emphysema at baseline were removed from the analyses to lessen the impact that malignant or chronic disease may have had on physical activity levels at baseline. Exposure information was gathered prior to cancer diagnosis, which precluded bias ascribable to discrepant recall of physical activity level by participants with and without a diagnosis of head and neck cancer.

Due to the large size of our cohort including more than 1,200 cases of head and neck cancer, insufficient statistical power is not likely to account for the null associations observed in our study. The large number of cases facilitated a detailed exploration of the relations with physical activity across strata of major risk factors for head and neck cancer. We observed null findings within all strata, which gave us confidence that we did not miss a strong inverse association between physical activity and head and neck cancer in our analyses.

In theory, physical activity has the potential to influence head and neck carcinogenesis through its effects on immune function. The impact of physical activity on immunomodulation varies according to the level of exercise. As compared to sitting, low-intensity physical activity, such as walking increases circulating levels of immune parameters, including blood counts for neutrophils, lymphocytes, monocytes, and natural killer cells [28]. Moderate levels of exercise also enhance mucosal immune parameters, such as salivary IgA [6, 7, 9]. In contrast, vigorous levels of exercise decrease T and B cells [29] and transiently suppress natural killer cell cytotoxicity [30] and salivary IgA [8]. We observed statistically non-significant relations for head and neck cancer both with vigorous activity and with less vigorous forms of activity. Even so, the possibility of a physical activity effect on the content or composition of saliva is intriguing, because saliva continuously permeates the mucosal epithelium of the oral cavity, the pharynx and, to a lesser extent the larynx, and therefore bears potential to influence head and neck cancer risk [10].

We conclude that despite the existence of a plausible biological mechanism, physical activity is not likely to substantially impact upon total head and neck cancer risk. Since definitive conclusions cannot be drawn on the basis of findings from the limited body of currently existing data on this topic, the relation of physical activity to head and neck cancer deserves continued attention in future epidemiologic research.

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論文名	Physical activity and head and neck cancer risk						
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対象の内訳		ヒト	動物	地域	欧米	研究の種類	縦断研究
	対象	一般健常者	空白		( )		コホート研究
	性別	男女混合	( )		( )		( )
	年齢	50～71(61.9歳)	[redacted]		( )		前向きコホート
	対象数	10000以上			( )		( )
調査の方法	質問紙	( )					
アウトカム	予防	なし	なし	ガン予防	なし		( )
	維持・改善	な し	な し	な し	なし	( )	( )
図表	なし						
図表掲載箇所							
概要 (800字まで)	＜目的＞頸部ガン発症と身体活動の関係を調査すること。＜方法＞コホート名：the NIH-AARP Diet and Health Study、対象者数：487732人、追跡期間：7.2年、身体活動評価方法詳細：他のthe NIH AAPと同様に　20分以上　汗をかくような運動を週何回行ったかを調べた。身体活動の単位は回/週で、身体活動の回数に応じて参加者を5つに分類した。分位1：なし、分位2：1回／週未満、分位3：1-2回／週、分位4：3-4回／週、分位5：5回／週以上。＜結果＞フォローアップの間、1,249人の参加者が頸部ガンになった。42.0%は口腔がん、18.9%は咽頭がん、32.5%喉頭がんであった。余暇身体活動と全頸部がん発症との関係は、分位1：1、分位2：0.87(0.72-1.05)、分位3：0.84(0.7-0.99)、分位4：0.82(0.69-0.97)、分位5：0.89(0.74-1.06であった。						
結論 (200字まで)	20分の息が弾むような運動を週あたり1-2回行うことで、アメリカ人男女の頸部ガンの発症を低下させる。						
エキスパートによるコメント (200字まで)	タバコの影響が強いと言われる頸部がんを身体活動で予防できるという知見は貴重である。						

担当者　　宮地元彦

Physical Activity Recommendations and Decreased Risk of Mortality

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Background: Whether national physical activity recommendations are related to mortality benefit is incompletely understood.

Methods: We prospectively examined physical activity guidelines in relation to mortality among 252 925 women and men aged 50 to 71 years in the National Institutes of Health–American Association of Retired Persons (NIH-AARP) Diet and Health Study. Physical activity was assessed using 2 self-administered baseline questionnaires.

Results: During 1 265 347 person-years of follow-up, 7900 participants died. Compared with being inactive, achievement of activity levels that approximate the recommendations for moderate activity (at least 30 minutes on most days of the week) or vigorous exercise (at least 20 minutes 3 times per week) was associated with a 27% (relative risk [RR], 0.73; 95% confidence interval [CI], 0.68-0.78) and 32% (RR, 0.68; 95% CI, 0.64-0.73) decreased mortality risk, respectively. Physical activity reflective of meeting both recommendations was related to substantially decreased mortality risk overall (RR, 0.50; 95% CI, 0.46-0.54) and in subgroups, including smokers (RR, 0.48; 95% CI, 0.44-0.53) and nonsmokers (RR, 0.54; 95% CI, 0.45-0.64), normal weight (RR, 0.45; 95% CI, 0.39-0.52) and overweight or obese individuals (RR, 0.48; 95% CI, 0.44-0.54), and those with 2 h/d (RR, 0.53; 95% CI, 0.44-0.63) and more than 2 h/d of television or video watching (RR, 0.50; 95% CI, 0.45-0.55). Engaging in physical activity at less than recommended levels was also related to reduced mortality risk (RR, 0.81; 95% CI, 0.76-0.86).

Conclusions: Following physical activity guidelines is associated with lower risk of death. Mortality benefit may also be achieved by engaging in less than recommended activity levels.

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PHYSICAL ACTIVITY PROMOTES health and longevity,[1,2] and increasing participation in regular exercise has been a major public health goal in the United States for decades.[3] The Office of the US Surgeon General (OSG), the Centers for Disease Control and Prevention (CDC), and the American College of Sports Medicine (ACSM) all endorse a minimum of 30 minutes of moderate activity on most days of the week, an amount and intensity of activity that is feasible for most Americans.[4,5] Recent nationally representative survey data[6] indicate that more than 50% of the adult US population do not meet the lower bound of the physical activity recommendations,[4,5] a proportion that has remained essentially unchanged throughout the last decade.[7] Commonly reported barriers to activity participation include lack of time and the perceived effort of exercise.[8]

Given the potential mortality benefit from achieving the physical activity guidelines, surprisingly little is known about current physical activity recommendations as they relate to mortality. The sparse epidemiologic data available suggest a 20% to 30% decreased mortality risk for subjects expending approximately 1000 kcal/wk—the equivalent of minimal adherence to the recommendations.[9] Moreover, the specific role of activity of at least moderate intensity is poorly understood.[10-12] Several investigations found an inverse association only for vigorous activity[13-18] or noted strong inverse relations with fitness,[19-21] whereas other studies[22-28] reported that moderate activity was also sufficient to decrease mortality risk.

We examined physical activity recommendations in relation to mortality in a large prospective cohort with comprehensive physical activity data. Our study differs from most previous investigations[2,9] in quantifying the dose-response associations in a manner that facilitates an application to the current guidelines.[4,5]

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METHODS

STUDY POPULATION

The National Institutes of Health–AARP (formerly known as the American Association of Retired Persons) (NIH-AARP) Diet and Health Study was established in 1995-1996, when 566 407 AARP members 50 to 71 years old who were residing in one of 6 US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) or 2 metropolitan areas (Atlanta, Georgia, and Detroit, Michigan) responded to a baseline questionnaire requesting information on medical history, diet, and structured exercise.[29] Within 6 months of the baseline questionnaire, subjects were asked to complete a second questionnaire that collected additional exposure information, including lifestyle activity. Eligible subjects for the present study were participants who responded to both questionnaires and who were alive and had not moved out of the study area before returning the second questionnaire (n=334 905). Of these, we excluded individuals who reported a previous diagnosis of cancer (n=19 479), cardiovascular disease (n=45 621), or emphysema (n=8123) and individuals with missing information on physical activity (n=8757). After these exclusions, the analytic cohort comprised 252 925 subjects (142 828 men and 110 097 women). The study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute. Completion of the self-administered baseline questionnaire was considered to imply informed consent.

COHORT FOLLOW-UP AND END POINT ASCERTAINMENT

Cohort members were followed up by annual linkage of the cohort to the National Change of Address database maintained by the US Postal Service, through processing undeliverable mail, by using other address change update services, and directly from cohort members' notifications. For matching purposes, we have virtually complete data on first and last name, address history, sex, and date of birth. Social security numbers are available for 85% of our cohort. Follow-up for vital status is performed by annual linkage of the cohort to the Social Security Administration Death Master File.[30] Verification of vital status and cause of death is provided by searches of the National Death Index (NDI) Plus.[31] We estimate that follow-up for deaths in our cohort is more than 93% complete.[30,31] Maintenance of the cohort also involves periodic linkage to the 8 state cancer registries serving our cohort.[32] The primary end point in the present analysis was mortality from any cause. We also investigated the 2 main causes of death: mortality from cardiovascular disease (*International Classification of Diseases, Ninth Revision* [*ICD-9*] codes 390.0-448.9) and mortality from cancer (*ICD-9* codes 140.0-208.9). In further analyses, we considered mortality from stroke and from a combination of cancers considered a priori to be associated with physical activity (ie, cancers of the colon, breast, prostate, lung, and endometrium).[33]

ASSESSMENT OF PHYSICAL ACTIVITY

The baseline questionnaire inquired about structured vigorous exercise during the previous year, defined as the frequency each week spent at activities such as exercise and sports that lasted 20 minutes or more and caused either increases in breathing or heart rate or working up a sweat. There were 6 possible response options: never; rarely; 1 to 3 times per month; 1 to 2 times per week; 3 to 4 times per week; and 5 or more times per week. We used that assessment to examine the ACSM physical activity guidelines that recommend at least 20 minutes of continuous vigorous exercise 3 times per week[34] as a means of improving cardiorespiratory fitness.

The second questionnaire requested information on the average time spent each week at activities of at least moderate intensity using categories of never; rarely; weekly, but less than 1 h/wk; 1 to 3 h/wk; 4 to 7 h/wk; and more than 7 h/wk. Specific examples included brisk walking/fast dancing, walking during golf, hiking/mountain climbing, cheerleading/drill team, tennis, biking, swimming, aerobics, jogging/running, rowing, basketball/baseball, football/soccer, handball/racquetball, weight lifting, heavy gardening, and heavy housework. We used 3 hours of activity of at least moderate intensity per week as a cut point to approximate the current OSG/CDC/ACSM physical activity recommendations[4,5] that emphasize the overall health benefits of 30 minutes of activity of moderate intensity on most days of the week.

Our physical activity assessment contains important elements of the Physical Activity Scale for the Elderly (PASE), which showed an intraclass correlation coefficient of 0.84 for 2 administrations of the questionnaire mailed 3 to 7 weeks apart[35] and a correlation coefficient of 0.58 comparing activity energy expenditure as assessed by the questionnaire with that using the doubly labeled water method.[36]

STATISTICAL ANALYSIS

Cox proportional hazards regression[37] with age as the time scale was used to estimate relative risks (RRs) and 95% confidence intervals (CIs) of mortality. Follow-up time was calculated from the scan date of the second questionnaire until death from any cause or the end of study on December 31, 2001. Terms for activity of at least moderate intensity and vigorous exercise were entered into the models simultaneously to assess their independent effects. The models were adjusted for age, sex, race/ethnicity, marital status, family history of cancer, education, smoking status, menopausal hormone therapy, aspirin, and intakes of multivitamins, vegetables, fruit, red meat, and alcohol. Information on family history of cardiovascular disease was unavailable. Because body mass index (BMI) and smoking[38] could be intermediate steps in the causal pathways linking physical activity to decreased mortality, we analyzed the data with and without inclusion of those variables in the model.

RESULTS

During 1 265 347 person-years of follow-up, we documented 7900 deaths. At baseline, half of the cohort (50.4%) reported engaging in activity of at least moderate intensity for more than 3 h/wk, and slightly less than half (47.8%) reported engaging in a minimum of 20 minutes of vigorous exercise 3 times per week. Subjects with increased levels of activity of at least moderate intensity or vigorous exercise tended to have a higher education level and, as expected, were leaner, showed less adulthood weight gain, and had greater intakes of total energy compared with less active subjects (**Table 1**).

Increased physical activity was associated with a clear decrease in risk of mortality from any cause (**Table 2**). Compared with the lowest category of no activity of at least moderate intensity, participants in the highest category of more than 7 h/wk had a multivariate RR of 0.68 (95% CI, 0.63-0.74). For vigorous exercise, any level above the inactive category was related to decreased mortality risk. Compared with no vigorous exercise, the multivariate RR was 0.71 (95% CI, 0.66-0.77) for the highest cat-

Table 1. Baseline Characteristics According to Activity of at Least Moderate Intensity and Vigorous Exercise

	Activity of at Least Moderate Intensity,[b] h/wk					Vigorous Exercise,[c] Times per Week				
Characteristic[a]	Inactive	<1	1-3	4-7	>7	Inactive	<1	1-2	3-4	≥5
Participants, No.	34 426	26 685	64 289	65 717	61 808	40 856	34 843	56 233	70 282	50 711
Age, y	62.3	62.0	62.2	62.5	62.9	62.5	61.7	62.1	62.7	62.9
Sex, %										
Women	44	44	44	43	44	54	45	42	41	38
Men	56	56	56	57	56	56	55	58	59	62
Race/ethnicity, %										
White	91	92	94	94	94	92	94	94	94	94
Black	5	4	3	3	3	5	3	3	3	3
Hispanic	2	2	2	2	2	2	2	2	2	2
Asian/Pacific Islander/Native American	2	2	1	1	1	2	1.	1	2	2
College education, %	70	76	78	79	76	66	75	78	80	79
Married or living as married, %	64	67	68	70	70	60	67	70	71	72
Family history of cancer, %	51	52	52	52	52	51	52	52	52	52
Current smoker, %	15	13	12	10	10	18	15	12	8	8
Past smoker, %	47	47	49	50	50	44	48	48	51	52
BMI	28.5	27.9	27.1	26.4	25.9	28.3	27.6	27.0	26.3	25.8
Weight gain since age 18 y, kg	21.1	19.8	17.7	15.5	13.9	20.8	19.2	17.7	15.4	13.3
Television or video watching, h/d	4	3	3	3	3	4	3	3	3	3
Current menopausal hormone therapy, %[d]	42	45	46	49	46	40	45	46	50	48
Past menopausal hormone therapy, %[d]	9	9	9	9	8	9	9	9	9	8
Regular aspirin use, %[e]	36	37	37	37	37	34	36	37	38	38
Total energy intake, kcal/d	1860	1809	1809	1829	1944	1835	1786	1838	1838	1960
Vegetable intake, servings/1000 kcal/d	1.6	1.7	1.8	1.9	1.9	1.6	1.7	1.8	1.9	2.0
Fruit intake, servings/1000 kcal/d	1.5	1.6	1.7	1.8	1.9	1.5	1.5	1.6	1.8	1.9
Red meat intake, g/1000 kcal/d	37	37	35	33	32	37	37	36	32	30
Alcohol intake, g/d	14	13	13	13	14	13	13	13	13	14
Multivitamin use, %	52	55	57	58	58	51	54	57	59	59

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
[a] *All values (except age) were directly standardized to the age distribution of the cohort.*
[b] Activity of at least moderate intensity is defined as activities with an estimated energy expenditure of greater than 3 metabolic equivalents (METs). The MET is defined as the ratio of work to resting energy expenditure (1 MET = 1 kcal/kg/h or 3.5-mL oxygen uptake/kg/min). Resting energy expenditure is assumed to be 1 MET.
[c] Vigorous exercise is defined as activities that lasted 20 minutes or more and caused either increases in breathing or heart rate or working up a sweat.
[d] *Among postmenopausal women.*
[e] Regular aspirin use is defined as use of aspirin or aspirin products once per week or more.

egory of at least 20 continuous minutes of vigorous exercise 5 or more times per week.

Adjustment for BMI had no appreciable effect on the risk estimates (Table 2). However, adjustment for smoking accounted for a considerable difference between the age- and sex-adjusted and multivariate findings for vigorous exercise. Inclusion of biological intermediary covariates that may mediate the effect of physical activity (hypertension, high cholesterol level, and diabetes) had no impact (data not shown).

To determine whether undiagnosed chronic disease may have caused a decrease in physical activity levels, thereby biasing our results, we excluded all deaths that occurred during the first 1, 2, and 3 years of follow-up and limited our analysis to subjects who reported undergoing regular cancer screening examinations at entry. Results were virtually unchanged (data not shown).

Much of the strong inverse association between physical activity and mortality was because of mortality from cardiovascular disease (Table 2). In contrast, physical activity was less strongly related to cancer mortality, but the decrease in risk was statistically significant. Compared with the lowest category of no activity of at least moderate intensity, amounts of more than 7 h/wk were related to significantly decreased risk of cancer mortality (RR, 0.83; 95% CI, 0.74-0.93). Compared with no vigorous exercise, the multivariate RR of cancer mortality for at least 20 minutes of vigorous exercise 3 to 4 times per week was 0.82 (95% CI, 0.74-0.92), and 5 or more times per week of vigorous exercise provided no additional benefit.

We next investigated the effects of activity of at least moderate intensity at levels that approximate the OSG/CDC/ACSM consensus guidelines for moderate activity (30 minutes on most days of the week)[4,5] and vigorous exercise as encouraged by the ACSM (20 minutes 3 or more times per week).[34] Activity levels reflective of meeting the recommendations of moderate activity and vigorous exercise both showed significant benefits for mortality (**Table 3**). Associations for mortality from cardiovascular disease were of comparable magnitude as those seen for mortality from any cause. Relations were weaker but evident for mortality from cancer.

We evaluated higher levels of physical activity by examining the effects of activity reflective of meeting both

Table 2. Relative Risk (RR) of Mortality From Any Cause and Mortality From Specific Causes According to Activity of at Least Moderate Intensity and Vigorous Exercise

Type of Activity[a]						*P* Value for Trend
Mortality From Any Cause						
Activity of at least moderate intensity, h/wk	Inactive	<1	1-3	4-7	>7	
No. of deaths	1683	937	1940	1794	1546	
Person-years	170 907	133 217	321 719	329 352	310 151	
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.80 (0.74-0.87)	0.72 (0.68-0.77)	0.68 (0.63-0.73)	0.61 (0.57-0.66)	<.001
Age- and sex-adjusted RR + BMI (95% CI)	1 [Reference]	0.81 (0.75-0.88)	0.74 (0.69-0.79)	0.70 (0.65-0.75)	0.63 (0.59-0.69)	<.001
Age- and sex-adjusted RR + smoking (95% CI)	1 [Reference]	0.82 (0.75-0.89)	0.74 (0.70-0.80)	0.70 (0.65-0.75)	0.63 (0.59-0.68)	<.001
Full multivariate RR (95% CI)[b]	1 [Reference]	0.85 (0.79-0.93)	0.79 (0.74-0.85)	0.76 (0.71-0.82)	0.68 (0.63-0.74)	<.001
Vigorous exercise, times per week	Inactive	<1	1-2	3-4	≥5	
No. of deaths	2000	1109	1682	1775	1334	
Person-years	202 815	174 174	281 371	352 635	254 352	
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.70 (0.65-0.75)	0.66 (0.62-0.71)	0.55 (0.51-0.59)	0.58 (0.53-0.62)	<.001
Age- and sex-adjusted RR + BMI (95% CI)	1 [Reference]	0.71 (0.66-0.77)	0.68 (0.63-0.73)	0.57 (0.53-0.61)	0.59 (0.55-0.64)	<.001
Age- and sex-adjusted RR + smoking (95% CI)	1 [Reference]	0.72 (0.67-0.78)	0.71 (0.66-0.76)	0.61 (0.57-0.66)	0.65 (0.60-0.70)	<.001
Full multivariate RR (95% CI)[b]	1 [Reference]	0.77 (0.71-0.83)	0.77 (0.72-0.82)	0.68 (0.63-0.73)	0.71 (0.66-0.77)	<.001
Mortality From Cardiovascular Disease						
Activity of at least moderate intensity, h/wk	Inactive	<1	1-3	4-7	>7	
No. of deaths	511	303	574	516	432	
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.86 (0.75-1.00)	0.71 (0.63-0.81)	0.64 (0.56-0.73)	0.56 (0.49-0.65)	<.001
Age- and sex-adjusted RR + BMI (95% CI)	1 [Reference]	0.88 (0.76-1.02)	0.74 (0.66-0.84)	0.68 (0.60-0.78)	0.60 (0.52-0.69)	<.001
Age- and sex-adjusted RR + smoking (95% CI)	1 [Reference]	0.88 (0.76-1.02)	0.73 (0.65-0.83)	0.67 (0.58-0.76)	0.58 (0.50-0.67)	<.001
Full multivariate RR (95% CI)[b]	1 [Reference]	0.94 (0.81-1.08)	0.80 (0.71-0.91)	0.75 (0.66-0.86)	0.65 (0.57-0.75)	<.001
Vigorous exercise, times per week	Inactive	<1	1-2	3-4	≥5	
No. of deaths	611	316	491	521	397	
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.65 (0.56-0.74)	0.63 (0.56-0.71)	0.53 (0.47-0.60)	0.57 (0.50-0.65)	<.001
Age- and sex-adjusted RR + BMI (95% CI)	1 [Reference]	0.66 (0.58-0.76)	0.65 (0.58-0.74)	0.56 (0.50-0.64)	0.61 (0.53-0.70)	<.001
Age- and sex-adjusted RR + smoking (95% CI)	1 [Reference]	0.67 (0.58-0.77)	0.67 (0.59-0.76)	0.59 (0.52-0.67)	0.64 (0.56-0.74)	<.001
Full multivariate RR (95% CI)[b]	1 [Reference]	0.72 (0.63-0.82)	0.74 (0.66-0.84)	0.66 (0.59-0.76)	0.71 (0.62-0.82)	<.001
Mortality From Cancer						
Activity of at least moderate intensity, h/wk	Inactive	<1	1-3	4-7	>7	
No. of deaths	645	392	884	894	818	
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.84 (0.74-0.95)	0.80 (0.72-0.89)	0.81 (0.72-0.90)	0.77 (0.68-0.86)	<.001
Age- and sex-adjusted RR + BMI (95% CI)	1 [Reference]	0.84 (0.74-0.96)	0.81 (0.73-0.90)	0.82 (0.73-0.91)	0.79 (0.69-0.87)	.002
Age- and sex-adjusted RR + smoking (95% CI)	1 [Reference]	0.86 (0.76-0.98)	0.83 (0.75-0.93)	0.84 (0.75-0.93)	0.79 (0.71-0.89)	.003
Full multivariate RR (95% CI)[b]	1 [Reference]	0.88 (0.78-1.00)	0.86 (0.78-0.96)	0.88 (0.79-0.98)	0.83 (0.74-0.93)	.02
Vigorous exercise, times per week	Inactive	<1	1-2	3-4	≥5	
No. of deaths	754	508	811	854	706	
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.84 (0.75-0.94)	0.82 (0.74-0.91)	0.66 (0.60-0.74)	0.75 (0.67-0.84)	<.001
Age- and sex-adjusted RR + BMI (95% CI)	1 [Reference]	0.85 (0.76-0.95)	0.83 (0.75-0.92)	0.67 (0.61-0.75)	0.76 (0.68-0.86)	<.001
Age- and sex-adjusted RR + smoking (95% CI)	1 [Reference]	0.87 (0.78-0.98)	0.89 (0.80-0.99)	0.76 (0.69-0.85)	0.88 (0.78-0.98)	.008
Full multivariate RR (95% CI)[b]	1 [Reference]	0.91 (0.81-1.02)	0.94 (0.85-1.04)	0.82 (0.74-0.92)	0.95 (0.85-1.07)	.23

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval.

[a] Activity of at least moderate intensity is defined as activities with an estimated energy expenditure of greater than 3 metabolic equivalents (METs). The MET is defined as the ratio of work to resting energy expenditure (1 MET=1 kcal/kg/h or 3.5-mL oxygen uptake/kg/min). Resting energy expenditure is assumed to be 1 MET. Vigorous exercise is defined as activities that lasted 20 minutes or more and caused either increases in breathing or heart rate or working up a sweat.

[b] The multivariate models used age as the underlying time metric and included the following covariates: sex (women; men), body mass index (<18.5; 18.5-24.9; 25.0-29.9; 30.0-34.9; 35.0-39.9; and ≥40.0), smoking (never smoking; past smoking of 1-19 cigarettes per day; past smoking of ≥20 cigarettes per day; current smoking of 1-19 cigarettes per day; and current smoking of ≥20 cigarettes per day), race/ethnicity (white; black; Hispanic; and Asian/Pacific Islander/Native American combined), education (<high school; high school; vocational school or some college; and college graduate), marital status (married or living as married; and divorced, separated, widowed, or never married), family history of cancer (yes; no), menopausal hormone therapy (never; current or former user of estrogen only; current user of estrogen and progestin combined; former user of estrogen and progestin combined; and not applicable), aspirin use (yes; no), multivitamin use (yes; no), intakes of vegetables (quintiles), fruit (quintiles), red meat (quintiles), and alcohol (0; 0.01-4.9; 5.0-14.9; 15.0-29.9; 30.0-49.9; and ≥50.0 g/d). The multivariate analyses of activity of at least moderate intensity and vigorous exercise were mutually adjusted.

recommendations for moderate activity and vigorous exercise (**Table 4**). Compared with subjects who were physically inactive, those with activity levels equivalent to meeting both recommendations showed a strong reduction in risk for mortality from any cause (multivariate RR, 0.50; 95% CI, 0.46-0.54). A similarly strong inverse association was noted for mortality from cardiovascular disease (multivariate RR, 0.48; 95% CI, 0.41-0.55) and mortality from stroke (multivariate RR, 0.40; 95% CI, 0.26-0.61), and a weaker relation was seen for mortality from cancer (multivariate RR, 0.74; 95% CI, 0.65-0.85) and mortality from physical activity–related cancers (multivariate RR, 0.73; 95% CI, 0.60-0.89). Those who reported doing some activity at less than recom-

Table 3. Relative Risk (RR) of Mortality From Any Cause and Mortality From Specific Causes According to Achievement of Physical Activity Recommendations

	Recommendation for MPA[a]			Recommendation for VPA[b]		
Variable	Inactive	No	Yes	Inactive	No	Yes
Mortality from any cause						
No. of deaths	1683	2877	3340	2000	2791	3109
Person-years	170 907	454 937	639 504	202 815	455 545	606 988
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.74 (0.70-0.79)	0.65 (0.61-0.69)	1 [Reference]	0.67 (0.63-0.71)	0.55 (0.52-0.59)
Full multivariate RR (95% CI)[c]	1 [Reference]	0.81 (0.76-0.86)	0.73 (0.68-0.78)	1 [Reference]	0.77 (0.72-0.81)	0.68 (0.64-0.73)
Mortality from cardiovascular disease						
No. of deaths	511	871	948	611	807	918
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.76 (0.68-0.85)	0.61 (0.54-0.69)	1 [Reference]	0.63 (0.57-0.70)	0.53 (0.48-0.60)
Full multivariate RR (95% CI)[c]	1 [Reference]	0.85 (0.75-0.95)	0.71 (0.63-0.80)	1 [Reference]	0.73 (0.66-0.82)	0.67 (0.60-0.75)
Mortality from cancer						
No. of deaths	645	1276	1712	754	1319	1560
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.81 (0.74-0.89)	0.79 (0.72-0.87)	1 [Reference]	0.82 (0.75-0.90)	0.69 (0.63-0.76)
Full multivariate RR (95% CI)[c]	1 [Reference]	0.87 (0.79-0.96)	0.87 (0.78-0.96)	1 [Reference]	0.92 (0.84-1.01)	0.87 (0.79-0.96)

Abbreviation: CI, confidence interval; MPA, moderate physical activity; VPA, vigorous physical activity.
[a] Recommendation for MPA: more than 3 hours of activity per week of at least moderate intensity corresponding to 30 minutes of activity of moderate intensity on most days of the week.
[b] Recommendation for VPA: 20 minutes of continuous vigorous exercise 3 or more times per week.
[c] Adjusted for the covariates listed in a footnote in Table 2. The multivariate analyses of recommendation for MPA and recommendation for VPA were mutually adjusted.

Table 4. Relative Risk (RR) of Mortality From Any Cause and Mortality From Specific Causes According to Joint Categories of Physical Activity Recommendations

Variable	Inactive	Neither Recommendation	Recommendation for MPA Only[a]	Recommendation for VPA Only[b]	Recommendation for Both MPA and VPA
Mortality from any cause					
No. of deaths	879	2520	1392	1161	1948
Person-years	74 139	361 407	222 814	190 298	416 690
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.59 (0.55-0.64)	0.51 (0.47-0.56)	0.47 (0.43-0.51)	0.36 (0.33-0.39)
Full multivariate RR (95% CI)[c]	1 [Reference]	0.70 (0.65-0.75)	0.62 (0.57-0.68)	0.61 (0.55-0.66)	0.50 (0.46-0.54)
Mortality from cardiovascular disease					
No. of deaths	278	761	379	349	569
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.56 (0.49-0.65)	0.44 (0.38-0.51)	0.44 (0.37-0.51)	0.32 (0.28-0.37)
Full multivariate RR (95% CI)[c]	1 [Reference]	0.68 (0.59-0.78)	0.56 (0.48-0.65)	0.58 (0.49-0.68)	0.48 (0.41-0.55)
Mortality from cancer					
No. of deaths	308	1082	683	531	1029
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.73 (0.64-0.83)	0.72 (0.63-0.82)	0.62 (0.54-0.72)	0.55 (0.48-0.62)
Full multivariate RR (95% CI)[c]	1 [Reference]	0.83 (0.73-0.94)	0.83 (0.72-0.95)	0.79 (0.68-0.91)	0.74 (0.65-0.85)

Abbreviations: CI, confidence interval; MPA, moderate physical activity; VPA, vigorous physical activity.
[a] Recommendation for MPA: more than 3 hours of activity of at least moderate intensity per week corresponding to 30 minutes of activity of moderate intensity on most days of the week.
[b] Recommendation for VPA: 20 minutes of continuous vigorous exercise 3 times per week.
[c] Adjusted for the covariates listed in a footnote in Table 2.

mended levels showed modest but significantly decreased risk of mortality from any cause, cardiovascular disease, and cancer.

Achievement of activity levels corresponding to the guidelines for either moderate activity or vigorous exercise or the combination of guidelines for moderate activity and vigorous exercise was inversely associated with mortality in subgroups defined by sex, age, race/ethnicity, education, smoking status, BMI, and television or video watching (**Table 5**), indicating no important effect modification (*P* value for interaction, >.05 for all). Vigorous exercise showed a particularly strong reduction in mortality risk among individuals with high (>2 h/d) television or video watching.

COMMENT

In this large prospective study, engaging in physical activity of at least moderate intensity for more than 3 h/wk was associated with a 27% decreased risk of mortality. Following the recommendation for vigorous exercise of 20 minutes 3 or more times per week was related to a 32% reduction in mortality risk. These data lend strong

Table 5. Multivariate Relative Risk of Mortality From Any Cause According to Joint Categories of Achievement of Recommendations for Activity of at Least Moderate Intensity and Vigorous Exercise in Subjects Defined by Selected Variables[a]

Variable	No. of Deaths	Inactive	Neither Recommendation	Recommendation for MPA Only[b]	Recommendation for VPA Only[c]	Recommendation for Both MPA and VPA
Sex						
Women	2661	1 [Reference]	0.70 (0.61-0.79)	0.65 (0.57-0.75)	0.62 (0.53-0.73)	0.53 (0.46-0.61)
Men	5239	1 [Reference]	0.70 (0.64-0.77)	0.60 (0.54-0.67)	0.60 (0.54-0.69)	0.49 (0.44-0.54)
Age at baseline, y						
<65	3454	1 [Reference]	0.69 (0.62-0.77)	0.64 (0.56-0.72)	0.60 (0.53-0.69)	0.50 (0.45-0.57)
≥65	4446	1 [Reference]	0.70 (0.63-0.78)	0.60 (0.54-0.68)	0.61 (0.54-0.68)	0.49 (0.44-0.55)
Race/ethnicity						
White	7409	1 [Reference]	0.70 (0.65-0.76)	0.62 (0.57-0.68)	0.62 (0.56-0.68)	0.51 (0.45-0.55)
Black	295	1 [Reference]	0.67 (0.47-0.96)	0.69 (0.46-1.05)	0.45 (0.29-0.68)	0.58 (0.39-0.86)
Hispanic	105	1 [Reference]	0.55 (0.30-0.99)	0.44 (0.22-0.88)	0.52 (0.26-1.03)	0.18 (0.09-0.39)
Asian/Pacific Islander/Native American	91	1 [Reference]	0.43 (0.22-0.85)	0.46 (0.22-0.96)	0.39 (0.19-0.82)	0.28 (0.14-0.57)
Education						
<High school	2371	1 [Reference]	0.69 (0.60-0.78)	0.61 (0.53-0.70)	0.53 (0.46-0.62)	0.48 (0.41-0.55)
College	5529	1 [Reference]	0.71 (0.64-0.78)	0.63 (0.57-0.71)	0.64 (0.57-0.72)	0.51 (0.46-0.57)
Current smoking status						
Smoker	6081	1 [Reference]	0.67 (0.61-0.73)	0.60 (0.54-0.66)	0.59 (0.53-0.65)	0.48 (0.44-0.53)
Nonsmoker	1819	1 [Reference]	0.74 (0.64-0.86)	0.64 (0.54-0.75)	0.63 (0.53-0.76)	0.54 (0.45-0.64)
BMI						
<25	2876	1 [Reference]	0.68 (0.59-0.77)	0.58 (0.50-0.67)	0.58 (0.49-0.67)	0.45 (0.39-0.52)
≥25	5024	1 [Reference]	0.67 (0.61-0.74)	0.60 (0.54-0.66)	0.58 (0.52-0.65)	0.48 (0.44-0.54)
Television or video watching, h/d						
≤2	2154	1 [Reference]	0.71 (0.59-0.84)	0.59 (0.49-0.72)	0.67 (0.56-0.81)	0.53 (0.44-0.63)
>2	5746	1 [Reference]	0.70 (0.64-0.77)	0.64 (0.58-0.70)	0.59 (0.53-0.65)	0.50 (0.45-0.55)

Abbreviations: BMI (calculated as weight in kilograms divided by height in meters squared); MPA, moderate physical activity; VPA, vigorous physical activity.
[a]Data are given as relative risk (95% confidence interval) unless otherwise specified. The multivariate models were adjusted for the covariates listed in a footnote in Table 2. In each case, the stratification variable was excluded from the model. Within each stratum, the category of inactive subjects served as the reference group.
[b]Recommendation for MPA: more than 3 hours of activity of at least moderate intensity per week corresponding to 30 minutes of activity of moderate intensity on most days of the week.
[c]Recommendation for VPA: 20 minutes of continuous vigorous exercise 3 or more times per week.

support to current physical activity guidelines, which endorse 30 minutes of moderate activity on most days of the week or 20 minutes of vigorous exercise 3 or more times per week.[4,5,34]

Apart from the present study, only 1 previous investigation[39] has quantified both moderate and vigorous activity in a manner that facilitates a direct comparison with the physical activity guidelines. That modestly sized study from Germany[39] included 943 deaths and examined mortality from any cause and found a statistically significant inverse relation of recommended levels of activity of moderate activity to risk of mortality in women (RR, 0.65; 95% CI, 0.51-0.82) but not in men (RR, 0.90; 95% CI, 0.77-1.01). Conversely, vigorous activity at recommended levels was statistically significantly inversely related to mortality risk in men (RR, 0.74; 95% CI, 0.68-0.94) but not in women (RR, 0.78; 95% CI, 0.57-1.08).

Previous epidemiologic studies of physical activity and mortality generally presented data in study-specific categories that do not readily compare with the guidelines or provided estimates of energy expenditure that require conversion into units of time before they can be translated into levels that correspond to the guidelines.[2,9] In those studies, an activity energy expenditure of approximately 1000 kcal/wk—an amount that corresponds to minimal adherence to the physical activity guidelines—was associated with a 20% to 30% reduction in mortality risk.[16,18,40-43]

Our study has numerous important strengths, including the substantial cohort size yielding precise risk estimates, the uniform criteria for ascertaining deaths, and the evaluation of cause-specific mortality. Subjects with preexisting chronic disease were excluded at baseline, thereby reducing the potential influence of chronic disease on physical activity levels. In secondary analyses, we further minimized the potential for bias due to undiagnosed chronic disease by excluding the initial follow-up period and excluding subjects without regular screening examinations.

Inclusion of BMI and cardiovascular risk factors in the models had little impact on the physical activity and mortality relation, suggesting that regulation of these factors explains only a small portion of the benefit of physical activity. In contrast, adjustment for smoking had an appreciable impact on the association between vigorous exercise and cancer mortality, indicating the importance of considering both vigorous exercise and smoking levels in the assessment of cancer mortality risk.

Our study has certain limitations. Information on physical activity was self-reported, which invariably entails some degree of misclassification.[44] However, the large cohort size prohibited us from using more accurate measures, such as activity monitors.[45] In addition, validation studies comparing physical activity assessments similar to those used in this cohort with referent methods suggest that the reliability and validity of our instrument is comparable to self-reported measures used in other cohorts.[46] Moreover, our activity measures were associated with current smoking, BMI, television or video watching, and total energy intake in the hypothesized directions, providing evidence of construct validity of our physical activity assessment. Using activity of at least moderate intensity to approximate the guidelines for moderate activity may have overstated the potential benefits of moderate activity because it includes vigorous activities. Likewise, our measure of vigorous exercise may have included some moderate activities, which would have understated the apparent protection afforded by vigorous exercise. We were unable to adjust for family history of cardiovascular disease, which may partly explain the stronger observed effects of physical activity on cardiovascular mortality than on cancer mortality.

Engaging in some activity at less than recommended levels provided protection from mortality. One potential explanation is overreporting of physical activity levels among active individuals. Notwithstanding, data from other studies[14,22,26,28,47] suggesting that lower-than-recommended activity levels may suffice to achieve mortality benefits are intriguing and require further evaluation.

Our findings showing that vigorous exercise was associated with a striking reduction in mortality risk among individuals with high television or video watching indicates that vigorous activity has the greatest potential for health benefits among those who are physically inactive. That individuals with greater activity levels consumed more calories than their less active counterparts suggests that apart from dietary intake, being physically inactive represents an important determinant of positive energy balance.

Numerous governmental agencies and private organizations have made recommendations for the appropriate amount of physical activity. The OSG, the CDC, the ACSM, the Institute of Medicine of the National Academy of Sciences, and the joint US Department of Agriculture/Department of Health and Human Services Dietary Guidelines for Americans all endorse a minimum of 30 minutes of moderate activity on most days of the week for overall health benefits.[4,5,48-50] In addition, several agencies and organizations have formulated complementary physical activity recommendations targeted at specific health goals such as weight control, cancer prevention, or cardiorespiratory fitness. Specifically, the Institute of Medicine recommends at least 60 minutes of moderate activity each day,[49] and the US Dietary Guidelines advocate 60 minutes of moderate to vigorous activity on most days of the week to prevent unhealthy adult weight gain.[50] The American Cancer Society calls for 45 to 60 minutes of moderate to vigorous activity on most days of the week to reduce the risk of developing obesity-related malignant conditions such as colon and breast cancers.[51] The ACSM distinguishes between physical activity vs fitness and promotes vigorous activities for at least 20 minutes 3 times a week to improve cardiorespiratory fitness.[34] Thus, physical activity recommendations vary depending on the particular health issue of interest.

Mechanistic studies show that the beneficial effects of physical activity and fitness involve biological processes that primarily mediate risk for cardiovascular disease and cancer.[4] Many biological mechanisms are likely to operate both with moderate and vigorous activity levels.[4,52] One study suggests that genetic factors do not account for physical activity–related mortality differences.[53] The independent nature of the association between physical activity and mortality that we observed following adjustment for and stratification by body mass index indicates that the metabolic pathways by which physical activity reduces mortality risk are not mediated through its impact on weight control. This suggests the value of regular exercise in promoting longevity not just for normal weight individuals but also for those who are overweight or obese.

In summary, engaging in more than 3 hours of at least moderate intensity activity per week decreases the risk of mortality by 27%. Substantial reduction in mortality risk can also be accomplished by 20 minutes of vigorous exercise 3 times per week. We conclude that following physical activity recommendations is associated with lower risk of death. In addition, our findings suggest that engaging in any physical activity by those who are currently sedentary represents an important opportunity to decrease the risk of mortality.

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対象の内訳

	ヒト	動物	地 域	欧米	研究の種類	縦断研究
対象	一般健常者	空白		( )		コホート研究
性別	男女混合	( )		( )		( )
年齢	50-71歳			( )		前向き研究
対象数	10000以上			( )		( )

調査の方法	質問紙	( )		

アウトカム

予 防	心疾患予防	な し	ガン予防	な し	死亡	( )
維持・改善	な し	な し	な し	な し	( )	( )

図 表

Table 2. Relative Risk (RR) of Mortality From Any Cause and Mortality From Specific Causes According to Activity of at Least Moderate Intensity and Vigorous Exercise

Type of Activity[a]						P Value for Trend
Mortality From Any Cause						
Activity of at least moderate intensity, h/wk	Inactive	<1	1-3	4-7	>7	
No. of deaths	1683	937	1940	1794	1546	
Person-years	173 907	133 217	321 719	329 352	310 151	
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.80 (0.74-0.87)	0.72 (0.68-0.77)	0.68 (0.63-0.73)	0.61 (0.57-0.66)	<.001
Age- and sex-adjusted RR + BMI (95% CI)	1 [Reference]	0.81 (0.75-0.88)	0.74 (0.69-0.79)	0.70 (0.65-0.75)	0.63 (0.59-0.68)	<.001
Age- and sex-adjusted RR + smoking (95% CI)	1 [Reference]	0.82 (0.75-0.89)	0.74 (0.70-0.80)	0.70 (0.65-0.75)	0.63 (0.59-0.68)	<.001
Full multivariate RR (95% CI)[b]	1 [Reference]	0.85 (0.79-0.93)	0.79 (0.74-0.85)	0.76 (0.71-0.82)	0.68 (0.63-0.74)	<.001
Vigorous exercise, times per week	Inactive	<1	1-2	3-4	≥5	
No. of deaths	2000	1109	1652	1775	1534	
Person-years	202 815	174 174	251 371	352 635	254 352	
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.70 (0.65-0.75)	0.66 (0.62-0.71)	0.55 (0.51-0.59)	0.58 (0.53-0.62)	<.001
Age- and sex-adjusted RR + BMI (95% CI)	1 [Reference]	0.71 (0.66-0.77)	0.68 (0.63-0.73)	0.57 (0.53-0.61)	0.59 (0.55-0.64)	<.001
Age- and sex-adjusted RR + smoking (95% CI)	1 [Reference]	0.72 (0.67-0.79)	0.71 (0.66-0.76)	0.61 (0.57-0.66)	0.65 (0.60-0.70)	<.001
Full multivariate RR (95% CI)[b]	1 [Reference]	0.77 (0.71-0.83)	0.77 (0.72-0.82)	0.68 (0.63-0.73)	0.71 (0.66-0.77)	<.001
Mortality From Cardiovascular Disease						
Activity of at least moderate intensity, h/wk	Inactive	<1	1-3	4-7	>7	
No. of deaths	511	303	574	516	432	
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.86 (0.75-1.00)	0.71 (0.63-0.81)	0.64 (0.56-0.73)	0.56 (0.49-0.65)	<.001
Age- and sex-adjusted RR + BMI (95% CI)	1 [Reference]	0.88 (0.76-1.02)	0.74 (0.66-0.84)	0.68 (0.60-0.78)	0.60 (0.53-0.69)	<.001
Age- and sex-adjusted RR + smoking (95% CI)	1 [Reference]	0.88 (0.76-1.02)	0.73 (0.65-0.83)	0.67 (0.58-0.76)	0.58 (0.50-0.67)	<.001
Full multivariate RR (95% CI)[b]	1 [Reference]	0.94 (0.81-1.08)	0.80 (0.71-0.91)	0.75 (0.66-0.86)	0.65 (0.57-0.75)	<.001
Vigorous exercise, times per week	Inactive	<1	1-2	3-4	≥5	
No. of deaths	611	316	491	521	397	
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.65 (0.56-0.74)	0.63 (0.56-0.71)	0.53 (0.47-0.60)	0.57 (0.50-0.66)	<.001
Age- and sex-adjusted RR + BMI (95% CI)	1 [Reference]	0.66 (0.58-0.76)	0.65 (0.58-0.74)	0.56 (0.50-0.64)	0.61 (0.53-0.70)	<.001
Age- and sex-adjusted RR + smoking (95% CI)	1 [Reference]	0.67 (0.58-0.77)	0.67 (0.59-0.76)	0.59 (0.52-0.67)	0.64 (0.56-0.74)	<.001
Full multivariate RR (95% CI)[b]	1 [Reference]	0.72 (0.63-0.83)	0.74 (0.66-0.84)	0.66 (0.59-0.76)	0.71 (0.62-0.82)	<.001
Mortality From Cancer						
Activity of at least moderate intensity, h/wk	Inactive	<1	1-3	4-7	>7	
No. of deaths	645	392	864	894	818	
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.84 (0.74-0.95)	0.80 (0.72-0.89)	0.81 (0.72-0.90)	0.77 (0.68-0.86)	<.001
Age- and sex-adjusted RR + BMI (95% CI)	1 [Reference]	0.84 (0.74-0.96)	0.81 (0.73-0.90)	0.82 (0.73-0.91)	0.79 (0.69-0.87)	.002
Age- and sex-adjusted RR + smoking (95% CI)	1 [Reference]	0.86 (0.76-0.98)	0.83 (0.75-0.93)	0.84 (0.75-0.93)	0.79 (0.71-0.88)	.003
Full multivariate RR (95% CI)[b]	1 [Reference]	0.88 (0.78-1.00)	0.86 (0.78-0.96)	0.88 (0.79-0.98)	0.83 (0.74-0.93)	.02
Vigorous exercise, times per week	Inactive	<1	1-2	3-4	≥5	
No. of deaths	754	508	811	854	706	
Age- and sex-adjusted RR (95% CI)	1 [Reference]	0.84 (0.75-0.94)	0.82 (0.74-0.91)	0.66 (0.60-0.74)	0.75 (0.67-0.84)	<.001
Age- and sex-adjusted RR + BMI (95% CI)	1 [Reference]	0.85 (0.76-0.95)	0.83 (0.75-0.92)	0.67 (0.61-0.75)	0.76 (0.68-0.86)	<.001
Age- and sex-adjusted RR + smoking (95% CI)	1 [Reference]	0.87 (0.78-0.98)	0.89 (0.80-0.99)	0.76 (0.69-0.85)	0.88 (0.78-0.98)	.006
Full multivariate RR (95% CI)[b]	1 [Reference]	0.91 (0.81-1.02)	0.94 (0.85-1.04)	0.82 (0.74-0.92)	0.95 (0.85-1.07)	.23

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval.

[a] Activity of at least moderate intensity is defined as activities with an estimated energy expenditure of greater than 3 metabolic equivalents (METs). The MET is defined as the ratio of work to resting energy expenditure (1 MET = 1 kcal/kg/h or 3.5-mL oxygen uptake/kg/min). Resting energy expenditure is assumed to be 1 MET. Vigorous exercise is defined as activities that lasted 20 minutes or more and caused either increases in breathing or heart rate or working up a sweat.

[b] The multivariate models used age as the underlying time metric and included the following covariates: sex (women, men), body mass index (<18.5; 18.5-24.9; 25.0-29.9; 30.0-34.9; 35.0-39.9; and ≥40.0), smoking (never smoking, past smoking of 1-19 cigarettes per day; past smoking of ≥20 cigarettes per day; current smoking of 1-19 cigarettes per day; and current smoking of ≥20 cigarettes per day), race/ethnicity (white; black; Hispanic; and Asian/Pacific Islander/Native American combined), education (<high school; high school; vocational school or some college; and college graduate), marital status (married or living as married; and divorced, separated, widowed, or never married), family history of cancer (yes; no), menopausal hormone therapy (never; current or former user of estrogen only; current user of estrogen and progestin combined; former user of estrogen and progestin combined; and not applicable), aspirin use (yes; no), multivitamin use (yes; no), intakes of vegetables (quintiles), fruit (quintiles), red meat (quintiles), and alcohol (0; 0.01-4.9; 5.0-14.9; 15.0-29.9; 30.0-49.9; and ≥50.0 g/d). The multivariate analyses of activity of at least moderate intensity and vigorous exercise were mutually adjusted.

図表掲載箇所	P2456, Table2
概 要(800字まで)	本研究は、アメリカのThe NIH-AARP Diet and HealthStudyに参加した男女252,925名を対象に5年間の追跡調査を行い、国が定める身体活動指針で示される身体活動量と全死因死亡リスクとの関連を検討したものである。質問紙により、20分以上の高強度身体活動を行った週当たりの頻度と、週当たりに行った中強度身体活動の平均時間を尋ねた。高強度活動については、不活動、1回/週未満、1-2回、3-4回、5回/週以上の5群に、中強度活動については、不活動、1時間/週未満、1-3時間、4-7時間、7時間/週以上の5群に分類した。アメリカにおける全身持久力向上のための身体活動推奨量は、20分以上の高強度活動を週3回以上であり、健康増進のための身体活動推奨量は中強度活動をほぼ毎日30分以上行うことである(本研究の3時間/週とほぼ同等)。中強度身体活動に関して、不活動な集団と比較すると、全ての集団で全死因死亡リスクが有意に減少した。相対リスクは順に、0.85(95%信頼区間:0.79-0.93)、0.79(0.74-0.85)、0.76(0.71-0.82)、0.68(0.63-0.74)であった(Ptrend<0.001)。高強度活動に関して、同様に全ての集団で全死因死亡リスクが有意に減少した。相対リスクは順に、0.77(0.71-0.83)。0.77(0.72-0.82)、0.68(0.63-0.73)、0.71(0.66-0.77)であった(Ptrend<0.001)。心疾患発症リスクについては、中強度活動を1時間/週以上からリスク減少がみられ(Ptrend<0.001)、高強度活動については、全ての集団で有意なリスク減少がみられた(Ptrend<0.001)。がん発症リスクは、中強度活動については1時間/週以上で、高強度活動については3回/週以上で有意なリスク減少がみられた。
結 論(200字まで)	本研究のコホートに対して、アメリカの身体活動推奨量は妥当であり、推奨量を実施することで全死因死亡リスク、心疾患発症リスク、およびがん発症リスクを大いに低下させることが明らかとなった。また、推奨量に達していない者も、不活動でいるよりは少しでも身体活動量を増やすことでそれらのリスクが減少することが明らかとなった。
エキスパートによるコメント(200字まで)	身体活動基準の策定に使用された研究である。基準で定められた身体活動量を満たさなくても、少しでも身体活動を増やすことの価値を示した点に意義がある。

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ORIGINAL ARTICLE

Recreational physical activity and prostate cancer risk (United States)

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Abstract
Objective To examine recreational physical activity (PA) and prostate cancer risk in a large cohort of men living in Washington State, focusing on frequency and type of physical activity at various times throughout life.
Methods In a prospective cohort study, we assessed physical activity in 34,757 men (50–76 years at baseline) using a questionnaire. Men were recruited into the study between 2000 and 2002. Five hundred and eighty-three men developed prostate cancer.
Results Using Cox proportional hazards regression, PA either in the 10 years before baseline or earlier in life was not associated with prostate cancer risk. However, compared to no activity, ≥10.5 MET-h per week (the median level) of PA was associated with a reduced prostate cancer risk among men who were normal weight (HR = 0.69, 95% CI 0.46–1.0), ≥65 years at diagnosis (HR = 0.75, 95% CI 0.55–1.0) and who had not had a recent PSA (HR = 0.47, 95% CI 0.28–0.81). Greater PA was associated with an increased risk among men who were obese (HR = 1.5, 95% CI 0.95–2.4), and no association among men <65 years or with a recent history of PSA screening (all p for interactions ≤0.02).
Conclusions PA was not associated with prostate cancer risk, except in subgroups defined by age, obesity, and screening history.

Keywords Prostate cancer · Physical activity · Obesity · Cohort

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Introduction

Prostate cancer is the most common cancer in US men, with 232,090 new cases and 30,350 deaths estimated for 2005 [1]. Researchers have identified few modifiable risk factors. While more than 35 studies have examined the association between physical activity and prostate cancer risk, results have been inconsistent [2–10]. An expert panel classified physical activity as a "probable" preventive factor for prostate cancer, as the evidence was strong enough to conclude that a causal relation was likely, but some uncertainty remained [11]. Seventeen studies have observed a reduced risk overall; the risks were statistically significantly reduced in 11 [2]. Average risk reductions were 10–30%. Even so, in at least three studies [12–14] higher levels of activity were statistically significantly associated with increased prostate cancer risks while the rest observed no association [2, 10, 15]. For aggressive or fatal prostate cancer, several well-conducted studies have observed statistically significantly reduced risks associated with increased physical activity [5, 8, 16]. Despite the equivocal findings, exercise is an appealing preventive factor because it has the potential to reduce the risk of prostate cancer as well as other chronic diseases, without the possible side effects of chemopreventive agents. Consequently, clarification of the role physical activity might play in prostate cancer initiation or progression is important.

A limitation of past studies is that most focused on recent physical activity, ignoring the long induction period for prostate cancer. The prevalence of sub-clinical prostate cancer in older men is extremely high, reaching over 60% at autopsy by age 80 [17, 18]. Given that prostate cancer has such a long preclinical phase, exposures long before diagnosis may be critically important. Furthermore, few previous studies collected detailed information on the frequency and type of activity performed, which may be an important determinant of risk. The aims of this study are to investigate whether the type, frequency, and timing of recreational physical activity are associated with prostate cancer risk overall, and in subgroups defined by tumor characteristics, age, and body mass index (BMI).

Methods

Recruitment and response rates

The VITamins And Lifestyle (VITAL) cohort includes both men and women between the ages of 50 and 76 who live in the 13-county area in western Washington State covered by the Surveillance, Epidemiology, and End Results (SEER) cancer registry [19]. Here, we describe recruitment of men because this study is limited to men. Between October 2000 and December 2002, we mailed 195,465 baseline questionnaires using names purchased from a commercial mailing list, followed by a post-card reminder 2 weeks later. Of the 38,143 questionnaires (19.5%) that were returned, 37,382 passed eligibility and questionnaire quality control checks. We excluded men with a history of prostate cancer at baseline ($n = 2013$), those who did not answer questions about history of prostate cancer ($n = 125$) or physical activity ($n = 485$), and two who were diagnosed with non-invasive prostate cancer, leaving 34,757 men for analysis.

Baseline questionnaire

Participants completed a 24-page self-administered, optically scanned questionnaire that inquired about anthropometric measures, physical activity, demographic characteristics, health history, family history of cancer, and other cancer risk factors. We calculated BMI as weight in kilograms divided by height in meters squared. Information about usual dietary intake over the past year was obtained from a 120-item, semi-quantitative food frequency section of the questionnaire that was adapted from food frequency questionnaires (FFQs) we developed for the Women's Health Initiative and other studies [20–22]. The measurement properties of earlier versions of this questionnaire have been published [21]. The FFQ analytic program is based on nutrient values from the Minnesota Nutrient Data System and yields estimated intakes of over 50 nutrients.

Physical activity measurement and measurement properties

We assessed recreational physical activity during the 10 years before baseline [23] since long-term physical activity may be more strongly related to cancer risk than activity at baseline alone [24]. Questions covered the frequency, duration and number of years for each of five types of exercise (walking, weight lifting, yoga, low-intensity activities such golf, and moderate/strenuous activities, such as jogging) over the previous 10 years. For walking, there was an additional question on pace, and for moderate/strenuous exercise, the participants selected from among nine types of activities. From this information, we computed average MET-hours per week (kcal per kg body weight per week) over the 10-year reference period by assigning an intensity code (MET) [25] to each activity, and multiplying this number by the average frequency per week, minutes per session (divided by 60 to get hours), and years in the last 10 (divided by 10), and summing across all activities. In addition, we calculated MET-hours per week of high- (i.e., activities with a MET of ≥6) and moderate-intensity activities (activities with MET ≥4–<6) [26]. To assess activity earlier in life, we also asked questions on frequency per week of exercise or sports (none, 1, 2–3, 4–5, 6–7) at ages 18, 30 and 45.

We conducted an inter-method reliability study of this physical activity questionnaire [23]. The correlation for total 10-year recreational activity between this instrument and a very detailed interview was 0.68 ($n = 217$). In the full cohort, BMI in men was inversely correlated with 10-year physical activity from the questionnaire ($r = -0.16$), which is a stronger correlation than that found between BMI and recent activity in validation studies of other questionnaires [27, 28]. Test–retest reliability (weighted kappa) of activity reported at 18, 30, and 45 was 0.61, 0.65, and 0.72, respectively [23].

Follow-up of participants for prostate cancer and censoring

Follow-up of the cohort for cancers and censoring date is described in detail elsewhere [19]. We identified new cases of invasive prostate cancer from baseline through 31 December 2003 by linking the study cohort to the western Washington Surveillance Epidemiology and End Results (SEER) cancer registry. We used SEER records to determine clinical stage (local, regional, or distant). Gleason score was categorized as 2–6 and 7–10, corresponding to grade (well- or moderately differentiated versus poorly differentiated cancers, respectively) [29]. As SEER implemented this categorization scheme beginning in 2003, we reclassified grade from the SEER abstraction forms for cancers diagnosed between 2000 and 2002. To incorporate both stage and grade into a single measure, we classified tumors based on their "aggressiveness." Tumors which were Gleason score 7–10 or regional/distant stage were classified as "aggressive" while those that were Gleason score 2–6 and local stage were classified as "non-aggressive."

The censored date for each subject was the earliest date of prostate cancer diagnosis (1.7%), withdrawal from the study (0.02%), death (2.0%), a move out of the 13-county catchment area of the SEER registry (3.0%), or the last date of SEER diagnoses (31 December 2003). To ascertain deaths, we linked to the Washington State death files. To identify moves out of the 13-county SEER registry area, we linked to the National Change of Address system, sent follow-up letters, and called those identified as having possibly moved with no forwarding address.

Statistical methods

We fit Cox proportional hazard models to estimate the hazard ratios of developing prostate cancer based on the average MET-hours per week in the 10 years before baseline as well as the type, frequency, and timing of physical activity, after adjusting for confounding factors [30]. Analysis time was defined as the participant's age, which effectively adjusts all analyses for age. Individuals first became at risk at the age they entered the study, and were censored at their age at the censored date, described in the previous section.

We modeled physical activity as a categorical variable by first creating a category of "no activity" and then either two or four additional categories in order to have approximately equal numbers in each (e.g., none, <median, ≥median of high-intensity MET-hours/week). We calculated hazard ratios, interpretable as relative risks of prostate cancer, and their confidence intervals for each category of exposure versus the lowest. To test for trends across the levels of a variable, we created a grouped linear variable, y that was assigned the median values of each category (e.g., 0, 2, 7, 15, and 32, respectively for each category of MET-hours/week of activity), and tested the parameter β in the model:

$$\ln \lambda(t) = \ln \lambda_0(t) + \beta y + \text{(other covariates)}$$

We evaluated whether the factors listed in Table 1 and as well as factors associated with PSA screening (sigmoidoscopy, Group Health Cooperative membership, benign prostatic hyperplasia (BPH) and medications for BPH including Proscar; Hytrin, Terazosin, Cardura, or Flomax) were confounders by including them individually in models and observing whether they changed the beta coefficient for the highest level of physical activity by 10% or more. We examined models both with, and without adjustment for current dietary factors (e.g., energy intake; percent energy from fat, carbohydrates, and protein; and servings per day of fruits and vegetables). Furthermore, we evaluated whether the association between physical activity and prostate cancer differed by age, family history, PSA screening, percent energy from fat, and BMI, by including a categorical predictor in our models and comparing the likelihood ratio test between a model with terms for the main effects and an interaction term (plus covariates) to a model with the terms for the main effects only (plus covariates). Finally, we assessed the HR of developing different types of prostate cancer (e.g., aggressive or regional/distant stage) by conducting analyses limited to men with that type of prostate cancer and controls.

We used tabular and graphical methods to evaluate the validity of the proportional hazards assumption. Schoenfeld residuals were plotted against time to determine whether the slope differed from zero, which is equivalent to testing that the log hazard ratio function is constant over time [30]. Analyses were conducted using STATA version 8.2 (StataCorp, College Station, Texas).

Results

Five hundred eighty-three men were diagnosed with prostate cancer during follow-up. Eight-four percent were local stage disease, while 15.5% were regional/distant, and only 1 (0.2%) was unknown stage. Moderate- to well-differentiated tumors (Gleason score 2–6, 68.3%) were more common than poorly differentiated tumors (Gleason score 7–10, 29.9%). Aggressive (Gleason score 7–10 or regional/distant stage) tumors made up 38.1% of all prostate cancers.

Table 1 gives the distributions of various demographic, medical, and dietary characteristics. Table 1 also gives the percentage of men reporting physical activity and the median MET-hours/week among those who were active by the same characteristics. Eighty-five percent of men reported some regular recreational physical activity in the 10 years before baseline, and the median MET-hours per week among those who were active were 10.5. Physical activity levels did not vary significantly by age at baseline. Hispanics, Blacks, and Asian or Pacific Islanders were more likely to report regular physical activity than were Whites, but the median MET-hours per week among those who were active were highest among Whites. As we would expect, physical activity prevalence was higher among men with higher levels of education and income, men screened for PSA, men without diabetes, and never or former smokers. Separated or divorced men were more active than

Table 1 Distribution of demographic, medical, screening, and dietary factors in the VITAL cohort and frequency of recreational physical activity within each group

Characteristic	*N*	%*	% reporting any activity	Median MET-hours per week (among those who are active)
Overall	34,757	100.0	85.0	10.5
Age at baseline				
50–54	8,316	23.9	84.5	10.5
55–59	7,980	23.0	84.5	10.0
60–64	6,540	18.8	84.1	10.2
65–69	5,797	16.7	86.4	10.5
70–74	6,124	17.6	85.8	10.5
Race				
White	31,994	93.2	84.9	10.5
Hispanic	293	0.9	89.4	9.6
Black	427	1.2	87.1	8.1
American Indian/Alaska Native	511	1.5	84.3	8.8
Asian or Pacific Islander	837	2.4	88.4	9.6
Other	264	0.8	83.0	9.6
Education				
Grade school/some HS	1,089	3.2	71.3	6.1
HS grad/ GED	4,363	12.7	76.3	7.3
Some college/technical school	12,030	35.0	82.3	8.8
College grad	9,422	27.4	88.7	11.4
Advanced degree	7,473	21.7	91.9	13.4
Income ($)[a]				
< 20,000	1,186	3.4	77.2	7.0
20,000–39,999	5,419	15.6	81.2	8.2
40,000–59,999	6,932	19.9	83.5	9.5
60,000–79,999	5,692	16.4	85.0	10.4
80,000+	10,134	29.2	89.6	12.5
Marital status				
Married	28,576	83.2	84.9	10.5
Living w/partner	838	2.4	83.6	10.6
Never married	1,126	3.3	84.6	10.9
Separated/divorced	2,844	8.3	86.5	11.3
Widowed	952	2.8	85.4	9.2
Family history of prostate cancer				
None	29,875	87.0	85.0	10.5
One 1st degree relative	4,198	12.2	85.1	10.5
≥ Two 1st degree relatives	280	0.8	85.0	8.9
PSA in previous 2 years				
No	9,622	28.0	80.2	9.2
Yes	24,709	72.0	86.7	10.6
Benign prostatic hyperplasia				
No	29,218	84.1	84.4	10.5
Yes	5,528	15.9	87.8	10.5
Diabetes				
No	31,936	91.9	85.2	10.5
Yes	2,818	8.1	82.6	7.2
Smoking status				
Never smoker	13,355	39.1	86.9	11.0
Current smoker	3,111	9.1	71.6	7.4
Former smoker (quit < 10 years ago)	2,576	7.5	80.3	7.2
Former smoker (quit ≥10 years ago)	15,159	44.3	87.0	10.5

Table 1 continued

Characteristic	*N*	%*	% reporting any activity	Median MET-hours per week (among those who are active)
Body mass index (kg/m²)				
< 25	9,291	27.5	87.2	12.3
25–29.9	16,424	48.7	86.5	10.9
≥30	8,040	23.8	79.9	6.5
Energy intake (kcal/day)[b]				
Q1 (800–1657)	8,037	25.0	86.4	9.6
Q2 (1658–2138)	8,046	25.0	85.7	10.5
Q3 (2139–2696)	8,024	25.0	85.6	10.6
Q4 (2697–4998)	8,049	25.0	82.8	10.8
% energy from fat[b]				
Q1 (4.5–29.9)	8,053	25.0	91.3	12.8
Q2 (30.0–35.2)	8,038	25.0	87.6	10.9
Q3 (35.3–40.1)	8,034	25.0	84.1	9.8
Q4 (40.2–73.6)	8,031	25.0	77.6	8.1
Intake of fruits & vegetables[c] *(servings/day)*				
Q1 (< 2.1)	7,961	25.0	78.7	7.6
Q2 (2.1–3.1)	7,988	25.1	83.9	9.6
Q3 (3.2–4.4)	7,953	25.0	87.4	10.9
Q4 (4.5–24.1)	7,972	25.0	90.6	13.5

*Unless otherwise noted, < 3% of persons were missing for each variable

[a] 15.5% missing income

[b] 7.5% missing energy intake and % energy from fat

[c] 8.3% missing intake of fruits and vegetables

married or widowed men. There was little difference in activity between men with and without a family history of prostate cancer. Activity was inversely associated with BMI, energy intake, and percent energy from fat, and positively associated with fruit and vegetable consumption.

There was a small, non-significant inverse association between any physical activity in the 10 years before baseline and prostate cancer risk (HR = 0.92, 95% CI 0.72–1.2), with little evidence of a trend when activity was categorized either by MET-hours per week (Table 2) or by sessions per week (data not presented). There were no statistically significant associations for moderate- and high-intensity activities with prostate cancer risk, or for specific activities, including walking, running, swimming, bicycling, and stair climbing. Furthermore, frequency of activity at ages 18, 30, or 45 was not associated with prostate cancer risk (Table 3).

Table 4 gives the association between physical activity and prostate cancer in subgroups of the cohort. The relationship of physical activity over the 10 years before baseline with prostate cancer varied by baseline BMI (p for interaction = 0.005). To make this complex relationship clearer, we used a single reference group (inactive normal weight men) for comparison to the other BMI categories. Among normal weight men, greater recreational physical activity was associated with a decreased risk of prostate cancer (≥10.5 MET-h/week versus none: HR=0.69, 95% CI 0.46–1.04, p for trend = 0.08). Among obese men, physical activity was associated with an increased risk (p for trend = 0.007). However, inactive obese men had a *decreased* prostate cancer risk (HR = 0.67, 95% CI 0.46–0.97) compared to inactive normal weight men. We also examined activity at earlier ages, stratified by BMI at that age. There were no consistent patterns (data not shown). Among men who had not been screened for PSA in the 2 years before baseline, greater MET-hours per week were associated with a lower prostate cancer risk (>10.5 MET-h/week versus none: HR = 0.47, 95% 0.28–0.81, p for trend = 0.02), while there was little association among men with a recent screening history (p for interaction = 0.02). Finally, we investigated whether the associations between physical activity and prostate cancer differed by grade, stage, or tumor aggressiveness. In these analyses, we stratified by age because there was evidence of non-proportional hazards for non-aggressive disease. Among men < 65 years at diagnosis, physical activity increased risk of non-aggressive disease (≥10.5 MET-h/week versus none: HR = 1.7, 95% CI 0.86–3.2, p-trend = 0.19). However among men ≥65 years, physical activity decreased risk of non-aggressive disease; HRs for no activity, < 10.5 MET-h/week, and ≥10.5 h/week were 1.0 (reference), 0.73 (95% CI 0.50–1.1), and 0.60 (95% CI 0.42–0.85), respectively, p-trend = 0.03. Physical activity was not associated with aggressive tumors. Results were similar when we classified

Table 2 Adjusted* hazard ratio (HR) of prostate cancer for 10-year average recreational physical activity measures and stair climbing

Physical activity measure	Cases		Cohort		Incidence (per 10^4)	HR* (95% CI)
	N	%[a]	*N*	%[a]		
Recreational physical activity						
None	83	14.4	5,225	15.0	73.7	1.0
Some	495	85.6	29,532	85.0	75.0	0.92 (0.72–1.2)
MET-hours/week (kcal/kg-hours × week)						
None	83	14.4	5,225	15.0	73.7	1.0 [b]
>0–3.9	120	20.8	7,382	21.2	76.1	0.95 (0.71–1.3)
4.0–10.4	123	21.3	7,266	20.9	79.0	0.96 (0.72–1.3)
10.5–21.0	121	20.9	7,501	21.6	74.9	0.84 (0.63–1.1)
21.1–157.25	131	22.7	7,383	21.2	81.9	0.93 (0.70–1.2)
Intensity of physical activity						
MET-hours week of high- and moderate-intensity activity[c]						
None	283	49.0	17,066	49.1	77.4	1.0 [b]
<8.1	139	24.1	8,763	25.2	73.7	1.0 (0.84–1.3)
≥8.1	156	27.0	8,928	25.7	80.9	1.1 (0.89–1.4)
MET-hours/week of high-intensity activity[c]						
None	437	75.6	24,774	71.3	82.2	1.0 [b]
<7.6	70	12.1	4,929	14.2	65.9	0.93 (0.71–1.2)
≥7.6	71	12.3	5,054	14.5	64.8	0.95 (0.75–1.2)
Pace of walking (per 5 MET-h/week)						
Slow walking (150 min/week)	50	8.6	3,583	10.2	–	0.78 (0.52–1.2)
Moderate walking (100 min/week)	226	39.3	13,022	37.5	–	0.94 (0.83–1.1)
Fast walking (75 min/week)	141	24.2	7,036	20.0	–	1.0 (0.93–1.1)
Type of other physical activities (per 5 MET-h/week)						
Jogging/running (33 min/week)[d]	59	10.1	5,098	14.5	–	1.0 (0.93–1.1)
Swimming (40 min/week)[d]	27	4.6	1,805	5.1	–	1.0 (0.83–1.3)
Slow cycling or stair machine (60 min/week)[d]	46	7.9	3,222	9.1	–	0.82 (0.58–1.2)
Fast cycling or stair machine (38 min/week) [d]	42	7.2	3,275	9.3	–	0.99 (0.87–1.1)
Stair climbing (flights/day)[d]						
0–1	194	33.6	10,799	30.8	83.8	1.0 [b]
2–4	169	29.3	9,250	26.4	84.4	1.2 (0.94–1.5)
5–9	122	21.1	7,832	22.4	71.7	0.97 (0.76–1.2)
10+	92	15.9	7,143	20.4	59.2	0.87 (0.67–1.1)

Numbers presented are those with non-missing values for covariates

*Adjusted for family history of prostate cancer and BMI, and stratified on income (categorical, with a category for missing income) and PSA in 2 years before baseline

[a]Also adjusted for MET-hours/week from other activities

[b]p for trend > 0.2

[c]8.1 and 7.6 MET-h/week were the median values for the respective categories

[d]For intensity of physical activity, pace of walking, and types of other physical activities, the percentage refers to the proportion of people reporting doing any of that type of activity

tumors by grade and stage. However, there were no consistent associations by tumor characteristics for activity at 18, 30, or 45. The association of physical activity with prostate cancer did not differ by family history.

Discussion

Overall, recreational physical activity either in the 10 years before baseline or earlier in life was not associated with prostate cancer risk. Our results generally agree with previous studies (see recent reviews [2–4, 15] and studies published since these reviews [5–10]), that suggest a weak protective effect, if any. Nevertheless, overall associations may obscure important differences by timing or type of physical activity, subgroup of the population, and prostate cancer tumor characteristics.

The critical time period for effects of physical activity or any other factor on prostate cancer risk has not been identified. We hypothesized that physical activity early in

Table 3 Adjusted* HR of prostate cancer for recreational physical activity at earlier ages

Recreational physical activity measure	Cases		Cohort		Incidence (per 10^4)	HR* (95% CI)
	N	%	*N*	%		
Days/week of exercise at age 18[a]						
None-1	125	22.8	8,592	25.8	67.4	1.0
2–5	317	57.9	18,433	55.2	80.2	1.17 (0.94–1.45)
6–7	106	19.3	6,341	19.0	77.4	1.09 (0.83–1.43)
p for trend						0.39
Days/week of exercise at age 30						
None	93	16.9	6,073	18.2	71.1	1.0
1–3	322	58.4	18,650	55.7	80.3	1.21 (0.95–1.55)
4–7	136	24.7	8,739	26.1	72.5	1.14 (0.87–1.50)
p for trend						0.87
Days/week of exercise at age 45						
None	126	22.9	7,991	23.6	73.3	1.0
1–3	301	54.6	17,808	52.7	78.5	1.10 (0.88–1.37)
4–7	124	22.5	8,015	23.7	72.0	0.99 (0.76–1.28)
p for trend						0.57

Numbers presented are those with non-missing values for covariates

*Adjusted for family history of prostate cancer and BMI at the same age and stratified on income (categorical, with a category for missing income) and PSA in 2 years before baseline

[a]Note: 16.3% of participants reported NO activity at age 18, 9.5% reported 1 day/week at age 18

life would be associated with a decreased risk because of prostate cancer's long latency period. Several studies have investigated occupational or recreational activity early in life, though results have not been consistent [3, 5, 9, 31–38]. Activity at ages 18, 30, and 45 was not associated with prostate cancer risk in the current study. Certainly, a limitation of this and other studies is reliance on recalled activity levels; non-differential misclassification due to poor recall could attenuate associations. Although recall of historical physical activity has been found to be relatively reliable, reliability decreases with increasing time, so evaluating early life physical activity retrospectively among older men is particularly challenging [38].

High-intensity activity may affect prostate cancer risk differently than low-intensity activity [5, 39], but only a limited number of studies have tried to investigate this hypothesis. At least two studies (one population-based Canadian case–control study [31] and one British cohort study [38]) observed reduced prostate cancer risks (30–75%) with high-intensity activity, while two large American cohort studies did not [5, 39]. In another study, high-intensity activity reduced the risk of advanced and fatal tumors by 70% in men 65 years or older, but was not associated with risk reduction in either men <65 years at diagnosis or men with local stage or low grade disease [5]. In the current study, high-intensity activity was not associated with prostate cancer risk overall, but there was an indication of an inverse association (p-trend = 0.08) for non-aggressive disease in men $\geqslant 65$ years at diagnosis.

Investigators have proposed that the effect of physical activity on prostate cancer risk may differ depending on family history, anthropometric measures, or age. Family history of prostate cancer did not appear to modify the association between physical activity and prostate cancer in the current study. Among men <65 years at diagnosis, physical activity was associated with a slightly increased risk of non-aggressive disease, but a decreased risk of non-aggressive disease in men ≥ 65 years. Poorly understood genetic factors, rather than lifestyle factors, may play a stronger role in prostate cancer diagnosed in younger men. However, results from previous studies show no consistent patterns in subgroups defined by age [3]. In the current study, physical activity in the 10 years before baseline was associated with a decreased risk of prostate cancer among lean men but an increased risk among obese men. Several other groups have examined this interaction, but associations of physical activity with prostate cancer risk did not differ statistically significantly by BMI [9, 10, 31].

Our findings for an inverse association of physical activity and prostate cancer risk among men not screened for PSA in the 2 years before baseline and in older men with non-aggressive tumors are difficult to interpret. Variation in PSA screening presents a challenge for prostate cancer researchers. Men who are screened are more likely to be diagnosed, and physically active men may be more likely to be screened. Indeed, the prevalence of PSA screening increased with increasing physical activity. Sixty-three percent of inactive men were screened while nearly 77% of the most active men were screened. A

Table 4 Adjusted* HR and 95% CI of prostate cancer by physical activity at baseline, stratified by various tumor and other demographic and health characteristics

Physical activity at baseline (MET-hours/week)	None	< 10.5[a]	≥10.5	p for trend
Total prostate cancer, HR (95% CI)	1.0 (ref)	0.95 (0.74–1.2)	0.89 (0.68–1.1)	0.32
Body mass index (kg/m²)[b]				
Normal weight (≤25)				
Cases/cohort	18/1,165	65/3,423	65/4,593	
HR (95% CI)	1.0 (ref)	0.90 (0.69–1.2)	0.69 (0.46–1.0)	0.08
Overweight (25–29.9)				
Cases/cohort	45/2,206	125/6,661	135/7,388	
HR (95% CI)	1.1 (0.73–1.5)	1.0 (0.69–1.5)	0.90 (0.63–1.3)	0.48
Obese (30±)				
Cases/cohort	18/1,589	46/3,933	45/2,411	
HR (95% CI)	0.67 (0.46–0.97)	0.67 (0.44–1.0)	1.0 (0.65–1.53)	0.007
PSA screening[c]				
Not screened in 2 years before baseline				
Cases/cohort	28/1,803	38/3,932	28/3,484	
HR (95% CI)	1.0 (ref)	0.62 (0.38–1.0)	0.47 (0.28–0.81)	0.02
Screened in 2 years before baseline				
Cases/cohort	49/3,040	190/9,789	210/10,656	
HR (95% CI)	1.0 (ref)	1.1 (0.82–1.5)	1.1 (0.79–1.5)	0.99
Tumor aggressiveness[‡] *and age at diagnosis*				
Non-aggressive prostate cancer, ≤65 years				
Cases/cohort	11/2,990	46/8,181	54/8,169	
HR (95% CI)	1.0 (ref)	1.4 (0.74–2.8)	1.7 (0.86–3.2)	0.19
Non-aggressive prostate cancer, 65± years				
Cases/cohort	36/1,721	87/5,131	89/5,509	
HR (95% CI)	1.0 (ref)	0.73 (0.50–1.1)	0.60 (0.41–0.88)	0.03
Aggressive				
Cases/cohort	28/4,907	91/13,872	92/14,239	
HR (95% CI)	1.0 (ref)	1.1 (0.71–1.7)	1.0 (0.67–1.6)	0.24

*Adjusted for family history of prostate cancer, BMI, stratified on PSA in 2 years before baseline and income

[a]The median MET-hours/week in the cohort were 10.5

[b]p for interaction = 0.005

[c]p for interaction = 0.02

[‡]Aggressive tumors are poorly differentiated (Gleason score 7–10) or regional/distant stage

limitation of our study is that we had no data on screening after baseline. Presumably, a history of PSA screening is a good predictor of future PSA testing, but it is clearly imperfect. To try to address this concern, we planned a priori to stratify on PSA screening because we assumed that associations observed in the unscreened group might be less likely to suffer from bias due to screening. Although we hypothesized that associations observed among men not screened would be similar to those for aggressive tumors, this was not the case, and in fact, the opposite was true. Surprisingly, there was very little difference in the proportion of aggressive disease by PSA screening; 36.6% of the cases who had a PSA in the 2 years before baseline developed aggressive disease compared to 38.8% of the cases who did not have a PSA. Thus, it is difficult to determine whether the associations we observed are causal or simply due to residual confounding or some other bias.

There are no straightforward mechanistic explanations for our finding of differential effects of physical activity in normal-weight and obese men. Alterations in endogenous hormones are the most widely accepted mechanisms for how both physical activity and obesity might influence prostate cancer risk, although our understanding of the complex relationships between steroid hormone concentrations and prostate cancer risk is incomplete. The literature on physical activity and hormones in men is sparse, but physical activity appears to increase SHBG and may lower testosterone levels [11, 40]. In contrast, obesity in