



Influence of physical activity on active surveillance discontinuation in men with low-risk prostate cancer

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Abstract

Purpose Epidemiologic data suggest that high levels of physical activity (PA) may reduce the risk of disease progression in men with prostate cancer (PCa), but it is unknown whether PA can delay the requirement for definitive treatment for those on active surveillance (AS). We investigated the influence of PA post-diagnosis on AS discontinuation in men with low-risk disease.

Methods The effect of PA on the time to AS discontinuation was assessed in 421 patients, of whom 107 underwent additional PCa treatment over a median of 2.5 years.

Results Using Cox regression models, we found that PA was not significantly associated with time to curative treatment initiation. Prostate-specific antigen (PSA) most proximal to AS initiation (HR, 1.11; 95% CI 1.03 to 1.21) and the number of positive cores (HR, 1.34; 95% CI 1.12 to 1.61) at diagnosis were associated with a significantly increased risk of discontinuing AS.

Conclusion Our findings suggest that PA during AS for PCa does not significantly influence time to curative treatment.

Keywords Prostate cancer · Low-risk disease · Active surveillance · Physical activity · Treatment

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Introduction

Active surveillance (AS) is a management approach to low-risk PCa that strives to minimize treatment-related morbidity while offering comparable long-term outcomes to those undergoing curative surgery and radiation [1]. Disease progression, identified by prostate-specific antigen (PSA) monitoring and repeat prostate biopsy, provide clinical indication for the use of alternate management strategies that are often associated with physical and psychosocial adverse effects that compromise quality of life (QOL). In the absence of disease progression, discontinuation of AS in favor of curative treatment may be initiated by the patient due to anxiety and/or distress related to delaying definitive therapy [2], yet the proportion of men who discontinue AS for non-clinical reasons appears to be relatively small [2]. In an effort to maximize the duration of time on AS, and consequently defer potentially problematic adverse effects associated with other treatments, strategies that can attenuate tumor progression and manage stress are particularly valuable [3].

Research shows that physical activity (PA) provides a number of physiological and psychological health benefits

to men with PCa. High levels of PA have been associated with reduced PCa progression and disease-specific mortality [4, 5] that may be explained by anti-neoplastic modulation of circulating growth and inflammatory cytokines, as well as infiltration of natural killer cells [6, 7]. Meta-analytic data have also shown that PA increases health-related QOL and decreases psychological distress in men with PCa [8]. Given the potential physiological and psychosocial benefits of PA for men with PCa and the potential reasons for AS discontinuation, we explored whether PA was associated with time from AS initiation to additional treatment.

Materials and methods

Retrospective data were retrieved from the electronic cancer care (ecc)Prostate Database at the Princess Margaret Cancer Centre between 2001 and 2016 and included 1062 men with PCa on AS. (Supplementary Fig. 1). The eccProstate Database was reviewed to ascertain participants' age, disease characteristics most proximal to active surveillance initiation and prior to curative treatment (if applicable), type of curative treatment (if applicable), and self-reported post-diagnosis PA throughout AS. Participants' PA was assessed at each follow-up visit every 3 to 6 months using the Godin Leisure-Time Exercise Questionnaire (GLTEQ) [9]. Patient consent was obtained for inclusion in our institutional database. This study was approved by the Research Ethics Board at the University Health Network. Participants were included in our analysis if they met AS criteria (PSA < 10 ng/ml, Clinical stage \leq T2a, and Gleason score 6 most proximal to diagnosis); \leq 75 years old at the time of diagnosis; completed a PA questionnaire within 24 months of AS initiation and prior to additional treatment; completed a minimum of three PA questionnaires until AS discontinuation or loss to follow-up.

PA was measured using the first, second, and final PA questionnaires after AS initiation until initiation of additional treatment or loss to follow-up. The GLTEQ was modified to include the average duration per session of PA per week for moderate and vigorous intensity activities to express PA volume in metabolic equivalent-minutes per week (MET-min/wk). Each participant's PA status across the study period was categorized as: inactive (< 210 MET-min/wk), insufficiently active (210–500 MET-min/wk), active/meeting PA guidelines (500–1000 MET-min/wk), or highly active (> 1000 MET-min/wk). Similar categorisation of PA has previously been used by Wang and colleagues [5]. Additionally, it is well-established that meeting PA guidelines corresponds to 500–1000 MET-min/wk of energy expenditure [10]. A sensitivity analysis was performed to detect differences in post-diagnosis PA status between men below and over 65 years old at baseline and over time. Time to discontinuation of AS was displayed for the entire cohort

using a Kaplan–Meier plot (see Supplementary data). Cox regression models were used to estimate the association between PA and risk of discontinuing AS, with adjustment for age, PSA most proximal to AS initiation, and number of positive cores from the diagnostic biopsy. PA was treated as a time-dependent variable to account for changes in participants' PA levels during the study. This statistical approach was undertaken after assessing the stability of participants' PA status indicated by the first, second, and final PA questionnaires. Within-participant variability in PA was associated with a change in PA categories in 43 and 48.5% of the cohort at the second and final PA questionnaire, respectively. Histopathological grade, the number of positive cores, and the percent involved of worst core from the biopsy prior to curative treatment, were used to assess disease progression in men who discontinued AS.

Of the 1062 AS cases in the database, 421 met the inclusion criteria. Most common reasons for exclusion included completion of the GLTEQ > 24 months after AS initiation ($n = 260$); completion of less than three PA questionnaires ($n = 209$); and a PSA value > 10 ng/ml ($n = 58$) (see Supplementary data).

Results

The mean age of participants at AS initiation was 61.8 years (SD = 6.5, range 44–75) (Table 1). The median durations of AS at the first, second, and final PA records were 3, 10, and 46 months. In the eligible cohort, 107 discontinued AS and underwent curative treatment and 314 were still on AS at the end of follow-up. The median time from AS initiation to curative treatment was 109 months. Additional treatment began as early as 7 months and as late as 116 months after AS initiation. Our sensitivity analysis showed that PA was not different between men above and below 65 years old at baseline or over time (data not shown). Cox regression analyses found no beneficial, consistent, or statistically significant association of PA with duration of AS (Table 2). In fact, the highest level of PA was associated with the highest risk of discontinuing AS (Table 2). In our multivariable model, only PSA most proximal to AS initiation (HR, 1.11; 95% CI 1.03 to 1.21) and the number of positive biopsy cores (HR, 1.34; 95% CI 1.12 to 1.61) at the time of diagnosis were associated with a significantly increased risk of discontinuing AS (Table 2).

Disease progression was assessed in men who discontinued AS ($n = 107$) and had available information on Gleason score ($n = 97$), number of positive cores ($n = 91$), and percent involved of worst core ($n = 89$) at AS initiation and prior to treatment. Compared to disease characteristics at AS initiation, Gleason score, the number of positive cores, and the percent involved of worst core increased in 68, 69, and 73%

Table 1 Participant characteristics according to PA questionnaire most proximal to AS initiation

Characteristics Mean (SD)	Inactive (n = 126)	Insufficiently active (n = 45)	Active (n = 84)	Highly active (n = 166)	All participants (n = 421)	Missing data Frequency (%) (n = 421)
Age (years)	62.8 (6.8)	63.1 (6.4)	61.3 (5.8)	61.0 (6.7)	61.8 (6.5)	0 (0)
PSA most proximal to AS initiation (ng/ml)	5.2 (2.8)	5.4 (2.8)	4.8 (2.5)	4.8 (2.4)	5.0 (2.6)	52 (12.3)
Number of positive cores from diagnostic biopsy	1.6 (0.9)	1.6 (0.8)	1.6 (1.0)	1.6 (0.9)	1.6 (0.9)	40 (9.5)
Percent involved of worst core from diagnostic biopsy (%)	9.2 (10.5)	7.8 (9.8)	10.7 (14.9)	9.3 (8.9)	9.4 (10.8)	55 (13.0)
MVPA most proximal to AS initiation (MET-min/wk)	11.3 (40.0)	375.7 (76.1)	730.5 (134.9)	2,080.3 (1018.8)	1,009.6 (1,105.9)	0 (0)

PA physical activity, AS active surveillance, *inactive* < 210 MET-min/wk, *insufficiently active* 210–500 MET-min/wk, *Active* 500–1000 MET-min/wk, *highly active* > 1000 MET-min/wk, SD standard deviation, PSA prostate-specific antigen, MVPA moderate-to-vigorous physical activity, MET-min/wk metabolic equivalent-minutes per week

Table 2 Risk of AS discontinuation relative to PA status post-diagnosis among men with PCa

Variable	HR (95% CI)	p trend
Unadjusted model (n = 421)		
Physical activity strata (MET-min/wk)		0.097
Inactive (< 210)	1.00 (ref.)	
Insufficiently active (210–500)	1.08 (0.53–2.23)	
Active (500–1,000)	0.78 (0.43–1.42)	
Highly active (> 1,000)	1.48 (0.94–2.34)	
Adjusted model (n = 338)		
Physical activity strata (MET-min/wk)		0.202
Inactive (< 210)	1.00 (ref.)	
Insufficiently active (210–500)	1.15 (0.51–2.57)	
Active (500–1000)	0.83 (0.43–1.59)	
Highly active (> 1000)	1.46 (0.89–2.43)	
Age (years)	0.97 (0.94–1.00)	0.143
PSA (ng/ml) most proximal to AS initiation	1.11 (1.03–1.21)	0.006
Number of positive cores from diagnostic biopsy	1.34 (1.12–1.61)	0.001

CI confidence interval, HR hazard ratio, ref. reference category, MET-min/wk metabolic equivalent-minutes per week, PSA prostate-specific antigen, AS active surveillance

of men prior to curative treatment initiation. Notably, ~ 11% of men who discontinued AS did not exhibit an increase in any of the aforementioned disease characteristics.

Discussion

Many studies have shown that higher levels of PA may protect against disease progression and survival after a PCa diagnosis [4, 5, 11]. Promising evidence from a randomized controlled trial suggests that intense lifestyle changes, including PA may downregulate tumor growth in men with low-risk PCa [12]. Similarly, Bourke and colleagues showed that 12 months of moderate-to-vigorous PA clinically

improves indices of physical and psychological health in men undergoing AS for PCa [13]. The aforementioned studies have acknowledged the value of PA as a disease-management strategy during AS; however, the utility of PA in extending the duration of AS requires further elucidation.

The present cohort study is the first to assess whether PA post-diagnosis can prolong the duration of AS in men with low-risk PCa. Our findings suggest that PA during AS does not significantly influence the time to initiation of curative treatment. Moreover, clinical indices, such as PSA most proximal to AS initiation and the number of positive cores from the diagnostic biopsy, were significantly associated with curative treatment initiation. The majority of men who discontinued AS experienced an increase

in histopathological grade had more positive cores and a greater tumor involvement of biopsy core prior to curative treatment. In contrast, a small proportion of men who underwent treatment (~ 11%) did not present progression in disease characteristics which may be indicative of AS termination due to non-clinical reasons (e.g., anxiety, fear of disease progression).

These results should be interpreted with caution for the following reasons. First, the effect of PA on AS discontinuation in our multivariate Cox regression model was assessed in 338 of the 421 participants due to missing data on PSA and the number of positive cores from diagnostic biopsy. Second, although we assessed changes in indices of disease progression in men who underwent curative treatment, we could not reliably and precisely determine the definitive reasons for AS discontinuation (i.e., clinically-indicated versus patient-directed), a distinction which might have helped disentangle the physiological and psychological effects of PA on AS duration. Third, we acknowledge the risk of social desirability bias in self-reported PA measurement [14]. In fact, findings from a recent cohort study suggest that self-reported PA overestimates actual moderate-to-vigorous PA in men with localized PCa [15]. Moreover, while body mass index (BMI) is often associated with physical activity status and has been implicated in prostate cancer progression [16], BMI data were not available for the majority of our participants and therefore not included in the analysis.

In conclusion, we did not find PA post-diagnosis to be significantly associated with the time on AS for men with low-risk PCa. While these data cannot conclusively determine whether PA affects clinical and non-clinical factors in men with low-risk disease, an area for future research relates to the exercise-related biological and psychological determinants that may influence the term of AS. Given the protective effects of PA for men with PCa and the limitations of the present study, further study/research is warranted.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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