Total energy expenditure and vigorous intensity physical activity are associated with reduced odds of reclassification among men on active surveillance

David E. Guy[1,2], Avi Vandersluis[2], Laurence H. Klotz[2], Neil Fleshner[4], Alexander Kiss[3], Chris Parker[5], Vasundara Venkateswaran[2]

[1]Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada, [2]Division of Urology, Department of Surgery, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [3]Evaluative Clinical Sciences, Sunnybrook Health Sciences Centre, [4]Division of Urology, Department of Surgery, Princess Margaret Hospital, Toronto, ON, Canada, [5]Institute of Cancer Research, Royal Marsden Hospital, Sutton, Surrey, UK

*Corresponding Author: Dr. Vasundara Venkateswaran
Associate Professor
Department of Surgery, University of Toronto
Division of Urology
Sunnybrook Health Sciences Centre
S-120, 2075 Bayview Avenue
Toronto, Ontario M4N 3M5, CANADA
Tel: (416) 480-6100 x 3127
E-mail: vasundara.venkateswaran@sunnybrook.ca

Running head: Physical activity and prostate cancer progression

Keywords: Prostate cancer, physical activity, progression, Active Surveillance

Abstract

Background: Research examining the association between physical activity (PA) and prostate cancer (PCa) has accumulated; however, few studies have examined this association in the context of active surveillance. The current study examines this among men initially diagnosed with favourable-risk PCa and managed by active surveillance at Sunnybrook Health Sciences Centre in Canada and the Royal Marsden Hospital in the United Kingdom.

Methods: Participants completed a questionnaire on daily participation in non-leisure, transport, and recreational PA. A logistic regression was employed using PA as the independent variable and whether the patient reclassified to higher-risk PCa while on active surveillance as the dependent variable. Demographic and lifestyle covariates were incorporated in the analysis to assess potential confounding and effect modification.

Results: Men from both hospitals presented with similar clinical and demographic characteristics. Total PA was inversely associated with odds of reclassification while on active surveillance (p-trend = 0.017). A weaker and non-significant inverse association was observed with recreational PA (p-trend = 0.30). Men who participated in weekly vigorous PA were less likely to reclassify than those who did not (OR [95%CI]: 0.40 [0.19-0.82]), owing to intensity of PA rather than duration.

Conclusions: Total and vigorous PA were inversely associated with odds of reclassification among men initially diagnosed with favourable-risk PCa and managed by active surveillance. Given the limitations of this study and that it is the first of its kind, more robust prospective observational studies involving objective PA measures are warranted to confirm findings.

Introduction

Prostate cancer (PCa) remains a major healthcare concern in Canada and globally (1). In 2016, 22,000 Canadian men were diagnosed with the disease, leading to considerable suffering and financial drain of healthcare resources (2). About half of these diagnoses were favorable-risk, which is unique in a sense that radical treatment is not initially required as it is with more aggressive phenotypes (3-5). Instead, favorable-risk patients are periodically assessed through analysis of serum biomarkers, histological grading and physical examination to classify disease risk (3), a management strategy known as active surveillance. During active surveillance, about one-third of men reclassify to higher risk disease and require radical treatment, leading to substantial disease- and treatment-related morbidity and mortality (3). Research examining factors in the progression of PCa during active surveillance will help to identify effective forms of tertiary prevention, so is of great value.

Physical activity (PA) has demonstrated influence in the evolution of PCa with increasing levels of participation being associated with reduced rates of PCa risk (6-8), biochemical recurrence (9), and PCa-specific death (10,11). However, few studies have examined the influence of PA on PCa in the context of active surveillance (12,13). Such studies also rely on surrogate outcomes of questionable validity (i.e. prostate-specific antigen (PSA)) and involve multiple lifestyle interventions, making it difficult to discern the main effect of PA alone (13,14). In light of this and considering that PCa grows relatively slow compared to other cancers (3), further investigation is required to distinguish whether PA significantly influences tumor progression among patients initially diagnosed with favourable-risk PCa and managed by active surveillance.

In a previous study, we demonstrated a protective association between healthier lifestyle characteristics and PCa progression (15). Of the six factors used to categorize a healthy lifestyle (PA, dietary intake, body mass index (BMI), waist-to-hip circumference ratio (WHR), tobacco use and alcohol use) only PA demonstrated consistent differences between favourable-risk and reclassified groups in both cohorts analyzed. Men who remained favorable-risk compared to those who reclassified to higher risk disease while on active surveillance demonstrated a 53.6% ($p=0.11$) and 41% ($p=0.061$) increase in total PA at Sunnybrook Health Sciences Centre in Canada (SHSC) and the Royal Marsden Hospital (RMH) in the United Kingdom, respectively (15). The current study re-evaluates this data more appropriately using tertiles instead of continuous PA data with a particular focus on PA as it relates to risk of PCa progression during active surveillance.

Methods

Participants

This study received ethics approval from The Research Ethics Board of SHSC. Participants were approached in clinic during their regular scheduled appointments/visits with intent to recruit during the period of each cohort. Informed consent was obtained from all patients approached. From 2010 to 2011, 133 men diagnosed with favourable-risk PCa between 1995 and 2011 and initially managed with active surveillance were recruited from SHSC. Two men were excluded from the study, as they opted for active surveillance despite initial recommendation for treatment upon diagnosis. The remaining 131 men were categorized into two groups: 1) those who were currently undergoing active surveillance ("favourable-risk") and 2) those who were initially managed with active surveillance but later reclassified to higher risk

disease and subsequently underwent radical treatment ("reclassified"). In 2013, 112 men diagnosed with favourable-risk PCa between 1999 and 2013 and initially managed with active surveillance were recruited from the RMH. 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 ("favourable-risk") and 2) those who initially presented with favourable-risk disease but later reclassified to higher risk disease and/or underwent radical treatment ("reclassified"). Categorizing men from the RMH cohort differently than those from the SHSC cohort was done in response to differences in available data.

"Favorable-risk" PCa was followed according to the D'Amico definition (Gleason score ≤ 6 (3+3), PSA < 10 mg/ml, and clinical stage ≤ T2a) with some exception (i.e. men with Gleason 7 (4+3), provided they are older than 70 years and only have a small proportion of Gleason 4 pattern) (16). Reclassification to higher risk disease was triggered by Gleason pattern 4 or 5 on repeat biopsy or when extensive increases in Gleason pattern 3 volume were found in patients under 55 years (16). Reclassification for men in the RMH cohort was similar; however, 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 a significant predictor of disease progression in this cohort (17).

Assessment of lifestyle characteristics

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, PA, dietary intake, medications and supplements, history of disease, and general health. Men were asked to recall information from the time they were on active

surveillance (i.e. reclassified men reported information from diagnosis to time of reclassification while men who remained favourable risk reported information from diagnosis to time of questionnaire. The PA section was identical to the Global Physical Activity Questionnaire (GPAQ), which has previously demonstrated weak to moderate strength correlation between self-report and objective measures (i.e. accelerometer and pedometer) of total PA (18). Height, weight, and WHR were also measured. The survey was administered to men in the SHSC cohort through personal interviews at the time of consent and to men in the RMH cohort as a take home survey (unmodified) right after consent was obtained.

Data regarding working/non-leisure, transport-related and recreational PA were collected. Non-leisure PA referred to PA done as part of paid or unpaid work, household maintenance, or study/training. Recreational physical activities included walking, jogging, swimming, sports, gym-based activities (e.g. treadmill, weight-lifting, etc.) and referred to planned activity for health benefit or enjoyment excluding non-leisure PA. Patients were also asked of their perceived intensity (i.e. moderate or vigorous) for each activity. Vigorous-intensity PA was defined as strenuous PA causing large increases and breathing and heart rate whereas moderate-intensity PA was defined as causing small increases in breathing and heart rate. Specific metabolic equivalent task (MET) values were assigned to all physical activities, according to the Compendium of Physical Activities (19). Values were further adjusted by BMI and age at diagnosis according to an equation established by Byrne et al (20), as shown below:

$$\text{Adjusted MET value for activity} = \text{Standard MET value for activity} * ([3.5 \text{ ml } O_2/\text{kg}\cdot\text{min}]/[3.6145 - (0.0367 * \text{BMI}) - (0.0038 * \text{age}) + (0.1790 * 2)])$$

Indices were developed to assess each patient's diet as a whole, as well as his fruit and vegetable intake. Details regarding this development have been reported previously (15). Briefly, for food groups thought to promote or hinder PCa growth, heavier consumption was allotted fewer and greater points, respectively. The overall dietary score was equivalent to the sum of points for each food group. The fruits and vegetable score 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. Scores were portioned into tertiles along with BMI, and WHR and were included as covariates in the regression model. Tobacco use was dichotomized as never and ever smoked, since few reported current tobacco use (n=7). Alcohol consumption was categorized as none, light (less than daily), moderate (daily but <3 drinks/day) and heavy (>3 drinks/day).

Statistical Analysis

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary NC). A power calculation was performed for the original study (15) and 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. A binary logistic regression analysis was performed with PA as the independent variable of interest and whether or not patients reclassified during their time on active surveillance as the dependent variable. Total and recreational PA were categorized into tertiles of MET-hrs/wk by cohort, since method of data collection might have influenced self-report values of PA (15,21). Since a substantial number of participants reported not participating in vigorous intensity PA (n = 88), it was dichotomized into any or no weekly participation. The first

model accounted for age at diagnosis, time on surveillance and recruitment centre. The second model further accounted for diet and BMI, and tobacco and alcohol use, and family history of PCa. Fruit and vegetable intake score and WHR were excluded after demonstrating notable muticollinearity (tolerance statistic <0.4) with dietary score and BMI, respectively. Since the latter two demonstrated a stronger association with the outcome and greater influence the association of interest, they were retained in the final model. We tested for evidence of a linear trend by modeling the median value of each tertile of total and recreational PA as a continuous term. We considered potential interactions of PA with age at diagnosis, time on surveillance and other lifestyle characteristics. Statistical significance for all analyses was denoted by a p-value <0.05.

Results

Both cohorts presented with similar clinical and demographic characteristics, as reported previously (15). Briefly, 93% of favorable-risk and 83% of reclassified men from the SHSC cohort had a Gleason score of 6, while men from RMH presented similarly with 96.1% and 93.3%, respectively. Seven percent and 13% from the favorabe-risk and reclassified groups were diagnosed with Gleason score 7 at SHSC, respectively, while this rate was only 3.9% and 3.3% at RMH. Patient characteristics by levels of PA are displayed in Table I. Briefly, men who completed greater levels of total PA also completed greater amounts of recreational PA and were more likely to participate in vigorous intensity PA. They were also, on average, younger at diagnosis and reclassification (reclassified only) or last follow-up (favourable-risk only). These trends were similar among levels of recreational PA and participation in vigorous PA as well. Higher levels of total PA and participation in vigorous PA seemed to be associated with shorter

time on active surveillance; however, when restricted to men who reclassified, time to reclassification was not associated with PA (15). Men who completed greater amounts of PA also had, on average, lower body mass indices.

Results from the binary logistic regression analysis are shown in Table II. Increasing levels of total PA were significantly associated with a reduction in odds of reclassification when data were pooled (p-trend = 0.027, respectively), but not when limited to either cohort (p-trend = 0.092 and 0.11). Increased MET-hrs/week of recreational PA were associated with a reduction in odds of reclassification (Tertile 2 vs. 1: 0.78 [0.38-1.58] and 3 vs. 1: 0.70 [0.34-1.44]), though this trend did not reach statistical significant in neither cohort (p-trend = 0.52 and 0.44) nor when the data were pooled (p-trend = 0.33). Participation in weekly vigorous PA was associated with a reduction in odds of reclassification in the SHSC and RMH cohorts (0.45 [0.16 – 1.27] and 0.27 [0.084 – 0.88], respectively). Results were highly significant upon pooled analysis (0.42 [0.20-0.85]).

Tests for interactions between categories of PA and participant characteristics were performed (Table 3). A borderline significant interaction was found between vigorous PA and diet score (p = 0.061) where a stronger inverse association was found at lower levels of diet score (first tertile 0.17 [0.052 – 0.53]; second tertile 0.38 [0.12 – 1.16]; third tertile 0.99 [0.36 – 2.76]). Similar findings were observed between total and recreational PA with diet score; however, these interactions were not significant (p = 0.67 and 0.40, respectively). A borderline significant interaction was also found between vigorous PA and WHR where stronger inverse associations were found among greater ratios (first tertile 0.67 [0.22 – 2.05]; second tertile 0.46 [0.16 – 1.36]; third tertile 0.13 [0.038 – 0.42]; p=0.079). This finding was similar for recreational

PA but not total PA (p=0.50 and 0.93, respectively). Notable interactions between total, recreational or vigorous PA and age at diagnosis, time on surveillance, BMI, or tobacco or alcohol use were not observed.

Discussion

The current study examined data collected from men initially diagnosed with favourable-risk PCa and managed by active surveillance at SHSC in Canada and RMH in the United Kingdom. The primary objective was to investigate the association between PA and PCa progression while on active surveillance. We found that increasing levels of total PA as expressed by MET-hrs/wk were inversely associated with odds of reclassification. Though this finding was not significant in either cohort alone, pooled results indicated a significant inverse linear trend. Lack of significance in single cohorts is probably due to the relatively small sample size, which increases the estimate of the standard error, thus reducing power to detect a significant reduction in odds of reclassification. The differences between odds of reclassification for the second vs. first tertile in the RMH and SHSC cohorts could be due to variation in the method of reclassification between cohorts among other healthcare and population variables. The inverse association between PA and PCa reclassification is consistent with previous literature indicating a protective effect of PA on PCa risk and progression (i.e. biochemical recurrence, bone metastasis, secondary treatment, and PCa death) (6-11).

Increasing levels of recreational PA appeared to be inversely associated with odds of reclassification in both cohorts, though this finding was not significant even when data were pooled. Lack of significance might be attributed to the small sample size given the weak nature of the association. However, a highly powered meta-analysis found that increased participation

in recreational PA to be only borderline significantly associated with a reduced risk of PCa (6). Vigorous PA was significantly associated with a reduction in odds of reclassification in both cohorts. Findings did not significantly or notably change when including total PA as a covariate, indicating that the association was due to intensity rather than duration of PA. These results are consistent with previous studies indicating an inverse association between vigorous PA and risk of PCa progression even with modest amounts of vigorous PA (i.e. biochemical recurrence, secondary treatment, bone metastasis, PCa death) (9,10).

The protective association between PA and PCa reclassification can be explained by a number of biological mechanisms (22). Of particular interest is the favorable modification of the hormonal milieu. Increased levels of PA have been found to reduce the bioavailability of androgens and insulin like growths factors (22-24). These hormones stimulate the androgen receptor in cancerous prostatic epithelial tissue, increasing proliferation and progression (25). Studies also suggest a possible association between increased PA and reduced androgen receptor content in prostatic epithelial tissue (26,27). The combined effect of reduced hormonal bioavailability and androgen receptor content would reduce androgen receptor stimulation, which is crucial in PCa proliferation (25). Other pathways such as reduced oxidative stress and inflammation, and increased immune surveillance have also been implicated in the protective association between increased PA and PCa (22).

Strengths and Limitations

This study is the first to examine the association between multiple categories of PA and PCa progression in the context of active surveillance. Strengths of our study design include classification of the outcome variable using a comprehensive set of clinical and pathological

parameters including Gleason score, measures of prostate-specific antigen and clinical staging. The PA section has been previously validated in nine countries and demonstrates weak to moderate reliability with objective measures (i.e. pedometer and accelerometer) (18). In addition, statistical control for a range of potential confounders was considered.

There are certain limitations of this study that should be considered. The retrospective nature of the study leaves data prone to recall bias. Since a number of factors may influence memory of participation in PA such as cognitive function, regularity of PA (e.g. scheduled fitness classes versus house maintenance) and memory assistance (e.g. presence of companion or family member), it is likely that recall bias would increase variation and bias findings toward the null. Though it has been found that cases (i.e. reclassified group) tend to remember exposures better than non-cases (i.e. favorable-risk) (28), it is unlikely that recall accuracy was enhanced among the reclassified compared to favorable-risk group, as variation in self-report PA was similar (15).

Differential questionnaire administration raises two major concerns. In-person compared to participant administration has been shown to elevate social desirability bias (21), which might explain increased PA participation among SHSC compared to RMH participants. Other variables such as geography (e.g. Canadians tend to travel greater distances between points of interest), and patient selection (i.e. differences in clinical guidelines might select different populations between cohorts that perform different amounts of PA) may also explain these discrepancies. The GPAQ was designed to be administered in-person, which might reduce variability due to individual interpretation. This might explain the narrower confidence intervals observed among the SHSC compared to the RMH cohort.

Another concern is that the reclassified group from the SHSC cohort included men who sought radical treatment regardless of disease status. Cancer-related anxiety has been found to independently predict receipt of radical treatment among men on active surveillance (29). Since PA might reduce such anxieties (30), the psychological effects might have contributed to our findings rather than just the biological effects of PA. However, only 3 men opted for treatment without clinical recommendation, and men who forewent treatment despite recommendation were excluded, making psychological influence a trivial concern. Finally, prostate-specific antigen screening was not examined as a covariate. Since it increases the likelihood of favourable-risk diagnosis and is associated with health-conscious behaviours (31), it has potential to confound the inverse association between PA and PCa progression noted here. However, lack of association and confounding among other health-conscious behaviors (e.g. diet, BMI, WHR and tobacco and alcohol use) suggests that inclusion of screening as a covariate would not significantly change study results.

Summary

The study finds increased levels of total and participation in vigorous PA to be associated with a reduction in odds of reclassification among men diagnosed with favourable-risk PCa and managed by active surveillance. Results for increased recreational PA were less convincing, though still favourable. These findings did not notably change at different age groups, or between cohorts lending further strength to our findings. In light of these results and considering that PA has been found safe and effective in improving overall health among PCa patients (13), oncologists should encourage men on active surveillance to increase levels of PA. Given the limitations of this study, suggesting specific PA levels sufficient in reducing PCa

progression would be inappropriate. Instead, oncologists should make a referral to professionals with experience in exercise programming for cancer patients (e.g. certified exercise physiologist) who can assess patients and provide tailored exercise programs that maximize health benefit and safety.

To overcome limitations within our study, future prospective observational studies with larger sample sizes of men undergoing active surveillance and objective measures of PA are warranted. Clinical trials are also warranted to understand the feasibility of exercise interventions among active surveillance patients and to accurately establish exercise prescriptions effective in tertiary prevention. A clinical trial involving lifestyle intervention in an active surveillance population is already underway, involving increased vegetable intake (32). Results suggest that clinical trials involving lifestyle intervention among active surveillance patients are feasible.

Acknowledgements

Funding was not required or mobilized for this project. No additional personnel significantly contributed to this study other than the authors.

Conflicts of Interest

The authors declare no conflicts of interest.

References

(1) Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: a cancer journal for clinicians. 2011;61(2):69-90.

(2) Canadian Cancer Society's Advisory Committee on Cancer Statistics: Canadian Cancer Statistics 2016. Toronto, Canadian Cancer Society, 2016.

(3) Klotz L. Active surveillance for low-risk prostate cancer. Curr Urol Rep. 2015;16(4):1-10.

(4) Klotz L, Emberton M. Management of low risk prostate cancer – active surveillance and focal therapy. Nat Rev Clin Oncol. 2014;11(6):324-34.

(5) Cooperberg MR, Carroll PR, Klotz L. Active surveillance for prostate cancer: progress and promise. J Clin Oncol. 2011 Sep 20;29(27):3669-76.

(6) Liu Y, Hu F, Li D, Wang F, Zhu L, Chen W, et al. Does physical activity reduce the risk of prostate cancer? A systematic review and meta-analysis. Eur Urol. 2011;60(5):1029-44.

(7) Antonelli JA, Jones LW, Bañez LL, Thomas J, Anderson K, Taylor LA, et al. Exercise and prostate cancer risk in a cohort of veterans undergoing prostate needle biopsy. J Urol. 2009;182(5):2226-31.

(8) De Nunzio C, Presicce F, Lombardo R, Cancrini F, Petta S, Trucchi A, et al. Physical activity as a risk factor for prostate cancer diagnosis: a prospective biopsy cohort analysis. BJU Int. 2016;117(6B).

(9) Richman EL, Kenfield SA, Stampfer MJ, Paciorek A, Carroll PR, Chan JM. Physical activity after diagnosis and risk of prostate cancer progression: data from the cancer of the prostate strategic urologic research endeavor. Cancer Res. 2011 Jun 1;71(11):3889-95.

(10) Kenfield SA, Stampfer MJ, Giovannucci E, Chan JM. Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. J Clin Oncol. 2011 Feb 20;29(6):726-32.

(11) Tai S, Hsieh H, Huang S, Wu M. Hair dye use, regular exercise, and the risk and prognosis of prostate cancer: multicenter case–control and case-only studies. BMC Cancer. 2016;16(1):242.

(12) Burton AJ, Martin RM, Donovan JL, Lane JA, Davis M, Hamdy FC, et al. Associations of lifestyle factors and anthropometric measures with repeat PSA levels during active surveillance/monitoring. Cancer Epidemiol Biomarkers Prev. 2012 Oct;21(10):1877-85.

(13) Ornish D, Weidner G, Fair WR, Marlin R, Pettengill EB, Raisin CJ, et al. Intensive lifestyle changes may affect the progression of prostate cancer. J Urol. 2005;174(3):1065-70.

(14) Hvid T, Lindegaard B, Winding K, Iversen P, Brasso K, Solomon TP, et al. Effect of a 2-year home-based endurance training intervention on physiological function and PSA doubling time in prostate cancer patients. Cancer Causes & Control. 2016;27(2):165-74.

(15) Vandersluis A, Guy D, Klotz L, Fleshner N, Kiss A, Parker C, et al. The role of lifestyle characteristics on prostate cancer progression in two active surveillance cohorts. Prostate Cancer Prostatic Dis. 2016 Jun 28;19:305-310.

(16) Klotz L. Active surveillance for prostate cancer: overview and update. Curr Treat Options Oncol. 2013 Mar 1;14(1):97-108.

(17) Ng MK, Van As N, Thomas K, Woode-Amissah R, Horwich A, Huddart R, et al. Prostate-specific antigen (PSA) kinetics in untreated, localized prostate cancer: PSA velocity vs PSA doubling time. BJU Int. 2009 Apr 1;103(7):872-6.

(18) Bull FC, Maslin TS, Armstrong T. Global physical activity questionnaire (GPAQ): nine country reliability and validity study. J Phys Act Health. 2009 Nov;6(6):790-804.

(19) Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32(9; SUPP/1):S498-S504.

(20) Byrne NM, Hills AP, Hunter GR, Weinsier RL, Schutz Y. Metabolic equivalent: one size does not fit all. J Appl Physiol. 2005 Sep;99(3):1112-9.

(21) Vuillemin A, Oppert J, Guillemin F, Essermeant L, Fontvieille A, Galan P, et al. Self-administered questionnaire compared with interview to assess past-year physical activity. Med Sci Sports Exerc. 2000;32(6):1119-24.

(22) Wekesa A, Harrison M, Watson R. Physical activity and its mechanistic effects on prostate cancer. Prostate cancer Prostatic Dis. 2015 Sep;18(3):197.

(23) Barnard RJ, Ngo TH, Leung P, Aronson WJ, Golding LA. A low-fat diet and/or strenuous exercise alters the IGF axis in vivo and reduces prostate tumor cell growth in vitro. Prostate. 2003;56(3):201-6.

(24) Schumann M, Mykkänen OP, Doma K, Mazzolari R, Nyman K, Häkkinen K. Effects of endurance training only versus same-session combined endurance and strength training on physical performance and serum hormone concentrations in recreational endurance runners. Appl Physiol Nutr Metab. 2014 Sep 15;40(1):28-36.

(25) Heinlein CA, Chang C. Androgen receptor in prostate cancer. Endocr Rev. 2004;25(2):276-308.

(26) Teixeira G, Fávaro W, Pinheiro P, Chuffa L, Amorim J, Mendes L, et al. Physical exercise on the rat ventral prostate: steroid hormone receptors, apoptosis and cell proliferation. Scand J Med Sci Sports. 2012;22(5):e86-e92.

(27) Deschenes MR, Maresh CM, Armstrong LE, Covault J, Kraemer WJ, Crivello JF. Endurance and resistance exercise induce muscle fiber type specific responses in androgen binding capacity. J Steroid Biochem Mol Biol. 1994;50(3):175-9.

(28) Patten, SB. Epidemiology for Canadian Students: principles, methods and critical appraisal. Canada: Brush Education Inc;2015.

(29) Latini DM, Hart SL, Knight SJ, Cowan JE, Ross PL, DuChane J, et al. The relationship between anxiety and time to treatment for patients with prostate cancer on surveillance. J Urol. 2007 Sep; 30178(3):826-32.

(30) Galvão DA, Taaffe DR, Spry N, Gardiner RA, Taylor R, Risbridger GP, et al. Enhancing active surveillance of prostate cancer: the potential of exercise medicine. Nat Rev Urol. 2016 May 1;13(5):258.

(31) Kristal AR, Stanford JL. Cruciferous vegetables and prostate cancer risk: confounding by PSA screening. Cancer Epidemiol Biomarkers Prev. 2004 Jul;13(7):1265.

(32) Parsons JK, Pierce JP, Mohler J, Paskett E, Jung SH, Morris MJ, et al. The Men's Eating and Living (MEAL) Study (CALGB 70807 [Alliance]): Recruitment Feasibility and Baseline Demographics of a Randomized Trial of Diet in Men on Active Surveillance for Prostate Cancer. BJU Int. 2017 May 21. DOI: 10.1111/bju.13890.