ORIGINAL REPORT

Physical Activity and Survival After Prostate Cancer Diagnosis in the Health Professionals Follow-Up Study

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A B S T R A C T

Purpose
To determine whether higher physical activity after prostate cancer (PCa) diagnosis decreases risk of overall and PCa-specific death.

Patients and Methods
We evaluated physical activity in relation to overall and PCa mortality among 2,705 men in the Health Professionals Follow-Up Study diagnosed with nonmetastatic PCa observed from 1990 to 2008. Proportional hazards models were used to evaluate physical activity and time to overall and PCa-specific death.

Results
Among men who lived at least 4 years after their postdiagnosis physical activity assessment, we documented 548 deaths, 20% of which were a result of PCa. In multivariable analysis, men who were physically active had lower risk of all-cause mortality ($P_{trend} < .001$) and PCa mortality ($P_{trend} = .04$). Both nonvigorous activity and vigorous activity were associated with significantly lower overall mortality. Those who walked $\geq$ 90 minutes per week at a normal to very brisk pace had a 46% lower risk of all-cause mortality (hazard ratio [HR] 0.54; 95% CI, 0.41 to 0.71) compared with shorter durations at an easy walking pace. Men with $\geq$ 3 hours per week of vigorous activity had a 49% lower risk of all-cause mortality (HR, 0.51; 95% CI, 0.36 to 0.72). For PCa-specific mortality, brisk walking at longer durations was suggestive inverse but not statistically significant. Men with $\geq$ 3 hours per week of vigorous activity had a 61% lower risk of PCa death (HR, 0.39, 95% CI, 0.18 to 0.84; $P = .03$) compared with men with less than 1 hour per week of vigorous activity. Men exercising vigorously before and after diagnosis had the lowest risk.

Conclusion
In men with PCa, physical activity was associated with lower overall mortality and PCa mortality. A modest amount of vigorous activity such as biking, tennis, jogging, or swimming for $\geq$ 3 hours a week may substantially improve PCa-specific survival.

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INTRODUCTION

Prostate cancer (PCa) is the most frequently diagnosed cancer in men in the United States; however, more than 80% of patients are diagnosed with localized disease,[1] with a relative 10-year survival rate of 93% for all stages combined.[2] More than two million men in the United States and 16 million men worldwide are PCa survivors. Observational studies report that breast and colon cancer survivors who engage in regular activity have significantly lower overall mortality and cancer-specific mortality compared with survivors who are inactive,[3-6] yet no studies have examined this association in PCa survivors.

We previously reported that vigorous activity was associated with reduced risk of incident advanced disease[7] and therefore hypothesized that vigorous activity may reduce the risk of PCa-specific and overall mortality in PCa survivors. Because walking and walking pace were inversely associated with risk of cardiovascular disease and total mortality previously observed within this cohort,[8,9] we also hypothesized that brisk walking may reduce the risk of PCa-specific and overall mortality. We prospectively assessed whether activity after diagnosis, specifically total, nonvigorous (including walking duration and pace), and vigorous activity, was inversely associated with these outcomes.

PATIENTS AND METHODS

Study Population
The Health Professionals Follow-Up Study is a prospective study of 51,529 US male health professionals who

enrolled in 1986 by completing a mailed questionnaire. Participants provided information about medical history and risk factors for chronic diseases, including cancer. Participants complete biennial follow-up questionnaires to collect information on new medical diagnoses and to update information on lifestyle factors (response rate, 96%). This study was approved by the Institutional Review Board of the Harvard School of Public Health.

Assessment of Physical Activity

Leisure time activity was assessed every 2 years. Beginning in 1986, men reported the average time per week spent on the following activities during the previous year: walking to work or for exercise (including golf); jogging ($>$ 10 min/mile); running ($\leq$ 10 min/mile); bicycling (including stationary); lap swimming; tennis; squash or racquetball; calisthenics or rowing; and number of flights of stairs climbed daily. Data on heavy outdoor work and weight training were added in 1988 and 1990, respectively. Walking pace, categorized as easy ($<$ 2 mph), normal (2 to 2.9 mph), brisk (3 to 3.9 mph), and very brisk ($\geq$ 4 mph), was also recorded and updated every 2 to 4 years. The physical activity assessment was validated using four 1-week seasonal diaries.[10] Each activity on the questionnaire was assigned a metabolic equivalent task (MET) value,[11] which is the energy expended compared with sitting at rest. Nonvigorous activities were those with an MET value of less than 6, and vigorous activities were those with an MET value of $\geq$ 6. We chose categories for analysis of total MET-hours per week to correspond to the equivalent of less than 1, 1 to less than 3, 3 to less than 8, 8 to less than 16, and $\geq$ 16 hours per week of walking at an average pace.

Ascertainment of PCa Diagnosis and Death

After a participant reported a diagnosis of PCa, medical records and pathology reports were sought to confirm the diagnosis and obtain information on pathology, treatments, and prostate-specific antigen (PSA) values. Participants completed biennial follow-up questionnaires to update data on treatments, PSA, and clinical progression. The primary outcomes were death from any cause and fatal PCa. Using reports of deaths from families and the National Death Index for nonrespondents, we ascertained more than 98% of deaths.[12] Causes of death were centrally adjudicated by study physicians who reviewed medical records and death certificates.

Population for Analysis

We excluded men diagnosed before 1990 to allow for adjustment for prediagnosis physical activity ascertained 4 years before diagnosis. We included in our analyses men who initially were free of a cancer diagnosis (except nonmelanoma skin cancer) in 1990 and had provided activity data before and after diagnosis (n = 3,032). To reduce the impact of advanced disease on activity duration and intensity, we excluded men who died within 4 years of their first postdiagnostic activity assessment (n = 200), had metastatic disease at diagnosis (n = 107), or reported metastasis before their first postdiagnostic questionnaire (n = 7) or in the 2-year period after their first postdiagnostic questionnaire (n = 13), leaving 2,705 men for analysis.

Covariates

Our final model for PCa-specific mortality included age at diagnosis (5-year categories), clinical stage (T1, T2, or T3/4), clinical Gleason score (score of $<$ 7, 7, or $>$ 7), primary treatment (categorical), prediagnosis activity (same categories as postdiagnosis activity), and body mass index (BMI; $<$ 25, 25 to $<$ 30, or $\geq$ 30 kg/m^2). We considered models that adjusted for PSA at diagnosis, race, height, family history of PCa, diabetes, smoking, and intakes of calcium, red meat, tomato sauce, fish, and α-linolenic acid, because these were previously associated with PCa incidence or progression in our study.[13,14] There was little evidence of confounding by these factors, so they were not included in our final models. Total energy consumption may mediate the relation between physical activity and our outcome, so we excluded energy from the final models; however, including it made no difference in the estimates. Our final model for overall mortality additionally included parental history of myocardial infarction (MI) at age 60 years or younger, high blood pressure, elevated cholesterol, diabetes, smoking (categorical) from the postdiagnostic questionnaire, and comorbidity status (considered to be yes if participant reported any of the following: MI, coronary artery bypass or coronary angioplasty, stroke, Parkinson's disease, and emphysema or chronic bronchitis) updated over follow-up.

Statistical Analysis

We used Cox proportional hazards models to calculate hazard ratios (HRs) of death from any cause or death from PCa. We checked the proportionality assumption by introducing a cross-product term of each specific physical activity variable by a function of time into the model and testing for its statistical significance. No significant violation of the proportionality assumption was found. In the main analysis for PCa mortality, deaths from other causes were censored, and competing risk Cox survival analysis was used.[15] We excluded participants who died within 4 years after the first assessment; therefore, person-years were calculated beginning 4 years from the date of the first postdiagnosis physical activity assessment until death or end of follow-up (January 1, 2008), whichever came first. Because of concerns of possible short-term effects of treatment on physical activity levels, if participants' first postdiagnosis physical activity questionnaires were within 6 months of primary treatment (n = 533), we did not use these data but entered these participants into the analysis upon the return of their next questionnaire. We performed a sensitivity analysis excluding these men completely from the study population, and the point estimates for physical activity did not change materially.

We updated activity every 2 years, maintaining a 4- to 6-year lag. For example, participants diagnosed with PCa between 1992 and 1994 entered the analysis in 1998. We applied their 1994 first postdiagnosis physical activity to deaths occurring between 1998 and 2000, their 1996 postdiagnosis physical activity to deaths occurring between 2000 and 2002, and so on. This approach allowed us to capture recent activity in relation to survival while minimizing reverse causation as a result of the effect of illness preceding death on physical activity.

Linear trends across categories were evaluated using the median of each category as a continuous variable.[16] When examining nonvigorous and vigorous physical activity, we mutually adjusted for both. We assessed interactions between physical activity and potential effect modifiers by entering the cross products of activity with those variables in multivariate models. All P values were two sided. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

We documented 548 deaths, 112 (20%) as a result of PCa, among the 2,705 PCa survivors. The median time from diagnosis to the first physical activity assessment (not including questionnaires completed within 6 months of primary treatment) was 18 months. The median duration of follow-up time from the first postdiagnosis physical activity assessment to censoring (either until death or the end of follow-up in January 2008) was 9.7 years for survivors and 7.8 years for men who died. Age-standardized characteristics after diagnosis are listed in Table 1. Compared with participants in the lowest categories of total and vigorous activity, those in the top category were slightly younger, smoked less, consumed more alcohol, and had a lower BMI. Consumption of relevant foods, energy-adjusted nutrients, and prognostic risk were similar between the groups.

Walking comprised 36% of total MET-hours per week and 52% of total time spent on physical activity (Table 2). Other significant contributors to total MET-hours included heavy outdoor work (22%) and bicycling (10%). Vigorous activity comprised 37% of total MET-hours and 24% of total time spent on physical activity.

Total Physical Activity

Each increasing category of total activity was associated with a decreased risk of all-cause mortality ($P_{\text{trend}} <$ .001; Table 3). HRs remained significant but were attenuated in multivariable analyses. Similar results were observed after further adjustment for prediagnosis physical activity. Men with $\geq$ 9 versus less than 9 MET-h/wk had a 33% reduction in all-cause mortality (HR, 0.67; 95% CI, 0.56 to 0.82; data not shown). We observed a significant trend with increasing MET-h/wk for

Table 1. Age-Standardized Baseline* Characteristics According to Physical Activity Category Among 2,705 Men With Prostate Cancer in the Health Professionals Follow-Up Study

Characteristic	Total Activity					Vigorous Activity		
	< 3 MET-h/wk	3 to < 9 MET-h/wk	9 to < 24 MET-h/wk	24 to < 48 MET-h/wk	≥ 48 MET-h/wk	< 1 h/wk	1 to < 3 h/wk	≥ 3 h/wk
No. of participants	302	373	710	660	660	1596	647	318
Mean age at diagnosis, years†	70.8	70.3	69.2	68.3	68.6	69.5	68.6	68.4
Mean total activity, MET-h/wk	0.9	5.8	16.3	34.4	87.3	23.4	34.5	75.1
Mean vigorous activity, MET-h/wk	0.05	1.0	4.5	11.1	30.3	0.5	12.0	49.1
Stage category, % of participants								
T1	44.8	50.8	52.8	49.8	49.8	49.0	53.0	51.6
T2	34.0	33.8	35.2	39.2	38.9	36.1	36.6	37.8
T3 or T4	2.1	3.5	2.0	2.2	2.1	2.3	2.0	2.1
Missing	19.1	11.9	9.9	8.8	9.2	12.5	8.4	8.6
Gleason score, % of participants								
< 7	50.8	51.5	55.9	59.5	53.8	53.2	58.1	57.3
7	15.3	19.8	18.6	15.7	19.3	18.2	17.3	17.1
> 7	5.4	6.8	4.9	5.3	4.8	5.1	6.1	4.8
Missing	28.5	22.0	20.6	19.6	22.1	23.5	18.6	20.9
Primary treatment, % of participants								
Radical prostatectomy	36.8	45.1	45.5	51.5	47.3	45.7	46.5	47.4
Radiation, seeds, or hormones	34.6	36.2	34.3	31.6	34.5	32.8	35.3	36.2
Watchful waiting	7.5	5.1	7.7	6.7	5.9	6.8	7.2	5.5
Other treatment	1.4	2.6	2.2	1.3	1.5	1.9	1.9	1.2
Missing treatment	19.6	11.1	10.2	8.8	11.0	12.9	9.1	9.8
Mean BMI, kg/m²	27.4	26.1	25.8	25.5	25.1	26.2	25.5	24.8
Family history of prostate cancer, % of participants	9.8	8.0	8.5	12.1	10.3	8.6	12.8	9.9
Diabetes, % of participants	12.5	10.1	6.7	8.3	6.0	8.7	8.6	5.6
High blood pressure, % of participants	50.3	48.1	41.8	43.7	39.4	45.6	42.0	39.6
Elevated cholesterol, % of participants	53.6	52.6	52.4	50.7	47.0	51.5	51.4	46.9
Parental history of MI at age ≤ 60 years, % of participants	9.6	11.8	12.0	11.7	10.4	11.0	11.3	11.9
Smoking status, % of participants								
Current smoker	5.8	5.9	4.8	3.3	2.7	5.1	3.7	1.5
Past smoker	52.7	52.0	50.1	51.5	49.2	51.2	50.8	49.1
Never smoker	41.5	42.0	45.1	45.2	48.1	43.7	45.5	49.3
Mean intake								
Calories per day	1,810	1,924	1,937	1,969	2,081	1,953	1,960	1,999
Calcium, mg/d	1,032	1,018	1,045	1,049	1,076	1,042	1,055	1,070
Red meat, servings/d	0.4	0.5	0.5	0.4	0.4	0.5	0.5	0.4
Tomato sauce, servings/wk	0.9	1.0	1.0	1.0	1.2	1.0	1.1	1.2
Fish, servings/d	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.4
Alcohol, % of participants								
Nondrinker	36.2	23.9	23.9	20.5	23.9	26.9	22.8	18.4
< 15 g/d	44.7	53.0	52.0	51.5	46.7	47.8	51.4	55.2
≥ 15 g/d	19.1	23.1	24.1	28.1	29.4	25.4	25.8	26.4

Abbreviations: MET, metabolic equivalent task; BMI, body mass index; MI, myocardial infarction.
*Baseline lifestyle factors are from participants' first postdiagnosis questionnaire. The subsequent questionnaire was used if first postdiagnosis questionnaire was completed within 6 months of primary treatment.
†Age is not age standardized.

PCa mortality (P_{trend} = .04). Comparing ≥ 9 versus less than 9 MET-h/wk, the HR for PCa mortality was 0.65 (95% CI, 0.43 to 1.00).

Nonvigorous Activity

We observed risk reductions for nonvigorous activity in relation to all-cause mortality starting at a modest level of 1 to less than 3 h/wk (Table 4). Compared with men with less than 1 h/wk of nonvigorous activity, men with 5 to less than 10 h/wk had a significant 28% reduction in total mortality, and men with ≥ 10 h/wk had a 51% risk reduction (P_{trend} < .001).

When evaluating walking separately, a significant benefit was observed at levels of ≥ 7 hours of walking per week (HR, 0.64; 95% CI, 0.47 to 0.86) versus < 20 minutes per week (P_{trend} = .003). Compared with men with an easy walking pace, men with a normal pace had a 37% lower risk of all-cause mortality (HR, 0.63; 95% CI, 0.50 to 0.78), and men with a brisk or very brisk pace had a 48% lower risk of all-cause mortality (HR, 0.52; 95% CI, 0.39 to 0.70; P_{trend} < .001, data not shown). An independent association of pace persisted after adjusting for walking duration. Compared with men who walked less than 90 minutes at an easy pace, those who walked ≥ 90 minutes at a normal to very brisk pace had a 46% lower risk of all-cause mortality (HR, 0.54, 95% CI, 0.41 to 0.71; Fig 1). No statistically significant inverse relation of nonvigorous activity

Table 2. Types of Activity Reported on First Postdiagnosis Questionnaire Among 2,705 Men With Prostate Cancer in the Health Professionals Follow-Up Study

Type of Activity	MET Value*	% of Total MET-Hours per Week†	% of Total Time Spent on Physical Activity
Walking to work or for exercise (including golf)	3 (for average pace)‡	36.2	52.4
Heavy outdoor work (eg, digging, chopping)	5.5	21.6	19.2
Bicycling (including stationary machine)	7	10.0	7.0
Tennis	7	8.3	4.7
Calisthenics, rowing, stair or ski machine, and so on	6	7.3	6.0
Weightlifting or weight machine	4.5	4.0	4.3
Running (10 min/mile or faster)	12	3.7	1.5
Jogging (slower than 10 min/mile)	7	3.3	2.3
Lap swimming	7	2.8	1.9
Squash or racquetball	12	1.7	0.7
Stair climbing	0.11	1.1	—

Abbreviation: MET, metabolic equivalent task.
*Nonvigorous activity included activities with an MET value of less than 6, and vigorous activities were those with an MET value of $\geq$ 6.
†MET-hours per week was calculated by multiplying the MET value by the number of hours per week engaged in that activity.
‡Walking pace and MET value were categorized as follows: easy (< 2 mph, 2.5 METs); normal (2 to 2.9 mph, 3 METs); brisk (3 to 3.9 mph, 4 METs); and very brisk ($\geq$ 4 mph, 4.5 METs).

(Table 4) or walking was observed for PCa mortality ($\geq$ 7 hours of walking per week [HR, 0.75; 95% CI, 0.39 to 1.43] v < 20 minutes of walking per week, P_{trend} = .53; brisk pace [HR, 0.66; 95% CI, 0.34 to 1.29] v easy pace, P_{trend} = .14; data not shown). However, men walking $\geq$ 7 h/wk at a brisk pace had a trend toward lower risk of PCa mortality compared with shorter durations or slower pace (Fig 1). Compared with men who walked less than 7 hours at a nonbrisk pace, men who walked $\geq$ 7 hours at a brisk pace had an HR of 0.44 (95% CI, 0.17 to 1.15) for PCa mortality (Fig 1).

Table 3. Age- and Multivariable-Adjusted HRs According to Physical Activity Category After Prostate Cancer Diagnosis

Measure	Total Activity					P for Trend
	< 3 MET-h/wk	3 to < 9 MET-h/wk	9 to < 24 MET-h/wk	24 to < 48 MET-h/wk	$\geq$ 48 MET-h/wk	
Median MET-hours per week on first postdiagnosis questionnaire	0.6	5.7	16	33.4	71.0	
All deaths (n = 548)						
No. of deaths	125	99	143	116	65	
Age-adjusted HR	1.00	0.79	0.63	0.57	0.33	< .001
95% CI		0.60 to 1.04	0.49 to 0.80	0.44 to 0.73	0.24 to 0.45	
Multivariable-adjusted HR*	1.00	0.81	0.70	0.66	0.40	< .001
95% CI		0.61 to 1.07	0.54 to 0.90	0.51 to 0.87	0.29 to 0.54	
Multivariable-adjusted HR†	1.00	0.80	0.69	0.65	0.38	< .001
95% CI		0.61 to 1.06	0.53 to 0.90	0.49 to 0.86	0.27 to 0.53	
Prostate cancer deaths (n = 112)						
No. of prostate cancer deaths	21	21	25	30	15	
Age-adjusted HR	1.00	0.90	0.61	0.85	0.41	.02
95% CI		0.49 to 1.67	0.34 to 1.10	0.48 to 1.50	0.21 to 0.80	
Multivariable-adjusted HR‡	1.00	0.96	0.65	0.93	0.46	.04
95% CI		0.51 to 1.80	0.36 to 1.20	0.51 to 1.68	0.23 to 0.92	
Multivariable-adjusted HR§	1.00	0.91	0.60	0.83	0.42	.04
95% CI		0.48 to 1.73	0.32 to 1.11	0.44 to 1.55	0.20 to 0.88	

NOTE. Physical activity was updated over follow-up. Men were alive for at least 4 years after their postdiagnosis physical activity assessments, and we only used activity information from 4 to 6 years before death.
Abbreviations: HR, hazard ratio; MET, metabolic equivalent task.
*Adjusted for age at diagnosis, months since diagnosis, clinical stage, Gleason score, treatment, parental history of myocardial infarction at age 60 years or younger, high blood pressure, elevated cholesterol, and diabetes status from the prediagnostic questionnaire; smoking status, body mass index, and alcohol intake from the first postdiagnostic questionnaire; and comorbidities (coded as yes if participant reported any of the following: myocardial infarction, coronary artery bypass or coronary angioplasty, stroke, Parkinson's disease, and emphysema or chronic bronchitis). This variable was updated over follow-up, and comorbidity status was applied one cycle prior to physical activity exposure.
†Additionally adjusted for prediagnosis physical activity.
‡Adjusted for age at diagnosis, months since diagnosis, clinical stage, Gleason score, treatment, and postdiagnosis body mass index.
§Additionally adjusted for prediagnosis physical activity.

Table 4. Age-and Multivariable-Adjusted HRs According to Duration of Nonvigorous and Vigorous Physical Activity After Prostate Cancer Diagnosis

Measure	Duration of Nonvigorous Activity					P for Trend	Duration of Vigorous Activity			P for Trend
	< 1 h/wk	1 to < 3 h/wk	3 to < 5 h/wk	5 to < 10 h/wk	≥ 10 h/wk		< 1 h/wk	1 to < 3 h/wk	≥ 3 h/wk	
Median duration per week on first postdiagnosis questionnaire, hours	0	1.6	3.5	6.0	15.5		0	1.5	5	
All deaths (n = 536)										
No. of deaths	178	148	31	126	53		371	122	43	
Age-adjusted HR	1.00	0.78	0.63	0.66	0.44	< .001	1.00	0.90	0.47	< .001
95% CI		0.62 to 0.98	0.43 to 0.94	0.52 to 0.84	0.32 to 0.61			0.73 to 1.11	0.34 to 0.65	
Multivariable-adjusted HR*	1.00	0.80	0.73	0.74	0.52	< .001	1.00	0.98	0.50	< .001
95% CI		0.64 to 1.01	0.49 to 1.08	0.58 to 0.95	0.37 to 0.71			0.79 to 1.22	0.36 to 0.70	
Multivariable-adjusted HR†	1.00	0.79	0.70	0.72	0.49	< .001	1.00	1.00	0.51	< .001
95% CI		0.63 to 1.00	0.47 to 1.04	0.56 to 0.93	0.35 to 0.69			0.80 to 1.25	0.36 to 0.72	
Prostate cancer deaths (n = 111)										
No. of prostate cancer deaths	26	33	11	29	12		71	31	9	
Age-adjusted HR	1.00	1.03	1.30	1.05	0.65	.21	1.00	1.10	0.33	.04
95% CI		0.61 to 1.74	0.63 to 2.70	0.61 to 1.80	0.32 to 1.32			0.71 to 1.70	0.08 to 1.37	
Multivariable-adjusted HR‡	1.00	1.04	1.47	1.12	0.75	.41	1.00	1.17	0.46	.06
95% CI		0.61 to 1.78	0.69 to 3.12	0.64 to 1.97	0.37 to 1.52			0.74 to 1.83	0.23 to 0.94	
Multivariable-adjusted HR§	1.00	1.08	1.46	1.13	0.79	.46	1.00	1.13	0.39	.03
95% CI		0.63 to 1.87	0.68 to 3.14	0.64 to 2.01	0.37 to 1.66			0.70 to 1.83	0.18 to 0.84	

NOTE. Physical activity was updated over follow-up. Men were alive for at least 4 years after their postdiagnosis physical activity assessments, and we only used activity information from 4 to 6 years before death. When examining nonvigorous and vigorous physical activity, we mutually adjusted for both. Twelve men who died (one from prostate cancer) did not contribute to analyses on duration of exercise because they only reported stair climbing as physical activity.

Abbreviation: HR, hazard ratio.

*Adjusted for age at diagnosis, months since diagnosis, clinical stage, Gleason score, treatment, parental history of myocardial infarction at age 60 years or younger, high blood pressure, elevated cholesterol, and diabetes status from the prediagnostic questionnaire; smoking status, body mass index, and alcohol intake from the first postdiagnostic questionnaire; and comorbidities (coded as yes if participant reported any of the following: myocardial infarction, coronary artery bypass or coronary angioplasty, stroke, Parkinson's disease, and emphysema or chronic bronchitis). This variable was updated over follow-up, and comorbidity status was applied one cycle prior to physical activity exposure.

†Additionally adjusted for prediagnosis physical activity.

‡Adjusted for age at diagnosis, months since diagnosis, clinical stage, Gleason score, treatment, and postdiagnosis body mass index.

§Additionally adjusted for prediagnosis physical activity.

Vigorous Activity

Vigorous activity was inversely associated with total mortality in models that included both vigorous and nonvigorous activity, and the effect per hour was stronger than that for nonvigorous activity. Men engaging in ≥ 3 hours versus less than 1 hour per week of vigorous activity had a 49% reduction in all-cause mortality (HR 0.51; 95% CI, 0.36 to 0.72). We observed a significant risk reduction for PCa mortality with increasing vigorous activity (P_{trend} = .03). Men with ≥ 3 h/wk of vigorous activity had a 61% lower risk of PCa-specific death (HR, 0.39; 95% CI, 0.18 to 0.84) compared with men with less than 1 h/wk of vigorous activity.

We evaluated the impact of change in vigorous activity, comparing participants' prediagnosis level to the postdiagnostic level immediately after diagnosis (excluding participants who completed the questionnaire within 6 months of their primary treatment). Compared with men with low levels (< 1 h/wk) of vigorous activity both before and after diagnosis (44.3%), men who reduced their activity from the highest category (≥ 3 h/wk) to a lower category (9.2%) had an HR of 1.08 (95% CI, 0.76 to 1.53) for total mortality. Men who increased their activity from a lower category to the highest category (7.6%) had an HR of 0.65 (95% CI, 0.44 to 0.97) for total mortality. Men in the highest category at both assessments (8.3%) had an HR of 0.61 (95% CI, 0.39 to 0.93) for total mortality. The corresponding estimates for PCa mortality were as follows: HR of 1.68 (95% CI, 0.91 to 3.11) for high to low; HR of 0.93 (95% CI, 0.43 to 1.99) for low to high; and HR of 0.40 (95% CI, 0.14 to 1.17) for staying in the highest category (data not shown). We found no significant interactions between activity and age at diagnosis, Gleason score, clinical stage, primary treatment, or BMI for all-cause or PCa-specific mortality.

DISCUSSION

In this population of men with PCa, men who exercised for ≥ 9 MET-h/wk had a 33% lower risk of death from any cause and a 35% lower risk of PCa-specific death, after adjustment for other risk factors for mortality and prediagnosis physical activity. Both nonvigorous activity and vigorous activity were associated with lower all-cause mortality. Only vigorous activity was associated with reduced PCa mortality, with a suggestion of a reduced risk for longer duration of brisk walking.

We considered the possibility that this association might be caused by undiagnosed metastatic cancer inducing a reduction in physical activity (reverse causation) and addressed this issue by excluding men with metastases at diagnosis and up to 2 years after their first postdiagnostic activity assessment and men who died within 4 years of this assessment. Additionally, we used activity information 4 to 6 years before death. The median time from metastasis to PCa death was 2.1 years, and the median time to death from other causes was also 2.1 years. This suggests that using activity information 4 to 6 years before death avoids much of the potential effect caused by reverse causation. Results were not materially different when using a longer lag time. On the basis of the analysis evaluating change in activity, the degree of reverse causation may not be severe because most of the reduction in risk was a result of men who were consistently high in
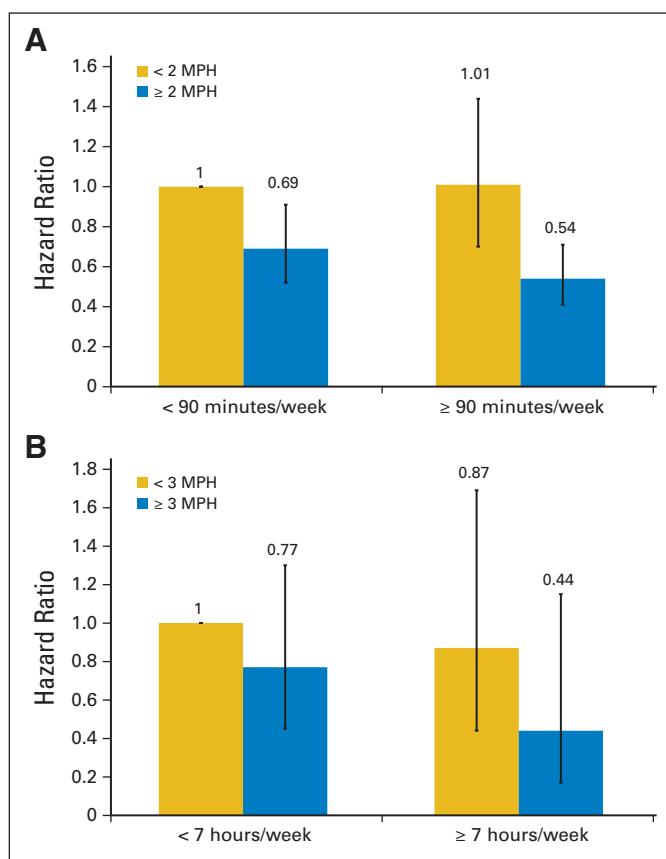
Fig 1. Multivariable-adjusted hazard ratios for (A) all-cause mortality and (B) prostate cancer mortality according to categories of walking duration and pace after prostate cancer diagnosis. An easy pace is less than 2 mile per hour (MPH), a normal pace is 2 to 2.9 MPH, and a brisk pace is ≥ 3 MPH. See footnotes in Table 3 for variables included in the multivariable models for overall and prostate cancer mortality.

activity or had moved from a lower category to the highest category and not mainly a result of an excess risk from men who reduced their activity. Additionally, in a sensitivity analysis in which we stopped updating activity before a diagnosis of metastasis, the results remained unchanged (data not shown).

Activity was self-reported and limited to a subset of common activities. However, this physical activity assessment has detected other well-established activity-disease relationships in cardiovascular disease[8,9] and cancer.[17,18] In addition, our population is homogenous by profession, so leisure time activity will capture most between-person variation in physical activity. Our physical activity assessment is a better measure of vigorous activity than nonvigorous activity[10]; nevertheless, we still observed a significant trend with increasing non-vigorous activity for all-cause mortality.

No prior studies have evaluated the relationship between physical activity after diagnosis and survival in men with PCa, but incidence studies suggest that vigorous activity could reduce risk for fatal disease. We previously reported a significant association between high levels of vigorous activity and reduced risk of advanced PCa in men age 65 years or older,[7] and several recent cohort studies support an association of recreational or occupational activity with reduced risk of advanced and fatal disease.[19-21] Patel et al[19] reported a significant 31% reduction in risk of aggressive PCa among men

engaged in more than 35 MET-h/wk of activity compared with men reporting no activity, whereas Johnson et al[21] reported no association for leisure time activity but a significant inverse association with advanced disease for manual occupational activity in the European Prospective Investigation Into Cancer and Nutrition (EPIC) cohort. Levels of leisure activity were much higher in EPIC compared with our study, with half of the men having ≥ 43 MET-hours of leisure activity per week, reducing the exposure contrast compared with our population.

Physical activity may affect cancer progression and mortality through the insulin/insulin-like growth factor (IGF) axis. The binding of IGFs and insulin to their receptors can influence cell proliferation, differentiation, apoptosis, adhesion, migration, and angiogenesis.[22] Physical activity increases insulin sensitivity and may affect IGF-1 bioactivity. Ma et al[23] reported that men in the highest quartile of prediagnostic plasma C-peptide (a marker of insulin production) had a 2.4-fold higher risk of dying from PCa compared with men in the lowest quartile. Laboratory studies have reported that exercise resulted in lower serum insulin and IGF-1 and higher IGF binding protein-1 compared with controls, and the serum from men engaged in regular aerobic exercise reduced cell growth, induced apoptosis, and increased p53 protein content in serum-stimulated LNCaP cells in vitro.[24,25]

Physical activity lowers inflammatory factors, increases anti-inflammatory cytokines, and inhibits the production of proinflammatory cytokines.[26-29] In a 12-month randomized controlled trial of a physical activity intervention among elderly persons, Nicklas et al[30] reported significantly lower circulating levels of inflammatory cytokine interleukin-6. Strong evidence supports a role of chronic inflammation in prostate carcinogenesis,[31] and the degree of inflammation in prostate tumors[32] and specific inflammatory markers[33] are associated with progression and can improve prediction for biochemical progression.[34] Stark et al[35] reported that in men with a BMI less than 25 kg/m^2, those with the highest level of IL-6 had an HR of 1.73 (95% CI, 0.86 to 3.51; $P_{trend} = .02$) for increased risk of lethal PCa compared with men with the lowest IL-6 level. Physical activity also increases adiponectin levels, which has anti-inflammatory and mitogenic actions,[36] and men with the highest compared with lowest quintile of adiponectin concentration had a 61% lower risk of PCa mortality (HR, 0.39; 95% CI, 0.17 to 0.85; $P_{trend} < .02$).[37]

Physical activity also affects the innate immune system.[38] Exercise in patients with breast cancer was associated with improved natural killer cell cytolytic activity,[39] monocyte function,[40] and proportion of circulating granulocytes.[40] Physical activity may also affect tumor angiogenesis.[41]

Although previous studies have focused on physical activity and improvement in fatigue, physical functioning, and quality of life,[42] we focused on physical activity after PCa diagnosis in relation to overall and PCa-specific mortality. The findings are based on prospective data, with activity data collected every 2 years, before and after diagnosis. Lastly, we had an adequate number of PCa deaths to evaluate this outcome after excluding participants who died within 4 years of diagnosis.

In conclusion, our results suggest that among men with PCa, moderate physical activity may improve overall survival, whereas a greater amount of activity is necessary to improve PCa-specific survival. A modest amount of vigorous activity such as biking, tennis, jogging, or swimming at levels of ≥ 3 h/wk may substantially improve PCa-specific survival. Mechanistic studies and randomized trials of physical activity interventions are needed in PCa

survivors to determine whether physical activity reduces PCa progression and what regimens are optimal.

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