Cigarette Smoking and Risk of Prostate Cancer in Middle-Aged Men[1]

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Abstract

Cigarette smoking may increase the risk of prostate cancer by affecting circulating hormone levels or through exposure to carcinogens. Although there are plausible mechanisms that could explain an association between smoking and prostate cancer, previous studies are inconsistent. The goal of this population-based case-control study was to assess this association in middle-aged men. Cases ($n = 753$) were men ages 40–64 years diagnosed with prostate cancer from 1993 to 1996 identified using the Seattle-Puget Sound Cancer Registry. Age-matched controls without prostate cancer from the same region ($n = 703$) were identified using random digit dialing. Participants completed detailed in-person interviews. Logistic regression was used to compute adjusted odds ratios (ORs) and 95% confidence intervals (CIs) to assess the prostate cancer-cigarette smoking relationship. Current smokers had an increased risk (OR = 1.4, 95% CI 1.0–2.0) relative to nonsmokers. A dose-response relationship was noted between number of pack-years smoked and prostate cancer risk (trend $P = 0.03$). The OR = 1.6 (95% CI 1.1–2.2) for men with >40 pack-years of smoking, with a stronger association observed in men with more aggressive disease (OR = 2.0, 95% CI 1.3–3.1). Smoking cessation resulted in a decline in risk (trend $P = 0.02$). Smoking is associated with a moderately increased relative risk of prostate cancer. Furthermore, a dose-response relationship exists between number of pack-years smoked and cancer risk. Given that smoking cessation seems to reduce these risks, results from this study have public health ramifications and suggest that prostate cancer should be added to the list of tumors for which cigarette smoking is a risk factor.

Introduction

Prostate cancer is the most frequent solid tumor diagnosed and the second leading cause of cancer death among American men (1). Certain risk factors for prostate cancer, such as advanced age, African-American race, and first-degree family history of the disease, have been identified, yet few causative environmental exposures for prostate cancer are known (2). It is likely that environmental influences play a role in the development of prostate cancer because migration studies of Japanese immigrants to the United States have found that the risk of prostate cancer increased 5-fold with the change of environment (3). It would be valuable to identify modifiable environmental risk factors for prostate cancer that can serve as targets for public health interventions that might lower the incidence of this common malignancy.

One such potential modifiable risk factor is cigarette smoking. There are several hypothetical mechanisms through which cigarette smoking may enhance prostate cancer risk. For example, cigarette smoking may alter circulating levels of steroid hormones. In particular, cigarette smoking has been associated with higher levels of bioavailable testosterone and lower levels of bioavailable estradiol in men (4). Studies found significant (Ps < 0.01) positive correlations between cigarettes smoked/day and serum total androstenedione as well as total and free testosterone in men (5). This is significant because testosterone and its more potent metabolite DHT[3] are necessary not only for normal prostate development and growth but also appear to enhance cell proliferation in the prostate, which potentially could be associated with malignant transformation. Conversely, estrogens act on the hypothalamus and pituitary to suppress secretion of gonadotropins, which may reduce testicular androgen production (6). Effectively, cigarette smoking may establish a hormonal milieu that is favorable for the development or progression of prostate cancer. In addition, cigarettes contain significant levels of cadmium, which has been linked to prostate carcinogenesis (7–9). Either or both of these mechanisms could support an association between cigarette smoking and prostate cancer.

Despite reasonable theoretical underpinnings for a relationship between smoking and prostate cancer, conclusive epidemiological evidence of this association is lacking. Hickey *et al.* (10) recently completed a structured review of the existing literature on cigarette smoking and prostate cancer. They found 23 prospective cohort studies, 5 nested case-control studies, 1 retrospective cohort study, and 36 case-control studies addressing this issue. Although most of the prospective cohort studies and all of the nested case-control studies found no relationship, 33% of the 15 population-based case-control studies showed a significant association between cigarette smoking and prostate cancer risk. Hickey *et al.* (10) concluded that these conflicting

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[3] The abbreviations used are: DHT, dihydrotestosterone: OR, odds ratio; CI, confidence interval; PSA, prostate-specific antigen; BPH, benign prostatic hyperplasia; SHBG, sex hormone-binding globulin.

findings may be because many of the previous studies suffered from methodological shortcomings such as differential measurement error in outcomes, attribution bias, surveillance bias, and inadequate adjustment for confounders. They suggest that future studies avoid these pitfalls by collecting a more comprehensive smoking history, with particular information on cessation, and by obtaining information on potential confounding factors such as dietary fat intake and history of prostate cancer screening.

The goal of the current study was to assess the association between cigarette smoking and prostate cancer while avoiding some of the methodological problems of prior research. Using a population-based case-control design, a detailed smoking history was obtained with particular attention to duration, amount of smoking, and smoking cessation. In addition, information was collected on stage and grade of cancer at diagnosis, which allowed examination of smoking associations according to clinical characteristics of the disease. Finally, we focused on men < age 65 years who are at relatively low baseline risk for prostate cancer in an effort to discover modest associations that might otherwise be undetectable in an older population at greater absolute risk for this complex disease.

Materials and Methods

Study Subjects. We conducted a population-based case-control study of risk factors for prostate cancer in middle-aged men, including lifetime history of cigarette smoking. Case patients included Caucasian and African-American male residents of King County in northwestern Washington, 40–64 years old, who were diagnosed with biopsy-proven prostate cancer between January 1, 1993, and December 31, 1996. Eligible cases were identified from the Seattle-Puget Sound SEER cancer registry and included 100% ages < 60 years and a random 75% sample of those who were ages 60–64 years at diagnosis.

A comparison group ($n = 703$) without a history of prostate cancer was identified through random digit dialing using a clustering factor of five residences/sampling unit (11). These individuals were male residents of King County, Washington, 40–64 years of age. Controls were frequency matched to case patient by age (same 5-year group) and recruited evenly throughout the ascertainment period of cases.

All study participants signed informed consent for participation. The Fred Hutchinson Cancer Research Center's Institutional Review Board approved study forms and procedures. Study subjects completed a structured in-person interview administered by a trained male interviewer. The questionnaire addressed the following areas: social and demographic factors; physical development, height, weight, and physical activity; reproductive history; detailed medical history, including history of BPH and prostate cancer screening; family structure and cancer history; dietary habits, including total dietary fat intake and servings of cruciferous vegetables consumed/week; lifetime smoking and alcohol consumption; lifetime sexual history; and occupational history. Clinical patient data were available from the cancer registry, including tumor grade and stage of disease at diagnosis. A detailed smoking history before reference date (date of diagnosis for cases and a similar assigned date for controls) was collected, including ages at onset and cessation, duration, and dose of cigarette smoking.

Statistical Methods. ORs were calculated to estimate the association between prostate cancer and the following smoking variables (continuous and categorized): smoking status (nonsmoker, current, former); duration of smoking (1–9, 10–19, 20–29, 30–39, ≥40 years); number of cigarettes smoked/day (1–10, 11–20, 21–30, 31–40, ≥41); total pack-years of smoking (>0–10, 11–20, 21–30, 31–40, >40); years since cessation in former smokers (>0–9, 10–19, 20–29, ≥30 years); and age first smoked (≤15, 16–17, 18–19, ≥20 years). Multivariate logistic regression (12) analysis was used to compute ORs and estimate 95% CIs adjusted for potential confounders such as age, race, family history of prostate cancer, body mass index, history of prostate cancer screening such as PSA testing (ever had a PSA, had a PSA > 1 year before reference date, number of PSA tests within the 5-years before reference date) or digital rectal examination > 1 year before reference date, dietary habits, physical activity, socioeconomic factors, and medical history. Any covariate that produced a change of >5% in the age-adjusted OR for the smoking status-prostate cancer association was included in the final model, *i.e.*, race, family history of prostate cancer in a first-degree relative, history of PSA testing >1 year before reference date, and a history of BPH. To examine if a dose-response relationship existed between smoking and prostate cancer, trend tests were performed using only cases and controls that were exposed to smoking (13).

To explore the hypothesis that smoking was associated with the development of more aggressive prostate cancer, additional analyses were completed using a polychotomous multivariate regression model (14). These models compared controls to cases with less aggressive (localized stage and Gleason score ≤ 7) and more aggressive (regional or distant stage disease or Gleason score 8–10) prostate cancer.

Results

During the ascertainment period, 1055 eligible prostate cancer patients were identified, and 138 were excluded because of the sampling protocol. Of the remaining 917 eligible patients, 753 (82%) with prostate cancer were interviewed. During the first step of random digit telephone dialing to identify controls, complete household census information was obtained for 94% of the 21,116 residential telephone numbers contacted. A total of 941 eligible men was identified and agreed to receive information on the study. Of these, 703 (75%) were interviewed, 228 (24%) refused, 6 were lost to follow-up, and 4 were too ill to participate (15).

Table 1 lists selected characteristics of cases and controls. The groups were similar according to age, but a higher proportion of cases than controls were black. More men with prostate cancer (19%) than without (10%) reported having a first-degree family member (*i.e.*, brother or father) with prostate cancer. Similarly, more cases (34%) had a history of BPH diagnosed ≥2 years before reference date than controls (17%), and more cases (71%) had undergone PSA testing > 1 year before the reference date than controls (34%).

Table 2 provides results of analyses of smoking variables and prostate cancer, adjusted for confounders. Current smoking was associated with a 40% increase in prostate cancer risk relative to nonsmokers (95% CI 1.0–2.0). Men who smoked for ≥40 years had a modest elevation in risk (OR = 1.5, 95% CI 1.0–2.2), as did those who smoked an average of >40 cigarettes/day (OR = 1.5; 95% CI 0.8–2.8). There was a significant positive trend in risk with pack-years of smoking (trend $P = 0.03$). Men who had a history of >40 pack-years of smoking had an OR of 1.6 (95% CI 1.1–2.2). When analyzed as a continuous variable, the ORs were 1.07 (95% CI 1.03–1.11) for 10 pack-years, 1.14 (95% CI 1.06–1.23) for 20 pack-years, and 1.22 (95% CI 1.08–1.37) for 30 pack-years of smoking. The elevations in risk estimates associated with >40 pack-years of

Table 1 Selected characteristics of prostate cancer cases and controls

Characteristics	Cases, *n* (%)	Controls, *n* (%)
Age, (yr)		
40–49	46 (6)	58 (8)
50–54	150 (20)	138 (20)
55–59	257 (34)	264 (38)
60–64	300 (40)	243 (35)
Race		
Caucasian	707 (94)	685 (97)
African American	46 (6)	18 (3)
Family history CAP[a]		
No	613 (81)	634 (90)
Yes	140 (19)	99 (10)
Education		
High school or less	162 (22)	133 (19)
Some college	210 (28)	191 (27)
College degree	202 (27)	192 (27)
Graduate degree	179 (24)	187 (27)
Annual income, $ United States		
<30,000	106 (14)	91 (13)
30,000–50,000	171 (23)	170 (24)
50,000–75,000	192 (26)	190 (27)
>75,000	274 (36)	243 (35)
Unknown	10 (1)	9 (1)
Weekly exercise		
None	149 (20)	107 (15)
<1	173 (23)	203 (29)
2–3	249 (33)	229 (33)
4–6	132 (18)	119 (17)
>6	50 (7)	45 (6)
Percentage of calories from fat		
≤30	126 (17)	138 (20)
31–37	181 (24)	152 (22)
38–42	159 (21)	151 (22)
≥43	149 (20)	153 (22)
Missing	138 (18)	109 (16)
Cruciferous vegetable/week		
<1	201 (27)	166 (24)
1–3	265 (35)	243 (35)
>3	149 (20)	185 (26)
Missing	138 (18)	109 (16)
Alcoholic drinks/week		
None	72 (10)	86 (12)
≤3	169 (22)	146 (21)
4–7	153 (20)	163 (23)
8–14	167 (22)	145 (21)
15–35	144 (19)	123 (17)
>35	48 (6)	40 (6)
History of PSA testing[b]		
No	218 (29)	464 (66)
Yes	535 (71)	239 (34)
History of BPH[c]		
No	500 (66)	581 (83)
Yes	253 (34)	122 (17)

[a] First-degree relative with prostate cancer.
[b] PSA test done >1 year before reference date.
[c] History of BPH.

Table 2 ORs and 95% CIs for prostate cancer associated with cigarette smoking

Smoking variable	Cases, *n* (%)	Controls, *n* (%)	OR[a] (95% CI)
Smoking status			
Nonsmoker	281 (37)	266 (38)	Referent
Former smoker	349 (46)	322 (46)	1.0 (0.8–1.3)
Current smoker	123 (16)	115 (16)	1.4 (1.0–2.0)
Smoking duration (yr)[b]			
Nonsmokers	281 (38)	266 (38)	Referent
<10	73 (10)	68 (10)	0.9 (0.6–1.4)
10–19	113 (15)	100 (14)	1.1 (0.8–1.5)
20–29	89 (12)	98 (14)	1.0 (0.7–1.4)
30–39	111 (14)	103 (14)	1.3 (0.9–1.8)
≥40	86 (11)	68 (10)	1.5 (1.0–2.2)
Cigarettes/day[c]			
Nonsmokers	281 (37)	266 (38)	Referent
1–10	91 (12)	75 (11)	1.1 (0.8–1.6)
11–20	216 (29)	230 (33)	1.0 (0.8–1.3)
21–30	74 (10)	75 (11)	1.1 (0.7–1.7)
31–40	62 (8)	37 (5)	1.8 (1.1–2.9)
>40	29 (4)	20 (3)	1.5 (0.8–2.8)
Pack-years of smoking[d]			
Nonsmoker	281 (37)	266 (38)	Referent
≤10	122 (16)	93 (13)	1.1 (0.8–1.6)
11–20	65 (9)	92 (13)	0.7 (0.5–1.1)
21–30	72 (10)	76 (11)	1.0 (0.7–1.5)
31–40	73 (10)	73 (10)	1.1 (0.8–1.7)
>40	140 (19)	103 (15)	1.6 (1.1–2.2)
Years since smoking cessation[e]			
Nonsmoker	281 (37)	266 (38)	Referent
Current smoker	123 (16)	115 (16)	1.4 (1.0–2.0)
<10	80 (11)	73 (10)	1.2 (0.8–1.7)
10–19	98 (13)	94 (13)	1.1 (0.8–1.6)
20–29	95 (13)	86 (12)	1.0 (0.7–1.5)
≥30	76 (10)	69 (10)	0.8 (0.6–1.2)

[a] ORs adjusted for age, race, family history of prostate cancer, history of PSA testing >1 year before reference date, and history of BPH.
[b] Trend test for smoking duration $P = 0.07$.
[c] Trend test for cigarettes per day $P = 0.09$.
[d] Pack-years = years smoked × cigarettes/day / 20; trend test for pack-years of smoking $P = 0.03$.
[e] Trend test for years since smoking cessation $P = 0.02$.

smoking were observed in both former (OR = 1.7, 95% CI 1.1–2.7) and current (OR = 1.5, 95% CI 1.0–2.3) smokers.

Former smokers were not at increased risk for prostate cancer when compared with nonsmokers (OR = 1.0, 95% CI 0.8–1.3). To additionally understand the relationship between smoking cessation and prostate cancer risk, we examined years since smoking cessation and prostate cancer. As shown in Table 2, men who stopped smoking <10 years before reference date had an OR of 1.2 (95% CI 0.8–1.7), whereas those who stopped ≥30 years prior were not at increased risk (OR = 0.8) for prostate cancer. Although none of the point estimates of risk reached statistical significance, the trend of declining ORs with increasing years since smoking cessation was significant (trend $P = 0.02$). Additional adjustment for total pack-years smoked slightly reduced the risk estimate in current smokers to 1.2 but did not change the OR of 0.8 in men who quit smoking ≥30 years ago; however, the trend test became nonsignificant. Recency and pack-years of smoking were highly correlated among cases and controls (Ps < 0.0001), with current smokers having a higher proportion of men with >40 pack-years of exposure.

To evaluate whether smoking was associated with the development of aggressive prostate cancer, cases were stratified into those with more or less aggressive disease (Table 3). Although the OR in current smokers was similar for men with more aggressive disease (OR = 1.5) and those with less aggressive disease (OR = 1.4), stronger associations with smoking history, measured as either smoking duration, number of cigarettes smoked/day, or total number of pack-years smoked, were observed in men with more aggressive prostate cancer. For example, men who had a >40 pack-year history of smoking had a 40% increase in risk (95% CI 1.0–2.0) of less aggressive disease, but a 100% increase in risk (95% CI 1.3–3.1) of developing more aggressive prostate cancer relative to nonsmokers. Earlier ages at which men first started smoking also

Table 3 ORs and 95% CIs for prostate cancer associated with cigarette smoking, stratified by disease aggressiveness

Smoking exposure	Controls, *n*	Cases, *n* Less aggressive	Cases, *n* More aggressive	OR[a] (95% CI) Less aggressive	OR[a] (95% CI) More aggressive
Smoking status					
Nonsmoker	266	197	84	Referent	Referent
Former smoker	322	220	129	0.9 (0.7–1.2)	1.3 (0.9–1.8)
Current smoker	115	81	42	1.4 (1.0–2.0)	1.5 (1.0–2.4)
Smoking duration (yr)					
Nonsmoker	266	197	84	Referent	Referent
<10	68	49	24	0.9 (0.6–1.4)	1.1 (0.6–1.8)
10–19	100	76	37	1.0 (0.7–1.5)	1.2 (0.7–1.9)
20–29	98	52	37	0.8 (0.5–1.2)	1.3 (0.8–2.1)
30–39	103	70	41	1.2 (0.8–1.7)	1.5 (1.0–2.4)
≥40	68	54	32	1.3 (0.8–2.0)	1.8 (1.1–3.1)
Cigarettes/day					
Nonsmokers	266	197	84	Referent	Referent
1–10	75	53	38	0.9 (0.6–1.4)	1.6 (1.0–2.5)
11–20	230	144	72	0.9 (0.7–1.3)	1.1 (0.8–1.6)
21–30	75	48	26	1.0 (0.7–1.6)	1.3 (0.8–2.2)
31–40	37	38	24	1.6 (0.9–2.7)	2.3 (1.3–4.1)
>40	20	18	11	1.3 (0.6–2.6)	1.9 (0.8–4.2)
Pack-years					
Nonsmoker	266	197	84	Referent	Referent
≤10	93	82	40	1.1 (0.8–1.6)	1.3 (0.8–2.0)
11–20	92	42	23	0.7 (0.4–1.1)	0.9 (0.5–1.5)
21–30	76	39	33	0.8 (0.5–1.2)	1.5 (0.9–2.4)
31–40	73	52	21	1.2 (0.8–1.8)	1.1 (0.6–1.9)
>40	103	86	54	1.4 (1.0–2.0)	2.0 (1.3–3.1)
Years since cessation					
Nonsmoker	266	197	84	Referent	Referent
Current smoker	115	81	42	1.4 (1.0–2.0)	1.5 (1.0–2.4)
<10	73	45	35	0.9 (0.6–1.4)	1.7 (1.0–2.7)
10–19	94	61	37	1.0 (0.7–1.5)	1.4 (0.9–2.2)
20–29	86	59	36	0.9 (0.6–1.4)	1.3 (0.8–2.1)
≥30	69	55	21	0.8 (0.5–1.3)	0.8 (0.5–1.4)
Age first smoked					
Nonsmoker	266	197	84	Referent	Referent
≤15 years	128	96	70	1.1 (0.8–1.5)	1.8 (1.2–2.7)
16–17 years	104	76	38	1.2 (0.8–1.7)	1.3 (0.8–2.1)
18–19 years	105	74	33	1.1 (0.7–1.6)	1.1 (0.7–1.8)
≥20 years	100	55	30	0.8 (0.5–1.2)	1.0 (0.6–1.7)

[a] ORs adjusted for age, race, family history of prostate cancer, history of PSA testing >1 year before reference date, and history of BPH.

appeared to be a stronger risk factor for more aggressive disease. Men who smoked before age 15 years had an OR = 1.1 (95% CI 0.8–1.5) for having aggressive cancer and an OR = 1.8 (95% CI 1.2–2.7) for more aggressive disease.

Discussion

Data from this population-based case-control study suggest that smoking is a risk factor for prostate cancer. In particular, current smokers appear to be at moderately increased risk (OR = 1.4) for this disease relative to nonsmokers. There also is a dose-response relationship, with a significant increase in risk estimates observed as the number of pack-years smoked increases. This is most pronounced in men with >40 pack-years of cumulative exposure who are 1.6 times more likely to have prostate cancer and are at a 2-fold increased relative risk of developing more aggressive forms of the disease. Importantly, if one stops smoking, there is a significant decline in risk, with men who stopped smoking ≥20 years previously at no greater risk than those who never smoked.

There are several potential mechanisms whereby cigarette smoking may increase risk of prostate cancer. One is the ability of cigarette smoking to increase bioavailable testosterone and decrease bioavailable estradiol, which may alter the hormonal milieu favoring higher androgenic exposure to the prostate (4, 16). Several lines of evidence suggest that hormones are involved in the etiology of benign and malignant prostate disease (17–21). *In vitro* animal models have been used to demonstrate that prolonged testosterone administration can induce and promote prostate tumors (22). Prior epidemiological studies have also demonstrated a relationship between alterations in serum androgen levels and risk of prostate cancer. Nomura *et al.* (23) showed that lower DHT levels and higher testosterone to DHT ratios were found in Asian men who subsequently developed prostate cancer during a 14-year follow-up. Gann *et al.* (17) reported that higher levels of circulating testosterone and lower levels of SHBG were associated with significantly increased relative risks of prostate cancer. To explore the possibility that changes in bioavailable testosterone were responsible, at least, in part, for the association of current smoking and prostate cancer noted in our study, we compared serum total testosterone and SHBG levels in current smokers to nonsmokers from 400 randomly selected controls. Current smokers had significantly higher levels of total testosterone (17.0 *versus* 14.9 nmol/liter, $P = 0.004$) and SHBG (29.7 *versus* 23.3 nmol/liter,

$P = 0.002$), lending support for the notion that smoking-induced changes in steroid hormone levels is a possible mechanism for the association between cigarette smoking and prostate cancer risk. Our observation of a decline in the relative risk within a decade of smoking cessation is also consistent with the theory that cigarette smoking induced hormonal changes may have a promotional effect on prostate tumor growth that diminishes fairly soon after exposure ceases.

Another possible mechanism for an association between smoking and prostate cancer is exposure to carcinogenic substances found in cigarettes. For example, cadmium is an inorganic toxicant that is widely used in industry and is also found in cigarettes (7–9). In 1993, the International Agency for Research on Cancer designated cadmium as a human carcinogen. Although not directly mutagenic in the prostate, cadmium has been shown to indirectly induce prostate carcinogenesis through interaction with the androgen receptor (24, 25). Ye *et al.* (24) have reported that cadmium has the property of activating the androgen receptor response in human prostate cancer cell lines in the absence of androgen but in the presence of the androgen receptor. Furthermore, when applied in combination with androgen, cadmium enhances androgen-mediated transcriptional activity in the prostate (24). Chronic cadmium exposure in rats has been shown to induce prostate tumors in the presence of normal testicular function (25). Therefore, chronic smoking in men with otherwise normal testicular function and androgen levels may effectively increase their androgen exposure through the interaction of cadmium with the androgen receptor and over the long term increase their risk of developing prostate cancer.

Other researchers have explored the relationship between smoking and prostate cancer using a variety of research designs. As the structured literature review by Hickey *et al.* (10) demonstrates, different studies have revealed conflicting results, depending upon the research design used and how well the study controlled for possible confounding factors. Hickey *et al.* (10) reviewed 65 prior studies of smoking and prostate cancer and found that most of the prospective studies and all of the nested case-control studies showed no association between current smoking and prostate cancer. In many of these studies, however, the lack of association may have been the result of inadequate ascertainment of smoking parameters or inadequate follow-up in these cohorts, yielding limited sample sizes. In the 31 studies that used a case-control design, 33% observed a positive association (10). Furthermore, the majority of prospective studies that used prostate cancer death as an outcome noted a positive association between current smoking and prostate cancer, supporting our findings of stronger effects in men with more aggressive disease (26–30). For example, the Health Professionals Follow-Up Study (28) found that men who smoked $\geq$15 pack-years were 1.8 times more likely to develop metastatic prostate cancer and 2.1 times more likely to die of prostate cancer than nonsmokers. This study and others (31–33) support our current findings.

Nevertheless, the exact relationship between smoking and prostate cancer remains unclear because there are numerous studies that have not been able to demonstrate any relationship. Giles *et al.* (34) used population-based tumor registries from Melbourne, Sydney, and Perth, Australia, to study 1498 men diagnosed with prostate cancer from 1994 to 1998. Controls were age matched at a ratio of one control/case. No relationship was noted between current smoking or number of pack-years smoked and prostate cancer risk. Furthermore, no relationship was seen between smoking and high-grade disease. However, the authors only controlled for age, location, and family history of prostate cancer.

The current study is also population-based and adheres to Hickey's *et al.* (10) recommendation that potential confounding factors such as dietary fat intake and history of screening be controlled in the analysis. This is particularly important for screening, where one might hypothesize that nonsmokers who live healthier lifestyles would be more likely to be screened, biasing results toward the null. In our control group, 36% of nonsmokers and 37% of former smokers had received one or more PSA test(s) a year or more before reference date. In contrast, only 21% of the current smokers and 27% of heavy smokers (>40 pack-years) reported having a PSA test. The age-adjusted OR for prostate cancer in current smokers increased from 1.03 to 1.43 after adding PSA screening to the regression model. Thus, PSA screening was a strong negative confounder of the smoking-prostate cancer relationship. The fact that the current population-based study adjusts for numerous potential confounders, including dietary fat and cruciferous vegetable intake and prostate cancer screening, is one strength of the study. These results highlight the importance of accounting for prostate cancer screening history in analyses of lifestyle risk factors for this disease.

Finally, the restriction of the study population to men under the age of 65 years who have a lower baseline incidence of prostate cancer than their older (>65 years) counterparts may have strengthened our ability to detect modest associations that might otherwise be missed (35). As suggested by Rothman and Poole (35), the strength of an exposure-disease association depends on the relative prevalence of other component causes for the same disease. By focusing on a subpopulation at lower absolute risk, it is possible to find stronger relations for those exposures that operate in the causal pathway to disease (35). This concept may be particularly applicable in studies of prostate cancer, which is a common and complex disease. Although the study was limited to men under age 65 years, there is no *a priori* reason to believe that smoking would not also be associated with prostate cancer risk in older men. However, given that the effect may be somewhat smaller in older men with more component causes, large studies of older men will be required to evaluate this association.

Some limitations of this study must also be considered when interpreting the results. Although the current study used rigorous methodology to collect detailed information on personal smoking history and duration of exposure, we were unable to account for exposure to second-hand tobacco smoke. Furthermore, we did not collect biological samples to validate smoking status. It is also possible that men who refused to participate in the study may have had different smoking patterns. Lastly, it is possible that unmeasured and yet unrecognized lifestyle factors that differ between smokers and nonsmokers could have confounded our results. We controlled for numerous lifestyle factors in the analysis (*i.e.*, education, income, marital status, physical activity, alcohol use, intake of cruciferous vegetables, and total fat as well as percentage of calories from fat), and none of these was found to substantially change the smoking-prostate cancer association.

In summary, the current population-based study demonstrates a modest positive association between smoking and risk of prostate cancer. In particular, current smokers, smokers of >40 years duration, and those with >40 pack-years of exposure have a 40–60% elevation in risk of prostate cancer relative to nonsmokers. Moreover, these positive associations are stronger in men with clinically more aggressive forms of prostate cancer. Men who quit smoking appear to reduce their risk of

prostate cancer ~10 or more years after cessation. These results have important public health implications and should be useful for educating physicians and patients about the adverse health effects of smoking and to promote primary prostate cancer prevention and smoking cessation strategies.

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