Cigarette Smoking and Prostate Cancer in a Prospective US Cohort Study

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Abstract

Smoking is an important risk factor for many cancers, yet the relationship between smoking and prostate cancer remains uncertain. We investigated whether smoking affected the risk of prostate cancers within a large prospective cohort study of dietary and environmental cancer risk factors among men ages 50 to 71 upon enrollment in 1995-1996 (n = 283,312). Cox proportional hazards regression models with hazard ratios (HR) and 95% confidence intervals (95% CI) were adjusted for age, race, education, height, body mass index, physical activity, family history of prostate cancer, diabetes, self-reported health status, prostate-specific antigen testing, digital rectal exam, total energy, α-tocopherol, calcium, α-linolenic acid, selenium, red meat, fish, and tomato intake. There were 14,810 nonadvanced and 1,830 advanced incident prostate cancers identified through 2003, and 394 men died of their disease through 2005. Current smokers had a decreased risk of nonadvanced prostate cancer (HR, 0.82; 95% CI, 0.77-0.88), but an increased risk of fatal prostate cancer (HR, 1.69; 95% CI, 1.25-2.27). Former smoking was also associated with decreased risk of nonadvanced prostate cancers (HR, 0.89; 95% CI, 0.86-0.92), but not fatal prostate cancers (HR, 1.03; 95% CI, 0.83-1.27). There was no apparent association between smoking and advanced prostate cancer. A number of biologically plausible mechanisms could explain these results, including the direct effects of carcinogens in tobacco smoke and the resulting changes in sex hormone or growth factor profiles. These findings suggest that current and former smokers may be at decreased risk of being diagnosed with prostate cancer and current smokers are at an increased risk of dying from prostate cancer. (Cancer Epidemiol Biomarkers Prev 2009;18(9): 2427–35)

Introduction

Prostate cancer is the most commonly diagnosed cancer in men in the United States, estimated to account for 186,320 new cases and 28,660 deaths in 2008 (1). The few well-established risk factors for prostate cancer incidence include increasing age, race/ethnicity (being African American or Jamaican), and having a positive family history (2). Smoking is an important risk factor for many cancers, yet most observational studies have not supported a link between cigarette smoking and prostate cancer (3). There are several biologically plausible mechanisms through which cigarette smoking could promote carcinogenesis in the prostate, including increased exposure to carcinogenic compounds in cigarettes, such as polycyclic aromatic hydrocarbons, heterocyclic aromatic amines, and nitrosamines (4). Important hormonal factors may also be influenced by smoking, as cross-sectional studies have shown that male smokers have elevated circulating levels of testosterone, androstenedione, and dihydrotestosterone (5-7) compared with nonsmokers, and some (5, 6), but not (7) all studies have also shown higher sex hormone–binding globulin levels in smokers. In addition, cigarette smokers also have lower insulin-like growth factor (IGF)-I and IGF binding protein-3 (IGFBP-3) serum concentrations (8), factors that have been positively associated with prostate cancer risk in some studies (9, 10). A recent pooled analysis of 18 prospective studies of prostate cancer risk and sex hormones found an inverse association with sex hormone–binding globulin, but no association with total testosterone, free testosterone, dihydrotestosterone, dehydroepiandrosterone sulfate, androenedione, androestanediol glucuronide, estradiol, or calculated free estradiol (11).

The vast majority of prostate cancers diagnosed do not result in death, indicating substantial variation in the disease, from microscopic, subclinical cases to highly aggressive, potentially fatal malignancies. Thus, factors that affect risk and disease progression should be examined separately for nonadvanced and fatal prostate cancers. Considerable data from large cohort studies suggest that cigarette smoking is associated with higher prostate cancer mortality (12-14), with some evidence for a dose-response relationship with the number of cigarettes smoked daily (12). Considering the relative consistency of these data, it is likely that smoking influences disease progression and survival.

Data from the NIH-AARP Diet and Health Study presents an opportunity to test the smoking-prostate cancer hypothesis in a large study population. In this report, we prospectively examined whether cigarette smoking affected the risk of incident and fatal prostate cancers in 283,112 men enrolled in the cohort in 1995 and 1996.

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Materials and Methods

Study Population. We used data from the NIH-AARP Diet and Health Study, a large prospective cohort study designed to investigate dietary and environmental risk factors and cancer (15). A questionnaire was mailed to AARP members ages 50 to 71 y in 1995-1996 and residing in one of eight states (California, Florida, Georgia, Louisiana, Michigan, New Jersey, North Carolina, and Pennsylvania). The NIH-AARP Diet and Health study was reviewed and approved by the Special Studies Institutional Review Board of the US National Cancer Institute. Of the 340,934 men who returned questionnaires with satisfactory complete data, we excluded those whose questionnaires were completed by proxies for the intended respondent (n = 15,760); those with a history of cancer, except nonmelanoma skin cancer, diagnosed before baseline (n = 27,240); and those who reported end stage renal disease at baseline (n = 626). In addition, we excluded individuals who reported extreme intakes (beyond two times the interquartile ranges of Box-Cox log-transformed intake) of total energy (n = 2,577) and those missing information on current smoking status (n = 11,619). After exclusions, the analytical cohort consisted of 283,112 men.

Cohort Follow-Up and Identification of Cancer Cases. We identified incident cases of prostate cancer (International Classification of Diseases for Oncology, 3rd Edition, code C619) through probabilistic linkage with the 11 state cancer registry databases (the eight states used at baseline plus Arizona, Nevada, and Texas) serving our study. These registries are certified by the North American Association of Central Cancer Registries as being 90% complete within 2 y of cancer occurrence. Information on prostate cancer stage and histologic grade was also obtained from cancer registry databases. Our case ascertainment method has been validated (16). Vital status was ascertained through annual linkage of the cohort to the Social Security Administration Death Master File in the United States, follow-up searches of the National Death Index Plus for participants who matched to the Social Security Administration Death Master File, cancer registry linkage, questionnaire responses, and responses to other mailings.

During follow-up through December 31, 2003, we identified 16,640 incident prostate cancer cases. When multiple cancers were diagnosed in the same participant, only the first malignancy diagnosed during the follow-up period was included as a prostate cancer case. We further classified prostate cancer as nonadvanced (n = 14,810), advanced (n = 1,830), and fatal (n = 394). Advanced prostate cancer cases were defined as those with clinical stages of T_3-T_4, N_1, or M_1 according to the American Joint Committee on Cancer's 1997 Tumor-Node-Metastasis classification system, as well as men who were diagnosed with and who died from prostate cancer during follow-up. The remaining cases were considered nonadvanced cases. Fatal cases were those who died from prostate cancer through December 31, 2005. Men who died between January 1, 2003 and December 31, 2005 were considered fatal cases, but not advanced incident cases. High-grade prostate cancer cases were defined as those with grade III by Surveillance, Epidemiology, and End Results coding, which is consistent with a Gleason score of $\geq$8, and low-grade prostate cancer cases were those with grade I or II (Gleason score of $\leq$7; ref. 17).

Data Collection. The baseline questionnaire contained questions about demographic information, medical history including family history of cancers, cigarette use, physical activity, and a food frequency questionnaire of 124 items including alcohol consumption. Participants were asked if they had smoked >100 cigarettes during their life (ever smokers), smoking intensity (cigarettes smoked per day), whether they were currently smoking or had quit smoking, and years since smoking cessation for former smokers. Information on age at smoking initiation and smokeless tobacco use was not collected. Those who reported quitting within the past year were considered current smokers for all analyses. We examined the years since smoking cessation at baseline via four categories: never smoked, stopped $\geq$10 y ago, stopped 5-9 y ago, and stopped 1-4 y ago. Participants reported their typical number of cigarettes smoked per day in six categories (1-10, 11-20, 21-30, 31-40, 41-60, and $\geq$61). For analyses, we merged these data with smoking status to create four categories of usual smoking intensity: never smokers, $\leq$1 pack/d, >1-2 packs/d, and >2 packs/d. We also created a variable, smoke-quit-dose, which combined never, former, or current smoking with usual dose into five categories: never smokers, former smokers who smoked $\leq$1 pack/d, former smokers who smoked >1 pack/d, current smokers who smoked <1 pack/d, and current smokers who smoked >1 pack/d.

Dietary consumption of fruits, vegetables, dairy, meats, and drinks of alcohol (beer, wine, and liquor) was calculated from the food frequency questionnaire data. Pyramid servings were defined by the US Department of Agriculture food guide pyramid, taking account of frequency and serving size (15, 18). Other categorical variables based on data from the baseline questionnaire included race (non-Hispanic White, non-Hispanic Black, other), education (<11 y, high school graduate, some college, and college and postgraduate), self-reported health status (excellent, very good, good, fair, poor), marital status (married, not married), and body mass index (BMI) in kg/m^2: (<20, 20-22.4, 22.5-24.9, 25-27.4, 27.5-29.9, 30-31.9, 32-33.9, $\geq$34). In a subsequently mailed questionnaire in 1996-1997 (63% response rate), we requested information on whether men had received prostate cancer screening using a prostate-specific antigen (PSA) test and/or digital rectal examination (DRE) during the past 3 y.

Statistical Analysis. We used Cox proportional hazard models (19) with person-years of follow-up as the underlying time metric to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) of prostate cancer. Person-years of follow-up were calculated from the date of study entry until the date of cancer diagnosis, death, moving out of the study area, or end of follow-up, whichever occurred first. The proportional hazards assumption was evaluated by modeling interaction terms of time and smoking and was upheld in all analyses. Median values for continuous variables and percentages for categorical variables of potential confounders and effect modifiers were generated by smoking status. Risk was calculated for all cases and separately for advanced, nonadvanced, and fatal cancers. All multivariate models adjusted for age at study entry, race, education, marital status, height, BMI, vigorous physical activity (times per week), family history of prostate cancer, personal history of diabetes, self-reported health status, PSA test, DRE,

Table 1. Selected characteristics according to smoking status among men in the NIH-AARP Diet and Health Study (*n* = 283,112)

Characteristic	Never (*n* = 85,795)		Former (*n* = 166,539)		Current (*n* = 30,755)	
	Number	% (IQR)	Number	% (IQR)	Number	% (IQR)
Median age (y)	62.2	(57.4, 66.3)	63.3	(58.4, 67.0)	60.9	(56.4, 65.6)
Race						
White, non-Hispanic	78,999	92.1	155,319	93.3	28,353	92.2
Black, non-Hispanic	2,199	2.6	4,092	2.5	1,187	3.9
Other/Unknown	4,597	5.4	7,128	4.3	1,215	4.0
College graduate	48,828	56.9	68,430	41.1	9,416	30.6
Married	73,851	86.1	143,505	86.2	23,606	76.8
Median height (m)	1.78	(1.73, 1.83)	1.78	(1.73, 1.83)	1.78	(1.73, 1.83)
Median BMI (kg/m^2)	26.3	(24.3, 29.0)	27.0	(24.8, 29.7)	25.9	(23.7, 28.7)
Median BMI at age 18 y (kg/m^2)	21.5	(19.7, 23.5)	21.3	(19.5, 23.4)	21.4	(19.6, 23.6)
Family history of prostate cancer (%)	7,349	8.6	14,023	8.4	2,365	7.7
Personal history of diabetes (%)	7,145	8.3	18,727	11.2	2,754	9.0
Vigorous physical activity (% ≥1 time/wk)	63,946	74.5	120,211	72.2	17,575	57.2
Physical activity at work (% mostly sitting)	28,801	33.6	53,206	32.0	9,263	30.1
Self-reported health status (% very good)	32,845	38.3	58,937	35.4	9,684	31.5
Digital rectal examination in the past 3 y (%)*	44,610	84.6	86,170	84.9	12,002	72.4
Screening for elevated PSA in the past 3 y (%)*	38,455	72.9	74,465	73.3	9,381	56.6
Multivitamin use (%)	55,408	64.6	106,980	64.2	17,919	58.3
Alcohol (median, drinks/d)						
0	20,789	24.2	31,996	19.2	5,917	19.2
<1	46,706	54.4	80,428	48.3	13,383	43.5
1-3	13,412	15.6	34,481	20.7	5,444	17.7
>3	4,888	5.7	19,634	11.8	6,011	19.5
Total energy intake (median, kcal/d)	1,831	(1416, 2360)	1849	(1425, 2386)	2083	(1570, 2747)
Daily dietary intakes						
Alcohol (median, g)	2.1	(0.2, 10.9)	4.5	(0.6, 18.2)	4.8	(0.6, 25.7)
α-linolenic acid (median, g)	1.2	(0.9, 1.7)	1.2	(0.9, 1.7)	1.4	(1.0, 2.0)
α-tocopherol (median, mg)	7.0	(5.2, 9.5)	6.9	(5.1, 9.4)	7.0	(5.1, 9.7)
Calcium (median, mg)	718	(514, 1007)	696	(502, 974)	716	(501, 1028)
Vitamin D (median, μg)	4.2	(2.7, 6.3)	4.1	(2.7, 6.1)	4.3	(2.7, 6.6)
Fish, (median, oz)	0.5	(0.3 0.9)	0.5	(0.3, 0.9)	0.5	(0.2, 0.8)
Red meat (median, oz)	1.8	(1.0, 3.0)	2.0	(1.1, 3.2)	2.7	(1.6, 4.1)
Selenium (median, μg)	94.7	(71.2, 124.6)	95.7	(71.9, 125.6)	102.1	(75.4, 137.0)
Tomatoes (median, cup equivalents)	0.3	(0.2, 0.5)	0.3	(0.2, 0.5)	0.3	(0.2, 0.5)
Fruits (median, cup equivalents)	1.9	(1.2, 2.9)	1.7	(1.0, 2.6)	1.1	(0.5, 2.0)
Vegetables (median, cup equivalents)	1.8	(1.2, 2.5)	1.8	(1.2, 2.5)	1.7	(1.1, 2.4)

Abbreviation: IQR, interquartile range.
*Information on DRE and PSA screening test comes from subsequently mailed questionnaire in 1996-1997 (available for approximately 60% of total sample); percentages in Table 1 compare only those who returned questionnaires.

total energy, and intake of α-tocopherol, calcium, red meat, fish, tomatoes, α-linolenic acid, and selenium. All dietary exposures were analyzed as quintiles of intake, except for total energy (continuous). Additional covariates that were considered but not included because they did not affect the smoking hazard ratio were personal history of heart disease, fruit and vegetable consumption, BMI at age 18, multivitamin use, leisure time physical activity, and workplace physical activity. Indicator variables were used for missing responses; generally <5% of values were missing. Effect modification was evaluated in stratified multivariate analyses and also tested by adding cross-product interaction terms and comparing *P* values for the likelihood ratio tests (<0.05) for the models with and without interaction terms. These included subgroups of BMI, alcohol consumption, race, family history of cancer, and PSA and DRE testing. We also examined whether the association between prostate cancer risk and smoking differed by years of smoking cessation, usual number of cigarettes smoked, and smoke-quit-dose. Age-adjusted incidence rates that were calculated according to Breslow and Day (20) were standardized to the entire NIH-AARP study population. All statistical tests were two-sided and $P \leq 0.05$ was considered statistically significant. Data analyses were conducted using Stata (version SE 10.1, STATA Corp.).

Results

Table 1 presents comparisons of baseline characteristics of men enrolled in the NIH-AARP Diet and Health Study for never, former, and current smokers. Current smokers tended to be slightly younger, less likely to have graduated college, and less likely to be married. There was little difference in BMI at age 18, but former smokers had the highest average BMI at baseline (27.0 versus 26.3 for never smokers and 25.9 for current smokers). Current smokers were less likely to have been screened with PSA (57%) than former and never smokers (both 73%) or have a DRE (72%) than former and never smokers (both 85%). Never smokers were more likely to not consume alcohol (24% versus 19% for former and current smokers), whereas current smokers were the most likely to consume >3 drinks/day (20%). Total energy was approximately 10% higher for current smokers (2,083 kcal) as compared with never (1,831 kcal) and former (1,849 kcal) smokers. Current smokers also reported higher intakes of red meat and selenium and lower consumption of fruits than never and former smokers.

Smoking seemed to decrease the risk of prostate cancer, but increased the risk of dying from prostate cancer (Table 2). Former (HR, 0.90; 95% CI, 0.87-0.93) and current (HR, 0.85; 95% CI, 0.80-0.90) smokers had lower

risks of being diagnosed with nonadvanced prostate cancer than never smokers in both the age-adjusted and multivariate models. Because 90% of the prostate cancers diagnosed in this cohort were nonadvanced, the estimates for all prostate cancers approximated those of nonadvanced cancers. Current, but not former, smokers were at increased risk of dying from prostate cancer (HR, 1.69) when compared with never smokers, but there was no apparent association between smoking status and advanced prostate cancer. The overall age-adjusted prostate cancer incidence rates were 946/100,000 person-years for never smokers, 840/100,000 person-years for former smokers, and 794/100,000 person-years for current smokers. The average follow-up time for prostate cancer–free men was 7.0 years; it was 3.9 years for men diagnosed with prostate cancer and 3.3 years for men who died of their disease.

We examined prostate cancer risk among never, former, and current smokers by age, family history of prostate cancer, PSA and DRE testing, BMI, and alcohol consumption (Table 3). Former and current smokers were less likely to be diagnosed with prostate cancer in nearly all categories of these factors, and current smokers had higher prostate cancer mortality across most categories. There were no statistically significant interactions between smoking and the factors examined for risk of incident or fatal prostate cancers. Regardless of whether men received DRE or PSA testing, current and former smokers were diagnosed with prostate cancer less often than never smokers. There seemed to be a stronger inverse association for current smokers missing information on PSA testing (HR, 0.79; 95% CI, 0.72-0.86) and DRE (HR, 0.79; 95% CI, 0.72-0.87). Data were missing for almost half of the study population because information about PSA or DRE testing was collected from a follow-up questionnaire. Current smokers who did not consume alcohol did not experience higher prostate cancer mortality.

Table 4 examines prostate cancer risk by patterns of smoking, including years of cessation, usual dose, and a smoke-quit-dose categorization. There were inverse linear trends with years since quitting smoking and usual number of cigarettes for incident prostate cancer, whereas only years since smoking cessation affected the HR for fatal disease. Again, divergent associations were observed for total and fatal prostate cancers. Among former smokers, the risk of prostate cancer was the lowest (HR, 0.85) for those with the most recent cessation period, 1 to 4 years prior to study entry, whereas prostate cancer mortality was highest in this group (HR, 1.70). Prostate cancer incidence declined in a dose-response manner with usual number of cigarettes smoked, with the lowest hazard ratios for those smoking ≥60 cigarettes per day (HR, 0.79). When smoking status, cessation time, and usual dose were combined into "smoke-quit-dose," current smokers who smoked >1 pack daily had the lowest risk of being diagnosed with prostate cancer (HR, 0.75) and were 1.54 times as likely to die from the disease.

In additional analyses of clinical factors not shown, we examined the smoking association by cancer grade, stage, and histology. Neither grade nor histology differed by smoking status, but current smokers were slightly less likely to be diagnosed with localized disease (81% versus 85% for former and never smokers) and more likely to have distant metastases (3% versus 1%, respectively). Consistent with this, localized and metastatic disease were less and more common, respectively, among the fatal cancers in current and former smokers. Current smokers who reported no DRE testing were significantly more likely to have distant metastases (9%) than never (2%) or former (3%) smokers upon diagnosis; however, adjustment for DRE did not alter the current smoking-fatal prostate cancer relationship.

Discussion

In this large prospective study, current and former smokers had decreased prostate cancer risk overall, but were more

Table 2. Hazard ratios of prostate cancer by smoking status

Smoking status	No. of cases	Age-adjusted rates*	Age-adjusted HR (95% CI)	Multivariate HR† (95% CI)
Total prostate cancer				
Never	5,512	946.2	1	1
Former	9,682	839.9	0.88 (0.85-0.91)	0.90 (0.87-0.93)
Current	1,446	793.7	0.83 (0.79-0.88)	0.85 (0.80-0.90)
P for trend			<0.001	<0.001
Nonadvanced cases				
Never	4,933	868.2	1	1
Former	8,622	774.3	0.88 (0.85-0.91)	0.89 (0.86-0.92)
Current	1,255	736.2	0.81 (0.76-0.86)	0.82 (0.77-0.88)
P for trend			<0.001	<0.001
Advanced cases				
Never	579	100.2	1	1
Former	1,060	95.2	0.93 (0.84-1.03)	0.97 (0.87-1.07)
Current	191	103.3	1.01 (0.85-1.18)	1.04 (0.88-1.24)
P for trend			0.56	0.96
Fatal cases				
Never	105	22.3	1	1
Former	225	24.3	1.06 (0.86-1.30)	1.03 (0.83-1.27)
Current	64	46.4	2.01 (1.52-2.67)	1.69 (1.25-2.27)
P for trend			<0.001	0.005

*Incidence rates (per 100,000 person-years) by smoking status were standardized to the male AARP population.
†Adjusted for age at study entry, race, education, marital status, height, BMI, vigorous physical activity, family history of prostate cancer, personal history of diabetes, self-reported health status, prostate-specific antigen screening test, digital rectal examination, total energy, and quintiles of intake of α-tocopherol, calcium, red meat, fish, tomato, α-linolenic acid, and selenium.

Table 3. Hazard ratios of prostate cancer by smoking status stratified by selected characteristics

Smoking status	Total prostate cancers			Fatal prostate cancers		
	No. of cases	Age-adjusted HR (95% CI)	Multivariate HR* (95% CI)	No. of cases	Age-adjusted HR (95% CI)	Multivariate HR (95% CI)
Less than median age at study entry (62.7 y)						
Never	2,145	1	1	28	1	1
Former	3,330	0.92 (0.87-0.97)	0.94 (0.89-1)	51	1.06 (0.70-1.61)	1.05 (0.68-1.61)
Current	623	0.76 (0.69-0.83)	0.79 (0.72-0.87)	16	1.47 (0.85-2.54)	1.27 (0.70-2.30)
P for trend		<0.001	<0.001		0.23	0.48
Equal to or above median age at study entry (62.7 y)						
Never	3,367	1	1	77	1	1
Former	6,352	0.88 (0.84-0.92)	0.89 (0.85-0.93)	174	1.08 (0.85-1.37)	1.05 (0.82-1.34)
Current	823	0.87 (0.81-0.94)	0.87 (0.80-0.94)	48	2.21 (1.59-3.06)	1.82 (1.29-2.57)
P for trend		<0.001	<0.001		<0.001	0.01
Positive family history of prostate cancer						
Never	736	1	1	6	1	1
Former	1,236	0.85 (0.78-0.93)	0.87 (0.79-0.96)	25	1.74 (0.83-3.65)	1.70 (0.77-3.74)
Current	179	0.84 (0.72-0.99)	0.76 (0.72-1.02)	4	1.57 (0.48-5.11)	1.35 (0.39-4.71)
P for trend		0.002	0.01		0.23	0.38
No family history of prostate cancer						
Never	4,538	1	1	94	1	1
Former	8,007	0.89 (0.86-0.92)	0.90 (0.87-0.94)	192	1 (0.80-1.25)	0.98 (0.78-1.23)
Current	1,203	0.84 (0.79-0.90)	0.85 (0.79-0.91)	58	2.06 (1.54-2.77)	1.75 (1.28-2.39)
P for trend		<0.001	<0.001	<0.001	0.01	
PSA testing						
Never	2,684	1	1	36	1	1
Former	4,574	0.86 (0.82-0.90)	0.87 (0.83-0.92)	90	1.04 (0.74-1.46)	0.97 (0.69-1.38)
Current	554	0.95 (0.86-1.04)	0.93 (0.85-1.03)	15	1.93 (1.15-3.25)	1.64 (0.95-2.83)
P for trend		<0.001	<0.001		0.08	0.25
No PSA testing						
Never	492	1	1	15	1	1
Former	888	0.96 (0.86-1.07)	0.95 (0.85-1.07)	36	1.17 (0.68-2.00)	1.13 (0.65-1.96)
Current	213	0.92 (0.78-1.08)	0.90 (0.76-1.06)	18	2.24 (1.19-4.20)	2.30 (1.18-4.48)
P for trend		0.27	0.20		0.02	0.02
Missing PSA testing info						
Never	2,336	1	1	54	1	1
Former	4,220	0.89 (0.85-0.94)	0.92 (0.87-0.97)	99	1.04 (0.76-1.40)	1.03 (0.75-1.41)
Current	679	0.76 (0.70-0.83)	0.79 (0.72-0.86)	31	1.73 (1.16-2.59)	1.49 (0.97-2.30)
P for trend		<0.001	<0.001		0.03	0.12
DRE testing						
Never	2,956	1	1	43	1	1
Former	5,062	0.86 (0.83-0.90)	0.88 (0.84-0.92)	102	0.98 (0.72-1.34)	1 (0.70-1.44)
Current	657	0.93 (0.85-1.01)	0.93 (0.85-1.02)	25	2.19 (1.41-3.41)	1.26 (0.59-2.68)
P for trend		<0.001	<0.001		0.02	0.56
No DRE testing						
Never	336	1	1	11	1	1
Former	602	0.90 (0.79-1.03)	0.89 (0.78-1.02)	28	1.28 (0.66-2.49)	1.67 (0.80-3.49)
Current	148	0.82 (0.68-1)	0.80 (0.65-0.98)	12	2.18 (1.01-4.72)	2.55 (0.96-6.76)
P for trend		0.04	0.02		0.15	0.05
Missing DRE testing info						
Never	2,220	1	1		1	1
Former	4,018	0.91 (0.86-0.95)	0.93 (0.88-0.98)	51	1.08 (0.79-1.47)	1.22 (0.85-1.75)
Current	641	0.77 (0.70-0.84)	0.79 (0.72-0.87)	95	1.65 (1.09-2.52)	1.33 (0.79-2.26)
P for trend		<0.001	<0.001	27	0.04	0.21
BMI 18.5-24.9 kg/m^2						
Never	1,879	1	1	30	1	1
Former	2,708	0.92 (0.86-0.97)	0.92 (0.87-0.98)	50	1.05 (0.69-1.60)	0.98 (0.64-1.50)
Current	554	0.83 (0.75-0.91)	0.85 (0.76-0.94)	23	2.35 (1.44-3.85)	1.69 (0.98-2.92)
P for trend		<0.001	<0.001		0.003	0.11
BMI 25-29.9 kg/m^2						
Never	2,670	1	1	44	1	1
Former	4,882	0.87 (0.83-0.91)	0.87 (0.83-0.92)	115	1.18 (0.87-1.59)	1.19 (0.88-1.63)
Current	640	0.81 (0.75-0.89)	0.82 (0.75-0.89)	30	2.21 (1.46-3.36)	1.85 (1.20-2.85)
P for trend		<0.001	<0.001		0.001	0.01
BMI >30 kg/m^2						
Never	857	1	1	28	1	1
Former	1,923	0.90 (0.83-0.98)	0.93 (0.85-1.00)	57	0.79 (0.52-1.20)	0.80 (0.52-1.22)
Current	215	0.89 (0.76-1.03)	0.94 (0.80-1.09)	10	1.50 (0.79-2.85)	1.35 (0.70-2.62)
P for trend		0.02	0.12		0.77	0.89
Alcohol consumption (0 drinks/d)						
Never	1,277	1	1	33	1	1
Former	1,657	0.84 (0.78-0.91)	0.89 (0.82-0.97)	49	1.15 (0.78-1.70)	0.92 (0.57-1.50)
Current	222	0.73 (0.63-0.84)	0.66 (0.52-0.83)	7	0.91 (0.42-1.94)	0.47 (0.11-1.96)
P for trend		<0.001	<0.001		0.82	0.30

(Continued on the following page)

Table 3. Hazard ratios of prostate cancer by smoking status stratified by selected characteristics (Cont'd)

Smoking status	Total prostate cancers			Fatal prostate cancers		
	No. of cases	Age-adjusted HR (95% CI)	Multivariate HR* (95% CI)	No. of cases	Age-adjusted HR (95% CI)	Multivariate HR (95% CI)
Alcohol consumption (1-3 drinks/d)						
Never	3,877	1	1	47	1	1
Former	6,762	0.89 (0.85-0.92)	0.91 (0.88-0.95)	103	1.09 (0.84-1.42)	1.06 (0.81-1.37)
Current	906	0.84 (0.78-0.90)	0.87 (0.80-0.93)	28	2.39 (1.70-3.37)	1.93 (1.34-2.77)
P for trend		<0.001	<0.001		<0.001	0.003
Alcohol consumption (>3 drinks/d)						
Never	358	1	1	20	1	1
Former	1,263	0.85 (0.75-0.95)	0.87 (0.77-0.98)	53	0.78 (0.34-1.82)	0.72 (0.31-1.69)
Current	318	0.82 (0.71-0.96)	0.87 (0.79-1.02)	16	2.32 (0.96-5.60)	1.91 (0.76-4.84)
P for trend		0.01	0.07		0.01	0.07

*Adjusted for age at study entry, race, education, marital status, height, BMI, vigorous physical activity, family history of prostate cancer, personal history of diabetes, self-reported health status, prostate-specific antigen screening test, digital rectal examination, total energy, and quintiles of intake of α-tocopherol, calcium, red meat, fish, tomato, α-linolenic acid, and selenium.

likely to die from their disease. Former smokers were also diagnosed with nonadvanced prostate cancer less often than never smokers, but did not differ with respect to prostate cancer mortality. Smoking-related comorbidities could contribute to other causes of death rather than prostate cancer as attributed on the death certificate; however, we observed the same relationship when indicators of general health, including self-reported health status, diabetes, heart disease, and physical activity, were included in the multivariate models. Furthermore, additional analysis showed no difference in the distribution of causes of death other than prostate cancer, when stratified by smoking status, between the general study population and those diagnosed with prostate cancer but did not die of their disease. Thus, it seems likely that smoking accelerated the course of the disease or its deleterious consequences.

Our study is the largest to date to investigate the relationship between tobacco use and prostate cancer incidence, and it confirms the majority of observational studies linking smoking to higher prostate cancer mortality (3, 13, 14, 21-25). For example, findings from the Cancer Prevention Study II, a prospective mortality study of 508,576 men, were similar to those presented here for fatal prostate cancer for current smokers (relative risk, 1.34) and former smokers (relative risk, 0.99). By contrast, most prior studies found null associations between smoking and prostate cancer incidence (3) or observed increased risk for smokers (12, 23). These studies have led to cigarette smoking not being considered a risk factor for prostate cancer, although the present findings, based on a very large cohort of men and >16,000 incident cases, suggest a protective relationship for both current and former smoking status and nonadvanced disease. Similar observations were made for current smokers and moderate grade tumors in an Australian case-control study (odds ratio, 0.76; 95% CI, 0.59-0.99; ref. 26), as well as for current and recent former smokers and low-grade tumors (Gleason ≤6; odds ratio, 0.84; 95% CI, 0.72-0.99) in the Health Professionals Follow-Up Study (14). Giles et al. (26) speculated that these findings were possibly explained by one of two factors: (*a*) smokers were less likely to seek medical care, which would result in fewer (early) diagnosed cancers from screening tests, or (*b*) there were spurious associations due to statistical chance. However, the Health Professionals Follow-Up Study follow-up included data before widespread PSA use (1986-1992) and afterwards (1992-2002), and noted that the smoking risk patterns were largely similar in the two time periods (14). The protective smoking association we observed was evident among men who had undergone DRE and PSA testing within the past 3 years and was independent of such screening. It is possible that in contrast to the present investigation, most prior studies did not show statistically significant results because of low power for a modest risk estimate. Further examination of a possible protective association between smoking and nonadvanced prostate cancer is warranted.

Differential detection of nonsymptomatic (and likely nonfatal) cancers through screening is of potential concern because current smokers were less likely than never and former smokers to report having a DRE or PSA test in the past 3 years, which could, in theory, contribute to the decreased prostate cancer "risk" in smokers. This relationship was also reflected in the 2003 California Health Interview Survey, a population-based, random digit dialing telephone survey, in which awareness of PSA testing was lower among current smokers (58%) compared with never (77%) and former (75%) male smokers ages >50 years with no history of prostate cancer (27). In fact, there was little difference in the risk of incident cancers between those in the NIH-AARP cohort who had and had not reported PSA testing, although the association was not statistically significant in those without PSA testing. For fatal cancers, current smokers without PSA testing had somewhat higher HR than those with PSA testing; controlling for smoking-related comorbidities failed to modify this association. Interestingly, current smokers with missing PSA data had fewer incident, but a similar number of fatal, cancers compared with those who were screened, suggesting that those who failed to return the follow-up survey may have had less screening and thus fewer nonadvanced prostate cancers, whereas the number of aggressive fatal cancers remained unchanged. Similar to PSA, current smokers who did not have DRE testing had lower incidence but higher prostate cancer mortality. Although differences in screening may partially explain the inverse relationship seen here between smoking and prostate cancer risk, it does not fully account for association as the overall association was unchanged by adjustment for DRE and PSA testing. These results suggest smoking may directly impact disease

progression and fatality in some manner other than early detection from screening.

There are a number of biologically plausible mechanisms through which smoking might adversely influence the development and progression of prostate cancer. Smoking affects sex hormones such that male smokers have higher bioavailable testosterone and lower estradiol (5, 6), which could lead to more aggressive, hormone-sensitive tumors, and thus decrease prostate cancer survival. Smokers are also exposed to myriad carcinogenic compounds, including cadmium, polycyclic aromatic hydrocarbons, heterocyclic aromatic amines, and nitrosamines, that could adversely affect prostate tumor development (3, 4). It has also been suggested that exposure to these carcinogens could lead to more aggressive tumors via mutations in tumor suppressor genes, such as *p53* (21). In addition, smokers present with higher-grade cancers (28, 29), which may provide evidence of true biological differences or could also reflect differential neglect of early symptoms or treatment referrals for smokers. In line with this, we found that current smokers were slightly more likely to present with metastatic disease (3%) than never smokers (1%), even though current smokers were at an overall lower risk of incident prostate cancer.

Few have investigated how smoking may play a protective role in prostate cancer; however, several biological pathways could be involved, including IGF and sex hormone–binding globulin. Higher IGF-I and IGFBF-3 have been associated with increased risk of prostate cancer, with a stronger association noted for IGF-I and low-grade cancers (10). Current smokers had lower IGFBP-3 levels and nonsignificantly decreased IGF-I levels as compared with never-smokers in one cross-sectional study (8). This association is particularly interesting considering the protective effect with nonadvanced (i.e., low-grade) prostate cancers observed in the present study. Male smokers also have higher circulating levels of sex hormone–binding globulin (6), which have been associated with decreased prostate cancer risk (11, 30). A protective effect of smoking also has been noted for benign prostatic hyperplasia (31, 32), which may be affected through similar pathways. Furthermore, PSA levels were approximately 10% lower in ever smokers compared with never smokers in 1,319 men in the 2001-2002 National Health and Nutrition Examination Survey (33), and PSA velocity was 33% lower in smokers than in nonsmokers in the placebo arm of the Prostate Cancer Prevention Trial (34). Smoking is associated with lower body mass (35), as evidenced by current smokers in this cohort who had lower baseline BMIs than former and never smokers, and obesity has been linked to increased high-grade and decreased low-grade prostate cancers (36). The relationship between obesity and prostate cancer risk is complex, with potential detection bias from both DRE (i.e., possibly more difficult in obese men) and PSA testing (i.e., lower levels in the obese; ref. 37). Adjustment for BMI, however, did not attenuate or seem to confound our estimates of risk.

When examining smoking patterns, we observed linear relationships between dose and length of smoking cessation and the risk of incident cancers, with prostate cancer mortality being highest for current smokers and those quitting within 4 years. A small population-based cohort

Table 4. Hazard ratios of prostate cancer by smoking pattern

Smoking pattern	Total prostate cancers			Fatal prostate cancers		
	No. of cases	Age-adjusted HR (95% CI)	Multivariate HR* (95% CI)	No. of cases	Age-adjusted HR (95% CI)	Multivariate HR (95% CI)
Cigarette smoking status						
Never	5,512	1	1	105	1	1
Former	9,682	0.88 (0.85-0.91)	0.90 (0.87-0.93)	225	1.06 (0.86-1.30)	1.03 (0.83-1.27)
Current	1,446	0.83 (0.79-0.88)	0.85 (0.80-0.90)	64	2.01 (1.52-2.67)	1.69 (1.25-2.27)
P for trend		<0.001	<0.001		<0.001	0.005
Years of cessation in former smokers prior to study entry						
Never Smokers	5,512	1	1	105	1	1
Stopped ≥10 y	7,784	0.89 (0.86-0.92)	0.90 (0.87-0.94)	163	1.02 (0.82-1.26)	1 (0.80-1.24)
Stopped 5-9 y	1,329	0.83 (0.77-0.89)	0.85 (0.79-0.92)	37	1.47 (1.00-2.15)	1.31 (0.89-1.93)
Stopped 1-4 y	569	0.83 (0.79-0.88)	0.85 (0.80-0.90)	25	2.02 (1.52-2.67)	1.70 (1.26-2.92)
P for trend		<0.001	<0.001		<0.001	<0.001
Usual no. of cigarettes smoked, current and former						
Never Smokers	5,512	1	1	105	1	1
1-10 cigs/d	2,433	0.95 (0.90-0.99)	0.93 (0.89-0.98)	55	1.14 (0.85-1.52)	1.07 (0.80-1.45)
11-20 cigs/d	3,680	0.90 (0.86-0.93)	0.90 (0.87-0.94)	94	1.17 (0.91-1.50)	1.11 (0.86-1.44)
21-30 cigs/d	2,330	0.86 (0.82-0.90)	0.88 (0.84-0.93)	63	1.15 (0.87-1.53)	1.10 (0.82-1.47)
31-40 cigs/ d	1,482	0.82 (0.78-0.87)	0.86 (0.81-0.91)	50	1.41 (1.04-1.92)	1.31 (0.96-1.79)
41-60 cigs/ d	962	0.83 (0.77-0.89)	0.87 (0.82-0.94)	21	1.03 (0.69-1.54)	0.96 (0.64-1.44)
≥60 cigs/d	241	0.71 (0.63-0.81)	0.79 (0.68-0.89)	6	1.21 (0.64-2.31)	1.09 (0.57-2.09)
P for trend		<0.001	<0.001		0.15	0.40
Smoke-quit-dose						
Never Smokers	5,512	1	1	105	1	1
Former smoker ≤1 pack/d	5,182	0.92 (0.88-0.95)	0.92 (0.88-0.95)	110	0.99 (0.78-1.26)	0.97 (0.76-1.24)
Former smoker >1 pack/d	4,500	0.85 (0.82-0.88)	0.88 (0.85-0.92)	115	1.13 (0.89-1.43)	1.09 (0.85-1.39)
Current smoker ≤1 pack/d	931	0.91 (0.85-0.97)	0.91 (0.84-0.97)	39	2.12 (1.53-2.94)	1.79 (1.27-2.52)
Current smoker >1 pack/d	515	0.73 (0.66-0.80)	0.75 (0.69-0.83)	25	1.86 (1.24-2.78)	1.54 (1.01-2.34)
P for trend		<0.001	<0.001		<0.001	0.02

*Adjusted for age at study entry, race, education, marital status, height, BMI, vigorous physical activity, family history of prostate cancer, personal history of diabetes, self-reported health status, prostate-specific antigen screening test, digital rectal examination, total energy, and quintiles of intake of α-tocopherol, calcium, red meat, fish, tomato, α-linolenic acid, and selenium.

study found that men who smoked at the time of diagnosis were at much higher risk of prostate-specific death (HR, 2.7), although the risk was attenuated for those quitting within 10 years (HR, 1.5; ref. 22). Prostate cancer mortality did not increase directly with smoking dose (i.e., cigarettes per day), similar to what was observed in Cancer Prevention Study II (13). By contrast, other large cohort studies reported dose-response relationships with the number of cigarettes among U.S. veterans, with highest risks for >39 cigarettes per day (relative risk, 1.5; 95% CI, 1.2-1.9; ref. 12), and with pack-years in a cohort study of health professionals with ≥15 pack-years (relative risk 2.1; 95% CI, 1.1-3.9; P trend = 0.02) compared with nonsmokers (21).

There are several notable strengths of our study. The availability of a large number of incident and fatal prostate cancer cases provided substantial power to detect modest potential associations that may have been obscured in smaller studies. The number of cases available was considerably larger than all previously published studies of incident prostate cancers and most studies of fatal cancers. Furthermore, information about cancers and smoking habits was ascertained prospectively, thus eliminating recall bias. Limitations include the lack of information on environmental tobacco smoke exposure and the age of smoking initiation, but age of smoking cessation was available. There is also the potential for misclassification because smoking was queried at one point in time. However, smoking was positively associated in a dose-response manner with the risk of smoking-related malignancies in our study, including lung cancer and head and neck cancers (38, 39). In addition, although up to 10 years of follow-up time was available, it is possible that this time period is too short to assess the true long-term effects of smoking on prostate cancer risk and mortality. Residual confounding by unmeasured or unexamined variables cannot be excluded; however, we controlled for numerous potential confounders and none substantially affected results.

In summary, we found that being a current or former smoker is associated with a decreased risk of prostate cancer, primarily nonadvanced disease. Smoking-related differences in PSA or DRE screening, BMI, or other potential confounders did not account for the observed protective relationship. Reexamination of this association in other prospective studies, and other investigations of the possible underlying biology would be informative. By contrast, current (but not former) smokers had higher prostate cancer mortality, suggesting that smoking cessation or abstinence could lead to improved prostate cancer survival. Our findings provide new evidence that current and former smokers may be at decreased risk of incident prostate cancer and bolster existing data linking smoking with fatal disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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