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Smoking and Fatal Prostate Cancer in a Large Cohort of Adult Men

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The authors examined the relation between smoking and the risk of fatal prostate cancer in a large prospective mortality study of 450,279 men who were cancer free at enrollment in 1982. During 9 years of follow-up, 1,748 deaths occurred from prostate cancer. Cox proportional hazards modeling was used to adjust for other risk factors Current cigarette smoking was associated with fatal prostate cancer (rate ratio = 1.34, 95% confidence interval (CI) 1.16–1.56). The rate ratio was greater at younger ages, decreasing from 1.83 (95% CI 1.04–3.24) among men below the age of 60 years to 1 11 (95% CI 0 79–1.58) among men aged 80 years and above (p for trend = 0.16). No trend in risk was observed with the number of cigarettes per day or with the duration of smoking among current smokers at baseline, and no increased risk was found among former smokers. Race did not significantly modify the association between cigarette smoking and fatal prostate cancer. These data, together with those of three other large prospective studies that find higher death rates from prostate cancer in current cigarette smokers, and inconsistent findings in incidence studies suggest that smoking may adversely affect survival in prostate cancer patients *Am J Epidemiol* 1997;145:466–75.

cohort studies; prostatic neoplasms; tobacco

Prostate cancer is the second leading cause of death among men in the United States (1), and the incidence and mortality rates among black American men are the highest in the world (2). Old age, black race, family history of prostate cancer, and a high saturated fat intake are the only factors consistently associated with increased risk (3). Two lines of evidence suggest that tobacco use may influence either the onset or the progression of prostate cancer: 1) certain nitrosamines that induce prostatic cancer in laboratory rats (4) are found in the urine of cigarette smokers, and 2) smokers have elevated levels of serum testosterone and androstenedione (5, 6), two steroids which may contribute to the progression of prostate cancer (3).

Seven (7–13) of 16 retrospective studies (7–22) (table 1) and one (23) of five prospective studies (23–27) have found some association between smoking and incident prostate cancer. Prospective studies of smoking and death from prostate cancer, however, have been more consistent. The largest three (28–30) of seven prospective mortality studies (28–34) found a modest (rate ratios < 2) association between current smoking and early death from prostate cancer.

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Abbreviations: CI, confidence interval; RR, rate ratio.

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The Cancer Prevention Study II provides an opportunity to supplement the prospective data on smoking and fatal prostate cancer and to examine this association in both white and black US males.

MATERIALS AND METHODS

Men in this study were selected from the 508,576 male participants in Cancer Prevention Study II, a prospective mortality study of 1.2 million American men and women enrolled in 1982 by more than 77,000 American Cancer Society volunteers in all 50 states, the District of Columbia, and Puerto Rico (35). Enrollment was restricted to persons aged 30 years and older where at least one household member was 45 years old or older. Participants completed a four-page baseline self-administered questionnaire in 1982 that included information on personal identifiers, demographic characteristics, height and weight, family history of cancer and other diseases, and various behavioral, environmental, occupational, and dietary exposures.

The median age of male study participants in 1982 was 57 years, 75 percent of the men were between 47 and 70 years of age, and none was younger than 30 years.

The vital status of study participants was determined from the month of enrollment through December 31, 1991, using two approaches. Volunteers made per-

TABLE 1. Smoking and prostate cancer: results from available studies

Study (ref no.)	Design	Use	Study size*	Rate ratio†	95% confidence interval
		Case-control studies			
Wynder et al., United States, 1971 (14)	Hospital-based case-control	Nonsmokers	40/39	1.00	
		Smokers	86/79	0.92	0.54–1.58
Schuman et al., Minneapolis, MN, 1977 (7)	Hospital-based case-control	Never	33/40	1.00	
		Ever	38/43	0.76	0.20–2.88
	Neighborhood controls	Never	33/40	1.00	
		Ever	22/35	2.79	0.86–9.29
Williams and Horm, TNCS,‡ United States, 1977 (15)	National Cancer Survey case-control§	Nonsmokers	NA‡	1.00	
		Smokers			
		Level 1	67	0.74	NA
		Level 2	59	0.74	NA
		Level 3	131	0 90	NA
Kolonel and Winkelstein, New York, NY, 1977 (16)	Hospital-based case-control	Nonsmokers	NA	1.00	
		Smokers	NA	1.1	NA
Mishina et al., Japan, 1985 (8)	Hospital cases-neighborhood controls	Nonsmokers	NA	1.00	
		Smokers	NA	1.63	$p = 0.76$
Checkoway et al., North Carolina, 1987 (9)	Hospital-based cases-BPH‡ controls	Never	7/17	1.00	
		Ever	33/47	1.71	0.58–5.2
Ross et al., California, 1987 (17)	Population-based case-control	Blacks			
		Never	NA	1.0	NA
		Current	NA	1.1	NA
		Whites			
		Never	NA	1.0	NA
		Current	NA	0.9	NA
Yu et al , United States, 1988 (18)	Hospital-based case-control	Whites			
		Never	233/624	1.0	
		Current	392/1,090	1.0	0.8–1.2
		Blacks			
		Never	32/57	1.0	
		Current	78/196	1.7	0.4–2.3
Siemiatycki et al., Canada, 1995 (19)	Hospital cases-population controls	Never	75/105	1.0	
		Ever	374/428	1.0	0.7–1.5
Honda et al., California, 1988 (10)	Population-based case-control	Never	44/69	1.0	
		1–9 years	10/11	1.7	0.6–4.4
		10–19 years	22/25	1.4	0.7–2.6
		20–39 years	90/78	1.9	1.1–3.1
		≥40 years	49/32	2.6	1.4–4.9
Oishi et al., Japan, 1989 (11)	Hospital-based case-control	No current	62/49	1.0	
		Current	38/51	0.59	0.34–1.03
		No former	51/60	1.00	
		Former	48/40	1.36	0.76–2.45
	Hospital cases-BPH controls	No current	62/69	1.00	
		Current	38/31	1.41	0.81–2.48
		No former	51/45	1.00	
		Former	48/55	0.77	0.44–1.35
Fincham et al., Canada, 1990 (20)	Population-based case-control	Never	106/153	1.00	
		Current	93/155	0.87	0.61–1.24

Table 1 continues

sonal inquiries in September 1984, 1986, and 1988 to determine whether their enrollees were alive or dead and to record the date and place of all deaths. Automated linkage using the National Death Index was used to extend follow-up through December 31, 1991 (36), and to identify deaths among 8,485 men lost to follow-up between 1982 and 1988. At the completion of mortality follow-up in December 1991, 431,046

TABLE 1. Continued

Study (ref no.)	Design	Use	Study size	Rate ratio	95% confidence interval
Slattery and West, Utah, 1993 (12)	Population-based case-control	Men ≤67 years¶			
		None	18/184	1.00	
		1–28.6 pack-years	9/96	0.96	0.43–2.09
		>28.6 pack-years	11/105	1.07	0.51–2.22
		Men >67 years¶			
		None	23/149	1.00	
		1–28.6 pack-years	11/80	0.89	0.43–1.81
		>28.6 pack-years	15/65	1.50	0.77–2.88
Talamini et al., Italy, 1993 (21)	Hospital-based case-control	Never	64/153	1.0	
		<10 cigarettes/day	20/39	1.03	0.53–2.00
		10–19 cigarettes/day	31/101	0.8	0.47–1.37
		20–29 cigarettes/day	26/80	0.9	0.52–1.62
		≥30 cigarettes/day	12/39	0.9	0.45–2.04
Van der Gulden et al., Netherlands, 1994 (13)	Population-based case-control	Never	16/134	1.00	
		Any	204/780	2.16	1.25–3.74
		1–14 cigarettes/day	98/364	2.23	1.26–3.94
		15–24 cigarettes/day	79/317	2.24	1.24–4.02
		>24 cigarettes/day	27/119	2.07	1.04–4.09
Hayes et al., Atlanta, GA, Detroit, MI, New Jersey, 1994 (22)	Population-based case-control	Blacks			
		None	88/116	1.0	
		Any	161/221	1.0	0.7–1.4
		<10 cigarettes/day	23/32	0.8	0.4–1.6
		10–19 cigarettes/day	47/59	1.1	0.6–1.8
		20–39 cigarettes/day	72/115	0.8	0.6–1.3
		≥40 cigarettes/day	19/14	1.9	0.9–4.2
		Whites			
		None	86/149	1.0	
		Any	116/177	1.2	0.8–1.7
		<10 cigarettes/day	4/7	0.8	0.2–3.2
		10–19 cigarettes/day	13/29	0.8	0.4–1.7
		20–39 cigarettes/day	72/104	1.2	0.8–1.8
		≥40 cigarettes/day	27/37	1.3	0.7–2.4
		Cohort studies			
Hammond, 25 states, United States, 1964 (31)	Mortality prospective (3 years' follow-up)	40–69 years			
		Never	36	1.00	
		Ever	88	0.97	NA
		70–89 years			
		Never	65	1.00	
		Ever	69	1.11	NA
Weir and Dunn, California, 1970 (32)	Mortality prospective	Nonsmokers	NA	1.00	
		Smokers	NA	0.78	NA
Doll et al., United Kingdom, 1994 (33)	Mortality prospective (40 years' follow-up)	Never	68	1.0	
		Current, any	67	1.0	NA
		1–14 cigarettes/day	54	0.8	NA
		15–24 cigarettes/day	73	1.1	NA
		≥25 cigarettes/day	85	1.2	NA
Carstensen et al., Sweden, 1987 (34)	Mortality prospective	Nonsmokers	77	1.0	
		1–7 cigarettes/day	26	1.1	NA
		8–15 cigarettes/day	31	0.8	NA
		≥16 cigarettes/day	15	0.9	NA

Table 1 continues

men (84.8 percent) were still living, 76,715 (15.1 percent) had died, and 815 (0.1 percent) had follow-up truncated in September 1988 because of insufficient data for National Death Index linkage. Death certificates were obtained for 97.9 percent of all men known to have died.

TABLE 1. Continued

Study (ref no.)	Design	Use	Study size	Rate ratio	95% confidence interval
Hsing et al., Lutheran Brotherhood of northeast United States, 1990 (28)	Mortality prospective	Never	19	1.0	
		Any	22	2.0	1.1–3.7
		Ever			
		1–19 cigarettes/day	12	1.6	0.8–3.3
		20–29 cigarettes/day	11	1.7	0.8–3.5
		≥30 cigarettes/day	3	1.4	0.4–4.4
Hsing et al., Veterans of United States, 1991 (29)	Mortality prospective (26 years' follow-up)	Never	4,607	1.0	
		Current	1,407	1.2	1.09–1.28
		1–9 cigarettes/day	260	1.1	0.97–1.27
		10–20 cigarettes/day	695	1.2	1.05–1.27
		21–39 cigarettes/day	374	1.2	1.09–1.38
		≥40 cigarettes/day	78	1.5	1.20–1.90
Coughlin et al., United States, 1996 (30)	Mortality prospective (16 years' follow-up)	Never	514	1.0	
		1–15 cigarettes/day	79	1.54	NA
		16–25 cigarettes/day	102	1.27	NA
		26–35 cigarettes/day	58	1.23	NA
		36–45 cigarettes/day	57	1.50	NA
		≥46 cigarettes/day	16	1.22	NA
Whittemore et al., college men of United States, 1984 (24)	Nested case-control	Never	NA	1.0	
		Every 10 pack-years of cigarettes	NA	1.1	1.0–1.3
Severson et al., Hawaii, 1989 (25)	Incidence prospective	Never	63	1.0	
		Current	65	0.9	0.61–1.23
Ross et al., California, 1990 (26)	Incidence prospective	Never	56	1.0	
		Former	73	0.8	NA
		Current	9	0.9	NA
Mills et al., Adventists of California, 1989 (27)	Incidence prospective	Never	90	1.00	
		Past	79	1.24	0.91–1.67
		Current	3	0.49	0.16–1.57
Hiatt et al., California, 1994 (23)	Nested case-control	Never	79	1.0	
		<1 pack/day	24	1.0	0.6–1.6
		≥1 pack/day	25	1.9	1.2–3.1

* In references 15, 23, 25–31, 33, 34, information on study size refers only to cases
† In references 7–22, values represent odds ratios.
‡ TNCS, Third National Cancer Survey; NA, not available; BPH, benign prostatic hypertrophy.
§ Controls are patients with cancer in other site.
¶ Results presented include only most aggressive tumors.

Prostate cancer deaths were defined as those deaths occurring among men through December 1991 with prostate cancer (*International Classification of Diseases*, Ninth Revision, code 185 (37)) as the underlying cause. One of the main objectives of the study was to assess the relation between smoking and fatal prostate cancer among black and white American men, since not enough men from other races were included in this cohort to examine their prostate cancer risk in relation to smoking separately. We excluded from the analysis (table 2) 2,399 men who had missing information on race and 9,247 men of races other than black or white. We also excluded 21,624 men who reported having cancer at study entry (except nonmelanoma skin cancer) and 21,747 men with no information on whether they had ever smoked or no information on smoking status (former or current smokers). The total cohort included in the analysis encompassed 450,279 men and 1,748 prostate cancer deaths.

In the baseline questionnaire, men completed information about their past and current smoking status. Ever cigarette smokers were defined as men who reported smoking at least one cigarette per day for at least 1 year and not smoking a pipe or cigars. Current smokers included persons who were ever cigarette smokers and who left blank the questions on former smoking. Former smokers were defined as ever cigarette smokers who indicated when they quit smoking. Several measures of cigarette smoking exposure level were investigated for their potential relation to fatal prostate cancer: the number of cigarettes per day

TABLE 2. Cohort eligible for analysis, Cancer Prevention Study II, United States, 1982–1991

	No of men	No of prostate cancer deaths
Total cohort	508,576	3,035
Exclusions		
Missing race	2,399 (0.5)*	10 (0.3)
Other race†	9,247 (1.8)	31 (1.0)
Reported at study entry		
Prostate cancer	3,280 (0.6)	826 (27.2)
Other cancer‡	21,624 (4.3)	268 (8.8)
Unclassified smoking status	21,747 (4 3)	152 (5.0)
Total no. of exclusions	58,297 (11 5)	1,287 (42.4)
Total available for analysis	450,279	1,748

* Numbers in parentheses, percentage.
† Includes Asian, Hispanic, and other race.
‡ Cancer at entry except non-melanoma skin cancer.

(<10, 10–19, 20, >20), the duration of exposure (<25, 25–35, >35–45, >45 years) among current smokers at study entry, and years since quitting at baseline (<6, 6–10, 11–15, 16–25, >25 years) among former smokers. Men who reported ever smoking pipes or cigars alone or in combination with cigarettes were defined in two separate categories: current smokers of pipes/cigars/cigarettes or former smokers of pipes/cigars/cigarettes.

We used Cox proportional hazards modeling (38) to examine the association of smoking and fatal prostate cancer while adjusting for other potential risk factors. All the analyses stratified on the exact year of age at enrollment and controlled for race (white and black). Potential confounders included in multivariate models were the following: family history of prostate cancer in a first degree relative; body mass index (weight (kg)/height $(m)^2$) (<20.7, 20.7–24.6, 24.7–27.7, 27.8–31.0, >31.0, unknown); years of education (less than high school, high school, some college, college graduate or graduate school, unknown); total physical activity at work or play (none, slight, moderate, heavy, unknown); alcohol use (none, any, unknown); vegetables (frequency per week of consuming six items (carrots, tomatoes, squash/corn, green leafy vegetables, raw vegetables, and cabbage/broccoli/brussels sprouts) divided into quartiles) (39); total fat meat (the frequency per week of consuming eight items (beef, pork meat, ham, hamburgers, liver, sausages, bacon, and smoked meats) divided into quartiles); and history of vasectomy (yes/no). Information on vasectomy was obtained through a question on types of surgical procedure prior to enrollment.

The test for linear trend was used to assess the statistical significance between the risk of prostate cancer death and levels of number of cigarettes smoked per day and years of exposure to cigarette smoking.

To test whether other factors modified the association between current smoking and fatal prostate cancer, we entered multiplicative interaction terms between smoking status (current, never) and each potential confounder into the multivariate models. In addition, to assess whether age modified the association between current smoking and fatal prostate cancer, we defined "attained age" (40, p. 337) for each study participant as a time-varying covariate (41). At each point in time during the follow-up period, attained age was calculated as the age at interview plus the time elapsed since the start of follow-up. For each man, attained age was incremented throughout the follow-up period until the man died or was lost to follow-up or until the study ended. Attained age was categorized into four age groups (<60 years, 60–69 years, 70–79 years, and ≥80 years), and both deaths and person-years at risk were allocated to each attained age category. A given study participant could contribute person-years at risk to more than one age group, depending on the ages attained by that participant during the study period. The statistical significance of the interaction was assessed at the $p = 0.05$ level using the likelihood ratio test (40). All statistical tests performed were two-sided tests of significance.

RESULTS

Of 450,279 men included in the analytic cohort, 118,308 (26 percent) had never smoked, 94,916 (21 percent) had ever smoked pipes or cigars alone or some combination of pipes, cigars, and cigarettes, 138,756 (31 percent) formerly smoked cigarettes only, and 98,299 (22 percent) were current cigarette smokers at study entry. Comparing current with never cigarette smokers at baseline, current smokers were more likely to be black, to have less education, to be thinner, to consume more alcohol, to eat fewer vegetables and more meat, and to exercise less than never smokers (table 3). They were also less likely to have a family history of prostate cancer or to have had a vasectomy.

There was no association between ever cigarette smoking (multivariate rate ratio (RR) = 1.02, 95 percent confidence interval (CI) 0.92–1.14) or former cigarette smoking (RR = 0.99, 95 percent CI 0.87–1.12) and risk of fatal prostate cancer (table 4). Results were similar among men who were current or former smokers of pipes/cigars only or a combination of pipes/cigars and cigarettes. However, men who were current cigarette smokers at study entry had 34 percent

TABLE 3. Distribution of potential prostate cancer risk factors and their association with cigarette smoking, Cancer Prevention Study II, United States, 1982–1991

Covariate	No of current smokers* (n = 98,299)	Age-adjusted % of current smokers	No of never smokers* (n = 118,308)	Age-adjusted % of never smokers
Race				
White	92,785	44.6	113,866	55.4
Black	5,514	55.3	4,442	44.7
Family history of prostate cancer				
No	95,900	45 2	114,572	54.8
Yes	2,399	39.0	3,736	61.0
Vasectomy				
No	96,790	45.2	116,160	54 8
Yes	1,509	38 5	2,148	61.5
Exercise				
None	2,802	61.7	1,847	38.3
Slight	24,124	50.5	23,541	49.5
Moderate	58,736	43.7	75,819	56.3
Heavy	11,716	40.5	15,861	59.5
Body mass index (kg/m^2)				
<20.7	6,028	62.6	4,012	37 4
≥20.7–<24.7	36,196	47.6	40,355	52.4
≥24.7–<27 8	33,126	42.6	43,170	57.4
≥27.8–<31.1	15,130	41 2	20,237	58.8
≥31.1	5,638	39 1	7,955	60.9
Education				
Less than high school	18,596	61.6	14,100	38.4
High school graduate	22,729	49.7	22,122	50.3
Some college	29,284	50 4	27,617	49.6
College graduate	26,217	32.2	52,977	67 8
Vegetable consumption				
First quartile	28,737	54 6	24,053	45.4
Second quartile	25,424	47.1	27,937	52.9
Third quartile	20,125	41.3	27,785	58.7
Fourth quartile	16,132	34.2	30,548	65 8
Fat meat consumption				
First quartile	15,815	35.3	29,969	64.7
Second quartile	22,393	42.6	29,696	57 4
Third quartile	24,885	47.3	26,809	52 7
Fourth quartile	27,325	52.5	23,849	47.5
Alcohol use				
None	9,868	27.4	26,310	72 6
Any	60,642	54.1	49,666	45.9

* Numbers do not add to total because of missing data.

higher death rates from prostate cancer (RR = 1.34, 95 percent CI 1.16–1.56) during the 9 years of follow-up than did never smokers.

Among current smokers of cigarettes exclusively, smoking was further characterized by cigarettes smoked per day at baseline and total years of smoking (table 4). The referent group for each smoking category was never smokers. The association of current smoking with fatal prostate cancer did not increase with the number of cigarettes per day or with the duration of smoking. However, the gradient of risk with duration among all current cigarette smokers could not be closely examined because age and the duration of smoking were highly correlated. The category for shorter smoking duration included men smoking as long as 25 years, and the mean smoking duration among all current cigarette smokers was 36 years (standard deviation = 10.65 years). Among former cigarette smokers, the number of years since quitting was not related to fatal prostate cancer.

There was no statistically significant modification of the positive association between current cigarette smoking and fatal prostate cancer by the attained age of study participants (p for interaction = 0.44). Although the risk of fatal prostate cancer associated with current cigarette smoking appeared to decrease with increasing attained age (table 5), the test for trend was not statistically significant (p = 0.16). The rate ratio for men younger than 60 years was 1.83 (95 percent CI 1.04–3.24), whereas no significant association was found among men older than 80 years (RR = 1.11, 95 percent CI 0.79–1.58).

TABLE 4. Prostate cancer mortality by smoking status, Cancer Prevention Study II, United States, 1982–1991

	Prostate cancer case patients	Person-years	Rate ratio*	Rate ratio†
Smoking status				
Never	485	1,050,238	1 00	1.00
Ever	1,263	2,877,901	1 05 (0 94–1.16)‡	1.02 (0.92–1.14)
Current cigarette only	339	843,342	1.37 (1 19–1.58)	1.34 (1.16–1.56)
Former cigarette only	558	1,205,037	1.01 (0.89–1.14)	0.99 (0.87–1.12)
Current pipe/cigar/cigarette	157	394,611	0.89 (0.74–1.06)	0.87 (0.73–1.05)
Former pipe/cigar/cigarette	209	434,911	0.93 (0.79–1.09)	0.91 (0.78–1.08)
		Among current cigarette smokers		
Cigarettes per day§				
Never	485	1,050,238	1.0	1.00
<10	42	73,303	1.34 (0.98–1 85)	1.33 (0.96–1.83)
≥10–<20	74	116,770	1.60 (1.25–2.04)	1.58 (1 23–2 03)
20	108	241,765	1.41 (1.14–1.74)	1.38 (1.10–1.71)
>20	107	394,941	1.30 (1.04–1.61)	1.25 (1.00–1.57)
			p for trend ¶ = 0 35	*p* for trend ¶ = 0 29
Duration (years)#				
Never	485	1,050,238	1 00	1.00
≤25	13	134,918	1.35 (0 77–2.38)	1.36 (0.77–2.38)
>25–≤35	43	278,686	1.67 (1.19–2.36)	1.65 (1.17–2.34)
>35–≤45	118	290,353	1.42 (1 14–1.78)	1.39 (1.11–1.75)
>45	155	129,760	1.28 (1 07–1.55)	1.26 (1.04–1 53)
			p for trend ¶ = 0.83	*p* for trend ¶ = 0 86
		Among former cigarette smokers		
Years since quit**				
Never	485	1,050,238	1 00	1.00
≥0–≤5	56	194,057	0 92 (0.70–1.22)	0.88 (0.67–1.17)
>5–≤10	68	176,408	1.08 (0 84–1.40)	1.04 (0.80–1.34)
>10–≤15	89	216,095	1.09 (0 87–1.36)	1.04 (0.83–1.31)
>15–≤25	178	368,874	1.12 (0.94–1.33)	1.08 (0.91–1 29)
>25	161	239,702	0.88 (0.74–1.05)	0.87 (0.73–1.05)

* Adjusted for age at enrollment and race

† Adjusted for age at enrollment, race, education, family history of prostate cancer, vasectomy, exercise, body mass index, alcohol use, and vegetable and fat meat intakes.

‡ Numbers in parentheses, 95% confidence interval.

§ Excludes eight case patients and 1,995 non-case subjects with missing information on cigarettes per day.

¶ Never smokers were excluded from trend test calculations.

Excludes 10 case patients and 1,166 non-case subjects with missing information on years smoked.

** Excludes five case patients and 1,085 non-case subjects with missing information on age that they quit smoking and one case patient and 117 non-case subjects with a negative value for years since they quit smoking

Race did not significantly modify the association between fatal prostate cancer and current cigarette smoking status at study entry ($p = 0.12$). White men who smoked at enrollment had a 33 percent increased risk of dying from prostate cancer (292 deaths in current smokers; RR = 1.33, 95 percent CI 1.13–1.57) compared with never smokers; this increased risk was 61 percent among black men (47 deaths; RR = 1.61, 95 percent CI 1.00–2.61).

The relation between current cigarette smoking and prostate cancer was significantly affected ($p < 0.05$) by family history of prostate cancer. Current smoking was associated with an increased risk of fatal prostate cancer among men without a family history of prostate cancer ($n = 332$ deaths among smokers; RR = 1.40, 95 percent CI 1.20–1.64) but not among men with a family history (n = seven deaths among smokers; RR = 0.61, 95 percent CI 0.27–1.39). The number of deaths in this latter group was small and the confidence interval wide. No other significant modifications of the association between current smoking and prostate cancer were observed.

We examined the possibility that the excess risk associated with being a current cigarette smoker at study entry was the result of a possible screening bias caused by the exclusion of men who reported prostate cancer at baseline. When fatal prostate cancer in the first 4 years of follow-up was excluded from the

TABLE 5. Prostate cancer risk by attained age of the study participants according to cigarette smoking status, Cancer Prevention Study II, United States, 1982–1991

Attained age	No. of deaths	Rate ratio*	Rate ratio†
<60 years			
Never smoker	15	1.00	1.00
Current cigarette smoker	31	1 90 (1 08–3.35)‡	1.83 (1.04–3 24)
≥60–<70 years			
Never smoker	98	1.00	1.00
Current cigarette smoker	119	1.45 (1.11–1.88)	1.41 (1.08–1.84)
≥70–<80 years			
Never smoker	207	1.00	1 00
Current cigarette smoker	147	1.39 (1.13–1 72)	1.37 (1 10–1.70)
≥80 years			
Never smoker	165	1.00	1 00
Current cigarette smoker	42	1.12 (0.80–1.58)	1.11 (0 79–1.58)
		p for trend § = 0.13	*p* for trend § = 0.16

* Adjusted for age at enrollment and race
† Adjusted for age at enrollment, race, education, family history of prostate cancer, vasectomy, exercise, body mass index, alcohol use, and vegetable and fat meat intakes.
‡ Numbers in parentheses, 95% confidence interval
§ Never smokers were excluded from trend test calculations.

analysis, the rate ratio for fatal prostate cancer among current cigarette smokers did not change (n = 283 deaths; RR = 1.44, 95 percent CI 1.21–1.70).

Among other covariates included in the multivariate model, being black (RR = 2.22, 95 percent CI 1.81–2.72), having a positive family history of prostate cancer (RR = 1.59, 95 percent CI 1.25–2.02), and low vegetable intake (RR = 1.26, 95 percent CI 1.07–1.48 for the lowest quartile of vegetable consumption) were associated with an increased risk for fatal prostate cancer.

DISCUSSION

Men who were cigarette smokers at the time of enrollment in the study had a 34 percent higher death rate from prostate cancer than never smokers during the 9 years of follow-up. This association was seen among both black and white current cigarette smokers but not among former smokers of any type of tobacco. The rate ratio did not increase with the number of cigarettes smoked or with years of smoking. Controlling for other prostate cancer risk factors did not alter these findings.

Several factors suggest that shortened survival among smokers with prostate cancer may be the explanation for the observed association. First, the increased risk associated with smoking is observed among current smokers in mortality studies. Three other large prospective mortality studies (28–30) have found higher prostate cancer death rates in smokers than in nonsmokers. These include the prospective Lutheran Brotherhood Cohort Study (28), the US military veterans' study (28–29, 42), and the Multiple Risk Factor Intervention Trial (MRFIT) (30). Like Cancer Prevention Study II, none of these studies can distinguish factors that influence survival from those that increase incidence, and no consistent association has been found in most of the studies on incident prostate cancer. Second, results from clinical studies (43, 44) have linked smoking with a higher likelihood of poorly differentiated, more aggressive prostate cancer at diagnosis, and with poorer 5-year survival, even in the absence of delayed diagnosis. Smokers have decreased natural killer cell activity (45) and immunoglobulin levels (45, 46) that would contribute to a poorer prognosis among prostate cancer patients. The association might be also mediated by hormonal factors. Tobacco seems to have an antiestrogen effect (47) that could alter the production, metabolism, and degradation of estrogen and decrease the estrogen available in the prostate (48). In addition, cigarette smoking increases the production of dihydrotestosterone, circulating levels of androgens (5, 6), and the ratio of androgens to estrogen at the target cell, which may contribute to the progression of prostate cancer (3, 48). It remains unclear, however, how the lack of a dose-response relation with the number of cigarettes observed in this study would fit with this hypothesis.

An alternative explanation for our findings is that the association between smoking and fatal prostate cancer is an artifact of reduced overall survival among smokers and reliance on death certificates to identify cases. Although the accuracy of death certificates for prostate cancer is reasonably high (49), the validity of

prostate cancer as the true underlying cause of death has not been assessed. It may be that prevalent nonfatal prostate cancers are sometimes recorded as the underlying cause of death. Therefore, because premature mortality from all causes is higher in smokers than nonsmokers (50), prostate cancer mortality among smokers could be artifactually raised. Lack of a dose-response with the number of cigarettes smoked observed in this and one of the other studies (30), however, would not support this explanation.

The possibility that the reported association could be due to more frequent screening for prostate cancer or earlier diagnosis among the nonsmokers than the smokers also seems unlikely. Although information on prostate cancer screening was not collected in Cancer Prevention Study II, no differences in the reported frequency of digital rectal examination for early diagnosis of prostate cancer were found between smokers and nonsmokers in the 1987 National Health Interview Survey (51). In addition, digital rectal examination, the most common prostate cancer screening modality in 1982 when Cancer Prevention Study II was begun, has limited ability to recognize early prostate cancer (52).

Finally, chance seems unlikely because of the internal consistency of the findings across different ages, race, different lengths of follow-up, and the agreement with the other larger prospective cohort studies on fatal prostate cancer (28–30). No dose-response trend was seen with the number of cigarettes smoked per day or with the duration of smoking, however, so chance cannot be totally ruled out.

The strengths of this study are its size, prospective design, and the exclusion of men with cancer at interview, minimizing the influence of disease status on reported smoking history. A limitation is that the data on smoking status were collected only once in 1982 and were not updated during follow-up. In a repeat survey of a subgroup of 90,000 men conducted in 1992–1993, it was found that almost 50 percent of male current smokers at the 1982 baseline had quit smoking in the interim. Less than 1 percent of the former smokers in 1982 had readopted the habit. Although the 1992–1993 subgroup was not a representative randomized sample of all original Cancer Prevention Study II participants, and although the percentage of men quitting the habit may be inflated, some misclassification of smoking could bias the risk estimates toward the null, so that the strength of the association with smoking might be stronger than has been reported here.

In conclusion, these results are consistent with the other large prospective cohort studies that have examined smoking and fatal prostate cancer. The lack of association between cigarette smoking and incident prostate cancer found in other studies suggests that these results are due to a reduction in prostate cancer survival in smokers compared with never smokers.

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