The Role of Lifestyle Characteristics on Prostate Cancer Progression in two Active Surveillance Cohorts

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Running head: Lifestyle and Prostate Cancer Progression

Keywords: Physical activity, nutrition, low-risk disease, conservative management

ABSTRACT

Background: Although much research has examined the relationship between lifestyle and prostate cancer (PCa) risk, few studies focus on the relationship between lifestyle and PCa progression. The present study examines this among men initially diagnosed with low- to intermediate-risk PCa and managed with active surveillance (AS).

Methods: Men enrolled in two separate AS programs were recruited for this study. Data regarding clinical, demographic and lifestyle characteristics were collected. Results were then compared between men whose disease remained low- to intermediate-risk and men whose disease progressed.

Results: Demographic, clinical and physical characteristics were similar between comparative groups and cohorts; with the exception that age at the time of diagnosis and questionnaire was increased among men whose disease progressed. Lifestyle scores among men who remained low to intermediate risk were higher than those who progressed; however, scores were only significant in one cohort upon univariable analysis. Upon multivariable analysis, the only predictor of progression was age at diagnosis. Physical activity was consistently higher in both low-risk groups, though this difference was insignificant. Consistent differences in other lifestyle variables were not observed.

Conclusions: Age remains an important predictor of PCa progression. Improving lifestyle characteristics among men initially managed with active surveillance might help to reduce the risk of progression. Given the limitations of this study, more rigorous investigation is required to confirm whether lifestyle characteristics influence the progression of low- to intermediate-risk PCa.

Introduction

With the introduction of PSA testing, the incidence of prostate cancer (PCa) has risen dramatically and is now the second-most frequently diagnosed cancer in the world [1]. While therapies such as surgery or radiation provide significant survival benefits for aggressive PCa, treatment for low risk disease can cause considerable morbidity and risk, unnecessarily [2, 3]. Low risk PCa typically progresses very slowly, and delaying treatment until signs of higher risk disease has not shown to decrease the likelihood of successful treatment [2, 4]. As such, active surveillance (AS), in which treatment is initially deferred, has become a sensible option for such patients [5].

While much research has examined the relationship between lifestyle and PCa risk, very few studies have focused on the effect of lifestyle on PCa progression. AS programs provide excellent opportunities to assess the impact of lifestyle on PCa progression without any confounding treatment effects. Although to date this potential has not been well realized, there is some indication that a healthy lifestyle, including physical activity, may delay the need for radical treatment in men on AS [6-8].

In the present study, we examined the association between lifestyle characteristics and disease progression in men diagnosed with low- to intermediate-risk PCa and initially managed with AS. The study consists of men from Sunnybrook Health Sciences Centre AS cohort (SB cohort) and the Institute of Cancer Research, Royal Marsden Hospital AS cohort (RMH cohort). It was hypothesized that men who were progressed to a higher risk disease would have lived less healthy lifestyles during the time they were managed with AS compared to those whose PCa has not yet progressed, suggesting that a healthy lifestyle may play a protective role in the progression of low- to intermediate-risk PCa.

Methods

Participants

The Research Ethics Board of Sunnybrook Health Sciences Centre in compliance with the Ontario Personal Health Information Act provided ethics approval. Informed consent was obtained from all participants. Recruitment of participants was accomplished by approaching patients with an intent to recruit those who came in to clinic for their regular scheduled appointments/visits during the period of recruitment for each cohort. All patients approached agreed to participate in the study. Between 2010 and 2011, 133 men diagnosed with low risk PCa and initially managed with AS were recruited from Sunnybrook Health Sciences Center. Two men were excluded from the study due to the fact that they opted for AS despite initial recommendation for treatment upon diagnosis. The remaining 131 participants were categorized into two groups: 1) those who were currently undergoing AS ("low risk") and 2) those who were initially managed with AS but later reclassified to a higher risk of disease progression and subsequently underwent radical treatment ("progressed"). Moreover in 2013, 112 men diagnosed with low risk PCa and initially managed with AS were recruited from the Royal Marsden Hospital. One hundred and six men returned the questionnaire with sufficient data and were categorized into two groups: 1) those who had low- to intermediate-risk disease ("low risk") and 2) those who initially presented with low risk disease but later reclassified to a higher risk of disease progression and/or underwent radical treatment ("progressed"). Categorizing men from the RMH cohort differently than those from the SB cohort was done in response to differences in available data.

AS is a form of conservative management for men with "low risk" PCa, which according to the D'Amico definition involves Gleason score of ≤ 6 (3+3), a PSA of less than 10 mg/ml, and a clinical stage of T1c or T2a. Some AS programs accept men with Gleason 7 (4+3), provided they are older than 70 years and only have a small proportion of Gleason 4 pattern [9]. Reclassification of patients to higher risk disease is triggered by the presence of Gleason pattern 4 or 5 on repeat biopsy or when extensive increases in volume of Gleason pattern 3 are found in patients under the age of 55, which warrants radical treatment [9]. Reclassification for men in the RMH cohort was similar; however in this study, the occurrence of adverse PSA kinetics (PSA doubling time of <3 years or a PSA velocity of >2.0 per year) without a confirmed biopsy upgrade warranted reclassification, as adverse PSA kinetics have been shown to be a significant predictor of disease progression in this cohort [10].

Lifestyle Assessment

A modified version of the WHO STEPwise approach to chronic disease risk factor surveillance- Instrument version 3 [11] was used to obtain information on demographics, tobacco use, alcohol use, physical activity, dietary intake, medications and supplements, history of disease, and general health. Height, weight, and waist to hip circumference ratio were also measured. The survey was administered to men in the SB cohort through personal interviews and to men in the RMH cohort as a take home survey at various time points post-diagnosis.

Indices were developed to assess each patient's diet as a whole, as well as his fruit and vegetable intake. For the food groups that have been thought to promote PCa (milk products [12, 13], fast food, and red meat [14]), heavy, moderate and light consumption

was given a score of 1, 2 and 3, respectively. For the food groups that have been reported to protect against PCa (fish [14], tomato products [14, 15], cruciferous vegetables [16], soy products [17], red grapes and/or red wine, and berries [18]), heavy, moderate, and light consumption were assigned a score of 3, 2, and 1, respectively. Raw scores for the overall dietary index (ranging from a minimum of 9 to a maximum of 27) were determined by calculating the total number of accrued points for all food groups, while the raw score for the fruits and vegetable index was equal to sum of the points accrued for regular consumption of tomato products, cruciferous vegetables, soy products, red grapes and/or red wine, and berries (min. 5, max. 15). Table I describes the interpretation of the raw scores for each index.

Data regarding working/non-leisure, travel, and recreational physical activity was collected. Values of energy expenditure (metabolic equivalent task hours per week or MET-hrs/week) for each activity were obtained from the Compendium of Physical Activities and adjusted according to body mass index and age with an equation established by Byrne et al [19]. Total, recreational and vigorous (activity requiring ≥6 MET-hrs) MET-hrs/week of physical activity was computed for each participant.

A lifestyle score was computed for each participant based on their total physical activity, dietary intake, body mass index, waist to hip circumference, tobacco use and alcohol use. Total MET hours/week of physical activity was split into quartiles per cohort and points were allotted to each participant according to their reported physical activity, with 0 points given to those in the least physically active quartile and 3 points given to those in the most physically active quartile. Diet scores were split into five levels (very poor, poor, average, good and excellent) and 0, 1, 2, 3, and 4 points were awarded

accordingly. Participants were also awarded 1 point if they had a body mass index of less than 30 kg/m^2, a waist to hip circumference ratio less than the median for each cohort, had never smoked or quit before their time on AS and had consumed less than 3 servings of alcohol daily. Increased physical activity was given a positive value, as previous research suggests a protective role with regard to PCa [7, 8, 20]. Body mass index [21, 22], waist to hip circumference ratio [23], tobacco use [24, 25] and alcohol use [26-28] provided negative contribution to the score, as they have been thought to promote PCa proliferation. Generalizing single unit values for each lifestyle factor and including multiple unit values with increased physical activity and diet quality was done in response to the lifestyle score developed by Kenfield *et al* (2015) [29]. In their study, an increased lifestyle score was associated with a reduced risk of lethal PCa.

Statistical Analysis

All statistical analyses were done using IBM SPSS 22.0 (SPSS Inc., Chicago, IL). A sample size of 68 individuals per group was determined a priori to enable the detection of a moderately sized effect of d = 0.43, with a power of 0.8 and one-sided α of 0.05, reflecting differences between the two groups on lifestyle factors. Data were tested for normality using the Shapiro-Wilk test and equality of variance using Levene's test. The two-tailed Student's t-test was used to compare continuous data of normal distribution. A one-sided Mann-Whitney U test was employed in the direction of the hypothesis to compare lifestyle scores while a two-sided Mann-Whitney U test was used to examine other non-parametric data. The chi-square or the Fisher's exact test was used to establish whether categorical data were independent between groups. To determine whether any lifestyle variables were correlated to either total time to progression (treated and reclassified groups only),

Pearson or Spearman correlation coefficients were used. Binary logistic regression analyses were performed for the lifestyle score, total MET-hrs/week, waist to hip circumference ratio, and overall dietary score adjusting for age at diagnosis and family history of PCa to determine the strength of predictability for progression to higher risk disease. Statistical significance for all analyses was denoted by a p-value <0.05.

Results

Clinical and demographic data are summarized in Table II. Of the 131 men in the SB cohort, 76 (58%) remained low risk and 55 (42%) progressed and subsequently underwent radical treatment. Of the 106 men in the RMH cohort, 76 (71.7%) remained low risk and 30 (28.3%) progressed to higher risk disease, as indicated by clinical parameters, with 15 having undergone radical treatment at the time of recruitment. At the time of diagnosis, men in SB and RMH cohorts were on average younger in the low risk versus the progressed groups (63 (40-81) vs. 67 (48-79); p=0.0089 and 64.5 (51-78) vs. 68.5 (68-83); p=0.0051). This was also the case for age at the time of questionnaire completion (67 (45-86) vs. 74 (48-89); p<0.0001 and 69.5 (53-83) vs. 71.5 (57-88); p=0.028).

The most common reasons for reclassification (or recommendation for definitive treatment) were Gleason score upgrade (31% and 37%), a combination of Gleason score upgrade and rising PSA values (20% and 3%), and abnormal PSA kinetics (27% and 47%). Three men (5%) from the SB cohort elected to undergo treatment due to cancer-related anxiety, despite showing no clinical signs of progression. Four men (13%) from the RMH cohort elected to undergo treatment for unknown reasons. However, patients from the RMH may have been recommended for treatment due to high PSA-density values (PSAD =

0.161, 0.279, 0.327 and 0.328 ng/mL^2). Although men from the low risk group remained on AS longer than men who progressed, total time on AS did not differ significantly between the comparative groups (p=0.62 and p=0.096).

There were no significant differences observed between groups with respect to baseline PSA values, body mass index, waist to hip circumference ratio, tobacco use, alcohol use, first-degree family history of PCa, and history of diabetes or cardiovascular disease/stroke. The majority of initial biopsies presented with Gleason 6 disease and a few with Gleason 7. Race distribution between groups was also similar.

Data regarding lifestyle characteristics and history of disease are summarized in Table III. In general, lifestyle scores were higher among men in the low risk compared to the progressed group in both cohorts (Figure 1). However, significance was only observed in the RMH cohort (p=0.046) and not in the SB cohort (p=0.14). On a binary logistic regression analysis, this difference was insignificant for both cohorts (95% CI = 0.77 to 1.16; p=0.29 and 95% CI = 0.55 to 1.02; p=0.066) (Table IV).

Although insignificant, median levels of total and recreational physical activity were generally increased among men from the low risk compared to the progressed groups (Figure 2A & B). However, total physical activity was not predictive of progression on the binary logistic regression analysis when adjusting for age and other lifestyle variables (95% CI = 0.99 to 1.01; p=0.62 and 95% CI = 0.99 to 1.00; p=0.24) (Table V).

Significant differences in the overall dietary intake score and the fruits and vegetables intake score were not observed (Table III). Overall, the use of micronutrients and medications was not significantly different between comparative groups in both cohorts (data not shown).

Significant correlations were not observed between age at diagnosis, total MET hrs/week, diet score and fruit and vegetable intake score and total time to progression (if applicable) (Table V). A significant positive correlation of moderate strength was observed between age at the time of treatment and total time to progression on AS (r=0.36; p=0.0073 and r=0.40; p=0.030) (Figure 3A & B).

All patients ranked their general health. On average, both groups reported "very good" physical and mental health and general quality of life. Overall pain and stress were ranked as "none". Reported feelings of fatigue were increased among men in the progressed groups compared to the low risk group, although this was only significant in the RMH cohort (p=0.24 and p=0.010).

Discussion

Lifestyle characteristics were examined among patients in the SB cohort with comparisons made between men who remained on the AS protocol (low risk) and those who reclassified to a higher risk of disease progression and subsequently underwent radical treatment (progressed). Men who progressed were significantly older than men who remained low risk at the time of PCa diagnosis as well as at the time of questionnaire completion. However, the two groups did not significantly differ in total years on AS, which suggests that increasing length of time on surveillance was not the determining cause of reclassification. These findings are consistent with results from the RMH cohort, which compared lifestyle behaviors of men who remained low risk (low risk) and those who reclassified to a higher risk of disease progression (progressed) and/or underwent treatment.

The primary objective was to investigate the role of lifestyle characteristics in protecting against progression of low- to intermediate-risk PCa in men on AS. Differences in lifestyle scores were modestly increased among men who remained low risk compared to those who progressed. One should note that this difference was only significant in the RMH cohort upon univariable analysis and borderline significant upon multivariable analysis. Using a similar scoring method, Kenfield *et al* (2015) demonstrated that a healthy lifestyle was associated with a reduced risk of lethal PCa among men from the Health Professionals Follow-up Study and men in the Physicians' Health Study [29]. Moreover, improved lifestyle behaviors have demonstrated a protective role against the incidence of indolent and aggressive disease as well as biochemical recurrence [7, 8].

Of the lifestyle characteristics examined, only physical activity demonstrated a consistent difference between comparative groups upon univariable analysis. That is, median total and recreational physical activity were increased among men from the low risk compared to the progressed group in both cohorts. However, this difference was not significant upon univariable or multivariable analyses.

Significant differences in the overall dietary index score and the fruits and vegetables index score were not observed between comparative groups in either cohort. This is inconsistent with previous studies that have demonstrated significant associations with dietary intake and PCa risk and progression [12, 14-17, 29]. The present study, however, collected information retrospectively, which negatively impacts recall when compared to prospective data collection. Moreover, the food frequency questionnaire used did not specify portion sizes for each serving. These limitations may explain the discrepancy in results with the previous studies, which collected data prospectively and

included information on portion sizes [12, 14-17, 29]. Furthermore, despite the fact that the strength of each dietary factor's role in PCa progression varies [18], equal weight was given to each dietary factor when calculating the index scores, likely leading to an over-generalization of the impact of diet.

A significant positive correlation was observed in both cohorts between age at the time of reclassification and total time to progression. This is consistent with data from Tsodikov *et al* (2006) and Chefo & Tsodikov (2009) indicating an increased delay time with increase in age at diagnosis [30, 31]. It is thought that more aggressive disease stems from the increased genetic burden in early onset PCa [32] relative to PCa diagnosed in older men. This is supported by research demonstrating an association between early onset PCa and an increase in the number of risk alleles [33].

This study is limited by its retrospective nature and that lifestyle data was self-reported and thus subject to the social desirability bias. Although consistent differences in lifestyle scores and physical activity were not significant upon multivariable analysis, the samples were small and may not have provided adequate power. As such, the occurrence of a type II error is possible. Moreover, there is a limited ability of self-report surveys to validly measure lifestyle behavior [34-36]. Future studies should consider the use of more objective measures in the assessment of lifestyle behaviors such as accelerometers or heart rate monitors to assess participation in physical activity and serum levels of nutrients indicative of dietary intake carotenoids, vitamin C and polyphenols to assess dietary intake [37, 38].

Summary

A healthy lifestyle as defined by increased physical activity, good nutritional habits, a healthy body weight and composition, reduced alcohol consumption, and no tobacco consumption may help slow the progression of low risk PCa in patients initially managed with AS, thereby delaying their need for definitive treatment. In light of these results and the fact that leading a healthy lifestyle is safe and has well-known physiological benefits, men diagnosed with low- to intermediate-risk PCa and initially managed with AS should be advised to improve lifestyle habits.

Implications from the present study also suggest that the use of a lifestyle assessment questionnaire may aid in predicting the progression of low- to intermediate-risk PCa in men enrolled in an AS program. Randomized control trials are warranted to more definitively determine the relationship between lifestyle characteristics and the progression of low- to intermediate-risk PCa.

Conflict of Interest

The authors have no conflict of interest to declare.

Figure 1. Comparison of the median and interquartile range of lifestyle scores between low risk and progressed groups from the Sunnybrook and Royal Marsden Hospital Cohorts.

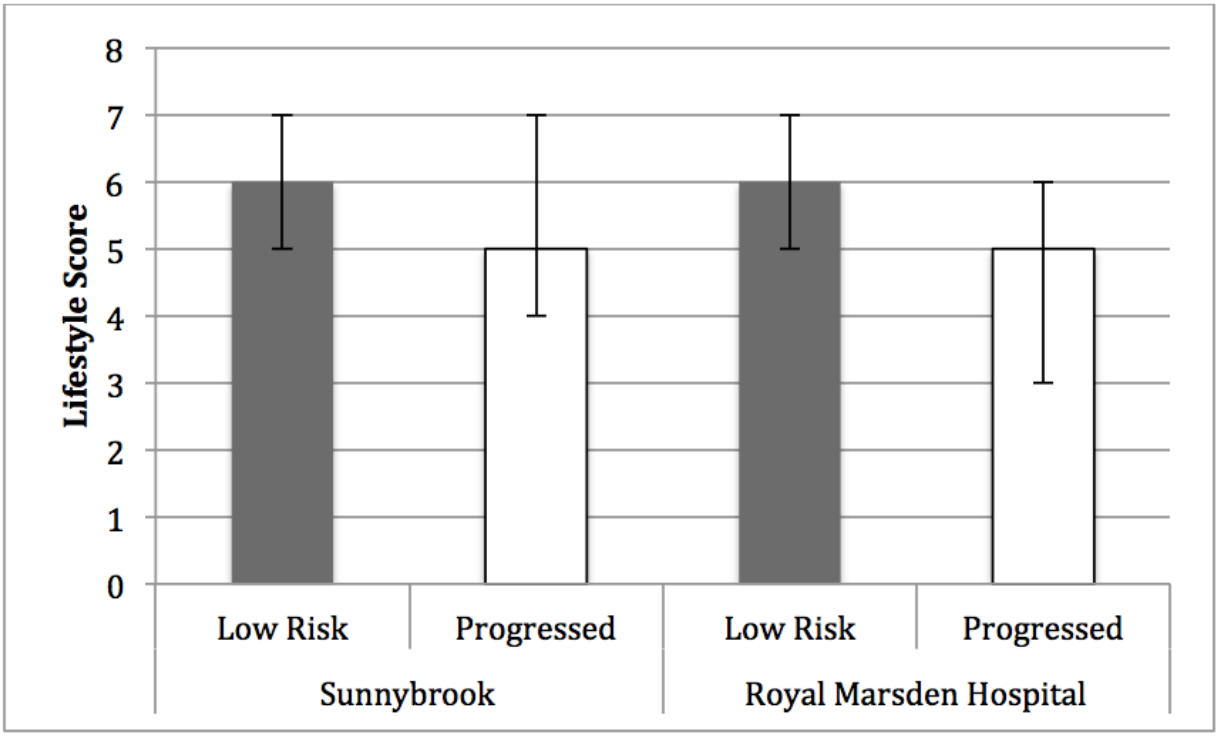

Figure 2. Comparison of the median and interquartile range of total physical activity (A) and recreational physical activity (B) in MET-hours/week performed by men in the low risk and progressed groups from the Sunnybrook cohort and Royal Marsden Hospital cohort.

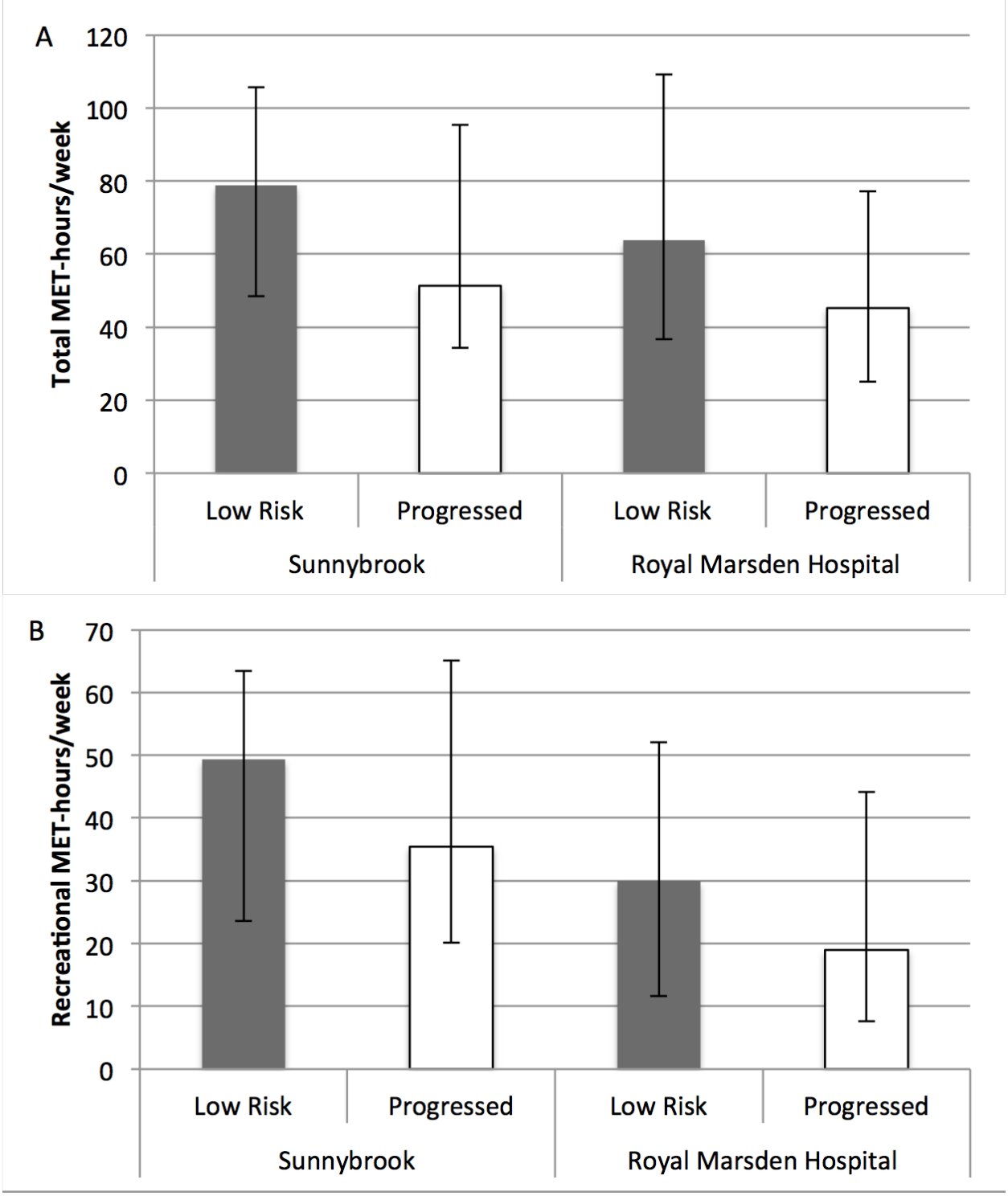

Figure 3. Correlation between age at the time of progression and total time to progression among men in the progressed group from the Sunnybrook cohort (A) and Royal Marsden Hospital (B) cohort.

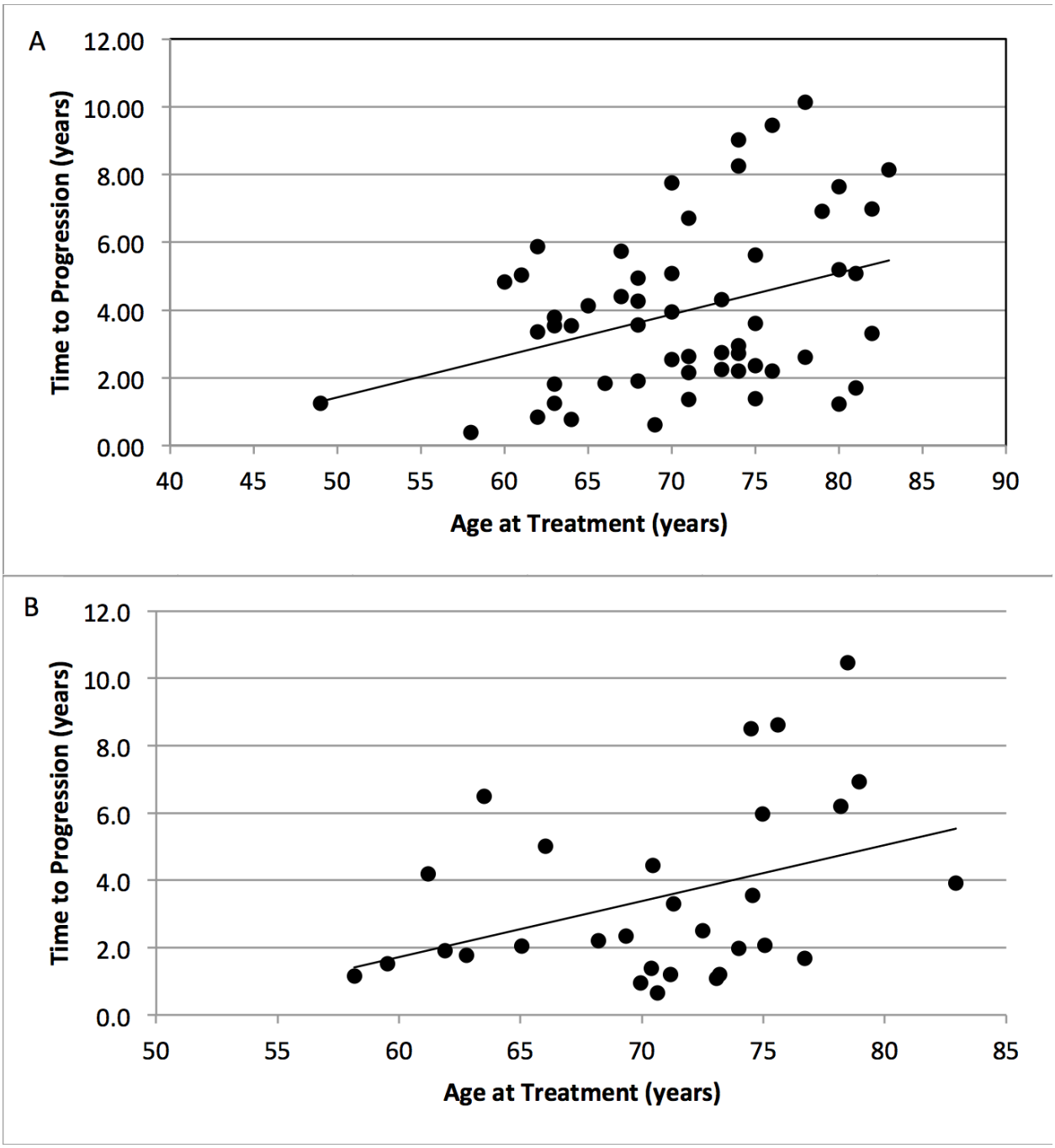

Table I. Interpretation of Overall Dietary and Fruits and Vegetables Indices

Overall Dietary Index		**Fruits and Vegetables Index**	
Raw Score	*Interpretation*	*Raw Score*	*Interpretation*
9-12	Very Poor		
13-16	Poor	5-8	Poor
17-20	Average	9-12	Average
21-24	Good	13-15	Good
25-27	Very Good		

Table II. Clinical and demographic data for men from the Sunnybrook Cohort and the Royal Marsden Hospital Cohort

Characteristic	Sunnybrook 2011			Royal Marsden Hospital 2013		
	Low Risk	Progressed	p-Value	Low Risk	Progressed	p-Value
Number of patients (%)	76 (58)	55 (42)		76 (71.7)	30 (28.3)	
Age at diagnosis, median (range)	63 (40-81)	67 (48-79)	0.0089	64.5 (51-78)	68.5 (58-83)	0.0051
Age at questionnaire, median (range)	67 (45-86)	74 (48-89)	<0.0001	69.5 (53-83)	71.5 (57-88)	0.028
Race, n (%)						
Caucasian	57 (75)	48 (87)		72 (94.7)	27 (90)	
Black	11 (14)	4 (7)		1 (1.3)	0 (0)	
Other	8 (11)	3 (6)		2 (2.6)	2 (6.7)	
Unknown	0 (0)	0 (0)		1 (1.3)	1 (3.3)	
Time on surveillance, median (range)	3.88 (0.16-15.90)	3.55 (0.38-10.13)	0.62	4.80 (0.6-10.7)	2.25 (0.6-10.5)	0.096
Baseline PSA, median (range)	5.33 (0.30-13.25)	5.63 (2.09-14.10)	0.46	6.25 (0.9-26.6)	6.17 (1.5-21.0)	0.51
Body mass index, median (range)	26.25 (20.53-26.01)	26.63 (20.37-39.75)	0.56	27.20 (20.2-40.8)	27.95 (22.2-39.4)	0.29
Gleason score at diagnosis, n (%)						
<6	0 (0)	1 (2)		0 (0)	1 (3.3)	
6 (3+3)	71 (93)	46 (83)		73 (96.1)	28 (93.3)	
7 (3+4)	5 (7)	7 (13)		3 (3.9)	1 (3.3)	
Unknown	0 (0)	1 (2)		0 (0)	0 (0)	
Waist to hip ratio, median (range)	0.98 (0.87-1.13)	0.97 (0.81-1.12)	0.35	0.95 (0.8-1.1)	0.96 (0.9-1.2)	0.19

Table III. Lifestyle characteristics and history of disease of men from the Sunnybrook Cohort and Royal Marsden Hospital Cohort

	Sunnybrook 2011			Royal Marsden Hospital 2013		
Characteristic	**Low Risk**	**Progressed**	**p-Value**	**Low Risk**	**Progressed**	**p-Value**
Lifestyle score, median (IQR)	6 (5-7)	5 (4-7)	0.14	6 (5-7)	5 (4-7)	0.046
Vigorous PA, MET hrs/wk, median (IQR)	24.90 (4.47-52.72)	26.95 (0.00-57.57)	0.79	0 (0-30.67)	0 (0-0)	0.11
Recreational PA, MET hrs/wk, median (IQR)	49.34 (23.60-63.48)	35.43 (20.09-65.03)	0.18	29.98 (11.64–52.01)	18.98 (7.60–44.20)	0.30
Total PA, MET hrs/wk, median (IQR)	78.79 (48.36-105.66)	51.30 (34.31-95.41)	0.11	63.78 (36.67-109.26)	45.19 (25.04-77.14)	0.12
Diet score, median (IQR)	17 (16-19)	18 (16-19)	0.88	15.5 (14-17)	15 (13.25-17)	0.68
Fruit and vegetable intake score, median (IQR)	10 (8-11)	9 (8-10.5)	0.59	14 (12-15)	13.5 (11.25-15)	0.55
Tobacco use, n (%)			0.47			0.37
Heavy smoker	2 (3)	1 (2)		0 (0)	1 (3.3)	
Light smoker	3 (4)	0 (0)		2 (2.6)	2 (6.7)	
Former smoker	42 (55)	30 (54)		38 (50)	11 (36.7)	
Non-smoker	29 (38)	24 (44)		35 (46.1)	15 (50)	
Unknown	0 (0)	0 (0)		0 (0)	1 (3.3)	
Alcohol use, n (%)			0.45			0.86
Heavy drinker	2 (3)	5 (9)		11 (14.5)	3 (10)	
Moderate drinker	23 (30)	15 (27)		16 (21.2)	7 (23.3)	
Light drinker	33 (43)	23 (42)		38 (50)	16 (53.3)	
Non-drinker	18 (24)	12 (22)		11 (14.5)	3 (10)	
Unknown	0 (0)	0 (0)		0 (0)	1 (3.3)	
Family history of Prostate Cancer, n (%)			0.77			0.55
Yes	15 (20)	12 (22)		12 (15.8)	7 (23.3)	
No	61 (80)	43 (78)		52 (68.4)	20 (66.7)	
Unknown	0 (0)	0 (0)		12 (15.8)	3 (10)	
History of diabetes, n (%)			0.94			0.26
Yes	10 (13)	7 (13)		6 (7.9)	3 (10)	
No	66 (87)	48 (87)		70 (92.1)	26 (86.7)	
Unknown	0 (0)	0 (0)		0 (0)	1 (3.3)	
History of CVD/stroke, n (%)			0.40			0.24
Yes	11 (14)	11 (20)		10 (13.2)	5 (16.7)	
No	65 (86)	44 (80)		66 (86.8)	24 (80)	
Unknown	0 (0)	0 (0)		0 (0)	1 (3.3)	

Table IV. Results from the binary logistic regression analysis using lifestyle variables as predictors for progression

	Sunnybrook 2011		Royal Marsden Hospital 2013	
Characteristic	***Multivariable OR (95% CI)**	**p-Value**	***Multivariable OR (95% CI)**	**p-Value**
Age at diagnosis	1.06 (1.01–1.11)	0.014	1.15 (1.04–1.26)	0.00067
Family history of prostate cancer	1.15 (0.48-2.76)	0.75	1.56 (0.49-4.93)	0.45
Lifestyle score	0.95 (0.77-1.16)	0.29	0.75 (0.55-1.02)	0.066
Total PA, MET hrs/wk	1.00 (0.99-1.01)	0.62	1.00 (0.99-1.00)	0.24
Diet score	0.99 (0.86 – 1.14)	0.88	0.89 (0.64-1.23)	0.47
Waist to hip ratio	0.029 (0.000-10.85)	0.24	4111.70 ($0.35\text{-}4.88\times10^{5}$)	0.082

*Multivariable analysis for lifestyle score, physical activity, diet score and waist to hip ratio were adjusted for by age at diagnosis and family history of prostate cancer. Physical activity, diet score and waist to hip ratio were further adjusted by each lifestyle characteristic.

Table V. Association between lifestyle variables and time to progression or treatment

	Sunnybrook 2011		Royal Marsden Hospital 2013	
Characteristic	**Time to progression**	**p-Value**	**Time to progression**	**p-Value**
Age at diagnosis, Pearson Coefficient (95% CI)	-0.01 (-0.27 to 0.21)	0.95	-0.039 (-0.32 to 0.23)	0.84
Age at treatment, Pearson Coefficient (95% CI)	0.36 (0.12 to 0.53)	0.0073	0.40 (0.10 to 0.61)	0.030
Total PA, MET hrs/wk, Spearman's rho (95% CI)	-0.11 (-0.38 to 0.17)	0.44	-0.22 (-0.57 to 0.18)	0.24
Diet score, Spearman's rho (95% CI)	0.15 (-0.13 to 0.39)	0.28	0.074 (-0.36 to 0.46)	0.70
Fruit and vegetable intake score, Pearson Coefficient (95% CI)	0.17 (-0.056 to 0.390)	0.22	-0.27 (-0.59 to 0.078)	0.15

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