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Physical Activity after Diagnosis and Risk of Prostate Cancer Progression: Data from the Cancer of the Prostate Strategic Urologic Research Endeavor

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Abstract

Vigorous activity after diagnosis was recently reported to be inversely associated with prostate cancer–specific mortality. However, men with metastatic disease may decrease their activity due to their disease; thus, a causal interpretation is uncertain. We therefore prospectively examined vigorous activity and brisk walking after diagnosis in relation to risk of prostate cancer progression, an outcome less susceptible to reverse causation, among 1,455 men diagnosed with clinically localized prostate cancer. Cox proportional hazards regression was used to examine vigorous activity, nonvigorous activity, walking duration, and walking pace after diagnosis and risk of prostate cancer progression. We observed 117 events (45 biochemical recurrences, 66 secondary treatments, 3 bone metastases, 3 prostate cancer deaths) during 2,750 person-years. Walking accounted for nearly half of all activity. Men who walked briskly for 3 h/wk or more had a 57% lower rate of progression than men who walked at an easy pace for less than 3 h/wk (HR = 0.43; 95% CI: 0.21–0.91; $P = 0.03$). Walking pace was associated with decreased risk of progression independent of duration (HR brisk vs. easy pace = 0.52; 95% CI: 0.29–0.91; $P_{trend} = 0.01$). Few men engaged in vigorous activity, but there was a suggestive inverse association (HR $\geq$3 h/wk vs. none = 0.63; 95% CI: 0.32–1.23; $P_{trend} = 0.17$). Walking duration and total nonvigorous activity were not associated with risk of progression independent of pace or vigorous activity, respectively. Brisk walking after diagnosis may inhibit or delay prostate cancer progression among men diagnosed with clinically localized prostate cancer. *Cancer Res; 71(11); 3889–95. ©2011 AACR.*

Introduction

More than 2.2 million men currently live with prostate cancer in the United States and approximately 217,000 new cases were diagnosed in 2010. The vast majority of new cases (92%) are diagnosed in the localized or regional stage and have a 5-year disease-specific survival approaching 100%; yet prostate cancer remains the second leading cause of cancer death among men in the United States (1). Little is known regarding the associations between modifiable lifestyle factors after diagnosis and risk of prostate cancer progression from localized to lethal disease.

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Our group was the first to report that postdiagnostic vigorous activity was associated with a statistically significant 61% reduction in risk of prostate cancer–specific mortality among men diagnosed with nonmetastatic prostate cancer (2). There is some concern that this association reflected a reduction in physical activity among men with metastatic disease. Thus, in an independent study population, we examined whether postdiagnostic vigorous activity and brisk walking were associated with reduced risk of prostate cancer progression, defined primarily by biochemical recurrence [e.g., prostate-specific antigen (PSA) increase]. Biochemical recurrence is an indicator of disease progression that manifests prior to the development of physical symptoms, thus avoiding potential bias due to reverse causation.

Vigorous activity is associated with lower levels of insulin, bioavailable insulin-like growth factor I (IGFI), and inflammatory cytokines, leading to a milieu that may inhibit proliferation and promote apoptosis of prostate cancer cells (3–7). Although brisk walking is classified as a moderate-intensity activity (8), it has also been associated with reductions in these factors (9, 10), as well as decreased risk of diseases affected by this milieu [e.g., total mortality (11), type II diabetes (12), coronary heart disease (13)]. Moreover, in our previous report, we observed a suggestive inverse association between brisk walking and risk of prostate cancer–specific mortality (2).

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On the basis of our previous findings and the potential biologic mechanisms, we hypothesized that both vigorous activity and brisk walking after diagnosis would inhibit prostate cancer progression among men diagnosed with localized disease. Thus, in this study, we prospectively examined vigorous activity, nonvigorous activity, walking duration, and walking pace after diagnosis and risk of prostate cancer progression among men diagnosed with clinically localized prostate cancer and participating in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE).

Materials and Methods

Study population

This analysis was based on a substudy of CaPSURE (14, 15). Starting in 1995, 40 urology clinics throughout the United States enrolled men with biopsy-verified prostate cancer. Participants completed a questionnaire on sociodemographics, medical symptoms, and use of health services at enrollment and every 6 months thereafter. Urologists reported clinical data at enrollment and subsequent clinic visits. During 2004–2005, 2,134 CaPSURE participants completed physical activity and dietary questionnaires; these men constitute the base population for this analysis. The Institutional Review Board of the University of California, San Francisco approved this study.

Physical activity assessment

Participants were asked how often (never to ≥11 h/wk) on average over the past year they participated in walking or hiking; jogging (>10 min/mile); running (≤10 min/mile); calisthenics, aerobics, rowing, Nordic track; bicycling; tennis, squash, racquetball; lap swimming; weightlifting; and other aerobic exercise (e.g., heavy outdoor work), as well as their usual walking pace and flights of stairs climbed daily. Our questionnaire was based on a well-validated questionnaire; the correlation between the average of four 1-week seasonal activity diaries and the original questionnaire was 0.58 for vigorous activity and 0.28 for nonvigorous activity (16).

A metabolic equivalent task (MET) value was assigned to each activity on the basis of the energy required by that activity relative to the resting metabolic rate (17). Activities were classified as vigorous if they required 6 or more METs (8). Physical activity was categorized on the basis of the distribution in the study population (Table 1): vigorous (0, 0.1–1.24, 1.25–2.9, ≥3 h/wk), nonvigorous (<1, 1–2.9, 3–4.9, 5–9.9, ≥10 h/wk), walking duration (<0.5, 0.5–1.4, 1.5–3.9, 4.0–6.9, ≥7 h/wk), and walking pace [<2, 2–2.9, ≥3 miles/h (mph)]. We also classified men according to their usual walking pace (≥3 vs. <3 mph) and duration (≥3 vs. <3 h/wk); 3 h/wk was the average walking duration in this population.

Clinical follow-up and outcome assessment

Urologists collected clinical data throughout follow-up and participants reported treatments, medications, and hospitalizations every 6 months. If a hospitalization was reported, we obtained all relevant medical records. We abstracted PSA levels, clinical stage, biopsy Gleason sum, treatment, and occurrence of metastases from urologists' reports and medical records. Mortality data were obtained via the National Death Index and Bureau of Vital Statistics.

The primary outcome was prostate cancer progression, defined as prostate cancer death, bone metastases from prostate cancer, biochemical recurrence, or secondary treatment. A death was attributed to prostate cancer if prostate cancer was listed as the primary, secondary, or tertiary cause of death on the death certificate and no other malignancy was listed as a higher-order cause. Bone metastases included urologist report of (i) prostate cancer progression to bone, (ii) positive bone scan, (iii) radiation for metastasis to a bone, or (iv) TNM stage M1b. Biochemical recurrence was defined as 2 consecutive PSA tests ≥0.2 ng/mL at least 8 weeks after radical prostatectomy or an increase of 2.0 ng/mL or more above postradiation nadir (18). Secondary treatments included any treatment initiated at least 6 months after primary treatment ended. Among men who had primary treatment, initiation of secondary treatment is indicative of biochemical or clinical evidence of disease progression (19, 20). The date of prostate cancer progression was the first of the following: prostate cancer death, diagnosis of bone metastases from prostate cancer, second PSA test ≥0.2 ng/mL after radical prostatectomy, first PSA test ≥2.0 ng/mL over postradiation nadir, or initiation of secondary treatment.

Inclusion criteria

The base population for this study included 2,134 men who completed the activity questionnaire in 2004–2005. We excluded men with nonlocalized disease at diagnosis (i.e., clinical T-stage T3+), men whose disease progressed prior to the questionnaire, and men who had not completed primary treatment prior to the questionnaire ($n = 548$). Men who reported an energy intake outside 800 to 4,200 kcal/d ($n = 67$) were excluded because their dietary information was considered unreliable and use of their dietary data could lead to incomplete adjustment for potential dietary confounders. We also excluded men missing physical activity data ($n = 11$) or clinical information at diagnosis ($n = 53$), leaving 1,455 men for analysis.

Statistical analysis

We used Cox proportional hazards regression to examine postdiagnostic vigorous activity, nonvigorous activity, walking duration, and walking pace in relation to risk of prostate cancer progression. Person-time was calculated from date of the questionnaire to date of progression, death from another cause, last contact, or August 21, 2009, whichever occurred first. Categories of physical activity were modeled by using indicator variables, and we conducted tests of trend by modeling the median of each exposure category continuously.

Our basic model (model 1) included age at diagnosis (continuous) and days from diagnosis to the questionnaire (continuous). Model 2 was additionally adjusted for biopsy Gleason sum (<7, 7, >7), PSA at diagnosis (tertiles), and primary treatment (radical prostatectomy, radiation therapy, other/watchful waiting, hormone therapy). We modeled PSA and treatment by using indicator variables and biopsy Gleason sum by using an ordinal variable. We adjusted vigorous and

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Table 1. Distribution of 10 leisure-time physical activities among 1,455 men diagnosed with clinically localized prostate cancer

	MET value	MET-hours/wk (%)[a,b]	Duration (%)[b]
Vigorous activities (≥6 METs)			
Running (≤10 min/mile)	12.0	2.8	1.2
Jogging (>10 min/mile)	7.0	2.2	1.6
Lap swimming	7.0	1.7	1.2
Bicycling (including stationary machine)	7.0	8.6	6.0
Tennis, squash, or racquetball	7.0	3.7	2.5
Calisthenics, aerobics, rowing, Nordic track	6.0	7.2	5.9
Nonvigorous activities (<6 METs)			
Other aerobic exercises (e.g., heavy outdoor work, raking, mowing)	5.5	37.5	33.3
Weightlifting or Nautilus	4.5	4.5	4.9
Walking or hiking (including walking for transportation or at golf)[c]	3.0	30.5	43.4
Flights of stairs[d]	0.11	1.2	

[a]MET-hours/wk calculated by multiplying the MET value assigned to an activity by the time spent engaged in that activity.
[b]Percentages may not add up to 100% due to rounding.
[c]METs assigned to walking depended on walking pace. Normal pace (2–2.9 mph) was assigned 3 METs.
[d]Duration of flights of stairs climbed per week was assumed negligible.

nonvigorous activity for each other, adjusted walking pace, and duration for each other, and examined nonvigorous activity, walking duration, and walking pace in relation to risk of progression among men who did not engage in vigorous activity. Adjustment for other risk factors for prostate cancer progression, including race, prostate cancer family history, smoking, diabetes, education, income, and intakes of tomato products, poultry with skin, dairy, cruciferous vegetables, and eggs, did not change our results (21–26).

Body mass index (BMI) may mediate the association between physical activity and prostate cancer progression. Therefore, we examined a third model adjusted for BMI (model 3). Additionally, we used likelihood ratio tests to examine whether biopsy Gleason sum (<7 vs. ≥7), age at diagnosis (continuous), BMI (<25 vs. ≥25 kg/m^2), or time from diagnosis to the questionnaire (continuous) modified the relation between physical activity and prostate cancer progression.

To examine whether men who had decreased their physical activity as a result of progression of their disease were influencing our results, we carried out a sensitivity analysis with a 1-year lag. We were also concerned that some men may undergo secondary treatment due to anxiety rather than a biologic change in their disease, hence we carried out analyses excluding watchful waiters ($n = 44$) or men who underwent secondary treatment without evidence of a preceding PSA increase ($n = 33$). Men treated close in time to the activity questionnaire may not have returned to their normal activity level, hence we carried out an analysis excluding men treated within 6 months prior to the questionnaire ($n = 204$). We also examined the results restricted to men diagnosed in 2000 or after ($n = 1,166$) and men who had radical prostatectomy as their primary treatment ($n = 922$).

All analyses were carried out by SAS version 9.1 (SAS Institute Inc.). *P* values were 2-sided and significant at 0.05 or less.

Results

We observed 117 events (45 biochemical progressions, 66 secondary treatments, 3 bone metastases, 3 prostate cancer deaths) among 1,455 men during 2,750 person-years. The median time from diagnosis to the questionnaire was 27 months [interquartile range (IQR): 15–46 months] and median follow-up after the questionnaire was 22 months (IQR: 9–31 months). Approximately 24% of participants ($n = 347$) withdrew from the study, were lost to follow-up, or declined clinical follow-up prior to the end of the study in August 21, 2009. These men did not differ materially from the remaining participants in terms of age at diagnosis, BMI, biopsy Gleason sum, primary treatment, clinical T-stage at diagnosis, vigorous activity, or usual walking pace.

Men who engaged in more vigorous activity or who walked at a brisk pace were younger, leaner, and less likely to be current smokers than the least active men (Table 2). In addition, more vigorously active men were more likely to have moderately differentiated disease (biopsy Gleason sum = 7) and less likely to have "other" treatment than less vigorously active men. Men who reported walking at a brisk pace were less likely to have a PSA ≥10 ng/mL at diagnosis, more likely to have radical prostatectomy as their primary treatment, and less likely to have radiation therapy as their primary treatment compared with men who reported walking at an easy pace.

Walking and other aerobic exercises (e.g., heavy outdoor work) each accounted for approximately one-third of energy expended by reported leisure-time physical activity, and together accounted for more than 75% of all time engaged in reported leisure-time activity in this population (Table 1). Vigorous activities accounted for approximately 26% of energy expended by reported leisure-time activity and 18% of total time spent in reported leisure-time activity.

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Table 2. Age-standardized characteristics of 1,455 men with clinically localized prostate cancer, by vigorous activity, usual walking pace, and overall

	Vigorous activity (h/wk)			Walking pace (mph)			Total; mean (SD) or *n* (%)
	0	≥3	P_{trend}[a]	< 2	≥3	P_{trend}[a]	
No. of participants	722	189		211	502		1,264
Age at diagnosis, mean (SD), y	65 (8)	64 (8)	0.007	69 (7)	62 (8)	<0.001	65 (8)
BMI, kg/m^2, %[b]							
<25	24	39	<0.001	22	35	<0.001	379 (27)
25–29.9	52	50	0.88	45	53	0.48	750 (53)
≥30	24	11	<0.001	32	13	<0.001	283 (20)
Current smokers, %	7	4	0.05	9	4	0.02	90 (6)
PSA at diagnosis ≥10 ng/mL, %	16	12	0.09	23	13	0.03	214 (15)
Clinical stage, %[b]							
T1	56	49	0.36	52	57	0.31	801 (55)
T2	44	51	0.36	48	43	0.31	654 (45)
Biopsy Gleason sum, %[b]							
2–6	74	68	0.02	73	69	0.35	1,034 (71)
7	20	28	0.004	20	25	0.28	347 (24)
8–10	6	4	0.32	7	6	0.90	74 (5)
Primary treatment, %[b]							
Radical prostatectomy	62	64	0.42	54	67	0.01	922 (63)
Radiation therapy	24	24	0.97	29	20	0.04	351 (24)
Hormonal therapy	5	6	0.34	8	5	0.23	110 (8)
Other/watchful waiting	9	5	0.04	9	8	0.69	72 (5)

[a]Calculated by using the median of each category as a continuous term.
[b]Percentages may not add to 100% due to rounding.

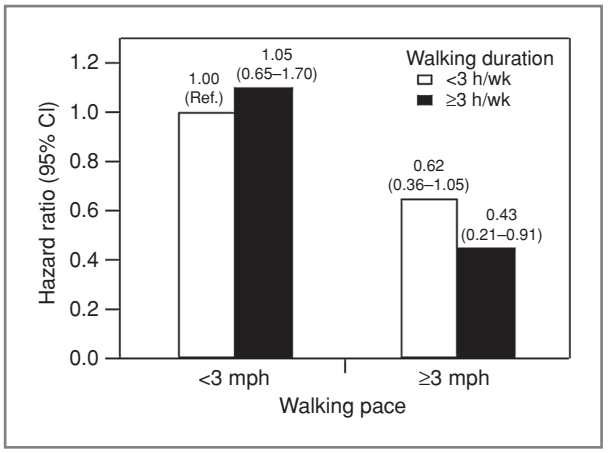

Figure 1. Postdiagnostic walking duration, walking pace, and risk of prostate cancer progression among 1,455 men diagnosed with clinically localized prostate cancer. Adjusted for age at diagnosis (continuous), days from diagnosis to questionnaire (continuous), primary treatment (radical prostatectomy, radiation, other/watchful waiting, hormone), biopsy Gleason sum (<7, 7, >7), and PSA at diagnosis (tertiles). Events/person-years: <3 mph, <3 h/wk = 66/1,289; <3 mph, ≥3 h/wk = 23/471; ≥3 mph, <3 h/wk = 18/569; ≥3 mph, ≥3 h/wk = 8/396. Ten participants (0.7%) who reported being unable to walk and reported no time spent walking were excluded.

Men who walked 3 or more hours per week at a brisk pace had a statistically significant 57% reduced rate of prostate cancer progression compared with men who walked less than 3 hours per week at a less than brisk pace (HR = 0.43; 95% CI: 0.21–0.91; $P = 0.03$; Fig. 1). These findings persisted after adjustment for BMI (HR = 0.48; 95% CI: 0.23–1.01; $P = 0.05$) and when restricting to the 722 men who did not engage in vigorous activity (HR = 0.37; 95% CI: 0.11–1.22; $P = 0.10$), although the CIs widened. Moreover, walking pace was associated with a statistically significant reduced risk of prostate cancer progression independent of walking duration (HR = 0.52; 95% CI: 0.29–0.91; $P_{trend} = 0.01$; Table 3). Adjustment for BMI did not material change the results (HR = 0.56; 95% CI: 0.32–1.00; $P_{trend} = 0.02$). Walking duration and total nonvigorous physical activity were not associated with risk of prostate cancer progression independent of walking pace and vigorous activity, respectively.

We observed a nonstatistically significant inverse association between vigorous activity and risk of prostate cancer progression. Men who engaged in 3 or more hours per week of vigorous activity had a 37% decreased risk of progression compared with men who engaged in no vigorous activity (HR = 0.63; 95% CI: 0.32–1.23; $P_{trend} = 0.17$). Few men engaged in vigorous activity in this population, which may explain the lack of statistical significance.

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Table 3. Postdiagnostic nonvigorous activity, vigorous activity, walking duration, and walking pace in relation to risk of prostate cancer progression among 1,455 men diagnosed with clinically localized prostate cancer

Nonvigorous (h/wk)	**0–0.9**	**1.0–2.9**	**3.0–4.9**	**5.0–9.9**	**≥10.0**	**P_{trend}**[a]
Events/person-year	22/456	34/774	13/269	23/697	25/554	
Model 1 HR (95% CI)[b]	1.0	0.91 (0.53–1.55)	0.97 (0.49–1.93)	0.73 (0.40–1.31)	0.96 (0.54–1.70)	0.89
Model 2 HR (95% CI)[c]	1.0	0.78 (0.45–1.33)	0.84 (0.42–1.69)	0.61 (0.34–1.11)	0.87 (0.49–1.56)	0.98
Model 3 HR (95% CI)[d]	1.0	0.80 (0.45–1.40)	0.90 (0.44–1.83)	0.71 (0.38–1.32)	0.96 (0.52–1.76)	0.76
Vigorous (h/wk)	**0.0**	**0.1–1.24**	**1.25–2.9**	**≥3.0**		**P_{trend}**[a]
Events/person-year	66/1,389	25/643	16/384	10/334		
Model 1 HR (95% CI)[b]	1.0	0.81 (0.51–1.28)	0.93 (0.54–1.60)	0.62 (0.32–1.21)		0.19
Model 2 HR (95% CI)[c]	1.0	0.88 (0.55–1.39)	0.84 (0.48–1.45)	0.63 (0.32–1.23)		0.17
Model 3 HR (95% CI)[d]	1.0	0.88 (0.55–1.41)	0.71 (0.40–1.28)	0.69 (0.35–1.36)		0.19
Walking duration (h/wk)	**0–0.4**	**0.5–1.4**	**1.5–3.9**	**4.0–6.9**	**≥7.0**	**P_{trend}**[a]
Events/person-year	25/515	38/851	23/507	16/475	15/402	
Model 1 HR (95% CI)[b]	1.0	0.95 (0.57–1.58)	0.98 (0.55–1.73)	0.79 (0.42–1.48)	0.89 (0.47–1.68)	0.95
Model 2 HR (95% CI)[c,e]	1.0	0.91 (0.53–1.54)	1.12 (0.62–2.05)	0.91 (0.46–1.77)	0.98 (0.50–1.92)	0.99
Model 3 HR (95% CI)[d,e]	1.0	0.81 (0.47–1.40)	0.94 (0.51–1.75)	0.74 (0.38–1.45)	0.80 (0.41–1.58)	0.86
Walking pace (mph)[e]	**Easy (<2.0)**	**Normal (2.0–2.9)**	**Brisk (≥3.0)**			**P_{trend}**[a]
Events/person-year	27/417	62/1,348	26/971			
Model 1 HR (95% CI)[b]	1.0	0.80 (0.50–1.26)	0.50 (0.28–0.86)			0.01
Model 2 HR (95% CI)[c]	1.0	0.94 (0.58–1.50)	0.52 (0.29–0.91)			0.01
Model 3 HR (95% CI)[d]	1.0	0.96 (0.60–1.56)	0.56 (0.32–1.00)			0.02

[a]Calculated by using the median of each category as a continuous term.

[b]Model 1 adjusted for age at diagnosis (continuous) and time from diagnosis to questionnaire (continuous).

[c]Model 2 adjusted for covariates in model 1 plus primary treatment (radical prostatectomy, radiation, other/watchful waiting, hormone), biopsy Gleason sum (<7, 7, >7), and PSA at diagnosis (tertiles). Vigorous and nonvigorous activities were adjusted for each other and walking duration and walking pace were adjusted for each other.

[d]Model 3 adjusted for covariates in model 2 plus BMI (<25, 25–29.9, ≥30 kg/m^2); 43 participants (3%) with missing BMI were not included.

[e]Ten participants (0.7%) who reported being unable to walk and reported no time spent walking were excluded from models with walking pace.

We found no evidence of effect modification by time from diagnosis to questionnaire, age at diagnosis, or BMI. However, there was a statistically significant interaction between biopsy Gleason sum and walking duration ($P_{interaction}$ = 0.006) and nonvigorous activity ($P_{interaction}$ = 0.03). For example, among men with biopsy Gleason sum <7 (n = 1,034), walking 7 or more hours per week was associated with a 61% reduction in risk of prostate cancer progression compared with walking less than half an hour per week (HR = 0.39; 95% CI: 0.11–1.41). There was no reduction in risk among men with biopsy Gleason sum ≥7 (n = 421; HR = 1.33; 95% CI: 0.54–3.29; data not shown in tables).

Our results did not materially change after excluding watchful waiters, events defined by secondary treatment without a preceding PSA increase, or men who completed their primary treatment within 6 months prior to the questionnaire. Our results were also robust in analyses that included a 1-year lag, or when restricting to men diagnosed since 2000 or men who had radical prostatectomy as their primary treatment.

Discussion

In this prospective study of physical activity among prostate cancer patients, we observed a strong inverse relation between walking pace after diagnosis and risk of prostate cancer progression. Men who walked briskly for 3 or more hours per week had the lowest risk of progression. There was also a suggestion of an inverse association for vigorous activity, but few men engaged in vigorous activity in this study population and this result was not statistically significant.

To our knowledge, only 1 other study has examined postdiagnostic physical activity in relation to clinical outcomes in prostate cancer survivors (2). In that study, men who engaged in 3 or more hours per week of vigorous activity experienced a 61% reduced rate of prostate cancer–specific mortality compared with men who engaged in less than 1 h/wk (HR = 0.39; 95% CI: 0.18–0.84; P_{trend} = 0.03). Additionally, men who walked briskly after diagnosis experienced a 48% reduction in all-cause mortality (HR = 0.52; 95% CI: 0.39–0.70; P_{trend} < 0.001) and a nonstatistically significant reduction in prostate cancer–specific mortality (HR = 0.66; 95% CI: 0.34–1.29)

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compared with men who walked at an easy pace. Reverse causation is a concern when examining the relation between physical activity and prostate cancer–specific mortality, in that men with metastatic disease may reduce their physical activity as a result of their disease, creating a spurious association between decreased activity and poor prognosis. Thus, a particular strength of this study is our outcome of prostate cancer progression, as this endpoint is far less susceptible to reverse causation given that the early indicators of progression occur prior to any symptoms.

Brisk walking may affect prostate cancer progression by reducing insulin resistance, decreasing bioavailable IGFI, and increasing adiponectin levels. Circulating levels of insulin, bioavailable IGFI, and adiponectin affect proliferation and apoptosis of prostate cancer cells *in vitro* (5, 6, 27) and *in vivo* (5), and have been associated with risk of advanced or fatal prostate cancer (28–30). In the Physician's Health Study, men in the highest quartile of prediagnostic C-peptide levels, a marker of insulin secretion, had a 2.38-fold increased risk of prostate cancer–specific mortality compared with men in the lowest quartile (HR = 2.38; 95% CI: 1.31–4.30; $P_{trend} = 0.008$; ref. 28). Among men with prostate cancer, men in the highest quintile of prediagnostic adiponectin had a 61% reduced risk of dying from prostate cancer compared with men in the lowest quintile (HR = 0.39; 95% CI: 0.17–0.85; $P_{trend} = 0.02$; ref. 30).

Further support for this mechanism comes from studies showing reduced cell growth and increased apoptosis of prostate cancer cells cultured in serum from healthy men who engaged in regular aerobic exercise. Serum from exercising men had lower insulin and IGFI and higher IGF binding protein-1 values compared with men who did not exercise; and addition of IGFI to the exercisers' serum removed its antiproliferative, proapoptotic effect (7, 31, 32).

Brisk walking may also affect prostate cancer progression by reducing inflammation. In a 12-month randomized controlled trial among elderly persons, walking "somewhat hard" was associated with lower circulating interleukin-6 (IL-6) (33). IL-6 promotes cell proliferation and inhibits apoptosis of prostate cancer cells *in vitro* (3), and high levels of IL-6 predicted a 73% increased risk of dying from prostate cancer among normal weight men (34).

We acknowledge that our study has several limitations. First, we had limited power due to a small number of events, including only 3 prostate cancer deaths, and low participation in vigorous activity. However, our progression-based outcome is less susceptible to reverse causation compared with prostate cancer–specific mortality, as physical symptoms of prostate cancer progression that may cause a decrease in physical activity are unlikely to precede biochemical recurrence. Furthermore, many elderly prostate cancer patients are not capable of doing vigorous activities, and thus our findings for brisk walking are particularly relevant for designing future intervention studies.

Second, we cannot eliminate nondifferential measurement error in our prospective physical activity assessment. Vigorous activities occur infrequently or sporadically in older persons and may be less accurately recalled than usual walking pace, which could partially explain the lack of a statistically significant association for vigorous activity. Third, we had no data on prediagnostic physical activity; however, data from the Health Professionals' Follow-up Study support an association between postdiagnostic activity and prostate cancer–specific mortality independent of prediagnostic activity (2). Fourth, 24% of the men who completed the physical activity questionnaire were lost to follow-up. These men did not differ from the remaining men in terms of their clinical prognostic factors, age at diagnosis, BMI, vigorous activity, or usual walking pace; therefore, although loss of these men reduced our statistical power, it is unlikely to have biased our results. Finally, the participants in our study were volunteers from a large population-based prostate cancer registry. The men who volunteered were younger at diagnosis, more likely to be white, and had better prognostic risk disease compared with the general CaPSURE population. Thus, our results may not be generalizable to non-Caucasian populations or populations with a different distribution of clinical prognostic factors.

In conclusion, we observed a statistically significant inverse association between brisk walking after diagnosis and risk of prostate cancer progression in men diagnosed with clinically localized prostate cancer. These results were based on a relatively small number of events among brisk walkers and thus further study is needed. However, our results are consistent with the only other study of physical activity after diagnosis and clinical outcomes in prostate cancer survivors, and suggest significant clinical benefits of brisk walking for men with prostate cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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