TABLE 3. Multivariate relative risk* of renal cell cancer in relation to level of physical activity, according to body mass index at baseline, NIH-AARP Diet and Health Study, 1995–2003†

Frequency or level of physical activity	Body mass index < 25.0			Body mass index ≥ 25.0		
	No. of cases	Multivariate RR‡	95% CI‡	No. of cases	Multivariate RR	95% CI
Current exercise/sports						
Never/rarely	53	1.00	Referent	205	1.00	Referent
1–3 times/month	27	0.67	0.42, 1.07	122	0.80	0.63, 1.00
1–2 times/week	50	0.70	0.47, 1.03	210	0.88	0.73, 1.07
3–4 times/week	93	0.88	0.62, 1.24	241	0.86	0.71, 1.05
≥5 times/week	56	0.63	0.43, 0.93	151	0.81	0.65, 1.00
p for trend		0.22			0.25	
Daily routine activity						
Mostly sitting	18	1.00	Referent	92	1.00	Referent
Sitting and walking	84	0.89	0.53, 1.48	334	0.95	0.76, 1.20
Walking and standing	118	0.88	0.53, 1.45	341	0.86	0.68, 1.09
Climbing stairs or hills or light lifting	53	0.80	0.47, 1.38	133	0.78	0.60, 1.03
Heavy work	6	0.63	0.25, 1.59	29	0.91	0.60, 1.39
p for trend		0.48			0.06	
Physical activity during adolescence						
Never/rarely	39	1.00	Referent	84	1.00	Referent
1–3 times/month	16	0.61	0.34, 1.10	65	1.12	0.81, 1.55
1–2 times/week	40	0.65	0.42, 1.02	144	1.06	0.81, 1.40
3–4 times/week	76	0.75	0.51, 1.11	192	0.79	0.61, 1.02
≥5 times/week	108	0.64	0.44, 0.94	444	0.92	0.72, 1.16
p for trend		0.18			0.09	

* Multivariate models included adjustment for age, sex, body mass index (weight (kg)/height $(m)^2$) at baseline (<25, 25–29.9, 30.0–34.9, 35.0–39.9, or ≥40), current height (m), race/ethnicity (White, Black, or other), smoking status (never smoker, current smoker of 1–10, 11–20, 21–30, 31–40, 41–60, or >60 cigarettes/day, or former smoker of 1–10, 11–20, 21–30, 31–40, 41–60, or >60 cigarettes/day), history of diabetes (yes/no), energy-adjusted protein intake (quintiles), and history of hypertension (yes/no).

† *P* values for interaction for current exercise/sports, routine physical activity, and physical activity during adolescence were 0.57, 0.93, and 0.09 respectively. Because of missing data, numbers of cases do not sum to the total number of cases available for analysis ($n = 1,238$).

‡ RR, relative risk; CI, confidence interval.

Qualitatively, physical activity was associated with greater reductions in renal cell cancer risk among participants who were normal-weight (body mass index < 25) than among those who were overweight, but the difference was not sufficient to reach statistical significance.

To our knowledge, no previous prospective studies have examined the association of physical activity during adolescence with renal cell cancer. Thus, we further explored this relation in several subgroups of potential interest (table 4). Among women, physical activity during adolescence had a graded dose-response relation with renal cell cancer, with a 38 percent reduction in risk being seen among women who were active five or more times per week. Age at menarche neither confounded nor modified this relation (*p* for interaction = 0.56), indicating that physical activity probably acts through a mechanism other than delayed exposure to estrogens to reduce renal cell cancer risk. Among men, physical activity during adolescence was not associated with reduced risk of renal cell cancer. Overall, however, a test for effect modification did not reveal statistically significant differences by sex (*p* for interaction = 0.28). Similarly, in analyses stratified by age, smoking status, or history of hypertension, we did not uncover any evidence of important effect modification (all *p*'s for interaction > 0.05).

With respect to current exercise/sports and routine activity, we found little evidence that the observed associations varied according to age, smoking status, or history of hypertension (all *p*'s for interaction > 0.05). However, men who engaged

TABLE 4. Relative risk of renal cell cancer in relation to frequency of physical activity during adolescence, NIH-AARP Diet and Health Study, 1995–2003*

	Frequency of physical activity during adolescence					p_{trend}
	Never/ rarely	1–3 times/ month	1–2 times/ week	3–4 times/ week	≥5 times/ week	
Sex						
Men						
No. of cases	63	53	131	201	481	
Person-years of follow-up	127,609	104,574	261,553	486,564	981,534	
Multivariate RR†	1.00	1.05	1.03	0.83	0.96	0.55
95% CI†	Referent	0.73, 1.51	0.76, 1.39	0.62, 1.10	0.72, 1.25	
Women						
No. of cases	66	29	53	76	85	
Person-years of follow-up	223,672	121,417	235,939	328,127	439,959	
Multivariate RR	1.00	0.82	0.77	0.77	0.62	<0.01
95% CI	Referent	0.53, 1.27	0.54, 1.11	0.55, 1.07	0.45, 0.86	
Age (years) at baseline						
<65						
No. of cases	72	49	108	151	327	
Person-years of follow-up	231,227	153,975	331,623	530,814	932,985	
Multivariate RR	1.00	0.96	0.93	0.75	0.84	0.15
95% CI	Referent	0.66, 1.37	0.69, 1.26	0.57, 1.00	0.65, 1.09	
≥65						
No. of cases	57	33	76	126	239	
Person-years of follow-up	120,054	72,016	165,869	283,877	488,508	
Multivariate RR	1.00	0.90	0.86	0.78	0.79	0.05
95% CI	Referent	0.59, 1.39	0.61, 1.21	0.57, 1.07	0.59, 1.06	
Smoking status						
Never smoker						
No. of cases	41	23	47	85	158	
Person-years of follow-up	141,168	83,038	183,175	284,237	492,925	
Multivariate RR	1.00	0.92	0.82	0.89	0.85	0.55
95% CI	Referent	0.55, 1.54	0.54, 1.25	0.64, 1.29	0.60, 1.21	
Former smoker						
No. of cases	64	45	105	148	311	
Person-years of follow-up	158,692	106,043	238,283	406,338	715,926	
Multivariate RR	1.00	1.00	0.99	0.77	0.85	0.10
95% CI	Referent	0.69, 1.47	0.72, 1.35	0.57, 1.03	0.65, 1.12	
Current smoker						
No. of cases	17	13	24	40	67	
Person-years of follow-up	38,918	28,455	59,334	96,155	162,148	
Multivariate RR	1.00	0.98	0.79	0.76	0.67	0.10
95% CI	Referent	0.48, 2.03	0.42, 1.47	0.43, 1.35	0.39, 1.15	
Hypertension status‡						
History of hypertension						
No. of cases	43	23	58	82	193	
Person-years of follow-up	79,566	49,292	109,437	179,612	315,734	
Multivariate RR	1.00	0.81	0.81	0.64	0.77	0.58
95% CI	Referent	0.49, 1.34	0.57, 1.27	0.47, 0.99	0.59, 1.16	
No history of hypertension						
No. of cases	30	19	39	65	117	
Person-years of follow-up	107,533	70,690	153,805	246,685	408,316	
Multivariate RR	1.00	0.90	0.81	0.76	0.74	0.19
95% CI	Referent	0.51, 1.60	0.50, 1.30	0.49, 1.18	0.49, 1.12	

* All p's for interaction > 0.05. Because of missing data, numbers of cases do not sum to the total number of cases available for analysis (n = 1,238).

† RR, relative risk, CI, confidence interval.

‡ Data were available only for those participants who answered the supplemental questionnaire (~60% of the cohort).

in routine physical activity had a reduced risk of renal cell cancer (for heavy work, multivariate RR = 0.78, 95 percent CI: 0.52, 1.18; p for trend = 0.04), whereas women did not (multivariate RR = 0.96, 95 percent CI: 0.33, 2.77; p for trend = 0.42; p for interaction = 0.01). No further statistically significant interactions were observed by sex. For example, men who engaged in exercise/sports five or more times per week had a 23 percent reduced risk of renal cell cancer (multivariate RR = 0.77, 95 percent CI: 0.62, 0.95), which was comparable to the 24 percent reduction observed in women who frequently exercised (multivariate RR = 0.76, 95 percent CI: 0.51, 1.11; p for interaction = 0.28).

DISCUSSION

In this large prospective cohort study of nearly 500,000 AARP members, we investigated three measures of physical activity—current exercise/sports, routine activity, and activity during adolescence—in relation to renal cell cancer. We found that each activity measure was related to reduced risk of renal cell cancer, with a borderline statistically significant association for exercise/sports and statistically significant associations for routine activity and activity during adolescence. Depending on the specific type of activity assessed, physical activity was associated with risk reductions ranging from 16 percent (for heavy work during daily routine) to 23 percent (for frequent exercise/sports at baseline) relative to inactivity. The associations between physical activity and renal cell cancer appeared to be more pronounced in persons who were normal-weight than in persons who were overweight. This may indicate that physical activity is unable to compensate for the adverse consequences of excess weight with respect to renal cell cancer risk. Alternatively, normal-weight persons may recall physical activity with greater accuracy.

To our knowledge, our study was the first prospective cohort investigation of the association between physical activity during adolescence and renal cell cancer. Among women but not among men, we found a graded inverse relation between activity during adolescence and renal cell cancer. Possible explanations for our findings include that physical activity may inhibit development of potential renal cell cancer precursors such as renal injury (23, 24) or that adolescent physical activity acts as a proxy for activity undertaken during a longer span of time, perhaps including the early years of adulthood.

Several biologic mechanisms have been proposed by which increased physical activity may be linked to lower renal cell cancer risk. In randomized controlled trials, physical activity has been demonstrated to reduce blood pressure (25, 26), a well-established risk factor for renal cell cancer (27). Exercise may also reduce lipid peroxidation (28), a process which may increase the frequency of DNA mutations in renal cells and hence induce renal cell cancer (28). Physical activity is associated with a decrease in serum insulin levels (5). Low insulin levels result in slower proliferation of renal cell cancer in vitro (29). Lower levels of insulin-like growth factor 1 have also been associated with decreased risk of renal cell cancer. Physical activity, through its insulin-reducing effects, may increase the concentration of insulin-like growth factor 1 binding proteins and thereby reduce the pool of bioactive insulin-like growth factor 1 (30). Physical activity may act through its correlate, low body weight, to promote renal health by decreasing oxidative stress (31) and renal atherosclerosis (32).

Despite biologic plausibility, previous prospective cohort studies have not consistently found that physical activity is related to reduced renal cell cancer risk. Reported findings have been as wide-ranging as increased risk (9), no association with risk (13), and reduced risk (10, 12, 17) of renal cell cancer with increasing activity level. In the largest of these prospective cohort studies, comprising 347 cases, physical activity was inversely related to renal cell cancer among women but not among men (17). In the second-largest prospective cohort study, comprising 275 cases, a high level of leisure-time physical activity was related to a nonsignificant reduced risk of renal cell cancer in men (multivariate RR = 0.74, 95 percent CI: 0.44, 1.23) but not in women (multivariate RR = 1.13, 95 percent CI: 0.56, 2.29) (13). Previous prospective cohort studies included relatively few cases, particularly in analyses stratified according to sex, which may have contributed to the inconsistency of their findings.

Case-control studies have reported similarly varying relations between physical activity and renal cell cancer (7, 11, 14–16). Case-control studies, however, are prone to selection and recall biases, which may explain their inconsistent results. In the case-control studies that found statistically significant associations, an increasing level of physical activity was associated with reductions in renal cell cancer risk ranging from 34 percent (17) to 54 percent (10). With respect to activity during adolescence, two case-control studies found a reduced risk of renal cell cancer with increasing adolescent activity level (11, 16), but another found no such link (7).

A major strength of our study is that it included a substantial number of renal cell cancer cases, thereby allowing us to detect a potentially modest association. The large sample size also allowed us to conduct exploratory analyses stratified by sex, age, race/ethnicity, smoking status, body mass index, and history of hypertension with reasonable statistical power. We were also able to examine multiple physical activity domains (i.e., current exercise/sports, activity during one's daily routine, and activity during adolescence). Additional strengths of our study included the prospective design and the availability of data on many important potential confounders.

Our study also had several important limitations. Because our study was observational, we cannot exclude the possibility that residual confounding explains some or all of the observed reduced risk of renal cell cancer associated with physical activity. In particular, we adjusted for self-reported body mass index as a proxy for adiposity. Consequently, incomplete adjustment for adiposity may partly explain our findings. Our assessments of physical activity, while incorporating elements of previously validated instruments (21), were based on self-reports and may have resulted in some degree of misclassification of physical activity levels. Our question concerning routine activity may not have captured activity arising from housework. Since women commonly engage in housework, this may explain why we

observed weaker relations with routine activity among women in our study. Because members of our study were at least 50 years of age at baseline, our inquiry into activity during adolescence required participants to recall activity from a period approximately 30–40 years in the past. Such distant recall may result in imprecise assessment and could result in error in the estimation of relative risks.

We also lacked information on blood pressure history for many of the participants in our study. High blood pressure is a known risk factor for renal cell cancer (27) and is also associated with physical activity and therefore may be a confounding factor. However, in a secondary analysis of only those participants who self-reported data on history of high blood pressure, we found that hypertension neither confounded nor modified the association between physical activity and renal cell cancer.

In conclusion, our study demonstrates that physical activity, including activity undertaken during adolescence, is associated with a reduced risk of renal cell cancer. Our results contribute to the accumulating evidence that physical inactivity predisposes people to cancer and further support the conclusion that physical activity is an important target for cancer prevention efforts.

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Conflict of interest: none declared.

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論文名	Physical activity during adulthood and adolescence in relation to renal cell cancer
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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(62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		( )
アウトカム 維持・改善	な し	な し	な し	なし	(	( )

図 表

TABLE 2. Relative risk of renal cell cancer in relation to level of physical activity, NIH-AARP Diet and Health Study, 1995–2003

Frequency or level of physical activity	No. of cases	Person-years of follow-up	Age- and sex-adjusted estimate		Multivariate estimate*		Mutually adjusted estimate†	
			RR‡	95% CI‡	RR	95% CI	RR	95% CI
Current exercise/sports								
Never/rarely	265	587,749	1.00	Referent	1.00	Referent	1.00	Referent
1–3 times/month	153	455,651	0.73	0.60, 0.89	0.77	0.63, 0.95	0.79	0.65, 0.97
1–2 times/week	266	723,952	0.77	0.65, 0.91	0.85	0.72, 1.01	0.89	0.74, 1.06
3–4 times/week	343	898,825	0.76	0.65, 0.89	0.89	0.75, 1.05	0.94	0.79, 1.11
≥5 times/week	211	644,770	0.63	0.53, 0.76	0.77	0.64, 0.92	0.81	0.67, 0.98
p for trend				<0.01		0.10		0.31
Daily routine activity								
Mostly sitting	113	261,331	1.00	Referent	1.00	Referent	1.00	Referent
Sitting and walking	428	1,087,126	0.85	0.69, 1.05	0.95	0.77, 1.17	0.97	0.79, 1.20
Walking and standing	471	1,278,083	0.75	0.61, 0.92	0.88	0.71, 1.09	0.91	0.74, 1.13
Climbing stairs or hills or light lifting	191	584,431	0.66	0.52, 0.83	0.80	0.63, 1.02	0.84	0.66, 1.07
Heavy work	35	99,978	0.72	0.49, 1.05	0.84	0.57, 1.22	0.89	0.60, 1.31
p for trend				<0.01		0.03		0.09
Physical activity during adolescence								
Never/rarely	129	351,281	1.00	Referent	1.00	Referent	1.00	Referent
1–3 times/month	82	225,991	0.93	0.71, 1.23	0.93	0.71, 1.23	0.95	0.72, 1.26
1–2 times/week	184	497,491	0.90	0.71, 1.12	0.90	0.72, 1.13	0.92	0.74, 1.16
3–4 times/week	277	814,691	0.78	0.63, 0.96	0.77	0.62, 0.95	0.79	0.64, 0.98
≥5 times/week	566	1,421,493	0.86	0.70, 1.04	0.82	0.68, 1.00	0.86	0.70, 1.04
p for trend				0.16		0.05		0.11

* Multivariate models included adjustment for age, sex, body mass index (weight (kg)/height (m)^2) at baseline (<25, 25–29.9, 30.0–34.9, 35.0–39.9, or ≥40), current height (m), race/ethnicity (White, Black, or other), smoking status (never smoker, current smoker of 1–10, 11–20, 21–30, 31–40, 41–60, or >60 cigarettes/day, or former smoker of 1–10, 11–20, 21–30, 31–40, 41–60, or >60 cigarettes/day), history of diabetes (yes/no), energy-adjusted protein intake (quintiles), and history of hypertension (yes/no).

† Mutually adjusted for current exercise/sports, routine physical activity, and physical activity during adolescence, in addition to the covariates included in the multivariate models.

‡ RR, relative risk; CI, confidence interval.

図表掲載箇所	
概 要 (800字まで)	<目的>身体活動と腎臓ガンの関係を明らかにすること。<方法>コホート名:the NIH-AARP Diet and Health Study、対象者数:482386人、追跡期間:8.2年、身体活動評価方法詳細:直近の1年間に"汗をかいたり、心拍数が上がるような20分以上の運動を週何回行いましたか?に対し、なし 1回未満 1～2回 3～4回 5回以上の回答に基づき5分位に分類。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5:5-7回/週であった。<結果>余暇身体活動と腎臓がん発症の関係は、分位1:1、分位2:0.79(0.65-0.97)、分位3:0.89(0.74-1.06)、分位4:0.94(0.79-1.11)、分位5:0.81(0.67-0.98であった。
結 論 (200字まで)	20分以上の息が弾む程度の運動を月に2-3回の行うことで腎臓がんの発症リスクが下がる。
エキスパートによるコメント (200字まで)	希少な腎臓がんの発症と運動との関係を大規模な研究で明らかにした研究で意義深い。

担当者 宮地元彦

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

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Abstract

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

Introduction

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

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

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Materials and Methods

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Results

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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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	男性	( )		( )		( )
年齢	50-71(62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		( )
アウトカム 維持・改善	な し	な し	な し	なし	(	( )

図　表

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

Physical activity	No. cases	Person-years	Age adjusted RR (95% CI)	Multivariate* RR (95% CI)	Mutually adjusted† RR (95% CI)
All prostate cancer cases					
Exercise at baseline					
Never/rarely	2,487	292,369	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1-3 times/mo	2,231	262,054	1.05 (0.99-1.11)	1.00 (0.95-1.06)	1.00 (0.95-1.06)
1-2 times/wk	3,869	441,674	1.05 (1.00-1.11)	0.99 (0.94-1.05)	1.00 (0.95-1.05)
3-4 times/wk	5,174	564,533	1.05 (1.00-1.10)	0.97 (0.93-1.02)	0.98 (0.93-1.03)
≥5 times/wk	4,111	430,500	1.08 (1.03-1.13)	1.01 (0.96-1.07)	1.02 (0.97-1.08)
P for trend			0.02	0.78	0.49
Activity during adolescence					
Never/rarely	1,131	130,091	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1-3 times/mo	921	106,070	1.03 (0.94-1.12)	1.01 (0.92-1.10)	1.01 (0.92-1.10)
1-2 times/wk	2,425	265,404	1.06 (0.99-1.14)	1.02 (0.95-1.10)	1.02 (0.95-1.10)
3-4 times/wk	4,457	493,204	1.03 (0.97-1.10)	0.99 (0.92-1.05)	0.99 (0.93-1.05)
≥5 times/wk	8,938	996,362	1.02 (0.96-1.08)	0.97 (0.91-1.03)	0.97 (0.91-1.03)
P for trend			0.51	0.03	0.03
Advanced prostate cancer cases					
Exercise at baseline					
Never/rarely	261	292,369	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1-3 times/mo	272	262,054	1.20 (1.01-1.42)	1.16 (0.98-1.37)	1.16 (0.97-1.37)
1-2 times/wk	400	441,674	1.03 (0.88-1.21)	0.99 (0.85-1.16)	0.99 (0.85-1.17)
3-4 times/wk	551	564,533	1.08 (0.93-1.25)	1.04 (0.89-1.21)	1.05 (0.90-1.22)
≥5 times/wk	458	430,500	1.17 (1.00-1.36)	1.14 (0.97-1.33)	1.16 (0.99-1.36)
P for trend			0.19	0.25	0.15
Activity during adolescence					
Never/rarely	123	130,091	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1-3 times/mo	95	106,070	0.96 (0.75-1.26)	0.94 (0.72-1.23)	0.93 (0.71-1.22)
1-2 times/wk	277	265,404	1.11 (0.90-1.37)	1.08 (0.87-1.33)	1.07 (0.86-1.33)
3-4 times/wk	490	493,204	1.04 (0.86-1.27)	1.00 (0.82-1.22)	1.00 (0.82-1.22)
≥5 times/wk	957	996,362	1.00 (0.85-1.21)	0.95 (0.78-1.14)	0.95 (0.77-1.13)
P for trend			0.48	0.18	0.12
Fatal prostate cancer cases‡					
Exercise at baseline					
Never/rarely	90	423,919	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1-3 times/mo	79	385,228	1.03 (0.76-1.39)	1.14 (0.84-1.54)	1.14 (0.84-1.55)
1-2 times/wk	112	651,165	0.83 (0.63-1.09)	0.98 (0.74-1.30)	0.98 (0.74-1.30)
3-4 times/wk	129	835,564	0.68 (0.52-0.89)	0.86 (0.65-1.14)	0.86 (0.65-1.14)
≥5 times/wk	103	637,901	0.70 (0.53-0.93)	0.90 (0.67-1.20)	0.90 (0.67-1.20)
P for trend			<0.01	0.12	0.12
Activity during adolescence					
Never/rarely	37	190,777	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1-3 times/mo	27	155,750	0.93 (0.57-1.53)	0.97 (0.59-1.59)	0.95 (0.58-1.56)
1-2 times/wk	62	390,893	0.83 (0.55-1.24)	0.90 (0.60-1.35)	0.89 (0.59-1.34)
3-4 times/wk	131	728,221	0.92 (0.64-1.32)	1.00 (0.69-1.44)	1.00 (0.69-1.46)
≥5 times/wk	256	1,468,137	0.89 (0.63-1.26)	0.96 (0.67-1.36)	0.98 (0.69-1.39)
P for trend			0.85	0.99	0.77

*Multivariate models are adjusted for age at baseline, age squared, history of digital rectal exam during the past 3 y (none, once, more than once), history of PSA exam during the past 3 y (none, once, more than once), BMI at baseline (<25, 25-29.9, 30.0-34.9, 35.0-39.9, 40+), BMI at age 18 (<25, 25-29.9, 30.0-34.9, 35.0-39.9, 40+), waist circumference (<35 inches, 35-38, 39-41, 42-44, 44+), history of diabetes (yes/no), highest level of education (did not complete high school, completed high school, some college, completed college and/or graduate school), marital status (married, divorced, separated, widowed, unmarried), smoking history (current smoker, former smoker, nonsmoker), family history of prostate cancer (yes/no), multivitamin use (yes/no), supplemental zinc use (yes/no), alcohol intake (quintiles), and quintiles of energy-adjusted intakes of red meat, processed meats, α-linolenic acid, γ-tocopherol, lycopene, fish, calcium (from the combination of food and supplements), and vitamin D (from the combination of food and supplements).
†Mutually adjusted for exercise at baseline and activity during adolescence in addition to the covariates included in the multivariate models.
‡For fatal prostate cancers, we also examined alternative models with a reduced set of covariates; age at baseline, history of digital rectal exam during the past 3 y, history of PSA exam during the past 3 y, BMI at baseline, BMI at age 18, smoking history, family history of prostate cancer, and intakes of γ-tocopherol and calcium. There were no substantial departures in the estimated β-coefficients (all changes less than 10%) or in the tests for trend (no models crossed the threshold of statistical significance).

図表掲載箇所	
概　要 (800字まで)	＜目的＞身体活動が前立腺がんの発症を抑制することはよく知られているが、進行性の前立腺がんでどうかは明らかではない。余暇身体活動と進行した致死性の前立腺がん発症との関係を検討した。＜方法＞コホート名：the NIH-AARP Diet and Health Study、対象者数：293902人、追跡期間：8.2年、身体活動評価方法詳細：アメリカスポーツ医学会の指針に則り20分間以上継続する汗がでるような運動を何回やっていますか？について、思春期と直近の3年について調べた。身体活動の単位：回/週。分位毎の身体活動は、分位1：なし、因子2：1回か2回／週、分位3：3-4回／週、分位4：5回／週であった。＜結果＞余暇身体活動と全前立腺がん発症リスクとの関係は、分位1：1、分位2：1(0.95-1.06)、分位3：1(0.95-1.05)、分位4：0.98(0.93-1.03)、分位5：1.02(0.97-1.08)であり、関連は見られなかった。また、進行性致死性がんに関しても関連は見られなかった。さらに思春期の身体活動も関係がなかった。
結　論 (200字まで)	思春期(18歳児)及び直近の運動習慣と前立腺ガンの発症は関係ない
エキスパートによるコメント (200字まで)	進行性前立腺がんと運動習慣には関連が弱いことを示した研究で、身体活動・運動によるがん予防の限界を明示した点で意味がある。

担当者　　宮地元彦

Combined Impact of Lifestyle-Related Factors on Total and Cause-Specific Mortality among Chinese Women: Prospective Cohort Study

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Abstract

Background: Although cigarette smoking, excessive alcohol drinking, obesity, and several other well-studied unhealthy lifestyle-related factors each have been linked to the risk of multiple chronic diseases and premature death, little is known about the combined impact on mortality outcomes, in particular among Chinese and other non-Western populations. The objective of this study was to quantify the overall impact of lifestyle-related factors beyond that of active cigarette smoking and alcohol consumption on all-cause and cause-specific mortality in Chinese women.

Methods and Findings: We used data from the Shanghai Women's Health Study, an ongoing population-based prospective cohort study in China. Participants included 71,243 women aged 40 to 70 years enrolled during 1996–2000 who never smoked or drank alcohol regularly. A healthy lifestyle score was created on the basis of five lifestyle-related factors shown to be independently associated with mortality outcomes (normal weight, lower waist-hip ratio, daily exercise, never exposed to spouse's smoking, higher daily fruit and vegetable intake). The score ranged from zero (least healthy) to five (most healthy) points. During an average follow-up of 9 years, 2,860 deaths occurred, including 775 from cardiovascular disease (CVD) and 1,351 from cancer. Adjusted hazard ratios for mortality decreased progressively with an increasing number of healthy lifestyle factors. Compared to women with a score of zero, hazard ratios (95% confidence intervals) for women with four to five factors were 0.57 (0.44–0.74) for total mortality, 0.29 (0.16–0.54) for CVD mortality, and 0.76 (0.54–1.06) for cancer mortality. The inverse association between the healthy lifestyle score and mortality was seen consistently regardless of chronic disease status at baseline. The population attributable risks for not having 4–5 healthy lifestyle factors were 33% for total deaths, 59% for CVD deaths, and 19% for cancer deaths.

Conclusions: In this first study, to our knowledge, to quantify the combined impact of lifestyle-related factors on mortality outcomes in Chinese women, a healthier lifestyle pattern—including being of normal weight, lower central adiposity, participation in physical activity, nonexposure to spousal smoking, and higher fruit and vegetable intake—was associated with reductions in total and cause-specific mortality among lifetime nonsmoking and nondrinking women, supporting the importance of overall lifestyle modification in disease prevention.

Please see later in the article for the Editors' Summary.

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Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MET, metabolic equivalent; PAR, population attributable risk; SES, socioeconomic; SWHS, Shanghai Women's Health Study; WHR, waist-hip ratio

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Introduction

Lifestyle-related factors—such as high adiposity, low or no exercise participation, unhealthy dietary habits, and environmental tobacco smoke—each have been linked to an increased risk of multiple chronic diseases and premature death [1–11]. However, few studies have investigated the combined impact of these lifestyle-related factors and mortality outcomes [2,12–15]. Research to quantify the overall impact of lifestyle-related factors on mortality outcomes will provide important information valuable for disease prevention. A recent prospective cohort study of 77,782 participants of the Nurse's Health Study (NHS) found a more than 4-fold increase in risk of all-cause mortality among women aged 34–59 y who reported ever smoking, a body mass index (BMI) $\geq$25 kg/m^2, <30 min per day of physical activity, an unhealthy diet score, and heavy or no alcohol drinking, compared to women with none of these risk factors [13]. Another prospective cohort study among 20,244 British men and women aged 45–79 y similarly reported a 4-fold increase in risk of all-cause mortality for participants with no health behaviors compared to participants who had four health behaviors (nonsmoker, plasma vitamin C levels indicative of $\geq$5 daily servings of fruits and vegetables, moderate alcohol intake, and physically active) [14].

Most studies of combinations of established lifestyle factors and mortality have been conducted in the United States and countries in Western Europe. Data are limited for other populations, including Chinese women, whose lifestyles differ considerably from their European counterparts [16,17]. Further, active smoking and alcohol consumption, which are two well-studied predictors of mortality [2,13], have been included in the previous studies. However, many women, and in particular Asian women [17], do not actively smoke or drink regularly, and thus it is important to study practical disease prevention measures for these women. Little is known, however, at present about the combined impact of lifestyle factors beyond that of active smoking and alcohol drinking on mortality.

In the Shanghai Women's Health Study, a population-based cohort study of approximately 75,000 middle-aged and older Chinese women, less than 3% of cohort members reported ever smoking and drinking alcohol regularly, providing a unique opportunity to quantify the overall impact of lifestyle factors other than active smoking and alcohol consumption on total and cause-specific mortality. Well-studied lifestyle-related factors relevant for this population were selected on the basis of prior knowledge of lifestyle factors in relation to mortality and with consideration of practical public health recommendations [1,3–9,18–24]. Specifically, the lifestyle factors selected included: (1) BMI, (2) waist-hip ratio (WHR), (3) exercise participation, (4) environmental tobacco smoke (assessed as exposure to spousal smoking), and (5) fruit and vegetable daily intake.

Methods

Study Population

Participants of this analysis are individuals in the Shanghai Women's Health Study (SWHS), an ongoing prospective cohort study of Chinese women. The study methods and rationale have been reported in detail elsewhere [17]. Briefly, participants were recruited from seven urban counties in Shanghai, China. A total of 74,942 women aged 40–70 y were recruited from December 1996 through May 2000 with a participation rate of 92.7%. The baseline survey included an in-person interview, self-administered questionnaire, and anthropometric measurements taken by trained interviewers using standardized protocols. Information was collected on demographics, lifestyle habits (e.g., diet, physical activity, alcohol, smoking), menstrual and reproductive history, medical history, occupational history, and select information from each participant's spouse (e.g., disease history, smoking and alcohol habits). Both the food frequency and physical activity questionnaires have been validated and reported elsewhere [25,26]. All participants provided written informed consent, and human participant Institutional Review Board (IRB) approval was obtained by the appropriate IRBs in China and the United States.

Follow-up for participants has included in-person interviews every 2–3 y to collect interim health history. Response rates were 99.8%, 98.7%, and 96.7% for the first, second, and third follow-up surveys, respectively. Data on vital status and cancer diagnoses also have been obtained by annual linkage to the population-based Shanghai cancer and vital statistics registries. Outcome data for the present analysis were censored at December 31, 2007.

Lifestyle-Related Factors

Data from the baseline interview were used to assess the lifestyle factors of interest. We were interested in lifestyle-related factors that are simple to assess and have been well-studied previously in relation to mortality. BMI, a measure of general adiposity, was calculated as measured weight in kilograms divided by measured height in meters squared and categorized using the World Health Organization (WHO) classifications [27]: underweight (<18.5 kg/m^2), normal weight (18.5–24.99 kg/m^2), overweight (25–29.99 kg/m^2), obese ($\geq$30 kg/m^2). Waist and hip circumference measurements were used to calculate the WHR (waist divided by hip circumference), a measure of central adiposity, and classified into three categories according to tertiles. During the baseline interview, participants were asked about regular exercise in the past 5 y ("regular" was defined as at least once per week, for more than 3 mo continuously). Information was also collected on type, intensity, and duration for up to three activities. We categorized exercise using standard metabolic equivalents (METs) as MET-hours/day (no exercise participation, >0 to 1.99 MET-h/d, and $\geq$2.0 MET-h/d) [26,28]. One MET-hour/day is approximately equivalent to about 15 min of participation in moderate-intensity activities [20,29]. Exposure to environmental tobacco smoke was defined as ever exposed to spousal smoking or never exposed. Grams per day of fruit and vegetable intake were assessed via a food frequency questionnaire for intake over the past 12 mo and categorized into tertiles.

Statistical Analyses

The primary study outcome was deaths from all causes. Cause of death information was collected from death certificates and coded according to the International Classification of Diseases, 9th Revision (ICD-9). Cause-specific deaths examined included deaths due to cardiovascular disease (CVD) (ICD-9 codes: 390–459) and cancer (ICD-9 codes: 140–208).

Among 74,942 women who completed the baseline assessment, 2,113 reported ever smoking (2.8%) and 1,678 reported ever drinking (2.2%); these women were excluded from the analyses (n = 3,513). We also excluded women with missing data on the lifestyle factors (anthropometric measures [n = 59] and FFQ items for main foods of interest [n = 11]), with extreme daily energy intake (defined as <500 or $\geq$3,500 kcal per day) (n = 108), and who were lost to follow-up shortly after the baseline recruitment (n = 8). In addition, women who did not have information on exposure to spousal smoking (n = 7,452) were excluded from analyses of environmental tobacco smoke and the combined effect of lifestyle factors on mortality. We compared select characteristics for women included in the current analyses to women in the entire SWHS cohort (Table S1). With the exception of age, other

characteristics were comparable across the three groups: (1) the entire cohort, (2) the cohort after excluding those who met any of the exclusion criteria stated above except exposure to spousal smoking, and (3) the cohort after further excluding women with missing data for spousal smoking. Due to the large sample size, the tests for several characteristics across these three groups were statistically significant. The cohorts included in the current analysis were somewhat younger than the entire cohort, particularly because of the exclusion of those who had missing data on exposure to spousal smoking, which was primarily due to a deceased spouse.

Two healthy lifestyle scores were created on the basis of previous research and public health recommendations [5,9,18,20,21,27], as well as consideration of adequate sample sizes for the five lifestyle factors. As shown in Table 1, a point was assigned to each category for the lifestyle factors BMI, WHR, exercise, and daily fruit and vegetable intake (zero [least healthy] to two [most healthy]), while for spousal smoking status a binary variable was used (ever, zero points and never, one point). Healthy lifestyle score 1 was assigned to each woman by summing the points for the five factors, with a possible range of 0–13. Healthy lifestyle score 2 (Table 1) was created by assigning points to simple binary indicators for each of the five factors with one point for having the healthy factor and again summing the points for the five factors to assign a score to each woman (range of 0–5 points). A higher score indicated a healthier lifestyle, and we hypothesized that mortality would decrease as number of healthy lifestyle factors increased.

Cox proportional hazards regression models were used to evaluate the associations of mortality with each lifestyle factor individually and then the healthy lifestyle scores. Adjusted hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) were derived from Cox models after adjusting for potential confounders. Age was used as the time-scale for all models [30], with entry time defined as age at baseline interview and exit time defined as age at death, last follow-up, or December 31, 2007, whichever came first. We first examined associations for each lifestyle factor with mortality adjusted for age and socioeconomic (SES) indicators (occupation [manual and agricultural workers/unknown, clerical, professional], education [≤elementary, junior high school, high school, >high school], and income/person [low, ≤5,000 CNY; middle, 5,000–9999 CNY; high ≥10,000 CNY]). Next, we additionally adjusted for the other lifestyle-factors. Both BMI and WHR remained associated with mortality outcomes after adjustment for each other and the other lifestyle factors; hence, both measures were included in the lifestyle scores. Linear trends were evaluated using the Wald test, treating the lifestyle score as a continuous variable. We examined the proportional hazards assumption, both graphically and by testing the significance of interaction terms for the two lifestyle scores and years of follow-up, and found no evidence for apparent departure from the assumption of proportional hazards.

For healthy lifestyle score 2, we calculated the total population attributable risk (PAR), via summing the exposure-category specific PARs, which estimates the proportion of deaths associated with not having the highest score (i.e., four to five healthy lifestyle-related factors) [31,32]. We used the following formula to estimate total PARs (percentage), which is appropriate for multicategory exposures and uses adjusted relative risks [31]:

$$\sum_{i=0}^{k} pd_i\left(\frac{RR_i-1}{RR_i}\right)\times 100,$$

where pd_i = proportion of cases in the ith exposure level; RR_i = relative risks for comparing women with no healthy factors ($i=1$), 1 healthy factor ($i=2$), two healthy factors ($i=3$), or 3 healthy factors ($i=4$), to women with four to five healthy lifestyle factors. PAR estimates are based on the assumption that the observed associations between the lifestyle factors and mortality are causal [31]. All analyses were performed using SAS version 9.2. Tests of statistical significance were based on two-sided probability, and p-values<0.05 were considered statistically significant.

Results

After an average of 9.1 y of follow-up (648,096 person-years), 2,860 deaths were identified among the 71,243 women who reported never smoking or drinking alcohol regularly, including 1,351 from cancer and 775 from CVDs. Compared to women who survived during follow-up, a higher percentage of deceased participants were classified as underweight, overweight or obese, had a higher WHR, reported not participating in exercise regularly, were exposed to spousal smoking, and had a lower daily intake of fruits and vegetables (Table 2).

Table 3 shows the HRs for each of the five lifestyle factors with total and cause-specific mortality. In age and SES-adjusted analyses, compared to obese women, those who were normal or overweight had significantly decreased HRs for total mortality, but women who were underweight had a significantly increased HR (Table 3). The association with underweight was no longer significant after excluding deaths in the first 3 y (HR = 1.19; 95% CI 0.93–1.52), suggesting an effect of reverse causation due to weight loss caused by preexisting chronic conditions. HRs for all-cause mortality were significantly decreased for women who had a lower WHR, were physically active, never exposed to spousal smoking, or had higher daily fruit and vegetable intake. Additional adjustment for all the other lifestyle factors did not appreciably change these results, although the associations were attenuated for normal weight, and the HR for spousal smoking status became marginally significant ($p=0.061$) as shown in Table 3. Similar patterns of associations with WHR were observed for cancer and cardiovascular deaths; findings were less consistent for BMI (Table 3). The patterns of associations with exercise participation, spousal smoking, and fruit and vegetable consumption were comparable to total mortality for deaths from CVD and generally weak or absent for cancer mortality (Table 3).

We also considered waist circumference as a measure of central adiposity, however, as compared to WHR, waist circumference was not as strongly associated with mortality outcomes. Compared with the highest waist circumference tertile (≥81 cm), the HRs for total mortality for the lowest tertile (<73 cm) and the middle tertile (73 to <81 cm) were 0.78 (95% CI 0.68–0.89) and 0.89 (95% CI 0.80–0.99), respectively, adjusting for SES indicators, BMI, exercise participation, spouse smoking status, and fruit and vegetable intake. Similar HRs were found for cardiovascular and cancer mortality, although the HRs for the middle tertile of waist circumference were not statistically significant (unpublished data).

A higher healthy lifestyle score 1 was significantly associated with a reduced risk of mortality from all-causes ($p_{trend}<0.01$), and from CVD ($p_{trend}<0.01$) and cancer ($p_{trend}=0.022$) (Table 4). For example, women with 7–9 points (most healthy), had a 47% reduction in risk of all-cause mortality (HR = 0.53; 95% CI 0.43–0.63), compared to women with 0–2 points (least healthy). Reductions in mortality associated with a higher lifestyle score were the strongest for deaths due to CVD. Similar patterns were generally seen for healthy lifestyle score 2 and total and cause-specific mortality (Table 4); hence, score 2 was used in subsequent analyses as it is simpler and easier to interpret than score 1. Not having four to five healthy lifestyle factors was associated with total

Table 1. Combined healthy lifestyle scores in the Shanghai Women's Health Study.

Lifestyle Factors Assessed at Baseline	Classification	Scoring Classification	
		Lifestyle Score 1	Lifestyle Score 2
BMI (kg/m^2)	<18.5, underweight	0	0
	≥30.0, obese	0	0
	25.0–29.99, overweight	1	0
	18.5–24.99, normal weight	2	1
WHR	Tertile 3, ≥0.830	0	0
	Tertile 2, 0.786 to <0.830	1	0
	Tertile 1, <0.786	2	1
Exercise participation (MET h/d)	No activity[a]	0	0
	>0 to 1.99[b]	1	0
	≥2.0[c]	2	1
Spouse smoke	Ever exposed to spouse's smoking	0	0
	Never	1	1
Fruit and vegetable daily intake (g)	Tertile 1, <404.3 g/d	0	0
	Tertile 2, 404.3 to <626.5 g/d	1	0
	Tertile 3, ≥626.5 g/d	2	1

[a]No exercise participation.
[b]~<30 min of moderate-intensity activity per day.
[c]~≥30 min of moderate-intensity activity per day.
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PARs of 33% for total mortality, 59% for CVD mortality, and 19% for cancer mortality (Table 4).

We examined the relation between all-cause mortality and healthy lifestyle score 2 among three subgroups of women classified by their chronic disease history at baseline: (1) women with potentially fatal chronic conditions including cancer, stroke, or coronary heart disease (CHD) ($n = 6{,}009$); (2) women with only less serious conditions, including hypertension and diabetes ($n = 12{,}209$); and (3) healthy women with no history of above-mentioned conditions ($n = 45{,}573$) (Table 5). Results for women in these three groups were fairly similar to overall findings, with significant trends for increasing number of healthy lifestyle factors in each subgroup. We also examined the association of all-cause mortality and healthy lifestyle score 2 by age (<55 y and ≥55 y). Results in these two age groups were similar to overall findings (unpublished data).

Sensitivity analyses were conducted to investigate the potential for bias due to the existence of subclinical diseases by excluding deaths occurring in the first 3 y of follow-up. Results from these analyses were similar to those shown in Table 4 for total mortality and mortality due to CVD and cancer. HRs for women with four to five healthy lifestyle factors compared to zero factors were 0.60 (95% CI 0.45–0.80; $p_{trend}<0.01$) for total mortality, 0.31 (95% CI 0.16–0.60; $p_{trend}<0.01$) for CVD mortality, and 0.75 (95% CI 0.51–1.11; $p_{trend} = 0.11$) for cancer mortality.

Figure 1 displays cumulative mortality estimates from the Cox proportional hazards regression model with age as the time-scale for score 2, adjusting for education, occupation, and income. The cumulative mortality for the healthy lifestyle score 2 by age at study exit was lowest for women with four to five healthy lifestyle factors and highest for women with zero factors (Figure 1).

Discussion

In this population-based prospective cohort study of Chinese women aged 40–70 y, we found that healthier lifestyle-related factors—including normal weight, lower WHR, participation in exercise, never being exposed to spousal smoking, and higher daily fruit and vegetable intake—were significantly and independently associated with lower risk of total and cause-specific mortality. Healthy lifestyle scores, composite measures of these five factors, were significantly associated with decreasing mortality as a number of healthy factors increased. The associations persisted for all women regardless of their baseline comorbidities. To our knowledge, this is the first large prospective cohort study specifically designed to quantify the combined impact of lifestyle-related factors on mortality outcomes among lifetime nonsmokers and nonalcohol drinkers. Results show that lifestyle factors other than active smoking and alcohol drinking have a major combined impact on mortality on a scale comparable to the effect of smoking as the leading cause of death in most populations [11,13,14].

In general, the literature is limited in regard to the study of combinations of lifestyle factors and mortality [2,12–14,33–38]. Further, most such studies have included alcohol and/or smoking [2,12,14,33–37], and little is known about the combined impact of lifestyle factors other than active smoking and drinking in relation to mortality. The answer to this question is of particular importance as there are a substantial number of people worldwide who are nonsmokers and do not drink excessively [14,39]. In an attempt to address this question, in a subgroup analysis among never-smokers in the Nurse's Health Study, van Dam and colleagues reported a 2-fold excess risk of all-cause mortality among women who had a high BMI, low physical activity, and unhealthy diet [13]. That study, however, did not consider environmental tobacco smoke or measures of central adiposity such as WHR.

Another limitation of previously published studies is that most studies have been conducted in the United States or Western Europe, and few studies have examined the combined impact of lifestyle factors in relation to mortality among Asian populations. We did, however, identify three reports from Japan, two