Smoking and Risk of Total and Fatal Prostate Cancer in United States Health Professionals[1]

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Abstract

Studies that have examined the relationship between cigarette use and prostate cancer incidence have yielded inconsistent results, although most studies have suggested that smoking is related to the occurrence of fatal prostate cancer. We evaluated prospectively the relationship between cigarette smoking and total, distant metastatic, and fatal prostate cancer in 47,781 male health professionals throughout the United States followed with questionnaires. From 1986 to 1994, we documented 1369 men with prostate cancer (excluding stage A1). One hundred fifty-two of the men had distant metastatic disease at diagnosis, and 103 fatal cases occurred from 1986 to 1994. Early (before age 30), late (within recent 10 years), and lifetime cumulative smoking history were unrelated to risk of total prostate cancer. However, men who had smoked 15 or more pack-years of cigarettes within the preceding 10 years were at higher risk of distant metastatic prostate cancer [multivariate relative risk (RR), 1.81; 95% confidence interval (CI), 1.05–3.11; *P* (trend), 0.03] and fatal prostate cancer [RR, 2.06; CI, 1.08–3.90; *P* (trend), 0.02] relative to nonsmokers. Within 10 years after quitting, the excess risk among smokers is eliminated. The higher rate of fatal prostate cancer among smokers did not appear to result from confounding by diet or other lifestyle factors, different screening behavior between smokers and nonsmokers, or from other smoking-related comorbidities. Our results indicate that although smoking was unrelated to prostate cancer incidence, recent tobacco use had a substantial impact on the occurrence of fatal prostate cancer.

Introduction

Cigarette use is the leading cause of death from cancer, but the relationship between smoking and prostate cancer has been inconsistent; some studies indicate no connection (1–5), whereas others suggest an elevated risk among smokers (6–10). In several studies, smokers had higher mortality rates from prostate cancer (11–14). A large investigation of United States veterans (12) found an elevated risk among current smokers at baseline during the initial 8.5 years of follow-up, but this risk was attenuated over the 26-year follow-up. This finding suggests that only relatively recent use of tobacco influenced risk of prostate cancer mortality because many smokers quit over time. A possible explanation for the more consistent results for mortality than incidence is that smokers may delay diagnosis and treatment, which could result in poorer survival. Alternatively, tobacco may theoretically induce prostate cancers to develop a more aggressive phenotype or may cause the development of a distinct subset of rapidly progressive cancers. For example, smoking-related carcinogens could possibly cause mutations in genes associated with tumor progression, or tobacco use may alter host factors, such as levels of hormones, which foster tumor progression. Indeed, two studies (15, 16) have found smokers more likely to be diagnosed with advanced stage or high histological grade prostate cancers.

The studies that found smokers to be at higher risk for prostate cancer mortality (11–14) could not distinguish whether this association was a result of delayed diagnosis and treatment among smokers, failure to control for confounding factors, or from direct effects from tobacco use. To better understand the nature of the relationship between smoking and prostate cancer, we examined smoking history and this malignancy in the Health Professionals Follow-Up Study.

Subjects And Methods

The Study Population and Follow-Up of the Cohort. The Health Professionals Follow-up Study is an ongoing prospective cohort study of the causes of cancer and heart disease in men (17). The cohort consists of 51,529 United States male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians who were 40–75 years when they responded to a mailed questionnaire in 1986. These men provided information on age, current and past tobacco use, marital status, height and weight, ancestry, medications, disease history, physical activity, and diet. For this analysis, we excluded men who reported cancer at baseline (other than nonmelanoma skin cancer). Because of the importance of controlling for dietary factors (17–19), we included only men who adequately completed a food frequency questionnaire (97% of the total). After these baseline exclusions, 47,781 participants formed the cohort for analysis beginning in 1986.

Follow-up questionnaires were sent in 1988, 1990, 1992, and 1994 to ascertain new cases of prostate cancer and to update exposure information. Most of the deaths in the cohort

were reported by family members or by the postal system in response to the follow-up questionnaires. In addition, we searched the National Death Index, a highly sensitive method (20), to identify deaths among nonrespondents. After repeated mailings, the follow-up response rate was 94% through 1994. We estimate having ascertained over 98% of the deaths in this cohort. This study was approved by the Harvard School of Public Health Human Research Committee.

Identification of Cases of Prostate Cancer. Whenever a diagnosis of prostate cancer was reported, we asked the participant or next of kin to permit us to obtain hospital records and pathology reports. Prostate cancers were staged by study physicians according to information from medical reports [stage A, occult or incidental finding (A1, focal; A2, diffuse); stage B, confined to prostate gland; stage C, localized to periprostatic area; stage D1, metastatic disease involving only regional lymph nodes; and Stage D2, metastases to other organs.) The classification was based on information from any work-up during the initial diagnosis including staging prostatectomy and bone scans. The study physicians were blinded to the participants' reported smoking status when they reviewed medical reports.

From 1986 to the end of this study period (January 31, 1994), we identified 1414 incident cases of prostate cancer. Of these, 1262 cases (89.3%) were confirmed by medical records, and of the remaining 152 cases, 130 men (85%) provided information regarding the basis of diagnosis. When we obtained pathology reports, a diagnosis of adenocarcinoma of the prostate was confirmed in 99% of the cases. Because stage A1 lesions are typically indolent and are especially prone to detection bias, we excluded these (3% of the total) and limited our analysis to the 1369 non-stage A1 cases.

Exposure Data. Current smoking status (cigarettes/day) was assessed on each biennial questionnaire. At baseline, we also inquired about past smoking, time since quitting (<1, 1–2, 3–5, 5–9, 10+ years), and the average number of cigarettes smoked per day before age 15 years, ages 15–19, 20–29, 30–39, 40–49, 50–59, and 60 and older. A pack was considered to be 20 cigarettes, and a pack-year is the equivalent of smoking 20 cigarettes a day for 1 year. We assessed dietary intake using a validated semiquantitative food frequency questionnaire (21). On each follow-up questionnaire, the participant was asked if he had had a digital rectal examination in the prior 2 years, and in 1994, the participant was asked whether he had ever had a PSA[3] determination.

Statistical Analysis. We calculated a cumulative cigarette pack-year history for each man during various periods throughout life, including total lifetime cumulative smoking, smoking before the age of 30 to assess smoking during adolescence and early adulthood, and recent smoking to assess any late-acting effect of smoking. Recent smoking history was defined as: (*a*) current smoking; (*b*) past-smoking within 10 years; and (*c*) total pack-years exposure in the 10 calendar years prior to follow-up. Because tobacco may influence the overall occurrence of prostate cancer or act specifically on progression, we conducted separate analyses of that subset of total cancers diagnosed at stage C or D (extraprostatic), stage D2 cases (distant metastases), and cases that led to death. For metastatic prostate cancer, we excluded 49 nonfatal stage D1 cases and only included 152 stage D2 cases because the diagnosis of stage D1 cases is based

on a diagnostic procedure (examining pelvic lymph nodes for tumor) and frequencies of various medical procedures vary by smoking status. We conducted an additional analysis of newly diagnosed cases of metastatic and fatal prostate cancer during 1988–1994 among men who had reported in 1988 having had a recent "negative" digital rectal examination, reasoning that these cases would represent a subset of particularly aggressive malignancies, and to reduce potential bias from any difference in screening behavior between smokers and nonsmokers.

Each man contributed to follow-up time (person-years) beginning on the month of return of the baseline questionnaire and ending on the month of diagnosis of prostate cancer, month of death from other causes, or the end of the study period (January 31, 1994). We calculated incidence rates of prostate cancer for men in a specific category of tobacco use by dividing the number of incident cases by the number of person-years. The RR was computed as the rate among men in the category of interest divided by the rate among men in the reference category, usually nonsmokers. We used the Mantel-Haenszel summary estimator (22) to adjust for age (across 2.5-year categories).

For multivariate analyses, we used pooled logistic regression, which accounts for varying time to the outcome event (23) and which is asymptotically equivalent to a Cox regression model with time-dependent covariates, given short time intervals and a low probability of outcome (24). A participant contributed up to four observations based on four 2-year time periods from 1986 to 1994; if a man had a diagnosis of prostate cancer or died from any cause, the subsequent 2-year time periods were censored. Each 2-year set of observations contributed by each subject was pooled in the logistic regression analysis. Age and current and past smoking status were updated biennially. In this paper, the term RR is equivalent to the incident rate ratio, given the low incidence rate of prostate cancer within each follow-up interval.

The basic multivariate model included age (updated every 2 years) and 1986 intakes (quintiles) of total fat (17), lycopene (18), vitamin E (25), and calcium (19), all of which have been associated with prostate cancer in this or other studies. We also included body mass index at age 21, which was inversely associated with risk of prostate cancer in this cohort (26). Other potential confounders considered included vasectomy, physical activity, alcohol, race, fructose, energy intake, and body mass index in 1986 and were included only if they altered the β coefficient for smoking variables by 10% when included individually in the basic multivariate model.

We tested for trends, controlling for multiple covariates by modeling the specific exposure as a continuous variable in a logistic model that included the covariates. All reported *P*s are two-sided.

Results

We first examined whether cigarettes smoked earlier in life might act as an initiator of prostate cancer. Analyses of total pack-years smoked prior to the age of 30 years did not yield an association with total prostate cancer incidence (age-adjusted RR, 1.08; 95% CI, 0.92–1.27, for >10 *versus* 0 pack-years; *P,* trend, 0.23), distant metastatic (RR, 1.04; 95% CI, 0.63–1.72; *P,* trend, 0.78), or fatal prostate cancer (RR, 1.10; 95% CI, 0.60–2.01; *P,* trend, 0.68). Moreover, analyzing cases accounting for various time lags of up to at least 40 years between onset of smoking and time period at risk did not indicate an increased risk of total or advanced prostate cancer among smokers (data not shown).

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[3] The abbreviations used are: PSA, prostate-specific antigen; RR, relative risk; CI, confidence interval; BPH, benign prostatic hypertrophy.

Table 1 Relative risk of prostate cancer according to smoking status updated every 2 years in the Health Professionals Follow-Up Study (1986–1994)

	Never smoked	Past smokers		Current smokers
		Stopped ≥10 years	Stopped <10 years	
Person-years	170,825	101,038	47,990	31,408
Total prostate cancer (*n*)[a]	580	503	174	112
Age-adjusted RR	1.0	0.99	1.04	1.05
RR[b]	1.0	0.99	1.03	1.04
95% CI		0.88–1.12	0.87–1.22	0.85–1.27
Distant metastatic[c]				
Prostate cancer (*n*)	58	55	26	13
Age-adjusted RR	1.0	1.06	1.58	1.23
RR[b]	1.0	1.07	1.56	1.23
95% CI		0.74–1.54	0.98–2.48	0.67–2.24
Fatal prostate cancer (*n*)	38	35	19	11
Age-adjusted RR	1.0	1.03	1.75	1.59
RR[b]	1.0	1.04	1.73	1.58
95% CI		0.66–1.64	1.00–3.01	0.81–3.10

[a] Excluding stage A1 cases.
[b] RR and 95% CI adjusted for age (in 2.5-year increments), body mass index at age 21 (six categories), and quintiles of intakes of calcium, total fat, vitamin E, and lycopene by multiple logistic regression. Age and smoking status are updated every 2 years.
[c] Includes all cases that were distant metastatic at diagnosis or fatal by 1994.

Table 2 RR of distant metastatic and fatal prostate cancer (1986–1994) according to total pack-years of cigarettes smoked in previous decade (1976–1986)

	Pack-years smoked during previous decade				*P*, trend[a]
	0	1–9	10–14	≥15	
Total person years	284,601	19,392	24,757	22,511	
Distant metastatic (*n*)	119	7	11	15	
Age-adjusted RR	1.0	1.16	1.28	1.85	
RR[b]	1.0	1.14	1.25	1.81	0.03
95% CI		0.53–2.45	0.67–2.32	1.05–3.11	
Fatal (*n*)	77	5	10	11	
Age-adjusted RR	1.0	1.29	1.80	2.11	
RR[b]	1.0	1.25	1.76	2.06	0.02
95% CI		0.50–3.10	0.91–3.42	1.08–3.90	

[a] Test for trend calculated using pack-years as a continuous variable in multiple logistic regression model.
[b] RR and 95% CI adjusted for age (in 2.5-year increments), body mass index at age 21 (6 categories), and quintiles of intakes of calcium, total fat, vitamin E, and lycopene by multiple logistic regression.

We next conducted a series of analyses to examine the influence of recent tobacco use. We found that neither current nor past smokers were at statistically significantly elevated risk for total prostate cancer (Table 1). However, men who had quit within the prior 10 years were at elevated risk for developing distant metastatic (RR, 1.56; 95% CI, 0.98–2.48) and fatal prostate cancer (RR, 1.73; 95% CI, 1.00–3.01), and current smokers had an elevated risk for fatal prostate cancer (RR, 1.58; 95% CI, 0.81–3.10), although this was not statistically significant. Next, we examined total smoking over the preceding 10 years in more detail. A dose-response relation existed between total pack-years of cigarettes smoked over the prior 10 years (1976–1986) and risk for metastatic and fatal prostate cancer in 1986–1994 (Table 2). Total lifetime cigarette pack-years was a risk factor for distant metastatic prostate cancer (RR, 1.14; 95% CI, 1.01–1.30 for a 20 pack-year increment) and fatal prostate cancer (RR, 1.18; 95% CI, 1.01–1.37). However, when we controlled for recent smoking history (1976–1986), lifetime cigarette pack-years smoked no longer remained a statistically significant risk factor for distant metastatic prostate cancer (RR, 1.09; 95% CI, 0.90–1.32) or fatal prostate cancer (RR, 1.07; 95% CI, 0.85–1.36). This suggests recent smoking history (for example, prior decade) is a better predictor of occurrence of aggressive prostate cancer than lifetime cumulative smoking history.

For recent smoking history (Tables 1 and 2), the age-adjusted and multivariate models provided nearly identical results, indicating little confounding by these factors. Further control for other potential confounders by including individually vasectomy, physical activity, alcohol, race, energy intake, and body mass index in 1986 in the basic multivariate model did not alter the results for smoking variables appreciably. For total metastatic prostate cancer, including stage D1 cases, results were nearly identical for current smoking and somewhat attenuated for recent past smoking compared with distant metastatic disease.

We explored whether lower frequency of screening at baseline among smokers, through a delay in diagnosis and treatment, may have accounted for the increase in mortality. In an analysis limited to men who had reported a negative digital rectal examination in 1986–1988, the only common screening test at the time, the associations between smoking and distant metastatic and fatal prostate cancer from 1988 to 1994 became even stronger (Table 3). The associations among men with a negative digital rectal examination were particularly strong for current smokers in 1986 [for metastatic prostate cancer RR (1–14 *versus* 0 cigarettes/day), 2.3 (95% CI, 0.9–6.0) and RR (≥15 *versus* 0 cigarettes/day), 4.2 (95% CI, 1.6–10.9]. For the occurrence of fatal prostate cancer, these respective RRs were 3.2 (95% CI, 1.1–9.5) and 5.8 (95% CI, 1.9–17.2).

We examined whether smokers, because of a higher frequency of medical conditions, were more likely to die from other causes after the diagnosis of prostate cancer and have their death attributed spuriously to prostate cancer. As expected, cigarette smoking was related to a higher risk of comorbidities (myocardial infarction, angina, cerebral vascular disease, other heart disease, and diabetes mellitus). Among men diagnosed with prostate cancer, having at least one of these conditions predicted death from other causes (RR, 1.63), but these conditions did not predict death attributed to prostate cancer (RR, 1.07). These findings suggest that prostate cancer fatalities among smokers were truly from the cancer and not from other smoking-related conditions. Because these comorbid conditions did not predict death from prostate cancer, results for smoking within the past 10 years (current, past, and total) and occurrence of metastatic or fatal prostate cancer were essentially unchanged when the presence of at least one comorbid condition was included as a covariate in the multivariate models.

To confirm a higher case fatality rate from prostate cancer among smokers, we conducted a survival analysis (using PHREG, SAS statistical software) beginning at the date of diagnosis, with failure time equal to the date of death from prostate cancer. Men were followed until the date of death from prostate cancer or other causes, or January 31, 1994. Relative to nonsmokers, we found a lower survival rate from prostate cancer among cases who were smokers in 1986 (age-adjusted mortality rate, 1.63; 95% CI, 0.88–3.02) or who had quit within the prior 10 years (RR, 1.64; 95% CI, 0.91–2.96). In contrast, men who developed prostate cancer but who had quit smoking for more than 10 years were not at higher risk of mortality (RR, 1.06; 95% CI, 0.67–1.68).

Table 3 RR of distant metastatic and fatal prostate cancer for an increment of 15 pack-years of cigarettes smoked in the prior decade (1976–1986) for all men (1986–1994) and RR among men (1988–1994) who reported a negative digital rectal examination in 1988

	n	RR[a] (95% CI)	*P*, trend
1986–1994 (total)			
Metastatic	152	1.55 (1.04–2.33)	0.03
Fatal	103	1.77 (1.11–4.07)	0.02
1988–1994 (negative digital rectal examination in 1988)			
Metastatic	57	2.05 (1.12–3.75)	0.02
Fatal	37	2.40 (1.17–4.91)	0.02

[a] RR and 95% CI adjusted for age (in 2.5-year increments), body mass index at age 21 (six categories), and quintiles of intakes of calcium, total fat, vitamin E, and lycopene by multiple logistic regression.

Discussion

In this study, cigarette smoking during the 10-year period preceding follow-up predicted the occurrence of metastatic and fatal prostate cancer. Men who had quit smoking within 10 years were at elevated risk, suggesting that continued smoking after the diagnosis was not necessary to increase mortality. The risk abated 10 years after smoking cessation. The associations with smoking were even stronger for cancers that were rapidly progressive, *i.e.,* those that were distantly metastatic or fatal in a relatively short time period after a negative digital rectal examination. These associations were not confounded by various factors considered, including diet, vasectomy, race, alcohol, physical activity, and body mass. Although we did not collect data on family history of prostate cancer (father, sibling) until 1990 and thus could not control for this prospectively, a positive family history was unlikely to confound our results because the prevalence of men with a positive family history was unrelated to smoking status (7.1% for never smokers, 7.1% for current smokers, and 7.0% for past smokers).

At least two scenarios could account for our results. If smokers tend to avoid medical contacts, their tumors could be diagnosed at later stages, and their higher mortality rate could be due to delayed treatment. Alternatively, tobacco could alter the behavior of prostate cancer, either directly on the tumor or by altering host characteristics. It is also possible that rapidly progressive tumors may represent a small, but important, distinct set of prostate cancers influenced by smoking.

We conducted various analyses to examine whether less intense medical surveillance among smokers may have accounted for their higher occurrence of fatal prostate cancer. Prior to 1990, the only practical and common screening test for prostate cancer was the digital rectal examination. Whether early detection by digital rectal examination has any appreciable impact on prostate cancer mortality is unlikely (27, 28); even if it does, a lower screening rate among smokers was unlikely to account for their higher mortality because the occurrence of fatal prostate cancer was even higher among smokers in an analysis limited to men who had had a recent negative digital rectal examination. If the association between smoking and metastatic prostate cancer resulted primarily from delayed diagnosis, attenuation rather than accentuation of relative risks would have been expected in this subgroup. In addition, in the biennial follow-up questionnaires, the report of a digital rectal examination in the prior 2 years was slightly higher among the past smokers, who had the highest occurrence for fatal prostate cancer, arguing strongly against less intense medical surveillance producing our findings (percentage with digital rectal examination for never, current, and past smokers, respectively,

by questionnaire years–1988: 62.0, 58.5, and 65.9; 1990: 62.9, 60.6, and 67.1; 1992: 69.5, 65.9, and 74.1; 1994: 71.8, 67.5, and 75.2).

Differential screening by PSA across strata of cigarette use was unlikely to account for our results, because the percentage of men who, by 1994, had had at least one PSA test varied little among never smokers (53% for men <65 years and 79% for those >65 years) and smokers who had quit within 10 years (53 and 78%) and was slightly lower among current smokers (50 and 70%). Also, the association between pack-years smoked in the prior 10 years and risk for distant metastatic prostate cancer (RR, 1.81; 95% CI, 1.07–3.06 for a 15 pack-year increment) and fatal prostate cancer (RR, 1.76; 95% CI, 0.98–3.15) was observed prior to 1990, before PSA screening became widely used.

Moreover, if tobacco use was related to substantially lower screening frequency, we would expect fewer localized prostate cancers among smokers, but current smokers in 1986 were not at lower risk for organ-confined prostate cancer (RR, 1.01; 95% CI, 0.78–1.32). Finally, although the impact of PSA screening on prostate cancer mortality remains unresolved, a substantial benefit is unlikely to occur within a few years (29). Other studies (11–14) that had also shown an association between tobacco use and fatal prostate cancer were conducted before widespread availability of the PSA test.

Another consideration is the possible impact of any relation between smoking and BPH on our results. Although BPH is generally not considered to be a direct precursor to prostate cancer, indirect relationships may occur from common diagnostic technologies. For example, stage A prostate cancers are diagnosed secondarily due to transurethral resections for BPH. However, we found no associations with early stage cancers but only for metastatic and fatal cancers, where issues regarding BPH are less important. The issue of detection was addressed directly by examination of digital rectal exam and PSA test frequency. In any case, because smoking was only weakly associated with risk of BPH in this cohort (30), BPH is unlikely to have a major impact on the association between smoking and prostate cancer risk.

We explored the possibility that because smokers have a higher death rate from various conditions, death among smokers could be attributed spuriously to a coincidental diagnosis of prostate cancer. Study physicians examined medical records blinded to exposure data and attempted to determine precise cause of death. Among men who were diagnosed with prostate cancer, smoking-related conditions predicted death from causes other than prostate cancer but not death from prostate cancer. Although our comorbidity score probably did not capture all tobacco-related comorbid conditions perfectly, it is unlikely that residual misclassification had a substantial impact because our findings were unchanged when we controlled for this variable. Men with other cancers at baseline were excluded from the analyses. Thus, deaths attributed to prostate cancer were most likely prostate cancer specific and not from vascular diseases or other cancers attributable to tobacco.

Our results agree with two recent reviews that concluded that tobacco use is not likely to be a major determinant of prostate cancer incidence (31, 32). In contrast, studies generally have found higher rates of fatal prostate cancer among smokers (11–14). A large study of prostate cancer mortality among United States veterans found a strong dose-response relation between current tobacco use at baseline and fatal prostate cancer (12). In the first 8.5 years of follow-up, the RR associated with >39 cigarettes per day was 2.42; with 26 years of follow-up, the RR was attenuated to 1.51 but remained statis-

tically significant ($P < 0.001$). If one's recent smoking history were the relevant factor, smoking status would be substantially misclassified for the later follow-up as a result of changing smoking patterns. Results for the Lutheran Brotherhood Cohort Study also showed about a doubling of risk of death from prostate cancer among cigarette smokers and users of smokeless tobacco (11). Among 348,874 black and white men who were screened as part of the MRFIT interventional trial and followed for an average of 16 years, those who smoked 1–25 cigarettes per day at baseline had a RR for prostate cancer mortality of 1.21 ($P = 0.04$), and for smokers of >25 cigarettes per day, the RR was 1.45 ($P = 0.0003$; Ref. 13). A recent study of the American Cancer Society cohort (CPS-II) found a higher risk of fatal prostate cancer (1.61) among black current smokers relative to black nonsmokers and white current smokers (1.33) relative to white nonsmokers (14).

Two studies (15, 16) examined smoking history in relation to tumor characteristics among prostate cancer patients and found that smokers were more likely to have stage D tumors and to have poorly differentiated tumors. A recent study (33) of only 69 total cases found current smokers to have a higher risk for total prostate cancer, but the association was considerably stronger for regional/distant disease compared to localized cancers.

Some studies showed relatively weak associations between cigarette use and prostate cancer mortality (34, 35). Most notably, a study of British doctors found no clear association between smoking reported in 1951 and updated in 1957, 1966, 1972, 1978, and 1990 and prostate cancer mortality up to 1991 (34). However, the heaviest smokers ($\geq$25 cigarettes per day) were at 24% elevated risk of fatal prostate cancer. Similarly, a large prospective study conducted in Sweden found current smokers to be at moderately elevated risk for prostate cancer mortality relative to never-smokers (RR, 1.26; 95% CI, 1.06–1.50; Ref. 35). However, current smoking was assessed in 1971–1975, and follow-up time accrued up to December 1991; smoking rates in Swedish men declined dramatically over the course of the study period (36). Several studies did not show a clear association between smoking and prostate cancer mortality, but these tended to be based on a single smoking assessment with follow-up periods up to several decades (37–39).

The higher rate of fatal prostate cancer among smokers, even accounting for screening differences, indicates that tobacco may enhance the aggressive behavior of prostate cancer or cause highly aggressive tumors. Presently, no tissue marker can reliably predict a distinct set of cancers with this aggressive phenotype, but such a group is suggested clinically by cancers that are rapidly progressive and fatal. The associations between recent past and current smoking were particularly strong for prostate cancers that caused death within several years of a negative digital rectal examination. Although it is likely that clones of premalignant cells, or even a small, undetectable cancer, were present at the time of the digital rectal examination, the observation of widespread metastasis and death within a short time period of apparent health suggests a specific "late" event that markedly enhances tumor aggressivity. A speculative candidate molecular event may be mutation of the *p53* tumor suppressor gene, which is observed only in a subset of prostate cancers and which correlates with aggressive behavior in prostate cancer (40–45).

The time course for a hypothetical smoking-induced event, possibly mutagenic, leading to metastatic prostate cancer corresponds with the changes in PSA levels before the diagnosis of metastatic prostate cancer. Using serum obtained over a 25-year period, one study (46) showed a sudden marked elevation in PSA levels occurred 5–10 years prior to a diagnosis of metastatic prostate cancer. The timing of this sharp increase in PSA level in relation to metastatic prostate cancers corresponds to our finding that only smoking during the prior 10 years or so is relevant and suggests that a specific event that enhances aggressive behavior occurs 5–10 years before metastatic prostate cancer becomes clinically apparent. Our use of 10 years was intended to capture a period of smoking relatively late in carcinogenesis and is not intended to be precise. For example, it is plausible that the risk of fatal prostate cancer drops within a shorter time period than 10 years after cessation of smoking, but our study size was too small to make such distinctions.

The pathogenic mechanisms that may underlie the observed association are unclear. Carcinogens from tobacco can enter and concentrate in prostate cells through the circulatory system (47). Smoking also may influence prostate carcinogenesis through its effect on levels of various hormones. High levels of testosterone and low levels of estrogens and sex hormone binding globulin have been shown to increase risk of prostate cancer (48). Hormones formed by the adrenal gland, DHEA, DHEAS, cortisol, and androstenedione, as well as total plasma testosterone, dihydrotestosterone and sex hormone-binding globulin are statistically significantly higher in smokers than nonsmokers (49–51). However, the full impact of these changes in hormonal levels in regards to fatal prostate cancer is not yet established.

Our findings indicate that tobacco use may have a substantial impact on mortality from prostate cancer. Within 10 years after quitting smoking, this excess risk is eliminated. Smoking cessation, even late in life, may reduce prostate cancer mortality.

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