A Prospective Study of Physical Activity and Incident and Fatal Prostate Cancer

Edward L. Giovannucci, MD, ScD; Yan Liu, MS; Michael F. Leitzmann, MD; Meir J. Stampfer, MD, DrPH; Walter C. Willett, MD, DrPH

Background: Whether physical activity has benefits against prostate cancer incidence or progression is unclear. Therefore, we assessed physical activity in relation to prostate cancer incidence, mortality, and Gleason histologic grade.

Methods: We used data from the Health Professionals Follow-up Study, a prospective cohort study, to determine the number of cases of incident, advanced (seminal vesicle invasion, metastasis, or fatal), fatal, and high-grade prostate cancer in a cohort of 47 620 US male health professionals, followed up from February 1, 1986, to January 31, 2000.

Results: During 14 years of follow-up, we documented 2892 new cases of prostate cancer, including 482 advanced cases (280 of which were fatal). For total prostate cancer, no association was observed for total, vigorous, and nonvigorous physical activity. In men 65 years or older, we observed a lower risk in the highest category of vigorous activity for advanced (multivariable relative risk, 0.33; 95% confidence interval, 0.17-0.62, for more than 29 vs 0 metabolic equivalent hours) and for fatal (relative risk, 0.26; 95% confidence interval, 0.11-0.66) prostate cancer. No associations were observed in younger men. Differential screening by prostate-specific antigen or a reduction in physical activity due to undiagnosed prostate cancer did not appear to account for the results. Among cases, men with high levels of physical activity were less likely to be diagnosed with poorly differentiated cancers (Gleason grade ≥7).

Conclusion: Although the mechanisms are not yet understood, these findings suggest that regular vigorous activity could slow the progression of prostate cancer and might be recommended to reduce mortality from prostate cancer, particularly given the many other documented benefits of exercise.

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Author Affiliations:
Departments of Nutrition (Drs Giovannucci, Stampfer, and Willett and Ms Liu) and Epidemiology (Drs Giovannucci, Stampfer, and Willett), Harvard School of Public Health, and Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital (Drs Giovannucci, Stampfer, and Willett), Boston, Mass; and Nutritional Epidemiology Branch, National Cancer Institute, Rockville, Md (Dr Leitzmann).
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Some studies[1-19] have suggested that more physically active men may have a lower risk of prostate cancer, but the associations have tended to be moderate, not always statistically significant, and sometimes only evident among older subgroups[6,9,11,16] or for substantially high, but not moderate, levels of activity.[9,16,18] However, many of the studies were not designed to examine physical activity in detail and could not adequately consider the amount, timing, and intensity of each type of activity.[20] In addition, prostate cancers are heterogeneous, and evidence suggests differences in etiology by different groups of men (eg, younger or older subgroups) or by type of end point (eg, high vs low grade, incident vs fatal). Moreover, the diagnosis of prostate cancer is currently largely influenced by the use of prostate-specific antigen (PSA) for screening, which could bias results.

Our group previously examined physical activity relative to risk of prostate cancer in the Health Professionals Follow-up Study, a prospective cohort study of US male health professionals who were followed up from February 1, 1986, to January 31, 1994.[16] In that analysis, which was based on 1362 total incident cases of prostate cancer, we found no relationship for total, vigorous, and nonvigorous physical activity. However, for metastatic prostate cancer we observed a statistically significant 54% lower risk in the highest category of vigorous activity only, which was due to a 69% risk reduction in older men (those ≥67.5 years of age) but not younger men. Now, with follow-up to 2000 and with 2982 incident cases in this cohort, we assessed the specific relationship between vigorous activity and risk of advanced prostate cancer in older men. In addition, we examined whether any benefit of physical activity occurs relatively soon or requires a long time lag, assessed

fatal prostate cancer and histologic tumor grade as additional end points, and accounted for PSA screening frequency.

METHODS

STUDY POPULATION

In 1986, 51 529 US male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians, aged 40 to 75 years, completed and returned a mailed questionnaire to initiate the Health Professionals Follow-up Study cohort. Through this 1986 baseline questionnaire, we elicited information on age, marital status, height and weight, ancestry, medications, smoking history, disease history, physical activity, and diet. Every 2 years, we mailed follow-up questionnaires to collect information on new medical diagnoses and lifestyle factors and to update data on physical activities. We updated dietary information through food frequency questionnaires that were administered every 4 years. Using reports from family members, the US Postal Service, and the National Death Index, we ascertained more than 98% of deaths.[21] Our follow-up response rate was 96%. This study was approved by the Human Subjects Committee of the Harvard School of Public Health, Boston, Mass.

IDENTIFICATION OF CASES OF PROSTATE CANCER

When participants reported new diagnoses in response to our questionnaires, we asked them for permission to obtain hospital records and pathology reports. Study investigators used the staging information received from any procedures or tests conducted during the initial diagnosis and treatment, including prostatectomies and bone scans. From 1986 to the end of this study period, we documented 3006 newly diagnosed cases of prostate adenocarcinoma in 596 756 person-years, after excluding 68 cases of stage T1a cancer (incidental histologic cancer found in ≤5% of tissue resected) because T1a cancers are relatively innocuous and especially prone to detection bias. Of the 3006 cases, we were able to document approximately 90% with the use of medical records and pathology reports; for most of the remaining 10%, participants provided information regarding the diagnosis and subsequent treatment. Based on the pathology report, we also recorded Gleason histologic grade, which was available for 2159 cases. Fatal prostate cancer was determined by study physicians after a review of the medical records.

ASSESSMENT OF PHYSICAL ACTIVITY

On the 1986 questionnaire, we asked men to report the average time per week 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 racquetball, and calisthenics or rowing. In addition, we asked about the number of flights of stairs climbed daily and the usual walking pace. We updated our physical activity assessment every 2 years. Heavy outdoor work was added in 1988 and weight training in 1990. To generate the total physical activity score, we summed activity-specific metabolic equivalent (MET)–hours per week. A MET-hour is the metabolic equivalent of sitting at rest for 1 hour. MET-hour values were obtained from a compendium of physical activities.[22] We also generated quintiles of total MET-hours per week for vigorous or high-intensity activities (running, jogging, biking, swimming, tennis, racquetball/squash, rowing/calisthenics, heavy outdoor work, and weight training) and nonvigorous activities (flights of stairs climbed and walking). The activity assessment has been previously validated.[23] Because the men are health professionals, occupational activity is low for most of them.

STATISTICAL ANALYSIS

After excluding men with diagnosed cancer (except for nonmelanoma skin cancer) at baseline and those who did not adequately complete a dietary or physical activity questionnaire, 47 620 men formed the analytic cohort. Each man accrued follow-up time beginning on the month of return of the baseline questionnaire and ending on the month of diagnosis for prostate cancer cases, or the month of death from other causes, or January 31, 2000, for noncases. We calculated incidence rates of prostate cancer for men in a specific category of physical activity level by dividing the number of incident total, advanced, nonadvanced, or fatal prostate cancer cases by the number of person-years in that category. Advanced cases were considered those with extension to the seminal vesicle or with evidence of metastasis to the lymph nodes or distant organs at the time of diagnosis, or those whose cases were fatal by January 31, 2000. The remaining cases, including those with minimal extension into the prostatic capsule, were considered nonadvanced.

Physical activity in MET-hours per week was categorized into quintiles. We considered separately total, vigorous, and nonvigorous physical activity. Because approximately half the cohort members reported no vigorous activity, those reporting no vigorous activity were considered in 1 category, and we then formed quartiles for those with any level of vigorous activity to form 5 total categories. To better assess timing of exposure to risk of prostate cancer, we examined baseline data (1986) without updating, with simple updating using the most recent assessment, and with cumulative updating, which uses the 1986 activity assessment to assess risk prospectively from 1986 to 1988, the average of the 1986 and 1988 assessments to assess risk prospectively from 1988 to 1990, and so forth. In addition, we considered 2-year and 4-year time lags (ie, updating information only up to 2 or 4 years, respectively), to the period of risk. For fatal prostate cancer, we updated data only until the time of the diagnosis.

We computed relative risks (RRs), which we defined as the incidence rate of disease in 1 category (eg, high level of vigorous activity) divided by the incidence rate in a specified reference category (eg, low activity level). We used the Mantel-Haenszel summary estimator to adjust for age (across 5-year categories). We used Cox proportional hazards modeling to control for multiple variables simultaneously and to compute 95% confidence intervals (CIs). Age (in 1-year intervals) and study period (in 2-year intervals) were controlled for as stratification variables in the Cox model. We tested for departures from the proportional hazards assumption by using likelihood tests. The following covariates were included in the models: body mass index at age 21 years, height, cigarette pack-years in the previous 10 years, family history of prostate cancer, history of diabetes mellitus, race, and intakes of total calories, red meat, fish, α-linolenic acid, calcium, zinc supplements, and tomato sauce.[24-29] When vigorous and nonvigorous activities were analyzed, they were mutually adjusted. We updated modifiable variables. We tested for trend across categories, controlling for multiple covariables by modeling the median values of categories of physical activity as a continuous variable in the multivariable model. We conducted tests for multiplicative interaction (Wald test) between age and physical activity by modeling si-

Table 1. Age-Standardized Characteristics of HPFS Men at 1986 Baseline

Characteristic	Total Activity			Vigorous Activity*		
	Q1	Q3	Q5	G1	G2	G3
Age, mean, y†	54.3	54.3	52.8	56.2	53.7	50.4
Total activity, mean, MET-h/wk	1.1	11.9	61.4	8.4	16.1	64.6
Vigorous activity, mean, MET-h/wk	0.1	5.3	41.3	0	8.0	56.0
BMI, mean	25.4	25.0	24.4	25.4	24.9	24.1
BMI at age 21 y, mean	22.9	22.9	23.2	23.0	23.0	23.1
Height, mean, cm	177.8	178.1	178.3	178.1	178.1	178.3
White, %	90.9	90.5	90.3	91.2	90.6	89.7
African American, %	1.4	0.95	0.8	1.0	1.0	0.96
Diabetes, %	4.3	3.1	2.2	3.7	2.7	2.1
Current smoker, %	14.6	9.5	6.4	13.8	8.1	4.7
Multivitamin use, %	37.1	42.2	44.5	36.3	44.8	46.7
Intake, mean‡						
Calories per day	1933	1978	2051	1980	1971	2014
Calcium, mg/d	862	893	923	866	904	942
α-Linolenic acid, g/d	1.09	1.08	1.05	1.08	1.08	1.05
Red meat, servings/d	0.68	0.61	0.54	0.69	0.58	0.48
Tomato sauce, servings/wk	0.90	0.95	1.04	0.93	0.95	1.04
Fish, servings/d	0.33	0.39	0.45	0.34	0.41	0.46

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent; Q, quintile.

*For vigorous activity, G1 indicates 0 MET-h/wk of vigorous activity; G2, second quartile of subjects with positive vigorous activity MET-hours; and G3, fourth quartile of subjects with positive vigorous activity MET-hours.

†Age is not age-standardized.

‡Red meat indicates beef, pork, or lamb as a main dish, and 1 serving equals 140 g; for tomato sauce, 1 serving equals 125 g; and for fish, 1 serving equals 112 g.

multaneously physical activity as a continuous variable, an indicator for age group (0 if <65 years; 1 if ≥65 years), and the product of age and vigorous activity (the interaction term). Using a case-case approach, we also assessed the odds ratio (OR) of being diagnosed as having a high-grade (Gleason grade ≥7) vs a low-grade (Gleason grade <7) cancer by using multivariable logistic regression. All reported *P* values are 2 sided.

RESULTS

AGE-STANDARDIZED CHARACTERISTICS ACCORDING TO PHYSICAL ACTIVITY LEVEL

Table 1 shows selected age-standardized characteristics in relation to total and vigorous physical activity. As expected, younger men tended to have more vigorous activity. In general, more physically active men had a more healthful lifestyle and diet.

TOTAL AND NONVIGOROUS PHYSICAL ACTIVITY

We examined total prostate cancer in relation to total physical activity by using the simple updated assessment (the most recent physical activity assessment) and found no association (multivariable-adjusted RR, 1.02 for the top vs bottom quintiles; 95%CI, 0.91-1.15; *P* for trend=.47), despite substantial power (approximately 600 cases per quintile). Moreover, no significant associations were observed for nonadvanced, advanced, or fatal prostate cancer. We found no evidence of a lower risk of total prostate cancer, or any subgroups of prostate cancer, associated with nonvigorous activities (data not shown). Use of baseline data (1986) without updating or cumulatively updated physical activity similarly yielded null results for total and nonvigorous activities.

VIGOROUS PHYSICAL ACTIVITY AND AGE STRATIFICATION

For vigorous physical activity in age-adjusted analyses, no appreciable association was observed with total prostate cancer (age-adjusted RR, 1.09; 95% CI, 0.97-1.23; *P* for trend=.05), and a modest positive association was noted for nonadvanced prostate cancer (age-adjusted RR, 1.21; 95% CI, 1.07-1.37; *P* for trend=.002). For advanced prostate cancer, in the Cox proportional regression analysis, there was strong evidence against the proportional hazards assumption (*P*<.001) because of strong heterogeneity by age, as was observed in a previous analysis by our group.[16] Thus, for the remaining analyses, we stratified the population into men younger than 65 years and those 65 years or older (**Table 2**). We found a decreased risk only in the older subgroup of men for advanced prostate cancer (*P*=.009, for interaction by age). The age-adjusted results (RRs across categories 1 through 5 for older men: 1.00, 0.88, 1.13, 1.03, and 0.31, respectively; *P* for trend=.001) were almost identical to the multivariable results (Table 2). For fatal prostate cancer, results were similar to those for advanced prostate cancer (*P*=.02, for interaction by age; multivariable RR for top vs bottom category, 0.26; 95% CI, 0.11-0.66). When we stratified advanced prostate cancer by study period and

Table 2. Relation Between Prostate Cancer and Vigorous Physical Activity in HPFS (1986-2000) by Age Group

Variable	MET-h/wk* 0	1-4	5-11	12-29	>29	*P* for Trend
Total prostate cancer						
Age <65 y, n	473	106	139	130	120	
RR (95% CI)†	1.00	0.95 (0.76-1.17)	1.15 (0.95-1.40)	1.03 (0.84-1.25)	1.08 (0.88-1.33)	.44
Age ≥65 y, n	1084	257	243	227	203	
RR (95% CI)†	1.00	1.06 (0.92-1.22)	0.99 (0.86-1.14)	1.08 (0.93-1.25)	1.09 (0.94-1.28)	.22
Nonadvanced prostate cancer						
Age <65 y, n	408	90	121	113	103	
RR (95% CI)†	1.00	0.94 (0.75-1.19)	1.17 (0.95-1.44)	1.02 (0.83-1.27)	1.06 (0.85-1.33)	.58
Age ≥65 y, n	874	217	192	189	193	
RR (95% CI)†	1.00	1.10 (0.95-1.28)	0.95 (0.81-1.12)	1.08 (0.92-1.27)	1.25 (1.06-1.46)	.009
Advanced prostate cancer‡						
Age <65 y, n	65	16	18	17	17	
RR (95% CI)†	1.00	0.98 (0.56-1.70)	1.06 (0.62-1.81)	1.02 (0.59-1.77)	1.23 (0.71-2.14)	.47
Age ≥65 y, n	210	40	51	38	10	
RR (95% CI)†	1.00	0.88 (0.63-1.25)	1.14 (0.83-1.56)	1.07 (0.75-1.52)	0.33 (0.17-0.62)	.003

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent; n, number of cases of prostate cancer; RR, relative risk.

*MET-hours of physical activity per week, updated every 2 years.

†Multivariable RR controlled for age, study period, body mass index at age 21 years, height, cigarette pack-years in the previous 10 years, family history of prostate cancer, history of diabetes mellitus, race, nonvigorous activity, and intake of total calories, red meat, fish, α-linolenic acid, calcium, zinc supplements, and tomato sauce.

‡A total of 280 of these cases were fatal.

Table 3. Relation Between Vigorous Physical Activity and Advanced Prostate Cancer in the HPFS (1986-2000)*

Study Period	MET-h/wk† 0	1-4	5-11	12-29	>29	*P* for Trend
1986 to January 1994 follow-up						
Age <65 y	1.00	1.22 (0.65-2.30)	1.16 (0.61-2.19)	1.28 (0.67-2.43)	1.19 (0.58-2.42)	.61
Age ≥65 y	1.00	0.83 (0.54-1.25)	1.00 (0.68-1.47)	1.05 (0.68-1.61)	0.35 (0.16-0.74)	.02
February 1994 to 2000 follow-up						
Age <65 y	1.00	0.53 (0.16-1.79)	0.85 (0.32-2.30)	0.62 (0.21-1.83)	1.32 (0.54-3.21)	.52
Age ≥65 y	1.00	1.00 (0.54-1.83)	1.46 (0.85-2.51)	1.07 (0.58-1.98)	0.27 (0.08-0.87)	.04

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent; RR, relative risk

*Analyses are stratified by study period and age group. Data are given as multivariable RR (95% CI), unless otherwise indicated. Multivariable RRs are controlled for age, study period, body mass index at age 21 years, height, cigarette pack-years in the previous 10 years, family history of prostate cancer, history of diabetes mellitus, race, nonvigorous activity, and intake of total calories, red meat, fish, α-linolenic acid, calcium, zinc supplements, and tomato sauce.

†MET-hours of physical activity per week, updated every 2 years.

Table 4. Relation Between Vigorous Physical Activity and Advanced Prostate Cancer for Men 65 Years or Older in the HPFS Accounting for Various Time Lags

Assessment	Q5 vs Q1, RR (95% CI)*	*P* for Trend
Simple updating	0.32 (0.17-0.61)	.002
Cumulative updating	0.62 (0.38-1.00)	.02
Cumulative updating, 2-y lag	0.65 (0.42-1.02)	.05
Cumulative updating, 4-y lag	0.47 (0.27-0.80)	.007

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-up Study; Q, quintile; RR, relative risk.

*Multivariable RR (see first footnote to Table 3) and 95% CI for high vs low category of vigorous physical activity.

age, a marked reduced risk in older men only was observed in both periods (**Table 3**).

TIME-LAGGED ANALYSES

Decreased risks of advanced prostate cancer for the high vs low category of physical activity for men 65 years or older were observed for simple updating, for cumulative updating (activity averaged for all questionnaires up to the period of risk), and for cumulative updating but considering 2-year or 4-year time lags (**Table 4**). Similar patterns were observed for fatal prostate cancer (data not shown). Furthermore, to determine whether morbidity from undiagnosed prostate cancer may have caused men to reduce their activity level, we examined the influence of recent changes in physical activity reported on the 2 questionnaires preceding the period of risk. Among men 65 years or older, relative to those who were consistently low in vigorous physical activity (ie, not in the top category), the multivariable RRs for advanced pros-

tate cancer were as follows: for men who had reduced their physical activity from a high to a low category, 1.53 (95% CI, 0.95-2.44); for men who had increased their physical activity from a low to a high category, 0.37 (95% CI, 0.15-0.90); and for men consistently in a high category, 0.32 (95% CI, 0.13-0.78). Thus, although a modest, nonsignificant increased risk of advanced prostate cancer was observed for men who reduced their activity level from the top category, the overall reduced risk was not caused solely by a reduction in vigorous activity level shortly before the diagnosis.

VIGOROUS PHYSICAL ACTIVITY AND GLEASON GRADE

For 2159 cases with data on the Gleason grade, 849 (39%) were Gleason grade 7 or higher (high-grade). In a case-only analysis, the multivariable OR of high-grade vs low-grade prostate cancer was significantly reduced for men in the top quintile of vigorous physical activity (OR, 0.64; 95% CI, 0.47-0.87; $P=.004$) relative to the lowest category, especially in men 65 years or older (OR, 0.53; 95% CI, 0.36-0.79; $P=.002$). To better distinguish high-grade from advanced-stage prostate cancer, we further limited the analysis to the 1871 nonadvanced cancers at diagnosis only (634 of these were high-grade cases). In this group, we also found that the multivariable OR was significantly reduced in men in the top quintile of vigorous physical activity (OR, 0.70; 95% CI, 0.51-0.97; $P=.03$) relative to the lowest category, particularly in men 65 years or older (OR, 0.64; 95% CI, 0.43-0.97; $P=.04$).

VIGOROUS ACTIVITY AND FREQUENCY OF PSA EXAMINATION

The respective percentages of men 65 years or older who reported at least 1 PSA examination by 2000 according to level of vigorous physical activity in 1992, from lowest to highest category, were 86%, 89%, 91%, 92%, and 92%. The respective percentages of men who reported having had a PSA test on at least 3 of the 4 biennial questionnaires from 1994 to 2000, across levels of vigorous activity (lowest to highest), were 73%, 71%, 75%, 76%, and 74%. Thus, the frequency of PSA tests did not differ appreciably across levels of vigorous activity.

COMMENT

In this cohort of male health professionals, we did not observe a monotonic association between total or nonvigorous nonoccupational physical activity and risk of total or advanced prostate cancer. However, as observed in an analysis based on less follow-up,[16] men who were 65 years or older had an approximately 70% reduction in advanced prostate cancer if they achieved 30 MET-h/wk, which is roughly equivalent to at least 3 hours of vigorous activity weekly. In addition, we now observe a similar reduction for fatal prostate cancer.

Several analyses indicate that our results were highly unlikely to have resulted from chance. First, statistically significant findings were observed initially in follow-up to 1994, and results were replicated with independent follow-up to 2000. Second, the inverse association was apparent for advanced prostate cancer at diagnosis, for fatal prostate cancer, and for high-grade prostate cancer, even among men with nonadvanced prostate cancer. Third, findings were observed when using the baseline questionnaire data, cumulative updated assessments, or simple updated assessments, and with various time lags between exposure and time of diagnosis.

Although the possibility of confounding cannot be entirely ruled out in an observational study, several facts argue against it. We controlled for numerous factors, and the age-adjusted and fully multivariable analyses provided similar results. The risk reduction was 3- to 4-fold, and a putative uncontrolled confounding factor would have to be strongly related to both high levels of physical activity and a substantially reduced risk of advanced prostate cancer.

Because the inverse association was observed for advanced prostate cancer and prostate cancer mortality but not nonadvanced prostate cancer, early diagnosis by PSA screening and treatment could possibly have reduced mortality among physically active men. However, PSA screening was common throughout the cohort and did not vary appreciably by level of vigorous physical activity. Furthermore, we observed a 3- to 4-fold reduction in risk in older men from 1986 to 1994,[16] before any effects of widespread PSA screening on metastasis and mortality could have taken effect.

Another consideration is that the lower mortality was caused by a reduction in physical activity among men who were ill with undiagnosed metastatic prostate cancer. However, we found that most of the reduction in risk was due to men who were consistently high in activity or who had moved from a lower to the highest category rather than due to an excess risk from men who had recently reduced their activity level. Moreover, this potential bias could not explain the higher likelihood of high-grade vs low-grade prostate cancer in those diagnosed as having organ-confined cancers.

The consistent finding that high levels of physical activity reduce risk in men 65 years or older may suggest variant etiologies for early-onset and later-onset cancers. Our group has previously found in this cohort that higher body mass index and waist circumference[25] are associated with a lower risk of prostate cancer in younger men but not older men. These findings led us to hypothesize that in younger men, androgen stimulation may be a more important factor because obesity is associated with lower circulating testosterone and with higher estrogen concentrations.[30-32] This apparent paradoxical "benefit" of obesity in younger men may explain the lack of an association with physical activity in that age group. Prostate cancers that are fatal by age 65 years tend to have a strong genetic component and may have a different etiology than those that occur in older men.

The mechanism whereby physical activity may be protective is unknown, but physical activity may influence a number of hormones hypothesized to enhance prostate cancer carcinogenesis, including insulinlike growth factor 1,[33] insulin,[34,35] leptin[36,37] and testosterone.[38,39] In one study,[40,41] an exercise and low-fat diet in-

tervention lowered circulating levels of insulinlike growth factor 1 and insulin in men, and increased levels of sex hormone–binding globulin and insulinlike growth factor binding protein 1. When used as a medium for cell culture to grow LNCaP cells, serum from the exercising men decreased proliferation by a third and increased apoptosis 4-fold.[42]

In conclusion, men 65 years or older engaging at least 3 hours of vigorous physical activity weekly had a markedly lower risk (almost 70%) of being diagnosed as having high-grade, advanced, or fatal prostate cancer. The findings were consistent over time, did not appear to be caused by bias or confounding, and are compatible with hormonal hypotheses regarding prostate cancer progression. Although the mechanisms still need to be understood, these findings suggest that vigorous activity could slow the progression of prostate cancer and might be recommended to reduce mortality from prostate cancer, particularly given the many other documented benefits of exercise.

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Correspondence: Edward L. Giovannucci, MD, ScD, Channing Laboratory, 181 Longwood Ave, Boston, MA 02115 (edward.giovannucci@channing.harvard.edu).
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