Physical Activity in Relation to Total, Advanced, and Fatal Prostate Cancer

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Abstract

Physical activity has been inconsistently related to total prostate cancer and few studies have examined whether this association varies by disease aggressiveness. We examined physical activity in relation to total, advanced, and fatal prostate cancer in the NIH-AARP Diet and Health Study. At baseline (1995-1996), 293,902 men ages 50 to 71 years completed a questionnaire inquiring about current frequency of vigorous exercise of at least 20 min of duration, as well as frequency of exercise during adolescence (ages 15-18). We used proportional hazards regression to calculate multivariate relative risks (RR) and 95% confidence intervals (95% CI). During up to 8.2 years of follow-up, 17,872 prostate cancer cases were identified, including 1,942 advanced and 513 fatal cases. Comparing frequent (5+ times per week) versus infrequent (less than once per week) vigorous exercise, exercise at baseline was not associated with risk of total prostate cancer (RR, 1.01; 95% CI, 0.96-1.07; P_{trend} = 0.78), advanced prostate cancer (RR, 1.14; 95% CI, 0.97-1.33; P_{trend} = 0.25), or fatal prostate cancer (RR, 0.90; 95% CI, 0.67-1.20; P_{trend} = 0.12). Increasing level of vigorous exercise during adolescence was associated with a small 3% reduction in total prostate cancer risk (frequent versus infrequent exercise during adolescence: RR, 0.97; 95% CI, 0.91-1.03; P_{trend} = 0.03) but was not associated with risk of advanced prostate cancer (RR, 0.95; 95% CI, 0.78-1.14; P_{trend} = 0.18) or fatal prostate cancer (RR, 0.96; 95% CI, 0.67-1.36; P_{trend} = 0.99). Neither vigorous exercise at baseline nor exercise during adolescence was related to risk of total, advanced, or fatal prostate cancer in this large prospective cohort. (Cancer Epidemiol Biomarkers Prev 2008;17(9):2458–66)

Introduction

Epidemiologic studies of the relationship between physical activity and prostate cancer have yielded mixed results (1). On balance, most studies have reported a null association regardless of whether examining occupational or leisure time physical activity (1) or vigorous versus less intense activity (2-5). However, some studies suggest that physical activity may reduce the risk of aggressive forms of this disease (6-8). Subsequently, it has been suggested that physical activity may decrease tumor progression or reduce the risk of aggressive cancer subtypes, even if it does not lower overall prostate cancer occurrence (7). Alternately, physically active men may receive prostate-specific antigen (PSA) screening or other screening more frequently than inactive men, and thus, different findings for total versus advanced cases may reflect potential screening biases.

Although initial evidence of a link between physical activity and reduced risk of aggressive prostate cancer is promising, much of this evidence is based on subgroup findings, such as in older men (8), or findings that were of borderline statistical significance (6). To rule out the possibility that these previous findings were due to chance, it is important to replicate them using a large study sample where subgroups were identified a priori. We therefore prospectively examined physical activity in relation to total, advanced, and fatal prostate cancer in a cohort of ~300,000 men enrolled in the NIH-AARP (formerly known as the American Association of Retired Persons) Diet and Health Study. Due to previous findings in the literature (6, 8), we hypothesized that physical activity is inversely associated with advanced or fatal prostate cancers, particularly among men ages ≥65 (8), or with total prostate cancer among men without recent PSA screening, among whom screening bias would be minimized (2).

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Materials and Methods

Study Population. The NIH-AARP Diet and Health Study was established in 1995 to 1996 when 567,169 AARP members 50 to 71 y old and residing in one of six states (California, Florida, Pennsylvania, New Jersey, North Carolina, and Louisiana) or two metropolitan areas (Atlanta, GA and Detroit, MI) responded to a baseline questionnaire eliciting information on demographic characteristics, physical activity, and other health-related behaviors (9). Within 6 mo from the mailing of the baseline questionnaire, a second questionnaire was mailed to participants who still lived in the study area and did not have prevalent cancer of the colon, breast, or prostate at baseline. The supplementary questionnaire inquired about history of digital rectal examinations and PSA screening in the past 3 y, weight at age 18, and waist circumference among other health-related questions. In total, 334,908 participants responded to the supplementary questionnaire.

Of the 567,169 respondents to the baseline questionnaire, we excluded participants who returned duplicate questionnaires (n = 179), who had died or moved out of the study area before baseline (n = 582), who withdrew from the study (n = 6), who had questionnaires completed by proxy respondents (n = 15,760), who were female (n = 225,468), who had a previous diagnosis of cancer (n = 27,248), or who were missing information on physical activity (n = 4,024). After these exclusions, data for 293,902 participants were available for analysis, including 176,678 men who completed the supplemental questionnaire.

The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the National Cancer Institute. All participants provided written informed consent.

Assessment of Physical Activity. Our exercise/sports assessment is based on the 1990 recommendation by the American College of Sports Medicine that all persons engage in the equivalent of at least 20 min of vigorous exercise three times per week (10). On the baseline questionnaire, participants were asked to report the number of bouts of exercise and/or sports per month during the past year that lasted at least 20 min and caused increased breathing or heart rate or a sweat (i.e., exercise at baseline). Study members were also asked about their frequency of sport and/or exercise at 15 to 18 y of age (i.e., exercise during adolescence). For each assessment of physical activity, participants selected their level of activity from six preestablished response options (never, rarely, one to three times per month, one to two times per week, three to four times per week, and five or more times per week). Our assessment of exercise at baseline is similar to a previous questionnaire with shown validity (percentage agreement = 0.71) based on comparison with an objective measure (i.e., a Computer Science and Applications activity monitor; ref. 11).

Ascertainment and Classification of Prostate Cancer Cases and Deaths. Incident, first primary prostate cancer cases (International Classification of Diseases for Oncology, Third Edition, code C619) were identified through December 31, 2003 by linkage of the NIH-AARP cohort database with state cancer registries. Information on the prostate cancer stage and histologic grade (93% complete) was also obtained from the state cancer registry databases. Localized prostate cancers were those tumors with a clinical or pathologic classification of T1a to T2b and N0M0 according to the American Joint Committee on Cancer 1997 tumor-lymph node-metastasis classification system (12). Advanced prostate cancer cases were defined as cases with clinical or pathologic tumor classifications of T3 or T4, N1 status, or M1 status, or as cases first identified by stage cancer registry and who subsequently died of prostate cancer between 1995 and 2003. Men who died from prostate cancer from 1995 to 2005 were classified as fatal cases, regardless of previous diagnosis. For individuals with information on both clinical and pathologic stage, the measure indicating worse disease was used. Low-grade prostate cancers were defined as grade 1 or 2 tumors by the Surveillance, Epidemiology, and End Results coding (13), which is consistent with a Gleason score of $\leq$7. High-grade prostate cancers were defined as grade 3 or 4 tumors (Gleason score of $\geq$8). In a previous validation study, the estimated sensitivity of cancer identification in our cohort was ~90% and the specificity was 99.5% (14).

Statistical Analysis. Participants were followed from the date of scan of the baseline questionnaire until diagnosis of first cancer, death, move out of the cancer registry ascertainment areas, or until the date of last follow-up on December 31, 2003. Deaths from prostate cancer as the underlying cause were ascertained through December 31, 2005 using the National Death Index.

Relative risks (RR) and 95% confidence intervals (95% CI) for prostate cancer were estimated using Cox proportional hazards regression according to categories of physical activity. We collapsed the bottom two categories of exercise at baseline and during adolescence to ensure sufficient numbers of cases in the reference category. For tests of trend, each category was assigned a single value indicating approximate frequency of physical activity bouts per week (never/rarely = 0.125, one to three times per month = 0.5, one to two times per week = 1.5, three to four times per week = 3.5, and five or more times per week = 5.5).

Covariates were included in multivariate models if previous studies consistently indicated an association with prostate cancer, or if the covariate was a statistically significant predictor of prostate cancer in the NIH-AARP Diet and Health cohort. For covariates for which information was not complete, we used a missing indicator variable to model the nonresponse. For analyses of fatal prostate cancers, we constructed alternative models using a reduced set of covariates (see Table 2, footnote) to address potential overfitting. In these models, there were no substantial departures in the estimated β-coefficients from those of the full models (all changes less than 10%) or in the tests for trend (no models crossed the threshold of statistical significance).

In models examining the risk of prostate cancer before age 65, only person-time before this age was counted and all individuals were censored on reaching age 65. In models examining the risk of prostate cancer after age 65, person-time was counted starting at age 65 and only for those individuals who had not previously been diagnosed with prostate cancer. For analyses stratified by

Table 1. Selected demographic and lifestyle characteristics according to exercise at baseline and during adolescence

Characteristic	All men	Exercise at baseline					Activity during adolescence				
		Never/ rarely	1-3 times/mo	1-2 times/wk	3-4 times/wk	>5 times/wk	Never/ rarely	1-3 times/mo	1-2 times/wk	3-4 times/wk	>5 times/wk
Participants (*n*)	293,902	44,717	38,641	64,766	82,719	63,059	19,151	15,577	39,054	72,841	147,279
Age (y)	62.1	62.2	61.4	61.7	62.4	62.6	62.1	61.7	62.0	62.1	62.2
Family history of prostate cancer (%)	8.8	8.1	8.7	8.8	8.9	8.9	8.3	8.2	8.4	8.8	9.0
Rectal exam during the past 3 y (%)*											
None	14.3	19.5	15.9	14.2	12.1	13.1	16.5	15.6	14.0	13.9	14.1
Once	27.0	30.2	28.9	27.9	25.4	25.4	27.5	26.9	27.2	27.1	26.9
More than once	58.7	50.4	55.1	57.9	62.5	61.5	56.0	57.5	58.8	59.0	59.0
PSA test during the past 3 y (%)*											
None	22.5	29.0	24.8	22.8	19.6	20.9	25.1	23.8	21.6	21.9	22.5
Once	26.2	27.8	27.5	27.4	25.5	24.4	25.8	26.3	26.6	26.4	26.1
More than once	51.3	43.3	47.6	49.8	54.9	54.6	49.1	49.9	51.8	51.7	51.4
Smoking status (%)											
Current smoker	11.0	18.1	14.4	11.6	8.0	7.3	10.6	11.3	11.0	11.2	10.9
Former smoker	58.8	56.9	57.8	58.0	60.8	60.4	58.1	59.6	60.0	60.0	58.2
Never smoker	30.2	25.0	28.4	31.0	32.0	32.6	31.3	28.8	29.5	29.2	31.2
College education (%)	45.7	33.2	43.0	46.4	50.3	49.0	39.4	41.9	44.9	44.6	47.6
BMI (kg/m^2)	27.3	28.4	28.0	27.5	26.9	26.4	27.2	27.0	27.0	27.1	27.5
History of diabetes (%)	10.2	15.6	10.5	9.4	8.9	8.5	11.3	9.9	10.1	9.8	10.3
Alcohol intake (g/d)	15.4	15.6	15.7	15.4	15.0	15.7	14.4	14.4	14.8	15.2	15.9
Red meat intake (g/d)	80.0	84.9	83.6	81.8	74.2	69.2	73.8	75.7	77.2	78.2	78.3
Lycopene intake (μg/d)	7,764	7,237	7,463	7,745	7,895	8,136	7,120	7,234	7,557	7,689	7,983
Multivitamin use (%)	15.4	13.6	15.0	14.9	16.3	16.3	15.5	15.4	15.3	15.1	15.6

*Rectal examination and PSA screening data are available only for those participants who answered the second questionnaire (~60% of cohort).

PSA screening, person-time was calculated starting from the date that the second questionnaire was returned, as these data were available only for respondents to the second questionnaire.

We formally tested for potential interactions of the physical activity and prostate cancer association using the likelihood ratio test (i.e., comparing the likelihood of models with and without multiplicative interaction terms). Interaction terms were calculated using the cross-product of the physical activity categories and the factor of interest (e.g., age).

Tests of the proportional hazards assumption did not reveal any departure from proportionality. All *P* values were based on two-sided tests. Statistical analyses were done using Statistical Analysis System release 9.1.3 (SAS Institute).

Table 2. RRs and 95% CIs for prostate cancer in relation to level of physical activity

Physical activity	No. cases	Person-years	Age adjusted RR (95% CI)	Multivariate* RR (95% CI)	Mutually adjusted † RR (95% CI)
All prostate cancer cases					
Exercise at baseline					
Never/rarely	2,487	292,369	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1-3 times/mo	2,231	262,054	1.05 (0.99-1.11)	1.00 (0.95-1.06)	1.00 (0.95-1.06)
1-2 times/wk	3,869	441,674	1.05 (1.00-1.11)	0.99 (0.94-1.05)	1.00 (0.95-1.05)
3-4 times/wk	5,174	564,533	1.05 (1.00-1.10)	0.97 (0.93-1.02)	0.98 (0.93-1.03)
≥5 times/wk	4,111	430,500	1.08 (1.03-1.13)	1.01 (0.96-1.07)	1.02 (0.97-1.08)
P for trend			0.02	0.78	0.49
Activity during adolescence					
Never/rarely	1,131	130,091	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1-3 times/mo	921	106,070	1.03 (0.94-1.12)	1.01 (0.92-1.10)	1.01 (0.92-1.10)
1-2 times/wk	2,425	265,404	1.06 (0.99-1.14)	1.02 (0.95-1.10)	1.02 (0.95-1.10)
3-4 times/wk	4,457	493,204	1.03 (0.97-1.10)	0.99 (0.92-1.05)	0.99 (0.93-1.05)
≥5 times/wk	8,938	996,362	1.02 (0.96-1.08)	0.97 (0.91-1.03)	0.97 (0.91-1.03)
P for trend			0.51	0.03	0.03
Advanced prostate cancer cases					
Exercise at baseline					
Never/rarely	261	292,369	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1-3 times/mo	272	262,054	1.20 (1.01-1.42)	1.16 (0.98-1.37)	1.16 (0.97-1.37)
1-2 times/wk	400	441,674	1.03 (0.88-1.21)	0.99 (0.85-1.16)	0.99 (0.85-1.17)
3-4 times/wk	551	564,533	1.08 (0.93-1.25)	1.04 (0.89-1.21)	1.05 (0.90-1.22)
≥5 times/wk	458	430,500	1.17 (1.00-1.36)	1.14 (0.97-1.33)	1.16 (0.99-1.36)
P for trend			0.19	0.25	0.15
Activity during adolescence					
Never/rarely	123	130,091	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1-3 times/mo	95	106,070	0.96 (0.73-1.26)	0.94 (0.72-1.23)	0.93 (0.71-1.22)
1-2 times/wk	277	265,404	1.11 (0.90-1.37)	1.08 (0.87-1.33)	1.07 (0.86-1.33)
3-4 times/wk	490	493,204	1.04 (0.86-1.27)	1.00 (0.82-1.22)	1.00 (0.82-1.22)
≥5 times/wk	957	996,362	1.00 (0.83-1.21)	0.95 (0.78-1.14)	0.95 (0.77-1.13)
P for trend			0.48	0.18	0.12
Fatal prostate cancer cases ‡					
Exercise at baseline					
Never/rarely	90	423,919	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1-3 times/mo	79	385,228	1.03 (0.76-1.39)	1.14 (0.84-1.54)	1.14 (0.84-1.55)
1-2 times/wk	112	651,165	0.83 (0.63-1.09)	0.98 (0.74-1.30)	0.98 (0.74-1.30)
3-4 times/wk	129	835,564	0.68 (0.52-0.89)	0.86 (0.65-1.14)	0.86 (0.65-1.14)
≥5 times/wk	103	637,901	0.70 (0.53-0.93)	0.90 (0.67-1.20)	0.90 (0.67-1.20)
P for trend			<0.01	0.12	0.12
Activity during adolescence					
Never/rarely	37	190,777	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1-3 times/mo	27	155,750	0.93 (0.57-1.53)	0.97 (0.59-1.59)	0.95 (0.58-1.56)
1-2 times/wk	62	390,893	0.83 (0.55-1.24)	0.90 (0.60-1.35)	0.89 (0.59-1.34)
3-4 times/wk	131	728,221	0.92 (0.64-1.32)	1.00 (0.69-1.44)	1.00 (0.69-1.46)
≥5 times/wk	256	1,468,137	0.89 (0.63-1.26)	0.96 (0.67-1.36)	0.98 (0.69-1.39)
P for trend			0.85	0.99	0.77

*Multivariate models are adjusted for age at baseline, age squared, history of digital rectal exam during the past 3 y (none, once, more than once), history of PSA exam during the past 3 y (none, once, more than once), BMI at baseline (<25, 25-29.9, 30.0-34.9, 35.0-39.9, 40+), BMI at age 18 (<25, 25-29.9, 30.0-34.9, 35.0-39.9, 40+), waist circumference (<35 inches, 35-38, 39-41, 42-44, 44+), history of diabetes (yes/no), highest level of education (did not complete high school, completed high school, some college, completed college and/or graduate school), marital status (married, divorced, separated, widowed, unmarried), smoking history (current smoker, former smoker, nonsmoker), family history of prostate cancer (yes/no), multivitamin use (yes/no), supplemental zinc use (yes/no), alcohol intake (quintiles), and quintiles of energy-adjusted intakes of red meat, processed meats, α-linolenic acid, γ-tocopherol, lycopene, fish, calcium (from the combination of food and supplements), and vitamin D (from the combination of food and supplements).

†Mutually adjusted for exercise at baseline and activity during adolescence in addition to the covariates included in the multivariate models.

‡For fatal prostate cancers, we also examined alternative models with a reduced set of covariates: age at baseline, history of digital rectal exam during the past 3 y, history of PSA exam during the past 3 y, BMI at baseline, BMI at age 18, smoking history, family history of prostate cancer, and intakes of γ-tocopherol and calcium. There were no substantial departures in the estimated β-coefficients (all changes less than 10%) or in the tests for trend (no models crossed the threshold of statistical significance).

Table 3. Multivariate RRs and 95% CIs for prostate cancer in relation to level of physical activity according to age at diagnosis

	Total		Advanced		Fatal*	
	No. cases	RR (95% CI)	No. cases	RR (95% CI)	No. cases	RR (95% CI)
Age at diagnosis <65						
Exercise at baseline						
Never/rarely	705	1.00 (Reference)	96	1.00 (Reference)	24	1.00 (Reference)
1-3 times/mo	747	1.01 (0.91-1.12)	111	1.13 (0.86-1.49)	24	1.13 (0.64-2.02)
1-2 times/wk	1,177	0.97 (0.88-1.07)	150	0.94 (0.72-1.21)	29	0.88 (0.50-1.53)
3-4 times/wk	1,409	1.00 (0.91-1.09)	186	1.01 (0.78-1.30)	27	0.67 (0.38-1.19)
≥5 times/wk	1,031	1.00 (0.91-1.10)	144	1.07 (0.82-1.40)	20	0.65 (0.35-1.21)
P for trend		0.91		0.76		0.04
Activity during adolescence						
Never/rarely	327	1.00 (Reference)	44	1.00 (Reference)	7	1.00 (Reference)
1-3 times/mo	281	0.96 (0.82-1.13)	35	0.88 (0.57-1.38)	8	1.33 (0.48-3.68)
1-2 times/wk	732	1.03 (0.90-1.17)	109	1.13 (0.80-1.61)	18	1.36 (0.56-3.28)
3-4 times/wk	1,274	0.97 (0.86-1.10)	172	0.96 (0.69-1.34)	34	1.37 (0.60-3.14)
≥5 times/wk	2,455	0.91 (0.81-1.02)	327	0.87 (0.63-1.19)	57	1.12 (0.50-2.50)
P for trend		0.003		0.07		0.62
Age at diagnosis ≥65						
Exercise at baseline						
Never/rarely	1,782	1.00 (Reference)	165	1.00 (Reference)	66	1.00 (Reference)
1-3 times/mo	1,484	1.00 (0.93-1.07)	161	1.18 (0.95-1.46)	55	1.14 (0.79-1.63)
1-2 times/wk	2,692	1.01 (0.95-1.07)	250	1.03 (0.84-1.26)	83	1.02 (0.74-1.42)
3-4 times/wk	3,765	0.97 (0.91-1.03)	365	1.06 (0.88-1.28)	102	0.93 (0.67-1.28)
≥5 times/wk	3,080	1.02 (0.96-1.09)	314	1.18 (0.98-1.43)	83	0.99 (0.71-1.39)
P for trend		0.67		0.20		0.52
Activity during adolescence						
Never/rarely	804	1.00 (Reference)	79	1.00 (Reference)	30	1.00 (Reference)
1-3 times/mo	640	1.02 (0.92-1.14)	60	0.97 (0.70-1.36)	19	0.86 (0.48-1.53)
1-2 times/wk	1,693	1.02 (0.94-1.11)	168	1.04 (0.79-1.36)	44	0.79 (0.49-1.25)
3-4 times/wk	3,183	0.99 (0.92-1.07)	318	1.02 (0.80-1.31)	97	0.90 (0.59-1.36)
≥5 times/wk	6,483	1.00 (0.92-1.07)	630	0.99 (0.78-1.25)	199	0.91 (0.62-1.35)
P for trend		0.44		0.68		0.76

NOTE: Multivariate models are adjusted for covariates indicated in Table 2.

*For fatal prostate cancers, we also examined alternative models with a reduced set of covariates, as indicated in Table 2. There were no substantial departures in the estimated β-coefficients (all changes less than 10%) or in the tests for trend (no models crossed the threshold of statistical significance).

Results

During up to 8.2 years of follow-up, we ascertained 17,872 incident cases of prostate cancer, including 1,942 cases of aggressive and 513 cases of fatal prostate cancer. At study baseline, approximately half of men (49.6%) engaged in at least 20 min of vigorous exercise three or more times per week, and thus, our study members were more physically active than men of similar age in the general population in 1996 (15). Approximately three quarters of men (74.9%) had engaged in exercise three or more days per week during adolescence. Participants who engaged in high levels of physical activity were more likely to have had a family history of prostate cancer, to have had one or more rectal examinations or PSA screenings during the past three years, to have attained a college or graduate level education, and to report a high lycopene intake than participants who never or rarely engaged in physical activity (Table 1). Men who exercised at baseline were also lighter [had a lower body mass index (BMI)] and were less likely to be current smokers, to eat red meat, and to have a history of diabetes than men who did not exercise at baseline. The correlation between exercise at baseline and during adolescence was 0.19.

Men who exercised five or more times per week (frequent exercise) were not at decreased risk of total prostate cancer in multivariate analyses (multivariate RR, 1.01; 95% CI, 0.96-1.07; $P_{trend} = 0.78$; Table 2) relative to men who never or rarely exercised (infrequent exercise). Men who exercised during adolescence had a slight but statistically significant trend toward reduced risk of total prostate cancer relative to men who never or rarely exercised during adolescence (RR, 0.97; 95% CI, 0.91-1.03; $P_{trend} = 0.03$). Results were similar regardless of whether models were adjusted for potential confounding factors.

Physical activity, defined either as exercise at baseline or exercise during adolescence, was not associated with risk of advanced or fatal prostate cancers. In analyses of exercise at baseline, the multivariate RRs of frequent versus infrequent exercise were 1.14 (95% CI, 0.97-1.33; $P_{trend} = 0.25$) for advanced cases and 0.90 (95% CI, 0.67-1.20; $P_{trend} = 0.12$) for fatal cases. For models of fatal prostate cancer, multivariate RRs were attenuated compared with age-adjusted RRs (age-adjusted RR of frequent versus infrequent exercise was 0.70; 95% CI, 0.53-0.93; $P_{trend} < 0.01$ compared with the multivariate RR of 0.90 reported above), suggesting potential confounding in age-adjusted models. Adjustment for smoking history and adiposity (i.e., current BMI, BMI at age 18, and waist circumference) was primarily responsible for this attenuation. With respect to exercise during adolescence, the multivariate RRs of frequent versus infrequent exercise were 0.95 (95% CI, 0.78-1.14; $P_{trend} = 0.18$) for advanced cases and 0.96 (95% CI, 0.67-1.36; $P_{trend} = 0.99$) for fatal cases.

To address the hypothesis that an inverse relation between physical activity and prostate cancer may be restricted to older men, we investigated the physical activity and prostate cancer relation according to whether the cancer was diagnosed relatively early (i.e., before age 65) or late (after age 65). Contrary to our hypothesis, we found that physical activity was unrelated to risk of total, advanced, or fatal prostate cancer after age 65. However, exercise at baseline was associated with decreased risk of prostate cancer mortality before age 65 (P_{trend} = 0.04; Table 3). In addition, exercise during adolescence was associated with decreased risk of total prostate cancer before age 65 (P_{trend} < 0.01).

We also hypothesized that the physical activity and prostate cancer relation may be most evident among men without recent prostate cancer screening. However, among men who had not undergone a PSA screening during the past three years, physical activity had no relation with total, advanced, or fatal prostate cancer (Table 4). On the other hand, among men who had undergone a PSA test during the past three years, exercise at baseline was associated with a reduced risk of prostate cancer mortality (P_{trend} = 0.05) and exercise during adolescence was associated with reduced risk of advanced prostate cancer (P_{trend} = 0.01).

Physical activity also had no evident relation to prostate cancer subtypes as defined by combinations of stage and grade (Table 5). For example, frequent exercisers and infrequent exercisers had nearly identical risks of localized low-grade prostate cancers (multivariate RR, 1.02; 95% CI, 0.96-1.08), localized high-grade prostate cancers (multivariate RR, 1.01; 95% CI, 0.87-1.17), and advanced low-grade prostate cancers (multivariate RR, 1.09; 95% CI, 0.88-1.36). Frequent exercisers had a suggestively elevated risk of advanced high-grade disease (multivariate RR, 1.26; 95% CI, 0.99-1.62), although there was no consistent dose-response relation (P_{trend} = 0.34), suggesting that this is a chance finding. Physical activity during adolescence was similarly unrelated to each prostate cancer subtype. In a separate analysis, we redefined low-grade cases as grade 1 cases but this did not affect the estimated association between physical activity and low-grade prostate cancers.

We also investigated the relation of physical activity to low-grade prostate cancers and high-grade prostate cancers without cross-classification by stage of disease. Conforming closely to our findings for total prostate cancer, we observed no relation between exercise at baseline and low-grade prostate cancer (P_{trend} = 0.56) and a slight but statistically significant association between exercise during adolescence and reduced risk of low-grade prostate cancer (for frequent versus infrequent exercise during adolescence: multivariate RR, 0.96; 95% CI, 0.90-1.03; P_{trend} = 0.04). Neither exercise

Table 4. Multivariate RRs and 95% CIs for prostate cancer in relation to level of physical activity according to history of PSA testing

	Total		Advanced		Fatal*	
	No. cases	RR (95% CI)	No. cases	RR (95% CI)	No. cases	RR (95% CI)
PSA test in the past 3 y						
Exercise at baseline						
Never/rarely	1,019	1.00 (Reference)	95	1.00 (Reference)	28	1.00 (Reference)
1-3 times/mo	987	0.97 (0.89-1.06)	115	1.20 (0.91-1.58)	26	1.08 (0.63-1.86)
1-2 times/wk	1,802	0.97 (0.89-1.04)	163	0.94 (0.73-1.21)	44	1.07 (0.66-1.73)
3-4 times/wk	2,531	0.91 (0.85-0.98)	257	1.03 (0.81-1.31)	57	0.97 (0.61-1.54)
≥5 times/wk	2,064	0.97 (0.90-1.05)	193	1.00 (0.78-1.30)	30	0.66 (0.38-1.12)
P for trend		0.35		0.69		0.05
Activity during adolescence						
Never/rarely	490	1.00 (Reference)	48	1.00 (Reference)	12	1.00 (Reference)
1-3 times/mo	437	1.08 (0.95-1.23)	41	1.01 (0.66-1.53)	13	1.39 (0.63-3.05)
1-2 times/wk	1,137	1.05 (0.94-1.17)	144	1.35 (0.97-1.87)	26	1.06 (0.53-2.11)
3-4 times/wk	2,132	1.02 (0.93-1.13)	205	1.00 (0.73-1.38)	51	1.08 (0.57-2.04)
≥5 times/wk	4,207	1.02 (0.93-1.13)	385	0.93 (0.69-1.26)	83	0.88 (0.48-1.62)
P for trend		0.56		0.01		0.17
No PSA test in the past 3 y						
Exercise at baseline						
Never/rarely	282	1.00 (Reference)	38	1.00 (Reference)	16	1.00 (Reference)
1-3 times/mo	249	1.05 (0.89-1.25)	34	1.09 (0.68-1.74)	8	0.65 (0.27-1.53)
1-2 times/wk	369	0.96 (0.82-1.13)	52	1.06 (0.69-1.63)	20	1.14 (0.58-2.24)
3-4 times/wk	448	0.98 (0.84-1.15)	56	1.00 (0.65-1.52)	21	1.02 (0.52-2.01)
≥5 times/wk	349	0.95 (0.81-1.12)	61	1.37 (0.90-2.08)	19	1.18 (0.59-2.37)
P for trend		0.40		0.19		0.41
Activity during adolescence						
Never/rarely	120	1.00 (Reference)	11	1.00 (Reference)	7	1.00 (Reference)
1-3 times/mo	91	0.95 (0.73-1.25)	12	1.39 (0.61-3.17)	4	0.76 (0.22-2.62)
1-2 times/wk	238	1.06 (0.85-1.32)	32	1.57 (0.79-3.13)	9	0.77 (0.28-2.10)
3-4 times/wk	425	0.98 (0.80-1.20)	64	1.67 (0.88-3.19)	16	0.66 (0.27-1.64)
≥5 times/wk	823	0.94 (0.77-1.14)	122	1.58 (0.85-2.96)	48	1.00 (0.44-2.26)
P for trend		0.20		0.36		0.46

NOTE: Multivariate models are adjusted for covariates indicated in Table 2. Analysis is limited to those participants who responded to the second questionnaire (~60% of cohort).

*For fatal prostate cancers, we also examined alternative models with a reduced set of covariates, as indicated in Table 2. There were no substantial departures in the estimated β-coefficients (all changes less than 10%) or in the tests for trend (no models crossed the threshold of statistical significance).

Table 5. Multivariate RRs and 95% CIs for prostate cancer in relation to level of physical activity according to combinations of stage and grade of cancer

	Localized, grade 1 or 2		Localized, grade 3 or 4		Advanced, grade 1 or 2		Advanced, grade 3 or 4	
	No. cases	RR (95% CI)	No. cases	RR (95% CI)	No. cases	RR (95% CI)	No. cases	RR (95% CI)
Exercise at baseline								
Never/rarely	1,731	1.00 (Reference)	309	1.00 (Reference)	138	1.00 (Reference)	102	1.00 (Reference)
1-3 times/mo	1,549	0.99 (0.92-1.06)	269	1.01 (0.85-1.19)	133	1.02 (0.80-1.30)	119	1.34 (1.03-1.76)
1-2 times/wk	2,807	1.02 (0.96-1.08)	430	0.93 (0.80-1.08)	227	1.01 (0.81-1.25)	146	0.97 (0.75-1.25)
3-4 times/wk	3,693	0.97 (0.92-1.03)	606	0.96 (0.83-1.10)	332	1.12 (0.92-1.38)	196	0.99 (0.77-1.26)
≥5 times/wk	2,936	1.02 (0.96-1.08)	488	1.01 (0.87-1.17)	243	1.09 (0.88-1.36)	191	1.26 (0.99-1.62)
P for trend		0.84		0.77		0.22		0.34
Activity during adolescence								
Never/rarely	804	1.00 (Reference)	139	1.00 (Reference)	66	1.00 (Reference)	46	1.00 (Reference)
1-3 times/mo	672	1.03 (0.93-1.14)	112	1.02 (0.79-1.31)	44	0.79 (0.54-1.16)	42	1.15 (0.75-1.74)
1-2 times/wk	1,710	1.00 (0.92-1.09)	289	1.02 (0.83-1.25)	150	1.04 (0.78-1.39)	107	1.16 (0.82-1.65)
3-4 times/wk	3,158	0.97 (0.90-1.05)	514	0.96 (0.79-1.15)	280	1.02 (0.78-1.33)	186	1.07 (0.77-1.48)
≥5 times/wk	6,372	0.97 (0.90-1.04)	1,048	0.95 (0.80-1.14)	533	0.93 (0.72-1.21)	373	1.04 (0.76-1.42)
P for trend		0.054		0.29		0.55		0.49

NOTE: Multivariate models are adjusted for covariates indicated in Table 2. For 1,227 cases, grade information was not available.

at baseline (P_{trend} = 0.45) nor exercise during adolescence (P_{trend} = 0.21) was related to high-grade prostate cancers.

The relationship of physical activity to prostate cancer did not vary according to BMI, history of diabetes, or family history of prostate cancer (all $P_{interaction} > 0.05$).

Discussion

In this large prospective study of men ages 50 to 71 years at entry, we found that physical activity was not related to prostate cancer risk. Men who exercised frequently at baseline had a risk of prostate cancer that was virtually identical to that of infrequent exercisers. Men who exercised frequently during adolescence had a statistically significant but modest 3% reduced risk of total prostate cancer. Moreover, contrary to our hypothesis, physical activity was not associated with advanced or fatal prostate cancers, including among men whose cancers were diagnosed after age 65 and men without a recent PSA screening. Physical activity was also unrelated to prostate cancer subtypes as defined by combinations of stage and grade.

Previous studies have not indicated a relationship between physical activity and prostate cancer among men with recent PSA screening (2) or between physical activity and prostate cases diagnosed before age 65 (2, 8). Nevertheless, in our study, increasing frequency of exercise was associated with reduced risk of death from prostate cancer before age 65. In addition, among men who had undergone a PSA test during the past three years, increasing frequency of exercise was related to reduced risk of mortality from prostate cancer. However, these specific subgroup findings did not correspond to our prior hypotheses and could have occurred as a consequence of multiple statistical tests. Thus, these subgroup findings should be treated with caution.

The biological effects of physical activity, including reduced levels of insulin (16, 17), androgens (17), and other growth factors, have led to investigations of a possible link with prostate cancer. Insulin has mitogenic and antiapoptotic activity and may exert these properties directly on prostate epithelial cells (18). In addition, hyperinsulinemia may affect prostate cancer risk by increasing levels of free (bioactive) insulin-like growth factor-I or testosterone (19). Although epidemiologic studies typically find no relation between serum androgens and prostate cancer (20), androgens are known to induce prostate cancer in rodents (21, 22), and androgen ablation reduces tumor growth (23). Furthermore, the use of finasteride, an androgen inhibitor, was found to reduce risk of prostate cancer in humans in a randomized clinical trial (24). By reducing levels of insulin and/or androgens, physical activity may plausibly reduce prostate cancer risk. Physical activity also enhances immune function and antioxidant defense mechanisms, which could potentially reduce prostate cancer risk (25).

Nevertheless, epidemiologic studies have primarily found no relationship between physical activity and prostate cancer, with reduced risk evident in only 14 of 42 available studies on this subject (1, 2, 6, 8, 26-33). Predominantly null results were found regardless of whether considering occupational or leisure time activity (1). Physical activity during adolescence has also not been consistently associated with prostate cancer risk (2, 4, 32, 34), although one study reported a borderline statistically significant inverse association (34). Thus, existing data do not strongly support an association between physical activity and prostate cancer.

More recently, epidemiologic studies have focused on clinically advanced prostate cancers (2, 6, 8, 31, 33, 35, 36), with several (6, 8, 31, 35) of these studies reporting reduced risk of advanced and fatal prostate cancer among physically active men. If confirmed, this would be an important finding as it suggests that physical activity may be a useful treatment modality to slow prostate cancer progression or that physical activity may reduce the risk of a clinically aggressive disease. One large early study based on U.S. census occupational codes indicated that high versus low physical activity professions were associated with a 16% decreased risk of fatal prostate cancer (35). However, of the three remaining studies that reported an inverse relation between physical activity and advanced or fatal prostate cancer, one study observed an association that was of only borderline statistical significance (P_{trend} = 0.06; ref. 6),

another study based its conclusions on only those men diagnosed after age 65 (8), and the third study was of modest size (266 advanced cases; ref. 31). In addition, several investigations have failed to find an association between physical activity and advanced or fatal prostate cancers (2, 33, 36). Our study was also unable to confirm an association between physical activity and advanced or fatal prostate cancers. Taken together, the preponderance of epidemiologic evidence suggests that the association between physical activity and advanced and fatal prostate cancers is either of modest size or null.

Previous investigations have speculated that screening bias may explain the lack of an association between physical activity and prostate cancer. In one previous study (2), restricting analysis to men without recent PSA screening resulted in an inverse association between physical activity and incident prostate cancer. In our study, physical activity was unrelated to prostate cancer among men without a recent PSA screen, including in analyses of advanced or fatal cases. Our data suggest that screening bias is an unlikely explanation for the null association observed between physical activity and prostate cancer. However, we were not able to fully address detection bias, which may occur if physically active men are more likely to be biopsied than inactive men. In the current health care setting, many men, sometimes 50% or more, who test positive in a PSA screen are not biopsied, with the likelihood depending in part on individual characteristics (37). The association of physical activity with the likelihood of biopsy among men who test positive in a PSA screen is currently unknown.

The strengths of our study include its prospective design and extensive available data on potential confounding factors. The large sample of men provided ample statistical power to analyze aggressive cases and to examine whether the physical activity and prostate cancer relation varied by age at diagnosis and history of PSA screening.

The primary limitation of our study is related to the assessment of physical activity. Physical activity in our study was self-reported rather than objectively assessed, captured only those activities of a vigorous intensity, and did not include the duration of physical activity bouts. Therefore, our measure of physical activity includes some misclassification of the relative physical activity levels of study participants, which may cause attenuation of the RR estimates. In addition, it is possible that only highly vigorous physical activity (e.g., running, swimming, and calisthenics) is related to reduced prostate cancer risk. In Giovannucci et al. (8), the authors examined primarily highly vigorous physical activity and found an association with reduced prostate cancer risk among older men. We were not able to examine separately vigorous and highly vigorous physical activity. Also, because members of our study were at least $\geq$50 years of age at baseline, our inquiry into activity during adolescence required participants to recall activity from a period approximately 30 to 40 years in the past. Such distant recall may have resulted in an imprecise assessment and could result in error in the estimation of RRs. History of PSA screening was ascertained by self-report, potentially affecting the precision of our adjustment for screening practices. However, our findings did not vary substantially according to history of PSA screening; thus, it is unlikely that error in the assessment of PSA screening explains our null findings. Gleason grade was not available for prostate cancer cases in this cohort; thus we cannot directly compare our grade-specific results with previously published work (38). However, the cancer grade data available from the cancer registries would likely correlate with the Gleason grade and would be expected to yield similar findings. As evidenced by the high proportion of men who engage in vigorous physical activity, participants in the AARP cohort population may be healthier than individuals in the general population. However, to the extent that our findings indicate a true biological association or lack thereof, our findings should be applicable to men from other populations.

In summary, we found that physical activity was not associated with risk of total prostate cancer, or aggressive or fatal prostate cancer. Our findings largely agree with the majority of previous studies on this topic, although our results for aggressive and fatal prostate cancer conflict with those of some previous studies. Although our data suggest that physical activity is unrelated to risk of prostate cancer, it is important to evaluate whether differences in the likelihood of screening practices, including likelihood of prostate biopsy between physically active and inactive men, contribute to these null findings.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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