Incorporating Germline Genetics into Personalised Risk-Assessment in the Detection of Prostate Cancer in Men with an Elevated Genetic Risk.

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Thesis submitted for MD (Res)

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Declaration

I hereby declare that the work presented in this thesis is the result of my own work. Assistance provided by other persons has been acknowledged within the chapter text. This work is original and has not been submitted for any other degree.

Holly Ni Raghallaigh

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Hypothesis

Prostate biopsy outcomes for men with a genetic predisposition to prostate cancer (PrCa) can be predicted from germline genetic profiling and clinical factors.

Abstract

Prostate cancer (PrCa) is the second most common male malignancy worldwide and has a large heritable component. The use of prostate specific antigen (PSA) as a screening test has limitations in both diagnostic accuracy and inability to discriminate between clinically significant and insignificant disease. Given that most men have a low lifetime risk of developing lethal PrCa, a proposed improved screening strategy could target certain populations of men at increased risk due to a genetic predisposition such as those with a family history (FH) of PrCa.

To date, approximately 170 common variants (SNPs) associated with PrCa risk exist and can be detected by analysing germline DNA. A polygenic risk score (PRS) can assign men a risk category. The use of prostate multiparametric MRI (mpMRI) has become the standard of care in men with a clinical suspicion of PrCa, with its clinical utility proving useful in helping target prostate biopsy towards a diagnosis of clinically significant prostate cancer. The clinical utility of mpMRI in men without a clinical suspicion of PrCa, but at increased risk of PrCa is undefined.

The PROFILE study offers up front mpMRI of the prostate and biopsy to men with a FH of PrCa, regardless of PSA in addition to SNP analysis. This thesis examined the association of PRS with biopsy outcome in addition to known clinical risk variables and biopsy outcome.

For this thesis, I performed an interim analysis of the PROFILE study participants' mpMRI, PRS and biopsy outcomes. The incidence of PrCa was 30%, occurring

across a spectrum of PSA values, but with 70% occurring at a PSA of 3.0ng/ml or less and 38% of significant cancers occurring at a PSA of 3.0ng/ml or less.

I found that PRS was associated with cancer detection and when men were categorised into percentiles of risk, those in the top 20% were the most affected. mpMRI performed well in detecting clinically significant prostate cancer, and a PIRADS 1-2 MRI showed high sensitivity at ruling out clinically significant disease. In men with an abnormal mpMRI, their predicted probability of cancer detection changed according to PRS. Overall mpMRI did not appear as specific in clinically significant cancer detection compared to PROMIS data, which is important to recognise in the use of PiRADS reporting in young men with a FH of PrCa if used as a risk-stratification or diagnostic tool on its own. Both PRS and MRI have the potential to play an important role in risk-stratifying men with a FH of PrCa and incorporation into targeted screening algorithms.

Abbreviations

ADT – Androgen deprivation therapy

ANOVA – Analysis of Variance

AS – Active surveillance

ASAP – Atypical Small Acinar Proliferation

AUC – Area under the curve

BCR – Biochemical recurrence

BPH – Benign prostatic hypertrophy

CSS – Cancer specific survival

DCE – Dynamic contrast enhancement

DDR – DNA damage response

DRE –Digital rectal examination

DWI – Diffusion weighted imaging

EAU – European Association of Urology

EPR – Electronic Patient Record

ERC – Endorectal coil

ERSPC – European randomised study of screening for prostate cancer

ESUR – European Society of Urological Radiology

FDR – First degree relative

FH – Family History

GGG – Gleason grade group

GRS – Genetic Risk Score

GWAS – Genome wide association studies

HGPIN – High Grade Prostatic Intraepithelial Neoplasia

HPC – Hereditary prostate cancer

ICR – Institute of Cancer Research

IQR – Interquartile range

ISUP –International Society of Urological Pathology

LR – Logistic regression

PrCa – Prostate Cancer

PFS – Progression free survival

PHS – Polygenic hazard score

PPV – Positive predictive value

PSAD – PSA Density

MCCL – Median cancer core length

MFS – Metastasis free survival

MMR –Mismatch repair

MRI – Magnetic resonance imaging

MpMRI – Multiparametric MRI

NCCN – National Comprehensive Cancer Network

NICE – National Institute of Clinical Excellence

NPV – Negative predictive value

NSC – National screening committee

OR – Odds ratio

OS – Overall survival

PCPT – Prostate cancer prevention trial

PHI – Prostate Health Index

PSA – Prostate specific antigen

PiRADS – Prostate Imaging - Reporting Data System

PLCO – Prostate, Lung, colorectal and Ovarian Cancer screening trial

PRS – Polygenic risk score

ROC – Receiver operator curve

RMH – Royal Marsden Hospital

RR –Relative risk

SIR –Standardised incidence ratio

SNP – Single nucleotide polymorphism

STHLM3 – Stockholm 3 Study

TCCL – Total cancer core length

TRUS – Transrectal ultrasound

UKGPCS – United Kingdom genetics prostate cancer study

USPSTF – United States preventative services taskforce

Contents

1 Chapter 1 –Introduction

1.1 Prostate Cancer

PrCa remains one of the most commonly diagnosed cancers in men in the western world, with 1.1 million new cases annually and 307,000 deaths [1]. It is the commonest cancer in the UK with Caucasian males having a lifetime risk of 13.2-15% of developing the disease [2]. However, not all men are at equal risk for developing the lethal form of the disease, and the vast majority will have unaffected overall survival (OS) [3].

Controversy exists as to the benefit of PSA-based screening for PrCa, as the screening test (PSA) has a propensity to detect a large amount of cancers ultimately destined to be clinically insignificant, and is poor at discriminating between men who may or may not harbour lethal disease, who would benefit from radical or early treatment.. Both the ProtecT and PIVOT studies of PSA screened men demonstrated no difference in disease-specific or all-cause mortality irrespective if men were treated or observed [4, 5]. The associated morbidity from radical prostatectomy or radiotherapy is significant ([6, 7]).

What we do know, is men with a FH of PrCa potentially have a susceptibility to earlier onset disease (with historic evidence suggesting aggressive histology and poor clinical outcomes) making them an ideal group of men in whom to establish robust screening tools to improve timely diagnosis and treatment (and survival although the impact of FH on overall and cancer specific-survival is unclear).

1.1.1 Family History

Not all men are at equal risk for developing PrCa which we now know is a polygenic disease with a large amount of heritability. Men with a brother or father affected with PrCa have at least a two-fold risk of developing PrCa compared to men without a FH, with the risk increasing further if the affected first degree relative (FDR) had early onset disease (≤55 years) with a relative risk (RR) of 3-5.[8]. Both monogenic and polygenic causes for PrCa exist, together explaining up to 40% of familial disease [9] .

This chapter will outline recent advances made in knowledge of PrCa characteristics in men with familial/hereditary PrCa with a focus on germline genetics and specific inheritable rare and common mutations contributing to PrCa risk, the use of polygenic risk scoring and current strategies underway to improve screening and diagnostics in this important group of men.

1.1.2 Hereditary Prostate Cancer (HPC)

This is a specifically defined scenario based on a man's pedigree, with three categories: 1) PrCa in three generations, 2) two cases of PrCa with an age of onset <55 years or 3) three first-degree relatives with the disease. It is still unclear if the biology of PrCa in men with HPC is more aggressive or different to those with 'sporadic' PrCa, but men with HPC do tend to have earlier onset disease. This specific subtype of familial PrCa was described by Carter et al in 1993, and accounts for approximately 3-5% of all prostate cancers [10] following segregation analyses and studies performed in twins and the Utah population database. In men with PrCa diagnosed at ≤55 years, it is found in up to 43% of cases [11] [12]. Mutations in the *HOXB13* gene have been implicated with this specific phenotype, as well as BRCA2, *HPC1, HPC2* and *CHEK2*.[13]. The mendelian inherence pattern of HPC has primarily been studied in Caucasian populations.

1.1.3 Familial Prostate Cancer

This describes the remainder of men with a 'FH' of PrCa (who do not fulfil the above criteria). Men with familial PrCa still have a significantly higher lifetime risk of developing the disease, with a 2-8 fold increase reported [14] and worsening risk with the number of relatives affected. Familial PrCa is likely caused by combination of dominant, moderate/high-risk genes, risk modulating-genes, common low-moderate risk variants, environmental exposures and advancing age (

Figure 1.1).

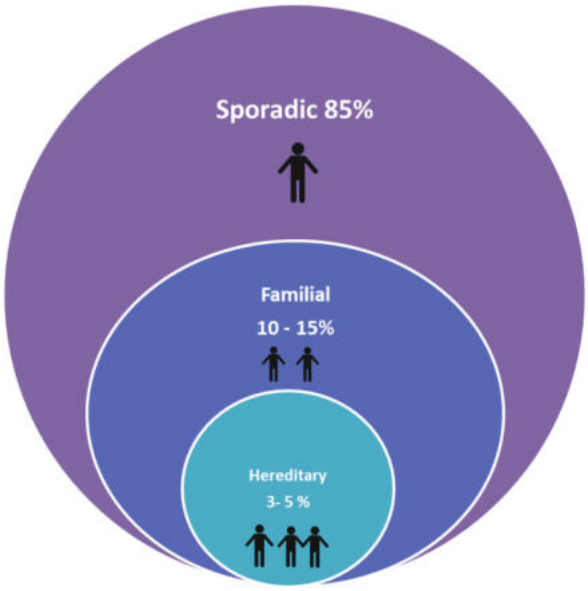

Figure 1.1 Schematic description of the proportion of PrCa attributable to either sporadic or inherited disease, adapted from Klein et al [13].

Men with a FH of prostate cancer have a significantly higher lifetime risk of developing the disease, with a 2-8 fold increase reported [14] and worsening risk with the number of first degree relatives affected. A Swedish study reporting from a family-database of over 9 million people reported a standardized incidence ratio (SIR) of 23.72 for men whose father and sibling were affected [15]. Further work in the same cohort established an SIR of 8.05 of developing PrCa before age 55, if a brother was affected before this age [16]. Another group screened 34 first-degree relatives (sons/brothers) of 17 sets of (two) brothers with PrCa, using a combination of PSA, digital rectal examination (DRE) and trans-rectal ultrasound guided (TRUS) biopsy. Clinically significant, asymptomatic PrCa was found in 8 (24%) men with a reported RR of developing PrCa of 5-11 [17]. In a retrospective assessment of American men with a FH of PrCa undergoing prostate biopsies for either a raised PSA or abnormal DRE, it was found these men were more significantly more likely to be diagnosed with both low-grade and high-grade PrCa [18].

Scandinavian twin studies have described the large effect of the heritability in PrCa in a study of over 44,000 pairs of both monozygotic (identical) and dizygotic (non-identical) twins. Lichenstein et al demonstrated concordance between identical and non-identical twins i.e the concordance for identical twins was 0.21 and 0.06 for non-identical twins meaning a man with an identical twin affected with PrCa has a 21% probability of having PrCa himself (6% for non-identical twins). They also showed a higher absolute risk (up to age 75) of PrCa in men with an affected identical twin (18%) compared to those with a non-identical twin (3%) and showed the difference in age of onset of PrCa was shorter in concordant pairs of identical twins (5.7 years) with PrCa than in concordant pairs of non-identical twins (8.8years). They estimated that 42% of PrCa risk in these (Swedish, Finnish and Danish) men was due to heritable factors [19].

A Swedish study reporting from a family-database of over 9 million reported a standardized incidence ratio (SIR) of 23.72 for men whose father and brother were affected [15]. Another group screened 34 first-degree relatives (sons/brothers) of 17 sets of (two) brothers with PrCa, using a combination of PSA, digital rectal examination (DRE) and trans-rectal ultrasound guided (TRUS) biopsy. Clinically significant, asymptomatic PrCa was found in 8 (24%) men with a reported RR of developing PrCa of 5-11 [17].

Elshafei et al assessed the risk of FH on having a positive prostate biopsy in men with a clinical suspicion of PrCa due to raised PSA or abnormal DRE in a single centre from 2000-2010. They found a significant association between FH status and the presence of both low grade and high grade cancer on initial biopsy. In all men with a positive biopsy, men who had a FH of PrCa were younger, less likely to be black and had a lower PSA than men without a FH. In multivariable analysis of men with a FH, prostate volume and PSA were significantly associated with high-grade disease [18].

1.1.4 Is the phenotype different?

Evidence for differing disease biology and trajectories between sporadic, familial and hereditary PrCa is varied. Work by Kupelin et al showed poorer biochemical-free relapse rates at five-years following radical prostatectomy in men with familial PrCa (one FDR affected with PrCa) compared to those without (n=529 with 12% of the cohort having a positive FH). FH remained an independent predictor of biochemical recurrence (BCR) after adjusting for age, histology, stage and surgical pathology variables [20] [21]. However in a similar analysis of 708 men undergoing radical prostatectomy published by Bova with longer follow-up [22], no differences in BCR were seen between men with familial PrCa or HPC compared with men with sporadic PrCa when were disease and age-matched.

With regards to clinical features including age at onset, histology and presenting PSA, Gronberg retrospectively analysed 74 families with familial and HPC in North

America compared to men without any FH. They showed that men with likely HPC harboured aggressive histology at diagnosis, had an earlier age of onset by 2 years and had worse stage at diagnosis than men with unlikely HPC and men with no FH [23]. In an analysis of 481,000 men in the Cancer Prevention Study II (CPS-II), 3% of men reported a FH of PrCa in one FDR and 0.05% reported a history in two FDRs. Men who had any FH of PrCa were 60% more likely to die from PrCa compared to those without, with a greater magnitude of effect if their affected relative was diagnosed before age 65 [24].

The Prostate Cancer Prevention Trial (PCPT) investigated the use of Finasteride, a 5-alpha-reductase-inhibitor (5ARI) in PrCa prevention. In the placebo arm of the study, men either underwent end of study biopsy (at 7 years) or a clinically-mandated biopsy if PSA was ≥4.0ng/ml or abnormal DRE at any of the men's' annual study visits up to year 7. In a separate analysis of 5,519 men in the placebo arm of this study, men with a FH (16% of the cohort) of PrCa had an odds ratio (OR) of 1.31 for harbouring PrCa on any form of prostate biopsy throughout study follow-up. Approximately 24% of men with a FH who underwent prostate biopsy had (any grade) PrCa compared with 17% of men without a FH. FH was not associated independently with high-grade disease. Approximately 95% of this cohort was Caucasian. [25] .

In a large Swedish analysis by Bratt et al of 51, 897 brothers of 32,807 men with PrCa, the risk of high-grade disease increased with the number of affected relatives (and with age) [26]. The same group also showed that brothers of men with high-grade (gleason 8-10) disease were at particular risk of developing high-grade disease themselves with a SIR of 2.53 (95% CI, 1.97-3.21) [27], with an OR of 3.82 (95% CI, 0.99-16.72) for monozygotic twins [28].

In an analysis of predictors of BCR in patients following radical prostatectomy, Liesenfeld et al specifically analysed long-term follow-up data of 2,480 men with more than 10-years of follow-up following surgery who still had no evidence of BCR. From years 10-20, age at surgery, PSA at diagnosis, pathological stage and gleason score were predictors for late BCR but FH status was not [29].

Brandt et al reported an increased risk of fatal PrCa in men whose father or brother had either had died from PrCa in an analysis of the Swedish Family Cancer database. They demonstrated a standardised mortality ratio (SMR) of death from PrCa in men with an affected father (2.04) or brother (2.75), with a risk of incident PrCa of 2.28 in men whose father died from PrCa and 3.25 in men whose' brother died from PrCa [30].

Interrogating the PLCO screening study data, Liss et al found that when they specifically analysed all study participants with a FH, those who were screened had a trend towards decreased PrCa specific mortality and time to death, with a significantly higher incidence of PrCa and cancer-specific mortality in those with a FH compared to those without [31].

Westerman et al reviewed the impact of FH in a first-degree relative on clinical and mortality outcomes in a surgical population of 16,472 men at the Mayo clinic undergoing radical prostatectomy from 1987-2010. Their cohort had a large incidence of FH (32.3%). They found men with a FH were significantly more likely to have localised disease, low-risk disease and higher 10-year cancer-specific (99% vs 97%) and overall survival (92% vs 85%) compared to men with no FH [32].

Lee et al also reported on an absence of effect of FH on survival outcomes in a longitudinal study of 1266 men in Korea who underwent radical prostatectomy, with a median follow-up of 40.5 months. No differences in histology characteristics were also found [33]. Similar survival results were also found in population of radical prostatectomy patients by Thalgott et al, however in contrast they found a higher proportion of patients with a FH had locally advanced disease and BCR [34].

Overall survival outcomes have been reported as superior in men with a FH of PrCa in a large Australian analysis of 9459 men by Ang et al [35] fter adjusting for NCCN risk category, age and year of treatment. In this analysis FH definition was a binary yes or no response relating to grandfather, father, uncle child or grandchild.

Recently, Urabe et al published a meta-analysis of 8 studies with 33,027 patients reporting no impact of FH on cancer specific mortality or the risk of biochemical recurrence (BCR) in localised PrCa patients [36].

1.1.5 FH analyses in ERSPC and PLCO trials

A subset analysis of European Randomised Screening Study of Prostate Cancer (ERSPC) (n=4,932) analysed the effect of FH in the Swiss cohort. Cumulative, screen-detected PrCa incidence over an 11 year period was significantly different between men with and without a FH (18% vs 12% respectively; HR 1.6). They reported FH along with age and baseline PSA as significant predictors of overall PrCa incidence, but only baseline PSA acted as an independent predictor for Gleason ≥7 cancer. When men were stratified by FH status. 5.1% of men with a FH of PrCa were found to have clinically significant cancer compared to 4% of men without a FH (no statistically significant difference). [37].

Prostate, Lung, Colorectal and Ovary (PLCO) trial data has also been interrogated for PrCa incidence in men with and without a FH. Abdel-Rahman analysed the relationship between PrCa incidence and a history of PrCa in FDR in 74,781 men. Similarly to ERSPC, a FH of PrCa was associated with a higher probability of cancer diagnosis (HR 1.59) with the number of affected first-degree relatives correlating positively with risk. By FH status (one FDR with PrCa) across both study arms, 10.5% of men without a FH were found to have PrCa compared with 16.5% of men with a FH. There was no difference in cancer stage, age or PSA at diagnosis between the groups. Mean PSA at cancer diagnosis for men with a FH was 9.8 compared to 11.8 for men without a FH. There was no statistically significant difference in tumour stage, histology, PSA or patient age between cancer cases in men with and without a FH. When analysing by screening arm vs non-screening arm, FH in a FDR and the number of FDRs was significantly associated with PrCa mortality (HR 1.89) in the non-screening arm compared to the interventional arm [38] suggesting a benefit to screening this group.

1.1.6 Family history analyses in the placebo arms of the PCPT and REDUCE trials

The Prostate Cancer Prevention Trial (PCPT) investigated the use of Finasteride, a 5-alpha-reductase-inhibitor (5ARI) in PrCa prevention. In the placebo arm of the study, men either underwent end of study biopsy (at 7 years) or a clinically-

mandated biopsy if PSA was ≥4.0ng/ml or abnormal DRE at any of the men's annual study visits up to year 7. Of the 4,692 men in the placebo arm who underwent evaluation, 1,147 cancers were detected (24%). Of those available for evaluation, 237 were Gleason 7,8, 9 or 10 (22%) [39]. In a separate analysis of 5,519 men in the placebo arm of this study, men with a FH (16% of the cohort) of PrCa had an odds ratio (OR) of 1.31 for harbouring PrCa on any form of prostate biopsy throughout study follow-up. The median PSA of this cohort at study entry was 1.5 ng/ml with 88% of men having a PSA ≤4.0ng/ml. Approximately 24% of men with a FH who underwent prostate biopsy had (any grade) PrCa compared with 17% of men without a FH. FH was not associated independently with high-grade disease. Approximately 95% of this cohort was Caucasian. [25] .

The REDUCE study was a 4-year RCT comparing efficacy of Dutasteride compared to placebo in preventing the development of PrCa in men defined at the study entry as being at an increased risk for PrCa (due to abnormal PSA/DRE). A sub-analysis of the study also examined the effect of FH on PrCa incidence at time of biopsy in both treatment and placebo arms. In the placebo arm, they found PrCa (all grades) in 23% of men undergoing biopsy with a FH compared to those without (19%) in the placebo arm, and found a 31% risk reduction (RR) in PrCa with Dutasteride [40] [41].

1.2 Specific Germline Genetic mutations involved in PrCa

Specific PrCa risk genes exist, occurring rarely in the general population (0.2-0.3%) but with emerging evidence suggesting enrichment in cases of advanced PrCa (Table 1.1).

Pritchard et al [42] highlighted the important role of DNA repair gene mutations in the biology of men presenting with advanced PrCa, demonstrating a relative risk (RR) of 18.6 for men with germline *BRCA2* mutations and 3.1 for men with *CHEK2* mutations. In their analysis of 692 men with metastatic PrCa, they found 11.8% of men carried a germline mutation in a DNA repair gene with 44% of all mutations found in the *BRCA2* gene (Figure 1.2). These men were unselected for age at diagnosis or FH status. This differed to men with localised PrCa, in whom a

frequency of germline mutations of 4.6% was found (however when specifically grouping men into NCCN risk criteria, 2% of men with low-intermediate risk had germline mutations in DNA repair genes and 6% in men with localised, high-risk PrCa) [43].

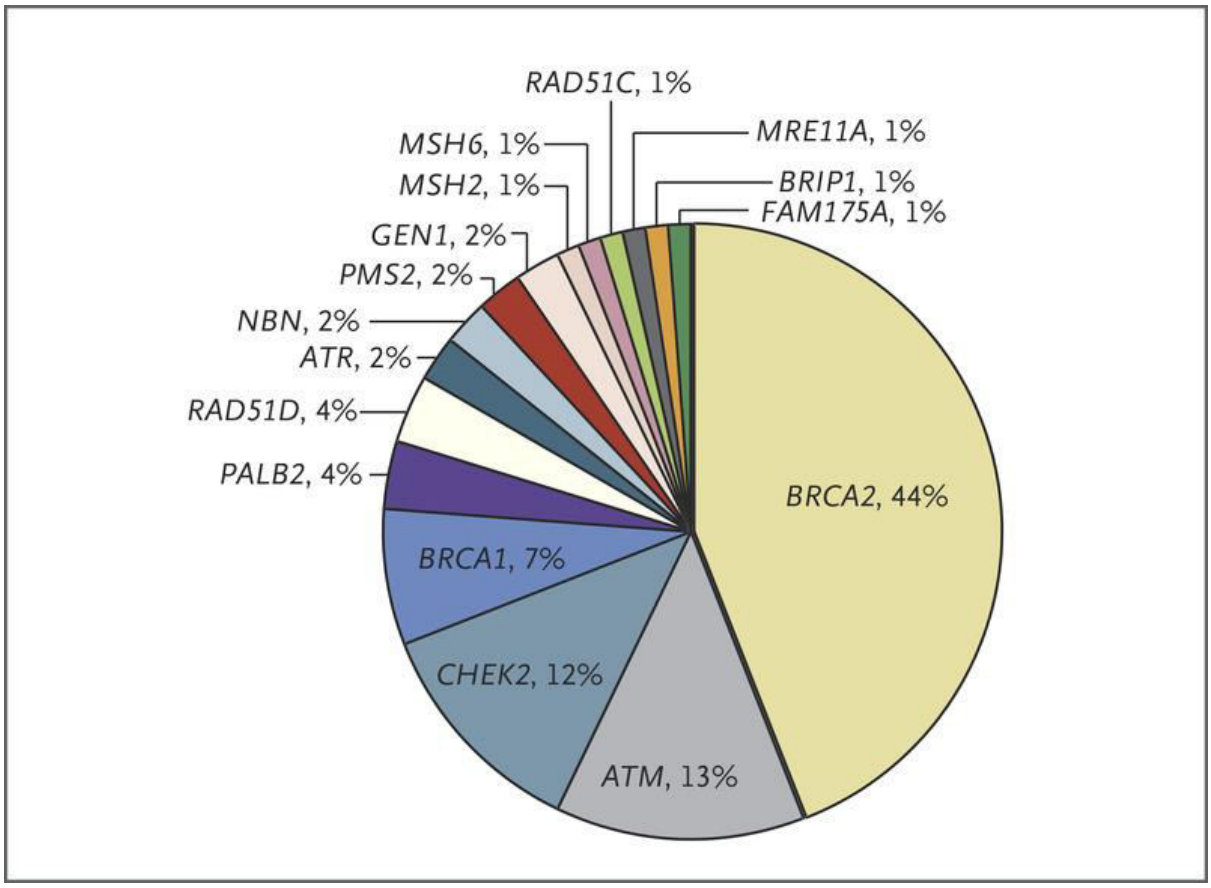

Figure 1.2 Reproduced from Pritchard et al. Pie chart demonstrating distribution of pathogenic germline mutations found across 16 DNA repair genes in 692 men with metastatic PrCa, unselected for age or FH status [42].

Nicolosi et al performed a cross-sectional study of 3607 men with PrCa, unselected for FH, age or disease stage referred to clinical genetics for germline testing between 2013 – 2018. They found 17.2% of men carried pathogenic germline mutations, of which 30.7% were *BRCA1/2* variants, 4.5% were due to *HOXB13*, 14.1% *CHEK2* and 9.6% due to *ATM [44].*

Mutations in *HPC1*, *HPC2*, *HOXB13* and *HPCX* have been linked via linkage and segregation analyses specifically to familial and HPC. Mutations in genes involved in DNA and mismatch repair such as *BRCA1/2*, *ATM, CHEK2,* and *MLH1* have been associated with an increased risk of developing PrCa in men with advanced PrCa unselected for FH as well as in men with familial PrCa.

In an analysis of a European cohort of men with a FH of PrCa in the United Kingdom Genetics Prostate Cancer Study (UKGPCS) [45], 7.3% of PrCa patients with a positive FH were found to carry a pathogenic germline mutation. The most frequent mutation was in *BRCA2* (28.57% of all mutations), and importantly there was a significant association between genetic mutation carrier status and nodal and metastatic disease (Figure 1.3).

Some of the specific genes when can be affected in the small number of men with PrCa due to a hereditary cancer predisposition syndrome are discussed below.

Gene	Chromosomal location	Function
BRCA1	17q21	Transcription, DNA repair of double-strand breaks and recombination
BRCA2	13q13	Homologous recombination pathway for double-strand DNA repair
HOXB13	17q21.32	Essential for vertebrate embryonic development
ATM	11q22	Codes for a protein which is an important cell-cycle checkpoint kinase, involved in signalling pathways required for cell responses to DNA damage and for genome stability
MLH1 (Lynch Syndrome)	3p22.2	DNA damage signalling and DNA damage repair. Freq mutated in HNPCC. Part of MMR genes

MSH6 (Lynch Syndrome)	2p16.3	Codes for protein essential to DNA repair. Belongs to MMR gene family
MSH2 (Lynch Syndrome)	2p21-p16.3	DNA damage signalling and DNA damage repair. Belongs to MMR gene family
NBN	8q21.3	Gene product is thought to be involved in DNA double-strand break repair and DNA damage-induced checkpoint activation.
CHEK2	22q12.1	Codes for a protein involved in cell-cycle checkpoint regulation and tumour supression
HPC1	1q24-q25	Associated with HPC. Found more often in men with early-onset disease. regulates cell proliferation and apoptosis through the interferon-regulated 2-5A pathway, and it had been a suggested tumor suppressor gene
HPC2/RNASEL	17p12	Associated with HPC. Coding for protein involved in tRNA processing and gene expression.
HPCX	Xq27-q28	X chromosome, previously studied within a Finnish founder population. Gene function unknown.

Table 1.1 moderate-high risk protein-coding genes involved in familial PrCa

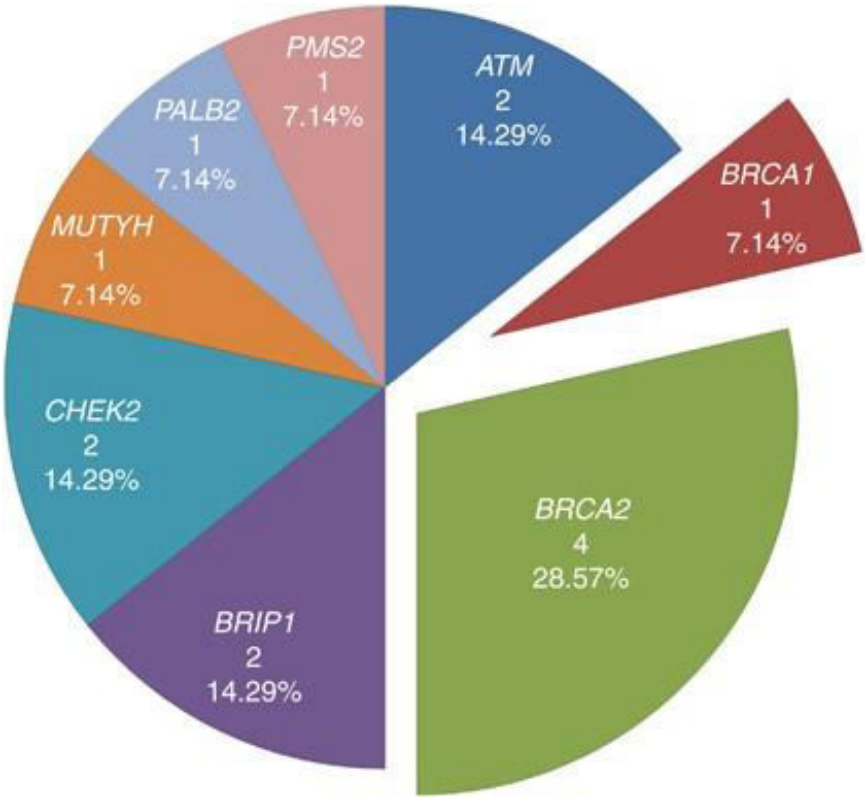

Figure 1.3 Reproduced from Leongamornlet et al. Distribution of pathogenic germline mutations in 191 men with at least ≥3 cases of PrCa in their family [45]

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1.2.1 NBN

Cybulski et al genotyped over 3,750 Polish men with PrCa for mutations in *BRCA1*, *CHEK2* and *NBN*. Mutation frequencies were higher in men with disease onset less than 60 years and in men with a FH of PrCa (positive/negative) (Table 1.2). A founder mutation (675del5) in *NBN* is found in approx. 1 in 750 of the Polish population with a three-fold increase in risk of PrCa and an apparent significant effect on overall survival after adjusting for age, stage and tumour grade. *CHEK2* mutations did not appear to have a similar effect on survival but were found more commonly in men with familial PrCa, and were more common than *BRCA1* mutations. It is estimated that mutations in *NBN* and *CHEK2* account for 1.4% and 5% of all prostate cancers in Poland respectively [46]. In a UK study of 139 aggressive PrCa cases, Mijuskovic et al found inherited protein truncating variants (PTVs) in several DNA repair genes including *NBN* (present in 5.8% of aggressive cases and no non-aggressive cases) which distinguished between aggressive and non-aggressive PrC [47]a.

	Controls (*n*=3956) No. (%)	Unselected cases (*n*=3750) No. (%)	OR	95% CI	*P*-value	Familial cases (*n*=412) No. (%)	OR	95% CI	**P Value**
Any *BRCA1* mutation	*17 **(0.4%)***	*14 (0.4%)*	*0.9*	*0.4–1.8*	*0.8*	*4 (**1.0%**)*	*2.3*	*0.8–6.8*	*0.3*
***NBN* 657del5**	23 **(0.6%)**	53 (1.4%)	2.5	1.5–4.0	0.0003	10 **(2.4%)**	4.3	2.0–9.0	0.0001
Any *CHEK2* mutation	228 **(5.8%)**	383 (10.2%)	1.9	1.6–2.2	<0.0001	59 **(14.3%)**	2.7	2.0–3.7	<0.0001

Table 1.2 Adapted from Cybulski et al. Frequency of germline mutations of *BRCA1*, *CHEK2* and *NBN* in controls, familial cases and cases unselcted for FH status [46]

1.2.2 CHEK2

CHEK2 mutations have been implicated in familial and hereditary PrCa, (Figure 1.3) and in particular in Slavic populations. Mutations of *CHEK2* are rare in men of Asian, Hispanic or African ancestry. Seppala et al genotyped 537 men with PrCa unselected for FH, 120 men with HPC and 480 healthy controls for the truncating 1100delc and missense 1157T *CHEK2* variants, both of which are Polish founder mutations. Both mutations were significantly associated with PrCa in men with HPC and not in unselected cases or controls [48]. A pooled OR of 1.98 and 3.39 for the*CHEK2* 1100delc variant for unselected and familial cases respectively was reported by Hale et al [49].

In a UK study of 191 men with 3 or more cases of PrCa in their family, Leongamornlert et al reported *CHEK2* germline mutations accounted for 14% of all germline loss of function (LoF) mutations discovered and was associated with more aggressive disease [45]..

1.2.3 HOXB13

HOXB13 is a protein-encoding gene belonging to the homeobox family, coding for a transcription factor essential in prostate development and also acts as a tumour suppressor gene. Carriers of a rare missense mutation (G84E) of the *HOXB13* gene have a 33% risk of developing PrCa, compared to a 12% risk of non-carriers when studied in a Swedish population, with themutation present in 1.3% of population controls and >4% of cases [50]. An analysis of 2,433 PrCa (European) families demonstrated this mutation in 5% of men with HPC, also describing a founder effect seen more commonly in Nordic populations [51] [50]. Further large-scale analysis of 4,000 PrCa cases in Finland for this specific mutation revealed a significantly higher carrier-rate amongst men with PrCa (3.5%) and those with a FH (8.4%) compared to controls [52].

In a separate study of 5,083 unrelated European subjects who had PrCa, Ewing et al found the carrier rate of the *G84E* mutation was increased by a factor of approximately 20. This mutation was significantly more common in men with disease at a young age and with a positive FH (1.4%), than those without (0.1%).[53]. There was no difference in Gleason grade between carriers and non-carriers [53]. This genetic mutation therefore seems particularly significant in young men with PrCa and with a strong FH in Finnish and Swedish populations.

Recently, Nyberg et al predicted age-specific cumulative risks for carriers of the G84E *HOXB13* variant for developing PrCa under varying pedigrees of FH. The average predicted PrCa risk by age 85 was 62% compared with 15% for non-carriers. For a mutation carrier with an affected father, the risk estimate ranged from 69% to 92% depending on the father's age at PrCa diagnosis, and for a man with two affected FDRs, the risk estimate ranged from 70% to 98% [54].

1.2.4 BRCA

Mutations in *BRCA1/2* are rare in the general population with an estimated prevalence of 0.2-0.3% in men and women. The Ashkenazi Jewish population is enriched for mutations in these genes with a frequency of approximately 2-2.5% of women carrying a mutation in *BRCA1/2* (12% of those with a history of breast cancer and 17% of those with ovarian cancer) and (3.2-4% of men with PrCa) [55].

Germline *BRCA2* mutations confer the highest risk of PrCa (8.6-fold in men aged ≤65 years) [56, 57], with the effect of mutations in *BRCA1* less significant (3.5-fold) [58]. In an Icelandic study, *BRCA1/2* mutation carriers were younger at diagnosis, (69 vs. 74 years) and presented with more advanced tumour (T) stage (T3-4: 79% vs. 36%) and poorly differentiated tumours (84% vs. 52.7%). Median cancer-specific survival (CSS) for carriers was 2.1 years compared with 12.4 years for non-carriers [59].

Poorer outcomes in these men compared to those without genetic mutations have also been reported. Edwards et al [13] compared overall survival (OS) after PrCa diagnosis in a series of *BRCA2* mutation carriers and controls. *BRCA2* mutation carriers had a median OS of 4.8 years vs with 8.5 years for non-carriers. Work by

Castro et al [60] reported a spectrum of pathogenic mutations in *BRCA1* and *BRCA2* confers a more aggressive PrCa phenotype more frequently associated with lymph node involvement and distant metastasis at diagnosis compared to non-carriers. *BRCA2* germline mutations were demonstrated as a prognostic factor for poorer OS and CSS, independently of other established prognostic factors including stage, Gleason score, and PSA and an Icelandic study showed a mean overall survival of only 2.1 years in men with PrCa with the specific 999del5 *BRCA2* mutation compared with non-carriers [61].

The most optimal treatment strategy for men with PrCa who carry a high-risk genetic mutation such as *BRCA2* is yet to be established. Castro et al retrospectively reviewed 1302 men (67 *BRCA1/2* mutation carriers) with PrCa, investigating metastases free survival (MFS) and CSS after either radical prostatectomy or radiotherapy. No direct comparison between the two treatments was possible however, a non-significant poorer MFS and CSS was noted after radiotherapy [62]. The PROREPAIR-B study reported shorter time to receiving androgen deprivation therapy (ADT) and a reduced median CSS in men with *BRCA2* mutations and demonstrated *BRCA2* mutation status as an independent prognostic factor affecting survival in men with metastatic castrate-resistant PrCa [63].

As described, men harbouring pathogenic mutations in *BRCA1/2* and *ATM* have a worse clinical phenotype with significantly elevated risks of adverse histology, shorter OSand poorer treatment responses. Men are increasingly choosing Active Surveillance (AS) as a treatment option for localised PrCa of favourable risk, due to the avoidance of the morbidity associated with radical surgery or radiotherapy. Carter et al [64] recently demonstrated a significant association between disease upgrade in men being treated with AS with germline mutations in *BRCA1/2/ATM* (Figs 19-20 of Gleason Grade Group (GGG) 1 upgrading to ≥GGG3 compared with non-carriers (five-fold greater risk; adjusted HR 2.40, p=0.046). (Figure 1.4). San Francisco et al [65] analysed predictors of progression in men with low-risk PrCa during AS (n=120). They found men with a FH of PrCa (at least one FDR or second-degree relative) were more likely to experience disease progression than men without (HR 1.93, 95% CI 0.96, 3.90; p=0.07) after a median follow-up of 2.4 years.

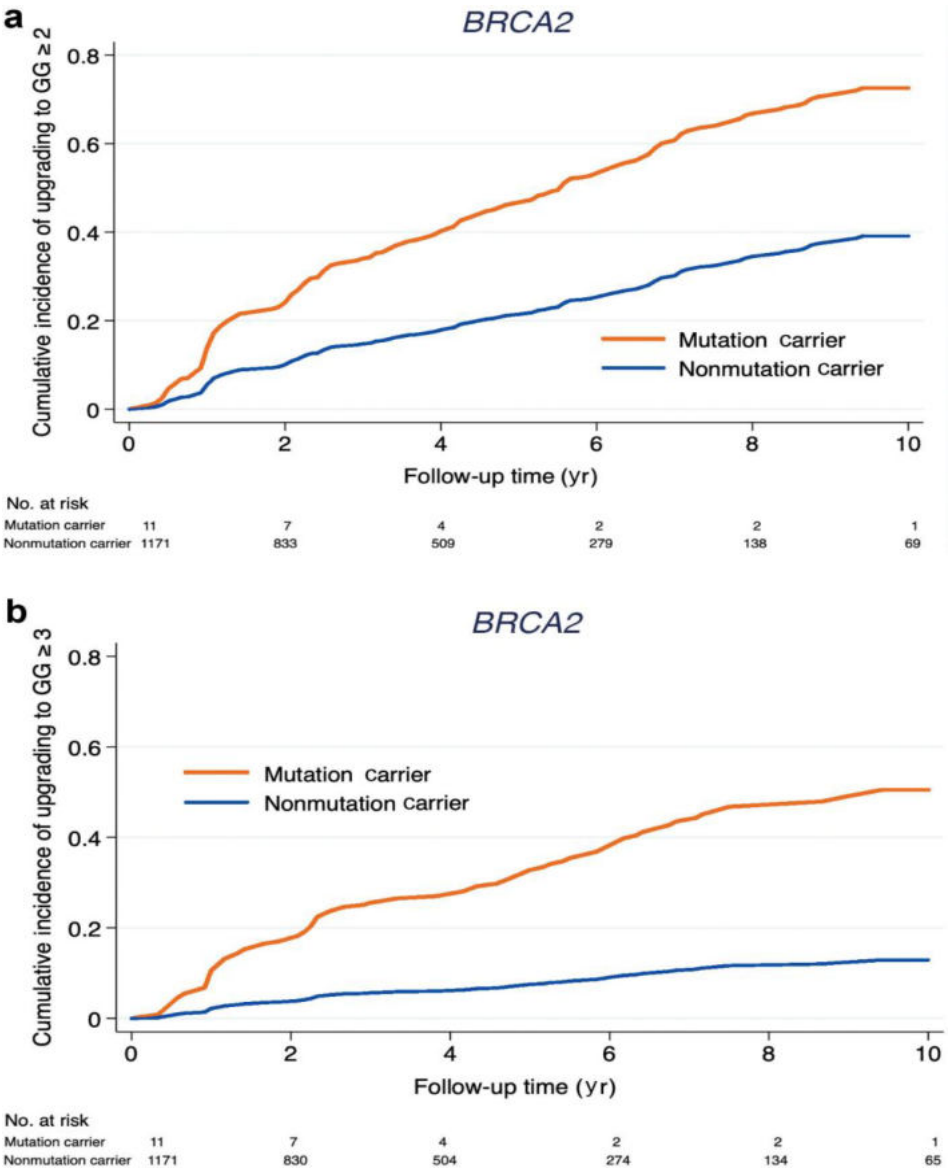

Figure 1.4 Reproduced from Carter et al. Risk of disease upgrading after diagnostic biopsy among carriers and non-carriers of mutations in *BRCA2* only who were initially diagnosed with grade group (GGG) 1 (Gleason score 3 + 3) (A) upgrading after diagnostic biopsy to GGG 2 or above (Gleason score 3 + 4 or above); (B) upgrading after diagnostic biopsy to GGG 3 or above (Gleason score 4 + 3 or above) [64]

1.2.5 Lynch Syndrome

Lynch syndrome is a multi-cancer syndrome caused by germline mutations in the miss-match repair (MMR) genes; *MLH1*, *MSH2* or *MSH6*. It has been estimated in a study investigating 106 men with MMR mutations that the cumulative risk of PrCa by the age of 70 in mutation carriers is 30%, compared with 9-12% in the general population. Of the cancers diagnosed with available histology, 5 cases (62.5%) were poorly differentiated, with a Gleason score ≥8 [54].

1.3 Single Nucleotide Polymorphisms (SNPs)

Risk alleles occurring in ≥1% of the population are known as a single-nucleotide polymorphism (SNPs). PrCa specific SNPs result in an elevated and potentially clinically relevant risk when multiple SNPs occur together, producing a cumulative effect. Increasing knowledge of polygenic disease heritability and susceptibility, the ability to perform large genome-wide association studies (GWAS) of thousands of cases/controls and disease-specific SNP discovery allows us to construct risk scores based on an individuals' germline genetics (polygenic risk scores or 'PRS'). PrCa risk SNPs have been found at many different chromosomal loci, outlined in Figure 1.7.

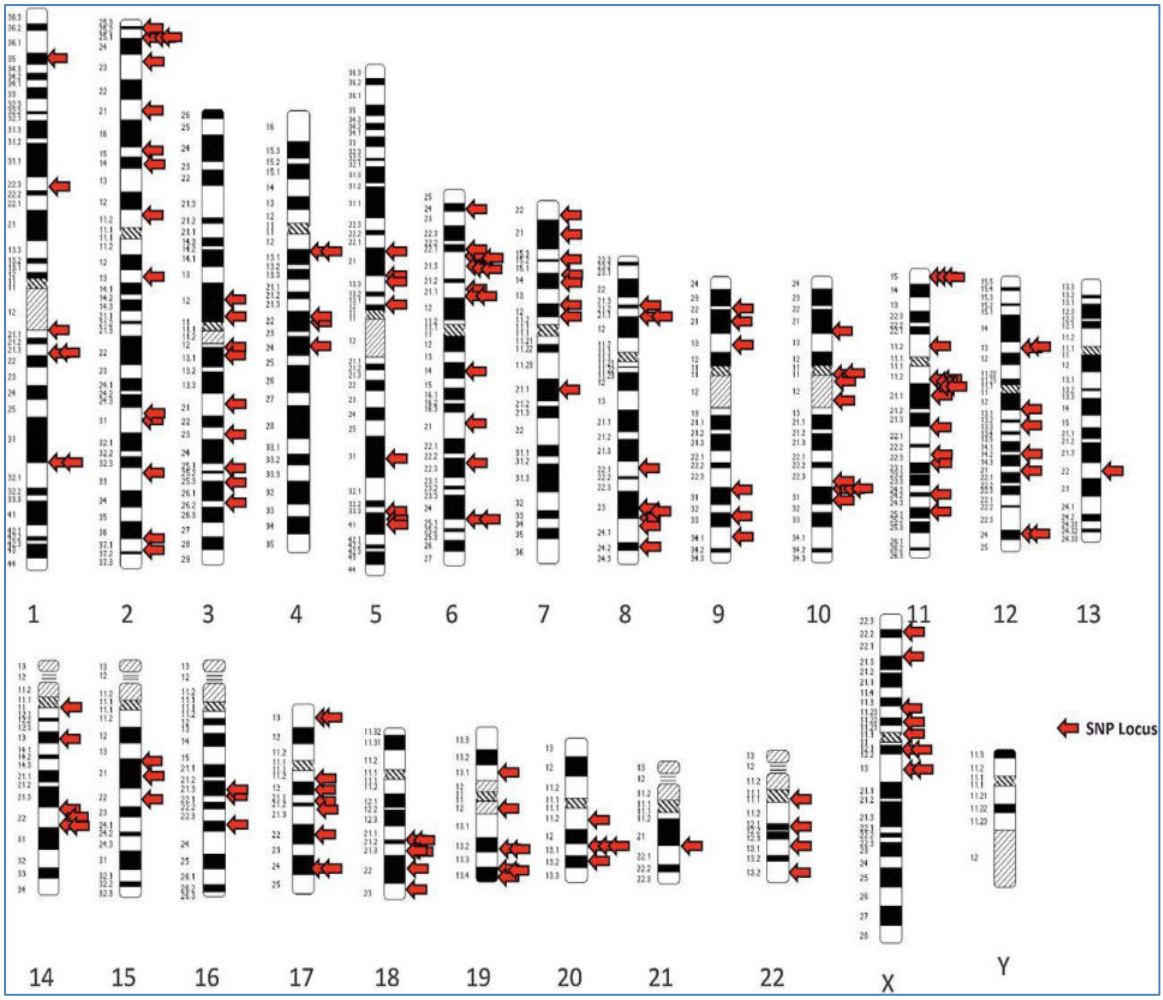

Figure 1.5 Reproduced from Benafif et al. Location of known PrCa risk SNPs per chromosome (each red arrow represents a SNP at its chromosomal loci [66]

Figure 1.6 Reproduced from Benafif et al. Location of known PrCa risk SNPs per chromosome (each red arrow represents a SNP at its chromosomal loci [66]

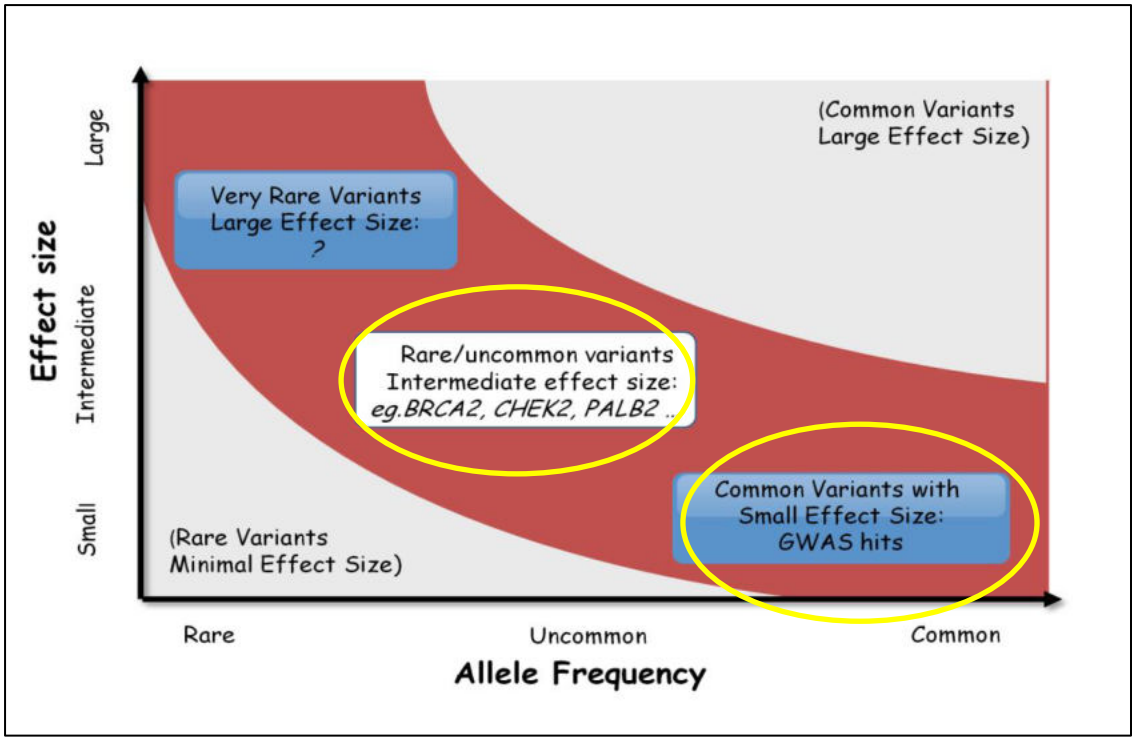

Figure 1.7 Adapted from Moniolo et al. Diagram showing the spectrum of genetic variants in polygenic disease i.e PrCa. The X-axis plots the risk allele frequency and effect size along the y-axis. The top right corner represents common variants with large effect sizes (none known). The bottom left corner represents rare variants with small effect size. Such variants would be of limited clinical interest. Candidate gene and linkage analyses have discovered rare variants (i.e *BRCA, HOXB13*) which produce moderate effect sizes. GWAS has discovered common variants conferring small to modest effect sizes. Those variants circled in yellow represent these germline genetic variations we incorporate into PRS (common variants) and panel testing (ie *BRCA2*) [67].

1.3.1 PRS based on PrCa-risk SNPs

An estimation of an individual's genetic risk for a disease or trait can be predicted using a polygenic risk score (PRS), (the sum of the risk SNPs, weighted by the log OR of each SNP)[68]. The effect of each allele has been mapped from published GWAS. By measuring the genetic burden for a specific disease/trait, PRS provides a clinically useful tool in identifying groups of people at risk of a disease, for example to stratify men into a screening regimens by only screening those at the greatest risk, i.e those we can justify exposing to potential hazards of screening tests.

An individuals' PRS in addition to clinical information and imaging may play a role in developing personalised screening strategies for PrCa. The value of PRS grew from

the genotyping of thousands of individuals initially with common non-cancerous conditions (i.e coronary artery disease) in order to discover disease-specific genetic variants and their effects (Figure 1.7).

Using 14 known PrCa associated SNPs and FH status, Xu et al built a risk prediction model. They found an OR of 4.92 for developing PrCa for men with a positive FH and ≥14 risk alleles for the Swedish cohort in their study [69] . Using data from the REDUCE trial, Kader and colleagues analysed germline DNA from 1,654 men undergoing prostate biopsy. They found adding a genetic score based on 33 risk SNPs with clinical variables was an independent PrCa risk predictor, and demonstrated their model's ability to reduce the number of biopsies required to diagnose PrCa [70].

As opposed to mass population or opportunistic screening, targeting 'high risk' men in whom early PrCa detection can offer a meaningful benefit seems pertinent instead of exposing all men to the harms of PrCa screening. In this vein, a PRS could stratify men into 'low' or 'high' risk groups, potentially opening up a door on which to base future screening decisions (i.e screening frequency/intensity) on. In 2018, the Oncoarray consortium published a meta-analysis and discovery of 63 new PrCa risk loci. Using a PRS of 147 SNPs, men falling in the top 1% of risk had an estimated RR of 5.71 when compared to men in the 25^{th}-75^{th} centiles of risk [71] (Table 1.3).

Risk category percentile	Relative risk	95% CI
<1	0.15	0.11-0.2
1-10	0.35	0.32-0.37
10-25	0.54	0.51-0.57
25-75	1 (baseline)	
75-90	1.74	1.67-1.82
90-99	2.69	2.55-2.82
>=99	5.71	5.04-6.48

Table 1.3 Reproduced from Schumacher et al. Estimation of PrCa risk by PRS using 147 risk SNPs. Men categorised into PRS percentiles based on the cumulative score distributed among controls [71].

Zheng & colleagues published their results examining the effect of the five commonest known SNPs associated with PrCa. They found their presence in combination with a FH accounted for 46% of the cases of PrCa in their cohort and conferred an odds ratio of 9.46 compared with men who had none of these factors, independent of PSA. MacInnis et al developed a model for predicting the probability of developing future PrCa based on 26 risk SNPs in men with familial PrCa [72], demonstrating the simultaneous effects of FH status and known PrCa susceptibility variants (Figure 1.8).

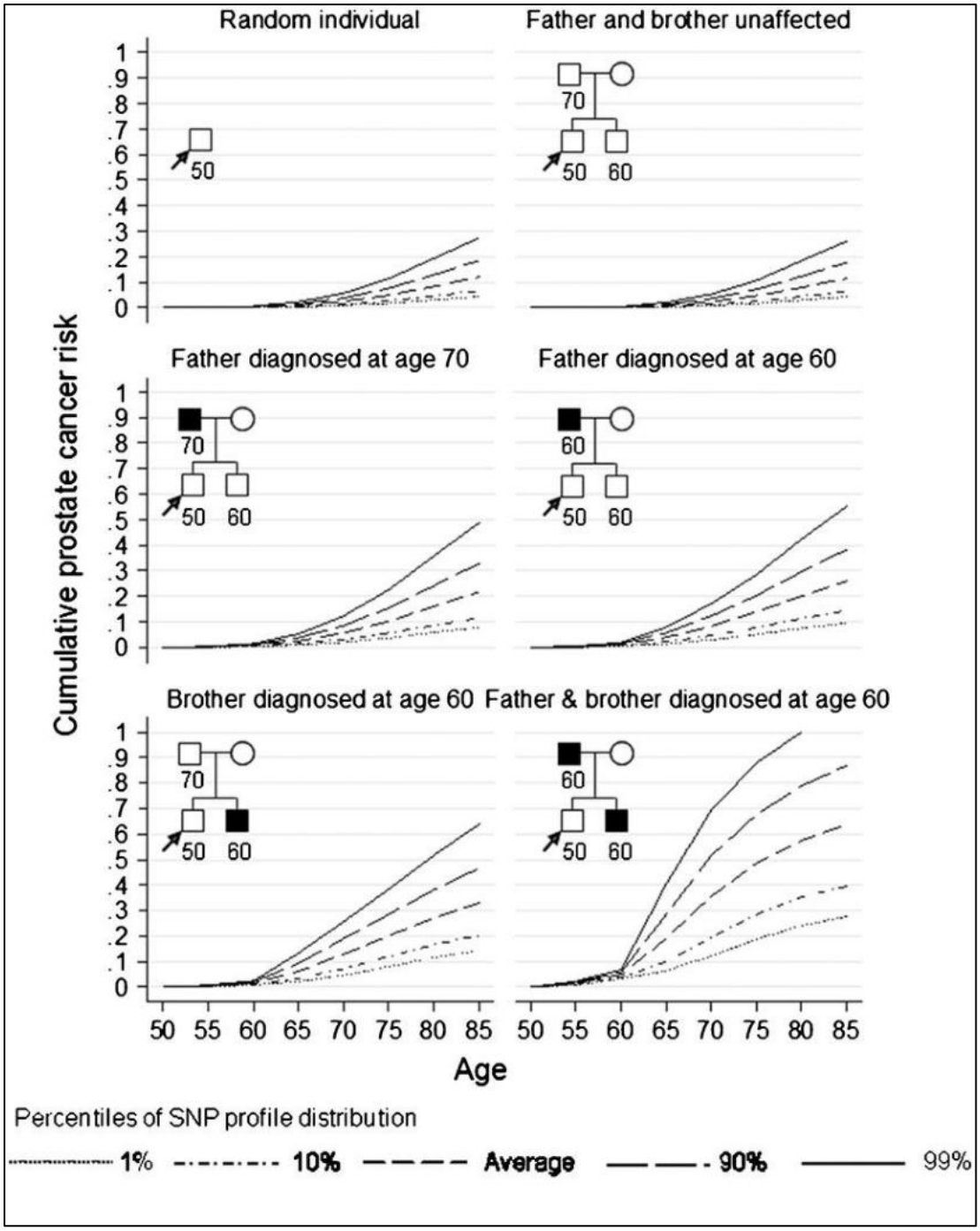

Figure 1.8 Reproduced from MacInnis et al. The lifetime PrCa risk is demonstrated depending on a man's FH status (i.e lifetime risk will vary depending on how many relatives affected and at what age) and PRS [72]

Lecarpentier and colleagues investigated the use of SNP profiling as a means of predicting PrCa risk in 1,802 men with *BRCA1/2* mutations, based on 103 known PrCa susceptibility loci (Figure 1.9). They demonstrated an increasing PrCa risk for increasing PRS quartiles, with an estimated risk of (any) PrCa of 61% by age 80 in men with *BRCA2* mutations who were in the 95th percentile of risk according to their PRS. This study provides valuable information on the additional benefit of SNP profiling in this group of men for risk stratification, which ultimately has the power to inform the patient and clinician on timing and type of screening/intervention decisions [73].

At present no formal UK or international guidance exists regarding screening programmes for men with additional PrCa risks (such as *BRCA1/2* mutation status or FH). These results indicate that a PRS could be informative in predicting individualised cancer risk for *BRCA* mutation carriers, a small but important group of men due to their high-risk status and could form the basis of an enhanced screening strategy for *BRCA* mutation carriers (Figure 1.9). Recently, Seibert et al used a polygenic hazard score (PHS) using 54 PrCa risk SNPs which showed ability in predicting age at diagnosis of any and also aggressive PrCa. In this study, the positive predictive value (PPV) of PSA also increased with increasing PHS [74].

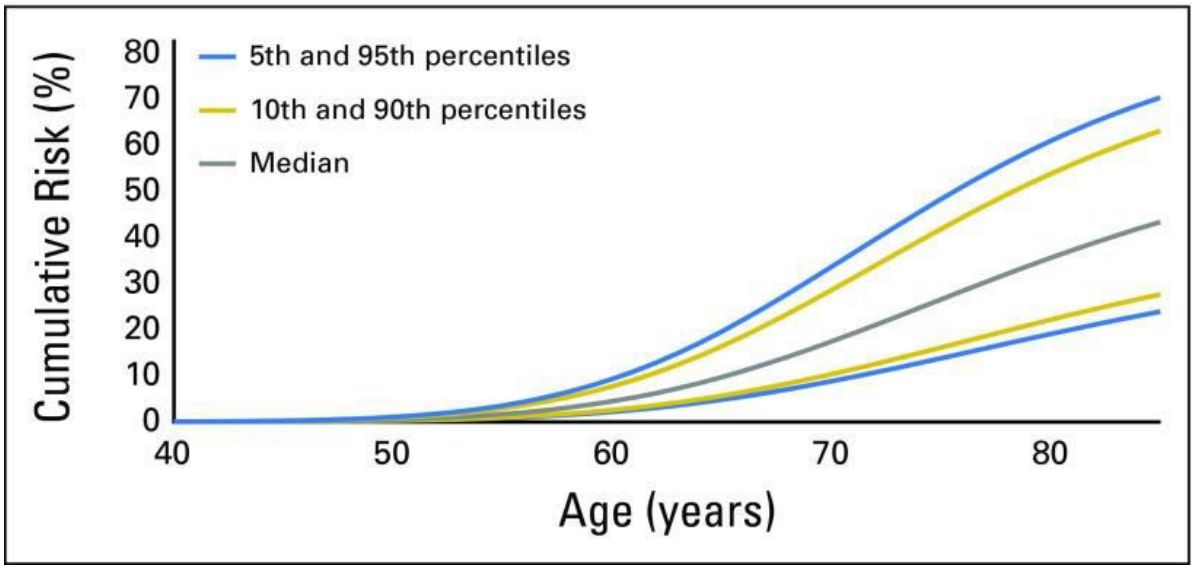

Figure 1.9 Reproduced from Lecarpentier et al. Predicted PrCa cumulative risk for male carriers of *BRCA2* mutations by percentiles of PrCa polygenic risk score that was constructed by using results from population-based studies [73]

1.4 Targeted Prostate Cancer Screening

PSA is not a diagnostic test for PrCa and has been deemed an unsatisfactory tool for population screening. Few other specialities have been as plagued with controversy as PrCa diagnostics, since the advent of PSA as a tumour marker after its isolation from the serum of 219 patients with PrCa by Papsidero in 1981 [75]. Work performed by Stamey in the 1980s [76] produced evidence that although PSA is related to PrCa, its levels also rose in the presence of BPH rendering its relationship to PrCa diagnosis in Stamey's own words as 'tenuous at best' [77]. The long natural history of PrCa and its biological variability is demonstrated in autopsy studies, demonstrating many men die with asymptomatic, localised PrCa [78, 79]. PSA screening agnostically taps into this reservoir of indolent disease, diagnosing men with a cancer which then exposes them to the morbidity and anxiety associated with PrCa diagnostics and radical treatments, without often a survival benefit.

In essence, PSA remains an imperfect screening tool in isolation for discriminating between a clinically significant cancer, and one which may have never affected a man during the course of his lifetime. Whilst the ERSPC study demonstrated a

reduction in PrCa-specific mortality (21%) after 13 years of follow up with a 4-yearly PSA screening interval, concerns regarding over-diagnosis and overtreatment exist [80]. The UK National Screening Committee (NSC) [81] [82] advises PSA is an unacceptable screening test with a recommendation made against a national screening programme.

In a report to the NSC in March 2013, the University of Sheffield assessed the outcomes of four different screening options; a single screen at age 50, screening every 4 years age 50-74, screening every 2 years age 50-74 and screening annually aged 50-74. They estimated all repeat screening policy options were associated with 45-65% risk of over-detection of PrCa, with a rate of 30-40% for a single screen policy and in order to obtain 1 additional year of life, repeat screening policies are associated within the region of 22-32 years of additional prostate cancer management. Finally, they estimated an overall expected survival benefit of 2-4 days per person invited for a single screen aged 50, and 20-60 days for the repeat screen policies [82].

The US Preventive Services Taskforce (USPSTF) cited the benefits of population PSA screening as 'small and potentially none, and the harms are moderate to substantial' [83]. Their 2017 PSA screening recommendation did acknowledge screening may offer greater benefits to men of African ancestry and men with a FH of PrCa compared with the general population. They strongly encouraged research regarding the most useful age to commence PrCa screening, optimal screening intervals and differences in outcomes in these two groups of men compared with men in the general population [84] **.**

Given that advanced and aggressive PrCa can significantly affect a man's quality and length of life [85], targeting men at a higher risk of cancer and clinically significant cancer would be the better target of a screening programme. However, no clear discriminatory test has materialised. It is in this scenario where clinical and genetic risk modelling may play a large part in future targeted screening strategies.

1.4.1 SNPs and PRS in PrCa risk stratification and screening

There is evidence to suggest genetic based scores improve PrCa detection and risk stratification. Using 14 known PrCa associated SNPs and the presence/absence of a FH of PrCa, Xu et al reported an OR of 4.92 for developing PrCa for men with a positive FH and ≥14 risk alleles for the Swedish cohort in their study [69] .

Using data from the REDUCE trial, which assessed the chemopreventative benefits of Dutasteride, Kader and colleagues analysed germline DNA from 1,654 controls. These men all had an initial negative prostate biopsy, with subsequent prostate biopsies at 2 and 4 years. They found adding a genetic score based on 33 risk SNPs with clinical variables was an independent predictor for PrCa on repeat prostate biopsy, and demonstrated the ability to reduce the number of repeat biopsies required [70].

Recently, Na et al investigated the association between a genetic risk score (GRS) and patient age at PrCa diagnosis compared to the association with FH. They performed a cohort study of 3225 white men (also from the REDUCE trial), and constructed a GRS based on 110 known PrCa risk SNPs for each participant. They found higher a GRS' was associated with earlier age at PrCa diagnosis, independent of FH status [86].

Callender et al investigated the cost-effectiveness and benefits/harms of using a PRS tailored screening program by way of a simulated model. They compared three screening models; no screening, age-based screening (PSA every 4 years from age 55-69) and risk-tailored screening (PSA every 4 years only in men whos' risk is at or above a certain absolute risk threshold based on their PRS). They compared cost, overdiagnosed cancers and amount of PrCa-related deaths averted due to screening between models. They found an age-based program prevented the most deaths but caused a greater amount of overdiagnosed cancers whereas a precision-based screening strategy averted a third more cases of overdiagnosis but averted fewer PrCa-specific deaths than the age-based model [87].

A risk-stratified approach to refining breast cancer screening was modelled by Pashayan et al [88] in a hypothetical UK cohort of over 300,000 women comparing no screening, age-based screening and a PRS-based model where only women in

the highest PRS were offered screening mammography. Reduced rates of breast cancer overdiagnosis and improved cost-effectiveness were found when women with low risk were not offered screening. A similar approach could be utilised in PrCa. The same author assessed the implications of using PRS in reducing PrCa over-diagnosis,

Pashayan et al assessed the implications of using polygenic risk scoring (PRS) on reducing over-diagnosis. They constructed a PRS on 17,000 men aged 50-69 from three large studies (ProtecT, SEARCH and UKGPCS) using 66 known PrCa risk SNPs, separating men with and without PrCa into risk quartiles. By using this method, they derived probabilities of overdiagnosis per risk quartile. They estimated from lowest risk quartile to the highest, a proportion of 43, 30, 25 and 19% of cancers were 'overdiagnosed' with the rate of overdiagnosis decreasing with increasing polygenic risk. They estimated a 56% reduction in over-diagnosis between the lowest risk quartile and the highest [89] suggesting a PRS could be used to risk-stratify men in higher risk categories who would benefit the most from screening and reducing harms of overdiagnosis.

In a separate study the same authors examined 43, 842 men within the ProtecT study alone, aged 50-69. A PSA threshold of ≥3.0 ng/ml^{-1} was used, with 3.5% of men being diagnosed with PrCa. It was estimated that 10-31% of these cases were over-diagnosed [90].

1.5 Future Directions for PRS and genetic-informed screening

It is unclear how PRS relates to the probability of detecting existing PrCa in asymptomatic men with a FH, many who will have low PSAs. The predictive value of SNP profiling in men presenting with a PSA of 1 - 3ng/ml was assessed by Nordstrom et al [23], finding that a risk score based on 49 SNPs was a significant predictor of a positive biopsy ($p = 0.028$). Based on current clinical practice if these men were following a PSA screening protocol, they would not fulfil clinical criteria for urological referral for prostate biopsy. In the PROFILE feasibility study, the predictive value of a PRS for men with a FH was analysed. No significant association between the PRS and PrCa diagnosis was found in 100 healthy men with a FH of PrCa

undergoing screening prostate biopsy irrespective of PSA. However, the number of cancers diagnosed in this group of men (mean age 53) with a low median PSA (1.3) was sizeable; 25% had PrCa found on screening biopsy of whom 48% had clinically significant disease. Twelve men with PrCa had a PSA <3 (52%). No adverse psychosocial variables were noted. [91].

Presently, the full PROFILE study (NCT02543905) is recruiting 350 men with a FH of PrCa and 350 men of African ancestry, investigating the role of targeted screening in men with a genetic susceptibility to PrCa. Germline genetic analysis of approximately 130 SNPs will be correlated with outcome at upfront prostate biopsy (regardless of PSA) at study entry in men aged 40-69. This prospective, targeted screening study will determine the association of genetic profiling with prostate biopsy result in those with a genetic susceptibility to PrCa undergoing targeted screening. PrCa incidence, aggressiveness and incidence of abnormal pre-biopsy MRI and its value in this cohort will also be assessed. An interim analysis of this cohort forms the basis of this thesis.

Currently, the IMPACT study (NCT00261456) has enrolled over 3,000 men (mutation carriers and controls) across multiple countries to investigate the outcomes of targeted PSA screening in men with *BRCA1/2* and MMR (*MSH2, MSH6, MLH1*) germline mutations with annual PSA and a biopsy threshold of 3.0 ng/ml. Early results in the *BRCA* cohort have suggested a screening strategy in this population is beneficial for men with a *BRCA2* mutation, with mutation carriers having with a higher rate of PrCa diagnosis, at a younger age and having more significant disease than non-carriers [92]. Baseline results for the Lynch Syndrome cohort show a higher proportion of aggressive disease in the MSH2 and MSH 6 cohorts and follow up data are awaited [93].

The STOCKHOLM3 study (STHLM3), [94] reported in 2015, was the first population based PrCascreening study that prospectively assessed a targeted screening approach. The study used a screening model combining liquid biomarkers (including PSA), 232 risk SNPs and known clinical variables (e.g. age, family history) and compared this with PSA alone (using a threshold of ≥3ng/ml) [94]. They reported the STHLM3 model improved the sensitivity for the detection of clinically significant PrCa with (AUC 0.74 vs 0.56) compared to PSA and also reduced the number of biopsies

performed by 32%.. Taking this approach further, the STHM3-MRI project aims to improve the PrCa diagnostic pathway by investigating the role of the STHLM3 test as a triage tool to assess non-inferiority to a standard diagnostic pathway using PSA and standard systematic biopsy. The pathway will randomise men at the point of diagnostic test after either a PSA ≥3ng/ml or STHLM3>11, with diagnostic test either being a traditional systematic or MRI-guided biopsy [95].

BARCODE1 will be the first prospective study to utilise a germline SNP profile to target PrCa screening in the general population, recruiting patients via their general practitioners (GPs). Screening in BARCODE1 is in the form of MRI guided biopsy. With the increasing interest in use of MRI as a triage tool to decide whether men presenting with symptoms or a raised PSA can safely avoid a biopsy, BARCODE1 will allow an assessment of the utility of MRI in men who have an increased genetic risk of prostate cancer based on their PRS. In the BARCODE1 pilot study, uptake via GPs was 26% with 25/303 identified for intervention based on a PRS falling in the top 10% of risk. 45% of these men had an abnormal MRI with (any) cancer detected in 38.8% [96].

Mano et al have published their results of prospectively screening 196 Israeli male *BRCA1/2* variant carriers (aged >40) for 5 cancers including PrCa. The rate of PrCa in *BRCA1* variant carriers (8.6%) was twice that of *BRCA2* variant carriers (3.8%), screening all men using annual PSA and DRE (neither PSA screening threshold or cancer characteristics reported) [97]. Within in the same institution, Golan et al reported germline genetic characteristics of 138 men referred to their Risk Clinic for germline genetic testing due to a FH of PrCa, a FH of multiple other malignancies or a known germline variant. Men with a FH of PrCa comprised 64% of their cohort, and 25% had a known germline variant. A total of 18% were found to carry a germline variant in *BRCA1/2*, *CHEK2*, *HPC2*, *ATM*, *MLH1*, *MSH2* or *MSH6*. This cohort is likely to be enriched for variants due to Jewish ethnicity [98]. Das et al have also reported their intention to study a prospective cohort of men with known germline variants, managed in a high-risk clinic [99]. Their ‘High-Risk’ clinic will utilise PSA, DRE, SelectMDx™ and MRI in a risk-algorithm.

1.6 Prostate MRI

The combination of PSA and transrectal ultrasound-guided (TRUS) biopsy without mpMRI guidance has limited accuracy for clinically significant cancer detection, contributing to the burden of PrCa overdiagnosis. Of the 20,188 TRUS biopsies performed in ERSPC following a 'positive' PSA, 63% did not yield PrCa. Of all cancers detected (7,408), 59.9% were low-risk [80]. Using PSA and systematic TRUS biopsy, estimates of overdiagnosed cases due to screening were demonstrated across both ERSPC and PLCO studies of up to 60% in subset analyses [100]. Efforts in improving PrCa diagnostics and managing men with AS are addressing the problem of PrCa overdiagnosis and subsequent overtreatment.

mpMRI has drastically changed our ability to diagnose PrCa. It allows us to risk-stratify men and select those who will benefit from a prostate biopsy by enabling targeted sampling; minimising the harms of over-diagnosis and over-treatment historically associated with systematic TRUS biopsy.

In the landmark PROMIS trial, using mpMRI as a triage tool compared to standard TRUS biopsy, increased the detection of clinically significant disease [101]. Discussion in the urological community then moved towards investigating if prostate biopsy could be avoided altogether in men with unremarkable prostate MRIs.

The PRECISION study randomised 500 men to undergo mpMRI with/without targeted prostate biopsy versus standard TRUS biopsy. In their analysis, fewer men received a diagnosis of clinically insignificant PrCa (9% vs 22%) in the MRI targeted group than in the standard TRUS group; 38% of men in the MRI-targeted group were found to have clinically significant PrCa, compared with 26% of the standard TRUS group. However in both groups of men, in those who went on to have radical prostatectomy the rates of Gleason upgrading on final pathology were similar (17% in the MRI-targeted group vs 15% in standard TRUS group) [102]. Debate continues if it is now 'safe' to avoid systematic sampling of the prostate and perform a targeted biopsy only.

1.6.1 Can MRI be used as a screening tool?

A small number of groups have investigated the use of MRI as a screening tool. Nam et al performed a pilot study in Toronto investigating the role of prostate MRI as a screening tool. The recruited 47 men from the population selected for absence of FH of PrCa, aged 50-75 with no prior prostate biopsy. A mpMRI, PSA, DRE and systematic TRUS biopsy (with cognitive targeting if required) was performed in all men. 38% of men had a diagnosis of PrCa. MRI was a superior predictor of (any) and ≥Gleason 7 cancer on biopsy and had superior PPV and NPV in men with a PSA ≤4ng/ml [103].

The ReIMAGINE Prostate Cancer Screening study (NCT04063566) is currently inviting PSA naive men in the general population aged 50-75 via their GP to undergo prostate MRI. Those with MRI lesions assigned a PIRADS score of ≥ 3 (or with a PSA density >0.12) will be referred for standard further PrCa diagnostic tests. This study will evaluate the feasibility of using prostate MRI as a population screening tool and the prevalence of MRI-detected PrCa across a spectrum of PSAs.

The PROSTAGRAM study performed community-based recruitment of 406 PSA-naïve men in the UK [104]. Each participant underwent a 'short' prostate MRI, ultrasound (US) and PSA. If one or more of the tests was 'positive' (i.e PSA >3.0, MRI PIRADS 3-5 or US visible lesion). Eldred-Evans et al reported that the use of T2-MRI (no contrast was administered) with a "screen-positive" definition of PIRADS 4-5, when compared to PSA screening using a threshold of 3ng/mL, was associated with increased rates of diagnosis of clinically significant PrCa without increasing diagnosis of clinically insignificant disease.

The STHLM3-MRI study aims to recruit 10,000 men by screening invitation, each of whom will have a PSA and an STHLM3 test. The STHLM3 test comprises genomic and clinical data including a polygenic risk score. It gives a man a percentage risk of ≥GGG2 cancer [105]. If either is abnormal (PSA 3.0/STHLM3 ≥11), the participant will be randomised to either systematic or MRI-targeted biopsy.

Relevant to the PROFILE study (which recruits men from aged 40) which reports on an interim analysis in this thesis, are the results of studies investigating the utility of MRI in younger men and if any differences in cancer detection rates exist, compared

to the ‘usual’ populations of men recruited to the aforementioned studies reporting the utility of pre-biopsy MRI in men with a clinical suspicion of PrCa. Importantly, the diffusion-weighted imaging (DWI) sequence of pre-biopsy MRI has been reported to vary with age [106]. Gieeelchinsky et al reported the reduced sensitivity of mpMRI in men younger than 50 for clinically significant cancer detection in a retrospective review of 1395 men who had had a pre-biopsy mpMRI and who had whole-gland final pathology available following radical prostatectomy, when adjusting for tumour volume and ISUP pathology score [107]. Stabile et al also reported a difference in the diagnostic performance of mpMRI in 930 men of varying ages. They found a higher rate of clinically significant cancer detection in men undergoing systematic-only biopsy compared to men aged ≤50, compared to those that were older, who had greater rates of clinically significant cancer detection on targeted cores [108].

2 Conclusions

We are now in a position to translate our understanding of the polygenic nature of PrCa risk to informing and improving screening strategies, by stratifying men into risk categories based on their genetic and FH status. The accuracy of modern, imaging-informed PrCa diagnostics, headlined by the PROMIS and PRECISION trials [101] [102] has been revolutionised by pre-biopsy MRI, improving cancer detection by targeting sampling to areas of abnormality in place of systematic TRUS biopsies ultimately reducing the rates of overdiagnosis.

The PROFILE study and the interim results discussed in this thesis will give practical insight into the role of genetic-based profiling in PrCa detection in high-risk men with a FH, and the potential ability of a genetic profile to form part of a targeted strategy to divert ‘low risk’ men from invasive diagnostics tests and funnel ‘high-risk’ men towards the most accurate test, whilst in parallel minimising the risk of overdiagnosis. Clinically useful results regarding the performance characteristics of mpMRI in this population will also be reported, which will provide valuable insight into its role in cancer detection both alone and alongside a genetic profile.

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4 Figures

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2 Chapter 2 – Materials & Methods

This chapter outlines The PROFILE Study which provided data for this thesis, and how an interim analysis of PROFILE study data forms the basis of this thesis. In this chapter, I will describe the overall methods of the PROFILE study and the methods applied to each data chapter (Chapters 3-5).

Baseline participant data are described in chapter 3, with specific data chapters analysing MRI and PRS in chapters 4 & 5 respectively.

2.1 Personal involvement and Role

In summary below is an outline of my specific, personal involvement with the PROFILE study

2.1.1 The PROFILE Pilot Study:

The aim of the PROFILE pilot study was to conduct a feasibility study in 100 men with a positive FH of PrCa (at least one first degree relative affected at <70 years, with diagnosis verified) to determine interest in the study, biopsy uptake and complication data over a two year period. After informed consent, patients provided blood samples to measure PSA level and for DNA extraction. All participants were asked to undergo a 12-core TRUS prostate biopsy regardless of baseline PSA result. Fifty participants were offered a T2-weighted with mpMRI prior to biopsy. In total 116 men were recruited and 102 biopsies completed. All patients were asymptomatic. A SNP analysis used 39 Pr Ca risk SNPs. The study was sponsored by the Institute of Cancer Research (ICR) and began recruitment in 2009 and was completed in 2012. The study demonstrated that prostate biopsy was acceptable and safe in men with a FH of PrCa, supporting a larger study powered to investigate the use of SNPs in PrCa risk stratification for targeted screening. This larger study took shape as the PROFILE study

During the course of my clinical fellowship, I managed men during their study follow-up from the pilot study including clinical queries, clinic appointments, MRI review, MDT discussion and performing study mandated prostate biopsies and delivering of cancer diagnose alongside data collection, cleaning, trial protocol ammendments and DMC attendance and data presentation.

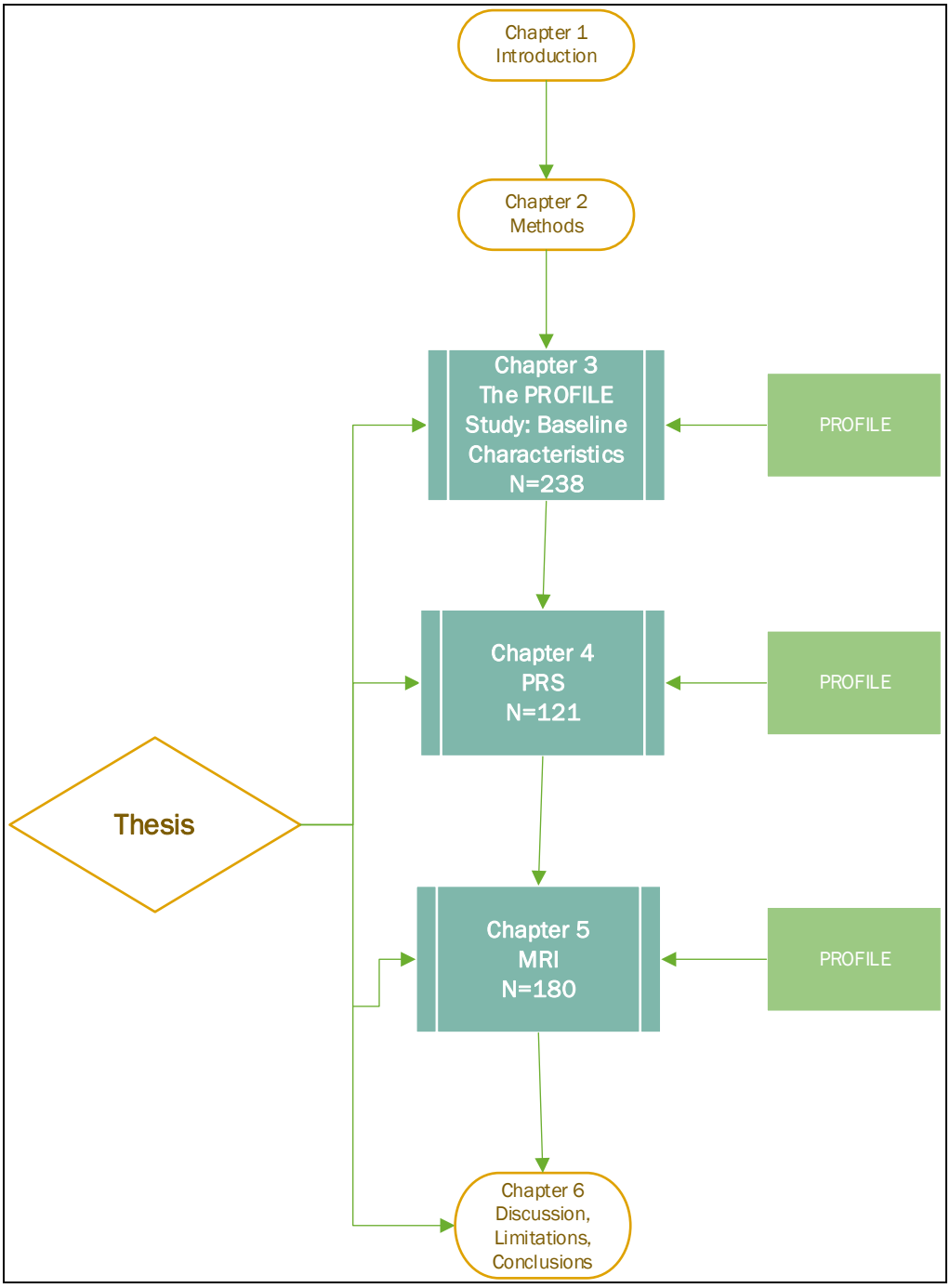
2.1.2 The PROFILE Study

The PROFILE study followed the aforementioned pilot, which demonstrated feasibility, uptake and safety. The aim of the PROFILE study is to correlate germline genotypes in men with an increased risk of PrCa due to a genetic predisposition with biopsy outcome. The additional contribution of mpMRI to PrCa screening in this cohort will also be assessed. The primary endpoint is the association of biopsy result with genetic profile in men having targeted prostate screening. This is to inform healthcare about the role of genetic profiling.

During the course of my clinical fellowship, I managed men during their study follow-up from the PROFILE study including clinical queries, MRI review, MDT discussion, consenting to study enrolment and performing study mandated prostate biopsies and delivering of cancer diagnoses. I have also been involved in study and protocol amendments, preparing study data for DMC meetings, presenting interim results at the ICR conference and Urology meetings and was involved in the reconfiguration of transitioning all prostate biopsies from TRUS to LA TP to improve the safety and accuracy profile of our participants' prostate biopsies.

2.2 Cohort for Analysis

An outline of the chapters and flow of this thesis is shown below.



2.3 The PROFILE Study: Overview and Rationale

The PROFILE study (NCT02543905) is sponsored by the ICR and began recruiting in 2015 (protocol in Appendix).

Following on from the PROFILE pilot study [1], the aim of the PROFILE study is to correlate germline genotypes in men with an increased risk of PrCa (men with a FH of PrCa and men of African Ancestry) due to a genetic predisposition with biopsy outcome and to assess the additional contribution of diffusion-weighted, mpMRI and new biomarkers to PrCa screening in this group.

This is to inform healthcare about the role of genetic profiling using PrCa germline risk variants which have been discovered by GWAS.

2.3.1 Aims

Aims explored in this thesis are as follows:

- Primary
    - To determine the association of genetic profile with prostate biopsy result in men at genetically higher PrCa risk (due to a FH) undergoing targeted PrCa screening
- Secondary
    - To determine the incidence and aggressiveness of PrCa in a cohort of men with a FH of PrCa
    - To investigate the value of T2-weighted in conjunction with DW-MRI as a screening tool in men with a FH of PrCa undergoing targeted PrCa screening

2.3.2 *Endpoints*

Endpoints explored in this thesis are as follows:

- Primary
    - To investigate the role of targeted PrCa screening in men at a higher genetic risk (with a FH of PrCa) and its association with specific genetic profiles

- Secondary
    - To determine the incidence and aggressiveness of PrCa in a cohort of men with a FH of PrCa
    - To determine the association of Diffusion Weighted MRI (DW-MRI) findings with prostate biopsy results in this cohort

2.3.3 *Study design*

The PROFILE study is recruiting two cohorts of men (men with a FH of PrCa and black men) with a genetic predisposition to PrCa, with 350 in each group. Each group following fulfilling inclusion criteria (listed in full in trial protocol in Appendix) will undergo upfront mpMRI and prostate biopsy, alongside donation of serum and urine ( ).

If men do not wish to undergo upfront biopsy with mpMRI, they can defer until their PSA reaches an age-related threshold which is study specific. Each participant will be followed up for a minimum of 5 years.

Only the FH cohort is henceforth described and the subject of this thesis' analysis.

2.3.4 Participants

A cohort with a FH defined as follows: (N=350)

- Men with a FDR (or second degree if through female line) with histologically or death certificate proven PrCa diagnosed at <70 years
- Men with two relatives on the same side of the family with histologically or death certificate proven PrCa where at least one is diagnosed at <70 years
- Men with three relatives on the same side of the family with histologically or death certificate proven PrCa diagnosed at any age

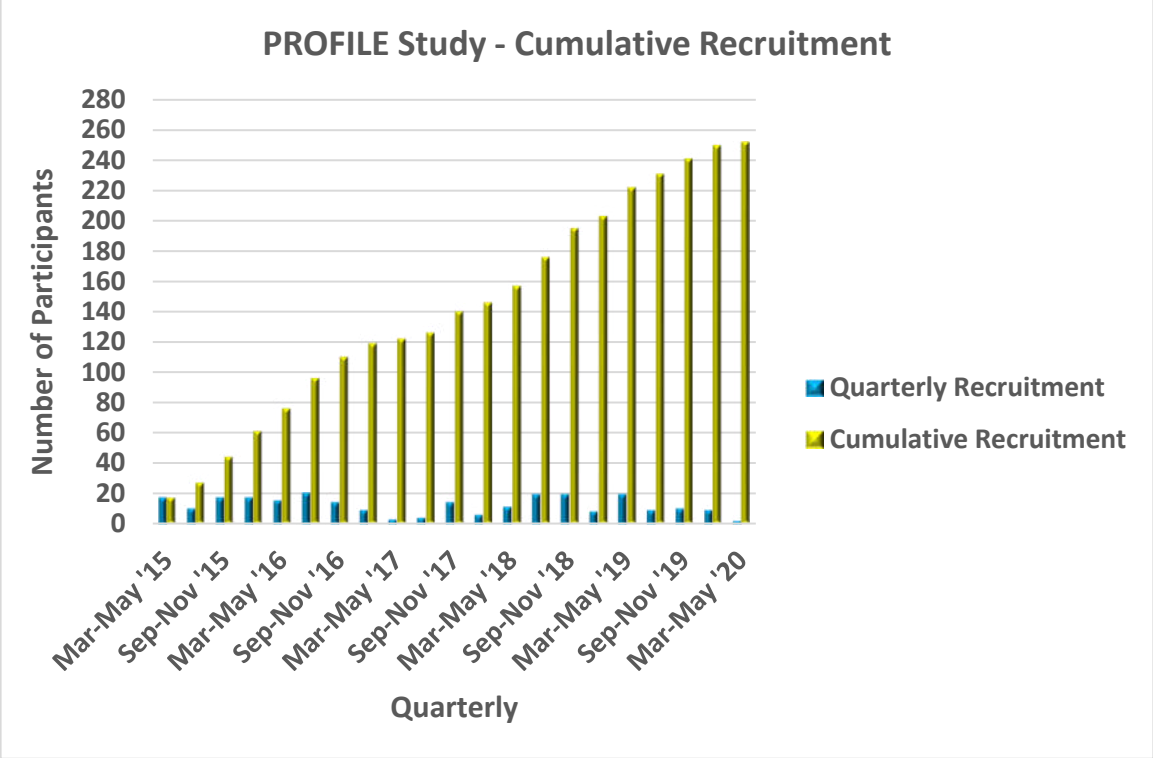


Figure 2.1 Recruitment and accrual trends from the time of study opening until the time of data freeze in February 2020

2.3.5 Study Interventions

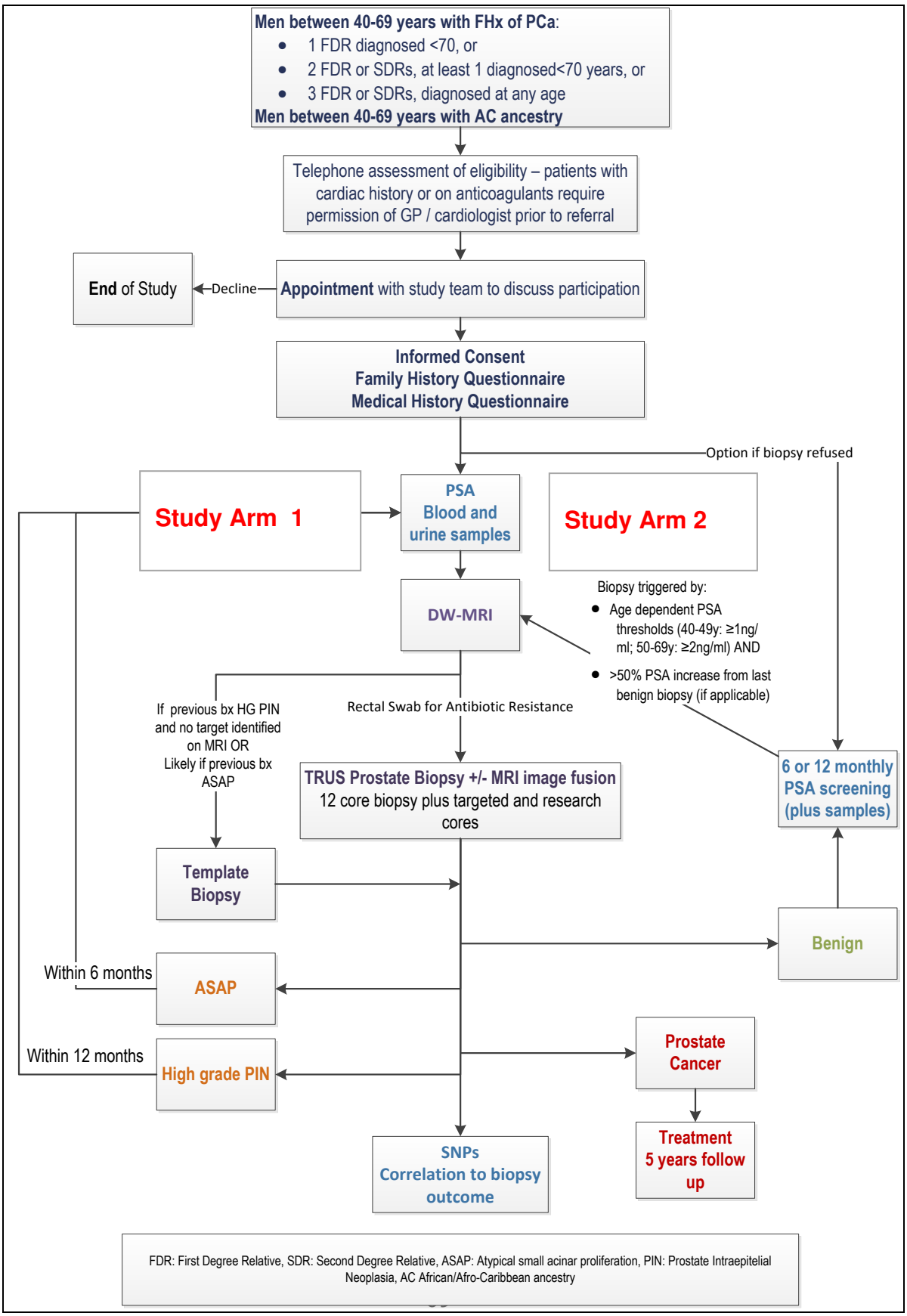
Men recruited to Study Arm 1 undergo upfront mpMRI and prostate biopsy, irrespective of PSA.

A second study arm (Study Arm 2) exists for men reluctant to undergo upfront MRI and prostate biopsy but who will accept a 'clinically triggered' prostate biopsy at an age-dependant (study defined) PSA threshold. These men have annual PSA testing and proceed to biopsy with preceding MRI if an age-related PSA threshold is reached ( ). The thresholds are as follows, with the rationale for these specific values arising from a study of PrCa detection in men with a FH of

PrCa using prostate biopsy; 25.3% of men had cancer with a PSA <4.0ng/ml, with a median PSA of 2.1ng/ml [2]

- PSAs of >1.0ng/ml in men aged 40-49
- PSAs of >2.0ng/ml in men aged 50-69.

Figure 2.2 Flowchart of the PROFILE study outlining both study arms (shown on next page)


Men between 40-69 years with FHx of PCa:
1 FDR diagnosed <70, or
2 FDR or SDRs, at least 1 diagnosed<70 years, or
3 FDR or SDRs, diagnosed at any age
Men between 40-69 years with AC ancestry
Telephone assessment of eligibility – patients with cardiac history or on anticoagulants require permission of GP / cardiologist prior to referral
Appointment with study team to discuss participation
Decline
End of Study
Informed Consent
Family History Questionnaire
Medical History Questionnaire
Option if biopsy refused
Study Arm 1
PSA
Blood and urine samples
Study Arm 2
DW-MRI
Biopsy triggered by:
Age dependent PSA thresholds (40-49y: ≥1ng/ml; 50-69y: ≥2ng/ml) AND
>50% PSA increase from last benign biopsy (if applicable)
If previous bx HG PIN and no target identified on MRI OR Likely if previous bx ASAP
Rectal Swab for Antibiotic Resistance
TRUS Prostate Biopsy +/- MRI image fusion
12 core biopsy plus targeted and research cores
6 or 12 monthly PSA screening (plus samples)
Template Biopsy
Benign
Within 6 months
ASAP
Within 12 months
High grade PIN
Prostate Cancer
Treatment
5 years follow up
SNPs
Correlation to biopsy outcome
FDR: First Degree Relative, SDR: Second Degree Relative, ASAP: Atypical small acinar proliferation, PIN: Prostate Intraepitelial Neoplasia, AC African/Afro-Caribbean ancestry

Additional blood, urine and tissue samples were taken for research purposes in order to investigate new biomarkers in this population using biochemistry, proteomic, metabolomic and microarray approaches. Urine samples were collected for further studies, for example biomarker studies PCA3 and the TMPRSS2:ERG translocation to correlate these with SNP profile, but biopsy decisions were not made on these results.

Blood was collected at study entry for retrospective SNP profiling, the results of which will are being fed back to patients at present. Unless there was a contraindication, T2 diffusion weighted (DW) contrast enhanced (CE) mpMRI was performed in all men prior to performing a prostate biopsy. The biopsy method until June 2020 was a 12 core systematic TRUS biopsy with additional cores targeting areas of abnormality on mpMRI using MR-US elastic fusion technology (Koelis™). Two extra cores, one from each side of the prostate (non-targeted) were taken and snap frozen for future molecular studies. In June 2020 due to ongoing efforts to minimise all infective-complication risks to patients undergoing invasive procedures at the Royal Marsden Hospital (RMH) due to the Covid19 pandemic, we changed our biopsy method changed to a local anaesthetic, trans-perineal approach (LA TP).The number and location of systematic cores was unchanged.

All men from the PROFILE study will be followed up for at least 5 years following participation. This will enable information to be collected on the development of PrCa beyond this protocol, and look at the treatment effects in men based on their genotype.

2.4 SNP assay

The design of the resulting 130 SNP assay used in all men in the PROFLE study for analysis is described below. I was not personally involved with the SNP assay design, or DNA extraction and genotyping or ICR QC procedures of PROFILE participants samples. These were carried out by my bioinformatics and scientific colleagues in the Oncogenetics team and are described for completeness.

2.4.1 SNP profile design

This genotyping assay was designed to be used in Oncogenetics studies in targeted PrCa screening being carried out by Professor Eeles' team in the ICR. SNPs associated with PrCa risk as a result of published genome wide association studies (GWAS) and meta-analyses were selected. At the start of assay development, 177 SNPs were submitted to Affymetrix® for inclusion in the design of the genotyping assay. These SNPs included:

- 99 SNPs identified in a previous GWAS and meta-analysis [3] and used in a previous genotyping assay
- 63 new SNPs identified in the most recent GWAS and meta-analysis [4]
- The *HOXB13* missense variant G84E [5]
- 14 SNPs identified by fine-mapping the 8q24 region [6]

DNA sequences for each SNP were submitted including 75bp either side of the variant. During the *in silico* assessment of submitted SNPs by Affymetrix®, 6 variants were identified to be 'un-designable' due to their location within single- or poly-nucleotide repeat sequences. These were replaced by proxy variants with good correlation with the variant of interest, i.e. $r^2>0.9$ (except one proxy SNP had $r^2=0.72$). A proxy SNP is a variant that has high linkage disequilibrium (represented by r^2) with the variant of interest.

Test plates of DNA samples with known genotypes were sent to Affymetrix® for the assay to be tested. After running the assay on 2 sets of test plates, 155 SNPs were found to be working well. A target SNP list of 147 was created based at the time, on the most uptodate GWAS of risk variants by Schumacher et al. After further development by Affymetrix® with the Oncogenetics team including more rounds of testing, assay optimisation and exclusion of non-European variants, a final SNP list of 132 was prepared. In-house QC at the ICR resulted in the loss of 2 SNPs due to low call rates leaving 130 risk SNPs (from a European population) in our panel (Table 2.1).

rsID	Chr	hg19 position	Risk Allele	Protective Allele	RAF	Risk Allele Beta	OR
rs56391074	1	88210715	AT	A	0.370	0.0466	1.05
rs17599629	1	150658287	G	A	0.218	0.0654	1.07
rs1043608	1	153909069	C	G	0.315	0.061	1.06
rs1218582	1	154834183	G	A	0.447	0.0457	1.05
rs4245739	1	204518842	A	C	0.738	0.0924	1.10
rs62106670	2	8597123	T	C	0.382	0.0524	1.05
rs9287719	2	10710730	C	T	0.467	0.0663	1.07
rs13385191	2	20888265	G	A	0.241	0.0528	1.05
rs1465618	2	43553949	T	C	0.214	0.0829	1.09
rs721048	2	63131731	A	G	0.182	0.0971	1.10
rs74702681	2	66652885	T	C	0.023	0.1586	1.17
rs10187424	2	85794297	T	C	0.574	0.0744	1.08
rs11691517	2	111893096	T	G	0.744	0.0635	1.07
rs12621278	2	173311553	A	G	0.941	0.2423	1.27
rs34925593	2	174234547	C	T	0.486	0.0466	1.05
rs59308963	2	202123479	T	TATTCTGTC	0.727	0.0505	1.05
rs7584330	2	238387228	G	A	0.229	0.0547	1.06

rs3771570	2	242382864	T	C	0.150	0.0841	1.09
rs2660753	3	87110674	T	C	0.103	0.1198	1.13
rs1283104	3	106962521	G	C	0.380	0.047	1.05
rs7611694	3	113275624	A	C	0.579	0.0831	1.09
rs10934853	3	128038373	A	C	0.277	0.0989	1.10
rs6763931	3	141102833	A	G	0.442	0.0428	1.04
rs142436749	3	169093100	G	A	0.012	0.2212	1.25
rs10936632	3	170130102	A	C	0.507	0.0972	1.10
rs10009409	4	73855253	T	C	0.311	0.0555	1.06
rs1894292	4	74349158	G	A	0.515	0.062	1.06
rs17021918	4	95562877	C	T	0.651	0.0852	1.09
rs7679673	4	106061534	C	A	0.592	0.1201	1.13
rs2242652	5	1280028	C	T	0.794	0.1598	1.17
rs12653946	5	1895829	T	C	0.425	0.0786	1.08
rs2121875	5	44365545	C	A	0.330	0.0481	1.05
rs76551843	5	169172133	A	G	0.991	0.2705	1.31
rs4976790	5	177968915	T	G	0.114	0.0737	1.08
rs4713266	6	11219030	C	T	0.517	0.0514	1.05
rs7767188	6	30073776	A	G	0.210	0.0544	1.06

rs12665339	6	30601232	G	A	0.164	0.0615	1.06
rs3096702	6	32192331	A	G	0.377	0.0559	1.06
rs3129859	6	32400939	G	C	0.670	0.0602	1.06
rs9296068	6	32988695	T	G	0.647	0.0477	1.05
rs1983891	6	41536427	T	C	0.277	0.0816	1.09
rs2273669	6	109285189	G	A	0.146	0.0694	1.07
rs339331	6	117210052	T	C	0.695	0.0837	1.09
rs1933488	6	153441079	A	G	0.579	0.076	1.08
rs9364554	6	160833664	T	C	0.283	0.1037	1.11
rs11452686	7	20414110	T	TA	0.564	0.0497	1.05
rs12155172	7	20994491	A	G	0.220	0.0925	1.10
rs10486567	7	27976563	G	A	0.763	0.1335	1.14
rs17621345	7	40875192	A	C	0.737	0.0715	1.07
rs56232506	7	47437244	A	G	0.451	0.054	1.06
rs6465657	7	97816327	C	T	0.464	0.1005	1.11
rs2928679	8	23438975	A	G	0.437	0.0534	1.05
rs11135910	8	25892142	T	C	0.153	0.0782	1.08
rs12543663	8	127924659	C	A	0.295	0.1114	1.12
rs10086908	8	128011937	T	C	0.697	0.1255	1.13

rs183373024	8	128104117	G	A	0.007	1.068	2.91
rs16901979	8	128124916	A	C	0.032	0.445	1.56
rs620861	8	128335673	C	T	0.631	0.1386	1.15
rs6983267	8	128413305	G	T	0.511	0.2004	1.22
rs1447295	8	128485038	A	C	0.107	0.345	1.41
rs1048169	9	19055965	C	T	0.379	0.0609	1.06
rs17694493	9	22041998	G	C	0.136	0.0726	1.08
rs1182	9	132576060	A	C	0.219	0.0581	1.06
rs61830900	10	871481	G	C	0.158	0.0773	1.08
rs76934034	10	46082985	T	C	0.917	0.1151	1.12
rs10993994	10	51549496	T	C	0.383	0.2075	1.23
rs1935581	10	90195149	C	T	0.623	0.0477	1.05
rs3850699	10	104414221	A	G	0.700	0.0704	1.07
rs4962416	10	126696872	C	T	0.267	0.0593	1.06
rs1881502	11	1507512	T	C	0.191	0.0581	1.06
rs7127900	11	2233574	A	G	0.199	0.1704	1.19
rs61890184	11	7547587	A	G	0.117	0.0706	1.07
rs2277283	11	61908440	C	T	0.311	0.0558	1.06
rs7931342	11	68994497	G	T	0.504	0.1565	1.17

rs11290954	11	76260543	AC	A	0.676	0.0609	1.06
rs11568818	11	102401661	T	C	0.550	0.0742	1.08
rs1800057	11	108143456	G	C	0.025	0.15	1.16
rs11214775	11	113807181	G	A	0.709	0.071	1.07
rs138466039	11	125054793	T	C	0.010	0.2806	1.32
rs878987	11	134266372	G	A	0.145	0.0639	1.07
rs2066827	12	12871099	T	G	0.756	0.0564	1.06
rs10845938	12	14416918	G	A	0.551	0.0572	1.06
rs80130819	12	48419618	A	C	0.908	0.0957	1.10
rs10875943	12	49676010	C	T	0.287	0.0688	1.07
rs902774	12	53273904	A	G	0.153	0.1258	1.13
rs7968403	12	65012824	T	C	0.641	0.0589	1.06
rs5799921	12	90160530	GA	G	0.699	0.0608	1.06
rs1270884	12	114685571	A	G	0.482	0.0697	1.07
rs7295014	12	133067989	G	A	0.342	0.0516	1.05
rs1004030	14	23305649	T	C	0.588	0.0462	1.05
rs11629412	14	37138294	C	G	0.582	0.0573	1.06
rs8008270	14	53372330	C	T	0.814	0.0832	1.09
rs7141529	14	69126744	C	T	0.499	0.0505	1.05

rs8014671	14	71092256	G	A	0.580	0.0466	1.05
rs4924487	15	40922915	C	G	0.839	0.0622	1.06
rs33984059	15	56385868	A	G	0.977	0.1761	1.19
rs201158093	16	82178893	TAA	TA	0.438	0.0487	1.05
rs684232	17	618965	C	T	0.353	0.0832	1.09
rs28441558	17	7803118	C	T	0.056	0.1507	1.16
rs11649743	17	36074979	G	A	0.806	0.1216	1.13
rs4430796	17	36098040	A	G	0.525	0.1973	1.22
rs138213197	17	46805705	T	C	0.002	1.3475	3.85
rs11650494	17	47345186	A	G	0.078	0.0992	1.10
rs2680708	17	56456120	G	A	0.605	0.0462	1.05
rs1859962	17	69108753	G	T	0.481	0.1606	1.17
rs8093601	18	51772473	C	G	0.440	0.0451	1.05
rs28607662	18	53230859	C	T	0.096	0.0746	1.08
rs12956892	18	56746315	T	G	0.301	0.0498	1.05
rs10460109	18	73036165	T	C	0.417	0.0441	1.05
rs7241993	18	76773973	C	T	0.695	0.0761	1.08
rs11666569	19	17214073	C	T	0.711	0.0516	1.05
rs118005503	19	32167803	G	C	0.912	0.0902	1.09

rs8102476	19	38735613	C	T	0.539	0.0902	1.09
rs11672691	19	41985587	G	A	0.737	0.0916	1.10
rs61088131	19	42700947	T	C	0.835	0.0624	1.06
rs2735839	19	51364623	G	A	0.853	0.1666	1.18
rs11480453	20	31347512	C	CA	0.603	0.0463	1.05
rs12480328	20	49527922	T	C	0.928	0.1071	1.11
rs6126982	20	52456445	T	G	0.474	0.0669	1.07
rs2427345	20	61015611	C	T	0.621	0.0452	1.05
rs6062509	20	62362563	T	G	0.698	0.0775	1.08
rs1041449	21	42901421	G	A	0.433	0.0509	1.05
rs9625483	22	28888939	A	G	0.027	0.1338	1.14
rs9623117	22	40452119	C	T	0.215	0.064	1.07
rs5759167	22	43500212	G	T	0.502	0.1423	1.15
rs2405942	X	9814135	A	G	0.783	0.0486	1.05
rs17321482	X	11482634	C	T	0.866	0.0671	1.07
rs5945619	X	51241672	C	T	0.364	0.1043	1.11
rs2807031	X	52896949	C	T	0.182	0.0581	1.06
rs5919432	X	67021550	T	C	0.801	0.0429	1.04

Table 2.1 130 SNPs included in final assay. rsID: reference SNP cluster ID. Chr: chromosome. hg19: Genome Reference Consortium Human Build 37 (GRCh37). RAF: Risk allele frequency.OR: odds ratio

2.4.2 DNA extraction

DNA extraction from blood was carried out externally by Tepnel Pharma Services (UK). Extracted DNA (minimum concentration 50ng/ul) was returned to the ICR and then sent to Affymetrix® (part of Thermo Fisher Scientific) in the USA for genotyping.

2.4.3 Genotyping

The genotyping assay utilises the Eureka™ Genomics protocol and is based on a ligation dependent polymerase chain reaction (PCR) that uses allele barcodes contained within the ligation probes as well as sample barcodes added by PCR. Once Eureka™ Genomics receive the extracted DNA, the main genotyping steps carried out are as follows:

1. DNA is heat denatured and mixed with a probe blend (three probes are required for each SNP to be interrogated)
2. For each SNP site, one of two left hybridisation sequence (LHS) probes (the two LHS probes are specific for the different alleles of the SNP) and a right hybridisation sequence (RHS) probe fully hybridise to the DNA.
3. Each LHS probe type contains a unique allele barcode sequence that provides the information for which SNP and allele the probe represents.
4. A ligase joins adjacent LHS and RHS probes to form a single fragment.

5. Sample identification barcode sequences (indexes) are added to the ligation products by PCR. Different barcode combinations are added to the different wells (one sample per well)
6. Each fragment therefore contains barcodes indicating which sample, SNP and allele it devolved from, so samples can be pooled after this step to generate the sequencing library. Fragments also contain the full Illumina® adapter sequences at this stage.
7. Sequence data are generated from the prepared libraries using an Illumina® MiSeq™ instrument.

Relative read counts for the two possible allele barcodes are used to determine genotype at the SNP position for each sample. Preliminary (QC and genotype calling are carried out at Affymetrix® and genotyping data is then sent back to the ICR Oncogenetics team for final in-house QC and downstream analysis.

2.4.4 ICR QC of genotyping data

Additional QC is performed on the raw computer assigned genotype calls, through manual examination of cluster plots using the Eureka Analysis Suite (https://www.thermofisher.com/uk/en/home/life-science/microarray-analysis/microarray-analysis-instruments-software-services/microarray-analysis-software/eureka-analysis-suite.html).

An in-house application has been developed by my colleagues in the Oncogenetics team using the Shiny R package. Genotyping data we receive from Eureka can be inputted to produce a PrCa risk PRS using the 130 SNPs for all oncogenetics study samples. It also enables users to compare PRS distribution across different cohorts or populations.

I did not carry out any of the aforementioned steps regarding SNP assay design, genotyping or ICR QC procedures but these are described for completeness. These were carried out by my bioinformatics and scientific colleagues in the Oncogenetics team.

2.4.5 Duplicate samples

SNPs for which the genotypes are called successfully in a sample will contribute to the PRS through either 0/1/2 x SNP beta (effect), depending on whether homozygous for the protective allele, heterozygous or homozygous for the risk allele respectively.

SNPs which are a 'no call' in any sample aren't set as 0 alleles with nothing added to the PRS as a result– you get a more accurate estimate by using the population relative allele frequency (RAF) as the allele count instead and multiplying that by the beta, effectively representing a probability that any individual in the population would have a risk allele for that SNP (given that many of these SNPs are common and therefore present in a large proportion of men).

In the case of a duplicate sample, that with the higher call rate was kept for analysis due to the greater accuracy in PRS resulting from lower missing data, if the call rates for duplicate samples were equal, the sample with the lower PRS was retained.

2.5 Polygenic Risk Scores

Once genotyping data is obtained for each study participant by use of the 130 SNP assay described, a polygenic risk score (PRS) is calculated. The background and rationale for this is described below.

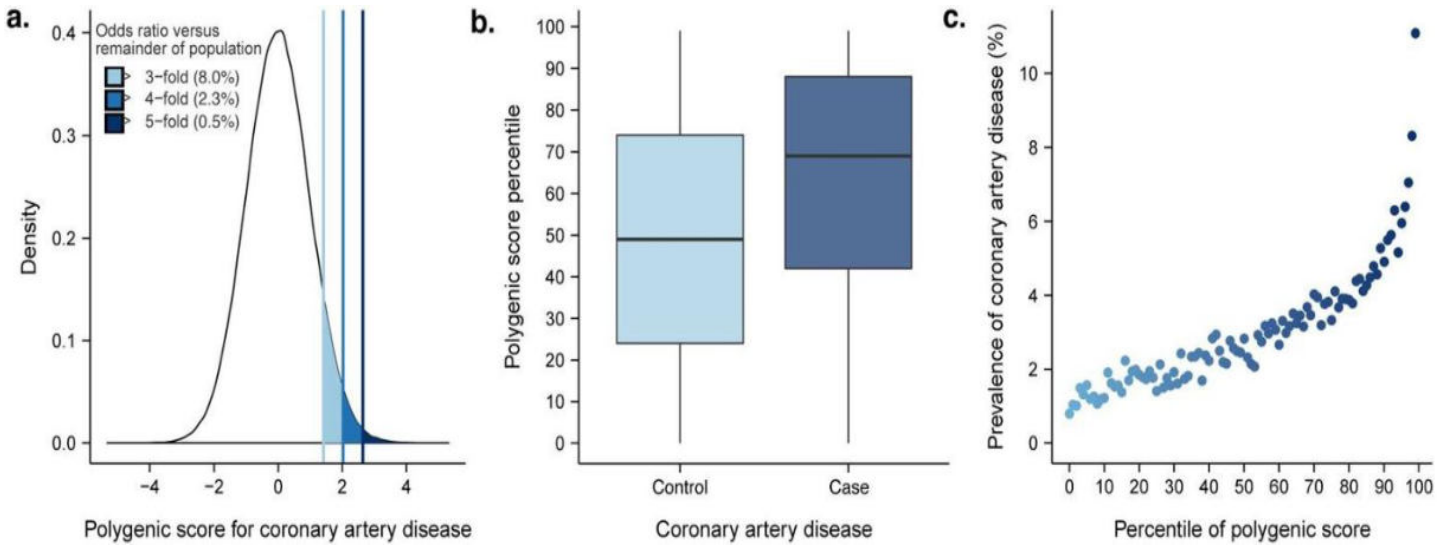


Figure 2.3

a) Distribution of PRS in the UK biobank testing dataset. PRS with values scaled from 0-1 is demonstrated on the X-axis, with proportions of the population with 3,4 and 5-fold risk compared to those in the average-risk category shaded. b) Box-plot demonstrating PRS percentile amongst cases of coronary artery disease in the UK biobank testing dataset (right) compared to controls (left). The box-plot demonstrates the lower mean PRS in the controls (left) compared to cases (right) c) Prevalence of coronary artery disease according to percentile of risk by PRS, demonstrating the highest prevalence of cases in those with the 'highest' PRS, ie those falling into the upper percentiles (Reproduced from Khera et al[7]).

PRS's aim to quantify the cumulative effects on a trait of a number of genetic variants and their associated weights. These variants usually individually have a small effect on susceptibility. PRS can be used to predict a person's likelihood of developing any disease with a genetic component. PRS provide a risk estimate relative to a defined reference point in the population, with the phenotype prevalence sharply rising in the highest percentiles. An example of how PRS is displayed and how values are distributed across a population are displayed in **Error! Reference source not found.** [7]

2.5.1 PRS calculation

After the sequencing of germline DNA for 130 PrCa risk SNPs (table 1), a PRS was calculated for each study participant based on their genotyping data, using R software, utilising the following formula:

$$Score_j = \sum_{i=1}^{N} \beta_i g_{ij}$$

Where:

N : Number of SNPs included in the assay (162)

g_{ij} : genotype at SNP locus *i* (0, 1, 2) for individual *j*. 0= homozygous for non-risk allele, 1=heterozygous for risk allele, 2=homozygous for risk allele

β_i : Per-allele log-odds ratio of SNP *i*

This formula produces the sum of weighted alleles for a set of SNPs (130 in this case) for an individual. When genotyping data were missing for a variant, 2x the risk allele frequency for that SNP was used. If the variant with missing data was a Chromosome X variant, then 1x the risk allele frequency was used. The PRS for each study participant was calculated as described above for the PROFILE cohort. This was carried out using statistical software 'R' by my colleagues in the oncogenetics team.

2.6 Relative Risk and percentile calculation

The mean PRS of a reference population (this population is described below) was used to calculate the risk of PrCa for each PROFILE participant *relative* to the reference population (i.e a population unselected for FH status). This was performed using the formula exp ($PRS_{subject}$ – $PRS_{Mean\ (ProtecT)}$). This generates a relative (RR) for each participant which describes that participants' relative risk of PrCa, compared to the general population.

2.6.1 ProtecT cohort

Relative risk (RR) estimates of PROFILE participants are relative to the mean PRS value of the genotyped men in the ProtecT control group who were treated as our best available estimate of average population risk.

The Prostate Testing for Cancer Treatment (ProtecT) trial was a PSA screening study where participants were recruited from GP surgeries across the UK.[8] aged 50-69. All participants provided written informed consent. A proportion of men (n=4518) with a PSA >3.0ng/ml underwent prostate biopsy during the diagnostic phase and went on to be randomised to surgery, active monitoring or radiotherapy.

Those screened but with a PSA of <3.0ng/ml or with a negative biopsy if their PSA was 3-<10ng/ml formed a 'control' group. The genotyping data for 2,571 of these men (aged 55-69 years) was used to calculate the PRS (using the same 130 SNPs used in the PROFILE participants). Mean age 61, IQR (58-64), median PSA 1.1, IQR (0.9-1.9), 94% no FH in a FDR (missing FH data on 321 men).

2.7 Prostate MRI

All eligible and consenting PROFILE participants had a mp MRI scan of the prostate which included T2W, DW and dynamic contrast enhanced (DCE) images with gadallinium. Scans were performed either at 3Tesla (3T) with endorectal coil (ERC) or at 1.5T with an external phased array coil and reported by a study appointed specialist uro-radiologist (Professor De Souza or Dr Aslam Sohaib).

Prostate lesions identified were scored 1-5 according to the Prostate Imaging Reporting and Data System PiRADS V2.0 system as developed by the European Society of Urogenital Radiology (ESUR) (https://www.acr.org/-/media/ACR/Files/RADS/Pi-RADS/PIRADS-V2.pdf). A PiRADS score of 1 indicated that clinically significant disease is highly unlikely to be present while a score of 5 indicated that clinically significant cancer is highly likely to be present. (Figure 2.4). Zonal anatomy for PiRADS reporting is shown in Figure 2.5.

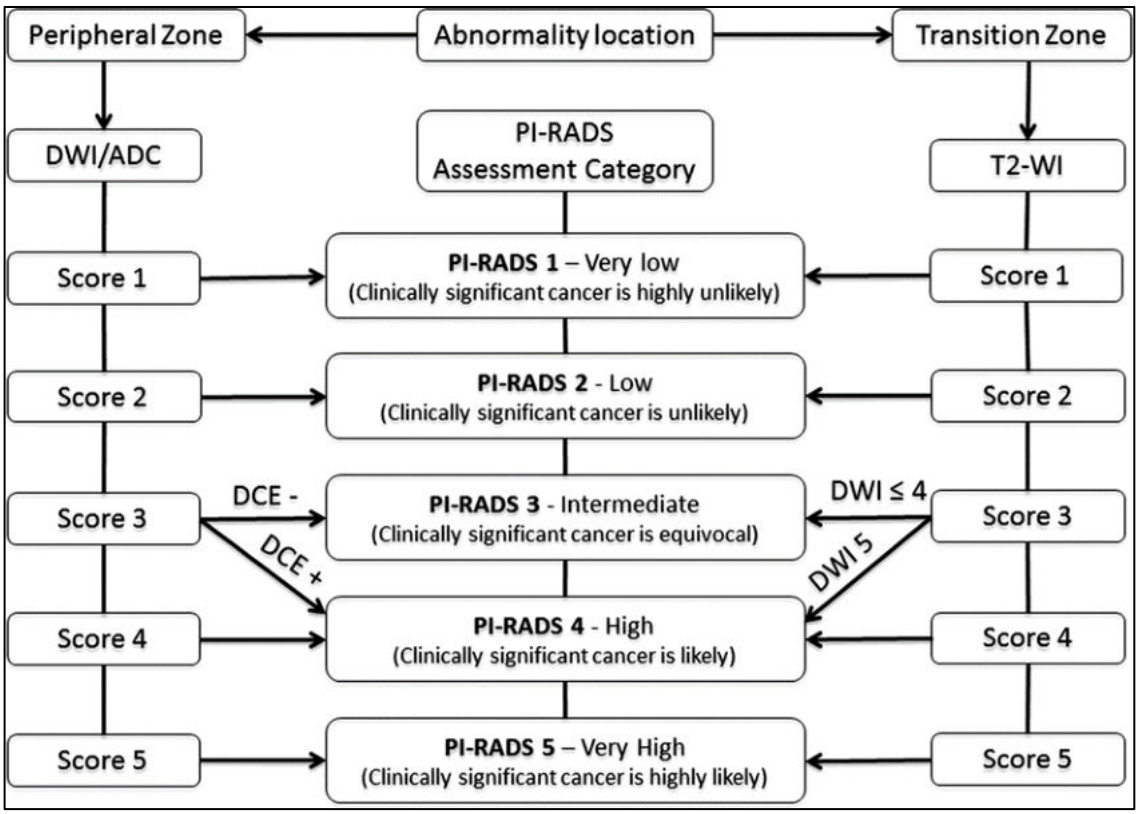


Figure 2.4 Flowchart showing the PI-RADS (Prostate Imaging Reporting and Data System) version 2 assessment categories. DCE = dynamic contrast-enhanced MR imaging, T2-WI = T2-weighted MR imaging. Reproduced from: "PI-RADS Version 2: A Pictorial Update" Purysko et al. RadioGraphics Vol. 36, No. 5: 1354-1372

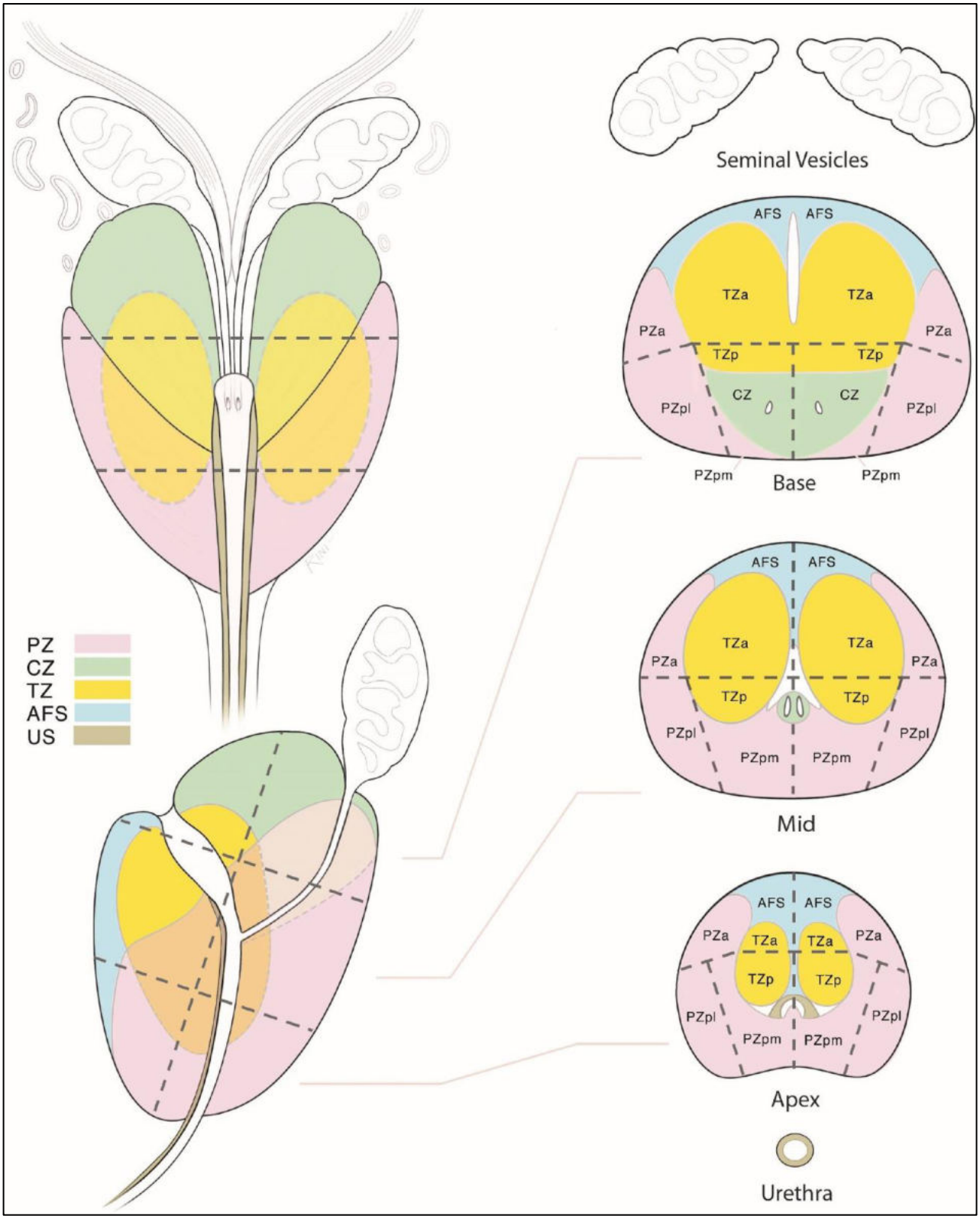

Seminal Vesicles
AFS
AFS
TZa
TZa
PZa
PZa
TZp
TZp
CZ
CZ
PZpl
PZpl
PZpm
PZpm
Base
Mid
Apex
Urethra
PZ
CZ
TZ
AFS
US

Figure 2.5 Sector map diagram for PIRADS version 2.1: the segmentation model used in PI-RADS v2.1 employs 38 sectors/regions for the prostate, two for the seminal vesicles, and one for the membranous urethra (total 41). Each of the right and left peripheral zones (PZs) at the prostate base, midgland, and apex is subdivided into three sections: anterior (a), posterior medial (pm), and posterior lateral (pl). Each of the right and left transition zones (TZs) at the prostate base, midgland, and apex is subdivided into two sections: anterior (a) and posterior (p). The anterior fibromuscular stroma is divided into right and left sections at the prostate base, midgland, and apex. The seminal vesicles are divided into right and left sections. AFS = anterior fibromuscular stroma; CZ = central zone; MRI = magnetic resonance imaging;.

Note. Reproduced from Turkbey et al [9]. The prostate sector diagram was modified by David A. Rini, MFA, CMI, FAMI, Associate Professor in the Department of Art as Applied to Medicine at the Johns Hopkins University, based on previously published figures by Villers et al. (Curr Opin Urol 2009;19:274–82) and Dickinson et al. (Eur Urol 2011;59:477–94) with anatomical correlation to the normal histology of the prostate by McNeal JE (Am J Surg Pathol 1988 Aug;12:619–33).

2.8 Prostate Biopsy

A mpMRI was followed by biopsy of the prostate. A systematic 12-core TRUS biopsy was carried out by the study urologist as shown in Figure 2.6. Two cores were also taken for research and future analyses. If a lesion(s) was identified on mpMRI, additional targeted sampling was undertaken (Koeils Urostation™) using elastic fusion technology. Prostate biopsy samples were examined by a specialist uro-pathologist at The RMH, and reported as per International Society of Urological Pathology (ISUP reporting procedures (described in PROFILE protocol, featured in Appendix).

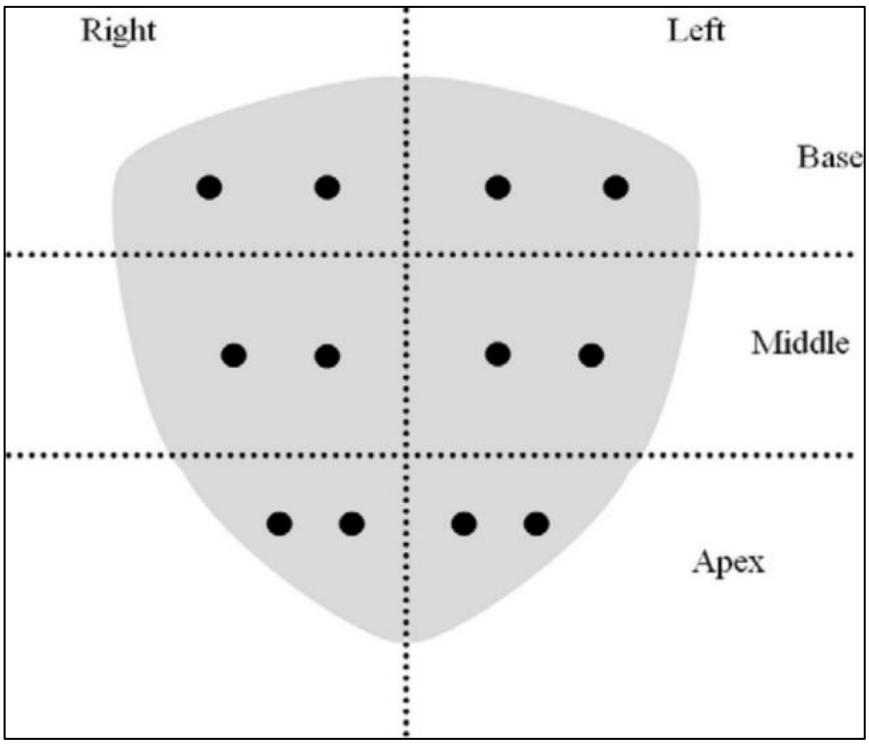


Fig 2.6 Schematic representation of a prostate in the coronal plane, highlighting the areas of standard systematic sampling. Reproduced from Hong et al [10].

2.9 Data collection

Clinical and genotyping data were collated and stored using the genetic data management system, Progeny Clinical [ref: Version 10 from Progeny Genetics (Copyright 2019. Reprinted with permission of Progeny Genetics LLC, Delray Beach, FL, www.progenygenetics.com)], which also allows for the construction and manipulation of genetic pedigrees. Accrual, clinical, radiological, and pathological data are prospectively and retrospectively recorded on study participants' CRF and electronically in Progeny, a web-based secure system used by the Oncogenetics team.

2.10 Methods of Chapter 3 – The PROFILE Study: Baseline Characteristic

2.10.1 Introduction

This chapter describes the baseline clinical characteristics (i.e PSA, Age, MRI) of all study participants who formed part of this thesis' interim analysis.

2.10.2 Patient Selection

Data were frozen at the end of February 2020. At this time point, there were 238 recruited, consented participants in the PROFILE FH cohort across both study arms with clinical data available for analysis.

A decision was made to not include men from the Black cohort due to the small numbers accrued (n=44) and to minimise a heterogeneous cohort. In addition, the current SNP assay is only inclusive of SNPs discovered in Caucasian, European populations.

2.10.3 Data Collection

PrCa diagnoses were confirmed from RMH clinical (electronic) patient records and pathology reports. Clinically significant cancer is defined as either intermediate or high-risk cancer (≥Gleason 3+4), as classified by D'Amico criteria [11] as per current NICE guidance [12] .

We collected data on age at diagnosis, PSA/PSAD at diagnosis, MRI prostate volume, MRI PiRADS score, staging data (TNM), method of biopsy, study arm, Gleason score, treatment, degree of FH, prior screening status and PRS..

Specific prostate biopsy and cancer characteristic data were also collected regarding MCCL, TCCL, total number of cores, number of positive and targeted cores, type of biopsy (systematic or targeted with systematic). Clinico-pathological data were extracted from our prospectively maintained study database (Progeny) and cross-referenced/double checked for accuracy with the RMH electronic patient record system (EPR).

2.10.4 Genotyping Methods

Germline DNA was extracted (blood) and sequenced for 130 known PrCa risk SNPs in 189 men in the FH cohort of the PROFILE study and in 95 men in the pilot study. DNA extraction, SNP assay design and genotyping carried out by other members of the oncogenetics team and collaborators has been described previously. Genotyping data are then kept on ICR server, in the Shiny App and downloaded for use to Microsoft Excel. (Genetic profiles and analysis are discussed in full in chapter 4).

2.10.5 Aims

To describe PROFILE recruitment processes and accrual at time of data freeze

To describe baseline characteristics of the PROFILE cohort

To describe the cancer characteristics of the PROFILE cohort

To describe differences in baseline characteristics between those with and without cancer in the PROFILE cohort

2.10.6 Statistical methods

All descriptive statistics, univariate analyses, logistic regression analyses and graphs were performed using a combination of GraphPad Prism 8.4.2 (Windows, GraphPad Software, San Diego, California USA, www.graphpad.com) and Stata SE 16.1 (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC.).

Normality of data distribution was assessed by QQ plots and the Shapiro-Wilk test. Where continuous data was normally distributed, the student T Test was used to compare means between two groups, or ANOVA if more than two groups.

Where continuous data was not normally distributed (PSA, PSA density, MRI volume), the Man-Whitney test was used to compare means between two groups or the Kruskal-Walis test was used where there were more than two groups. When comparing groups of categorical data (prior screening status, degree of FH and MRI), Fishers' Exact or the Chi^2 tests were used.

2.10.7 Power calculations

For the PROFILE study, a sample size of 318 in each group will provide 80% power to detect a RR of 2 for detection of PrCa at a 5% significance level, compared with an expected detection rate in the general population of 3%. A sample size of 350 per group therefore allows for a drop-out rate of 9 – 10%.

This analysis is therefore underpowered (n=238) in its present format to make conclusive associations between cancer detection on biopsy and any clinical variables or association analyses performed.

2.11 Methods for Chapter 4 – MRI

2.11.1 Introduction

This chapter describes in detail the MRI characteristics of all men with data available for analysis (who underwent both MRI and prostate biopsy).

The distribution of PiRADS scores is described, along with summary statistics of clinical variables (PSA, PSAD, age, prior PSA screening status and FH degree) are described per PiRADS category.

Association analyses are performed to investigate the performance characteristics of MRI in this cohort and its association with cancer detection in this cohort of unaffected men, with a FH of PrCa. MRI is also analysed in a logistic regression model to examine its effect in combination with PRS and other clinical variables in predicting the probability of PrCa.

2.11.2 Patient selection

All MRIs performed within Study Arms 1 & 2 are included for descriptive analysis (n=180). For association of MRI with prostate biopsy outcome, only MRIs where a biopsy also occurred were included (n=151). Repeat MRIs (n=26) within the study period were performed as per study protocol due to either initial HGPIN/ASAP on initial prostate biopsy or if a study participants' PSA rose above ≥50% of his (initial) pre-biopsy PSA, and were followed by repeat biopsy (this occurred in 16 men).

2.11.3 Data collection

Data for all recruited, consented participants were frozen in at the end of February 2020. Data were collated and stored using the genetic data management system, Progeny Clinical: Version 10 from Progeny Genetics [ref], All analyses were performed in Stata SE 16.1 [[StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC .]

Genotyping and MRI methods are already described.

All PSA measurements were taken from two sites in the RMH (Sutton or Chelsea). PSAD was measured by dividing the MRI prostatic volume by the PSA at the time of study entry/pre-biopsy. In addition to baseline participant data described in Chapter 3, specific MRI-focussed data included: PiRADS lesion(s) per MRI, method of biopsy and the presence of (MRI-fusion) lesion targeting and biopsy histology were collected for each MRI/biopsy combination performed, MRI prostate volume, and biopsy characteristics including as previously described.

All MRIs were performed in the RMH (Sutton or Chelsea) and reported by either Professor Nandita DeSouza or Dr Aslam Sohaib, Consultant Radiologists. MRI scans were performed across two RMH sites, Chelsea and Sutton. MRIs performed in Sutton were in a 3T machine with an endorectal coil (ERC) and those performed in Chelsea on a 1.5T machine with no ERC.

All prostate biopsies were performed in the RMH (Chelsea) by either HNR or Mr Pardeep Kumar, Consultant Urological Surgeon. All biopsy samples were processed and examined in the RMH (Chelsea) by Dr Steve Hazell, Consultant Urological Histopathologist.

Clinico-pathological data were extracted from our prospectively maintained study database (Progeny) and cross-referenced/double checked for accuracy with the EPR.

2.11.4 Aims

Describe the frequency of normal and abnormal MRI in the PROFILE FH cohort

Describe the incidence of clinically significant and insignificant cancer across all PiRADS scores in men undergoing targeted screening in the PROFILE study

Describe the performance of pre biopsy MRI in the PROFILE FH cohort

To define sensitivity, specificity, NPV and PPV of MRI in the PROFILE FH cohort

Describe the performance of pre biopsy MRI in combination with other clinical variables in predicting cancer in the PROFILE FH cohort

2.11.5 Statistical methods

The relationship of individual PiRADS score with clinical factors such (i.e PSA, PSAD , Age) is described.

An abnormal MRI is described by categorization into two categorical variables (PiRADS 1-2 vs 3-5 and PiRADS 1-3 vs 4-5).

The relationship of an abnormal MRI with outcome at prostate biopsy and its role in cancer detection in combination with other clinical variables is investigated using Fishers' Exact test, Chi^2 test and multiple logistic regression (StataCorp). AUC/ROC analyses are also performed.

2.12 Methods of Chapter 5 – PRS

2.12.1 Introduction

This chapter describes the genotyping data analyses of all study participants with an available PRS and prostate biopsy data (n=121). and reports on differences between those with and without cancer, and those with and without clinically significant cancer. The data were frozen in February 2020, when the number of recruited, consented men in the full PROFILE study (not including Pilot data) available for analysis was 238.

2.12.2 Patient selection

Of these 238 participants, 8 men had no PRS due to either failure of DNA extraction (low volume or low concentration, n=4), sample not taken at enrolment (n=4), or still awaiting DNA extraction (n=41). Following Eureka Genomics and in-house ICR QC procedures (described previously), a PRS was available for 187 men. For men who underwent either a biopsy in (Study arm 1 or Study arm 2), a PRS was available for 121/187 i.e. the PRS available for the remaining 66 men did not form part of any association analyses due to the fact there was no biopsy to prove presence or absence of PrCa.

Men from the PROFLE FH cohort who had not had a prostate biopsy (both study arms) were excluded from any analyses with cancer outcome. Men from the pilot study were also excluded from any analyses relating to cancer outcome due to significant differences in prostate biopsy practices which were felt to have potentially biased cancer detection rates between the two cohorts due to the absence of PiRADS scoring of the majority of pre-biopsy MRIs in the pilot cohort not allowing for targeted sampling as was the case for all men in the full study cohort.

A PRS was available for 95 men in the Pilot cohort who had undergone prostate biopsy. Due to differences in pre-biopsy MRI reporting and the potential influence on cancer-detection at prostate biopsy, these 95 pilot men were not included in any analysis of PRS or MRI association with biopsy outcome but they were included in the cohort for describing PRS characteristics of the study cohort described in (Chapter 5, Figure 5.1). .

2.12.3 Data collection

Germline DNA which had been extracted and sequenced for all FH cohort participants at the time of data freezing in February 2020 underwent QC procedures described. The PRS for each participant was computed by a member of the oncogentics team and passed to me for downstream clinical analysis. . Clinico-pathological data were extracted from our prospectively maintained study database (Progeny) and cross-referenced/double checked for accuracy with the RMH EPR.

Clinic-pathological data for the 121 men with a PRS was collated (PSA, PSAD, age, prior screening status, FH degree), reviewed and compared between those with and without cancer.

2.12.4 Aims

To describe the distribution of PRS in men with a FH of PrCa

To describe the difference in PRS between men with and without a FH of PrCa

To describe the effect of degree of FH on PRS

To describe the association of PRS with cancer detection on men with a FH of Pr Ca undergoing targeted screening

To describe if the association of PRS with outcome at prostate biopsy changes in men with a FH of PrCa when adjusting for other clinical variables

To investigate if PRS with/without other clinical variables can predict outcome at prostate biopsy in men with a FH of PrCa

2.12.5 Statistical methods

Univariate analyses for each variable were performed using summary statistics (mean, median, SD, IQR). Comparison of means was performed using the student t test for normally distributed data and the Mann Whitney test for abnormally distributed data. Fishers' exact test was used to compare categorical variables. A combination of the two-sample t test, Mann-Whitney and ANOVA tests were used to compare means between (continuous data) groups and Pearson chi-squared and Fisher's exact tests for categorical data. Where the mean differed largely from the median, the median is reported with the interquartile range (IQR). *P* values are considered significant if <0.05. All continuous variables (PSA, PSAD, MRI volume and age) were tested for normality using the Shapiro-Wilks test and plotted using quantile-quantile plots.

The effect of PRS on cancer outcome was analysed both alone and with other variables of interest in a logistic regression model, for the outcome of any cancer and the outcome of clinically significant cancer. Following univariate analysis, each individual predictor variable of interest was regressed against cancer outcome with PRS to assess for a significant relationship and interaction. PRS, PSA, PSAD, category of PSA, category of PSAD, age and MRI all demonstrated a significant relationship with (any) cancer outcome. To refine our understanding of how the probability of cancer at both a 'low' and 'high' PRS differs due to age, PSA, PSAD or an abnormal MRI, I performed marginal analyses of the specific predictor variables (i.e PSA/PSAD/Age) at different PRS points. To investigate the effect of FH on PRS testing was performed with ANOVA using Bonferroni correction. Where small numbers of significant cancers were grouped by PRS as a categorical variable, a Firth logistic regression was performed.

In order to display the PRS distributions across the PROFILE and other populations/subgroups, kernel density plots were constructed using genotyping data. Where percentiles of risk are described, the means and SD of the control population (ProtecT) were used to cut PROFILE participants into risk percentiles so as to compare their risk to that of the general population. All analyses performed and graphs were generated using Stata 16.1 SE [StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC.].

2.13 References

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3 Chapter 3 – Baseline Characteristics

Table of Contents

3.1 Introduction

The use of PSA as a PrCa screening tool in the general population remains a controversial topic. Mortality benefits are emerging with long-term follow-up of ERSCPC [1], but ultimately no recommendation for population screening using PSA exists at present. However, not all men are at equal risk of PrCa, and this has generated interest in developing screening strategies that could be targeted to a specific population subgroup who stand to benefit more from exposure to the harms of screening tests.

Recent updates to EAU and NCCN guidance highlight the important differentiation between men at average risk and men at increased risk, e.g. those of black ethnicity, those with a personal or family history of germline mutations in DNA repair genes, and men with a Family History (FH) of PrCa. Updated EAU guidance now also recommends PSA screening for men with a known mutation in *BRCA2*.

Healthy, unaffected men with a FH of PrCa present an important and potentially challenging group of men to manage in the early detection setting. If presenting at a young age for screening, decades of intervention potentially lie ahead. The opportunity for intervening in this group to treat clinically significant disease should not be missed. However, the traditional screening tests of PSA and DRE may not perform well in this population.

This chapter describes the baseline clinical characteristics of all men with a FH with available clinical and biopsy data from the PROFILE Study. The PROFILE Study is introduced, and baseline descriptive characteristics and univariable associations are given for variables of interest (PSA, age, PSAD, prostate volume, prior screening status, and degree of FH). A brief summary of MRI and PRS is also given, but these two parameters are discussed in detail in their own chapters 4 and 5 respectively. Finally, I discuss implications for ongoing research as well as future clinical pathways.

3.2 Methods

Methods are described in Chapter 2 (Materials & Methods). Statistical methods

Statistical methods for this chapter are described in Chapter 2 (Materials & Methods).

3.3 Results

The baseline clinical characteristics of the PROFILE study participants forming the subject of this thesis' interim analysis are described in table format first, and subsequently discussed below.

Descriptive statistics categorised by insignificant cancer/no cancer/clinically significant cancer are shown as well as univariate analysis for each clinical variable of interest including ORs, marginal predictions and AUC.

	No Cancer		Insignificant Cancer		Significant Cancer		Total	
	N	(%)	N	(%)	N	(%)	N	(%)
Age								
40 - 49	38	(36.2)	12	(36.4)	1	(7.7)	51	(33.8)
50 - 59	52	(49.5)	17	(51.5)	3	(23.1)	72	(47.7)
≥60	15	(14.3)	4	(12.1)	9	(69.2)	28	(18.5)
MRI								
PiRADS 1-2	81	(77.1)	21	(63.6)	1	(7.7)	103	(68.2)
PiRADS 3-5	24	(22.9)	12	(36.4)	12	(92.3)	48	(31.8)
Biopsy outcome								
PiRADS 1-2	82	(77.4)	20	(62.5)	1	(7.7)	103	(68.2)
PiRADS 3-5	24	(22.6)	12	(37.5)	12	(92.3)	48	(31.8)
PRS (quintiles)								
<20	16	(20.0)	3	(10.0)	1	(9.1)	20	(16.5)
20 - <40	14	(17.5)	3	(10.0)	1	(9.1)	18	(14.9)
40 - <60	14	(17.5)	3	(10.0)	0	(0.0)	17	(14.0)
60 - <80	19	(23.8)	4	(13.3)	2	(18.2)	25	(20.7)
≥80	17	(21.3)	17	(56.7)	7	(63.6)	41	(33.9)
PSA								
0 - <1	53	(50.5)	6	(18.2)	0	(0.0)	59	(39.1)
1 - <2	23	(21.9)	16	(48.5)	3	(23.1)	42	(27.8)
2 - <3	15	(14.3)	5	(15.2)	2	(15.4)	22	(14.6)
≥3	14	(13.3)	6	(18.2)	8	(61.5)	28	(18.5)

PSAD								
	<0.15	102	(97.1)	32	(97.0)	9	(69.2)	143	(94.7)
	≥0.15	3	(2.9)	1	(3.0)	4	(30.8)	8	(5.3)
Prior PSA								
	Y	53	(62.4)	21	(80.8)	8	(66.7)	82	(66.7)
	N	32	(37.6)	5	(19.2)	4	(33.3)	41	(33.3)
	Unknown	7		3		1		11	
FH								
	1 rel, age <70	44	(47.8)	10	(31.3)	4	(30.8)	58	(42.3)
	2 rels	27	(29.3)	13	(40.6)	7	(53.8)	47	(34.3)
	3+ rels	21	(22.8)	9	(28.1)	2	(15.4)	32	(23.4)

Table 3.1 descriptive statistics of clinical variables of interest

		Univariable Analysis					
		Any cancer			Clinically significant cancer		
		Odds Ratio	(95% C.I.)	*P*	Odds Ratio	(95% C.I.)	*P*
Age							
	As continuous	1.056	(1.0, 1.1)	0.034	1.197	(1.1, 1.3)	0.002
	40 - 49	Ref.			Ref.		
	50 - 59	1.124	(0.5, 2.5)	0.778	2.174	(0.2, 21.5)	0.507
	≥60	2.533	(1.0, 6.7)	0.061	23.684	(2.8, 199.8)	0.004
MRI vol		1.012	(1.0, 1.0)	0.255	0.995	(1.0, 1.0)	0.793
MRI							
	PiRADS 1-2	Ref.			Ref.		
	PiRADS 3-5	3.6	(1.7, 7.6)	0.001	33.99	(4.2, 270)	0.001
PRS (continuous)		3.12	(1.68, 5.89)	0.001	3.996	(1.4, 11.29)	0.001
PRS (quintiles)							
	<20	1.167	(0.2, 6.1)	0.856	2.692	(0.1, 70.48)	0.552
	20 - <40	1.333	(0.2, 7.0)	0.736	3	(0.11, 78.8)	0.51
	40 - <60	Ref.			Ref.		
	60 - <80	1.474	(0.3, 6.9)	0.624	3.723	(0.1, 82.5)	0.406
	≥80	6.588	(1.6, 26.5)	0.008	7.609	(0.00, 141.0)	0.173
PSA							
	As continuous	1.437	(1.1, 1.9)	0.006	1.71	(1.2, 2.4)	0.001
	0 - <1.0	Ref.			Ref.		
	1 - <2.0	7.297	(2.6, 20.6)	0.000	10.544	(0.5, 209.8)	0.123
	2 - <3.0	4.122	(1.2, 14.1)	0.024	14.512	(0.7, 315.0)	0.088

	≥3.0	8.833	(2.9, 27.2)	0.000	49.341	(2.7, 893.2)	0.008
PSAD							
	As continuous	1.015	(1.0, 1.0)	0.006	1.018	(1.0, 1.0)	0.000
	<0.15	Ref.			Ref.		
	≥0.15	4.146	(0.9, 18.2)	0.059	14.158	(3.3, 61.1)	0.000
Prior PSA							
	Y	1.945	(0.8, 4.6)	0.132	1	(0.3, 3.5)	1.000
	N	Ref.			Ref.		
	Unknown	2.032	(0.4, 8.5)	0.333	0.925	(0.0, 9.2)	
FH							
	1 rel, age <70	Ref.			Ref.		
	2 rels	2.328	(1.0, 5.4)	0.047	2.363	(0.6, 8.6)	0.193
	3+ rels	1.646	(0.6, 4.2)	0.301	0.9	(0.2, 5.2)	0.906

Table 3.2 clinical variables of interest and predicted probability of cancer detection; odds ratio (OR), 95% confidence intervals (CI)

		Any cancer				
Model		**ROC, %**	**Sens., %**	**Spec., %**	**PPV, %**	**NPV, %**
Age		0.6	0	100	0	69.5
MRI vol (cc)		0.58	0	100	0	30.7
MRI	**PiRADS 1-2 vs 3-5**	0.6500	53.3	77.4	50	79.6
	PiRADS 1-3 vs 4-5	0.6100	31.1	91.5	60.9	75.8
PRS		0.74	39.5	91.5	68.2	76.5
PSA (ng/ml)		0.72	19.6	94.3	60	72.8
PSAD (ng/ml)		0.67	13	96.2	60	71.6
Prior PSA		0.56	69	42.4	35.4	75

		Significant cancer				
Model		**ROC, %**	**Sens., %**	**Spec., %**	**PPV, %**	**NPV, %**
Age		0.8	0	100	0	91.4
MRI vol (cc)		0.5	0	100	0	91.3
MRI	**PiRADS 1-2 vs 3-5**	0.83	92.3	73.9	25	99
	PiRADS 1-3 vs 4-5	0.8	69.2	89.9	39.1	96.9
PRS		0.7200	0.0	100.0	0.0	90.91
PSA (ng/ml)		0.86	7.7	98.5	33.3	91.9
PSAD (ng/ml)		0.84	15.4	98.6	50	92.5
Prior PSA		0.5	61.5	38.8	9.8	90.4

Table 3.3 Performance characteristics of individual clinical variables of interest for the diagnosis of any cancer or significant cancer

	No Cancer				Insignificant Cancer				Significant Cancer				Total			
	PiRADS 1-2		PiRADS 3-5		PiRADS 1-2		PiRADS 3-5		PiRADS 1-2		PiRADS 3-5		PiRADS 1-2		PiRADS 3-5	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
PRS (quintiles)																
<20	13	(21.3)	3	(16.7)	2	(9.5)	1	(11.1)	0	(0.0)	1	(10.0)	15	(18.1)	5	(13.5)
20 - <40	10	(16.4)	4	(22.2)	3	(14.3)	0	(0.0)	0	(0.0)	1	(10.0)	13	(15.7)	5	(13.5)
40 - <60	10	(16.4)	4	(22.2)	2	(9.5)	1	(11.1)	0	(0.0)	0	(0.0)	12	(14.5)	5	(13.5)
60 - <80	16	(26.2)	3	(16.7)	3	(14.3)	1	(11.1)	0	(0.0)	2	(20.0)	19	(22.9)	6	(16.2)
≥80	12	(19.7)	4	(22.2)	11	(52.4)	6	(66.7)	1	(100.0)	6	(60.0)	24	(28.9)	16	(43.2)
PSA (ng/ml)																
0 - <1	43	(53.1)	10	(41.7)	6	(28.6)	0	(0.0)	0	(0.0)	0	(0.0)	49	(47.6)	10	(20.8)
1 - <2	20	(24.7)	3	(12.5)	11	(52.4)	5	(41.7)	1	(100.0)	2	(16.7)	32	(31.1)	10	(20.8)
2 - <3	11	(13.6)	4	(16.7)	3	(14.3)	2	(16.7)	0	(0.0)	2	(16.7)	14	(13.6)	8	(16.7)
≥3	7	(8.6)	7	(29.2)	1	(4.8)	5	(41.7)	0	(0.0)	8	(66.7)	8	(7.8)	20	(41.7)
PSAD (ng/ml)																
<0.15	79	(97.5)	23	(95.8)	21	(100.0)	11	(91.7)	1	(100.0)	8	(66.7)	101	(98.1)	42	(87.5)
≥0.15	2	(2.5)	1	(4.2)	0	(0.0)	1	(8.3)	0	(0.0)	4	(33.3)	2	(1.9)	6	(12.5)
Age																
40 - 49	31	(37.8)	8	(33.3)	9	(45.0)	2	(16.7)	0	(0.0)	1	(8.3)	40	(38.8)	11	(22.9)
50 - 59	40	(48.8)	12	(50.0)	9	(45.0)	8	(66.7)	0	(0.0)	3	(25.0)	49	(47.6)	23	(47.9)
≥60	11	(13.4)	4	(16.7)	2	(10.0)	2	(16.7)	1	(100.0)	8	(66.7)	14	(13.6)	14	(29.2)

Table 3.4 clinical variables of interest described by individual PiRADS score and cancer status

3.3.1 Biopsy characteristics

Biopsy outcomes including median cancer core length (MCCL), total cancer core length (TCCL), number of cores taken (total), number of positive cores (if cancer present) and number of targeted cores taken described by cancer outcome.

The incidence of clinically significant prostate cancer was 8.6% (21.9% low-grade PrCa). Overall, the incidence of PrCa was approximately 30%. There were significant differences in MCCL, TCCL, number of positive and targeted cores between clinically significant and insignificant cancers. According to D'Amico classification, 71.7% of cancers (n=46) detected were low risk, 10.9% intermediate risk and 17.4% high risk.

	Cancer		
	Significant	**Insignificant/Benign**	P Value
MCCL median (IQR)	3.5 (3 – 6.5)	1.5 (1 – 2.5)	*0.0003*
TCCL median (IQR)	9 (6 – 16.5)	2 (3.2 – 6.8)	*0.0001*
No +ve cores mean (SD)	4.8 (2.11)	1.7 (1.77)	*0.0001*
Total no cores mean (SD)	15.0 (4.66)	13.4 (3.03)	0.0771
No targeted cores mean (SD)	2.77 (1.74)	0.63 (1.29)	*0.0003*

Table 3.5 Histology characteristics of participants

3.3.2 PSA

23.08% of all clinically significant cancers were found in men with a PSA of 1.0-1.9ng/ml and 61.54% of all clinically significant cancers were found in men with a PSA of ≥3.0ng/ml (Figure 3.1).

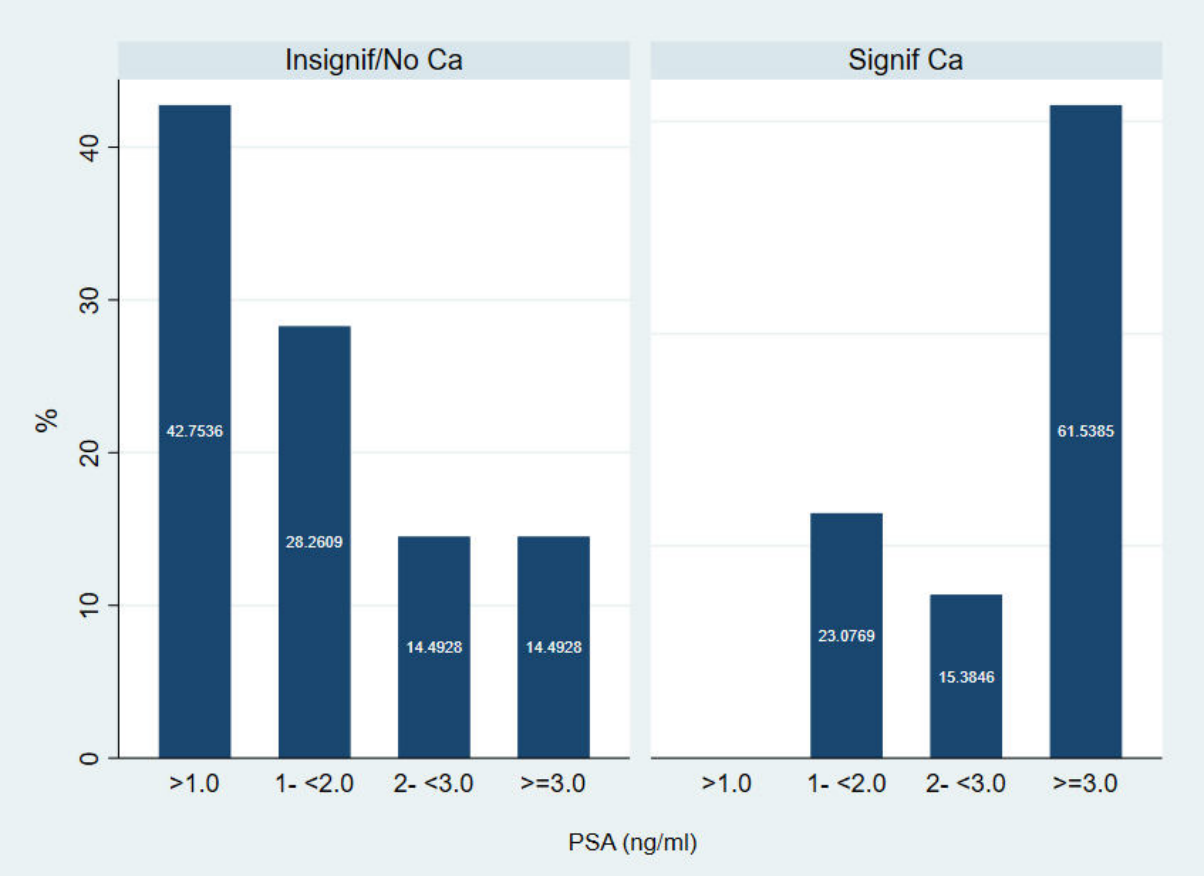

Figure 3.1 This figure describes the spread of PSA values in men by insignificant/non cancers vs clinically significant cancers found.

PSA (as a continuous variable) was positively associated with detection of clinically significant cancer (OR, 1.71, p=0.001). ie for each unit increase in PSA there was

1.71 increase in the odds of detecting significant cancer compared to those with insignificant cancer/no cancer.

Using a PSA of <1.0ng/ml as the reference, only a PSA of >=3.0ng/ml was significantly associated with significant cancer (OR 49.3) in a logistic regression model (p=0.008).

Adjusted predictions describe an (average) probability of significant cancer of 5%, 12% and 33% in men with a PSA of 1-<2.0ng/ml, 2-<3.0ng/ml and >=3.0ng/ml respectively.

PSA as a continuous variable was significantly associated with any cancer outcome. At the mean PSA of 1.83ng/ml, the adjusted predicted probability of cancer was 33.3% (p=0.001).

On average, men with a PSA <1ng/ml had a 10.2% risk of cancer. Men with a PSA of 2-<3ng/ml had a greater probability at 31.8%, with those in the highest PSA category having an (average) probability of 50%.

3.3.3 PSA & MRI

In all men with a PSA between 0-1.0ng/ml (n=59), 16.9% had an abnormal (PiRADS 3-5) MRI. In men with a PSA of ≥3.0ng/ml, 71.4% had an abnormal MRI.

In the 6 men who had PrCa (any) with a PSA of 0-<1.0ng/ml, all had a normal (PiRADS 1-2) MRI. None of these cancers were clinically significant. In the 14 men who had PrCa (any) with a PSA of ≥3.0ng/ml, 92.8% had an abnormal MRI (8 of these were clinically significant).

In men with clinically significant cancer, no men had a PSA of 0-<1.0ng/ml. Most men with clinically significant cancer at other ‘low’ categories of PSA had an abnormal MRI (n=4/5). All 8 men who had clinically significant cancer and a PSA of ≥3.0ng/ml had an abnormal MRI.

In men in the lowest PSA category (0-<1.0ng/ml; n=59), 49 (83%) had a normal (PiRADS 1-2) and 10 (17%) had an abnormal (PiRADS 3-5) MRI. Of the men in the lowest PSA category with a normal MRI, no significant cancer was found. In those with an abnormal MRI, no clinically significant cancer was found. All of the clinically insignificant cancer detected in this category was in those with a normal MRI.

In men in the highest PSA category (≥3.0ng/ml; n=28), 8 men (28.6%) had a normal MRI and 20 (71.4%) had an abnormal MRI. In those with a normal MRI, no clinically significant cancer was found, whereas in those with an abnormal MRI, clinically significant cancer was found in 8 men (40%) and insignificant cancer in 25% of men (highlighted in red).

In all men with clinically significant cancer (n=13), 61.5% (8/13) were found in men with a PSA in the highest category (≥3.0ng/ml).

3.3.4 Age

In men aged 60 or greater, 46.4% had any cancer detected vs 25.4% of those aged 40-49. 69% of all clinically significant cancers were found in men aged 60 or older; 7.69% of all cinically significant cancers (1/13) were found in men aged 40-49.

On average, the predicted probability of clinically significant cancer detection in men aged 40-49 was 2%, 4% in those aged 50-59 and 32% in those aged ≥60 (Figure 3.2).

Age was significantly associated with significant cancer detection (OR 1.05, p=0.034). At the mean age (53.45 years) the probability of cancer was 33.3%.

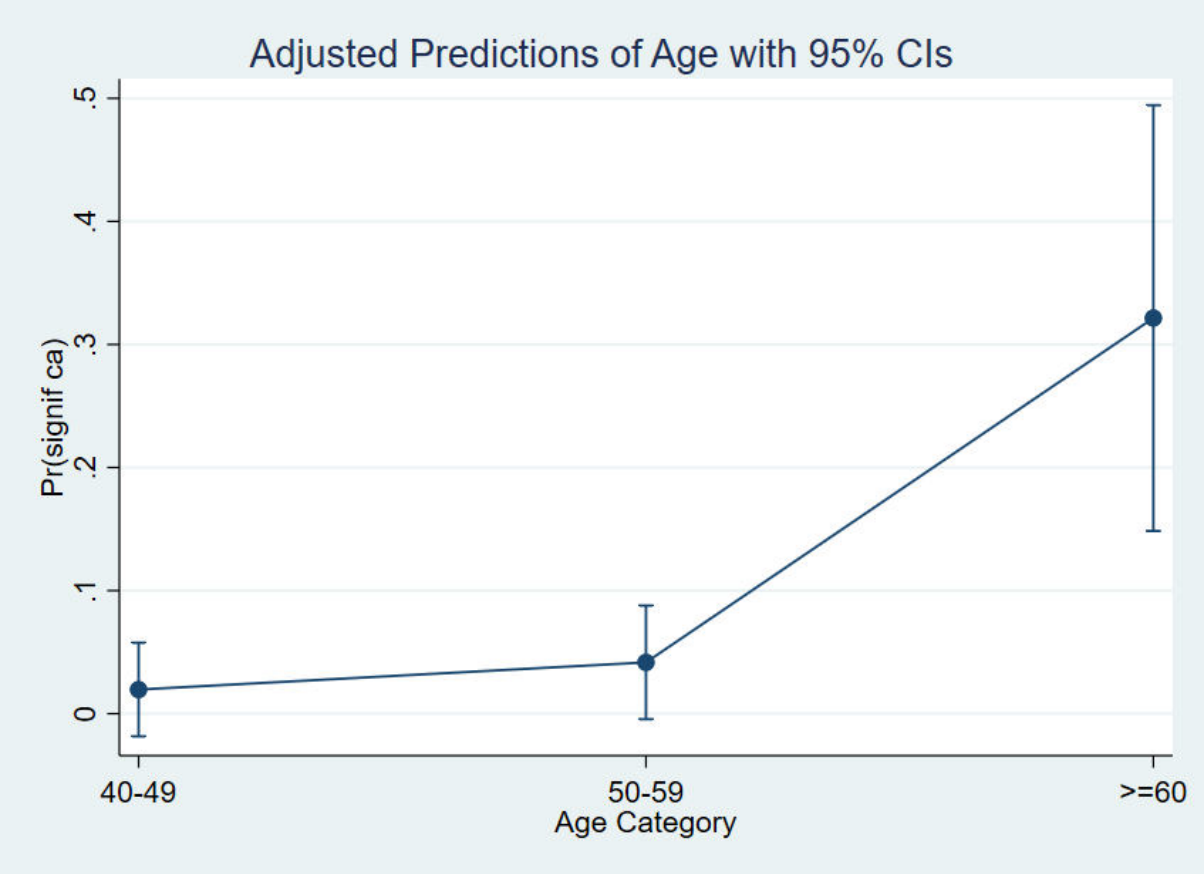

Figure 3.2. This graph displays the marginal predictions of age on the probability of clinically significant cancer detection.

3.3.5 Age & MRI

Just over 78% of men aged 40-49 had a 'normal' MRI (PiRADS 1-2). The highest proportion of abnormal MRI was in those aged 60 and above (50%); approximately one third of all men aged 50-59 had an abnormal MRI (PiRADS 3-5).

The highest percentage of men with an abnormal MRI was in those aged 60 or above (26.7%). In young men (aged 40-49) with any PrCa, only 25% had an abnormal MRI. Whereas in those aged 60 and above, 77% had an abnormal MRI.

Almost all men, in any age category with clinically significant cancer had an abnormal MRI (88-100%).

3.3.6 PSAD

For each unit increase in PSAD there was a positive association with a diagnosis of clinically significant cancer (OR1.018) and this was statistically significant ($p<0.001$). A PSAD ≥0.15ng/ml was positively associated with a diagnosis of clinically significant cancer (OR 14.1) and this was statistically significant ($p<0.001$).

The proportion of men with a PSAD <0.15ng/ml who had no cancer/insignificant cancer was 93.7% or clinically significant cancer (6.29%), and those who had a PSAD ≥0.15 who had no cancer/insignificant cancer (50%) or clinically significant cancer (50%) (Figure 3.3,Table 3.1).

3.3.7 PSAD & MRI

29% of men with a PSAD <0.15 had an abnormal MRI whereas 75% of men with a PSAD≥0.15 had an abnormal MRI. All men with a PSAD ≥0.15 who had clinically significant cancer, also had an abnormal MRI.

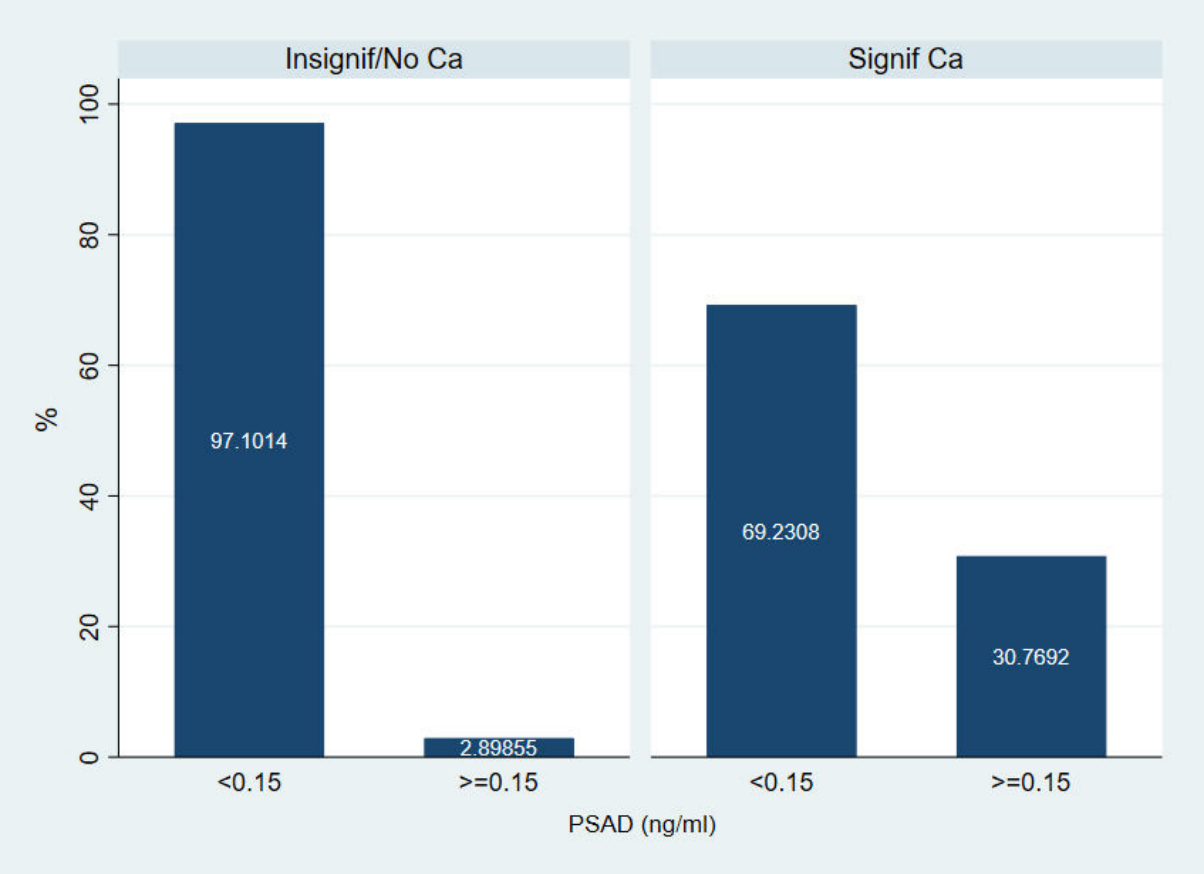

Figure 3.3. This figure displays the proportion of men with either no cancer/insignificant cancer or clinically significant cancer who had a PSAD ≥0.15; ie 30.7% of men with clinically significant cancer had a PSAD ≥0.15 compared to 2.8% of those with no cancer/insignificant cancer.

3.3.8 MRI Volume

There was no significant association between prostatic volume and any cancer detection or clinically significant cancer detection.

3.3.9 Degree of FH

The proportion of men in the study cohort whose FH of PrCa was in 1 relative (first degree) aged <70years (42%); 2 relatives, at least one being a FDR (34.3%) and those who had three relatives on the same side of the family with a history of PrCa (any age); 23.3%.

6.2% of men with a FH of PrCa in 3 or more relatives had clinically significant cancer, 14.8% in those who had a FH in 2 relatives and 6.9% in men with a FH of

PrCa in 1 FDR<70 years old. Of all men with a FH of PrCa in 3 or more relatives, approximately 68% had had a prior PSA before entering the study. For men with a history of PrCa in one FDR, 53% had had prior PSA screening. 34% of men with a FH of PrCa in 3 or more relatives had a diagnosis of (any) cancer, 42.5% in those who had a FH in 2 relatives and 24.1% in men with a FH of PrCa in 1 FDR<70 years old.

3.3.10 Biopsy method

Almost three quarters of all insignificant cancers/no cancers were detected on systematic biopsies, with 90% of all significant cancers detected by fusion biopsies. Only one significant cancer was found on systematic biopsy. Of all systematic-only biopsies in this group, 98% yielded insignificant cancer/no cancer. Of all the fusion biopsies performed (for PiRADS 3-5), 25% yielded clinically significant cancer.

3.4 Discussion

3.4.1 Cancer incidence and aggressiveness

The majority of cancers detected in this study were classified as D'Amico Low risk. The majority of D'Amico High risk & intermediate risk classified cancers occurred in men with a PiRADS 3-5 MRI (87-100%) with approximately three quarters of D'Amico Low risk classified cancers occurring in men with a PiRADS 1-2 MRI.

The published incidence of indolent and high-grade PrCa at low PSA levels is not negligible [2] and has been well described amongst just under 3,000 men in the placebo arm of the REDUCE trial with a PSA ≤4.0ng/ml by Thompson et al [3]. Although their cohort was significantly older than ours (age range 62-91) and had a low FH rate (16.2%), they diagnosed 15.2% of men with PrCa (with 14.9% of those being ≥Gleason 3+4). They calculated a prevalence of (any) PrCa of 6.6% in men with a PSA of 0-0.5ng/ml, 10.1% among those with a PSA of 0.6-1.0ng/ml, 17% of those with a PSA of 1.1 – 2.0ng/ml, 23.9% in those with a PSA of 2.1-3.0ng/ml and 26.9% in those with a PSA of 3.1-4.0ng/ml.

In our (younger, FH selected and MRI-informed biopsy) cohort; 13.04% of all cancers occurred in those with a PSA <1.0ng/ml, 41.3% in those with a PSA 1.0-1.9ng/ml, 15.22% in those with a PSA of 2.0-2.9ng/ml and 30.43% in those with a PSA ≥3.0ng/ml.

3.4.2 Age

The association of advancing age and PrCa is well described [4, 5], with a high proportion of older men expected to harbour indolent PrCa with the risk increasing from approximately age 40 [6, 7]. The most common age-range for our cohort was 50-59 (61%).

As both a categorical and continuous variable, age was significantly associated with clinically significant PrCa (Table 3.2). When age was categorised into three brackets; 40-49, 50-59 and ≥60, only those in the latter category had a statistically significant predicted probability of significant cancer (OR 23, p=0.004) compared to those in the youngest category. For men aged 60 and above, the average predicted probability of clinically significant PrCa was 32%.

3.4.3 Prior screening

PSA screening gives rise to higher incidences of PrCa detection and has been reported to result in fewer diagnoses of aggressive disease [8, 9]. There was a high rate of prior PSA screening in our cohort (61%) but no statistically significant association between prior PSA screening and a lower probability of PrCa. Those with a FH of PrCa in 1 relative had a slightly lower frequency of prior PSA screening than those with a FH in 2 or 3 relatives (53% vs 65-68%) but there was no statistically significant difference found.

3.4.4 MRI Volume

Prostate volume has been reported as being a potential factor in PrCa incidence and aggressiveness [10-12]. Interestingly we found no statistically significant association between prostate volume and any cancer or clinically significant cancer detection in this cohort, with a mean volume of 34.8cc (SD 15.8, median 30.5). Given the known association of age with benign prostatic hypertrophy (BPH), and the average age of our study population being younger than that featuring in study populations in many papers investigating the role of prostate size in PrCa development, this may account for the lack of a positive finding in this clinical variable.

3.4.5 PSA

The association of a raised PSA with PrCa is well described [13-16], allowing for well-known limitations in sensitivity and a high false positive rate due to the competing influences of prostate size/BPH/urinary tract infection/sexual activity etc.

PSA was significantly associated with any and significant cancer detection in our cohort. The majority of significant cancers were detected in those with a PSA ≥3.0 (range 0.2-8.4ng/ml) but a proportion were found in men with a PSA of 1.0-2.9 (34%). Clinically insignificant cancers were found throughout the PSA spectrum and this is in-keeping with published literature.

3.4.6 PSAD

The association of PSAD with clinically significant PrCa detection is well described [17] [18] with cut offs of 0.08 [19] and 0.15 [20] [21, 22] suggested as cut points, below which there is a significantly lower incidence of clinically significant PrCa.

The proportion of men with a PSAD <0.15 who had no cancer/insignificant cancer was 93.7% and 6.29% for those with clinically significant cancer. For those who had a PSAD ≥0.15 who had no cancer/insignificant cancer, the frequency was 50% and for clinically significant cancer was 50%.

There was a significant difference in the probability of clinically significant cancer detection between those with a PSAD ≥ 0.15ng/ml (OR 14.1, p<0.001) and those without. PSAD as a continuous variable was also associated with significant PrCa detection (OR 1.01, p<0.001).

3.4.7 FH degree

The influence of the number and closeness of relatives on the incidence and aggressiveness of PrCa has been described [23-26]. Recently published data from a large multi-institutional study demonstrated an adjusted OR of 1.77 for high grade PrCa if men had a FH of PrCa in a FDR compared to second-degree [27]. In our cohort, there was no statistically significant difference in clinically significant cancer outcomes between different pedigrees of family history, when each category was compared to the ‘baseline’ category (1 FDR <70 years) or when each category was also compared to each other although the ORs were positive.

There was a statistically significant difference noted in those with a FH in two relatives compared to those with one (OR 2.32) for a diagnosis of any cancer, whereas there was no association between those with a FH in three relatives compared to those with one (p=0.301).

3.5 Limitations

The small number of men with a PSAD≥0.15ng/ml minimises our ability to analyse the value of this category in predicting the probability of any/clinically significant cancer. An age and PSA matched cohort unselected for FH would provide a useful comparator, and would potentially allow for more robust conclusions and recommendations if a fundamentally different screening process should be employed for men with a FH of PrCa compared to those without, and if clinical variables including MRI and PRS behave 'differently' in an age/PSA matched population.

Ideally, we would have a PSA naïve population, however in the modern day it is not uncommon for men with a FH of PrCa to have sought PSA screening from a young age and our population therefore reflects more of a real life clinical setting.

For absolute uniformity of prostate biopsy accuracy, each biopsy could have been performed by the same clinician and MRI reported by the same radiologist.

3.6 Conclusion

PSA, PSAD and age were significantly associated with clinically significant cancer detection in healthy men selected for a FH of PrCa undergoing targeted screening. All three variables performed 'well' according area under the ROC curve (Table 3.3). There was no difference in rates of clinically significant cancer detection in men with the highest number of relatives with PrCa compared to those with the lowest, but having two relatives with PrCa was significantly associated with any cancer detection. Despite high levels of prior PSA screening there was no statistically significant association found as yet between those with and without prior screening and a diagnosis of PrCa. These variables of interest may therefore have limited use in any risk prediction strategy for unaffected men with a FH of PrCa. Modern day rates of cancer detection must be compared with caution to those quoted from older (but larger) screening studies given the enormous shift in PrCa diagnostics to MRI guided prostate biopsy.

3.7 Tables

3.8 Figures

3.9 References

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4 Chapter 4 – MRI

4.1 Introduction

This chapter investigates the association of pre-biopsy MRI with outcome of cancer (both clinically significant cancer and 'any' cancer) at systematic prostate biopsy (with targeted sampling as guided by MRI), in men with a FH of PrCa undergoing targeted screening in the PROFILE study.

4.2 Background

Pre-biopsy MRI has become the standard of care in PrCa diagnostics in men referred with a clinical suspicion of PrCa, either due to a raised PSA or abnormal DRE, and is now features in the most recent EAU [1] and NICE [2] guidance.

Little is known of the clinical utility of pre-biopsy MRI in the 'at risk' but clinically unsuspected setting i.e. in unaffected men without a clinical suspicion of PrCa but who possess a higher than average population risk of the disease. Such men are likely to be young, with smaller prostate glands in whom PSA may not be the best screening tool for early PrCa detection. A pathway involving MRI as a screening tool in these men is un-investigated, although the STHLM-3 MRI study has recently reported results from 2293 men randomised to either biparametric MRI followed by targeted and systematic prostate biopsy, or non-image guided, systematic biopsy only following an 'abnormal' STHLM3 result which incorporates a PRS [3]. The study reported the STLMH-3 test combined with MRI-targeted biopsy was associated with a higher detection rate of significant PrCa compared to PSA and systematic biopsy.

Following a description of the aims below, descriptive MRI characteristics for all men undergoing pre-biopsy MRI are described followed by regression analyses investigating performance of MRI in predicting the probability of cancer at prostate biopsy.

4.3 Aims

Describe the incidence of clinically significant and insignificant cancer across all PiRADS scores in men undergoing targeted screening in the PROFILE FH cohort

Describe the performance of pre biopsy MRI in the PROFILE FH cohort

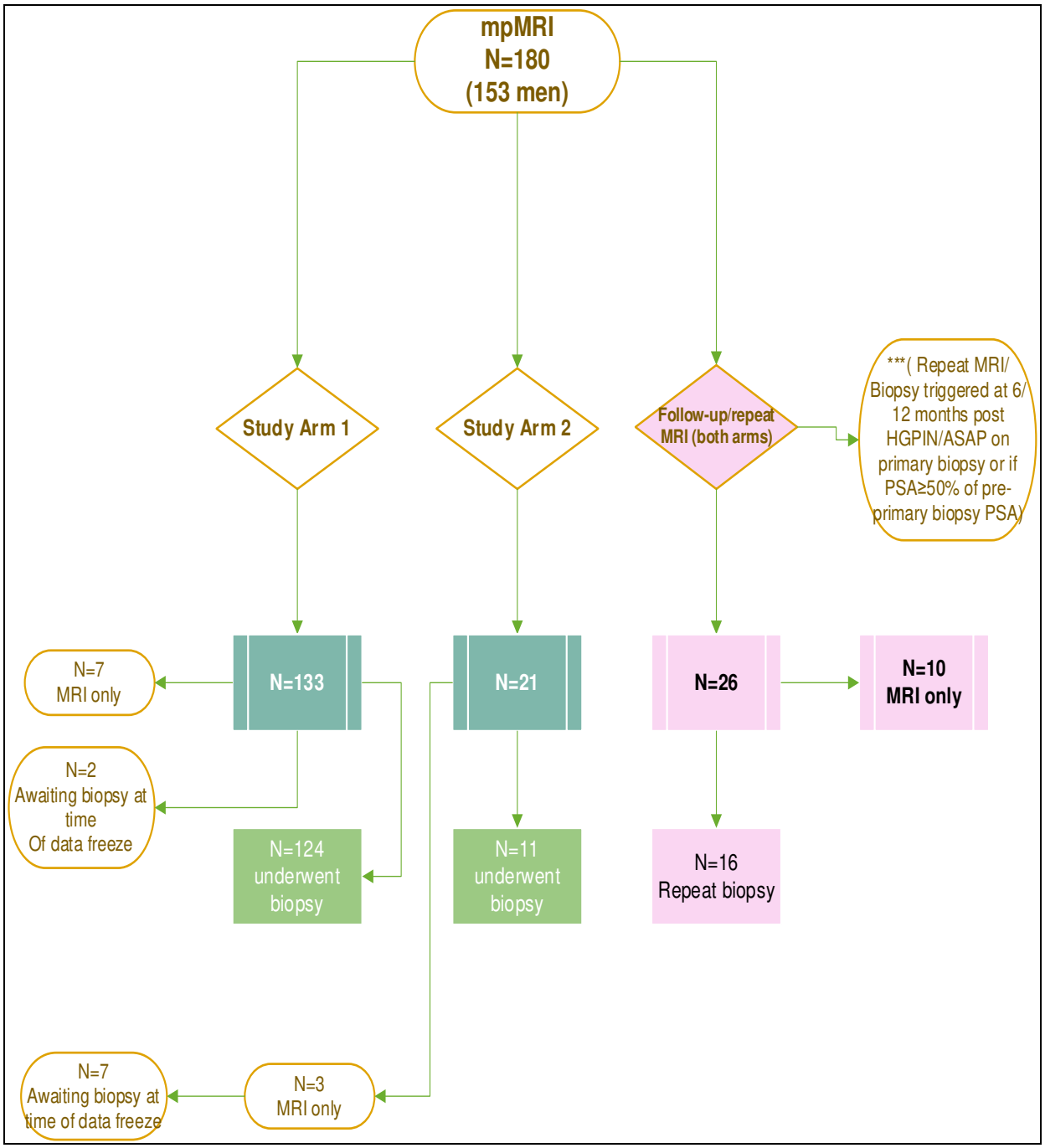
To define sensitivity, specificity, NPV and PPV of MRI in the PROFILE FH cohort

Describe the performance of pre biopsy MRI in combination with other clinical variables in predicting cancer in the PROFILE FH cohort

4.4 Methods

All MRIs performed prior to either a primary or repeat biopsy are described (n=151), with a full account of the methods described in Chapter 2. Figure below outlines the numbers of MRIs per study arm.

Figure 4.1 Flowchart displaying numbers of men with a pre-biopsy MRI available according to primary biopsy (study arm 1 or 2) and repeat biopsy.



4.5 Results

For the purposes of analysis and to investigate which cut off of 'abnormal' PIRADS may be useful, MRIs are presented as two categorical variables: 'abnormal' if pre-biopsy MRI was PiRADS 3-5, and a second definition of 'abnormal' if PiRADS 4-5.

The proportion of benign disease, insignificant and significant cancer is described per individual PIRADS score in Figure 4.2 below. Insignificant cancer was seen throughout the spectrum of PIRADS apart from PIRADS 5. Approximately 11% of all PIRADS 3 MRIs yielded a diagnosis of clinically significant PrCa, a PIRADS score that is defined as 'equivocal' with not all men proceeding to biopsy. Given the mean age of men in our study was young (53.5), such a diagnosis is meaningful in this age group and therefore PIRADS 3 MRI in this cohort of men may be best included as definitely 'abnormal' alongside PIRADS 4-5.

Baseline Characteristics	Total Number	Significant Ca	Non-significant /No Ca	P value
PRS, mean (SD)	120	11.16 (0.244)	10.52 (0.0656)	0.0051
Age, mean (SD)	151	63.3 (57.4 – 66.2)	53.8 (45.5 – 58.7)	0.0003
PSA, median (IQR)	151	3.5 (2.4 – 4.8)	1.15 (0.8 – 2.2)	0.0001
PSA Density, mean (SD)	151	0.307 (0.480)	0.052 (0.2247)	0.0039
MRI Volume, median (IQR)	151	29cc (27 – 39)	31cc (25 – 39)	0.9619
FH variable N (%)	137			
1<70	58 (42.34)	4 (6.9)	54 (93.1)	0.345
2	47 (34.310	7 (14.89)	40 (85.1)	
3	32 (23.36)	2 (6.25)	30 (93.75)	
Prior PSA N (%)	134			
Yes	82	8	74	0.997

	(61.19)	(9.76)	(90.24)	
No	41	4	37	
	(30.6)	(9.76)	(90.24)	
Unknown	11	1	10	
	(8.21)	(9.09)	(90.91)	
PiRADS				
N	151			
(%)				
1	9	0	9	
	(5.96)	(0)	(6.52)	<0.001
2	94	1	93	
	(62.25)	(7.69)	(67.39)	
	26	3	23	
3	(17.22)	(23.08)	(16.67)	
	19	7	12	
4	(12.58)	(53.85)	(8.7)	
	3	2	1	
5	(1.99)	(15.4)	(0.72)	
Mode of Detection				0.286
Study arm 1	124	11	110	
		(84.62)	(81.48)	
Study arm 2	11	2	9	
		(15.38)	(6.66)	
Follow-up	16	0	16	
			(11.86)	

Table 4.1 baseline clinical characteristics of all men with a pre-biopsy mpMRI and biopsy histology available for analysis (n=151). Of these men, 121 had genotyping available (described in more detail in chapter 5).

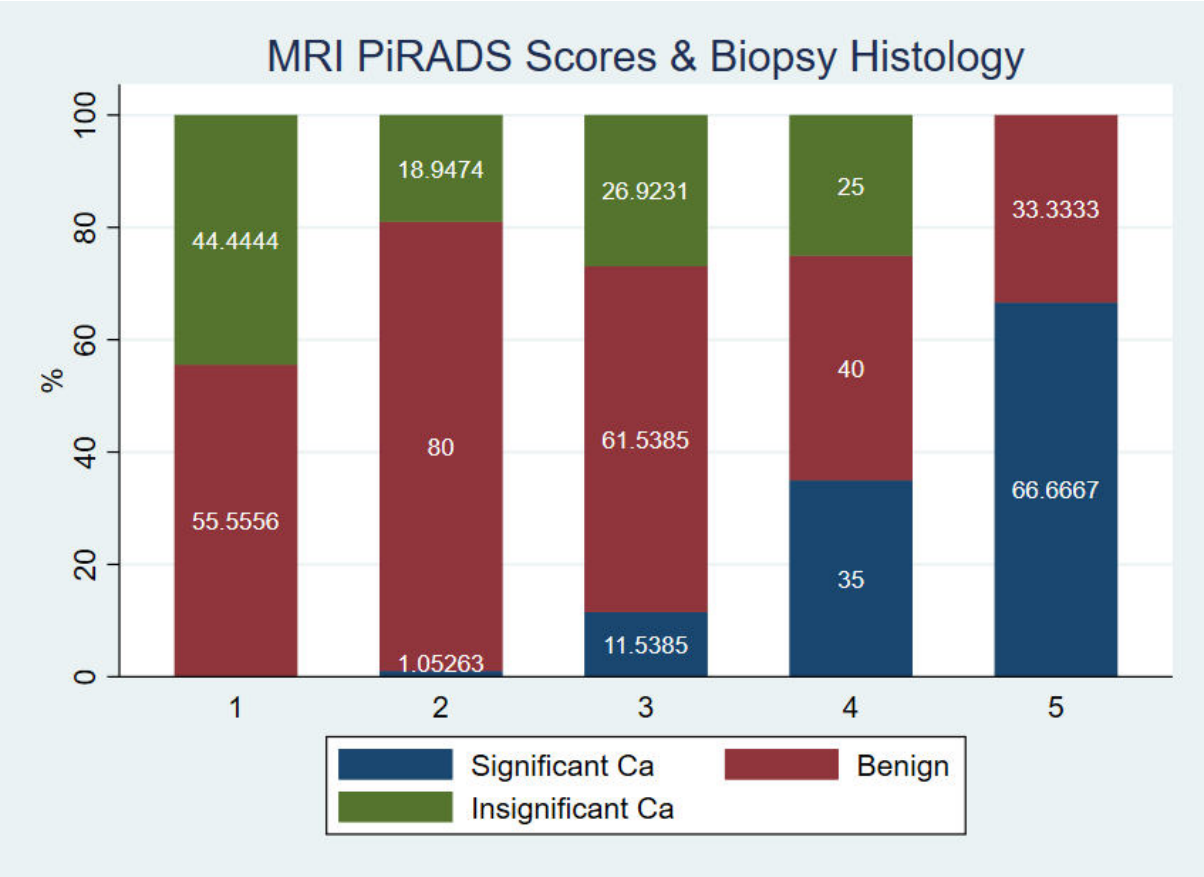


Figure 4.2 Stacked bar chart displaying all MRIs by PiRADS score, with proportions of insignificant/no cancer and significant cancers.

A stacked bar chart displaying the frequency of individual pre biopsy PiRADS scores in men with insignificant/no cancer vs significant cancer is shown below in Figure 4.3. The majority of men with insignificant/no cancer had a PiRADS score of 2, whereas the most frequently seen PiRADS score in men with significant cancer was PiRADS 4.

The same chart is displayed for 'any cancer' vs no cancer in Figure 4.4. here, the majority of men with no cancer had a PiRADS score of 2, and the most frequently

seen PiRADS score in men **any** cancer was PiRADS 2, likely reflecting the larger number of insignificant cancers detected in this cohort.

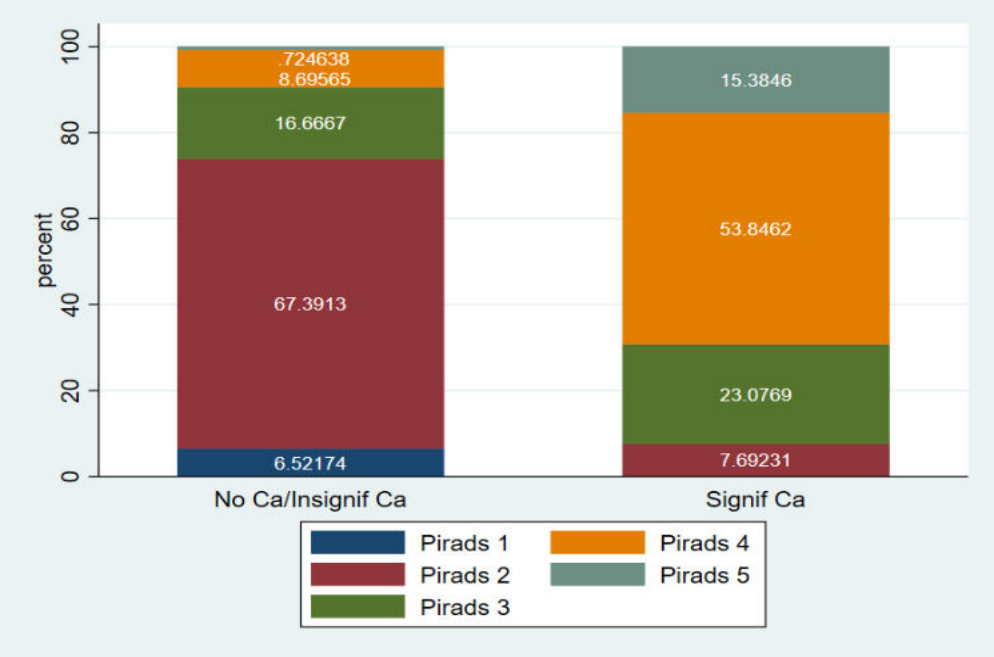


Figure 4.3 Stacked bar chart. Significant cancer vs no cancer/insignificant cancer

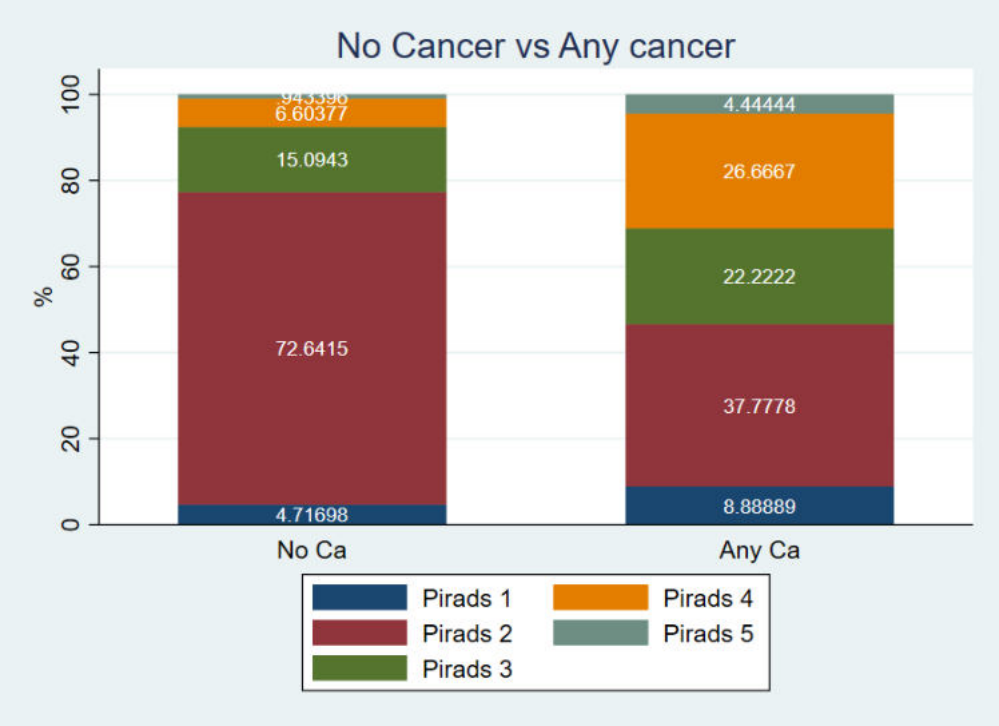


Figure 4.4 Stacked bar chart. Any cancer vs no cancer

Biopsy histology is also demonstrated below in categories of PIRADS, for both definitions of 'abnormal i.e PiRADS 1-2 vs PIRADS 3-5 and PIRADS 1-3 vs PIRADS 4-5 (Figure 4.6 Stacked bar chart displaying biopsy histology outcome according to 'normal (PiRADS 1-3) vs 'abnormal' (PiRADS 4-5) MRI. , **Error! Reference source not found.**). Approximately 50% of all PIRADS 3-5 MRIs yielded (any) cancer, with 24% showing a significant cancer. The overwhelming majority of PIRADS1-2 MRIs yielded either no cancer or clinically insignificant cancer with 1% having significant disease.

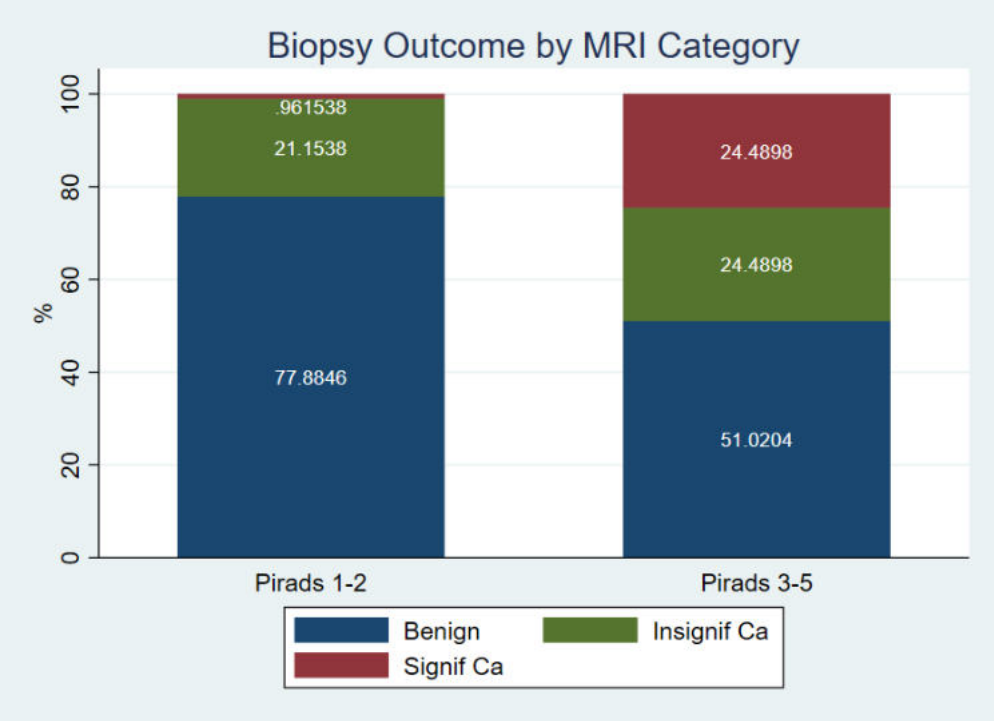


Figure 4.5 Stacked bar chart displaying biopsy histology outcome according to 'normal (PiRADS 1-3) vs 'abnormal' (PiRADS 4-5) MRI.

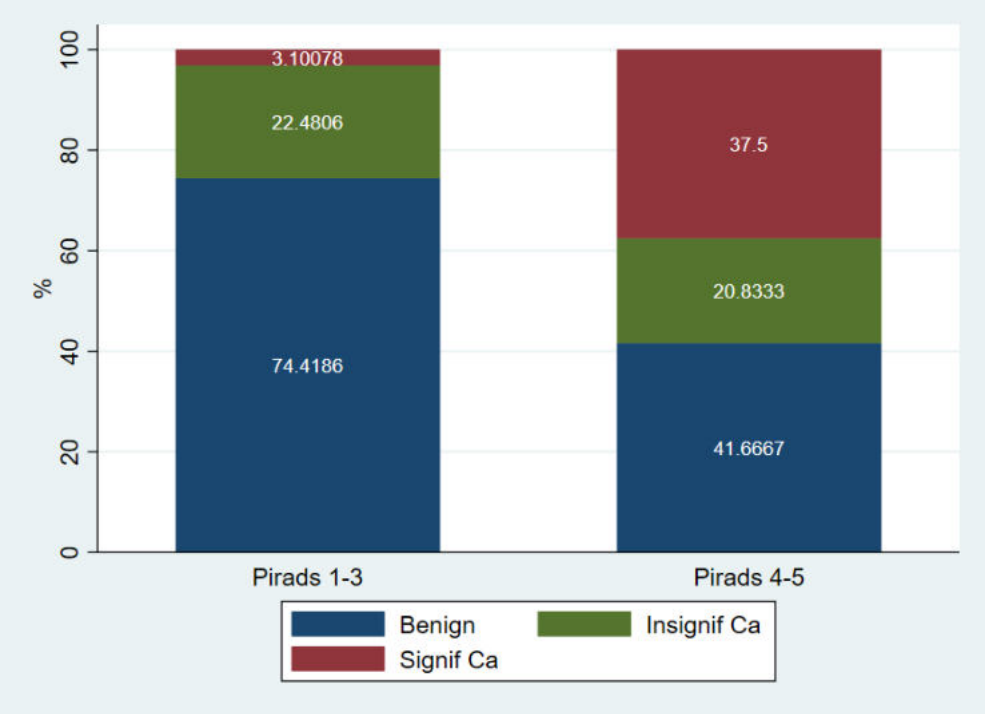


Figure 4.6 Stacked bar chart displaying biopsy histology outcome according to 'normal (PiRADS 1-3) vs 'abnormal' (PiRADS 4-5) MRI.

A table of results describing the baseline clinical variables of interest by individual PiRADS score is featured below in Table 4.2 and by PiRADS 1-2 vs 3-5 in Table 4.3, and cancer classification according to D'Amico/NCCN in Table 4.4. For reference, a graph displaying the results of PROMIS data (biopsy outcome by PiRADS score) is shown in Figure 4.7.

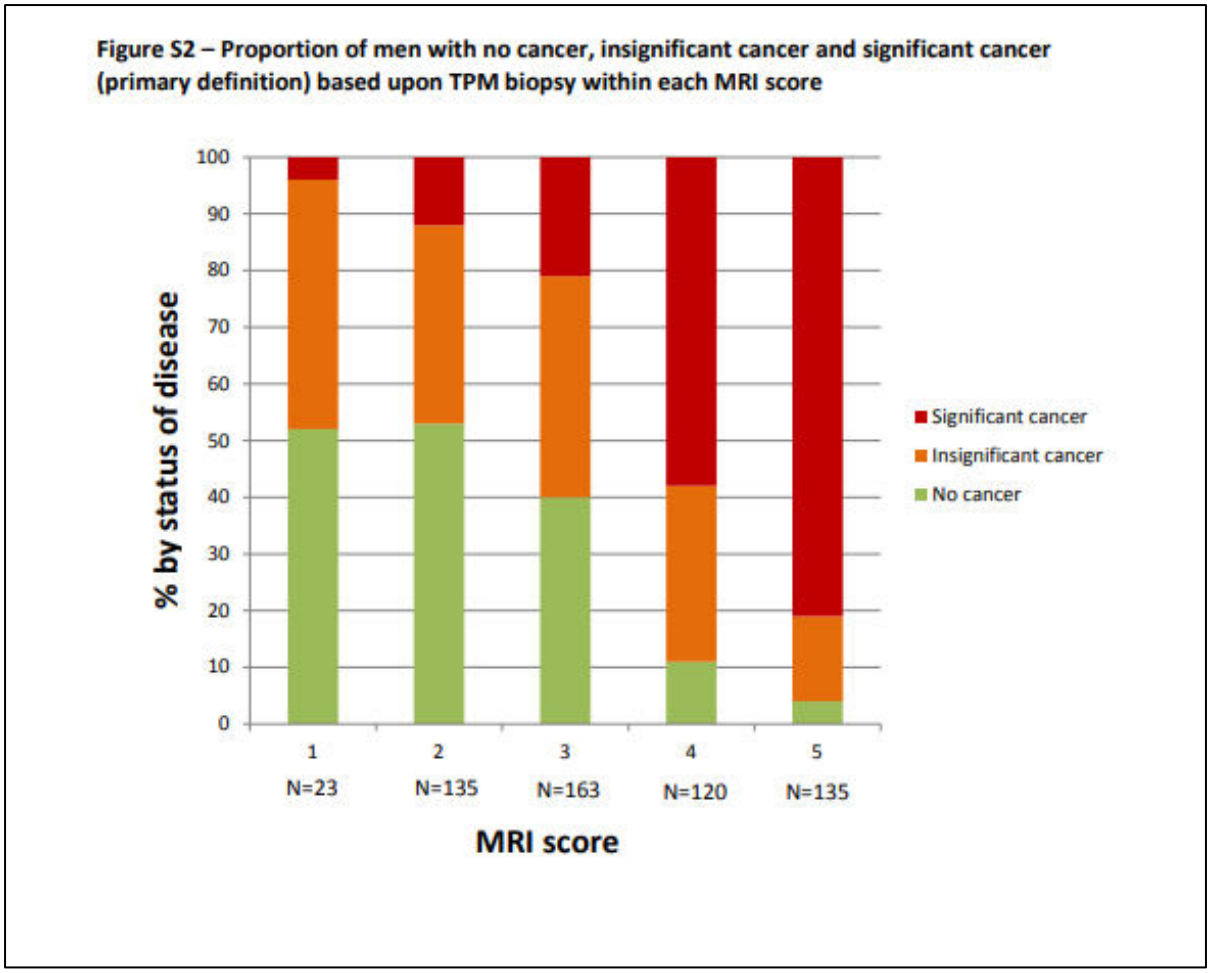


Figure 4.7 Reproduced from Ahmed et al, supplemental material [4]

	PIRADS 1		PIRADS 2		PIRADS 3		PIRADS 4		PIRADS 5	
	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median
Age (years)	52.3 (7.4)	52.528	52.38 (7.3)	52.528	53.2 (6.3)	54.121	59.4 (7.5)	60.583	60.747 (4.8)	58.511
PSA (ng/ml)	1.473 (1.3)	1.1	1.41809 (1.2)	1.1	2.17692 (1.5)	1.85	2.9 (1.5)	2.3	4.8 (1.9)	3.7
PSAD (ng/ml)	0.06 (0.04)	0.0359	0.04 (0.04)	0.34	0.06 (0.04)	0.04	0.08 (0.1)	0.07	0.2 (0.1)	0.2
Prostate volume (ml)	33 (13.6)	29.5	32.7 (12.9)	30	38.7692 (18.2)	32.5	41.26316 (22.1)	36	29.3 (2.1)	30

Table 4.2 Description of clinical variables of all participants categorised by individual PiRADS score

	PIRADS 1-2		PIRADS 3-5	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Age (years)	52.3 (7.4)	52.5 (44.9-58.2)	56.1 (7.4)	57.5 (51.1-61.3)
PSA (ng/ml)	1.5 (1.3)	1.1 (0.7-2.0)	2.6 (1.7)	2.4 (1.1-3.7)
PSAD (ng/ml)	0.05 (0.04)	0.04 (0.0-0.1)	0.1 (0.1)	0.06 (0.0-0.1)
Prostate volume (cc)	32.9 (13.6)	29.5 (25.0-38.0)	39.2 (19.3)	32.5 (26.0-44.0)

Table 4.3 Clinical variables of participants categorised by PiRADS 1-2 MRI vs PiRADS 3-5

	PIRADS 1-2		PIRADS 3-5		Total	(%)
	N	(%)	N	(%)		
Damico						
Low	21	(64)	12	(36)	33	(71.7)
Intermediate	0	(0)	5	(100)	5	(10.9)
High	1	(12.5)	7	(85.5)	8	(17.4)
NCCN						
Very low	18	(94.7)	1	(5.3)	19	(41.3)
Low	3	(21.4)	11	(78.6)	14	(30.4)
Intermediate favourable	0	(0)	9	(100)	9	(19.6)
Intermediate unfavourable	1	(25)	3	(75)	4	(8.7)

Table 4.4 Cancer outcomes by D'Amico and NCCN classification categorised by PiRADS 1-2 vs 3-5 MRI

4.6 MRI – Univariate analysis

Univariate analysis of MRI, MRI with one and MRI with two other clinical variables are presented and discussed below in tables.

Multivariable Models (MRI + one other)		Any cancer			Clinically significant cancer		
		Odds Ratio	(95% C.I.)	*P*	Odds Ratio	(95% C.I.)	*P*
MRI	**PiRADS 1-2**	Ref.			Ref.		
	PiRADS 3-5	2.7	(1.2, 5.9)	0.0	24.2	(2.8, 204.2)	0.003
PSA*		1.3	(1.0, 1.7)	0.017	1.6	(1.1, 2.4)	0.01
MRI	**PiRADS 1-3**	Ref.			Ref.		
	PiRADS 4-5	3.0	(1.1, 8.2)	0.02	11.8	(3.0, 46.5)	0.0001
PSA*		1.3	(1.0, 1.7)	0.017	1.5	(1.0, 2.2)	0.01
MRI	**PiRADS 1-2**	Ref.			Ref.		
	PiRADS 3-5	3.0	(1.3, 6.8)	0.006	21.6	(2.5, 183.5)	0.01
PSA (≥3.0)		1.7	(0.6, 4.3)	0.2	3.5	(0.9, 13.3)	0.06
MRI	**PiRADS 1-3**	Ref.			Ref.		
	PiRADS 4-5	3.7	(1.3, 9.9)	0.009	12.1	(3.0, 48.9)	0.00
PSA (≥3.0)		1.8	(0.7, 4.7)	0.18	4.2	(1.0, 16.8)	0.04
MRI	**PiRADS 1-2**	Ref.			Ref.		
	PiRADS 3-5	2.9	(1.3, 6.4)	0.006	23.5	(2.8, 196)	0.004
PSAD*		1	(0.9, 1.0)	0.06	1.01	(1.0, 1.2)	0.007
MRI	**PiRADS 1-3**	Ref.			Ref.		
	PiRADS 4-5	3.3	(1.2, 9.1)	0.017	11.6	(2.9, 46.5)	0.001
PSAD*		1	(0.9, 1.0)	0.077	1.01	(1.0 1.2)	0.015

MRI	**PiRADS 1-2**	Ref.			Ref.		
	PiRADS 3-5	3.3	(1.5, 7.1)	0.002	27.4	(3.3, 223.2)	0.002
PSAD (≥0.15)		2.5	(0.5, 12.1)	0.2	7.6	1.3, 44.2)	0.02
MRI	**PiRADS 1-3**	Ref.			Ref.		
	PiRADS 4-5	4.1	(1.6, 10.7)	0.003	15.6	(4.2, 64.2)	0.0001
PSAD (≥0.15)		2.7	(0.5, 13.1)	0.2	9.2	(1.3, 61.3)	0.02

Table 4.5 results of logistic regression analyses for outcomes of clinically significant vs insignificant PrCa

Multivariable Models (MRI + one other)		Any cancer			Clinically significant cancer		
		Odds Ratio	(95% C.I.)	*P*	Odds Ratio	(95% C.I.)	*P*
MRI	**PiRADS 1-3**	Ref.			Ref.		
	PiRADS 4-5	4.1	(1.6, 10.7)	0.003	15.6	(4.2, 64.2)	0.0001
PSAD (≥0.15)		2.7	(0.5, 13.1)	0.2	9.2	(1.3, 61.3)	0.02
MRI	**PiRADS 1-2**	Ref.			Ref.		
	PiRADS 3-5	3.3	(1.5, 7.0)	0.002	25.8	(3.1, 212)	0.003
Age*		1.03	(0.9, 1.0)	0.2	1.1	(1.0, 1.3)	0.007
MRI	**PiRADS 1-3**	Ref.			Ref.		
	PiRADS 4-5	3.9	(1.4, 10.5)	0.007	10.5	(2.5, 42.5)	0.001
Age*		1	(0.9, 1.0)	0.4	1.1	(1.0, 1.2)	0.035
MRI	**PiRADS 1-2**	Ref.			Ref.		
	PiRADS 3-5	3.4	(1.6, 7.2)	0.001	29.8	(3.4, 254)	0.002
Age	**40-49**	Ref.			Ref.		

	50-59	0.9	(0.4, 2.2)	0.9	1.5	(0.1, 16.7)	0.7
	>60	1.8	(0.6, 5.2)	0.2	16.8	91.7, 161)	0.014
MRI	**PiRADS 1-3**	Ref.			Ref.		
	PiRADS 4-5	4	(1.4, 10.9)	0.006	10.4	(2.5, 42.9)	0.001
Age	**40-49**	Ref.			Ref.		
	50-59	0.9	(0.4, 2.2)	0.9	1.4	(0.13, 15.3)	0.7
	>60	1.4	(0.5, 4.3)	0.5	9.1	(0.9, 88.3)	0.057

Table 4.6 Multivariable models (MRI and one other variable)

Multivariable Models (MRI + two others)		Any cancer			Clinically significant cancer		
		Odds Ratio	(95% C.I.)	*P*	Odds Ratio	(95% C.I.)	*P*
MRI	**PiRADS 1-2**	Ref.			Ref.		
	PiRADS 3-5	2.6	(1.1, 5.8)	0.016	17.9	(2.1, 153)	0.008
PSA*		1.3	(1.0, 1.7)	0.035	1.5	(1.0, 2.3)	0.046
Age*		1	(0.9, 1.0)	0.5	1.1	(1.02, 1.3)	0.02
MRI	**PiRADS 1-2**	Ref.			Ref.		
	PiRADS 3-5	2.7	(1.2, 5.9)	0.013	17.2	(1.9, 152)	0.01
PSAD*		1	(0.9, 1.0)	0.08	1	(1.0, 1.03)	0.01
Age*		1	(0.9, 1.0)	0.3	1.1	(1.04, 1.4)	0.009

Table 4.7 three variable modles, including MRI, Age and either PSA or PSAD

MRI PiRADS 3-5 was positively associated with clinically significant cancer detection (OR 34) compared with men with a PiRADS 1-3 MRI (p=0.001). Men with a PiRADS 1-2 MRI on average, had a 1% probability of clinically significant cancer detection on biopsy. Men with a PiRADS 3-5 MRI on average, had a 25% probability of clinically significant cancer detection on biopsy. Men with a PiRADS 3-5 MRI had a 24% increase in (average) probability of clinically significant cancer detection (Table 1, Appendix).

MRI PiRADS 4-5 was positively associated with clinically significant cancer detection (OR 19.9) compared to men with a PiRADS 1-3 MRI (p=0.001). Men with a PiRADS 1-3 MRI on average, had a 3% probability of clinically significant cancer detection on biopsy. Men with a PiRADS 4-5 MRI on average, had a 39% probability of clinically significant cancer detection on biopsy. men with a PiRADS 4-5 MRI had a 36% increase in (average) probability of clinically significant cancer detection (p=0.001) (Table 1 Appendix).

4.7 MRI and one other variable

In a model with PSA, MRI PiRADS 3-5 was positively associated with clinically significant cancer detection (OR 24.2) compared with men with a PiRADS 1-2 MRI (p=0.003) (Figure 4.8). PSA (OR 1.66) was also positively associated with clinically significant cancer detection (p=0.008) but less so than MRI. At a mean PSA of 1.8ng/ml, the average predicted probability of signifcant cancer in men with a PiRADS 1-2 MRI was 0.8%, and 16.1% in those with a PiRADS 3-5 MRI.

At the lowest levels of PSA, men with a PiRADS 3-5 MRI had a similar predicted probability of clinically significant cancer to those with a PiRADS 1-2 MRI (0-11%). At higher levels of PSA, men with and without a PiRADS 3-5 MRI had significantly different predicted probabilities of cancer (ie at a PSA of 8.0ng/ml, men with a PiRADS 1-2 MRI had a 15% predicted probability, and men with a PiRADS 3-5 MRI had an 81% predicted probability of clinically significant cancer detection).

Below a PSA of 1.0ng/ml, there was no statistically significant difference in effect between men with and without a PiRADS 3-5 MRI; i.e. men at this very low PSA level appeared to have a very low probability of significant cancer even in the presence of an ‘abnormal’ MR; i.e. at a PSA of 3.0ng/ml, men with a PiRADS 3-5 MRI had, on average a 24% increase in probability of clinically significant cancer detection than men with a PIRADS 1-2 MRI. This is for example, compared with 8% at a PSA of 0.5ng/ml.

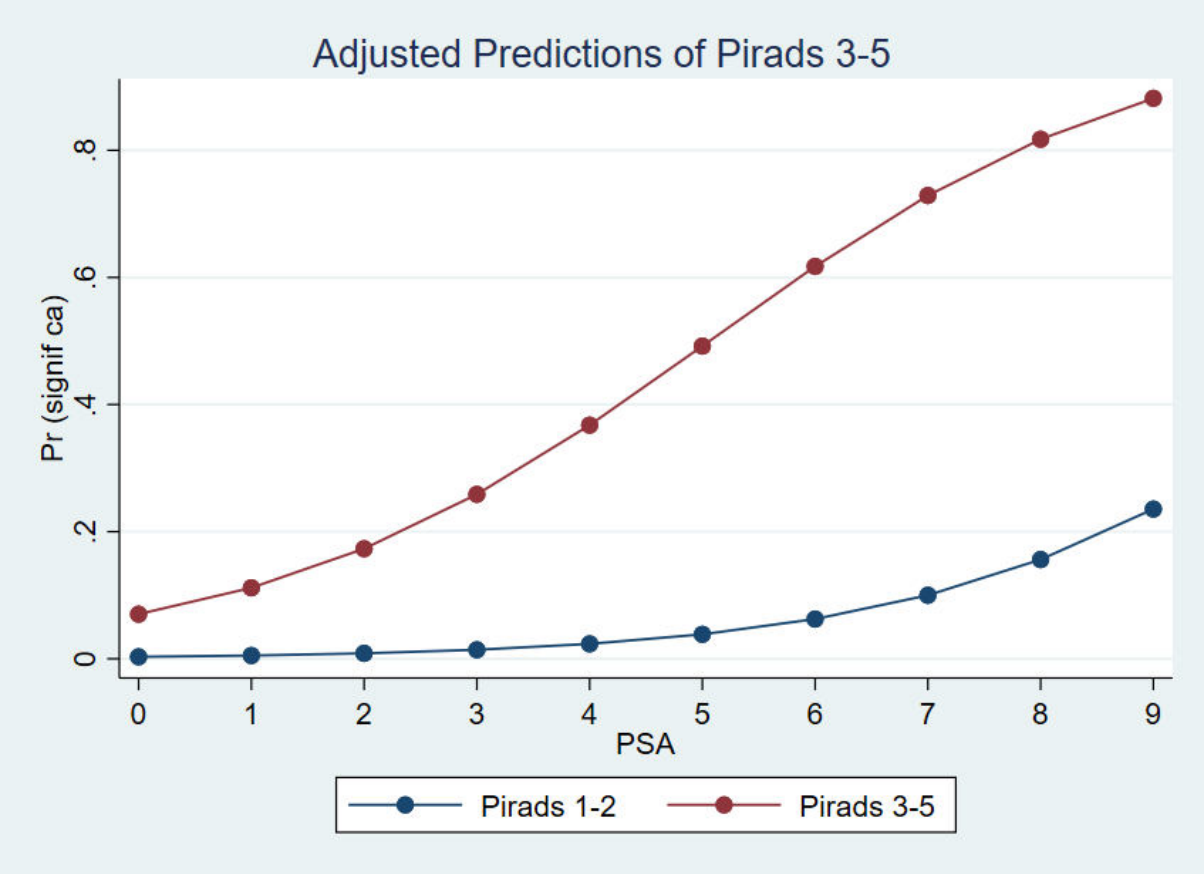


Figure 4.8 Graph depicting the probability of significant PrCa by PSA and PiRADS

MRI PiRADS 4-5 was positively associated with clinically significant cancer detection (OR 11.8) compared with men with a PiRADS 1-3 MRI ($p<0.0001$) (Figure 4.9). In a logistic regression model with PIRADS 4-5 MRI and PSA, PSA (OR 1.57) was also positively associated with clinically significant cancer detection ($p=0.018$) but less so than MRI. At a mean PSA of 1.8ng/ml, the average predicated probability of significant cancer in men with a PiRADS 1-3 MRI was 2.7% and 25.1% in those with a PiRADS 4-5 MRI. At the lowest levels of PSA, men with a PiRADS 4-5 MRI had different predicted probabilities of clinically significant cancer to those with a PiRADS 1-3 MRI but these were not statistically significant.

At higher levels of PSA, men with and without a PiRADS 4-5 MRI had significantly different predicted probabilities of cancer (ie at a PSA of 8.0ng/ml, men with a PiRADS 1-3 MRI had a 31% predicted probability, and men with a PiRADS 4-5 MRI

had an 84% predicted probability of clinically significant cancer detection). At a PSA of 3.0ng/ml, men with a PiRADS 4-5 MRI had, on average a 31.7% increase in probability of clinically significant cancer detection than men with a PIRADS 1-3 MRI. This was 13% at a PSA of 0.5ng/ml.

The inclusion of men with a PIRADS 3 MRI in the 'normal' definition will inflate this group for cancers due to the cancer detection rate of 11% and 26% for clinically significant and insignificant cancer respectively.

Overall, PSA appeared to further define men's predicted probability of cancer detection with a normal or abnormal MRI. Not all men's probability of cancer was the same and at very low/low levels of PSA, the probability of cancer remained low even in the face of an abnormal MRI. This could reflect 'over-reporting' of cancer likelihood in this cohort of men which would account for lower than expected significant cancer detection rates in our PIRADS 3,5 and 5 MRIs when compared to PROMIS data (Figure 4.7). However, the PROMIS trial was conducted in a population of older men than this cohort, with clinical suspicion of PrCa due to a raised PSA or abnormal DRE.

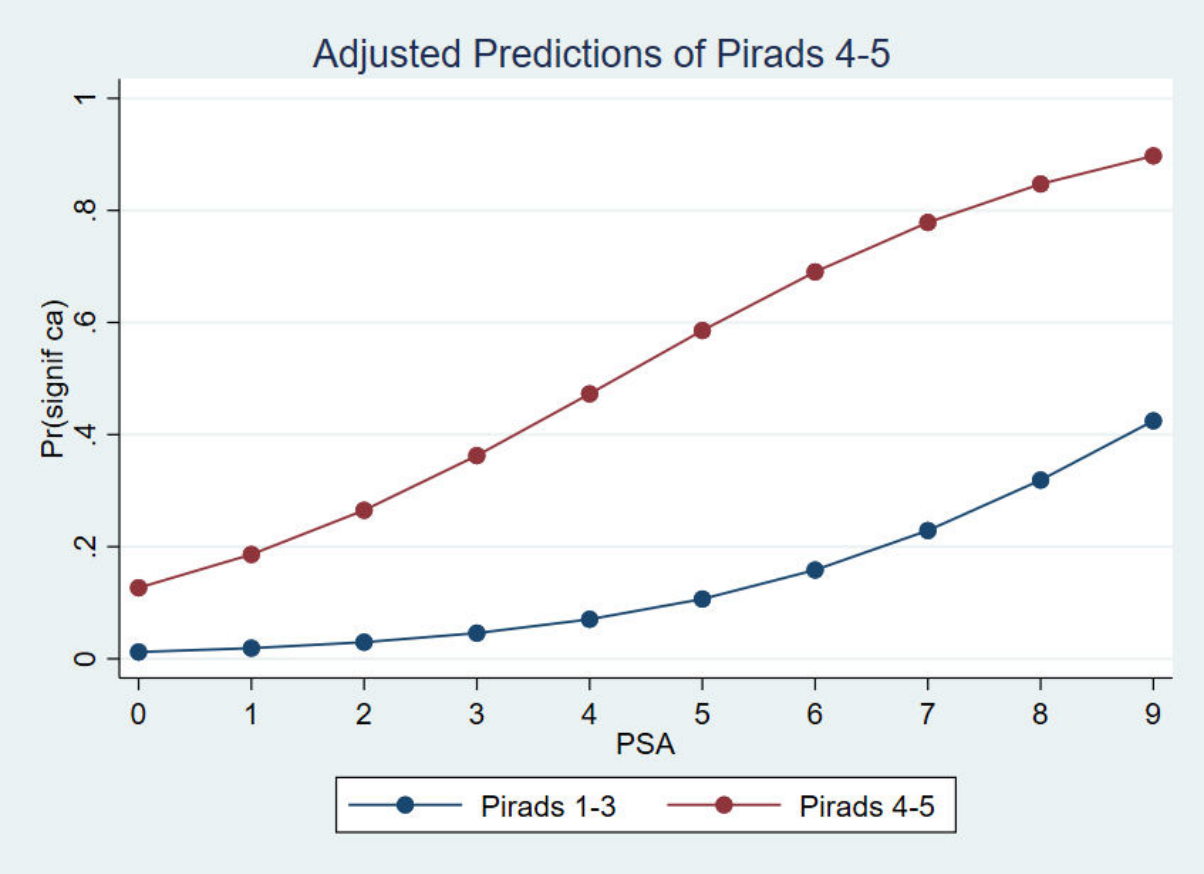


Figure 4.9 Adjusted predictions of PiRADS 4-5 MRI at one unit increments of PSA (ng/ml), graphically depicted from the coefficients described in a logistic regression model.

PSAD ≥0.15ng/ml was positively associated with significant PrCa (OR 7.6; p=0.024) and a PiRADS 3-5 MRI was also positively associated with significant PrCa (OR 27.43; p=0.002). PSAD as a continuous variable was positively associated with significant PrCa (OR 1.015; p=0.007) and a PiRADS 3-5 MRI remained positively associated with significant PrCa (OR 23.5; p=0.004) (Figure 4.10). The (average) predicted probability of clinically significant cancer remained low in men with a PiRADS 1-2 MRI irrespective of their PSAD. Men with a PiRADS 3-5 MRI had an increasing predicted probability of cancer as PSAD increased.

At the mean PSAD of 0.05ng/ml, the average predicted probability of clinically significant PrCa in men with a PiRADS 1-2 MRI was 0.9% and 17.3% in men with a

PiRADS 3-5 MRI. At a PSAD of 0.15, men with PiRADS 3-5 MRI had a predicted probability of significant PrCa of 44%, compared to 3% in those with a PiRADS 1-2 MRI. The (average) predicted probability of clinically significant cancer remained low in men with a PiRADS 1-2 MRI irrespective of their PSAD. Men with a PiRADS 3-5 MRI had an increasing predicted probability of cancer as PSAD increased.

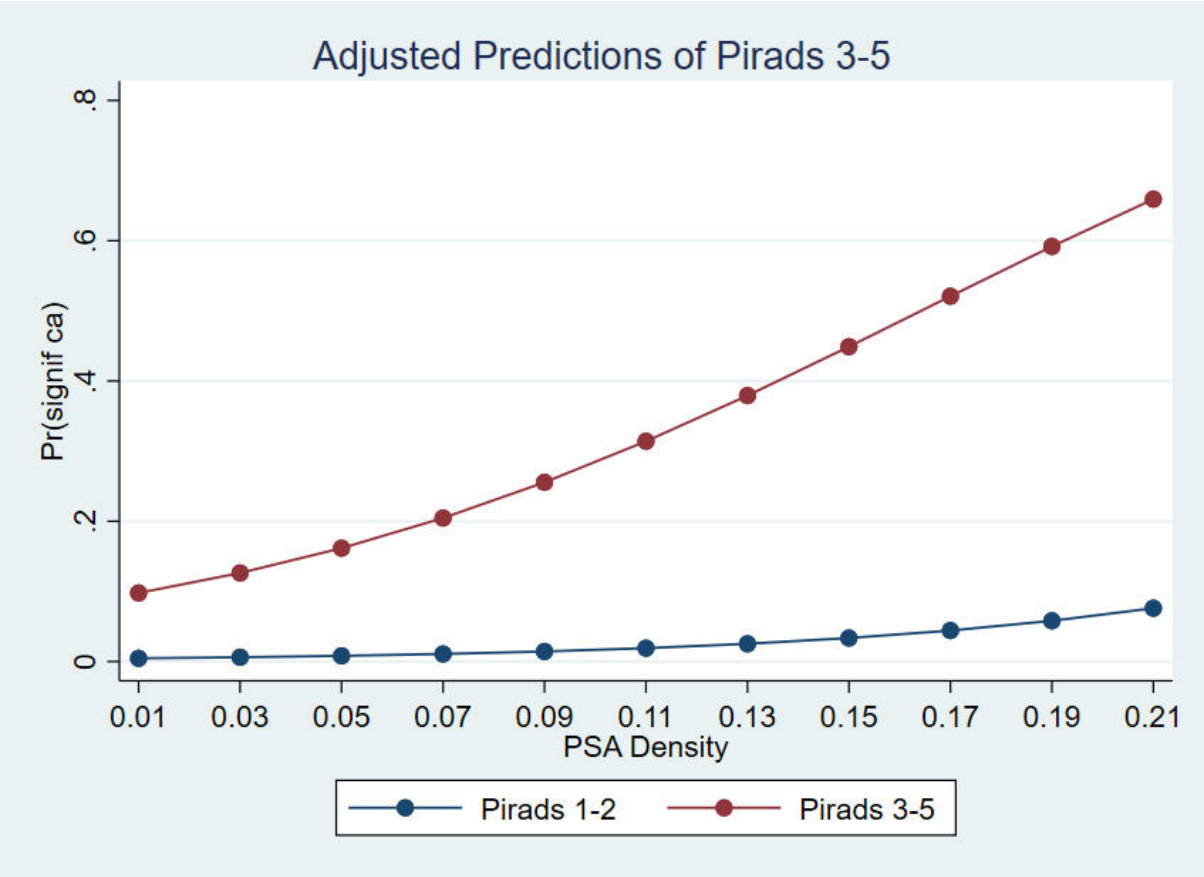


Figure 4.10 Adjusted predictions of PiRADS 3-5 MRI at varying levels of PSAD

Only age at or greater than 60years old was statistically significantly associated with clinically significant PrCa (OR 16.88, p=0.014) (Figure 4.11). A PiRADS 3-5 MRI remained significantly associated with significant cancer outcome (OR 29) compared to men with a PiRADS 1-2 MRI (p=0.002). PiRADS 3-5 MRI was positively associated with clinically significant cancer (OR 25.7) in a model with age as a continuous variable (Table 4.6) which was also positively and significantly associated with clinically significant cancer detection (OR 1.17).

At all ages, predicted probability of clinically significant PrCa remained low in the presence of a PiRADS 1-2 MRI. The predicted probabilty of significant PrCa remained low in the presence of an abnormal MRI at younger ages (age 40-50). As age increased so did the predicted probability of significant cancer (Figure 4.11).

At the mean study age (53.5 years), the predicated probability of clinically significant cancer detection in a man with a PiRADS 1-2 MRI was 0.6%, and 13.6% with a PiRADS 3-5 MRI. Men aged 40 with a PiRADS 1-2 MRI have an (average) probability of 0.1% of clinically significant cancer detection. This remains low even at the oldest age of 70 (8.4%). At the same ages, the probability was 1.7% and 70.2% in those with a PiRADS 3-5 MRI. The predicted probabilty of significant PrCa remained low in the presence of an abnormal MRI at younger ages (age 40-50). As age increased so did the predicted probability of significant cancer. Men aged 50 with a PiRADS 3-5 MRI have a 7.8% increase in probability of clinically significant cancer detection compared with men with a PiRADS 1-2 MRI (this changes to 61% in men aged 70).

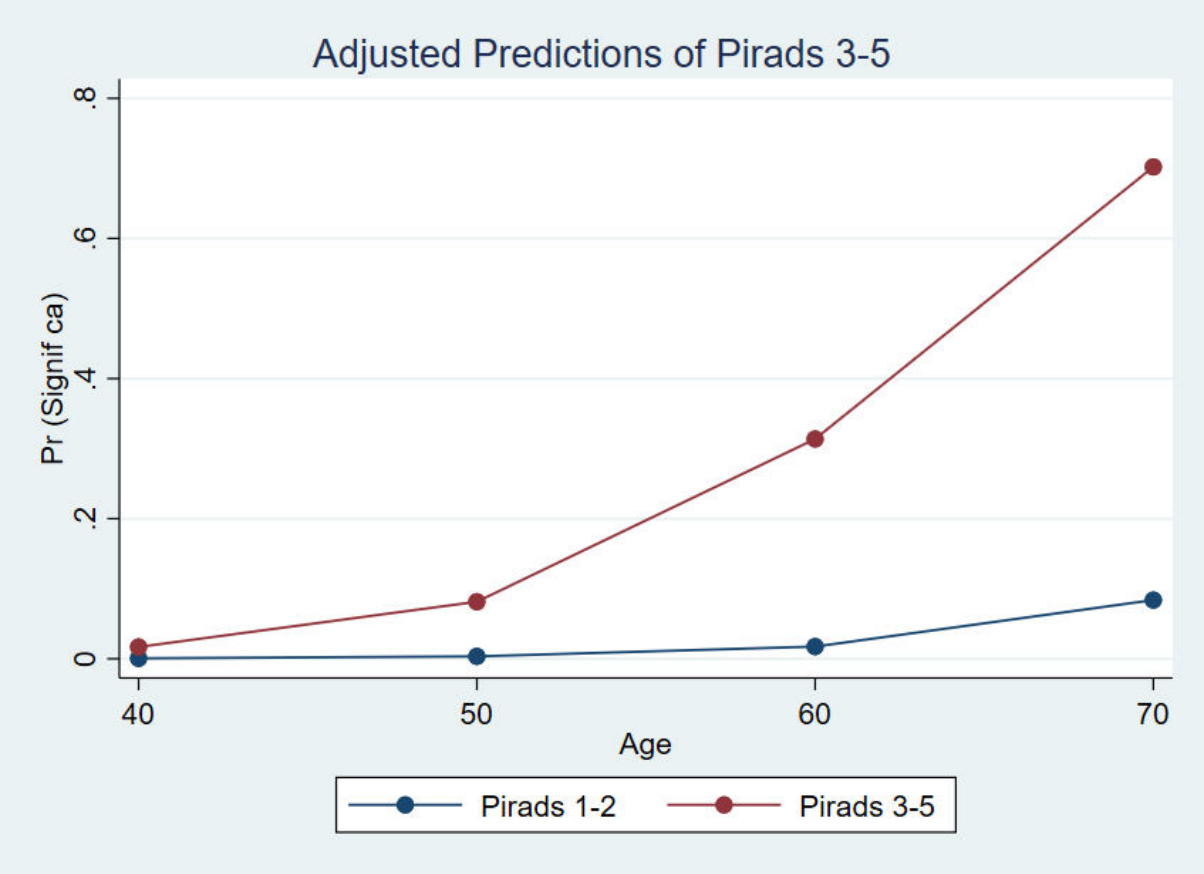


Figure 4.11 Predicted probability of significant PrCa depending on age and MRI status.

4.8 MRI and two other variables

Age and PSA were together included in a logistic regression model with PIRADS 3-5 MRI for the detection of clinically significant PrCa. PiRADS 3-5 MRI was positively associated with significant cancer (OR 17.9; p=0.008), as were age (OR 1.16, p= 0.022) and PSA (OR 1.52, p=0.046).

At a mean PSA of 1.83ng/ml and age of 53.5 years, the percentage probability of detecting clinically significant PrCa on biopsy was 0.6% in men with a PiRADS 1-2 MRI and 9.1% in men with a PiRADS 3-5 MRI (

Figure 4.12). In men with the lowest PSAs and a normal MRI, the predicted probability (on average) remained lower even at the oldest age (13%). In the presence of an abnormal MRI (PiRADS 3-5) at the same PSA values, the predicted probabilities were significantly higher but only in the older age range.

In men aged 40 with a PiRADS 1-2 MRI, the (average) predicted probability of clinically significant cancer was 0%, 0.1%, 0.1%, 0.1% and 0.2% at PSA values of 0, 1, 2, 3 and 4ng/ml. In men aged 70 with a PiRADS 1-2 MRI, the (average) predicted probability of clinically significant cancer was 19%, 27%, 36%, 46% and 56% at PSA values of 5, 6, 7, 8 and 9ng/ml.

All of the above analyses were completed for PIRADS 4-5 MRI and are described further in the Appendix.

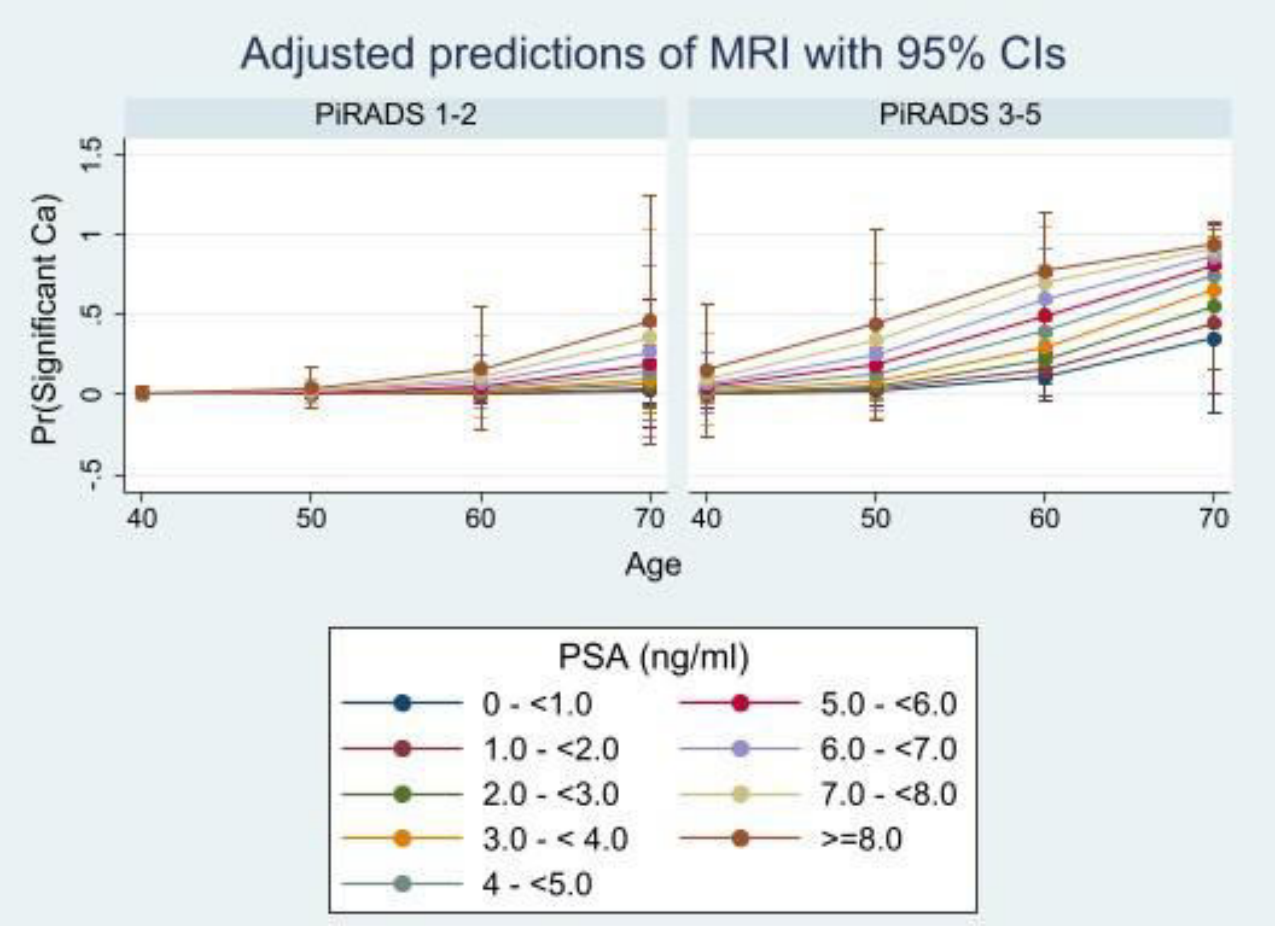


Figure 4.12 Graph of adjusted predictions of significant PrCa probability at various levels of PSA and age in the presence of a PIRADS 1-2 or PIRADS 3-5 MRI.

MRI was then examined with PSAD and Age (Figure 4.13). PiRADS 3-5 MRI was positively associated with significant cancer outcome at prostate biopsy (OR 17.1; p=0.011), as were age and PSAD (with lower ORs;Table 4.7).

An increase in probaility of cancer was only observed at the oldest age for those with a normal MRI. This was similar to PSA. In those with an abnormal (PiRADS 3-5 MRI), older age and PSAD appeared to have more of an impact.

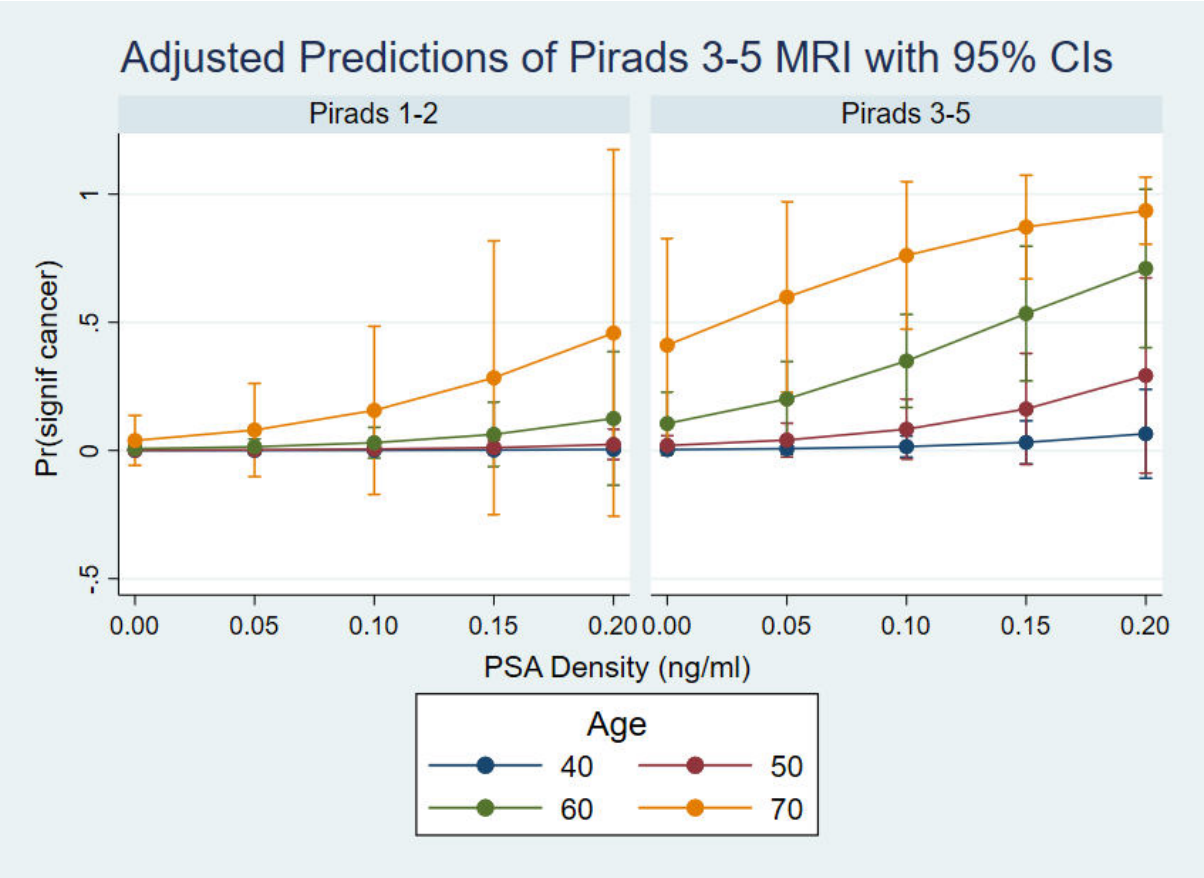


Figure 4.13 Predicted probabilites of significant PrCa at margins of age and PSAD by category of MRI.

All of the above analyses was completed for PIRADS 4-5 MRI and is described further in the Appendix.

4.9 MRI alone for the detection of '**any**' cancer

The detection of 'any' prostate cancer (including low grade disease) is not the goal of clinician or a screening test. The indolent nature of low-grade disease has been shown to not adversely impact a man's length of life and any radical treatment performed for disease of this nature therefore comes with the unnecessary morbidity risk of erectile dysfunction and incontinence.

MRI PiRADS 3-5 was positively associated with any significant cancer detection (OR 3.682) compared to men with a PiRADS 1-2 MRI (p=0.001). Men with a PiRADS 1-2 MRI on average, had a 21% probability of any cancer on their biopsy. Men with a PiRADS 3-5 MRI had a 50% chance of any cancer being detected on their prostate biopsy.

MRI PiRADS 4-5 was positively associated with clinically significant cancer detection (OR 4.667) compared with men with a PiRADS 1-3 MRI (p=0.001). Men with a PiRADS 1-3 MRI on average, had a 25% probability of any cancer on their biopsy. Men with a PiRADS 4-5 MRI had a 60% chance of **any** cancer being detected on their prostate biopsy.

At the mean study age of 53, or mean PSA of 1.83ng/ml, men with a PIRADS 1-2 MRI had on average, a probability of any cancer detection of 21% and 22% respectively (Table 2 in Appendix). These results highlight that potentially using MRI alone in young men with a FH as an early cancer detection tool, who have a normal MRI (PIRADS 1-2) would not yield anything other than insignificant cancer if a biopsy was performed (Figure 4.5). Other clinical variables (i.e PSA) did provide further information. At a PSA of 0-<1.0ng/ml with a PiRADS 1-2 MRI, the (average) predicted probability of any cancer was 14% and 31% with a PiRADS 3-5 MRI. At a PSA of 3.0ng/ml with a PiRADS 1-2 MRI the (average) predicted probability of any cancer was 29% and 53% with a PiRADS 3-5 MRI. At the higher levels of PSA (8-9ng/ml), there was no significant difference in the predicted probability of PrCa

between a normal and abnormal MRI i.e a normal MRI was not reassuring if the PSA was high (Figure 4.14).

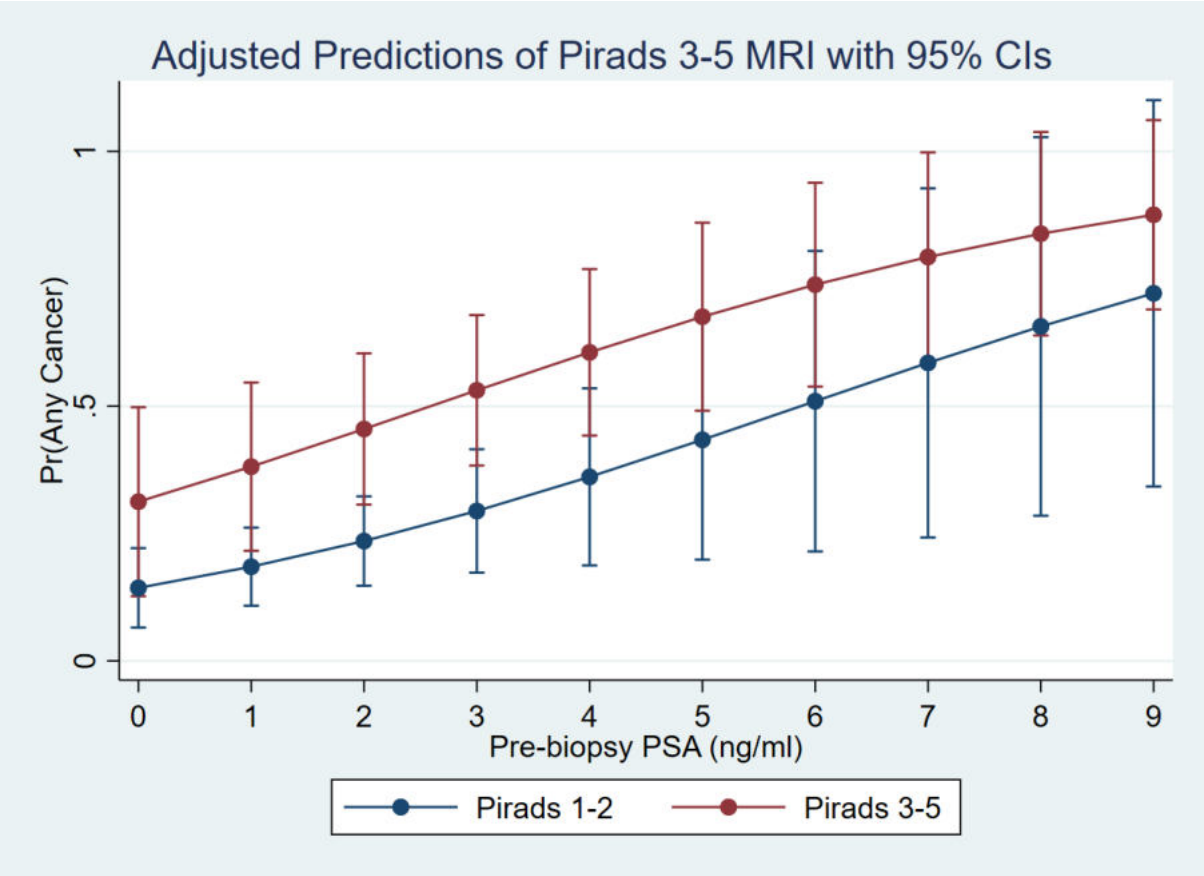


Figure 4.14 The predicted probability of any PrCa rose as the PSA rose, whether in the presence of a normal or abnormal MRI.

4.10 Discussion

MRI is felt to currently outperform PSA in the diagnostic setting, with PROMIS [4] and PRECISION [5] describing its potential and ability to help certain men avoid a prostate biopsy altogether in the absence of a radiological abnormality, and the 4M [6] and MRI-First [7] trials reporting MRI's ability to aid in the diagnosis of clinically significant PrCa by guiding targeted prostate biopsy in place of systematic sampling.

The clinical utility of pre-biopsy MRI heralds the potential to be expanded upon, and potentially be used either as a more sensitive assessment/screening tool in men than PSA, or as an adjunct with clinical information (i.e. PSA/Age/PRS). Both Nam [8] and Emberton (NCT04063566, [9]) are proposing its use in this way in the general population, leaving the area of its use in 'high-risk' men in the population with a FH of PrCa uninvestigated.

4.10.1 Frequency of an abnormal MRI

The most commonly encountered PiRADS score was PiRADS 2 (64%), followed by PIRADS 3 (17%) and PiRADS 4 (12%). Approximately one third of men had an 'abnormal' MRI, or PiRADS 3-5 suggesting conservatively that this amount of men may face a prostate biopsy according to currently practised clinical criteria in PrCa diagnostics.

The amount of PiRADS 5 lesions, those with a very high likelihood of cancer was low (2%).

Clinically insignificant cancer was observed across the spectrum of PiRADS 1-4 lesions. Clinically significant cancer was most commonly found in PiRADS 3-4 MRIs,

specifically 11% of all PiRADS 3 MRIs yielded a diagnosis of clinically significant cancer.

4.10.2 MRI Chaacteristics

4.10.3 Any Cancer

In men with a FH of PrCa, an 'abnormal' MRI was significantly associated with an outcome of any cancer (PiRADS 3-5; OR 3.68 PiRADS 4-5; OR 4.66) at prostate biopsy. It is important to note, that in the context of diagnosing a man with (any) Prca, that in this cohort, men with a PiRADS 1-2 MRI on average, had a 21% probability of any cancer on their biopsy. Men with a PiRADS 3-5 MRI had a 50% chance of any cancer being detected on their prostate biopsy, this rose to 60% if PIRADS 4-5.

The fact that we may find PrCa in approximately 20% (at least) of men with a FH of PrCa 'screening' biopsy has important implications for implementing an MRI-based strategy in such men; 62% of all clinically insignificant cancers occurred in men with a PIRADS 1-2 MRI; in particular, if PiRADS 1-2 areas are biopsied systematically (ie we may be overdetecting insignificant disease). Long-term follow-up of this cohort will inform us what disease trajectory these patients have.

4.10.4 Significant Cancer

4.10.4.1 MRI

In men with a FH of PrCa, an 'abnormal' MRI was significantly associated with an outcome of significant cancer (PiRADS 3-5; OR 33.99 & PiRADS 4-5; OR 19.92). The probability of clinically significant cancer detection in the presence of a PIRADS 1-2 MRI was low at 1%, and 25% for PIRADS 3-5. The sensitivity, specificity, NPV and PPV of a PIRADS 3-5 MRI was 92%, 73%, 99% and 25%.

In one of the only available studies of screening unselected men with mpMRI by Nam et al [8], their pilot results described MRI as the only significant predictor for the presence of PrCa (OR 2.7, 95% CI 1.4-5.4). In 47 men, the PiRADS score was 1 in 6/47 (13%), 2 in 15/47 (32%), 3 in 9/47 (19%), 4 in 7/47 (15%) and 5 in 10/47 (21%) with an average volume of 52.2cc and average age of 61 years (IQR 55-68). Our cohort is younger (mean age 53.5; IQR 46-59 years) with smaller prostates (mean volume 34.87cc) and is selected for a FH of PrCa with a mean PSA of 1.8ng/ml (IQR 0.8-2.4). We found PiRADS 3-5 MRI in 31.8% of men compared to 55% of those screened by Nam et al. Excluding men who underwent a repeat MRI, we detected an MRI PiRADS score of 3-5 in approx. 33% of men.

We found less clinically insignificant cancer in men with PIRADS 3 (27%; Figure 4.2) change when compared to PROMIS (40%) and less clinically significant cancer (11.5% vs 20%) with a greater proportion of benign histology (61.5% vs 40%). Clearly comparing MRI performance in our study cohort to that of the PROMIS cohort is difficult, given the significant differences in PSA, age and prostate characteristics. However, our clinically significant cancer detection rate is interesting considering the mean PSA of all our PiRADS 3 lesions was 2.1ng/ml (Table 4.2). The overall mean PSA in PROMIS was 7.9ng/ml, (SD 2.9, range 0.5 – 15), however PROMIS did not report the PSA characteristics per category of PiRADS.

If considering PiRADS 3 ‘abnormal’, just over 90% of our clinically significant cancers detected had an abnormal pre-biopsy MRI (Figure 4.3). If considering only PiRADS 4-5 as abnormal, this reduces to 63% (Figure 4.3). Only 1/8 D’Amico high risk cancers was found in a PiRADS 1-2 MRI, with the rest found in men with a PiRADS 3-5 MRI. For Intermediate risk D’Amico cancers, all were detected in men with a PiRADS 3-5 MRI. Given that 23% of all clinically significant cancers in this cohort had a PiRADS 3 lesion, including PIRADS 3 as an ‘abnormal’ predictor variable as opposed to ‘equivocal’ in this cohort of young men is proposed (Figure 4.2).

Using the same definition of clinical significance for PrCa as within this study (≥Gleason 3+4), the sensitivity of MRI in PROMIS was 88%, specificity 45%, PPV

65% and NPV 76%. MRI in our cohort had a sensitivity of 92%, specificity of 73%, PPV of 25% and NPV of 99% (AUC 0.83). For any cancer detection, MRI had an inferior AUC (0.64) with a low sensitivity and PPV (52% and 50% respectively).

4.10.4.2 MRI with other variables

Men with PiRADS 4-5 change were older, had higher PSAs and PSA densities () all of which are known to associate with prostate cancer. Our best performing models for clinically significant cancer detection according to AUC included MRI (PiRADS 3-5), with PSA/PSAD and age as continuous variables.

Exploring the marginal effect of PSA, PSAD and age in men with a PiRADS 1-2 MRI, men in this category at a young age maintained a low predicted probability of significant cancer even at high PSAs (Figure 4.12). A similar finding was noted for PSAD (Figure 4.13). This finding with an MRI PiRADS 1-2 NPV of 99% provides early evidence that young men with a FH of PrCa could safely avoid prostate biopsy, in the presence of a normal MRI even at high PSA or PSAD.

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Men with a low PSA and a PiRADS 1-2 MRI had a low predicted probability of cancer. Below a PSA of 1.0ng/ml, there was no statistically significant difference in effect between men with and without a PiRADS 3-5 MRI; i.e. men at this very low PSA level appeared to have a very low probability of significant cancer even in the presence of an 'abnormal' MRI.

At a mean study PSA of 1.83ng/ml and mean study age of 53.5 years, the percentage probability of detecting clinically significant PrCa on biopsy was 0.6% in men with a PiRADS 1-2 MRI and 9.1% in men with a PiRADS 3-5 MRI. In men with **low** PSAs and a normal MRI, the predicted probability (on average) remained low, at 13% at the oldest age. In the presence of an abnormal MRI (PiRADS 3-5) at the same PSA values (

Figure 4.12). i.e in men aged 40 with a PiRADS 1-2 MRI, the (average) predicted probability of clinically significant cancer was 0%, 0.1%, 0.1%, 0.1% and 0.2% at PSA values of 0, 1, 2, 3 and 4ng/ml.

Men aged 40 with a PiRADS 1-2 MRI had an (average) probability of 0.1% of clinically significant cancer detection. This remains low even at the oldest age of 70 (8.4%). At the same ages, the probability is 1.7% and 70.2% in those with a PiRADS 3-5 MRI (Figure 4.11).

MRI was statistically significantly associated with an outcome of clinically significant cancer in men with a PiRADS 3-5 score, in the presence of age; (OR 25.7, P=0.003), PSA (OR 24.2, p=0.003) and PSAD (OR 23.5, p=0.004) or if PiRADS 4-5; (age; OR 10.5, p=0.001; PSA; OR 11.8, p=0.000 and PSAD; OR 11.6, p=0.00).

4.11 Limitations

The most significant limiting factor remains the small sample size (n=151) of this analysis which is in its present form underpowered. We also do not have a comparator group without any MRI which would also inform on the benefit of MRI in the detection of PrCa at screening prostate biopsy. There was also a low number of PiRADS 5 MRIs, limiting our ability to truly understand its association with clinically significant (or any) cancer. Lack of long or intermediate-term follow-up for men diagnosed with clinically insignificant cancer limits our ability to investigate if a subgroup may fail active surveillance, in those with ‘normal’ MRI but for example, a high PSA or PSAD.

4.12 Conclusions

The role of pre-biopsy MRI in men undergoing a) targeted screening or b) specifically in men with a FH of PrCa has been the subject of limited published research. Evidence exists on the incidence of PrCa (including clinically significant cancers) at low PSA levels, as per interrogation of the REDUCE trial in men in the placebo arm with a PSA of ≤4.0ng/ml [10]. MRI could be particularly useful in this group if able to, with a higher degree of certainty than PSA, ‘rule out’ clinically significant PrCa either

alone or in combination with other clinical information, thereby allowing young men the opportunity to avoid a prostate biopsy unless clinically necessary. The incidence of clinically significant cancer was lower than expected in those with an ‘abnormal’ MRI, raising the possibility that in this cohort of young men with relatively low PSAs, PiRADS classification has a propensity to overcall lesions which may appear radiologically more concerning than proven on biopsy.

4.13 References

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4.14 Figures

4.15 Tables

5 Chapter 5 - Polygenic Risk Score (PRS)

Table of Contents

5.1 Introduction

This chapter investigates the association of PRS with outcome at prostate biopsy in in the PROFILE FH cohort.

As not all men recruited to the study underwent prostate biopsy (i.e. a proportion of men were recruited to study arm 2 and only had a prostate biopsy if the study age-defined PSA threshold was met), and as such biopsy information (or cancer outcome) is available only for men who underwent a biopsy either in study arm 1 (n=124) or study arm 2 (n=11). As described in Chapter 2 (Materials & Methods), a small number of men (n=16) underwent a second or third (n=1) biopsy as per study protocol if their initial biopsy (any study arm) yielded HGPIN or ASAP.

Also as described in Chapter 2 (Materials & Methods), genotyping data (PRS) was only available for 121 men who had also undergone prostate biopsy. Therefore all analyses performed to investigate the correlation of prostate biopsy outcome (i.e. cancer detection) with PRS or MRI described in this chapter are performed in this n=121 cohort,

5.2 Aims

To describe the distribution of PRS in men with a FH of PrCa

To describe the difference in PRS between men with and without a FH of PrCa

To describe the effect of degree of FH on PRS

To describe the association of PRS with cancer detection on men with a FH of Pr Ca undergoing targeted screening

To describe if the association of PRS with outcome at prostate biopsy changes in men with a FH of PrCa when adjusting for other clinical variables

To investigate if PRS with/without other clinical variables can predict outcome at prostate biopsy in men with a FH of PrCa

5.3 Methods

This is described in detail in Chapter 2 (Materials & Methods)

5.4 Statistical Analyses

This is described in Chapter 2 (Materials & Methods)

5.5 Results

As described, 46 cancers have been detected in 135 men (151 prostate biopsies). For reference, a summary of the baseline characteristics of this cohort is described below in **Error! Reference source not found.**. There were significant differences in P RS, PSA, age, PSAD and individual PIRADS scores in men with and without cancer. MRI volume, degree of FH (i.e. number of relatives) or study arm did not differ between men with and without cancer.

PRS is described in a univariable analysis, with subsequent multi-variable analyses investigating PRS in a logistic regression model with clinical variables of interest used in clinically diagnosis or risk assessing men for PrCa (i.e PSA, PSAD and age).

			Cancer		P value
		All	Significant	Non-significant/No cancer	
PRS, mean (SD)		10.58 (0.71)	11.16 (0.81)	10.53 (0.68)	0.0052
Age (study entry), mean (SD)		53.7 (7.91)	61.2 (7.1)	52.7 (7.5)	0.0008
PSA, median (IQR)		1.3 (0.8 - 2.3)	3.3 (1.9 - 4.8)	1.2 (0.78 - 2.1)	0.0003
PSAD median (IQR)		0.04 (0.02 - 0.06)	0.08 (0.05 - 0.18)	0.04 (0.02 - 0.06)	0.0003
MRI Volume median (IQR)		31 (25 - 39)	30.0 (25 - 42)	31.0 (25-39)	0.8497
FH variable) N, (%)	**1<70**	52 (43.33)	4 (36.36)	48 (43.64)	0.717
	2	38 (31.67)	5 (45.45)	34 (30.91)	
	3	30 (25)	2 (18.18)	28 (25.45)	
Prior PSA N (%)					
	Yes	77 (63.64)	8 (72.73)	68 (61.2)	0.451
	No	37 (3.58)	2 (18.18)	6 (5.45)	
	Unknown	7 (5.79)	1 (9.09)	35 (31.82)	
PiRADS					

N (%)					
	1	8 (6.67)	0 (0)	8 (7.34)	0.000
	2	74 (61.67)	1 (9.09)	73 (66.97)	
	3	20 (16.67)	3 (27.27)	17 (15.6)	
	4	16 (13.33)	6 (54.55)	10 (9.17)	
	5	2 (1.67)	1 (9.09)	1 (0.92)	
Mode of Detection					
	Study arm 1	32 (78.1)	9 (81.9)	102 (90.3)	0.422
	Study arm 2	6 (14.7)	2 (18.1)	8 (7.1)	
	Follow-up	3 (7.3)	0 (0)	3 (2.6)	

Table 5.1 Baseline characteristics of men who underwent prostate biopsy with available genotyping data, described by any cancer outcome.

Model	Multivariable Models (PRS + one other)		Any cancer			Clinically significant cancer		
			Odds Ratio	(95% C.I.)	*P*	Odds Ratio	(95% C.I.)	*P*
1	Prior PSA	Y	2.4	(0.9, 6.5)	0.07	2.1	(0.4, 11.0)	0.4
		N	Ref.			Ref.		
	PRS	(cont.)	3.2	(1.7, 6.0)	0	4.1	(1.4, 11.8)	0.009
2	Age	40 - 49	Ref.			Ref.		
		50 - 59	0.3	(-0.6, 1.3)	0.5	1.4	(0.1, 17.3)	0.8
		≥60	1.1	(0.0, 2.2)	0.06	24.5	(2.6, 233.6)	0.005
	PRS	(cont.)	1.1	(0.5, 1.8)	0	4.7	(1.4, 15.3)	0.01
3	Age	(cont.)	1.1	(1.0, 1.1)	0.04	1.2	(1.1, 1.4)	0.003
	PRS	(cont.)	3.1	(1.7, 5.9)	0	4.2	(1.4, 12.9)	0.01
4	PSA	(cont.)	2.2	(1.4, 3.4)	0.001	1.7	(1.2, 2.4)	0.003
	PRS	(cont.)	3.7	(1.2, 11.9)	0.029	4.1	(1.3, 13.4)	0.02
5	PSA	0 - <1	Ref.			Ref.		
		1 - <2	3.0	(0.9, 10.3)	0.08	0.11	(0.1, 0.6)	0.02
		2 - <3	6.5	(1.8, 22.7)	0.004	0.3	(0.1, 1.8)	0.2
		≥3	8.4	(2.1, 33.5)	0.003	1 (omitted due to collinearity)		
	PRS	(cont.)	2.7	(1.4, 5.5)	0.005			0.04
6	PSAD	(cont.)	1.0	(1.0, 1.0)	0.04	1.0	(1.0, 1.0)	0.003
	PRS	(cont.)	2.7	(1.4, 5.1)	0.002	3.2	(0.9, 10.6)	0.06

	Multivariable Models (PRS + one other)		Any cancer			Clinically significant cancer		
			Odds Ratio	(95% C.I.)	*P*	Odds Ratio	(95% C.I.)	*P*
7	MRI	PiRADS 1-2	Ref.			Ref.		
		PiRADS 3-5	2.7	(1.2, 6.5)	0.2	28.6	(3.4, 241.9)	0.002
	PRS	(cont.)	3.1	(1.6, 5.8)	0.001	3.7	(1.2, 11.5)	0.03
8	MRI	PiRADS 1-3	Ref.			Ref.		
		PiRADS 4-5	4.1	(1.3, 12.9)	0.02	12.4	(3.0, 52.0)	0.001
	PRS	(cont.)	2.9	(1.5, 5.5)	0.001	3.1	(1.0, 9.5)	0.05
9	FH	1 rel, age <70	Ref.			Ref		
		2 rels	2.5	(1.0, 6.5)	0.06	1.5	(0.4, 6.6)	0.5
		3+ rels	1.0	(0.4, 3.0)	0.9	0.7	(0.1, 4.5)	0.7
	PRS	(cont.)	3.2	(1.7, 6.1)	0	3.8	(1.3, 10.8)	0.02

Table 5.2 Table of results displaying logistic regression analyses (with OR, 95% CI and P values) of PRS in a model with one other clinical variable of interest

Multivariable Models (PRS + two others)		Any cancer			Clinically significant cancer		
		Odds Ratio	(95% C.I.)	*P*	Odds Ratio	(95% C.I.)	*P*
(MRI vs. PSA)							
PSA	(cont.)	1.5	(1.0, 2.1)	0.014	1.6	(1.1, 2.3)	0.02
PRS	(cont.)	2.9	(1.5, 5.4)	0.002	3.9	(1.2, 13.3)	0.03
Age	(cont.)	1.03	(0.9, 1.09)	0.27	1.2	(1.0, 1.4)	0.01
MRI	PiRADS 1-2	Ref.			Ref.		
	PiRADS 3-5	2.32	(0.9, 5.7)	0.06	27.5	(2.7, 275.6)	0.005
PRS	(cont.)	3	(1.6, 5.8)	0.001	5.0	(1.3, 19.0)	0.02
Age	(cont.)	1	(0.9, 1.1)	0.12	1.2	(1.0, 1.4)	0.01
MRI	PiRADS 1-3	Ref.			Ref.		
	PiRADS 4-5	3.1	(0.9, 10.6)	0.07	5.4	(1.1, 25.7)	0.04
PRS	(cont.)	2.9	(1.6, 5.6)	0.001	3.6	(1.1, 11.4)	0.03
Age	(cont.)	1	(0.9, 1.0	0.26	1.2	(1.0, 1.3)	0.04

Table 5.3 Table of results describing logistic regression models including PRS and two other clinical variables of interest

Model	Multivariable Models	Any cancer				
		ROC, %	Sens., %	Spec., %	PPV, %	NPV, %
1	Prior PSA + PRS (cont.)	0.772	45.9	92.7	73.9	79.2
2	Age (cat.) + PRS (cont.)	0.7721	39.5	86.6	57.7	75.5
3	Age (cont.) + PRS (cont.)	0.768	42.1	90.2	66.7	77
4	PSA (cont.) + PRS (cont.)	0.794	50	89	67.9	79.4
5	PSA (cat.) + PRS (cont.)	0.745	52.6	87.8	66.7	80
6	PSAD (cont.) + PRS (cont.)	0.763	42.1	87.8	61.5	76.6
7	MRI (1-2 vs. 3-5) + PRS (cont.)	0.768	44.7	85.4	58.6	76.9
8	MRI (1-3 vs. 4-5) + PRS (cont.)	0.7644	39.5	87.8	60	75.8
9	FH (cat.) + PRS (cont.)	0.739	40.5	91.5	68.2	77.3
	Multivariable Models -					
10	Age + PSA + PRS	0.79	50	90.2	70.4	79.6
11	MRI (1-2 vs. 3-5) + PRS (cont.) + Age	0.77	50	89	67.9	79.4
12	MRI (1-2 vs. 3-5) + PRS (cont.) + PSA	0.79	50	90.2	70.4	79.6
	MRI (1-3 vs. 4-5) + PRS (cont.) + Age	0.77	39.5	91.5	68.2	76.5
	MRI (1-3 vs. 4-5) + PRS (cont.) + PSA	0.79	52.6	90.2	71.4	80.4

Table 5.4 Table of results describing the ROC (AUC), sensitivity, specificity, NPV and PPV of each multivariable model including PRS for any cancer detection

Model	Multivariable Models	Significant Cancer				
		ROC, %	Sens., %	Spec., %	PPV, %	NPV, %
1	Prior PSA + PRS (cont.)	0.749	0	100	0	90.8
2	Age (cat.) + PRS (cont.)	0.87	36.4	99	80	93.9
3	Age (cont.) + PRS (cont.)	0.856	27.3	99	75	93.1
4	PSA (cont.) + PRS (cont.)	0.85	27.3	99	75	93.1
5	PSA (cat.) + PRS (cont.)	0.85	36.7	99	80	93.9
6	PSAD (cont.) + PRS (cont.)	0.8	27.3	99	75	93.1
7	MRI (1-2 vs. 3-5) + PRS (cont.)	0.9058	27.3	98.2	60	93
8	MRI (1-3 vs. 4-5) + PRS (cont.)	0.824	45.6	99	83.3	94.7
9	FH (cat.) + PRS (cont.)	0.73	0	100	0	90
	Multivariable Models					
10	Age + PSA + PRS	0.91	45.6	98.2	71.4	94.7
11	MRI (1-2 vs. 3-5) + PRS (cont.) + Age	0.94	45.6	97.3	62.5	94.6
12	MRI (1-2 vs. 3-5) + PRS (cont.) + PSA	0.93	36.4	98.2	66.7	93.9
13	MRI (1-3 vs. 4-5) + PRS (cont.) + Age	0.87	45.5	99	83.3	94.7
14	MRI (1-3 vs. 4-5) + PRS (cont.) + PSA	0.89	36.4	99	80	93.9

Table 5.5 Table of results describing the ROC (AUC), sensitivity, specificity, NPV and PPV of each multivariable model including PRS for clinically significant cancer detection

5.5.1 Baseline characteristics

The baseline clinical characteristics of the 121 men described in this chapter are displayed in Table 5.1. Men with significant cancer were older, had a higher PSA, PSAD (although this was still less than 0.15ng/ml) and had more PiRADS 3-5 MRIs than men with either no cancer or low grade cancer.

5.5.2 Effect of FH status on PRS

The PROFILE cohort is a group of healthy men without a personal history of PrCa but all participants as described, have a FH of PrCa (of varying degrees, with one FDR diagnosed or died at age <70 as a minimum entry criterion). The PRS was calculated for the PROFILE cohort and is compared to the PRS of a control cohort (the ProtecT cohort), aimed to represent the general population. There is a low FH rate in the control (ProtecT) population (described in Chapter 2 Materials & Methods).

The mean PRS differs between PROFILE and a control population, ($p<0.001$) and the curve is shifted to the right (Figure 5.1). Blue and red solid lines represent the mean PRS of the PROFILE (10.6, SD 0.7, 95% CI 10.5 – 10.7) and control (10.3, SD 0.6, 95% CI 10.3 – 10.4) cohorts respectively.

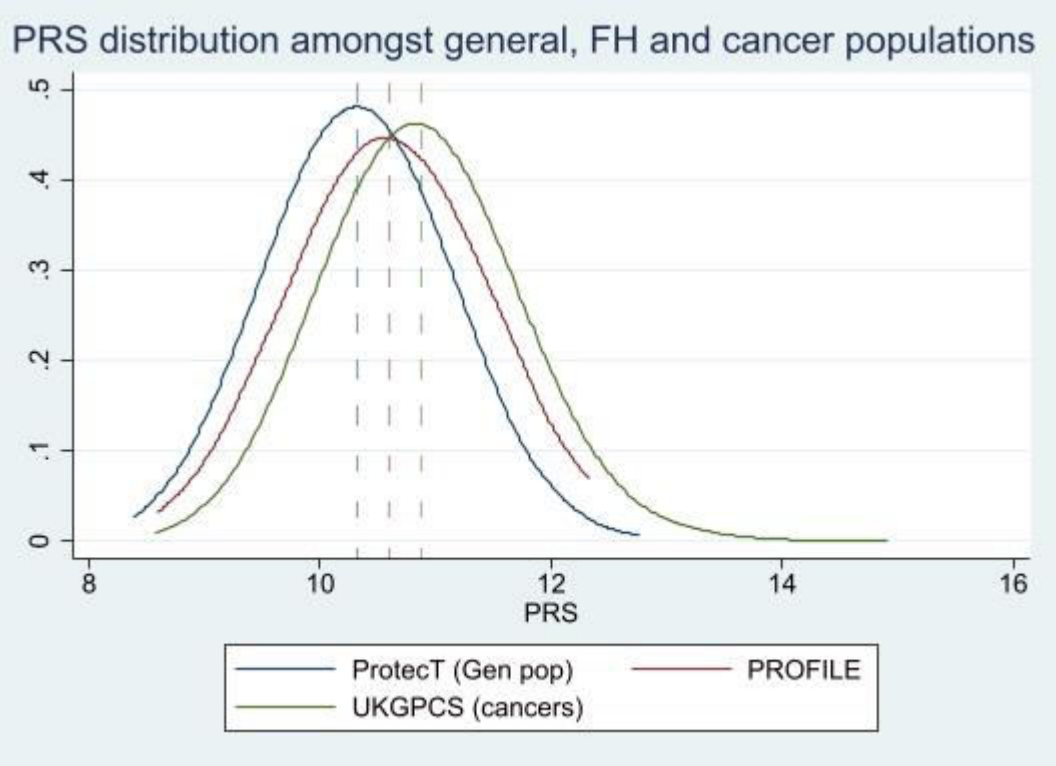

Figure 5.1 PRS distribution amongst different 'at risk' populations. The general population (represented by ProtecT), the FH population (represented by PROFILE) and a prostate cancer population (UKGPCS). Dashed lines represent the mean of each cohort; ProtectT N=2751. PROFILE N = 284. UKGPCS N = 11,972.

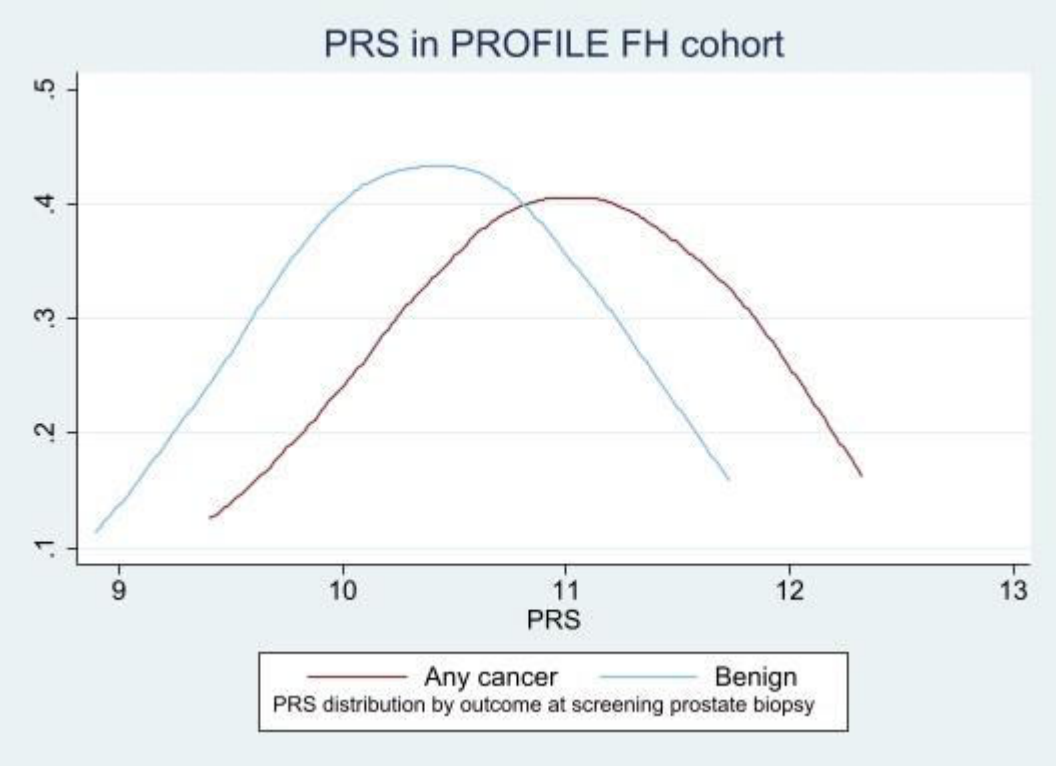

Figure 5.2 The difference in PRS between men with (any) cancer and those without in the PROFILE study. Two sample T test with equal variances. P value 0.0001.Any Cancer N = 41. No cancer N=81

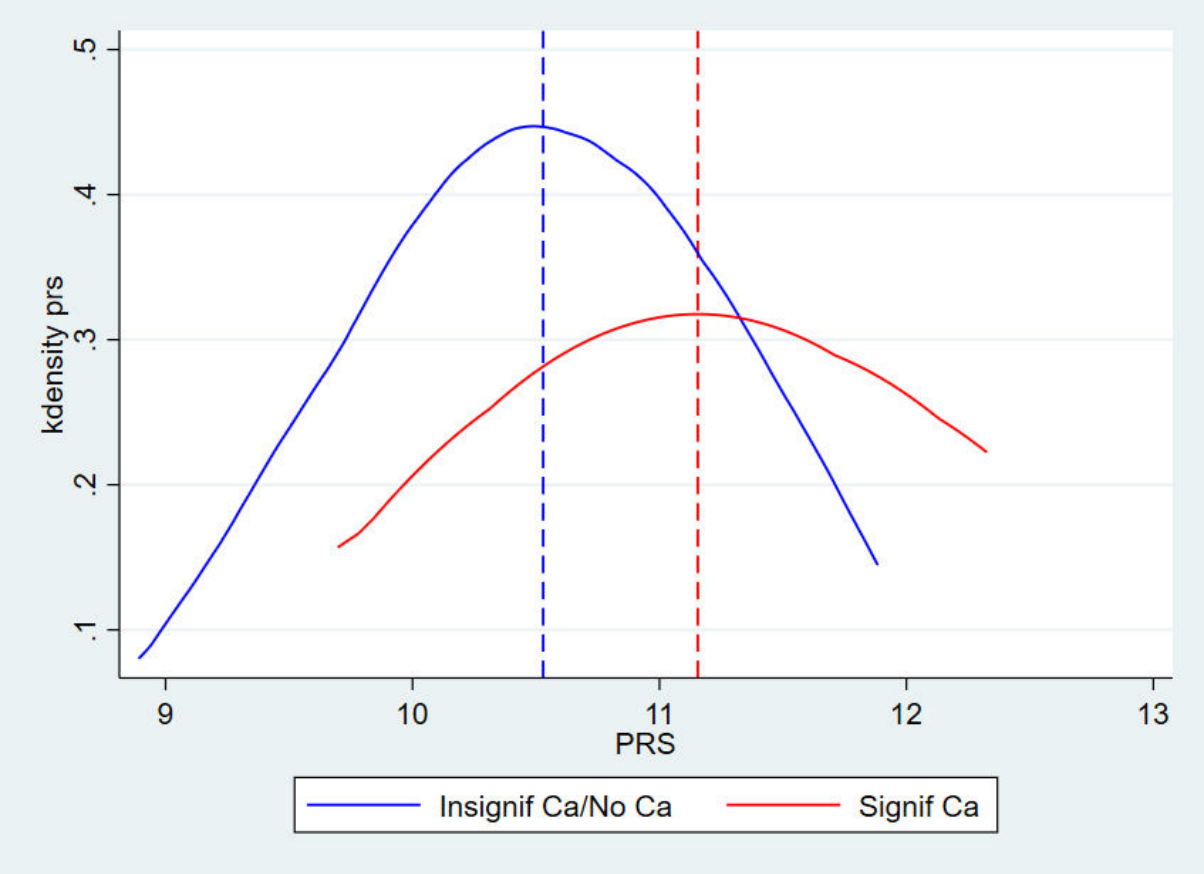

Figure 5.3 Kernel density plot of PRS in men with Insignificant cancer/No cancer vs men with significant cancer. Dashed lines indicate the mean.

As described by Schumacher et al, PRS associates with PrCa, with men harbouring PrCa displaying a higher PRS [1] than those without. This difference was observed in our cohort of men (i.e selected for a FH of PrCa) (Figure 5.2, Figure 5.2).

To examine this finding in a larger cohort, the PRS of men with PrCa was examined in the UKGPCS study (green line) (Figure 5.1). The PRS of the PROFILE cohort (mean PRS 10.6, SD 0.7 95%CI 10.5 – 10.7) lies approximately halfway between a cancer population (UKGPCS cohort - mean PRS 10.9, SD 0.7 95% CI 10.9 – 10.9) and a 'normal' (or non-cancer)' population (ProtecT cohort - mean PRS 10.3, SD 0. 95%CI 10.3 – 10.4) (Figure 5.1). The cancer population chosen for comparison (UKGPCS) includes all cases both with and without a FH, and also includes those

with an unknown FH status. This finding is similar to that described in Pharoah and Chaterjee et al [2-4].

In the PROFILE study, the mean PRS is higher for men diagnosed with (any) cancer (mean PRS 10.9, SD 0.7, 95%CI 10.70031 – 11.) than those with benign histology (10.4, SD 0.7, 95% CI 10.3 – 10.6) (Figure 5.2). There was a difference (P=0.005) between the mean PRS of those with significant cancer (mean PRS 11.1; SE .2, SD, .8, 95% CI 10.6– 11.7) vs those with no cancer/insignificant cancer (mean PRS 10.5; SE 0.06, SD 0.7, 95% CI 10.400 – 10.7) but these results must be interpreted with caution due to small numbers and no confirmation in the published literature of proven ability of PRS to discriminate between significant and insignificant PrCa (Figure 5.3).

There was no difference in the mean PRS between differing degrees of FH i.e. the degree of FH did not appear to change or 'increase' the PRS.

5.5.3 PRS & Cancer Outcome at Prostate Biopsy

This section describes a description of PRS with outcome at prostate biopsy. PRS is analysed as both a categorical variable (categorized into percentiles of risk) and a continuous variable.

Cancers occurred across the spectrum of polygenic risk, graphically demonstrated below (Figure 5.4). The RR of cancer appears greater in those men who fall into the top percentiles of risk, as demonstrated below. Superimposed on the graph are prostate biopsy results, including no cancer (green), insignificant cancer (red) and significant cancer (blue). A red arrow is placed at the mean PRS.

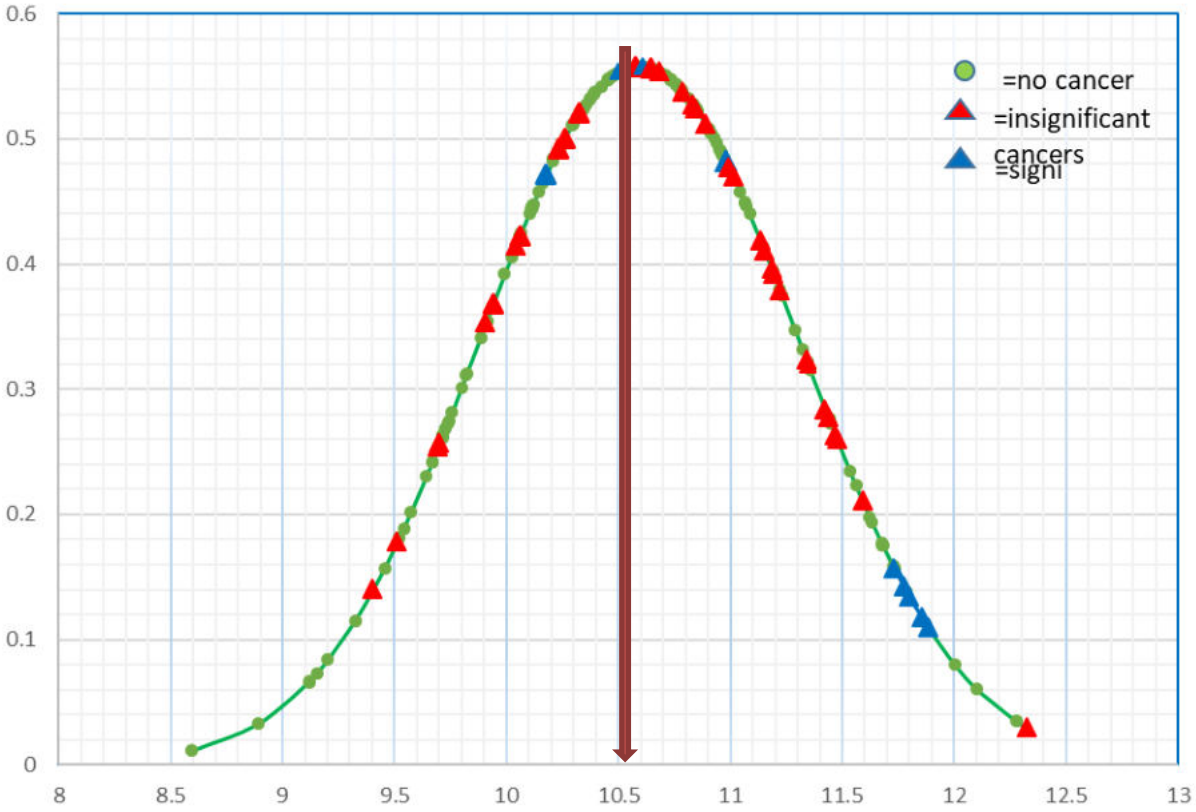

Figure 5.4 Frequency distribution PRS in the PROFILE study population. PRS is defined on the X-axis and the proportion in the population is defined on the Y-axis

For risk stratification purposes, men were separated into percentiles of risk (methods described in Chapter 2 Materials & Methods), with percentile cut points generated from the mean and SD of our reference (ProtecT) population (Table 5.6). We split the PRS into quintiles because of the relatively low number of participants in this analysis. This table demonstrates the PRS values at which percentile cut points applied. i.e. men with PRS less than 9.78 fell into the lowest quintile (<20th) of risk. Men with a PRS above this value but less than 10.17 fell into the second lowest quintile of risk (20 - <40th) etc. Men with a PRS greater than 10.88 fell into the highest percentile of risk (≥80th).

PRS Percentiles	PRS (Upper limit) cut points
< 20th	9.782938
20 - <40th	10.16469
40 - <60th	10.49349
60 - <80th	10.87524
≥ 80th	>10.87524
*90th - <99th**	*11.83872*
*≥99th**	*>11.83872*
Mean PRS 10.58679, Median PRS 10.6281, SD 0.7151105, Min 8.8907, Max 12.32632 ****These cut points are not used in any analysis due to small numbers of participants falling within these categories and are included in this table and results for descriptive purposes only***	

Table 5.6 table displaying cut points of PRS at each percentile

In a logistic regression model of PRS category and cancer outcome, the average probability of cancer in the lowest PRS category (PRS <20th quintile) was 20% and 58% (≥80th quintile) in the highest category. Figure 5.5 shows the marginal effects for each PRS quintile compared to the 'middle' quintile (treated as the average). There appears to be small differences between each PRS quintile category and the middle (40-<60th),and a large increase in the predicted probability of cancer for men with a PRS at or above the 80th quintile, compared to the middle (and all other PRS centiles). Figure 5.6 shows the marginal effects for each PRS category compared to the 'middle' quintile (treated as the average) including a 90-99th centile category. Both figures display the increase in predicted probability of PrCa in those men with a PRS in the highest category (at or above the 80th quintile).

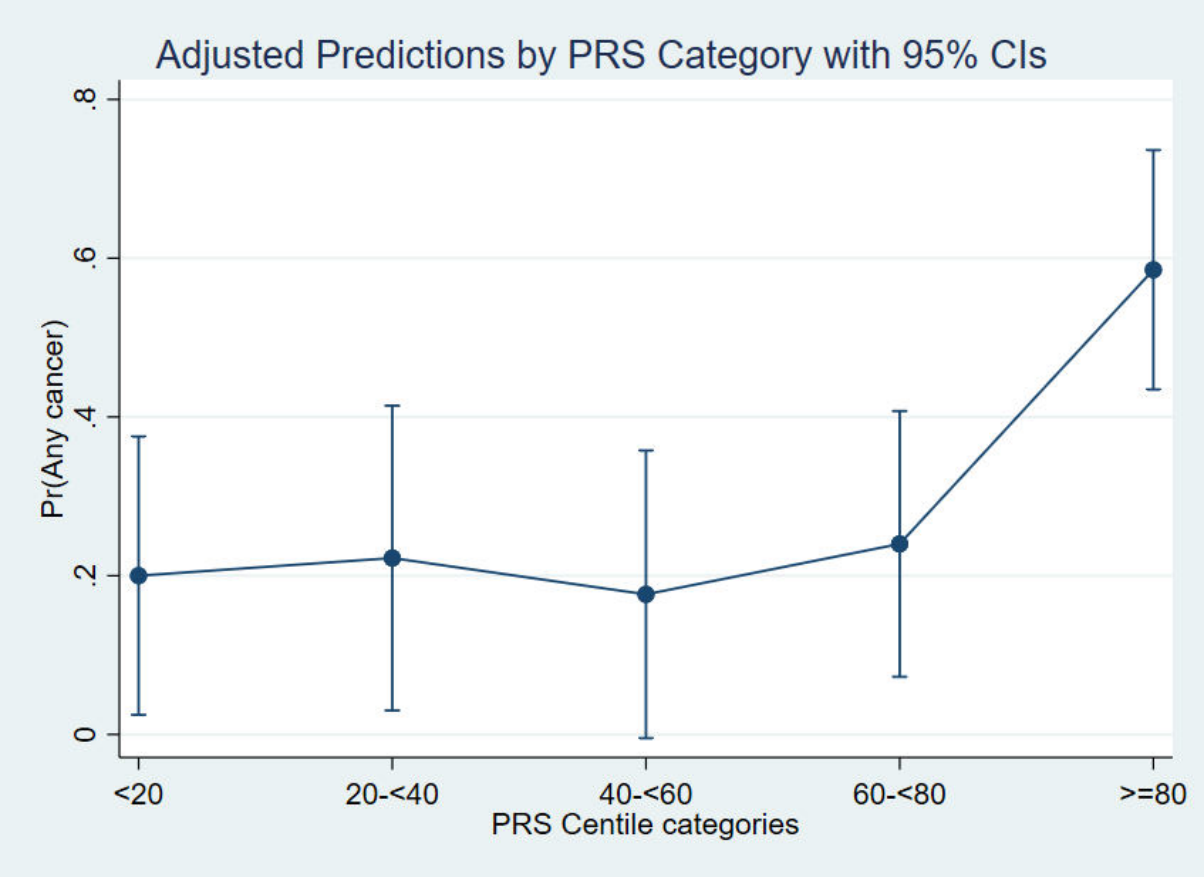

Figure 5.5 Average predicted probabilities of (any) cancer for each PRS percentile category.

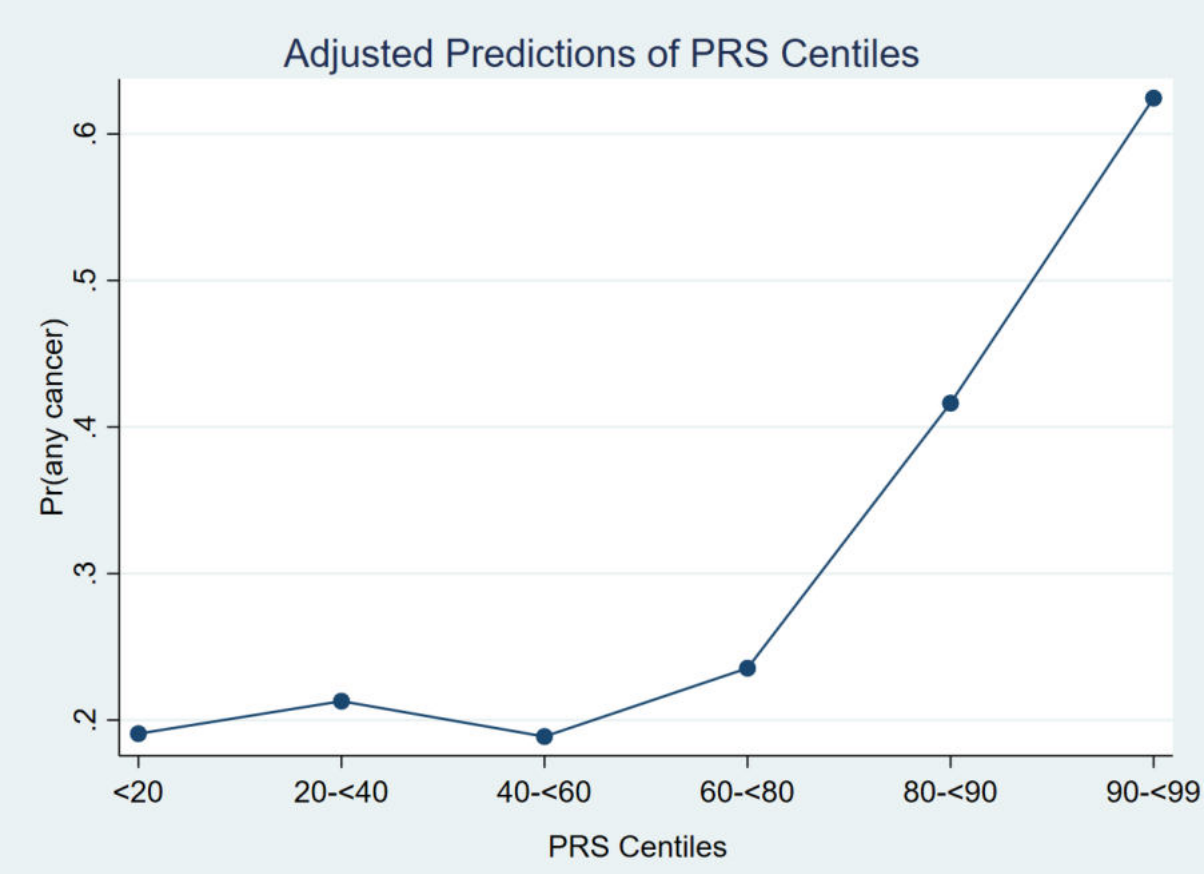

Figure 5.6 Predicted probability of (any) cancer at each PRS centile, including two 'higher' categories – 80th- <90th and ≥90th

PRS as a continuous variable had an OR of 3.13 (P<0.01) with any outcome of any cancer at prostate biopsy. This means the average probability of having (any) PrCa at a PRS of 8.0 is 2.3%, which moves to 5.7% at a PRS of 8.8 (Figure 5.7). The difference in effect between each of these predictions is not statistically significant.

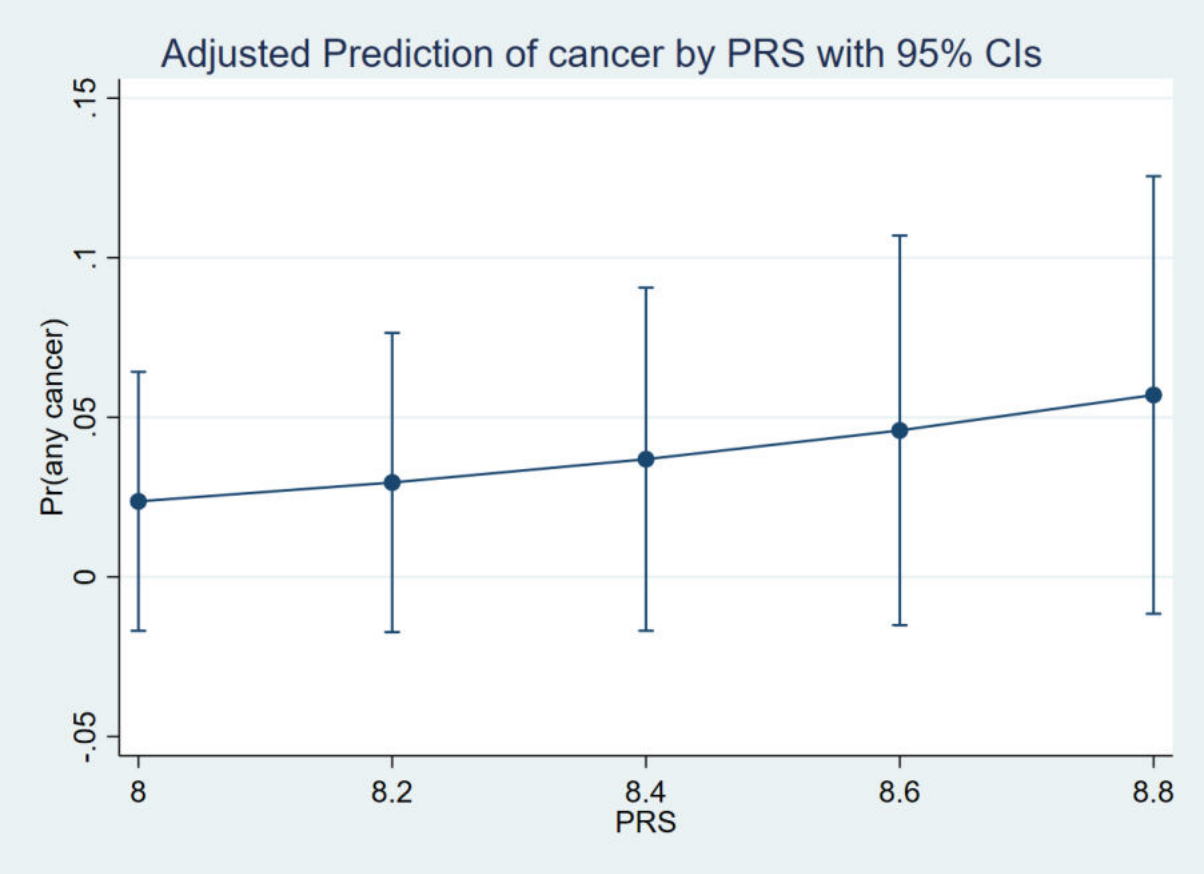

Figure 5.7 Probability of (any) cancer if PRS 8.0– 8.8 (i.e. low)

The average predicted probability of (any) cancer is 7% at a PRS of 9.0 moving to 70% at a PRS of 12 (Figure 5.8). This curve demonstrates the increase in probability of cancer at the 'top' end (≥80%) of polygenic risk score compared to that described in the previous figure (i.e the 'low' end of the polygenic risk).

The mean PRS in PROFILE is 10.586. The 'average' man in PROFILE therefore has adjusted predicted probability of cancer of 31.7%.

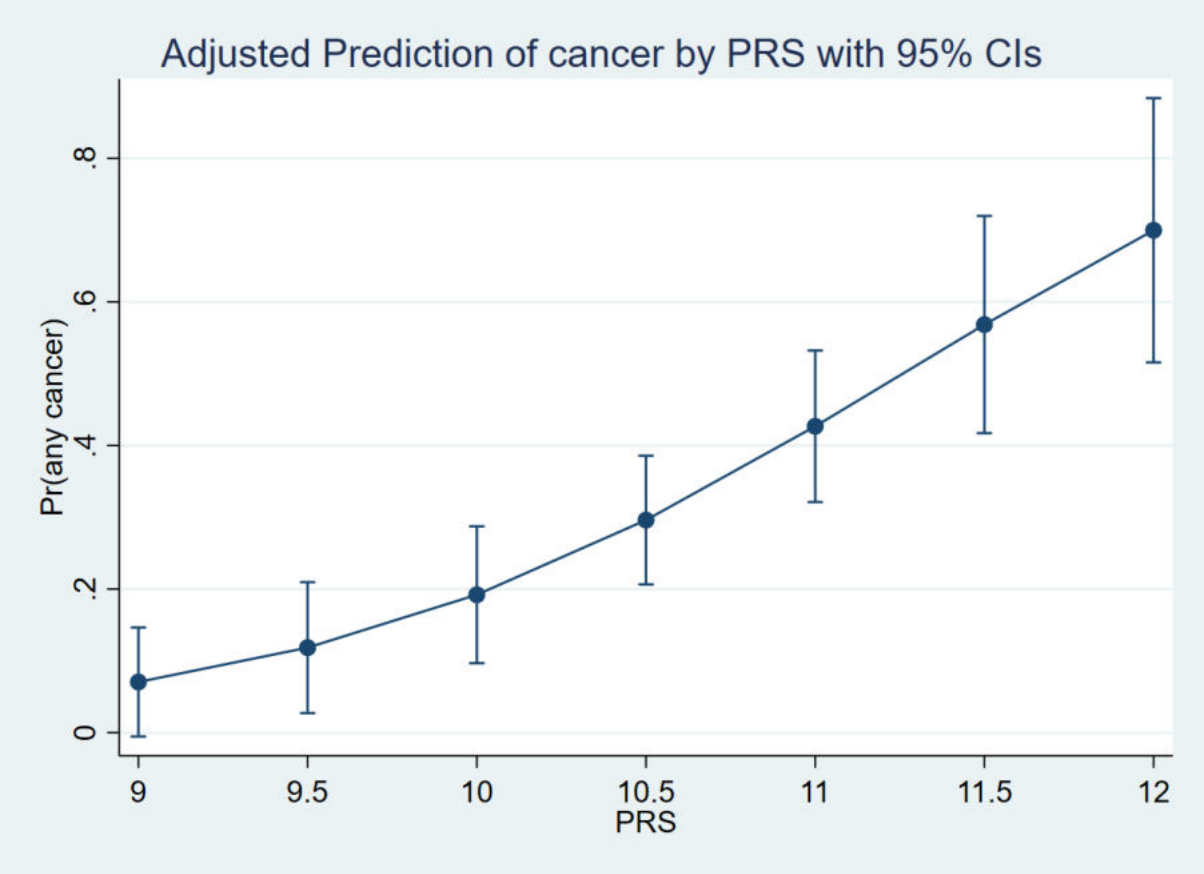

Figure 5.8 Adjusted predictions at a PRS of 9 and above.

63.64% of all **significant** cancers occurred in those with a PRS at or above the 80th centile and 9.09% of all significant cancers occurred in those with a PRS less than the 20th centile. Of all men with significant cancer, 63% had a PRS at or above the 80th centile. For men with insignificant ca/no cancer, 30% had a PRS at or above the 80th centile (Chapter 3, table 1),

A bar chart showing the spectrum of cancer across all PRS quintiles is shown in Figure 5.9. i.e. 63% of all clinically significant cancers occurred in men with a PRS at or above the 80th centile (7/11).

A bar chart displaying the reverse is shown in Figure 5.10. i.e. 95% of men in the bottom 20% of risk either had insignificant cancer or no cancer. 17% of men in the top 20% of risk had significant cancer.

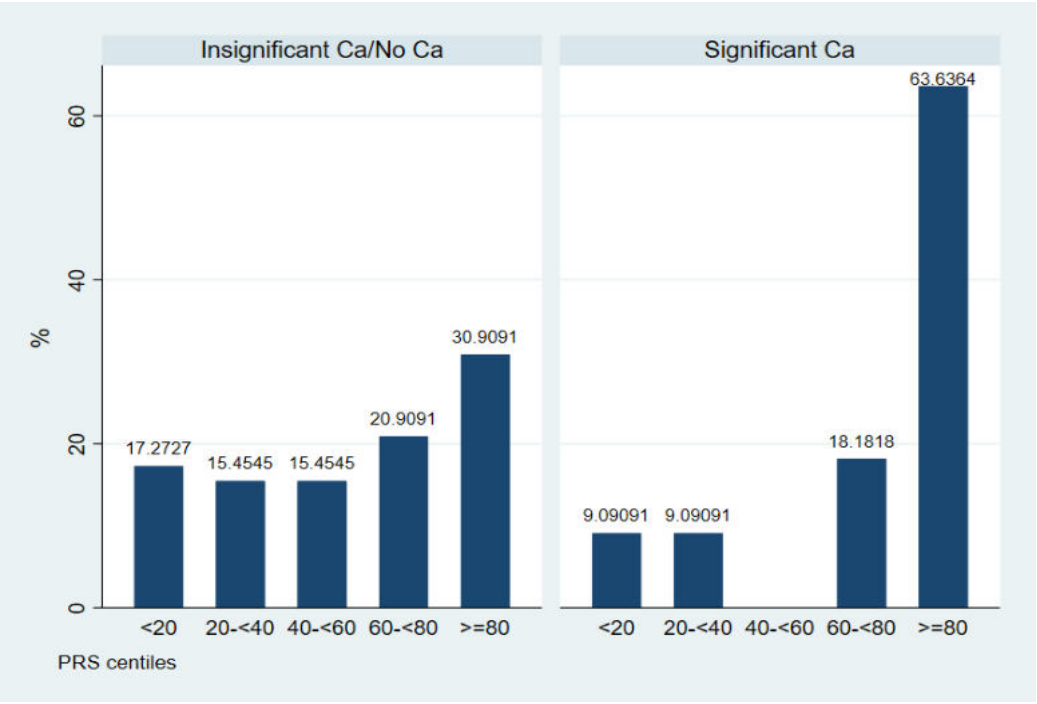

Figure 5.9 Distribution of PRS per prostate biopsy outcome of significant cancer vs no cancer/insignificant cancer

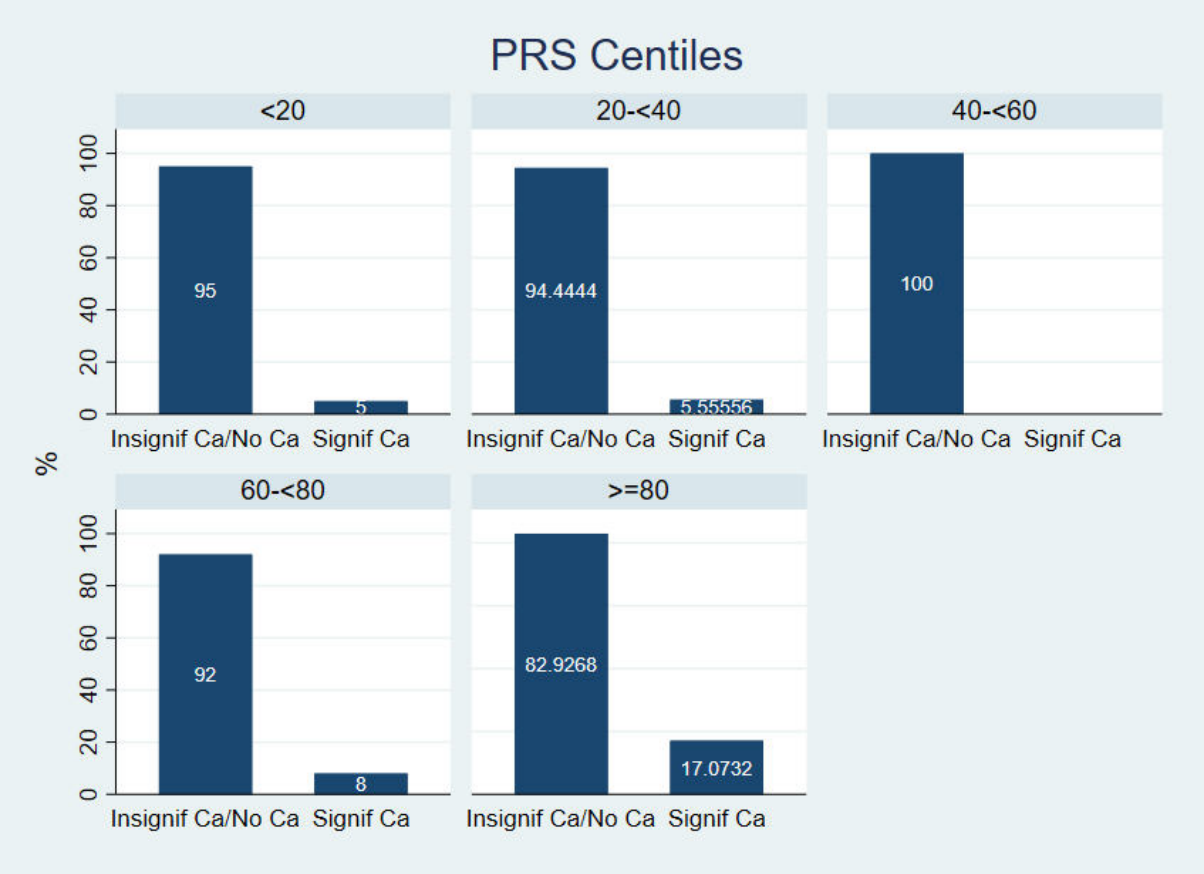

Figure 5.10 Proportion of significant cancer vs nocancer/insignificant cancer per PRS quintile

PRS was positively associated with significant cancer detection with the highest OR for the highest risk category (≥80th centile), but not statistically significantly so when using the middle PRS category as the reference. The probability of significant cancer detection in men with a PRS at or above the 80th centile was significantly increased compared with men with a PRS below the 80th centile (OR 3.696). As a continuous variable, PRS was associated with significant cancer detection (OR 3.996, P=0.009).

5.5.3.1 PRS in Multivariable Models

PRS and clinical (continuous) variables of interest (i.e PSA, PSAD, Age etc) and categorical variables (ie Prior screening status, MRI) described in Chapter 3 were investigated in a multivariable logistic regression model with PRS. Marginal analyses were performed at varying continuous variable and are described below.

5.5.3.2 PRS and one clinical variable

In a model with PRS and prior PSA screening (yes/no/unknown), PRS was positively associated with (any) cancer detection (OR 3.209; 95% CI 1.7, 6; (p<0.0001). unknown prior PSA screening status and prior PSA screening were positively associated with PrCa detection (OR 3.4, 2.4 respectively), but not statistically significantly so (p=0.18, 0.07 respectively). The model overall showed significance (p<0.001), but this is likely due to the effect of PRS. This finding was replicated when the outcome was clinically significant cancer.

In a model with PRS as a continuous variable and age as a categorical variable, age ≥60 was positively associated with any cancer detection, but not statistically significantly so (p=0.06; OR 1.08). PRS remained positively associated with cancer detection (OR of 1.149 (p=<0.01). With age as a continuous variable, both age (OR 1.05; p=0.03) and PRS (OR 3.15, p<0.001) were positively associated with any cancer detection, with PRS showing a stronger association. This relationship is expanded upon below by way of marginal effects (Figure 5.11). At the lower limits of PRS, an older age did not appear to greatly influence the likelihood of cancer. At a young age, those with the highest probability of cancer were those with a high PRS.

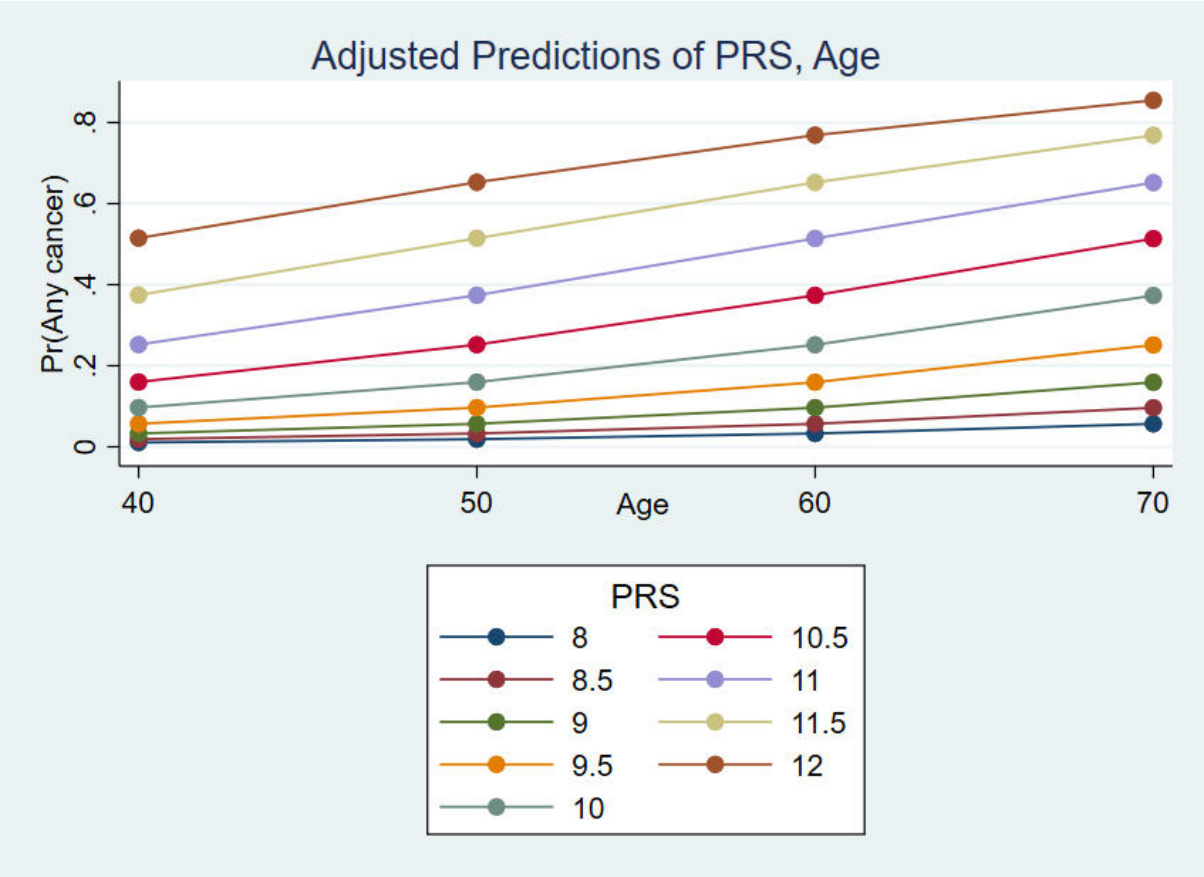

Figure 5.11 Effects of age and PRS on predicted probability of (any) cancer.

In a model with PRS as a continuous variable and PSA as a categorical variable, only a PSA of 2ng/ml or greater was statistically significantly associated with (any) cancer detection compared to those with a PSA of <1.0ng/ml. Compared with a PSA <1.0ng/ml, men with a PSA of 1-<2, 2-<3 or ≥3 had an OR of 3.0 (p=0.75), 6.45

(p=0.004) and 8.4 (p=0.003) of (any) cancer detection. PSA as a continuous variable was positively (OR 1.36) and significantly (p=0.024) associated with PrCa detection in a model with PRS.

Margins of effect of age and PRS on the predicted probability of significant cancer are shown below. At the lower scale of PRS, the probaility of significant cancer remained relatively low despite older age. At the highest PRS, the probability increases as age increases.

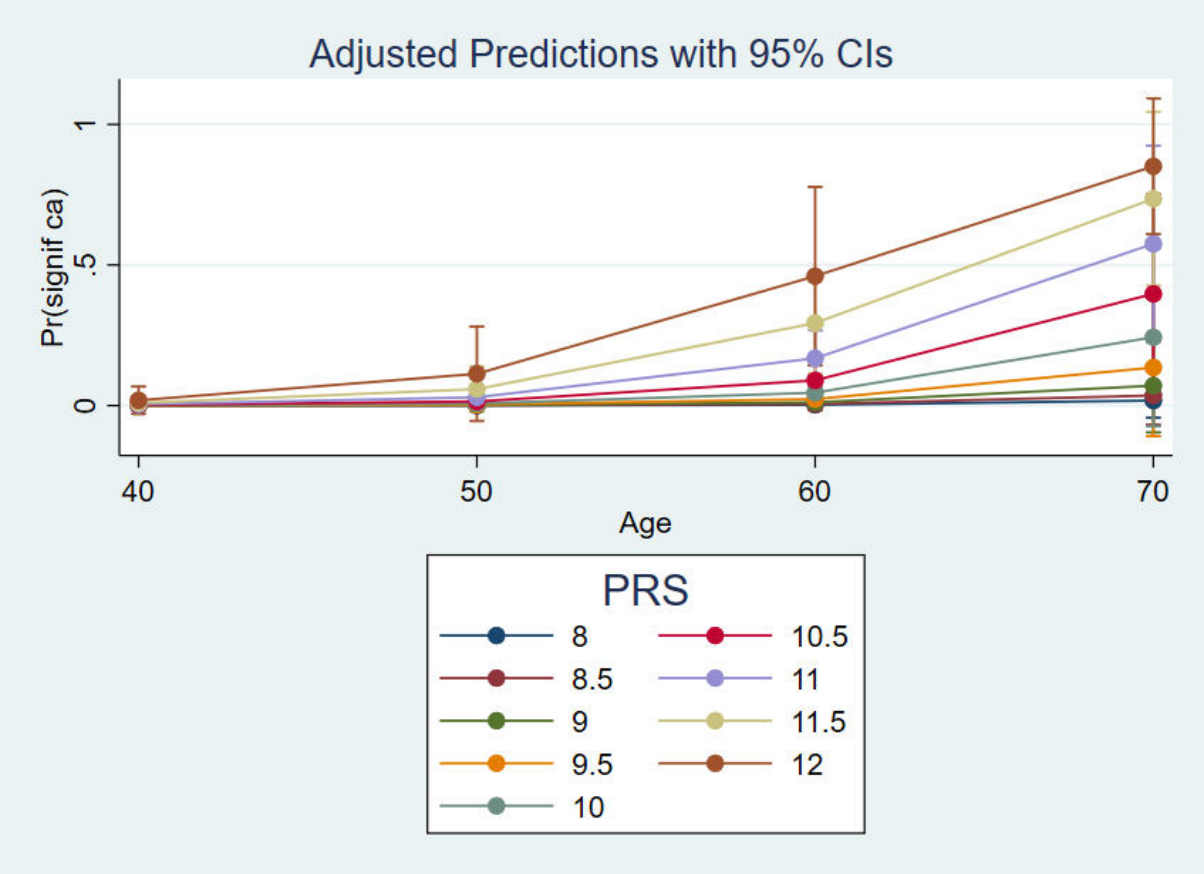

Figure 5.12 Margins of effect of age and PRS on the predicted probability of significant cancer.

To highlight the relationship between PSA and PRS, the lowest limit of PRS is graphed below in Figure 5.13. At a low PRS, there was no significant increase in the probability of (any) cancer in men with either the lowest or highest PSA.

The relationship at the rest of the PRS spectrum is graphed in Figure 5.14. At the lowest category of PSA (<1ng/ml), the average probability increased from 1-37% as the PRS increased. At the highest category of PSA (≥3.0ng/ml), the average probability increased from 8 – 83%.

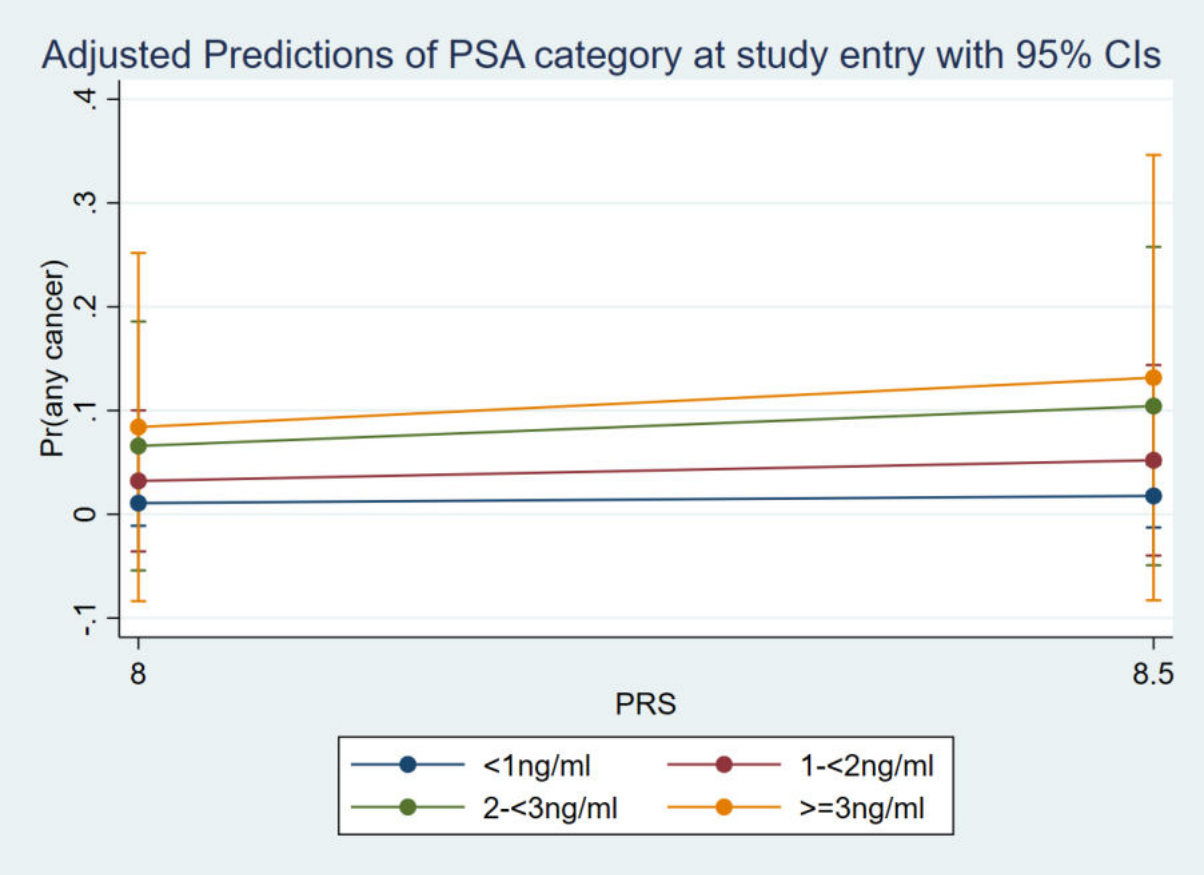

Figure 5.13 Adjusted predicted probability of (any) cancer by PSA category in the presence of a PRS from 8-8.5 or the 'lower' end of polygenic risk.

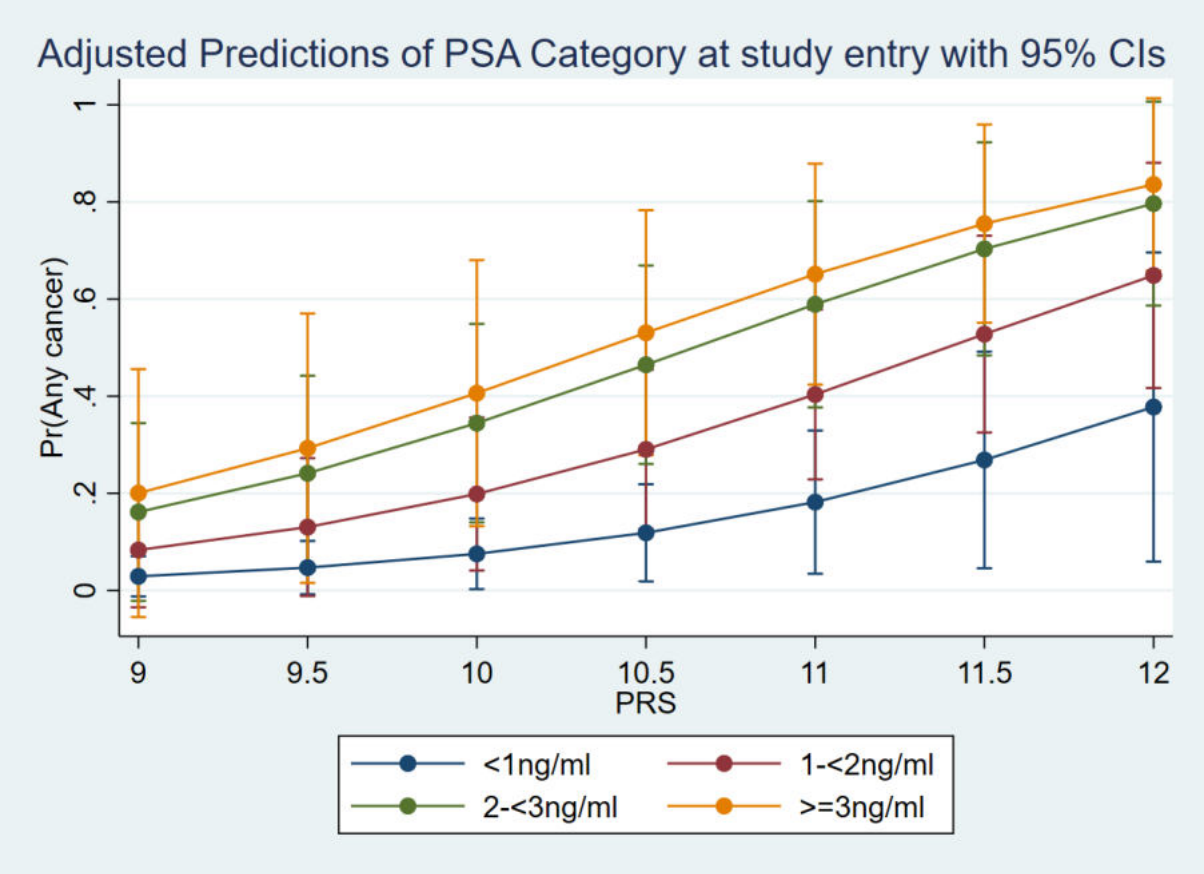

Figure 5.14 Average probability of cancer detection by category of PSA in the presence of a PRS in the middle and higher end of risk.

PSA (OR 1.7; p=0.003) and PRS (OR 4.1; p=p=0.018) were positively and statistically significantly associated with the probability of significant cancer (p<0.01). At the lower scale of PRS, the probaility of significant cancer (Figure 5.15) remained relatively low despite a high PSA. At the highest PRS, the probability increases as PSA increases. A similar relationship was seen with PSAD (Figure 5.16).

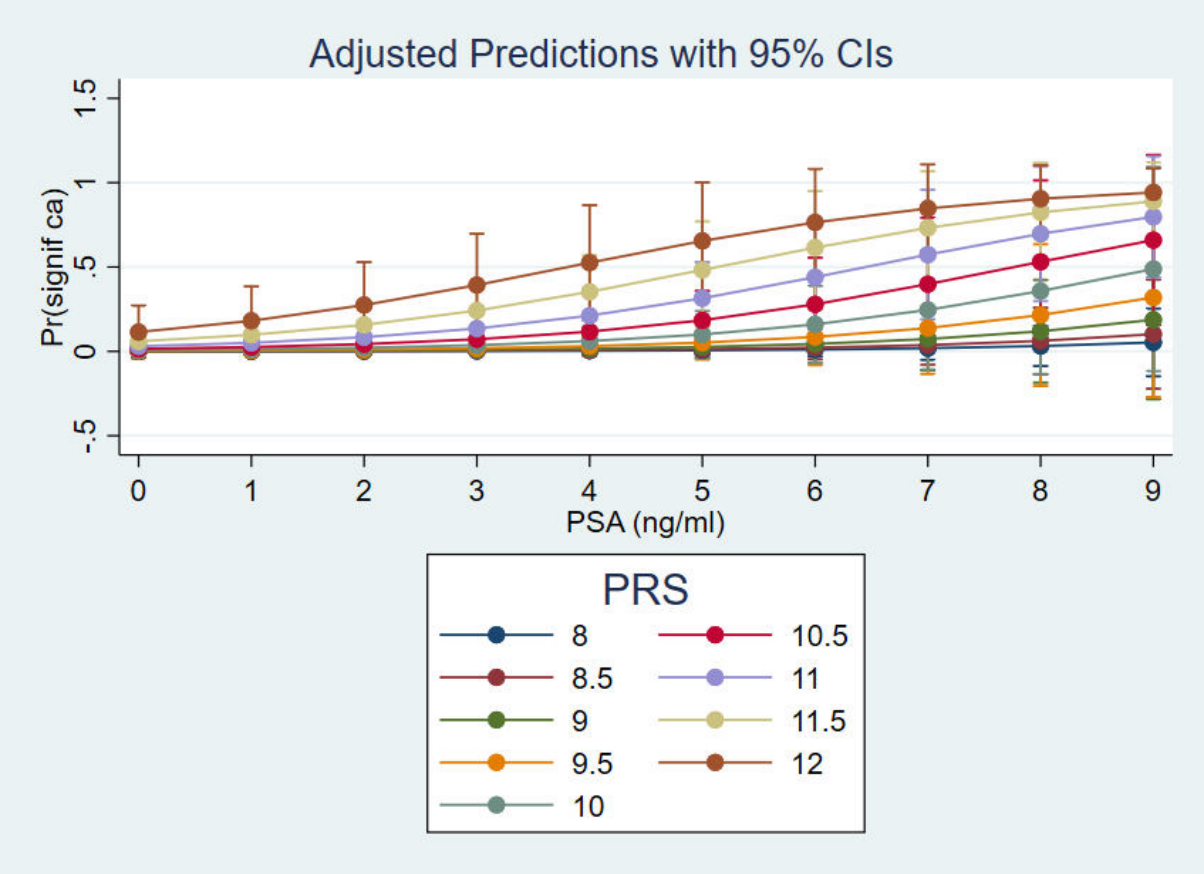

Figure 5.15 Margins of effect of PSA and PRS on the predicted probability of significant cancer.

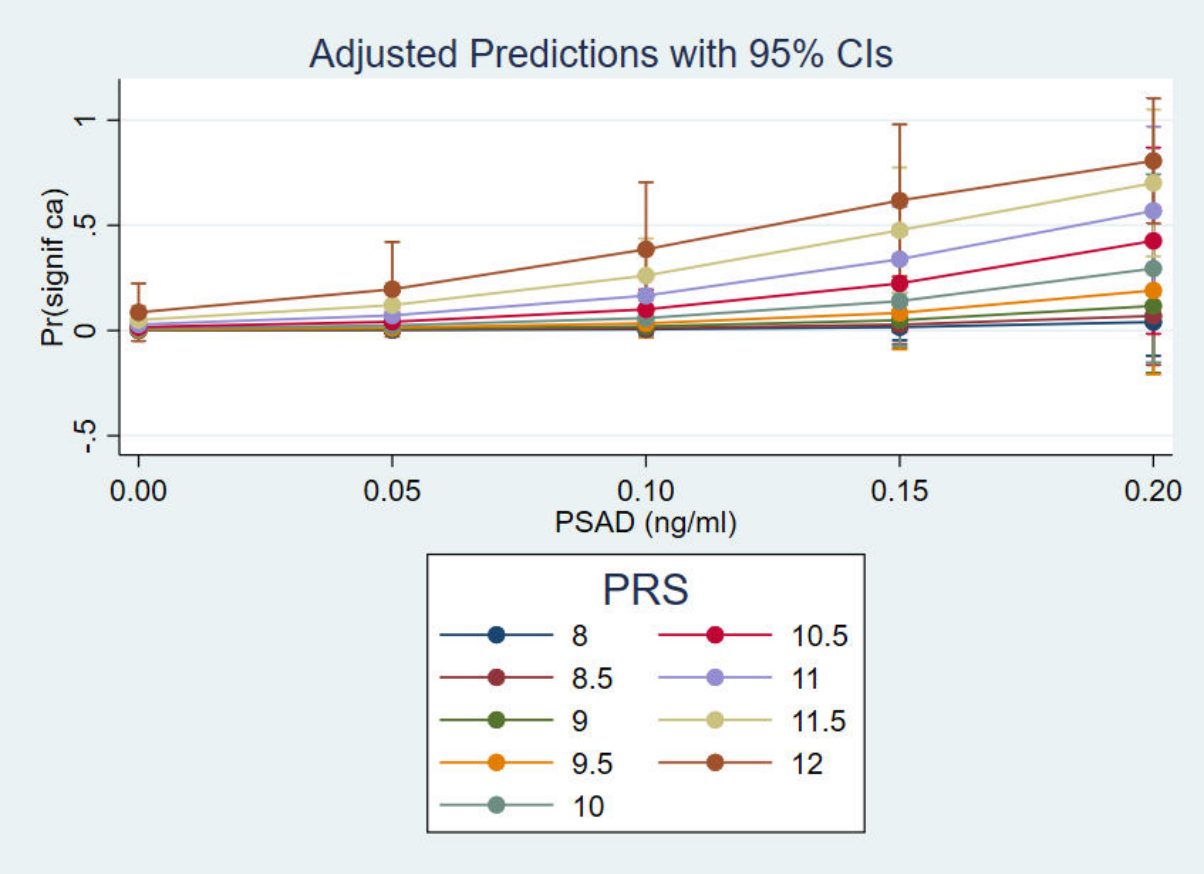

Figure 5.16 Margins of effect of PSAD and PRS on the predicted probability of significant cancer. A the lower scale of PRS, the probaility of significant cancer remained relatively low despite a high PSAD. At the highest PRS, the probability increases as PSAD increases.

In men with no cancer on screening biopsy (n=89), 18.7% of those in the lowest PRS centile (<20th) had an abnormal MRI. For those in the 'middle' PRS risk category (40-<60th centile), 28.6% had an abnormal MRI and for those in the highest risk PRS centile (≥80th), 25% had an abnormal MRI.

In men with (any) cancer on screening biopsy (n=41), 50% in the lowest PRS centile (<20th) had an abnormal MRI. For those in the 'middle' PRS risk category (40-<60th), 66.7% had an abnormal MRI and for those in the highest PRS centile (<80th), 50% had an abnormal MRI.

In men in the lowest quintile of PRS (n=20), 15 (75%) had a normal (PiRADS 1-2) and 5 (25%) had an abnormal (PiRADS 3-5) MRI. Of the men in the lowest PRS risk centile with a normal MRI, no significant cancer was found. In those with an abnormal MRI, clinically significant cancer was found in 1 man (20%) and insignificant cancer in 1 man (20%).

In men in the 'average' or middle PRS quintile (40-<60th; n=17), 12 had a normal MRI (70.6%) and 5 had an abnormal MRI (29.4%). No clinically significant cancer was found in any man with a normal or abnormal MRI. Insignificant cancer was found in 16.7% and 20% of men with a normal and abnormal MRI respectively.

In men in the highest PRS quintile (≥80th; n=40; highlighted in red), 24 men (60%) had a normal MRI and 16 (40%) had an abnormal MRI. In those with a normal MRI, clinically significant cancer was found in 1 man (4.2%), whereas in those with an abnormal MRI clinically significant cancer was found in 6 men (37.5%) (Chapter 3, Table 3.4).

A logistic regression model including PRS as a continuous variable and PiRADS 3-5 MRI demonstrated men with a PiRADS 3-5 MRI (compared to those with a PIRADS 1-2 MRI) had an increased probability of (any) cancer detection (OR 2.727). In this model with PRS which remained statistically significantly associated with any cancer detection (OR 3.05; p=0.001) and the AUC of this model (0.74) was superior to that of PRS alone (0.70) or MRI alone (0.61). The relationship between the predicted probabilities of any cancer detection is demonstrated below along the spectrum of PRS in men with and without an abnormal MRI (Figure 5.17). The predicted probability of (any) cancer varied across the PRS spectrum for men with normal and abnormal MRIs i.e. the predicted probability of any cancer in men with a normal MRI was higher if their PRS was higher. The marginal effects were greatest from a PRS of approx. 9.5 onwards.

The results were similar in a model with PIRADS 4-5 MRI. PRS was positively and significantly associated (OR 2.92, p=0.001) and PIRADS 4-5 MRI (OR 4.13, p=0.015).

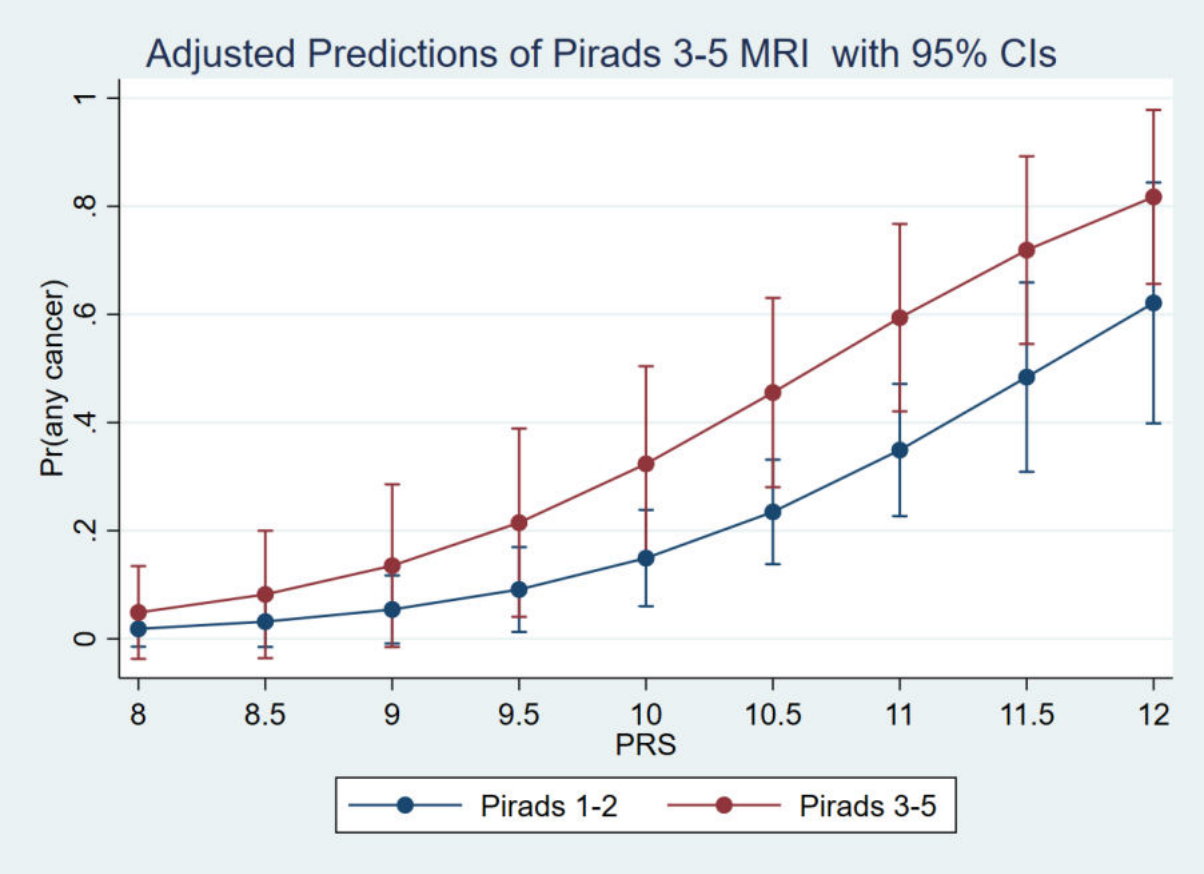

Figure 5.17 Adjusted predictions for probability of (any) cancer for men with PiRADS 1-2 MRI vs PiRADS 3-5 MRI.

The probability of clinically significant cancer detection increased with increasing PRS in men with an abnormal (PiRADS 3-5) MRI. The probability of significant cancer was greater in men with a PiRADS 3-5 MRI compared to those without (p=0.002) in the presence of PRS (OR 28.6; p=0.003). The average probability of significant cancer detection in men with a PiRADS 1-2 MRI remained low even at the

highest PRS values (0-9.8%). The average probability of significant cancer detection in men with a PiRADS 3-5 MRI ranged from 30-75% at the same high values of PRS. For men with an abnormal MRI, or PiRADS 3-5, at low levels of PRS there was lower predicted cancer probability (0-18%) compared to at the higher end of the PRS scale (30-75%). This relationship is graphed below in Figure 5.18.

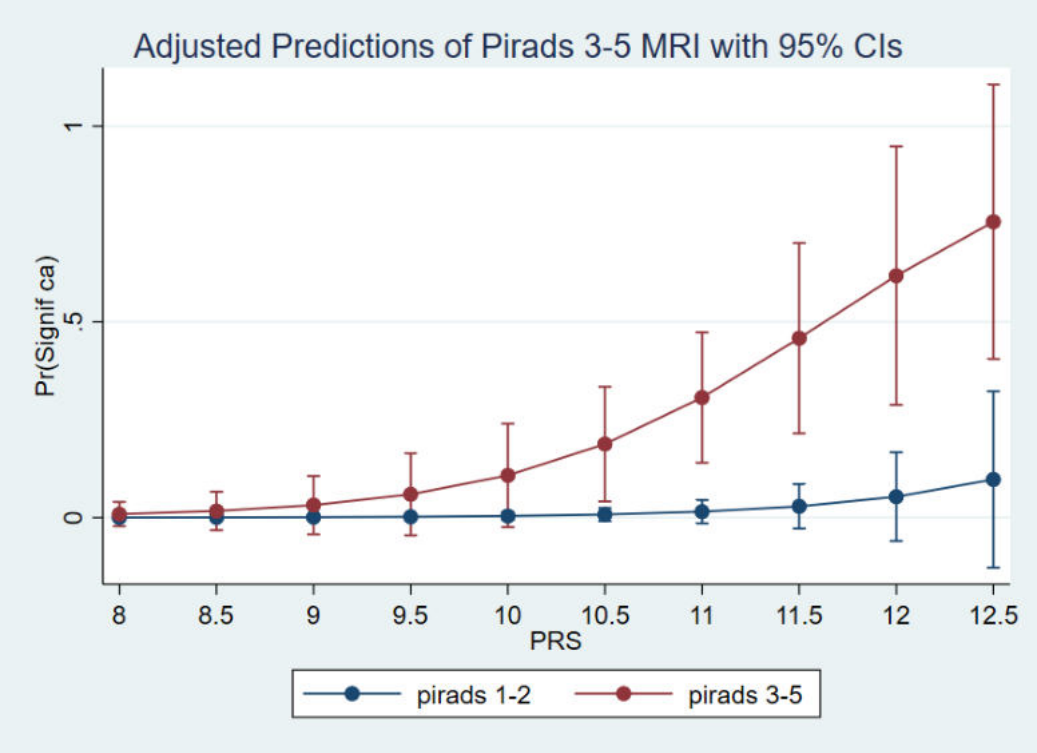

Figure 5.18 Predicted probability of significant cancer at variations of PRS of men with an MRI with a PiRADS score of 3-5 compared to those with a PiRADS 1-2.

Overall, a model incorporating PRS and the degree of FH was significant (p<0.0001). PRS as a continuous variable was positively associated with (any) cancer detection (OR 3.218). There was almost a statistically significant difference between (any) cancer probability men with 2 relatives with PrCa (compared to those with PrCa in 1 relative aged <70 years old; p=0.057). A graph demonstrating this is shown below in Figure 5.19. Those with 2 relatives have a greater 'baseline' risk at every unit of PRS. There is no difference in cancer probability if men had one or three relatives with PrCa.

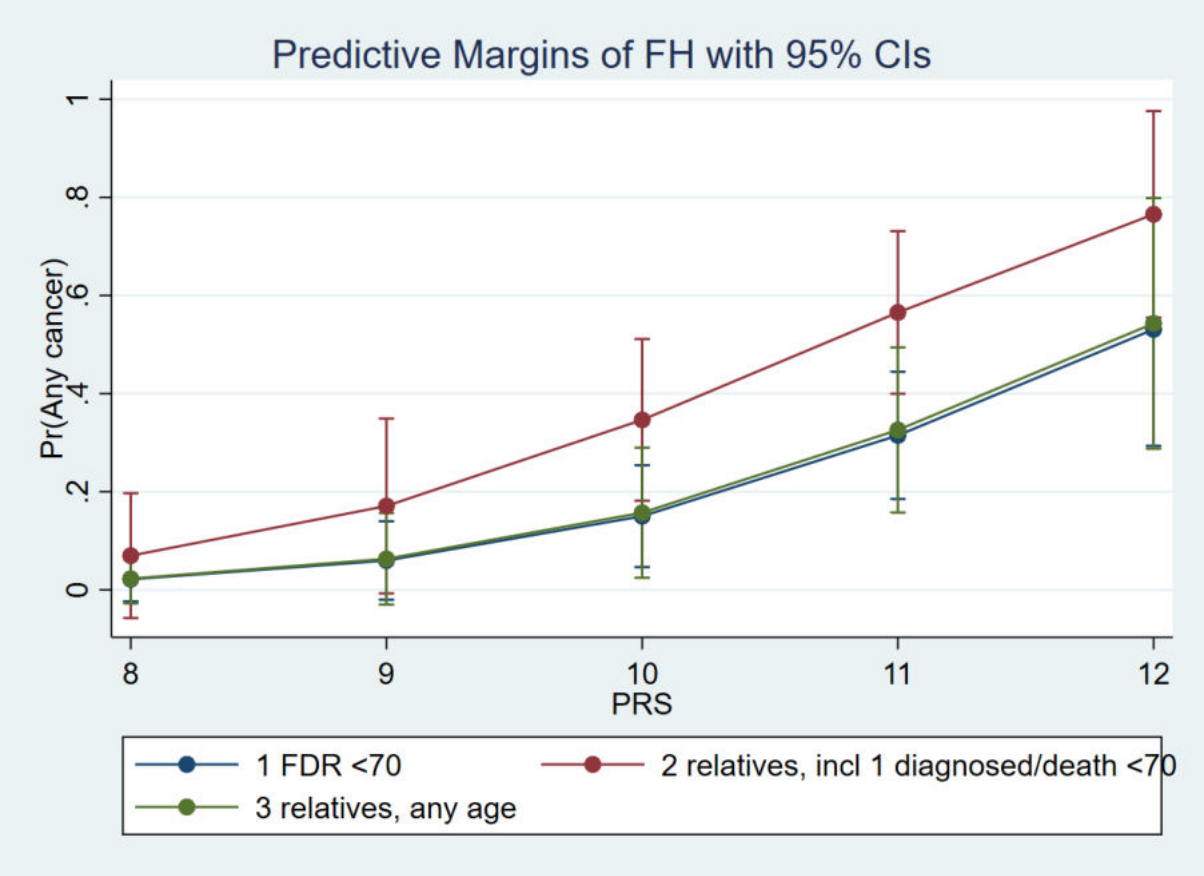

Figure 5.19 Probability of cancer depending on degree of FH and PRS.

The only variables of interest which maintained statistically significance in a multivariate model (with 3 or more variables) were PRS, category of PSA at study entry (≥2ng/ml) and a FH in 2 relatives. Of note MRI and age lost their significance.

5.5.3.3 PRS and two clinical variables

The best performing model for significant cancer detection according to AUC parameters (0.89) excluding MRI was comprised of PRS, age and PSA. All three variables positively and statisrtically significantly were associated with significant cancer; OR 3.92 (p=p=0.028), OR 1.56 (p=0.021) and OR 1.19 (p=0.011) respectively.

The best performing model for significant cancer detection according to AUC parameters (0.94) including MRI was comprised of PRS, MRI PIRADS 3-5 and age. PiRADS 3-5 MRI was positively associated with significant cancer (OR 27.5, p=0.005), as were age (OR 1.2, p=0.011) and PRS (OR 5.0, p=0.018). The relationship between these variables is graphed below in Figure 5.20.

In men with a PiRADS 1-2 MRI, the predicted probability of clinically significant cancer detection was low unless men were 70 years old with a high PRS. i.e with a low/very low PRS, even at older age the predicted probability was low.

In men with a PiRADS 3-5 MRI, the probability of clinically significant cancer detection was low only at the youngest ages (40-50) and at the lowest PRS. The highest risk was in those of an older age *and* a higher PRS i.e. men aged 70 with a 'low' PRS had an average probability of clinically significant cancer detection of 2-13% (PRS 8-9).

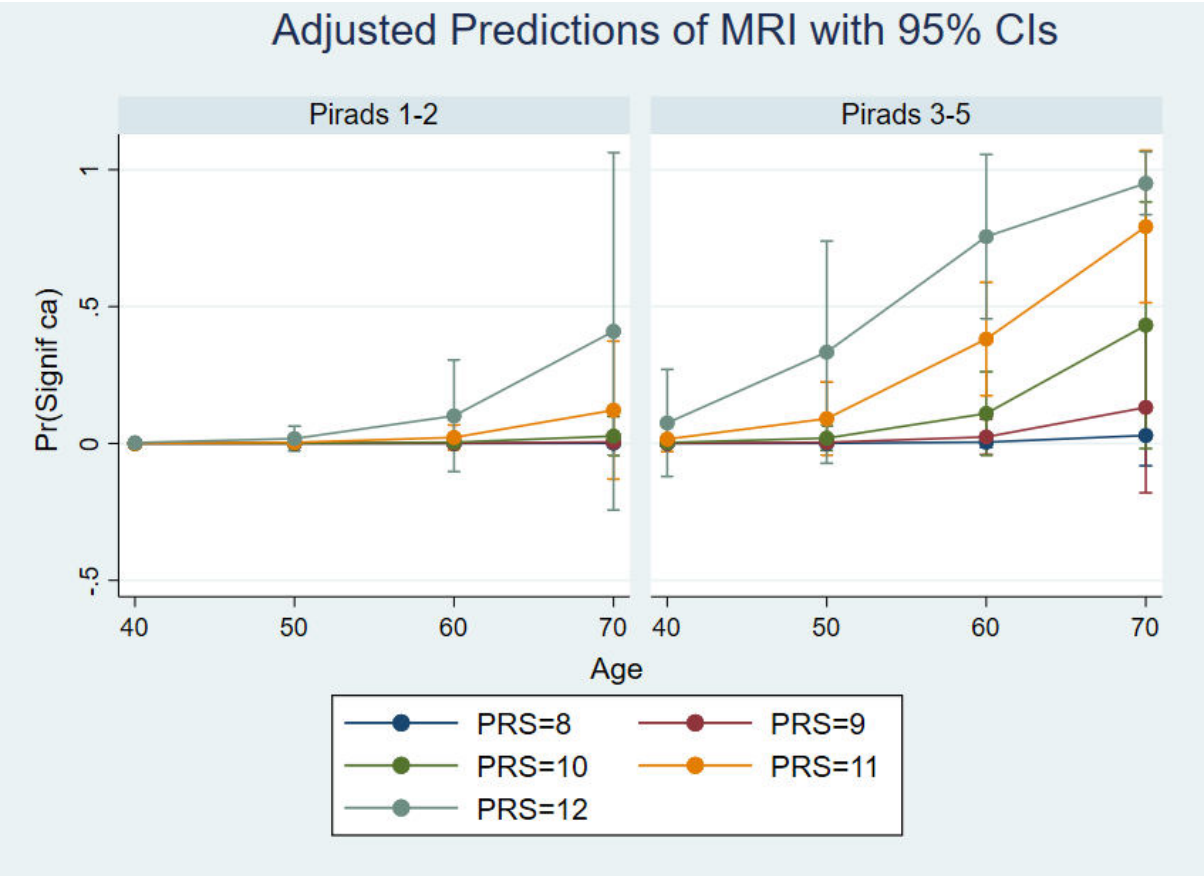

Figure 5.20 Predicted probability of (significant) cancer at different values of PRS and age levels by PIRADS 1-2 vs 3-5 MRI.

The model was repeated with PIRADS 4-5 MRI and results are displayed below in Figure 5.21. In men with PiRADS 1-3 MRI, the probability of clinically significant cancer detection was low until men were at least 60 years old with a higher PRS values

In men with PiRADS 4-5 MRI, the probability of clinically significant cancer detection differed depending on age and PRS. The highest risk was in those with a higher PRS from age 60 onwards (ie men aged 60 and older with a 'low' PRS had an average probability of clinically significant cancer detection of 4-12% (PRS 8-9).

The youngest men (aged 40) with the highest PRS had an average probability of significant cancer detection of 10%, men aged 50 (highest PRS) had a probability of

31%, men aged 60 (at the highest PRS) had a probability of 65% and men aged 70 9at the highest PRS) a probability of 88%

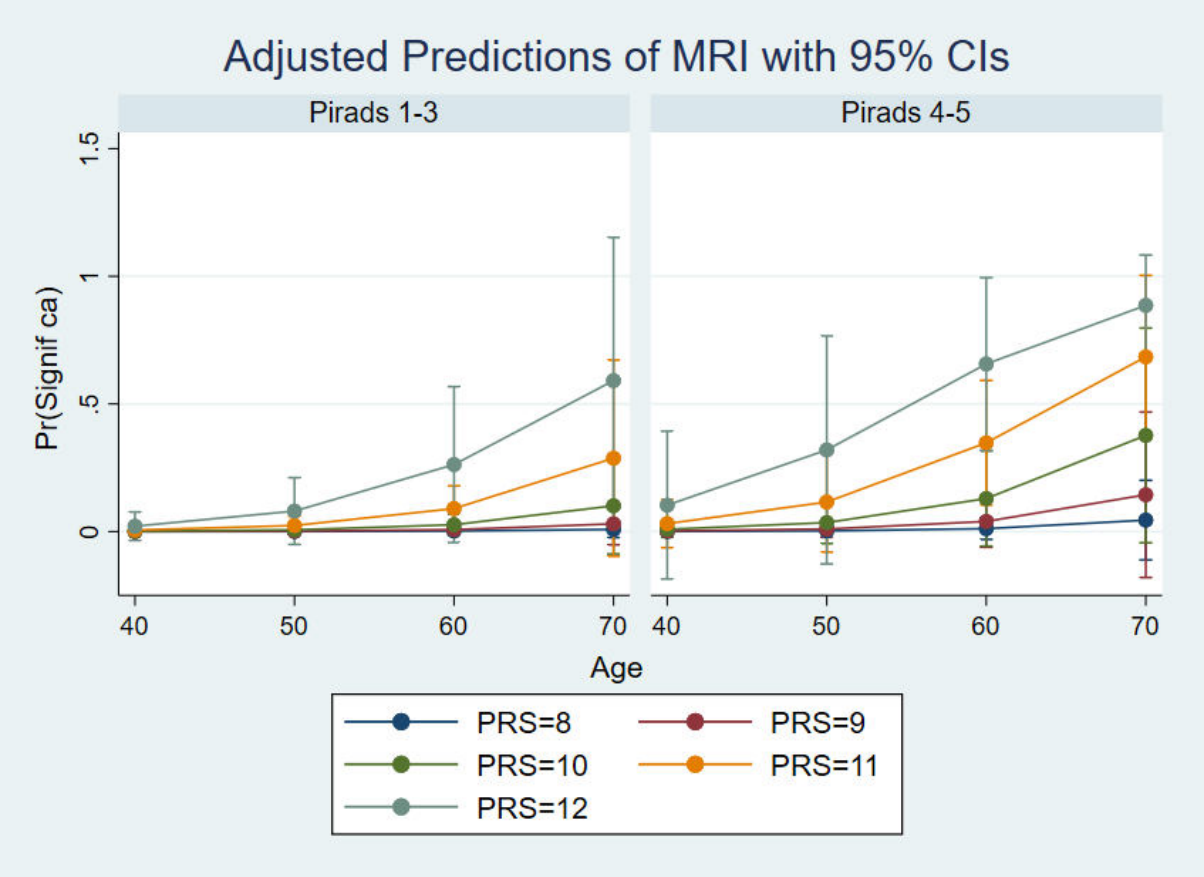

Figure 5.21 Adjusted predictions of (clinically significant) cancer probability at varying levels of PRS and age. Predicted probability of (significant) cancer at different covariate levels (age/PRS) by normal/abnormal MRI.

5.6 Discussion

5.6.1 PRS

PRS was associated with outcome of (any) cancer at prostate biopsy (OR 3.13) and this was especially true for men in the highest 10% of polygenic risk (p=0.001) (Figure 5.6).

The probability of cancer was not the same in all percentiles of polygenic risk. Using men with a PRS between 20th - <80th quintile as the 'average' category, there was a significant difference between those in the top 20% (OR 6.58) compared to the baseline (p=0.008). There was a positive association with the other percentile categories compared to the average but none reached statistical significance. There was a greater increase in cancer probability in the top 20% of risk (40%) compared to the baseline than for any other category (2-6%).

The association of a PRS with PrCa in European populations is well-described, by Schumacher at al [1], Tasa et al [5] and in a multi-ancestral analysis by Conti et al [6]. Our findings of a higher predicted probability of (any) cancer in the highest percentiles of polygenic risk (compared to men in the reference/average percentile) are comparable to those found by Tasa et al (seen below in Figure 5.22 and Figure 5.23) when they analysed approximately 9,000 men using a 121 SNP assay for PrCa risk prediction.

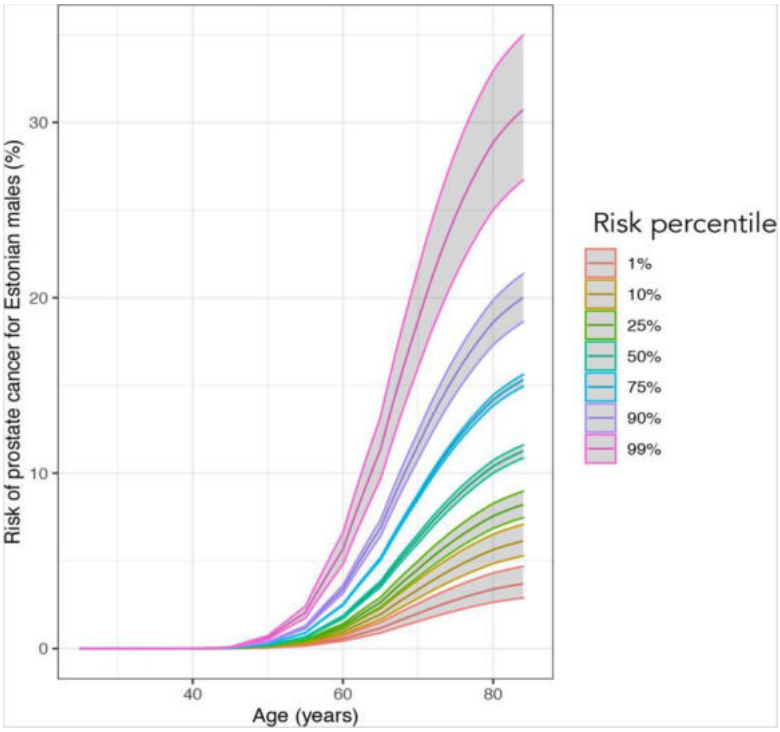

Figure 5.22 Cummulative risk of PrCa by varying PRS percentiles in the cohort described by Tasa et al.

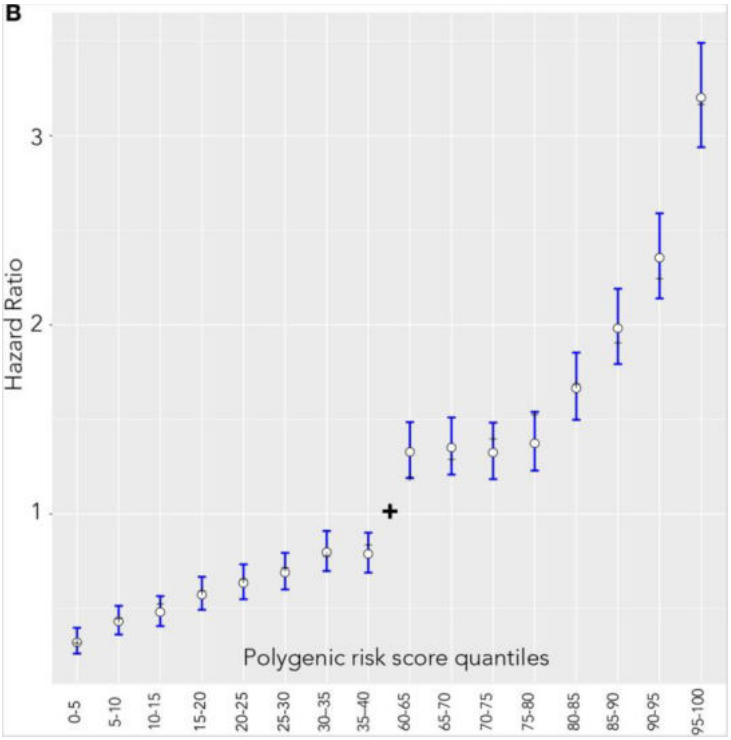

Figure 5.23 Reprinted from Tasa et al [5]. HR estimates between quantiles 40-60 of their best performing PRS model and categorised 5% bins in their incident dataset in the UK biobank

PRS in our cohort was associated with clinically significant PrCa, (OR 3.9) and specifically for a PRS at or above the 80th centile (OR 3.69). This finding should be interpreted with caution; due to small numbers of men with significant cancer in this cohort and a lack of SNPs validated (at present) for high-grade PrCa.

At the lower scale of PRS, the probability of significant cancer remained relatively low despite older age (Figure 5.12). The majority of men with clinically significant cancer detection in our cohort were 60 or older (72%), with a median PSA of 3.3ng/ml (29.17% of men ≥60 had a PSA of ≥3.0ng/ml, compared to 18.18% of men aged 50-59 and 2.38% of men aged 40-49). The predicted probability of cancer for men increased as their PSA rose and this was also affected by their PRS (Figure 5.24).

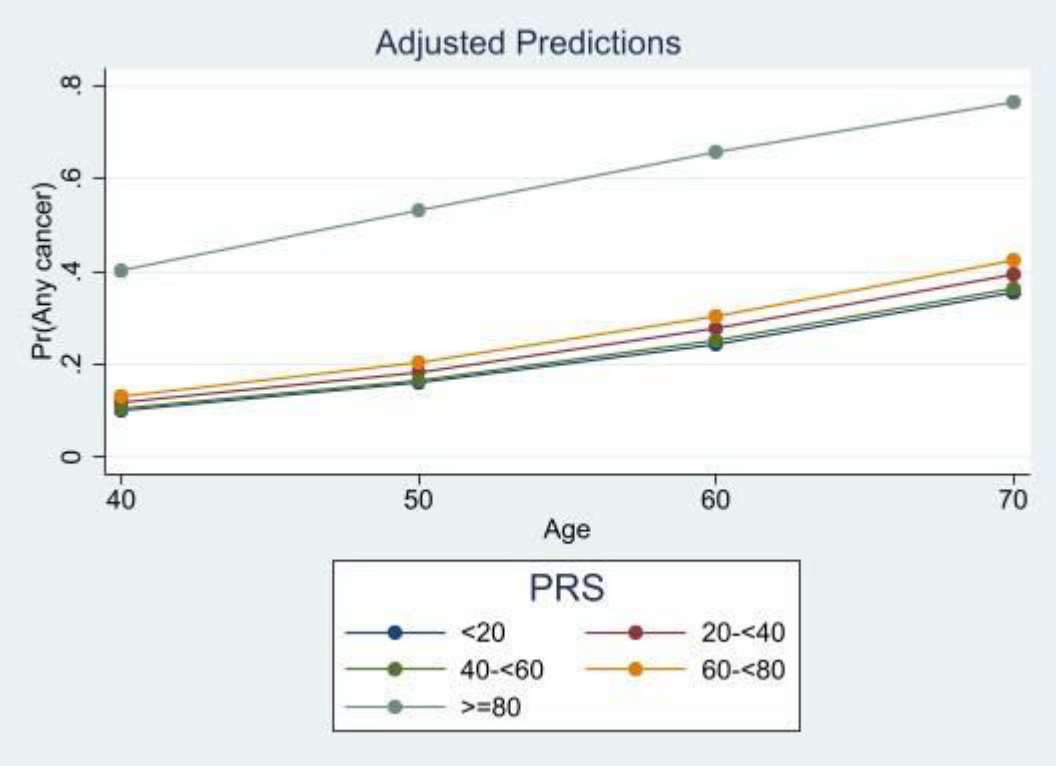

Figure 5.24 predicted probability of (any) cancer by age group and PRS. There was a significant difference between those in the highest quintile of risk (regardless of age) compared to those in all other quintiles.

At the lowest category of PSA (<1ng/ml), the average probability of any cancer increased from 1-37% as the PRS increased. At the highest category of PSA (≥3.0ng/ml), the average probability increased from 8 – 83% (Figure 5.13, Figure 5.14). A the lower scale of PRS, the probability of significant cancer was relatively low despite a high PSA or PSAD (Figure 5.15, Figure 5.16). The predicted probability of cancer categorized by age also appeared to be affected/modified by PRS (Figure 5.11). Age, as well as PSA is a known risk factor PrCa detection. In older men, the predicted probability was lower in men with a low PRS than those with a high PRS. If these findings remained true in a large and powered cohort, future research could establish if men despite known risk factors being present (i.e. older age) could avoid diagnostic intervention to detect PrCa if their PRS was low enough.

5.6.2 MRI & PRS

The average probability of significant cancer detection in men with a PiRADS 1-3 MRI was 0.02% at the lowest PRS and 22% at the highest. The predicted probabilities were generally higher than in those previously described with a PiRADS 1-2 MRI, which is likely accounted for by the inclusion of PiRADS 3 MRIs (27% of all significant cancers occurred in men with a PiRADS 3 lesion).

For men with a PiRADS 4-5 MRI, the average probability of clinically significant cancer detection was not high (2-17%) in men with a PRS in the lower risk end, and was 39-67% in men with a 'higher' PRS (according to a logistic regression model). In all cases of significant cancer (n=11), 63.64% occurred in men in the top 20% of polygenic risk; of all cases of significant cancer, this was the same for a PiRADS 4-5 MRI (i.e 63.64% occurred in men with a PiRADS 4-5 MRI).

The performance of an 'abnormal' MRI alone in clinically significant cancer detection (AUC 0.83) was improved by the addition of PRS in a logistic regression model (AUC 0.90). Given that in this cohort, 27.27% of significant cancers detected were in men with a PiRADS 3 MRI (54.5% PiRADS 4 and 9.09% PiRADS 5), it would seem sensible to include PiRADS 3 lesions in any definition of 'abnormal' in this cohort as opposed to equivocal (the AUC of a PiRADS 4-5 MRI alone in significant cancer detection was lower at 0.79).

Not all 'abnormal' MRIs yielded significant cancer. In the 121 men described in this chapter; 15% of PiRADS 3 MRIs revealed clinically significant cancer, 35.5% of PiRADS 4 and 50% of PiRADS 5 (these numbers are significantly lower than described in PROMIS data). Overall, approximately 25% of men with either insignificant or no cancer had an abnormal MRI or were 'overcalled'. This has implications when offering (for example) a young man with a FH of PrCa a prostate biopsy based on a PiRADS 3-5 MRI and counselling him about the likelihood of low-grade cancer detection and the impact this may have on many aspects of his life including a possible long period of surveillence with repeat biopsies, multiple MRIs and a formal diagnosis of cancer..

Precise clinical factors influencing this are unknown. Inter-observer and intra-observer variability of MRI reporting and inaccurate biopsy sampling during lesion targeting are likely to play a role. The interplay between clinical information such as age, PSA and PRS and the radiological ruling 'in' or 'out' of PrCa is therefore likely to be important in (1) deciding if a primary biopsy simply may have missed the target or (2) biologically the tissue is more likely to be benign due to a low PRS/PSA/young age in combination with MRI findings. A combination approach of informing an MRI result with PRS and age for example, could be helpful in decision to perform a second prostate biopsy, or perform closer (or less) frequent PSA screening. This could have an impact on decisions as to when to screen; for example men ≥60 but with a low PRS could avoid immediate intervention/biopsy whereas men of the same age but with a high PRS may wish to undergo further investigations sooner.

For men with a PiRADS 1-2 MRI, the probability of clinically significant cancer at a high PRS was low. For men with a PiRADS 3-5 MRI, at low levels of PRS there was a lower predicted cancer probability (0-18%) compared to those at the higher end of the PRS scale (30-75%). At present, this is the first analysis investigating PRS in a population selected for FH of PrCa and exploring its utility in targeted PrCa screening. Although clearly larger numbers are required to evaluate further, PRS may be able to play a role in improving the pathway for men undergoing mpMRI in the modern diagnostic era.

These early findings may indicate that men with an abnormal MRI with a low PRS do not have the same risk of clinically significant cancer as men with an abnormal MRI and a high PRS. A specific area of interest to evaluate further would be the role of PRS in determining the need for prostate biopsy and the likely yield of significant cancer in men specifically with PiRADS 3 lesions which at present commonly yield low to low-moderate cancer diagnoses.

5.7 Limitations

The small number of men with clinically significant PrCa (n=11) and incomplete genotyping data for all men with available MRI and prostate biopsy results (n=121) in this analysis limits any conclusions and recommendations at present regarding any of the significant associations found between PRS and outcome of clinically significant cancer in men with a FH of PrCa undergoing targeted screening. Our early findings of an association of PRS with clinically significant cancer and a greater likelihood of significant disease in men with PiRADS 3-5 lesions will need further re-examination in a larger dataset and with an up to date SNP assay taking into account new variants discovered prior to finishing this interim analysis.

5.8 Conclusions

PRS is associated with cancer detection in men undergoing targeted screening, in particular in men in the top 20% of polygenic risk. This may be important as at present studies using PRS to stratify populations often only consider the top 10% of the PRS for intensive screening; this is the case in our unit's BARCODE 1 study and would have implications for expanding this study intervention to the top 20% of the PRS distribution. A greater-powered sample size will also enable a finer examination of the top 10% and top 1%, to further gauge the risk in this group. PRS appeared to modify the predicted probability of both any and significant cancer detection according to mpMRI and age, suggesting, for example, that there are subtle factors within the MRI risk profile which can further risk stratify men to low or high risk for PrCa detection. Future work should aim to investigate if PRS in combination with MRI could help some men avoid a prostate biopsy and identify who is at the greatest risk of PrCa in those with an abnormal MRI, given the published variation in cancer detection rates.

As described in chapter 4, the Incidence of clinically significant cancer was lower than expected in those with an 'abnormal' MRI, raising the possibility that in this

cohort of young men with relatively low PSAs, PIRADS classification has a propensity to over-call lesions which may appear radiologically more concerning than proven on biopsy. The PiRADS MRI reporting system which is routinely used to report the majority of mpMRIs in the UK, may not be the best platform to assess for radiological evidence of cancer In such men, with other systems such as Likert which takes clinical parameters into account [7].

PRS therefore may be able to play a role in deciphering who will benefit most from no further intervention or prostate biopsy based on the interaction of their PRS and MRI findings.

5.9 References

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5.10 Figures

5.11 Tables

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6 Chapter 6 – Discussion

This thesis reports the main findings of an analysis of clinical variables associated with outcome at prostate biopsy in healthy, unaffected men selected for FH of PrCa undergoing targeted screening in the PROFILE study. Men's germline genetic profile in the form of a PRS based on 130 PrCa risk SNPs and its association with outcome at prostate biopsy is discussed, in addition to the role of pre-biopsy mpMRI and its ability to detect clinically insignificant and significant cancer in the same study population.

Recruitment and study interventions continue for the PROFILE study in the FH cohort, with a full analysis expected once recruitment reaches 350.

The relative findings are discussed below.

6.1.1 PRS

In our cohort, PRS was associated with PrCa detection. When stratified into percentiles (or quintiles) of risk, men in the top 20% had a significantly higher predicted probability of PrCa detection. This association is in keeping with published data ([1-3]. In over 400,000 men (unselected for FH status), data from the UK Biobank showed that a significant proportion of the population can be identified as being at higher risk of PrCa by using a PRS (147 SNPs), with those in the highest quintile of risk having a three-fold greater risk than those in the lowest quintile [4]. Similar to Schumacher et al (RR 2.69), men in our PROFILE analysis in the highest percentiles of risk had a significantly greater risk of PrCa (OR 6.5) with an AUC of 0.70. Results from Sipeky et al [2] also demonstrated the clinical utility of a PRS (55 SNPs) for PrCa risk prediction (OR 2.8) in Finnish men with an AUC of 0.61.

Of note, men were tested for the presence of pathogenic variants in DNA repair genes and were excluded if any were present. Tasa et al investigated the performance of a 121 SNP PRS in an Estonian databank and the UK Biobank. They reported an AUC of 0.63 for any PrCa detection with a HR of 1.65 with similar appearing frequency distribution data to ours (Chapter 5; Figure 5.22 and Figure 5.23) [5]

Our cohort differs generally from those in published studies in that all men had an additional genetic predisposition to PrCa i.e. a FH. There is a lack of suitable studies for direct comparison to ours, investigating the role of a SNP assay to predict PrCa outcome at an MRI-informed prostate biopsy in men **selected** for FH status. Xu et al also described the predictive ability of their (72 SNP) PRS with similar results when adjusting for FH status with a 1.5-3.9-fold increase in odds of PrCa development in 4,372 men in the 2nd-4th quartiles of risk, compared to those in the first quantile [6]. ORs for those with and without a FH of PrCa (any FH, yes or no) were similar (OR 1.9; 95% CI 1.5-2.4; OR 1.65, 95% CI 1.4-1.8 respectively). They reported that FH status did not add predictive or discriminatory power over a PRS.

Compared to our control population of unaffected men, the median PRS in our study population was significantly higher (Chapter 5; Fig 5.1), and appeared to be shifted towards that of the median PRS of a cancer population. This indicates our population is enriched for undiagnosed or 'destined' to be diagnosed cancers (as we know a higher PRS, i.e. above the median is associated with cancer) presumably due to low-penetrance, common PrCa germline risk variants. Sipeky et al described a third of their cases of PrCa occurring in men in the highest quartile of risk, and also described 75.4% of their cohort with metastatic disease had a PRS above the control median. Our cohort had no metastases, and we found 64% of all significant cancers occurred in men with a PRS in the top 20% (Chapter 5; Figure 5.9), with an OR of 3.9 for significant cancer (PRS as a continuous variable; Chapter 3; Table 3.2), or an OR of 7.6 if men were in the top 20% of polygenic risk (Chapter 5; Table 3.2) compared with men with a PRS below the 80th centile. Our AUC for clinically significant cancer detection was 0.72 (Chapter 3; Table 3.3).

There is not yet a widely accepted set of unique SNPs or SNP that is convincingly associated with the prediction of clinically significant or lethal PrCa exclusively despite some authors' reports. Siebert et al reported an association with men in the 98th and higher percentile of polygenic hazard score (PHS) calculated from 54 SNPs with aggressive PrCa (HR 2.9) when compared to men with an average PHS (30-70th percentile). They also reported the PPV of PSA rose as the PHS rose [7].

The use of SNPs and/or a PRS is likely to play a part in the future risk stratification of men undergoing assessment or facing PrCa diagnostic procedures. The use of SNPs in breast cancer risk prediction in combination with mammography has been shown to improve case identification [8] and is under investigation as part of a PRS-based breast cancer screening program in the PROCAS, WISDOM and CORDIS trials [9, 10] .

Men with abnormal MRIs did not all have the same risk of cancer when other variables were examined into a model. PRS in addition to MRI in a logistic regression model for the predicted probability of clinically significant cancer performed well with OR of 28.6 and 3.65 respectively (Chapter 5, Table 5.2) and an AUC of 0.90 (Chapter 5, Table 5.5). In the presence of an abnormal MRI, men at the low end of the PRS scale did not have the same predicated probability of cancer as those with a high PRS i.e. if this finding is replicated in a large dataset this could mean men's risk of cancer as dictated by their MRI can be further informed by a PRS and men with an abnormal MRI but a 'reassuring' PRS may be able to avoid or defer biopsy.

When I examined the predicted probability of cancer in a logistic regression model adding MRI and age to PRS, I found that PRS drew out men at higher risk who have other 'normalising' or reassuring features such as a PiRADS 1-2 MRI and young age (Chapter 5; Figure 5.20) . Men with an abnormal MRI were also found to have differing probabilities of cancer detected depending on their PRS and age. For example, men with an abnormal MRI, a high PRS and older age had a significantly different risk than men with an abnormal MRI but with a low PRS (Chapter 5; Figure 5.20).

Clearly a much larger and population level study, the STHLM3-MRI trial (which randomized 2,293 healthy men to undergo a PSA or STHLM3 test, with FH status incorporated into the STHLM3 test result) provides a practical and large scale comparison to the theme within the PROFILE study, of incorporating risk factors into a model with MRI in aiming to improve both PrCa diagnostic accuracy and deciding if a test incorporating genetic information can usefully risk stratify men. The STHLM3-MRI study is described further below.

6.1.2 MRI

We found no clinically significant cancers in men with a PSA <1.0ng and a normal MRI, indicating a potential role for such criteria in risk stratifying men presenting for PrCa screening with a FH. This would support the findings by Lilja et al that a PSA of <1ng/ml at < 60 years is predictive of a low risk of clinically significant PrCa [11].

Age remained a significant factor, with 32% of all men aged ≥-60 biopsied in our cohort having clinically significant PrCa compared with 2% of those aged 40-49. An abnormal MRI (PiRADS 3-5) was more common in men aged 60 or older (50%) than those aged 40-49 (21.6%), and of those aged ≥60 with clinically significant cancer, 88% had an abnormal MRI.

In men selected for other genetic predispositions (i.e *BRCA1/2* status), screening algorithms/protocols often involve up front MRI. Margel et al recruited 185 men to undergo screening PSA, DRE and MRI. They reported a PPV of 24% and found few MRIs detected cancers in men younger than 50 [12]. In their later analysis using multiple specific screening strategies [13], they reported 57% of all screened participants had either an abnormal PSA or MRI, of which 85% underwent prostate biopsy. Their findings of lower numbers of PiRADS 5 lesions (3%), lower numbers of MRI abnormalities in those aged 40-50 and low median PSA (1.0ng/ml) and prostate volume (30mls) were similar to ours. They found that among men younger than 55, PSA values were low and not useful for (any) cancer prediction with MRI having the

highest net benefit. However, in older patients, PSA triaging before MRI was better than MRI alone.

An interesting MRI analysis in young men by Gielchinsky et al is important to discuss in light of our findings. They found a lower sensitivity of PiRADS 4-5 MRI for clinically significant cancer detection in younger men (median age 47) compared to older (median age 62) men (49% vs 72.5%) [14].

In a similar vein but in a much larger cohort, Stabile et al reported the performance of MRI in significant cancer detection according to age in 930 men. In men <50 years old, they found the performance of systematic prostate biopsy had a higher yield for significant PrCa detection than (PiRADS reported) MRI-targeted biopsies reflecting a lower accuracy of MRI in younger men [15].

For clinically significant PrCa, the NPV of an abnormal MRI (PiRADS 3-5) in our cohort was high (99%) but PPV low (25%) (Chapter 3, Table 3.3). We found different biopsy/histology characteristics in PIRADS 3 lesions in this cohort of men compared to PROMIS data. This raises the question whether young men with small prostates and low PSAs should be subject to the same reporting system used for men with suspicious features. In a LR model including PRS the PPV of MRI was increased to 60% with an AUC of 0.90.

In this cohort, the frequency of PiRADS 5 MRI was low. This is not unexpected given we invited healthy men with no suspicion of PrCa for study recruitment. When Nam et al performed a pilot study evaluating MRI in the general population as a PrCa screening tool in 50 men, the frequency of PiRADS 5 MRI was 21%, with a median PSA of 3.03ng/ml, median age of 61 and mean prostate volume of 52.2cc [16].

In the UK, Eldred-Evans et al performed an imaging-based screening study in 408 men ('The IP1-PROSTAGRAM Study'). They reported that 17.7% of men screened from the general population had a PiRADS 3-5 MRI, at a 10% FH rate of PrCa in a FDR [17].

The frequency of significant cancer in those with PiRADS 3-5 MRIs was also lower than 'expected' compared to PROMIS data. If this is not a finding simply affected by

our cohort size, this may indicate other clinical features play a part i.e. the PiRADS classification system may have a lower or more limited ability to detect cancer in this population (i.e young men, smaller prostates, lower PSAs, 'young tissue') and tests such as PRS may assist in identifying men at risk of cancer in addition to MRI. A larger cohort size will help answer this question.

Our data eventually may provide a valuable insight into the 'normal' radiological appearances of young, unaffected men with a genetic predisposition to PrCa due to a FH. This may in time become a group who increasingly may wish to explore PrCa screening options undoubtedly of which MRI will feature. Current MRI reporting tools such as PiRADS as described, have traditionally been used and reported in men with a clinical suspicion of PrCa, either with a significantly raised PSA, and or an abnormal DRE and often at an older age. Our cohort of men with both an MRI and biopsy provides valuable information as to how a PiRADS reported MRI correlates with biopsy outcome in this unique group of men. Our MRI data also may complement that of the REIMAGINE (NCT04063566) MRI data, where Emberton & colleagues will screen 300 healthy men in the community with bi-parametric MRI instead of PSA and assess the feasibility of such a screening approach, alongside the ability of MRI to detect cancers in unaffected, PSA-naïve men.

6.2 Future Work

6.2.1 Stockholm3

The Stockholm 3 (STHLM3) study group reported their model's ability to reduce the amount of unnecessary prostate biopsies [18] whilst still detecting clinically significant PrCa. The STHLM3 test is a blood test including clinical markers (PSA, free PSA, intact PSA, hK2, MSMB, MIC1), SNPs and clinical information regarding DRE, age, prior biopsy and FH status. It has reported higher sensitivity and specificity than PSA [19]. In a community based study, investigators recommended GPs in the Stavanger region of Norway to change from PSA to the STHLM3 test. They reported the implementation of the test in primary care as a new tool for PrCa

detection was feasible, reduced onward urology referrals by 28% and increased the proportion of clinically significant cancer detected by 23% [20]. The STHLM3 test is being prospectively evaluated in a multi-ethnic cohort (SEPTA trial) in Chicago (NCT04583072) and is also being evaluated in a pathway incorporating MRI in the STHLM3MRI study, which combines a paired and randomized study design [21], the results of which have recently been published [22].

Nordstrom & colleagues reported that compared to screening for PrCa using PSA and systematic biopsies, the STHLM3 test combined with MRI-targeted biopsies with associated systematic biopsies was associated with 69 percent fewer low-grade cancers (95%CI 52-80; 45 vs 142 per 10,000 tested men) and 52 percent fewer biopsies (95%CI 43-58; 409 vs 853 per 10,000 tested men) when compared to PSA screening followed by systematic biopsy . This test combination shows significant promise for minimising the risk of cancer overdetection with its associated harms of overtreatment whilst still detecting clinically significant disease.

6.2.2 New Risk Stratification Pathways

An ‘MRI only’ pathway is appealing; in so far as it allows men (in whom anxiety regarding prostate biopsy is not uncommon) to avoid a prostate biopsy if their risk is deemed low enough. Questions beyond this, regarding intensity of further screening if the initial screen test is negative remain unanswered. Dahut et al describe a PrCa screening protocol targeted to men with pathogenic variants in known or suspected high-penetrance cancer predisposition genes i.e. *BRCA2* [23]. They will screen 500 men with upfront mpMRI, (age-defined) PSA and DRE with repeat screening interventions every two years or as clinically dictated (aged 30 – 49 PSA threshold <2.0ng/ml, aged 50-75 PSA threshold >2.5ng/ml).

Given the seemingly different characteristics of prostate biopsy histology in young men with ‘equivocal’ MRIs as demonstrated in our cohort and others ([14, 24]), future work should focus on elucidating the unique radiological appearances of ‘young’ prostates, considering how this can inform newer, updated versions of our lesion

scoring systems (PiRADS/Likert) and consider redefining PiRADS 3 lesions in such men from equivocal to suspicious. Our unique cohort of young men in the FH cohort presents a good opportunity to assess the performance of MRI in young men in addition to those having repeat MRI and biopsy.

Using a PRS as an initial risk stratification tool to help identify which men may benefit from intervention if their risk of cancer is sufficiently high is attractive. This represents a one off, safe intervention and with potentially large cost benefits given the rapidly reducing cost of sequencing technology. Other tumour sites, i.e. breast are presently incorporating PRS into screening programs in the PROCAS, CORDIS and WISDOM trials. For example, the BOADICEA risk prediction model which incorporates 313 breast cancer risk SNPs, risk-stratifies women and provides individualised risk to aid clinical decision making, and provides a better level of risk stratification than mammography schedules dictated by age alone [25] [26]. The most up to date guidance from the NCCN regarding early detection of PrCa recommends high risk monogene mutation panel testing for men with a FH of PrCa fulfilling specific criteria [27] [28], but no recommendation for screening/risk stratifying men based on SNP testing exists.

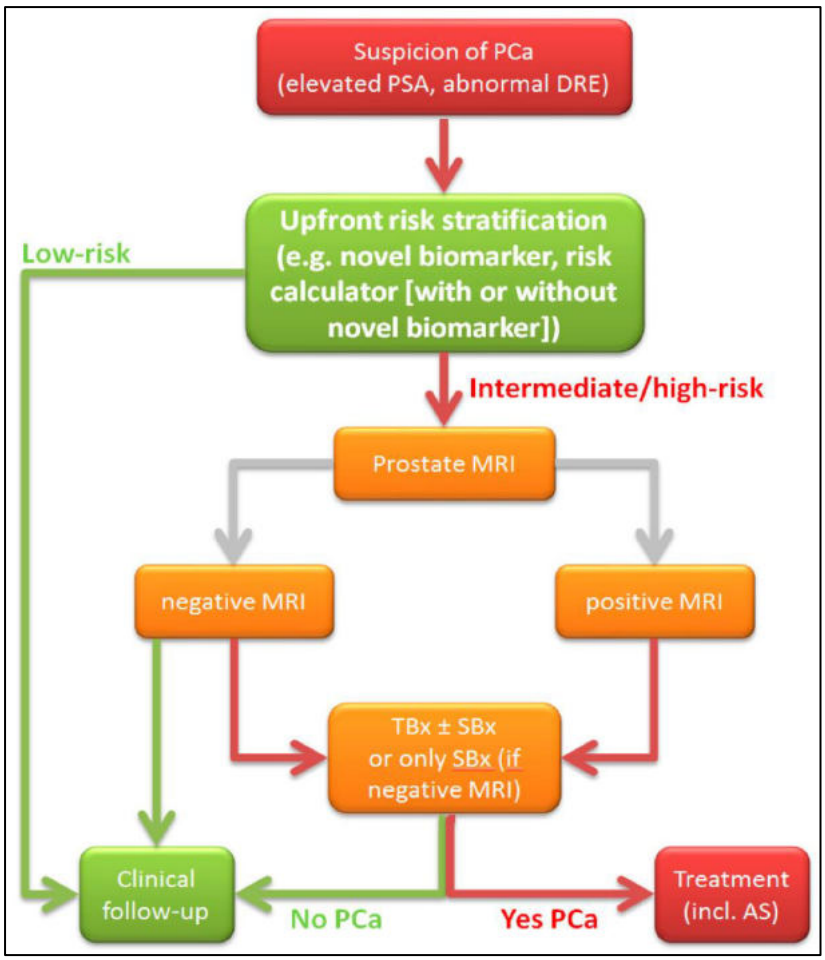

Figure 6.1 Flowchart proposing a workflow for risk stratification of men with a clinical suspicion of PrCa incorporating risk calculators and MRI after the point of aligning men into a risk category (reproduced from Osses et al) [29].

Alberts et al incorporated mpMRI into the ERSPC risk calculator (RC) and reported a higher AUC (0.84) for high-grade PrCa when including PiRADS score from a pre-biopsy mpMRI compared to ERSPC RC alone (AUC 0.76) [30], however FH status was not included in their model.

MRI as part of a risk-prediction model alongside novel liquid biomarkers (i.e. Prostate Health Index/PHI) has also been investigated by Druskin et al [31]. They reported that of the 104 men who underwent MRI, PiRADS score was complementary to PHI, with a PiRADS score ≥3 or, if PiRADS score ≤2, a PHI ≥0.44, detecting 100% of clinically significant disease.

6.2.3 Other high-risk groups

The work of the PROFILE study can also be extrapolated to other high-risk groups such as men of African ancestry (provided the PRS is ancestry-appropriate) or men with pathogenic variants in DNA damage-repair genes. Future work includes extending the PROFILE protocol of mpMRI and SNP analysis to men of African ancestry with a separate analysis and a unique, ethnically-appropriate SNP assay incorporating PrCa SNPs specific to this population of men generated from GWAS in African populations [32, 33], i.e. the risk variant at 8q24, rs72725854 described by Darst [34] and at 17q21 as described by Haiman [35]. Conti et al recently reported the results of a multi-ethnic GWAS [36]. This multi-ancestry analysis discovered 86 new genetic risk variants independently associated with PrCa risk, with different genetic risk scores (GRS) depending on whether men were of Asian, African or European ancestry. This brings the total known number of PrCa risk SNPs to 269.

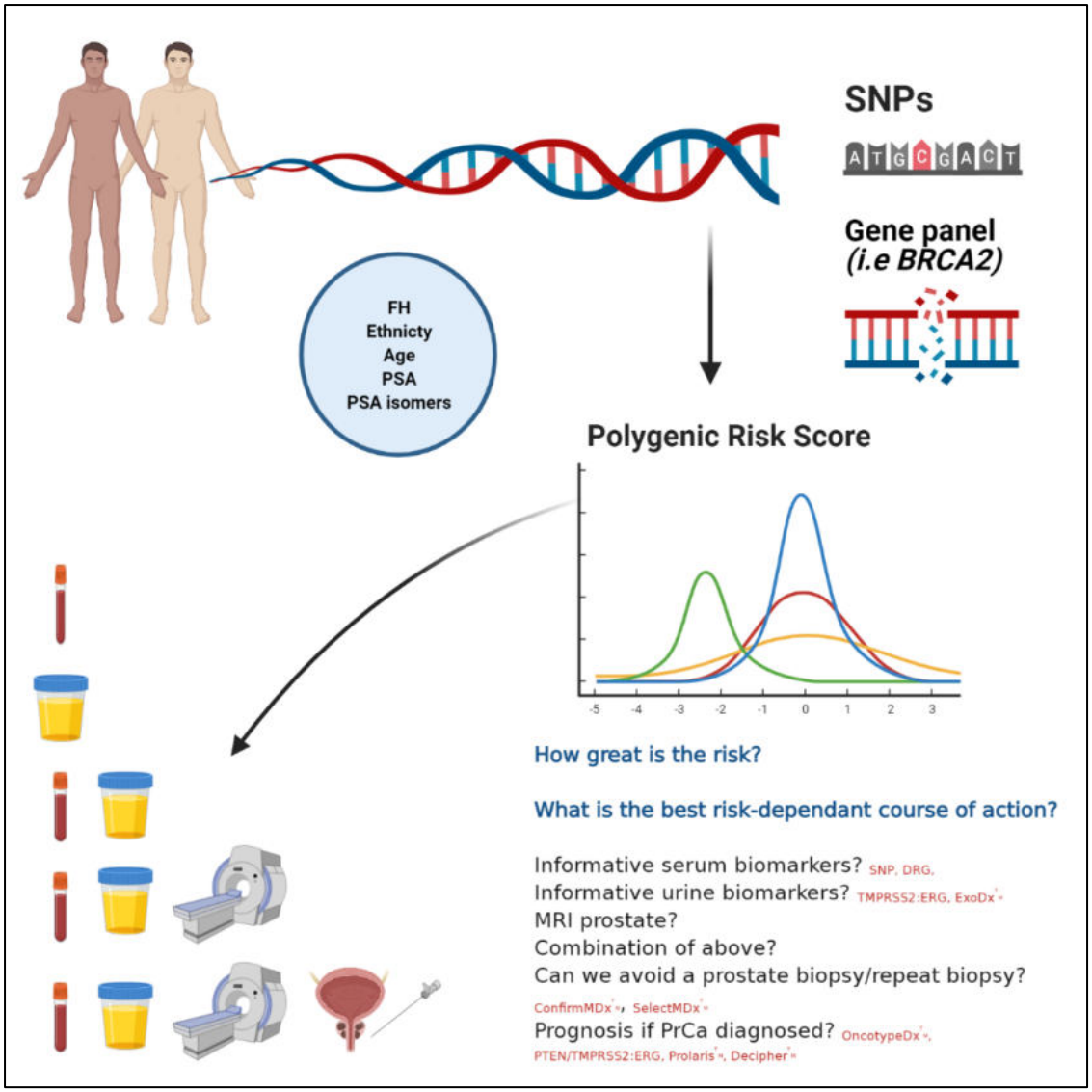

Figure 6.2 My diagram of a potential sequence of tools used in early PrCa detection in men with a suspected genetic predisposition to PrCa. Text in red names specific genomic informative tests (prolaris, decipher, Oncotype Dx, ConfirmMDx, TMPRSS2:ERG, ExoDx and DRG = Damage Repair Genes

6.3 Limitations

6.3.1 Sample Size

The PROFILE protocol lists the expected population detection rate of PrCa of 3% (amongst other studies, Sun et al showed that 4.4% of men <50 years ol have PrCa) [37]) with an expected RR of 2 (at least) for those with a FH of PrCa . For 80% power at a 5% significance level, this requires a sample size of 318 men, with the overall aim of 350 decided to allow for drop out.

Assessing the sample size of our cohort of men for analysis in this thesis (n=135 who underwent biopsy) means our analysis is underpowered for investigating the association of PRS and MRI with outcome at prostate biopsy, with a power calculated of 0.5259.

6.3.2 Study design Cohort

A direct comparison group unselected for FH (age matched) undergoing the same interventional protocol would have allowed us to truly compare any differences in MRI and PRS utility, MRI performance and cancer detection by PiRADS, In addition, an entirely PSA-Naïve study cohort would have allowed for the examination of MRI as a screening tool in this cohort.

6.3.3 PRS

Limitations of PRS at present include their use in determining risk of aggressive, life-limiting disease. As yet, there is no clear confirmed association between any specific risk-loci and risk of lethal PrCa and the PRS predicts overall disease. Also, a high risk score does not mean that a person will definitely develop a condition, and a low score does not mean that disease cannot occur. PRS scores, although informative,

are not diagnostic. They provide an individualised, estimated risk of disease occurrence relative to the general population, but do not provide information on when (i.e. at the time of genotyping) a man will develop PrCa if he is 'high risk' or whether he currently harbours it. The accuracy of PRS is diminished in individuals not from the same ancestral population as that in which the score was developed (most risk loci have been discovered from large GWAS in mainly European – origin populations). Our study assay is likely to require 'updating' in the near future to incorporate SNP profiles relevant to groups of other ancestries.

6.3.4 MRI

MRI as a diagnostic tool has not been extensively studied in young men with low PSAs, without a clinical suspicion of PrCa, or at a low PSA. MRI has not been extensively studied (yet) as a screening tool in unaffected, healthy men, and results of the REIMAGINE study will inform us of the usefulness and cancer detection rate of MRI in this setting. The PiRADS scoring system (version 1) of cancer suspicion was developed in 2012 by a European Society of Urological Radiology (ESUR) working group [38], with evidence underpinning the recommendations based on mpMRI studies in men with PrCa, radical prostatectomy specimens or in men with a clinical suspicion of PrCa due to either a raised PSA or abnormal DRE [39] [40, 41]. Version 2 has since superseded PiRADS V1 [42]. The small number of PiRADS 5 MRIs in our sample size also limits our ability to assess the cancer detection rate of PiRADS 5 scored MRIs in this cohort.

6.4 Conclusions

We have shown that PRS and MRI show early promise in cancer detection, and have the potential to inform a modern risk-stratification strategy for men with a genetic predisposition to PrCa which could also be expanded to men in the general population. We have also described the favourable NPV of mpMRI, but its lower PPV of PiRADS reported mpMRI in young men and the possibility of 'overcalling' lesions.

Despite modernisation of prostate biopsy in the form of LATP techniques, availability of fusion technology and the improved safety profile compared to TRUS, hesitation amongst men undergoing prostate biopsy is common. Clear risk-adapted screening protocols for men with a FH of PrCa which avoid unnecessary biopsies are required (Figure 6.1, Figure 6.2). When a biopsy is advised, systematic sampling is still likely to be required given the lack of certainty regarding safety in practising target-only biopsies in this population (entirely selected for FH status, in contrast to the populations studied in PRECISION [43]), given the occasional propensity for MRI to miss clinically significant cancer [44]. However, in our cohort - the likelihood of detecting insignificant PrCa during systematic sampling was not negligible (44% and 19% of PiRADS 1 & PiRADS 2 MRIs yielded insignificant cancer respectively) and so adjunct tests to inform MRI will be helpful in this space to minimise overdetection.

Long-term follow-up of PROFLE participants will allow for knowledge on the natural history of men with a FH of PrCa, and the role of PSA and MRI in the detection of PrCa in this cohort. Long-term follow-up will also allow for a further analysis of impact of PRS on cancer detection over time and the role of repeat MRI in this population. More intelligent screening, use of risk stratification tools, more accurate diagnostics will allow for a safer, more effective pathway for PrCa patients, minimising screening, overdiagnosis and overtreatment harms. The PROFILE study contributes to this effort and a fully powered analysis of the performance of PRS and mpMRI in cancer detection will move PrCa early detection further forward into the personalised medicine era.

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6.6 Table of Figures

Appendix Chapter 2

The PROFILE study: Germline genetic profiling: correlation with targeted prostate cancer screening and treatment

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1. Background

Introduction – the genetics of prostate cancer

Prostate cancer (PrCa) is now the commonest cancer in men in the Western world, with over 49,000 new cases per annum and a lifetime risk of 1 in 11 in the United Kingdom (UK) (Cancer Research UK CancerStats, 2012). However, its aetiology remains very poorly understood. The substantial worldwide variation in incidence rates suggests that lifestyle risk factors are important. To date, however, no definite lifestyle risk factors have been identified.

Aside from demographic factors, the only well established risk factor for PrCa is family history. Genetic studies, in particular genome-wide association analyses have identified over 70 genetic variants associated with PrCa risk, (reviewed in Goh et al, 2012; Eeles et al 2013). The risk of the disease in first degree relatives of cases is approximately twice that in the general population (Carter et al., 1992; Goldgar et al., 1994; Eeles et al., 1999; Hemminki et al., 2002; Gronberg 2003; Edwards and Eeles, 2004). This familial risk is greater amongst young cases, being more than fourfold for cases below age 60. Higher risks have been shown for men with two or more affected relatives. There is a higher risk in Afro-Caribbeans who have a 2.87-3.19-fold increased risk compared with whites in the UK (Ben-Shlomo et al, 2008). Analyses based on the Nordic twin registries have found higher risks in monozygotic than dizygotic twins, supporting the hypothesis that much of this familial aggregation is due to genetic rather than shared lifestyle factors (Lichtenstein et al., 2000).

Genetic predisposition arises from rare highly-penetrant mutations, and/or from common variants conferring more moderate risks. We, and others, have found the former using direct candidate gene mutation analysis (e.g. Dong et al., 2003; Edwards et al., 2003, 2012; Guisti et al 2003; Cybulski et al., 2004; Kote-Jarai et al., 2011; Leongamornlert et al., 2012). Sequencing of a linkage region on 17q has revealed a high risk PrCa predisposition gene, *HOXB13* which has a relative risk of 4-20 in families and is present in about 3.4% of European populations. (Ewing et al, 2012; Zu et al, 2012; Witte et al, 2013). Genome-wide association studies (GWAS) identify common variants, present in >5% of the population. In GWAS, susceptibility variants [usually single nucleotide polymorphisms (SNPs)] are identified by finding a difference in genotype frequency between cases and controls.

The total number of PrCa susceptibility alleles reported to date from GWAS is shown in Table 1. It is very likely that further low penetrance, common PrCa susceptibility loci will be reported in the next 18 months since (i) GWAS meta analyses are planned over this time and may yield further hits; (ii) further follow up genotyping is planned (The Oncoarray GAME-ON initiative) in both our sample sets and others, some of which are in ethnic minority groups which have to date been only sparsely studied.

Based on the estimated relative risks of currently known SNPs (Table 1), approximately 30% of the familial risk of PrCa can now be explained and the top 1% of the risk profile has a 4.7-fold risk compared with the average of the population.

It is estimated that nearly 2000 SNPs may be associated with PrCa risk (Eeles et al., Nature Genetics 2013) and the proposed Oncoarray initiative which will run 600 000 SNPs in 80 000 PrCa blood DNA samples and controls (cases:controls in a 3:1 ratio) is likely to find further hits.

Table 1. Common susceptibility loci for prostate cancer identified through GWAS; Goh et al., 2012 and Eeles et al, Nat Genetics 2013

Locus	SNP	Ref Allele	Effect Allele	Effect allele frequency*	Per allele OR*	Nearby genes
1q21	rs1218582	A	G	0.45	1.06 (1.03-1.09)	*KCNN3*
1q32	rs4245739	A	C	0.25	0.91 (0.88-0.95)	*MDM4, PIK3C2B*
2p11	rs10187424	A	G	0.41	0.92 (0.89-0.94)	*GGCX/VAMP8*
2p15	rs721048	G	A	0.19	1.15 (1.10-1.21)	*EHBP1*
2p21	rs1465618	G	A	0.23	1.08 (1.03-1.12)	*THADA*
2p24	rs13385191	A	G	0.56	1.15 (1.10-1.21)	*C2orf43*
2p25	rs11902236	G	A	0.27	1.07 (1.03-1.10)	*TAF1B:GRHL1*
2q31	rs12621278	A	G	0.06	0.75 (0.70-0.80)	*ITGA6*
2q37	rs2292884	A	G	0.25	1.14 (1.09-1.19)	*MLPH*
2q37	rs3771570	G	A	0.15	1.12 (1.08-1.17)	*FARP2*
3p11	rs2055109	T	C	0.9	1.20 (1.13-1.29)	
3p12	rs2660753	C	T	0.11	1.18 (1.06-1.31)	
3q13	rs7611694	A	C	0.41	0.91 (0.88-0.93)	*SIDT1*
3q21	rs10934853	C	A	0.28	1.12 (1.08-1.16)	*EEFSEC*
3q23	rs6763931	C	T	0.45	1.04 (1.01-1.07)	*ZBTB38*
3q26	rs10936632	A	C	0.48	0.90 (0.88-0.93)	*CLDN11/SKIL*
4q13	rs1894292	G	A	0.48	0.91 (0.89-0.94)	*AFM, RASSF6*
4q22	rs17021918	C	T	0.34	0.90 (0.87-0.93)	*PDLIM5*
4q22	rs12500426	C	A	0.46	1.08 (1.05-1.12)	*PDLIM5*
4q24	rs7679673	C	A	0.45	0.91 (0.88-0.94)	*TET2*
5p12	rs2121875	T	G	0.34	1.05 (1.02-1.08)	*FGF10*
5p15	rs2242652	G	A	0.19	0.87 (0.84-0.90)	*TERT*
5p15	rs12653946	C	T	0.44	1.26 (1.20-1.33)	*IRX4*
5q35	rs6869841	G	A	0.21	1.07 (1.04-1.11)	*FAM44B (BOD1)*
6p21	rs130067	T	G	0.21	1.05 (1.02-1.09)	*CCHCR1*
6p21	rs1983891	C	T	0.41	1.15 (1.09-1.21)	*FOXP4*
6p21	rs3096702	G	A	0.4	1.07 (1.04-1.10)	*NOTCH4*
6p21	rs2273669	A	G	0.15	1.07 (1.03-1.11)	*ARMC2, SESN1*
6q22	rs339331	C	T	0.63	1.22 (1.15-1.28)	*RFX6*

6q25	rs9364554	C	T	0.29	1.17 (1.08-1.26)	*SLC22A3*
6q25	rs1933488	A	G	0.41	0.89 (0.87-0.92)	*RSG17*
7p15	rs10486567	A	G	0.77	0.74 (0.66-0.83)	*JAZF1*
7p21	rs12155172	G	A	0.23	1.11 (1.07-1.15)	*SP8*
7q21	rs6465657	T	C	0.46	1.12 (1.05-1.20)	*LMTK2*
8p21	rs2928679	C	T	0.42	1.05 (1.01-1.09)	*SLC25A37*
8p21	rs1512268	G	A	0.45	1.18 (1.14-1.22)	*NKX3.1*
8p21	rs11135910	G	A	0.16	1.11 (1.07-1.16)	*EBF2*
8q24	rs1447295	C	A	0.13	1.62	
8q24	rs6983267	T	G	0.5	1.26 (1.13-1.41)	
8q24	rs16901979	C	A	0.09	1.79 (1.36-2.34)	
8q24	rs10086908	T	C	0.3	0.87 (0.81-0.94)	
8q24	rs12543663	A	C	0.31	1.08 (1.00-1.16)	
8q24	rs620861	C	T	0.39	0.90 (0.84-0.96)	
9q31	rs817826	T	C	0.08	1.41 (1.29-1.54)	*RAD23B-KLF4*
9q33	rs1571801	C	A	0.25	1.27 (1.10-1.48)	*DAB21P*
10q11	rs10993994	C	T	0.4	1.25 (1.17-1.34)	*MSMB*
10q24	rs3850699	A	G	0.29	0.91 (0.89-0.94)	*TRIM8*
10q26	rs4962416	T	C	0.27	1.20 (1.07-1.34)	*CTBP2*
10q26	rs2252004	T	G	0.77	1.16 (1.10-1.22)	
11p15	rs7127900	G	A	0.2	1.22 (1.17-1.27)	
11q12	rs1938781	T	C	0.3	1.16 (1.11-1.21)	*FAM111A*
11q13	rs7931342	G	T	0.49	0.84 (0.79-0.90)	
11q22	rs11568818	A	G	0.44	0.91 (0.88-0.94)	*MMP7*
12q13	rs10875943	T	C	0.31	1.07 (1.04-1.10)	*TUBA1C/PRPH*
12q13	rs902774	G	A	0.15	1.17 (1.11-1.24)	*KRT8*
12q24	rs1270884	G	A	0.49	1.07 (1.04-1.10)	*TBX5*
13q22	rs9600079	G	T	0.38	1.18 (1.12-1.24)	
14q22	rs8008270	G	A	0.18	0.89 (0.86-0.93)	*FERMT2*
14q24	rs7141529	A	G	0.5	1.09 (1.06-1.12)	*RAD51L1*
17p13	rs684232	A	G	0.36	1.10 (1.07-1.14)	*VPS53, FAM57A*
17q12	rs4430796	G	A	0.49	1.22 (1.15-1.30)	*HNF1B*

17q12	rs11649743	A	G	0.8	1.28 (1.07-1.52)	*HNF1B*
17q21	rs7210100	A	G	0.05	1.51 (1.35-1.69)	*ZNF652*
17q21	rs11650494	G	A	0.08	1.15 (1.09-1.22)	*HOXB13, SPOP*
17q24	rs1859962	T	G	0.46	1.20 (1.14-1.27)	
18q23	rs7241993	G	A	0.3	0.92 (0.89-0.95)	*SALL3*
19q13	rs2735839	G	A	0.15	0.83 (0.75-0.91)	*KLK2/KLK3*
19q13	rs8102476	T	C	0.54	1.12 (1.08-1.15)	
19q13	rs11672691	G	A	0.76	1.12 (1.03-1.21)	
19q13	rs103294	T	C	0.24	1.28 (1.21-1.36)	*LILRA3*
20q13	rs2427345	G	A	0.37	0.94 (0.91-0.97)	*GATAS, CABLES2*
20q13	rs6062509	A	C	0.3	0.89 (0.66-0.92)	*ZGPAT*
22q13	rs5759167	G	T	0.47	0.86 (0.83-0.88)	*BIL/TTLL1*
Xp11	rs5945619	T	C	0.36	1.19 (1.07-1.31)	*NUDT11*
Xp22	rs2405942	A	G	0.21	0.88 (0.83-0.92)	*SHROOM2*
Xq12	rs5919432	A	G	0.19	0.94 (0.89-0.98)	*AR*

*Data for Effect allele frequency and per allele OR (odds ratio) are taken from the original publications. 95% confidence intervals are given in brackets where available.

These results may have clinical implications for targeted screening and there are also potential implications for risk counselling. Individually each SNP confers a modest effect on relative risk, however, the combined effects of these SNPs are thought to be multiplicative and therefore may be substantial, and as other SNPs are identified it may be possible to define genotypes that are sufficiently predictive of risk to be useful clinically. MacInnis et al., (2011) have described a model – the P model, which incorporates SNP data and family history. Antoniou (*personal communication*) has modelled lifetime risks from family history alone and then considered the additional effects of SNP profiling. This shows that an unaffected man aged 50 years with a father who had PrCa diagnosed at age 60 would have a lifetime risk of 22% and this rises to just over 55% if a 27 SNP profile is added to the model. Similar results have been reported in data from the PLCO and Swedish prostate screening studies using data from 5 and 14 alleles (Zheng et al., 2008; Sun et al., 2008; Xu et al., 2009).

Such SNP profiles have already been modelled for use to target ages at which to start breast cancer mammographic screening (Pharoah et al., 2008). In men, where there is more doubt about which populations to target for PSA screening, it is possible that SNP profiling may be of even more use in planning targeted screening by identifying whom to biopsy. It has been suggested that SNP profiling in other common cancers may be used to modify screening protocols (Pharoah et al, 2008) and modelling has shown that SNP profiling could target screening for PrCa and reduce unnecessary screens and be economically viable (Pashayan et al., 2011). A study from Sweden has suggested a similar result (Aly et al., 2011).

Rare genetic variants

Over the last few years, evidence has grown for the role of rarer higher-risk gene mutations (notably in the *BRCA1/2* genes) in PrCa susceptibility. *BRCA2* and other DNA-repair genes are associated with more aggressive disease. Germline *BRCA2* mutations are the genetic events that confer the highest risk of PrCa known to date (8.6-fold in men aged ≤65 years) (Edwards et al., 2003; Kote-Jarai et al., 2011; Chalasani., 1999) whilst the effect of *BRCA1* is relatively modest (3.5-fold) but clinically important. Pathogenic germline mutations in both the *BRCA1* and *BRCA2* genes (particularly *BRCA2*) have been associated with more aggressive disease, and poorer clinical outcomes (Leongamornlert et al., 2014; Carter et al., 2019; Castro et al., 2015; Castro et al., 2015). We have reported that there was no difference in disease outcome after radical prostatectomy in men with or without germline *BRCA* mutations, but a worse outcome in mutation carriers after radical radiotherapy (Castro et al., 2015); and Carter et al. (2019) reported a higher upgrading on re-biopsy in men on active surveillance who have germline mutations in *ATM* or *BRCA1/2* compared with non-carriers (Carter et al., 2019). These high-risk but moderate penetrance genes are likely modified by SNPs and in the future, testing for both common and rare genetic variants will become standard practice.

Recently in the USA, the National Comprehensive Cancer Network (NCCN) introduced guidelines to offer germline genetic testing to men at PrCa diagnosis with high-risk (Gleason >7) and specific family history features or metastatic PrCa (www.nccn.org). Testing recommendations are limited to *BRCA1*, *BRCA2* and *ATM*. Cheng et al have modified these guidelines and suggested offering testing to PrCa patients with any one of the following: known mutation in the family or hereditary breast and ovarian cancer syndrome; metastatic disease; high-risk localised PrCa (Gleason >8, WHO grade group >3, or PSA >20); or those with mutations in hereditary PrCa genes in tumour sequencing (e.g. *BRCA1/2*, *MMR*, *ATM*). Following reports of responses to PARP inhibitors (Pritchard et al., 2016; Mateo et al., 2015), platinum agents and immunotherapy (Mateo et al., 2017) in PrCa patients with germline *BRCA*, *ATM* and *MMR* gene mutations respectively, recommendations to include germline testing for these genes in men with metastatic PrCa are likely to become adopted by the National Genetic Testing Directory (NGTD) over the coming years. Recently, several groups, including our own, have shown that limiting testing to these genes is too narrow; the most commonly mutated genes are *BRCA2*, *ATM*, *HOXB13*, *BRCA1* and *CHEK2*, but we have shown that 14.5% of PrCa cases diagnosed under 60 years of age harbour germline mutations in 23 DNA repair genes (Leongamornlert et al., 2014 and 2019; Mateo et al., 2015). Importantly, previous research from our team shows that defects in DNA repair genes are not only associated with higher rates of PrCa development, but are also associated with a higher probability of nodal disease and metastatic spread at presentation and therefore shorter survival (Chief Medical Officer Annual report 2016). We have shown that a *BRCA2* germline mutation is an independent prognostic factor for this in multivariate analysis (Castro et al., 2013 and 2015). Other groups have shown that mutations in *ATM* also have a poorer prognosis (Carter et al., 2019; Na et al., 2017). There is increasing evidence that mutations in the mis-match repair genes *MSH2*, *MSH6*, and *MLH1* also cause aggressive disease (Page et al., 2019; Kote-Jarai et al., 2011; Castro et al., 2015; Grindedal et al., 2009; Mitra et al., 2011; Bancroft et al., 2014; Barrow et al., 2013).

Genetic testing for germline mutations will therefore have an important role in screening and diagnostics in the future as for men with a high-risk mutation, this would impact on treatment recommendations and improve clinical outcomes. For example, through diverting men with localised disease away from active surveillance to undergo radical curative treatments would reduce the rate of disease progression in men with localised disease. Men with advanced disease could be offered targeted therapies that will reduce toxicities of ineffective therapies, extend survival and improve quality of life.

Prostate Screening

PrCa PSA screening studies of the general population to date have reported conflicting effects on mortality from the disease.

To date there are several population based screening studies which have used a threshold of PSA to determine whether to undertake prostate biopsy (Andriole et al, 2009; Schroder et al, 2009; Hugosson et al, 2010; Schroder et al, 2012). The problem with PSA is that it has false positive and negative outcomes. Two of three of these studies have shown a reduction of mortality from such screening and the study which showed no reduction (PLCO) was from the USA and had a large contamination of screening in the control group. 44% of controls had a PSA prior to entry into the study, therefore a large proportion of participants had been 'pre-screened' (Andriole et al, 2009). However the US and European guidelines are not to offer population PrCa screening as 12-48 men need to be treated to save one life and the attendant morbidities of treatment do not yet justify the benefits (Chou et al, 2011; Heidenreich et al, 2011). This compares with a 3:1 ratio for breast screening which has been adopted in national screening programmes in Europe. We have shown using theoretical modeling that genetic profiling of 27 SNPs in a population rather than the use of an age cut-off of 55 years for PrCa PSA screening would predict that 16% of men could avoid screening at the expense of missing 3% of cases Pashayan et al, 2011). We have undertaken a pilot PROFILE study using primary prostate biopsy (12 core trans-rectal ultrasound biopsy irrespective of PSA in men aged 40-69 years) in 100 men with a family history of PrCa who are at ≥2-fold risk compared with the general population. We have found that they have double the number of clinically significant, (as defined on UK NICE treatment guidelines which determine which PrCas need radical treatment rather than active surveillance), PrCas detected compared with population based PSA screening from the ERSPC trial. There are various risk calculator algorithms associated with the screening and prevention trials, ERSPC and PCPT (Ankerst et al, 2012). We plan to add genetic data to the ERSPC Prostate Cancer Risk Calculator, (www.prostatecancer-riskcalculator.com) and the PCPT trial in our analyses. From such data it is therefore predicted that genetic profiling to guide PrCa screening would result in an improved benefit/risk ratio. It is expected that a more extensive genetic profile such as that now available would improve this benefit further.

We are already conducting a targeted screening study (IMPACT) in men who carry rarer higher risk mutations in the *BRCA1* or *BRCA2* genes and so PROFILE is a natural extension of our work in targeted screening as it will investigate the role of common genetic variant SNP profiling in determining targeted PrCa screening (Mitra et al, 2008; 2011).

The Prostate Cancer Prevention Trial (PCPT) detected PrCa in 22% of men with a PSA between 2.1-3.0ng/ml and 27% of men with PSAs between 3.1-4.0ng/ml ie the normal range (age ranges 62-91; Thompson et al., 2004). This prompted many in the US to suggest lowering the threshold for prostate biopsy to 2.0mg/ml (Thompson, Goodman et al. 2003, Thompson, Pauler et al. 2004, Catalona, Loeb et al. 2006). This was using 6 or more biopsy cores and data suggest that 12 vs 6 cores detect 31% more cancer i.e. in PCPT the figures would raise to 36% and 29% respectively at ages 62-91 (Eichler et al, 2006). We would therefore expect lower detection rates of cancer at younger age groups than this.

The ERSPC study investigators argue against the lowering of this threshold, however, as the interval PrCa rate was low in the ERSPC with a threshold PSA of 3ng/ml (Roobol, Grenabo et al. 2007); they believe that this level of 3ng/ml is adequately low to detect clinically significant PrCa in men ≥ 55 years in the general population. In the general population it has been shown that that clinically detectable PrCa is present in 13-20% of men within 3 to 5 years of a PSA measurement between 2.5-4.0 mg/ml and 25-30% of men with a level above 4.0ng/ml (Gann et al, 1995; Karazanashvili et al, 2003). Currently, the ERSPC and ProtecT studies are using a PSA level for biopsy of ≥3ng/ml for screening the general population with an interval of 4 years in men greater than or equal to 55 years of age.

It is important to consider not just the number of cancers that are detected but the ability of a screening modality to distinguish between clinically significant disease, i.e. disease causing a significant risk to the patient's life or wellbeing, versus disease that would pose no threat if left untreated. The definition of clinically significant localized PrCa is defined using the NICE criteria for intermediate / high risk disease, which comprises a Gleason score of ≥7, and /or ≥T2b, N1, M1 (http://guidance.nice.org.uk/CG58). The use of a lower PSA threshold for biopsy in the general population could potentially lead to a higher detection of clinically insignificant PrCa. However, in moderate / high risk groups targeted screening is being evaluated and pilot data from PrCas associated with *BRCA* gene mutations, suggest that this does indeed improve the efficiency of prostate screening (Mitra et al, 2008).

The Targeted PSA Screening (TAPS) study looked at the feasibility of targeting screening at high risk groups (Melia et al, 2006) and identified a number of key issues. The aims of this study were to investigate the uptake rate of screening using prostate specific antigen (PSA) testing, and the referral rate in male relatives of men already diagnosed with PrCa below the age of 65 years. This study recruited relatives of men with PrCa aged between 45-69 years and contacted eligible men via their affected relatives. The results of the study found that discussing the study in person with PrCa patients yielded a higher recruitment rate compared with postal invites. They also found that there was a high level of previous PSA screening within this cohort. Interestingly they found that men were far more likely to opt for screening within the study if they were married / co-habiting versus men who were single. The results of this study have important implications for the design of targeted screening programmes in higher-risk groups and highlights that further research is needed into the management of higher risk groups.

Several studies have looked at interest in genetic testing among men with a family history of PrCa and have found a very high level of interest, with studies reporting 90-98% of men expressing interest in testing if it was to become available (Bratt et al., 2000; Cormier et al., 2002; Cowan et al., 2008). Weinrich et al, (2002) and Myers et al, (2000) have reported a very high level of interest (86-87%) in genetic testing among African-American men without a family history of PrCa. This suggests that there could be a very high level of interest among the target population.

PSA screening

Factors known to affect the total serum PSA level include age, race, prostatic inflammation and benign prostate hyperplasia (BPH). PSA is known to increase with advancing age signifying the normal physiological enlarging of the prostate gland (Oesterling, Jacobsen et al. 1993).Although PSA sensitivity is 72-90% at a threshold of 4ng/ml, its specificity is not high (Dall'era, 2002). Therefore, efforts to improve the sensitivity and specificity of serum PSA using different diagnostic parameters have been

developed. These include age-adjusted PSA, free to total fraction PSA, PSA density and PSA velocity. The most applicable components of these are age-adjusted PSA and free to total fraction PSA. Oesterling et al (2001) found that PSA level increases with age. Data from Sun et al. (2007) show that 4.4% of men <50 years have PrCa and that using a threshold of ≥2ng/ml would detect 75% of these cancers. In a study by Canby-Hagino et al (2007) PrCa was diagnosed at biopsy in 25.3% of men with a family history of PrCa with a PSA level of <4.0ng/ml. The median PSA in the men with cancer was 2.1ng/ml (age range 50-80). Therefore we plan to use a threshold of >2ng/ml for biopsy in men aged ≥50 years who choose to have PSA follow-up. Data from many different studies have shown that the mean PSA cut-off for men aged 40-49 years is 2.14ng/ml compared with 3.40ng/ml for men aged 50-59 years old. However, age adjusted PSA cut-offs are not recommended for men 60 years or older because of the danger of overlooking a significant number of PrCas. Benchikh et al., 2010 showed that the used of a 4 marker panel can reduce the number of biopsies needed in a population based screening trial and increase the probability that a intermediate/high risk cancer would be found.

Early screening of men for PSA may serve to stratify the male population by risk of future clinically significant prostate cancer. Data from the Malmö Preventive Project cohort were used to develop an evidence based pathway for prostate cancer testing. Measurement of PSA concentration in early midlife can identify a small group of men at increased risk of prostate cancer metastasis several decades later. Risk of death from prostate cancer was associated with baseline PSA; 44% (95% confidence interval 34% to 53%) of deaths occurred in men with a PSA concentration in the highest 10th of the distribution of concentrations at age 45-49 (≥1.6 µg/L),(Vickers, Ulmert et al. 2013). Similar findings were reported within the Danish 'Diet, Cancer and Health' study of 27,179 men aged 50 to 64. Baseline total PSA and free/total PSA ratio were associated with risk of developing prostate cancer 14 years later. The median level of PSA for cases was 3.7ng/ml, significantly higher than controls 1.07ng/ml. Individuals with a PSA in the upper quintile were not only more likely to develop prostate cancer, but they were also more likely to develop an aggressive cancer (>T3,GS>7). A lower ratio of free/total PSA (<0.15) was associated with a higher risk of prostate cancer and also an increased risk of aggressive disease.(Larsen, Brasso et al. 2013) A panel of tests including total, free and intact PSA and kallikrein-related peptidase 2 can potentially be used as a non-invasive alternative to clinical invasive tests in prostate cancer screening. In order to answer this question, 3,654 men participating in the European Randomized Study of Screening for Prostate Cancer from 2 centres, Rotterdam and Goteborg, who underwent a TRUS guided prostate biopsy for an elevated PSA (>3ng/ml) were recruited. The predicitive accuracy of the laboratory model was significant with an AUC of 0.766. Using invasive clinical tests like TRUS-estimated prostate volume or Digital Rectal examination did not improve discrimation for any cancer.(Carlsson, Peltola et al. 2013)

Digital Rectal Examination (DRE) and TransRectal Ultrasound (TRUS)

DRE and TRUS are thought to add little to sensitivity of screening for localized disease. The positive predictive value of DRE is between 8-10% and most of the cancers diagnosed by this method have favourable prognostic features (Schröder et al., 1998; Schröder et al., 2000).

Ultrasound shear wave elastography of the prostate is a new ultrasound technique that has been reported to increase the sensitivity, specificity and positive predictive value in the detection of prostate cancer and provide better diagnostic accuracy than grey-scale ultrasound imaging.

Prostate screening and family history/genetic factors

There are preliminary data on PSA threshold and PSA screening alone without DRE in high risk populations based on genetic analyses or family history (Mitra et al, 2011). A few reported studies of PSA screening in first degree relatives within PrCa clusters show an increased proportion of raised PSA levels compared with a non-targeted population. This translates into a three-fold higher detection of clinically significant PrCa (McWhorter et al, 1992; Neuhausen et al, 1997; Matikainen et al, 1999; Valeri et al, 2002). A study of men with at least one first or second degree relative with PrCa who underwent prostate biopsy showed that 25.3% had PrCa (Canby-Hagino et al., 2007). Nam et al (2009) studied the effect of 25 SNPs in men who had biopsy and PSA screening. In 3,004 patients, 1,389 (46.2%) were found to have PrCa. Fifteen of the 25 SNPs studied were significantly associated with PrCa on biopsy ($P=0.02\text{-}7x10^{-8}$). He selected a combination of 4 SNPs with the best predictive value for further study. After adjusting for other predictive factors, the odds ratio for patients with all four of the variant genotypes compared with men with no variant genotype was 5.1 (95% confidence interval, 1.6-16.5; P=0.006). When incorporated into a nomogram, genotype status contributed more significantly than PSA, family history, ethnicity, urinary symptoms, and digital rectal examination (area under the curve=0.74). The positive predictive value of the PSA test ranged from 42% to 94% depending on the number of variant genotypes carried ($P=1x10^{-15}$).

PCA3, a molecular urinary assay (an mRNA that is highly over expressed in PrCa cells) has also been shown to be useful in the prediction of PrCa. Independent of prostate volume, serum PSA and the number of previous biopsies, PCA3 levels have been shown to correlate with total tumour volume and post-prostatectomy Gleason score (Deras et al., 2008; Nakanishi et al., 2008). It is purported to have particular use in the prediction of positive repeat biopsies after a negative biopsy with an equivocal PSA of 3-10ng/ml, a situation in which PSA is not always helpful (Haese et al., 2008).

The TMPRSS2-ERG translocation is present in over two thirds of PrCas. A urine test has been developed and the presence of the translocation has been shown to be associated with PrCa burden at prostatectomy (Young et al., 2012).

We will therefore collect serum, plasma, urine, saliva and prostate tissue samples with the aim of conducting proteomics and metabolomics to look for further markers.

Imaging and prostate cancer diagnosis

Diffusion weighted Magnetic Resonance Imaging (MRI) is a technique that is being evaluated in the research arena and used in conjunction with conventional T2W imaging has been shown have a high level of sensitivity in detecting clinically significant PrCa (Haider et al, 2007; Reinsberg et al, 2007; Kozlowski et al, 2008). The PROMIS study evaluated the diagnostic accuracy of MRI prior to prostate biopsy, demonstrating a quarter of men could safely avoid prostate biopsy based on only exposing men to a biopsy based on a Likert course of ≥3. Approximately 10% of men with a Likert score of 1-2 had clinically significant PrCa on biopsy, although the study cohort were men with referred with a clinical suspicion of PrCa with a median PSA of 7.1. The PRECISION study investigated the use of MRI-targeted biopsy compared to TRUS biopsy, with men who did not demonstrate any MRI abnormality (Likert score 1-2) not invited for prostate biopsy. The found fewer diagnoses of clinically insignificant PrCa and also found higher clinically significant PrCa detection rate in men undergoing MRI-targeted biopsies versus those undergoing standard biopsy (Kasivasanathan, 2018). These studies recruited cohorts of men unselected for family history, and with symptoms suggestive of prostate cancer.

The PROFILE Pilot study

The aim of the PROFILE study is to correlate germline genotypes in men with an increased risk of PrCa due to a genetic predisposition with biopsy outcome and also to assess the additional contribution of DW-MRI and new biomarkers to PrCa screening in this group. An initial pilot has been undertaken to inform the main study. The aim of the pilot PROFILE study was to conduct a feasibility study in 100 men with a positive family history of PrCa (at least one first degree relative affected at <70 years, with diagnosis verified) to determine the interest in the study, biopsy uptake and complication data. The rationale behind the study design of this protocol where at risk groups are identified on family history and are retrospectively profiled rather than taking a specific SNP profile as a criterion for screening and biopsy is that if the latter design were employed, then as new profiles are published (which is likely to be over the next 18 months), the eligibility criteria of the study would be continually changing and also would potentially add bias to the results.

The pilot PROFILE study recruited eligible men aged 40-69 years with a family history of PrCa over a two year period. After informed consent, patients provided blood samples to measure PSA level and for DNA extraction. All participants were asked to undergo a 12 core prostate biopsy regardless of baseline PSA result. Participants without previous prostate biopsy or who underwent biopsy >1 year ago were also offered a T2-weighted with DW-MRI prior to biopsy in 50 of the participants.

In total 116 men were recruited and 102 biopsies completed. All patients were asymptomatic. Based on SNP analysis of 39 PrCa risk SNPs, a total of 53 men had a predicted relative risk <1 (median age 55 yrs; median PSA 1.20). In this subgroup, 8 men (15.1%) were diagnosed with PrCa (median age 62.0 yrs, median PSA 2.50). Amongst the 48 men with a relative risk >1 (median age 51.0 yrs; median PSA 1.4) 13 PrCas (27.1%) have been identified (median age 56.0 yrs, median PSA 2.7). T2 weighted in conjunction with DW-MRI had 33% false positives and 10% false negatives. The AUC of T2 weighted in conjunction with DW-MRI was 0.83. Twelve men with PrCa had a PSA <3 (52%). No adverse psychosocial variables were noted.

Conclusions from the pilot study:

Prostate biopsy as a means of PrCa screening is feasible and acceptable in men with a family history of PrCa. The findings support a larger study investigating the use of SNPs in PrCa risk stratification for targeted screening.

Based on the pilot data, the main PROFILE study would require 350 men in each of two cohorts, (i) Caucasian men with a family history and (ii) men who are of African/Afro-Caribbean origin irrespective of family history with pre-biopsy T2-weighted DW-MRI in all cases.

2. Study overview and rationale

The PROFILE study has been developed to investigate the role of targeted PrCa screening in men at a higher genetic risk and its association with specific genetic profiles and biomarkers (both biological samples and imaging - T2-weighted in conjunction with DW-MRI and shear wave elastography).

The primary endpoint is the association of biopsy result with genetic profile in men having targeted prostate screening. This is to inform healthcare about the role of genetic profiling as PrCa germline

genetic risk variants are discovered. Secondary endpoints are the association of apparent diffusion coefficient metrics and biological sample biomarkers with biopsy outcome.

The study will be composed of three cohorts of men aged 40-69: (1) a cohort with a family history defined as at least one first degree (or second degree if through the female line) relative with PrCa diagnosed at <70 years (diagnosis verified); (2) a cohort of Black African or Caribbean men irrespective of family history and (3) men known to carry a mutation in a high-risk gene. The first cohort will consist of men of Caucasian ethnicity given the lack of studies validating PrCa SNPs in other ethnicities and the utility of the genetic profile that will be used in unknown in other populations.

It is anticipated that there will be a number of men who express an interest in the study and donate blood for genetic profiling but who later decide not to proceed with biopsy. These men will be put into a separate arm of the study (arm 2) and followed up within the study protocol with annual PSA testing and will proceed to biopsy if an age-related PSA threshold is reached. The thresholds that will be used are PSAs of >1.0ng/ml in men aged 40-49 and PSAs of >2.0ng/ml in men aged 50-69.

Additional blood, urine, saliva and tissue samples will be taken for research purposes in order to investigate new biomarkers in this population using biochemistry, proteomic, metabolomic and microarray approaches. Samples will be collected from urine for further studies, for example biomarker studies PCA3 and the TMPRSS2 ERG translocation to correlate these with SNP profile, but biopsy decisions will not be made on these results.

Blood will be collected at study entry for retrospective SNP profiling, the results of which will be fed back to patients at the end of the study, including cohort 3 where the role of SNP profile together with a high-risk mutation will be evaluated. T2 weighted DW MRI will be offered to all men pre biopsy. The biopsy will be a 12 core biopsy with additional cores targeting areas of abnormality on MRI. Two extra cores, one from each side of the prostate (non-targeted) will be taken and snap frozen for future molecular studies.

The PROFILE study will be undertaken at The Royal Marsden NHS Foundation Trust in London and Sutton. A sister study will invite this cohort of men to take part in a study evaluating the psychosocial impact of receiving genetic profiling results within the context of this study.

All men from the PROFILE study will be followed up for at least 5 years following participation. This will enable information to be collected on the development of PrCa beyond this protocol, and look at the treatment effects in men based on their genotype.

3. Aims

- **Primary:** To determine the association of genetic status with prostate cancer detection in men at genetically higher PrCa (PrCa) risk undergoing targeted PrCa screening

- **Secondary**: To determine:
  - Incidence and aggressiveness of PrCa in these cohorts.

  - To investigate the value of T2-weighted in conjunction with DW-MRI as a cancer detection tool in men at genetically higher PrCa (PrCa) risk undergoing targeted PrCa screening.

  - To determine the incidence of abnormal imaging using 3D ultrasound, shear wave elastography and biopsy outcome and to correlate standard 12 core prostate biopsies with targeted biopsies based on abnormalities identified at T2-weighted in conjunction with DW-MRI.

  - To determine the association of biomarker profile with cancer detection in men at genetically higher PrCa risk undergoing targeted PrCa screening.

  To determine the association of polygenic risk score (PRS) with prostate cancer detection in men at genetically higher risk of PrCa undergoing targeted PrCa screening.

  - To determine the efficacy of PrCa screening in men at genetically high-risk of PrCa.

  - The psychosocial impact of undergoing prostate screening and genetic profiling as part of this study (see associated protocol).

4. Study Design

This screening study is designed to look at the correlation of cancer incidence with genetic profile. The aim is to evaluate targeted screening for PrCa in men at a genetically higher risk to estimate the incidence of PrCa and the sensitivity and specificity of PSA screening in these populations and correlate this with genetic profiles and biological endpoints. Additionally the study aims to identify serum and/or urine markers (for example PCA3, hK2 and free: total PSA ratio) and imaging technologies (eg MRI and new imaging techniques) predictive of the risk of developing PrCa and to correlate these with genetic risk.

5. End Points

Primary Endpoint

To investigate the role of targeted Prostate Cancer screening in men at a higher genetic risk (i.e. family history, ethnicity, gene mutation status) and its association with specific genetic profiles and biomarkers

Secondary Endpoints

1. To determine the incidence and aggressiveness of prostate cancer in the cohorts studied.

2. To determine the association of Diffusion Weighted MRI (DW-MRI) findings with prostate biopsy results.

3. To determine the incidence of abnormal imaging using 3D ultrasound, shear wave elastography and biopsy outcome and to correlate standard 12 core prostate biopsies with targeted biopsies based on abnormalities identified at DWMRI.

4. To determine the association of biological sample biomarker profile and quantitative imaging biomarkers e.g. apparent diffusion coefficient metrics with prostate biopsy result in men at genetically higher prostate cancer risk undergoing targeted prostate screening

6. Inclusion/ Exclusion Criteria

- Number of subjects:
  - Family History Cohort: 350 men
  - Afro-Caribbean cohort: 350 men
  - High-risk gene mutation cohort: 350 men

- **Inclusion Criteria:**
  - Either:
    (1) Caucasian men with a positive family history of PrCa defined as:

    - Men with a first degree relative (or second degree if through female line) with histologically or death certificate proven PrCa diagnosed at <70 years
    - Men with two relatives on the same side of the family with histologically or death certificate proven PrCa where at least one is diagnosed at <70 years
    - Men with three relatives on the same side of the family with histologically or death certificate proven PrCa diagnosed at any age

    Or (2) Men of African or Caribbean ancestry defined as:

    - Both parents and all 4 grandparents from that origin

    Or (3) Men with a pathogenic mutation in a gene thought to cause a higher-risk of prostate cancer: (including B*RCA1, BRCA2, ATM, PALB2, MLH1, MSH2, MSH6, CHEK2* and other DNA repair gene mutations as listed in appendix G)

  - Age 40-69 years
  - WHO performance status 0-2 (see Appendix A)
  - Absence of any psychological, familial, sociological or geographical situation potentially hampering compliance with the study protocol and follow-up schedule.

- **Exclusion criteria**
  - Previous cancer with a life-expectancy of less than five years.
  - Previous PrCa
  - Negative biopsy within one year before recruitment
  - Co-morbidities making prostate biopsy risk unacceptable (anticoagulants or antiplatelet medication including Warfarin, Clopidogrel, Apixaban, Dabigatran or other NOAC (Novel Oral Anti-Coagulant); poorly controlled diabetes, cardiovascular/respiratory disease, immunosuppressive medication or splenectomy)
  - Men with body mass index (BMI) 40 and above.
  - Men with BMI 35 and above plus other co-morbidities.
  - Contraindications to having an MRI (pacemakers, aneurysm clips, metallic cardiac valve/stent, Ventriculo-Peritoneal (VP) shunt, cochlear implant, neurotransmitter, metallic foreign bodies in eye(s), other metalwork, claustrophobia)
  - Neither Caucasian or Afro-Caribbean ethnicity
  - Any significant psychological conditions that may be worsened or exacerbated by participation in the study

- **Subject Withdrawal**
  - Subjects may withdraw from the study at any time if they so wish without giving a reason. No further data will be collected about that individual, and any unused samples will be destroyed. Data collected up to that point will be retained for audit purposes.

7. Methodology

The target population is a group of 350 men in each of the three cohorts. Potential participants will be identified through advertisements in the press, use of social media (in collaboration with press offices of the ICR/RMH, the funders of the study), posters and leaflets about the study that will be placed in GP surgeries, hospitals and other community organisations. Men will also be recruited through GP surgeries from mail-outs; relatives of cancer patients at collaborating centres and through relatives of participants from the UK Genetic Prostate Cancer Study (REC reference: 06/MRE02/4; permission to invite the men and their relatives to collaborative research studies is already in place). The PROFILE

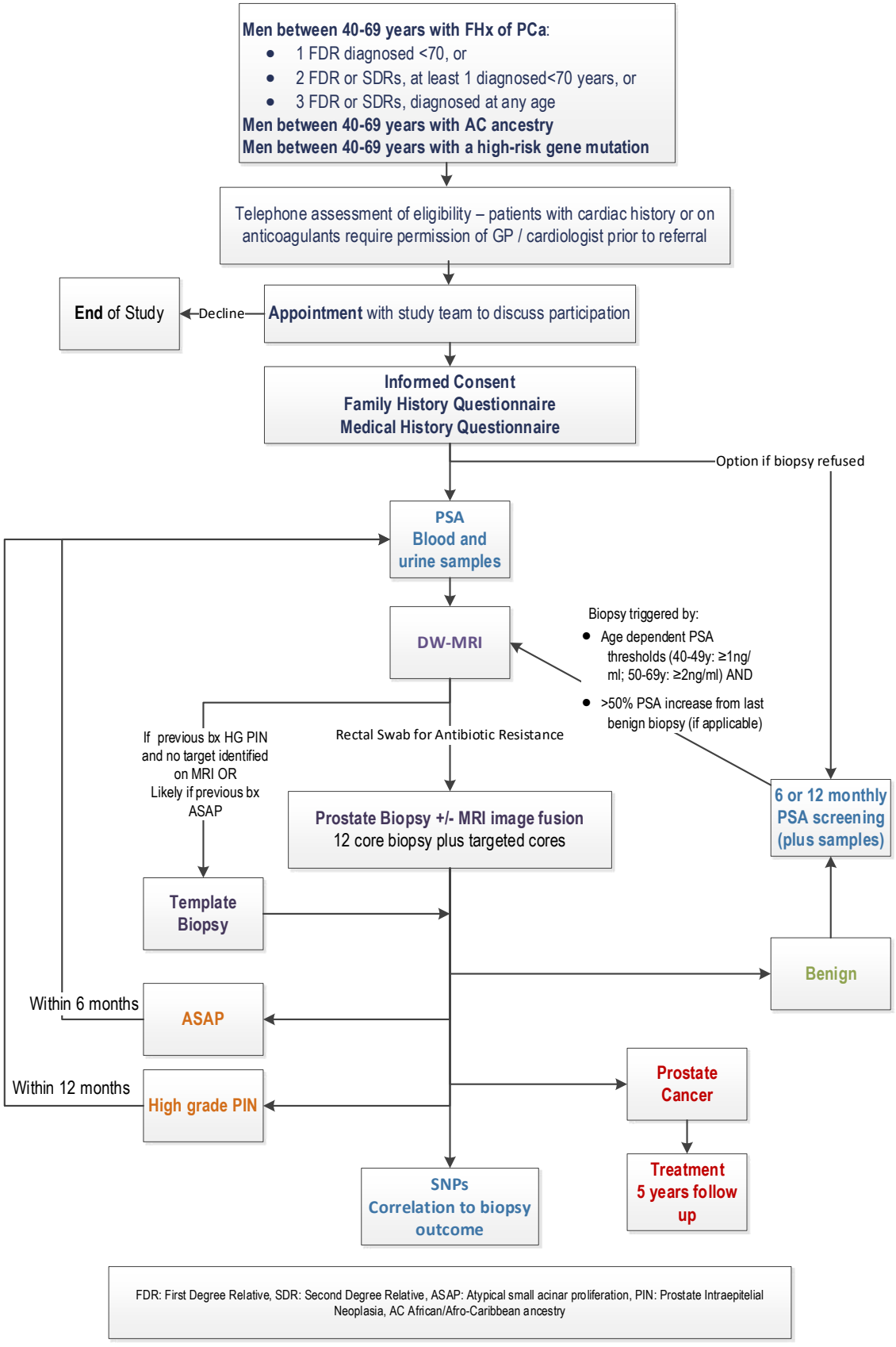
study and/or raising risk awareness, especially in the Afro-Caribbean community will be promoted by use of press releases as well as support from funders of this study. Funders aim to raise awareness on their websites, use of internal communication such as newsletters aimed at health professionals, social media, flyers to be displayed/distributed at professional education events and awareness events. Where possible during such coverage, contact details of the study team will be included so that those interested can contact the study team directly for further information about the study and guidance on how to take part. Promoting the study in this way will enable information about the study to be transmitted to the wider community, especially the Afro-Caribbean community where recruitment is challenging. By extending the study into Primary Care and by including GP Practices as Participant Identification Centres, this will allow promotion of the study to the wider community and will enable us to reach our target population.

Individuals expressing an interest in taking part in the study will be sent a patient information sheet. This explains the study in lay terms and gives the contact details for the research team. Individuals will be requested to complete a reply slip and those that confirm their interest will be telephoned by the research team to confirm eligibility (this will include confirmation of the diagnoses in relatives and collection of previous PSA results where applicable) and they will be asked to seek a GP referral, if they are not already registered at the Royal Marsden Hospital. Once the referral is received, an appointment will be scheduled to meet with the local study team.

For men with a cardiac history or those taking aspirin, permission to join the study will be required from their cardiologist and/or GP and discussed with the PROFILE study clinical fellow/PI.

For men taking finasteride, their PSA value will be doubled to obtain their true PSA value.

Study Algorithm



Enrolment

The enrolment appointment will last approximately 45-60 minutes during which the participant will be counselled about all study procedures including undergoing prostate biopsy and the potential side-effects, DW-MRI of the prostate (if eligible), the current status of PSA testing and genetic profiling. They will be asked to give their written consent before any investigations are initiated and before any biological samples are obtained. Men can provide written consent during this first appointment or they can have the opportunity to go away and think about whether they would like to take part. For the latter, if the team has not heard from them within two weeks they will be telephoned to answer any further questions and to either schedule another appointment to seek consent or to confirm that they do not wish to take part in the study. All men will be asked to complete a family history questionnaire and a short medical history questionnaire. These will be sent to the men in advance of their first appointment to be completed at home where possible.

A 50ml blood sample, a saliva sample and urine samples pre and post prostatic massage will be obtained from all consenting participants when possible. The baseline PSA level of all participants will be measured in the same laboratory.

Men will be offered a prostate biopsy (with preceding DW-MRI) regardless of their baseline PSA result. Investigations will be offered to participants on a voluntary basis and those accepting will form study arm 1. As this is a cohort of healthy volunteers, participants can decline a prostate biopsy and prefer to only undergo further investigations if PSA is above their age-related threshold will form study arm 2.

Recruitment will continue until 350 men have undergone MRI and biopsy regardless of which study arm they enter.

Diffusion Weighted MRI

DW-MRI will be offered to all men who are medically suitable for MRI.

The DW-MRI scans last approximately 30-45 minutes. Co-registration with 3 dimensional Ultrasound is optional and will depend on local facilities and expertise. If any incidental adverse findings are discovered, the participant will be reviewed in the hospital as per departmental guidelines and referred to the appropriate clinician. If the participant would like, additional support can be provided at this stage.

Prostate Biopsy

A twelve core prostate biopsy (see Appendix C) will be taken for diagnostic purposes (with additional targeted biopsies where appropriate) and a further 2 samples obtained for research (where possible). The biopsy will either be via the transrectal or transperineal route. Consent to take the 2 extra samples for research may be sought before the biopsy procedure commences (optional for patient and collected when facilities are available) and will be immediately snap frozen in dry ice for future DNA and RNA analyses.

In the case of a visible, anterior prostate suspicious lesion on MRI, then a transperineal biopsy upfront would be preferable, in view of the risk of a false negative TRUS biopsy in this setting.

The volume of the prostate gland will be measured and recorded as a standard part of the TRUS procedure. In addition measurements will be taken to calculate the anoscrotal distance and anogenital distance (see Appendix E). These measurements are being taken in collaboration with Dr Manolis Kogevinas, MD, PhD, Professor and co-Director, Centre for Research in Environmental Epidemiology (CREAL) at IMIM (Hospital del Mar Research Institute), Barcelona and the rationale for recording these measurements are listed in Appendix E. A one page questionnaire will also accompany this part of the study.

All biopsies will be reviewed by one pathologist at each centre using an agreed standardised procedure (See Appendix D). If any of the cores identify the presence of PrCa, the subject will receive treatment as advised by their local centre. All cases will be scanned into a virtual central review database for review by a panel of expert urological pathologists.

Those cases whose first biopsy detects Atypical Small Acinar Proliferation (ASAP) or High Grade Prostatic Intra-epithelial Neoplasia (HG-PIN) will be re-biopsied within 6 to 12 months, or sooner according to local guidelines. A repeat DW-MRI will be performed, adding in extra cores depending on the MRI appearance. The repeat biopsy will either be a transperineal template biopsy or TRUS biopsy depending on the MRI findings.

Outcome of biopsy

1. Prostate cancer – treatment as advised by local guidelines
2. ASAP / HG PIN detected – repeat PSA, DW-MRI and biopsy in 6 months to 1 year.
3. No abnormalities identified - PSA follow up annually for 5 years

Rectal Swab

Rectal Swab in order to identify Ciprofloxacin resistance could be offered to those patients who received antibiotic treatment within the last 3 months or travelled extensively, according to local guidelines.

Follow-up post study biopsy

Following study participation, those men with a PSA of $\geq$1.0ng/ml if <50 years or $\geq$2.0ng/ml if $\geq$50 years who have a negative biopsy will be asked to continue with annual PSA for at least five years screening through the study and a repeat biopsy if PSA value increases by more than 50%.

The outcome of different treatments in these men with PrCa has not been studied; therefore treatment data will be collected for a further 5 years' in order to compare treatment outcomes retrospectively.

All study participants will be asked for their updated medical and family history information for 5 years. Where men are not seen in person for continued PSA screening a short postal questionnaire will be sent.

Those men who are eligible and come for appointment 1 and consent to follow up but subsequently decide against a biopsy will be followed up with annual PSA screening and SNP profiled to correlate SNP profile with PSA values. If their PSA is above the threshold where biopsy is recommended and they decline undergoing biopsy they will be withdrawn from the study.

Participants may be flagged by the cancer registry to confirm a diagnosis of prostate cancer, a date of death and cause of death. This will be done via the Data linkage Service (formerly known as Medical Research Information Service), using records maintained by The NHS Information Centre and the Health & Social Care Information Centre.

8. Data Acquisition

At enrolment

Each subject will complete the following:

- Sign the study consent form
- Complete the Family History Questionnaire
- Complete the Medical History Questionnaire.
- Provide 50ml blood sample and 30ml urine sample (first pass) pre and post prostatic massage for total PSA level, free:total PSA, PCA3 and other studies (Appendix B – Guidelines for Sample Collection)

At MRI scan

Each subject will complete the following:

- Sign the local hospital MRI consent form (where required)

At Biopsy

Each subject will complete the following:

- Sign the local hospital biopsy consent form

If PrCa is diagnosed

The staging and further investigation of the disease is as directed by the collaborating uro-oncology unit. Management is based on the immediately available pathology report, not on the later central review.

Minimum information required by the study centre will be:

- Clinical T stage
- Gleason score of biopsy and extent of involvement (in percentage of tissue involved an absolute length of core in millimeter)
- Treatment and management plan
- Radiological TNM stage
- Histopathology report for men undergoing radical surgery
- Slides should be scanned into PathXL for central review after the local clinical report has been issued.
- Following a diagnosis of PrCa, a treatment questionnaire will be required annually for a minimum of 5 years.

Results

- The Biopsy results will be discussed with the participant either in person or by telephone (for negative results only and at the clinician's discretion)
- The genetic profiling results will be disclosed to the participant either at a telephone appointment or at their next screening visit and written information will be provided alongside these results to explain their significance based on current knowledge.

Follow-up

All participants will be followed up with a 12-monthly PSA test for at least 5 years (until the last recruit has completed 5 years of screening). GP follow-up is advised and we will collect the data, if this is not possible then the follow up will be at the Royal Marsden Hospital.

Participants may be flagged by the cancer registry to confirm a diagnosis of prostate cancer, a date of death and cause of death. This will be done via the Data linkage Service (formerly known as Medical Research Information Service), using records maintained by The NHS Information Centre and the Health & Social Care Information Centre.

Potential adverse events

Side-effects of biopsy:

Prostate biopsy should be carried out in accordance with the study protocol (Appendix C) and antibiotic prophylaxis should be given as per local hospital protocol. The number of biopsy cores will remain the same but the method of obtaining biopsy may be either transrectal (TR) or transperineal (TP), according to local RMH practice and/or service availability.

The procedure is uncomfortable and associated with the following risks

▪ Painful or difficult voiding	13%
▪ Haematuria	60-90%
▪ Significant haematuria requiring hospital admission	0.4-1%
▪ Haematospermia	60%
▪ Rectal bleeding	20-30%
▪ Fever/Uncomplicated urinary tract infection	3-5%
▪ Prostatitis	0.5-6%
▪ Septicaemia/hospital admission	3-5% TR; 1-2% TP
▪ Acute urinary retention	1% TR; 1-10% TP

- Vaso-vagal 2.4-10%
- Mortality (30 day) 0.03-0.9%
- Erectile problems requiring intervention (14%)

(Taken from Crundwell et al. 1999; Raaijmakers et al. 2002; Loeb et al, 2013; Carlsson et al, 2010; Ozden, E et al 2009; Ahmed et al, 2017 and Wagenlehner et al. 2013)

For this reason subjects will be followed carefully and be able to contact the urology department in case of problems. The research team will follow up any complications and will facilitate admission locally or at the Royal Marsden if necessary. The reported complication rate from the pilot study was close to 6%, with the main issue being prostatitis. Mild lower urinary tract symptoms were not recorded. The rate of infections in the pilot study is in keeping with published data.

Venepuncture

Venepuncture a risk of
- Feeling faint,
- Bruising at venepuncture site,
- Excessive bleeding,
- Hitting a nerve
- Hitting an artery

The procedure should be carried out by those with adequate training and in accordance with local hospital protocol.

9. Data Analysis

- All biopsy interventions and results will be reported to the data centre as they occur. Biopsy results will be reviewed by a central team of pathologists.
- PrCa diagnosis will be reported immediately. The diagnosis and treatment will be based on histological confirmation. A later research central review will be undertaken by a central team of pathologists. If there is disagreement the local diagnosis will be the overriding one for treatment.
- Cause of death will be reported by the participating centre and verified from cancer registry data.
- Data completeness (Questionnaires and CRFs) will be evaluated
- Initial translational studies will use the stored serum/urine samples and will include assays for free:total PSA levels and human kallikrein 2 (hK2) and other markers and proteomics, PCA3 and translocations for research only.
- An Independent Data Monitoring Committee will review the study data 6 monthly

10. Study Organisation/ Trial Monitoring and Management Strategy

Administrative Responsibilities

The CI, Clinical Fellow and Study Coordinator will be responsible for writing the protocol, submitting to the Committee for Clinical Research and for local management R&D approval, reviewing all case report forms and documenting evaluation forms, discussing the contents of the reports with the Statistician, and for writing the draft of the study results. The CI will also generally be responsible for answering all clinical questions concerning eligibility, treatment, and the evaluation of the subjects.

Steering Committee

It will be the responsibility of the CI to report changes to the protocol and data updates to the study Steering Committee.

Independent Data Monitoring Committee (IDMC)

An IDMC has been set up chaired by Professor Stephen Duffy who is an international expert in screening. Other members of the committee are Dr Peter White (former Head of UKNEQAS for PSA tests), Mr Paul Cathcart (Consultant Urological Surgeon) and Mr John McGrath (Consultant Urological Surgeon). This IDMC also monitors the other international screening targeted screening study based on genotype in *BRCA1/2* mutation carriers (IMPACT).

11. Adverse Events

Definitions

Adverse Events (AE) are any untoward medical occurrence or experience in a patient or clinical investigation subject which occurs following participation in the trial regardless of the causal relationship. This can include any unfavourable and unintended signs or symptoms, an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the use of the study, for example:

- death
- a life-threatening event (i.e. the subject was at immediate risk of death at the time the reaction was observed)
- hospitalisation or prolongation of hospitalisation
- persistent or significant disability/incapacity
- any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed above).

Reporting procedure

Non-serious adverse events

All Adverse Events (AE), occurring during the study until the end of the period of follow-up must be recorded on an adverse event form. All adverse events will be reported to the data centre and logged in accordance with to the local sites Standard Operating Procedures for Adverse Events.

The Chief Investigator will decide if those events are related to the study intervention (i.e. unrelated, unlikely, possible, probable, definitely and not assessable) and the decision will be recorded on the

adverse event forms. AEs definitely not study related (i.e. reported as unrelated) will not be considered as adverse events in study analyses, but reported separately. The assessment of causality is made by the investigator using the following definitions:

Relationship	Description
UNRELATED	There is no evidence of any causal relationship
UNLIKELY	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the subject's clinical condition, other concomitant treatments).
POSSIBLE	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the subject's clinical condition, other concomitant treatments).
PROBABLE	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
DEFINITELY	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
NOT ASSESSABLE	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Serious adverse events

All Serious Adverse Events (SAE), related or not to the study, occurring during the study period and within 30 days after the last study intervention (eg. biopsy) will be reported and logged in accordance with to the local sites Standard Operating Procedures for Adverse Events.

Original SAE reports will be filed in the PROFILE trial master file.

12. Statistical Considerations

Power calculations

A sample size of 318 in each group will provide 80% power to detect a relative risk of 2 for detection of prostate cancer at a 5% significance level, compared with an expected detection rate in the general population of 3%. A sample size of 350 per group therefore allows for a drop out rate of 9 – 10%.

Analysis plan

The proportion of men detected with prostate cancer at biopsy will in each group will be calculated both on an 'intention to treat' basis for all men recruited, and in those actually biopsied; exact binomial

95 % confidence intervals will be calculated for each group, and for subgroups according to previous negative biopsy.

Recruitment timeframes

It is anticipated that the study will complete recruitment within 36 months. The study team will meet monthly to discuss recruitment and will report to the Steering Committee and Data Monitoring Committee six monthly. If there are problems with meeting the target recruitment this will be discussed at the Steering Committee meetings.

End of study

The end of study is defined as the date of the last appointment of the last participant.

13. Regulatory & Ethics Committee Approval

Subject protection

The responsible investigator will ensure that this study is conducted in accordance with the Good Clinical Practice (GCP) guidelines, the Data Protection Act 1998 (DPA) and the Human Tissue Act 2004 (HTA) and Codes of Practice for consent issued by the Human Tissue Authority. All staff at each Trust are required to abide by the Data Protection Act 1998 and also in accordance with the Confidentiality Code of Practice and Data Protection Policy and Procedure. The protocol was approved by the Committee for Clinical Research at the Royal Marsden NHS Foundation Trust and Institute of Cancer Research and the Research and by the London-Riverside Research Ethics Committee.

Subject identification

A sequential identification number will be automatically attributed to each subject registered in the trial. This number will identify the subject and must be included on all case report forms. In order to avoid identification errors, subjects' initials (maximum of 4 letters), date of birth and hospital number (if available) will also be reported on the case report forms.

Informed consent

All subjects will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he will be exposed. Each participant will be informed about the strict procedures used to protect the confidentiality of his patient data, and that his medical records may be reviewed for trial purposes by authorised individuals other than their treating physician.

It will be emphasised that participation is voluntary and that the subject is allowed to refuse further participation in the protocol whenever he wants. This will not prejudice the subject's subsequent care. Documented informed consent must be obtained, according to the principals of GCP, for all subjects included in the study before they are registered at the Data Centre.

The informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative".

Provision of results from the genetic profiling

There is considerable uncertainty about how genetic profile relates to predicted risk of PrCa. For this reason individualized written information will be provided to each participant receiving a polygenic risk score (PRS) result, putting any research results in the context of the current population risks. Patients can opt not to receive results of genetic profiling or biomarker results. It will be stressed that these are research results only and that we do not fully understand the meaning of the results. A psychosocial study is being run concurrently and will explore these issues in more depth and the participants' experience of receiving these results will be an important component of the evaluation of this study.

Other well-known genetic causes of prostate cancer will be likely also be evaluated. This analysis is complementary to the genetic profiling. These are changes that are rare but can cause a large increase in risk on their own. These include mutations in genes such as *BRCA1*, *BRCA2* and Lynch Syndrome genes. In order to interpret the results from the first genetic profile analysis, this second analysis must also be done as they are not mutually exclusive.

In addition to these results being used for interpretation in the research context, it is possible that clinically significant mutations may be discovered. The research team consists of those experienced in interpreting and disseminating genetic results (including geneticists, genetic counsellors/nurses and bioinformaticians). This team will evaluate which variants are classified as 'clinically significant' in the context of the research study. Only these genetic results will be reported back to the participant.

Over diagnosis of prostate cancer

One limitation of prostate screening is the detection of PrCas that would not otherwise have been detected and that may not be of clinical significance. However, these are cohorts of men at genetically higher risk of PrCa and the data obtained from the pilot study indicated that this is unlikely to be the case. In addition, this cohort is a young cohort and the detection of PrCa within this age group is likely to be of greater clinical significance due to longer life expectancy. Therefore while this risk of over diagnosis is recognised it is felt to be justified in this particular cohort. This will be discussed with every participant during the consent process as well as all potential treatment options.

14. Data Handling and Record Keeping

Control of data consistency

Data forms will be entered in the database at the Data Centre. Computerised and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the Data Manager to be entered on the master database. Inconsistent forms will be kept "on-hold" until resolution of the inconsistencies.

External review of histology

Histological assessment of prostate biopsies is subject to inter observer variation, particularly with reference to assessing Gleason grade. For this reason biopsies will routinely be reviewed and representative samples will be re-examined by the study pathologists. Clinical decisions will be based on local assessment and a routine review to confirm diagnosis will not be required. If the review in retrospect reports a cancer which was not reported locally then this case will be subject to expert

pathological review by the study panel pathologists in conjunction with the local reporting pathologist and an MDT decision taken as to the outcome.

15. Financing, Indemnity & Insurance

The Funders of the study are:

- Cancer Research UK (Research Nurse and Statistical Support)
- The Ronald and Rita McAulay Foundation (Clinical Research Fellow)
- PCUK Movember Centre of Excellence
- National Institute for Health Research Biomedical Research Centre at RMH/ICR

The standard NHS indemnity procedures will apply at each collaborating hospital. Each participating site is responsible for ensuring insurance and indemnity arrangements are in place to cover the liability of the Principal Investigator.

Liability rests with the study sponsor – the Institute of Cancer Research and a Research Agreement will be in place with each collaborating centre specifying the liability arrangements.

The study sponsor, the Institute of Cancer Research has no special compensation arrangements for this study. Resources will be accounted for the prostate biopsies and the MRI scans will be funded by a CRUK imaging grant. Prostate biopsies will be conducted by the research fellow and/or the RMH urology team. The NHS Litigation Authority covers standard clinical negligence of NHS employees, staff and health professionals under its Clinical Negligence Scheme for Trusts.

16. Publication Policy

The Chief Investigator together with the team at the data centre will write the final publication of the study results. A draft manuscript will be submitted to all co-authors (the study team, two named individuals from each collaborating centre and all members of the steering committee) for comments. After revision by all co-authors the manuscript will be sent to a major scientific journal.

The CI, the Study Coordinator and the Data Centre must approve all publications, abstracts and presentations based on subjects included in this study. This is applicable to any individual subject registered in the trial, or any subgroup of the trial subjects.

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APPENDIX A

WHO scale for performance status

Grade	Performance scale
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

APPENDIX B

GUIDELINES FOR SAMPLE COLLECTION

For all samples blood should be drawn:-

a) Prior to any manipulation of the prostate
b) At least 24h following ejaculation (if within 24h the time should be noted)
c) 6 weeks after resolution of prostatitis

Each centre must record for each sample:-

a) The tube used to collect the sample (should include full details of tube type and manufacturer)
b) All sample manipulations eg
   a. Time of blood draw
   b. Time and temperature of centrifugation (where appropriate)
   c. Time and temperature of storage

Details of the initial study PSA test used:

1) Manufacturer (eg DPC, Roche, Bayer)

2) Kit (eg DPC IMMULITE Third Generation test)

Samples to be collected:

- Please note that ideally all samples should be processed and frozen as soon as possible on the day that they were taken.
- If samples can not be processed on the day then samples should be processed in the lab chronologically.
- All blood tubes should be gently inverted (10-15 times) before being placed in the centrifuge.

1) **<u>Sample collection for local PSA testing</u>**
Normally serum but some centres may be using tests that recommend plasma.

2) **<u>Serum for routine quality control</u>**
Collection tubes: Plain –BD Vacutainer SST II Advance 8.5ml (sterile, gel, plain to promote clotting, plastic) is recommended.

Centrifuge: Leave the sample to clot for approximately 30 minutes and then centrifuge at ~2200rcf for 15 minutes.

Aliquots: Remove serum with a sterile pipette and aliquot into 4 equal volumes (approximately 0.5mL) in 1.8mL Nunc Cryotubes

Storage: The aliquots should be transferred to a -80^{o}C freezer as soon as possible. (The samples may be stored at 4^{o}C for up to 24 hours).

3) **Plasma Heparin**

Collection tubes: Plasma Heparin – BD Vacutainer LH PST II 8.0ml (sterile, gel, heparin to prevent clotting, plastic) is recommended

Centrifuge: Leave the sample to clot for approximately 30 minutes and then centrifuge at ~2200rcf for 20 minutes.

Aliquots: Remove plasma with a sterile pipette and aliquot into 4 equal volumes (approximately 0.5mL) in 1.8mL Nunc Cryotubes

Storage: The aliquots should be transferred to a -80^{o}C freezer as soon as possible. (The samples may be stored at 4^{o}C for up to 24 hours).

4) **Serum**

Collection tubes: Plain –BD Vacutainer SST II Advance 8.5ml (sterile, gel, plain to promote clotting, plastic) is recommended.

Centrifuge: Leave the sample to clot for approximately 30 minutes and then centrifuge at ~2200rcf for 10-20 minutes.

Aliquots: Remove serum with a sterile pipette and aliquot into 4 equal volumes (approximately 0.5mL) in 1.8mL Nunc Cryotubes

Storage: The aliquots should be transferred to a -80^{o}C freezer as soon as possible. (The samples may be stored at 4^{o}C for up to 24 hours).

5) **Plasma EDTA**

Collection tubes: EDTA –BD PPT, K2E 15.8mg, 8.5ml (sterile, gel, EDTA to prevent clotting, plastic) is recommended.

Centrifuge: Centrifuge at ~2200rcf for 20 minutes as soon as possible.

Aliquots: Remove serum with a sterile pipette and aliquot into 4 equal volumes (approximately 0.5mL) in 1.8mL Nunc Cryotubes

Storage: The aliquots should be transferred to a -80^{o}C freezer as soon as possible. (The samples may be stored at 4^{o}C for up to 24 hours).

6) **Sodium Citrate**

Collection tubes: Vacutainer Light Blue top 2.7ml tubes with 0.109m Sodium Citrate (pH 5.7) #363083) is recommended.

Centrifuge: Centrifuge at ~2200rcf for 20 minutes as soon as possible.

Aliquots: Remove serum with a sterile pipette and aliquot into 4 equal volumes (approximately 0.5mL) in 1.8mL Nunc Cryotubes

Storage: The aliquots should be transferred to a -80^{o}C freezer as soon as possible. (The samples may be stored at 4^{o}C for up to 24 hours).

7) Whole Blood for DNA extraction

Collection tubes: EDTA –BD Vacutainer KTE 10.8mg, 6ml (sterile, EDTA to prevent clotting, plastic, for DNA extraction) is recommended.

Storage: No processing required. Transfer to -80°C freezer as soon as possible. (The samples may be stored at 4°C for up to 24 hours).

8) Saliva for DNA extraction

Collection tubes: Oragene saliva collection tubes

Storage: No processing required. The samples should be stored at room temperature until DNA extracted.

9) RNA for expression studies

Collection tubes: Either PAXgene™ Blood RNA Tube, PreAnalytiX GmbH, Homobrechtikon, CH, 2.5ml, Vacutainer Brand plug.

Or Applied Biosystems

Storage: No processing required. The samples should be left overnight at room temperature before freezing at –80°C.

10) Urine collection pre prostatic massage

Collection tubes: 30ml in a universal plastic container.

Procedure: The first pass urine should be collected

Storage: The samples should either be or kept in the original container (if freezable) or decanted directly into two approximately 10 ml aliquots in freezable falcon tubes and transferred to a –80°C freezer as soon as possible. Do not overfill these containers as this could cause cracking on freezing due to volume expansion.

11) Urine collection post prostatic massage (for PCA3)
Massage prostate three times with finger via DRE

Collection tubes: 40mL in a 60mL universal plastic container.

Procedure: The first pass urine will be collected following a DRE. The physician will perform a DRE as follows. *Apply firm pressure on the prostate from the base to the apex and from the lateral to the median line of each lobe. Apply enough pressure to slightly depress the prostate surface. Perform exactly 3 strokes per lobe.*
Following DRE, the subject will collect the first 40 mL of urine in a labelled 60 mL urine collection cup. If the subject cannot stop his urine flow and provides more than the 40 mL, the entire volume will be kept. If the subject is unable to provide this quantity, collect at least 20 mL. Record the time and volume of urine collection on the Case Report form.

In order to test the urine sample with the PCA3 assay, the sample must be processed with the urine specimen collection kit per the PCA3 assay package insert instructions. Urine samples should be maintained at 2 to 8°C and refrigerated for no longer than 4 hours if not processed immediately.
1. Invert urine sample (in urine collection cup) 5 times to re-suspend cells.

2. Using the transfer pipette, transfer 2.5 mL of urine to an appropriately labelled PCA3 transport tube. The correct volume of urine has been added to the transport tube when the fluid level is within the black fill lines.
3. Screw cap on the PCA3 transfer tube tightly, then invert the transport tube 5x to mix.
4. Two additional aliquots of processed urine specimens will be made by following the same procedures in steps 1 through 3 above, volume permitting. There should be a total of 3 processed urine specimens; extra processed urine specimens will be used for repeat testing, if necessary, and research studies as described in this protocol.
5. Screw cap on the PCA3 transfer tube tightly, then invert the cup 5x to mix.
6. The remaining urine will be transferred to a 50 mL transfer tube with orange cap containing 4 mL of 0.5M EDTA.
7. Screw cap on the 50 ml transfer tube tightly, then invert the transport tube 5x to mix.
Storage: TBC.

12) Biopsy samples

Collection tubes: Each sample should be placed directly into a 1.8mL Nunc Cryotube with no preservative and placed immediately into dry ice.

Storage: The cryotubes should be transferred to a -80^{o}C freezer as soon as possible after the procedure.

APPENDIX C

The 12 biopsy cores should be taken from the following locations:

1. Right peripheral zone base

2. Right transitional zone base

3. Right peripheral zone mid

4. Right transitional zone mid

5. Right peripheral zone apex

6. Right transitional zone apex

7. Left peripheral zone base

8. Left transitional zone base

9. Left peripheral zone mid

10. Left transitional zone mid

11. Left peripheral zone apex

12. Left transitional zone apex

In addition to these 12 standard cores, cores should also be targeted according to MRI findings (where applicable).

Two research cores should be obtained in addition to the above, one from the right side and one from the left side of the prostate. For storage / processing, see Appendix B.

APPENDIX D

PROCESSING AND REPORTING PROSTATIC BIOPSIES

By Professor Chris Foster

1. Number of Cores

Multiple reports form the U.S. and Europe have confirmed that “sextant” sampling methods “miss” a significant percentage of cancers in the first biopsy procedure and that an extended biopsy approach yields higher detection rates. The number of cores recommended in these studies is variable ranging from a minimum of 8 cores to extensive biopsy schema. Most reports have advocated 10-12 cores (Fink, Hutarew et al. 2001, Stewart, Leibovich et al. 2001, Bott, Young et al. 2002, Durkan, Sheikh et al. 2002, Haggarth, Ekman et al. 2002, Taylor, Gancarczyk et al. 2002, Matlaga, Eskew et al. 2003). It might be argued that the precise technique adopted in an individual patient depends upon whether radiographic abnormalities have been identified within the prostate or whether prostatic biopsy is being employed as a “blind” screening procedure following detection of an elevated PSA or digital rectal abnormality. However, if performed correctly, a standard protocol-based procedure should identify, locate and map all the essential information with respect to the majority of prostate cancers. At the initial biopsy, a minimum of 12 cores should be taken in standard positions with extra cores targeted to areas of MR abnormality (Damiano, Autorino et al. 2003). The use of 12 as opposed to 6 cores increases prostate cancer detection frequency by 23.5% and the greatest benefit is in those with a PSA of <4ng/ml which is the most likely scenario in PROFILE (Thiesler et al., 2007)

2. Location, Anatomic Source of the Cores

All the above-cited studies reported significantly improved cancer detection when the most lateral “subcapsular” peripheral zone of the prostate including the anterior “horns” and the apex were biopsied. Sampling these compartments according to different studies results in reducing the sextant false negative rates by 20-35%, with a recent report indicating that the extended biopsy schemes minimizes PSA and age related detection rates. The recommended scheme i.e. a modification of that introduced by Presti et al, comprising 10 biopsies, (6 sextant and 2 lateral and apical on each side) (Presti, Chang et al. 2000). This approach limits the biopsy scheme to 6 central cores with an emphasis on the lateral peripheral zones (de la Taille, Antiphon et al. 2003). This 10-core biopsy protocol that emphasises lateral and apical placement (Bauer, Zeng et al. 2000) enhances detection of peripheral zone cancers, as we demonstrated in a comparative study (Philip J et al, 2004). We further confirmed the positive effect of sampling the peripheral region of the prostate, even when using a 12-core technique (Philip J et al., 2006). Without this lateral direction, 12-core biopsies may be negative despite a very high index of suspicion of prostatic malignancy (Abd, Goodman et al. 2011, Serefoglu, Altinova et al. 2012). This is probably because many cancers originate peripherally (Presti, Chang et al. 2000). Any hypoechoic areas in the peripheral zone should be included in the biopsy strategy. In addition, it may be necessary to perform digitally guided biopsies of an indurated or suspicious area. Recommendations to maximise cancer detection have included strategies incorporating more regions such as transition and lateral peripheral zones (Epstein, Walsh et al. 1997, Levine, Ittman et al. 1998).

3. Considerations for Gland Volume

Detecting prostate cancers in larger prostates is often more difficult than in smaller glands. While more studies suggest that obtaining more cores from larger prostates can increase the rate of cancer detection, a recent report on 750 patients acknowledged the inverse relationship between gland volume and ability to detect prostate cancer in larger glands, disputes the value of more core biopsies (Durkan, Sheikh et al. 2002). Thus, it may be beneficial to obtain more biopsy cores from large volume glands. However, there are no objective evidence-based data to support such a presumption.

4. Length and Diameter of Cores, Type of Needles Used

It is important to provide adequate diagnostic material with an effort to obtain intact cores. This is directly dependent on the type of needle biopsy gun employed and the training and dexterity of the operator. Assessment of training and efficiency should be monitored by audit.

5. Maintaining Source Identification of Individual Cores When Sent for Pathological Examination

To alleviate workload in the laboratory, it has been suggested that cores from the apex, mid and base from one side of the prostate can be submitted in one container and reported collectively. Adopting such a protocol is suboptimal and contravenes established WHO (Bostwick, Foster et al. 2000) and European (Boccon-Gibod, van der Kwast et al. 2004) guidelines. Whatever the employed protocol, it is important to maintain separation of biopsy samples according to side (right/left) throughout submission and pathology reporting. Samples obtained via modifications of the sampling protocol (such as few cores from a palpable abnormality), need to be oriented and kept separately for processing and reporting.

Assessment of a patient as a potential candidate for locus-specific treatment (i.e. radical prostatectomy or selective radiotherapy) requires the comprehensive accumulation of data from several distinct clinical, radiological and pathological sources. Key to this assessment is a detailed understanding of the precise location, and possible extent, of an identified prostate cancer. Therefore, individual prostatic tissue core biopsies, taken separately, should be retained and processed separately and not “lumped together” in single cassettes. Furthermore, the practice of attempting to arrange multiple needle-cores of tissue into single cassettes in some sort of sequence marked by the presence of some identifiable agent, or non-prostatic tissue (e.g. mouse liver has been suggested) should be discouraged as unnecessary:

- Introduction of unwarranted complexity.
- Increased likelihood of error with respect to identification of individual cases.
- Increased handling of tissues.
- Increased need to cut multiple sections to fully examine each of the tissue cores with consequent loss of tissue for additional studied (e.g. immuno-histochemistry).

While apparently pragmatic, it is probable that a cost-benefit assessment of “tissue aggregation” is likely to indicate the compromise of detailed information for the unlikely gain of speed in tissue processing, and hence should be discouraged.

6. Guidelines for Adequate Prostatic Needle Biopsy Processing

Irrespective of any screening programme, heightened awareness of prostate cancer in the general population, together with increased digital rectal examination and use of PSA testing has increased the detection of early prostatic neoplasia. By definition, many of these lesions tend to be smaller in size and to approximate closer to the normal range of morphological appearances, thus making diagnosis more difficult (Epstein 2004). Some guidance is suggested that might assist in resolving this dilemma:

The number of biopsies embedded in one cassette

Urologists want to know at which site the prostate cancer is located. This information may help to decide whether a unilateral nerve sparing prostatectomy is possible. In cases of lesions suspect for adenocarcinoma, it is important to know their localization for site-specific repeat biopsy. It is considered preferable that each biopsy core is embedded in a manner that it may be identified uniquely. Originally, this was considered to be separately (Boccon-Gibod, van der Kwast et al. 2004). However, indelible colour-marking at the time of grossing and cassetting allows several cores to be aligned parallel to one another and processed simultaneously. This recommendation was not given explicitly in previous guidelines (Bostwick, Foster et al. 2000).

The procedure of embedding of needle biopsies into paraffin wax

The objective is to achieve a maximum amount of tissue for microscopic evaluation since this correlates with the cancer detection rate (Iczkowski, Casella et al. 2002, van der Kwast, Lopes et al. 2003). However, needle biopsies tend to become curved after fixation and flat embedding of the biopsy cores enhances the amount of tissue that is examined by the pathologist. Strengthening of biopsy cores can be achieved by stretching the needle biopsy tissue between two nylon meshes or by wrapping them in a piece of paper. This can be done even after initial formalin fixation. Such manipulations are not recommended because manual handling, however minimal, is associated with traumatisation to the tissue and impaired morphology.

The number of sections from each biopsy core (levels of sectioning)

Earlier reports (Bostwick, Foster et al. 2000, Iczkowski, Casella et al. 2002) have demonstrated that it is mandatory to cut several sections of each biopsy core at different levels in order not to miss small foci of adenocarcinoma. Cutting biopsy cores at different levels may allow a definite diagnosis of adenocarcinoma when a small focus is found at a single level. Practically, laboratories need to agree a single strategy for cutting and staining prostatic needle biopsy specimens. Reyes and Humphrey provide strong evidence that complete histologic sampling with serial sections entirely through the paraffin wax block is unnecessary (Reyes and Humphrey 1998). Their study of 200 consecutive cases showed that the initial three slides, each containing several sections, identified all of the contained cancers, thus making further work redundant. Furthermore, after an initial diagnosis of pure high-trade PIN, generation of additional sections is also unnecessary. Rather, the patient should undergo clinical follow-up and full rebiopsy. It is recommended that sections of a core at two different levels are sufficient. Ribbons between the two levels can be stored for cases where additional histologic slides or immunohistochemistry are required.

The length of each biopsy core should be recorded as an integrated part of the macroscopic description for comparison with the length on the glass slide.

7. Guidelines for Uniform Reporting of Prostate Lesions

Reporting of the histopathology of prostatic needle biopsies is performed in accordance with ISUP 2005 guidelines (Epstein et al 2005) and should be as unequivocal and concise as possible. This means that the nomenclature of prostatic lesions in pathology reports should be uniform. Terms like “atypical glands”, “glandular atypia”, “probably malignant”, but “benign not excluded” should be avoided, since it is not clear to the urologist, which further action should be taken. The adequacy of prostatic needle biopsies should be mentioned in the pathology report. An inadequate prostatic core biopsy core is defined as a core lacking glandular structures, is traumatized or is fragmented such that a diagnosis of prostate cancer cannot be reliable confirmed or excluded. The underlying terms seem to have proven their value and consistency in the last several years:

Benign

This includes fibromuscular or glandular hyperplasia, various forms of atrophy as well as foci of chronic (lymphocytic) inflammation. Although multiple biopsies with post-atrophic hyperplasia may be reported as such, in itself this finding has no clinical consequence. Distinctions between the above entities are of limited clinical relevance and subject to considerable inter-observer variation (Oppenheimer, Kahane et al. 1997). Pathologists should make themselves aware of benign prostatic lesions that mimic carcinoma (Foster and Sakr 2001).

Acute inflammation

This lesion is characterized by damage to glandular structures. This finding might explain increased serum PSA levels.

Chronic granulomatous inflammation

Includes xanthogranulomatous inflammation. This condition can cause strongly elevated PSA levels and cause a false positive digital rectal examination.

Adenosis

Adenosis fortunately is a very rare finding in peripheral zone derived needle biopsies. Adenosis which is characterised by a condensation of small glands surrounded by sporadic basal cells is also known as atypical adenomatous hyperplasia (Bostwick, Srigley et al. 1993). The latter term is not recommended because the term “atypical” may suggest a relation with malignancy.

Prostatic intra-epithelial neoplasia (PIN)

Although initially low grade and high grade PIN were distinguished, only (high grade) PIN is reported. Cytological and nuclear abnormalities contributing to the various entities recognised as “low grade” PIN

has no prognostic relevance. Only “high grade” PIN is associated with an adverse risk of developing prostate cancer. Therefore, HGPIN is now reported simply as ‘PIN’. The extent and architectural pattern of PIN may also be reported, since some of these variants (solid, comedo and cribriform) may be associated with unfavourable prostate cancer as they may represent intraductal spread of high-grade cancer (Cohen, McNeal et al. 2000). Isolated diagnosis of HG PIN necessitates a repeat biopsy within six months. There is a strong association of previous PIN with cancer (Meng, Shinohara et al. 2003). Men with PIN have been reported to have up to 36% cancer detection rates in subsequent biopsies (Davidson, Bostwick et al. 1995, Goeman, Joniau et al. 2003).

Atypical small acinar proliferation (ASAP)

This entity is not *per se* malignant, but may be a harbinger, if not a precursor, of malignancy and therefore requires to be identified and reported. Prostate needle biopsies occasionally contain cytologically and architecturally atypical small acinar proliferations (ASAP) that are suspicious for, but not diagnostic of, adenocarcinoma. These histological appearances include the number of acini per focus of ASAP, number of foci, variation in acinar size, nuclear enlargement, presence of luminal mucin, crystalloids, adjacent focal chronic inflammation, adjacent atrophy, and adjacent prostatic intraepithelial neoplasia (PIN). Stratification of suspicion in cases of ASAP without PIN results in "favor benign”, “uncertain”, and “favor carcinoma". In an otherwise benign biopsy, the high predictive value of ASAP for subsequent adenocarcinoma promotes a repeat biopsy. Nevertheless, no single clinical or pathologic feature has been identified that increases the likelihood of subsequent cancer.

Adenocarcinoma

The location(s) of the foci of adenocarcinoma should be recorded. In this way the number of positive biopsies is implicitly known to the clinician. If a small focus (< 3 mm) of adenocarcinoma is present in only one needle biopsy this may be recorded in the conclusion as “focal adenocarcinoma”. It is also recommended to estimate the proportion of tumour involvement of the needle biopsies, particularly with the advent of quantitative prostate biopsy for prediction of organ confined disease (Haese, Chaudhari et al. 2003). The extent of cancer involvement may be given in percentage of the biopsy core lengths (e.g. > 5%, 10%, 20%, etc).

Appearance suspicious, but not diagnostic, of adenocarcinoma

If the lesion is too small and/or lacks sufficient criteria to be able to make a definite diagnosis of adenocarcinoma (Cheville, Reznicek et al. 1997, Epstein 1999).

The possibility of other malignancies, including carcinosarcoma, sarcoma and adenocarcinoma of the colon etc. masquerading as prostatic carcinoma should be considered. When adenocarcinoma, high grade PIN, or lesions suspicious for adenocarcinoma are present at separate sites, these should also be reported separately.

Reporting grades of differentiation

It is recommended to use the Gleason scoring system. Advantages of this grading system are its general use and the large amount of data in the literature on its prognostic impact and accuracy. As advocated by Epstein (Epstein 2000) Gleason scores of 2 to 4 to prostatic adenocarcinoma should not be attributed on peripheral zone needle biopsies. It is recommended that the lowest Gleason growth

pattern that can be assessed in needle biopsies is growth pattern 3, implying that a Gleason score of 6 is the lowest possible on peripheral zone needle biopsies (Epstein, Allsbrook et al. 2005).

An important feature of the Gleason system is that it takes into account the heterogeneity of prostate cancer by including the two most prominent growth patterns. Thus, in sextant needle biopsies the Gleason score can range from 6 to 10. The location of a separate area of high grade (Gleason growth pattern 4 or 5) cancer should always be reported irrespective of its extent in the needle biopsy (Srigley, Amin et al. 2000). In radical prostatectomy specimens a second growth pattern that comprises less than 5% of the tumour area is not included in the Gleason score. This rule does not apply for high-grade cancer in prostatic needle biopsies: Irrespective of the amount of the second growth pattern it is included in the Gleason score. If, in addition to growth pattern 3, both pattern 4 and 5 are present in the needle biopsies the pattern 5 will be included in the Gleason score (i.e. 3 + 5 = 8).

Immunohistochemistry

Of all special investigations available to diagnostic surgical pathologists only immunohistochemistry has yet found a regular place in the compendium of techniques routinely-accepted techniques. Antibodies to detect high-molecular weight cytokeratins (Brawer, Peehl et al. 1985, Purnell, Heatfield et al. 1987, Grignon, Ro et al. 1988, Hedrick and Epstein 1989, Devaraj and Bostwick 1993) and to αMeCo racemase (Xu, Stolk et al. 2000, Jiang, Woda et al. 2001, Luo, Zha et al. 2002, Rubin, Zhou et al. 2002) are principally employed. Antibody 34βE12 (previously known as “keratin 903” and generated by Gown and Vogel in 1982 (Gown and Vogel 1982) reveals absence of basal cells from glandular epithelial structures to be indicative (but not diagnostic) of malignant change. Conversely, enhanced expression of αMeCo racemase (identified as P504S and first reported by Xu et al. (Xu, Stolk et al. 2000) occurs in neoplastic prostatic epithelial cells of both luminal and basal types (Evans 2003). Both reagents should be used by experienced immunohistochemistry and interpreted with caution by experienced diagnostic pathologists to avoid erroneous interpretation of appearances. It cannot be emphasized strongly enough that underpinning such diagnostic adjuncts is the “Gold Standard” of good morphological assessment.

Quality control indicators

The standardization of processing and reporting on prostate needle biopsies, will be increasingly important in order to assure quality and to avoid medico-legal complications.

As a quality indicator the average length of needle biopsies and the percentage of inadequate biopsies can be used. The frequency of suspect lesions might give an indication as to the level of certainty reached by the pathologist. This is of course related to several factors, including the population under study, the quality of needle biopsies and their processing as well as the staining and the confidence of the pathologist. The percentage of suspect lesions should not rise above 5% since this will lead to a too frequent indication of repeat biopsies.

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APPENDIX E

ANOGENITAL DISTANCE MEASUREMENT PROTOCOL

INTRODUCTION

The importance of fetal exposure with respect to the development of prostate cancer was proposed in the early 1990s [1], although little evidence has been provided subsequently. Androgens are critical for the development of the male reproductive system during gestation and they stimulate the growth of the perineal region in male offspring [2]. Anogenital distance (i.e. the distance between the centre of the anus and the genitals) is a sexually dimorphic phenotype that tracks through life, with men having longer anogenital distances than women. In animals, anogenital distance has been shown to be related to the action of fetal androgens, and exposure to chemicals such as dioxins that exhibit antiandrogenic activity results in shorter distances in male rats [3]. In studies conducted in children, anogenital distance has been associated with endocrine disruptors such as phthalates [4]. In a recent study conducted by CREAL, AGD was also associated with dioxins [5]. Studies conducted in young adults reported that a shorter anoscrotal distance was a predictor of a low sperm concentration [6], and a longer anoscrotal distance was associated with fatherhood, a higher sperm density and a higher total motile sperm count [7]. A recent study we conducted in Barcelona, we found that longer anogenital distance, comprising a phenotype associated with normal *in utero* sexual development in men, was associated with a lower risk of prostate cancer [8]. In the present study, we aim to evaluate the association of anogenital distance with the risk of prostate cancer and also evaluate whether it is associated with clinical characteristics and prognosis.

This is among the first studies on AGD in adults. We do not know well what factors are associated with AGD and so several major factors related to health and cancer have been included, such as information about diet. We would like to evaluate which factors, if any, may influence AGD and/or prostate cancer risk and their possible relationships. AGD will be performed on a subgroup of PROFILE participants who consent to take part in this sub-study.

MATERIAL AND METHODS

Equipment required

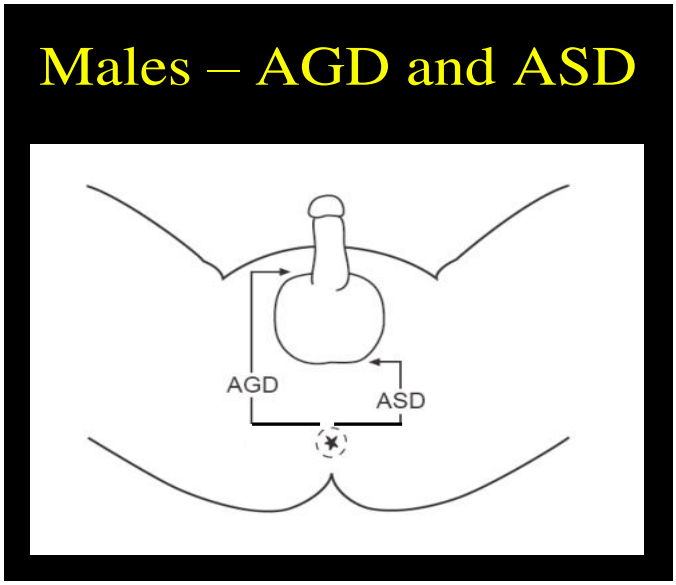
- Caliper (20 cm long – 15 cm is sometimes enough)
- Alcohol 70% (to clean the caliper)
- Hygienic wet towel (to clean the anogenital area before the measurements)
- Gynecological examination chair or medical chair with leg support

Measurements

1. Anogenital distance (AGD or AGD_{AP}): distance from anus (upper edge) to upper penis

2. Anoscrotal distance (ASD or AGD_{AS}): distance from anus (upper edge) to scrotum. It is necessary to hold the scrotum in order to be able to perform the measurement

3. A one page participant questionnaire will accompany this part of the study



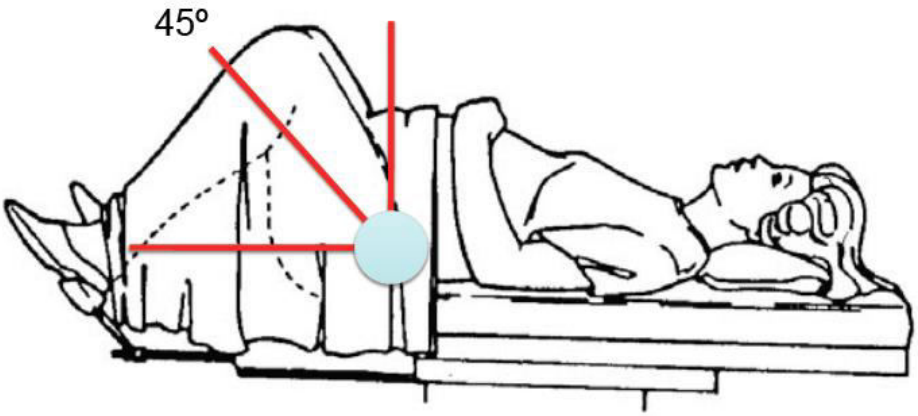
How to proceed with the measurements

Before starting the measurements:

- Adjust both leg supports of the medical chair at the same height and put the back rest in horizontal position. If the subject has vertigo or cervical problems and is not able to stay in a horizontal position, adjust the back rest of the chair at 30º respect to the horizontal.

- The subject has to be naked from the waist down. We offer the subject a hygienic wet towel to clean the anogenital area and a hospital gown to cover himself.

- To proceed with the measurements, the subject should lie down on the medical chair, with the buttocks in the edge of the chair and his feet on the leg support (typical position for a gynecological exam), with his thighs at a 45° angle to the medical chair (see below). It is very important that the subject is correctly positioned before proceeding with the measurements. If there is any reason (hip fracture, low flexibility, etc.) that impedes the subject to adopt the correct position, it will not be possible to do the measurements.



Measuring:

1. To facilitate the procedure and do the correct measurement, the subject has to be in a still position.
2. Always clean the caliper with alcohol before using it.
3. Before the measurement of AGD, open the caliper to around 70-100mm to facilitate the positioning of the caliper into the genital area.
4. Keeping the subject in the correct position, put the upper edge of the caliper in the upper part of the measurement (upper penis or scrotum).
5. Keep opening the caliper till the superior vertex of the anus.
6. Check that the upper edge is still in the correct position. If not, correct it.
7. Write down the measure of the caliper (in mm and 2 decimals).
8. Take the caliper out, close it and adjust it again to zero.
9. Repeat the measurement (steps 4-8) two more times (within-examiner variability)
10. Adjust the caliper to zero and then proceed with the second measure.

When NOT do the measurements?

We will not proceed with the measurements in the following circumstances:

1. The subject cannot take the correct position (flexibility, fractures, surgery in the area, etc.)
2. If the subject has an erection, wait till it suppresses and then proceed with the measurements
3. If the subject has any condition that changes the anatomy of the area: external hemorrhoids, surgery, etc.
4. If the subject has an active infection in the external genital area (genital herpes, HPV warts)

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APPENDIX F

(See Prostate Imaging – Reporting and Data Systems (PIRADS) V2.0, 2015 (separate document))
https://www.acr.org/-/media/ACR/Files/RADS/Pi-RADS/PIRADS-V2.pdf

APPENDIX G

Clinically relevant genes for patient and family*	Potentially clinically relevant genes for patient and family ^	Genes not considered clinically relevant for family members (but believed to be involved in the development of prostate cancer)			
BRCA1	*ATM*	*ALKBH3*	*FANCM**	*PER1*	*TOP2B*
BRCA2	*BAP1*	*ANO7*	*GADD45A*	*PMS1*	*TOP3A*
MLH1	*BRIP1*	*APEX1*	*GEN1*	*PNKP*	*TP53BP1*
MSH2	*CDH1*	*AR*	*GTF2H2*	*POLK*	*WRN*
MSH6	*CDK4*	*ATR*	*GTF2H3*	*POLM*	*XAB2*
PMS2	*CDKN2A*	*ATRIP*	*GTF2H4*	*POLN*	*XPA**
RB1	*CHEK2*	*BARD1*	*HOXB13*	*POLQ*	*XPC**
	PALB2	*BLM**	*HUS1*	*PRSS1*	*XRCC1*
	POLD1	*CCNH*	*LIG1*	*RAD1*	*XRCC2*
	POLE	*CDC25C*	*LIG3*	*RAD50*	*XRCC4*
	POT1	*CHD1*	*LIG4*	*RAD51B*	*XRCC5 (Ku)*
	PTCH1	*CHEK1*	*MLH3*	*RAD52*	
	PTEN	*CLK2*	*MMS19*	*RAD54B*	
	RAD51C	*DCLRE1A*	*MNAT1*	*RAD54L*	
	RAD51D	*EME1*	*MPG*	*RECQL*	
	SMAD4	*EME2*	*MRE11A*	*RECQL4*	
	SMARCA4	*ERCC2*	*MSH5*	*RECQL5*	
	STK11	*ERCC5*	*MSR1*	*RINT1*	
	TP53	*ERCC6*	*MUTYH**	*RNASEL*	
		ESR2	*NABP2*	*RPA1*	
		EXO1	*NBN**	*SETMAR*	
		FAM175A	*NEIL1*	*SLX4*	
		*FANCA**	*NEIL2*	*SMUG1*	

		*FANCD2**	*NTHL1*	*SPOP*	
		ALKBH3	*FANCM**	*PER1*	
		ANO7	*GADD45A*	*PMS1*	

***** Mutations in these genes will be confirmed in a clinically accredited laboratory so that predictive testing can be offered to relatives where appropriate.

^ Mutations in these genes will be confirmed in a clinically accredited laboratory only when an appropriate family history is also present and where the patient is affected with prostate cancer themselves. For unaffected men with an alive relative, we would invite them to be tested through the study and where the affected man is also mutation positive, then clinical testing would be performed.

Appendix Chapter 3

Raw stata data output

Significant Cancer – ROC curves for all variables

3.1.1 PRS

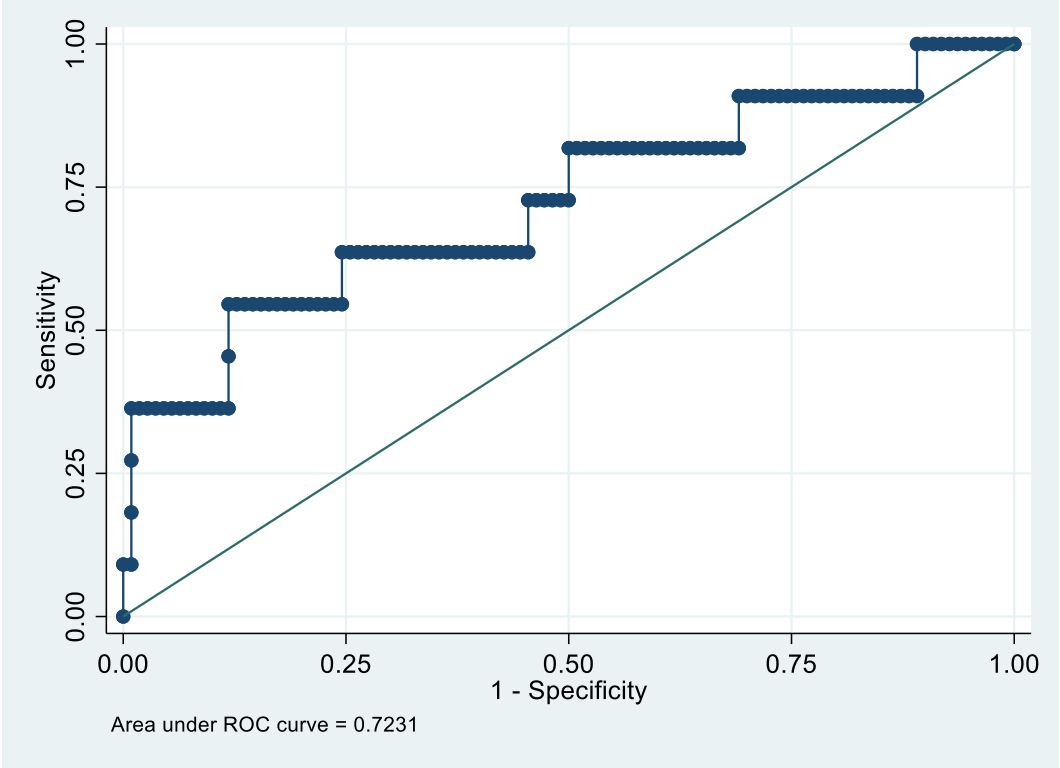


Figure 0.1 Area under the ROC curve for predictor variable PRS (continuous variable) for clinically significant cancer detection

3.1.2 PSA

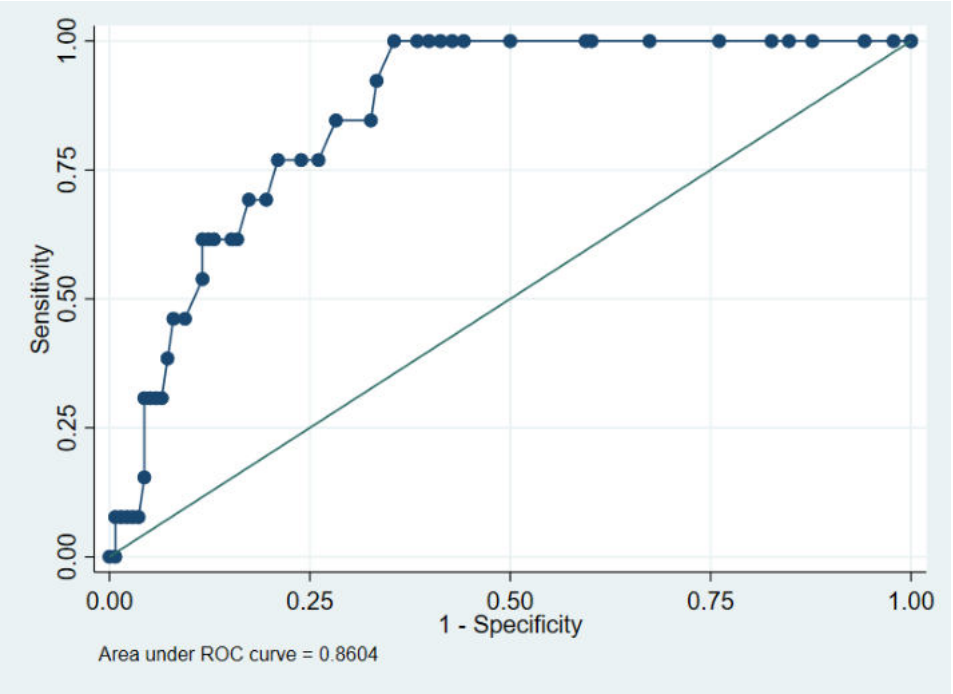


Figure 0.2. graph displaying the area under the ROC curve for predictor variable (PSA) for clinically significant cancer detection.

3.1.3 PSAD

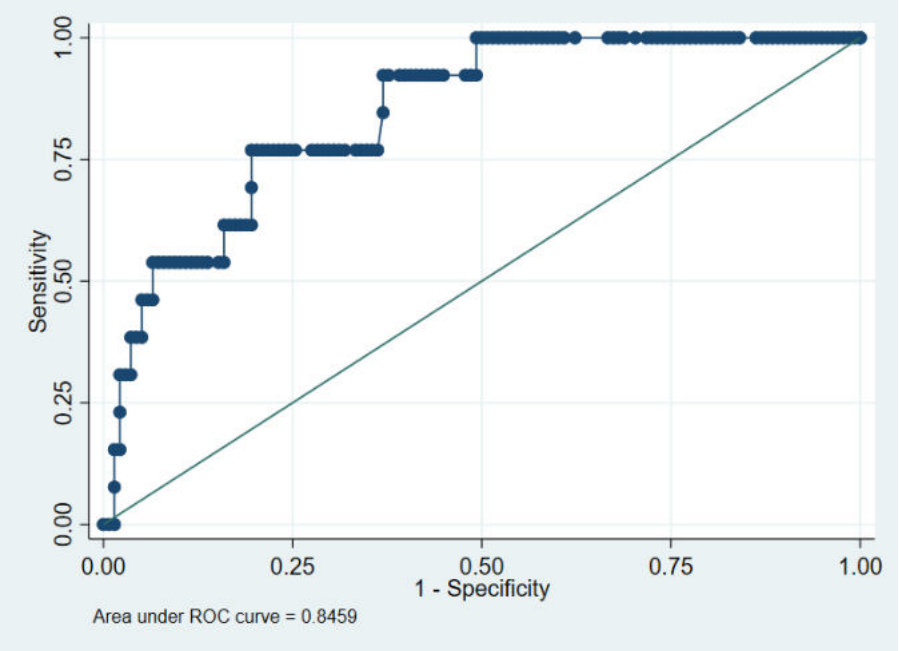


Figure 0.3. graph displaying the area under the ROC curve for predictor variable (PSAD) for clinically significant cancer detection.

3.1.4 Age

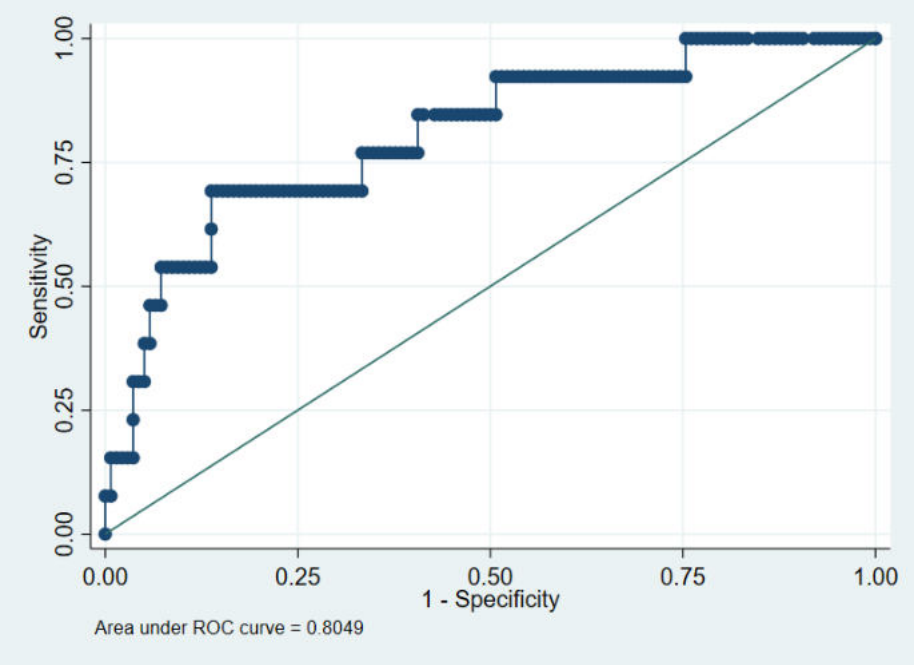


Figure 0.4. graph displaying the area under the ROC curve for predictor variable (age) for clinically significant cancer detection.

3.1.5 Prostate Vol

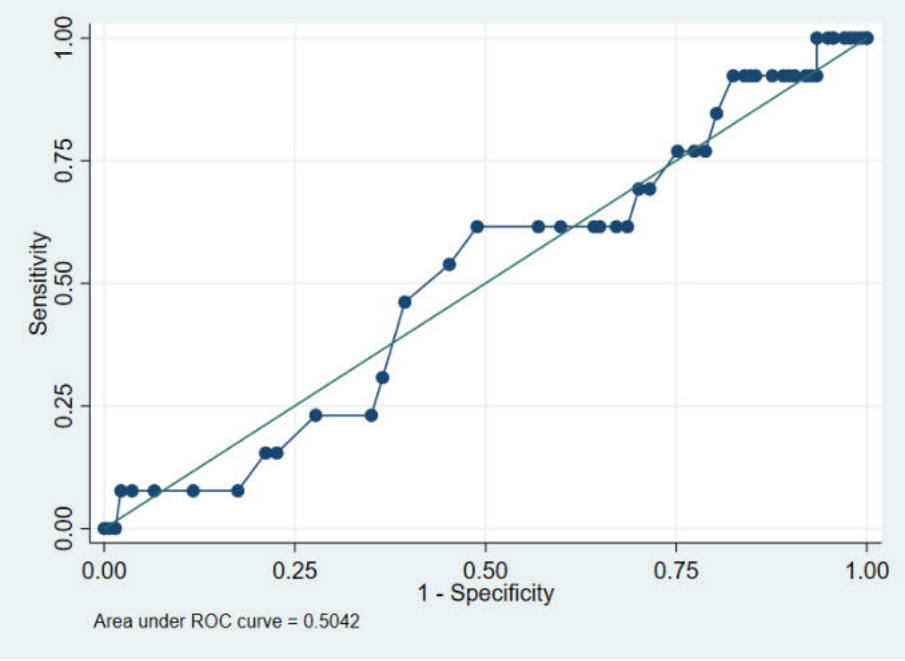


Figure 0.5. graph displaying the area under the ROC curve for predictor variable (prostate volume) for clinically significant cancer detection.

3.2 Any Cancer – ROC curves for all variables

3.2.1 PRS

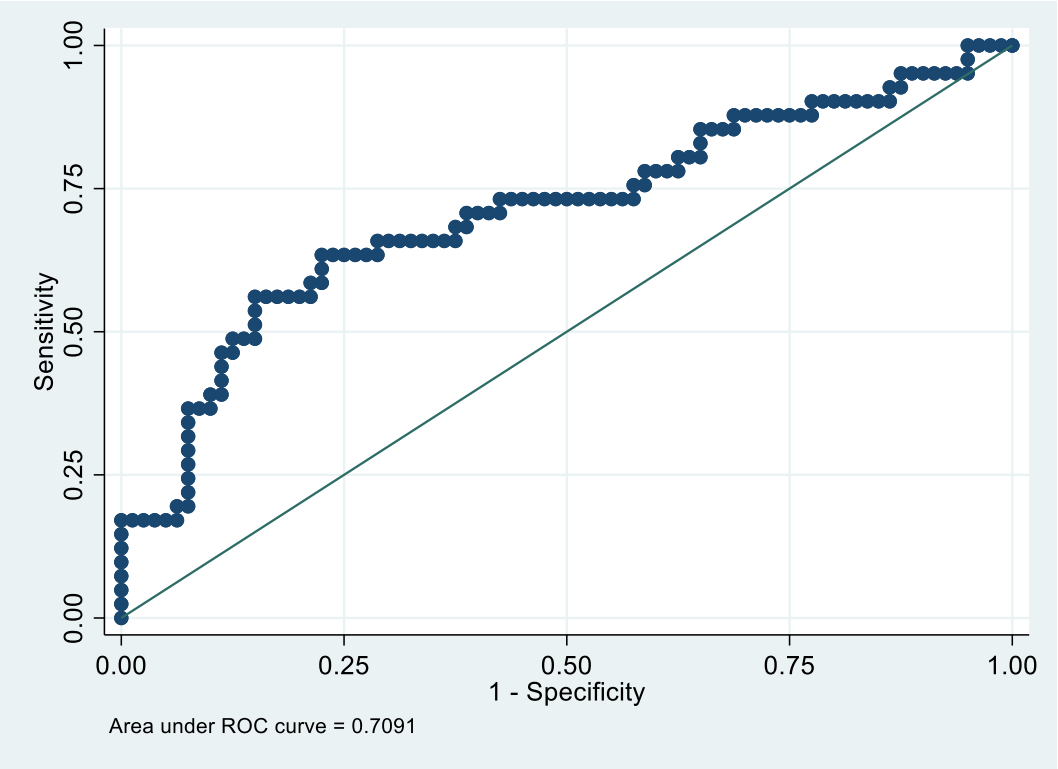


Figure 0.6 graph displaying the area under the ROC curve for predictor variable (PRS as a continuous variabe) for any cancer detection.

3.2.2 PSA

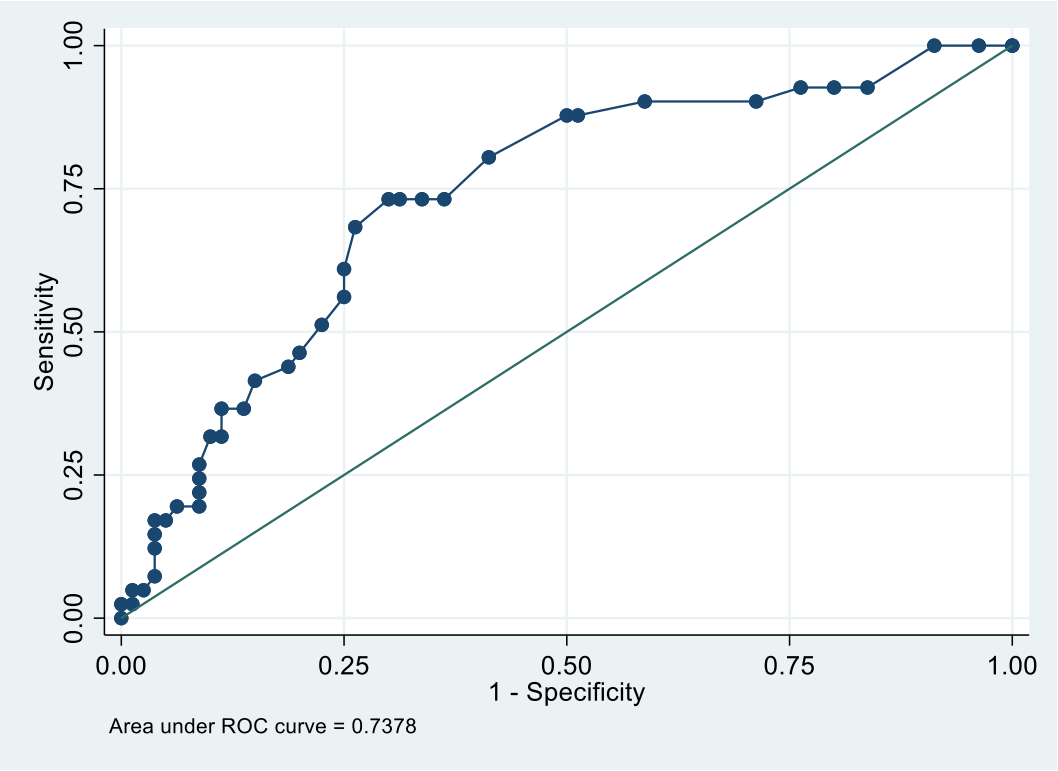


Figure 0.7 graph displaying the area under the ROC curve for predictor variable (PSA as a continuous variable) for any cancer detection.

3.2.3 PSAD

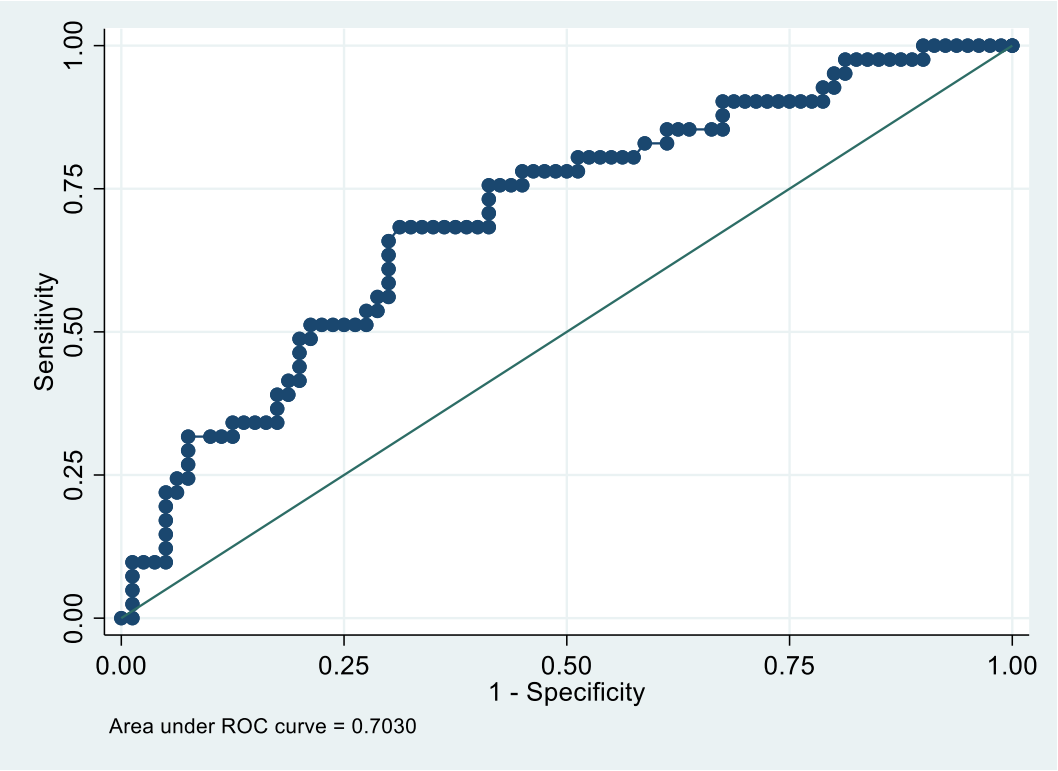


Figure 0.8 graph displaying the area under the ROC curve for predictor variable (PSAD as a continuous variable) for any cancer detection.

3.2.4 Age

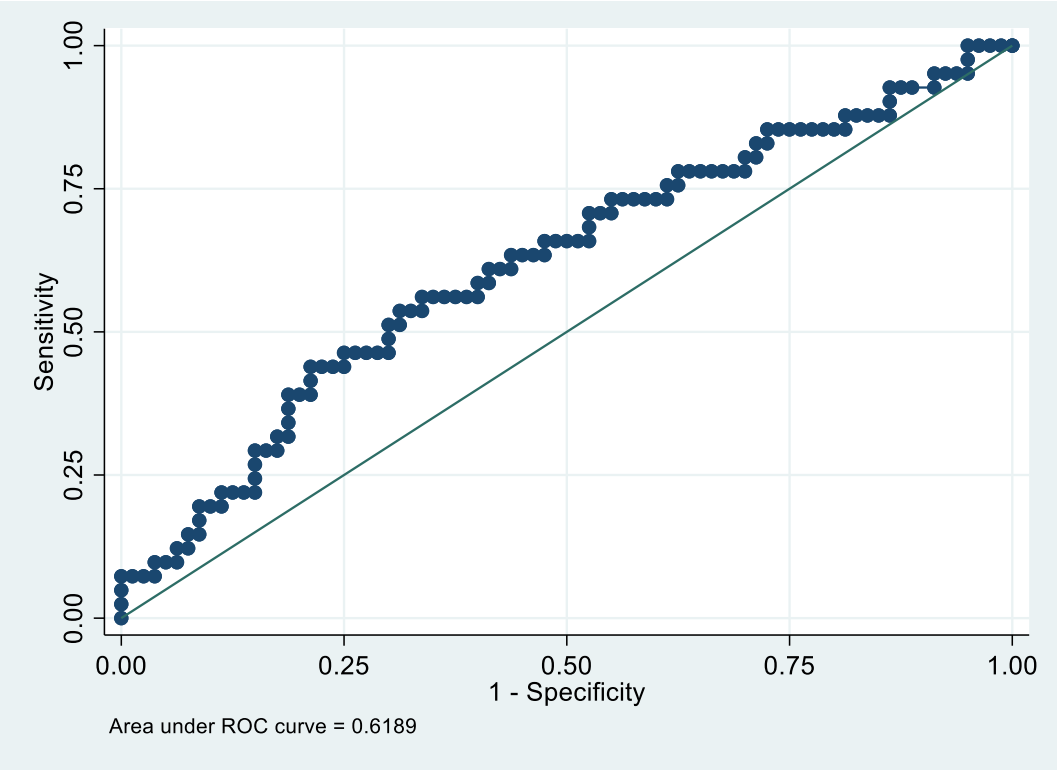


Figure 0.9 graph displaying the area under the ROC curve for predictor variable (age as a continuous variable) for any cancer detection.

3.2.5 Prostate Vol

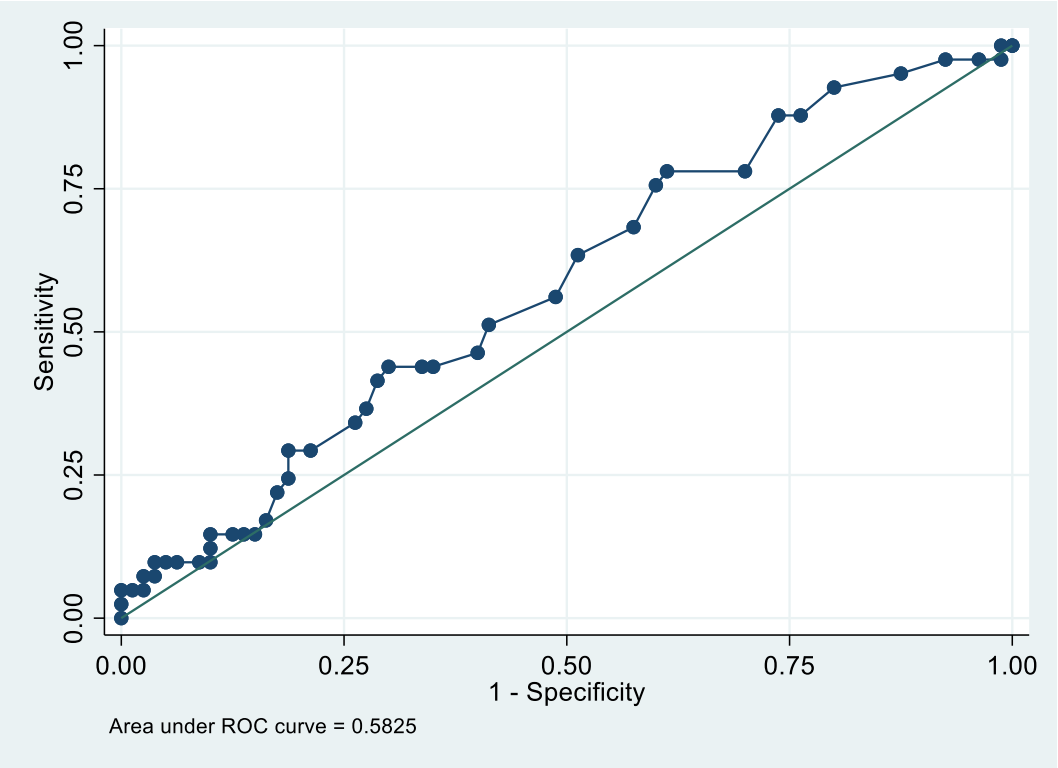


Figure 0.10 graph displaying the area under the ROC curve for predictor variable (prostate volume as a continuous variable) for any cancer detection.

PSA	Pirads	Obs	Rank	Sum
	1	9		691.000
	2	94		6060.000
	3	26		2221.000
	4	19		2083.000
	5	3		421.000

chi-squared = 25.473 with 4 d.f.
probability = 0.0001

chi-squared with ties = 25.531 with 4 d.f.
probability = 0.0001

Table 1

PSAD	Pirads	Obs	Rank	Sum
	1	9		794.000
	2	94		6059.500
	3	26		2149.000
	4	19		2031.500
	5	3		442.000

chi-squared = 25.325 with 4 d.f.
probability = 0.0001
chi-squared with ties = 25.327 with 4 d.f.
probability = 0.0001

Table 2

Table 9. Kruskal-Wallis equality-of-populations rank test for PSAD, to assess for difference in means between PSA in each category of Pirads.

Age	Pirads	Obs	Rank	Sum
	1	9		571.000
	2	94		6543.000
	3	26		1944.500
	4	19		2071.000
	5	3		346.500

chi-squared = 16.036 with 4 d.f.
probability = 0.0030

chi-squared with ties = 16.036 with 4 d.f.
probability = 0.0030

Table 10. Kruskal-Wallis equality-of-populations rank test for age, to assess for difference in means between PSA in each category of Pirads.

Table 3

MRI Vol	Pirads	Obs	Rank	Sum
	1	9		618.000
	2	93		6592.500
	3	26		2179.000
	4	19		1729.000
	5	3		206.500

chi-squared = 4.711 with 4 d.f.
probability = 0.3183
chi-squared with ties = 4.719 with 4 d.f.
probability = 0.3174

Table 4 - Kruskal-Wallis equality-of-populations rank test for MRI Volume, to assess for difference in means between PSA in each category of Pirads.

PSAD	Pirads	Obs	Rank	Sum
	1	9		794.000
	2	94		6059.500
	3	26		2149.000
	4	19		2031.500
	5	3		442.000

chi-squared = 25.325 with 4 d.f.
probability = 0.0001
chi-squared with ties = 25.327 with 4 d.f.
probability = 0.0001

Table 5 - Kruskal-Wallis equality-of-populations rank test for PSAD, to assess for difference in means between PSA in each category of Pirads.

PSA	Pirads 3-5	Obs	Rank	Sum
	N	103		6751.000
	Y	48		4725.000

chi-squared = 18.522 with 1 d.f.
probability = 0.0001
chi-squared with ties = 18.564 with 1 d.f.
probability = 0.0001

Table 19. Kruskal-Wallis equality-of-populations rank test for age, to assess for difference in means between PSA in category of Pirads, grouped by Pirads 1-2 vs Pirads 3-5

MRI Vol	Pirads 3-5	Obs	Rank	Sum
	N	102		7210.500
	Y	48		4114.500

chi-squared = 3.905 with 1 d.f.
probability = 0.0481

Table 20. Kruskal-Wallis equality-of-populations rank test for age, to assess for difference in means between MRI vol in category of Pirads, grouped by Pirads 1-2 vs Pirads 3-5

chi-squared with ties = 3.912 with 1 d.f.
probability = 0.0479

Age	Pirads 3-5	Obs	Rank	Sum
	N	103		7114.000
	Y	48		4362.000

chi-squared = 8.141 with 1 d.f.
probability = 0.0043
chi-squared with ties = 8.141 with 1 d.f.
probability = 0.0043

Table 21. Kruskal-Wallis equality-of-populations rank test for age, to assess for difference in means between age in category of Pirads, grouped by Pirads 1-2 vs Pirads 3-5

PSAD	Pirads 3-5	Obs	Rank	Sum
	N	103		6853.500
	Y	48		4622.500

chi-squared = 15.164 with 1 d.f.
probability = 0.0001
chi-squared with ties = 15.165 with 1 d.f.
probability = 0.0001

Table 22. Kruskal-Wallis equality-of-populations rank test for age, to assess for difference in means between PSAD in category of Pirads, grouped by Pirads 1-2 vs Pirads 3-5

Age	Pirads 4-5	Obs	Rank	Sum
	0	128		8927.500
	1	23		2548.500

chi-squared = 17.184 with 1 d.f.
probability = 0.0001
chi-squared with ties = 17.184 with 1 d.f.
probability = 0.0001

Table 23. Kruskal-Wallis equality-of-populations rank test for age, to assess for difference in means between age in category of Pirads, grouped by Pirads 1-3 vs Pirads 4-5

PSA	Pirads 4-5	Obs	Rank	Sum
	0	128		8831.000
	1	23		2645.000

chi-squared = 21.577 with 1 d.f.
probability = 0.0001
chi-squared with ties = 21.625 with 1 d.f.
probability = 0.0001

Table 24. Kruskal-Wallis equality-of-populations rank test for age, to assess for difference in means between PSA in category of Pirads, grouped by Pirads 1-3 vs Pirads 4-5

MRI Vol	Pirads 4-5	Obs	Rank	Sum
	0	127		9242.500
	1	23		2082.500

chi-squared = 3.257 with 1 d.f.
probability = 0.0711
chi-squared with ties = 3.263 with 1 d.f.
probability = 0.0709

Table 25. Kruskal-Wallis equality-of-populations rank test for age, to assess for difference in means between MRI Volume in category of Pirads, grouped by Pirads 1-3 vs Pirads 4-5

PSAD	Pirads 4-5	Obs	Rank	Sum
	0	128		8901.500
	1	23		2574.500

chi-squared = 18.318 with 1 d.f.
probability = 0.0001
chi-squared with ties = 18.320 with 1 d.f.
probability = 0.0001

Table 26. Kruskal-Wallis equality-of-populations rank test for age, to assess for difference in means between PSAD in category of Pirads, grouped by Pirads 1-3 vs Pirads 4-5

Adjusted predictions **Number of obs = 151**
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()
1._at : prebiopsypsa = 0
2._at : prebiopsypsa = .5
3._at : prebiopsypsa = 1
4._at : prebiopsypsa = 1.5
5._at : prebiopsypsa = 2
6._at : prebiopsypsa = 2.5
7._at : prebiopsypsa = 3
8._at : prebiopsypsa = 3.5

9._at : prebiopsypsa = 4
10._at : prebiopsypsa = 4.5
11._at : prebiopsypsa = 5
12._at : prebiopsypsa = 5.5
13._at : prebiopsypsa = 6
14._at : prebiopsypsa = 6.5
15._at : prebiopsypsa = 7
16._at : prebiopsypsa = 7.5
17._at : prebiopsypsa = 8
18._at : prebiopsypsa = 8.5
19._at : prebiopsypsa = 9

Delta-method

	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#abnormalMRI						
1#N	0.003	0.004	0.820	0.411	-0.004	0.011
1#Y	0.070	0.046	1.530	0.125	-0.019	0.160
2#N	0.004	0.005	0.860	0.391	-0.005	0.013
2#Y	0.089	0.050	1.770	0.077	-0.010	0.187
3#N	0.005	0.006	0.890	0.373	-0.006	0.017
3#Y	0.112	0.054	2.060	0.039	0.006	0.218
4#N	0.007	0.007	0.920	0.357	-0.007	0.021
4#Y	0.140	0.057	2.440	0.015	0.027	0.252
5#N	0.009	0.009	0.950	0.343	-0.009	0.026
5#Y	0.173	0.060	2.880	0.004	0.055	0.291
6#N	0.011	0.011	0.970	0.332	-0.011	0.033
6#Y	0.213	0.063	3.360	0.001	0.089	0.337
7#N	0.014	0.014	0.980	0.325	-0.014	0.042
7#Y	0.259	0.069	3.760	0.000	0.124	0.393
8#N	0.018	0.018	0.990	0.321	-0.018	0.054
8#Y	0.311	0.078	4.000	0.000	0.158	0.463
9#N	0.023	0.024	0.990	0.321	-0.023	0.070
9#Y	0.368	0.091	4.040	0.000	0.189	0.546
10#N	0.030	0.030	0.990	0.324	-0.030	0.090
10#Y	0.429	0.108	3.980	0.000	0.218	0.640
11#N	0.038	0.040	0.970	0.330	-0.039	0.116
11#Y	0.492	0.125	3.930	0.000	0.246	0.738
12#N	0.049	0.051	0.960	0.339	-0.051	0.150
12#Y	0.556	0.141	3.930	0.000	0.278	0.833
13#N	0.062	0.067	0.940	0.348	-0.068	0.193
13#Y	0.617	0.154	4.020	0.000	0.316	0.918
14#N	0.079	0.086	0.920	0.358	-0.090	0.248
14#Y	0.676	0.160	4.210	0.000	0.361	0.990
15#N	0.100	0.111	0.900	0.367	-0.117	0.317
15#Y	0.729	0.161	4.520	0.000	0.413	1.045
16#N	0.125	0.141	0.890	0.374	-0.151	0.402
16#Y	0.776	0.157	4.950	0.000	0.469	1.084
17#N	0.156	0.177	0.880	0.378	-0.191	0.504
17#Y	0.817	0.148	5.520	0.000	0.527	1.108
18#N	0.193	0.219	0.880	0.379	-0.237	0.622
18#Y	0.853	0.136	6.270	0.000	0.586	1.119
19#N	0.236	0.266	0.890	0.376	-0.285	0.757
19#Y	0.882	0.122	7.220	0.000	0.642	1.121

Table 6 significant cancer. Psa + pirads 3-5 MRI

Logistic regression

signifvsinsignifor~a	Coef.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
1b.priorPSA	1	.	.	.	.	.	
2.priorPSA	.925	1.085	-0.07	.947	.093	9.226	
3.priorPSA	1	.645	0.00	1	.283	3.538	
Constant	.108	.057	-4.23	0	.039	.303	***

Mean dependent var	0.097	SD dependent var	0.297
Pseudo r-squared	0.000	Number of obs	134.000
Chi-square	0.005	Prob > chi2	0.997
Akaike crit. (AIC)	91.346	Bayesian crit. (BIC)	100.039

*** *p*<.01, ** *p*<.05, * *p*<.1

Table 7 LR model for Prior PSA + signif ca

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()
1._at : ageatstudy~y = 40
prebiopsypsa = 0
2._at : ageatstudy~y = 40
prebiopsypsa = 1
3._at : ageatstudy~y = 40
prebiopsypsa = 2
4._at : ageatstudy~y = 40
prebiopsypsa = 3
5._at : ageatstudy~y = 40
prebiopsypsa = 4
6._at : ageatstudy~y = 40
prebiopsypsa = 5
7._at : ageatstudy~y = 40
prebiopsypsa = 6
8._at : ageatstudy~y = 40
prebiopsypsa = 7
9._at : ageatstudy~y = 40
prebiopsypsa = 8
10._at : ageatstudy~y = 40
prebiopsypsa = 9
11._at : ageatstudy~y = 50
prebiopsypsa = 0
12._at : ageatstudy~y = 50
prebiopsypsa = 1
13._at : ageatstudy~y = 50
prebiopsypsa = 2
14._at : ageatstudy~y = 50
prebiopsypsa = 3
15._at : ageatstudy~y = 50
prebiopsypsa = 4

```
16._at     : ageatstudy~y  =       50
             prebiopsypsa  =        5
17._at     : ageatstudy~y  =       50
             prebiopsypsa  =        6
18._at     : ageatstudy~y  =       50
             prebiopsypsa  =        7
19._at     : ageatstudy~y  =       50
             prebiopsypsa  =        8
20._at     : ageatstudy~y  =       50
             prebiopsypsa  =        9
21._at     : ageatstudy~y  =       60
             prebiopsypsa  =        0
22._at     : ageatstudy~y  =       60
             prebiopsypsa  =        1
23._at     : ageatstudy~y  =       60
             prebiopsypsa  =        2
24._at     : ageatstudy~y  =       60
             prebiopsypsa  =        3
25._at     : ageatstudy~y  =       60
             prebiopsypsa  =        4
26._at     : ageatstudy~y  =       60
             prebiopsypsa  =        5
27._at     : ageatstudy~y  =       60
             prebiopsypsa  =        6
28._at     : ageatstudy~y  =       60
             prebiopsypsa  =        7
29._at     : ageatstudy~y  =       60
             prebiopsypsa  =        8
30._at     : ageatstudy~y  =       60
             prebiopsypsa  =        9
31._at     : ageatstudy~y  =       70
             prebiopsypsa  =        0
32._at     : ageatstudy~y  =       70
             prebiopsypsa  =        1
33._at     : ageatstudy~y  =       70
             prebiopsypsa  =        2
34._at     : ageatstudy~y  =       70
             prebiopsypsa  =        3
35._at     : ageatstudy~y  =       70
             prebiopsypsa  =        4
36._at     : ageatstudy~y  =       70
             prebiopsypsa  =        5
37._at     : ageatstudy~y  =       70
             prebiopsypsa  =        6
38._at     : ageatstudy~y  =       70
             prebiopsypsa  =        7
39._at     : ageatstudy~y  =       70
             prebiopsypsa  =        8
40._at     : ageatstudy~y  =       70
             prebiopsypsa  =        9
```

	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#abnormalMRI						
1#N	0.000	0.001	0.570	0.566	-0.001	0.002
1#Y	0.006	0.009	0.670	0.506	-0.012	0.024
2#N	0.001	0.001	0.600	0.551	-0.001	0.002
2#Y	0.009	0.013	0.710	0.480	-0.016	0.035
3#N	0.001	0.001	0.610	0.540	-0.002	0.003
3#Y	0.014	0.019	0.740	0.460	-0.023	0.051
4#N	0.001	0.002	0.620	0.536	-0.003	0.005
4#Y	0.021	0.028	0.760	0.449	-0.034	0.076
5#N	0.002	0.003	0.620	0.539	-0.004	0.008
5#Y	0.032	0.042	0.760	0.446	-0.051	0.115
6#N	0.003	0.005	0.600	0.547	-0.006	0.012
6#Y	0.048	0.064	0.750	0.452	-0.077	0.173
7#N	0.004	0.007	0.580	0.562	-0.010	0.019
7#Y	0.071	0.097	0.730	0.463	-0.119	0.262
8#N	0.006	0.012	0.550	0.579	-0.016	0.029
8#Y	0.105	0.147	0.720	0.475	-0.183	0.393
9#N	0.010	0.019	0.530	0.599	-0.027	0.047
9#Y	0.152	0.216	0.700	0.483	-0.272	0.575
10#N	0.015	0.030	0.500	0.619	-0.044	0.074
10#Y	0.214	0.305	0.700	0.483	-0.384	0.812
11#N	0.002	0.002	0.740	0.461	-0.003	0.006
11#Y	0.027	0.026	1.010	0.314	-0.025	0.078
12#N	0.002	0.003	0.790	0.430	-0.003	0.008
12#Y	0.040	0.034	1.170	0.242	-0.027	0.107
13#N	0.004	0.004	0.830	0.408	-0.005	0.012
13#Y	0.060	0.045	1.330	0.182	-0.028	0.147
14#N	0.005	0.006	0.850	0.398	-0.007	0.018
14#Y	0.088	0.060	1.460	0.145	-0.030	0.206
15#N	0.008	0.010	0.840	0.402	-0.011	0.027
15#Y	0.128	0.085	1.500	0.134	-0.039	0.296
16#N	0.012	0.015	0.810	0.419	-0.018	0.042
16#Y	0.183	0.124	1.470	0.141	-0.061	0.427
17#N	0.019	0.024	0.760	0.445	-0.029	0.066
17#Y	0.254	0.179	1.420	0.155	-0.096	0.605
18#N	0.028	0.039	0.710	0.476	-0.049	0.105
18#Y	0.342	0.244	1.400	0.161	-0.136	0.820
19#N	0.042	0.064	0.660	0.507	-0.082	0.167
19#Y	0.442	0.307	1.440	0.150	-0.160	1.044
20#N	0.063	0.101	0.620	0.535	-0.136	0.261
20#Y	0.547	0.352	1.550	0.120	-0.143	1.237
21#N	0.007	0.008	0.820	0.410	-0.009	0.023
21#Y	0.108	0.077	1.410	0.159	-0.042	0.258
22#N	0.010	0.011	0.900	0.367	-0.012	0.032
22#Y	0.155	0.081	1.910	0.056	-0.004	0.315
23#N	0.015	0.016	0.960	0.335	-0.016	0.047
23#Y	0.219	0.081	2.720	0.007	0.061	0.377
24#N	0.023	0.023	1.000	0.318	-0.022	0.069
24#Y	0.299	0.081	3.690	0.000	0.140	0.459
25#N	0.035	0.035	1.000	0.319	-0.034	0.104
25#Y	0.394	0.098	4.040	0.000	0.203	0.586
26#N	0.052	0.054	0.960	0.336	-0.054	0.159
26#Y	0.498	0.131	3.810	0.000	0.242	0.754
27#N	0.078	0.085	0.910	0.362	-0.089	0.244
27#Y	0.602	0.164	3.670	0.000	0.281	0.923
28#N	0.114	0.132	0.860	0.388	-0.145	0.372
28#Y	0.697	0.183	3.810	0.000	0.339	1.056
29#N	0.163	0.198	0.820	0.409	-0.225	0.551

29#Y	0.778	0.183	4.250	0.000	0.420	1.137
30#N	0.229	0.284	0.810	0.419	-0.327	0.785
30#Y	0.843	0.167	5.040	0.000	0.515	1.170
31#N	0.029	0.039	0.730	0.463	-0.048	0.106
31#Y	0.349	0.234	1.490	0.137	-0.111	0.808
32#N	0.043	0.055	0.790	0.427	-0.064	0.151
32#Y	0.449	0.223	2.020	0.044	0.012	0.886
33#N	0.065	0.076	0.850	0.396	-0.085	0.214
33#Y	0.554	0.199	2.790	0.005	0.164	0.944
34#N	0.095	0.107	0.890	0.371	-0.113	0.304
34#Y	0.654	0.171	3.820	0.000	0.319	0.990
35#N	0.138	0.149	0.930	0.352	-0.153	0.430
35#Y	0.743	0.147	5.070	0.000	0.455	1.030
36#N	0.197	0.204	0.960	0.336	-0.204	0.597
36#Y	0.815	0.126	6.490	0.000	0.569	1.061
37#N	0.271	0.271	1.000	0.317	-0.260	0.803
37#Y	0.870	0.106	8.190	0.000	0.662	1.078
38#N	0.362	0.341	1.060	0.288	-0.306	1.030
38#Y	0.911	0.088	10.390	0.000	0.739	1.083
39#N	0.464	0.398	1.170	0.244	-0.316	1.244
39#Y	0.940	0.070	13.360	0.000	0.802	1.077
40#N	0.569	0.427	1.330	0.183	-0.269	1.406
40#Y	0.960	0.055	17.490	0.000	0.852	1.067

Contrasts of adjusted predictions **Number of obs = 151**
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()

1._at : ageatstudy~y = 40
prebiopsypsa = 0
2._at : ageatstudy~y = 40
prebiopsypsa = 1
3._at : ageatstudy~y = 40
prebiopsypsa = 2
4._at : ageatstudy~y = 40
prebiopsypsa = 3
5._at : ageatstudy~y = 40
prebiopsypsa = 4
6._at : ageatstudy~y = 40
prebiopsypsa = 5
7._at : ageatstudy~y = 40
prebiopsypsa = 6
8._at : ageatstudy~y = 40
prebiopsypsa = 7
9._at : ageatstudy~y = 40
prebiopsypsa = 8
10._at : ageatstudy~y = 40
prebiopsypsa = 9
11._at : ageatstudy~y = 50
prebiopsypsa = 0
12._at : ageatstudy~y = 50
prebiopsypsa = 1
13._at : ageatstudy~y = 50
prebiopsypsa = 2

14._at : ageatstudy~y = 50
prebiopsypsa = 3
15._at : ageatstudy~y = 50
prebiopsypsa = 4
16._at : ageatstudy~y = 50
prebiopsypsa = 5
17._at : ageatstudy~y = 50
prebiopsypsa = 6
18._at : ageatstudy~y = 50
prebiopsypsa = 7
19._at : ageatstudy~y = 50
prebiopsypsa = 8
20._at : ageatstudy~y = 50
prebiopsypsa = 9
21._at : ageatstudy~y = 60
prebiopsypsa = 0
22._at : ageatstudy~y = 60
prebiopsypsa = 1
23._at : ageatstudy~y = 60
prebiopsypsa = 2
24._at : ageatstudy~y = 60
prebiopsypsa = 3
25._at : ageatstudy~y = 60
prebiopsypsa = 4
26._at : ageatstudy~y = 60
prebiopsypsa = 5
27._at : ageatstudy~y = 60
prebiopsypsa = 6
28._at : ageatstudy~y = 60
prebiopsypsa = 7
29._at : ageatstudy~y = 60
prebiopsypsa = 8
30._at : ageatstudy~y = 60
prebiopsypsa = 9
31._at : ageatstudy~y = 70
prebiopsypsa = 0
32._at : ageatstudy~y = 70
prebiopsypsa = 1
33._at : ageatstudy~y = 70
prebiopsypsa = 2
34._at : ageatstudy~y = 70
prebiopsypsa = 3
35._at : ageatstudy~y = 70
prebiopsypsa = 4
36._at : ageatstudy~y = 70
prebiopsypsa = 5
37._at : ageatstudy~y = 70
prebiopsypsa = 6
38._at : ageatstudy~y = 70
prebiopsypsa = 7
39._at : ageatstudy~y = 70
prebiopsypsa = 8

40._at : ageatstudy~y = 70
prebiopsypsa = 9

	df	chi2	P>chi2
abnormalMRI@_at			
1	1	0.440	0.509
2	1	0.490	0.483
3	1	0.540	0.463
4	1	0.570	0.452
5	1	0.570	0.449
6	1	0.560	0.454
7	1	0.540	0.464
8	1	0.510	0.474
9	1	0.500	0.480
10	1	0.510	0.477
11	1	0.990	0.320
12	1	1.320	0.250
13	1	1.710	0.191
14	1	2.040	0.153
15	1	2.170	0.141
16	1	2.110	0.146
17	1	2.020	0.155
18	1	2.030	0.154
19	1	2.280	0.131
20	1	2.970	0.085
21	1	1.920	0.166
22	1	3.430	0.064
23	1	6.470	0.011
24	1	10.710	0.001
25	1	12.510	0.000
26	1	12.010	0.001
27	1	12.300	0.001
28	1	14.250	0.000
29	1	15.190	0.000
30	1	9.680	0.002
31	1	2.290	0.131
32	1	4.240	0.039
33	1	8.020	0.005
34	1	13.550	0.000
35	1	16.600	0.000
36	1	12.900	0.000
37	1	7.190	0.007
38	1	3.600	0.058
39	1	1.850	0.174
40	1	1.020	0.312
Joint	4	17.580	0.002

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()
1._at : ageatstudy~y = 40
prebiopsypsa = 0
2._at : ageatstudy~y = 40
prebiopsypsa = 1
3._at : ageatstudy~y = 40
prebiopsypsa = 2
4._at : ageatstudy~y = 40

prebiopsypsa = 3
5._at : ageatstudy~y = 40
prebiopsypsa = 4
6._at : ageatstudy~y = 40
prebiopsypsa = 5
7._at : ageatstudy~y = 40
prebiopsypsa = 6
8._at : ageatstudy~y = 40
prebiopsypsa = 7
9._at : ageatstudy~y = 40
prebiopsypsa = 8
10._at : ageatstudy~y = 40
prebiopsypsa = 9
11._at : ageatstudy~y = 50
prebiopsypsa = 0
12._at : ageatstudy~y = 50
prebiopsypsa = 1
13._at : ageatstudy~y = 50
prebiopsypsa = 2
14._at : ageatstudy~y = 50
prebiopsypsa = 3
15._at : ageatstudy~y = 50
prebiopsypsa = 4
16._at : ageatstudy~y = 50
prebiopsypsa = 5
17._at : ageatstudy~y = 50
prebiopsypsa = 6
18._at : ageatstudy~y = 50
prebiopsypsa = 7
19._at : ageatstudy~y = 50
prebiopsypsa = 8
20._at : ageatstudy~y = 50
prebiopsypsa = 9
21._at : ageatstudy~y = 60
prebiopsypsa = 0
22._at : ageatstudy~y = 60
prebiopsypsa = 1
23._at : ageatstudy~y = 60
prebiopsypsa = 2
24._at : ageatstudy~y = 60
prebiopsypsa = 3
25._at : ageatstudy~y = 60
prebiopsypsa = 4
26._at : ageatstudy~y = 60
prebiopsypsa = 5
27._at : ageatstudy~y = 60
prebiopsypsa = 6
28._at : ageatstudy~y = 60
prebiopsypsa = 7
29._at : ageatstudy~y = 60
prebiopsypsa = 8
30._at : ageatstudy~y = 60
prebiopsypsa = 9
31._at : ageatstudy~y = 70
prebiopsypsa = 0
32._at : ageatstudy~y = 70
prebiopsypsa = 1
33._at : ageatstudy~y = 70
prebiopsypsa = 2
34._at : ageatstudy~y = 70
prebiopsypsa = 3
35._at : ageatstudy~y = 70

```
          prebiopsypsa    =          4
36._at     : ageatstudy~y    =         70
          prebiopsypsa    =          5
37._at     : ageatstudy~y    =         70
          prebiopsypsa    =          6
38._at     : ageatstudy~y    =         70
          prebiopsypsa    =          7
39._at     : ageatstudy~y    =         70
          prebiopsypsa    =          8
40._at     : ageatstudy~y    =         70
          prebiopsypsa    =          9
```

Delta-method

	Contrast	Std.Err.	z	P>z
abnormalMRI@_at				
(Y vs base) 1	0.006	0.009	0.660	0.509
(Y vs base) 2	0.009	0.012	0.700	0.483
(Y vs base) 3	0.013	0.018	0.730	0.463
(Y vs base) 4	0.020	0.027	0.750	0.452
(Y vs base) 5	0.030	0.040	0.760	0.449
(Y vs base) 6	0.045	0.061	0.750	0.454
(Y vs base) 7	0.067	0.092	0.730	0.464
(Y vs base) 8	0.099	0.138	0.720	0.474
(Y vs base) 9	0.142	0.201	0.710	0.480
(Y vs base) 10	0.199	0.280	0.710	0.477
(Y vs base) 11	0.025	0.025	0.990	0.320
(Y vs base) 12	0.038	0.033	1.150	0.250
(Y vs base) 13	0.056	0.043	1.310	0.190
(Y vs base) 14	0.083	0.058	1.430	0.153
(Y vs base) 15	0.120	0.081	1.470	0.141
(Y vs base) 16	0.171	0.117	1.450	0.146
(Y vs base) 17	0.236	0.166	1.420	0.155
(Y vs base) 18	0.314	0.220	1.430	0.154
(Y vs base) 19	0.400	0.265	1.510	0.131
(Y vs base) 20	0.484	0.281	1.720	0.085
(Y vs base) 21	0.101	0.073	1.380	0.166
(Y vs base) 22	0.145	0.078	1.850	0.064
(Y vs base) 23	0.204	0.080	2.540	0.011
(Y vs base) 24	0.276	0.084	3.270	0.001
(Y vs base) 25	0.359	0.102	3.540	0.000
(Y vs base) 26	0.446	0.129	3.470	0.001
(Y vs base) 27	0.524	0.150	3.510	0.000
(Y vs base) 28	0.584	0.155	3.770	0.000
(Y vs base) 29	0.615	0.158	3.900	0.000
(Y vs base) 30	0.613	0.197	3.110	0.002
(Y vs base) 31	0.320	0.211	1.510	0.131
(Y vs base) 32	0.406	0.197	2.060	0.039
(Y vs base) 33	0.490	0.173	2.830	0.005
(Y vs base) 34	0.559	0.152	3.680	0.000
(Y vs base) 35	0.604	0.148	4.070	0.000
(Y vs base) 36	0.618	0.172	3.590	0.000
(Y vs base) 37	0.599	0.223	2.680	0.007
(Y vs base) 38	0.549	0.289	1.900	0.058
(Y vs base) 39	0.476	0.350	1.360	0.174
(Y vs base) 40	0.391	0.386	1.010	0.312

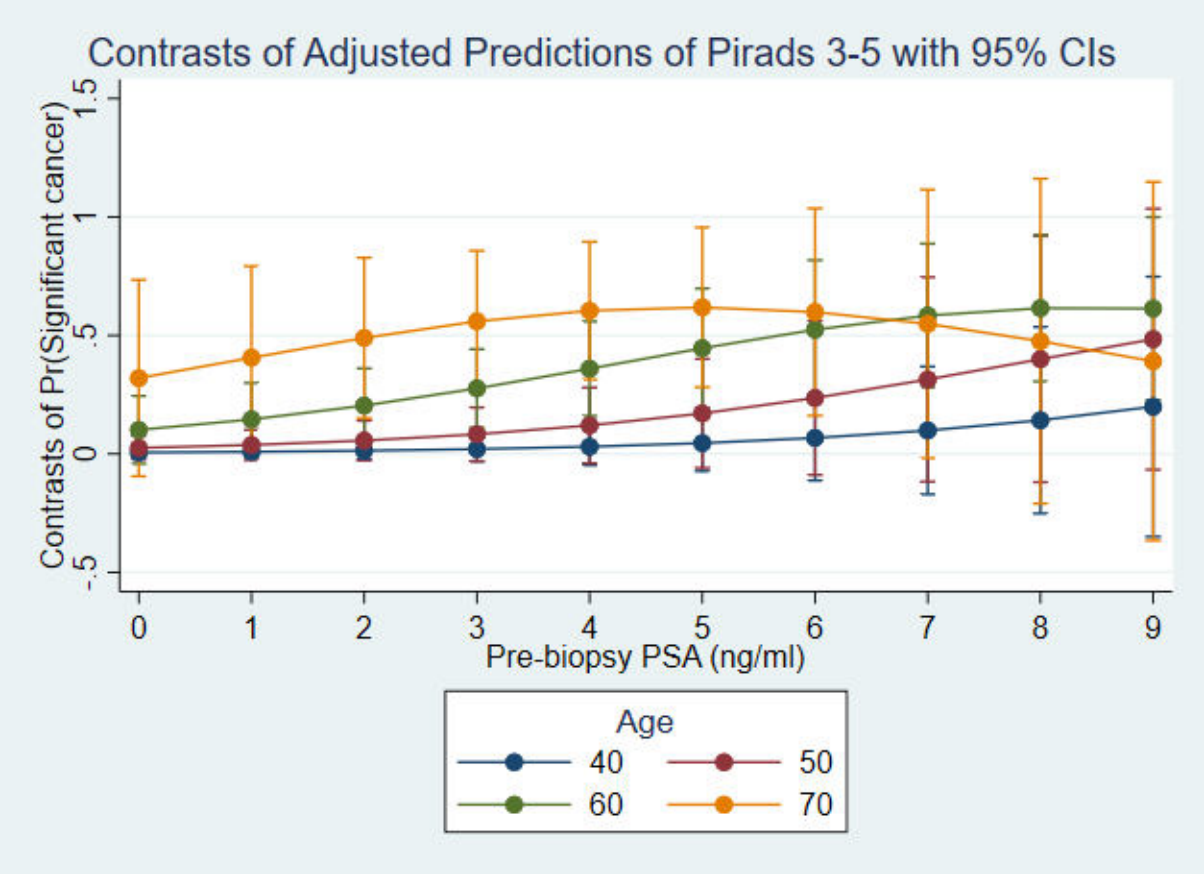


Figure 11

Adjusted predictions **Number of obs = 151**
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()
1._at : ageatstudy~y = 40
prebiopsypsa = 0
2._at : ageatstudy~y = 40
prebiopsypsa = 1
3._at : ageatstudy~y = 40
prebiopsypsa = 2
4._at : ageatstudy~y = 40
prebiopsypsa = 3
5._at : ageatstudy~y = 40
prebiopsypsa = 4
6._at : ageatstudy~y = 40
prebiopsypsa = 5
7._at : ageatstudy~y = 40
prebiopsypsa = 6
8._at : ageatstudy~y = 40
prebiopsypsa = 7
9._at : ageatstudy~y = 40
prebiopsypsa = 8
10._at : ageatstudy~y = 40
prebiopsypsa = 9

```
11._at      : ageatstudy~y   =       50
              prebiopsypsa   =        0
12._at      : ageatstudy~y   =       50
              prebiopsypsa   =        1
13._at      : ageatstudy~y   =       50
              prebiopsypsa   =        2
14._at      : ageatstudy~y   =       50
              prebiopsypsa   =        3
15._at      : ageatstudy~y   =       50
              prebiopsypsa   =        4
16._at      : ageatstudy~y   =       50
              prebiopsypsa   =        5
17._at      : ageatstudy~y   =       50
              prebiopsypsa   =        6
18._at      : ageatstudy~y   =       50
              prebiopsypsa   =        7
19._at      : ageatstudy~y   =       50
              prebiopsypsa   =        8
20._at      : ageatstudy~y   =       50
              prebiopsypsa   =        9
21._at      : ageatstudy~y   =       60
              prebiopsypsa   =        0
22._at      : ageatstudy~y   =       60
              prebiopsypsa   =        1
23._at      : ageatstudy~y   =       60
              prebiopsypsa   =        2
24._at      : ageatstudy~y   =       60
              prebiopsypsa   =        3
25._at      : ageatstudy~y   =       60
              prebiopsypsa   =        4
26._at      : ageatstudy~y   =       60
              prebiopsypsa   =        5
27._at      : ageatstudy~y   =       60
              prebiopsypsa   =        6
28._at      : ageatstudy~y   =       60
              prebiopsypsa   =        7
29._at      : ageatstudy~y   =       60
              prebiopsypsa   =        8
30._at      : ageatstudy~y   =       60
              prebiopsypsa   =        9
31._at      : ageatstudy~y   =       70
              prebiopsypsa   =        0
32._at      : ageatstudy~y   =       70
              prebiopsypsa   =        1
33._at      : ageatstudy~y   =       70
              prebiopsypsa   =        2
34._at      : ageatstudy~y   =       70
              prebiopsypsa   =        3
35._at      : ageatstudy~y   =       70
              prebiopsypsa   =        4
36._at      : ageatstudy~y   =       70
              prebiopsypsa   =        5
```

37._at : ageatstudy~y = 70
prebiopsypsa = 6
38._at : ageatstudy~y = 70
prebiopsypsa = 7
39._at : ageatstudy~y = 70
prebiopsypsa = 8
40._at : ageatstudy~y = 70
prebiopsypsa = 9

Delta-method

	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#abnormalMRI45						
1 0	0.002	0.003	0.700	0.483	-0.003	0.007
1 1	0.012	0.020	0.620	0.535	-0.026	0.051
2 0	0.003	0.004	0.740	0.459	-0.005	0.010
2 1	0.019	0.028	0.660	0.511	-0.037	0.074
3 0	0.004	0.005	0.770	0.441	-0.007	0.015
3 1	0.028	0.041	0.690	0.491	-0.052	0.108
4 0	0.006	0.008	0.790	0.431	-0.010	0.023
4 1	0.042	0.059	0.720	0.474	-0.074	0.159
5 0	0.010	0.013	0.790	0.431	-0.015	0.034
5 1	0.064	0.086	0.740	0.460	-0.105	0.233
6 0	0.015	0.019	0.770	0.440	-0.023	0.053
6 1	0.094	0.125	0.760	0.450	-0.150	0.339
7 0	0.023	0.031	0.750	0.456	-0.037	0.083
7 1	0.138	0.178	0.770	0.439	-0.211	0.486
8 0	0.035	0.049	0.710	0.476	-0.061	0.130
8 1	0.196	0.246	0.800	0.425	-0.286	0.679
9 0	0.052	0.077	0.680	0.497	-0.098	0.203
9 1	0.273	0.326	0.840	0.402	-0.365	0.911
10 0	0.078	0.120	0.650	0.516	-0.157	0.312
10 1	0.365	0.403	0.900	0.366	-0.425	1.155
11 0	0.006	0.006	1.050	0.292	-0.005	0.018
11 1	0.040	0.044	0.930	0.352	-0.045	0.126
12 0	0.009	0.008	1.190	0.234	-0.006	0.025
12 1	0.061	0.058	1.050	0.292	-0.052	0.174
13 0	0.014	0.011	1.310	0.191	-0.007	0.036
13 1	0.090	0.076	1.180	0.236	-0.059	0.239
14 0	0.022	0.016	1.370	0.170	-0.009	0.053
14 1	0.132	0.101	1.310	0.190	-0.065	0.329
15 0	0.033	0.024	1.350	0.176	-0.015	0.081
15 1	0.189	0.133	1.420	0.157	-0.073	0.450
16 0	0.050	0.039	1.270	0.203	-0.027	0.126
16 1	0.263	0.175	1.500	0.133	-0.080	0.606
17 0	0.074	0.064	1.170	0.243	-0.050	0.199
17 1	0.353	0.222	1.590	0.112	-0.082	0.789
18 0	0.109	0.102	1.070	0.285	-0.091	0.310
18 1	0.456	0.266	1.710	0.087	-0.066	0.978
19 0	0.158	0.159	1.000	0.319	-0.153	0.470
19 1	0.562	0.294	1.910	0.056	-0.014	1.139
20 0	0.224	0.234	0.960	0.339	-0.235	0.683
20 1	0.663	0.298	2.230	0.026	0.079	1.247
21 0	0.021	0.016	1.320	0.186	-0.010	0.052
21 1	0.126	0.090	1.400	0.162	-0.051	0.303
22 0	0.031	0.020	1.590	0.112	-0.007	0.070
22 1	0.181	0.100	1.810	0.070	-0.015	0.377
23 0	0.047	0.026	1.850	0.064	-0.003	0.098

23 1	0.253	0.105	2.410	0.016	0.047	0.460
24 0	0.071	0.036	1.990	0.046	0.001	0.141
24 1	0.342	0.110	3.110	0.002	0.127	0.558
25 0	0.105	0.054	1.920	0.054	-0.002	0.211
25 1	0.444	0.121	3.660	0.000	0.206	0.681
26 0	0.152	0.087	1.750	0.080	-0.018	0.322
26 1	0.550	0.139	3.950	0.000	0.277	0.822
27 0	0.215	0.136	1.590	0.112	-0.051	0.481
27 1	0.652	0.155	4.220	0.000	0.349	0.955
28 0	0.296	0.199	1.490	0.136	-0.093	0.686
28 1	0.742	0.159	4.680	0.000	0.431	1.052
29 0	0.392	0.266	1.470	0.140	-0.129	0.913
29 1	0.815	0.149	5.460	0.000	0.522	1.107
30 0	0.497	0.322	1.550	0.122	-0.133	1.127
30 1	0.871	0.131	6.670	0.000	0.615	1.127
31 0	0.068	0.066	1.020	0.306	-0.062	0.197
31 1	0.331	0.210	1.570	0.115	-0.081	0.743
32 0	0.100	0.087	1.140	0.252	-0.071	0.271
32 1	0.431	0.205	2.100	0.036	0.029	0.834
33 0	0.146	0.115	1.260	0.206	-0.080	0.372
33 1	0.538	0.188	2.850	0.004	0.168	0.907
34 0	0.207	0.151	1.370	0.170	-0.089	0.503
34 1	0.641	0.166	3.860	0.000	0.315	0.966
35 0	0.286	0.195	1.470	0.142	-0.095	0.667
35 1	0.732	0.144	5.080	0.000	0.449	1.015
36 0	0.380	0.241	1.580	0.114	-0.091	0.852
36 1	0.807	0.124	6.520	0.000	0.565	1.050
37 0	0.485	0.279	1.740	0.083	-0.063	1.032
37 1	0.865	0.104	8.300	0.000	0.661	1.069
38 0	0.590	0.299	1.970	0.048	0.004	1.177
38 1	0.908	0.085	10.640	0.000	0.740	1.075
39 0	0.688	0.294	2.340	0.019	0.111	1.265
39 1	0.938	0.068	13.840	0.000	0.805	1.071
40 0	0.772	0.268	2.890	0.004	0.248	1.296
40 1	0.958	0.052	18.310	0.000	0.856	1.061

Table 8 adj preds mri 4-5, psa and age

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()
1._at : ageatstudy~y = 40
prebiopsypsa = 0
2._at : ageatstudy~y = 40
prebiopsypsa = 1
3._at : ageatstudy~y = 40
prebiopsypsa = 2
4._at : ageatstudy~y = 40
prebiopsypsa = 3
5._at : ageatstudy~y = 40
prebiopsypsa = 4
6._at : ageatstudy~y = 40
prebiopsypsa = 5
7._at : ageatstudy~y = 40
prebiopsypsa = 6
8._at : ageatstudy~y = 40

prebiopsypsa = 7
9._at : ageatstudy~y = 40
prebiopsypsa = 8
10._at : ageatstudy~y = 40
prebiopsypsa = 9
11._at : ageatstudy~y = 50
prebiopsypsa = 0
12._at : ageatstudy~y = 50
prebiopsypsa = 1
13._at : ageatstudy~y = 50
prebiopsypsa = 2
14._at : ageatstudy~y = 50
prebiopsypsa = 3
15._at : ageatstudy~y = 50
prebiopsypsa = 4
16._at : ageatstudy~y = 50
prebiopsypsa = 5
17._at : ageatstudy~y = 50
prebiopsypsa = 6
18._at : ageatstudy~y = 50
prebiopsypsa = 7
19._at : ageatstudy~y = 50
prebiopsypsa = 8
20._at : ageatstudy~y = 50
prebiopsypsa = 9
21._at : ageatstudy~y = 60
prebiopsypsa = 0
22._at : ageatstudy~y = 60
prebiopsypsa = 1
23._at : ageatstudy~y = 60
prebiopsypsa = 2
24._at : ageatstudy~y = 60
prebiopsypsa = 3
25._at : ageatstudy~y = 60
prebiopsypsa = 4
26._at : ageatstudy~y = 60
prebiopsypsa = 5
27._at : ageatstudy~y = 60
prebiopsypsa = 6
28._at : ageatstudy~y = 60
prebiopsypsa = 7
29._at : ageatstudy~y = 60
prebiopsypsa = 8
30._at : ageatstudy~y = 60
prebiopsypsa = 9
31._at : ageatstudy~y = 70
prebiopsypsa = 0
32._at : ageatstudy~y = 70
prebiopsypsa = 1
33._at : ageatstudy~y = 70
prebiopsypsa = 2
34._at : ageatstudy~y = 70

prebiopsypsa = 3
35._at : ageatstudy~y = 70
prebiopsypsa = 4
36._at : ageatstudy~y = 70
prebiopsypsa = 5
37._at : ageatstudy~y = 70
prebiopsypsa = 6
38._at : ageatstudy~y = 70
prebiopsypsa = 7
39._at : ageatstudy~y = 70
prebiopsypsa = 8
40._at : ageatstudy~y = 70
prebiopsypsa = 9

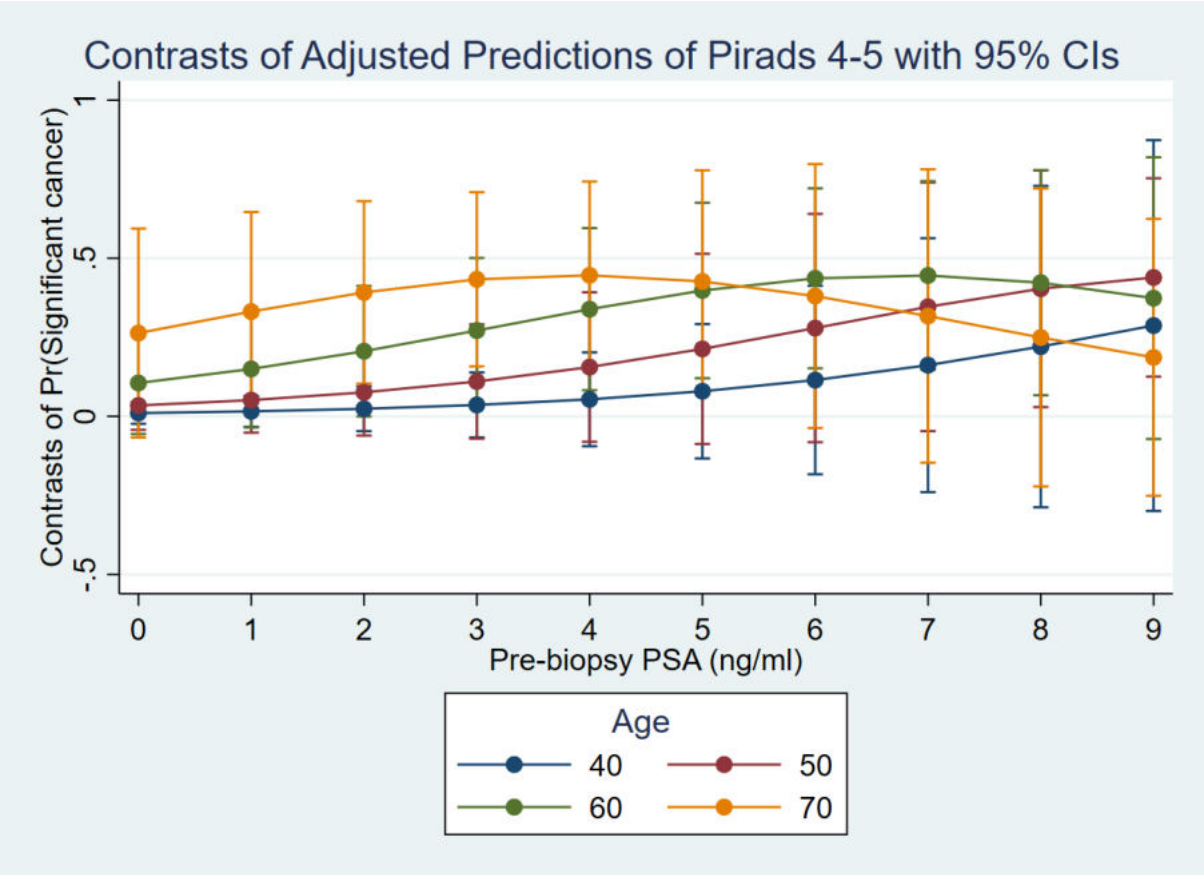
	df	chi2	P>chi2
abnormalMRI45@_at			
1	1	0.360	0.550
2	1	0.400	0.528
3	1	0.440	0.509
4	1	0.470	0.492
5	1	0.500	0.478
6	1	0.530	0.465
7	1	0.570	0.450
8	1	0.620	0.429
9	1	0.720	0.395
10	1	0.920	0.337
11	1	0.760	0.383
12	1	0.960	0.328
13	1	1.180	0.277
14	1	1.430	0.233
15	1	1.670	0.196
16	1	1.930	0.165
17	1	2.300	0.129
18	1	2.980	0.084
19	1	4.470	0.035
20	1	7.520	0.006
21	1	1.640	0.201
22	1	2.510	0.113
23	1	3.830	0.050
24	1	5.370	0.021
25	1	6.720	0.010
26	1	7.910	0.005
27	1	9.030	0.003
28	1	8.570	0.003
29	1	5.420	0.020
30	1	2.700	0.100
31	1	2.440	0.118
32	1	4.250	0.039
33	1	7.090	0.008
34	1	9.510	0.002
35	1	8.700	0.003
36	1	5.670	0.017
37	1	3.190	0.074
38	1	1.800	0.180
39	1	1.080	0.299
40	1	0.700	0.404
Joint	4	11.730	0.019

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()
1._at : ageatstudy~y = 40
prebiopsypsa = 0
2._at : ageatstudy~y = 40
prebiopsypsa = 1
3._at : ageatstudy~y = 40
prebiopsypsa = 2
4._at : ageatstudy~y = 40
prebiopsypsa = 3
5._at : ageatstudy~y = 40
prebiopsypsa = 4
6._at : ageatstudy~y = 40
prebiopsypsa = 5
7._at : ageatstudy~y = 40
prebiopsypsa = 6
8._at : ageatstudy~y = 40
prebiopsypsa = 7
9._at : ageatstudy~y = 40
prebiopsypsa = 8
10._at : ageatstudy~y = 40
prebiopsypsa = 9
11._at : ageatstudy~y = 50
prebiopsypsa = 0
12._at : ageatstudy~y = 50
prebiopsypsa = 1
13._at : ageatstudy~y = 50
prebiopsypsa = 2
14._at : ageatstudy~y = 50
prebiopsypsa = 3
15._at : ageatstudy~y = 50
prebiopsypsa = 4
16._at : ageatstudy~y = 50
prebiopsypsa = 5
17._at : ageatstudy~y = 50
prebiopsypsa = 6
18._at : ageatstudy~y = 50
prebiopsypsa = 7
19._at : ageatstudy~y = 50
prebiopsypsa = 8
20._at : ageatstudy~y = 50
prebiopsypsa = 9
21._at : ageatstudy~y = 60
prebiopsypsa = 0
22._at : ageatstudy~y = 60
prebiopsypsa = 1
23._at : ageatstudy~y = 60
prebiopsypsa = 2
24._at : ageatstudy~y = 60
prebiopsypsa = 3
25._at : ageatstudy~y = 60
prebiopsypsa = 4
26._at : ageatstudy~y = 60
prebiopsypsa = 5
27._at : ageatstudy~y = 60
prebiopsypsa = 6
28._at : ageatstudy~y = 60

```
          prebiopsypsa   =         7
29._at     : ageatstudy~y   =        60
          prebiopsypsa   =         8
30._at     : ageatstudy~y   =        60
          prebiopsypsa   =         9
31._at     : ageatstudy~y   =        70
          prebiopsypsa   =         0
32._at     : ageatstudy~y   =        70
          prebiopsypsa   =         1
33._at     : ageatstudy~y   =        70
          prebiopsypsa   =         2
34._at     : ageatstudy~y   =        70
          prebiopsypsa   =         3
35._at     : ageatstudy~y   =        70
          prebiopsypsa   =         4
36._at     : ageatstudy~y   =        70
          prebiopsypsa   =         5
37._at     : ageatstudy~y   =        70
          prebiopsypsa   =         6
38._at     : ageatstudy~y   =        70
          prebiopsypsa   =         7
39._at     : ageatstudy~y   =        70
          prebiopsypsa   =         8
40._at     : ageatstudy~y   =        70
          prebiopsypsa   =         9
```

	Delta-method			
	Contrast	Std.Err.	z	P>z
abnormalMRI45@_at				
(1 vs base) 1	0.010	0.017	0.600	0.550
(1 vs base) 2	0.016	0.025	0.630	0.528
(1 vs base) 3	0.024	0.036	0.660	0.509
(1 vs base) 4	0.036	0.052	0.690	0.492
(1 vs base) 5	0.054	0.076	0.710	0.478
(1 vs base) 6	0.079	0.108	0.730	0.465
(1 vs base) 7	0.115	0.152	0.750	0.450
(1 vs base) 8	0.162	0.205	0.790	0.429
(1 vs base) 9	0.221	0.259	0.850	0.395
(1 vs base) 10	0.287	0.299	0.960	0.337
(1 vs base) 11	0.034	0.039	0.870	0.383
(1 vs base) 12	0.051	0.053	0.980	0.328
(1 vs base) 13	0.076	0.070	1.090	0.277
(1 vs base) 14	0.110	0.092	1.190	0.232
(1 vs base) 15	0.156	0.121	1.290	0.196
(1 vs base) 16	0.213	0.153	1.390	0.165
(1 vs base) 17	0.279	0.184	1.520	0.129
(1 vs base) 18	0.346	0.201	1.730	0.084
(1 vs base) 19	0.404	0.191	2.110	0.035
(1 vs base) 20	0.439	0.160	2.740	0.006
(1 vs base) 21	0.106	0.083	1.280	0.201
(1 vs base) 22	0.150	0.094	1.590	0.113
(1 vs base) 23	0.206	0.105	1.960	0.050
(1 vs base) 24	0.271	0.117	2.320	0.021
(1 vs base) 25	0.339	0.131	2.590	0.010
(1 vs base) 26	0.398	0.142	2.810	0.005
(1 vs base) 27	0.436	0.145	3.010	0.003
(1 vs base) 28	0.445	0.152	2.930	0.003
(1 vs base) 29	0.423	0.182	2.330	0.020
(1 vs base) 30	0.374	0.227	1.640	0.100
(1 vs base) 31	0.263	0.168	1.560	0.118
(1 vs base) 32	0.331	0.161	2.060	0.039

(1 vs base) 33	0.392	0.147	2.660	0.008
(1 vs base) 34	0.433	0.140	3.080	0.002
(1 vs base) 35	0.446	0.151	2.950	0.003
(1 vs base) 36	0.427	0.179	2.380	0.017
(1 vs base) 37	0.380	0.213	1.790	0.074
(1 vs base) 38	0.317	0.237	1.340	0.180
(1 vs base) 39	0.249	0.240	1.040	0.300
(1 vs base) 40	0.186	0.223	0.830	0.404



Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(canceranybiopsy), predict()
1._at : prebiopsypsa = 0
ageatstudy~y = 40
2._at : prebiopsypsa = 0
ageatstudy~y = 50
3._at : prebiopsypsa = 0
ageatstudy~y = 60
4._at : prebiopsypsa = 0
ageatstudy~y = 70
5._at : prebiopsypsa = 1
ageatstudy~y = 40

6._at : prebiopsypsa = 1
ageatstudy~y = 50
7._at : prebiopsypsa = 1
ageatstudy~y = 60
8._at : prebiopsypsa = 1
ageatstudy~y = 70
9._at : prebiopsypsa = 2
ageatstudy~y = 40
10._at : prebiopsypsa = 2
ageatstudy~y = 50
11._at : prebiopsypsa = 2
ageatstudy~y = 60
12._at : prebiopsypsa = 2
ageatstudy~y = 70
13._at : prebiopsypsa = 3
ageatstudy~y = 40
14._at : prebiopsypsa = 3
ageatstudy~y = 50
15._at : prebiopsypsa = 3
ageatstudy~y = 60
16._at : prebiopsypsa = 3
ageatstudy~y = 70
17._at : prebiopsypsa = 4
ageatstudy~y = 40
18._at : prebiopsypsa = 4
ageatstudy~y = 50
19._at : prebiopsypsa = 4
ageatstudy~y = 60
20._at : prebiopsypsa = 4
ageatstudy~y = 70
21._at : prebiopsypsa = 5
ageatstudy~y = 40
22._at : prebiopsypsa = 5
ageatstudy~y = 50
23._at : prebiopsypsa = 5
ageatstudy~y = 60
24._at : prebiopsypsa = 5
ageatstudy~y = 70
25._at : prebiopsypsa = 6
ageatstudy~y = 40
26._at : prebiopsypsa = 6
ageatstudy~y = 50
27._at : prebiopsypsa = 6
ageatstudy~y = 60
28._at : prebiopsypsa = 6
ageatstudy~y = 70
29._at : prebiopsypsa = 7
ageatstudy~y = 40
30._at : prebiopsypsa = 7
ageatstudy~y = 50
31._at : prebiopsypsa = 7
ageatstudy~y = 60
32._at : prebiopsypsa = 7
ageatstudy~y = 70
33._at : prebiopsypsa = 8
ageatstudy~y = 40
34._at : prebiopsypsa = 8
ageatstudy~y = 50
35._at : prebiopsypsa = 8
ageatstudy~y = 60
36._at : prebiopsypsa = 8
ageatstudy~y = 70

37._at : prebiopsypsa = 9
ageatstudy~y = 40
38._at : prebiopsypsa = 9
ageatstudy~y = 50
39._at : prebiopsypsa = 9
ageatstudy~y = 60
40._at : prebiopsypsa = 9
ageatstudy~y = 70

Delta-method

	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#abnormalMRI						
1#N	0.125	0.048	2.630	0.009	0.032	0.218
1#Y	0.274	0.110	2.480	0.013	0.057	0.490
2#N	0.143	0.040	3.590	0.000	0.065	0.221
2#Y	0.305	0.094	3.230	0.001	0.120	0.491
3#N	0.163	0.056	2.880	0.004	0.052	0.273
3#Y	0.339	0.109	3.100	0.002	0.124	0.554
4#N	0.185	0.094	1.970	0.049	0.001	0.369
4#Y	0.374	0.153	2.440	0.015	0.074	0.675
5#N	0.159	0.056	2.830	0.005	0.049	0.269
5#Y	0.333	0.116	2.880	0.004	0.106	0.559
6#N	0.181	0.039	4.590	0.000	0.103	0.258
6#Y	0.368	0.087	4.240	0.000	0.198	0.538
7#N	0.205	0.055	3.720	0.000	0.097	0.312
7#Y	0.404	0.095	4.240	0.000	0.217	0.591
8#N	0.231	0.098	2.350	0.019	0.038	0.424
8#Y	0.442	0.140	3.150	0.002	0.167	0.717
9#N	0.200	0.072	2.790	0.005	0.060	0.340
9#Y	0.397	0.124	3.200	0.001	0.154	0.641
10#N	0.226	0.047	4.830	0.000	0.134	0.317
10#Y	0.435	0.083	5.210	0.000	0.272	0.598
11#N	0.254	0.058	4.410	0.000	0.141	0.367
11#Y	0.473	0.083	5.720	0.000	0.311	0.636
12#N	0.284	0.104	2.730	0.006	0.080	0.489
12#Y	0.512	0.126	4.060	0.000	0.265	0.759
13#N	0.249	0.095	2.620	0.009	0.062	0.435
13#Y	0.466	0.137	3.400	0.001	0.197	0.735
14#N	0.279	0.066	4.230	0.000	0.149	0.408
14#Y	0.505	0.089	5.670	0.000	0.330	0.679
15#N	0.311	0.070	4.460	0.000	0.174	0.447
15#Y	0.543	0.078	6.950	0.000	0.390	0.696
16#N	0.345	0.114	3.030	0.002	0.122	0.568
16#Y	0.581	0.115	5.080	0.000	0.357	0.806
17#N	0.305	0.126	2.420	0.016	0.058	0.551
17#Y	0.536	0.152	3.530	0.000	0.238	0.834
18#N	0.338	0.095	3.570	0.000	0.153	0.524
18#Y	0.574	0.102	5.640	0.000	0.375	0.774
19#N	0.374	0.092	4.060	0.000	0.193	0.554
19#Y	0.611	0.083	7.320	0.000	0.448	0.775
20#N	0.410	0.128	3.200	0.001	0.159	0.661
20#Y	0.648	0.108	6.010	0.000	0.436	0.859
21#N	0.367	0.161	2.270	0.023	0.051	0.683
21#Y	0.605	0.165	3.660	0.000	0.281	0.929
22#N	0.403	0.129	3.130	0.002	0.151	0.656
22#Y	0.641	0.116	5.510	0.000	0.413	0.869
23#N	0.441	0.121	3.660	0.000	0.205	0.678
23#Y	0.676	0.094	7.200	0.000	0.492	0.860
24#N	0.480	0.146	3.290	0.001	0.193	0.766
24#Y	0.709	0.105	6.730	0.000	0.502	0.915
25#N	0.434	0.198	2.200	0.028	0.047	0.822

25#Y	0.669	0.174	3.850	0.000	0.328	1.010
26#N	0.472	0.163	2.900	0.004	0.153	0.792
26#Y	0.703	0.128	5.500	0.000	0.452	0.953
27#N	0.511	0.150	3.410	0.001	0.218	0.804
27#Y	0.734	0.103	7.120	0.000	0.532	0.936
28#N	0.549	0.164	3.350	0.001	0.228	0.871
28#Y	0.763	0.104	7.310	0.000	0.558	0.967
29#N	0.504	0.230	2.190	0.029	0.053	0.955
29#Y	0.728	0.176	4.130	0.000	0.382	1.074
30#N	0.542	0.193	2.810	0.005	0.164	0.921
30#Y	0.758	0.133	5.690	0.000	0.496	1.019
31#N	0.580	0.175	3.320	0.001	0.238	0.923
31#Y	0.785	0.108	7.270	0.000	0.573	0.997
32#N	0.617	0.179	3.460	0.001	0.267	0.968
32#Y	0.810	0.102	7.920	0.000	0.609	1.010
33#N	0.573	0.255	2.250	0.024	0.074	1.072
33#Y	0.780	0.172	4.530	0.000	0.443	1.117
34#N	0.611	0.215	2.840	0.005	0.189	1.032
34#Y	0.805	0.133	6.070	0.000	0.546	1.065
35#N	0.647	0.192	3.370	0.001	0.271	1.023
35#Y	0.828	0.108	7.690	0.000	0.617	1.040
36#N	0.681	0.187	3.650	0.000	0.315	1.047
36#Y	0.849	0.098	8.680	0.000	0.658	1.041
37#N	0.640	0.268	2.390	0.017	0.115	1.166
37#Y	0.824	0.162	5.090	0.000	0.507	1.142
38#N	0.675	0.227	2.980	0.003	0.230	1.119
38#Y	0.846	0.127	6.680	0.000	0.598	1.094
39#N	0.708	0.200	3.550	0.000	0.317	1.099
39#Y	0.865	0.103	8.390	0.000	0.663	1.067
40#N	0.739	0.188	3.940	0.000	0.371	1.106
40#Y	0.882	0.091	9.680	0.000	0.703	1.060

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(canceranybiopsy), predict()
1._at : prebiopsypsa = 0
ageatstudy~y = 40
2._at : prebiopsypsa = 0
ageatstudy~y = 50
3._at : prebiopsypsa = 0
ageatstudy~y = 60
4._at : prebiopsypsa = 0
ageatstudy~y = 70
5._at : prebiopsypsa = 1
ageatstudy~y = 40
6._at : prebiopsypsa = 1
ageatstudy~y = 50
7._at : prebiopsypsa = 1
ageatstudy~y = 60
8._at : prebiopsypsa = 1
ageatstudy~y = 70
9._at : prebiopsypsa = 2
ageatstudy~y = 40
10._at : prebiopsypsa = 2
ageatstudy~y = 50
11._at : prebiopsypsa = 2
ageatstudy~y = 60
12._at : prebiopsypsa = 2
ageatstudy~y = 70

13._at : prebiopsypsa = 3
ageatstudy~y = 40
14._at : prebiopsypsa = 3
ageatstudy~y = 50
15._at : prebiopsypsa = 3
ageatstudy~y = 60
16._at : prebiopsypsa = 3
ageatstudy~y = 70
17._at : prebiopsypsa = 4
ageatstudy~y = 40
18._at : prebiopsypsa = 4
ageatstudy~y = 50
19._at : prebiopsypsa = 4
ageatstudy~y = 60
20._at : prebiopsypsa = 4
ageatstudy~y = 70
21._at : prebiopsypsa = 5
ageatstudy~y = 40
22._at : prebiopsypsa = 5
ageatstudy~y = 50
23._at : prebiopsypsa = 5
ageatstudy~y = 60
24._at : prebiopsypsa = 5
ageatstudy~y = 70
25._at : prebiopsypsa = 6
ageatstudy~y = 40
26._at : prebiopsypsa = 6
ageatstudy~y = 50
27._at : prebiopsypsa = 6
ageatstudy~y = 60
28._at : prebiopsypsa = 6
ageatstudy~y = 70
29._at : prebiopsypsa = 7
ageatstudy~y = 40
30._at : prebiopsypsa = 7
ageatstudy~y = 50
31._at : prebiopsypsa = 7
ageatstudy~y = 60
32._at : prebiopsypsa = 7
ageatstudy~y = 70
33._at : prebiopsypsa = 8
ageatstudy~y = 40
34._at : prebiopsypsa = 8
ageatstudy~y = 50
35._at : prebiopsypsa = 8
ageatstudy~y = 60
36._at : prebiopsypsa = 8
ageatstudy~y = 70
37._at : prebiopsypsa = 9
ageatstudy~y = 40
38._at : prebiopsypsa = 9
ageatstudy~y = 50
39._at : prebiopsypsa = 9
ageatstudy~y = 60
40._at : prebiopsypsa = 9
ageatstudy~y = 70

	df	chi2	P>chi2
abnormalMRI@_at			
1	1	3.080	0.079
2	1	3.850	0.050

3	1	4.070	0.044
4	1	3.870	0.049
5	1	3.730	0.053
6	1	4.680	0.030
7	1	5.040	0.025
8	1	5.000	0.025
9	1	4.400	0.036
10	1	5.360	0.021
11	1	5.770	0.016
12	1	5.880	0.015
13	1	5.090	0.024
14	1	5.870	0.015
15	1	6.170	0.013
16	1	6.260	0.012
17	1	5.770	0.016
18	1	6.180	0.013
19	1	6.230	0.013
20	1	6.060	0.014
21	1	6.210	0.013
22	1	6.150	0.013
23	1	5.880	0.015
24	1	5.350	0.021
25	1	5.860	0.015
26	1	5.480	0.019
27	1	5.010	0.025
28	1	4.310	0.038
29	1	4.600	0.032
30	1	4.240	0.039
31	1	3.830	0.050
32	1	3.220	0.072
33	1	3.130	0.077
34	1	2.960	0.085
35	1	2.720	0.099
36	1	2.320	0.128
37	1	2.040	0.153
38	1	1.990	0.158
39	1	1.880	0.170
40	1	1.650	0.199
Joint	4	7.510	0.111

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(canceranybiopsy), predict()
1._at : prebiopsypsa = 0
ageatstudy~y = 40
2._at : prebiopsypsa = 0
ageatstudy~y = 50
3._at : prebiopsypsa = 0
ageatstudy~y = 60
4._at : prebiopsypsa = 0
ageatstudy~y = 70
5._at : prebiopsypsa = 1
ageatstudy~y = 40
6._at : prebiopsypsa = 1
ageatstudy~y = 50
7._at : prebiopsypsa = 1
ageatstudy~y = 60
8._at : prebiopsypsa = 1
ageatstudy~y = 70

```
9._at       : prebiopsypsa   =        2
              ageatstudy~y   =       40
10._at      : prebiopsypsa   =        2
              ageatstudy~y   =       50
11._at      : prebiopsypsa   =        2
              ageatstudy~y   =       60
12._at      : prebiopsypsa   =        2
              ageatstudy~y   =       70
13._at      : prebiopsypsa   =        3
              ageatstudy~y   =       40
14._at      : prebiopsypsa   =        3
              ageatstudy~y   =       50
15._at      : prebiopsypsa   =        3
              ageatstudy~y   =       60
16._at      : prebiopsypsa   =        3
              ageatstudy~y   =       70
17._at      : prebiopsypsa   =        4
              ageatstudy~y   =       40
18._at      : prebiopsypsa   =        4
              ageatstudy~y   =       50
19._at      : prebiopsypsa   =        4
              ageatstudy~y   =       60
20._at      : prebiopsypsa   =        4
              ageatstudy~y   =       70
21._at      : prebiopsypsa   =        5
              ageatstudy~y   =       40
22._at      : prebiopsypsa   =        5
              ageatstudy~y   =       50
23._at      : prebiopsypsa   =        5
              ageatstudy~y   =       60
24._at      : prebiopsypsa   =        5
              ageatstudy~y   =       70
25._at      : prebiopsypsa   =        6
              ageatstudy~y   =       40
26._at      : prebiopsypsa   =        6
              ageatstudy~y   =       50
27._at      : prebiopsypsa   =        6
              ageatstudy~y   =       60
28._at      : prebiopsypsa   =        6
              ageatstudy~y   =       70
29._at      : prebiopsypsa   =        7
              ageatstudy~y   =       40
30._at      : prebiopsypsa   =        7
              ageatstudy~y   =       50
31._at      : prebiopsypsa   =        7
              ageatstudy~y   =       60
32._at      : prebiopsypsa   =        7
              ageatstudy~y   =       70
33._at      : prebiopsypsa   =        8
              ageatstudy~y   =       40
34._at      : prebiopsypsa   =        8
              ageatstudy~y   =       50
35._at      : prebiopsypsa   =        8
              ageatstudy~y   =       60
36._at      : prebiopsypsa   =        8
              ageatstudy~y   =       70
37._at      : prebiopsypsa   =        9
              ageatstudy~y   =       40
38._at      : prebiopsypsa   =        9
              ageatstudy~y   =       50
39._at      : prebiopsypsa   =        9
              ageatstudy~y   =       60
```

40._at : prebiopsypsa = 9
ageatstudy~y = 70

Delta-method

	Contrast	Std.Err.	z	P>z
abnormalMRI@_at				
(Y vs base) 1	0.149	0.085	1.750	0.079
(Y vs base) 2	0.163	0.083	1.960	0.050
(Y vs base) 3	0.176	0.087	2.020	0.044
(Y vs base) 4	0.190	0.096	1.970	0.049
(Y vs base) 5	0.174	0.090	1.930	0.053
(Y vs base) 6	0.187	0.087	2.160	0.031
(Y vs base) 7	0.200	0.089	2.250	0.025
(Y vs base) 8	0.211	0.094	2.240	0.025
(Y vs base) 9	0.197	0.094	2.100	0.036
(Y vs base) 10	0.209	0.090	2.320	0.021
(Y vs base) 11	0.219	0.091	2.400	0.016
(Y vs base) 12	0.227	0.094	2.430	0.015
(Y vs base) 13	0.218	0.096	2.260	0.024
(Y vs base) 14	0.226	0.093	2.420	0.015
(Y vs base) 15	0.233	0.094	2.480	0.013
(Y vs base) 16	0.237	0.095	2.500	0.012
(Y vs base) 17	0.232	0.096	2.400	0.016
(Y vs base) 18	0.236	0.095	2.490	0.013
(Y vs base) 19	0.238	0.095	2.500	0.013
(Y vs base) 20	0.237	0.096	2.460	0.014
(Y vs base) 21	0.238	0.095	2.490	0.013
(Y vs base) 22	0.237	0.096	2.480	0.013
(Y vs base) 23	0.234	0.097	2.420	0.015
(Y vs base) 24	0.229	0.099	2.310	0.021
(Y vs base) 25	0.235	0.097	2.420	0.015
(Y vs base) 26	0.230	0.098	2.340	0.019
(Y vs base) 27	0.223	0.100	2.240	0.025
(Y vs base) 28	0.213	0.103	2.080	0.038
(Y vs base) 29	0.224	0.105	2.140	0.032
(Y vs base) 30	0.215	0.105	2.060	0.039
(Y vs base) 31	0.205	0.105	1.960	0.050
(Y vs base) 32	0.192	0.107	1.800	0.073
(Y vs base) 33	0.207	0.117	1.770	0.077
(Y vs base) 34	0.195	0.113	1.720	0.085
(Y vs base) 35	0.182	0.110	1.650	0.099
(Y vs base) 36	0.168	0.111	1.520	0.128
(Y vs base) 37	0.184	0.129	1.430	0.153
(Y vs base) 38	0.171	0.121	1.410	0.158
(Y vs base) 39	0.157	0.114	1.370	0.170
(Y vs base) 40	0.143	0.111	1.280	0.199

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(canceranybiopsy), predict()
1._at : prebiopsypsa = 0
ageatstudy~y = 40
2._at : prebiopsypsa = 0
ageatstudy~y = 50
3._at : prebiopsypsa = 0
ageatstudy~y = 60
4._at : prebiopsypsa = 0
ageatstudy~y = 70
5._at : prebiopsypsa = 1

ageatstudy~y = 40
6._at : prebiopsypsa = 1
ageatstudy~y = 50
7._at : prebiopsypsa = 1
ageatstudy~y = 60
8._at : prebiopsypsa = 1
ageatstudy~y = 70
9._at : prebiopsypsa = 2
ageatstudy~y = 40
10._at : prebiopsypsa = 2
ageatstudy~y = 50
11._at : prebiopsypsa = 2
ageatstudy~y = 60
12._at : prebiopsypsa = 2
ageatstudy~y = 70
13._at : prebiopsypsa = 3
ageatstudy~y = 40
14._at : prebiopsypsa = 3
ageatstudy~y = 50
15._at : prebiopsypsa = 3
ageatstudy~y = 60
16._at : prebiopsypsa = 3
ageatstudy~y = 70
17._at : prebiopsypsa = 4
ageatstudy~y = 40
18._at : prebiopsypsa = 4
ageatstudy~y = 50
19._at : prebiopsypsa = 4
ageatstudy~y = 60
20._at : prebiopsypsa = 4
ageatstudy~y = 70
21._at : prebiopsypsa = 5
ageatstudy~y = 40
22._at : prebiopsypsa = 5
ageatstudy~y = 50
23._at : prebiopsypsa = 5
ageatstudy~y = 60
24._at : prebiopsypsa = 5
ageatstudy~y = 70
25._at : prebiopsypsa = 6
ageatstudy~y = 40
26._at : prebiopsypsa = 6
ageatstudy~y = 50
27._at : prebiopsypsa = 6
ageatstudy~y = 60
28._at : prebiopsypsa = 6
ageatstudy~y = 70
29._at : prebiopsypsa = 7
ageatstudy~y = 40
30._at : prebiopsypsa = 7
ageatstudy~y = 50
31._at : prebiopsypsa = 7
ageatstudy~y = 60
32._at : prebiopsypsa = 7
ageatstudy~y = 70
33._at : prebiopsypsa = 8
ageatstudy~y = 40
34._at : prebiopsypsa = 8
ageatstudy~y = 50
35._at : prebiopsypsa = 8
ageatstudy~y = 60
36._at : prebiopsypsa = 8

```
          ageatstudy~y   =        70
37._at     : prebiopsypsa   =         9
          ageatstudy~y   =        40
38._at     : prebiopsypsa   =         9
          ageatstudy~y   =        50
39._at     : prebiopsypsa   =         9
          ageatstudy~y   =        60
40._at     : prebiopsypsa   =         9
          ageatstudy~y   =        70
```

Delta-method

	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#abnormalMRI45						
1 0	0.152	0.055	2.750	0.006	0.043	0.260
1 1	0.342	0.164	2.090	0.037	0.021	0.664
2 0	0.163	0.043	3.820	0.000	0.080	0.247
2 1	0.362	0.140	2.590	0.010	0.088	0.636
3 0	0.175	0.059	2.980	0.003	0.060	0.291
3 1	0.382	0.141	2.710	0.007	0.105	0.659
4 0	0.188	0.095	1.980	0.048	0.002	0.375
4 1	0.403	0.170	2.360	0.018	0.069	0.737
5 0	0.195	0.063	3.060	0.002	0.070	0.319
5 1	0.412	0.168	2.450	0.014	0.083	0.742
6 0	0.208	0.039	5.300	0.000	0.131	0.286
6 1	0.434	0.134	3.240	0.001	0.172	0.696
7 0	0.223	0.056	3.990	0.000	0.113	0.333
7 1	0.455	0.128	3.560	0.000	0.204	0.706
8 0	0.238	0.100	2.370	0.018	0.042	0.435
8 1	0.477	0.156	3.060	0.002	0.171	0.782
9 0	0.246	0.079	3.120	0.002	0.091	0.400
9 1	0.487	0.171	2.850	0.004	0.152	0.822
10 0	0.262	0.044	5.910	0.000	0.175	0.349
10 1	0.508	0.128	3.970	0.000	0.257	0.759
11 0	0.279	0.057	4.930	0.000	0.168	0.390
11 1	0.530	0.114	4.630	0.000	0.306	0.754
12 0	0.297	0.107	2.790	0.005	0.088	0.506
12 1	0.551	0.139	3.980	0.000	0.280	0.823
13 0	0.306	0.103	2.980	0.003	0.105	0.507
13 1	0.561	0.173	3.250	0.001	0.223	0.900
14 0	0.324	0.064	5.080	0.000	0.199	0.450
14 1	0.583	0.125	4.660	0.000	0.337	0.828
15 0	0.344	0.068	5.060	0.000	0.211	0.477
15 1	0.604	0.105	5.750	0.000	0.398	0.809
16 0	0.363	0.116	3.140	0.002	0.136	0.591
16 1	0.624	0.123	5.070	0.000	0.383	0.865
17 0	0.373	0.133	2.800	0.005	0.112	0.634
17 1	0.634	0.172	3.670	0.000	0.296	0.971
18 0	0.393	0.094	4.200	0.000	0.210	0.577
18 1	0.653	0.125	5.230	0.000	0.409	0.898
19 0	0.414	0.090	4.580	0.000	0.237	0.592
19 1	0.673	0.101	6.650	0.000	0.474	0.871
20 0	0.435	0.130	3.360	0.001	0.181	0.690
20 1	0.692	0.111	6.210	0.000	0.473	0.910
21 0	0.445	0.166	2.690	0.007	0.120	0.770
21 1	0.700	0.169	4.140	0.000	0.369	1.031
22 0	0.467	0.127	3.680	0.000	0.218	0.716
22 1	0.718	0.125	5.750	0.000	0.473	0.963
23 0	0.488	0.118	4.130	0.000	0.257	0.720
23 1	0.735	0.100	7.320	0.000	0.538	0.932
24 0	0.510	0.146	3.490	0.000	0.223	0.797
24 1	0.752	0.103	7.270	0.000	0.549	0.954

25 0	0.520	0.196	2.660	0.008	0.137	0.903
25 1	0.759	0.162	4.700	0.000	0.442	1.076
26 0	0.542	0.157	3.440	0.001	0.233	0.850
26 1	0.775	0.123	6.320	0.000	0.535	1.015
27 0	0.563	0.145	3.890	0.000	0.280	0.847
27 1	0.789	0.099	7.940	0.000	0.594	0.984
28 0	0.584	0.162	3.610	0.000	0.267	0.901
28 1	0.803	0.097	8.270	0.000	0.613	0.994
29 0	0.594	0.217	2.730	0.006	0.168	1.020
29 1	0.810	0.150	5.390	0.000	0.515	1.104
30 0	0.615	0.181	3.410	0.001	0.261	0.969
30 1	0.823	0.117	7.040	0.000	0.594	1.052
31 0	0.635	0.164	3.860	0.000	0.313	0.958
31 1	0.835	0.096	8.690	0.000	0.647	1.023
32 0	0.655	0.172	3.800	0.000	0.317	0.993
32 1	0.847	0.090	9.360	0.000	0.669	1.024
33 0	0.664	0.229	2.910	0.004	0.216	1.112
33 1	0.852	0.136	6.270	0.000	0.586	1.118
34 0	0.683	0.193	3.540	0.000	0.304	1.062
34 1	0.862	0.108	7.990	0.000	0.651	1.074
35 0	0.702	0.175	4.010	0.000	0.359	1.045
35 1	0.872	0.090	9.710	0.000	0.696	1.049
36 0	0.719	0.175	4.100	0.000	0.376	1.063
36 1	0.882	0.083	10.650	0.000	0.719	1.044
37 0	0.728	0.228	3.190	0.001	0.281	1.174
37 1	0.886	0.120	7.400	0.000	0.651	1.120
38 0	0.744	0.195	3.820	0.000	0.362	1.126
38 1	0.894	0.097	9.240	0.000	0.705	1.084
39 0	0.760	0.176	4.330	0.000	0.416	1.105
39 1	0.902	0.081	11.070	0.000	0.743	1.062
40 0	0.776	0.171	4.540	0.000	0.441	1.111
40 1	0.910	0.074	12.290	0.000	0.765	1.055

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(canceranybiopsy), predict()
1._at : prebiopsypsa = 0
ageatstudy~y = 40
2._at : prebiopsypsa = 0
ageatstudy~y = 50
3._at : prebiopsypsa = 0
ageatstudy~y = 60
4._at : prebiopsypsa = 0
ageatstudy~y = 70
5._at : prebiopsypsa = 1
ageatstudy~y = 40
6._at : prebiopsypsa = 1
ageatstudy~y = 50
7._at : prebiopsypsa = 1
ageatstudy~y = 60
8._at : prebiopsypsa = 1
ageatstudy~y = 70
9._at : prebiopsypsa = 2
ageatstudy~y = 40
10._at : prebiopsypsa = 2
ageatstudy~y = 50
11._at : prebiopsypsa = 2
ageatstudy~y = 60
12._at : prebiopsypsa = 2
ageatstudy~y = 70

13._at : prebiopsypsa = 3
ageatstudy~y = 40
14._at : prebiopsypsa = 3
ageatstudy~y = 50
15._at : prebiopsypsa = 3
ageatstudy~y = 60
16._at : prebiopsypsa = 3
ageatstudy~y = 70
17._at : prebiopsypsa = 4
ageatstudy~y = 40
18._at : prebiopsypsa = 4
ageatstudy~y = 50
19._at : prebiopsypsa = 4
ageatstudy~y = 60
20._at : prebiopsypsa = 4
ageatstudy~y = 70
21._at : prebiopsypsa = 5
ageatstudy~y = 40
22._at : prebiopsypsa = 5
ageatstudy~y = 50
23._at : prebiopsypsa = 5
ageatstudy~y = 60
24._at : prebiopsypsa = 5
ageatstudy~y = 70
25._at : prebiopsypsa = 6
ageatstudy~y = 40
26._at : prebiopsypsa = 6
ageatstudy~y = 50
27._at : prebiopsypsa = 6
ageatstudy~y = 60
28._at : prebiopsypsa = 6
ageatstudy~y = 70
29._at : prebiopsypsa = 7
ageatstudy~y = 40
30._at : prebiopsypsa = 7
ageatstudy~y = 50
31._at : prebiopsypsa = 7
ageatstudy~y = 60
32._at : prebiopsypsa = 7
ageatstudy~y = 70
33._at : prebiopsypsa = 8
ageatstudy~y = 40
34._at : prebiopsypsa = 8
ageatstudy~y = 50
35._at : prebiopsypsa = 8
ageatstudy~y = 60
36._at : prebiopsypsa = 8
ageatstudy~y = 70
37._at : prebiopsypsa = 9
ageatstudy~y = 40
38._at : prebiopsypsa = 9
ageatstudy~y = 50
39._at : prebiopsypsa = 9
ageatstudy~y = 60
40._at : prebiopsypsa = 9
ageatstudy~y = 70

	df	chi2	P>chi2
abnormalMRI45@_at			
1	1	2.090	0.148
2	1	2.540	0.111

3	1	2.830	0.092
4	1	2.930	0.087
5	1	2.580	0.108
6	1	3.080	0.079
7	1	3.450	0.063
8	1	3.660	0.056
9	1	3.160	0.075
10	1	3.630	0.057
11	1	3.980	0.046
12	1	4.210	0.040
13	1	3.840	0.050
14	1	4.170	0.041
15	1	4.370	0.037
16	1	4.470	0.035
17	1	4.500	0.034
18	1	4.590	0.032
19	1	4.560	0.033
20	1	4.370	0.036
21	1	4.780	0.029
22	1	4.660	0.031
23	1	4.400	0.036
24	1	3.930	0.047
25	1	4.250	0.039
26	1	4.120	0.042
27	1	3.800	0.051
28	1	3.240	0.072
29	1	3.160	0.075
30	1	3.160	0.075
31	1	2.940	0.087
32	1	2.490	0.115
33	1	2.150	0.143
34	1	2.220	0.136
35	1	2.120	0.145
36	1	1.840	0.175
37	1	1.450	0.229
38	1	1.540	0.215
39	1	1.510	0.220
40	1	1.350	0.246
Joint	4	9.750	0.045

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(canceranybiopsy), predict()
1._at : prebiopsypsa = 0
ageatstudy~y = 40
2._at : prebiopsypsa = 0
ageatstudy~y = 50
3._at : prebiopsypsa = 0
ageatstudy~y = 60
4._at : prebiopsypsa = 0
ageatstudy~y = 70
5._at : prebiopsypsa = 1
ageatstudy~y = 40
6._at : prebiopsypsa = 1
ageatstudy~y = 50
7._at : prebiopsypsa = 1
ageatstudy~y = 60
8._at : prebiopsypsa = 1
ageatstudy~y = 70

9._at : prebiopsypsa = 2
ageatstudy~y = 40
10._at : prebiopsypsa = 2
ageatstudy~y = 50
11._at : prebiopsypsa = 2
ageatstudy~y = 60
12._at : prebiopsypsa = 2
ageatstudy~y = 70
13._at : prebiopsypsa = 3
ageatstudy~y = 40
14._at : prebiopsypsa = 3
ageatstudy~y = 50
15._at : prebiopsypsa = 3
ageatstudy~y = 60
16._at : prebiopsypsa = 3
ageatstudy~y = 70
17._at : prebiopsypsa = 4
ageatstudy~y = 40
18._at : prebiopsypsa = 4
ageatstudy~y = 50
19._at : prebiopsypsa = 4
ageatstudy~y = 60
20._at : prebiopsypsa = 4
ageatstudy~y = 70
21._at : prebiopsypsa = 5
ageatstudy~y = 40
22._at : prebiopsypsa = 5
ageatstudy~y = 50
23._at : prebiopsypsa = 5
ageatstudy~y = 60
24._at : prebiopsypsa = 5
ageatstudy~y = 70
25._at : prebiopsypsa = 6
ageatstudy~y = 40
26._at : prebiopsypsa = 6
ageatstudy~y = 50
27._at : prebiopsypsa = 6
ageatstudy~y = 60
28._at : prebiopsypsa = 6
ageatstudy~y = 70
29._at : prebiopsypsa = 7
ageatstudy~y = 40
30._at : prebiopsypsa = 7
ageatstudy~y = 50
31._at : prebiopsypsa = 7
ageatstudy~y = 60
32._at : prebiopsypsa = 7
ageatstudy~y = 70
33._at : prebiopsypsa = 8
ageatstudy~y = 40
34._at : prebiopsypsa = 8
ageatstudy~y = 50
35._at : prebiopsypsa = 8
ageatstudy~y = 60
36._at : prebiopsypsa = 8
ageatstudy~y = 70
37._at : prebiopsypsa = 9
ageatstudy~y = 40
38._at : prebiopsypsa = 9
ageatstudy~y = 50
39._at : prebiopsypsa = 9
ageatstudy~y = 60

40._at : prebiopsypsa = 9
ageatstudy~y = 70

Delta-method

	Contrast	Std.Err.	z	P>z
abnormalMRI45@_at				
(1 vs base) 1	0.190	0.132	1.450	0.148
(1 vs base) 2	0.199	0.125	1.590	0.111
(1 vs base) 3	0.207	0.123	1.680	0.092
(1 vs base) 4	0.214	0.125	1.710	0.087
(1 vs base) 5	0.218	0.136	1.610	0.108
(1 vs base) 6	0.225	0.128	1.760	0.079
(1 vs base) 7	0.232	0.125	1.860	0.063
(1 vs base) 8	0.238	0.124	1.910	0.056
(1 vs base) 9	0.241	0.135	1.780	0.075
(1 vs base) 10	0.246	0.129	1.910	0.057
(1 vs base) 11	0.250	0.126	1.990	0.046
(1 vs base) 12	0.254	0.124	2.050	0.040
(1 vs base) 13	0.256	0.131	1.960	0.050
(1 vs base) 14	0.258	0.126	2.040	0.041
(1 vs base) 15	0.260	0.124	2.090	0.037
(1 vs base) 16	0.261	0.123	2.110	0.035
(1 vs base) 17	0.261	0.123	2.120	0.034
(1 vs base) 18	0.260	0.121	2.140	0.032
(1 vs base) 19	0.258	0.121	2.140	0.033
(1 vs base) 20	0.256	0.122	2.090	0.037
(1 vs base) 21	0.255	0.117	2.190	0.029
(1 vs base) 22	0.251	0.116	2.160	0.031
(1 vs base) 23	0.247	0.118	2.100	0.036
(1 vs base) 24	0.242	0.122	1.980	0.047
(1 vs base) 25	0.239	0.116	2.060	0.039
(1 vs base) 26	0.233	0.115	2.030	0.042
(1 vs base) 27	0.226	0.116	1.950	0.051
(1 vs base) 28	0.219	0.122	1.800	0.072
(1 vs base) 29	0.216	0.121	1.780	0.075
(1 vs base) 30	0.208	0.117	1.780	0.075
(1 vs base) 31	0.200	0.117	1.710	0.087
(1 vs base) 32	0.192	0.121	1.580	0.115
(1 vs base) 33	0.188	0.128	1.470	0.143
(1 vs base) 34	0.179	0.120	1.490	0.136
(1 vs base) 35	0.171	0.117	1.460	0.145
(1 vs base) 36	0.162	0.120	1.350	0.175
(1 vs base) 37	0.158	0.132	1.200	0.229
(1 vs base) 38	0.150	0.121	1.240	0.215
(1 vs base) 39	0.142	0.116	1.230	0.220
(1 vs base) 40	0.134	0.115	1.160	0.246

Contrasts of adjusted predictions Number of obs = 92
Model VCE : OIM
Expression : Pr(signif ca), predict()

Delta-method

	Contrast	Std.Err.	z	P>z
PSA Cat				
(2- <3.0 vs <1.0)	0.019	0.073	0.270	0.790
(≥3.0 vs <1.0)	0.214	0.094	2.280	0.023

Table 0.9. contrasts of adjusted predictions

Logistic regression (Any cancer)	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
PSA	1.437	.189	2.75	.006	1.11	1.859	***
Constant	.257	.083	-4.23	0	.137	.482	***

Mean dependent var	0.339	SD dependent var	0.475
Pseudo r-squared	0.055	Number of obs	121.000
Chi-square	8.537	Prob > chi2	0.003
Akaike crit. (AIC)	150.407	Bayesian crit. (BIC)	155.999

**** p<.01, ** p<.05, * p<.1*

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
<1.0	1	.	.	.	.	.	
1-<2	7.297	3.873	3.74	0	2.579	20.648	***
2-3	4.122	2.591	2.25	.024	1.203	14.13	**
>=3	8.833	5.062	3.80	0	2.873	27.159	***
Constant	.113	.049	-5.06	0	.049	.263	***

Mean dependent var	0.305	SD dependent var	0.462
Pseudo r-squared	0.122	Number of obs	151.000
Chi-square	22.674	Prob > chi2	0.000
Akaike crit. (AIC)	170.978	Bayesian crit. (BIC)	183.047

*** p<.01, ** p<.05, * p<.1

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(any cancer), predict()

	Delta-method					
	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
PSA Cat						
<1.0	0.102	0.039	2.580	0.010	0.025	0.179
1-<2	0.452	0.077	5.890	0.000	0.302	0.603
2-3	0.318	0.099	3.200	0.001	0.124	0.513
≥3	.5	0.094	5.290	0.000	0.315	0.685

Table 0.10. Marginal predictions of cancer probability by category of PSA at study entry. On average, men with a PSA <1ng/ml had a 10.2% risk of cancer. Men with a PSA of 2-<3ng/ml have a greater probability at 31.8%, with those in the highest PSA category having an (average) probability of 50%.

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(any cancer), predict()

	Delta-method			
	Contrast	Std.Err.	z	P>z
PSA Cat				

(1.0-1.9 vs <1.0)	0.351	0.086	4.060	0.000
(2.0-2.9 vs <1.0)	0.216	0.107	2.030	0.043
(≥3.0 vs <1.0)	0.398	0.102	3.890	0.000

Table 0.11. this table shows the contrasts of the marginal predictions described above in Table 0.10. On average, men with a PSA of <1.0 had a 35% lower probability of any cancer than men with a PSA of 1.0-1.9ng/ml, 21.6% lower than men with a PSA of 2.0-2.9ng/ml and 39.9% lower than men with a PSA of ≥3.0.

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(any cancer), predict()

	Delta-method					
	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
PSA Cat						
<1.0	0.102	0.039	2.580	0.010	0.025	0.179
1-<2	0.452	0.077	5.890	0.000	0.302	0.603
2-3	0.318	0.099	3.200	0.001	0.124	0.513
≥3	.5	0.094	5.290	0.000	0.315	0.685

Table 0.12.

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(any cancer), predict()

	Delta-method			
	Contrast	Std.Err.	z	P>z
PSA Cat				
(1.0-1.9 vs <1.0)	0.351	0.086	4.060	0.000
(2.0-2.9 vs <1.0)	0.216	0.107	2.030	0.043
(≥3.0 vs <1.0)	0.398	0.102	3.890	0.000

Table 0.13. this table shows the contrasts of the marginal predictions described above in Table 0.10. On average, men with a PSA of <1.0 had a 35% lower probability of any cancer than men with a PSA of 1.0-1.9ng/ml, 21.6% lower than men with a PSA of 2.0-2.9ng/ml and 39.9% lower than men with a PSA of ≥3.0.

Appendix Chapter 4

	Clinically significant cancer		
	Contrast of Adj Preds*	**Marginal Adj Pred****	**(95% C.I.)**
PIRADS 1-2		0.01	(0.009, 0.02)
PIRADS 3-5	0.24	0.25	(0.12, 0.37)
PIRADS 1-3		0.031	(0.001, 0.06)
PIRADS 4-5	0.36	0.39	(0.19, 0.59)
	Any cancer		
	Contrast of Adj Preds	**Marginal Adj Pred**	**(95% C.I.)**
PIRADS 1-2		0.21	(0.13, 0.29)
PIRADS 3-5	0.28	0.5	(0.35, 0.64)
PIRADS 1-3		0.25	(0.17, 0.32)
PIRADS 4-5	0.35	0.6	(0.4, 0.8)

Table 0.1 adjusted marginal predictions of any cancer and significant cancer by PiRADS category

PiRADS 4-5 MRI

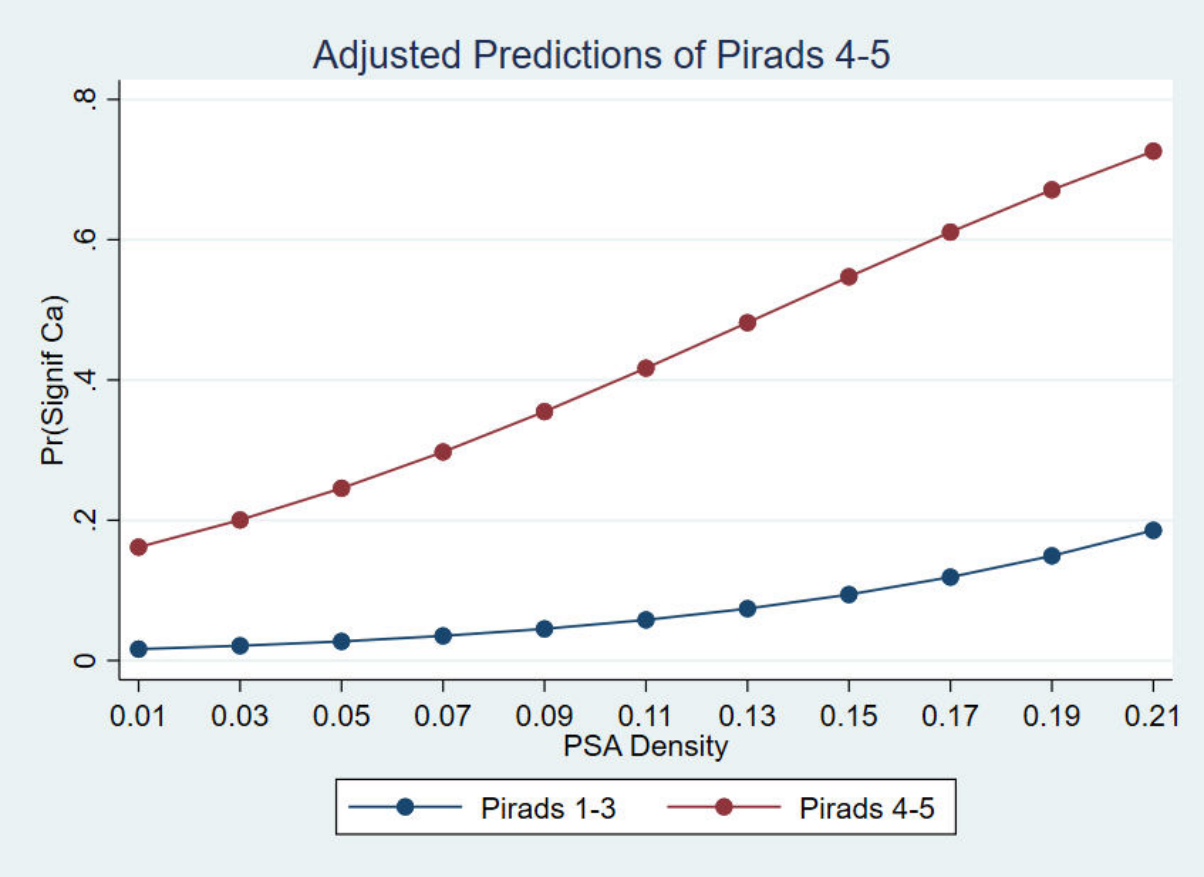


Figure 0.1 Adjusted predictions of Pirads 4-5 MRI at varying levels of PSAD; the (average) predicted probability of clinically significant cancer remained low in men with a Pirads 1-3 MRI irrespective of their PSAD. Men with a Pirads 4-5 MRI had an increasing predicted probability of cancer as PSAD increased.

A PSA Density ≥0.15 was positively associated with significant PrCa (OR 9.26; p=0.021) and a Pirads 4-5 MRI was also positively associated with significant PrCa (OR 16.49; p<0.01). AUC for this model was 0.8358. PSA Density as a continuous variable was postitively assocated with significant PrCa (OR 1.013; p=0.015) and a Pirads 4-5 MRI remained positively associated with significant PrCa (OR 11.63; p=0.001).

At the mean PSAD of 0.05ng/ml, the average predicted probability of clinically significant cancer in men with a Pirads 1-2 MRI was 2% and 26% in men with a Pirads 4-5 MRI. At a PSAD of 0.15, men with Pirads 4-5 MR had a predicted probability of cancer of 54%, compared to 9% in those with a Pirads 1-3 MRI. The (average) predicted probability of clinically significant cancer remained low in men with a Pirads 1-3 MRI irrespective of their PSAD. Men with a Pirads 4-5 MRI had an

increasing predicted probability of cancer as PSAD increased. at a PSAD of 0.05, men with a Pirads 4-5 MRI had a 21% increase in probability of clinically significant cancer detection compared to men with a Pirads 1-3 MRI. This rose to 54% at the highest level of PSAD (0.21). The difference in predicted probability of significant PrCa between men with and without a Pirads 4-5 MRI grew as PSAD values rose.

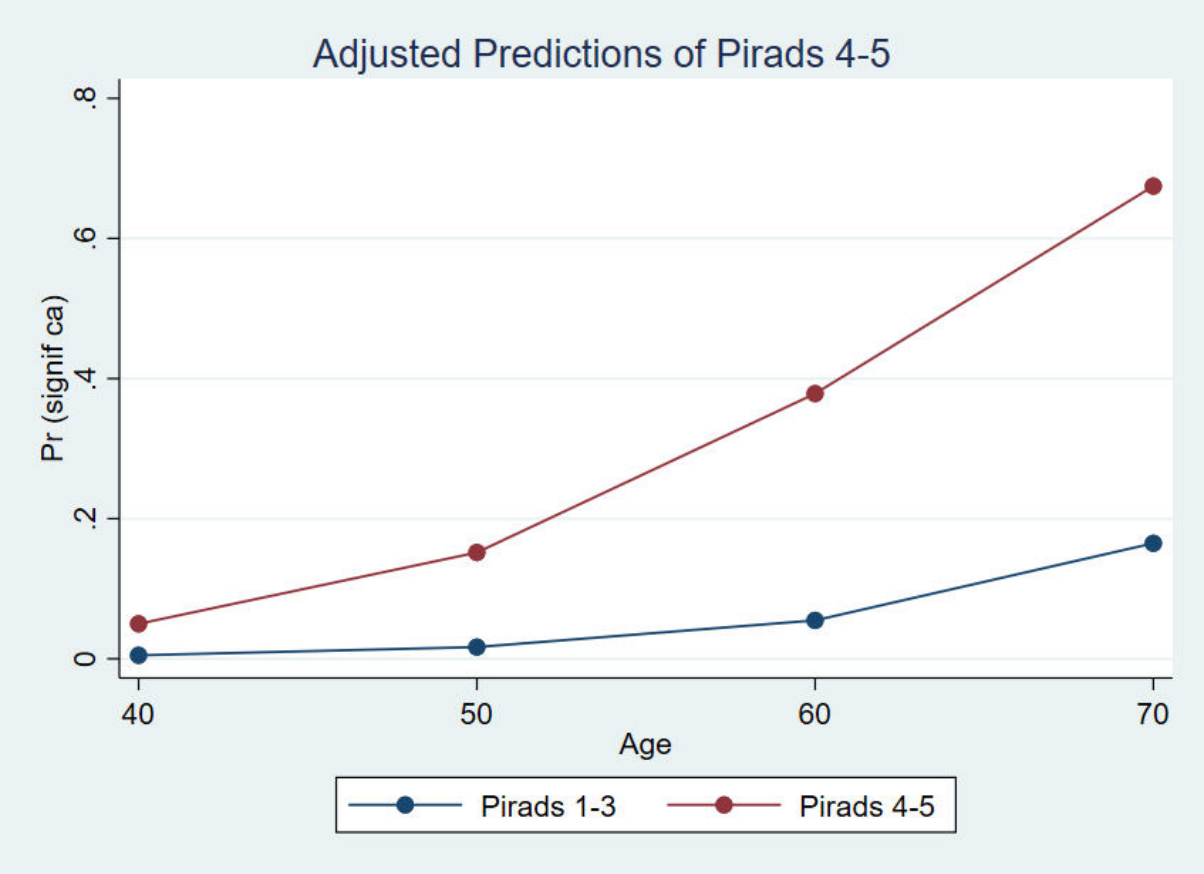


Figure 0.2 At all ages, predicted probability of clinically significant PrCa remained low in the presence of a Pirads 1-3 MRI. The predicted probabilty of significant PrCa remained low in the presence of an abnormal (Pirads 4-5) MRI at younger ages (age 40-50). As age increased so did the predicted probability of significant cancer

In a Logistic regression model describing age and Pirads 4-5 MRI as categorical variables. Overall the model is significant. Only age at or greater than 60years old approached statistical significance (OR 9.10, p=0.057). Age 50-60 was positively associated (OR 1.439) but not statistically, compared to men aged 40-<50 (p=0.763). A Pirads 4-5 MRI remained significantly associated with signifcnat cancer outcome (OR 10.42) compared to men with a Pirads 1-3 MRI (p=0.001). PIrads 4-5 MRI is positively associated with clinically significant cancer (OR 10.5) in the presence of age which is also positively associated with clinically significant cancer detection (OR 1.13, p=0.035). At the mean study age (53.5), the predicated probability of clinically significant cancer detection in a man with a Pirads 1-3 MRI is 2%, and 21% with a

Pirads 4-5 MRI. Men aged 40 with a Pirads 1-3 MRI have an (average) probability of 0.5% of clinically significant cancer detection (highlighted in blue). This remains relatively low at the oldest age of 70 (16%; highlighted in red). At the same ages, the probability is 5% and 67% in those with a Pirads 4-5 MRI (highlighted in green). At all ages, predicted probability of clinically significant PrCa remained low in the presence of a Pirads 1-3 MRI. The predicted probabilty of significant PrCa remained low in the presence of an abnormal (Pirads 4-5) MRI at younger ages (age 40-50). As age increased so did the predicted probability of significant cancer. Ie men aged 50 with a Pirads 4-5 MRI there is a 13% increase in probability of clinically significant cancer detection compared to men with a Pirads 1-3 MRI (this changes to 51% in men aged 70). The largest difference in predicted probability (coefficients above in Table 0.43) of signifciant PrCa between men with and without an abnormal (Pirads 4-5) MRI was in older men i.e aged 50 and above.

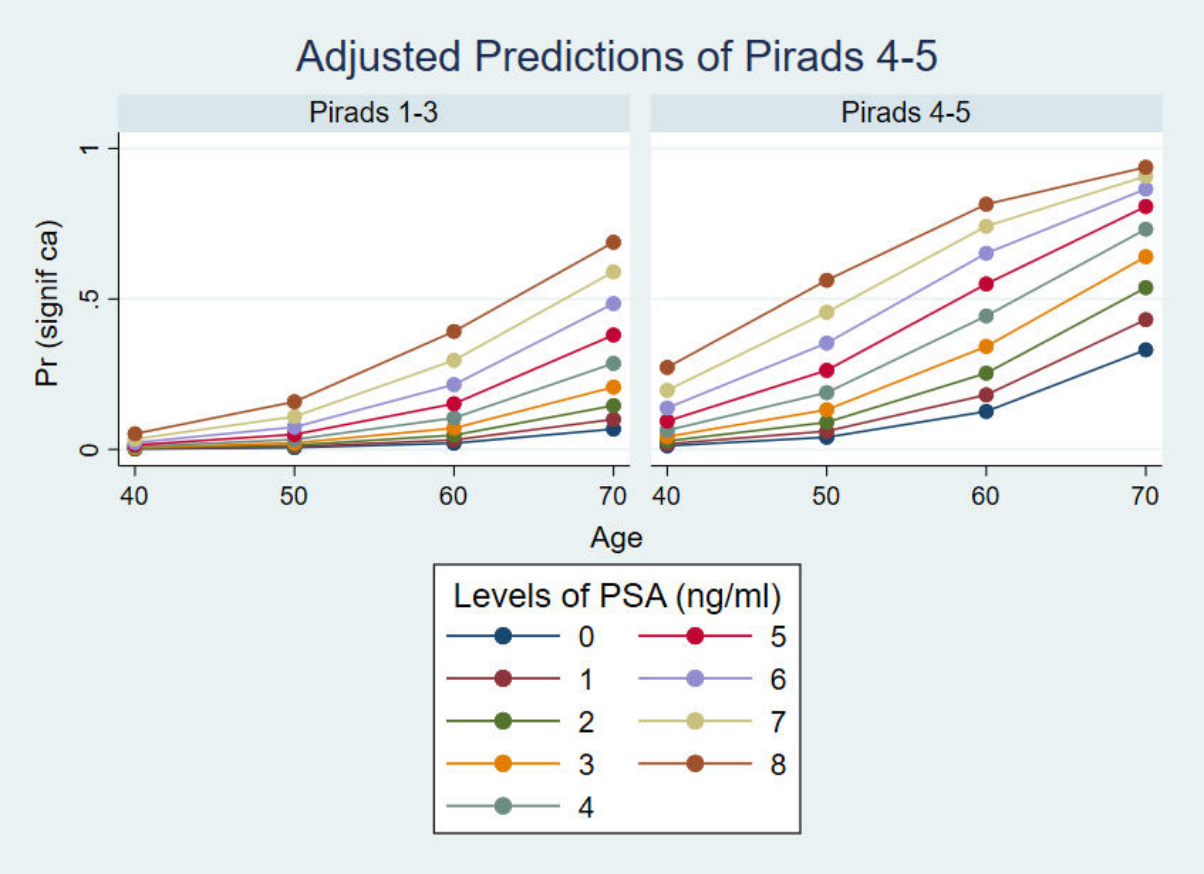


Figure 0.3 Graph of adjusted predictions of significant PrCa probability at various levels of PSA and age in the presence of a normal or abnormal MRI. i.e in men with low PSAs and a normal MRI, the predicted proability (on average) remained low even at the oldest age. In the presence of an abnormal MRI (pirads 3-5) at the same PSA values, the trend was similar but only in the younger age range.

Logistic regression model incorporating MRI as a categorical (predictor) variable and age and PSA as continuous (predictor) variables, with clinically significant PrCa as outcome. Pirads 4-5 MRI was positively associated with significant cancer outcome. At a mean PSA of 1.83ng/ml and age of 53.5 years, the percentage probability of detecting clinically significant PrCa on biopsy was 2% in men with a Pirads 1-3 MRI and 12.5% in men with a Pirads 4-5 MRI. Further adjusted predictions of PrCa probability at PSA and age values outside the mean values are listed in Appendix C and graphed in **Error! Reference source not found.Error! Reference source not found.**at prostate biopsy (OR 6.81; p=0.01), as were age (OR 1.13, p= 0.054) and PSA (OR 1.53, p=0.025). in men with low PSAs and a normal MRI, the predicted proability (on average) remained low even at the oldest age. In the presence of an abnormal MRI (pirads 3-5) at the same PSA values, the trend was similar but only in the younger age range. A full list of the specific coefficients/adjusted predictions which produced this graph in addition to contrasts of the adjusted predictions are listed in Appendix.

Clinically significant cancer				
	Contrast of Adj Preds*	Marginal Adj Pred**		(95% C.I.)
Mean Age	**53.5**			
PIRADS 1-2			0.006	(0.007, 0.019)
PIRADS 3-5			0.136	(0.016, 0.25)
PIRADS 1-3			0.026	(0.002, 0.05)
PIRADS 4-5			0.216	(0.004, 0.427)
Mean PSA	**1.83ng/ml**			
PIRADS 1-2			0.008	(0.009, 0.02)
PIRADS 3-5			0.161	(0.04, 0.27)
PIRADS 1-3			0.027	(0.001, 0.05)
PIRADS 4-5			0.251	(0.05, 0.44)
Mesn PSAD	**0.055ng/ml**			

PIRADS 1-2		0.009	(0.009, 0.02)
PIRADS 3-5		0.173	(0.05, 0.28)
PIRADS 1-3		0.015	(0.00, 0.05)
PIRADS 4-5		0.26	(0.06, 0.45)

***the average difference in probability of cancer detection between the two variables**
****the average probability of cancer detection in men with a PIRADS 1-2/3-5 etc MRI**

Any cancer

		Contrast of Adj Preds	**Marginal Adj Pred**	**(95% C.I.)**
Mean Age	**53.5**			
PIRADS 1-2			0.21	(0.13, 0.29)
PIRADS 3-5			0.47	(0.33, 0.62)
PIRADS 1-3			0.25	(0.17, 0.33)
PIRADS 4-5			0.57	(0.35, 0.79)

Mean PSA	**1.83ng/ml**		
PIRADS 1-2		0.22	(0.14, 0.31)
PIRADS 3-5		0.44	(0.29, 0.53)
PIRADS 1-3		0.25	(0.17, 0.33)
PIRADS 4-5		0.51	(0.28, 0.74)
Mesn PSAD	**0.055ng/ml**		
PIRADS 1-2		0.22	(0.14, 0.30)
PIRADS 3-5		0.46	(0.31, 0.60)
PIRADS 1-3		0.25	(0.18, 0.33)
PIRADS 4-5		0.53	(0.31, 0.76)

Table 0.1

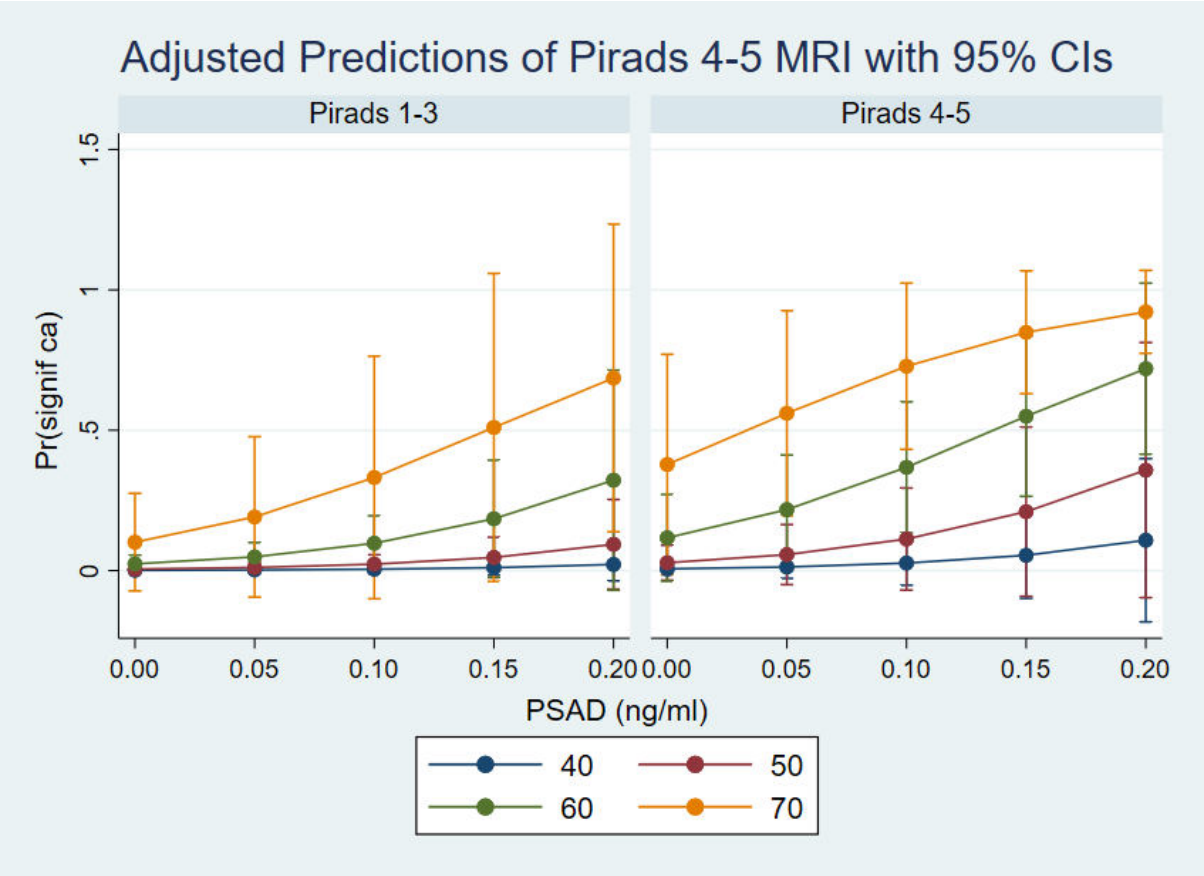


Figure 0.4 Predicted probabilites of significant PrCa at margins of age and PSAD by category of MRI. An increase in probaility of cancer was only observed at the oldest for those with a normal MRI. In those with an abnormal (Pirads 4-5 MRI), older age and PSAD appeared to have more of an impact.

Logistic regression model incorporating MRI as a categorical (predictor) variable and age and PSAD as continuous (predictor) variables, with clinically significant PrCa as outcome. Pirads 4-5 MRI was positively associated with significant cancer outcome at prostate biopsy (OR 2.86; p=0.05), as was age (OR 1.02, p= 0.364) but not PSAD (OR 1298.436*, p=0.082).

Any Cancer detection

MRI 3-5 and one other variable – Any Cancer

In a logistic regression model with MRI, PSA as a categorical variable, was positively associated with any PrCa compared to those with a PSA of 0-1.0ng/ml. only a PSA of >=4.0ng/ml was significantly associated with (any) cancer (OR 5.15, p=0.008). Pirads 3-5 MRI was significantly and positively associated with any cancer (OR 3.0, p=0.011).

In a logistic regression model with MRI, PSA as a continuous variable was positively associated with any PrCa (OR 1.35, p=0.017). Pirads 3-5 MRI was significantly and positively associated with any cancer (OR 2.7, p=0.013). At a mean PSA of 1.83ng/ml, the percentage probability of detecting any PrCa on biopsy was 22% in men with a Pirads 1-2 MRI and 44% in men with a Pirads 3-5 MRI.

At the higher end of the PSA scale (i.e at a PSA of 8ng/ml), the (average) predicted probability of any cancer was 65% with a pirads 1-2 MRI and 83% with a Pirads 3-5 MRI. The predicted probability of any PrCa rose as the PSA rose, whether in the presence of a normal or abnormal MRI.

Abnormal MRI Definition : Pirads 4-5 and PSA for Any Cancer

In a logistic regression model with MRI, PSA as a categorical variable was positively associated with any PrCa compared to those with a PSA of 0-1.0ng/ml. only a PSA of >=4.0ng/ml was significantly associated with (any) cancer (OR 5.85, p=0.004). Pirads 4-5 MRI was significantly and positively associated with any cancer (OR 2.78, p=0.048).

In a logistic regression model with MRI, PSA as a continuous variable was positively associated with any PrCa (OR 1.36, p=0.017). Pirads 4-5 MRI was significantly and positively associated with any cancer (OR 3.0, p=0.029).

At a mean PSA of 1.83ng/ml, the percentage probability of detecting any PrCa on biopsy was 25% in men with a Pirads 1-3 MRI and 51% in men with a Pirads 4-5 MRI. Further adjusted predictions of PrCa probability at PSA values outside the mean values are listed in the Appendix. At a PSA of 0-<1.0ng/ml with a Pirads 1-3 MRI, the (average) predicted probability of any cancer was 16% and 37% with a Pirads 4-5 MRI.

At a PSA of 3ng/ml with a Pirads 1-3 MRI the (average) predicted probability of any cancer was 33% and 60% with a Pirads 4-5 MRI. At the higher end of the PSA scale

(i.e at a PSA of 8ng/ml, the (average) predicted probability of any cancer was 70% with a pirads 1-3 MRI and 87% with a Pirads 4-5 MRI.

The predicted probability of any PrCa rose as the PSA rose, whether in the presence of a normal or abnormal MRI. At the higher levels of PSA (6-9ng/ml), there was no significant difference in the predicted probability of PrCa between a normal and abnormal MRI. The greatest difference in the predicted probability of PrCa between those with a normal and abnormal MRI was in those with a PSA of 3-5ng/ml (coefficients in Appendix).

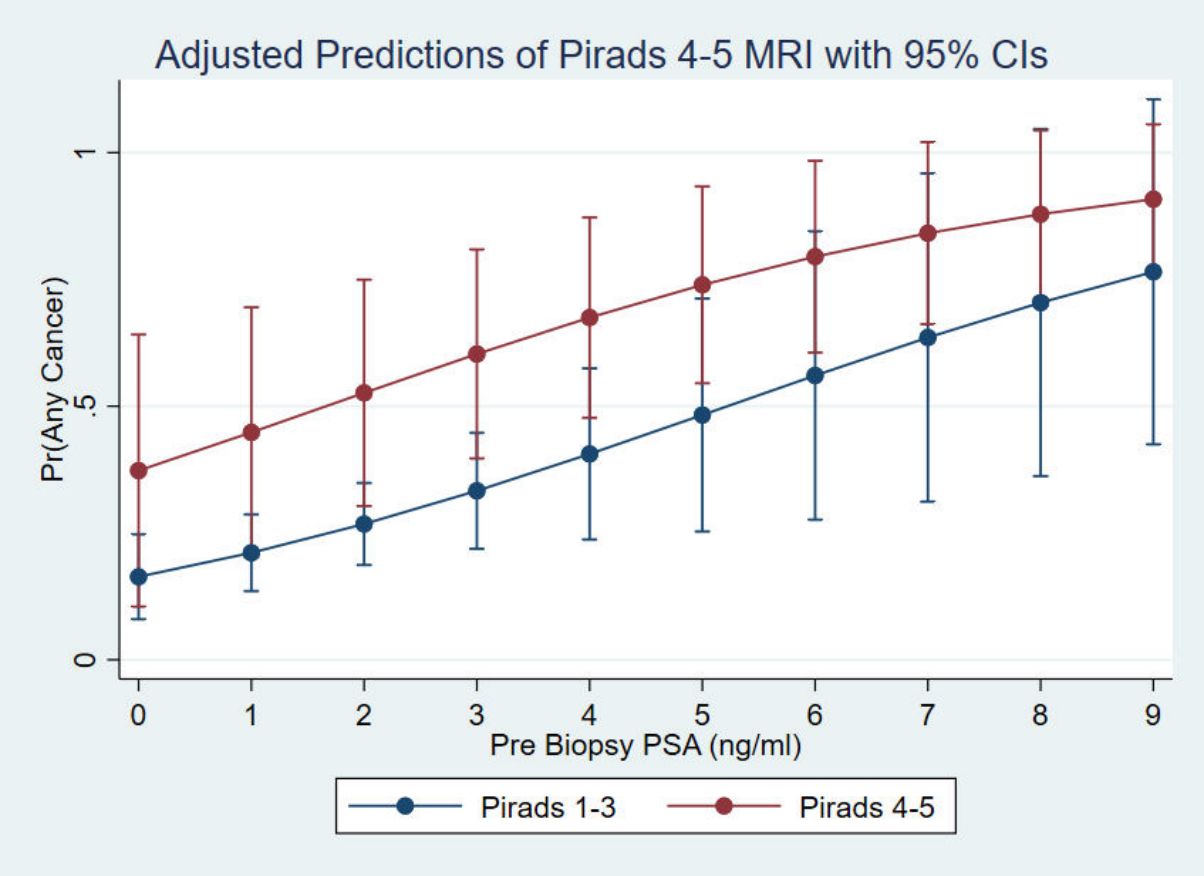


Figure 0.1 The predicted probability of any PrCa rose as the PSA rose, whether in the presence of a normal or abnormal MRI.

Abnormal MRI Definition : Pirads 3-5 and PSA Density

A PSAD≥0.15ng/ml was associated with any cancer detection on prostate biopsy (OR 2.58, p=0.23) but not statistically significantly so in a model with Pirads 3-5 MRI (OR 3.36, p=0.002).

PSAD (continuous variable) was positively associated with any cancer detection on prostate biopsy (OR 1.00, p=0.063) but not statistically significantly so in a model with Pirads 3-5 MRI (OR 2.95, p=0.006).

At a mean PSAD of 0.055ng/ml, the percentage probability of detecting any PrCa on biopsy was 22% in men with a Pirads 1-2 MRI and 46% in men with a Pirads 3-5 MRI.

Abnormal MRI Definition : Pirads 4-5 and PSA Density

A PSAD≥0.15ng/ml was associated with any cancer detection on prostate biopsy (OR 2.7`, p=0.21) but not statistically significantly so in a model with Pirads 4-5 MRI (4.15, p=0.003).

PSAD (continuous variable) was positively associated with any cancer detection on prostate biopsy (OR 1.00, p=0.077) but not statistically significantly so in a model with Pirads 4-5 MRI (OR 2.95, p=0.017).

At a mean PSAD of 0.055ng/ml, the percentage probability of detecting any PrCa on biopsy was 25% in men with a Pirads 1-3 MRI and 53% in men with a Pirads 4-5 MRI.

Abnormal MRI Definition : Pirads 3-5 and Age

Age as a categorical variable was positively associated with any cancer detection (ORs 0.97 & 1.86) but not statistically significantly so. A Pirads 3-5 MRI remained significantly associated with any cancer detection (OR 3.39) compared to men with a Pirads 1-2 MRI (p=0.001). PIrads 3-5 MRI is positively associated with any cancer (OR 3.30; p=0.002)) in the presence of age as a continuous variable, which is also significantly associated with any cancer detection (OR 1.03) but not statistically significantly so (p=0.192). At the mean study age (53.5 years), the predicated probability of any cancer detection in a man with a Pirads 1-2 MRI is 21%, and 47%

with a Pirads 3-5 MRI. Age as a categorical variable was positively associated with any cancer detection (ORs 0.97 & 1.4) but not statistically significantly so.

Abnormal MRI Definition : Pirads 4-5 and Age

A Pirads 4-5 MRI remained significantly associated with any cancer detection (OR 4.0) compared to men with a Pirads 1-3 MRI (p=0.006). PIrads 4-5 MRI is positively associated with any cancer (OR 3.93; p=0.007)) in the presence of age which is also significantly associated with any cancer detection (OR 1.02) but not statistically significantly so (p=0.339). At the mean study age (53.5 years), the predicated probability of any cancer detection in a man with a Pirads 1-3 MRI is 25%, and 57% with a Pirads 4-5 MRI.

Abnormal MRI Definition : Pirads 3-5 , PSA and Age

In a logistic regression model incorporating age and PSA as continuous predictor variables and MRI as a categorical predictor variable with (any) cancer as the outcome, Pirads 3-5 MRI was positively and significantly associated with cancer detection OR2.63, p=0.016). PSA was also significantly associated (OR 1.32, p=0.035) but age was not. At a mean age of 53.5 years and PSA of 1.8ng/ml, the average probability of (any) cancer detection was 22% in those with a Pirads 1-2

MRI and 43% in those with a Pirads 3-5 MRI . A large increase in probaility of cancer was not seen due to age. PSA appeared to have the greatest impact upon probability with an abnormal (Pirads 3-5) MRI. A full table of coefficients and contrasts of adjusted predictions is listed in Appendix.

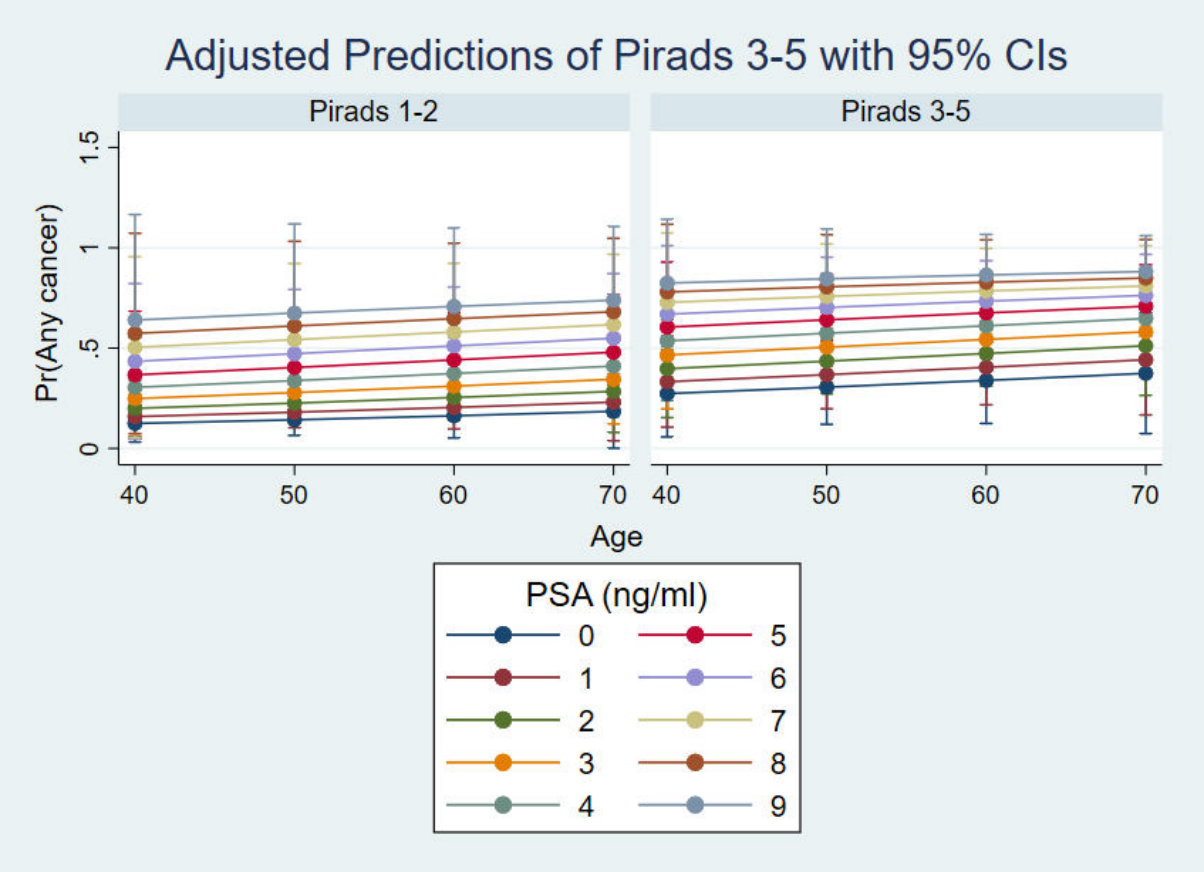


Figure 0.2 predicted probabilites of (any) PrCa at margins of age and PSA by category of MR. A large increase in probaility of cancer was not seen due to age. PSA appeared to have the greatest impact upon probability with an abnormal (Pirads 3-5) MRI. A full table of coefficients and contrasts of adjusted predictions is listed in Appendix.

Abnormal MRI Definition : Pirads 4-5, Age and PSA

In a logistic regression model incorporating age and PSA as continuous predictor variables and MRI as a categorical predictor variable with (any) cancer as the outcome, Pirads 4-5 MRI was positively and significantly associated with cancer detection OR 2.9, p=0.044). PSA was also significantly associated (OR 1.35, p=0.027) but age was not (p=0.755). At a mean age of 53.5 years and PSA of 1.8ng/ml, the average probability of (any) cancer detection was 25% in those with a Pirads 1-3 MRI and 50% in those with a Pirads 4-5 MRI. A large increase in probaility of cancer was not seen due to age. PSA appeared to have the greatest impact upon probability with an abnormal (Pirads 4-5) MRI. A full table of coefficients and contrasts of adjusted predictions is listed in Appendix.

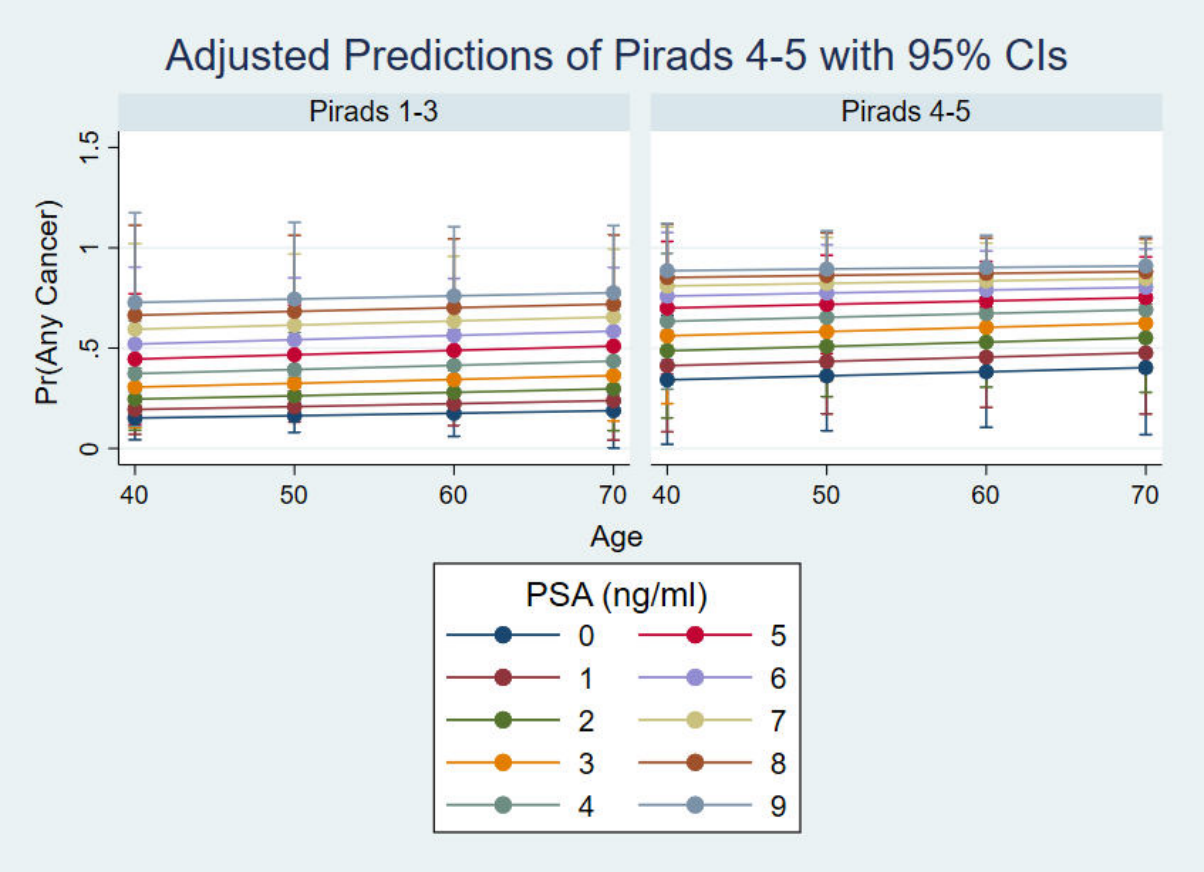


Figure 0.3 predicted probabilites of (any) PrCa at margins of age and PSA by category of MRI. A large increase in probaility of cancer was not seen due to age. PSA appeared to have the greatest impact upon probability with an abnormal (Pirads 4-5) MRI. A full table of coefficients and contrasts of adjusted predictions is listed in Appendix.

Abnormal MRI Definition : Pirads 3-5, Age and PSAD

Logistic regression model incorporating MRI as a categorical (predictor) variable and age and PSAD as continuous (predictor) variables, with clinically significant PrCa as outcome. Pirads 3-5 MRI was positively associated with significant cancer outcome at prostate biopsy (OR 2.70; p=0.013), as were age (OR 1.03, p= 0.261) but not PSAD (OR 1064.702*, p=0.082). An increase in probaility of cancer was observed with an increasing age and PSAD, for both normal and abnormal MRIs. A full table of coefficients and contrasts of adjusted predictions is listed in Appendix.

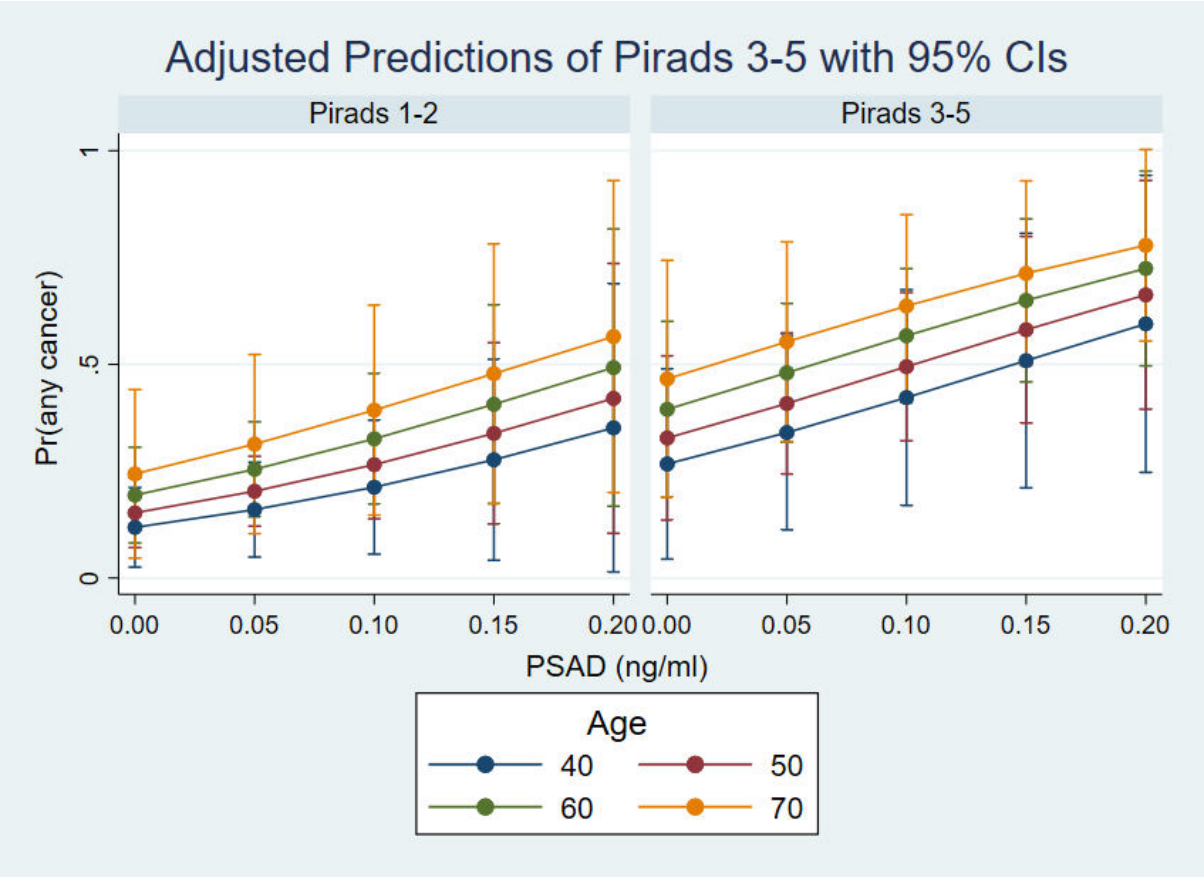


Figure 0.4 Predicted probabilites of (any) PrCa at margins of age and PSAD by category of MRI. An increase in probaility of cancer was observed with an increasing age and PSAD, for both normal and abnormal MRIs. A full table of coefficients and contrasts of adjusted predictions is listed in Appendix.

Abnormal MRI Definition : Pirads 4-5, Age and PSAD

Logistic regression model incorporating MRI as a categorical (predictor) variable and age and PSAD as continuous (predictor) variables, with clinically significant PrCa as

outcome. Pirads 4-5 MRI was positively associated with significant cancer outcome at prostate biopsy (OR 2.86; p=0.05), as were age (OR 1.02, p= 0.364) but not PSAD (OR 1298.436*, p=0.082). Predicted probabilites of (any) PrCa at margins of age and PSAD by category of MRI. An increase in probaility of cancer was observed with an increasing age and PSAD, for both normal and abnormal MRIs. A full table of coefficients and contrasts of adjusted predictions is listed in Appendix.

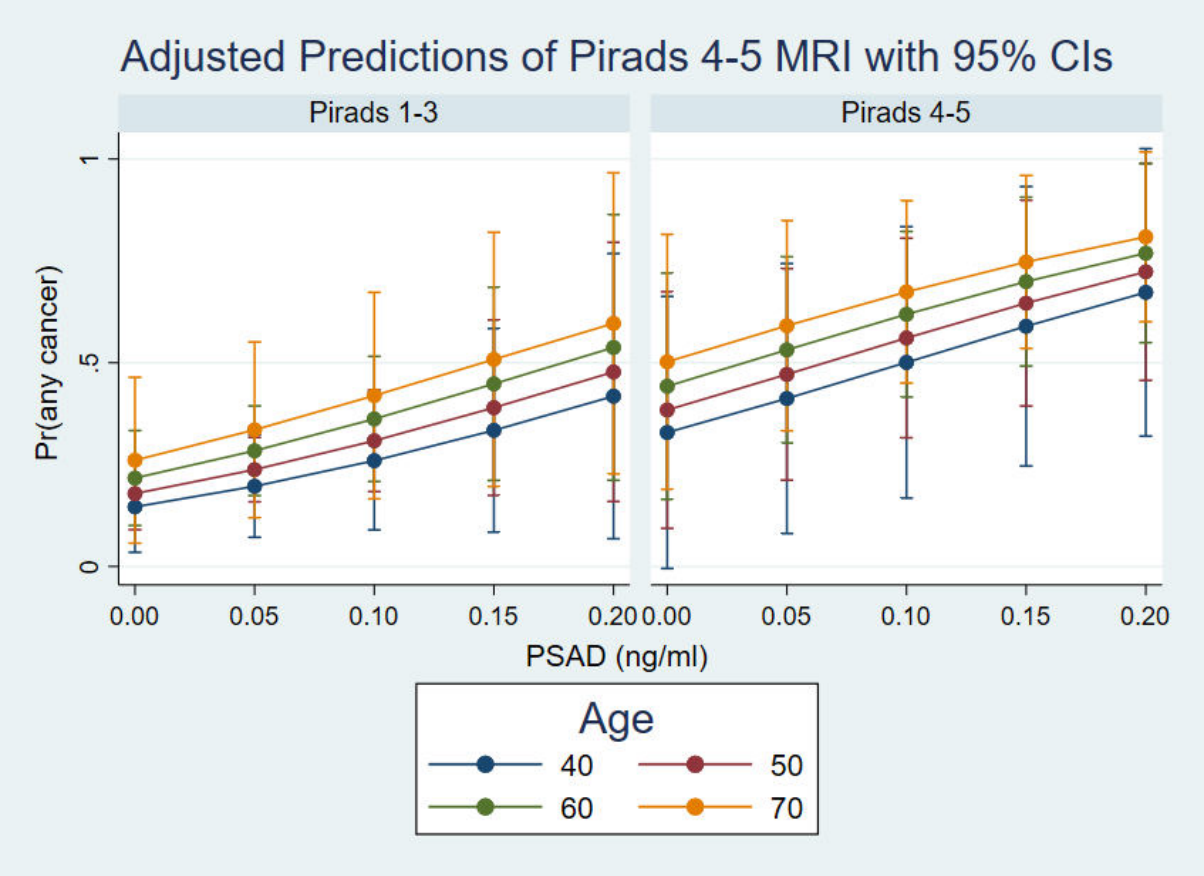


Figure 0.5 Predicted probabilites of (any) PrCa at margins of age and PSAD by category of MRI. An increase in probaility of cancer was observed with an increasing age and PSAD, for both normal and abnormal MRIs. A full table of coefficients and contrasts of adjusted predictions is listed in Appendix.

Raw data and STATA output

(for reference and evidence only if required)

PSA	Pirads	Obs	Rank	Sum
	1	9		691.000
	2	94		6060.000
	3	26		2221.000
	4	19		2083.000
	5	3		421.000

chi-squared = 25.473 with 4 d.f.
probability = 0.0001

chi-squared with ties = 25.531 with 4 d.f.
probability = 0.0001

Table 0.1

PSAD	Pirads	Obs	Rank	Sum
	1	9		794.000
	2	94		6059.500
	3	26		2149.000
	4	19		2031.500
	5	3		442.000

chi-squared = 25.325 with 4 d.f.
probability = 0.0001
chi-squared with ties = 25.327 with 4 d.f.

Table 9. Kruskal-Wallis equality-of-populations rank test for PSAD, to assess for difference in means between PSA in each category of Pirads.

probability = 0.0001

Table 0.2

Age	Pirads	Obs	Rank	Sum
	1	9		571.000
	2	94		6543.000
	3	26		1944.500
	4	19		2071.000
	5	3		346.500

chi-squared = 16.036 with 4 d.f.
probability = 0.0030

chi-squared with ties = 16.036 with 4 d.f.
probability = 0.0030

Table 10. Kruskal-Wallis equality-of-populations rank test for age, to assess for difference in means between PSA in each category of Pirads.

Table 0.3

MRI Vol	Pirads	Obs	Rank	Sum
	1	9		618.000
	2	93		6592.500
	3	26		2179.000
	4	19		1729.000
	5	3		206.500

chi-squared = 4.711 with 4 d.f.
probability = 0.3183

chi-squared with ties = 4.719 with 4 d.f.
probability = 0.3174

Table 0.4 - Kruskal-Wallis equality-of-populations rank test for MRI Volume, to assess for difference in means between PSA in each category of Pirads.

PSAD	Pirads	Obs	Rank	Sum
	1	9		794.000
	2	94		6059.500
	3	26		2149.000
	4	19		2031.500
	5	3		442.000

chi-squared = 25.325 with 4 d.f.
probability = 0.0001
chi-squared with ties = 25.327 with 4 d.f.
probability = 0.0001

Table 0.5 - Kruskal-Wallis equality-of-populations rank test for PSAD, to assess for difference in means between PSA in each category of Pirads.

PSA	Pirads 3-5	Obs	Rank	Sum
	N	103		6751.000
	Y	48		4725.000

chi-squared = 18.522 with 1 d.f.
probability = 0.0001
chi-squared with ties = 18.564 with 1 d.f.
probability = 0.0001

Table 19. Kruskal-Wallis equality-of-populations rank test for age, to assess for difference in means between PSA in category of Pirads, grouped by Pirads 1-2 vs Pirads 3-5

MRI Vol	Pirads 3-5	Obs	Rank	Sum
	N	102		7210.500
	Y	48		4114.500

chi-squared = 3.905 with 1 d.f.
probability = 0.0481
chi-squared with ties = 3.912 with 1 d.f.
probability = 0.0479

Table 20. Kruskal-Wallis equality-of-populations rank test for age, to assess for difference in means between MRI vol in category of Pirads, grouped by Pirads 1-2 vs Pirads 3-5

Age	Pirads 3-5	Obs	Rank	Sum
	N	103		7114.000
	Y	48		4362.000

chi-squared = 8.141 with 1 d.f.
probability = 0.0043
chi-squared with ties = 8.141 with 1 d.f.
probability = 0.0043

Table 21. Kruskal-Wallis equality-of-populations rank test for age, to assess for difference in means between age in category of Pirads, grouped by Pirads 1-2 vs Pirads 3-5

PSAD	Pirads 3-5	Obs	Rank	Sum
	N	103		6853.500
	Y	48		4622.500

chi-squared = 15.164 with 1 d.f.
probability = 0.0001
chi-squared with ties = 15.165 with 1 d.f.
probability = 0.0001

Table 22. Kruskal-Wallis equality-of-populations rank test for age, to assess for difference in means between PSAD in category of Pirads, grouped by Pirads 1-2 vs Pirads 3-5

Age	Pirads 4-5	Obs	Rank	Sum
	0	128		8927.500
	1	23		2548.500

chi-squared = 17.184 with 1 d.f.
probability = 0.0001
chi-squared with ties = 17.184 with 1 d.f.
probability = 0.0001

Table 23. Kruskal-Wallis equality-of-populations rank test for age, to assess for difference in means between age in category of Pirads, grouped by Pirads 1-3 vs Pirads 4-5

PSA	Pirads 4-5	Obs	Rank	Sum
	0	128		8831.000
	1	23		2645.000

chi-squared = 21.577 with 1 d.f.
probability = 0.0001
chi-squared with ties = 21.625 with 1 d.f.
probability = 0.0001

Table 24. Kruskal-Wallis equality-of-populations rank test for age, to assess for difference in means between PSA in category of Pirads, grouped by Pirads 1-3 vs Pirads 4-5

MRI Vol	Pirads 4-5	Obs	Rank	Sum
	0	127		9242.500
	1	23		2082.500

chi-squared = 3.257 with 1 d.f.
probability = 0.0711
chi-squared with ties = 3.263 with 1 d.f.
probability = 0.0709

Table 25. Kruskal-Wallis equality-of-populations rank test for age, to assess for difference in means between MRI Volume in category of Pirads, grouped by Pirads 1-3 vs Pirads 4-5

PSAD	Pirads 4-5	Obs	Rank	Sum
	0	128		8901.500
	1	23		2574.500

chi-squared = 18.318 with 1 d.f.

probability = 0.0001
chi-squared with ties = 18.320 with 1 d.f.
probability = 0.0001

Table 26. Kruskal-Wallis equality-of-populations rank test for age, to assess for difference in means between PSAD in category of Pirads, grouped by Pirads 1-3 vs Pirads 4-5

Significant cancer

Abnormal MRI Definition : Pirads 3-5

Logistic regression

Signif Ca	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Pirads 1-2	1	.	.	.	.	.	
Pirads 3-5	34	35.997	3.33	.001	4.269	270.816	***
Constant	.01	.01	-4.60	0	.001	.07	***

Mean dependent var	0.086	SD dependent var	0.281
Pseudo r-squared	0.264	Number of obs	151.000
Chi-square	23.364	Prob > chi2	0.000
Akaike crit. (AIC)	69.244	Bayesian crit. (BIC)	75.278

*** p<.01, ** p<.05, * p<.1

Table 0.1 logistic regression results, for significant cancer as outcome and MRI Pirads 3-5 MRI as a predictor categorical variable. MRI Pirads 3-5 was positively associated with clinically significant cancer detection (OR 34) compare to men with a Pirads 1-3 MRI (p=0.001).

Adjusted predictions **Number of obs = 151**
Model VCE : OIM
Expression : Pr(signif ca), predict()

	Delta-method Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
Pirads 3-5						
N	0.010	0.010	1.000	0.315	-0.009	0.029
Y	.25	0.063	4.000	0.000	0.128	0.372

Table 0.2 Marginal adjusted predictions of (average) clinically significant cancer probability. Men with a Pirads 1-2 MRI on average, had a 1% probability of clinically significant cancer detection on biopsy. ***Men with a Pirads 3-5 MRI on average, had a 25% probability of clinically significant cancer detection on biopsy.***

Contrasts of adjusted predictions **Number of obs = 151**
Model VCE : OIM
Expression : Pr(signif ca), predict()

	df	chi2	P>chi2
Pirads 3-5	1	14.440	0.000

Table 0.3 There was a statistically significant difference in effect between men with and without a Pirads 3-5 MRI (contrast of adjusted predictions; p<0.0001). ***Men with a Pirads 3-5 MRI had a 24% increase in (average) probability of clinically significant cancer detection.***

Logistic regression

Signif Ca	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Pirads 1-3	1	.	.	.	.	.	
Pirads 4-5	19.929	13.228	4.51	0	5.426	73.196	***
Constant	.032	.016	-6.76	0	.012	.087	***

Mean dependent var	0.086	SD dependent var	0.281
Pseudo r-squared	0.251	Number of obs	151.000
Chi-square	22.219	Prob > chi2	0.000
Akaike crit. (AIC)	70.389	Bayesian crit. (BIC)	76.423

*** p<.01, ** p<.05, * p<.1

Table 0.4 logistic regression results, for significant cancer as outcome and MRI Pirads 4-5 MRI as a predictor categorical variable. ***MRI Pirads 4-5 was positively associated with clinically significant cancer detection (OR 19.9) compare to men with a Pirads 1-3 MRI (p=0.001).***

Adjusted predictions **Number of obs = 151**
Model VCE : OIM
Expression : Pr(signif ca), predict()

	Delta-method					
	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
Pirads 4-5						
No	0.031	0.015	2.030	0.042	0.001	0.061
Yes	0.391	0.102	3.850	0.000	0.192	0.591

Table 0.5 Marginal adjusted predictions of (average) clinically significant cancer probability. ***Men with a Pirads 1-3 MRI on average, had a 3% probability of clinically significant cancer detection on biopsy. Men with a Pirads 4-5 MRI on average, had a 39% probability of clinically significant cancer detection on biopsy.***

Contrasts of adjusted predictions **Number of obs = 151**
Model VCE : OIM
Expression : Pr(signif ca), predict()

	df	chi2	P>chi2
Pirads 4-5	1	12.240	0.001

Table 0.6 There was a statistically significant difference in effect between men with and without a Pirads 4-5 MRI (contrast of adjusted predictions; p=0.001). men with a Pirads 4-5 MRI had a 36% increase in (average) probability of clinically significant cancer detection.

Abnormal MRI Definition : Pirads 3-5 and PSA

Logistic regression

Signif ca	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
PSA	1.666	.318	2.67	.008	1.146	2.423	***
Pirads 1-2	1	.	.	.	.	.	
Pirads 3-5	24.208	26.343	2.93	.003	2.868	204.292	***
Constant	.003	.004	-4.73	0	0	.034	***

Mean dependent var	0.086	SD dependent var	0.281
Pseudo r-squared	0.346	Number of obs	151.000
Chi-square	30.700	Prob > chi2	0.000
Akaike crit. (AIC)	63.908	Bayesian crit. (BIC)	72.959

*** p<.01, ** p<.05, * p<.1

Table 0.7 Logistic regression results, for significant cancer as outcome, MRI Pirads 3-5 MRI as a predictor (categorical) variable and PSA (continuous variable). ***MRI Pirads 3-5 was positively associated with clinically significant cancer detection (OR 24.2) compared to men with a Pirads 1-2 MRI (p=0.003). PSA (OR 1.66) was also positively associated with clinically significant cancer detection (p=0.008) but less so than MRI.***

Adjusted predictions **Number of obs = 151**
Model VCE : OIM
Expression : Pr(signif ca), predict()
at : 1.abnormal~l = .6821192 (mean)
2.abnormal~l = .3178808 (mean)
PSA = 1.833775 (mean)

	Delta-method					
	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
Pirads 3-5						
No	0.008	0.008	0.940	0.347	-0.009	0.024
Yes	0.161	0.059	2.730	0.006	0.045	0.277

Table 0.8 ***At a mean PSA of 1.8ng/ml, the average predicted probability of signifcant cancer in men with a Pirads 1-2 MRI was 0.8%, and 16.1% in those with a Pirads 3-5 MRI.***

Adjusted predictions **Number of obs = 151**
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()
1._at : prebiopsypsa = 0
2._at : prebiopsypsa = .5
3._at : prebiopsypsa = 1
4._at : prebiopsypsa = 1.5

5._at : prebiopsypsa = 2
6._at : prebiopsypsa = 2.5
7._at : prebiopsypsa = 3
8._at : prebiopsypsa = 3.5
9._at : prebiopsypsa = 4
10._at : prebiopsypsa = 4.5
11._at : prebiopsypsa = 5
12._at : prebiopsypsa = 5.5
13._at : prebiopsypsa = 6
14._at : prebiopsypsa = 6.5
15._at : prebiopsypsa = 7
16._at : prebiopsypsa = 7.5
17._at : prebiopsypsa = 8
18._at : prebiopsypsa = 8.5
19._at : prebiopsypsa = 9

Delta-method

	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#pirads 3-5 MRI						
1#N	0.003	0.004	0.820	0.411	-0.004	0.011
1#Y	0.070	0.046	1.530	0.125	-0.019	0.160
2#N	0.004	0.005	0.860	0.391	-0.005	0.013
2#Y	0.089	0.050	1.770	0.077	-0.010	0.187
3#N	0.005	0.006	0.890	0.373	-0.006	0.017
3#Y	0.112	0.054	2.060	0.039	0.006	0.218
4#N	0.007	0.007	0.920	0.357	-0.007	0.021
4#Y	0.140	0.057	2.440	0.015	0.027	0.252
5#N	0.009	0.009	0.950	0.343	-0.009	0.026
5#Y	0.173	0.060	2.880	0.004	0.055	0.291
6#N	0.011	0.011	0.970	0.332	-0.011	0.033
6#Y	0.213	0.063	3.360	0.001	0.089	0.337
7#N	0.014	0.014	0.980	0.325	-0.014	0.042
7#Y	0.259	0.069	3.760	0.000	0.124	0.393
8#N	0.018	0.018	0.990	0.321	-0.018	0.054
8#Y	0.311	0.078	4.000	0.000	0.158	0.463
9#N	0.023	0.024	0.990	0.321	-0.023	0.070
9#Y	0.368	0.091	4.040	0.000	0.189	0.546
10#N	0.030	0.030	0.990	0.324	-0.030	0.090
10#Y	0.429	0.108	3.980	0.000	0.218	0.640
11#N	0.038	0.040	0.970	0.330	-0.039	0.116
11#Y	0.492	0.125	3.930	0.000	0.246	0.738
12#N	0.049	0.051	0.960	0.339	-0.051	0.150
12#Y	0.556	0.141	3.930	0.000	0.278	0.833
13#N	0.062	0.067	0.940	0.348	-0.068	0.193
13#Y	0.617	0.154	4.020	0.000	0.316	0.918
14#N	0.079	0.086	0.920	0.358	-0.090	0.248
14#Y	0.676	0.160	4.210	0.000	0.361	0.990
15#N	0.100	0.111	0.900	0.367	-0.117	0.317
15#Y	0.729	0.161	4.520	0.000	0.413	1.045
16#N	0.125	0.141	0.890	0.374	-0.151	0.402
16#Y	0.776	0.157	4.950	0.000	0.469	1.084
17#N	0.156	0.177	0.880	0.378	-0.191	0.504
17#Y	0.817	0.148	5.520	0.000	0.527	1.108
18#N	0.193	0.219	0.880	0.379	-0.237	0.622
18#Y	0.853	0.136	6.270	0.000	0.586	1.119
19#N	0.236	0.266	0.890	0.376	-0.285	0.757
19#Y	0.882	0.122	7.220	0.000	0.642	1.121

*Table 0.9 Marginal adjusted predictions clinically significant cancer probability according to differing levels of PSA (**Error! Reference source not found.**)*

*At the lowest levels of PSA, men with a Pirads 3-5 MRI had a similar predicted probability of clinically significant cancer to those with a Pirads 1-2 MRI (0-11%). **At higher levels of PSA, men with and without a Pirads 3-5 MRI had significantly different predicted probabilities of cancer (ie at a PSA of 8.0ng/ml, men with a Pirads 1-2 MRI had a 15% predicted probability, and men with a Pirads 3-5 MRI had an 81% predicted probability of clinically significant cancer detection).***

Contrasts of adjusted predictions **Number of obs = 151**
Model VCE : OIM
Expression : Pr(signif ca), predict()

1._at	: prebiopsypsa	=	0
2._at	: prebiopsypsa	=	.5
3._at	: prebiopsypsa	=	1
4._at	: prebiopsypsa	=	1.5
5._at	: prebiopsypsa	=	2
6._at	: prebiopsypsa	=	2.5
7._at	: prebiopsypsa	=	3
8._at	: prebiopsypsa	=	3.5
9._at	: prebiopsypsa	=	4
10._at	: prebiopsypsa	=	4.5
11._at	: prebiopsypsa	=	5
12._at	: prebiopsypsa	=	5.5
13._at	: prebiopsypsa	=	6
14._at	: prebiopsypsa	=	6.5
15._at	: prebiopsypsa	=	7
16._at	: prebiopsypsa	=	7.5
17._at	: prebiopsypsa	=	8
18._at	: prebiopsypsa	=	8.5
19._at	: prebiopsypsa	=	9

	df	chi2	P>chi2
Pirads 3-5 MRI@_at			
1	1	2.310	0.129
2	1	3.050	0.081
3	1	4.100	0.043
4	1	5.610	0.018
5	1	7.630	0.006
6	1	10.010	0.002
7	1	12.160	0.001
8	1	13.400	0.000
9	1	13.660	0.000
10	1	13.480	0.000
11	1	13.410	0.000
12	1	13.810	0.000
13	1	14.880	0.000
14	1	16.750	0.000
15	1	19.220	0.000
16	1	21.160	0.000
17	1	20.180	0.000
18	1	15.550	0.000
19	1	10.150	0.001

Joint	3	21.160	0.000

Table 0.10 Contrasts of adjusted predictions. ***Below a PSA of 1.0ng/ml, there was no statistically significant difference in effect between men with and without a Pirads 3-5 MRI. Ie men at this very low PSA level appeared to have a very low probability of significant cancer even in the presence of an 'abnormal' MRI.***

Contrasts of adjusted predictions **Number of obs = 151**
Model VCE : OIM
Expression : Pr(signif ca), predict()

1._at : prebiopsypsa = 0
2._at : prebiopsypsa = .5
3._at : prebiopsypsa = 1
4._at : prebiopsypsa = 1.5
5._at : prebiopsypsa = 2
6._at : prebiopsypsa = 2.5
7._at : prebiopsypsa = 3
8._at : prebiopsypsa = 3.5
9._at : prebiopsypsa = 4
10._at : prebiopsypsa = 4.5
11._at : prebiopsypsa = 5
12._at : prebiopsypsa = 5.5
13._at : prebiopsypsa = 6
14._at : prebiopsypsa = 6.5
15._at : prebiopsypsa = 7
16._at : prebiopsypsa = 7.5
17._at : prebiopsypsa = 8
18._at : prebiopsypsa = 8.5
19._at : prebiopsypsa = 9

	Delta-method			
	Contrast	Std.Err.	z	P>z
Pirads 3-5 MRI@_at				
(Y vs base) 1	0.067	0.044	1.520	0.128
(Y vs base) 2	0.085	0.049	1.750	0.081
(Y vs base) 3	0.107	0.053	2.030	0.043
(Y vs base) 4	0.133	0.056	2.370	0.018
(Y vs base) 5	0.165	0.060	2.760	0.006
(Y vs base) 6	0.202	0.064	3.160	0.002
(Y vs base) 7	0.244	0.070	3.490	0.000
(Y vs base) 8	0.292	0.080	3.660	0.000
(Y vs base) 9	0.344	0.093	3.700	0.000
(Y vs base) 10	0.399	0.109	3.670	0.000

(Y vs base) 11	0.454	0.124	3.660	0.000
(Y vs base) 12	0.506	0.136	3.720	0.000
(Y vs base) 13	0.555	0.144	3.860	0.000
(Y vs base) 14	0.596	0.146	4.090	0.000
(Y vs base) 15	0.629	0.143	4.380	0.000
(Y vs base) 16	0.651	0.142	4.600	0.000
(Y vs base) 17	0.661	0.147	4.490	0.000
(Y vs base) 18	0.660	0.167	3.940	0.000
(Y vs base) 19	0.646	0.203	3.190	0.001

Table 0.11 Contrasts of adjusted predictions with coefficients. ***le at a PSA of 3.0ng/ml, men with a Pirads 3-5 MRI had, on average a 24% increase in probability of clinically significant cancer detection than men with a Pirad 1-2 MRI. This was 8% at a PSA of 0.5ng/ml.***

Sensitivity	7.69%
Specificity	98.55%
Positive predictive value	33.33%
Negative predictive value	91.89%
Correctly classified	90.73%

Table 0.12 Sensitivity, specificity, NPV and PPV values for the logistic regression model described in Table 0.7 including Pirads 3-5 MRI and PSAD.

Logistic regression

Signif ca	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
PSA	1.577	.29	2.48	.013	1.099	2.261	**
Pirads 1-3	1	.	.	.	.	.	
Pirads 4-5	11.843	8.271	3.54	0	3.013	46.551	***
Constant	.012	.009	-6.04	0	.003	.051	***

Mean dependent var	0.086	SD dependent var	0.281
Pseudo r-squared	0.316	Number of obs	151.000
Chi-square	27.982	Prob > chi2	0.000

Akaike crit. (AIC)	66.626	Bayesian crit. (BIC)	75.678

*** p<.01, ** p<.05, * p<.1

Table 0.13 logistic regression results, for significant cancer as outcome, MRI Pirads 4-5 MRI as a predictor (categorical) variable and PSA (continuous variable). MRI Pirads 4-5 was positively associated with clinically significant cancer detection (OR 11.8) compared to men with a Pirads 1-3 MRI (p<0.0001). PSA (OR 1.57) was also positively associated with clinically significant cancer detection (p=0.018) but less so than MRI.

Adjusted predictions **Number of obs = 151**
Model VCE : OIM
Expression : Pr(signif ca), predict()
at : 0.abnorma~45 = .8476821 (mean)
1.abnorma~45 = .1523179 (mean)
PSA = 1.833775 (mean)

	Delta-method					
	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
Pirads 4-5						
No	0.027	0.015	1.870	0.061	-0.001	0.056
Yes	0.251	0.100	2.520	0.012	0.055	0.446

Table 0.14 At a mean PSA of 1.8ng/ml, the average predicated probability of significant cancer in men with a Pirads 1-3 MRI was 2.7% and 25.1% in those with a Pirads 4-5 MRI.

Adjusted predictions **Number of obs = 151**
Model VCE : OIM
Expression : Pr(signif ca), predict()
1._at : prebiopsypsa = 0
2._at : prebiopsypsa = .5
3._at : prebiopsypsa = 1
4._at : prebiopsypsa = 1.5
5._at : prebiopsypsa = 2
6._at : prebiopsypsa = 2.5
7._at : prebiopsypsa = 3
8._at : prebiopsypsa = 3.5
9._at : prebiopsypsa = 4
10._at : prebiopsypsa = 4.5
11._at : prebiopsypsa = 5
12._at : prebiopsypsa = 5.5
13._at : prebiopsypsa = 6
14._at : prebiopsypsa = 6.5
15._at : prebiopsypsa = 7
16._at : prebiopsypsa = 7.5
17._at : prebiopsypsa = 8
18._at : prebiopsypsa = 8.5
19._at : prebiopsypsa = 9

	Delta-method					
	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#pirads 4-5 MRI						
1 0	0.012	0.009	1.390	0.165	-0.005	0.029
1 1	0.127	0.084	1.510	0.132	-0.038	0.292
2 0	0.015	0.010	1.520	0.129	-0.004	0.035
2 1	0.154	0.090	1.720	0.086	-0.022	0.330
3 0	0.019	0.011	1.660	0.097	-0.003	0.041
3 1	0.186	0.094	1.970	0.049	0.001	0.371

4 0	0.024	0.013	1.790	0.073	-0.002	0.050
4 1	0.223	0.098	2.280	0.023	0.031	0.415
5 0	0.030	0.015	1.910	0.056	-0.001	0.060
5 1	0.265	0.100	2.640	0.008	0.068	0.462
6 0	0.037	0.019	1.980	0.047	0.000	0.073
6 1	0.312	0.103	3.030	0.002	0.110	0.513
7 0	0.046	0.023	2.010	0.045	0.001	0.091
7 1	0.362	0.106	3.420	0.001	0.155	0.570
8 0	0.057	0.029	1.970	0.049	0.000	0.113
8 1	0.417	0.111	3.760	0.000	0.199	0.634
9 0	0.070	0.037	1.900	0.058	-0.002	0.143
9 1	0.473	0.118	4.020	0.000	0.242	0.703
10 0	0.087	0.048	1.800	0.072	-0.008	0.182
10 1	0.530	0.126	4.210	0.000	0.283	0.776
11 0	0.107	0.063	1.690	0.091	-0.017	0.230
11 1	0.586	0.134	4.380	0.000	0.324	0.847
12 0	0.130	0.082	1.590	0.112	-0.030	0.291
12 1	0.640	0.140	4.570	0.000	0.365	0.914
13 0	0.158	0.105	1.510	0.132	-0.048	0.365
13 1	0.690	0.144	4.810	0.000	0.409	0.972
14 0	0.191	0.133	1.440	0.151	-0.070	0.452
14 1	0.737	0.144	5.120	0.000	0.455	1.019
15 0	0.229	0.165	1.390	0.166	-0.095	0.552
15 1	0.778	0.141	5.530	0.000	0.503	1.054
16 0	0.271	0.200	1.360	0.175	-0.121	0.664
16 1	0.815	0.135	6.050	0.000	0.551	1.079
17 0	0.319	0.237	1.340	0.179	-0.146	0.784
17 1	0.847	0.126	6.710	0.000	0.600	1.094
18 0	0.370	0.274	1.350	0.176	-0.167	0.907
18 1	0.874	0.116	7.530	0.000	0.647	1.102
19 0	0.425	0.307	1.380	0.167	-0.178	1.027
19 1	0.897	0.105	8.540	0.000	0.691	1.103

Table 0.15 Marginal adjusted predictions clinically significant cancer probability according to differing levels of PSA. At the lowest levels of PSA, men with a Pirads 4-5 MRI had different predicted probabilities of clinically significant cancer to those with a Pirads 1-3 MRI but these were not statistically significant.

At higher levels of PSA, men with and without a Pirads 4-5 MRI had significantly different predicted probabilities of cancer (ie at a PSA of 8.0ng/ml, men with a Pirads 1-3 MRI had a 31% predicted probability, and men with a Pirads 4-5 MRI had an 84% predicted probability of clinically significant cancer detection).

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signif ca), predict()
1._at : prebiopsypsa = 0
2._at : prebiopsypsa = .5
3._at : prebiopsypsa = 1
4._at : prebiopsypsa = 1.5
5._at : prebiopsypsa = 2
6._at : prebiopsypsa = 2.5
7._at : prebiopsypsa = 3
8._at : prebiopsypsa = 3.5
9._at : prebiopsypsa = 4
10._at : prebiopsypsa = 4.5
11._at : prebiopsypsa = 5
12._at : prebiopsypsa = 5.5

13._at : prebiopsypsa = 6
14._at : prebiopsypsa = 6.5
15._at : prebiopsypsa = 7
16._at : prebiopsypsa = 7.5
17._at : prebiopsypsa = 8
18._at : prebiopsypsa = 8.5
19._at : prebiopsypsa = 9

	df	chi2	P>chi2
Pirads 4-5 MRI@_at			
1	1	2.070	0.150
2	1	2.640	0.104
3	1	3.390	0.066
4	1	4.370	0.037
5	1	5.590	0.018
6	1	7.010	0.008
7	1	8.500	0.004
8	1	9.950	0.002
9	1	11.330	0.001
10	1	12.740	0.000
11	1	14.380	0.000
12	1	16.460	0.000
13	1	18.890	0.000
14	1	20.790	0.000
15	1	20.140	0.000
16	1	16.050	0.000
17	1	10.870	0.001
18	1	6.870	0.009
19	1	4.340	0.037
Joint	3	21.190	0.000

Table 0.16

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signif ca), predict()
1._at : prebiopsypsa = 0
2._at : prebiopsypsa = .5
3._at : prebiopsypsa = 1
4._at : prebiopsypsa = 1.5
5._at : prebiopsypsa = 2
6._at : prebiopsypsa = 2.5
7._at : prebiopsypsa = 3
8._at : prebiopsypsa = 3.5
9._at : prebiopsypsa = 4
10._at : prebiopsypsa = 4.5
11._at : prebiopsypsa = 5
12._at : prebiopsypsa = 5.5
13._at : prebiopsypsa = 6
14._at : prebiopsypsa = 6.5
15._at : prebiopsypsa = 7
16._at : prebiopsypsa = 7.5
17._at : prebiopsypsa = 8

18._at : prebiopsypsa = 8.5
19._at : prebiopsypsa = 9

	Delta-method Contrast	Std.Err.	z	P>z
Pirads 4-5 MRI@_at				
(1 vs base) 1	0.115	0.080	1.440	0.150
(1 vs base) 2	0.139	0.086	1.620	0.105
(1 vs base) 3	0.167	0.091	1.840	0.066
(1 vs base) 4	0.199	0.095	2.090	0.037
(1 vs base) 5	0.235	0.100	2.360	0.018
(1 vs base) 6	0.275	0.104	2.650	0.008
(1 vs base) 7	0.317	0.109	2.920	0.004
(1 vs base) 8	0.360	0.114	3.150	0.002
(1 vs base) 9	0.402	0.120	3.370	0.001
(1 vs base) 10	0.443	0.124	3.570	0.000
(1 vs base) 11	0.479	0.126	3.790	0.000
(1 vs base) 12	0.509	0.126	4.060	0.000
(1 vs base) 13	0.532	0.122	4.350	0.000
(1 vs base) 14	0.546	0.120	4.560	0.000
(1 vs base) 15	0.550	0.122	4.490	0.000
(1 vs base) 16	0.544	0.136	4.010	0.000
(1 vs base) 17	0.528	0.160	3.300	0.001
(1 vs base) 18	0.504	0.192	2.620	0.009
(1 vs base) 19	0.473	0.227	2.080	0.037

Table 0.17 Contrasts of adjusted predictions with coefficients.le at a PSA of 3.0ng/ml, men with a Pirads 4-5 MRI had, on average a 31.7% increase in probability of clinically significant cancer detection than men with a Pirad 1-3 MRI. This was 13% at a PSA of 0.5ng/ml.

Sensitivity	**23.08%**
Specificity	97.83%
Positive predictive value	50.00%
Negative predictive value	93.10%
Correctly classified	91.39%

Table 0.18 Sensitivity, specificity, NPV and PPV values for the logistic regression model described in Table 0.13 including Pirads 4-5 MRI and PSA.

Logistic regression

Significant cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Pirads 1-2 MRI	1	.	.	.	.	.	

Pirads 3-5 MRI	27.434	29.346	3.10	.002	3.371	223.25	***
PSA Density <0.15	1	.	.	.	.	.	
PSA Density≥0.15	7.605	6.836	2.26	.024	1.306	44.279	**
Constant	.009	.009	-4.68	0	.001	.064	***

Mean dependent var	0.086	SD dependent var	0.281
Pseudo r-squared	0.322	Number of obs	151.000
Chi-square	28.560	Prob > chi2	0.000
Akaike crit. (AIC)	66.048	Bayesian crit. (BIC)	75.099

*** p<.01, ** p<.05, * p<.1

Table 0.19 Logistic regression model for outcome of significant cancer with Pirads 3-5 MRI and a PSA Density ≥0.15 as categorical predictor variables. Overall the model is significant (prob>chi2 0.000). A PSA Density ≥0.15 was positively associated with significant PrCa (OR 7.6; p=0.024) and a Pirads 3-5 MRI was also positively associated with significant PrCa (OR 27.43; p=0.002). AUC for this model was 0.8640.

Logistic regression

Signif ca	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Pirads 1-2 MRI	1	.	.	.	.	.	
Pirads 3-5 MRI	23.508	25.44	2.92	.004	2.819	196.055	***
PSAD	1.015	.005	2.71	.007	1.004	1.025	***
Constant	.004	.004	-4.90	0	0	.036	***

Mean dependent var	0.086	SD dependent var	0.281
Pseudo r-squared	0.353	Number of obs	151.000
Chi-square	31.316	Prob > chi2	0.000
Akaike crit. (AIC)	63.292	Bayesian crit. (BIC)	72.344

*** p<.01, ** p<.05, * p<.1

Table 0.20 Logistic regression model for outcome of significant cancer with Pirads 3-5 MRI and a PSA Density as categorical and continuous predictor variables respectively. Overall the model is significant. PSA Density was postitively assocated with significant PrCa (OR 1.015; p=0.007) and a Pirads 3-5 MRI was remained positively associated with significant PrCa (OR 23.5; p=0.004). AUC for this model is graphed below in ***Error! Reference source not found.***

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signif ca), predict()
at : 1.abnormal~l = .6821192 (mean)
2.abnormal~l = .3178808 (mean)
PSAD = .0557596 (mean)

	Delta-method Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
Pirads 3-5 MRI						
N	0.009	0.009	0.970	0.330	-0.009	0.027
Y	0.173	0.059	2.930	0.003	0.057	0.289

Table 0.21 At the mean PSAD of 0.05, the average predicted probability of clinically significant PrCa in men with a Pirads 1-2 MRI was 0.9% and 17.3% in men with a Pirads 3-5 MRI.

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()
1._at : psad = .01
2._at : psad = .03
3._at : psad = .05
4._at : psad = .07
5._at : psad = .09
6._at : psad = .11
7._at : psad = .13
8._at : psad = .15
9._at : psad = .17
10._at : psad = .19
11._at : psad = .21

	Delta-method Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#pirads 3-5 MRI						
1#N	0.005	0.005	0.910	0.363	-0.005	0.014
1#Y	0.098	0.050	1.950	0.052	-0.001	0.196
2#N	0.006	0.006	0.940	0.346	-0.007	0.019
2#Y	0.126	0.054	2.320	0.020	0.020	0.233
3#N	0.008	0.008	0.970	0.333	-0.008	0.025
3#Y	0.162	0.058	2.790	0.005	0.048	0.275
4#N	0.011	0.011	0.990	0.324	-0.011	0.032
4#Y	0.205	0.062	3.280	0.001	0.082	0.327
5#N	0.014	0.014	1.000	0.319	-0.014	0.043
5#Y	0.255	0.069	3.690	0.000	0.120	0.391
6#N	0.019	0.019	1.000	0.320	-0.019	0.057
6#Y	0.314	0.081	3.880	0.000	0.155	0.473
7#N	0.025	0.026	0.990	0.324	-0.025	0.076
7#Y	0.379	0.098	3.880	0.000	0.188	0.571
8#N	0.033	0.035	0.970	0.332	-0.034	0.101
8#Y	0.449	0.118	3.820	0.000	0.218	0.680
9#N	0.044	0.047	0.950	0.343	-0.047	0.136
9#Y	0.521	0.137	3.790	0.000	0.252	0.790
10#N	0.058	0.063	0.920	0.355	-0.065	0.181
10#Y	0.592	0.153	3.870	0.000	0.292	0.892
11#N	0.076	0.084	0.900	0.367	-0.089	0.241
11#Y	0.659	0.162	4.060	0.000	0.341	0.978

Table 0.22 Adjusted predictions of Pirads 3-5 MRI at varying levels of PSAD. I.e at a PSAD of 0.15, men with Pirads 3-5 MRI had a predicted probability of significant PrCa of 44%, compared to 3% in those with a Pirads 1-2 MRI.

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()
1._at : psad = .01
2._at : psad = .03
3._at : psad = .05
4._at : psad = .07
5._at : psad = .09
6._at : psad = .11
7._at : psad = .13

8._at : psad = .15
9._at : psad = .17
10._at : psad = .19
11._at : psad = .21

	df	chi2	P>chi2
abnormalMRI@_at			
1	1	3.620	0.057
2	1	5.070	0.024
3	1	7.080	0.008
4	1	9.490	0.002
5	1	11.610	0.001
6	1	12.710	0.000
7	1	12.880	0.000
8	1	12.800	0.000
9	1	13.100	0.000
10	1	14.160	0.000
11	1	16.210	0.000
Joint	3	27.300	0.000

Table 0.23 Contrasts of adjusted predictions. There is a statistically significant difference in significant PrCa probability between men with and without a Pirads 3-5 MRI at all levels of PSAD, apart from the lowest (i.e PSAD = 0.01).

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()
1._at : psad = .01
2._at : psad = .03
3._at : psad = .05
4._at : psad = .07
5._at : psad = .09
6._at : psad = .11
7._at : psad = .13
8._at : psad = .15
9._at : psad = .17
10._at : psad = .19
11._at : psad = .21

	Delta-method Contrast	Std.Err.	z	P>z
Pirads 3-5 MRI @_at				
Base = pirads 1-2 MRI				
(Y vs base) 1	0.093	0.049	1.900	0.057
(Y vs base) 2	0.120	0.053	2.250	0.024
(Y vs base) 3	0.154	0.058	2.660	0.008
(Y vs base) 4	0.194	0.063	3.080	0.002
(Y vs base) 5	0.241	0.071	3.410	0.001
(Y vs base) 6	0.295	0.083	3.570	0.000
(Y vs base) 7	0.354	0.099	3.590	0.000
(Y vs base) 8	0.415	0.116	3.580	0.000
(Y vs base) 9	0.477	0.132	3.620	0.000
(Y vs base) 10	0.534	0.142	3.760	0.000
(Y vs base) 11	0.583	0.145	4.030	0.000

Table 0.24 Contrasts of adjusted predictions with coefficients (graphically depicted below in Figure 0.1). I.e at a PSAD of 0.05, men with a Pirads 3-5 MRI had a 15% increase in probability of clinically significant cancer detection compared to men with a Pirads 1-2 MRI. This rose to 58% at the highest level of PSAD (i.e at a PSAD of 0.21).

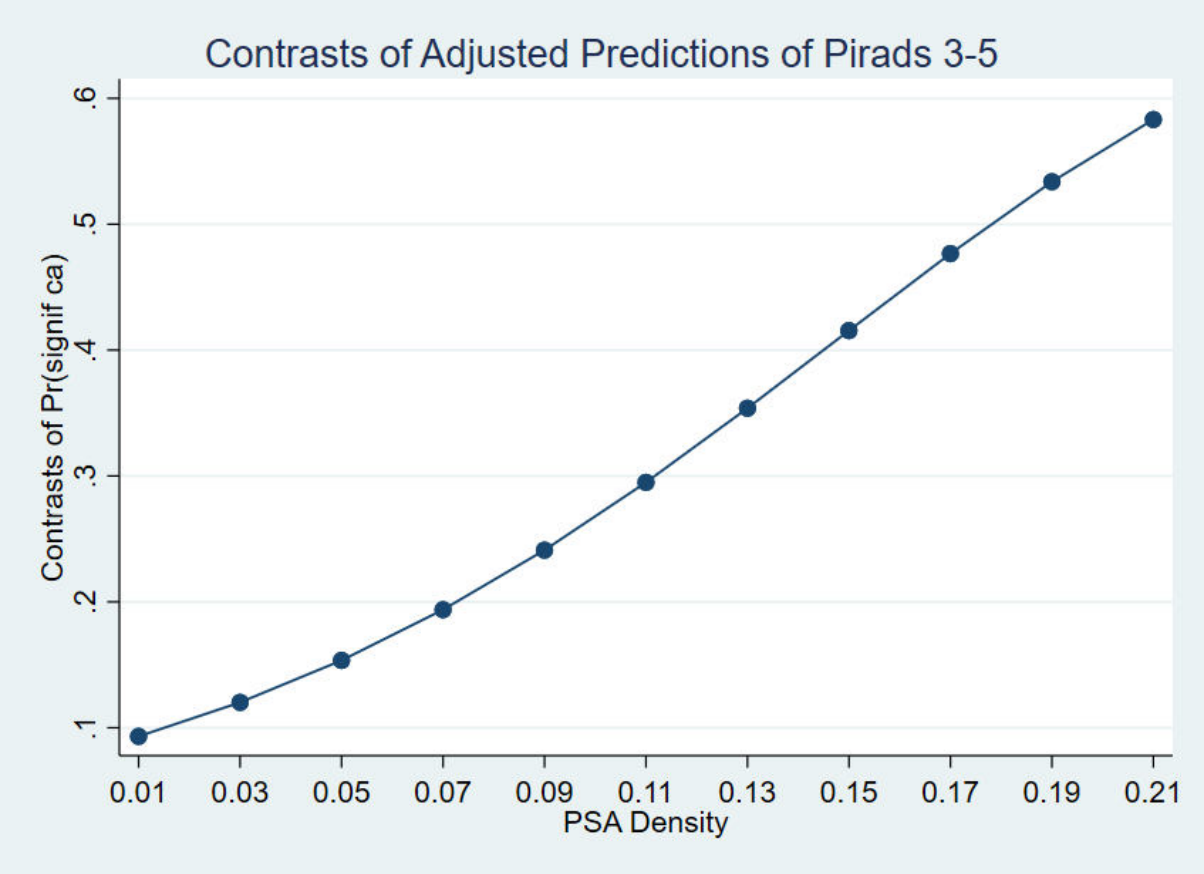


Figure 0.1 Graph of contrasts of adjusted predictions (coefficients described above in Table 0.24).

Sensitivity	30.77%
Specificity	98.55%
Positive predictive value	66.67%
Negative predictive value	93.79%
Correctly classified	92.72%

Table 0.25 Sensitivity, specificity, NPV and PPV values for the logistic regression model (Table 0.20) including Pirads 3-5 MRI and PSAD as a continuous variable.

Logistic regression

Significant cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Pirads 1-3	1	.	.	.	.	.	
Pirads 4-5	16.496	11.446	4.04	0	4.234	64.271	***
PSA Density <0.15	1	.	.	.	.	.	
PSA Density≥0.15	9.266	8.936	2.31	.021	1.399	61.352	**
Constant	.027	.014	-6.71	0	.009	.077	***

Mean dependent var	0.086	SD dependent var	0.281
Pseudo r-squared	0.310	Number of obs	151.000
Chi-square	27.499	Prob > chi2	0.000
Akaike crit. (AIC)	67.109	Bayesian crit. (BIC)	76.161

*** p<.01, ** p<.05, * p<.1

Table 0.26 Logistic regression model for outcome of significant cancer with Pirads 4-5 MRI and a PSA Density ≥0.15 as categorical predictor variables. Overall the model is significant (prob>chi2 0.000). A PSA Density ≥0.15 was positively associated with significant PrCa (OR 9.26; p=0.021) and a Pirads 4-5 MRI was also positively associated with significant PrCa (OR 16.49; p<0.01). AUC for this model was 0.8358.

Logistic regression

Signif Ca	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Pirads 1-3	1	.	.	.	.	.	
Piras 4-5	11.631	8.225	3.47	.001	2.909	46.511	***
PSAD	1.013	.005	2.44	.015	1.003	1.024	**
Constant	.015	.01	-6.37	0	.004	.053	***

Mean dependent var	0.086	SD dependent var	0.281
Pseudo r-squared	0.318	Number of obs	151.000
Chi-square	28.216	Prob > chi2	0.000
Akaike crit. (AIC)	66.392	Bayesian crit. (BIC)	75.443

*** p<.01, ** p<.05, * p<.1

Table 0.27 Logistic regression model for outcome of significant cancer with Pirads 4-5 MRI and a PSA Density as categorical and continuous predictor variables respectively. Overall the model is significant. PSA Density was postitively assocated with significant PrCa (OR 1.013; p=0.015) and a Pirads 4-5 MRI was remained positively associated with significant PrCa (OR 11.63; p=0.001). ROC curve with AUC for this model is graphed below in ***Error! Reference source not found.****.*

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signif ca), predict()
at : 0.abnorma~45 = .8476821 (mean)
1.abnorma~45 = .1523179 (mean)
PSAD = .0557596 (mean)

	Delta-method Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
Pirads 4-5 MRI						

No	0.029	0.015	1.940	0.052	-0.000	0.059
Yes	0.260	0.101	2.580	0.010	0.063	0.457

Table 0.28 at the mean PSAD of 0.55, the average predicted probability of clinically significant cancer in men with a Pirads 1-2 MRI was 2% and 26% in men with a Pirads 4-5 MRI.

Adjusted predictions **Number of obs = 151**
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()
1._at : psad = .01
2._at : psad = .03
3._at : psad = .05
4._at : psad = .07
5._at : psad = .09
6._at : psad = .11
7._at : psad = .13
8._at : psad = .15
9._at : psad = .17
10._at : psad = .19
11._at : psad = .21

	Delta-method Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#abnormalMRI45						
1 0	0.016	0.010	1.610	0.107	-0.004	0.036
1 1	0.162	0.091	1.770	0.076	-0.017	0.340
2 0	0.021	0.012	1.770	0.076	-0.002	0.044
2 1	0.200	0.096	2.090	0.037	0.012	0.389
3 0	0.027	0.014	1.910	0.056	-0.001	0.055
3 1	0.246	0.100	2.460	0.014	0.050	0.441
4 0	0.035	0.018	2.000	0.046	0.001	0.070
4 1	0.297	0.103	2.890	0.004	0.095	0.499
5 0	0.045	0.023	2.010	0.045	0.001	0.089
5 1	0.355	0.107	3.300	0.001	0.144	0.565
6 0	0.058	0.030	1.940	0.052	-0.001	0.116
6 1	0.417	0.114	3.650	0.000	0.193	0.641
7 0	0.074	0.040	1.830	0.067	-0.005	0.153
7 1	0.482	0.123	3.910	0.000	0.240	0.723
8 0	0.094	0.055	1.700	0.089	-0.014	0.202
8 1	0.547	0.133	4.100	0.000	0.286	0.809
9 0	0.119	0.075	1.580	0.114	-0.029	0.267
9 1	0.611	0.142	4.290	0.000	0.332	0.890
10 0	0.149	0.101	1.470	0.141	-0.049	0.348
10 1	0.671	0.148	4.520	0.000	0.380	0.962
11 0	0.186	0.133	1.390	0.164	-0.076	0.447
11 1	0.726	0.150	4.850	0.000	0.433	1.020

Table 0.29 adjusted predictions of Pirads 3-5 MRI at varying levels of PSAD. Ie at a PSAD of 0.15, men with Pirads 4-5 MR had a predicted probability of cancer of 54%, compared to 9% in those with a Pirads 1-3 MRI. Coefficients within this table are graphed below in ***Error! Reference source not found.***

Contrasts of adjusted predictions **Number of obs = 151**
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()

1._at : psad = .01
2._at : psad = .03
3._at : psad = .05
4._at : psad = .07
5._at : psad = .09
6._at : psad = .11
7._at : psad = .13
8._at : psad = .15
9._at : psad = .17
10._at : psad = .19
11._at : psad = .21

	df	chi2	P>chi2
abnormalMRI45@_at			
1	1	2.770	0.096
2	1	3.680	0.055
3	1	4.890	0.027
4	1	6.340	0.012
5	1	7.910	0.005
6	1	9.440	0.002
7	1	10.910	0.001
8	1	12.510	0.000
9	1	14.570	0.000
10	1	17.240	0.000
11	1	19.730	0.000
Joint	3	23.050	0.000

Table 0.30 contrasts of adjusted predictions. There is a statistically significant difference in cancer probability between men with and without a Pirads 4-5 MRI at all levels of PSAD, from a level of 0.05ng/ml upwards.

Contrasts of adjusted predictions **Number of obs = 151**
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()

1._at : psad = .01
2._at : psad = .03
3._at : psad = .05
4._at : psad = .07
5._at : psad = .09
6._at : psad = .11
7._at : psad = .13
8._at : psad = .15
9._at : psad = .17
10._at : psad = .19
11._at : psad = .21

	Delta-method Contrast	Std.Err.	z	P>z
abnormalMRI45@_at				
(1 vs base) 1	0.145	0.087	1.660	0.096

(1 vs base) 2	0.179	0.093	1.920	0.055
(1 vs base) 3	0.218	0.099	2.210	0.027
(1 vs base) 4	0.262	0.104	2.520	0.012
(1 vs base) 5	0.310	0.110	2.810	0.005
(1 vs base) 6	0.359	0.117	3.070	0.002
(1 vs base) 7	0.408	0.123	3.300	0.001
(1 vs base) 8	0.453	0.128	3.540	0.000
(1 vs base) 9	0.492	0.129	3.820	0.000
(1 vs base) 10	0.522	0.126	4.150	0.000
(1 vs base) 11	0.541	0.122	4.440	0.000

Table 0.31 contrasts of adjusted predictions with coefficients. Ie at a PSAD of 0.05, men with a Pirads 4-5 MRI had a 21% increase in probability of clinically significant cancer detection compared to men with a Pirads 1-3 MRI. This rose to 54% at the highest level of PSAD (0.21). Coefficients within this table are graphed below in Figure 0.2

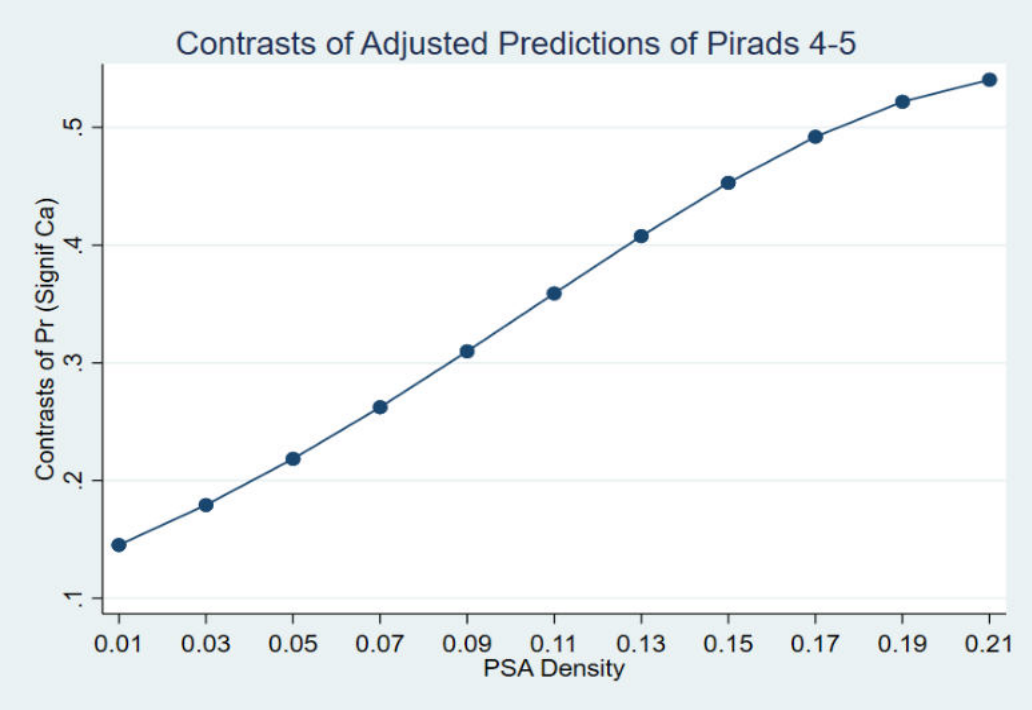


Figure 0.2 Contrasts of predicted probability of significant PrCa at various levels of PSAD. The difference in predicted probability of significant PrCa between men with and without a Pirads 4-5 MRI grew as PSAD values rose.

Sensitivity	30.77%
Specificity	99.28%
Positive predictive value	80.00%
Negative predictive value	93.84%
Correctly classified	93.38%

Table 0.32 Sensitivity, specificity, NPV and PPV values for the logistic regression model described (Table 0.27) including Pirads 4-5 MRI and PSAD.

Logistic regression

Significant cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Pirads 1-2 MRI	1	.	.	.	.	.	
Pirads 3-5 MRI	29.84	32.642	3.10	.002	3.497	254.633	***
Age 40-<50	1	.	.	.	.	.	
Age 50-<60	1.572	1.896	0.38	.708	.148	16.706	
Age >=60	16.881	19.454	2.45	.014	1.764	161.554	**

Constant	.003	.004	-4.13	0	0	.047	***

Mean dependent var	0.086	SD dependent var	0.281
Pseudo r-squared	0.416	Number of obs	151.000
Chi-square	36.853	Prob > chi2	0.000
Akaike crit. (AIC)	59.755	Bayesian crit. (BIC)	71.824

*** p<.01, ** p<.05, * p<.1

Table 0.33 Logistic regression model describing age and Pirads 3-5 MRI as categorical variables. Overall the model is significant. Only age at or greater than 60years old was statistically significantly associated with significant PrCa (OR 16.88, p=0.014). Age 50-60 was positively associated (OR 1.57) but not statistically, compared to men aged 40-<50. A Pirads 3-5 MRI remained significantly associated with signifcnat cancer outcome (OR 29) compared to men with a Pirads 1-2 MRI (p=0.002).

Logistic regression

Signif Ca	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Age	1.178	.072	2.70	.007	1.046	1.327	***
Pirads 1-2	1	.	.	.	.	.	
Pirads 3-5	25.762	27.747	3.02	.003	3.12	212.696	***
Constant	0	0	-3.68	0	0	.002	***

Mean dependent var	0.086	SD dependent var	0.281
Pseudo r-squared	0.376	Number of obs	151.000
Chi-square	33.336	Prob > chi2	0.000
Akaike crit. (AIC)	61.272	Bayesian crit. (BIC)	70.324

*** p<.01, ** p<.05, * p<.1

Table 0.34 logistic regression model incorporating age as a continuous variable, and MRI Pirads 3-5 as a categorical variable. Overall the model is significant (p<0.0001). PIrads 3-5 MRI is positively associated with clinically significant cancer (OR 25.7) in the presence of age which is also significantly associated with clinically significant cancer detection (1.17).

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()
at : ageatstudy~y = 53.51148 (mean)
1.abnormal~l = .6821192 (mean)
2.abnormal~l = .3178808 (mean)

	Delta-method Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
Pirads 3-5						
N	0.006	0.007	0.930	0.353	-0.007	0.019
Y	0.136	0.062	2.210	0.027	0.016	0.257

Table 0.35 At the mean study age (53), the predicated probability of clinically significant cancer detection in a man with a Pirads 1-2 MRI is 0.6%, and 13.6% with a Pirads 3-5 MRI.

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signif ca), predict()
1._at : ageatstudy~y = 40

2._at : ageatstudy~y = 50
3._at : ageatstudy~y = 60
4._at : ageatstudy~y = 70

	Delta-method					
	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#pirads 4-5						
1#N	0.001	0.001	0.640	0.525	-0.001	0.003
1#Y	0.017	0.021	0.810	0.415	-0.024	0.058
2#N	0.003	0.004	0.850	0.394	-0.004	0.011
2#Y	0.081	0.052	1.570	0.115	-0.020	0.183
3#N	0.017	0.017	1.010	0.315	-0.017	0.051
3#Y	0.314	0.079	3.960	0.000	0.159	0.469
4#N	0.084	0.091	0.920	0.357	-0.095	0.262
4#Y	0.702	0.152	4.610	0.000	0.404	1.000

Table 0.36 Adjusted predicted probabilities of clinically significant cancer detection at varing levels of age. Ie. Men aged 40 with a Pirads 1-2 MRI have an (average) probability of 0.1% of clinically significant cancer detection. This remains low even at the oldest age of 70 (8.4%). At the same ages, the probability is 1.7% and 70.2% in those with a Pirads 3-5 MRI. Graph depiction of coefficients shown below in ***Error! Reference source not found.***

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()
1._at : Age = 40
2._at : Age = 50
3._at : Age = 60
4._at : Age = 70

	Delta-method			
	Contrast	Std.Err.	z	P>z
Pirads 3-5 MRI @_at				
(Y vs base) 1	0.016	0.020	0.810	0.417
(Y vs base) 2	0.078	0.050	1.560	0.120
(Y vs base) 3	0.296	0.081	3.660	0.000
(Y vs base) 4	0.618	0.138	4.480	0.000

Table 0.37 Contrasts of adjusted predictions with coefficients. Ie men aged 50 with a Pirads 3-5 MRI have a 7.8% increase in probability of clinically significant cancer detection compared to men with a Pirads 1-2 MRI (this changes to 61% in men aged 70). Graph depiction of coefficients shown below in Figure 0.3

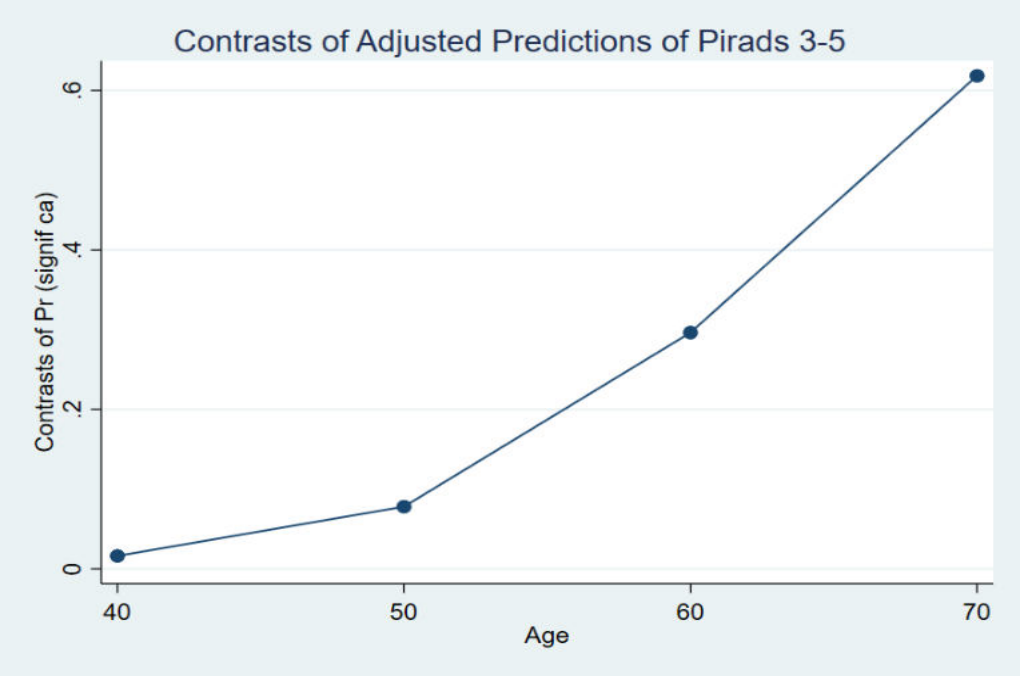


Figure 0.3 Contrasts of predicted probability of signifcant PrCa between men with and without an abnormal MRI (pirads 3-5) as age increases. The greatest difference in predicted probability is in older men i.e even if a man has an 'abnormal' MRI (pirads 3-5), if he is 40-<50 years old, the difference in his predicted probability is not that much greater than those with a normal MRI.

Sensitivity	**30.77%**
Specificity	98.55%
Positive predictive value	66.67%
Negative predictive value	93.79%
Correctly classified	92.72%

Table 0.38 Sensitivity, specificity, NPV and PPV values for the logistic regression model described (Table 0.34) including Pirads 3-5 MRI and age.

Logistic regression

Significant cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Pirads 1-3 MRI	1	.	.	.	.	.	
Pirads 4-5 MRI	10.425	7.533	3.24	.001	2.529	42.97	***
Age 40-<50	1	.	.	.	.	.	
Age 50-<60	1.439	1.74	0.30	.763	.135	15.384	
Age >=60	9.109	10.562	1.91	.057	.939	88.397	*
Constant	.015	.016	-4.03	0	.002	.116	***

Mean dependent var	0.086	SD dependent var	0.281
Pseudo r-squared	0.337	Number of obs	151.000
Chi-square	29.825	Prob > chi2	0.000
Akaike crit. (AIC)	66.783	Bayesian crit. (BIC)	78.852

*** p<.01, ** p<.05, * p<.1

Table 0.39 Logistic regression model describing age and Pirads 4-5 MRI as categorical variables. Overall the model is significant. Only age at or greater than 60years old approached statistical significance (OR 9.10, p=0.057). Age 50-60 was positively associated (OR 1.439) but not statistically, compared to men aged 40-<50 (p=0.763). A Pirads 4-5 MRI remained significantly associated with signifcnat cancer outcome (OR 10.42) compared to men with a Pirads 1-3 MRI (p=0.001).

Logistic regression

Signif Ca	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Age	1.13	.066	2.11	.035	1.009	1.267	**
Pirads 1-3	1	.	.	.	.	.	
Pirads 4-5	10.504	7.499	3.29	.001	2.592	42.563	***
Constant	0	0	-3.00	.003	0	.029	***

Mean dependent var	0.086	SD dependent var	0.281
Pseudo r-squared	0.312	Number of obs	151.000
Chi-square	27.612	Prob > chi2	0.000
Akaike crit. (AIC)	66.996	Bayesian crit. (BIC)	76.048

*** p<.01, ** p<.05, * p<.1

Table 0.40 Logistic regression model incorporating age as a continuous variable, and MRI Pirads 4-5 as a categorical variable. Overall the model is significant (p<0.0001). PIrads 4-5 MRI is positively associated with clinically significant cancer (OR 10.5) in the presence of age which is also positively associated with clinically significant cancer detection (OR 1.13, p=0.035).

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()
at : Age = 53.51148 (mean)
0.abnorma~45 = .8476821 (mean)
1.abnorma~45 = .1523179 (mean)

	Delta-method Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
Pirads 4-5						

No	0.026	0.014	1.800	0.072	-0.002	0.053
Yes	0.216	0.108	2.000	0.045	0.004	0.427

Table 0.41 At the mean study age (53.5), the predicated probability of clinically significant cancer detection in a man with a Pirads 1-3 MRI is 2%, and 21% with a Pirads 4-5 MRI.

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signif ca), predict()
1._at : ageatstudy~y = 40
2._at : ageatstudy~y = 50
3._at : ageatstudy~y = 60
4._at : ageatstudy~y = 70

	Delta-method					
	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#abnormalMRI45						
1 0	0.005	0.006	0.870	0.384	-0.006	0.016
1 1	0.050	0.062	0.800	0.423	-0.072	0.172
2 0	0.017	0.011	1.490	0.137	-0.005	0.039
2 1	0.152	0.102	1.480	0.138	-0.049	0.352
3 0	0.055	0.027	2.000	0.046	0.001	0.109
3 1	0.379	0.108	3.510	0.000	0.167	0.590
4 0	0.165	0.121	1.360	0.173	-0.072	0.402
4 1	0.675	0.150	4.500	0.000	0.381	0.969

Table 0.42 Adjusted predicted probabilities of clinically significant cancer detection at varing levels of age. Ie. Men aged 40 with a Pirads 1-3 MRI have an (average) probability of 0.5% of clinically significant cancer detection (highlighted in blue). This remains relatively low at the oldest age of 70 (16%; highlighted in red). At the same ages, the probability is 5% and 67% in those with a Pirads 4-5 MRI (highlighted in green). Coefficients are graphed below in ***Error! Reference source not found.****.*

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signif ca), predict()
1._at : ageatstudy~y = 40
2._at : ageatstudy~y = 50
3._at : ageatstudy~y = 60
4._at : ageatstudy~y = 70

	Delta-method			
	Contrast	Std.Err.	z	P>z
Pirads 4-5 MRI @_at				
(1 vs base) 1	0.045	0.058	0.780	0.435
(1 vs base) 2	0.135	0.097	1.400	0.162
(1 vs base) 3	0.324	0.112	2.880	0.004
(1 vs base) 4	0.510	0.123	4.150	0.000

Table 0.43 Contrasts of adjusted predictions with coefficients. Ie men aged 50 with a Pirads 4-5 MRI there is a 13% increase in probability of clinically significant cancer detection compared to men with a Pirads 1-3 MRI (this changes to 51% in men aged 70). Coefficients are graphed below in Figure 0.4

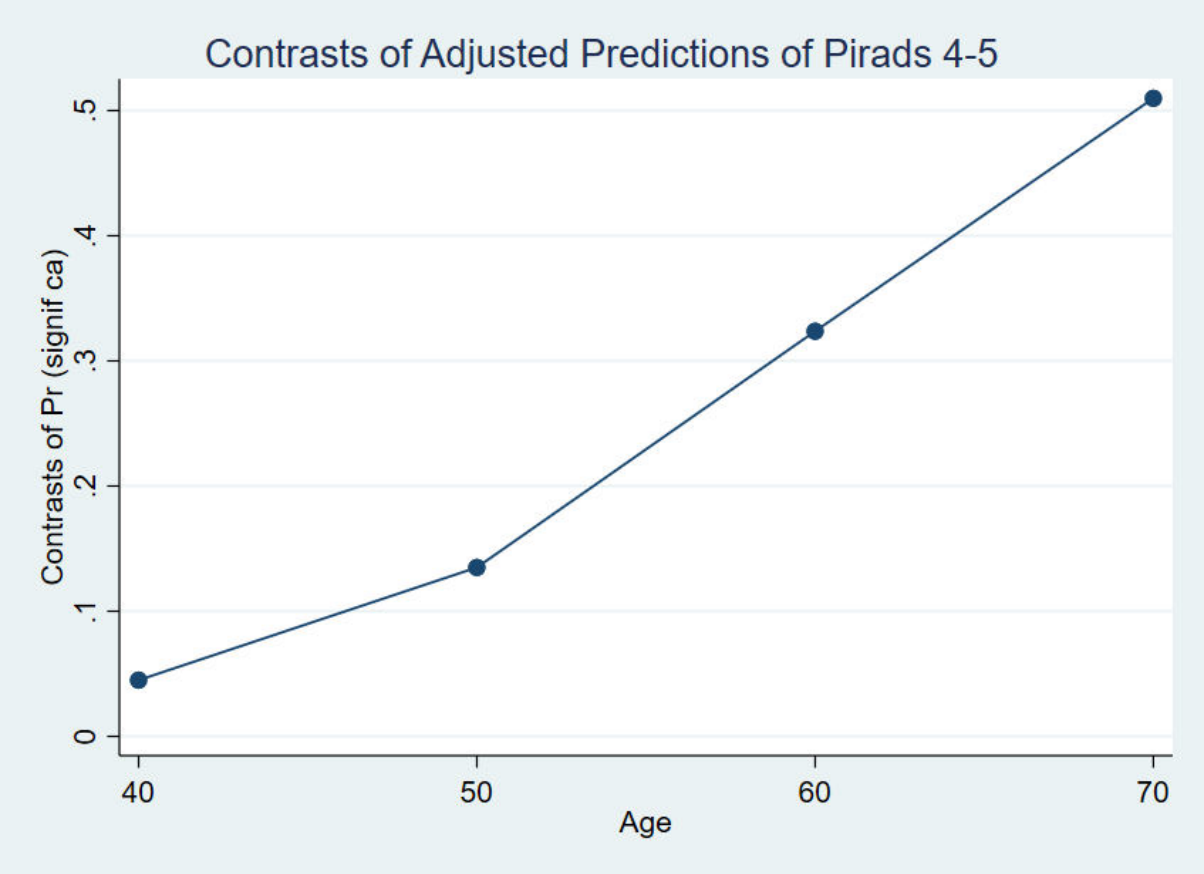


Figure 0.4 The largest difference in predicted probability (coefficients above in Table 0.43) of signifciant PrCa between men with and without an abnormal (Pirads 4-5) MRI was in older men i.e aged 50 and above

Table 0.44 Sensitivity, specificity, NPV and PPV values for the logistic regression model described (Table 0.40) including Pirads 4-5 MRI and PSA.

Sensitivity	**30.77%**
Specificity	97.10%
Positive predictive value	50.00%
Negative predictive value	93.71%
Correctly classified	91.39%

Logistic regression

Signif Ca	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Pirads 1-2	1	.	.	.	.	.	
Pirads 3-5	36.22	38.561	3.37	.001	4.495	291.859	***
No prior PSA	1	.	.	.	.	.	
Unknown	.655	.818	-0.34	.735	.057	7.581	
Prior PSA	1.205	.858	0.26	.794	.298	4.866	
Constant	.01	.011	-4.08	0	.001	.092	***

Mean dependent var	0.097	SD dependent var	0.297
Pseudo r-squared	0.278	Number of obs	134.000
Chi-square	23.732	Prob > chi2	0.000
Akaike crit. (AIC)	69.619	Bayesian crit. (BIC)	81.211

*** p<.01, ** p<.05, * p<.1

Table 0.45 Logistic regression model incorporating pirads 3-5 MRI and prior PSA screening status.

The model is significant but only Pirads 3-5 MRI has a statistically significant association (p=0.001); prior PSA was positively associated (OR 1.2) compared to those with no prior screening but not significantly so (p=0.794). The AUC for this model was 0.8311. The overall statiscally significant prob>chi2 is likely derived from the performance of the variable MRI; in the absence of MRI Prior PSA has an OR of 0.644, p=1.0 with an overall model prob >ch2 = 0.9974; AUC 0.5209; Appendix C

Abnormal MRI Definition : Pirads 4-5 and Prior PSA Screening

Logistic regression

Signif Ca	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Pirads 1-3	1	.	.	.	.	.	
Pirads 4-5	22.984	16.092	4.48	0	5.827	90.656	***
No prior PSA	1	.	.	.	.	.	
Unknown	1.101	1.47	0.07	.942	.08	15.066	
Pior PSA	1.78	1.352	0.76	.448	.402	7.886	
Constant	.024	.019	-4.71	0	.005	.114	***

Mean dependent var	0.097	SD dependent var	0.297
Pseudo r-squared	0.266	Number of obs	134.000
Chi-square	22.729	Prob > chi2	0.000
Akaike crit. (AIC)	70.623	Bayesian crit. (BIC)	82.214

*** p<.01, ** p<.05, * p<.1

Table 0.46 Logistic regression model incorporating pirads 4-5 MRI and prior PSA screening status.

The model is significant but only Pirads 4-5 MRI has a statistically significant association (p<0.01); prior PSA was positively associated (OR 1.78) compared to those with no prior screening but not significantly so (p=0.448). The AUC for this model was 0.8471. The overall statiscally significant prob>chi2 is likely derived from the

performance of the variable MRI; in the absence of MRI Prior PSA has an OR of 0.644, p=1.0 with an overall model Prob>ch2 = 0.9974; AUC 0.5209; Appendix C

Abnormal MRI Definition : Pirads 3-5, Age and PSA

Logistic regression

Signif Ca	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Pirads 1-2	1	.	.	.	.	.	
Pirads 3-5	17.982	19.672	2.64	.008	2.107	153.469	***
Age	1.161	.075	2.30	.022	1.022	1.318	**
PSA	1.524	.321	2.00	.046	1.008	2.304	**
Constant	0	0	-3.46	.001	0	.002	***

Mean dependent var	0.086	SD dependent var	0.281
Pseudo r-squared	0.420	Number of obs	151.000
Chi-square	37.204	Prob > chi2	0.000
Akaike crit. (AIC)	59.404	Bayesian crit. (BIC)	71.473

**** p<.01, ** p<.05, * p<.1*

Table 0.47 Logistic regression model incorporating MRI as a categorical (predictor) variable and age and PSA as continuous (predictor) variables, with clinically significant PrCa as outcome. Pirads 3-5 MRI was positively associated with significant cancer outcome at prostate biopsy (OR 17.9; p=0.008), as were age (OR 1.16, p= 0.022) and PSA (OR 1.52, p=0.046).

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signif ca), predict()
at : 1.abnormal~l = .6821192 (mean)
2.abnormal~l = .3178808 (mean)
PSA = 1.833775 (mean)
Age~y = 53.51148 (mean)

	Delta-method Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
Pirads 3-5 MRI						
No	0.006	0.006	0.890	0.371	-0.007	0.018
Yes	0.091	0.053	1.710	0.088	-0.013	0.194

Table 0.48 At a mean PSA of 1.83ng/ml and age of 53.5 years, the percentage probability of detecting clinically significant PrCa on biopsy was 0.6% in men with a Pirads 1-2 MRI and 9.1% in men with a Pirads 3-5 MRI. Further adjusted predictions of PrCa probability at PSA and age values outside the mean are listed in Appendix C and graphed in ***Error! Reference source not found.*** *below*

i.e in men with ***low*** *PSAs and a normal MRI, the predicted proability (on average) remained low even at the oldest age (13%). In the presence of an abnormal MRI (pirads 3-5) at the same PSA values, the predicted probabilities were significantly higher but only in the older age range (highlighted in green below in Table 0.49). Examples of specific coefficients to complement this figure listed below in Table 0.49. Contrasts for these adjusted predictions are listed in Appendix C*

Delta-method

	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#abnormalMRI						
Age 40						
PSA = 0#Pirads1-2	0.000	0.001	0.570	0.566	-0.001	0.002
PSA = 0#Pirads3-5	0.006	0.009	0.670	0.506	-0.012	0.024
PSA = 1#Pirads 1-2	0.001	0.001	0.600	0.551	-0.001	0.002
PSA = 1#Pirads3-5	0.009	0.013	0.710	0.480	-0.016	0.035
PSA = 2#Pirads 1-2	0.001	0.001	0.610	0.540	-0.002	0.003
PSA = 2#Pirads 3-5	0.014	0.019	0.740	0.460	-0.023	0.051
PSA =3#Pirads1-2	0.001	0.002	0.620	0.536	-0.003	0.005
PSA = 3#Pirads3-5	0.021	0.028	0.760	0.449	-0.034	0.076
PSA = 4#Pirads1-2	0.002	0.003	0.620	0.539	-0.004	0.008
PSA = 4#Pirads3-5	0.032	0.042	0.760	0.446	-0.051	0.115
Age 60						
PSA=0#Pirads 3-5	0.108	0.077	1.410	0.159	-0.042	0.258
PSA=1#Pirads 3-5	0.155	0.081	1.910	0.056	-0.004	0.315
PSA=2#Pirads 3-5	0.219	0.081	2.720	0.007	0.061	0.377
PSA=3#Pirads 3-5	0.299	0.081	3.690	0.000	0.140	0.459
PSA=4#Pirads 3-5	0.394	0.098	4.040	0.000	0.203	0.586
Age 70						
PSA=0#pirads 3-5	0.349	0.234	1.490	0.137	-0.111	0.808
PSA=1#pirads 3-5	0.449	0.223	2.020	0.044	0.012	0.886
PSA=2#pirads 3-5	0.554	0.199	2.790	0.005	0.164	0.944
PSA=3#pirads 3-5	0.654	0.171	3.820	0.000	0.319	0.990
PSA=4#pirads 3-5	0.743	0.147	5.070	0.000	0.455	1.030
Age 70						
PSA=5#Pirads1-2	0.197	0.204	0.960	0.336	-0.204	0.597
PSA=5#Pirads3-5	0.815	0.126	6.490	0.000	0.569	1.061
PSA=6#Pirads1-2	0.271	0.271	1.000	0.317	-0.260	0.803
PSA=6#Pirads3-5	0.870	0.106	8.190	0.000	0.662	1.078
PSA=7#Pirads1-	0.362	0.341	1.060	0.288	-0.306	1.030

2						
PSA=7#Pirads3-5	0.911	0.088	10.390	0.000	0.739	1.083
PSA=8#Pirads1-2	0.464	0.398	1.170	0.244	-0.316	1.244
PSA=9#Pirads3-5	0.940	0.070	13.360	0.000	0.802	1.077
PSA=9#Pirads1-2	0.569	0.427	1.330	0.183	-0.269	1.406
PSA=9#Pirads3-5	0.960	0.055	17.490	0.000	0.852	1.067

Table 0.49 Examples of coefficients of adjusted predictions at varying PSA levels and age for abnormal/normal MRI. i.e in men aged 40 with a pirads 1-2 MRI, the (average) predicted probability of clinically significant cancer was 0%, 0.1%, 0.1%, 0.1% and 0.2% at PSA values of 0, 1, 2, 3 and 4ng/ml (highlighted in blue). In men aged 70 with a pirads 1-2 MRI, the (average) predicted probability of clinically significant cancer was 19%, 27%, 36%, 46% and 56% at PSA values of 5, 6, 7, 8 and 9ng/ml (highlighted in red).

Sensitivity	**46.15%**
Specificity	98.55%
Positive predictive value	75.00%
Negative predictive value	95.10%
Correctly classified	94.04%

Table 0.50 Sensitivity, specificity, NPV and PPV values for the logistic regression model described above (Table 0.47) including Pirads 3-5 MRI, PSA and age

Logistic regression

Signif Ca	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Pirads 1-3	1	.	.	.	.	.	
Pirads 4-5	6.819	5.081	2.58	.01	1.583	29.375	***
Age	1.131	.072	1.93	.054	.998	1.282	*
PSA	1.533	.293	2.23	.025	1.054	2.229	**
Constant	0	0	-2.93	.003	0	.024	***

Mean dependent var	0.086	SD dependent var	0.281
Pseudo r-squared	0.365	Number of obs	151.000
Chi-square	32.358	Prob > chi2	0.000
Akaike crit. (AIC)	64.250	Bayesian crit. (BIC)	76.319

*** p<.01, ** p<.05, * p<.1

Table 0.51 Logistic regression model incorporating MRI as a categorical (predictor) variable and age and PSA as continuous (predictor) variables, with clinically significant PrCa as outcome. Pirads 4-5 MRI was positively associated with significant cancer outcome at prostate biopsy (OR 6.81; p=0.01), as were age (OR 1.13, p= 0.054) and PSA (OR 1.53, p=0.025).

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signif ca), predict()
at : 0.abnorma~45 = .8476821 (mean)

1.abnorma~45 = .1523179 (mean)
PSA = 1.833775 (mean)
age~y = 53.51148 (mean)

	Delta-method Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
Pirads 4-5 MRI						
No	0.020	0.013	1.570	0.117	-0.005	0.046
Yes	0.125	0.084	1.480	0.139	-0.040	0.289

Table 0.52 At a mean PSA of 1.83ng/ml and age of 53.5 years, the percentage probability of detecting clinically significant PrCa on biopsy was 2% in men with a Pirads 1-3 MRI and 12.5% in men with a Pirads 4-5 MRI. Further adjusted predictions of PrCa probability at PSA and age values outside the mean values are listed in Appendix C and graphed in ***Error! Reference source not found.Error! Reference source not found.****.*

Sensitivity	46.15%
Specificity	98.55%
Positive predictive value	75.00%
Negative predictive value	95.10%
Correctly classified	94.04%

Table 0.53 Sensitivity, specificity, NPV and PPV values for the logistic regression model described above in Table 0.51 including Pirads 4-5 MRI, PSA and age

Logistic regression

Signif ca	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Pirads 1-2	1	.	.	.	.	.	
Pirads 3-5	17.17	19.133	2.55	.011	1.933	152.504	**
Age	1.195	.082	2.61	.009	1.045	1.366	***
PSAD	3924140.1	23096890	2.58	.01	38.344	4.016e+11	***
Constant	0	0	-3.62	0	0	.001	***

Mean dependent var	0.086	SD dependent var	0.281
Pseudo r-squared	0.460	Number of obs	151.000
Chi-square	40.775	Prob > chi2	0.000
Akaike crit. (AIC)	55.833	Bayesian crit. (BIC)	67.902

*** p<.01, ** p<.05, * p<.1*

Table 0.54 Logistic regression model incorporating MRI as a categorical (predictor) variable and age and PSAD as continuous (predictor) variables, with clinically significant PrCa as outcome. Pirads 3-5 MRI was positively associated with significant cancer outcome at prostate biopsy (OR 17.1; p=0.011), as were age (OR 1.19, p= 0.009) and PSAD (OR 3924140.1, p=0.01).* * OR value inflated due to nature of variable

Sensitivity	38.46%
Specificity	98.55%

Positive predictive value	71.43%
Negative predictive value	94.44%
Correctly classified	93.38%

Table 0.55 Sensitivity, specificity, NPV and PPV values for the logistic regression model described above in Table 0.54 including Pirads 3-5 MRI, PSAD and age

Logistic regression

Signif ca	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Pirads 1-3	1	.	.	.	.	.	
Pirads 4-5	5.394	4.21	2.16	.031	1.169	24.9	**
Age	1.165	.079	2.24	.025	1.019	1.331	**
PSAD	2727260	15584418	2.59	.01	37.299	1.994e+11	***
Constant	0	0	-3.12	.002	0	.008	***

Mean dependent var	0.086	SD dependent var	0.281
Pseudo r-squared	0.394	Number of obs	151.000
Chi-square	34.887	Prob > chi2	0.000
Akaike crit. (AIC)	61.721	Bayesian crit. (BIC)	73.790

*** p<.01, ** p<.05, * p<.1

Table 0.56 Logistic regression model incorporating MRI as a categorical (predictor) variable and age and PSAD as continuous (predictor) variables, with clinically significant PrCa as outcome. Pirads 4-5 MRI was positively associated with significant cancer outcome at prostate biopsy (OR 5.39; p=0.031), as were age (OR 1.16, p= 0.025) and PSAD (OR 2726260, p=0.01).* * OR value inflated due to nature of variable

Sensitivity	38.46%
Specificity	98.55%
Positive predictive value	71.43%
Negative predictive value	94.44%
Correctly classified	93.38%

Table 0.57 Sensitivity, specificity, NPV and PPV values for the logistic regression model described above in Table 0.56 including Pirads 4-5 MRI, PSAD and age

Any cancer

Abnormal MRI Definition : Pirads 3-5

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Pirads 1-2	1	.	.	.	.	.	

Pirads 3-5	3.682	1.383	3.47	.001	1.763	7.688	***
Constant	.272	.065	-5.42	0	.17	.435	***

Mean dependent var	0.609	SD dependent var	0.924
Pseudo r-squared	0.066	Number of obs	151.000
Chi-square	12.262	Prob > chi2	0.000
Akaike crit. (AIC)	177.390	Bayesian crit. (BIC)	183.424

*** p<.01, ** p<.05, * p<.1

Table 0.1 Logistic regression results, for any cancer as outcome and MRI Pirads 3-5 MRI as a predictor (categorical) variable. MRI Pirads 3-5 was positively associated with clinically significant cancer detection (OR 3.682) compared to men with a Pirads 1-2 MRI (p=0.001).

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(any cancer), predict()

	Delta-method					
	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
Pirads 3-5						
N	0.214	0.040	5.290	0.000	0.134	0.293
Y	.50	0.072	6.930	0.000	0.359	0.641

Table 0.2 Marginal adjusted predictions of (average) cancer probability (any cancer). Men with a Pirads 1-2 MRI on average, had a 21% probability of any cancer on their biopsy. Men with a Pirads 3-5 MRI had a 50% chance of any cancer being detected on their prostate biopsy.

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(any cancer), predict()

	Delta-method			
	Contrast	Std.Err.	z	P>z
Pirads 3-5 MRI (Y vs base)	0.286	0.083	3.460	0.001

Table 0.3 There was, on average a 28% difference in predicted probability of any cancer between men with and without a Pirads 3-5 MRI, and this difference was statistically significant.

Abnormal MRI Definition : Pirads 4-5

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Pirsds 1-3	1	.	.	.	.	.	
Pirads 4-5	4.667	2.21	3.25	.001	1.845	11.805	***
Constant	.333	.068	-5.38	0	.223	.497	***

Mean dependent var	0.609	SD dependent var	0.924
Pseudo r-squared	0.059	Number of obs	151.000
Chi-square	10.905	Prob > chi2	0.001
Akaike crit. (AIC)	178.747	Bayesian crit. (BIC)	184.781

*** p<.01, ** p<.05, * p<.1

Table 0.4 Logistic regression results, for any cancer as outcome and MRI Pirads 4-5 MRI as a predictor (categorical) variable. MRI Pirads 4-5 was positively associated with clinically significant cancer detection (OR 4.667) compared to men with a Pirads 1-3 MRI (p=0.001).

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(Caanybiopsy), predict()

	Delta-method					
	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
Pirads 4-5						
No	.25	0.038	6.530	0.000	0.175	0.325
Yes	0.609	0.102	5.980	0.000	0.409	0.808

Table 0.5 Marginal adjusted predictions of (average) cancer probability (any cancer). Men with a Pirads 1-3 MRI on average, had a 25% probability of any cancer on their biopsy. Men with a Pirads 4-5 MRI had a 60% chance of any cancer being detected on their prostate biopsy.

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(any cancer), predict()

	Delta-method			
	Contrast	Std.Err.	z	P>z
Pirads 4-5				
(Yes vs base)	0.359	0.109	3.300	0.001

Table 0.6 There was, on average a 35% difference in predicted probability of any cancer between men with and without a Pirads 4-5 MRI, and this difference was statistically significant.

Abnormal MRI Definition : Pirads 3-5 and PSA

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
PSA 0-<1	1	.	.	.	.	.	
PSA 1-<2	7.307	3.958	3.67	0	2.527	21.125	***
PSA 2-<3	3.421	2.211	1.90	.057	.964	12.14	*
PSA <4	5.154	3.164	2.67	.008	1.547	17.165	▪▪▪
Pirads 1-2	1	.	.	.	.	.	
Pirads 3-5	3.044	1.33	2.55	.011	1.293	7.168	**
Constant	.087	.04	-5.34	0	.035	.213	***
Mean dependent var		0.305	SD dependent var			0.462	

Pseudo r-squared	0.158	Number of obs	151.000
Chi-square	29.269	Prob > chi2	0.000
Akaike crit. (AIC)	166.383	Bayesian crit. (BIC)	181.469

*** p<.01, ** p<.05, * p<.1

Table 0.7 Logistic regression mode with any cancer as outcome, and PSA and MRI Pirads score as categorical, predictor variables. PSA in all categories was positively associated with any PrCa compared to those with a PSA of 0-1.0ng/ml. only a PSA of >=4.0ng/ml was significantly associated with (any) cancer (OR 5.15, p=0.008). Pirads 3-5 MRI was significantly and positively associated with any cancer (OR 3.0, p=0.011).

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
PSA	1.356	.172	2.40	.017	1.057	1.739	**
Pirads 1-2	1	.	.	.	.	.	
Pirads 3-5	2.716	1.09	2.49	.013	1.237	5.965	**
Constant	.167	.054	-5.52	0	.089	.316	***

Mean dependent var	0.609	SD dependent var	0.924
Pseudo r-squared	0.098	Number of obs	151.000
Chi-square	18.254	Prob > chi2	0.000
Akaike crit. (AIC)	173.398	Bayesian crit. (BIC)	182.450

*** p<.01, ** p<.05, * p<.1

Table 0.8 Logistic regression mode with any cancer as outcome, and PSA and MRI Pirads score as continuous and categorical respoectively, predictor variables. PSA was positively associated with any PrCa (OR 1.35, p=0.017). Pirads 3-5 MRI was significantly and positively associated with any cancer (OR 2.7, p=0.013).

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(any cancer), predict()
at : 1.abnormal~l = .6821192 (mean)
2.abnormal~l = .3178808 (mean)
PSA = 1.833775 (mean)

	Delta-method Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
Pirads 3-5 MRI						
N	0.226	0.043	5.260	0.000	0.142	0.311
Y	0.443	0.077	5.770	0.000	0.292	0.593

Table 0.9 At a mean PSA of 1.83ng/ml, the percentage probability of detecting any PrCa on biopsy was 22% in men with a Pirads 1-2 MRI and 44% in men with a Pirads 3-5 MRI. Further adjusted predictions of PrCa probability at PSA values outside the mean values are listed below in Table 0.10 and graphed in ***Error! Reference source not found.***

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(any cancer), predict()
1._at : prebiopsypsa = 0
2._at : prebiopsypsa = 1
3._at : prebiopsypsa = 2
4._at : prebiopsypsa = 3
5._at : prebiopsypsa = 4
6._at : prebiopsypsa = 5
7._at : prebiopsypsa = 6

8._at : prebiopsypsa = 7
9._at : prebiopsypsa = 8
10._at : prebiopsypsa = 9

	Delta-method Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#pirads 3-5 MRI						
1#N	0.143	0.040	3.600	0.000	0.065	0.221
1#Y	0.312	0.095	3.300	0.001	0.127	0.498
2#N	0.185	0.039	4.730	0.000	0.108	0.261
2#Y	0.381	0.084	4.530	0.000	0.216	0.546
3#N	0.235	0.045	5.260	0.000	0.148	0.323
3#Y	0.455	0.076	6.010	0.000	0.307	0.604
4#N	0.294	0.062	4.760	0.000	0.173	0.415
4#Y	0.531	0.075	7.050	0.000	0.384	0.679
5#N	0.361	0.089	4.070	0.000	0.187	0.535
5#Y	0.606	0.083	7.270	0.000	0.442	0.769
6#N	0.434	0.120	3.610	0.000	0.199	0.669
6#Y	0.676	0.094	7.180	0.000	0.491	0.860
7#N	0.510	0.150	3.390	0.001	0.215	0.805
7#Y	0.738	0.102	7.230	0.000	0.538	0.939
8#N	0.585	0.175	3.350	0.001	0.242	0.928
8#Y	0.793	0.105	7.570	0.000	0.588	0.998
9#N	0.656	0.190	3.460	0.001	0.285	1.028
9#Y	0.838	0.102	8.230	0.000	0.639	1.038
10#N	0.721	0.193	3.730	0.000	0.342	1.101
10#Y	0.876	0.095	9.230	0.000	0.690	1.061

*Table 0.10 Coefficients representing the marginal effects of PSA and Pirads 3-5 MRI on the predicted probability of (any) cancer (also graphed below in **Error! Reference source not found.**). Ie at a PSA of 0-<1.0ng/ml with a Pirads 1-2 MRI, the (average) predicted probability of any cancer was 14% and 31% with a Pirads 3-5 MRI (highlighted in blue). At a PSA of 3ng/ml with a Pirads 1-2 MRI the (average) predicted probability of any cancer was 29% and 53% with a Pirads 3-5 MRI (highlighted in green). At the higher end of the PSA scale (i.e at a PSA of 8ng/ml, the (average) predicted probability of any cancer was 65% with a pirads 1-2 MRI and 83% with a Pirads 3-5 MRI (highlighted in red).*

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(any cancer), predict()
1._at : prebiopsypsa = 0
2._at : prebiopsypsa = 1
3._at : prebiopsypsa = 2
4._at : prebiopsypsa = 3
5._at : prebiopsypsa = 4
6._at : prebiopsypsa = 5
7._at : prebiopsypsa = 6
8._at : prebiopsypsa = 7
9._at : prebiopsypsa = 8
10._at : prebiopsypsa = 9

	df	chi2	P>chi2
Pirads 3-5@_at			
1	1	4.150	0.042
2	1	5.190	0.023
3	1	6.040	0.014
4	1	6.590	0.010
5	1	6.760	0.009

6	1	6.380	0.012
7	1	5.310	0.021
8	1	3.910	0.048
9	1	2.680	0.102
10	1	1.820	0.178
Joint	3	8.060	0.045

Table 0.11 There were significant differences in the predicted probability of PrCa between a normal and abnormal (pirads 3-5) MRI (highlighted in blue).

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(any cancer), predict()
1._at : prebiopsypsa = 0
2._at : prebiopsypsa = 1
3._at : prebiopsypsa = 2
4._at : prebiopsypsa = 3
5._at : prebiopsypsa = 4
6._at : prebiopsypsa = 5
7._at : prebiopsypsa = 6
8._at : prebiopsypsa = 7
9._at : prebiopsypsa = 8
10._at : prebiopsypsa = 9

	Delta-method			
	Contrast	Std.Err.	z	P>z
Pirads 3-5@_at				
(Y vs base) 1	0.169	0.083	2.040	0.042
(Y vs base) 2	0.196	0.086	2.280	0.023
(Y vs base) 3	0.220	0.089	2.460	0.014
(Y vs base) 4	0.237	0.092	2.570	0.010
(Y vs base) 5	0.244	0.094	2.600	0.009
(Y vs base) 6	0.242	0.096	2.530	0.012
(Y vs base) 7	0.229	0.099	2.300	0.021
(Y vs base) 8	0.208	0.105	1.980	0.048
(Y vs base) 9	0.182	0.111	1.640	0.102
(Y vs base) 10	0.154	0.114	1.350	0.178

Table 0.12 At the higher levels of PSA (8-9ng/ml), there was no significant difference in the predicted probability of PrCa between a normal and abnormal MRI. The greatest difference in the predicted probability of PrCa between those with a normal and abnormal MRI was in those with a PSA of 2-5ng/ml (highlighted in green).

Sensitivity	32.61%
Specificity	92.38%
Positive predictive value	65.22%
Negative predictive value	75.78%
Correctly classified	74.17%

Table 0.13 For a logistic regression model including Pirads 3-5 MRI and PSA as predictor variables (Table 0.8), post-estimation test results are listed above

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
PSA 0-<1	1	.	.	.	.	.	
PSA 1-<2	6.476	3.475	3.48	0	2.262	18.539	***
PSA 2-<3	3.433	2.207	1.92	.055	.974	12.105	*
PSA <4	5.859	3.604	2.87	.004	1.755	19.565	▪▪▪▪
Pirads 1-3	1	.	.	.	.	.	
Pirads 4-5	2.786	1.446	1.97	.048	1.008	7.703	**
Constant	.11	.048	-5.10	0	.047	.257	***

Mean dependent var	0.305	SD dependent var	0.462
Pseudo r-squared	0.144	Number of obs	151.000
Chi-square	26.668	Prob > chi2	0.000
Akaike crit. (AIC)	168.984	Bayesian crit. (BIC)	184.070

*** p<.01, ** p<.05, * p<.1*

Table 0.14 Logistic regression mode with any cancer as outcome, and PSA and MRI Pirads score as categorical, predictor variables. PSA in all categories was positively associated with any PrCa compared to those with a PSA of 0-1.0ng/ml. only a PSA of >=4.0ng/ml was significantly associated with (any) cancer (OR 5.85, p=0.004). Pirads 4-5 MRI was significantly and positively associated with any cancer (OR 2.78, p=0.048).

Logistic regression

Any	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
PSA	1.367	.178	2.39	.017	1.058	1.765	**
Pirads 1-3	1	.	.	.	.	.	
Pirads 4-5	3.039	1.55	2.18	.029	1.118	8.256	**
Constant	.196	.061	-5.23	0	.106	.361	***

Mean dependent var	0.305	SD dependent var	0.462
Pseudo r-squared	0.091	Number of obs	151.000
Chi-square	16.894	Prob > chi2	0.000
Akaike crit. (AIC)	174.758	Bayesian crit. (BIC)	183.810

*** p<.01, ** p<.05, * p<.1*

Table 0.15 Logistic regression mode with any cancer as outcome, and PSA and MRI Pirads score as continuous and categorical respoectively, predictor variables. PSA was positively associated with any PrCa (OR 1.36, p=0.017). Pirads 4-5 MRI was significantly and positively associated with any cancer (OR 3.0, p=0.029).

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(any cancer), predict()
at : 0.abnorma~45 = .8476821 (mean)
1.abnorma~45 = .1523179 (mean)
prebiopsypsa = 1.833775 (mean)

Delta-method

	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
Pirads 4-5 MRI						
No	0.258	0.040	6.460	0.000	0.179	0.336
Yes	0.513	0.116	4.440	0.000	0.287	0.740

Table 0.16 At a mean PSA of 1.83ng/ml, the percentage probability of detecting any PrCa on biopsy was 25% in men with a Pirads 1-3 MRI and 51% in men with a Pirads 4-5 MRI. Further adjusted predictions of PrCa probability at PSA values outside the mean values are listed below in Table 0.17 and graphed in Figure 0.1.

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(any cancer), predict()
1._at : prebiopsypsa = 0
2._at : prebiopsypsa = 1
3._at : prebiopsypsa = 2
4._at : prebiopsypsa = 3
5._at : prebiopsypsa = 4
6._at : prebiopsypsa = 5
7._at : prebiopsypsa = 6
8._at : prebiopsypsa = 7
9._at : prebiopsypsa = 8
10._at : prebiopsypsa = 9

	Delta-method Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#abnormalMRI45						
1 0	0.164	0.043	3.830	0.000	0.080	0.247
1 1	0.373	0.137	2.730	0.006	0.105	0.641
2 0	0.211	0.039	5.470	0.000	0.135	0.287
2 1	0.448	0.126	3.570	0.000	0.202	0.695
3 0	0.268	0.041	6.490	0.000	0.187	0.349
3 1	0.526	0.114	4.620	0.000	0.303	0.749
4 0	0.333	0.058	5.720	0.000	0.219	0.447
4 1	0.603	0.105	5.740	0.000	0.397	0.809
5 0	0.406	0.086	4.710	0.000	0.237	0.574
5 1	0.675	0.101	6.690	0.000	0.477	0.872
6 0	0.483	0.117	4.120	0.000	0.253	0.712
6 1	0.739	0.099	7.470	0.000	0.545	0.933
7 0	0.560	0.145	3.860	0.000	0.276	0.845
7 1	0.795	0.096	8.240	0.000	0.606	0.984
8 0	0.635	0.165	3.850	0.000	0.312	0.959
8 1	0.841	0.092	9.180	0.000	0.662	1.021
9 0	0.704	0.175	4.030	0.000	0.362	1.046
9 1	0.879	0.084	10.420	0.000	0.713	1.044
10 0	0.765	0.174	4.410	0.000	0.425	1.105
10 1	0.908	0.075	12.070	0.000	0.761	1.056

*Table 0.17 Coefficients representing the marginal effects of PSA and Pirads 4-5 MRI on the predicted probability of (any) cancer (also graphed below in Figure 0.1**Error! Reference source not found.**). Ie at a PSA of 0-<1.0ng/ml with a Pirads 1-3 MRI, the (average) predicted probability of any cancer was 16% and 37% with a Pirads 4-5 MRI (highlighted in blue). At a PSA of 3ng/ml with a Pirads 1-3 MRI the (average) predicted probability of any cancer was 33% and 60% with a Pirads 4-5 MRI (highlighted in green). At the higher end of the PSA scale (i.e at a PSA of 8ng/ml, the (average) predicted probability of any cancer was 70% with a pirads 1-3 MRI and 87% with a Pirads 4-5 MRI (highlighted in red).*

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(any cancer), predict()
1._at : prebiopsypsa = 0
2._at : prebiopsypsa = 1
3._at : prebiopsypsa = 2
4._at : prebiopsypsa = 3
5._at : prebiopsypsa = 4

6._at : prebiopsypsa = 5
7._at : prebiopsypsa = 6
8._at : prebiopsypsa = 7
9._at : prebiopsypsa = 8
10._at : prebiopsypsa = 9

	df	chi2	P>chi2
Pirads 4-5 MRI@_at			
1	1	2.960	0.085
2	1	3.720	0.054
3	1	4.450	0.035
4	1	5.060	0.024
5	1	5.390	0.020
6	1	5.160	0.023
7	1	4.290	0.038
8	1	3.150	0.076
9	1	2.190	0.139
10	1	1.520	0.218
Joint	3	10.550	0.015

Table 0.18 There were significant differences in the predicted probability of PrCa between a normal and abnormal (pirads 4-5) MRI (highlighted in blue).

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(any cancer), predict()
1._at : prebiopsypsa = 0
2._at : prebiopsypsa = 1
3._at : prebiopsypsa = 2
4._at : prebiopsypsa = 3
5._at : prebiopsypsa = 4
6._at : prebiopsypsa = 5
7._at : prebiopsypsa = 6
8._at : prebiopsypsa = 7
9._at : prebiopsypsa = 8
10._at : prebiopsypsa = 9

	Delta-method			
	Contrast	Std.Err.	z	P>z
Pirads 4-5 MRI@_at				
(1 vs base) 1	0.209	0.122	1.720	0.085
(1 vs base) 2	0.237	0.123	1.930	0.054
(1 vs base) 3	0.259	0.123	2.110	0.035
(1 vs base) 4	0.270	0.120	2.250	0.024
(1 vs base) 5	0.269	0.116	2.320	0.020
(1 vs base) 6	0.257	0.113	2.270	0.023
(1 vs base) 7	0.234	0.113	2.070	0.038
(1 vs base) 8	0.206	0.116	1.780	0.076
(1 vs base) 9	0.174	0.118	1.480	0.139
(1 vs base) 10	0.143	0.116	1.230	0.218

Table 0.19 At the higher levels of PSA (6-9ng/ml), there was no significant difference in the predicted probability of PrCa between a normal and abnormal MRI. The greatest difference in the predicted probability of PrCa between those with a normal and abnormal MRI was in those with a PSA of 3-5ng/ml (highlighted in green).

Sensitivity	28.26%

Specificity	91.43%
Positive predictive value	59.09%
Negative predictive value	74.42%
Correctly classified	72.19%

Table 0.20 For a logistic regression model including Pirads 4-5 MRI and PSA as predictor variables (Table 0.15), post-estimation test results are listed above

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Pirads 1-2 MRI	1	.	.	.	.	.	
Pirads 3-5 MRI	3.364	1.291	3.16	.002	1.586	7.138	***
PSAD<0.15	1	.	.	.	.	.	
PSAD≥0.15	2.584	2.044	1.20	.23	.548	12.181	
Constant	.265	.064	-5.48	0	.165	.427	***

Mean dependent var	0.305	SD dependent var	0.462
Pseudo r-squared	0.074	Number of obs	151.000
Chi-square	13.749	Prob > chi2	0.001
Akaike crit. (AIC)	177.903	Bayesian crit. (BIC)	186.955

*** p<.01, ** p<.05, * p<.1

Table 0.21 logistic regression model; any cancer as outcome with both PSA Density (PSAD) and MRI as categorical, predictor variables. A PSAD≥0.15ng/ml was associated with any cancer detection on prostate biopsy (OR 2.58, p=0.23) but not statistically significantly so in a model with Pirads 3-5 MRI (OR 3.36, p=0.002).

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
PSA Density	1.007	.004	1.86	.063	1	1.015	*
Pirads 1-3	1	.	.	.	.	.	
Pirads 3-5	2.951	1.167	2.74	.006	1.359	6.405	***
Constant	.192	.06	-5.31	0	.104	.352	***

Mean dependent var	0.609	SD dependent var	0.924
Pseudo r-squared	0.086	Number of obs	151.000
Chi-square	15.886	Prob > chi2	0.000
Akaike crit. (AIC)	175.766	Bayesian crit. (BIC)	184.818

*** p<.01, ** p<.05, * p<.1

Table 0.22 logistic regression model; any cancer as outcome with both PSA Density (PSAD) and MRI as continuous and categorical, predictor variables respectively. PSAD was positively associated with any cancer detection on prostate biopsy (OR 1.00, p=0.063) but not statistically significantly so in a model with Pirads 3-5 MRI (OR 2.95, p=0.006).

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(any cancer), predict()
at : PSA D = .0557596 (mean)
1.abnormal~I = .6821192 (mean)

2.abnormal~l = .3178808 (mean)

	Delta-method Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
Pirads 3-5 MRI						
N	0.224	0.042	5.290	0.000	0.141	0.307
Y	0.460	0.076	6.070	0.000	0.312	0.609

Table 0.23 At a mean PSAD of 0.055ng/ml, the percentage probability of detecting any PrCa on biopsy was 22% in men with a Pirads 1-2 MRI and 46% in men with a Pirads 3-5 MRI.

Sensitivity	26.09%
Specificity	93.33%
Positive predictive value	63.16%
Negative predictive value	74.24%
Correctly classified	72.85%

Table 0.24 For a logistic regression model including Pirads 3-5 MRI and PSA as predictor variables (Table 0.22), post-estimation test results are listed above

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
PSAD <0.15	1	.	.	.	.	.	
PSAD >=0.15	2.718	2.187	1.24	.214	.562	13.154	
Pirads 1-3 MRI	1	.	.	.	.	.	
Pirads 4-5 MRI	4.159	2.013	2.94	.003	1.61	10.741	***
Constant	.321	.067	-5.47	0	.214	.482	***

Mean dependent var	0.305	SD dependent var	0.462
Pseudo r-squared	0.067	Number of obs	151.000
Chi-square	12.476	Prob > chi2	0.002
Akaike crit. (AIC)	179.176	Bayesian crit. (BIC)	188.228

*** p<.01, ** p<.05, * p<.1

Table 0.25 logistic regression model; any cancer as outcome with both PSA Density (PSAD) and MRI as categorical, predictor variables. A PSAD≥0.15ng/ml was associated with any cancer detection on prostate biopsy (OR 2.7`, p=0.21) but not statistically significantly so in a model with Pirads 4-5 MRI (4.15, p=0.003).

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
PSAD	1.007	.004	1.77	.077	.999	1.015	*
Pirads 1-3	1	.	.	.	.	.	

Pirads 4-5	3.365	1.711	2.39	.017	1.242	9.114	**
Constant	.232	.069	-4.94	0	.13	.414	***

Mean dependent var	0.609	SD dependent var	0.924
Pseudo r-squared	0.076	Number of obs	151.000
Chi-square	14.140	Prob > chi2	0.001
Akaike crit. (AIC)	177.512	Bayesian crit. (BIC)	186.564

*** p<.01, ** p<.05, * p<.1

Table 0.26 logistic regression model; any cancer as outcome with both PSA Density (PSAD) and MRI as continuous and categorical, predictor variables respectively. PSAD was positively associated with any cancer detection on prostate biopsy (OR 1.00, p=0.077) but not statistically significantly so in a model with Pirads 4-5 MRI (OR 2.95, p=0.017).

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(any cancer), predict()
at : PSAD = 55.75958 (mean)
0.abnorma~45 = .8476821 (mean)
1.abnorma~45 = .1523179 (mean)

	Delta-method					
	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
Pirads 4-5						
No	0.258	0.040	6.520	0.000	0.180	0.335
Yes	0.539	0.114	4.720	0.000	0.315	0.763

Table 0.27 At a mean PSAD of 0.055ng/ml, the percentage probability of detecting any PrCa on biopsy was 25% in men with a Pirads 1-3 MRI and 53% in men with a Pirads 4-5 MRI.

Sensitivity	26.09%
Specificity	91.43%
Positive predictive value	57.14%
Negative predictive value	73.85%

Correctly classified	71.52%

Table 0.28 For a logistic regression model including Pirads 4-5 MRI and PSA as predictor variables (Table 0.26Table 0.22), post-estimation test results are listed above

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
40-<50	1	.	.	.	.	.	
50-<60	.979	.423	-0.05	.961	.42	2.283	
≥60	1.866	.978	1.19	.234	.668	5.211	
Pirads 1-2	1	.	.	.	.	.	
Pirads 3-5	3.392	1.303	3.18	.001	1.598	7.203	***
Constant	.249	.087	-3.97	0	.125	.495	***

Mean dependent var	0.305	SD dependent var	0.462
Pseudo r-squared	0.077	Number of obs	151.000
Chi-square	14.206	Prob > chi2	0.003
Akaike crit. (AIC)	179.446	Bayesian crit. (BIC)	191.515

*** p<.01, ** p<.05, * p<.1

Table 0.29 Logistic regression model describing age and Pirads 3-5 MRI as categorical variables. Overall the model is significant. Age as a categorical variable was positively associated with any cancer detection (ORs 0.97 & 1.86) but not statistically significantly so. A Pirads 3-5 MRI remained significantly associated with any cancer detection (OR 3.39) compared to men with a Pirads 1-2 MRI (p=0.001).

Logistic regression

Any cancer	OR	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Age	1.034	.026	1.30	.192	.983	1.087	
Pirads 1-2	1	.	.	.	.	.	
Pirads 3-5	3.301	1.27	3.10	.002	1.553	7.016	***
Constant	.047	.065	-2.22	.027	.003	.702	**

Mean dependent var	0.609	SD dependent var	0.924
Pseudo r-squared	0.075	Number of obs	151.000
Chi-square	13.982	Prob > chi2	0.001
Akaike crit. (AIC)	177.670	Bayesian crit. (BIC)	186.722

*** p<.01, ** p<.05, * p<.1

Table 0.30 logistic regression model incorporating age as a continuous variable, and MRI Pirads 3-5 as a categorical variable. PIrads 3-5 MRI is positively associated with any cancer (OR 3.30; p=0.002)) in the presence of age which is also significantly associated with any cancer detection (OR 1.03) but not statistically significantly so (p=0.192).

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(any cancer), predict()
at : Age = 53.51148 (mean)
1.abnormal~l = .6821192 (mean)
2.abnormal~l = .3178808 (mean)

Delta-method

	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
Pirads 3-5						
N	0.217	0.041	5.290	0.000	0.137	0.298

Y	0.478	0.074	6.430	0.000	0.333	0.624

Table 0.31 At the mean study age (53.5 years), the predicated probability of any cancer detection in a man with a Pirads 1-2 MRI is 21%, and 47% with a Pirads 3-5 MRI.

Sensitivity	32.61%
Specificity	90.48%
Positive predictive value	60.00%
Negative predictive value	75.40%
Correctly classified	72.85%

Table 0.32 For a logistic regression model including Pirads 3-5 MRI and age as predictor variables (Table 0.30Table 0.26Table 0.22), post-estimation test results are listed above

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
40-<50	1	.	.	.	.	.	
50-<60	.976	.416	-0.06	.955	.423	2.252	
≥60	1.478	.817	0.71	.48	.5	4.365	
Pirads 1-3	1	.	.	.	.	.	
Pirads 4-5	4.022	2.05	2.73	.006	1.482	10.92	***
Constant	.32	.104	-3.50	0	.169	.606	***

Mean dependent var	0.305	SD dependent var	0.462
Pseudo r-squared	0.063	Number of obs	151.000
Chi-square	11.606	Prob > chi2	0.009
Akaike crit. (AIC)	182.045	Bayesian crit. (BIC)	194.115

*** p<.01, ** p<.05, * p<.1

Table 0.33 Logistic regression model describing age and Pirads 4-5 MRI as categorical variables. Overall the model is significant. Age as a categorical variable was positively associated with any cancer detection (ORs 0.97 & 1.4) but not statistically significantly so. A Pirads 4-5 MRI remained significantly associated with any cancer detection (OR 4.0) compared to men with a Pirads 1-3 MRI (p=0.006).

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Age	1.025	.027	0.96	.339	.974	1.079	
Pirads 1-3	1	.	.	.	.	.	
Pirads 4-5	3.935	1.982	2.72	.007	1.466	10.563	***
Constant	.089	.125	-1.73	.084	.006	1.387	*

Mean dependent var	0.609	SD dependent var	0.924

Pseudo r-squared	0.064	Number of obs	151.000
Chi-square	11.824	Prob > chi2	0.003
Akaike crit. (AIC)	179.828	Bayesian crit. (BIC)	188.880

*** p<.01, ** p<.05, * p<.1

Table 0.34 logistic regression model incorporating age as a continuous variable, and MRI Pirads 4-5 as a categorical variable. PIrads 4-5 MRI is positively associated with any cancer (OR 3.93; p=0.007)) in the presence of age which is also significantly associated with any cancer detection (OR 1.02) but not statistically significantly so (p=0.339).

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(any cancer), predict()
at : Age~y = 53.51148 (mean)
0.abnorma~45 = .8476821 (mean)
1.abnorma~45 = .1523179 (mean)

	Delta-method					
	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
Pirads 4-5						
No	0.254	0.039	6.530	0.000	0.178	0.330
Yes	0.572	0.112	5.130	0.000	0.353	0.791

Table 0.35 At the mean study age (53.5 years), the predicated probability of any cancer detection in a man with a Pirads 1-3 MRI is 25%, and 57% with a Pirads 4-5 MRI.

Sensitivity	30.43%
Specificity	91.43%
Positive predictive value	60.87%
Negative predictive value	75.00%
Correctly classified	72.85%

Table 0.36 For a logistic regression model including Pirads 4-5 MRI and age as predictor variables (Table 0.34Table 0.26Table 0.22), post-estimation test results are listed above

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
No prior PSA	1	.	.	.	.	.	
unknown	1.838	1.416	0.79	.429	.406	8.317	

Prior PSA	2.245	1.05	1.73	.084	.898	5.613	*
		.	.	.	.	.	
Pirads 1-2	1						
Pirads 3-5	3.986	1.626	3.39	.001	1.792	8.867	***
	.156	.069	-4.17	0	.065	.373	***
Constant							

Mean dependent var	0.627	SD dependent var	0.931
Pseudo r-squared	0.086	Number of obs	134.000
Chi-square	14.414	Prob > chi2	0.002
Akaike crit. (AIC)	160.234	Bayesian crit. (BIC)	171.825

*** p<.01, ** p<.05, * p<.1

Table 0.37 in a logistic regression model including prior PSA screening and MRI as predictor, categorical variables, Pirads 3-5 MRI was positively and statistically significantly associated with any cancer detection (OR 3.98, p=0.001). Pior PSA screening was positively associated with any cancer detection with an OR of 2.24 but this did not reach statistical significance (p=0.084) compared to those without prior screening.

Abnormal MRI Definition : Pirads 4-5 and Prior PSA

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
No prior PSA	1	.	.	.	.	.	
Unknown	2.432	1.904	1.14	.256	.525	11.278	
Prior PSA	2.611	1.272	1.97	.049	1.005	6.784	**
		.	.	.	.	.	
Pirads 1-3	1						
Pirads 4-5	5.813	3.08	3.32	.001	2.058	16.424	***
Constant	.167	.074	-4.01	0	.069	.4	***

Mean dependent var	0.627	SD dependent var	0.931
Pseudo r-squared	0.086	Number of obs	134.000
Chi-square	14.401	Prob > chi2	0.002
Akaike crit. (AIC)	160.247	Bayesian crit. (BIC)	171.838

*** p<.01, ** p<.05, * p<.1

Table 0.38 in a logistic regression model including prior PSA screening and MRI as predictor, categorical variables, Pirads 4-5 MRI was positively and statistically significantly associated with any cancer detection (OR 5.81, p=0.001). Prior PSA screening was positively associated with any cancer detection with an OR of 2.61 and this did reach statistical significance (p=0.049) compared to those without prior screening.

Abnormal MRI Definition : Pirads 3-5, Age and PSA

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
PSA	1.324	.176	2.11	.035	1.02	1.718	**
Age	1.016	.028	0.56	.572	.963	1.072	
Pirads 1-2	1	.	.	.	.	.	

Pirads 3-5	2.639	1.068	2.40	.016	1.194	5.831	**
Constant	.077	.109	-1.80	.071	.005	1.247	*

Mean dependent var	0.305	SD dependent var	0.462
Pseudo r-squared	0.100	Number of obs	151.000
Chi-square	18.573	Prob > chi2	0.000
Akaike crit. (AIC)	175.079	Bayesian crit. (BIC)	187.148

*** p<.01, ** p<.05, * p<.1

Table 0.39 In a logistic regression model incorporating age and PSA as continuous predictor variables and MRI as a categorical predictor variable with (any) cancer as the outcome, Pirads 3-5 MRI was positively and significantly associated with cancer detection OR2.63, p=0.016). PSA was also significantly associated (OR 1.32, p=0.035) but age was not.

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(any cancer), predict()
at : PSA = 1.833775 (mean)
Age~y = 53.51148 (mean)
1.abnormal~l = .6821192 (mean)
2.abnormal~l = .3178808 (mean)

	Delta-method					
	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
Pirads 3-5						
N	0.227	0.043	5.260	0.000	0.143	0.312
Y	0.437	0.078	5.640	0.000	0.285	0.589

Table 0.40 At a mean age of 53.5 years and PSA of 1.8ng/ml, the average probability of (any) cancer detection was 22% in those with a Pirads 1-2 MRI and 43% in those with a Pirads 3-5 MRI.

Sensitivity	34.78%
Specificity	91.43%
Positive predictive value	64.00%
Negative predictive value	76.19%
Correctly classified	74.17%

Table 0.41 For a logistic regression model including Pirads 4-5 MRI and age as predictor variables (Table 0.39Table 0.26Table 0.22), post-estimation test results are listed above

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
PSA	1.35	.183	2.22	.027	1.036	1.761	**
Age	1.009	.028	0.31	.755	.955	1.065	
Pirads 1-3	1	.	.	.	.	.	
Pirads 4-5	2.907	1.537	2.02	.044	1.031	8.195	**
Constant	.126	.182	-1.44	.151	.008	2.131	

Mean dependent var	0.305	SD dependent var	0.462

Pseudo r-squared	0.092	Number of obs	151.000
Chi-square	16.991	Prob > chi2	0.001
Akaike crit. (AIC)	176.661	Bayesian crit. (BIC)	188.730

*** p<.01, ** p<.05, * p<.1

Table 0.42 In a logistic regression model incorporating age and PSA as continuous predictor variables and MRI as a categorical predictor variable with (any) cancer as the outcome, Pirads 4-5 MRI was positively and significantly associated with cancer detection OR 2.9, p=0.044). PSA was also significantly associated (OR 1.35, p=0.027) but age was not (p=0.755).

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(Any cancer), predict()
at : PSA = 1.833775 (mean)
Age~y = 53.51148 (mean)
0.abnorma~45 = .8476821 (mean)
1.abnorma~45 = .1523179 (mean)

	Delta-method Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
Pirads 4-5						
No	0.259	0.040	6.450	0.000	0.180	0.337
Yes	0.503	0.120	4.190	0.000	0.268	0.739

Table 0.43 At a mean age of 53.5 years and PSA of 1.8ng/ml, the average probability of (any) cancer detection was 25% in those with a Pirads 1-3 MRI and 50% in those with a Pirads 4-5 MRI.

Sensitivity	28.26%
Specificity	92.38%
Positive predictive value	61.90%
Negative predictive value	74.62%
Correctly classified	72.85%

Table 0.44 For a logistic regression model including Pirads 4-5 MRI and age as predictor variables (Table 0.42 Table 0.26 Table 0.22), post-estimation test results are listed above

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Pirads 1-2	1	.	.	.	.	.	
Pirads 3-5	2.709	1.093	2.47	.013	1.229	5.972	**
Age	1.03	.027	1.12	.261	.979	1.083	
PSAD	1064.702	4260.58	1.74	.082	.418	2713015	*
Constant	.042	.059	-2.26	.024	.003	.655	**

Mean dependent var	0.305	SD dependent var	0.462
Pseudo r-squared	0.092	Number of obs	151.000
Chi-square	17.158	Prob > chi2	0.001
Akaike crit. (AIC)	176.494	Bayesian crit. (BIC)	188.563

*** p<.01, ** p<.05, * p<.1

Table 0.45 Logistic regression model incorporating MRI as a categorical (predictor) variable and age and PSAD as continuous (predictor) variables, with clinically significant PrCa as outcome. Pirads 3-5 MRI was positively

associated with significant cancer outcome at prostate biopsy (OR 2.70; p=0.013), as were age (OR 1.03, p= 0.261) but not PSAD (OR 1064.702, p=0.082).* * OR value inflated due to nature of variable

Sensitivity	34.78%
Specificity	91.43%
Positive predictive value	64.00%
Negative predictive value	76.19%
Correctly classified	74.17%

Table 0.46 For a logistic regression model including Pirads 3-5 MRI, PSAD and age as predictor variables (Table 0.45Table 0.42Table 0.26Table 0.22), post-estimation test results are listed above

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Pirads 1-3	1	.	.	.	.	.	
Pirads 4-5	2.862	1.536	1.96	.05	1	8.195	*
Age	1.024	.027	0.91	.364	.972	1.079	
PSAD	1298.436	5353.521	1.74	.082	.402	4197307	*
Constant	.065	.094	-1.90	.058	.004	1.094	*

Mean dependent var	0.305	SD dependent var	0.462
Pseudo r-squared	0.081	Number of obs	151.000
Chi-square	14.967	Prob > chi2	0.002
Akaike crit. (AIC)	178.684	Bayesian crit. (BIC)	190.754

*** p<.01, ** p<.05, * p<.1

Table 0.47 Logistic regression model incorporating MRI as a categorical (predictor) variable and age and PSAD as continuous (predictor) variables, with clinically significant PrCa as outcome. Pirads 4-5 MRI was positively associated with significant cancer outcome at prostate biopsy (OR 2.86; p=0.05), as were age (OR 1.02, p= 0.364) b PSAD (OR 1298.436, p=0.082).* * OR value inflated due to nature of variable

Sensitivity	28.26%
Specificity	92.38%
Positive predictive value	61.90%
Negative predictive value	74.62%
Correctly classified	72.85%

Table 0.48 For a logistic regression model including Pirads 4-5 MRI and age as predictor variables (Table 0.47 Table 0.26 Table 0.22), post-estimation test results are listed above

Adjusted predictions **Number of obs = 151**

Model VCE : OIM

Expression : Pr(signifvsinsignifornoca), predict()

1._at : prebiopsypsa = 0
2._at : prebiopsypsa = .5
3._at : prebiopsypsa = 1
4._at : prebiopsypsa = 1.5
5._at : prebiopsypsa = 2
6._at : prebiopsypsa = 2.5
7._at : prebiopsypsa = 3
8._at : prebiopsypsa = 3.5
9._at : prebiopsypsa = 4
10._at : prebiopsypsa = 4.5
11._at : prebiopsypsa = 5
12._at : prebiopsypsa = 5.5
13._at : prebiopsypsa = 6
14._at : prebiopsypsa = 6.5
15._at : prebiopsypsa = 7
16._at : prebiopsypsa = 7.5
17._at : prebiopsypsa = 8
18._at : prebiopsypsa = 8.5
19._at : prebiopsypsa = 9

Delta-method

	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#abnormalMRI						
1#N	0.003	0.004	0.820	0.411	-0.004	0.011

1#Y	0.070	0.046	1.530	0.125	-0.019	0.160
2#N	0.004	0.005	0.860	0.391	-0.005	0.013
2#Y	0.089	0.050	1.770	0.077	-0.010	0.187
3#N	0.005	0.006	0.890	0.373	-0.006	0.017
3#Y	0.112	0.054	2.060	0.039	0.006	0.218
4#N	0.007	0.007	0.920	0.357	-0.007	0.021
4#Y	0.140	0.057	2.440	0.015	0.027	0.252
5#N	0.009	0.009	0.950	0.343	-0.009	0.026
5#Y	0.173	0.060	2.880	0.004	0.055	0.291
6#N	0.011	0.011	0.970	0.332	-0.011	0.033
6#Y	0.213	0.063	3.360	0.001	0.089	0.337
7#N	0.014	0.014	0.980	0.325	-0.014	0.042
7#Y	0.259	0.069	3.760	0.000	0.124	0.393
8#N	0.018	0.018	0.990	0.321	-0.018	0.054
8#Y	0.311	0.078	4.000	0.000	0.158	0.463
9#N	0.023	0.024	0.990	0.321	-0.023	0.070
9#Y	0.368	0.091	4.040	0.000	0.189	0.546
10#N	0.030	0.030	0.990	0.324	-0.030	0.090
10#Y	0.429	0.108	3.980	0.000	0.218	0.640
11#N	0.038	0.040	0.970	0.330	-0.039	0.116
11#Y	0.492	0.125	3.930	0.000	0.246	0.738
12#N	0.049	0.051	0.960	0.339	-0.051	0.150
12#Y	0.556	0.141	3.930	0.000	0.278	0.833
13#N	0.062	0.067	0.940	0.348	-0.068	0.193
13#Y	0.617	0.154	4.020	0.000	0.316	0.918
14#N	0.079	0.086	0.920	0.358	-0.090	0.248
14#Y	0.676	0.160	4.210	0.000	0.361	0.990
15#N	0.100	0.111	0.900	0.367	-0.117	0.317
15#Y	0.729	0.161	4.520	0.000	0.413	1.045
16#N	0.125	0.141	0.890	0.374	-0.151	0.402
16#Y	0.776	0.157	4.950	0.000	0.469	1.084
17#N	0.156	0.177	0.880	0.378	-0.191	0.504
17#Y	0.817	0.148	5.520	0.000	0.527	1.108
18#N	0.193	0.219	0.880	0.379	-0.237	0.622
18#Y	0.853	0.136	6.270	0.000	0.586	1.119
19#N	0.236	0.266	0.890	0.376	-0.285	0.757
19#Y	0.882	0.122	7.220	0.000	0.642	1.121

Table 0.49 significant cancer. Psa + pirads 3-5 MRI

Logistic regression

signifvsinsignifor~a	Coef.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
1b.priorPSA	1	.	.	.	.	.	
2.priorPSA	.925	1.085	-0.07	.947	.093	9.226	
3.priorPSA	1	.645	0.00	1	.283	3.538	
Constant	.108	.057	-4.23	0	.039	.303	***

Mean dependent var	0.097	SD dependent var	0.297
Pseudo r-squared	0.000	Number of obs	134.000
Chi-square	0.005	Prob > chi2	0.997
Akaike crit. (AIC)	91.346	Bayesian crit. (BIC)	100.039

*** *p<.01, ** p<.05, * p<.1*

Table 0.50 LR model for Prior PSA + signif ca

```
Adjusted predictions                    Number of obs     =        151
Model VCE    : OIM
Expression   : Pr(signifvsinsignifornoca), predict()
1._at        : ageatstudy~y    =         40
               prebiopsypsa    =          0
2._at        : ageatstudy~y    =         40
               prebiopsypsa    =          1
3._at        : ageatstudy~y    =         40
               prebiopsypsa    =          2
4._at        : ageatstudy~y    =         40
               prebiopsypsa    =          3
5._at        : ageatstudy~y    =         40
               prebiopsypsa    =          4
6._at        : ageatstudy~y    =         40
               prebiopsypsa    =          5
7._at        : ageatstudy~y    =         40
               prebiopsypsa    =          6
8._at        : ageatstudy~y    =         40
               prebiopsypsa    =          7
9._at        : ageatstudy~y    =         40
               prebiopsypsa    =          8
10._at       : ageatstudy~y    =         40
               prebiopsypsa    =          9
11._at       : ageatstudy~y    =         50
               prebiopsypsa    =          0
12._at       : ageatstudy~y    =         50
               prebiopsypsa    =          1
13._at       : ageatstudy~y    =         50
               prebiopsypsa    =          2
14._at       : ageatstudy~y    =         50
               prebiopsypsa    =          3
15._at       : ageatstudy~y    =         50
               prebiopsypsa    =          4
16._at       : ageatstudy~y    =         50
               prebiopsypsa    =          5
17._at       : ageatstudy~y    =         50
               prebiopsypsa    =          6
18._at       : ageatstudy~y    =         50
               prebiopsypsa    =          7
19._at       : ageatstudy~y    =         50
               prebiopsypsa    =          8
20._at       : ageatstudy~y    =         50
               prebiopsypsa    =          9
21._at       : ageatstudy~y    =         60
               prebiopsypsa    =          0
22._at       : ageatstudy~y    =         60
               prebiopsypsa    =          1
23._at       : ageatstudy~y    =         60
               prebiopsypsa    =          2
24._at       : ageatstudy~y    =         60
               prebiopsypsa    =          3
25._at       : ageatstudy~y    =         60
```

prebiopsypsa = 4
26._at : ageatstudy~y = 60
prebiopsypsa = 5
27._at : ageatstudy~y = 60
prebiopsypsa = 6
28._at : ageatstudy~y = 60
prebiopsypsa = 7
29._at : ageatstudy~y = 60
prebiopsypsa = 8
30._at : ageatstudy~y = 60
prebiopsypsa = 9
31._at : ageatstudy~y = 70
prebiopsypsa = 0
32._at : ageatstudy~y = 70
prebiopsypsa = 1
33._at : ageatstudy~y = 70
prebiopsypsa = 2
34._at : ageatstudy~y = 70
prebiopsypsa = 3
35._at : ageatstudy~y = 70
prebiopsypsa = 4
36._at : ageatstudy~y = 70
prebiopsypsa = 5
37._at : ageatstudy~y = 70
prebiopsypsa = 6
38._at : ageatstudy~y = 70
prebiopsypsa = 7
39._at : ageatstudy~y = 70
prebiopsypsa = 8
40._at : ageatstudy~y = 70
prebiopsypsa = 9

Delta-method

	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#abnormalMRI						
1#N	0.000	0.001	0.570	0.566	-0.001	0.002
1#Y	0.006	0.009	0.670	0.506	-0.012	0.024
2#N	0.001	0.001	0.600	0.551	-0.001	0.002
2#Y	0.009	0.013	0.710	0.480	-0.016	0.035
3#N	0.001	0.001	0.610	0.540	-0.002	0.003
3#Y	0.014	0.019	0.740	0.460	-0.023	0.051
4#N	0.001	0.002	0.620	0.536	-0.003	0.005
4#Y	0.021	0.028	0.760	0.449	-0.034	0.076
5#N	0.002	0.003	0.620	0.539	-0.004	0.008
5#Y	0.032	0.042	0.760	0.446	-0.051	0.115
6#N	0.003	0.005	0.600	0.547	-0.006	0.012
6#Y	0.048	0.064	0.750	0.452	-0.077	0.173
7#N	0.004	0.007	0.580	0.562	-0.010	0.019
7#Y	0.071	0.097	0.730	0.463	-0.119	0.262
8#N	0.006	0.012	0.550	0.579	-0.016	0.029
8#Y	0.105	0.147	0.720	0.475	-0.183	0.393
9#N	0.010	0.019	0.530	0.599	-0.027	0.047
9#Y	0.152	0.216	0.700	0.483	-0.272	0.575

10#N	0.015	0.030	0.500	0.619	-0.044	0.074
10#Y	0.214	0.305	0.700	0.483	-0.384	0.812
11#N	0.002	0.002	0.740	0.461	-0.003	0.006
11#Y	0.027	0.026	1.010	0.314	-0.025	0.078
12#N	0.002	0.003	0.790	0.430	-0.003	0.008
12#Y	0.040	0.034	1.170	0.242	-0.027	0.107
13#N	0.004	0.004	0.830	0.408	-0.005	0.012
13#Y	0.060	0.045	1.330	0.182	-0.028	0.147
14#N	0.005	0.006	0.850	0.398	-0.007	0.018
14#Y	0.088	0.060	1.460	0.145	-0.030	0.206
15#N	0.008	0.010	0.840	0.402	-0.011	0.027
15#Y	0.128	0.085	1.500	0.134	-0.039	0.296
16#N	0.012	0.015	0.810	0.419	-0.018	0.042
16#Y	0.183	0.124	1.470	0.141	-0.061	0.427
17#N	0.019	0.024	0.760	0.445	-0.029	0.066
17#Y	0.254	0.179	1.420	0.155	-0.096	0.605
18#N	0.028	0.039	0.710	0.476	-0.049	0.105
18#Y	0.342	0.244	1.400	0.161	-0.136	0.820
19#N	0.042	0.064	0.660	0.507	-0.082	0.167
19#Y	0.442	0.307	1.440	0.150	-0.160	1.044
20#N	0.063	0.101	0.620	0.535	-0.136	0.261
20#Y	0.547	0.352	1.550	0.120	-0.143	1.237
21#N	0.007	0.008	0.820	0.410	-0.009	0.023
21#Y	0.108	0.077	1.410	0.159	-0.042	0.258
22#N	0.010	0.011	0.900	0.367	-0.012	0.032
22#Y	0.155	0.081	1.910	0.056	-0.004	0.315
23#N	0.015	0.016	0.960	0.335	-0.016	0.047
23#Y	0.219	0.081	2.720	0.007	0.061	0.377
24#N	0.023	0.023	1.000	0.318	-0.022	0.069
24#Y	0.299	0.081	3.690	0.000	0.140	0.459
25#N	0.035	0.035	1.000	0.319	-0.034	0.104
25#Y	0.394	0.098	4.040	0.000	0.203	0.586
26#N	0.052	0.054	0.960	0.336	-0.054	0.159
26#Y	0.498	0.131	3.810	0.000	0.242	0.754
27#N	0.078	0.085	0.910	0.362	-0.089	0.244
27#Y	0.602	0.164	3.670	0.000	0.281	0.923
28#N	0.114	0.132	0.860	0.388	-0.145	0.372
28#Y	0.697	0.183	3.810	0.000	0.339	1.056
29#N	0.163	0.198	0.820	0.409	-0.225	0.551
29#Y	0.778	0.183	4.250	0.000	0.420	1.137
30#N	0.229	0.284	0.810	0.419	-0.327	0.785
30#Y	0.843	0.167	5.040	0.000	0.515	1.170
31#N	0.029	0.039	0.730	0.463	-0.048	0.106
31#Y	0.349	0.234	1.490	0.137	-0.111	0.808
32#N	0.043	0.055	0.790	0.427	-0.064	0.151
32#Y	0.449	0.223	2.020	0.044	0.012	0.886
33#N	0.065	0.076	0.850	0.396	-0.085	0.214
33#Y	0.554	0.199	2.790	0.005	0.164	0.944
34#N	0.095	0.107	0.890	0.371	-0.113	0.304
34#Y	0.654	0.171	3.820	0.000	0.319	0.990
35#N	0.138	0.149	0.930	0.352	-0.153	0.430
35#Y	0.743	0.147	5.070	0.000	0.455	1.030
36#N	0.197	0.204	0.960	0.336	-0.204	0.597
36#Y	0.815	0.126	6.490	0.000	0.569	1.061
37#N	0.271	0.271	1.000	0.317	-0.260	0.803
37#Y	0.870	0.106	8.190	0.000	0.662	1.078
38#N	0.362	0.341	1.060	0.288	-0.306	1.030
38#Y	0.911	0.088	10.390	0.000	0.739	1.083
39#N	0.464	0.398	1.170	0.244	-0.316	1.244
39#Y	0.940	0.070	13.360	0.000	0.802	1.077

40#N	0.569	0.427	1.330	0.183	-0.269	1.406
40#Y	0.960	0.055	17.490	0.000	0.852	1.067

Contrasts of adjusted predictions **Number of obs = 151**
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()

1._at : ageatstudy~y = 40
prebiopsypsa = 0
2._at : ageatstudy~y = 40
prebiopsypsa = 1
3._at : ageatstudy~y = 40
prebiopsypsa = 2
4._at : ageatstudy~y = 40
prebiopsypsa = 3
5._at : ageatstudy~y = 40
prebiopsypsa = 4
6._at : ageatstudy~y = 40
prebiopsypsa = 5
7._at : ageatstudy~y = 40
prebiopsypsa = 6
8._at : ageatstudy~y = 40
prebiopsypsa = 7
9._at : ageatstudy~y = 40
prebiopsypsa = 8
10._at : ageatstudy~y = 40
prebiopsypsa = 9
11._at : ageatstudy~y = 50
prebiopsypsa = 0
12._at : ageatstudy~y = 50
prebiopsypsa = 1
13._at : ageatstudy~y = 50
prebiopsypsa = 2
14._at : ageatstudy~y = 50
prebiopsypsa = 3
15._at : ageatstudy~y = 50
prebiopsypsa = 4
16._at : ageatstudy~y = 50
prebiopsypsa = 5
17._at : ageatstudy~y = 50
prebiopsypsa = 6
18._at : ageatstudy~y = 50
prebiopsypsa = 7
19._at : ageatstudy~y = 50
prebiopsypsa = 8
20._at : ageatstudy~y = 50
prebiopsypsa = 9
21._at : ageatstudy~y = 60
prebiopsypsa = 0
22._at : ageatstudy~y = 60
prebiopsypsa = 1

23._at : ageatstudy~y = 60
prebiopsypsa = 2
24._at : ageatstudy~y = 60
prebiopsypsa = 3
25._at : ageatstudy~y = 60
prebiopsypsa = 4
26._at : ageatstudy~y = 60
prebiopsypsa = 5
27._at : ageatstudy~y = 60
prebiopsypsa = 6
28._at : ageatstudy~y = 60
prebiopsypsa = 7
29._at : ageatstudy~y = 60
prebiopsypsa = 8
30._at : ageatstudy~y = 60
prebiopsypsa = 9
31._at : ageatstudy~y = 70
prebiopsypsa = 0
32._at : ageatstudy~y = 70
prebiopsypsa = 1
33._at : ageatstudy~y = 70
prebiopsypsa = 2
34._at : ageatstudy~y = 70
prebiopsypsa = 3
35._at : ageatstudy~y = 70
prebiopsypsa = 4
36._at : ageatstudy~y = 70
prebiopsypsa = 5
37._at : ageatstudy~y = 70
prebiopsypsa = 6
38._at : ageatstudy~y = 70
prebiopsypsa = 7
39._at : ageatstudy~y = 70
prebiopsypsa = 8
40._at : ageatstudy~y = 70
prebiopsypsa = 9

	df	chi2	P>chi2
abnormalMRI@_at			
1	1	0.440	0.509
2	1	0.490	0.483
3	1	0.540	0.463
4	1	0.570	0.452
5	1	0.570	0.449
6	1	0.560	0.454
7	1	0.540	0.464
8	1	0.510	0.474
9	1	0.500	0.480
10	1	0.510	0.477
11	1	0.990	0.320
12	1	1.320	0.250
13	1	1.710	0.191
14	1	2.040	0.153
15	1	2.170	0.141

16	1	2.110	0.146
17	1	2.020	0.155
18	1	2.030	0.154
19	1	2.280	0.131
20	1	2.970	0.085
21	1	1.920	0.166
22	1	3.430	0.064
23	1	6.470	0.011
24	1	10.710	0.001
25	1	12.510	0.000
26	1	12.010	0.001
27	1	12.300	0.001
28	1	14.250	0.000
29	1	15.190	0.000
30	1	9.680	0.002
31	1	2.290	0.131
32	1	4.240	0.039
33	1	8.020	0.005
34	1	13.550	0.000
35	1	16.600	0.000
36	1	12.900	0.000
37	1	7.190	0.007
38	1	3.600	0.058
39	1	1.850	0.174
40	1	1.020	0.312
Joint	4	17.580	0.002

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()
1._at : ageatstudy~y = 40
prebiopsypsa = 0
2._at : ageatstudy~y = 40
prebiopsypsa = 1
3._at : ageatstudy~y = 40
prebiopsypsa = 2
4._at : ageatstudy~y = 40
prebiopsypsa = 3
5._at : ageatstudy~y = 40
prebiopsypsa = 4
6._at : ageatstudy~y = 40
prebiopsypsa = 5
7._at : ageatstudy~y = 40
prebiopsypsa = 6
8._at : ageatstudy~y = 40
prebiopsypsa = 7
9._at : ageatstudy~y = 40
prebiopsypsa = 8
10._at : ageatstudy~y = 40
prebiopsypsa = 9
11._at : ageatstudy~y = 50
prebiopsypsa = 0
12._at : ageatstudy~y = 50
prebiopsypsa = 1
13._at : ageatstudy~y = 50
prebiopsypsa = 2
14._at : ageatstudy~y = 50
prebiopsypsa = 3
15._at : ageatstudy~y = 50

	prebiopsypsa	=	4
16._at	: ageatstudy~y	=	50
	prebiopsypsa	=	5
17._at	: ageatstudy~y	=	50
	prebiopsypsa	=	6
18._at	: ageatstudy~y	=	50
	prebiopsypsa	=	7
19._at	: ageatstudy~y	=	50
	prebiopsypsa	=	8
20._at	: ageatstudy~y	=	50
	prebiopsypsa	=	9
21._at	: ageatstudy~y	=	60
	prebiopsypsa	=	0
22._at	: ageatstudy~y	=	60
	prebiopsypsa	=	1
23._at	: ageatstudy~y	=	60
	prebiopsypsa	=	2
24._at	: ageatstudy~y	=	60
	prebiopsypsa	=	3
25._at	: ageatstudy~y	=	60
	prebiopsypsa	=	4
26._at	: ageatstudy~y	=	60
	prebiopsypsa	=	5
27._at	: ageatstudy~y	=	60
	prebiopsypsa	=	6
28._at	: ageatstudy~y	=	60
	prebiopsypsa	=	7
29._at	: ageatstudy~y	=	60
	prebiopsypsa	=	8
30._at	: ageatstudy~y	=	60
	prebiopsypsa	=	9
31._at	: ageatstudy~y	=	70
	prebiopsypsa	=	0
32._at	: ageatstudy~y	=	70
	prebiopsypsa	=	1
33._at	: ageatstudy~y	=	70
	prebiopsypsa	=	2
34._at	: ageatstudy~y	=	70
	prebiopsypsa	=	3
35._at	: ageatstudy~y	=	70
	prebiopsypsa	=	4
36._at	: ageatstudy~y	=	70
	prebiopsypsa	=	5
37._at	: ageatstudy~y	=	70
	prebiopsypsa	=	6
38._at	: ageatstudy~y	=	70
	prebiopsypsa	=	7
39._at	: ageatstudy~y	=	70
	prebiopsypsa	=	8
40._at	: ageatstudy~y	=	70
	prebiopsypsa	=	9

Delta-method

	Contrast	Std.Err.	z	P>z
abnormalMRI@_at				
(Y vs base) 1	0.006	0.009	0.660	0.509
(Y vs base) 2	0.009	0.012	0.700	0.483
(Y vs base) 3	0.013	0.018	0.730	0.463
(Y vs base) 4	0.020	0.027	0.750	0.452
(Y vs base) 5	0.030	0.040	0.760	0.449
(Y vs base) 6	0.045	0.061	0.750	0.454

(Y vs base) 7	0.067	0.092	0.730	0.464
(Y vs base) 8	0.099	0.138	0.720	0.474
(Y vs base) 9	0.142	0.201	0.710	0.480
(Y vs base) 10	0.199	0.280	0.710	0.477
(Y vs base) 11	0.025	0.025	0.990	0.320
(Y vs base) 12	0.038	0.033	1.150	0.250
(Y vs base) 13	0.056	0.043	1.310	0.190
(Y vs base) 14	0.083	0.058	1.430	0.153
(Y vs base) 15	0.120	0.081	1.470	0.141
(Y vs base) 16	0.171	0.117	1.450	0.146
(Y vs base) 17	0.236	0.166	1.420	0.155
(Y vs base) 18	0.314	0.220	1.430	0.154
(Y vs base) 19	0.400	0.265	1.510	0.131
(Y vs base) 20	0.484	0.281	1.720	0.085
(Y vs base) 21	0.101	0.073	1.380	0.166
(Y vs base) 22	0.145	0.078	1.850	0.064
(Y vs base) 23	0.204	0.080	2.540	0.011
(Y vs base) 24	0.276	0.084	3.270	0.001
(Y vs base) 25	0.359	0.102	3.540	0.000
(Y vs base) 26	0.446	0.129	3.470	0.001
(Y vs base) 27	0.524	0.150	3.510	0.000
(Y vs base) 28	0.584	0.155	3.770	0.000
(Y vs base) 29	0.615	0.158	3.900	0.000
(Y vs base) 30	0.613	0.197	3.110	0.002
(Y vs base) 31	0.320	0.211	1.510	0.131
(Y vs base) 32	0.406	0.197	2.060	0.039
(Y vs base) 33	0.490	0.173	2.830	0.005
(Y vs base) 34	0.559	0.152	3.680	0.000
(Y vs base) 35	0.604	0.148	4.070	0.000
(Y vs base) 36	0.618	0.172	3.590	0.000
(Y vs base) 37	0.599	0.223	2.680	0.007
(Y vs base) 38	0.549	0.289	1.900	0.058
(Y vs base) 39	0.476	0.350	1.360	0.174
(Y vs base) 40	0.391	0.386	1.010	0.312

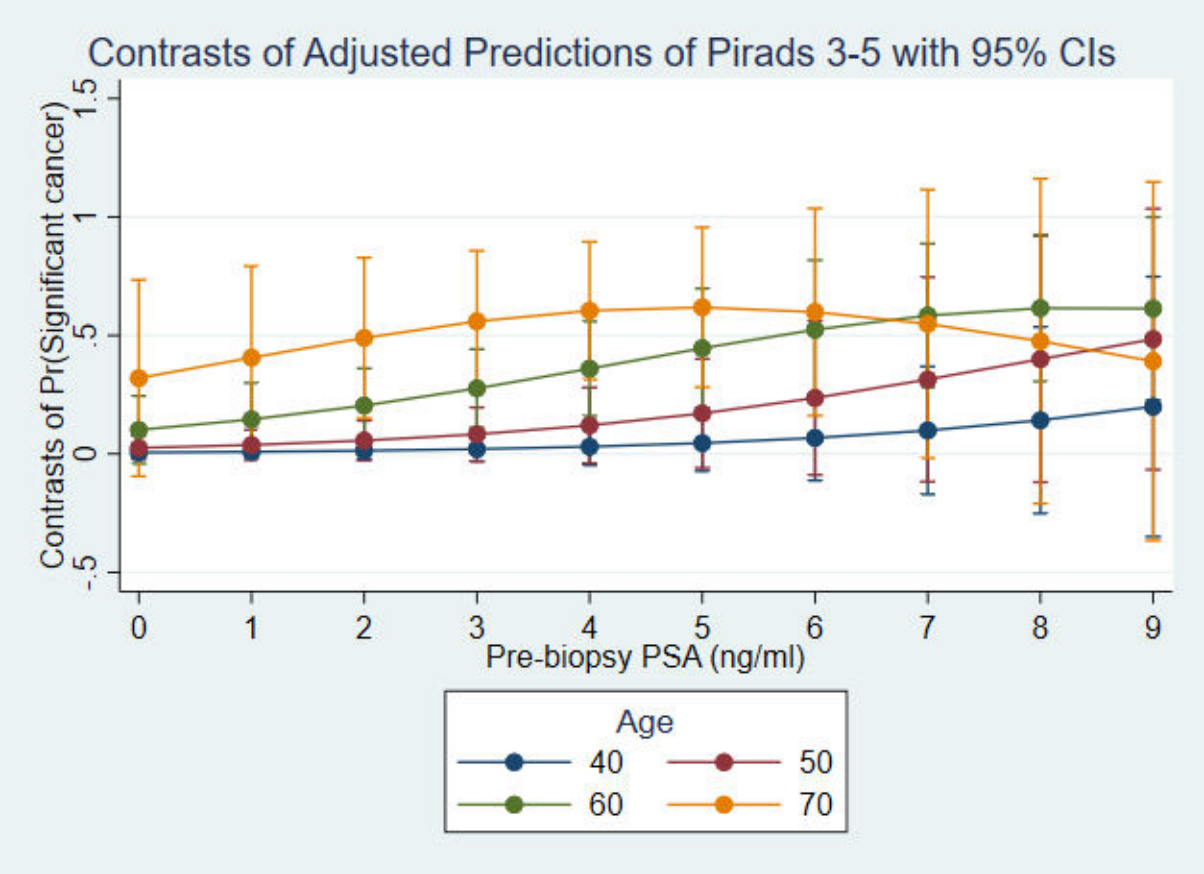


Figure 0.1

Adjusted predictions **Number of obs = 151**
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()
1._at : ageatstudy~y = 40
prebiopsypsa = 0
2._at : ageatstudy~y = 40
prebiopsypsa = 1
3._at : ageatstudy~y = 40
prebiopsypsa = 2
4._at : ageatstudy~y = 40
prebiopsypsa = 3
5._at : ageatstudy~y = 40
prebiopsypsa = 4
6._at : ageatstudy~y = 40
prebiopsypsa = 5
7._at : ageatstudy~y = 40
prebiopsypsa = 6
8._at : ageatstudy~y = 40
prebiopsypsa = 7
9._at : ageatstudy~y = 40
prebiopsypsa = 8
10._at : ageatstudy~y = 40
prebiopsypsa = 9

```
11._at      : ageatstudy~y  =       50
              prebiopsypsa  =        0
12._at      : ageatstudy~y  =       50
              prebiopsypsa  =        1
13._at      : ageatstudy~y  =       50
              prebiopsypsa  =        2
14._at      : ageatstudy~y  =       50
              prebiopsypsa  =        3
15._at      : ageatstudy~y  =       50
              prebiopsypsa  =        4
16._at      : ageatstudy~y  =       50
              prebiopsypsa  =        5
17._at      : ageatstudy~y  =       50
              prebiopsypsa  =        6
18._at      : ageatstudy~y  =       50
              prebiopsypsa  =        7
19._at      : ageatstudy~y  =       50
              prebiopsypsa  =        8
20._at      : ageatstudy~y  =       50
              prebiopsypsa  =        9
21._at      : ageatstudy~y  =       60
              prebiopsypsa  =        0
22._at      : ageatstudy~y  =       60
              prebiopsypsa  =        1
23._at      : ageatstudy~y  =       60
              prebiopsypsa  =        2
24._at      : ageatstudy~y  =       60
              prebiopsypsa  =        3
25._at      : ageatstudy~y  =       60
              prebiopsypsa  =        4
26._at      : ageatstudy~y  =       60
              prebiopsypsa  =        5
27._at      : ageatstudy~y  =       60
              prebiopsypsa  =        6
28._at      : ageatstudy~y  =       60
              prebiopsypsa  =        7
29._at      : ageatstudy~y  =       60
              prebiopsypsa  =        8
30._at      : ageatstudy~y  =       60
              prebiopsypsa  =        9
31._at      : ageatstudy~y  =       70
              prebiopsypsa  =        0
32._at      : ageatstudy~y  =       70
              prebiopsypsa  =        1
33._at      : ageatstudy~y  =       70
              prebiopsypsa  =        2
34._at      : ageatstudy~y  =       70
              prebiopsypsa  =        3
35._at      : ageatstudy~y  =       70
              prebiopsypsa  =        4
36._at      : ageatstudy~y  =       70
              prebiopsypsa  =        5
```

37._at : ageatstudy~y = 70
prebiopsypsa = 6
38._at : ageatstudy~y = 70
prebiopsypsa = 7
39._at : ageatstudy~y = 70
prebiopsypsa = 8
40._at : ageatstudy~y = 70
prebiopsypsa = 9

Delta-method

	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#abnormalMRI45						
1 0	0.002	0.003	0.700	0.483	-0.003	0.007
1 1	0.012	0.020	0.620	0.535	-0.026	0.051
2 0	0.003	0.004	0.740	0.459	-0.005	0.010
2 1	0.019	0.028	0.660	0.511	-0.037	0.074
3 0	0.004	0.005	0.770	0.441	-0.007	0.015
3 1	0.028	0.041	0.690	0.491	-0.052	0.108
4 0	0.006	0.008	0.790	0.431	-0.010	0.023
4 1	0.042	0.059	0.720	0.474	-0.074	0.159
5 0	0.010	0.013	0.790	0.431	-0.015	0.034
5 1	0.064	0.086	0.740	0.460	-0.105	0.233
6 0	0.015	0.019	0.770	0.440	-0.023	0.053
6 1	0.094	0.125	0.760	0.450	-0.150	0.339
7 0	0.023	0.031	0.750	0.456	-0.037	0.083
7 1	0.138	0.178	0.770	0.439	-0.211	0.486
8 0	0.035	0.049	0.710	0.476	-0.061	0.130
8 1	0.196	0.246	0.800	0.425	-0.286	0.679
9 0	0.052	0.077	0.680	0.497	-0.098	0.203
9 1	0.273	0.326	0.840	0.402	-0.365	0.911
10 0	0.078	0.120	0.650	0.516	-0.157	0.312
10 1	0.365	0.403	0.900	0.366	-0.425	1.155
11 0	0.006	0.006	1.050	0.292	-0.005	0.018
11 1	0.040	0.044	0.930	0.352	-0.045	0.126
12 0	0.009	0.008	1.190	0.234	-0.006	0.025
12 1	0.061	0.058	1.050	0.292	-0.052	0.174
13 0	0.014	0.011	1.310	0.191	-0.007	0.036
13 1	0.090	0.076	1.180	0.236	-0.059	0.239
14 0	0.022	0.016	1.370	0.170	-0.009	0.053
14 1	0.132	0.101	1.310	0.190	-0.065	0.329
15 0	0.033	0.024	1.350	0.176	-0.015	0.081
15 1	0.189	0.133	1.420	0.157	-0.073	0.450
16 0	0.050	0.039	1.270	0.203	-0.027	0.126
16 1	0.263	0.175	1.500	0.133	-0.080	0.606
17 0	0.074	0.064	1.170	0.243	-0.050	0.199
17 1	0.353	0.222	1.590	0.112	-0.082	0.789
18 0	0.109	0.102	1.070	0.285	-0.091	0.310
18 1	0.456	0.266	1.710	0.087	-0.066	0.978
19 0	0.158	0.159	1.000	0.319	-0.153	0.470
19 1	0.562	0.294	1.910	0.056	-0.014	1.139
20 0	0.224	0.234	0.960	0.339	-0.235	0.683
20 1	0.663	0.298	2.230	0.026	0.079	1.247
21 0	0.021	0.016	1.320	0.186	-0.010	0.052
21 1	0.126	0.090	1.400	0.162	-0.051	0.303
22 0	0.031	0.020	1.590	0.112	-0.007	0.070
22 1	0.181	0.100	1.810	0.070	-0.015	0.377
23 0	0.047	0.026	1.850	0.064	-0.003	0.098

23 1	0.253	0.105	2.410	0.016	0.047	0.460
24 0	0.071	0.036	1.990	0.046	0.001	0.141
24 1	0.342	0.110	3.110	0.002	0.127	0.558
25 0	0.105	0.054	1.920	0.054	-0.002	0.211
25 1	0.444	0.121	3.660	0.000	0.206	0.681
26 0	0.152	0.087	1.750	0.080	-0.018	0.322
26 1	0.550	0.139	3.950	0.000	0.277	0.822
27 0	0.215	0.136	1.590	0.112	-0.051	0.481
27 1	0.652	0.155	4.220	0.000	0.349	0.955
28 0	0.296	0.199	1.490	0.136	-0.093	0.686
28 1	0.742	0.159	4.680	0.000	0.431	1.052
29 0	0.392	0.266	1.470	0.140	-0.129	0.913
29 1	0.815	0.149	5.460	0.000	0.522	1.107
30 0	0.497	0.322	1.550	0.122	-0.133	1.127
30 1	0.871	0.131	6.670	0.000	0.615	1.127
31 0	0.068	0.066	1.020	0.306	-0.062	0.197
31 1	0.331	0.210	1.570	0.115	-0.081	0.743
32 0	0.100	0.087	1.140	0.252	-0.071	0.271
32 1	0.431	0.205	2.100	0.036	0.029	0.834
33 0	0.146	0.115	1.260	0.206	-0.080	0.372
33 1	0.538	0.188	2.850	0.004	0.168	0.907
34 0	0.207	0.151	1.370	0.170	-0.089	0.503
34 1	0.641	0.166	3.860	0.000	0.315	0.966
35 0	0.286	0.195	1.470	0.142	-0.095	0.667
35 1	0.732	0.144	5.080	0.000	0.449	1.015
36 0	0.380	0.241	1.580	0.114	-0.091	0.852
36 1	0.807	0.124	6.520	0.000	0.565	1.050
37 0	0.485	0.279	1.740	0.083	-0.063	1.032
37 1	0.865	0.104	8.300	0.000	0.661	1.069
38 0	0.590	0.299	1.970	0.048	0.004	1.177
38 1	0.908	0.085	10.640	0.000	0.740	1.075
39 0	0.688	0.294	2.340	0.019	0.111	1.265
39 1	0.938	0.068	13.840	0.000	0.805	1.071
40 0	0.772	0.268	2.890	0.004	0.248	1.296
40 1	0.958	0.052	18.310	0.000	0.856	1.061

Table 0.51 adj preds mri 4-5, psa and age

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()
1._at : ageatstudy~y = 40
prebiopsypsa = 0
2._at : ageatstudy~y = 40
prebiopsypsa = 1
3._at : ageatstudy~y = 40
prebiopsypsa = 2
4._at : ageatstudy~y = 40
prebiopsypsa = 3
5._at : ageatstudy~y = 40
prebiopsypsa = 4
6._at : ageatstudy~y = 40
prebiopsypsa = 5
7._at : ageatstudy~y = 40
prebiopsypsa = 6
8._at : ageatstudy~y = 40

prebiopsypsa = 7
9._at : ageatstudy~y = 40
prebiopsypsa = 8
10._at : ageatstudy~y = 40
prebiopsypsa = 9
11._at : ageatstudy~y = 50
prebiopsypsa = 0
12._at : ageatstudy~y = 50
prebiopsypsa = 1
13._at : ageatstudy~y = 50
prebiopsypsa = 2
14._at : ageatstudy~y = 50
prebiopsypsa = 3
15._at : ageatstudy~y = 50
prebiopsypsa = 4
16._at : ageatstudy~y = 50
prebiopsypsa = 5
17._at : ageatstudy~y = 50
prebiopsypsa = 6
18._at : ageatstudy~y = 50
prebiopsypsa = 7
19._at : ageatstudy~y = 50
prebiopsypsa = 8
20._at : ageatstudy~y = 50
prebiopsypsa = 9
21._at : ageatstudy~y = 60
prebiopsypsa = 0
22._at : ageatstudy~y = 60
prebiopsypsa = 1
23._at : ageatstudy~y = 60
prebiopsypsa = 2
24._at : ageatstudy~y = 60
prebiopsypsa = 3
25._at : ageatstudy~y = 60
prebiopsypsa = 4
26._at : ageatstudy~y = 60
prebiopsypsa = 5
27._at : ageatstudy~y = 60
prebiopsypsa = 6
28._at : ageatstudy~y = 60
prebiopsypsa = 7
29._at : ageatstudy~y = 60
prebiopsypsa = 8
30._at : ageatstudy~y = 60
prebiopsypsa = 9
31._at : ageatstudy~y = 70
prebiopsypsa = 0
32._at : ageatstudy~y = 70
prebiopsypsa = 1
33._at : ageatstudy~y = 70
prebiopsypsa = 2
34._at : ageatstudy~y = 70

prebiopsypsa = 3
35._at : ageatstudy~y = 70
prebiopsypsa = 4
36._at : ageatstudy~y = 70
prebiopsypsa = 5
37._at : ageatstudy~y = 70
prebiopsypsa = 6
38._at : ageatstudy~y = 70
prebiopsypsa = 7
39._at : ageatstudy~y = 70
prebiopsypsa = 8
40._at : ageatstudy~y = 70
prebiopsypsa = 9

	df	chi2	P>chi2
abnormalMRI45@_at			
1	1	0.360	0.550
2	1	0.400	0.528
3	1	0.440	0.509
4	1	0.470	0.492
5	1	0.500	0.478
6	1	0.530	0.465
7	1	0.570	0.450
8	1	0.620	0.429
9	1	0.720	0.395
10	1	0.920	0.337
11	1	0.760	0.383
12	1	0.960	0.328
13	1	1.180	0.277
14	1	1.430	0.233
15	1	1.670	0.196
16	1	1.930	0.165
17	1	2.300	0.129
18	1	2.980	0.084
19	1	4.470	0.035
20	1	7.520	0.006
21	1	1.640	0.201
22	1	2.510	0.113
23	1	3.830	0.050
24	1	5.370	0.021
25	1	6.720	0.010
26	1	7.910	0.005
27	1	9.030	0.003
28	1	8.570	0.003
29	1	5.420	0.020
30	1	2.700	0.100
31	1	2.440	0.118
32	1	4.250	0.039
33	1	7.090	0.008
34	1	9.510	0.002
35	1	8.700	0.003
36	1	5.670	0.017
37	1	3.190	0.074
38	1	1.800	0.180
39	1	1.080	0.299
40	1	0.700	0.404
Joint	4	11.730	0.019

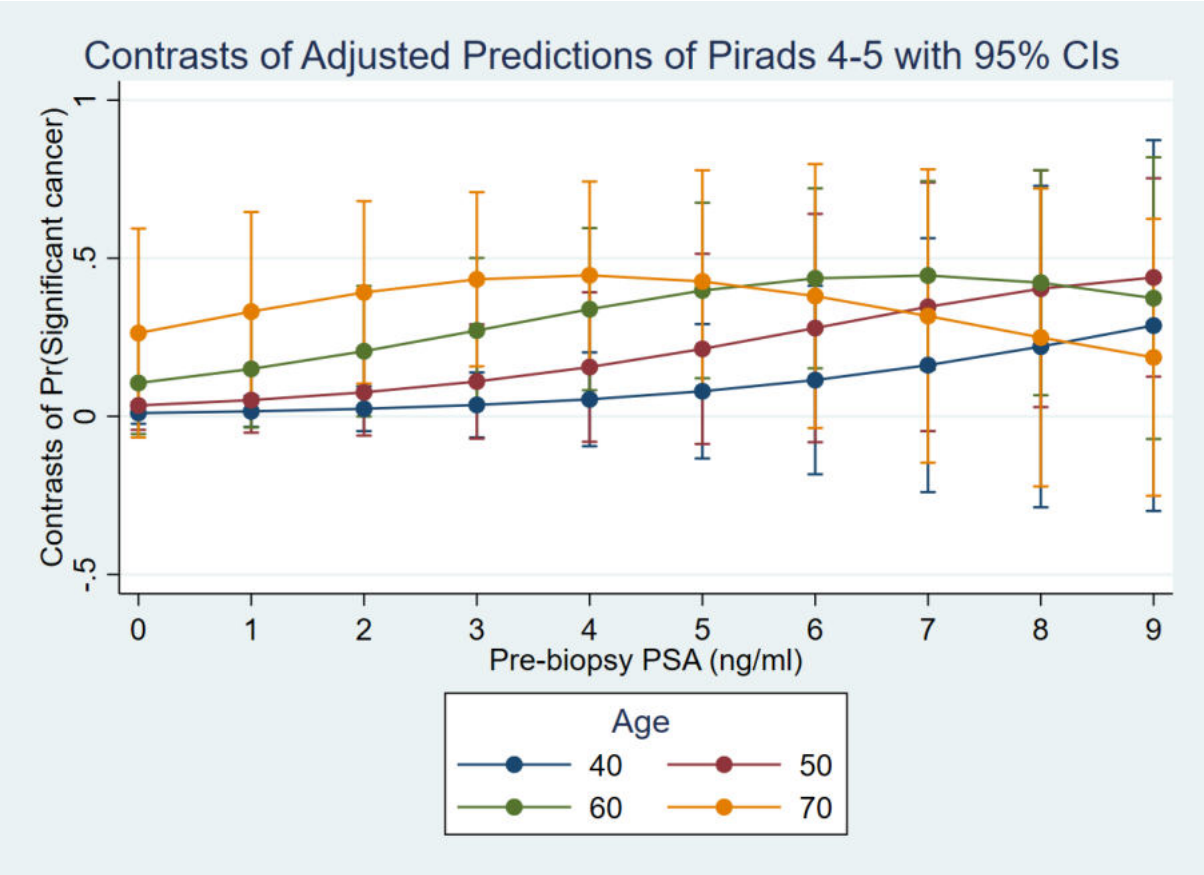
Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()
1._at : ageatstudy~y = 40
prebiopsypsa = 0
2._at : ageatstudy~y = 40
prebiopsypsa = 1
3._at : ageatstudy~y = 40
prebiopsypsa = 2
4._at : ageatstudy~y = 40
prebiopsypsa = 3
5._at : ageatstudy~y = 40
prebiopsypsa = 4
6._at : ageatstudy~y = 40
prebiopsypsa = 5
7._at : ageatstudy~y = 40
prebiopsypsa = 6
8._at : ageatstudy~y = 40
prebiopsypsa = 7
9._at : ageatstudy~y = 40
prebiopsypsa = 8
10._at : ageatstudy~y = 40
prebiopsypsa = 9
11._at : ageatstudy~y = 50
prebiopsypsa = 0
12._at : ageatstudy~y = 50
prebiopsypsa = 1
13._at : ageatstudy~y = 50
prebiopsypsa = 2
14._at : ageatstudy~y = 50
prebiopsypsa = 3
15._at : ageatstudy~y = 50
prebiopsypsa = 4
16._at : ageatstudy~y = 50
prebiopsypsa = 5
17._at : ageatstudy~y = 50
prebiopsypsa = 6
18._at : ageatstudy~y = 50
prebiopsypsa = 7
19._at : ageatstudy~y = 50
prebiopsypsa = 8
20._at : ageatstudy~y = 50
prebiopsypsa = 9
21._at : ageatstudy~y = 60
prebiopsypsa = 0
22._at : ageatstudy~y = 60
prebiopsypsa = 1
23._at : ageatstudy~y = 60
prebiopsypsa = 2
24._at : ageatstudy~y = 60
prebiopsypsa = 3
25._at : ageatstudy~y = 60
prebiopsypsa = 4
26._at : ageatstudy~y = 60
prebiopsypsa = 5
27._at : ageatstudy~y = 60
prebiopsypsa = 6
28._at : ageatstudy~y = 60

	prebiopsypsa	=	7
29._at	: ageatstudy~y	=	60
	prebiopsypsa	=	8
30._at	: ageatstudy~y	=	60
	prebiopsypsa	=	9
31._at	: ageatstudy~y	=	70
	prebiopsypsa	=	0
32._at	: ageatstudy~y	=	70
	prebiopsypsa	=	1
33._at	: ageatstudy~y	=	70
	prebiopsypsa	=	2
34._at	: ageatstudy~y	=	70
	prebiopsypsa	=	3
35._at	: ageatstudy~y	=	70
	prebiopsypsa	=	4
36._at	: ageatstudy~y	=	70
	prebiopsypsa	=	5
37._at	: ageatstudy~y	=	70
	prebiopsypsa	=	6
38._at	: ageatstudy~y	=	70
	prebiopsypsa	=	7
39._at	: ageatstudy~y	=	70
	prebiopsypsa	=	8
40._at	: ageatstudy~y	=	70
	prebiopsypsa	=	9

Delta-method

	Contrast	Std.Err.	z	P>z
abnormalMRI45@_at				
(1 vs base) 1	0.010	0.017	0.600	0.550
(1 vs base) 2	0.016	0.025	0.630	0.528
(1 vs base) 3	0.024	0.036	0.660	0.509
(1 vs base) 4	0.036	0.052	0.690	0.492
(1 vs base) 5	0.054	0.076	0.710	0.478
(1 vs base) 6	0.079	0.108	0.730	0.465
(1 vs base) 7	0.115	0.152	0.750	0.450
(1 vs base) 8	0.162	0.205	0.790	0.429
(1 vs base) 9	0.221	0.259	0.850	0.395
(1 vs base) 10	0.287	0.299	0.960	0.337
(1 vs base) 11	0.034	0.039	0.870	0.383
(1 vs base) 12	0.051	0.053	0.980	0.328
(1 vs base) 13	0.076	0.070	1.090	0.277
(1 vs base) 14	0.110	0.092	1.190	0.232
(1 vs base) 15	0.156	0.121	1.290	0.196
(1 vs base) 16	0.213	0.153	1.390	0.165
(1 vs base) 17	0.279	0.184	1.520	0.129
(1 vs base) 18	0.346	0.201	1.730	0.084
(1 vs base) 19	0.404	0.191	2.110	0.035
(1 vs base) 20	0.439	0.160	2.740	0.006
(1 vs base) 21	0.106	0.083	1.280	0.201
(1 vs base) 22	0.150	0.094	1.590	0.113
(1 vs base) 23	0.206	0.105	1.960	0.050
(1 vs base) 24	0.271	0.117	2.320	0.021
(1 vs base) 25	0.339	0.131	2.590	0.010
(1 vs base) 26	0.398	0.142	2.810	0.005
(1 vs base) 27	0.436	0.145	3.010	0.003
(1 vs base) 28	0.445	0.152	2.930	0.003
(1 vs base) 29	0.423	0.182	2.330	0.020
(1 vs base) 30	0.374	0.227	1.640	0.100
(1 vs base) 31	0.263	0.168	1.560	0.118
(1 vs base) 32	0.331	0.161	2.060	0.039

(1 vs base) 33	0.392	0.147	2.660	0.008
(1 vs base) 34	0.433	0.140	3.080	0.002
(1 vs base) 35	0.446	0.151	2.950	0.003
(1 vs base) 36	0.427	0.179	2.380	0.017
(1 vs base) 37	0.380	0.213	1.790	0.074
(1 vs base) 38	0.317	0.237	1.340	0.180
(1 vs base) 39	0.249	0.240	1.040	0.300
(1 vs base) 40	0.186	0.223	0.830	0.404



Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(canceranybiopsy), predict()
1._at : prebiopsypsa = 0
ageatstudy~y = 40
2._at : prebiopsypsa = 0
ageatstudy~y = 50
3._at : prebiopsypsa = 0
ageatstudy~y = 60
4._at : prebiopsypsa = 0
ageatstudy~y = 70
5._at : prebiopsypsa = 1
ageatstudy~y = 40

6._at : prebiopsypsa = 1
ageatstudy~y = 50
7._at : prebiopsypsa = 1
ageatstudy~y = 60
8._at : prebiopsypsa = 1
ageatstudy~y = 70
9._at : prebiopsypsa = 2
ageatstudy~y = 40
10._at : prebiopsypsa = 2
ageatstudy~y = 50
11._at : prebiopsypsa = 2
ageatstudy~y = 60
12._at : prebiopsypsa = 2
ageatstudy~y = 70
13._at : prebiopsypsa = 3
ageatstudy~y = 40
14._at : prebiopsypsa = 3
ageatstudy~y = 50
15._at : prebiopsypsa = 3
ageatstudy~y = 60
16._at : prebiopsypsa = 3
ageatstudy~y = 70
17._at : prebiopsypsa = 4
ageatstudy~y = 40
18._at : prebiopsypsa = 4
ageatstudy~y = 50
19._at : prebiopsypsa = 4
ageatstudy~y = 60
20._at : prebiopsypsa = 4
ageatstudy~y = 70
21._at : prebiopsypsa = 5
ageatstudy~y = 40
22._at : prebiopsypsa = 5
ageatstudy~y = 50
23._at : prebiopsypsa = 5
ageatstudy~y = 60
24._at : prebiopsypsa = 5
ageatstudy~y = 70
25._at : prebiopsypsa = 6
ageatstudy~y = 40
26._at : prebiopsypsa = 6
ageatstudy~y = 50
27._at : prebiopsypsa = 6
ageatstudy~y = 60
28._at : prebiopsypsa = 6
ageatstudy~y = 70
29._at : prebiopsypsa = 7
ageatstudy~y = 40
30._at : prebiopsypsa = 7
ageatstudy~y = 50
31._at : prebiopsypsa = 7
ageatstudy~y = 60
32._at : prebiopsypsa = 7
ageatstudy~y = 70
33._at : prebiopsypsa = 8
ageatstudy~y = 40
34._at : prebiopsypsa = 8
ageatstudy~y = 50
35._at : prebiopsypsa = 8
ageatstudy~y = 60
36._at : prebiopsypsa = 8
ageatstudy~y = 70

37._at : prebiopsypsa = 9
ageatstudy~y = 40
38._at : prebiopsypsa = 9
ageatstudy~y = 50
39._at : prebiopsypsa = 9
ageatstudy~y = 60
40._at : prebiopsypsa = 9
ageatstudy~y = 70

Delta-method

	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#abnormalMRI						
1#N	0.125	0.048	2.630	0.009	0.032	0.218
1#Y	0.274	0.110	2.480	0.013	0.057	0.490
2#N	0.143	0.040	3.590	0.000	0.065	0.221
2#Y	0.305	0.094	3.230	0.001	0.120	0.491
3#N	0.163	0.056	2.880	0.004	0.052	0.273
3#Y	0.339	0.109	3.100	0.002	0.124	0.554
4#N	0.185	0.094	1.970	0.049	0.001	0.369
4#Y	0.374	0.153	2.440	0.015	0.074	0.675
5#N	0.159	0.056	2.830	0.005	0.049	0.269
5#Y	0.333	0.116	2.880	0.004	0.106	0.559
6#N	0.181	0.039	4.590	0.000	0.103	0.258
6#Y	0.368	0.087	4.240	0.000	0.198	0.538
7#N	0.205	0.055	3.720	0.000	0.097	0.312
7#Y	0.404	0.095	4.240	0.000	0.217	0.591
8#N	0.231	0.098	2.350	0.019	0.038	0.424
8#Y	0.442	0.140	3.150	0.002	0.167	0.717
9#N	0.200	0.072	2.790	0.005	0.060	0.340
9#Y	0.397	0.124	3.200	0.001	0.154	0.641
10#N	0.226	0.047	4.830	0.000	0.134	0.317
10#Y	0.435	0.083	5.210	0.000	0.272	0.598
11#N	0.254	0.058	4.410	0.000	0.141	0.367
11#Y	0.473	0.083	5.720	0.000	0.311	0.636
12#N	0.284	0.104	2.730	0.006	0.080	0.489
12#Y	0.512	0.126	4.060	0.000	0.265	0.759
13#N	0.249	0.095	2.620	0.009	0.062	0.435
13#Y	0.466	0.137	3.400	0.001	0.197	0.735
14#N	0.279	0.066	4.230	0.000	0.149	0.408
14#Y	0.505	0.089	5.670	0.000	0.330	0.679
15#N	0.311	0.070	4.460	0.000	0.174	0.447
15#Y	0.543	0.078	6.950	0.000	0.390	0.696
16#N	0.345	0.114	3.030	0.002	0.122	0.568
16#Y	0.581	0.115	5.080	0.000	0.357	0.806
17#N	0.305	0.126	2.420	0.016	0.058	0.551
17#Y	0.536	0.152	3.530	0.000	0.238	0.834
18#N	0.338	0.095	3.570	0.000	0.153	0.524
18#Y	0.574	0.102	5.640	0.000	0.375	0.774
19#N	0.374	0.092	4.060	0.000	0.193	0.554
19#Y	0.611	0.083	7.320	0.000	0.448	0.775
20#N	0.410	0.128	3.200	0.001	0.159	0.661
20#Y	0.648	0.108	6.010	0.000	0.436	0.859
21#N	0.367	0.161	2.270	0.023	0.051	0.683
21#Y	0.605	0.165	3.660	0.000	0.281	0.929
22#N	0.403	0.129	3.130	0.002	0.151	0.656
22#Y	0.641	0.116	5.510	0.000	0.413	0.869
23#N	0.441	0.121	3.660	0.000	0.205	0.678
23#Y	0.676	0.094	7.200	0.000	0.492	0.860
24#N	0.480	0.146	3.290	0.001	0.193	0.766
24#Y	0.709	0.105	6.730	0.000	0.502	0.915
25#N	0.434	0.198	2.200	0.028	0.047	0.822

25#Y	0.669	0.174	3.850	0.000	0.328	1.010
26#N	0.472	0.163	2.900	0.004	0.153	0.792
26#Y	0.703	0.128	5.500	0.000	0.452	0.953
27#N	0.511	0.150	3.410	0.001	0.218	0.804
27#Y	0.734	0.103	7.120	0.000	0.532	0.936
28#N	0.549	0.164	3.350	0.001	0.228	0.871
28#Y	0.763	0.104	7.310	0.000	0.558	0.967
29#N	0.504	0.230	2.190	0.029	0.053	0.955
29#Y	0.728	0.176	4.130	0.000	0.382	1.074
30#N	0.542	0.193	2.810	0.005	0.164	0.921
30#Y	0.758	0.133	5.690	0.000	0.496	1.019
31#N	0.580	0.175	3.320	0.001	0.238	0.923
31#Y	0.785	0.108	7.270	0.000	0.573	0.997
32#N	0.617	0.179	3.460	0.001	0.267	0.968
32#Y	0.810	0.102	7.920	0.000	0.609	1.010
33#N	0.573	0.255	2.250	0.024	0.074	1.072
33#Y	0.780	0.172	4.530	0.000	0.443	1.117
34#N	0.611	0.215	2.840	0.005	0.189	1.032
34#Y	0.805	0.133	6.070	0.000	0.546	1.065
35#N	0.647	0.192	3.370	0.001	0.271	1.023
35#Y	0.828	0.108	7.690	0.000	0.617	1.040
36#N	0.681	0.187	3.650	0.000	0.315	1.047
36#Y	0.849	0.098	8.680	0.000	0.658	1.041
37#N	0.640	0.268	2.390	0.017	0.115	1.166
37#Y	0.824	0.162	5.090	0.000	0.507	1.142
38#N	0.675	0.227	2.980	0.003	0.230	1.119
38#Y	0.846	0.127	6.680	0.000	0.598	1.094
39#N	0.708	0.200	3.550	0.000	0.317	1.099
39#Y	0.865	0.103	8.390	0.000	0.663	1.067
40#N	0.739	0.188	3.940	0.000	0.371	1.106
40#Y	0.882	0.091	9.680	0.000	0.703	1.060

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(canceranybiopsy), predict()
1._at : prebiopsypsa = 0
ageatstudy~y = 40
2._at : prebiopsypsa = 0
ageatstudy~y = 50
3._at : prebiopsypsa = 0
ageatstudy~y = 60
4._at : prebiopsypsa = 0
ageatstudy~y = 70
5._at : prebiopsypsa = 1
ageatstudy~y = 40
6._at : prebiopsypsa = 1
ageatstudy~y = 50
7._at : prebiopsypsa = 1
ageatstudy~y = 60
8._at : prebiopsypsa = 1
ageatstudy~y = 70
9._at : prebiopsypsa = 2
ageatstudy~y = 40
10._at : prebiopsypsa = 2
ageatstudy~y = 50
11._at : prebiopsypsa = 2
ageatstudy~y = 60
12._at : prebiopsypsa = 2
ageatstudy~y = 70

13._at : prebiopsypsa = 3
ageatstudy~y = 40
14._at : prebiopsypsa = 3
ageatstudy~y = 50
15._at : prebiopsypsa = 3
ageatstudy~y = 60
16._at : prebiopsypsa = 3
ageatstudy~y = 70
17._at : prebiopsypsa = 4
ageatstudy~y = 40
18._at : prebiopsypsa = 4
ageatstudy~y = 50
19._at : prebiopsypsa = 4
ageatstudy~y = 60
20._at : prebiopsypsa = 4
ageatstudy~y = 70
21._at : prebiopsypsa = 5
ageatstudy~y = 40
22._at : prebiopsypsa = 5
ageatstudy~y = 50
23._at : prebiopsypsa = 5
ageatstudy~y = 60
24._at : prebiopsypsa = 5
ageatstudy~y = 70
25._at : prebiopsypsa = 6
ageatstudy~y = 40
26._at : prebiopsypsa = 6
ageatstudy~y = 50
27._at : prebiopsypsa = 6
ageatstudy~y = 60
28._at : prebiopsypsa = 6
ageatstudy~y = 70
29._at : prebiopsypsa = 7
ageatstudy~y = 40
30._at : prebiopsypsa = 7
ageatstudy~y = 50
31._at : prebiopsypsa = 7
ageatstudy~y = 60
32._at : prebiopsypsa = 7
ageatstudy~y = 70
33._at : prebiopsypsa = 8
ageatstudy~y = 40
34._at : prebiopsypsa = 8
ageatstudy~y = 50
35._at : prebiopsypsa = 8
ageatstudy~y = 60
36._at : prebiopsypsa = 8
ageatstudy~y = 70
37._at : prebiopsypsa = 9
ageatstudy~y = 40
38._at : prebiopsypsa = 9
ageatstudy~y = 50
39._at : prebiopsypsa = 9
ageatstudy~y = 60
40._at : prebiopsypsa = 9
ageatstudy~y = 70

	df	chi2	P>chi2
abnormalMRI@_at			
1	1	3.080	0.079
2	1	3.850	0.050

3	1	4.070	0.044
4	1	3.870	0.049
5	1	3.730	0.053
6	1	4.680	0.030
7	1	5.040	0.025
8	1	5.000	0.025
9	1	4.400	0.036
10	1	5.360	0.021
11	1	5.770	0.016
12	1	5.880	0.015
13	1	5.090	0.024
14	1	5.870	0.015
15	1	6.170	0.013
16	1	6.260	0.012
17	1	5.770	0.016
18	1	6.180	0.013
19	1	6.230	0.013
20	1	6.060	0.014
21	1	6.210	0.013
22	1	6.150	0.013
23	1	5.880	0.015
24	1	5.350	0.021
25	1	5.860	0.015
26	1	5.480	0.019
27	1	5.010	0.025
28	1	4.310	0.038
29	1	4.600	0.032
30	1	4.240	0.039
31	1	3.830	0.050
32	1	3.220	0.072
33	1	3.130	0.077
34	1	2.960	0.085
35	1	2.720	0.099
36	1	2.320	0.128
37	1	2.040	0.153
38	1	1.990	0.158
39	1	1.880	0.170
40	1	1.650	0.199
Joint	4	7.510	0.111

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(canceranybiopsy), predict()
1._at : prebiopsypsa = 0
ageatstudy~y = 40
2._at : prebiopsypsa = 0
ageatstudy~y = 50
3._at : prebiopsypsa = 0
ageatstudy~y = 60
4._at : prebiopsypsa = 0
ageatstudy~y = 70
5._at : prebiopsypsa = 1
ageatstudy~y = 40
6._at : prebiopsypsa = 1
ageatstudy~y = 50
7._at : prebiopsypsa = 1
ageatstudy~y = 60
8._at : prebiopsypsa = 1
ageatstudy~y = 70

9._at : prebiopsypsa = 2
ageatstudy~y = 40
10._at : prebiopsypsa = 2
ageatstudy~y = 50
11._at : prebiopsypsa = 2
ageatstudy~y = 60
12._at : prebiopsypsa = 2
ageatstudy~y = 70
13._at : prebiopsypsa = 3
ageatstudy~y = 40
14._at : prebiopsypsa = 3
ageatstudy~y = 50
15._at : prebiopsypsa = 3
ageatstudy~y = 60
16._at : prebiopsypsa = 3
ageatstudy~y = 70
17._at : prebiopsypsa = 4
ageatstudy~y = 40
18._at : prebiopsypsa = 4
ageatstudy~y = 50
19._at : prebiopsypsa = 4
ageatstudy~y = 60
20._at : prebiopsypsa = 4
ageatstudy~y = 70
21._at : prebiopsypsa = 5
ageatstudy~y = 40
22._at : prebiopsypsa = 5
ageatstudy~y = 50
23._at : prebiopsypsa = 5
ageatstudy~y = 60
24._at : prebiopsypsa = 5
ageatstudy~y = 70
25._at : prebiopsypsa = 6
ageatstudy~y = 40
26._at : prebiopsypsa = 6
ageatstudy~y = 50
27._at : prebiopsypsa = 6
ageatstudy~y = 60
28._at : prebiopsypsa = 6
ageatstudy~y = 70
29._at : prebiopsypsa = 7
ageatstudy~y = 40
30._at : prebiopsypsa = 7
ageatstudy~y = 50
31._at : prebiopsypsa = 7
ageatstudy~y = 60
32._at : prebiopsypsa = 7
ageatstudy~y = 70
33._at : prebiopsypsa = 8
ageatstudy~y = 40
34._at : prebiopsypsa = 8
ageatstudy~y = 50
35._at : prebiopsypsa = 8
ageatstudy~y = 60
36._at : prebiopsypsa = 8
ageatstudy~y = 70
37._at : prebiopsypsa = 9
ageatstudy~y = 40
38._at : prebiopsypsa = 9
ageatstudy~y = 50
39._at : prebiopsypsa = 9
ageatstudy~y = 60

40._at : prebiopsypsa = 9
ageatstudy~y = 70

Delta-method

	Contrast	Std.Err.	z	P>z
abnormalMRI@_at				
(Y vs base) 1	0.149	0.085	1.750	0.079
(Y vs base) 2	0.163	0.083	1.960	0.050
(Y vs base) 3	0.176	0.087	2.020	0.044
(Y vs base) 4	0.190	0.096	1.970	0.049
(Y vs base) 5	0.174	0.090	1.930	0.053
(Y vs base) 6	0.187	0.087	2.160	0.031
(Y vs base) 7	0.200	0.089	2.250	0.025
(Y vs base) 8	0.211	0.094	2.240	0.025
(Y vs base) 9	0.197	0.094	2.100	0.036
(Y vs base) 10	0.209	0.090	2.320	0.021
(Y vs base) 11	0.219	0.091	2.400	0.016
(Y vs base) 12	0.227	0.094	2.430	0.015
(Y vs base) 13	0.218	0.096	2.260	0.024
(Y vs base) 14	0.226	0.093	2.420	0.015
(Y vs base) 15	0.233	0.094	2.480	0.013
(Y vs base) 16	0.237	0.095	2.500	0.012
(Y vs base) 17	0.232	0.096	2.400	0.016
(Y vs base) 18	0.236	0.095	2.490	0.013
(Y vs base) 19	0.238	0.095	2.500	0.013
(Y vs base) 20	0.237	0.096	2.460	0.014
(Y vs base) 21	0.238	0.095	2.490	0.013
(Y vs base) 22	0.237	0.096	2.480	0.013
(Y vs base) 23	0.234	0.097	2.420	0.015
(Y vs base) 24	0.229	0.099	2.310	0.021
(Y vs base) 25	0.235	0.097	2.420	0.015
(Y vs base) 26	0.230	0.098	2.340	0.019
(Y vs base) 27	0.223	0.100	2.240	0.025
(Y vs base) 28	0.213	0.103	2.080	0.038
(Y vs base) 29	0.224	0.105	2.140	0.032
(Y vs base) 30	0.215	0.105	2.060	0.039
(Y vs base) 31	0.205	0.105	1.960	0.050
(Y vs base) 32	0.192	0.107	1.800	0.073
(Y vs base) 33	0.207	0.117	1.770	0.077
(Y vs base) 34	0.195	0.113	1.720	0.085
(Y vs base) 35	0.182	0.110	1.650	0.099
(Y vs base) 36	0.168	0.111	1.520	0.128
(Y vs base) 37	0.184	0.129	1.430	0.153
(Y vs base) 38	0.171	0.121	1.410	0.158
(Y vs base) 39	0.157	0.114	1.370	0.170
(Y vs base) 40	0.143	0.111	1.280	0.199

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(canceranybiopsy), predict()
1._at : prebiopsypsa = 0
ageatstudy~y = 40
2._at : prebiopsypsa = 0
ageatstudy~y = 50
3._at : prebiopsypsa = 0
ageatstudy~y = 60
4._at : prebiopsypsa = 0
ageatstudy~y = 70
5._at : prebiopsypsa = 1

ageatstudy~y = 40
6._at : prebiopsypsa = 1
ageatstudy~y = 50
7._at : prebiopsypsa = 1
ageatstudy~y = 60
8._at : prebiopsypsa = 1
ageatstudy~y = 70
9._at : prebiopsypsa = 2
ageatstudy~y = 40
10._at : prebiopsypsa = 2
ageatstudy~y = 50
11._at : prebiopsypsa = 2
ageatstudy~y = 60
12._at : prebiopsypsa = 2
ageatstudy~y = 70
13._at : prebiopsypsa = 3
ageatstudy~y = 40
14._at : prebiopsypsa = 3
ageatstudy~y = 50
15._at : prebiopsypsa = 3
ageatstudy~y = 60
16._at : prebiopsypsa = 3
ageatstudy~y = 70
17._at : prebiopsypsa = 4
ageatstudy~y = 40
18._at : prebiopsypsa = 4
ageatstudy~y = 50
19._at : prebiopsypsa = 4
ageatstudy~y = 60
20._at : prebiopsypsa = 4
ageatstudy~y = 70
21._at : prebiopsypsa = 5
ageatstudy~y = 40
22._at : prebiopsypsa = 5
ageatstudy~y = 50
23._at : prebiopsypsa = 5
ageatstudy~y = 60
24._at : prebiopsypsa = 5
ageatstudy~y = 70
25._at : prebiopsypsa = 6
ageatstudy~y = 40
26._at : prebiopsypsa = 6
ageatstudy~y = 50
27._at : prebiopsypsa = 6
ageatstudy~y = 60
28._at : prebiopsypsa = 6
ageatstudy~y = 70
29._at : prebiopsypsa = 7
ageatstudy~y = 40
30._at : prebiopsypsa = 7
ageatstudy~y = 50
31._at : prebiopsypsa = 7
ageatstudy~y = 60
32._at : prebiopsypsa = 7
ageatstudy~y = 70
33._at : prebiopsypsa = 8
ageatstudy~y = 40
34._at : prebiopsypsa = 8
ageatstudy~y = 50
35._at : prebiopsypsa = 8
ageatstudy~y = 60
36._at : prebiopsypsa = 8

```
          ageatstudy~y   =          70
37._at     : prebiopsypsa   =           9
          ageatstudy~y   =          40
38._at     : prebiopsypsa   =           9
          ageatstudy~y   =          50
39._at     : prebiopsypsa   =           9
          ageatstudy~y   =          60
40._at     : prebiopsypsa   =           9
          ageatstudy~y   =          70
```

Delta-method

	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#abnormalMRI45						
1 0	0.152	0.055	2.750	0.006	0.043	0.260
1 1	0.342	0.164	2.090	0.037	0.021	0.664
2 0	0.163	0.043	3.820	0.000	0.080	0.247
2 1	0.362	0.140	2.590	0.010	0.088	0.636
3 0	0.175	0.059	2.980	0.003	0.060	0.291
3 1	0.382	0.141	2.710	0.007	0.105	0.659
4 0	0.188	0.095	1.980	0.048	0.002	0.375
4 1	0.403	0.170	2.360	0.018	0.069	0.737
5 0	0.195	0.063	3.060	0.002	0.070	0.319
5 1	0.412	0.168	2.450	0.014	0.083	0.742
6 0	0.208	0.039	5.300	0.000	0.131	0.286
6 1	0.434	0.134	3.240	0.001	0.172	0.696
7 0	0.223	0.056	3.990	0.000	0.113	0.333
7 1	0.455	0.128	3.560	0.000	0.204	0.706
8 0	0.238	0.100	2.370	0.018	0.042	0.435
8 1	0.477	0.156	3.060	0.002	0.171	0.782
9 0	0.246	0.079	3.120	0.002	0.091	0.400
9 1	0.487	0.171	2.850	0.004	0.152	0.822
10 0	0.262	0.044	5.910	0.000	0.175	0.349
10 1	0.508	0.128	3.970	0.000	0.257	0.759
11 0	0.279	0.057	4.930	0.000	0.168	0.390
11 1	0.530	0.114	4.630	0.000	0.306	0.754
12 0	0.297	0.107	2.790	0.005	0.088	0.506
12 1	0.551	0.139	3.980	0.000	0.280	0.823
13 0	0.306	0.103	2.980	0.003	0.105	0.507
13 1	0.561	0.173	3.250	0.001	0.223	0.900
14 0	0.324	0.064	5.080	0.000	0.199	0.450
14 1	0.583	0.125	4.660	0.000	0.337	0.828
15 0	0.344	0.068	5.060	0.000	0.211	0.477
15 1	0.604	0.105	5.750	0.000	0.398	0.809
16 0	0.363	0.116	3.140	0.002	0.136	0.591
16 1	0.624	0.123	5.070	0.000	0.383	0.865
17 0	0.373	0.133	2.800	0.005	0.112	0.634
17 1	0.634	0.172	3.670	0.000	0.296	0.971
18 0	0.393	0.094	4.200	0.000	0.210	0.577
18 1	0.653	0.125	5.230	0.000	0.409	0.898
19 0	0.414	0.090	4.580	0.000	0.237	0.592
19 1	0.673	0.101	6.650	0.000	0.474	0.871
20 0	0.435	0.130	3.360	0.001	0.181	0.690
20 1	0.692	0.111	6.210	0.000	0.473	0.910
21 0	0.445	0.166	2.690	0.007	0.120	0.770
21 1	0.700	0.169	4.140	0.000	0.369	1.031
22 0	0.467	0.127	3.680	0.000	0.218	0.716
22 1	0.718	0.125	5.750	0.000	0.473	0.963
23 0	0.488	0.118	4.130	0.000	0.257	0.720
23 1	0.735	0.100	7.320	0.000	0.538	0.932
24 0	0.510	0.146	3.490	0.000	0.223	0.797
24 1	0.752	0.103	7.270	0.000	0.549	0.954

25 0	0.520	0.196	2.660	0.008	0.137	0.903
25 1	0.759	0.162	4.700	0.000	0.442	1.076
26 0	0.542	0.157	3.440	0.001	0.233	0.850
26 1	0.775	0.123	6.320	0.000	0.535	1.015
27 0	0.563	0.145	3.890	0.000	0.280	0.847
27 1	0.789	0.099	7.940	0.000	0.594	0.984
28 0	0.584	0.162	3.610	0.000	0.267	0.901
28 1	0.803	0.097	8.270	0.000	0.613	0.994
29 0	0.594	0.217	2.730	0.006	0.168	1.020
29 1	0.810	0.150	5.390	0.000	0.515	1.104
30 0	0.615	0.181	3.410	0.001	0.261	0.969
30 1	0.823	0.117	7.040	0.000	0.594	1.052
31 0	0.635	0.164	3.860	0.000	0.313	0.958
31 1	0.835	0.096	8.690	0.000	0.647	1.023
32 0	0.655	0.172	3.800	0.000	0.317	0.993
32 1	0.847	0.090	9.360	0.000	0.669	1.024
33 0	0.664	0.229	2.910	0.004	0.216	1.112
33 1	0.852	0.136	6.270	0.000	0.586	1.118
34 0	0.683	0.193	3.540	0.000	0.304	1.062
34 1	0.862	0.108	7.990	0.000	0.651	1.074
35 0	0.702	0.175	4.010	0.000	0.359	1.045
35 1	0.872	0.090	9.710	0.000	0.696	1.049
36 0	0.719	0.175	4.100	0.000	0.376	1.063
36 1	0.882	0.083	10.650	0.000	0.719	1.044
37 0	0.728	0.228	3.190	0.001	0.281	1.174
37 1	0.886	0.120	7.400	0.000	0.651	1.120
38 0	0.744	0.195	3.820	0.000	0.362	1.126
38 1	0.894	0.097	9.240	0.000	0.705	1.084
39 0	0.760	0.176	4.330	0.000	0.416	1.105
39 1	0.902	0.081	11.070	0.000	0.743	1.062
40 0	0.776	0.171	4.540	0.000	0.441	1.111
40 1	0.910	0.074	12.290	0.000	0.765	1.055

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(canceranybiopsy), predict()
1._at : prebiopsypsa = 0
ageatstudy~y = 40
2._at : prebiopsypsa = 0
ageatstudy~y = 50
3._at : prebiopsypsa = 0
ageatstudy~y = 60
4._at : prebiopsypsa = 0
ageatstudy~y = 70
5._at : prebiopsypsa = 1
ageatstudy~y = 40
6._at : prebiopsypsa = 1
ageatstudy~y = 50
7._at : prebiopsypsa = 1
ageatstudy~y = 60
8._at : prebiopsypsa = 1
ageatstudy~y = 70
9._at : prebiopsypsa = 2
ageatstudy~y = 40
10._at : prebiopsypsa = 2
ageatstudy~y = 50
11._at : prebiopsypsa = 2
ageatstudy~y = 60
12._at : prebiopsypsa = 2
ageatstudy~y = 70

13._at : prebiopsypsa = 3
ageatstudy~y = 40
14._at : prebiopsypsa = 3
ageatstudy~y = 50
15._at : prebiopsypsa = 3
ageatstudy~y = 60
16._at : prebiopsypsa = 3
ageatstudy~y = 70
17._at : prebiopsypsa = 4
ageatstudy~y = 40
18._at : prebiopsypsa = 4
ageatstudy~y = 50
19._at : prebiopsypsa = 4
ageatstudy~y = 60
20._at : prebiopsypsa = 4
ageatstudy~y = 70
21._at : prebiopsypsa = 5
ageatstudy~y = 40
22._at : prebiopsypsa = 5
ageatstudy~y = 50
23._at : prebiopsypsa = 5
ageatstudy~y = 60
24._at : prebiopsypsa = 5
ageatstudy~y = 70
25._at : prebiopsypsa = 6
ageatstudy~y = 40
26._at : prebiopsypsa = 6
ageatstudy~y = 50
27._at : prebiopsypsa = 6
ageatstudy~y = 60
28._at : prebiopsypsa = 6
ageatstudy~y = 70
29._at : prebiopsypsa = 7
ageatstudy~y = 40
30._at : prebiopsypsa = 7
ageatstudy~y = 50
31._at : prebiopsypsa = 7
ageatstudy~y = 60
32._at : prebiopsypsa = 7
ageatstudy~y = 70
33._at : prebiopsypsa = 8
ageatstudy~y = 40
34._at : prebiopsypsa = 8
ageatstudy~y = 50
35._at : prebiopsypsa = 8
ageatstudy~y = 60
36._at : prebiopsypsa = 8
ageatstudy~y = 70
37._at : prebiopsypsa = 9
ageatstudy~y = 40
38._at : prebiopsypsa = 9
ageatstudy~y = 50
39._at : prebiopsypsa = 9
ageatstudy~y = 60
40._at : prebiopsypsa = 9
ageatstudy~y = 70

	df	chi2	P>chi2
abnormalMRI45@_at			
1	1	2.090	0.148
2	1	2.540	0.111

3	1	2.830	0.092
4	1	2.930	0.087
5	1	2.580	0.108
6	1	3.080	0.079
7	1	3.450	0.063
8	1	3.660	0.056
9	1	3.160	0.075
10	1	3.630	0.057
11	1	3.980	0.046
12	1	4.210	0.040
13	1	3.840	0.050
14	1	4.170	0.041
15	1	4.370	0.037
16	1	4.470	0.035
17	1	4.500	0.034
18	1	4.590	0.032
19	1	4.560	0.033
20	1	4.370	0.036
21	1	4.780	0.029
22	1	4.660	0.031
23	1	4.400	0.036
24	1	3.930	0.047
25	1	4.250	0.039
26	1	4.120	0.042
27	1	3.800	0.051
28	1	3.240	0.072
29	1	3.160	0.075
30	1	3.160	0.075
31	1	2.940	0.087
32	1	2.490	0.115
33	1	2.150	0.143
34	1	2.220	0.136
35	1	2.120	0.145
36	1	1.840	0.175
37	1	1.450	0.229
38	1	1.540	0.215
39	1	1.510	0.220
40	1	1.350	0.246
Joint	4	9.750	0.045

Contrasts of adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(canceranybiopsy), predict()
1._at : prebiopsypsa = 0
ageatstudy~y = 40
2._at : prebiopsypsa = 0
ageatstudy~y = 50
3._at : prebiopsypsa = 0
ageatstudy~y = 60
4._at : prebiopsypsa = 0
ageatstudy~y = 70
5._at : prebiopsypsa = 1
ageatstudy~y = 40
6._at : prebiopsypsa = 1
ageatstudy~y = 50
7._at : prebiopsypsa = 1
ageatstudy~y = 60
8._at : prebiopsypsa = 1
ageatstudy~y = 70

9._at : prebiopsypsa = 2
ageatstudy~y = 40
10._at : prebiopsypsa = 2
ageatstudy~y = 50
11._at : prebiopsypsa = 2
ageatstudy~y = 60
12._at : prebiopsypsa = 2
ageatstudy~y = 70
13._at : prebiopsypsa = 3
ageatstudy~y = 40
14._at : prebiopsypsa = 3
ageatstudy~y = 50
15._at : prebiopsypsa = 3
ageatstudy~y = 60
16._at : prebiopsypsa = 3
ageatstudy~y = 70
17._at : prebiopsypsa = 4
ageatstudy~y = 40
18._at : prebiopsypsa = 4
ageatstudy~y = 50
19._at : prebiopsypsa = 4
ageatstudy~y = 60
20._at : prebiopsypsa = 4
ageatstudy~y = 70
21._at : prebiopsypsa = 5
ageatstudy~y = 40
22._at : prebiopsypsa = 5
ageatstudy~y = 50
23._at : prebiopsypsa = 5
ageatstudy~y = 60
24._at : prebiopsypsa = 5
ageatstudy~y = 70
25._at : prebiopsypsa = 6
ageatstudy~y = 40
26._at : prebiopsypsa = 6
ageatstudy~y = 50
27._at : prebiopsypsa = 6
ageatstudy~y = 60
28._at : prebiopsypsa = 6
ageatstudy~y = 70
29._at : prebiopsypsa = 7
ageatstudy~y = 40
30._at : prebiopsypsa = 7
ageatstudy~y = 50
31._at : prebiopsypsa = 7
ageatstudy~y = 60
32._at : prebiopsypsa = 7
ageatstudy~y = 70
33._at : prebiopsypsa = 8
ageatstudy~y = 40
34._at : prebiopsypsa = 8
ageatstudy~y = 50
35._at : prebiopsypsa = 8
ageatstudy~y = 60
36._at : prebiopsypsa = 8
ageatstudy~y = 70
37._at : prebiopsypsa = 9
ageatstudy~y = 40
38._at : prebiopsypsa = 9
ageatstudy~y = 50
39._at : prebiopsypsa = 9
ageatstudy~y = 60

40._at : prebiopsypsa = 9
ageatstudy~y = 70

Delta-method

	Contrast	Std.Err.	z	P>z
abnormalMRI45@_at				
(1 vs base) 1	0.190	0.132	1.450	0.148
(1 vs base) 2	0.199	0.125	1.590	0.111
(1 vs base) 3	0.207	0.123	1.680	0.092
(1 vs base) 4	0.214	0.125	1.710	0.087
(1 vs base) 5	0.218	0.136	1.610	0.108
(1 vs base) 6	0.225	0.128	1.760	0.079
(1 vs base) 7	0.232	0.125	1.860	0.063
(1 vs base) 8	0.238	0.124	1.910	0.056
(1 vs base) 9	0.241	0.135	1.780	0.075
(1 vs base) 10	0.246	0.129	1.910	0.057
(1 vs base) 11	0.250	0.126	1.990	0.046
(1 vs base) 12	0.254	0.124	2.050	0.040
(1 vs base) 13	0.256	0.131	1.960	0.050
(1 vs base) 14	0.258	0.126	2.040	0.041
(1 vs base) 15	0.260	0.124	2.090	0.037
(1 vs base) 16	0.261	0.123	2.110	0.035
(1 vs base) 17	0.261	0.123	2.120	0.034
(1 vs base) 18	0.260	0.121	2.140	0.032
(1 vs base) 19	0.258	0.121	2.140	0.033
(1 vs base) 20	0.256	0.122	2.090	0.037
(1 vs base) 21	0.255	0.117	2.190	0.029
(1 vs base) 22	0.251	0.116	2.160	0.031
(1 vs base) 23	0.247	0.118	2.100	0.036
(1 vs base) 24	0.242	0.122	1.980	0.047
(1 vs base) 25	0.239	0.116	2.060	0.039
(1 vs base) 26	0.233	0.115	2.030	0.042
(1 vs base) 27	0.226	0.116	1.950	0.051
(1 vs base) 28	0.219	0.122	1.800	0.072
(1 vs base) 29	0.216	0.121	1.780	0.075
(1 vs base) 30	0.208	0.117	1.780	0.075
(1 vs base) 31	0.200	0.117	1.710	0.087
(1 vs base) 32	0.192	0.121	1.580	0.115
(1 vs base) 33	0.188	0.128	1.470	0.143
(1 vs base) 34	0.179	0.120	1.490	0.136
(1 vs base) 35	0.171	0.117	1.460	0.145
(1 vs base) 36	0.162	0.120	1.350	0.175
(1 vs base) 37	0.158	0.132	1.200	0.229
(1 vs base) 38	0.150	0.121	1.240	0.215
(1 vs base) 39	0.142	0.116	1.230	0.220
(1 vs base) 40	0.134	0.115	1.160	0.246

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(canceranybiopsy), predict()
1._at : ageatstudy~y = 40
psad = 0
2._at : ageatstudy~y = 40
psad = .05
3._at : ageatstudy~y = 40
psad = .1
4._at : ageatstudy~y = 40
psad = .15
5._at : ageatstudy~y = 40

psad = .2
6._at : ageatstudy~y = 50
psad = 0
7._at : ageatstudy~y = 50
psad = .05
8._at : ageatstudy~y = 50
psad = .1
9._at : ageatstudy~y = 50
psad = .15
10._at : ageatstudy~y = 50
psad = .2
11._at : ageatstudy~y = 60
psad = 0
12._at : ageatstudy~y = 60
psad = .05
13._at : ageatstudy~y = 60
psad = .1
14._at : ageatstudy~y = 60
psad = .15
15._at : ageatstudy~y = 60
psad = .2
16._at : ageatstudy~y = 70
psad = 0
17._at : ageatstudy~y = 70
psad = .05
18._at : ageatstudy~y = 70
psad = .1
19._at : ageatstudy~y = 70
psad = .15
20._at : ageatstudy~y = 70
psad = .2

Delta-method

	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#abnormalMRI						
1#N	0.118	0.048	2.490	0.013	0.025	0.212
1#Y	0.267	0.114	2.350	0.019	0.044	0.489
2#N	0.160	0.057	2.820	0.005	0.049	0.271
2#Y	0.340	0.116	2.930	0.003	0.113	0.568
3#N	0.212	0.080	2.660	0.008	0.056	0.369
3#Y	0.422	0.129	3.280	0.001	0.170	0.675
4#N	0.277	0.120	2.310	0.021	0.041	0.512
4#Y	0.509	0.152	3.350	0.001	0.211	0.807
5#N	0.351	0.172	2.040	0.041	0.014	0.689
5#Y	0.595	0.177	3.350	0.001	0.247	0.942
6#N	0.152	0.041	3.680	0.000	0.071	0.234
6#Y	0.328	0.098	3.340	0.001	0.136	0.520
7#N	0.203	0.042	4.870	0.000	0.121	0.285
7#Y	0.408	0.084	4.850	0.000	0.243	0.573
8#N	0.265	0.065	4.100	0.000	0.139	0.392
8#Y	0.494	0.088	5.590	0.000	0.321	0.668
9#N	0.338	0.108	3.130	0.002	0.126	0.551
9#Y	0.581	0.111	5.220	0.000	0.363	0.799
10#N	0.420	0.161	2.610	0.009	0.105	0.736
10#Y	0.663	0.137	4.850	0.000	0.395	0.930
11#N	0.194	0.057	3.400	0.001	0.082	0.306
11#Y	0.395	0.105	3.760	0.000	0.189	0.601
12#N	0.254	0.057	4.480	0.000	0.143	0.366
12#Y	0.480	0.083	5.800	0.000	0.318	0.642
13#N	0.326	0.078	4.180	0.000	0.173	0.479
13#Y	0.567	0.080	7.080	0.000	0.410	0.724

14#N	0.406	0.119	3.420	0.001	0.174	0.639
14#Y	0.650	0.097	6.680	0.000	0.459	0.840
15#N	0.492	0.166	2.980	0.003	0.168	0.817
15#Y	0.724	0.116	6.230	0.000	0.496	0.952
16#N	0.244	0.101	2.420	0.015	0.046	0.441
16#Y	0.466	0.142	3.290	0.001	0.189	0.743
17#N	0.313	0.107	2.930	0.003	0.104	0.523
17#Y	0.553	0.119	4.640	0.000	0.319	0.787
18#N	0.393	0.125	3.130	0.002	0.147	0.638
18#Y	0.637	0.109	5.840	0.000	0.423	0.850
19#N	0.478	0.155	3.090	0.002	0.175	0.782
19#Y	0.713	0.110	6.450	0.000	0.496	0.929
20#N	0.565	0.186	3.030	0.002	0.200	0.930
20#Y	0.779	0.114	6.810	0.000	0.554	1.003

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(canceranybiopsy), predict()
1._at : ageatstudy~y = 40
psad = 0
2._at : ageatstudy~y = 40
psad = .05
3._at : ageatstudy~y = 40
psad = .1
4._at : ageatstudy~y = 40
psad = .15
5._at : ageatstudy~y = 40
psad = .2
6._at : ageatstudy~y = 50
psad = 0
7._at : ageatstudy~y = 50
psad = .05
8._at : ageatstudy~y = 50
psad = .1
9._at : ageatstudy~y = 50
psad = .15
10._at : ageatstudy~y = 50
psad = .2
11._at : ageatstudy~y = 60
psad = 0
12._at : ageatstudy~y = 60
psad = .05
13._at : ageatstudy~y = 60
psad = .1
14._at : ageatstudy~y = 60
psad = .15
15._at : ageatstudy~y = 60
psad = .2
16._at : ageatstudy~y = 70
psad = 0
17._at : ageatstudy~y = 70
psad = .05
18._at : ageatstudy~y = 70
psad = .1
19._at : ageatstudy~y = 70
psad = .15
20._at : ageatstudy~y = 70
psad = .2

Delta-method

	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#abnormalMRI45						
1 0	0.146	0.057	2.570	0.010	0.035	0.258
1 1	0.329	0.170	1.930	0.054	-0.005	0.663
2 0	0.197	0.064	3.080	0.002	0.072	0.322
2 1	0.412	0.169	2.440	0.015	0.081	0.743
3 0	0.260	0.087	2.990	0.003	0.090	0.429
3 1	0.501	0.170	2.950	0.003	0.168	0.834
4 0	0.334	0.128	2.620	0.009	0.084	0.584
4 1	0.589	0.175	3.370	0.001	0.246	0.932
5 0	0.418	0.179	2.340	0.019	0.068	0.768
5 1	0.673	0.180	3.740	0.000	0.320	1.025
6 0	0.179	0.045	3.950	0.000	0.090	0.267
6 1	0.384	0.148	2.590	0.010	0.093	0.674
7 0	0.238	0.040	5.890	0.000	0.159	0.317
7 1	0.471	0.132	3.560	0.000	0.212	0.731
8 0	0.308	0.064	4.850	0.000	0.184	0.433
8 1	0.561	0.125	4.490	0.000	0.316	0.806
9 0	0.390	0.110	3.550	0.000	0.174	0.605
9 1	0.646	0.129	5.020	0.000	0.394	0.899
10 0	0.477	0.162	2.940	0.003	0.159	0.795
10 1	0.723	0.136	5.320	0.000	0.457	0.990
11 0	0.217	0.059	3.650	0.000	0.100	0.333
11 1	0.442	0.142	3.120	0.002	0.165	0.720
12 0	0.284	0.056	5.060	0.000	0.174	0.394
12 1	0.532	0.117	4.560	0.000	0.303	0.760
13 0	0.362	0.078	4.620	0.000	0.208	0.516
13 1	0.619	0.104	5.970	0.000	0.416	0.822
14 0	0.448	0.121	3.710	0.000	0.211	0.685
14 1	0.699	0.106	6.610	0.000	0.492	0.906
15 0	0.537	0.166	3.230	0.001	0.211	0.864
15 1	0.769	0.112	6.870	0.000	0.549	0.988
16 0	0.261	0.104	2.510	0.012	0.057	0.464
16 1	0.502	0.160	3.150	0.002	0.189	0.815
17 0	0.335	0.110	3.050	0.002	0.120	0.551
17 1	0.591	0.132	4.490	0.000	0.333	0.849
18 0	0.419	0.129	3.240	0.001	0.166	0.673
18 1	0.674	0.114	5.900	0.000	0.450	0.898
19 0	0.508	0.159	3.190	0.001	0.196	0.820
19 1	0.747	0.108	6.900	0.000	0.535	0.959
20 0	0.597	0.189	3.160	0.002	0.227	0.966
20 1	0.809	0.106	7.610	0.000	0.601	1.017

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()
1._at : ageatstudy~y = 40
psad = 0
2._at : ageatstudy~y = 40
psad = .05
3._at : ageatstudy~y = 40
psad = .1
4._at : ageatstudy~y = 40
psad = .15
5._at : ageatstudy~y = 40
psad = .2
6._at : ageatstudy~y = 50
psad = 0

```
7._at       : ageatstudy~y   =         50
              psad           =        .05
8._at       : ageatstudy~y   =         50
              psad           =         .1
9._at       : ageatstudy~y   =         50
              psad           =        .15
10._at      : ageatstudy~y   =         50
              psad           =         .2
11._at      : ageatstudy~y   =         60
              psad           =          0
12._at      : ageatstudy~y   =         60
              psad           =        .05
13._at      : ageatstudy~y   =         60
              psad           =         .1
14._at      : ageatstudy~y   =         60
              psad           =        .15
15._at      : ageatstudy~y   =         60
              psad           =         .2
16._at      : ageatstudy~y   =         70
              psad           =          0
17._at      : ageatstudy~y   =         70
              psad           =        .05
18._at      : ageatstudy~y   =         70
              psad           =         .1
19._at      : ageatstudy~y   =         70
              psad           =        .15
20._at      : ageatstudy~y   =         70
              psad           =         .2
```

Delta-method

	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#abnormalMRI						
1#N	0.000	0.000	0.540	0.589	-0.001	0.001
1#Y	0.003	0.005	0.620	0.532	-0.007	0.014
2#N	0.000	0.001	0.570	0.566	-0.001	0.002
2#Y	0.007	0.010	0.680	0.497	-0.013	0.028
3#N	0.001	0.001	0.600	0.552	-0.002	0.004
3#Y	0.015	0.021	0.720	0.473	-0.026	0.056
4#N	0.002	0.003	0.600	0.548	-0.004	0.008
4#Y	0.032	0.043	0.740	0.462	-0.053	0.116
5#N	0.004	0.007	0.590	0.556	-0.009	0.018
5#Y	0.065	0.088	0.740	0.461	-0.108	0.239
6#N	0.001	0.002	0.720	0.472	-0.002	0.004
6#Y	0.019	0.019	1.000	0.317	-0.019	0.058
7#N	0.002	0.003	0.790	0.432	-0.004	0.009
7#Y	0.041	0.034	1.210	0.226	-0.025	0.106
8#N	0.005	0.006	0.820	0.410	-0.007	0.018
8#Y	0.083	0.060	1.390	0.164	-0.034	0.200
9#N	0.011	0.014	0.820	0.412	-0.015	0.038
9#Y	0.162	0.110	1.470	0.142	-0.054	0.379
10#N	0.024	0.030	0.780	0.436	-0.036	0.083
10#Y	0.292	0.194	1.500	0.132	-0.088	0.673
11#N	0.007	0.008	0.860	0.391	-0.009	0.022
11#Y	0.105	0.062	1.690	0.091	-0.017	0.227
12#N	0.014	0.015	0.950	0.343	-0.015	0.044
12#Y	0.201	0.074	2.700	0.007	0.055	0.347
13#N	0.030	0.031	0.990	0.321	-0.030	0.090
13#Y	0.349	0.093	3.770	0.000	0.168	0.531
14#N	0.063	0.064	0.980	0.329	-0.063	0.188
14#Y	0.534	0.134	3.990	0.000	0.272	0.797
15#N	0.125	0.133	0.940	0.347	-0.136	0.385

15#Y	0.710	0.158	4.500	0.000	0.401	1.019
16#N	0.039	0.050	0.790	0.432	-0.058	0.136
16#Y	0.411	0.212	1.940	0.053	-0.005	0.827
17#N	0.080	0.093	0.860	0.389	-0.102	0.262
17#Y	0.598	0.190	3.160	0.002	0.227	0.970
18#N	0.156	0.167	0.930	0.350	-0.172	0.485
18#Y	0.761	0.147	5.190	0.000	0.473	1.049
19#N	0.284	0.273	1.040	0.298	-0.250	0.818
19#Y	0.872	0.103	8.450	0.000	0.670	1.074
20#N	0.458	0.365	1.260	0.209	-0.257	1.174
20#Y	0.936	0.067	14.020	0.000	0.805	1.066

Adjusted predictions Number of obs = 151
Model VCE : OIM
Expression : Pr(signifvsinsignifornoca), predict()
1._at : ageatstudy~y = 40
psad = 0
2._at : ageatstudy~y = 40
psad = .05
3._at : ageatstudy~y = 40
psad = .1
4._at : ageatstudy~y = 40
psad = .15
5._at : ageatstudy~y = 40
psad = .2
6._at : ageatstudy~y = 50
psad = 0
7._at : ageatstudy~y = 50
psad = .05
8._at : ageatstudy~y = 50
psad = .1
9._at : ageatstudy~y = 50
psad = .15
10._at : ageatstudy~y = 50
psad = .2
11._at : ageatstudy~y = 60
psad = 0
12._at : ageatstudy~y = 60
psad = .05
13._at : ageatstudy~y = 60
psad = .1
14._at : ageatstudy~y = 60
psad = .15
15._at : ageatstudy~y = 60
psad = .2
16._at : ageatstudy~y = 70
psad = 0
17._at : ageatstudy~y = 70
psad = .05
18._at : ageatstudy~y = 70
psad = .1
19._at : ageatstudy~y = 70
psad = .15
20._at : ageatstudy~y = 70
psad = .2

Delta-method

	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#abnormalMRI45						

1 0	0.001	0.002	0.670	0.506	-0.002	0.005
1 1	0.006	0.011	0.570	0.566	-0.015	0.027
2 0	0.002	0.003	0.720	0.471	-0.004	0.009
2 1	0.013	0.021	0.620	0.534	-0.028	0.054
3 0	0.005	0.007	0.760	0.450	-0.008	0.018
3 1	0.027	0.040	0.660	0.507	-0.052	0.106
4 0	0.011	0.014	0.760	0.447	-0.017	0.038
4 1	0.055	0.078	0.700	0.485	-0.099	0.208
5 0	0.022	0.030	0.740	0.461	-0.036	0.080
5 1	0.108	0.148	0.730	0.466	-0.183	0.399
6 0	0.005	0.005	1.060	0.290	-0.005	0.015
6 1	0.028	0.032	0.880	0.379	-0.034	0.090
7 0	0.011	0.009	1.240	0.214	-0.006	0.029
7 1	0.057	0.055	1.040	0.297	-0.050	0.164
8 0	0.023	0.017	1.340	0.180	-0.011	0.057
8 1	0.112	0.093	1.210	0.226	-0.069	0.294
9 0	0.047	0.037	1.280	0.200	-0.025	0.119
9 1	0.210	0.154	1.370	0.172	-0.091	0.511
10 0	0.094	0.081	1.150	0.250	-0.066	0.253
10 1	0.358	0.232	1.540	0.123	-0.096	0.812
11 0	0.024	0.016	1.510	0.132	-0.007	0.055
11 1	0.117	0.079	1.480	0.138	-0.038	0.271
12 0	0.049	0.026	1.880	0.060	-0.002	0.100
12 1	0.217	0.099	2.190	0.029	0.023	0.412
13 0	0.097	0.050	1.950	0.052	-0.001	0.196
13 1	0.368	0.119	3.090	0.002	0.135	0.601
14 0	0.185	0.106	1.730	0.083	-0.024	0.393
14 1	0.550	0.146	3.780	0.000	0.265	0.835
15 0	0.322	0.200	1.610	0.107	-0.070	0.714
15 1	0.719	0.155	4.630	0.000	0.415	1.024
16 0	0.101	0.089	1.140	0.253	-0.072	0.275
16 1	0.378	0.200	1.890	0.059	-0.014	0.771
17 0	0.191	0.146	1.310	0.189	-0.094	0.477
17 1	0.561	0.186	3.010	0.003	0.195	0.926
18 0	0.332	0.220	1.500	0.132	-0.100	0.764
18 1	0.728	0.151	4.820	0.000	0.432	1.024
19 0	0.510	0.280	1.820	0.068	-0.039	1.059
19 1	0.849	0.112	7.610	0.000	0.630	1.067
20 0	0.686	0.279	2.450	0.014	0.138	1.234
20 1	0.922	0.075	12.220	0.000	0.774	1.070

Chapter 5 Appendix

Raw Data output from Stata (for reference only if required relating to statistical analyses) is included below.

PRS

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
<20th	1.167	.988	0.18	.856	.222	6.135	
20-<40th	1.333	1.136	0.34	.736	.251	7.084	
40-60th (ref)	1	.	.	.	.	.	
60-<80th	1.474	1.164	0.49	.624	.313	6.932	
>=80th	6.588	4.683	2.65	.008	1.636	26.535	***
Constant	.214	.136	-2.42	.015	.062	.746	**

Mean dependent var	0.339	SD dependent var	0.475
Pseudo r-squared	0.109	Number of obs	121.000
Chi-square	16.824	Prob > chi2	0.002
Akaike crit. (AIC)	148.121	Bayesian crit. (BIC)	162.100

*** p<.01, ** p<.05, * p<.1

Table 0.1 LR output of association between PRS category and cancer outcome. Examining the marginal effect at each PRS category, the probability of cancer in the lowest category was 20% and 58% in the highest category (table below).

Adjusted predictions Number of obs = 121
Model VCE : OIM
Expression : Pr(any cancer), predict()

	Delta-method Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
PRS						
<20	.2	0.089	2.240	0.025	0.025	0.375
20-<40	0.222	0.098	2.270	0.023	0.030	0.414
40-<60	0.176	0.092	1.910	0.056	-0.005	0.358
60-<80	.24	0.085	2.810	0.005	0.073	0.407
>=80	0.585	0.077	7.610	0.000	0.435	0.736

Table 0.2 Marginal predictions of PRS category on cancer outcome

Contrasts of adjusted predictions Number of obs = 121
Model VCE : OIM
Expression : Pr(canceranybiopsy), predict()

	Delta-method Contrast	Std.Err.	z	P>z
PRS centile				
base = 40-<60th				
(<20 vs base)	0.024	0.129	0.180	0.855
(20-<40 vs base)	0.046	0.135	0.340	0.734
(60-<80 vs base)	0.064	0.126	0.500	0.614
(>=80 vs base)	0.409	0.120	3.400	0.001

Table 0.3 A measure of the difference in effect between each PRS risk category, confirming no large difference in effect until the highest quintile (40.9% difference) is compared to the middle/reference centile (highlighted in red)

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
PRS	3.131	.993	3.60	0	1.682	5.829	***
Constant	0	0	-3.76	0	0	.002	***

Mean dependent var	0.339	SD dependent var	0.475
Pseudo r-squared	0.098	Number of obs	121.000
Chi-square	15.195	Prob > chi2	0.000
Akaike crit. (AIC)	143.750	Bayesian crit. (BIC)	149.341

*** p<.01, ** p<.05, * p<.1

Adjusted predictions Number of obs = 121
Model VCE : OIM
Expression : Pr(any cancer), predict()
at : PRS = 10.58679 (mean)

	Delta-method Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_cons	0.317	0.046	6.940	0.000	0.228	0.407

Table 0.4 The average predicted probability of (any) PRS in men with a PRS at the mean (10.58) is 31.7%

PRS PSA CAT

Adjusted predictions **Number of obs = 121**

Model VCE : OIM
Expression : Pr(any cancer), predict()
1._at : prs = 8
2._at : prs = 8.5

	Delta-method Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#PSA Cat						
1#<1	0.011	0.011	0.970	0.333	-0.011	0.033
1#1-<2	0.032	0.035	0.930	0.354	-0.036	0.100
1#2-3	0.066	0.061	1.080	0.282	-0.054	0.186
1#>=3	0.084	0.086	0.980	0.326	-0.084	0.252
2#<1	0.018	0.016	1.140	0.254	-0.013	0.048
2#1-<2	0.052	0.047	1.110	0.266	-0.040	0.144
2#2-3	0.104	0.078	1.330	0.183	-0.049	0.258
2#>=3	0.132	0.109	1.200	0.229	-0.083	0.346

Table 0.1 Coefficients of the marginal predicated probabilities of cancer detection for each PSA category in the presence of the lowest levels of PRS; graphed below in **Error! Reference source not found.**

Adjusted predictions Number of obs = 121
Model VCE : OIM
Expression : Pr(any cancer), predict()
1._at : prs = 8
2._at : prs = 9
3._at : prs = 10
4._at : prs = 11
5._at : prs = 12

	Delta-method Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#psacat						
1#<1	0.011	0.011	0.970	0.333	-0.011	0.033
1#1-<2	0.032	0.035	0.930	0.354	-0.036	0.100
1#2-3	0.066	0.061	1.080	0.282	-0.054	0.186
1#>=3	0.084	0.086	0.980	0.326	-0.084	0.252
2#<1	0.029	0.021	1.370	0.170	-0.012	0.070
2#1-<2	0.083	0.060	1.380	0.167	-0.035	0.201
2#2-3	0.161	0.093	1.730	0.084	-0.022	0.344
2#>=3	0.200	0.130	1.540	0.124	-0.055	0.456
3#<1	0.075	0.037	2.030	0.042	0.003	0.148
3#1-<2	0.199	0.080	2.470	0.014	0.041	0.356
3#2-3	0.344	0.104	3.300	0.001	0.140	0.549
3#>=3	0.406	0.140	2.910	0.004	0.132	0.680
4#<1	0.182	0.075	2.420	0.016	0.034	0.329
4#1-<2	0.403	0.089	4.520	0.000	0.229	0.578
4#2-3	0.589	0.108	5.440	0.000	0.377	0.802
4#>=3	0.651	0.116	5.610	0.000	0.424	0.879

5#<1	0.378	0.162	2.330	0.020	0.059	0.696
5#1-<2	0.649	0.118	5.480	0.000	0.417	0.881
5#2-3	0.797	0.107	7.430	0.000	0.587	1.007
5#>=3	0.836	0.091	9.230	0.000	0.659	1.014

PRS MRI

Adjusted predictions **Number of obs = 120**
Model VCE : OIM
Expression : Pr(any cancer), predict()
1._at : prs = 8
2._at : prs = 9
3._at : prs = 10
4._at : prs = 11
5._at : prs = 12

	Delta-method					
	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#PiRADS 3-5						
1#N	0.018	0.017	1.100	0.273	-0.015	0.051
1#Y	0.049	0.044	1.110	0.266	-0.037	0.134
2#N	0.054	0.032	1.690	0.091	-0.009	0.117
2#Y	0.135	0.077	1.760	0.078	-0.015	0.286
3#N	0.149	0.045	3.280	0.001	0.060	0.238
3#Y	0.324	0.092	3.510	0.000	0.143	0.504
4#N	0.349	0.062	5.600	0.000	0.227	0.471
4#Y	0.594	0.088	6.720	0.000	0.421	0.767
5#N	0.621	0.114	5.470	0.000	0.399	0.844
5#Y	0.817	0.082	9.960	0.000	0.656	0.978

Table 0.1 The average probability of cancer with a PiRADS 3-5 MRI reaches 81% compared to 62% for a 'normal' MRI at the top end of polygenic risk i.e with a PRS of 12 – highlighted in red.

Table 0.2 Adjusted predications for probability of (any) cancer. **Error! Reference source not found.**

Adjusted predictions **Number of obs = 120**
Model VCE : OIM
Expression : Pr(any cancer), predict()
1._at : prs = 8
2._at : prs = 9
3._at : prs = 10
4._at : prs = 11
5._at : prs = 12

	Delta-method				
	Margin	Std.Err.	z	P>z	Interval]

					[95%Conf.	
_at#PiRADS 4-5						
1 0	0.023	0.021	1.110	0.266	-0.018	0.064
1 1	0.089	0.084	1.050	0.293	-0.077	0.254
2 0	0.065	0.037	1.750	0.080	-0.008	0.137
2 1	0.222	0.135	1.650	0.100	-0.042	0.486
3 0	0.168	0.046	3.630	0.000	0.077	0.258
3 1	0.454	0.145	3.130	0.002	0.170	0.739
4 0	0.371	0.058	6.410	0.000	0.257	0.484
4 1	0.709	0.111	6.370	0.000	0.491	0.927
5 0	0.633	0.111	5.710	0.000	0.416	0.849
5 1	0.877	0.073	12.060	0.000	0.734	1.019

Table 0.2 The average probability of cancer with a PiRADS 4-5 MRI reaches 87% compared to 63% for a 'normal' MRI at the top end of polygenic risk i.e with a PRS of 12 – highlighted in red. Graphical representation of this tables coefficients is shown below in **Error! Reference source not found.**

Contrasts of adjusted predictions **Number of obs = 120**
Model VCE : OIM
Expression : Pr(any cancer), predict()
1._at : prs = 8
2._at : prs = 9
3._at : prs = 10
4._at : prs = 11
5._at : prs = 12

	Delta-method Contrast	Std.Err.	z	P>z
abnormalMRI4-5@_at				
base = PiRADS 1-3 MRI				
(1 vs base) 1	0.066	0.068	0.970	0.334
(1 vs base) 2	0.157	0.113	1.390	0.164
(1 vs base) 3	0.287	0.139	2.070	0.039
(1 vs base) 4	0.338	0.122	2.760	0.006
(1 vs base) 5	0.244	0.095	2.580	0.010

Table 36 – contrasts of adjusted predictions. Those with a PiRADS 4-5 MRI and a PRS of 10, 11 or 12 had a 28%, 33% and 24% increase in probability of (any) cancer detection compared to men with a PiRADS 1-3 MRI, and these differences were statistically significant (highlighted in red).

If mens' PRS was 'low', there were non-statistically significant differences in cancer probability between those with and without a PiRADS 4-5 MRI.

Contrasts of adjusted predictions Number of obs = 120
Model VCE : OIM
Expression : Pr(signifca), predict()
1._at : prs = 8
2._at : prs = 8.5
3._at : prs = 9

4._at : prs = 9.5
5._at : prs = 10
6._at : prs = 10.5
7._at : prs = 11
8._at : prs = 11.5
9._at : prs = 12
10._at : prs = 12.5

	Delta-method Contrast	Std.Err.	z	P>z
abnormalMRI@_at				
(base = MRI PiRADS 1-2)				
(Y vs base) 1	0.009	0.015	0.560	0.572
(Y vs base) 2	0.016	0.024	0.680	0.499
(Y vs base) 3	0.031	0.037	0.840	0.400
(Y vs base) 4	0.057	0.052	1.110	0.267
(Y vs base) 5	0.104	0.065	1.590	0.113
(Y vs base) 6	0.180	0.074	2.440	0.015
(Y vs base) 7	0.292	0.086	3.380	0.001
(Y vs base) 8	0.430	0.123	3.480	0.000
(Y vs base) 9	0.565	0.155	3.630	0.000
(Y vs base) 10	0.658	0.147	4.490	0.000

Table 0.3 contrasts of adjusted predictions between men with and without a PiRADS 3-5 MRI.

At the higher end of the PRS scale (ie at a PRS of 12), men with an abnormal MRI had a 56% increase in probability of clinically significant cancer compared to men with a PiRADS 1-2 MRI.

At the mean PRS (10.5), men with an abnormal MRI had an 18% increase in probability of significant cancer detection compared to those with a normal MRI.

Contrasts of adjusted predictions Number of obs = 120
Model VCE : OIM
Expression : Pr(signifca), predict()
1._at : prs = 8
2._at : prs = 8.5
3._at : prs = 9
4._at : prs = 9.5
5._at : prs = 10
6._at : prs = 10.5
7._at : prs = 11
8._at : prs = 11.5
9._at : prs = 12
10._at : prs = 12.5

	Delta-method Contrast	Std.Err.	z	P>z
abnormalMRI 4-5@_at				
base = normal MRI/PiRADS 1-3				
(1 vs base) 1	0.020	0.035	0.560	0.574
(1 vs base) 2	0.034	0.051	0.670	0.502
(1 vs base) 3	0.059	0.071	0.830	0.406
(1 vs base) 4	0.098	0.091	1.080	0.280

(1 vs base) 5	0.158	0.107	1.480	0.138
(1 vs base) 6	0.243	0.116	2.090	0.036
(1 vs base) 7	0.346	0.127	2.740	0.006
(1 vs base) 8	0.451	0.142	3.180	0.001
(1 vs base) 9	0.529	0.141	3.770	0.000
(1 vs base) 10	0.558	0.126	4.420	0.000

Table 0.4 Men with a PiRADS 4-5 MRI had no significant increase in cancer probability compared to men with a normal MRI until approx. a PRS of 10.5.

At a PRS of 12, men with an abnormal MRI had a 52% greater increase in probability of clinically significant cancer detection than men with a PiRADS 1-3 (highlighted in red). MRI. At the mean study PRS (10.5), men with an abnormal MRI had a 24% greater probability of significant cancer detection than those with a PiRADS 1-3 MRI (highlighted in blue)

PRS &MRI

Sensitivity	**45.45%**
Specificity	99.08%
PPV	83.33%
NPV	94.74%
Correctly classified	94.17%

Table 0.5 Sensitivity, specificity, NPV and PPV values for a logistic regression models' performance in clinically significant cancer detection, incorporating PRS as a continuous variable and MRI as a categorical variable.

PRS PSA Age

Sensitivity	**36.36%**
Specificity	97.27%
NPV	93.86%
PPV	57.14%
Correctly classified	91.74%

Table 0.1 Sensitivity, specificity, NPV and PPV values for a logistic regression models' performance (Table 0.10) in clinically significant cancer detection, incorporating PRS, PSA and age as continuous variables.

PRS Age

28 Adjusted predictions **Number of obs = 121**
Model VCE : OIM
Expression : Pr(canceranybiopsy), predict()
1._at : ageatstudy~y = 40
prs = 8
2._at : ageatstudy~y = 40
prs = 8.5
3._at : ageatstudy~y = 40

prs = 9
4._at : ageatstudy~y = 40
prs = 9.5
5._at : ageatstudy~y = 40
prs = 10
6._at : ageatstudy~y = 40
prs = 10.5
7._at : ageatstudy~y = 40
prs = 11
8._at : ageatstudy~y = 40
prs = 11.5
9._at : ageatstudy~y = 40
prs = 12
10._at : ageatstudy~y = 50
prs = 8
11._at : ageatstudy~y = 50
prs = 8.5
12._at : ageatstudy~y = 50
prs = 9
13._at : ageatstudy~y = 50
prs = 9.5
14._at : ageatstudy~y = 50
prs = 10
15._at : ageatstudy~y = 50
prs = 10.5
16._at : ageatstudy~y = 50
prs = 11
17._at : ageatstudy~y = 50
prs = 11.5
18._at : ageatstudy~y = 50
prs = 12
19._at : ageatstudy~y = 60
prs = 8
20._at : ageatstudy~y = 60
prs = 8.5
21._at : ageatstudy~y = 60
prs = 9
22._at : ageatstudy~y = 60
prs = 9.5
23._at : ageatstudy~y = 60
prs = 10
24._at : ageatstudy~y = 60
prs = 10.5
25._at : ageatstudy~y = 60
prs = 11
26._at : ageatstudy~y = 60
prs = 11.5
27._at : ageatstudy~y = 60
prs = 12
28._at : ageatstudy~y = 70
prs = 8
29._at : ageatstudy~y = 70
prs = 8.5
30._at : ageatstudy~y = 70
prs = 9
31._at : ageatstudy~y = 70
prs = 9.5
32._at : ageatstudy~y = 70
prs = 10
33._at : ageatstudy~y = 70

prs = 10.5
34._at : ageatstudy~y = 70
prs = 11
35._at : ageatstudy~y = 70
prs = 11.5
36._at : ageatstudy~y = 70
prs = 12

	Delta-method Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at						
1	0.011	0.011	1.000	0.316	-0.010	0.032
2	0.019	0.016	1.170	0.240	-0.013	0.050
3	0.033	0.023	1.410	0.159	-0.013	0.079
4	0.057	0.033	1.720	0.085	-0.008	0.122
5	0.097	0.045	2.140	0.032	0.008	0.186
6	0.160	0.061	2.610	0.009	0.040	0.280
7	0.252	0.085	2.990	0.003	0.087	0.418
8	0.375	0.116	3.240	0.001	0.148	0.601
9	0.515	0.145	3.540	0.000	0.230	0.800
10	0.019	0.017	1.110	0.267	-0.014	0.052
11	0.033	0.024	1.350	0.176	-0.015	0.081
12	0.057	0.033	1.730	0.084	-0.008	0.122
13	0.097	0.041	2.350	0.019	0.016	0.177
14	0.160	0.046	3.470	0.001	0.070	0.250
15	0.252	0.048	5.260	0.000	0.158	0.346
16	0.374	0.059	6.350	0.000	0.259	0.490
17	0.515	0.084	6.120	0.000	0.350	0.679
18	0.653	0.105	6.210	0.000	0.447	0.859
19	0.033	0.029	1.140	0.253	-0.023	0.089
20	0.057	0.040	1.410	0.159	-0.022	0.136
21	0.097	0.053	1.830	0.067	-0.007	0.200
22	0.159	0.062	2.560	0.011	0.037	0.282
23	0.252	0.065	3.880	0.000	0.125	0.379
24	0.374	0.063	5.930	0.000	0.250	0.497
25	0.514	0.070	7.390	0.000	0.378	0.651
26	0.652	0.083	7.850	0.000	0.490	0.815
27	0.769	0.087	8.800	0.000	0.598	0.940
28	0.057	0.052	1.090	0.275	-0.045	0.159
29	0.096	0.073	1.320	0.186	-0.046	0.239
30	0.159	0.095	1.670	0.094	-0.027	0.346
31	0.251	0.113	2.220	0.027	0.029	0.473
32	0.373	0.122	3.060	0.002	0.134	0.612
33	0.514	0.120	4.270	0.000	0.278	0.749
34	0.652	0.112	5.820	0.000	0.433	0.871
35	0.769	0.098	7.810	0.000	0.576	0.962
36	0.855	0.080	10.630	0.000	0.697	1.013

PSAD PRS

Adjusted predictions Number of obs = 121
Model VCE : OIM

Expression : Pr(canceranybiopsy), predict()

1._at	: psadstu~1000	=	0
	prs	=	8
2._at	: psadstu~1000	=	0
	prs	=	8.5
3._at	: psadstu~1000	=	0
	prs	=	9
4._at	: psadstu~1000	=	0
	prs	=	9.5
5._at	: psadstu~1000	=	0
	prs	=	10
6._at	: psadstu~1000	=	0
	prs	=	10.5
7._at	: psadstu~1000	=	0
	prs	=	11
8._at	: psadstu~1000	=	0
	prs	=	11.5
9._at	: psadstu~1000	=	0
	prs	=	12
10._at	: psadstu~1000	=	.05
	prs	=	8
11._at	: psadstu~1000	=	.05
	prs	=	8.5
12._at	: psadstu~1000	=	.05
	prs	=	9
13._at	: psadstu~1000	=	.05
	prs	=	9.5
14._at	: psadstu~1000	=	.05
	prs	=	10
15._at	: psadstu~1000	=	.05
	prs	=	10.5
16._at	: psadstu~1000	=	.05
	prs	=	11
17._at	: psadstu~1000	=	.05
	prs	=	11.5
18._at	: psadstu~1000	=	.05
	prs	=	12
19._at	: psadstu~1000	=	.1
	prs	=	8
20._at	: psadstu~1000	=	.1
	prs	=	8.5
21._at	: psadstu~1000	=	.1
	prs	=	9
22._at	: psadstu~1000	=	.1
	prs	=	9.5
23._at	: psadstu~1000	=	.1
	prs	=	10
24._at	: psadstu~1000	=	.1
	prs	=	10.5
25._at	: psadstu~1000	=	.1
	prs	=	11
26._at	: psadstu~1000	=	.1
	prs	=	11.5
27._at	: psadstu~1000	=	.1
	prs	=	12
28._at	: psadstu~1000	=	.15
	prs	=	8
29._at	: psadstu~1000	=	.15
	prs	=	8.5
30._at	: psadstu~1000	=	.15
	prs	=	9
31._at	: psadstu~1000	=	.15

	prs	=	9.5
32._at	: psadstu~1000	=	.15
	prs	=	10
33._at	: psadstu~1000	=	.15
	prs	=	10.5
34._at	: psadstu~1000	=	.15
	prs	=	11
35._at	: psadstu~1000	=	.15
	prs	=	11.5
36._at	: psadstu~1000	=	.15
	prs	=	12
37._at	: psadstu~1000	=	.2
	prs	=	8
38._at	: psadstu~1000	=	.2
	prs	=	8.5
39._at	: psadstu~1000	=	.2
	prs	=	9
40._at	: psadstu~1000	=	.2
	prs	=	9.5
41._at	: psadstu~1000	=	.2
	prs	=	10
42._at	: psadstu~1000	=	.2
	prs	=	10.5
43._at	: psadstu~1000	=	.2
	prs	=	11
44._at	: psadstu~1000	=	.2
	prs	=	11.5
45._at	: psadstu~1000	=	.2
	prs	=	12

Delta-method

	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at						
1	0.019	0.018	1.100	0.271	-0.015	0.054
2	0.031	0.024	1.330	0.184	-0.015	0.078
3	0.051	0.031	1.650	0.098	-0.009	0.111
4	0.080	0.038	2.130	0.033	0.006	0.155
5	0.126	0.045	2.780	0.005	0.037	0.214
6	0.191	0.056	3.410	0.001	0.081	0.300
7	0.279	0.077	3.610	0.000	0.127	0.430
8	0.388	0.111	3.510	0.000	0.171	0.605
9	0.510	0.146	3.500	0.000	0.224	0.795
10	0.019	0.018	1.100	0.271	-0.015	0.054
11	0.032	0.024	1.330	0.184	-0.015	0.078
12	0.051	0.031	1.650	0.098	-0.009	0.111
13	0.081	0.038	2.130	0.033	0.006	0.155
14	0.126	0.045	2.780	0.005	0.037	0.214
15	0.191	0.056	3.410	0.001	0.081	0.300
16	0.279	0.077	3.610	0.000	0.128	0.430
17	0.388	0.111	3.510	0.000	0.171	0.605
18	0.510	0.146	3.500	0.000	0.225	0.795
19	0.019	0.018	1.100	0.270	-0.015	0.054
20	0.032	0.024	1.330	0.184	-0.015	0.078
21	0.051	0.031	1.650	0.098	-0.009	0.111
22	0.081	0.038	2.130	0.033	0.006	0.155
23	0.126	0.045	2.780	0.005	0.037	0.214
24	0.191	0.056	3.410	0.001	0.081	0.300
25	0.279	0.077	3.620	0.000	0.128	0.430
26	0.388	0.110	3.510	0.000	0.172	0.605
27	0.510	0.146	3.500	0.000	0.225	0.795
28	0.019	0.018	1.100	0.270	-0.015	0.054

29	0.032	0.024	1.330	0.184	-0.015	0.078
30	0.051	0.031	1.650	0.098	-0.009	0.111
31	0.081	0.038	2.130	0.033	0.006	0.155
32	0.126	0.045	2.780	0.005	0.037	0.214
33	0.191	0.056	3.410	0.001	0.081	0.300
34	0.279	0.077	3.620	0.000	0.128	0.430
35	0.388	0.110	3.520	0.000	0.172	0.605
36	0.510	0.146	3.510	0.000	0.225	0.795
37	0.019	0.018	1.100	0.270	-0.015	0.054
38	0.032	0.024	1.330	0.184	-0.015	0.078
39	0.051	0.031	1.650	0.098	-0.009	0.111
40	0.081	0.038	2.130	0.033	0.006	0.155
41	0.126	0.045	2.780	0.005	0.037	0.214
42	0.191	0.056	3.420	0.001	0.081	0.301
43	0.279	0.077	3.620	0.000	0.128	0.430
44	0.388	0.110	3.520	0.000	0.172	0.605
45	0.510	0.145	3.510	0.000	0.225	0.795

PRS age

Adjusted predictions Number of obs = 121
Model VCE : OIM
Expression : Pr(signifca), predict()
1._at : ageatstudy~y = 40
prs = 8
2._at : ageatstudy~y = 40
prs = 8.5
3._at : ageatstudy~y = 40
prs = 9
4._at : ageatstudy~y = 40
prs = 9.5
5._at : ageatstudy~y = 40
prs = 10
6._at : ageatstudy~y = 40
prs = 10.5
7._at : ageatstudy~y = 40
prs = 11
8._at : ageatstudy~y = 40
prs = 11.5
9._at : ageatstudy~y = 40
prs = 12
10._at : ageatstudy~y = 50
prs = 8
11._at : ageatstudy~y = 50
prs = 8.5
12._at : ageatstudy~y = 50
prs = 9
13._at : ageatstudy~y = 50
prs = 9.5
14._at : ageatstudy~y = 50
prs = 10
15._at : ageatstudy~y = 50
prs = 10.5
16._at : ageatstudy~y = 50
prs = 11
17._at : ageatstudy~y = 50
prs = 11.5
18._at : ageatstudy~y = 50

	prs	=	12
19._at	: ageatstudy~y	=	60
	prs	=	8
20._at	: ageatstudy~y	=	60
	prs	=	8.5
21._at	: ageatstudy~y	=	60
	prs	=	9
22._at	: ageatstudy~y	=	60
	prs	=	9.5
23._at	: ageatstudy~y	=	60
	prs	=	10
24._at	: ageatstudy~y	=	60
	prs	=	10.5
25._at	: ageatstudy~y	=	60
	prs	=	11
26._at	: ageatstudy~y	=	60
	prs	=	11.5
27._at	: ageatstudy~y	=	60
	prs	=	12
28._at	: ageatstudy~y	=	70
	prs	=	8
29._at	: ageatstudy~y	=	70
	prs	=	8.5
30._at	: ageatstudy~y	=	70
	prs	=	9
31._at	: ageatstudy~y	=	70
	prs	=	9.5
32._at	: ageatstudy~y	=	70
	prs	=	10
33._at	: ageatstudy~y	=	70
	prs	=	10.5
34._at	: ageatstudy~y	=	70
	prs	=	11
35._at	: ageatstudy~y	=	70
	prs	=	11.5
36._at	: ageatstudy~y	=	70
	prs	=	12

Delta-method

	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at						
1	0.000	0.000	0.420	0.671	-0.000	0.000
2	0.000	0.000	0.470	0.638	-0.000	0.001
3	0.000	0.000	0.520	0.600	-0.001	0.001
4	0.001	0.001	0.580	0.559	-0.001	0.002
5	0.001	0.002	0.650	0.518	-0.002	0.004
6	0.002	0.003	0.710	0.481	-0.004	0.008
7	0.004	0.006	0.750	0.455	-0.007	0.016
8	0.009	0.012	0.760	0.446	-0.014	0.033
9	0.019	0.025	0.750	0.455	-0.030	0.068
10	0.000	0.001	0.500	0.614	-0.001	0.002
11	0.001	0.001	0.580	0.561	-0.002	0.004
12	0.002	0.002	0.680	0.495	-0.003	0.007
13	0.003	0.004	0.820	0.414	-0.005	0.012
14	0.007	0.007	0.990	0.321	-0.007	0.021
15	0.014	0.012	1.200	0.229	-0.009	0.038
16	0.029	0.021	1.380	0.167	-0.012	0.071
17	0.058	0.041	1.420	0.157	-0.022	0.139
18	0.113	0.086	1.320	0.188	-0.055	0.281
19	0.003	0.005	0.560	0.573	-0.007	0.012
20	0.006	0.008	0.670	0.502	-0.011	0.022

21	0.011	0.014	0.830	0.409	-0.015	0.038
22	0.023	0.021	1.070	0.284	-0.019	0.065
23	0.046	0.031	1.500	0.134	-0.014	0.106
24	0.090	0.039	2.300	0.021	0.013	0.166
25	0.168	0.051	3.330	0.001	0.069	0.267
26	0.293	0.092	3.190	0.001	0.113	0.473
27	0.460	0.162	2.840	0.005	0.143	0.778
28	0.018	0.031	0.570	0.570	-0.043	0.079
29	0.036	0.053	0.680	0.499	-0.068	0.139
30	0.071	0.085	0.830	0.404	-0.095	0.237
31	0.135	0.125	1.080	0.278	-0.109	0.380
32	0.243	0.162	1.500	0.133	-0.074	0.560
33	0.397	0.181	2.200	0.028	0.043	0.752
34	0.575	0.178	3.230	0.001	0.226	0.924
35	0.736	0.158	4.670	0.000	0.427	1.044
36	0.851	0.123	6.910	0.000	0.610	1.092

PRS PSA

Adjusted predictions Number of obs = 121
Model VCE : OIM
Expression : Pr(signifca), predict()
1._at : baselinepsa = 0
prs = 8
2._at : baselinepsa = 0
prs = 8.5
3._at : baselinepsa = 0
prs = 9
4._at : baselinepsa = 0
prs = 9.5
5._at : baselinepsa = 0
prs = 10
6._at : baselinepsa = 0
prs = 10.5
7._at : baselinepsa = 0
prs = 11
8._at : baselinepsa = 0
prs = 11.5
9._at : baselinepsa = 0
prs = 12
10._at : baselinepsa = 1
prs = 8
11._at : baselinepsa = 1
prs = 8.5
12._at : baselinepsa = 1
prs = 9
13._at : baselinepsa = 1
prs = 9.5
14._at : baselinepsa = 1
prs = 10
15._at : baselinepsa = 1
prs = 10.5

16._at : baselinepsa = 1
prs = 11
17._at : baselinepsa = 1
prs = 11.5
18._at : baselinepsa = 1
prs = 12
19._at : baselinepsa = 2
prs = 8
20._at : baselinepsa = 2
prs = 8.5
21._at : baselinepsa = 2
prs = 9
22._at : baselinepsa = 2
prs = 9.5
23._at : baselinepsa = 2
prs = 10
24._at : baselinepsa = 2
prs = 10.5
25._at : baselinepsa = 2
prs = 11
26._at : baselinepsa = 2
prs = 11.5
27._at : baselinepsa = 2
prs = 12
28._at : baselinepsa = 3
prs = 8
29._at : baselinepsa = 3
prs = 8.5
30._at : baselinepsa = 3
prs = 9
31._at : baselinepsa = 3
prs = 9.5
32._at : baselinepsa = 3
prs = 10
33._at : baselinepsa = 3
prs = 10.5
34._at : baselinepsa = 3
prs = 11
35._at : baselinepsa = 3
prs = 11.5
36._at : baselinepsa = 3
prs = 12
37._at : baselinepsa = 4
prs = 8
38._at : baselinepsa = 4
prs = 8.5
39._at : baselinepsa = 4
prs = 9
40._at : baselinepsa = 4
prs = 9.5
41._at : baselinepsa = 4
prs = 10
42._at : baselinepsa = 4
prs = 10.5
43._at : baselinepsa = 4
prs = 11
44._at : baselinepsa = 4
prs = 11.5
45._at : baselinepsa = 4
prs = 12
46._at : baselinepsa = 5
prs = 8

47._at : baselinepsa = 5
prs = 8.5
48._at : baselinepsa = 5
prs = 9
49._at : baselinepsa = 5
prs = 9.5
50._at : baselinepsa = 5
prs = 10
51._at : baselinepsa = 5
prs = 10.5
52._at : baselinepsa = 5
prs = 11
53._at : baselinepsa = 5
prs = 11.5
54._at : baselinepsa = 5
prs = 12
55._at : baselinepsa = 6
prs = 8
56._at : baselinepsa = 6
prs = 8.5
57._at : baselinepsa = 6
prs = 9
58._at : baselinepsa = 6
prs = 9.5
59._at : baselinepsa = 6
prs = 10
60._at : baselinepsa = 6
prs = 10.5
61._at : baselinepsa = 6
prs = 11
62._at : baselinepsa = 6
prs = 11.5
63._at : baselinepsa = 6
prs = 12
64._at : baselinepsa = 7
prs = 8
65._at : baselinepsa = 7
prs = 8.5
66._at : baselinepsa = 7
prs = 9
67._at : baselinepsa = 7
prs = 9.5
68._at : baselinepsa = 7
prs = 10
69._at : baselinepsa = 7
prs = 10.5
70._at : baselinepsa = 7
prs = 11
71._at : baselinepsa = 7
prs = 11.5
72._at : baselinepsa = 7
prs = 12
73._at : baselinepsa = 8
prs = 8
74._at : baselinepsa = 8
prs = 8.5
75._at : baselinepsa = 8
prs = 9
76._at : baselinepsa = 8
prs = 9.5
77._at : baselinepsa = 8
prs = 10

78._at : baselinepsa = 8
prs = 10.5
79._at : baselinepsa = 8
prs = 11
80._at : baselinepsa = 8
prs = 11.5
81._at : baselinepsa = 8
prs = 12
82._at : baselinepsa = 9
prs = 8
83._at : baselinepsa = 9
prs = 8.5
84._at : baselinepsa = 9
prs = 9
85._at : baselinepsa = 9
prs = 9.5
86._at : baselinepsa = 9
prs = 10
87._at : baselinepsa = 9
prs = 10.5
88._at : baselinepsa = 9
prs = 11
89._at : baselinepsa = 9
prs = 11.5
90._at : baselinepsa = 9
prs = 12

Delta-method

	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at						
1	0.000	0.001	0.490	0.622	-0.001	0.002
2	0.001	0.002	0.570	0.567	-0.002	0.004
3	0.002	0.003	0.680	0.496	-0.003	0.007
4	0.004	0.004	0.830	0.406	-0.005	0.012
5	0.008	0.007	1.040	0.297	-0.007	0.022
6	0.015	0.011	1.330	0.185	-0.007	0.038
7	0.030	0.019	1.590	0.111	-0.007	0.068
8	0.060	0.037	1.620	0.105	-0.012	0.132
9	0.114	0.080	1.430	0.152	-0.042	0.271
10	0.001	0.001	0.510	0.611	-0.002	0.004
11	0.002	0.003	0.600	0.551	-0.004	0.007
12	0.003	0.004	0.720	0.472	-0.005	0.012
13	0.006	0.007	0.900	0.369	-0.007	0.020
14	0.013	0.011	1.170	0.240	-0.009	0.034
15	0.026	0.016	1.600	0.109	-0.006	0.057
16	0.051	0.024	2.080	0.038	0.003	0.099
17	0.098	0.047	2.080	0.038	0.006	0.191
18	0.181	0.104	1.740	0.082	-0.023	0.385
19	0.001	0.002	0.520	0.602	-0.004	0.006
20	0.003	0.004	0.620	0.538	-0.006	0.011
21	0.005	0.007	0.750	0.453	-0.009	0.019
22	0.011	0.011	0.960	0.338	-0.011	0.033
23	0.022	0.017	1.300	0.193	-0.011	0.054
24	0.043	0.023	1.910	0.056	-0.001	0.087
25	0.084	0.031	2.720	0.007	0.023	0.144
26	0.157	0.060	2.630	0.009	0.040	0.274
27	0.274	0.130	2.110	0.035	0.020	0.529
28	0.002	0.004	0.530	0.595	-0.006	0.010
29	0.004	0.007	0.630	0.529	-0.009	0.018
30	0.009	0.012	0.770	0.439	-0.014	0.032
31	0.018	0.018	1.000	0.317	-0.018	0.054

32	0.037	0.026	1.390	0.163	-0.015	0.088
33	0.072	0.033	2.150	0.032	0.006	0.137
34	0.136	0.042	3.220	0.001	0.053	0.218
35	0.242	0.079	3.060	0.002	0.087	0.397
36	0.393	0.155	2.530	0.011	0.089	0.697
37	0.004	0.007	0.540	0.592	-0.010	0.018
38	0.008	0.012	0.640	0.524	-0.016	0.031
39	0.015	0.020	0.790	0.432	-0.023	0.054
40	0.031	0.030	1.020	0.308	-0.029	0.090
41	0.061	0.043	1.430	0.153	-0.023	0.145
42	0.117	0.053	2.190	0.029	0.012	0.221
43	0.212	0.067	3.160	0.002	0.080	0.343
44	0.353	0.110	3.200	0.001	0.137	0.569
45	0.526	0.174	3.030	0.002	0.185	0.866
46	0.006	0.012	0.540	0.591	-0.017	0.030
47	0.013	0.020	0.640	0.523	-0.027	0.053
48	0.026	0.033	0.790	0.432	-0.039	0.092
49	0.052	0.051	1.020	0.309	-0.048	0.152
50	0.100	0.071	1.410	0.159	-0.039	0.239
51	0.184	0.089	2.070	0.038	0.010	0.358
52	0.315	0.109	2.880	0.004	0.100	0.529
53	0.483	0.147	3.290	0.001	0.195	0.770
54	0.655	0.177	3.700	0.000	0.308	1.001
55	0.011	0.021	0.530	0.593	-0.029	0.051
56	0.022	0.035	0.630	0.526	-0.046	0.091
57	0.044	0.057	0.780	0.436	-0.067	0.155
58	0.086	0.085	1.000	0.316	-0.082	0.253
59	0.160	0.116	1.370	0.170	-0.068	0.388
60	0.279	0.141	1.970	0.049	0.002	0.556
61	0.440	0.159	2.760	0.006	0.128	0.752
62	0.615	0.171	3.600	0.000	0.280	0.950
63	0.764	0.161	4.740	0.000	0.448	1.081
64	0.019	0.035	0.530	0.597	-0.051	0.088
65	0.037	0.060	0.630	0.531	-0.080	0.154
66	0.073	0.095	0.770	0.442	-0.113	0.259
67	0.138	0.139	0.990	0.321	-0.135	0.411
68	0.246	0.180	1.360	0.173	-0.108	0.599
69	0.398	0.201	1.980	0.048	0.004	0.792
70	0.574	0.196	2.930	0.003	0.189	0.958
71	0.732	0.171	4.280	0.000	0.397	1.067
72	0.847	0.133	6.380	0.000	0.587	1.108
73	0.032	0.061	0.520	0.602	-0.087	0.150
74	0.062	0.100	0.620	0.536	-0.135	0.259
75	0.119	0.155	0.770	0.444	-0.185	0.423
76	0.215	0.214	1.000	0.315	-0.205	0.635
77	0.358	0.252	1.420	0.156	-0.136	0.852
78	0.531	0.246	2.160	0.031	0.048	1.014
79	0.697	0.204	3.420	0.001	0.298	1.096
80	0.824	0.150	5.510	0.000	0.531	1.117
81	0.905	0.101	8.960	0.000	0.707	1.103
82	0.053	0.102	0.520	0.605	-0.148	0.254
83	0.102	0.165	0.620	0.536	-0.221	0.425
84	0.188	0.240	0.780	0.435	-0.284	0.659
85	0.319	0.301	1.060	0.289	-0.271	0.909
86	0.488	0.309	1.580	0.114	-0.117	1.093
87	0.660	0.257	2.560	0.010	0.155	1.164
88	0.798	0.183	4.360	0.000	0.439	1.156
89	0.889	0.118	7.530	0.000	0.658	1.120
90	0.942	0.072	13.020	0.000	0.800	1.084

Predictive margins Number of obs = 121

PRS FH degree

Model VCE : OIM
Expression : Pr(any cancer), predict()
1._at : prs = 8
2._at : prs = 9
3._at : prs = 10
4._at : prs = 11
5._at : prs = 12

	Delta-method					
	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#fhvariable_1						
1 1	0.021	0.022	0.940	0.347	-0.023	0.065
1 2	0.069	0.065	1.070	0.284	-0.057	0.196
1 3	0.022	0.025	0.890	0.375	-0.027	0.072
2 1	0.059	0.040	1.470	0.143	-0.020	0.139
2 2	0.172	0.091	1.880	0.060	-0.007	0.351
2 3	0.063	0.047	1.330	0.184	-0.030	0.155
3 1	0.151	0.053	2.840	0.005	0.047	0.255
3 2	0.350	0.084	4.150	0.000	0.185	0.515
3 3	0.157	0.068	2.330	0.020	0.025	0.290
4 1	0.317	0.066	4.790	0.000	0.188	0.447
4 2	0.571	0.083	6.840	0.000	0.407	0.734
4 3	0.328	0.086	3.820	0.000	0.160	0.497
5 1	0.536	0.120	4.450	0.000	0.300	0.772
5 2	0.771	0.105	7.360	0.000	0.566	0.976
5 3	0.547	0.130	4.220	0.000	0.293	0.802

Table 13 adjusted predictions at degree of FH at different values of PRS

Contrasts of adjusted predictions **Number of obs = 121**
Model VCE : OIM
Expression : Pr(any cancer), predict()
1._at : prs = 8
2._at : prs = 8.5
3._at : prs = 9
4._at : prs = 9.5
5._at : prs = 10
6._at : prs = 10.5
7._at : prs = 11
8._at : prs = 11.5
9._at : prs = 12

	Delta-method			
	Contrast	Std.Err.	z	P>z
fhvariable_1@_at				
(2 vs base) 1	0.024	0.023	1.020	0.309
(2 vs base) 2	0.040	0.034	1.190	0.236
(2 vs base) 3	0.067	0.048	1.390	0.163
(2 vs base) 4	0.106	0.066	1.620	0.105
(2 vs base) 5	0.154	0.086	1.800	0.071

(2 vs base) 6	0.201	0.105	1.910	0.056
(2 vs base) 7	0.226	0.115	1.960	0.050
(2 vs base) 8	0.217	0.110	1.970	0.048
(2 vs base) 9	0.178	0.096	1.850	0.064
(3 vs base) 1	0.001	0.009	0.080	0.938
(3 vs base) 2	0.001	0.015	0.080	0.938
(3 vs base) 3	0.002	0.026	0.080	0.938
(3 vs base) 4	0.003	0.043	0.080	0.938
(3 vs base) 5	0.005	0.068	0.080	0.938
(3 vs base) 6	0.008	0.097	0.080	0.938
(3 vs base) 7	0.010	0.123	0.080	0.938
(3 vs base) 8	0.010	0.134	0.080	0.937
(3 vs base) 9	0.010	0.123	0.080	0.937

Table 39 - Contrasts of adjusted predictions of degree of FH at different values of PRS displayed above in table 40. There is a statistically significant difference in (any) cancer probability in men with 2 relatives compared with those with 1 relatives, at the higher end of PRS.

PRS PIRADS 3-5

Adjusted predictions Number of obs = 120
Model VCE : OIM
Expression : Pr(signifca), predict()
1._at : prs = 8
2._at : prs = 8.5
3._at : prs = 9
4._at : prs = 9.5
5._at : prs = 10
6._at : prs = 10.5
7._at : prs = 11
8._at : prs = 11.5
9._at : prs = 12
10._at : prs = 12.5

	Delta-method Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#pirads 3-5 MRI						
1#N	0.000	0.001	0.490	0.628	-0.001	0.002
1#Y	0.009	0.016	0.570	0.572	-0.022	0.040
2#N	0.001	0.001	0.550	0.581	-0.002	0.003
2#Y	0.017	0.025	0.680	0.499	-0.032	0.066
3#N	0.001	0.002	0.630	0.526	-0.002	0.005
3#Y	0.032	0.038	0.840	0.399	-0.042	0.106
4#N	0.002	0.003	0.730	0.464	-0.004	0.008
4#Y	0.059	0.053	1.110	0.265	-0.045	0.164
5#N	0.004	0.005	0.840	0.399	-0.006	0.014
5#Y	0.108	0.067	1.600	0.109	-0.024	0.240
6#N	0.008	0.008	0.950	0.345	-0.009	0.025
6#Y	0.188	0.075	2.510	0.012	0.041	0.334
7#N	0.015	0.015	1.000	0.316	-0.015	0.045
7#Y	0.307	0.085	3.610	0.000	0.140	0.473
8#N	0.029	0.029	0.990	0.322	-0.028	0.086
8#Y	0.458	0.124	3.700	0.000	0.215	0.701
9#N	0.053	0.058	0.920	0.356	-0.060	0.167
9#Y	0.618	0.168	3.670	0.000	0.288	0.948

10#N	0.098	0.115	0.850	0.396	-0.128	0.323
10#Y	0.756	0.179	4.230	0.000	0.405	1.106

PRS PIRADS 4-5

Adjusted predictions Number of obs = 120
Model VCE : OIM
Expression : Pr(signifca), predict()
1._at : prs = 8
2._at : prs = 8.5
3._at : prs = 9
4._at : prs = 9.5
5._at : prs = 10
6._at : prs = 10.5
7._at : prs = 11
8._at : prs = 11.5
9._at : prs = 12
10._at : prs = 12.5

	Delta-method Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#pirads 4-5						
1 0	0.002	0.003	0.560	0.574	-0.004	0.008
1 1	0.022	0.038	0.570	0.571	-0.053	0.097
2 0	0.003	0.005	0.660	0.507	-0.006	0.012
2 1	0.038	0.055	0.680	0.498	-0.071	0.146
3 0	0.006	0.007	0.810	0.420	-0.008	0.019
3 1	0.064	0.076	0.840	0.399	-0.085	0.214
4 0	0.010	0.009	1.020	0.310	-0.009	0.028
4 1	0.108	0.098	1.100	0.269	-0.083	0.299
5 0	0.017	0.013	1.330	0.184	-0.008	0.042
5 1	0.175	0.113	1.550	0.122	-0.047	0.397
6 0	0.029	0.017	1.750	0.079	-0.003	0.062
6 1	0.272	0.119	2.290	0.022	0.039	0.505
7 0	0.050	0.025	2.040	0.041	0.002	0.099
7 1	0.397	0.124	3.200	0.001	0.153	0.640
8 0	0.085	0.046	1.850	0.065	-0.005	0.176
8 1	0.536	0.145	3.700	0.000	0.252	0.821
9 0	0.141	0.093	1.510	0.132	-0.042	0.324
9 1	0.670	0.167	4.010	0.000	0.342	0.998
10 0	0.224	0.174	1.290	0.199	-0.118	0.565
10 1	0.782	0.168	4.650	0.000	0.452	1.111

PRS AGE MRI

Adjusted predictions Number of obs = 120
Model VCE : OIM
Expression : Pr(signifca), predict()
1._at : prs = 8
ageatstudy~y = 40

2._at : prs = 8
ageatstudy~y = 50
3._at : prs = 8
ageatstudy~y = 60
4._at : prs = 8
ageatstudy~y = 70
5._at : prs = 9
ageatstudy~y = 40
6._at : prs = 9
ageatstudy~y = 50
7._at : prs = 9
ageatstudy~y = 60
8._at : prs = 9
ageatstudy~y = 70
9._at : prs = 10
ageatstudy~y = 40
10._at : prs = 10
ageatstudy~y = 50
11._at : prs = 10
ageatstudy~y = 60
12._at : prs = 10
ageatstudy~y = 70
13._at : prs = 11
ageatstudy~y = 40
14._at : prs = 11
ageatstudy~y = 50
15._at : prs = 11
ageatstudy~y = 60
16._at : prs = 11
ageatstudy~y = 70
17._at : prs = 12
ageatstudy~y = 40
18._at : prs = 12
ageatstudy~y = 50
19._at : prs = 12
ageatstudy~y = 60
20._at : prs = 12
ageatstudy~y = 70

Delta-method

	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#MRI Pirads 3-5						
1#N	0.000	0.000	0.310	0.759	-0.000	0.000
1#Y	0.000	0.000	0.350	0.725	-0.001	0.001
2#N	0.000	0.000	0.350	0.723	-0.000	0.000
2#Y	0.001	0.002	0.420	0.674	-0.003	0.004
3#N	0.000	0.000	0.400	0.690	-0.001	0.001
3#Y	0.005	0.010	0.490	0.627	-0.015	0.025
4#N	0.001	0.003	0.420	0.674	-0.004	0.006
4#Y	0.029	0.056	0.520	0.603	-0.081	0.140
5#N	0.000	0.000	0.370	0.713	-0.000	0.000
5#Y	0.001	0.001	0.440	0.661	-0.002	0.004
6#N	0.000	0.000	0.450	0.655	-0.000	0.001
6#Y	0.004	0.007	0.570	0.568	-0.010	0.018
7#N	0.001	0.002	0.520	0.601	-0.002	0.004
7#Y	0.024	0.033	0.720	0.469	-0.041	0.089
8#N	0.005	0.010	0.550	0.582	-0.014	0.025
8#Y	0.132	0.159	0.830	0.408	-0.180	0.443
9#N	0.000	0.000	0.440	0.657	-0.000	0.001

9#Y	0.003	0.006	0.560	0.577	-0.008	0.015
10#N	0.001	0.001	0.580	0.563	-0.002	0.003
10#Y	0.020	0.023	0.850	0.393	-0.025	0.064
11#N	0.004	0.006	0.720	0.472	-0.008	0.017
11#Y	0.110	0.078	1.410	0.160	-0.043	0.262
12#N	0.027	0.036	0.740	0.459	-0.044	0.098
12#Y	0.432	0.230	1.880	0.060	-0.018	0.882
13#N	0.001	0.001	0.520	0.602	-0.002	0.003
13#Y	0.016	0.023	0.690	0.492	-0.030	0.061
14#N	0.004	0.005	0.730	0.468	-0.006	0.013
14#Y	0.091	0.068	1.330	0.183	-0.043	0.225
15#N	0.022	0.023	0.950	0.345	-0.024	0.067
15#Y	0.381	0.106	3.610	0.000	0.175	0.588
16#N	0.122	0.129	0.950	0.345	-0.130	0.374
16#Y	0.792	0.142	5.580	0.000	0.514	1.070
17#N	0.003	0.005	0.560	0.576	-0.007	0.013
17#Y	0.075	0.100	0.750	0.453	-0.121	0.271
18#N	0.018	0.023	0.770	0.442	-0.028	0.063
18#Y	0.334	0.207	1.610	0.107	-0.072	0.739
19#N	0.101	0.104	0.970	0.332	-0.103	0.305
19#Y	0.756	0.153	4.940	0.000	0.456	1.056
20#N	0.410	0.333	1.230	0.219	-0.243	1.062
20#Y	0.950	0.059	16.240	0.000	0.836	1.065

Adjusted predictions Number of obs = 120
Model VCE : OIM
Expression : Pr(signifca), predict()
1._at : prs = 8
ageatstudy~y = 40
2._at : prs = 8
ageatstudy~y = 50
3._at : prs = 8
ageatstudy~y = 60
4._at : prs = 8
ageatstudy~y = 70
5._at : prs = 9
ageatstudy~y = 40
6._at : prs = 9
ageatstudy~y = 50
7._at : prs = 9
ageatstudy~y = 60
8._at : prs = 9
ageatstudy~y = 70
9._at : prs = 10
ageatstudy~y = 40
10._at : prs = 10
ageatstudy~y = 50
11._at : prs = 10
ageatstudy~y = 60
12._at : prs = 10
ageatstudy~y = 70
13._at : prs = 11
ageatstudy~y = 40
14._at : prs = 11
ageatstudy~y = 50
15._at : prs = 11
ageatstudy~y = 60
16._at : prs = 11
ageatstudy~y = 70

17._at : prs = 12
ageatstudy~y = 40
18._at : prs = 12
ageatstudy~y = 50
19._at : prs = 12
ageatstudy~y = 60
20._at : prs = 12
ageatstudy~y = 70

Delta-method

	Margin	Std.Err.	z	P>z	[95%Conf.	Interval]
_at#abnormalMRI45						
1 0	0.000	0.000	0.410	0.679	-0.000	0.001
1 1	0.001	0.002	0.390	0.699	-0.003	0.004
2 0	0.001	0.001	0.490	0.624	-0.002	0.003
2 1	0.003	0.006	0.460	0.643	-0.009	0.015
3 0	0.002	0.004	0.540	0.589	-0.006	0.010
3 1	0.011	0.021	0.530	0.595	-0.031	0.053
4 0	0.009	0.016	0.530	0.596	-0.023	0.041
4 1	0.045	0.080	0.560	0.573	-0.111	0.201
5 0	0.000	0.001	0.510	0.608	-0.001	0.002
5 1	0.002	0.005	0.470	0.641	-0.008	0.013
6 0	0.002	0.003	0.660	0.508	-0.004	0.007
6 1	0.010	0.017	0.610	0.543	-0.022	0.043
7 0	0.008	0.010	0.770	0.439	-0.012	0.027
7 1	0.040	0.051	0.770	0.439	-0.061	0.141
8 0	0.030	0.042	0.730	0.468	-0.052	0.113
8 1	0.144	0.165	0.870	0.383	-0.180	0.468
9 0	0.002	0.003	0.640	0.525	-0.003	0.007
9 1	0.009	0.016	0.560	0.574	-0.022	0.040
10 0	0.007	0.007	0.960	0.338	-0.007	0.021
10 1	0.035	0.042	0.840	0.399	-0.047	0.117
11 0	0.027	0.021	1.270	0.204	-0.015	0.068
11 1	0.129	0.095	1.360	0.173	-0.057	0.316
12 0	0.101	0.096	1.050	0.294	-0.088	0.290
12 1	0.377	0.215	1.760	0.079	-0.044	0.797
13 0	0.006	0.008	0.740	0.459	-0.010	0.022
13 1	0.031	0.048	0.650	0.517	-0.063	0.125
14 0	0.024	0.018	1.310	0.191	-0.012	0.059
14 1	0.116	0.100	1.160	0.247	-0.080	0.312
15 0	0.090	0.045	1.990	0.046	0.001	0.179
15 1	0.348	0.125	2.790	0.005	0.103	0.592
16 0	0.287	0.196	1.470	0.143	-0.097	0.672
16 1	0.684	0.163	4.200	0.000	0.365	1.004
17 0	0.021	0.028	0.740	0.459	-0.035	0.077
17 1	0.104	0.148	0.700	0.483	-0.186	0.393
18 0	0.080	0.067	1.210	0.228	-0.050	0.211
18 1	0.320	0.228	1.400	0.160	-0.127	0.766
19 0	0.262	0.156	1.680	0.092	-0.043	0.568
19 1	0.657	0.172	3.810	0.000	0.319	0.995
20 0	0.591	0.286	2.070	0.039	0.030	1.152
20 1	0.886	0.101	8.800	0.000	0.689	1.083

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
No Prior PSA	1	.	.	.	.	.	

(ref)							
Unknown	3.448	3.22	1.33	.185	.553	21.506	
Prior PSA	2.482	1.226	1.84	.066	.942	6.536	*
			.	.	.	.	
PRS	3.209	1.027	3.64	0	1.714	6.011	***
Constant	0	0	-3.94	0	0	.001	***

Mean dependent var	0.342	SD dependent var	0.476
Pseudo r-squared	0.126	Number of obs	120.000
Chi-square	19.490	Prob > chi2	0.000
Akaike crit. (AIC)	142.622	Bayesian crit. (BIC)	153.772

*** p<.01, ** p<.05, * p<.1

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
No Prior PSA (ref)	1	.	.	.	.	.	
Unknown	3.448	3.22	1.33	.185	.553	21.506	
Prior PSA	2.482	1.226	1.84	.066	.942	6.536	*
			.	.	.	.	
PRS	3.209	1.027	3.64	0	1.714	6.011	***
Constant	0	0	-3.94	0	0	.001	***

Mean dependent var	0.342	SD dependent var	0.476
Pseudo r-squared	0.126	Number of obs	120.000
Chi-square	19.490	Prob > chi2	0.000
Akaike crit. (AIC)	142.622	Bayesian crit. (BIC)	153.772

*** p<.01, ** p<.05, * p<.1

Table 0.1 Overall, the model is significant (p<0.0001).

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Age	1.059	.029	2.08	.038	1.003	1.117	**
PRS	3.146	1.008	3.58	0	1.678	5.897	***
Constant	0	0	-4.14	0	0	0	***

Mean dependent var	0.339	SD dependent var	0.475
Pseudo r-squared	0.127	Number of obs	121.000
Chi-square	19.694	Prob > chi2	0.000
Akaike crit. (AIC)	141.250	Bayesian crit. (BIC)	149.637

*** p<.01, ** p<.05, * p<.1

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
PRS	2.73	.966	2.84	.005	1.365	5.461	***
PSA (ng/ml)							
<1 (ref)	1	.	.	.	.	.	
1-<2	3.042	1.9	1.78	.075	.894	10.349	*
2-<3	6.452	4.144	2.90	.004	1.833	22.719	***
>=3	8.403	5.925	3.02	.003	2.11	33.465	***

Constant	0	0	-3.32	.001	0	.006	***

Mean dependent var	0.339	SD dependent var	0.475
Pseudo r-squared	0.187	Number of obs	121.000
Chi-square	28.923	Prob > chi2	0.000
Akaike crit. (AIC)	136.021	Bayesian crit. (BIC)	150.000

*** p<.01, ** p<.05, * p<.1

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
PSAD	1.011	.005	2.02	.044	1	1.022	**
PRS	2.691	.881	3.02	.002	1.417	5.113	***
Constant	0	0	-3.39	.001	0	.007	***

Mean dependent var	0.339	SD dependent var	0.475
Pseudo r-squared	0.130	Number of obs	121.000
Chi-square	20.099	Prob > chi2	0.000
Akaike crit. (AIC)	140.845	Bayesian crit. (BIC)	149.232

*** p<.01, ** p<.05, * p<.1

Table 0.2 Logistic regression model investigating PSAD and PRS as continuous variables

Logistic regression		Number of obs =	121	
	LR chi2(2) =	20.70		
	Prob > chi2 =	0.0000		
Log likelihood = -67.120604		Pseudo R2 =	0.1336	
canceranybiopsy Odds ratio	Std. err.	z	P>z [95% conf.	interval]
prs 2.894509	.9392746	3.28	0.001 1.53235	5.467536
baselinepsa 1.360386	.1853658	2.26	0.024 1.041544	1.776833
_cons 3.33e-06	.0000117	-3.61	0.000 3.53e-09	.0031518
Note: _cons estimates baseline	odds.			

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
PiRADS 3-5 MRI	2.727	1.202	2.28	.023	1.15	6.468	**
PRS	3.058	.992	3.44	.001	1.619	5.776	***
Constant	0	0	-3.69	0	0	.002	***

Mean dependent var	0.342	SD dependent var	0.476
Pseudo r-squared	0.134	Number of obs	120.000
Chi-square	20.623	Prob > chi2	0.000

Akaike crit. (AIC)	139.489	Bayesian crit. (BIC)	147.852

*** p<.01, ** p<.05, * p<.1

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
		.	.	.	.	.	
PiRADS 4-5	4.131	2.398	2.44	.015	1.324	12.888	**
		.	.	.	.	.	
PRS	2.922	.956	3.28	.001	1.54	5.547	***
Constant	0	0	-3.51	0	0	.004	***

Mean dependent var	0.342	SD dependent var	0.476
Pseudo r-squared	0.141	Number of obs	120.000
Chi-square	21.684	Prob > chi2	0.000
Akaike crit. (AIC)	138.428	Bayesian crit. (BIC)	146.790

*** p<.01, ** p<.05, * p<.1

Table 0.3 Overall, a model incorporating MRI PiRADS 4-5 and PRS was statistically significant (p<0.0001). PRS was positively associated with (any) cancer (OR 2.92) and this was statistically significant (p=0.001). MRI PiRADS 4-5 was positively associated with (any) cancer detection (OR 4.1) compared to men without (i.e PiRADS 1-3).

Logistic regression

Any cancer	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
I rel <70 (ref)	1	.	.	.	.	.	
2 rels	2.519	1.222	1.90	.057	.973	6.521	*
3.rels	1.043	.558	0.08	.937	.366	2.974	
PRS	3.218	1.037	3.63	0	1.711	6.053	***
Constant	0	0	-3.86	0	0	.001	***

Mean dependent var	0.339	SD dependent var	0.475
Pseudo r-squared	0.126	Number of obs	121.000
Chi-square	19.471	Prob > chi2	0.000
Akaike crit. (AIC)	143.473	Bayesian crit. (BIC)	154.656

*** p<.01, ** p<.05, * p<.1

Table 0.4

Signif ca	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
No Prior PSA	1	.	.	.	.	.	
Unknown	3.711	5.068	0.96	.337	.255	53.947	
Prior PSA	2.078	1.764	0.86	.389	.394	10.972	
PRS	4.099	2.21	2.62	.009	1.425	11.791	***
Constant	0	0	-3.00	.003	0	.002	***

Mean dependent var	0.092	SD dependent var	0.290
Pseudo r-squared	0.127	Number of obs	120.000
Chi-square	9.356	Prob > chi2	0.025
Akaike crit. (AIC)	72.175	Bayesian crit. (BIC)	83.325

*** p<.01, ** p<.05, * p<.1

Table 0.5 In a model with PRS, the presence of pior PSA screening prior to stufy entry was not associated with significnt cancer detection (OR 2.0, p0.389).

Logistic regression

Signif ca	PR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Age	1.209	.078	2.96	.003	1.066	1.372	***
PRS	4.217	2.408	2.52	.012	1.377	12.914	**
Constant	0	0	-3.64	0	0	0	***

Mean dependent var	0.091	SD dependent var	0.289
Pseudo r-squared	0.288	Number of obs	121.000
Chi-square	21.262	Prob > chi2	0.000
Akaike crit. (AIC)	58.460	Bayesian crit. (BIC)	66.847

*** p

Logistic regression

Signif ca	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
Age 40-<50	1	.	.	.	.	.	
Age 50-<60	1.449	1.832	0.29	.77	.121	17.274	
Age≥60	24.547	28.218	2.78	.005	2.579	233.623	***
PRS	4.711	2.837	2.57	.01	1.447	15.336	**
Constant	0	0	-3.03	.002	0	.001	***

Mean dependent var	0.091	SD dependent var	0.289
Pseudo r-squared	0.338	Number of obs	121.000
Chi-square	24.940	Prob > chi2	0.000
Akaike crit. (AIC)	56.782	Bayesian crit. (BIC)	67.965

*** p<.01, ** p<.05, * p<.1

Table 0.6 In two models, one with with PRS and age as a categorical variable and the other with age as a continuous variable, age greater or equalled to 60 years old was significantly associated with significant cancer outcome (OR 24.5; p=0.005).

Logistic regression

Signif ca	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
PSA	1.711	.307	3.00	.003	1.205	2.431	***
PRS	4.131	2.478	2.36	.018	1.275	13.386	**
Constant	0	0	-2.82	.005	0	.003	***
Mean dependent var		0.091	SD dependent var			0.289	
Pseudo r-squared		0.241	Number of obs			121.000	
Chi-square		17.733	Prob > chi2			0.000	
Akaike crit. (AIC)		61.989	Bayesian crit. (BIC)			70.376	

*** p<.01, ** p<.05, * p<.1

Table 0.7 PSA (OR 1.7; p=0.003) and PRS (OR 4.1; p=p=0.018) were positively and statistically significantly associated with the probability of significant cancer (p<0.01)

Logistic regression

Signif ca	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
PSAD	1.019	.006	3.02	.003	1.007	1.032	***
PRS	3.159	1.95	1.86	.063	.942	10.595	*
Constant	0	0	-2.37	.018	0	.061	**
Mean dependent var		0.091	SD dependent var			0.289	
Pseudo r-squared		0.263	Number of obs			121.000	
Chi-square		19.404	Prob > chi2			0.000	
Akaike crit. (AIC)		60.318	Bayesian crit. (BIC)			68.706	

*** p<.01, ** p<.05, * p<.1

Table 0.8 PSAD (OR 1.019) and PRS (3.159) were positively and statistically significantly associated with the probability of significant cancer (p<0.01)

Logistic regression

Signif ca	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
PiRADS 3-5 MRI	28.641	31.179	3.08	.002	3.391	241.899	***
PRS	3.658	2.132	2.22	.026	1.167	11.463	**
Constant	0	0	-2.82	.005	0	.004	***
Mean dependent var		0.092	SD dependent var			0.290	
Pseudo r-squared		0.348	Number of obs			120.000	
Chi-square		25.595	Prob > chi2			0.000	
Akaike crit. (AIC)		53.935	Bayesian crit. (BIC)			62.298	

*** p<.01, ** p<.05, * p<.1

Table 0.9 PRS was associated with significant cancer (OR 3.65) detection. The probability of significant cancer

Logistic regression

Signif ca	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
PRS	3.926	2.446	2.20	.028	1.158	13.314	**
PSA	1.56	.3	2.31	.021	1.07	2.272	**
Age	1.195	.083	2.56	.011	1.042	1.37	**
Constant	0	0	-3.38	.001	0	0	***
Mean dependent var		0.091	SD dependent var			0.289	
Pseudo r-squared		0.362	Number of obs			121.000	
Chi-square		26.674	Prob > chi2			0.000	
Akaike crit. (AIC)		55.048	Bayesian crit. (BIC)			66.231	

*** p<.01, ** p<.05, * p<.1

Table 0.10 logistic regression model including PRS, PSA and age as contiuous variables.

Age was then added to the models incorporating MRI and PRS, with the following results.

Logistic regression MRI PiRADS 3-5, Age, PRS

Signif ca	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
PiRADS 3-5	27.52	32.35	2.82	.005	2.748	275.59	***
PRS	5.012	3.406	2.37	.018	1.323	18.99	**
Age	1.2	.086	2.54	.011	1.043	1.38	**
Constant	0	0	-3.24	.001	0	0	***
Mean dependent var		0.092	SD dependent var			0.290	
Pseudo r-squared		0.474	Number of obs			120.000	
Chi-square		34.853	Prob > chi2			0.000	
Akaike crit. (AIC)		46.678	Bayesian crit. (BIC)			57.827	

*** p<.01, ** p<.05, * p<.1

Logistic regression MRI PiRADS 4-5, Age, PRS

Signif ca	OR.	St.Err.	t-value	p-value	[95% Conf	Interval]	Sig
PiRADS 4-5	5.3771	4.291	2.11	.035	1.125	25.697	**
PRS	3.588	2.113	2.17	.03	1.132	11.377	**
Age	1.151	.078	2.07	.039	1.007	1.314	**
Constant	0	0	-3.02	.003	0	0	***
Mean dependent var		0.092	SD dependent var			0.290	
Pseudo r-squared		0.349	Number of obs			120.000	
Chi-square		25.663	Prob > chi2			0.000	
Akaike crit. (AIC)		55.868	Bayesian crit. (BIC)			67.018	

**** p<.01, ** p<.05, * p<.1*

Table 0.11 Logistic regression model incorporating PRS and age as continuous variables and MRI PiRADS 4-5.