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A Prospective Study of Physical Activity and Prostate Cancer in Male Health Professionals[1]

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ABSTRACT

Because the role of exercise in prostate cancer is unclear, we examined the relationship between leisure time physical activity and risk of prostate cancer in the Health Professionals Follow-up Study, a prospective cohort study of male health professionals in the United States. In 1986, 47,542 men 40–75 years of age and free of cancer responded to a mailed questionnaire that included an assessment of physical activity. The reported average time per week spent on each of a variety of nonoccupational activities was multiplied by its typical energy expenditure requirements expressed in metabolic equivalents (METs) and summed to yield a total weekly MET-hour score. We also examined MET-hours from all vigorous activities, defined as those requiring energy expenditures of six or more METs, and nonvigorous activities. From 1986 until January 31, 1994, we identified 1362 incident cases of total prostate cancer (excluding stage A1), 419 advanced (extraprostatic) cases, and 200 metastatic cases. No relationship with total or advanced prostate cancer was evident for total, vigorous, and nonvigorous physical activity. For metastatic prostate cancer, we also found no linear trends for these activities, but did observe a significantly lower risk in the highest category of vigorous activity (multivariate relative risk = 0.46; 95% confidence interval = 0.24–0.89 for >25 *versus* 0 MET-hours), controlling for age, vasectomy, history of diabetes, height, smoking, and dietary factors. This highest category included 15% of the population and reflects at least 3 h/week of participation in vigorous activities. Differences in disease surveillance according to activity level could not account for our findings. The results from this cohort indicate that physical activity is unlikely to influence the incidence of total prostate cancer appreciably; however, the suggestion of a lower risk of metastatic prostate cancer in men engaging in high levels of vigorous activities warrants further study.

INTRODUCTION

A number of studies have examined either occupational or recreational physical activity and the risk of prostate cancer (1–16), and most have suggested a moderately lower risk of prostate cancer among more physically active men (1–13). However, the relationships have tended to be moderate, not always statistically significant, and sometimes only evident among older subgroups (5, 8, 10). In an earlier prospective study of 419 cases, men who maintained a substantially high level of physical expenditure (≥4000 kcal/week) had about one-half the risk of prostate cancer; however, lower levels of activity were not associated with any reduced risk (8). This apparent high threshold, which included the top 4% of that population, is consistent with studies indicating that substantially high levels of vigorous activity lower circulating testosterone levels acutely and chronically (17) and that circulating testosterone level correlates with prostate cancer risk (18).

The evidence supporting a benefit of physical activity on lowering prostate cancer risk, although promising, has been hampered by difficulties in assessing long-term physical activity levels and in excluding confounding factors such as diet. Moreover, the influence of a specific type of physical activity, as well as the intensity and duration of exercise, on cancer risk is poorly characterized. Because of these limitations, we examined the relationship between physical activity and risk of prostate cancer in the Health Professionals Follow-up Study, a cohort of men who completed physical activity questionnaires at multiple times and who provided detailed data on diet and other lifestyle and health-related factors.

PATIENTS AND METHODS

The Study Population and Follow-up of the Cohort. The Health Professionals Follow-up Study is an ongoing prospective cohort study of the causes of cancer and heart disease in men (19). The cohort consists of 51,529 male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians in the United States, who were 40 to 75 years of age and responded to a mailed questionnaire in 1986. These men provided information on age, physical activity, tobacco use, marital status, height and weight, ancestry, medications, disease history, and diet. To form the analytic cohort for this study, we excluded men who did not complete the physical activity assessment or who reported cancer at baseline (other than non-melanoma skin cancer). Because of the importance of controlling for dietary factors, we included only men who adequately completed a food frequency questionnaire (97% of the total). After these baseline exclusions, 47,542 participants remained.

Follow-up questionnaires were sent in 1988, 1990, 1992, and 1994 to ascertain new cases of a variety of diseases, including prostate cancer, and to update exposure information, including physical activity. Most deaths in the cohort were reported by family members or by the postal system in response to the follow-up questionnaires and additionally through the National Death Index (20). We estimate having ascertained >98% of the deaths in this cohort, and the overall follow-up response was 94%.

Identification and Classification of Cases of Prostate Cancer. For every reported prostate cancer, we asked the participant, or the next-of-kin for deceased men, for permission to obtain relevant hospital records and pathology reports (21). A study physician staged prostate cancers according to information received from medical reports [stage A: occult or incidental finding in prostate tissue surgically removed for benign prostatic hyperplasia (A1: focal; A2: diffuse); stage B: confined to prostate gland; stage C: extraprostatic extension localized to periprostatic area; stage D1: metastatic disease involving only regional lymph nodes; and stage D2: those that have metastasized to other organs]. These classification criteria included information from any work-up during the initial diagnosis, including prostatectomy and bone scans. Because stage A1 lesions are typically indolent and are especially prone to detection bias, we excluded these (3% of the total) from our primary analysis. From 1986 to January 31, 1994, we identified 1362 total incident cases of non-stage A1 prostate cancer, 419 advanced (stages C and D) cases, and 200 metastatic cases.

Assessment of Physical Activity. In 1986 we asked participants to report the average time per week (none, 1–4 min, 5–19 min, 20–39 min, 40–80 min, 1.5 h, 2–3 h, 4–6 h, 7–10 h, or 11+ h) that they engaged in the following activities during the past year: walking or hiking outdoors (including walking at golf), jogging (slower than 10 min/mile), running (10 min/mile or faster), bicycling (including stationary machine), lap swimming, tennis, squash or

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Table 1 *Age-standardized baseline characteristics according to category of physical activity in 47,542 men in the Health Professionals Follow-up Study*

	Physical activity (range of MET-hours/week[a])				
	0–2.7	2.8–7.7	7.8–16.5	16.6–32.5	≥32.6
Participants (*n*)	9,585	9,317	9,508	9,554	9,578
Mean age in 1986 (yr)	54.8	55.3	54.5	53.9	53.4
Mean BMI (kg/m^2)	25.4	25.3	25.1	24.7	24.4
Mean height (inches)	69.9	70.1	70.1	70.2	70.2
Current smoker (%)	14.5	10.8	9.3	7.1	6.5
Past smoker (%)	40.2	40.5	42.7	43.9	41.8
History of vasectomy (%)	19.4	20.2	21.8	22.4	22.5
History of diabetes (%)	4.2	3.3	3.1	2.8	2.3
Routine rectal exam 1986–1988 (%)	56.8	59.8	62.3	63.7	62.7
Ever tested for serum PSA level (%)	58.6	58.9	61.6	63.3	62.8
Multivitamin use (%)	37.0	40.1	42.9	44.1	44.8
Mean daily intakes[b]					
Total energy (kcal/day)	1,935	1,983	1,979	1,987	2,049
Total fat (g/day)	72.1	72.5	71.1	69.6	69.9
Calcium (mg/day)	829	873	881	909	935
Lycopene (μg/day)	9,198	9,730	9,951	10,431	11,132
Monosaccharide fructose (g/day)	24.3	25.5	25.9	26.8	28.9
Fructose from sucrose (g/day)	22.3	22.9	22.4	22.5	23.6

[a] MET-hours/week, sum of the average time/week spent in each activity × MET value of each activity. MET-value = caloric need/kg body weight/h activity/caloric need/kg body weight/h at rest.
[b] Nutrients are adjusted for total energy intake.

racquet ball, calisthenics, or rowing. We also asked the number of flights climbed daily and walking pace [easy (<2 mph), average (2–2.9 mph), brisk (3–3.9 mph), or striding (4+ mph)]. To generate the total physical activity score, we summed activity-specific MET[3]-hours/week in 1986. A MET-hour is the metabolic equivalent of sitting at rest for 1 h. MET values were obtained from a compendium of physical activities (22). The activity specific values were as follows: stairs, flights/day × 0.11 (multiplier includes conversion to weekly); jogging, h/week × 7.0; running, h/week × 10.0; biking, h/week × 7.0; swimming, h/week × 7.0; tennis, h/week × 7.0; racquetball/squash, h/week × 12.0; and rowing/calisthenics, h/week × 6.0. The MET value assigned to walking was dependent on pace (h/week walking × pacing, where pacing was rated as follows: easy = 2.5, average = 3.0, brisk = 4.0, and striding = 4.5). We also generated quintiles of total MET-hours/week for vigorous or high-intensity activities (running, jogging, biking, swimming, tennis, racquetball/squash, and rowing/calisthenics) and nonvigorous intensity activities (flights of stairs climbed and walking). Because these men are health professionals, occupational activity is low.

Validation of Physical Activity Questionnaire. The validity of the physical activity questionnaire was investigated in a subset of 238 study participants who completed a past-week recall and an open-ended 1-week activity diary during 4 different seasons throughout 1 year beginning in August of 1991 (23). The men had completed one activity questionnaire in 1990 and an additional one in 1992. In addition, a subset of these men took a step test in 1992 to measure fitness. The Pearson correlation between diary-based and questionnaire-based activity scores for vigorous activity was 0.54 for the 1990 questionnaire and 0.58 for the 1992 questionnaire. The median vigorous MET-hours/week was 5.7 for the diary records, 4.2 for the 1990 questionnaire, and 6.4 for the 1992 questionnaire. The similarity of the medians of the diary records and the questionnaires indicates that the majority of activities contributing to vigorous activities were captured by the questionnaire. The correlation between questionnaire-based vigorous activity and resting pulse was −0.45; for pulse after stepping, the correlation was −0.41. Among the nonvigorous activities, the correlation between the diary measurements and the questionnaire was 0.40 for walking and 0.60 for stair climbing. Nonvigorous activities were not correlated with pulse. The capability of our questionnaire to assess physical activity in this cohort was also evidenced by the detection of inverse linear associations between physical activity and colon cancer and adenoma (24), diverticular disease (25), gallstones (26), and benign prostatic hyperplasia (27).

Statistical Analysis. Each man accrued follow-up time beginning on the month of return of the baseline questionnaire and ending on the month of diagnosis of prostate cancer, month of death from other causes, or January 31, 1994, whichever came first. We calculated incidence rates of prostate cancer for men in a specific category of physical activity level in 1986 by dividing the number of incident cases by the number of person-years. These analyses were conducted for total, advanced, and metastatic prostate cancer and for total, vigorous, and nonvigorous activity. The relative risk was computed as the rate among men in the category of interest divided by the rate among men in the specified reference category. All categories were defined before analyses were conducted. We used the Mantel-Haenszel summary estimator (28) to adjust for age (across 2.5-year categories). To estimate relative risks when controlling for multiple risk factors, we used pooled logistic regression, which accounts for the varying times to the outcome event (29) and which is asymptotically equivalent to Cox regression modeling (30). Confounding by various factors related to either total, advanced, or metastatic prostate cancer was evaluated through multivariate models in this population, including age, history of vasectomy (31), history of diabetes mellitus (32), smoking, height (33), intake of energy-adjusted total fat (19), calcium, monosaccharide fructose, fructose from sucrose (21), and lycopene (34) at baseline. We additionally considered the impact of BMI, which could be an intermediate factor in the causal pathway between physical activity and prostate cancer. We tested for trends, controlling for multiple covariates by modeling the specific exposure as a continuous variable in a multiple logistic regression model that included the covariates. In addition, the shape of the relationship between physical activity and prostate cancer was evaluated using restricted cubic splines (35). All reported *P* values are from two-sided tests.

RESULTS

We examined the relationship between physical activity and established or potential risk factors for prostate cancer (Table 1) to assess the potential for confounding. The more physically active men tended to be slightly younger and to have a lower BMI, and were less likely to be current smokers and more likely to have had a vasectomy. The more active men were also slightly more likely to have had a routine digital rectal examination and a PSA test by 1994. Among the more physically active, total energy intake was higher, consistent with greater energy expenditure, and the fat composition of the diet was slightly lower, whereas calcium and lycopene intakes were higher.

We next examined non-stage A1 prostate cancer risk in relation to total physical activity and to vigorous and nonvigorous activity. As shown in Table 2, no relationship was evident in age-adjusted and multivariate analyses. In addition, for advanced (stages C and D) prostate cancer, no trends across levels of physical activity were observed (Table 3). Although an ~25% reduction in risk was observed in the second lowest quintile compared with the lowest quintile for both total and vigorous activity, no further trend was noted for

[3] The abbreviations used are: MET, metabolic equivalent; BMI, body mass index; PSA, prostate-specific antigen; RR, relative risk; CI, confidence interval.

Table 2 *RR of total prostate cancer (non-stage A1) in relation to total physical activity and vigorous and nonvigorous activity in the Health Professionals Follow-up Study (1986–1994)*

	Category					
	1	2	3	4	5	*P* value for trend[a]
Total physical activity						
Median MET-hours	1.0	4.8	11.3	22.7	46.8	
Cases/person-years	293/72,194	274/70,564	263/72,197	288/72,868	244/72,666	
Age-adjusted RR	1.0	0.90	0.90	1.03	0.92	0.99
Multivariate RR[b]	1.0	0.89	0.89	1.01	0.90	0.88
95% CI		(0.75–1.05)	(0.75–1.05)	(0.85–1.19)	(0.76–1.07)	
Vigorous activity[c]						
Median MET-hours[b]	0	1.4	7.0	17.5	41.0	
Cases/person-years	630/134,242	224/61,606	194/54,263	168/55,731	146/54,648	
Age-adjusted RR	1.0	0.97	1.00	1.04	1.03	0.63
Multivariate RR[b]	1.0	0.96	0.99	1.03	1.03	0.59
95% CI		(0.82–1.12)	(0.84–1.17)	(0.87–1.23)	(0.85–1.24)	
Nonvigorous Activity[d]						
Median MET-hours[b]	0.3	1.6	3.8	7.6	21.3	
Cases/person-years	250/80,640	231/66,359	269/71,964	272/71,064	340/70,463	
Age-adjusted RR	1.0	1.11	1.02	0.98	0.99	0.35
Multivariate RR[b]	1.0	1.11	1.03	0.96	0.97	0.25
95% CI		(0.93–1.33)	(0.85–1.21)	(0.81–1.15)	(0.82–1.15)	

[a] *P* value for trend based on modeling the continuous variable in a multiple logistic model.
[b] RR controlled for age (2.5-year categories); history of vasectomy (yes or no); history of diabetes mellitus (yes or no); smoking (never, former, three levels of current smoking); height (five categories); intake of energy-adjusted total fat (quintiles), calcium (six categories), monosaccharide fructose (quintiles), fructose from sucrose (quintiles), and lycopene (quintiles).
[c] Controlled for nonvigorous activity.
[d] Controlled for vigorous activity.

quintiles 2–5. The essentially null relationships between physical activity and total and advanced prostate cancer were similar for younger and older men, and over calendar time (data not shown).

When physical activity in relation to metastatic prostate cancer was examined, no linear trends were noted for total, vigorous, and nonvigorous activities (Table 4). However, for vigorous activity, a significantly lower risk of metastatic prostate cancer was observed in the highest quintile (multivariate RR = 0.46). In analyses limited to stage D2 (distant metastatic) cancers, a similar reduced risk was also observed among the most physically active men (RR = 0.52; 95% CI, 0.25–1.09). The lower risk for metastatic cancers was specific for this highest level of activity; indeed, in the second highest quintile, there was a slight, nonsignificant increased risk. Excluding the first 2 or 4 years of follow-up did not appreciably alter the RR for metastatic prostate cancer in the top quintile of vigorous activity (RR = 0.56 after excluding first 2 years; RR = 0.57 excluding first 4 years). Comparing the top quintile to the bottom four quintiles yielded relative risks of 0.75 (95% CI, 0.50–1.13) for total activity and 0.48 (95% CI, 0.25–0.92) for vigorous activity. This inverse association with vigorous activity persisted after men who did not have a PSA examination by 1994 were excluded (RR = 0.45).

Because of the *a priori* hypothesis that only high levels of vigorous activity reduce risk of prostate cancer (8), we conducted analyses to examine the dose-response relationship. First, a cubic spline analysis was conducted; this showed a relatively flat association until ~20 MET-hours of vigorous activity per week and an inverse association thereafter. In another analysis, we created additional variables, which equaled zero unless vigorous activity exceeded a specified level (for example, "variable" = 0 if vigorous MET-hours ≤20 and "variable" = vigorous MET-hours if vigorous MET-hours >20). We then conducted logistic regression analysis for metastatic prostate cancer, which included the new variable along with total vigorous activity

Table 3 *RR of advanced prostate cancer (stages C and D) in relation to total physical activity and vigorous and nonvigorous activity in the Health Professionals Follow-up Study (1986–1994)*

	Category					
	1	2	3	4	5	*P* for trend[a]
Total physical activity						
Median MET-hours	1.0	4.8	11.3	22.7	46.8	
Cases/person-years	100/72,347	77/70,742	79/72,346	87/73,030	76/72,800	
Age-adjusted RR	1.0	0.74	0.79	0.91	0.84	0.77
Multivariate RR[b]	1.0	0.73	0.78	0.89	0.82	0.73
95% CI		(0.54–0.98)	(0.58–1.05)	(0.66–1.19)	(0.60–1.11)	
Vigorous activity[c]						
Median MET-hours	0	1.4	7.0	17.5	41.0	
Cases/person-years	206/134,608	58/61,738	60/54,376	55/55,810	40/54,734	
Age-adjusted RR	1.0	0.76	0.94	1.03	0.84	0.59
Multivariate RR[b]	1.0	0.75	0.93	1.03	0.87	0.73
95% CI		(0.56–1.01)	(0.69–1.25)	(0.76–1.40)	(0.61–1.23)	
Nonvigourous activity[d]						
Median MET-hours	0.3	1.6	3.8	7.6	21.3	
Cases/person-years	78/80,771	63,66,497	89/72,125	83/1,212	106/70,661	
Age-adjusted RR	1.0	0.96	1.08	0.97	0.99	0.86
Multivariate RR[b]	1.0	0.97	1.08	0.94	0.94	0.84
95% CI		(0.69–1.36)	(0.79–1.46)	(0.68–1.28)	(0.70–1.27)	

[a] *P* value for trend based on modeling the continuous variable in a multiple logistic model.
[b] RR controlled for age; history of vasectomy; history of diabetes mellitus; smoking; height; and intake of energy-adjusted total fat, calcium, monosaccharide fructose, fructose from sucrose, and lycopene.
[c] Controlled for nonvigorous activity.
[d] Controlled for vigorous activity.

Table 4 *RR of metastatic prostate cancer (stage D) in relation to total physical activity, and vigorous and nonvigorous activity in the Health Professionals Follow-up Study (1986–1994)*

	Category					
	1	2	3	4	5	*P* value for trend[a]
Total physical activity						
Median MET-hours	1.0	4.8	11.3	22.7	46.8	
Cases/person-years	45/72,401	39/70,775	39/72,383	48/73,062	29/72,841	
Age-adjusted RR	1.0	0.83	0.88	1.12	0.71	0.33
Multivariate RR[b]	1.0	0.84	0.89	1.14	0.72	0.38
95% CI		(0.54–1.29)	(0.58–1.38)	(0.75–1.72)	(0.44–1.17)	
Vigorous activity[c]						
Median MET-hours	0	1.4	7.0	17.5	41.0	
Cases/Person-years	105/134,695	26/61,770	29/54,402	30/55,837	10/54,758	
Age-adjusted RR	1.0	0.68	0.91	1.15	0.43	0.23
Multivariate RR[b]	1.0	0.68	0.91	1.17	0.46	0.24
95% CI		(0.44–1.04)	(0.59–1.37)	(0.77–1.78)	(0.24–0.89)	
Nonvigorous activity[d]						
Median MET-hours	0.3	1.6	3.8	7.6	21.3	
Cases/person-years	30/80,816	29/66,536	42/72,160	47/71,244	52/70,706	
Age-adjusted RR	1.0	1.15	1.31	1.42	1.22	0.82
Multivariate RR[b]	1.0	1.13	1.29	1.38	1.16	0.98
95% CI		(0.69–1.89)	(0.81–2.08)	(0.87–2.18)	(0.74–1.84)	

[a] *P* value for trend based on modeling the continuous variable in a multiple logistic model.
[b] Relative risk controlled for age; history of vasectomy; history of diabetes mellitus; smoking; height; intake of energy-adjusted total fat, calcium, monosaccharide fructose, fructose from sucrose, and lycopene.
[c] Controlled for nonvigorous activity.
[d] Controlled for vigorous activity.

(MET-hours), and tested for a statistically significant improvement over the multivariate model that included total vigorous activity but not this new variable, using the likelihood ratio test. This procedure was repeated in separate models for different values for this variable. The *P* values for each of the following values of this variable were as follows: $P > 0.9$ for 15 MET-hours; $P = 0.04$ for 20 MET-hours and 25 MET-hours, $P = 0.32$ for 30 MET-hours; and $P > 0.9$ for 35 MET-hours. These results suggest a change in the slope (in the inverse direction) at vigorous activity level in the 20–25 MET-hours range.

For our major analyses (presented above), we did not control for BMI, a potentially intermediate variable influenced by physical activity. In multivariate models controlling additionally for BMI at age 21 and in 1986, all results were nearly identical as to the multivariate models presented. In addition, the impact of physical activity on prostate cancer did not vary across tertiles of BMI in 1986 and waist and hip circumferences assessed in 1987.

Because some previous studies found inverse associations between activity and prostate cancer limited to older men (>60–70 years of age; 5, 8, 10), we examined these associations separately for younger and older men, dichotomizing by the median age of diagnosis (67.5 years). None of the types of activity were related appreciably to total or advanced prostate cancer in either age group. Among the older men only, an inverse association was noted for vigorous activity, and the reduction in risk was mostly for the most physically active men (Table 5).

We further examined the association (from 1988 to 1994) between activity and prostate cancer risk by comparing men consistently in the high quintile of activity, using questionnaires in 1986 and 1988 to men consistently falling in the low quintile. Total physical activity was unrelated to total, advanced, or metastatic prostate cancer (data not shown). Vigorous activity was also unrelated to total (RR = 1.10) or advanced prostate cancer (RR = 0.99) and was related only weakly to metastatic prostate cancer (RR = 0.84; 95% CI = 0.38–1.87).

None of the individual activities were related to risk of total or advanced prostate cancer (all *P* values for trend >0.10). For metastatic prostate cancer, the individual vigorous activities tended to have nonsignificant inverse trends, but only the trend for racquet sports approached statistical significance ($P = 0.09$). The RR for high *versus* low tertiles were 0.63 (95% CI, 0.31–1.29) for racquet sports and 0.75 (95% CI, 0.38–1.47) for rowing and calisthenics. Thus, the reduced risk for metastatic prostate cancer associated with high levels of vigorous activities was not related to a particular kind of activity, but rather was observed in men who engaged extensively in one of a variety of activities or in a combination of several activities.

DISCUSSION

In this cohort of health professionals, no linear relationship between nonoccupational physical activity and total or advanced prostate can-

Table 5 *RR of prostate cancer in relation to vigorous physical activity among younger (40–67.5 years) and older (>67.5 years) populations of men in the Health Professionals Follow-up Study (1986–1994)*

Variable (median MET-hours/week)	Total (non-stage A1)				Advanced (stages C and D)				Metastatic (stage D)			
	Age, 40–67.5 years[a] (*n* = 627)		Age, ≥67.5 years[a] (*n* = 735)		Age, 40–67.5 years[a] (*n* = 199)		Age, ≥67.5 years[a] (*n* = 220)		Age, 40–67.5 years[a] (*n* = 91)		Age, ≥67.5 years[a] (*n* = 109)	
	RR[b]	95%CI	RR[b]	95%CI	RR[b]	95%CI	RR[b]	95%CI	RR[b]	95%CI	RR[b]	95%CI
Vigorous activity												
0	1.0		1.0		1.0		1.0		1.0		1.0	
1.4	1.02	0.81–1.29	0.91	0.74–1.13	0.97	0.63–1.48	0.63	0.42–0.95	0.76	0.34–1.30	0.71	0.40–1.25
7.0	1.04	0.82–1.33	0.95	0.76–1.19	1.15	0.75–1.76	0.79	0.53–1.19	0.66	0.32–1.36	1.13	0.68–1.89
17.5	1.19	0.94–1.52	0.87	0.67–1.13	1.41	0.94–2.13	0.71	0.43–1.15	1.77	1.03–3.03	0.63	0.29–1.32
41.0	1.02	0.78–1.33	1.07	0.82–1.39	1.05	0.65–1.68	0.74	0.44–1.26	0.63	0.28–1.43	0.31	0.10–0.99
P value for trend[c]	0.70		0.68		0.54		0.21		0.74		0.04	

[a] Age updated every 2 years.
[b] RR controlled for age (continuous); history of vasectomy; history of diabetes mellitus; smoking; height; intake of energy-adjusted total fat, calcium, monosaccharide fructose, fructose from sucrose, and lycopene; and nonvigorous activity.
[c] *P* for trend based on modeling the continuous variable in a multiple logistic model.

cer emerged; however, men engaging in substantially high levels of vigorous activities had approximately one-half the likelihood of being diagnosed with metastatic prostate cancer. Each of several analytic approaches indicated that the inverse association began at ~20–25 MET-hours/week, equivalent to at least 3 h of vigorous activity weekly. When we examined subsequent risk among men who were consistently in the high quintile in 1986 and 1988 to those who were consistently low, the inverse association for metastatic prostate cancer weakened (RR = 0.84), although the CIs were wide due to the small numbers (CI, 0.38–1.87) and compatible with our overall findings. The finding of a reduced risk only at the highest category of activity primarily among older men, although statistically significant, could be a chance finding; however, it does replicate closely findings from the Harvard Alumni Study (8). Because our activity assessment was completed before the diagnosis of prostate cancer, recall bias was unlikely, and confounding from diet did not account for our findings.

Apart from chance, possible explanations of our findings are that either physical activity reduces progression, but not overall occurrence, of prostate cancer or that physically active men undergo screening more frequently, which causes their cancer to be detected at an earlier stage. Several facts argue against the latter explanation. First, although higher levels of physical activity were associated with a slightly higher frequency of digital rectal examination or PSA screening, these differences were minor (Table 1). Notably, men in the second highest physical activity category had a slightly greater frequency for screening but were at 2.5-fold higher risk for metastatic prostate cancer than the most active men. Moreover, after excluding non-cases who had not had a PSA examination by 1994, results were similar (RR = 0.45 for quintile 5 *versus* quintiles 1–4). Finally, if men in the highest category had undergone greater surveillance for prostate cancer, we would expect elevated detection rates of early-stage (organ-confined) tumors among them; however, this was not observed.

Some risk factors may primarily influence metastasis; for example, constitutional (*e.g.*, height; 33) and genetic factors (*e.g.*, polymorphism in the androgen receptor gene; 36), which are unlikely to be related to screening behaviors, have been associated specifically with metastatic prostate cancer. Unlike our study, some previous studies found an inverse relationship between total prostate cancer and activity. Possibly, this discrepancy could be a result of PSA screening, which has substantially increased the frequency of diagnosis of early-stage prostate cancers in recent years. The proportion of newly diagnosed cancers with clinical evidence of distant metastases approached 50% several decades ago, but represented only 14.6% in this recent cohort. Any true association limited only to aggressive prostate cancers with the capacity to metastasize would be attenuated in analyses for total prostate cancer at the present time, but may have been detected in earlier studies when prostate cancer was frequently diagnosed as a result of symptoms induced by aggressive cancers.

Our study has several strengths and limitations: the activity assessment was prospective and validated; we measured potentially confounding variables such as diet; the follow-up response rate was high; and the number of cases was relatively large. In addition, we had information on digital rectal examinations and PSA testing, which allowed us to address the potential for detection bias. One limitation was that, as in most studies, we were only able to consider the impact of relatively recent physical activity levels; we could not address exercise during adolescence or early adulthood, or cumulative lifetime activity. Another limitation was that occupational activity was uniformly low in these health professionals. Nonetheless, a wide range in leisure time activity levels existed, and our results are pertinent to the large proportion of men in economically developed countries who experience relatively low levels of occupational physical activity.

Several approaches have been used to examine the relationship between physical activity levels in adulthood and prostate cancer risk. Among studies that have evaluated occupational activity based on job classification, men in occupations that require relatively low energy expenditure have been at ~10–50% higher risk of prostate cancer (1–4). One occupational study found no association between low energy expenditure and higher risk of prostate cancer among men <70 years of age but one-half the risk of prostate cancer among men >70 years who had spent most of their life in sedentary jobs (5). Of the studies that have focused on recreational activities or a combination of occupational and recreational activities, one case-control study (6) and several prospective studies (7–12, 16) have found results similar to the occupational studies. A recent prospective study in Finland found moderate risk reduction for occupational walkers but not for heavy laborers (16). Occupational walkers who also had moderate to heavy levels of leisure activity had a 60% reduction in risk. Another study found no association between prostate cancer risk and occupational activity, but a borderline statistically significant 23% risk reduction with recreational or home-related activity (13). A multicenter population-based case-control study found no strong evidence for a relationship (14); another case-control study found a suggestion of a positive association (15). Although most studies have tended to support an inverse association, the relationships have tended to be moderate, not always statistically significant, and sometimes only evident in subgroups, and potential confounders such as dietary differences have not been addressed adequately.

Our finding of a benefit against metastatic disease only with substantially high levels of physical activity, beginning at least 3 h/week of vigorous activity, is probably not simply an artifact of our questionnaire because in this cohort, linear inverse associations with activity have been observed for colon cancer and adenoma (24), diverticular disease (25), gallstones (26), and benign prostatic hyperplasia (27). Our results are also consistent with the findings of Lee *et al.* (8) who, using similar methodology, found a lower risk of prostate cancer only among men at the highest level of physical expenditure, and like us, also found the association strongest for older men (≥70 years). A Norwegian cohort study found an inverse association only in men >60 years of age (10), and a case-control study conducted in Hawaii found occupational activity protective only in men >70 years of age (5). A study by Oliveria *et al.* (12) found, across approximate quartiles of physical fitness determined by maximal treadmill test, RRs of 1.0, 1.1, 0.73, and 0.26, although the dose-response displayed for physical fitness cannot be assumed to have the same pattern as physical activity. A limitation of the latter study was a high nonresponse rate to follow-up (53%).

One potential mechanism whereby physical activity may influence prostate carcinogenesis is through the modulation of testosterone level. Abnormally low levels of testosterone, as in castrates (37), inhibits prostate carcinogenesis, and prostate cancer is sensitive to androgens and often regresses when androgen stimulation is withdrawn (37). That lower risk of prostate cancer is associated with testosterone levels within the low-normal range, over which physical activity may be relevant, was demonstrated in a prospective study (18).

At least 15 studies (17) have found that an episode of prolonged submaximal exercise may induce a transient rise in testosterone level during the exercise period, followed by a reduction. The drop in testosterone could be in the range of 25–50% if the activity was conducted for 2 h or longer, and concentrations returned to a normal range within 24–72 h. In endurance-trained men, resting total and free testosterone levels were only 60–85% of those in age-matched, untrained men (17). Three intervention studies that have examined the impact of exercise training on hormone levels reported a significant reduction in testosterone after 1–6 months of intensive training (38–

40). For example (40), 15 healthy sedentary men who underwent 6 months of supervised running training with mileage increasing progressively to a mean of ~35 miles/week had an ~30% reduction in total testosterone and the testosterone/sex hormone-binding globulin ratio (index of free testosterone). Two studies of 2–3 months duration did not show a significant reduction (41, 42).

Alternatively, physical activity may act through mechanisms not involving testosterone. Epithelial cell division in the prostate gland is stimulated by the release of growth factors from adjacent stromal cells that are heavily innervated with α-1-adrenergic receptors (43, 44). Recently, Gann *et al.* (45) hypothesized that local neurotrophic factors in the prostate gland, associated with central sympathetic nervous activity, may underlie the direct association these investigators observed between resting heart rate and prostate cancer mortality. Thus, an alternative, although speculative, mechanism may be that exercise lowers sympathetic activity, which reduces growth factor release from stromal cells.

Overall, our results do not support the hypothesis that physical activity within the range observable in male health professionals in the United States is a major factor for prostate cancer incidence. However, a suggestion of a potential benefit against metastatic disease at substantially high levels of activity warrants further study.

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