Early Life Risk Factors for Prostate Cancer: A Population-based Case-Control Study in Sweden[1]

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Abstract

We undertook a population-based case-control study to investigate early life risk factors for prostate cancer. Information on dietary habits during childhood and adolescence, childhood environment, pubertal development, and physical activity was collected by face-to-face interviews with 256 (74.6%) of all eligible cases and 252 (76.6%) of all selected controls, frequency matched by age. All potential controls were screened for prostate cancer with negative findings. Odds ratios with 95% confidence intervals were estimated by logistic regression. Analyses of localized (T_{0-2}, M_0) and more advanced cancers were made separately. In general, there was no clear association between diet and prostate cancer risk. An increased risk associated with childhood living in more densely populated, compared with rural, areas was found (odds ratio = 2.1; 95% confidence interval = 1.3–3.5); this effect was most apparent for localized cancers (odds ratio = 3.2; 95% confidence interval = 1.7–6.2). There was no substantial association between adult height or body mass index and prostate cancer, but exercise appeared negatively associated with risk (*P* value for trend, 0.13).

We conclude that our study provides some indications that exposures early in life are important in the etiology of prostate cancer.

Introduction

Despite considerable research, the etiology of prostate cancer remains obscure. A few risk factors have been identified, namely age, black race, and possibly high dietary fat (1), but these explain little of the risk of the disease. To date, most epidemiological studies of this cancer have focused on potential risk factors in adult life. However, it takes at least one generation for men in migrant families to assume the cancer risks of their host country (2), suggesting the importance of early life factors. Moreover, it has been hypothesized that early hormonal events, such as androgen surges during adolescence, may influence the risk of the disease (3). Indeed, it has recently been argued that the increased incidence of disorders of the reproductive tract of the male, such as testicular cancer and urethral abnormalities, may be related to increased estrogen exposure *in utero* (4).

Data on the relationship between early exposures and subsequent risk of prostate cancer are sparse. However, suggestions that cases may differ from controls with respect to sexual development in adolescence (3) support such an association. Serum levels of androgens can be affected by diet (5) and physical activity (6, 7), an influence which could in turn have an impact on the prostate. Thus, a role of diet and physical activity in early life is also plausible, although the little previous research on these topics has not shown firm support for this (8–11).

Using data from a population-based case-control study, we examine below early exposures such as diet, childhood environment, pubertal development, and physical activity as possible risk factors for prostate cancer.

Subjects and Methods

Subjects. The study base consisted of all men under 80 years old, born in Sweden, and living in Örebro county during January 1989 through September 1992. This fairly stable and compact source population comprised around 270,000 individuals in 1988 (12). In this population all men suspected as having prostatic cancer were referred to one of three hospitals (Örebro, Karlskoga, or Lindesberg) for further diagnostic work-up and treatment. The study was approved by the local ethical review board of Örebro County Council.

Eligible as cases were all patients with a newly diagnosed, cytologically and/or histologically confirmed prostatic cancer. Operationally, these subjects were identified through records at the three county hospitals noted above. Surveillance of the only department of pathology which serves the study area, and of the regional cancer registry, indicated that all eligible cases had been identified in this manner. All tumors were graded and staged in accordance with the WHO (13) and Union Internationale Contre le Cancer (14) classifications, respectively. The presence of skeletal metastases was assessed routinely by skeletal scintigraphy and skeletal radiography if needed. The tumors were classified as localized (T_{0-2}, M_0) or advanced (T_{3-4}, M_0; T_{0-4}, M_1).

During the study period, male controls were selected randomly every third month from the county population register and frequency matched by age (<50, 50–59, 60–69, and 70–79) to the cases. All potential controls provided

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a blood specimen and underwent digital rectal examination by one investigator (S-O. A.). Men with a palpable nodule and/or elevated serum levels (>10 μg/l) of prostate-specific antigen were investigated further by ultrasound-guided biopsies. They were accepted as controls only if these biopsies showed no evidence of cancer. Less than 3% of potential controls actually had prostate cancer.

Data Collection. Exposure data were collected in three ways. First, a comprehensive self-administered food frequency questionnaire about recent diet and diet 20 years previously was mailed to all potential study participants. They were collected and completed at the time of a subsequent personal interview. Subjects referred to the hospital for suspected prostate cancer were sent the questionnaire before work-up, *i.e.*, before the diagnosis had been established. However, in many patients there was no suspicion of cancer on admission to hospital, and some patients did not respond to this initial contact. Hence, in a majority of cases it was not possible to secure a completed questionnaire before diagnosis and enrollment in the study effectively began after the patient was notified of the presence of cancer.

Second, all subjects were seen at home by professional female interviewers who were blinded to case-control status and unaware of 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 questionnaire was divided into two parts. One part focused on childhood and adolescence and included questions about place of residence, occupation of the parents, pubertal development, weight, physical activity, education, and food habits. We assessed pubertal development by means of questions regarding age of voice breaking and of first beard growth. In addition, the respondent was asked to compare his own age at puberty with that of his classmates. Physical activity and weight around the time of puberty were assessed similarly in relation to classmates. The second part of the interview focused on adult life and included questions about body size, marital status, religious preference, occupational history, sexual history, medical history, smoking habits, alcohol intake, and family history. Finally, clinical data were obtained at physical examination of both cases and controls. BMI[3] was calculated as weight/(height)^2.

Assessment of Adolescent Diet. A food frequency questionnaire was used to assess dietary habits during adolescence. The questionnaire comprised 20 questions regarding food items of *a priori* interest, namely dairy products (milk, cheese), foods rich in fat and cholesterol, and selected other foods. This limited questionnaire was thus designed to obtain estimates of total fat and cholesterol intake, but not other nutrients. Eight food frequency options were offered, ranging from "never or seldom" to >4 times/day or more. Portion sizes were not requested. The responses were converted into frequencies per month and converted into quantitative fat and cholesterol intakes by using the food composition data base system (KOST) developed at the Swedish National Food Administration (15). This system is based on measurements of nutrients and calories in foods from the 1970s and onwards.

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

Statistical Analysis. Odds ratios 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, and multivariate adjustment in others as indicated. Continuous variables such as height, weight, and BMI were analyzed in original continuous form, as well as in categorized form. Since the apparent effects of childhood environment could be confounded by adult environment, adjustment was made in some analyses for adult occupation as a farmer. This marker (albeit indirect) of living in an agricultural area was the only measurement we had available of adult social environment. In separate analyses, this exposure was found to be related to prostate cancer risk.

Categorization of the continuous variables was principally based on quartiles derived from the distribution among the controls. However, when necessary, other cutoff points were used to obtain suitable categories. Tests of linear trends are based on "semi-continuous" variables created from the categorized variables, using consecutive integers to identify ordered categories. Upper cutoff values between categories of consumption for selected food items are shown in the Appendix.

Results

Of 343 eligible cases, 256 (74.6%) were included in the study. Sixty-three (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%) had died. Of the 329 invited control subjects, 252 (76.6%) completed the interview. Forty-two (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 ± SD of the 256 prostate cancer patients (70.0 ± 6.1 years) agreed closely with that of the 252 controls (69.8 ± 6.2 years). Of the 256 cases included, 68 were discovered unexpectedly after a transurethral resection for presumed benign prostatic hyperplasia (T_0 tumors). All other cases had papable cancers (T_2–T_4) staged by digital rectal examination and clinical examination to evaluate the presence of metastases. There were 118 localized cases (46.5%) and 136 with advanced tumors (53.5%). More of the advanced cases (69.9%) had high grade tumors (G_2–G_3) than the localized ones (23.7%).

Table 1 shows the distribution of selected demographic characteristics of cases and controls and corresponding odds ratios. There was a 2-fold increased risk (OR = 2.1; 95% CI = 1.3–3.5) associated with urban living during childhood, compared to residence in an agricultural area. Correspondingly, sons of farmers had a reduced risk compared to blue collar workers (OR = 0.6; 95% CI = 0.4–1.0). A higher level of education was also associated with an increased risk of prostate cancer. However, in multivariate models including grade of urbanization, father's occupation, level of education, and adult farming, the OR associated with childhood urban living decreased to 1.7 (95% CI = 1.0–3.1), the protective effect of being the son of a farmer diminished (OR = 0.8; 95% CI = 0.4–1.3), and the effect of education disappeared. Table 2 presents separate age-adjusted risk estimates for localized and advanced tumors. Differences by grade of urbanization were somewhat more marked for localized cancers (OR = 3.2; 95% CI = 1.7–6.2) for city living *versus* agricultural area than for advanced cancers (OR = 1.6; 95% CI = 0.9–2.9).

Table 3 summarizes the association between pubertal

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Table 1 Age-adjusted odds ratios with 95% CI of prostate cancer according to grade of urbanization during childhood and adolescence, father's occupation, and level of education

Variable	No. of cases/controls	Age-adjusted OR (95% CI)	Multivariate OR (95% CI)
Grade of urbanization[a]			
Agricultural area	77/91	1.0 (ref.)	1.0 (ref.)
Woodland	21/34	0.7 (0.4–1.4)	0.6 (0.3–1.2)
Village	50/56	1.1 (0.7–1.7)	0.9 (0.5–1.5)
Small town	41/34	1.4 (0.8–2.4)	1.1 (0.6–2.0)
City	64/36	2.1 (1.3–3.5)	1.7 (1.0–3.1)
Father's occupation[b]			
Blue-collar worker	105/106	1.0 (ref.)	1.0 (ref.)
Farmer	50/78	0.6 (0.4–1.0)	0.8 (0.4–1.3)
Craftsman	31/23	1.4 (0.7–2.5)	1.3 (0.7–2.3)
Civil servant	29/16	1.8 (0.9–3.5)	1.6 (0.8–3.2)
Own businessman	28/18	1.5 (0.8–2.9)	1.5 (0.8–2.8)
Other	9/9	1.0 (0.4–2.7)	1.1 (0.4–2.8)
Level of education[b]			
Years in school			
≤6	141/156	1.0 (ref.)	1.0 (ref.)
7–9	65/61	1.2 (0.8–1.8)	1.0 (0.7–1.6)
≥10	47/35	1.5 (0.9–2.5)	1.1 (0.7–1.9)
P value for trend		0.12	0.64

[a] Multivariate estimates adjusted for age and adult farming.
[b] Multivariate estimates adjusted for age, urbanization (city *versus* countryside), and adult farming.

Table 2 Age-adjusted odds ratios of localized and advanced prostate cancers according to grade of urbanization during childhood and adolescence, father's occupation, and level of education

Variables	Localized cases		Advanced cases	
	No. of cases/controls	OR (95% CI)	No. of cases	OR (95% CI)
Grade of urbanization				
Agricultural area	26/91	1.0 (ref.)	49	1.0 (ref.)
Woodland	9/34	0.9 (0.4–2.2)	12	0.7 (0.3–1.4)
Village	28/56	1.7 (0.9–3.2)	22	0.7 (0.4–1.3)
Small town	20/34	2.0 (1.0–4.0)	21	1.1 (0.6–2.2)
City	33/36	3.2 (1.7–6.2)	31	1.6 (0.9–2.9)
Father's occupation				
Blue-collar worker	48/106	1.0 (ref.)	57	1.0 (ref.)
Farmer	20/78	0.6 (0.3–1.0)	28	0.7 (0.4–1.1)
Craftsman	17/23	1.7 (0.8–3.4)	14	1.1 (0.5–2.4)
Civil servant	12/16	1.6 (0.7–3.6)	17	2.0 (0.9–4.2)
Own businessman	14/18	1.6 (0.7–3.6)	14	1.4 (0.7–3.1)
Other	4/9	1.1 (0.3–3.7)	5	1.0 (0.3–3.2)
Level of education				
Years in school				
≤6	56/156	1.0 (ref.)	83	1.0 (ref.)
7–9	36/61	1.6 (0.9–2.7)	29	0.9 (0.5–1.6)
≥10	24/35	1.9 (1.0–3.5)	23	1.3 (0.7–2.3)
P value for trend		0.03		0.58

development and the prostate cancer risk. Developmental events were difficult to recall with certainty and missing data prevented detailed analysis. Early age at onset of beard growth tended to be associated with an increased risk of cancer (OR = 2.4; 95% CI = 0.9–6.6), but weight at puberty in relation to classmates did not differ substantially between cases and controls. Physical activity was negatively associated with risk (OR for higher activity = 0.7; 95% CI = 0.4–1.0; *P* for trend = 0.06). No substantial change was noted in multivariate analysis after adjustment for childhood urbanization and adult farming. Analysis of pubertal events and risks for prostate cancer by degree of tumor aggressiveness was not possible because of the limited numbers of men in the different exposure categories.

Table 3 ORs for prostate cancer, with 95% CIs according to exposures during puberty

Variable	No. of cases/controls	Age-adjusted OR (95% CI)	Multivariate OR[a] (95% CI)
Age at onset of beard growth (years)			
≤14	14/6	2.4 (0.9–6.6)	2.6 (0.9–7.1)
15–16	92/98	1.0 (ref.)	1.0 (ref.)
17–18	93/76	1.3 (0.9–2.0)	1.3 (0.8–1.9)
≥19	17/21	0.9 (0.4–1.7)	0.8 (0.4–1.6)
Unknown	40/51		
P value for trend		0.64	0.41
Weight during puberty[b]			
Less	23/22	0.9 (0.5–1.7)	0.9 (0.5–1.7)
Same	217/204	1.0 (ref.)	1.0 (ref.)
More	9/9	1.0 (0.4–2.5)	1.1 (0.4–2.9)
Unknown	7/17		
P value for trend		0.87	0.69
Level of physical activity during puberty[b]			
Lower	9/7	1.2 (0.4–3.3)	1.3 (0.5–3.6)
Same	205/184	1.0 (ref.)	1.0 (ref.)
Higher	38/52	0.7 (0.4–1.0)	0.7 (0.4–1.1)
Unknown	4/9		
P value for trend		0.06	0.13

[a] Multivariate analysis including age, grade of urbanization (city *versus* countryside), and adult farming.
[b] In comparison with classmates.

Table 4 presents the ORs associated with the consumption of selected food items during adolescence. We found no suggestion that the intake of high fat foods was associated with increased risk; the highest quartile of intake had an associated OR of 0.6 (95% CI = 0.4–1.1; *P* for trend = 0.07). Multivariate analysis did not substantially change the risk estimates. Moreover, dairy products as a group (milk, butter, cheese, and cream) showed no association with risk. Indices for total fat and cholesterol were also calculated, with ORs close to unity. Consumption of fish was, if anything, positively associated with prostate cancer risk (OR = 1.8; 95% CI = 1.0–3.5 for the highest intake level). No associated risks were found for the other foods studied. Localized and advanced cancers displayed similar patterns, and multivariate analysis did not substantially change the risk estimates (data not shown).

Table 5 gives the ORs for prostate cancer according to height, weight, and BMI at age 20. Overall, height, weight, and BMI appeared to have little impact, but for advanced cancers there were suggestions that increased height was associated with a modestly increased risk and high BMI with a decreased risk (data not shown). Both patterns were consistent with chance, however. Adjustment for childhood urbanization and adult farming left these risk estimates essentially unchanged. Height, weight, and BMI analyzed as continuous variables provided no additional information. Risk estimates for BMI at age 20 were unaffected when adjustment was made for BMI 20 and 2 years prior to interview.

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Table 4 Age-adjusted odds ratios (with 95% CI) for prostate cancer according to adolescent consumption of selected food items and indices for total fat and cholesterol[a]

Food item	OR_2	OR_3	OR_4	*P* value for trend
Whole milk	0.8 (0.5–1.3)	0.8 (0.4–1.3)	0.8 (0.5–1.4)	0.47
Cheese	0.8 (0.5–1.4)	1.0 (0.7–1.6)	0.8 (0.4–1.6)	0.80
Butter	1.1 (0.7–1.9)	0.6 (0.3–1.4)	0.6 (0.4–1.1)	0.07
Cream	1.3 (0.9–2.1)	1.4 (0.8–2.4)	0.7 (0.4–1.2)	0.45
Total dairy products	1.4 (0.8–2.3)	1.1 (0.6–1.8)	0.8 (0.4–1.3)	0.24
Margarine	2.2 (0.8–6.2)	1.6 (0.5–5.3)		0.49
Egg	1.0 (0.6–1.6)	1.2 (0.7–2.0)		0.52
Fish	1.0 (0.6–1.6)	1.8 (1.0–3.5)		0.09
Meat/sausage	1.0 (0.6–1.5)	1.1 (0.7–1.8)	0.7 (0.3–1.4)	0.71
Liver	0.9 (0.6–1.40)	1.5 (0.9–2.5)		0.22
Carrots[b]	1.1 (0.7–1.7)	0.9 (0.6–1.4)		0.67
Cookies, crackers and pastery	1.1 (0.7–1.6)	1.0 (0.6–1.8)	1.6 (0.9–2.9)	0.18
Total fat	0.7 (0.4–1.2)	1.0 (0.7–1.7)	0.7 (0.4–1.1)	0.38
Cholesterol	1.0 (0.6–1.7)	0.8 (0.5–1.3)	0.9 (0.5–1.4)	0.36

[a] For cutoff values for levels of consumption, see Appendix; reference categories are the lowest exposure categories.
[b] Weighted consumption during summer and winter.

Table 5 Age-adjusted odds ratios for prostate cancer according to height, weight, and BMI at age 20 analyzed both as continuous and categorized into quartiles

Variable	No. of cases/ controls	Age-adjusted odds ratio (95% CI)	Multivariate odds ratio (95% CI)[a]
Continuous (10 cm)	255/235	1.2 (0.9–1.6)	1.1 (0.8–1.6)
Height (cm) in quartiles			
≤170	60/64	1.0 (ref.)	1.0 (ref.)
171–174	60/61	1.0 (0.6–1.7)	1.1 (0.6–1.8)
175–178	65/58	1.2 (0.7–1.9)	1.1 (0.7–1.9)
>178	70/52	1.4 (0.8–2.3)	1.4 (0.8–2.3)
Weight continuous (10 kg)	212/204	0.9 (0.7–1.2)	1.0 (0.8–1.3)
Weight (kg) in quartiles			
≤63	64/57	1.0 (ref.)	1.0 (ref.)
64–69	54/48	1.1 (0.6–1.8)	1.2 (0.7–2.0)
70–72.5	41/48	0.8 (0.5–1.4)	0.9 (0.5–1.6)
>72.5	53/51	1.0 (0.6–1.6)	1.1 (0.6–1.9)
BMI continuous (5 kg/m^2)	211/193	0.8 (0.5–1.2)	1.0 (0.6–1.5)
BMI (kg/m^2) in quartiles			
≤20.83	61/49	1.0 (ref.)	1.0 (ref.)
20.84–22.49	56/48	1.0 (0.6–1.6)	1.1 (0.6–1.9)
22.50–23.81	47/48	0.8 (0.4–1.4)	0.8 (0.5–1.5)
>23.81	47/48	0.8 (0.5–1.4)	1.0 (0.6–1.8)

[a] Multivariate analysis including age, grade of urbanization (city *versus* countryside), and adult farming.

Discussion

The main finding in this population-based case-control study of early life risk exposures was the lack of association between adolescent diet and the risk of prostate cancer. We also found a decreased risk associated with childhood residence in an agricultural area and an increased risk associated with living in more densely populated areas, most notably for localized cancers. Exercise during adolescence appeared to be negatively associated with risk.

Our finding of an increased risk for prostate cancer associated with urban living during childhood was most pronounced for localized cancers. This pattern might be partially explained by a greater access to medical care (including transurethral resection of the prostate) among subjects growing up in a city. However, a real increase in exposure to risk factors in densely populated areas cannot be excluded. In previous studies, education has demonstrated variable relationships to prostate cancer risk (15–18). In our study, the positive association for localized cancers was eliminated after adjustment for living in an agricultural area during childhood and adult life.

The finding of a negative association between physical activity and prostate cancer is in agreement with some (19–23) but not all (10, 11, 24) previous studies. However, most research has focused on lifetime physical activity, not specifically with that in early life. There are reports that trained athletes have lower basal levels of circulating testosterone than do untrained men (6, 25), and that testosterone levels are decreased immediately after exercise (6, 7). Because testosterone has been implicated in the etiology of prostate cancer (26), this could be a mechanism through which physical activity might act there. The indication we found of a positive association of early onset of puberty with risk of prostate cancer also supports a role for androgens. However, the number of subjects was too small to permit any firm conclusions.

Our dietary questionnaire for adolescence was too limited to permit analysis of most nutrients; however, an index of total fat intake was unassociated with risk. In view of the lack of overall effect of dairy products, the possible inverse association of butter intake with risk is most plausibly the result of chance. There is a little previously published data regarding dietary habits during childhood or adolescence and subsequent risk of prostate cancer. Two cohort studies (8, 9) found little indication of an effect. This could be due to inaccuracies in recalled data or limited power, but it is also possible that early diet is of minor importance for tumor initiation and acts as a tumor promoter later in life. Even the results from case-control and cohort studies of fat intake in adult life and subsequent risk of prostate cancer have not been consistent (9, 15, 27–38).

Our finding of a weak negative association of BMI at age 20 with prostate cancer (all cancers) did not remain when adjustment was made for place of living during childhood and adult life. Again, most studies on BMI and prostate cancer risk refer to the adult weight. In one cohort study (39), BMI at age 25 was found to be weakly positively associated with risk of prostate cancer.

This population-based study was focused on exposures

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in childhood and adolescence; consequently the quality of information collected on exposures as remote as 70 years previously will of course suffer from misclassification. Because there is no clear widely held hypothesis regarding the etiology of prostate cancer, there is no reason to believe that differential recall would substantially affect cases and controls. Hence, the ORs are likely biased toward unity. This is most likely to be an issue for exposures measured with imprecision: diet and adolescent development, for example. Factors such as height, weight, and childhood environment are less likely to be affected.

Our study has several strengths. Most epidemiological investigations of prostate cancer will suffer from misclassification of disease status because the prevalence of latent cancer is relatively high (40), implying an impaired discrimination between cases and controls. We were able to overcome this, however, by screening all potential controls for prostate cancer, and conducting separate analyses for localized and advanced cancers. Moreover, the existence of a cancer registry completely covering the study area enabled us to ascertain reliably all incident cases, and the participation rate among both cases and controls was reasonably high.

In summary, we have found some suggestions that pubertal events affect prostate cancer risk, and that childhood environment (urbanization) plays a role as well. The impact of early diet, however, appears small.

Appendix

Upper cutoff points between categories of consumption for selected food items and indices[a]

Foods	R_1	R_2	R_3	R_4
Whole milk (glasses/day)	3.0	4	5	10
Cheese (slices/month)	6.0	14	30	75
Butter (sandwiches/day)	5.0	6	7	15
Cream	2.0	6	14	75
Margarine (sandwiches/day)[b]	4.0	6	10	
Egg (eggs/month)[b]	2.0	6	75	
Fish[b]	2.0	6	30	
Meat/sausage	6.0	14	22	30
Liver[b]	0.5	2	120	
Carrots[b]	2.0	5	30	
Cookies, crackers and pastery[b]	2.0	6	14	75
Total fat index (g/day)	78.0	97	119	226
Cholesterol index (mg/day)	292.0	401	508	1428
Total dairy products	122.0	157	195	389

[a] Unless otherwise stated, the unit used is times/month, and divisions based on quartiles.
[b] Categories arbitrarily chosen to obtain groups of suitable size.

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