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A Case-Cohort Study on Prostate Cancer Risk in Relation to Family History of Prostate Cancer

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We investigated the risk of prostate cancer in relation to a family history of prostate cancer in 58,279 men ages 55–69 years. We found 704 incident cases after 6.3 years of follow-up. Rate ratios and 95% confidence intervals for having an affected *vs* nonaffected father and brother were, respectively 1.44 (0.80–2.58) and 5.57 (1.61–19.26). We found no evidence for an increasing risk with an increasing percentage of affected family members. The associations we observed were stronger for cases diagnosed before age 70 compared with cases diagnosed after age 70 and for advanced compared with localized tumors. (Epidemiology 1999;10:192–195)

Keywords: Prospective case-cohort study, prostate cancer risk, family history, age.

Despite a high incidence of prostate cancer in Western countries, few risk factors are known. A positive family history has been reported to be associated with risk,[1,2] but limited data from prospective studies are available. With data from the Netherlands Cohort Study, we were able to investigate not only a positive family history, but also to take the number of brothers into account as well as the age at diagnosis of brothers and fathers. We were also able to investigate case subgroups (localized and advanced tumors) separately.

Methods

The Cohort

The study design has been described in detail elsewhere.[3] Briefly, in 1986, 58,279 men ages 55–69 years who originated from 204 municipal population registries throughout the country completed a self-administered questionnaire on personal and family history of cancer, usual diet, and other risk factors for cancer. We used a case-cohort approach for analysis[4]: for calculation of cancer incidence rates, the number of cases for the entire cohort was used as the numerator, while person years at risk (denominator) were estimated using a random male sample of controls, the subcohort (N = 1688). We identified incident prostate cancer cases using computerized record linkage with all nine cancer registries in The Netherlands.[5] The control subcohort has been followed up biennially for vital status information. Completeness of cancer follow-up was at least 96%; no subcohort member has been lost to follow-up.[6] After 6.3 years of follow-up (September 1986-December 1992), 704 incident, primary prostate cancer cases were identified. During this period, systematic screening for prostate cancer was not instituted in the Netherlands.

Data Collection and Analysis

Subjects were asked to report how many brothers they had, whether their father or brother(s) had ever been diagnosed with prostate cancer, and if so, at what age. To take family size into account in analyses, we computed the percentage of family members with prostate cancer: the number of affected family members (fathers and brothers) divided by the number of brothers plus one (father). A percentage was also computed for brothers only.

We excluded subjects with prevalent cancer at baseline other than skin cancer and subjects with incomplete or inconsistent dietary data according to criteria described earlier.[7] A total of 642 cases and 1525 subcohort members remained for analysis. First, we examined potential confounding factors including age, educational level, fat intake, and consumption of vegetables and fruit. Second, we computed rate ratios (RRs) and 95% confidence intervals (CI). We assumed that survival times were exponentially distributed in the follow-up period.[8] We also computed RRs for subgroups of cases diagnosed before and after age 70 and for localized (T0–2, M0) and advanced (T3–4, M0; T0–4, M1) tumors.

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TABLE 1. Distribution of Potential Confounding Factors among Subcohort Members and Cases with a Negative and Positive Family History of Prostate Cancer

Variables	Person-Years in Subcohort (%)		Number of Cases (%)	
	No Family History	Positive Family History	No Family History	Positive Family History
Age				
55–59	3417 (38.5)	119 (47.0)	92 (15.0)	6 (21.4)
60–64	3095 (34.9)	100 (39.1)	217 (35.3)	12 (42.9)
65–69	2355 (26.6)	35 (13.9)	305 (49.7)	10 (35.7)
Educational level*				
Low	4176 (47.1)	81 (31.7)	275 (45.2)	10 (35.7)
Medium	3065 (34.6)	123 (48.5)	212 (34.8)	10 (35.7)
High	1574 (17.7)	44 (17.3)	122 (20.0)	8 (28.6)
Fat intake (quintiles)				
1 (low)	1763 (19.9)	43 (16.9)	135 (22.0)	5 (17.9)
2	1753 (19.8)	54 (21.3)	130 (21.2)	7 (25.0)
3	1771 (20.0)	69 (27.2)	123 (20.0)	6 (21.4)
4	1787 (20.2)	38 (14.8)	119 (19.4)	4 (14.3)
5 (high)	1794 (20.2)	50 (19.8)	107 (17.4)	6 (21.4)
Vegetable consumption (quintiles)				
1 (low)	1800 (20.3)	62 (24.3)	121 (19.7)	6 (21.4)
2	1702 (19.2)	82 (32.1)	130 (21.2)	2 (7.1)
3	1760 (19.8)	57 (22.2)	122 (19.9)	9 (32.1)
4	1828 (20.6)	35 (13.9)	141 (23.0)	6 (21.4)
5 (high)	1778 (20.0)	19 (7.4)	100 (16.3)	5 (17.9)
Fruit consumption (quintiles)				
1 (low)	1810 (20.4)	31 (12.4)	116 (18.9)	
2	1748 (19.7)	57 (22.2)	110 (17.9)	9 (32.1)
3	1768 (19.9)	47 (18.4)	101 (16.4)	5 (17.9)
4	1778 (20.1)	50 (19.8)	140 (22.8)	6 (21.4)
5 (high)	1763 (19.9)	69 (27.2)	147 (23.9)	8 (28.6)

* Because of missing information, percentages may not add up to 100%; low is defined as primary school with/without lower level vocational education, medium as secondary school or medium level vocational education, high as university or higher level vocational education.

Results

Of subcohort members and cases, 2.5% and 4.1%, respectively, had a father or brother with prostate cancer. Table 1 shows descriptive information on subcohort members and cases. Subcohort members and cases with a positive family history were younger compared with subjects without a family history. Furthermore, they less often had a lower educational level. Fat intake and consumption of vegetables and fruit also differed between subjects with and without a family history of prostate cancer but patterns in the distribution were less clear.

Age-adjusted and multivariate adjusted RRs for prostate cancer according to family history were comparable (Table 2). A positive *vs* negative family history was associated with an increased prostate cancer risk (RR = 1.77). For an affected father, the estimate was 1.38 with a 95% CI of 0.76–2.49; for one or more affected brothers, the RR was 5.54 (1.75–17.50). The RR for subjects with less than 50% of family members affected was 3.09 (1.60–5.98) and 0.95 (0.34–2.66) when more than 50% was affected. For subjects with less than 50% of their brothers affected, the RR was 12.26 (2.34–64.35); it was 2.60 (0.51–13.26) when more than 50% of their brothers were affected. Age at diagnosis of affected family members before age 75 was associated with a higher relative risk (RR = 2.36, 95% CI: 1.10–5.07) compared with age at diagnosis at age 75 years or older (RR = 1.36, 95% CI: 0.64–2.89).

In the subgroup of cases diagnosed before age 70, the RRs for a positive family history were increased while in the subgroup of cases diagnosed after age 70, only the RR for having a brother with prostate cancer was increased (Table 3). RRs for a family history of prostate cancer were higher for advanced prostate tumors than for localized tumors (Table 4).

Discussion

An important strength of our study is its prospective design, making information bias unlikely. Another strength is that there is no loss to follow-up of cases and subcohort members.[6,9] On the other hand, small numbers limited certain analyses. Furthermore, family history is subject to nondifferential misclassification. Nevertheless, it has been shown that the accuracy of reported family history of cancer[10] or prostate cancer[11,12] in first degree relatives is high. Another limitation is that we could not take into account the age distribution of family members.

A positive association between family history and prostate cancer risk has been previously reported.[12–14] In several,[12,15–19] but not all[2,11] studies, estimated risks were higher for affected brothers (RRs varying from 1.9 to 5.3) than for affected fathers (RRs varying from 1.2 to 3.5). These findings support an X-linked or recessive model of inheritance,[20] but greater misclassification of the reporting of fathers' history compared with brothers' history of prostate cancer could have influenced results.

TABLE 2. Rate Ratios (RRs) and 95% Confidence Intervals (95% CI) for Prostate Cancer According to the Number and Percentage of Affected First Degree Family Members and Age at Diagnosis of These Family Members

Exposure	Age-Adjusted		Multivariate Adjusted*	
	No of Cases†/ Person-Years in Subcohort	RR (95% CI)	No of Cases†/ Person-Years in Subcohort	RR (95% CI)
No. of affected family members				
None‡	614/8868	1.00	609/8814	1.00
≥1	28/254	1.77 (1.06–2.96)	28/248	1.77 (1.05–2.97)
Father with prostate cancer				
No‡	622/8893	1.00	617/8839	1.00
Yes	20/229	1.36 (0.75–2.45)	20/223	1.38 (0.76–2.49)
Brother(s) with prostate cancer				
No‡	634/9097	1.00	629/9037	1.00
Yes	8/25	6.29 (1.92–20.55)	8/25	5.54 (1.75–17.50)
% of affected family members				
None‡	614/8868	1.00	609/8814	1.00
1–49	20/125	3.00 (1.83–4.89)	20/118	3.09 (1.60–5.98)
≥50	6/86	0.99 (0.50–1.97)	6/86	0.95 (0.34–2.66)
% of affected brothers				
None‡	504/7232	1.00	500/7175	1.00
1–49	5/13	12.74 (3.06–53.00)	5/13	12.26 (2.34–64.35)
≥50	3/13	3.50 (0.95–12.86)	3/13	2.60 (0.51–13.26)
Age (years) at diagnosis family member§				
No affected family member‡	614/8868	1.00	609/8814	1.00
≥75	11/111	1.37 (0.80–2.33)	11/111	1.36 (0.64–2.89)
<75	13/113	2.38 (1.41–4.03)	13/107	2.36 (1.10–5.07)
Age (years) at diagnosis father				
No affected father‡	622/8893	1.00	617/8839	1.00
≥75	11/111	1.35 (0.64–2.86)	11/111	1.34 (0.63–2.86)
<75	7/94	1.58 (0.61–4.06)	7/88	1.64 (0.63–4.23)

* Adjusted for age at baseline (continuous), educational level (low, medium, high), total fat intake (continuous), and total vegetable and total fruit consumption (both continuous).
† Because of missing information, numbers may not add up to 642.
‡ Reference category.
§ In case of more than one affected family member, the youngest age at diagnosis was used.

An autosomal dominant gene has also been proposed as a model of inheritance.[21,22]

Some studies have reported an increasing risk of prostate cancer with increasing numbers of affected first degree family members.[2,11,12,16] Our estimates, based on small numbers, did not confirm this pattern. Some studies, such as the Netherlands Cohort Study, showed a higher risk associated with a younger age at diagnosis of affected family members,[12,16] but not all.[11] We were unable to adjust for the age of family members, but controlling for the age of the subjects might have, albeit indirectly and partially, controlled for family age. When family members were affected, risk of developing prostate cancer before age 70 was increased whereas risk of prostate cancer after age 70 was not. This finding comports with those in one cohort study[23] and two case-control studies.[16,24] In one cohort[2] and one case-control study,[25] associations were not clearly different for younger and older cases. In general, hereditary cancers are known to have earlier onset. Therefore, our findings

TABLE 3. Rate Ratios (RRs) and 95% Confidence Intervals (95% CI) for Prostate Cancer According to Age at Diagnosis and Family History

Characteristic	Cases Diagnosed before Age 70 (N = 369)		Cases Diagnosed at Age 70 and Older (N = 273)	
	Cases/Person-Years in Subcohort	RR* (95% CI)	Cases/Person-Years in Subcohort	RR* (95% CI)
No. of affected family members				
None†	343/8814	1.00	266/8814	1.00
≥1	21/248	2.22 (1.37–3.59)	7/248	0.90 (0.32–2.51)
Father with prostate cancer				
No†	350/8839	1.00	267/8839	1.00
Yes	14/223	1.61 (0.88–2.95)	6/223	0.79 (0.27–2.32)
Brother(s) with prostate cancer				
No†	357/9037	1.00	272/9037	1.00
Yes	7/25	6.96 (2.19–22.12)	1/25	4.58 (0.41–50.96)

* Adjusted for age at baseline (continuous), educational level (low, medium, high), total fat intake (continuous), and total vegetable and total fruit consumption (both continuous).
† Reference category.

TABLE 4. Rate Ratios (RRs) and 95% Confidence Intervals (95% CI) for Localized (T0–2, M0) and Advanced (T3–4, M0; T0–4, M1) Prostate Tumors According to Family History

Characteristic	Localized Tumors (N = 226)		Advanced Tumors (N = 213)	
	Cases/Person-Years in Subcohort	RR* (95% CI)	Cases/Person-Years in Subcohort	RR* (95% CI)
No. of affected family members				
None†	214/8814	1.00	198/8814	1.00
≥1	10/248	1.85 (0.90–3.81)	12/248	2.37 (1.22–4.62)
Father with prostate cancer				
No†	216/8839	1.00	201/8839	1.00
Yes	8/223	1.61 (0.72–3.56)	9/223	1.98 (0.93–4.24)
Brother(s) with prostate cancer				
No†	222/9037	1.00	207/9037	1.00
Yes	2/25	4.30 (0.81–22.86)	3/25	5.33 (1.36–20.85)

* Adjusted for age at baseline (continuous), educational level (low, medium, high), total fat intake (continuous), and total vegetable and total fruit consumption (both continuous).
† Reference category.

might indicate a hereditary component for early prostate cancer.

We found stronger associations for advanced prostate tumors than for localized tumors. Our findings, therefore, do not support the suggestion that men with a positive family history of prostate cancer get diagnosed at an early stage because of increased awareness. If men with a positive family history are at increased risk of aggressive growing prostate tumors, this tendency might counteract the possibility of more early stage diagnoses and the similar proportions in our study might be the net result of these two possibilities. In two other studies no different association for localized and advanced tumors was reported.[15,16]

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