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Prostate Cancer

Interim Results from the IMPACT Study: Evidence for Prostate-specific Antigen Screening in *BRCA2* Mutation Carriers

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Abstract

Background: Mutations in *BRCA2* cause a higher risk of early-onset aggressive prostate cancer (PrCa). The IMPACT study is evaluating targeted PrCa screening using prostate-specific-antigen (PSA) in men with germline *BRCA1/2* mutations.
Objective: To report the utility of PSA screening, PrCa incidence, positive predictive value of PSA, biopsy, and tumour characteristics after 3 yr of screening, by BRCA status.
Design, setting, and participants: Men aged 40–69 yr with a germline pathogenic *BRCA1/2* mutation and male controls testing negative for a familial *BRCA1/2* mutation were recruited. Participants underwent PSA screening for 3 yr, and if PSA > 3.0 ng/ml, men were offered prostate biopsy.
Outcome measurements and statistical analysis: PSA levels, PrCa incidence, and tumour characteristics were evaluated. Statistical analyses included Poisson regression offset by person-year follow-up, chi-square tests for proportion *t* tests for means, and Kruskal-Wallis for medians.
Results and limitations: A total of 3027 patients (2932 unique individuals) were recruited (919 *BRCA1* carriers, 709 *BRCA1* noncarriers, 902 *BRCA2* carriers, and 497 *BRCA2* noncarriers). After 3 yr of screening, 527 men had PSA > 3.0 ng/ml, 357 biopsies were performed, and 112 PrCa cases were diagnosed (31 *BRCA1* carriers, 19 *BRCA1* noncarriers, 47 *BRCA2* carriers, and 15 *BRCA2* noncarriers). Higher compliance with biopsy was observed in *BRCA2* carriers compared with noncarriers (73% vs 60%). Cancer incidence rate per 1000 person years was higher in *BRCA2* carriers than in noncarriers (19.4 vs 12.0; $p = 0.03$); *BRCA2* carriers were diagnosed at a younger age (61 vs 64 yr; $p = 0.04$) and were more likely to have clinically significant disease than *BRCA2* noncarriers (77% vs 40%; $p = 0.01$). No differences in age or tumour characteristics were detected between *BRCA1* carriers and *BRCA1* noncarriers. The 4 kallikrein marker model discriminated better (area under the curve [AUC] = 0.73) for clinically significant cancer at biopsy than PSA alone (AUC = 0.65).
Conclusions: After 3 yr of screening, compared with noncarriers, *BRCA2* mutation carriers were associated with a higher incidence of PrCa, younger age of diagnosis, and clinically significant tumours. Therefore, systematic PSA screening is indicated for men with a *BRCA2* mutation. Further follow-up is required to assess the role of screening in *BRCA1* mutation carriers.
Patient summary: We demonstrate that after 3 yr of prostate-specific antigen (PSA) testing, we detect more serious prostate cancers in men with *BRCA2* mutations than in those without these mutations. We recommend that male *BRCA2* carriers are offered systematic PSA screening.

1. Introduction

It is well established that *BRCA2* gene mutations cause a higher risk of prostate cancer (PrCa), with an estimated relative risk of 2.5–8.6-fold by age 65 yr [1,2], and are associated with earlier-onset, clinically significant disease. A number of retrospective studies report higher rates of lymph node involvement, distant metastasis at diagnosis, and higher mortality rates in mutation carriers [3–6]. Germline *BRCA2* mutation status is reported to be an independent prognostic factor for poorer outcome [3]. Furthermore, tumours of *BRCA2* mutation carriers with localised PrCa have been demonstrated to exhibit genomic instability more typically seen in metastatic castration-resistant PrCa [7].

There is debate about whether there is an increased risk of PrCa for *BRCA1* mutation carriers, with an estimated relative risk of 1.8–3.75-fold by age 65 yr [8] and some evidence of more clinically significant disease [3,9]; however, this warrants further research. It is hypothesised that targeted screening in *BRCA1/2* carriers facilitates early detection.

The controversies of using prostate-specific antigen (PSA) screening in the general population are well documented, but PSA remains the most effective PrCa biomarker currently available [10–12]. Efforts to improve sensitivity and specificity of PSA by incorporating other biological markers, such as the 4 kallikrein (4 K) marker panel [13,14], PrCa risk calculators [15,16], magnetic resonance imaging (MRI) [17,18], and genetic markers [19,20], into screening algorithms are under evaluation.

The IMPACT study (Identification of Men with a genetic predisposition to ProstAte Cancer: Targeted screening in men at higher genetic risk and controls; http://impact.icr.ac.uk/) is an international, multicentre study evaluating targeted PrCa screening in men with *BRCA1/2* mutations. IMPACT aims to evaluate the utility of PSA screening in detecting clinically significant PrCa (defined as intermediate- or high-risk disease using the National Institute for Health and Care Excellence [NICE] guidelines [21]), PrCa incidence, positive predictive value (PPV) of biopsy using a PSA threshold of 3.0 ng/ml, and tumour characteristics in order to establish whether PSA screening detects clinically significant disease in this population compared with the noncarrier control group.

An analysis of the baseline screen for nearly 2500 men enrolled in IMPACT supported the use of targeted PSA screening in *BRCA1/2* mutation carriers, suggesting that screening detects a high proportion of clinically significant tumours [22]. Moreover, we have also demonstrated that PSA is more predictive of PrCa in *BRCA1/2* carriers than in noncarriers [23]. It has been reported that men with germline *BRCA1/ BRCA2* mutations, on active surveillance for low-risk PrCa, are at a higher risk of reclassification to higher-grade PrCa than noncarriers [24].

National Comprehensive Cancer Network guidelines advise PrCa screening to begin at 45 yr for male *BRCA2* carriers, consider the same for *BRCA1* carriers, and perform routine *BRCA1/2* testing for men with high-risk PrCa, family history, or metastatic disease [25,26].

The aims of this study were to evaluate the utility of PSA screening, by assessing PrCa prevalence/incidence, PPV of biopsy, and tumour characteristics. A secondary aim was to evaluate the addition of 4 K markers to the algorithm predicting biopsy outcome (full details of this analysis can be found in the Supplementary material).

2. Patients and methods

The IMPACT study design has been reported previously [22,27,28] and is summarised in Fig. 1. The protocol was approved by the West-Midlands Research and Ethics Committee in the UK (reference: 05/MRE07/25) and subsequently by each participating institution's local committee. All participants provided written consent, and interim analyses are presented to the Independent Data and Safety Monitoring Committee biannually.

The target sample is 500 *BRCA1* and 350 *BRCA2* mutation carriers, and a control group of 850 men who have undergone predictive testing and tested negative for a pathogenic *BRCA1/2* mutation known to be present in their family. IMPACT has been powered to detect a two-fold PrCa risk over 5 yr of screening, with 80% power at the $p < 0.01$ level.

Between October 2005 and February 2013, men aged 45–69 yr in The Netherlands and 40–69 yr in all other countries were recruited from families with known pathogenic *BRCA1* or *BRCA2* mutations. Further detail of the inclusion criteria were described previously [22,27,28]. Participants were screened annually in all centres except for those in The Netherlands, which screened biennially in accordance with local regulations. Recruitment was extended to December 2015, and a subset of 95 *BRCA2* noncarriers was sequenced for *BRCA1/2* mutations and used as the control group to cover the loss of numbers that resulted in removing The Netherlands cohort from cumulative analyses and include them as *BRCA1* noncarriers.

All participants underwent annual PSA testing for four screening rounds. If PSA was >3.0 ng/ml, transrectal ultrasound–guided prostate biopsy (PB) was recommended. Decision to biopsy was based on this single PSA level; PSA was not repeated prior to biopsy unless clinically indicated. Centres were requested to follow a standard biopsy protocol, consisting of 10 and 12 biopsy cores taken from specific locations within the prostate gland. Individuals with a benign PB continued annual PSA follow-up. A repeat PB was recommended if PSA was >50% of the pre-PB PSA [29] (Fig. 1). The local histopathologist at each centre reported the biopsy results to guide treatment in accordance with local guidelines. Cancers were defined using the NICE criteria, and were deemed "clinically significant" if classified as of intermediate or high risk according to these guidelines [21]. Whenever high-grade prostate intraepithelial neoplasia or atypical small acinar proliferation was detected, the biopsy was repeated within 3–6 mo.

The IMPACT results have been compared with the Göteborg cohort of the ERPSC study. This Swedish general population cohort of men aged 50–64 yr was offered biennial PSA screening with further investigations for PSA > 3.0 ng/ml and therefore were the closest general population group available for comparison.

2.1. Statistical analysis

Statistical analyses were undertaken using Stata 14.2 StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP and GraphPad QuickCalcs Web site: https://www.graphpad.com/quickcalcs (accessed August 2019).

PrCa prevalence for individuals with PSA > 3.0 ng/ml at the first PSA test was calculated. The cumulative incidence was calculated at the fourth screening round, stratified by age group, tumour-node-metastasis stage, and Gleason score, and compared by mutation status using Poisson regression offset by person-year follow-up, adjusted for age, ethnicity, and country. Proportions of screen-detected disease and PPV of PB were compared between groups using the chi-square test. Fisher's exact and Kruskal-Wallis tests were used to compare median age, PSA, and tumour characteristics between groups.

Analyses were performed on the whole cohort and by *BRCA* status. Secondary analyses were conducted excluding prevalent cancers (cancers diagnosed within <12 mo of enrolment). A p value of <0.05 was considered statistically significant.

3. Results

3.1. Study population

A total of 3027 persons (2932 unique individuals) were recruited from 65 centres in 20 countries over 120 mo (Supplementary Table 1): 919 *BRCA1* carriers, 709 *BRCA1* noncarriers, 902 *BRCA2* carriers, and 497 *BRCA2* noncarriers. Ninety-five *BRCA2* noncarriers sequenced for both *BRCA1*/2 mutations were included in both control cohorts. The cohorts were overrecruited, as advised by the study's Independent Data Monitoring Committee. The rationale was that overrecruitment would only strengthen the data and would compensate for any participants who withdrew from the study.

The majority of participants were Caucasian (97%), highly educated, and in work (Supplementary Table 2);

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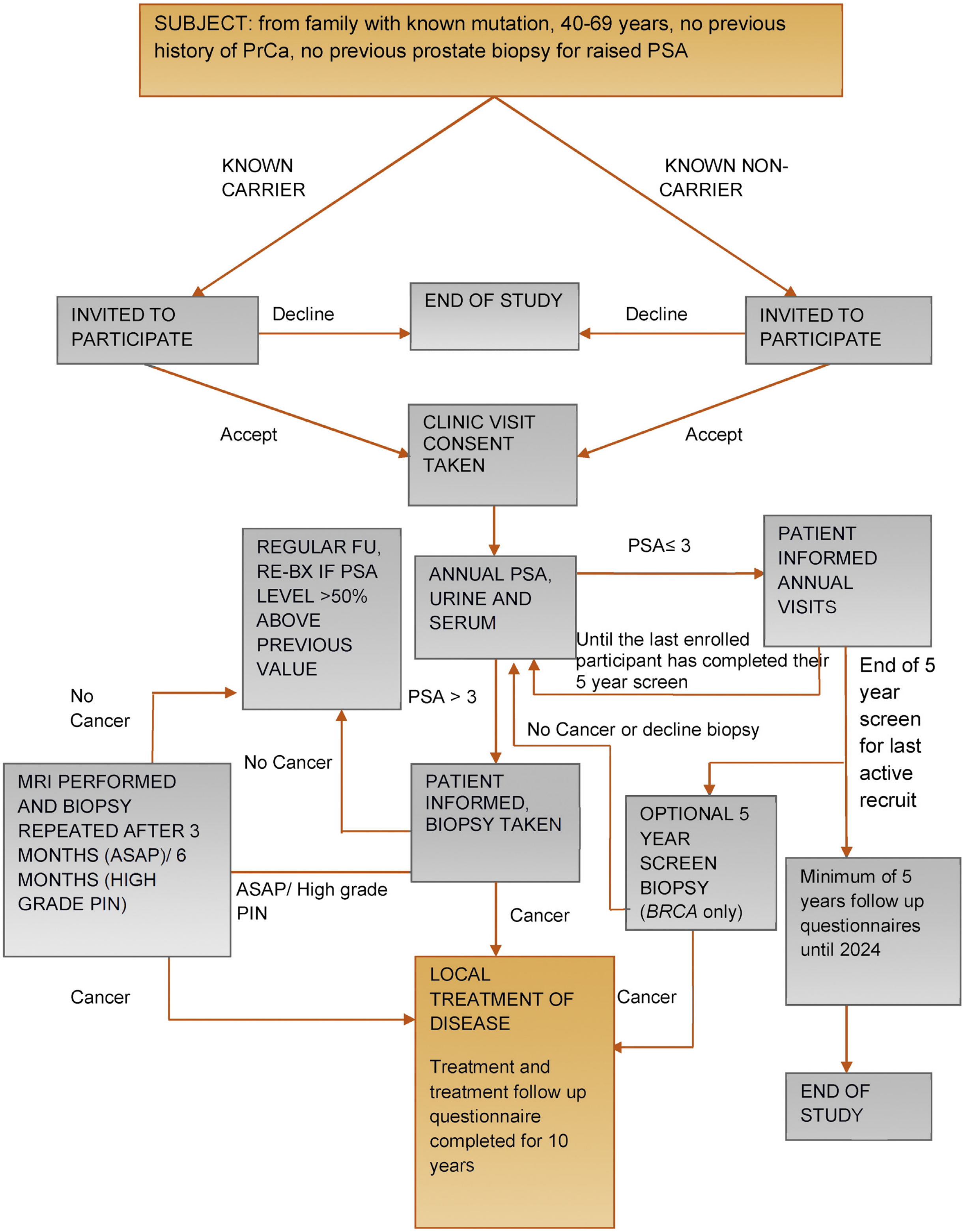

Fig. 1 – Study design algorithm.

median enrolment age was 54 yr; 24% of men reported urinary symptoms and 36% previously had at least one PSA test; and 31% reported a family history of PrCa. No statistically significant differences were observed in socio-demographic variables, symptoms, or previous screening between groups.

3.2. *PrCa detection rates after 3 yr of screening and PPV of biopsy*

At baseline, 2932 participants had a PSA test, 228 (7.7%) had PSA > 3.0 ng/ml, and 69 (2.4%) had cancers diagnosed from 195 biopsies.

Table 1 – Prostate cancer detection rates after four rounds of screening.

	Total cohort[a]	Mutation status			
		BRCA2+	BRCA2–	BRCA1+	BRCA1–
Baseline ("yr 1")					
Unique individuals, *n* (%)	2932	902 (30)	497(16)	919 (30)	709 (24)
Total PSAs taken, *n*	2931	902	497	919	708
Median PSA (IQR)	0.9 (0.6-1.5)	0.9 (0.5-1.5)	0.9 (0.6-1.4)	0.9 (0.5-1.4)	1.0 (0.6-1.7)
PSA > 3 ng/ml, *n* (%)	228 (7.5)	68 (7.5)	29 (5.8)	73 (7.9)	61 (8.6)
PSA > 3 ng/ml requiring action, *n*	228	68	29	73	61
Biopsies, *n* (biopsy rate %)	180 (79)	56 (82)	19 (66)	57 (78)	49 (75)
Including repeats, *n*	195	61	21	62	52
Benign, *n*	107	29	12	32	35
ASAP/HG PIN, *n*	13	5	0	6	2
Malignant (PrCa incidence), *n* (%, 95 CI)	69 (2.4, 1.8-3.0)	25 (2.8, 1.7-3.8)	7 (1.4, 3.7-2.4)	24 (2.6, 1.6-3.6)	13 (1.8, 0.8-2.8)
Diff. in detection rate: BRCA + vs BRCA– (%, 95 CI)		(1.4, -0.1-2.9)		(0.8, -0.6-2.2)	
p value for detection rate: BRCA + vs BRCA–		0.10		0.3	
Diagnosed within 6 mo of entry, *n*	65	25	6	22	12
Diagnosed within 12 mo of entry, *n*	68	25	7	23	13
PPV of biopsy (%, 95 CI)	(35, 29-43)	(41, 29-53)	(33, 13-53)	(39, 27-51)	(25, 13-37)
Diff. in PPV, biopsy: BRCA + vs BRCA– (%, 95 CI)		(8, −16-31)		(14, −3-31)	
p value for PPV, biopsy: BRCA + vs BRCA–		0.5		0.12	
PPV of PSA > 3 ng/ml requiring action (%, 95 CI)	(30, 24-37)	(37, 25-48)	(24, 9-40)	(33, 22-44)	(21, 11-32)
Diff. in PPV, PSA > 3: BRCA + vs BRCA– (%, 95 CI)		(13, −7-32)		(12, −3-26)	
p value for PPV, PSA > 3: BRCA + vs BRCA–		0.2		0.14	
3-yr follow-up ("yr 4")					
Total PSAs taken, *n* (%)	9363	3108 (32)	1600 (16)	2847 (29)	2183 (22)
Median PSA (IQR)	0.9 (0.6-1.5)	0.9 (0.6-1.5)	0.9 (0.6-1.5)	0.9 (0.5-1.5)	1.0 (0.6-1.7)
PSA > 3 ng/ml, *n* (%)	695 (7.4)	200 (6.4)	117 (7.3)	218 (7.7)	182 (8.3)
PSA > 3 ng/ml requiring action, *n* (%)	527 (5.6)	150 (4.8)	84 (5.3)	138 (4.8)	126 (5.8)
Biopsies, *n* (biopsy rate%)	332 (63)	110 (73)	50 (60)	93 (67)	89 (71)
Including repeats, *n*	357	122	54	98	95
Benign, *n*	208	59	32	60	67
ASAP/HG PIN, *n*	26	10	5	7	6
Malignant (PrCa incidence), *n* (%, 95 CI)	112 (3.8, 3.2-4.6)	47 (5.2, 3.8-6.7)	15 (3.0, 1.5-4.5)	31 (3.4, 2.2-4.5)	19 (2.7, 1.5-3.9)
Diff. in detection rate: BRCA + vs BRCA– (%, 95 CI)		(2.2, 0.1-4.2)		(0.7, −0.9-2.3)	
p value for detection rate: BRCA + vs BRCA–		0.057		0.4	
PPV of biopsy (%, 95 CI)	(31, 27-36)	(39, 30-47)	(28, 16-40)	(32, 22-41)	(20, 12-28)
Diff. in PPV, biopsy: BRCA + vs BRCA– (%, 95 CI)		(11, −4-25)		(12, −0.6-24)	
p value for PPV, biopsy: BRCA + vs BRCA–		0.17		0.065	
PPV of PSA > 3 ng/ml requiring action (%, 95 CI)	(21, 18-25)	(31, 24-39)	(18, 10-26)	(23, 16-29)	(15, 9-21)
Diff. in PPV, PSA > 3: BRCA + vs BRCA– (%, 95 CI)		(13, 2-25)		(7, −2-17)	
p value for PPV, PSA > 3: BRCA + vs BRCA–		0.025		0.13	
Prevalence of PrCa in all PSAs (%, 95 CI)	(1.2, 1-1.4)	(1.5, 1.1-1.9)	(0.9, 0.5-1.4)	(1.1, 0.7-1.5)	(0.9, 0.5-1.2)
Diff. in prevalence of PrCa: BRCA + vs BRCA– (%, 95 CI)		(0.6, −0.1-1.2)		(0.2, −0.3-0.8)	
p value for prevalence of PrCa: BRCA + vs BRCA–		0.10		0.4	
Follow-up time (yr), median (IQR)					
Noncancers	3.0 (2.18, 3.12)	3.0 (2.91, 3.14)	3.0 (2.17, 3.11)	3.0 (2.09, 3.12)	3.0 (2.12, 3.10)
Cancers	0.3 (0.12, 2.05)	0.4 (0.18, 2.27)	1.0 (0.12, 2.28)	0.2(0.10, 1.12)	0.2 (0.06, 1.43)
Total follow-up time, person yrs					
Noncancers	7185	2371	1227	2206	1674
Cancers	110	57	20	19	14
Cancer incidence rate (per 1000 person yrs)	15	19	12	14	11
Incidence rate ratio (crude), (95 CI)		1.61 (0.90-2.88)		1.24 (0.70-2.19)	
IRR, adjusted for age, ethnicity, country (95 CI) (*p* value)		1.95 (1.06-3.56) (0.031)		1.36 (0.75-2.45) (0.3)	

ASAP = atypical small acinar proliferation; CI = confidence interval; Diff. = difference; HG PIN = high-grade prostate intraepithelial neoplasia; IQR = interquartile range; IRR = incidence rate ratio; PPV = positive predictive value; PrCa = prostate cancer; PSA = prostate-specific antigen.
[a] A total of 95 individuals contribute to both BRCA1 and BRCA2 controls; therefore, the sum of mutation status will not match the total cohort.

Cumulatively, after four PSA screens, 527 individuals (18%) had PSA > 3.0 ng/ml and 112 cancers diagnosed from 357 biopsies. In the *BRCA2* cohort, 47 (5.2%) cancers were diagnosed in carriers and 15 (3.0%) in noncarriers; 31 cancers (3.4%) were diagnosed in *BRCA1* carriers compared with 19 (2.7%) in noncarriers (Table 1 and Fig. 2).

Overall PrCa detection rate was 3.8% (112/2932), and the cancer incidence rate per 1000 person years was 15. The cancer incidence rates were 19 and 12 in *BRCA2* carriers and noncarriers, respectively (incidence rate ratio [IRR] = 1.95, *p* = 0.031), and 14 and 11 in *BRCA1* carriers and noncarriers, respectively (IRR = 1.36, *p* = 0.3).

Overall, PPV of PB was 31%, with 39% and 28% in *BRCA2* carriers and noncarriers, respectively (*p* = 0.17), and 32% and 20% in *BRCA1* carriers and noncarriers, respectively (*p* = 0.065).

The overall PPV of PSA > 3.0 ng/ml was 21%, with 31% and 18% in *BRCA2* carriers and noncarriers, respectively (*p* =

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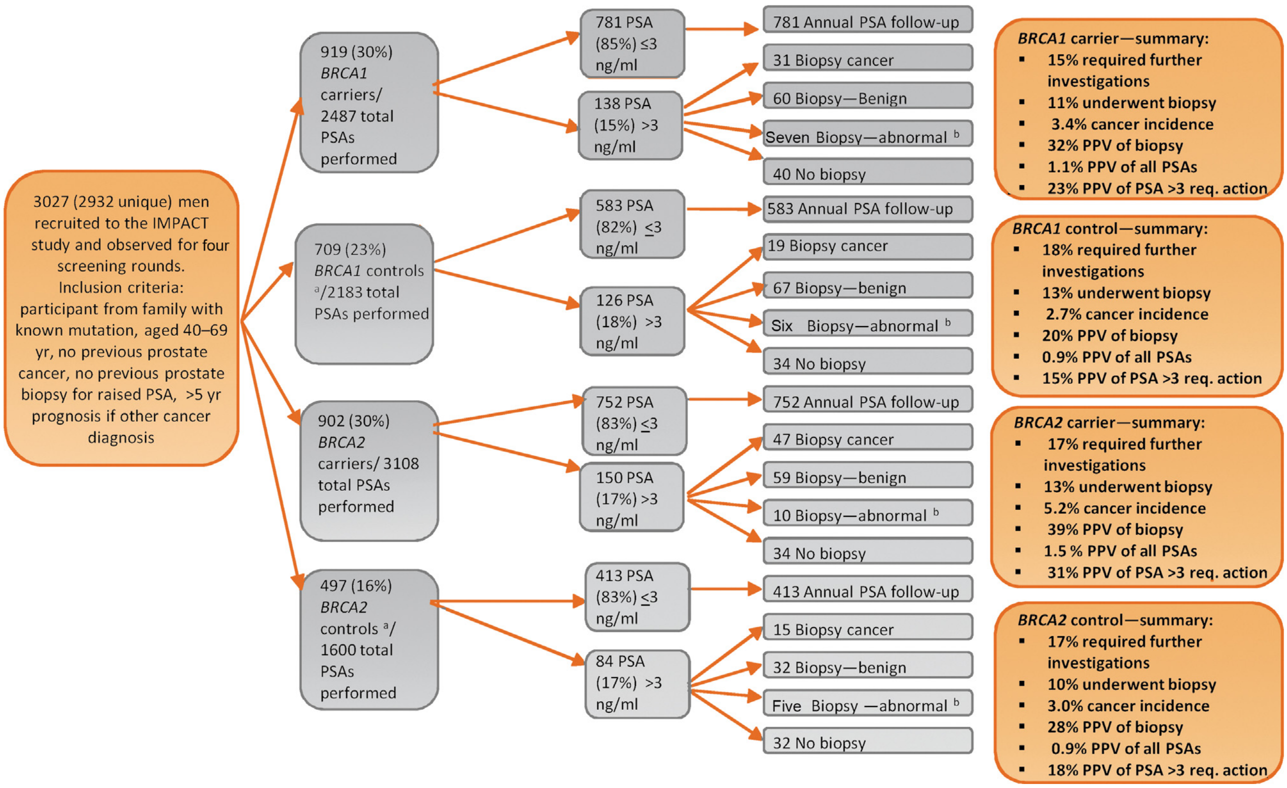

Fig. 2 – A consort diagram of the IMPACT study after four screening rounds. ASAP = atypical small acinar proliferation; PIN = prostate intraepithelial neoplasia; PPV = positive predictive value; PSA = prostate-specific-antigen.
[a]Controls were men who had a negative predictive genetic test for the BRCA mutation in their family.
[b]Biopsy—abnormal refers to high-grade PIN and ASAP.

0.025), and 23% and 15% in *BRCA1* carriers and noncarriers, respectively ($p = 0.13$).

To compare results with the population-based Göteborg cohort [30], we restricted the IMPACT cohort to entry ages 50–64 yr (Supplementary Table 3). The Göteborg study report 2.5% PrCa incidence (confidence interval [CI]: 2.2%, 2.8%) after 4 yr [30,31] compared with 5.3% (CI: 4.2–6.5) in IMPACT.

PPV for PB is 30% in the Göteborg cohort and is 26% for PSA (above threshold). PPV for PB is 33% in IMPACT, restricted to the Göteborg age range, and 24% for PSA > 3.0 ng/ml. When comparing PPVs in the Göteborg cohort with IMPACT for clinically significant disease, we see a higher incidence in the *BRCA2* carriers for both PSA ($p \leq 0.001$) and PB ($p \leq 0.001$).

As a sensitivity analysis, analyses were repeated excluding centres in The Netherlands (Supplementary Table 4) that screened patients biennially. No differences in the distributions of cancer incidence, incidence rate, or PPV of PB were observed. To rule out the *BRCA2* control group being an outlier, the analyses were repeated combining the control groups, and all significant differences remained.

Analyses were repeated removing cancers diagnosed within <12 mo of study entry (Supplementary Table 5). These analyses show increased PrCa incidence in *BRCA2* carriers; however, these analyses are currently underpowered.

During the first four screening rounds, the biopsy compliance rate for raised PSA (>3) was 73% in *BRCA2* carriers, 60% in *BRCA2* noncarriers, 67% in *BRCA1* carriers, and 71% in *BRCA1* noncarriers. From the 357 biopsies performed including repeat biopsies, the median age at biopsy of *BRCA2* carriers was 60 yr, compared with 64 yr in *BRCA2* noncarriers ($p \leq 0.001$). No differences were observed in the *BRCA1* cohort (Table 2). When comparing by genetic status, no differences were seen in median PSA, which triggered biopsy, time (in days) between PSA test and biopsy, age at biopsy, and number of diagnostic cores taken at biopsy.

3.3. *Cancer characteristics*

Table 3 and Supplementary Table 6 show the characteristics of all screen-detected PrCa cases diagnosed in patients with a PSA level of >3.0 ng/ml during the first four screening rounds.

The median age at PrCa diagnosis was 61 yr (interquartile range [IQR]: 56, 64) in *BRCA2* carriers and 64 yr (IQR: 60, 66) in *BRCA2* noncarriers ($p = 0.044$, Kruskal-Wallis). In the *BRCA1* cohort, there was no difference in median age at diagnosis ($p = 0.33$).

Looking at the overall risk category, 37/48 (77%) *BRCA2* carriers had intermediate- or high-risk PrCa (clinically significant disease), compared with six/15 (40%) *BRCA2* noncarriers ($p = 0.011$, Fisher's exact). There were no

Table 2 – Summary of characteristics of men who underwent biopsies in the first four screening rounds of the IMPACT study.

	Total	BRCA1+	BRCA1−	*p* value	BRCA2+	BRCA2−	*p* value
Total biopsies (*n*)	357[a]	98	95		122	54	
Biopsy compliance (%)	68	71	75		81	64	
Median PSA (ng/ml) to trigger biopsy (IQR)	4.2 (3.5–5.6)	4.2 (3.7–5.6)	4.0 (3.5–4.8)	0.1	4.5 (3.5–5.9)	4.2 (3.4–6.2)	0.8
Median age (yr) at biopsy (IQR)	61 (56–65)	61 (56–64)	61 (56–65)	0.9	60 (56–64)	64 (60–67)	<0.001
Median time difference (d) PSA to biopsy (IQR)	51 (27–89)	56 (28–72)	42 (22–79)	0.3	57 (28–94)	50 (25–87)	0.1
Median cores taken, *n* (IQR)	10 (8–12)	10 (9–12)	10 (8–12)	0.5	10 (8–12)	10 (8–12)	1

IQR = interquartile range; PSA = prostate-specific antigen.
[a] Twelve biopsies contribute to both BRCA1 and BRCA2 controls, therefore the sum of mutation status will not match total cohort.

Table 3 – Summary of cancer characteristics of PSA detected cancers using final clinical pathology (ie, if available after prostatectomy)[a].

Genetic status	BRCA2+ (n = 48)	BRCA2− (n = 15)	*p* value	BRCA1+ (n = 33)	BRCA1− (n = 20)	*p* value
Median age (yr) at diagnosis	61 (56, 64)	64 (60, 66)	0.044	62 (57, 66)	61 (58, 62)	0.3
Median PSA (ng/ml) at diagnosis (IQR)	4.5 (3.6, 5.5)	4.2 (3.4, 6.1)	0.9	4.4(3.8, 5.9)	4.4 (3.6, 5.3)	0.7
Gleason score 6	18 (38)	11 (73)	0.019[b]	18 (55)	13 (65)	0.6[a]
Gleason score 7 (3 + 4)	15 (31)	1 (7)		9 (27)	4 (20)	
Gleason score 7 (4 + 3)	9 (19)	2 (13)		4 (12)	3 (15)	
Gleason score 8+	6 (12)	1 (7)		2 (6)	0	
T stage—T1/T2a	16 (35)	8 (57)	0.2[b]	9 (31)	8 (40)	0.6[a]
T Stage—T2b	2 (4)	2 (14)		0	1 (5)	
T Stage—T2c/T3	28 (61)	4 (29)		20 (69)	11 (55)	
Risk category[c]—low	11 (23)	9 (60)	0.011[b]	10 (30)	4 (20)	0.5[a]
Risk category[c]—intermediate	7 (14.5)	1 (7)		3 (9)	6 (30)	
Risk category[c]—high	30 (62.5)	5 (33)		20 (61)	10 (50)	
Screening round diagnosed—1	25 (52)	7 (47)		23 (70)	13 (65)	
Screening round diagnosed—2	7 (14.5)	1 (7)		3 (9)	3 (15)	
Screening round diagnosed—3	9 (19)	5 (33)		6 (18)	2 (10)	
Screening round diagnosed—4	7 (14.5)	2 (13)		1 (3)	2 (10)	
Active surveillance	8 (17)	7 (47)		5 (17)	6 (30)	
Radical prostatectomy	32 (70)	6 (40)		22 (76)	12 (60)	
Nonsurgical treatment	6 (13)	2 (13)		2 (7)	2 (10)	

IQR = interquartile range; NICE = National Institute for Health and Care Excellence; PSA = prostate-specific antigen.
Some pathology information is not available from sites yet.
Values are presented as median (IQR) and *n* (%).
[a] Note four cancers included in this analysis were diagnosed as a result of additional off-protocol repeat biopsies in men with high PSA.
[b] *p* values calculated on difference between clinically significant disease and non–clinically significant disease.
[c] Risk category classification system using NICE guidelines [21].

statistically significant differences between *BRCA1* carriers (70%) and noncarriers (80%; Fig. 3).

Limiting to incident cases, 48 cancers were diagnosed: 23 in *BRCA2* carriers, eight in *BRCA2* noncarriers, 10 in *BRCA1* carriers, and seven in *BRCA1* noncarriers; there is no significant difference by carrier status. No significant difference was also seen when limiting to incident cases and excluding men who had had a previous benign biopsy (*n* = 9).

After four screening rounds, no deaths from PrCa were reported in the IMPACT study participants.

4. Discussion

The IMPACT study is the only international prospective PrCa screening study conducted exclusively in families with *BRCA1/2* mutations. IMPACT will screen all but the Dutch patients for a total of five screening rounds, and collect cancer incidence and mortality data for a further 5 yr.

Controversy about PSA level that used to trigger PB continues, and we have demonstrated that using a PSA level of >3.0 ng/ml, after four screening rounds, 13% of the total cohort was recommended to have a PB with a 3.8% cancer detection rate. The IMPACT study continues to collect screening data, and a further component of the protocol is to offer men the option of undergoing PB after the completion of five screening rounds, irrespective of the PSA level. This will provide the opportunity to evaluate the number of clinically significant cancers missed in carriers and non-carriers when using a PSA threshold of 3.0 ng/ml.

We have demonstrated that the trends reported after the baseline screen are strengthened after 3 yr of follow-up. The PPV of PSA > 3.0 ng/ml was significantly higher in *BRCA2* mutation carriers (31%) compared with noncarriers (18%; *p* = 0.025). When compared with the Göteborg cohort, the PPV of PB in *BRCA2* carriers was 41% compared with 30%, therefore biopsying fewer men unnecessarily. As previously reported, no significant differences were detected between *BRCA1* carriers and noncarriers [19].

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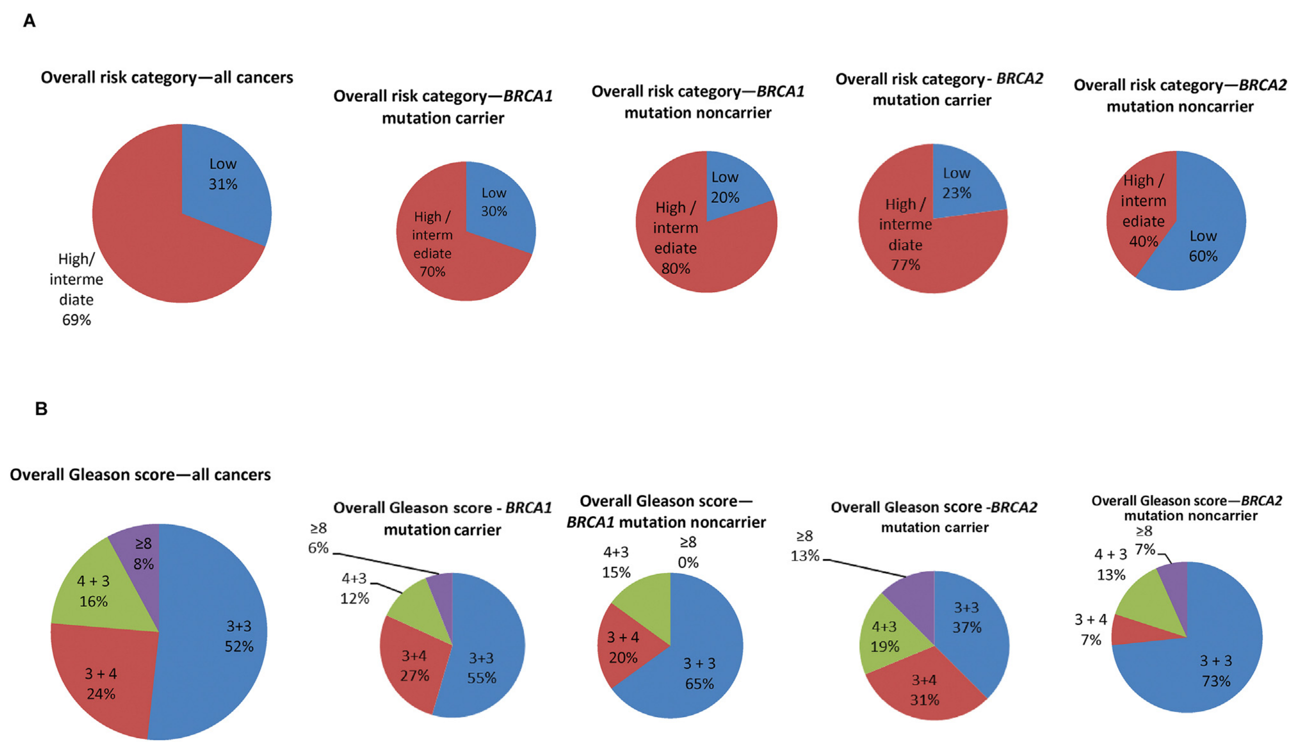

Fig. 3 – (A) Pie charts showing the overall prostate cancer risk category (as defined by the NICE guidelines—www.nice.org.uk: low: PSA < 10 and Gleason ≤6 and T1/T2a; intermediate: PSA 10–20 or Gleason 7 or T2b; and high: PSA > 20 or Gleason 8–10 or ≥ T2c), for all study PSA-detected cancers in screening rounds 1–4 and broken down by genetic status. (B) Pie charts showing the overall Gleason score, for all study PSA-detected cancers in screening rounds 1–4 and broken down by genetic status.
NICE = National Institute for Health and Care Excellence; PSA = prostate-specific-antigen.

After four screening rounds, *BRCA2* carriers have a statistically significantly higher cancer incidence rate (19) per 1000 person years compared with noncarriers (12; $p =$ 0.03). With a higher number of cancers detected than reported previously [22], we have confirmed that *BRCA*2 carriers are diagnosed at a younger age ($p =$ 0.044) than *BRCA*2 noncarriers and that a significantly greater proportion of cancers were intermediate- or high-risk disease ($p =$ 0.011). Overall, 77% of cancers diagnosed in *BRCA2* carriers were clinically significant, compared with 49% in the general population [11]. The youngest age of diagnosis of clinically significant disease was 41 yr for *BRCA2* carriers and 43 yr for *BRCA1* carriers, which may suggest screening from an early age. Regarding the number of men needed to screen to detect one clinically significant PrCa after four screening rounds, screening 60 *BRCA2* carriers aged 40–54 yr and 13 carriers aged 55–69 yr will detect one clinically significant PrCa, respectively. Eventually, long-term follow-up data on the clinical benefit of early detection are needed to determine the best starting age.

Analyses of the cancer detection rates, PPV, and characteristics were repeated excluding prevalent cancers (PrCa diagnosed within 12 mo of baseline PSA). It was found that whilst not statistically significant, there was greater PrCa incidence in *BRCA2* carriers than in noncarriers (9.1 vs 6.4), and substantially higher numbers of intermediate- and high-risk cancers were detected in *BRCA*2 carriers than in noncarriers ($p =$ 0.074). Owing to the relatively small number of cancers diagnosed in the *BRCA2* noncarriers, we also re-ran these analyses combining the two noncarrier control groups, and statistically significant differences in tumour characteristics remained. In addition, clinically significant cancers were diagnosed at every screening round, supporting the use of systematic PSA screening. After 3 yr of follow-up, it is possible that disease was present, but not detectable by PSA, at study entry. A further aim of the IMPACT study is to offer PB to all men after five screening rounds, to evaluate the utility of a baseline biopsy irrespective of the PSA level with respect to cancer prevalence and tumour characteristics. However, it is reassuring to see from the data presented that using a cut-off of 3 ng/ml, the majority of the tumours detected were at an early stage.

No statistically significant differences were detected in age of onset or cancer characteristics between *BRCA1* carriers and noncarriers. Further follow-up is required to conclude the clinical management of *BRCA1* carriers.

Similar to our report for the IMPACT baseline screen [22], the ProtecT score using the 4 K panel (Supplementary material) was able to predict PB outcome, with a discrimination of 0.73 for high-grade disease. This adds further evidence to support the use of additional biological markers, such as the 4 K panel in improving the detection of clinically significant PrCa.

4.1. Limitations

A limitation of IMPACT is that not all men comply with the study protocol, and therefore cancers may be missed either in men who refuse PB, or in men who are advised locally to have MRI or repeat PSA instead of a PB. Genetic status may play a role in protocol compliance with fewer noncarriers, particularly *BRCA2* noncarriers, proceeding with a PB (73% vs 60%). This differential biopsy rate is likely to have underestimated the PrCa incidence in both *BRCA2* carriers and noncarriers. Complete data would be expected to strengthen the power to detect the difference in clinically significant disease between these groups. As follow-up will continue for a further 5 yr, these data will become available as part of future analyses. The higher observed biopsy rate within *BRCA2* carriers could represent variation in how health professionals counsel men with high PSA levels, with a bias towards encouraging biopsy in *BRCA2* carriers. Of note, no variation was seen between the number of cores taken at biopsy and mutation status. Variation was observed between sites and across the course of the study as the protocol increased from 10 to 12 biopsy cores as standard practice changed.

Given the rarity of *BRCA1/2* mutations, it was not possible to restrict the protocol to those with no prior urinary symptoms or PSA testing. Those with a prior PB were excluded. There was no difference in cancer incidence rates in those with symptoms or prior PSA testing.

In comparing with the Göteborg cohort, we acknowledge that this general population cohort is not stratified for *BRCA* status; however, the population frequency of *BRCA1/2* mutations is low. This study also used biennial rather than yearly PSA and was restricted to sextant PB, and therefore cancer detection rates at PB may be lower than that in IMPACT.

IMPACT started in 2005, prior to the implementation of multiparametric MRI in PrCa screening [17,18]. Without a systematic evaluation of the use of MRI in men at genetically high risk, it is difficult to extrapolate general population data to this setting and needs further research.

The Dutch protocol, as outlined above, screened men every 2 yr, and also included digital rectal examination and PCA3 in the algorithm of whether to proceed to biopsy or not. Therefore, some men with PSA < 3.0 ng/ml were biopsied, some of whom were diagnosed with cancer. However, despite this differing protocol in this cohort, sensitivity analyses excluding the Dutch data demonstrate that this approach did not affect the overall results.

A challenge of a longitudinal study such as IMPACT is in balancing the standardisation of procedures and changes in practice. For example, there have been changes in PB during the course of this study; the protocol has been updated to increase the number of diagnostic cores from 10 to 12 during the study's duration. Some centres have used the transperineal approach in line with local practice guidelines.

5. Conclusions

We demonstrate that, after four annual PSA screening rounds, *BRCA2* mutation carriers have a higher incidence of PrCa, are diagnosed at a younger age, and present with more clinically significant tumours than *BRCA2* noncarriers. Further follow-up is required to assess the role of screening in *BRCA1* mutation carriers. Therefore, these data support the use of systematic PSA screening in male *BRCA2* carriers.

Author contributions: Rosalind A. Eeles had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Aaronson, Ardern-Jones, Bancroft, Bangma, Castro, Dearnaley, Eccles, Evans, Eyfjord, Falconer, Foster, Gronberg, Hamdy, Johannsson, Khoo, Kote-Jarai, Lilja, Lindeman, Lubinski, Mahle, Mikropoulos, Mitra, Moynihan, Page, Rennert, Suri.
Acquisition of data: All authors.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Page, Bancroft, Brook, Assel, Vickers, Lilja.
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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2019.08.019.

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