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Development and Application of a Lifestyle Score for Prevention of Lethal Prostate Cancer

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Abstract

Background: Several lifestyle factors have been associated with risk of lethal prostate cancer, but little is known about their combined effect. Our objective was to develop and apply a lifestyle score for prevention of lethal prostate cancer.

Methods: We developed a lifestyle score among 42 701 men in the Health Professionals Follow-up Study (HPFS) followed from 1986 to 2010 and applied it among 20 324 men in the Physicians' Health Study (PHS) followed from 1982 to 2010. One point was given for each of: not currently smoking or quit 10 or more years ago, body mass index under 30 kg/m^2, high vigorous physical activity, high intake of tomatoes and fatty fish, and low intake of processed meat. Diet-only scores (range = 0–3) and total scores (range = 0–6) were calculated. We used multivariable Cox proportional hazards regression to estimate the risk of lethal prostate cancer, adjusting for potential risk factors of lethal prostate cancer. All statistical tests were two-sided.

Results: We observed 576 lethal prostate cancer events in HPFS and 337 in PHS. Men with 5–6 vs 0–1 points had a 68% decreased risk of lethal prostate cancer (hazard ratio [HR] = 0.32, 95% confidence interval [CI] = 0.19 to 0.52) in HPFS and a non-statistically significant 38% decreased risk (HR = 0.62, 95% CI = 0.30 to 1.26) in PHS. For dietary factors only, men with 3 vs 0 points had a 46% decreased risk (HR = 0.54, 95% CI = 0.30 to 0.96) in the HPFS and a non-statistically significant 30% decreased risk (HR = 0.70, 95% CI = 0.40 to 1.23) in PHS.

Conclusions: Adhering to a healthy lifestyle, defined by not smoking, normal body weight, high physical activity, and a healthy diet, may lower risk of lethal prostate cancer.

Prostate cancer is the most frequently diagnosed cancer (1) and the second leading cause of cancer death among men in the United States (2). Most patients are diagnosed with clinically indolent tumors without lethal potential. Substantial evidence suggests that risk factors for lethal prostate cancer differ from those for indolent disease (3). Chemoprevention trials for prostate cancer have tested antioxidant supplements (selenium, vitamin E), phytochemicals (soy isoflavones, green tea polyphenols), and 5-alpha reductase inhibitors (4,5). Although some of these agents may have promise, trials have typically focused on prevention of total incident prostate cancer, with little evidence bearing on lethal disease.

Increasing evidence suggests that specific lifestyle factors affect risk of lethal prostate cancer (6). In the present analysis, we focus on six factors that have been identified as potential independent, modifiable risk factors for lethal and advanced

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prostate cancer in the Health Professionals Follow-up Study (HPFS) and multiple other observational cohorts of healthy men: body mass index (BMI) (7–9), vigorous physical activity (8,10), smoking (8,11,12), and tomato (8,13,14), fatty fish (15,16), and processed meat intake (17–19). The combined effect of these dietary and lifestyle factors is unknown.

We developed a lifestyle score based on these six factors and examined the relation of this score with risk of lethal prostate cancer in the HPFS, a large prospective cohort of US men. We hypothesized that men who adhered to more healthy behaviors would have reduced risk of lethal prostate cancer. We then sought to test our findings within an independent cohort, the Physicians' Health Study.

Methods

Study Populations

This study received institutional review board approval at each participating institution. The HPFS began in 1986 as a prospective study of 51 529 US male health professionals age 40 to 75 years at baseline. The baseline questionnaire assessed demographics, lifestyle, medical history, and included a validated, semiquantitative food frequency questionnaire (FFQ) (20). Participants complete biennial follow-up questionnaires (response rate = 96%); diet information is updated every four years.

The Physicians' Health Study (PHS) began in 1982 as a randomized trial of aspirin and beta-carotene among 22 071 healthy US male physicians age 40 to 84 years (21). Information on medical history and lifestyle factors was collected at enrollment, and yearly follow-up questionnaires updated disease status, medical history, and lifestyle factors. Ten follow-up questionnaires included an abbreviated food list, and the 2000–2002 questionnaire included a 61-item FFQ.

Identification of Prostate Cancer Cases and Outcomes

Self-reported, incident cases of prostate cancer in the PHS (1982–2010) and HPFS (1986–2010) were confirmed through medical record and pathology report review. Clinical T-stage, Gleason score, prostate cancer treatments, prostate-specific antigen (PSA) values at diagnosis and throughout follow-up and occurrence of metastases were ascertained from medical records and questionnaires sent to prostate cancer survivors and their physicians after diagnosis. An endpoint committee determined cause of death through death certificates and medical record review and, secondarily, via next of kin. The primary outcome for this analysis was lethal prostate cancer, defined as prostate cancer death or metastasis to the bones or other organs, excluding lymph nodes.

Assessment of Exposure Variables

The questionnaires used to assess diet, physical activity, and self-reported body weight in the HPFS have been validated, as previously described (20,22–24). The FFQ in the PHS was modeled after the HPFS FFQ, and we expect the validity in PHS to be similar to HPFS, given their similar professions and distribution of demographic characteristics.

Body mass index (BMI; kg/m^2): At baseline, men reported their current height and weight. Body weight was updated biennially in HPFS and nine times over follow-up in PHS. Physical activity was assessed at baseline and biennially in the HPFS. Men reported the average time per week spent over the past year doing leisure-time physical activities, as previously described (23). Activities were classified according to their metabolic equivalent of task (MET) value; those that require six or more METs were considered vigorous (25). Walking pace was updated every two to four years. In the PHS, physical activity was assessed at baseline and four times during follow-up. Participants were asked how often they "exercised to sweat" in six categories, ranging from rarely/never to daily. Current smoking status was assessed biennially in the HPFS and at baseline and four times over follow-up in the PHS. Past smokers at baseline reported when they quit.

Dietary exposures: Participants reported how often they consumed a specified portion size, from never or less than one serving per month to six or more servings per day for approximately 140 items in HPFS and 61 items in PHS. We calculated the average cumulative intake during follow-up when possible (26). For example, the average intake from 1986, 1990, and 1994 HPFS FFQs was used for the 1994 to 1998 exposure. In the PHS, there were too few dietary measures to calculate cumulative average intake; fatty fish was evaluated once between 1982 and 1985, and processed meat was evaluated as hot dog intake once between 1982 and 1985 and as hot dogs/bacon/processed meats once between 2000 and 2002.

Population for Analysis

The populations for analysis included cohort participants alive and free of diagnosed cancer, except nonmelanoma skin cancer at the start of analysis (1990 for HPFS and 1987 for PHS), after imposing a four-year lag to reduce the potential for an effect of undiagnosed aggressive prostate cancer on these lifestyle behaviors (reverse causation). For example, we applied participants' 1994 lifestyle score to deaths occurring between 1998 and 2000, their 1996 lifestyle score to deaths occurring between 2000 and 2002, and so on. We excluded 6.5% of men in HPFS and 4.0% of men in PHS who were missing the lifestyle score, leaving 42 701 men in HPFS and 20 324 in PHS in the final analysis.

Development of the Healthy Lifestyle Score in HPFS

We dichotomized each lifestyle factor in the HPFS based on standard definitions (BMI) or previously reported cut-points (all other factors) from the HPFS, as well as other independent cohorts (7,10,11,14,18,27). Men were assigned one point for each healthy lifestyle factor (range = 0–6). Healthy lifestyle factors were: BMI of less than 30 kg/m^2, high vigorous physical activity, never smoker or quit 10 or more years ago, high intake of tomatoes and fatty fish, and low intake of processed meat. To evaluate the role of diet independent of BMI, smoking status, and physical activity, we also calculated a score using only the dietary factors (range = 0–3).

Application of the Healthy Lifestyle Score in PHS

The phrasing of certain questions and the categorical responses varied somewhat between HPFS and PHS. For example, the HPFS questionnaire assessed five tomato items and PHS questionnaire assessed two tomato items. Thus, when necessary, we applied different but comparable cut-points in the PHS (Table 1). All cut-point definitions were determined prior to data analysis in the PHS (a priori) to avoid overfitting the data.

Statistical Analyses

Participants contributed person-time from the date of return of the 1990 questionnaire in HPFS and from 1987 in PHS until lethal prostate cancer diagnosis, death, or end of follow-up, whichever occurred first. End of follow-up was January 2010 in both HPFS and PHS. The event date for lethal prostate cancers was the date of diagnosis of metastases or death from prostate cancer, whichever occurred first. We updated exposure throughout follow-up until development of lethal disease, ignoring date of initial diagnosis, because we hypothesized that this exposure window would be most etiologically relevant to the development and progression of lethal prostate cancer. Secondarily, we conducted an analysis in which we stopped updating exposures at the date of prostate cancer diagnosis. To evaluate the potential of confounding by PSA screening, we also conducted a sensitivity analysis limited to an intensely screened HPFS subcohort, defined as men who reported PSA screening on 50% or more of the follow-up questionnaires from 1994 onward (PSA screening was first evaluated in 1994). We also considered models adjusted for height, intake of calcium, low fat dairy, whole milk, and coffee, energy, and selenium supplementation. There was little evidence of confounding by these factors, so they were not included in our final models. In the HPFS, we carried forward exposure data from the most recent questionnaire if data were missing (on average, 10.4% of men per cycle). In the PHS, we carried forward exposure data if: 1) the lifestyle factor was not assessed in a given cycle (number of assessments listed in Table 1) or 2) data were missing (on average, 4.4% of men per cycle).

We used Cox proportional hazards regression to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of the lifestyle score and risk of lethal prostate cancer. Age-adjusted models used age as the time scale, stratified by calendar time in two-year intervals in the HPFS and one-year intervals in the PHS (the frequency of follow-up questionnaires). Cross-product terms of the scores by a function of time were added to the models to check the proportionality assumption; no violation was found. Multivariable models were additionally adjusted for race (white, nonwhite, missing), diabetes (yes, no, missing), multivitamin use (yes, no, missing), vitamin E use (yes, no, missing), and random assignment status (aspirin, beta-carotene, both, or neither) for PHS. When examining the diet score, we adjusted for smoking, BMI, and vigorous physical activity (see categories in Table 1). When examining the association of each of the six individual factors with lethal prostate cancer risk, we adjusted for the other five factors. All statistical analyses were performed in SAS, version 9.3 (SAS Institute, Inc; Cary, NC). All *P* values were from two-sided tests; results with a two-sided *P* value of less than .05 were considered statistically significant.

Population-attributable risk (PAR): We estimated the percentage of lethal prostate cancer cases occurring in the United States that could be prevented if all men engaged in the six healthy lifestyle factors, assuming our observed associations represent causal relations. The distributions of the six lifestyle factors in the general US population were estimated based on 812 cancer-free males above age 60 years who participated in the National Health and Nutrition Examination Survey (NHANES) between 2003 and 2006 (28). To calculate the PAR, we used the following formula (29,30):

Table 1. Definitions of the lifestyle score in the Health Professionals Follow-up Study and Physicians' Health Study*

	Definition of lifestyle score		Number of times assessed	
Health factors	HPFS	PHS	HPFS	PHS
BMI	<30 kg/m² = 1 point; else 0 points		10	10
Physical activity†	≥3 h/wk vigorous activity (activities requiring ≥6 METs) and/or ≥7 h/wk brisk walking = 1 point; else 0 points	Baseline assessment: exercised to sweat ≥2 times/wk = 1 point Follow-up assessments: exercised to sweat ≥3 times/wk = 1 point; else 0 points	10	5
Smoking status	Never smoked or quit ≥ 10 years ago = 1 point; else 0 points		10	5
Tomatoes†	≥7 servings/wk raw tomatoes, tomato juice, tomato sauce, salsa, pizza = 1 point; else 0 points	≥4 servings/wk tomatoes, tomato juice = 1 point; else 0 points (note: does not include tomato sauce)	5	11
Fatty fish†	≥1 serving/wk mackerel, salmon, sardines, bluefish, swordfish = 1 point; else 0 points	≥1 serving/wk of dark fish = 1 point; else 0 points	5	1
Processed meat†	<3 servings/wk of beef or pork hot dogs, bacon, salami, bologna, or other processed meat sandwiches, and other processed meats = 1 point; else 0 points	First assessment: <1 serving/wk of hot dogs = 1 point Second assessment: <3 servings/wk of hot dogs, bacon, processed meats = 1 point; else 0 points	5	2

* The lifestyle score was calculated by adding one point per healthy factor (range = 0–6). The diet-only score was calculated by adding points from tomato, fatty fish, and processed meat intake (range = 0–3). The different cut-points for each study were based on the questions asked within each cohort. BMI = body mass index; HPFS = Health Professionals Follow-up Study; MET = metabolic equivalent of task; PHS = Physicians' Health Study.

† Questions used to assess physical activity differed between the HPFS (23) and PHS. Differences in the types of foods captured for each food item are displayed in the table.

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$$PAR = p_e(HR - 1) / [1 + p_e(HR - 1)]$$

where p_e is the exposed proportion in NHANES and HR is the hazard ratio from the multivariable model estimates from HPFS.

Results

Among 42 701 men in HPFS and 20 324 men in PHS initially free of cancer, 5597 men in HPFS and 3083 men in PHS were diagnosed with prostate cancer, and 576 and 337 of these were lethal, respectively. The median follow-up time to lethal prostate cancer diagnosis (metastasis or prostate cancer-specific death) was 12.2 (interquartile range [IQR] = 7.3–16.3) years in the HPFS and 11.0 (IQR = 8.1–18.0) years in the PHS.

Distributions of the lifestyle score, diet score, individual lifestyle factors, and select covariates in 1986 and 2002 are shown in Table 2. The PHS participants were slightly older than the HPFS. Distributions were similar across cohorts and time. Differences in the consumption of processed meats are likely because of fewer processed meat items queried on the PHS FFQ than the HPFS FFQ (Table 1).

Table 3 shows the age-adjusted and multivariable model results for the lifestyle and diet-only scores and risk of lethal prostate cancer. In both cohorts, a higher lifestyle score was inversely associated with risk, although the results were not statistically significant in PHS. Men with 5 to 6 vs 0 to 1 points had a 68% decreased risk of lethal prostate cancer (HR = 0.32, 95% CI = 0.19 to 0.52, $P_{trend} < .001$) in the HPFS and 38% decreased risk (HR= 0.62, 95% CI = 0.30 to 1.26, $P_{trend} = .09$) in the PHS. A 1-point increase in the score was associated with a 20% decreased risk in the HPFS (95% CI = 0.73 to 0.87, $P_{trend} < .001$) and 9% decreased risk in the PHS (95% CI = 0.81 to 1.02, $P_{trend} = .12$).

Similarly, an inverse association was observed when examining the diet-only score, but the relation was statistically significant only in the HPFS. Men with 3 vs 0 points had a 46% decreased risk of lethal prostate cancer (HR = 0.54, 95% CI = 0.30 to 0.96, $P_{trend =}$ .0007) in the HPFS and a 30% decreased risk (HR = 0.70, 95% CI = 0.40 to 1.23, $P_{trend} = .25$) in the PHS, adjusting for potential confounders as well as BMI, physical activity, and smoking status (Table 3). A 1-point increase in the diet-only score was associated with a 19% decreased risk (95% CI = 0.71 to 0.91, $P_{trend} = .0007$) in the HPFS and 9% decreased risk in the PHS (95% CI = 0.78 to 1.07, $P_{trend} = .25$). Our results were similar when we stopped updating exposures at the time of prostate cancer diagnosis (Table 3).

The results were similar when restricting to men in the HPFS who reported frequent PSA tests (n = 29 330, 400 events). Compared with men with 0 to 1 points, those with 2, 3, 4, and 5 to 6 points for the lifestyle score had hazard ratios of: 0.59 (95% CI = 0.38 to 0.89), 0.56 (95% CI = 0.38 to 0.83), 0.37 (95% CI = 0.24 to 0.57), and 0.27 (95% CI = 0.15 to 0.49), respectively. The hazard ratios for the dietary score for men with 1, 2, and 3 points were 0.78 (95% CI = 0.60 to 1.00), 0.68 (95% CI = 0.49 to 0.95), and 0.53 (95% CI = 0.26 to 1.06), respectively. We could not conduct this sensitivity analysis in PHS because of insufficient data on PSA screening.

Hazard ratios and 95% confidence intervals for the individual lifestyle factors are presented in Table 4 for age-adjusted and multivariable models and show the relative contribution of each variable to the score: Factors with stronger hazard ratios contributed to a greater degree to the overall score compared with the factors with weaker hazard ratios. Results

Table 2. Characteristics of men in the Health Professionals Follow-up Study and the Physicians' Health Study at baseline and during follow-up

	HPFS		PHS	
Characteristics	in 1986	in 2002	in 1986	in 2002
No. of participants	42 701	34 213	19 881*	15 390
Age, y, mean ± SD	53.5±9.6	67.6±8.6	60.7±9.1	74.0±7.4
Lifestyle score†, %				
0–1 (less healthy)	8.2	4.4	3.0	2.6
2	25.0	20.2	16.7	14.0
3	37.8	45.2	41.6	41.8
4	21.1	22.8	30.1	31.8
5–6 (more healthy)	7.9	7.4	8.7	9.8
Diet-only score‡, %				
0–1 (less healthy)	74.3	76.4	59.2	59.4
2	21.5	20.4	35.6	35.2
3 (more healthy)	4.2	3.2	5.3	5.4
BMI < 30 kg/m²§, %	91.8	85.7	95.9	91.0
High vigorous physical activity‖, %	19.4	20.0	14.0	14.4
Never smoker or quit ≥ 10 y¶, %	77.2	89.8	78.4	90.7
High tomato intake#, %	20.2	20.9	41.9	42.2
High fatty fish intake**, %	20.7	10.5	12.7	12.5
Low processed meat intake††, %	66.7	82.4	82.7	82.1
Personal history of diabetes (covariate), %	3.0	9.0	2.8	6.5
Multivitamin use (covariate), %	41.7	58.6	19.4	43.1
Vitamin E use (covariate), %	19.0	44.4	5.0	36.0

* Four hundred forty-three men in the Physicians' Health Study did not have information on all six exposures in 1986 and were added to the analysis when they completed a later questionnaire with relevant exposure information. BMI = body mass index; HPFS = Health Professionals Follow-up Study; PHS = Physicians' Health Study.

† Lifestyle score is determined by number of healthy lifestyle factors: 0 (least healthy) - 6 (more healthy).

‡ Diet score is determined by number of healthy diet factors: 0 (least healthy) - 3 (more healthy).

§ Current height and weight were assessed at baseline. Weight was assessed biennially in the HPFS and nine times over follow-up in the PHS.

‖ HPFS: Physical activity was assessed biennially. Low: <3 hrs/wk vigorous and <7 hrs/wk brisk walking. High: ≥3 hrs/wk vigorous and/or ≥7 hrs/wk brisk walking. PHS: Days per week of vigorous physical activity (*enough to sweat*) assessed at baseline and four times over follow-up. Low: <5 days/wk. High: ≥5 days/wk.

¶ HPFS: Smoking status assessed biennially. PHS: Smoking status assessed at baseline and four times over follow-up.

HPFS: Average of cumulative tomato (raw), tomato juice, tomato sauce, salsa, and pizza intake, assessed every four years. Low: <7 serv/wk. High: ≥7 serv/wk. PHS: Average of cumulative intake of tomato and tomato juice, assessed at baseline and 10 times over follow-up. Low: <4 serv/wk. High: ≥4 serv/wk.

** HPFS: Average of cumulative fatty fish intake (eg, mackerel, salmon, sardines, bluefish, swordfish), assessed every four years. Low: <1 serv/wk. High: ≥1 serv/wk. PHS: Fatty fish intake assessed once between 1982 and 1985. Low: <1 serv/wk. High: ≥ 1 serv/wk.

†† HPFS: Average of cumulative processed meat intake assessed every four years. One serving of total processed red meat = one beef or pork hot dog; two slices of bacon; salami, bologna, or other processed meat sandwich; 57 g or two links of other processed meats (eg, sausage, kielbasa, etc.). Low: <3 serv/wk. High: ≥3 serv/wk. PHS: One serving of total processed red meat = one hot dog; two slices of bacon; one piece/slice of sausage, salami, bologna, or other processed meat. Hot dog intake assessed once between 1981 and 1985. Low: <1 serv/wk. High: ≥1 serv/wk. Hot dogs, bacon, and other processed meat assessed once between 1997 and 2001. Change cut-point to Low: <3 serv/wk. High: ≥3 serv/wk.

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Table 3. Hazard ratios and 95% confidence intervals for risk of lethal prostate cancer by lifestyle score in HPFS (1990–2010) and PHS (1987–2010)*

	Exposures updated over follow-up				Exposures updated until date of diagnosis			
Lifestyle scores	Person-years of follow-up	No. of lethal prostate cancer cases	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)†	Person-years of follow-up	No. of lethal prostate cancer cases	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)†
Lifestyle score, HPFS‡								
0–1 (less healthy) (Ref)	44 744	46	1	1	44 860	50	1	1
2	164 717	128	0.66 (0.46 to 0.92)	0.65 (0.46 to 0.92)	164 927	126	0.61 (0.43 to 0.84)	0.60 (0.43 to 0.84)
3	317 101	278	0.62 (0.45 to 0.85)	0.62 (0.45 to 0.85)	316 540	256	0.54 (0.39 to 0.73)	0.53 (0.39 to 0.73)
4	163 946	101	0.46 (0.32 to 0.65)	0.45 (0.31 to 0.64)	164 107	116	0.48 (0.34 to 0.68)	0.48 (0.34 to 0.68)
5–6 (more healthy)	52 493	23	0.32 (0.19 to 0.54)	0.32 (0.19 to 0.52)	52 567	28	0.37 (0.23 to 0.59)	0.37 (0.23 to 0.59)
P_{trend}			<.001	<.001			<.001	<.001
Diet score, HPFS§								
0 (less healthy) (Ref)	126 403	123	1	1	126 792	126	1	1
1	449 206	346	0.72 (0.59 to 0.89)	0.74 (0.60 to 0.91)	448 956	333	0.69 (0.56 to 0.85)	0.71 (0.57 to 0.87)
2	144 098	94	0.61 (0.47 to 0.81)	0.64 (0.49 to 0.84)	144 052	103	0.66 (0.51 to 0.86)	0.69 (0.53 to 0.91)
3 (more healthy)	23 293	13	0.50 (0.28 to 0.89)	0.54 (0.30 to 0.96)	23 201	14	0.54 (0.31 to 0.94)	0.58 (0.33 to 1.01)
P_{trend}			.0002	.0007			.001	.005
Lifestyle score, PHS‡								
0–1 (less healthy) (Ref)	10 362	11	1	1	10 369	11	1	1
2	57 896	48	0.71 (0.36 to 1.41)	0.76 (0.38 to 1.52)	58 191	55	0.80 (0.41 to 1.58)	0.86 (0.43 to 1.70)
3	159 279	134	0.61 (0.32 to 1.17)	0.67 (0.35 to 1.29)	159 615	134	0.61 (0.32 to 1.16)	0.66 (0.34 to 1.28)
4	121 601	104	0.53 (0.28 to 1.03)	0.57 (0.29 to 1.10)	121 238	100	0.53 (0.27 to 1.01)	0.57 (0.29 to 1.11)
5–6 (more healthy)	40 079	40	0.54 (0.27 to 1.10)	0.62 (0.30 to 1.26)	39 805	37	0.52 (0.26 to 1.06)	0.62 (0.30 to 1.27)
P_{trend}			.05	.09			.009	.03
Diet score, PHS§								
0 (less healthy) (Ref)	33 741	39	1	1	33 672	31	1	1
1	192 483	150	0.66 (0.45 to 0.97)	0.71 (0.48 to 1.05)	193 033	160	0.80 (0.53 to 1.19)	0.89 (0.59 to 1.33)
2	138 906	132	0.67 (0.45 to 0.99)	0.70 (0.47 to 1.04)	138 704	125	0.75 (0.50 to 1.13)	0.83 (0.54 to 1.24)
3 (more healthy)	24 088	16	0.63 (0.36 to 1.09)	0.70 (0.40 to 1.23)	23 808	21	0.65 (0.36 to 1.17)	0.78 (0.44 to 1.41)
P_{trend}			.19	.25			.15	.30

* Cox proportional hazards regression with two-sided P values. We used a four- to six-year lag for all exposures to reduce the potential for reverse causation. Follow-up for the Health Professionals Follow-up Study began in 1990, using exposures ascertained in 1986. Follow-up for PHS started in 1987, using exposures ascertained starting in 1982. CI = confidence interval; HPFS = Health Professionals Follow-up Study; HR = hazard ratio; PHS = Physicians' Health Study.

† Adjusted for age in months (continuous), race (white, non-white, missing), diabetes (yes, no, missing), multivitamin use (yes, no, missing), and vitamin E use (yes, no, missing). We used age as the time scale, stratified by calendar time in months (HPFS) and two-year intervals (PHS). Additionally adjusted for randomization status (aspirin, beta-carotene, both, or neither) in the PHS. The multivariable model for the diet score was additionally adjusted for body mass index, physical activity, and smoking status.

‡ Lifestyle score is determined by number of healthy lifestyle factors: 0 (least healthy) - 6 (more healthy).

§ Diet score is determined by number of healthy diet factors: 0 (least healthy) - 3 (more healthy).

Table 4. Hazard ratios and 95% confidence intervals for risk of lethal prostate cancer by select lifestyle factors in HPFS (1990–2010) and PHS (1987–2010)*

	Exposures updated over follow-up					Exposures updated until date of diagnosis for case patients				
Life	Person-years of follow-up	No. of lethal prostate cancer cases	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)†	Multivariable-adjusted HR (95% CI)‡	Person-years of follow-up	No. of lethal prostate cancer cases	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)†	Multivariable-adjusted HR (95% CI)‡
Lifestyle factors, HPFS										
BMI, kg/m²§										
<30	659 766	516	0.88 (0.67 to 1.16)	0.88 (0.67 to 1.16)	0.93 (0.71 to 1.23)	660 041	518	0.91 (0.69 to 1.20)	0.90 (0.68 to 1.19)	0.93 (0.71 to 1.23)
≥30 (Ref)	83 234	60	1	1	1	82 959	58	1	1	1
Vigorous physical activity‖										
Low (Ref)	587 119	503	1	1	1	586 337	483	1	1	1
High	155 881	73	0.62 (0.48 to 0.79)	0.61 (0.47 to 0.78)	0.64 (0.50 to 0.82)	156 663	93	0.79 (0.63 to 0.99)	0.80 (0.64 to 1.00)	0.83 (0.66 to 1.05)
Smoking status¶										
Never or quit ≥10 y	624 248	496	0.83 (0.65 to 1.06)	0.83 (0.65 to 1.06)	0.88 (0.69 to 1.13)	623 662	484	0.72 (0.57 to 0.90)	0.72 (0.57 to 0.91)	0.75 (0.59 to 0.95)
Current or quit <10 y (Ref)	118 752	80	1	1	1	119 338	92	1	1	1
Tomato intake#										
Low (Ref)	604 899	496	1	1	1	605 273	494	1	1	1
High	138 101	80	0.80 (0.63 to 1.01)	0.80 (0.63 to 1.01)	0.82 (0.65 to 1.05)	137 728	82	0.83 (0.65 to 1.05)	0.84 (0.66 to 1.06)	0.85 (0.67 to 1.08)
Fatty fish intake**										
Low (Ref)	598 883	508	1	1	1	598 883	501	1	1	1
High	144 118	68	0.77 (0.59 to 0.99)	0.76 (0.58 to 0.98)	0.83 (0.64 to 1.07)	144 118	75	0.85 (0.66 to 1.09)	0.86 (0.67 to 1.10)	0.91 (0.71 to 1.17)
Processed meat intake††										
Low	570 057	425	0.75 (0.62 to 0.91)	0.75 (0.62 to 0.91)	0.78 (0.64 to 0.94)	569 682	424	0.76 (0.63 to 0.91)	0.76 (0.62 to 0.91)	0.78 (0.64 to 0.94)
High (Ref)	172 944	151	1	1	1	173 318	152	1	1	1
Lifestyle factors, PHS										
BMI, kg/m²§										
<30	362 901	309	0.72 (0.48 to 1.07)	0.72 (0.48 to 1.08)	0.74 (0.49 to 1.10)	363 167	312	0.80 (0.52 to 1.21)	0.78 (0.51 to 1.20)	0.79 (0.52 to 1.21)
≥30 (Ref)	26 316	28	1	1	1	26 050	25	1	1	1
Vigorous physical activity‖										
Low (Ref)	330 472	277	1	1	1	330 612	282	1	1	1
High	58 745	60	1.07 (0.80 to 1.43)	1.12 (0.83 to 1.49)	1.14 (0.85 to 1.52)	58 605	55	0.97 (0.72 to 1.31)	1.04 (0.77 to 1.40)	1.07 (0.79 to 1.45)
Smoking status¶										
Never or quit ≥10 y	329 936	284	0.74 (0.55 to 1.01)	0.79 (0.58 to 1.08)	0.81 (0.59 to 1.11)	329 214	273	0.61 (0.46 to 0.81)	0.65 (0.49 to 0.87)	0.66 (0.49 to 0.88)
Current or quit <10 y (Ref)	59 281	53	1	1	1	60 003	64	1	1	1
Tomato intake#										
Low (Ref)	227 745	173	1	1	1	228 043	175	1	1	1
High	161 472	164	1.09 (0.88 to 1.36)	1.08 (0.86 to 1.35)	1.09 (0.87 to 1.36)	161 174	162	1.09 (0.87 to 1.35)	1.08 (0.87 to 1.35)	1.10 (0.88 to 1.37)

Table 4. *Continued*

Life	Exposures updated over follow-up					Exposures updated until date of diagnosis for case patients				
	Person-years of follow-up	No. of lethal prostate cancer cases	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)†	Multivariable-adjusted HR (95% CI)‡	Person-years of follow-up	No. of lethal prostate cancer cases	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)†	Multivariable-adjusted HR (95% CI)‡
Fatty fish intake**										
Low (Ref)	330 186	287	1	1	1	330 926	296	1	1	1
High	59 031	60	0.79 (0.56 to 1.12)	0.82 (0.58 to 1.16)	0.80 (0.57 to 1.14)	58 291	43	0.66 (0.46 to 0.95)	0.70 (0.49 to 1.01)	0.69 (0.48 to 0.99)
Processed meat intake††										
Low	322 053	265	0.72 (0.55 to 0.94)	0.73 (0.55 to 0.96)	0.75 (0.57 to 0.99)	322 400	270	0.79 (0.60 to 1.04)	0.82 (0.62 to 1.08)	0.86 (0.64 to 1.14)
High (Ref)	67 164	72	1	1	1	66 817	67	1	1	1

* Cox proportional hazards regression with two-sided *P* values. We used a four- to six-year lag for all exposures to reduce the potential for reverse causation. Follow-up for the Health Professionals Follow-up Study began in 1990, using exposures ascertained in 1986. Follow-up for the Physicians' Health Study started in 1987, using exposures ascertained starting in 1982. CI = confidence interval; HPFS = Health Professionals Follow-up Study; HR = hazard ratio; PFS = Physicians' Health Study.

† Adjusted for age in months (continuous), race (white, nonwhite, missing), diabetes (yes, no, missing), multivitamin use (yes, no, missing), and vitamin E use (yes, no, missing). We used age as the time scale, stratified by calendar time in two-year intervals. Additionally adjusted for random assignment status (aspirin, beta-carotene, both, or neither) in the PHS. The six individual factors were additionally adjusted for the other five factors.

‡ The six individual factors were additionally adjusted for the other five factors.

§ Current height and weight were assessed at baseline. Weight was assessed biennially in the HPFS and nine times over follow-up in the PHS.

|| HPFS: Physical activity was assessed biennially. Low: <3 hrs/wk vigorous and <7 hrs/wk brisk walking. High: ≥3 hrs/wk vigorous and/or ≥7 hrs/wk brisk walking. PHS: Days per week of vigorous physical activity (enough to sweat) assessed at baseline and four times over follow-up. Low: <5 days/wk. High: ≥5 days/wk.

¶ HPFS: Smoking status assessed biennially. PHS: Smoking status assessed at baseline and four times over follow-up.

HPFS: Average of cumulative tomato (raw), tomato juice, tomato sauce, salsa, and pizza intake, assessed every four years. Low: <7 serv/wk. High: ≥7 serv/wk. PHS: Average of cumulative intake of tomato and tomato juice, assessed at baseline and ten times over follow-up. Low: <4 serv/wk. High: ≥4 serv/wk.

** HPFS: Average of cumulative fatty fish intake (eg, mackerel, salmon, sardines, bluefish, swordfish), assessed every four years. Low: <1 serv/wk. High: ≥1 serv/wk. PHS: Fatty fish intake assessed once between 1982 and 1985. Low: <1 serv/wk. High: ≥1 serv/wk.

†† HPFS: Average of cumulative processed meat intake assessed every four years. One serving of total processed red meat = one beef or pork hot dog; two slices of bacon; salami, bologna, or other processed meat sandwich; 57 g or two links of other processed meats (eg, sausage, kielbasa, etc.). Low: <3 serv/wk. High: ≥3 serv/wk. PHS: One serving of total processed red meat = one hot dog; two slices of bacon; one piece/slice of sausage, salami, bologna, or other processed meat. Hot dog intake assessed once between 1981 and 1985. Low: <1 serv/wk. High: ≥ 1 serv/wk. Hot dogs, bacon, and other processed meat assessed once between 1997 and 2001. Change cut-point to Low: <3 serv/wk. High: ≥3 serv/wk.

from all models within each cohort were qualitatively similar. Factors associated with a statistically significantly decreased risk of lethal prostate cancer in multivariable models from the primary analysis included high vigorous physical activity (HR = 0.64, 95% CI = 0.50 to 0.82) and low consumption of processed meat (HR = 0.78, 95% CI = 0.64 to 0.94) in the HPFS. Low processed meat was also associated with a statistically significant decreased risk in the PHS (HR = 0.75, 95% CI = 0.57 to 0.99). We observed greater inverse associations between vigorous physical activity and lethal prostate cancer when updating until four years prior to lethal event or censoring in the HPFS, compared with updating until date of diagnosis, while smoking prior to diagnosis (vs continuing to update exposure postdiagnosis) was more strongly associated with lethal prostate cancer in both cohorts.

Population-Attributable Risk

Using data from the NHANES, we calculated that 47% of hypothetical lethal prostate cancer cases could potentially be prevented if US adult men had five or more vs zero to four of the lifestyle factors (Table 5), assuming that our findings represent causal associations. Engaging in vigorous physical activity had the highest potential impact on prevention of lethal prostate cancer (34%).

Discussion

In two large-scale prospective studies, a lifestyle score that included healthy weight, vigorous physical activity, not smoking, and consumption of tomatoes, fatty fish, and reduced intake of processed meat was associated with decreased risk of lethal prostate cancer. The score results were more pronounced in the HPFS compared with the PHS. Although we made the variables comprising the score as similar as possible across cohorts, differences in the phrasing and frequency of certain questions and foods collected—particularly for vigorous activity and tomatoes—could partially explain the different associations, as we collected more detailed information in HPFS. While we cannot be certain that these associations are causal, our results suggest that a healthy lifestyle may substantially reduce the risk of lethal prostate cancer. We also observed a modestly stronger inverse association in men who had PSA levels measured more frequently.

Our study has limitations. First, because of the self-reported exposure data, there is potential for measurement error. However, the questionnaires have been previously validated (20,23,24) as reliable sources of the exposure information, and any misclassification of exposure was likely random with respect to the outcome. As a result, it is possible that our findings underestimate the true relation between the lifestyle score and lethal prostate cancer. Second, while we cannot eliminate the potential for residual or unmeasured confounding, we carefully controlled for numerous factors and the age-adjusted and multivariable analyses provided similar results. Third, we dichotomized the lifestyle factors and assigned them one point for simplicity, but recognize that the associations between the factors and risk of lethal prostate cancer are likely continuous, not dichotomous. Hence, the reported hazard ratios for individual factors may be attenuated because of including men who may still derive a benefit at levels below our cut-points. Fourth, the HPFS and PHS are mostly white men with high socioeconomic status. However, each factor has been associated with lethal prostate cancer in other cohorts, suggesting that our results are generalizable to more diverse populations. Fifth, we acknowledge that the number of lethal outcomes in some of the subgroups is small, limiting our statistical power. A randomized trial of these lifestyle factors on risk of lethal prostate cancer is not feasible. Thus, further exploration in independent prospective cohorts is needed.

None of the several comprehensive reviews about prevention of advanced and lethal prostate cancer through diet and lifestyle (31–33) have attempted to quantify the combined effect of these factors on risk of lethal prostate cancer. Because these healthy behaviors are often correlated and potentially act through similar biologic mechanisms including hyperinsulinemia, insulin resistance, insulin-like growth factors and associated binding proteins, sex hormone regulation, inflammation, adipokine production and signaling, and oxidative stress (34,35), the combined score helps conceptualize lethal prostate cancer prevention as a constellation of lifestyle factors. For example, many of these mechanisms may underlie the relationship between obesity, physical activity, and lethal prostate cancer (36–40). Indeed, our PAR analysis suggests that even a modest adoption of two or more lifestyle factors potentially could prevent many lethal prostate cancers in the general population.

In addition to the observed inverse association between the combined lifestyle score and lethal prostate cancer risk, our results for each individual factor, though not all statistically significant, are generally consistent with the current literature. In particular, high BMI has been strongly associated with increased risk of advanced and lethal prostate cancer in numerous observational studies and four meta-analyses (9,41–43). The proposed biologic mechanisms involve the insulin/insulin-like growth factor axis (44–46), altered levels of sex hormones (47), and adipokine signaling (48–50). These mechanisms may be similar to those underlying the benefit of vigorous physical activity (51). High prediagnostic C-peptide levels and low prediagnostic adiponectin levels, which are altered by BMI and physical activity, have been shown to be statistically significantly associated with lower risk of prostate cancer mortality (45).

Table 5. Population-attributable risk percentages in NHANES

Lifestyle factors	No. (%) of NHANES participants	Multivariable-adjusted HR* in HPFS	PAR %
BMI < 30 kg/m²†	579 (71.3)	0.93	2.11
High physical activity‡	80 (9.9)	0.64	33.65
Never smoker or quit >10 y§	600 (73.9)	0.88	3.44
≥7 servings tomato per wk‖	166 (20.4)	0.82	14.87
≥1 servings fish intake per wk¶	11 (1.4)	0.83	16.81
<3 servings processed meat per wk#	409 (50.4)	0.78	12.28
≥2 lifestyle factors (vs 0–1)	637 (78.5)	0.56	14.48
≥3 lifestyle factors (vs 0–2)	332 (40.9)	0.75	16.46
≥4 lifestyle factors (vs 0–3)	76 (9.4)	0.64	33.77
≥5 lifestyle factors (vs 0–4)	9 (1.1)	0.53	46.72

* Cox proportional hazards regression. For the population-attributable risk % formula, please refer to formula in the Methods section. HPFS = Health Professionals Follow-up Study; HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; PAR = population-attributable risk.
† Compared with people with BMI ≥ 30 kg/m².
‡ Exercised more than others of same age in the last 30 days.
§ Compared with current smokers and those that quit less than 10 years ago.
‖ Compared with <7 serv/wk.
¶ Compared with <1 serv/wk. NHANES did not distinguish fatty fish from other types of fish. We used the 2006 HPFS diet data to calculate the percentage of total fish intake that came from fatty fish and applied this to the NHANES population to estimate fatty fish intake.
# Compared with ≥3 serv/wk.

ARTICLE

Mounting evidence suggests that current smoking increases risk of aggressive and lethal prostate cancer (52,53). Smokers tend to have more advanced disease at diagnosis and worse outcomes after treatment (54,55). In our analyses, nonsmoking or quitting 10 or more years prior to diagnosis was statistically significantly inversely associated with lethal prostate cancer only when we stopped updating smoking status at diagnosis, suggesting that quitting early is important.

Fish consumption was unrelated to total prostate cancer in a meta-analysis of 12 cohort studies but with a statistically significant 63% reduction for prostate cancer mortality in a meta-analysis of four cohort studies (27). High intake of fatty fish was related to a non-statistically significantly decreased risk of lethal prostate cancer in the present analysis. Likewise, tomato and lycopene consumption have been associated with lower risk of advanced and lethal prostate cancer in previous analyses of the HPFS (13) and in the PLCO (14) and EPIC (56) cohorts. In the present study, high tomato intake was associated with a non-statistically significant lower risk of lethal prostate cancer in HPFS but not in PHS; the HPFS questionnaire included tomato sauce intake (the major source of absorbable lycopene), which drove the association in HPFS, whereas the PHS questionnaire did not include that item.

High intake of processed meat was independently associated with increased risk of lethal prostate cancer in the HPFS and PHS. A meta-analysis of eight cohort studies reported a non-statistically significantly increased risk for high-grade or high-stage prostate cancer associated with high processed meat intake, though this is an imperfect surrogate for lethal disease (57). We previously reported a non-statistically significant positive association with incident lethal prostate cancer (HR = 1.52, 95% CI = 0.89 to 2.61) for processed red meat at levels of three or more servings per week (17,18).

In conclusion, our analysis suggests that specific lifestyle-related factors, including engaging in vigorous physical activity, maintaining a healthy body weight, not smoking, consuming fatty fish and tomatoes, and limiting intake of processed meat, may reduce risk of lethal prostate cancer. We estimated that 47% of lethal prostate cancer cases could be prevented in the United States if adult men over age 60 years had five or more of these healthy lifestyle factors.

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