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Research Article

Cancer Prevention Research

Physical Activity from Early Adulthood and Risk of Prostate Cancer: A 24-Year Follow-Up Study among Icelandic Men

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Abstract

Physical activity in adult life may reduce prostate cancer risk. Data are scarce on the role of activity during early adulthood, as well as combined recreational and occupational physical activity on prostate cancer risk and mortality. We undertook a prospective study of 8,221 Icelandic men (born 1907 to 1935) in the population-based Reykjavik Study. At enrollment, between 1967 and 1987, the men provided information on regular recreational physical activity since the age of 20 years as well as current occupational activity. Through linkage to nationwide cancer and mortality registers, the men were followed for prostate cancer diagnosis and mortality through 2009. We used Cox models to calculate the relative risk of prostate cancer by level of physical activity. During a mean follow-up of 24.8 years, 1,052 men were diagnosed with prostate cancer, of whom 349 had advanced disease (stage 3+ or prostate cancer death). Neither recreational nor occupational physical activity was, independently or combined, associated with overall or localized prostate cancer. Compared with physically inactive men, we observed a nonsignificant lower risk of advanced prostate cancer [HR, 0.67; 95% confidence interval (CI), 0.42–1.07] among men reporting both recreational and occupational physical activities (P value for interaction = 0.03). Awaiting confirmation in larger studies with detailed assessment of physical activity, our data suggest that extensive physical activity beginning in early adulthood may reduce the risk of advanced prostate cancer. *Cancer Prev Res; 8(10); 905–11. ©2015 AACR.*

Introduction

Prostate cancer is the second most common cancer among men worldwide, but with a striking international variation in incidence rates (1). Widespread PSA testing has led to a rise in the detection of indolent tumors from the large but silent reservoir of latent prostate cancer (2). It is therefore important to distinguish between risk factors for aggressive and indolent disease.

Increasing evidence, including a recent meta-analysis (3), suggests that physical activity and fitness may play a preventive role in prostate cancer development and progression (3–6). Results of the numerous studies addressing physical activity and risk of prostate cancer have though been found to be inconsistent (3–6), perhaps due to methodological differences across studies, including inability to distinguish lethal from indolent prostate cancers, variation in follow-up time, and methods for ascertainment of physical activity. Importantly, it is not known whether persistent activity or physical activity during specific periods of life affects prostate cancer risk (3, 5). Moreover, very few studies have assessed the role of detailed lifetime physical activity, including both early life activity and combined recreational and occupational activity (7–9).

Leveraging the population-based Reykjavik Study (10) with more than 24 years of follow-up and the nationwide Icelandic Cancer Registry (11), we conducted a prospective analysis of regular recreational physical activity in adulthood (from the age of 20 years until time of enrollment) and occupational physical activity at enrollment and risk of prostate cancer. We hypothesized that the combined effect of physical activity in leisure time and at work would be associated with decreased risk of prostate cancer, particularly for advanced disease.

Materials and Methods

Study population

The prospective Reykjavik Study is a population-based cohort initiated in 1967 by the Icelandic Heart Association (10). All men born from 1907 to 1935 and living in the Reykjavik area in December 1966 were identified (n = 14,923), of whom 12,842 were randomly selected and invited to participate in the study (in

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waves from 1967 to 1987). The response rate was 71% (n = 9,115). At entry, participants who were aged 33 to 79 years underwent a detailed medical examination. They also completed a questionnaire regarding health and lifestyle factors, including questions on physical activity in leisure time and at work. For the present study, men with diagnosed prostate cancer at baseline ($n = 19$), incomplete follow-up ($n = 20$), and incomplete information on physical activity (n = 855) were excluded, leaving 8,221 men in our cohort.

Assessment of physical activity

At entry to the Reykjavik Study, participants reported whether they were mostly sitting, mostly standing, or mostly on the move at their current work. Based on the responses, two categories were defined for occupational physical activity: low (mostly sitting or mostly standing) and high (mostly on the move). Participants were also asked whether they had regularly participated in sports or exercised since the age of 20 years. Only men reporting regular leisure physical activity were then asked when in life they were active, given the following age categories (in years) to respond to: 20–29, 30–39, 40–49, and 50–59. A variable for current recreational physical activity was created, matching the information on participation in recreational physical activity to the age at enrollment.

To study the combined effect of physical activity in leisure time and in current work, participants were cross classified into four different physical activity groups: (i) no leisure activity—low work activity, (ii) leisure activity—low work activity, (iii) no leisure activity—high work activity, and (iv) leisure activity—high work activity. For combined activity, there were complete data on recreational and occupational physical activity for 8,221 men (reduced to 8,152 men when using information on current activity).

Follow-up and ascertainment of prostate cancer

The men were followed from entry to the Reykjavik study (between 1967 and 1987) until diagnosis of prostate cancer, death, or the end of the study period (December 31, 2009). Follow-up was virtually complete (99%; ref. 12). Furthermore, data from a recent study indicate that the Icelandic Cancer Registry is 99.15% complete with respect to nationwide registration of all cancer cases in Iceland (13).

Data on prostate cancer diagnoses until the end of 2009 were obtained via record linkage to the Icelandic Cancer Registry (11). Information on prostate cancer as the underlying cause of death was retrieved from Statistics Iceland (14). Classification of stage of disease at diagnosis was based on medical records using the tumor–node–metastasis stage classification: stage I (incidental finding), including T1a, NX/0, and MX/0; stage II (tumor confined to prostate gland), including T1b/1c/1/2, NX/0, and MX/0; stage III (tumor extending through prostatic capsule), including T3, NX/0, and MX/0; or stage IV (locally advanced or metastatic disease), including T4, NX/0, MX/0 or any T, N1 and/or M1. Stage information was available for approximately 60% of cases. Men were classified as having advanced prostate cancer if they died from the disease or were diagnosed with a stage III or IV tumor. Other cases were classified as localized.

Statistical analysis

We used two sample t-tests for continuous variables and χ^2 test for categorical variables (95% confidence level) to compare baseline demographic and health characteristics of participants by level of combined physical activity.

Cox proportional hazards modeling was used to calculate HRs and 95% confidence intervals (CIs) for localized, advanced, and total prostate cancer across levels of recreational and occupational activities. We examined associations with both recreational and occupational activity separately as well as combined leisure- and work based activity. Our main analysis for combined activity was performed using recreational physical activity since the age of 20 years, but in a secondary analysis, we used current recreational physical activity (at time of enrollment). Due to observed interaction between physical activity in leisure time and at work, we further made a stratified analysis of recreational physical activity, according to level of occupational activity (data reported in Supplementary Table S2).

Multivariate models were used for controlling for the following covariates (values at baseline): birth-year (continuous), age (continuous), height (continuous), body mass index (continuous), type 2 diabetes (yes/no), smoking (never/former/current), family history of prostate disease (yes/no), regular health check-ups (yes/no), educational attainment (elementary/secondary school, college education, or university education), and residency in early life (Reykjavik, seaside village, rural area, or combination of seaside village and rural area; ref. 15). Weight, blood pressure, serum cholesterol, serum glucose, and erythrocyte sedimentation rate were not included in the multivariate models as these variables were not important predictors for prostate cancer or significant confounders in the statistical analysis.

A sensitivity analysis was performed to address the potential effect of an existing undiagnosed prostate cancer on physical activity, where participants diagnosed with the disease within the first 3 years from entry to the study were excluded.

We used SAS software, version 9.2 (SAS Institute Inc.; www.sas.com) for all statistical analyses. The study protocol was approved by the Icelandic Ethical Review Board (VSNb2007120014/03-7) and the Icelandic Data Protection Authority.

Results

The mean age of participants (n = 8,221) when entering the Reykjavik Study was 51.7 years (SD = 8.1). During an average follow-up time of 24.8 years (SD = 10.7), 1,052 men were diagnosed with prostate cancer, of whom 349 had advanced disease. Mean age at cancer diagnosis was 73.6 years. A minority of participants reported being physically active in their leisure time from early adulthood (n = 2,164, 26%) and still fewer at time of enrollment (n = 1,072, 12%). The correlation (kappa coefficient) between regular physical activity since the age of 20 years and baseline recreational physical activity was 0.52.

Somewhat fewer men were occupied in physically demanding jobs (n = 3,798, 46%) than in sedentary occupations (n = 4,423, 54%). Participation in regular recreational physical activity from the age of 20 years was lower among men in physically demanding occupations as compared with men in sedentary jobs: 20% versus 32%, respectively.

Characteristics according to physical activity level

Table 1 shows the characteristics of the cohort by level of leisure physical activity, stratified for occupational physical activity (low and high). For both strata of occupational activity, men participating in leisure physical activity were taller and had lower blood

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Table 1. Demographic and health characteristics (at baseline) by level of recreational physical activity (RPA), stratified for occupational physical activity (OPA)

	Total ($n = 8,221$)					
	Low OPA ($n = 4,423$)			High OPA ($n = 3,798$)		
	Non-RPA/low OPA ($n = 3,023$)	RPA/low OPA ($n = 1,400$)		Non-RPA/high OPA ($n = 3,034$)	RPA/high OPA ($n = 764$)	
	Mean (SD)	Mean (SD)	*P* value	Mean (SD)	Mean (SD)	*P* value
Age, years	51.3 (8.0)	51.6 (8.2)	0.2523	52.0 (8.1)	52.6 (8.0)	0.0710
Height, cm	177.0 (6.2)	177.9 (6.4)	<0.0001	175.7 (6.2)	176.3 (6.3)	0.0445
Weight, kg	81.3 (12.8)	82.2 (11.4)	0.0198	79.0 (11.8)	79.6 (11.1)	0.1738
Body mass index, kg/m^2	25.9 (3.6)	26.0 (3.2)	0.6435	25.5 (3.4)	25.6 (3.2)	0.6633
Diastolic blood pressure, mm Hg	89.0 (10.5)	87.6 (10.4)	<0.0001	87.9 (10.1)	86.6 (9.9)	0.0015
Systolic blood pressure, mm Hg	140.7 (18.9)	138.1 (18.5)	<0.0001	139.9 (18.6)	138.0 (18.1)	0.0134
Serum cholesterol, mmol/L	6.40 (1.1)	6.37 (1.0)	0.3523	6.40 (1.1)	6.33 (1.0)	0.1079
Serum glucose, mg/dl	83.4 (15.5)	81.7 (11.3)	<0.0001	82.6 (13.5)	82.8 (17.6)	0.7718
	n (%)	*n* (%)	*P* value	*n* (%)	*n* (%)	*P* value
Diabetes, type 2	139 (4.6)	51 (3.6)	0.145	114 (3.8)	28 (3.7)	0.9029
Smoking status			<0.0001			<0.0001
Never smoker	552 (18.3)	342 (24.4)		625 (20.6)	216 (28.3)	
Former smoker	710 (23.5)	358 (25.6)		625 (20.6)	169 (22.1)	
Current smoker	1,761 (58.2)	700 (50.0)		1,783 (58.8)	379 (49.6)	
Regular health check-up	643 (21.3)	412 (29.4)	<0.0001	496 (16.3)	166 (21.7)	0.0005
Prostate disease in the family	299 (9.9)	169 (12.1)	0.0283	203 (6.7)	51 (6.7)	0.9878
Education			<0.0001			<0.0001
Primary and secondary	2,173 (71.9)	683 (48.8)		2,863 (94.4)	652 (85.4)	
College	467 (15.4)	356 (25.4)		136 (4.5)	85 (11.1)	
University	383 (12.7)	361 (25.8)		35 (1.1)	27 (3.5)	
Location of first residence[a]			<0.0001			<0.0001
Reykjavik	1,106 (36.9)	645 (46.1)		955 (31.5)	342 (44.8)	
Seaside village	1,008 (33.3)	395 (28.2)		1,115 (36.8)	238 (31.2)	
Rural area	750 (24.8)	294 (21.0)		794 (26.2)	160 (20.9)	
Combination of rural area and seaside village	105 (3.5)	38 (2.7)		116 (3.8)	20 (2.6)	

[a]Numbers do not add up to 100% due to missing values.

pressure than those physically inactive in their leisure time. The recreationally active men tended to smoke less but have more regular health check-ups, a higher educational level, and be raised in the capital area (Reykjavik) in childhood compared with men inactive in their leisure time. Among men with low occupational physical activity, those participating in recreational physical activity were also heavier, had lower serum glucose levels, and were more likely to have prostate disease in the family than men not physically active in their leisure time.

Physical activity and prostate cancer

For total, localized, and advanced disease, no significant association was observed in independent analysis between either recreational or occupational physical activity and prostate cancer (Tables 2 and 3). A marginally reduced risk of advanced prostate cancer was observed among men who reported being physically active in their leisure time since the age of 20 years (HR, 0.82; 95% CI, 0.63–1.06) compared with nonactive men in leisure time.

In the cross-classified analysis, there was no significant association observed between combined physical activity and total prostate cancer or localized disease (Table 4). A marginally reduced risk of advanced prostate cancer was observed for the most active men (leisure activity and high work activity) as compared with the least active men (no leisure activity and low work activity), with HR of 0.67 (95% CI, 0.42–1.07). Similar results were obtained in the secondary analysis for current combined activity (see Supplementary Table S1). A statistically significant interaction was found between recreational and occupational physical activity in the cross-classified analysis ($P = 0.03$, advanced disease).

When the recreational analysis was stratified for occupational activity (Supplementary Table S2), we observed no significant association between recreational physical activity and total prostate cancer or localized disease, for both high and low levels of occupational activity. However, we found a significantly reduced risk of advanced prostate cancer for men physically active both in their leisure time and at work, with HR of 0.59 (95% CI, 0.37–0.94), compared with those who were not participating in recreational physical activity but employed in a physically demanding job. When we further adjusted for current recreational physical activity, the HR became 0.62 (95% CI, 0.35–1.10). Similar results, albeit nonsignificant, were obtained in the secondary analysis for current physical activity (see Supplementary Tables S1 and S3). Adjusting additionally for regular leisure physical activity since the age of 20 years resulted in a higher HR between current physical activity and advanced disease.

Sensitivity analysis

Excluding men who were diagnosed with prostate cancer within the first 3 years from study entry (seven men with advanced disease) did not alter the point estimates significantly from that of the unrestricted multivariate analysis. For our main combined analysis, we obtained an HR of 0.66 (95% CI, 0.41–1.05) for advanced disease when comparing the most active men with the least active men (corresponding HR for the secondary analysis of current combined activity was 0.66; 95% CI, 0.32–1.35).

Discussion

In this population-based prospective cohort study, we observed a statistically significant interaction between occupational activity

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Table 2. Prostate cancer risk by regular recreational physical activity (RPA) from the age of 20 years

	Number of participants					
	Total	Without PCa	With PCa	IR per 1,000 person-year	Age-adjusted HR (95% CI)	Multivariate HR[a] (95% CI)
Total PCa	8,221					
Number of cases	1,052					
RPA		1,870	294	5.40	0.98 (0.86–1.13)	0.93 (0.81–1.07)
Non-RPA		5,299	758	5.08	1.0	1.0
Localized PCa	7,872					
Number of cases	703					
RPA		1,870	206	3.92	1.03 (0.88–1.22)	0.99 (0.83–1.17)
Non-RPA		5,299	497	3.46	1.0	1.0
Advanced PCa	7,518					
Number of cases	349					
RPA		1,870	88	1.77	0.87 (0.69–1.13)	0.82 (0.63–1.06)
Non-RPA		5,299	261	1.89	1.0	1.0

Abbreviations: IR, incidence rate; PCa, prostate cancer.
[a]Adjustment was made for the following covariates (values at baseline): birth-year, age, height, body mass index, type 2 diabetes, smoking, family history of prostate cancer, education, residency in early life, and regular health check-ups.
Data on RPA were incomplete for 292 men, leaving 8,784 men in the analytic cohort.
Number of individuals in multiadjusted analysis was 3% to 4% lower than in the age-adjusted analysis (due to missing values for covariates).

and recreational physical activity since early adult life and risk of advanced prostate cancer. Men in the highest level of combined recreational and occupational physical activity were marginally at lower risk of advanced prostate cancer compared with the least active men. We observed no association of physical activity levels and total or localized prostate cancer. Reduced risk of advanced prostate cancer was not seen in independent analysis of physical activity at work, but marginally significant results were seen for physical activity in leisure time since the age of 20 years. These results suggest that the effects of physical activity may be accumulative over time and/or need to be continuous during the induction time of prostate cancer, which tends to be long (3, 5, 6). The total amount of physical activity may also be important.

Previous cohort studies exploring the association between physical activity and prostate cancer risk have reported inconsistent results (3, 5, 6, 7, 16–36). That may, at least partly, be due to different methodologies used across studies. A majority of the studies have focused on recreational activity (16–27), and only few have studied combined physical activity from work and leisure time (7, 29, 32, 36). Moreover, most of the studies only contain information on current physical activity from the midlife period or later in life except for few studies with lifetime data (7, 16, 19, 33). Most importantly, though, may be the fact that prostate cancer endpoints differ between mentioned studies; only 11 studies (7, 17–20, 23, 25, 26, 33, 34, 36) have disentangled advanced disease from incident prostate cancer.

Our results, although not statistically significant, of substantial risk reduction of advanced prostate cancer for the most active men is in an agreement with the results of three of the four previous cohort studies exploring combined physical activity at work and in leisure (7, 29, 32). A Swedish study by Orsini and colleagues (7), using lifetime physical activity data, found a 25% reduced risk of advanced prostate cancer (16% for total prostate cancer). In studies by Hartman and colleagues (32) and Clarke and Whittemore (29), the risk of prostate cancer was reduced for the most active men, but the methodology, however, differed from ours as they used information on recent but not lifetime physical activity in their analysis with total prostate cancer as the sole endpoint. Results of a study by Grotta and colleagues (36) disagree with our

Table 3. Prostate cancer risk by occupational physical activity (OPA)

	Number of participants					
	Total	Without PCa	With PCa	IR per 1,000 person-year	Age-adjusted HR (95% CI)	Multivariate HR[a] (95% CI)
Total PCa	8,221					
Number of cases	1,052					
Mostly sitting		2,799	454	5.63	1.0	1.0
Mostly standing		1,022	148	5.01	0.89 (0.74–1.08)	0.97 (0.80–1.17)
Mostly on the move		3,348	450	4.94	0.84 (0.74–0.96)	0.91 (0.79–1.06)
Localized PCa	7,872					
Number of cases	703					
Mostly sitting		2,799	306	3.95	1.0	1.0
Mostly standing		1,022	106	3.70	0.95 (0.76–1.19)	1.01 (0.80–1.27)
Mostly on the move		3,348	291	3.22	0.81 (0.69–0.96)	0.87 (0.72–1.04)
Advanced PCa	7,518					
Number of cases	349					
Mostly sitting		2,799	148	2.00	1.0	1.0
Mostly standing		1,022	42	1.56	0.77 (0.55–1.09)	0.88 (0.62–1.26)
Mostly on the move		3,348	159	1.83	0.90 (0.72–1.12)	1.01 (0.78–1.30)

Abbreviation: PCa, prostate cancer.
[a]Adjustment was made for the following covariates (values at baseline): birth-year, age, height, body mass index, type 2 diabetes, smoking, family history of prostate cancer, education, residency in early life, and regular health check-ups.
Data on OPA were missing for 587 men.
Number of individuals in multiadjusted analysis was 3% to 4% lower than in the age-adjusted analysis (due to missing values for covariates).

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Table 4. Prostate cancer risk by combined recreational and occupational physical activity

	Number of participants				
	Total	Without PCa	With PCa	Age-adjusted HR (95% CI)	Multivariate HR[a] (95% CI)
Total PCa	8,221				
Non-RPA, low OPA		2,625	398	1.0	1.0
Non-RPA, high OPA		2,674	360	0.87 (0.76–1.01)	0.92 (0.79–1.07)
RPA, low OPA		1,196	204	1.03 (0.87–1.22)	0.94 (0.79–1.13)
RPA, high OPA		674	90	0.83 (0.66–1.05)	0.83 (0.65–1.04)
Localized PCa	7,872				
Non-RPA, low OPA		2,625	275	1.0	1.0
Non-RPA, high OPA		2,674	222	0.79 (0.67–0.95)	0.83 (0.69–1.00)
RPA, low OPA		1,196	137	1.03 (0.84–1.26)	0.94 (0.76–1.16)
RPA, high OPA		674	69	0.92 (0.71–1.20)	0.88 (0.67–1.16)
Advanced PCa	7,518				
Non-RPA, low OPA		2,625	123	1.0	1.0
Non-RPA, high OPA		2,674	138	1.06 (0.83–1.36)	1.15 (0.89–1.49)
RPA, low OPA		1,196	67	1.08 (0.80–1.46)	0.98 (0.72–1.35)
RPA, high OPA		674	21	0.61 (0.39–0.97)	0.67 (0.42–1.07)

Abbreviations: OPA, occupational physical activity; PCa, prostate cancer; RPA, recreational physical activity.
[a]Adjustment was made for the following covariates (values at baseline): birth-year, age, height, body mass index, type 2 diabetes, smoking, family history of prostate disease, education, and regular health check-ups.
Number of individuals in multiadjusted analysis was 3% to 4% lower than in the age-adjusted analysis (due to missing values for covariates).
Data on OPA and/or RPA were missing or incomplete for 855 men, leaving 8,221 men in the analytic cohort.

results for advanced disease, where no association was found between combined physical activity and advanced prostate cancer. The study used recent physical activity, not lifetime physical activity (36). A few case–control studies have analyzed combined recreational and occupational physical activity and prostate cancer risk, two studies reported reduced risk for the most active men (8, 37), whereas others have found borderline association (38) or no association (9, 39). Only two of the studies (8, 9) used lifetime physical activity.

The correlation between current and regular adult life physical activity (used mainly in this study) of 0.52 indicates that these variables are not conveying similar information. In addition, adjustment for current recreational activity had only minor effect on the point estimate of the observed reduced risk of advanced disease for the most active men which points toward an importance of accumulated physical activity over the life course. Furthermore, adjusting for regular adult life physical activity in the analysis of current combined physical activity and advanced disease resulted in a higher point estimate of the observed HR for the most active men.

The exact biologic pathways through which physical activity might reduce prostate cancer risk or progression remain unclear, but several mechanisms have been suggested. Physical activity may lower the levels of some of the endogenous growth factors and hormones that have been implicated in prostate cancer risk such as testosterone (40), serum insulin (41), and insulin-like growth factor-1 (42). Being physically active is a key element in weight control and prevention of obesity, which has been associated with advanced prostate cancer risk (43). However, in the present study, the point estimates did not change when adjusting for body weight. Physical activity may also improve immune function (44) and prevent chronic low-grade inflammation (45), and antioxidant defense mechanism may be augmented (46). Finally, regular recreational physical activity combined with being in a physically demanding job might affect the quality of sleep during nights, where better sleep might offer a protection against advanced prostate cancer, as has been suggested among elderly men in a subgroup within this cohort (47).

Our study has several strengths. We used a large and well-described population-based cohort, with information on regular physical activity in leisure time from early adulthood and onwards. The available data on potential covariates were also extensive, well characterized, and obtained at the same time as the information on exposure. Another major strength of this study is the long and virtually complete follow-up for prostate cancer diagnosis and deaths via the linkage to the Icelandic cancer and mortality registries. As the recent meta-analysis by Liu and colleagues (3) indicates, length of the follow-up may be crucial when exploring the potential effects of physical activity on prostate cancer risk; their observed association between these two variables seemed to be confined to studies with a long follow-up time, like ours. The number of advanced prostate cancer cases in the current study is also substantial, enhancing the power of our statistical analysis. Finally, diminishing concerns of reverse causality, our sensitivity analysis excluding those participants diagnosed with prostate cancer within the first 3 years from entry to the study did not change the association results observed for the full-size cohort.

Limitations of this study include the fact that information on physical activity was crudely assessed through questionnaires at entry to the study only and not evaluated throughout the follow-up period. The men's reporting of leisure time physical activity in the distant past is likely to suffer from some recall-related error. However, it is not likely that such error is related to subsequent diagnosis of advanced prostate cancer, and thus such nondifferential misclassification would tend to drive the observed point estimates toward the null (48). Although the use of questionnaires for historical recall of physical activity shows limited reliability and validity, especially at the individual level (48, 49), it is the only way to assess past activity and is believed to be useful as an activity-ranking instrument for large study populations (48). Another limitation of the study is the high number of missing information on physical activity levels, reducing the effective sample size in our analysis. Also, we had no information on the frequency or intensity of physical activity which prohibited us from assessing potential reduction in risk of advanced prostate cancer by these factors. Another disadvantage is

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the fact that the classification of physical activity at work was based on current occupational activity at baseline and did not take into account previous or later occupations. Present study lacks information on total energy intake; however, we adjusted for body mass index measured in midlife, which correlates with total energy intake (50). The follow-up period was long and it is quite possible that some participants experienced a significant change in important covariates during follow-up from baseline assessment, e.g., in body weight or smoking habits, yet it is difficult to predict the magnitude of bias to our observed point estimates. Finally, the incomplete data on tumor stage may have resulted in misclassification of disease level. Some men in our study with advanced prostate cancer at diagnosis might not have been classified as such, most likely leading to underestimation of the association between physical activity and advanced prostate cancer.

In summary, our data suggest that being physically active in leisure time since early adulthood as well as during working hours is in combination associated with marginally reduced risk of a diagnosis of advanced prostate cancer later in life. Meanwhile, we found no association between physical activity level and risk of total or localized prostate cancer. Large studies with long-term follow-up and detailed assessment of activity levels (e.g., frequency and intensity) are needed to confirm these suggestive findings.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S.M. Hrafnkelsdóttir, J.E. Torfadóttir, T. Aspelund, U.A. Valdimarsdóttir
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