Lifestyle Factors and Prostate Cancer Risk: A Case-Control Study in Sweden[1]

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Abstract

We examined associations between lifestyle factors and subsequent risk of prostate cancer in a population-based case-control study. Information on smoking and alcohol habits, socioeconomic factors, marital status, family history, and sexual habits were obtained from a questionnaire and a face-to-face interview with 256 (74.6%) eligible patients and 252 (76.6%) selected controls, frequency matched by age and screened for prostate cancer with negative findings. Unconditional logistic regression was used to estimate the odds ratios (ORs).

Risk was elevated among current smokers of cigarettes (OR, 1.8) and current users of hard liquor (OR, 1.4); however, the lack of dose-response trend for both of these exposures argues against a causal association. We found tentative evidence that early first intercourse, a larger number of sexual partners, and other indices of high sexual activity are associated with increased risk. Similarly, adult height, an indicator of nutrition during childhood and adolescence, was weakly positively associated with risk, although larger studies are needed to establish this link. Unmarried men had a lower risk than married men (OR, 0.3), and socioeconomic status did not appear to be strongly associated with prostate cancer. Men with a father who had prostate cancer had a more than 2-fold increased risk of prostate cancer, whereas those with a brother affected had about a 5-fold risk.

Introduction

The strikingly large international differences in prostate cancer incidence suggest that environmental factors play a major etiological role for this malignancy. Indeed, Japanese migrants to Hawaii themselves experience a substantial increase in incidence in comparison to nonemigrants (1). Nonetheless, current knowledge of the etiology of prostate cancer is minimal. Aside from age and race, and possibly dietary fat, no clear risk factors have been identified.

Cigarette smoking is an emerging controversy. Use of tobacco is generally not considered to be a risk factor for prostate cancer (2), although in a few recent studies (3–6) excess risks have been found, particularly among heavy smokers. Studies on alcohol use have also yielded conflicting findings (2–4, 7, 8) Available data with regard to socioeconomic factors, marital status, and sexual activity are inconsistent (2) as are those for occupational exposures (2). Several studies (9–11), but not all (12), have found increased prostate cancer incidence in male relatives of patients with prostate cancer, suggesting that familial factors, either shared environmental or genetic influences, may play an etiological role.

Using data from a population-based case-control study, we examined the association of prostate cancer risk with lifestyle factors such as smoking and alcohol habits, anthropometric measures, socioeconomic status, marital status, and sexual activity as well as a family history of this disease.

Subjects and Methods. The study base consisted of all men under the age of 80 years, born in Sweden, and living in Örebro County during January 1989 through September 1991. This fairly stable and compact source population was comprised of about 270,000 individuals in 1988 (13). In this population, all men suspected of having prostate cancer were referred to one of three hospitals (Örebro, Karlskoga, or Lindesberg) for further diagnostic work-up and treatment.

The study protocol was approved by the ethical review board of the Örebro County Council. All patients with a newly diagnosed, cytologically and/or histologically confirmed prostate cancer were eligible. In practice, hospital records were used to identify cases. The completeness of case reporting was confirmed through surveillance of the only Department of Pathology which serves the study area and through reports from the regional cancer registry. All tumors were graded and staged in accordance with the WHO (14) and TNM (15) classifications, respectively. The presence of skeletal metastases was assessed routinely using skeletal scintigraphy and skeletal radiography if needed. The tumors were classified anatomically as localized (T_{0-2}, M_0) or advanced (T_{3-4}, M_0; T_{0-4}, M_1) and pathologically as highly (G1), moderately (G2), or poorly (G3) differentiated.

Male controls were randomly selected from the county population register every third month and frequency matched by age (<50, 50–59, 60–69, and 70–79 years) to the cases. All potential controls underwent digital rectal examination by one examiner (S-O. A.) and provided a blood specimen. Males with a palpable nodule and/or elevated serum levels (>10 μg/liter) of prostate-specific antigen were investigated further using ultrasound-guided biopsies. They were accepted as controls

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only if these biopsies showed no evidence of cancer. Less than 3% of the potential controls actually had prostate cancer.

Exposure data were collected in three ways. First, a comprehensive self-administered food frequency questionnaire was mailed to all potential study participants. It was collected and completed at the time of a subsequent personal interview. Second, all subjects were seen at home by professional female interviewers who were blinded to case-control status and unaware of the study hypotheses. Each interviewer saw both cases and controls. No proxy interviews were conducted. The mean duration of an interview was 79 min for cases and 78 min for controls. The interview questionnaire included questions about body size, socioeconomic status, marital status and sexual history, smoking and alcohol habits, and occupational and family history. Finally, clinical data were obtained at physical examination of both subjects and controls. BMI[3] was calculated as weight/height^2 (kg/m^2).

We considered nonsmokers to be individuals with a total lifetime consumption of <100 cigarettes, or individuals smoking a pipe on a regular basis for <6 months. Former smokers were individuals who stopped smoking >2 years before the interview, and current smokers were those still smoking or those who stopped smoking <2 years before the interview. Information was obtained on the type of smoking (filtered cigarettes, nonfiltered cigarettes, or a pipe), age at which smoking started, mean number of cigarettes smoked daily, and duration of smoking. Similarly, a nondrinker was defined as an individual who had used alcoholic beverages (light beer excluded) on a regular basis for <6 months; a former drinker as an individual who stopped drinking >2 years before the interview, and a current drinker as an individual still drinking or who stopped drinking <2 years before the interview. Information was obtained regarding type of alcoholic beverages consumed (beer, wine, or hard liquor) as well as the amount and duration of use. Total daily alcohol intake was determined by adding ethanol from all alcoholic beverages after taking into account the frequency of consumption and the amount and ethanol content of specific drinks.

A measure of the SES of the interviewee was derived from his main occupation. The classification devised by Statistics Sweden (16) was used to score occupations as: 1, unskilled manual worker; 2, skilled manual worker; 3, lower nonmanual worker; or 4, higher nonmanual worker. The average score for a subject's lifetime occupational experience was calculated, weighing the component scores by the duration of each position. Furthermore, if an interviewee had been a self-employed person or a farmer for 20 years or more, he was classified as such. The interviewees were then grouped into five classes: unskilled manual workers, skilled manual workers, nonmanual workers, self-employed persons, and farmers.

The ORs and 95% CIs were used as measures of association, estimated by unconditional logistic regression, using maximum likelihood methods. Adjustment for age was made in all analyses. Continuous variables such as height, weight, and BMI were analyzed in original continuous form as well as in categorized form, principally based on quartiles derived from the control distribution. Tests of the linear trend were based on score variables created from the categorized variables, using consecutive integers to identify ordered categories.

[3] The abbreviations used are: BMI, body mass index; SES, socioeconomic status; OR, odds ratio; CI, confidence interval.

Table 1 Age-adjusted ORs with 95% CIs for prostate cancer according to smoking habits

Variable	No. of		OR	95% CI
	Cases	Controls		
Smoking status (cigarettes)				
Nonsmoker	68	86	1.0	ref[a]
Former smoker	107	97	1.4	0.9–2.1
Current smoker	60	42	1.8	1.1–3.0
Consumption (number of cigarettes/day)				
Nonsmoker	68	86	1.0	ref
≤5	46	40	1.5	0.9–2.5
6–10	58	36	2.0	1.2–3.5
11–15	18	18	1.2	0.6–2.6
>15	37	30	1.5	0.9–2.7
P value for trend			0.10	
Duration (yr)				
Nonsmoker	68	86	1.0	ref
≤19	36	36	1.2	0.7–2.2
20–35	39	35	1.4	0.8–2.4
36–46	55	34	2.0	1.2–3.4
>46	36	33	1.4	0.8–2.5
P value for trend			0.03	
Type of cigarettes				
Nonsmoker	68	86	1.0	ref
Nonfiltered	67	77	1.1	0.7–1.7
Filtered	55	27	2.6	1.5–4.5
Mixed (filtered/nonfiltered)	46	37	1.6	0.9–2.7
Smoking status (pipe)				
Nonsmoker	68	86	1.0	ref
Former smoker	98	83	1.5	1.0–2.3
Current smoker	19	27	0.9	0.4–1.7
Use of oral snuff				
No	221	210	1.0	ref
Yes	31	41	0.7	0.4–1.2

[a] ref, reference category.

Results

Of 343 eligible cases, 256 (74.6%) were included in the study, 63 (18.4%) refused, 20 (5.8%) were unable to take part due to mental or physical illness other than prostate cancer, and 4 (1.2%) died before interview. Of the 330 invited control subjects, 252 (76.6%) completed the interview, 42 (12.5%) refused, and 36 (10.9%) did not take part for other reasons (*e.g.*, unable to be contacted, moved out from study area). The mean age and SD of the cases (70.0 ± 6.1 years) agreed closely with those of the controls (69.8 ± 6.2 years). Of the cases included, 68 (26.6%) were discovered unexpectedly after surgery for presumed benign prostatic hyperplasia (T_0 tumors). Forty-three cases (16.8%) were diagnosed accidentally at routine check-ups due to symptoms unrelated to prostate cancer, yet, many of these tumors were locally advanced. The remaining 145 cases (56.6%) were symptomatic. No screening activity for prostate cancer was in progress in this area. The tumors were staged by digital rectal examination and clinical examination for the presence of metastases. There were 118 (46.5%) localized cases and 136 (53.5%) with advanced tumors. More of the advanced cases (69.9%) had moderately-poorly differentiated tumors (G2-G3) than the localized ones (23.7%).

Smoking Habits. The ORs associated with cigarette and pipe smoking are shown in Table 1. Current cigarette smokers had a higher risk than those who never smoked, and smoking of filtered cigarettes was associated with a higher risk than unfiltered brands. However, there was no clear pattern of increasing risk with increasing numbers of cigarettes smoked, and no

Table 2 Age-adjusted ORs with 95% CIs for prostate cancer according to alcohol habits

Variable	No. of		OR	95% CI
	Cases	Controls		
Beer				
Nondrinker	106	121	1.0	ref[a]
Former drinker	7	7	1.2	0.4–3.4
Current drinker	18	21	1.0	0.5–2.0
Wine				
Nondrinker	106	120	1.0	ref
Former drinker	3	2	1.7	0.3–10.3
Current drinker	23	25	1.0	0.6–2.0
Liquor				
Nondrinker	106	121	1.0	ref
Former drinker	13	20	0.8	0.4–1.6
Current drinker	122	99	1.4	1.0–2.0
Duration (yr)				
Nondrinker	106	121	1.0	ref
≤38	15	30	0.5	0.3–1.1
39–48	49	35	1.5	0.9–2.5
49–53	45	28	1.9	1.1–3.2
54–61	26	26	1.2	0.7–2.3
P value for trend			0.04	
Total consumption of alcohol (g/wk)				
Nondrinker	106	121	1.0	ref
≤24.4	18	24	0.9	0.4–1.7
24.4–48.5	23	23	1.1	0.6–2.1
48.6–96	29	23	1.4	0.8–2.6
>96	31	23	1.5	0.8–2.8
P value for trend			0.11	

[a] ref, reference category.

Table 3 Age-adjusted ORs with 95% CIs for prostate cancer according to height, weight, and BMI 2 years prior to the interview, analyzed both as a continuous variable and categorized into quartiles

Variable	No. of		OR	95% CI
	Cases	Controls		
Height (cm)				
Quartiles				
≤170	60	64	1.0	ref[a]
171–174	60	61	1.1	0.6–1.8
175–178	65	58	1.2	0.7–1.9
>178	70	52	1.4	0.9–2.4
P value for trend			0.17	
Height, continuous (10 cm)	255	235	1.2	0.9–1.6
P value for trend			0.26	
Weight (kg)				
Quartiles				
≤72	68	73	1.0	ref
73–78	54	55	1.1	0.6–1.8
79–84	59	56	1.1	0.7–1.8
>84	69	61	1.2	0.7–1.9
P value for trend			0.46	
Weight, continuous (10 kg)	250	245	1.1	0.9–1.3
P value for trend			0.61	
BMI (kg/m^2)				
Quartiles				
≤23.84	59	57	1.0	ref
23.85–25.37	53	57	0.9	0.6–1.6
25.38–27.36	70	58	1.2	0.7–1.9
>27.36	67	56	1.2	0.7–2.0
P value for trend			0.39	
BMI, continuous (5 kg/m^2)	249	228	1.0	0.8–1.4
P value for trend			0.83	

[a] ref, reference category.

regular trend with the duration of smoking. Age at initiation of smoking was also not associated with risk (data not shown). Adjustment for alcohol intake changed the risk estimates only modestly. Pipe smoking and use of snuff (typically p.o.) were not associated with risk. Use of cigars or chewing tobacco were reported by too few subjects for meaningful analysis. In general, localized and advanced cancers displayed similar patterns regarding tobacco habits (data not shown).

Drinking Habits. The ORs associated with drinking habits are shown in Table 2. Current use of beer or wine was not associated with prostate cancer risk, but there was a slightly increased risk for current users of hard liquor. There were weak indications of a trend with the duration of alcohol use (*P* value for trend, 0.04), but no increasing risk with an increased amount of alcohol currently consumed (*P* value for trend, 0.11). Risk patterns were similar for localized and advanced cancers (data not shown). Adjustment for smoking reduced the alcohol estimates modestly (data not shown).

Medical and Sexual History. A history of testicular disorders was not significantly associated with prostate cancer risk, nor was most previous surgery (*e.g.*, inguinal hernia, circumcision, or urinary calculus). Vasectomy was associated with an 8-fold increase in risk (OR, 8.4; 95% CI, 1.0–67.7), although this estimate was hampered by the small number of subjects who underwent the procedure (eight cases and one control).

We made a considerable effort to obtain detailed and reliable information on sexual history. Nevertheless, the analyses were hampered by a high proportion of nonresponse to these questions: 40% for the question about age at first intercourse and 48.4% for number of sexual partners. There were indications that men who reported a late age at first intercourse had a lower risk than those with an earlier debut (OR, 0.6; 95% CI, 0.3–1.1 for >21 *versus* ≤17 years), whereas those with a high number of lifetime sexual partners was positively associated with risk (OR, 1.6; 95% CI, 0.8–3.1 for >6 partners *versus* 1 partner). The association with the number of partners was more pronounced for advanced cancers (OR, 2.4; 95% CI, 1.0–5.6).

Anthropometric Measures. In Table 3, ORs for selected anthropometric measures are presented. Height, weight, and BMI 2 years prior to the interview were not significantly associated with prostate cancer risk, whether analyzed in the categorized or continuous form. However, there was evidence of a weak-positive association between height and prostate cancer risk. Associations with BMI and weight appeared to be more pronounced for advanced than for localized cancers. The ORs for BMI in the highest quartiles were 1.4 (95% CI, 0.8–2.6) and 0.9 (95% CI, 0.5- 1.8) for advanced and localized cancers, respectively. The corresponding ORs for weight were 1.5 (95% CI, 0.8–2.6) and 0.9 (95% CI, 0.5–1.7), respectively. Weight and BMI 20 years prior to the interview were not associated with risk (data not shown).

Socioeconomic Variables, Marital Status, and Family History. ORs for SES and family history are presented in Table 4. In general, SES was not strongly associated with risk for prostate cancer, although we found tentative evidence (based on small numbers) that self-employed men were at an increased risk and farmers were at a decreased risk.

Unmarried men experienced a lower risk for prostate cancer than married men or those living with a stable partner (OR, 0.3). Divorced men and widowers also had a low risk (OR, 0.6), but this was compatible with a chance finding. Separate anal-

Table 4 Age-adjusted ORs with 95% CIs for prostate cancer according to SES, marital status, and family history

Variable	No. of		OR	95% CI
	Cases	Controls		
SES				
Unskilled manual workers	69	77	1.0	ref[a]
Skilled manual workers	87	84	1.1	0.7–1.8
Nonmanual workers	72	62	1.3	0.8–2.1
Self-employed	14	6	2.7	1.0–7.3
Farmers	11	23	0.6	0.3–1.2
Marital status				
Married/living with stable partner	237	215	1.0	ref
Unmarried	10	27	0.3	0.2–0.7
Divorced/widower	6	9	0.6	0.2–1.8
Family history				
Affected relatives				
None	237	244	1.0	ref
Father	19	8	2.4	1.0–5.6
None	241	249	1.0	ref
Brother[b]	15	3	5.2	1.5–18.1
None	225	241	1.0	ref
Father and/or brother	31	11	3.0	1.5–6.1
<70 yr	14	5	2.6	0.9–7.6
≥70 yr	17	6	3.3	1.3–8.7

[a] ref, reference category.
[b] Any brother.

yses of localized and advanced cancers did not provide any further information. The number of marriages, age at first marriage, or number of children were not related to prostate cancer risk (data not shown).

A family history of prostate cancer was strongly associated with risk. Men with a father affected were more than twice as likely to develop the cancer as men without an affected father (OR, 2.4; 95% CI, 1.0–5.6). One hundred seventy-three cases and 175 controls had at least one brother. The risk for men with at least one brother affected was increased more than 5-fold (OR, 5.2; 95% CI, 1.5–18.1). The mean age at diagnosis for the affected fathers of cases and controls was 70.6 ± 7.4 and 71.0 ± 9.1 years, respectively, and the corresponding mean ages for the affected brothers was 73.1 ± 7.0 and 67.7 ± 3.2 years, respectively. To explore whether a positive family history was associated with a higher relative risk of developing prostate cancer at a young age, we undertook a stratified analysis. However, if anything, the association between prostate cancer in a first-degree relative and risk was weaker before age 70 than after 70 years of age.

Discussion

In this population-based study of prostate cancer, we found inconsistent indications of the effect of cigarette smoking. This modest smoking association is in agreement with some previous investigations (3–6), while other studies (2, 8) reported no association. A large prospective study of smoking and prostate cancer in Sweden also showed no clear relationship, further emphasizing that the weak association we found may not be causal.[4]

Similarly, the available epidemiological data do not point to a clear causal role of alcohol in prostate cancer (2, 4, 6–8), although our finding of a slightly elevated risk for current use of hard liquor is supported by some previous reports (17, 18). Furthermore, no obvious biological mechanism has been proposed that would explain such an association. Indeed, alcohol has been found to decrease plasma testosterone (19), an effect which might be expected to decrease prostate cancer risk.

In our analysis of medical history, we found an increased risk among subjects who had had a vasectomy, a finding limited both by imprecision and possible recall bias. No study published before 1990 showed any significant elevation in risk, whereas several studies published after 1990 have reported an association (20, 21). No established biological mechanism exists to explain a causal relationship, although some hypotheses have been proposed, including an increase in circulating androgen levels after a vasectomy, a decrease in local immune factors, and an increase in local production of growth factors. Overall, existing data do not permit any firm conclusion (20).

The absence of an association in our data among height, weight, BMI, and prostate cancer is in agreement with several previous reports, but contradictory to others (2). Substantially larger studies are needed to ascertain weak associations between anthropometric measures and prostate cancer because they can provide important etiological clues. For instance, an association between adult height, a crude indicator of nutrition during childhood and adolescence, and breast cancer has clearly indicated the importance of early life exposures in the etiology of this malignancy (22, 23). The risk of prostate cancer may also be influenced early in life as suggested by studies in migrants (1) and other recent investigations (24).

Regarding socioeconomic variables, farming was associated with a decreased risk, a finding which has been reported previously (25). However, other studies suggest that farmers are at increased risk (26). The reason for these discrepancies is unclear. Possibly, the risk enhancement is related to specific farming exposures, which are not present in our area. Alternatively, our finding also could be a chance finding since it was not statistically significant. In Sweden, socioeconomic variables are generally not strongly associated with cancer risk (27).

Reports of the association between marital status and risk of prostate cancer have been inconsistent in previous studies. Our finding of a decreased risk among unmarried men is supported by some previous reports (28–30) but contradicts others (31–33). The number of marriages and children were, however, not associated with risk. We were unable, despite considerable effort, to establish clearly associations between sexual activity and prostate cancer. Although some leads appeared, they need cautious interpretation because of the nonresponse from many participants. If not biased by a possible selection of respondents, these findings may reflect hormonal influences that might be of importance in the etiology of prostate cancer.

We found a markedly increased risk associated with a positive family history, a known risk factor from several previous studies (9, 10, 34). In these studies, a 2–4-fold increase in risk was reported for first-degree relatives of men with prostate cancer. In the study by Steinberg *et al.* (34), the relative risk escalated with the number of affected first-degree relatives to 4.9 for men with two affected first-degree relatives and 10.9 for those with more than three. In additional segregation and linkage analyses, early-onset prostate cancer appeared to be inherited in an autosomal dominant fashion of a rare high-risk allele (11). This form of prostate cancer may account for a significant number (40%) of early-onset cases, while overall these cases only represent a small proportion (9% by age 85

[4] H-O. Adami, R. Bergström, G. Engholm, A. Englund, O. Nyrén, submitted for publication.

years). Two factors were particularly important determinants of risk, namely, early onset in the relatives and multiple affected family members. In our study, the mean age at diagnosis was 70 years, with few individuals under 60 years old. We did not find any association between age at diagnosis and the number of affected family members. However, it has to be pointed out that our study had limited ability to address this issue. Our finding of an excess risk of prostate cancer in men with affected brothers compared to those with affected fathers is consistent with the hypothesis of an X-linked model of inheritance (35). The total impact of the genetic component has, however, not been fully elucidated. Family members also share a common environment, which makes it difficult to separate the genetic liability.

Our study has potential methodological limitations that must be considered when interpreting the results. In particular, the study had limited power to detect some associations. As in most case-control studies, response bias and nonresponse could have distorted our findings. However, since there is no clear widely held hypothesis regarding the etiology of prostate cancer, there is no strong reason to believe that differential recall would substantially affect cases and controls. Hence, the risk estimates are likely biased toward unity, although differential misclassification could also have influenced some of the results, notably for exposures generally perceived as harmful such as smoking and alcohol.

Strengths of our study include the population-based design; all cases and controls were listed in the County population register. Careful data collection was carried out by professional interviewers who were unaware of the study hypotheses. The lack of any screening activity for prostate cancer is another advantage; such screening would lead to a selective concentration of asymptomatic cases among health-conscious men. Finally, this is one of the few studies of prostate cancer in which controls have been systematically screened for the malignancy. Controls identified with prostate cancer were excluded from the control group. Less than 3% of the controls actually were diagnosed with prostate cancer, and it seems unlikely that this would have any substantial impact on the outcome of the study. It is possible that the nonrespondent individuals differed in some way from those who responded. However, because our response rates were reasonably high and almost identical in cases and controls, major bias from nonresponse seems unlikely.

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