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Original Paper

The Risk of Malignant Tumours in First-degree Relatives of Men with Early Onset Prostate Cancer: A Population-based Cohort Study

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Previous studies have indicated that hereditary prostate cancer is common among men with early onset prostate cancer. The aim of this study was to investigate the incidence of malignant tumours in first-degree relatives of men with early onset prostate cancer. All prostate cancer cases diagnosed before the age of 51 years from 1958 to 1994 were identified in the population-based Swedish Cancer Register. The first-degree relatives of clinical cases were identified through parish data. Their vital status and cancer incidence were studied in the Swedish Cancer Register, the Cause of Death Register and the Census Register. The expected incidence of malignant tumours for the first-degree relatives were calculated using regional cancer register data. Cause-specific standardised incidence ratios (SIR) and 95% confidence intervals (CI) were calculated. The study included 423 first-degree relatives of 89 men with clinical prostate cancer. The first-degree relatives' SIR for malignant tumours was 0.99 (95% CI 0.78–1.23). The SIR for prostate cancer diagnosed at any age was 1.43 (95% CI 0.82–2.33), and 3.37 for first-degree relatives diagnosed before the age of 70 years (95% CI 1.36–6.94). There was no significantly increased risk of any non-prostatic malignant tumour. Only in five of the families did the pedigree show a pattern of hereditary prostate cancer. The first-degree relatives of men with early onset prostate cancer had more than a 3-fold increase in the risk of developing prostate cancer before the age of 70 years, but their total cancer risk was not increased. This study does not support the assumption that dominantly inherited susceptibility is a major cause of early onset prostate cancer.

Key words: prostatic neoplasms, relatives, cancer risk, epidemiology, cohort study
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INTRODUCTION

PROSTATE CANCER is the most common malignant tumour in Sweden [1], but its aetiology is still poorly understood. An important risk factor of prostate cancer is a family history of the disease [2]. Several large epidemiological studies have shown that brothers and sons of men with prostate cancer have approximately a doubled risk of prostate cancer [3–10]. Recent research has focused on the possibility of an inherited predisposition to prostate cancer as an explanation of these epidemiological findings. Based on a segregation analysis of first-degree relatives of 691 men with localised prostate cancer, Carter and associates raised the hypothesis of a highly penetrant autosomal dominantly inherited prostate cancer susceptibility gene [11]. They calculated that a rare high-risk allele is responsible for 9% of all prostate cancer cases, and as much as 43% of cases diagnosed before the age of 55 years. Just recently, an inherited predisposition for prostate cancer was linked to a region of chromosome 1 [12], but the gene(s) involved have not yet been identified. Whether hereditary prostate cancer is associated with an increased risk of non-prostatic tumours is presently not known.

The aim of this population-based study was to investigate the risk of malignant tumours in first-degree relatives of men with early onset prostate cancer, and to assess the prevalence of dominantly inherited cancer syndromes in their families.

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PATIENTS AND METHODS

Since 1958 all newly diagnosed cancer cases in Sweden have been registered by the Swedish Cancer Registry. From this register, we identified all men diagnosed with prostate cancer before 51 years of age in the Southern healthcare region, which today has approximately 1.5 million inhabitants. We found 118 men diagnosed from 1958 to December 1994. These 118 cases constituted 0.48% of the total number of prostate cancers diagnosed during this period. The median age at diagnosis of prostate cancer in the population was 75 years.

The pathology reports, relevant clinical records and autopsy reports were studied to ascertain the accuracy of the prostate cancer diagnosis for the 118 cases. In 7 cases where the diagnosis seemed uncertain, re-examination of the original pathological specimens with immunohistochemistry verified the diagnosis of prostatic adenocarcinoma. 29 cases were excluded from the study: 19 cases of small, localised, low-grade prostatic cancers accidentally diagnosed at autopsy; 4 cases with microscopic foci of low-grade prostate cancer diagnosed at pathological examination of the prostate following cystoprostatectomy for bladder cancer; 2 cases where a cytological diagnosis of a low-grade prostate adenocarcinoma was revised and the patients had no further signs of prostate cancer for more than 20 years; 2 cases for which the records could not be found; 1 case of prostatic rhabdomyosarcoma; and 1 case where no evidence of prostate cancer was found in the records, which was considered to be an error in the notification of the Cancer Register. Altogether 89 cases of clinical adenocarcinoma of the prostate were included.

In all, 503 first-degree relatives of the 89 clinical cases were identified with assistance from the census registers held by the parish authorities. For 48 of them no information concerning their civic registration numbers could be found, and 32 were dead before 1958. These 80 first-degree relatives could not be evaluated in the Cancer Register, and were thus excluded. The remaining 423 first-degree relatives (58 fathers, 92 brothers, 66 sons, 56 mothers, 81 sisters and 70 daughters) were included in the cohort. None of the relatives were also index cases. Their vital status and cancer incidence were observed from 1 January 1958 until 30 June 1996 using the population-based Swedish Cancer Register, Cause of Death Register and Census Register. Each individual could have more than one malignant tumour registered. The expected number of cases was then calculated for the various tumour types using retrospective age-, gender- and calendar-year specific data from the South Swedish Regional Tumour Registry with the population stratified into 5-year age groups. We used the person-years method: for every single calendar year the expected risk of developing a specific malignant tumour was calculated for each individual.

Cause-specific standardised incidence ratios (SIR) and 95% confidence intervals (CI) were calculated. *P* values were calculated using the Poisson distribution if the expected number of cases was less than 10, otherwise by the chi-squared distribution. All tests were two-tailed.

RESULTS

The 423 first-degree relatives in the cohort were observed for 13 962 person-years. A total of 80 malignant tumours were diagnosed in the first-degree relatives during the period of observation. The calculated expected number of cancer cases was 81, which gave an SIR of 0.99 (95% CI: 0.78–1.23). There was no significantly increased or decreased risk for any tumour site (Table 1).

There were 16 cases (4 brothers and 12 fathers) of prostate cancer among the 216 male first-degree relatives (SIR = 1.43, 95% CI: 0.82–2.33). The mean age at diagnosis of these 16 cases was 72 years. The SIR for prostate cancer was higher for younger first-degree relatives (Table 2). The SIR for non-Hodgkin's lymphoma, rectal cancer and for the total incidence of malignant tumours also increased successively for the younger first-degree relatives, although not reaching statistical significance. The SIR for these sites for first-degree relatives younger than 70 years were: non-Hodgkin's lymphoma 3.79 (95% CI: 0.46–13.70), rectal cancer 3.29 (95% CI: 0.68–9.60), and for the total incidence of malignant tumours 1.35 (95% CI: 0.84–2.07).

The pedigrees in families with two or more prostate cancer cases were further expanded in the registers to include

Table 1. Incidence of malignant tumours in first-degree relatives of men diagnosed with prostate cancer before the age of 51 years

ICD 7	Tumour	Obs.	Exp.	SIR	95% CI
140–209	All malignant tumours	80	81.0	0.99	0.78–1.23
151	Stomach	5	4.9	1.03	0.33–2.40
153	Large bowel	6	7.0	0.86	0.31–1.86
154	Rectum	4	4.0	0.99	0.27–2.53
157	Pancreas	2	2.6	0.76	0.09–2.75
162	Bronchus or lung	7	5.4	1.28	0.52–2.65
170	Breast	4	8.1	0.49	0.13–1.26
172	Uterine body	2	1.7	1.15	0.14–4.15
175	Ovary	3	2.0	1.53	0.31–4.46
177	Prostate	16	11.0	1.43	0.82–2.33
180	Kidney	2	2.5	0.81	0.10–2.93
190	Malignant melanoma	3	2.0	1.51	0.31–4.43
191	Skin (melanoma excluded)	7	4.3	1.61	0.65–3.33
193	Brain	2	2.5	0.81	0.10–2.93
200	Non-Hodgkin's lymphoma	4	2.1	1.92	0.52–4.90
204–209	Leukaemias	2	2.2	0.90	0.12–3.48

Number of first-degree relatives: 423. Number of person-years at risk: 13 962. Tumour sites with two or more observed cases are shown in the table. At each following tumour site 1 case was observed: mouth, liver, biliary tract, larynx and uterine cervix. Five cases had a tumour of unknown origin. Obs., observed number of cases; Exp., expected number of cases; SIR, standardised incidence ratio; CI, confidence interval.

Table 2. Incidence of prostate cancer in male first-degree relatives of men diagnosed with prostate cancer before the age of 51 years

Age at diagnosis	Obs.	Exp.	SIR	95% CI	*P* value
All ages	16	11.0	1.43	0.82–2.33	0.17
< 80 years	11	6.1	1.80	0.90–3.21	0.064
< 70 years	7	2.1	3.37	1.36–6.94	0.006

Obs., observed number of cases; Exp., expected number of cases; SIR, standardised incidence ratio; CI, confidence interval.

second-degree relatives. In 5 of these 14 families the pedigree revealed a pattern of hereditary prostate cancer: 1 pedigree with 4 cases of prostate cancer in 2 successive generations, 2 pedigrees with 3 prostate cancer cases within a nuclear family, and 2 pedigrees with prostate cancer occurring in 3 successive generations. The mean age at diagnosis of prostate cancer in these 5 families was 63 years (69 years if the index cases were excluded), compared with 75 years in the population. Besides these 5 families, there was no pedigree indicating the existence of a dominantly inherited cancer susceptibility syndrome.

DISCUSSION

We studied the cancer incidence for first-degree relatives of men diagnosed with prostate cancer before the age of 51 years. As expected, there was an increased risk of prostate cancer in male first-degree relatives (SIR = 1.43), which was more pronounced for younger relatives (SIR 3.37 for first-degree relatives younger than 70 years at diagnosis). A similar age dependence has also been found by others [3–5, 7, 9]. The first-degree relatives' total incidence of malignant tumours was not different from the population's. This is in perfect agreement with previous studies of cancer risk for first-degree relatives of prostate cancer patients [9, 10, 13].

Our study showed no significantly increased risk of any non-prostatic malignant tumour for the first-degree relatives. However, as indicated by the wide confidence intervals, the power of the study did not permit exclusion of moderate risk increases. There have been reports of a slightly increased risk of brain tumours in families of prostate cancer patients [9, 13]. Others have reported an increased risk of prostate cancer for male first-degree relatives of colon and breast cancer patients [9, 14–16], and for men in families with hereditary breast and ovarian cancer [17–20]. In a study by Anderson and associates, the presence of a family member with prostate cancer significantly increased the risk of breast cancer for first-degree relatives of breast cancer patients [21]. These findings lead to the hypothesis of common environmental or genetic risk factors for these tumours. However, our study showed no connection between early onset prostate cancer and colorectal cancer, breast cancer or ovarian cancer. Besides the five families with hereditary prostate cancer, we found no evidence of any hereditary cancer syndrome in the studied families. The FDRs' breast cancer risk was even reduced. In a study of FDRs of prostate cancer patients by Goldgar and coworkers, there was a slightly increased risk of colorectal carcinomas, but the risks of breast and ovarian cancer were not increased [9]. Isaacs and associates and Mettlin and associates found no increased risk of tumours at these three sites [10, 13]. These negative findings are not in conflict with the observations of an increased risk of prostate cancer in families with hereditary breast and ovarian cancer. Since male carriers of breast and ovarian cancer susceptibility genes certainly contribute to only a small fraction of prostate cancer cases, they should not greatly influence the incidence of breast and ovarian cancer in studies of relatives of men with prostate cancer.

Considering our selection of cases diagnosed at a very early age, the SIR for prostate cancer in this study was surprisingly low. It is unlikely that any methodological bias caused the relatively low number of prostate cancer cases among the first-degree relatives. Since data were collected from registers only, selection bias and recall bias were eliminated. The Swedish Cancer Register is accurate [22], and it is unlikely that a significant number of prostate cancer cases among the first-degree relatives were not registered there. The method for calculation of the expected cancer incidence was based on data from the regional cancer register and has been used in several studies without giving suspicion of inaccuracy [23, 24]. Furthermore, the SIR for the total incidence of malignant tumours was close to one in our study, which is consistent with previous studies [9, 10, 13] and thus implies that our methods were correct.

In previous large population-based register studies, the relative risk of prostate cancer for male first-degree relatives of prostate cancer patients has ranged from 1.7 to 2.4 [3, 5, 9]. In these and other studies the risk increased even more for first-degree relatives of younger prostate cancer cases [3–5, 7, 9]. In the study by Carter and associates, the risk for first-degree relatives of patients diagnosed at the age of 50 years was twice as high as for first-degree relatives of cases diagnosed at the age of 70 years [11], and they calculated that hereditary prostate cancer accounted for 43% of the prostate cancer cases diagnosed before the age of 55 years. Based on these studies, we expected to find an SIR for prostate cancer of approximately 3–4 in our study (30–40 cases among the first-degree relatives), but it turned out to be only 1.43 (16 cases). Even the upper end of the 95% CI of the SIR (2.33) was less than our estimate. In only 5 families did the extended pedigree show a pattern of hereditary prostate cancer, according to its clinical definition [13]. In all 5 pedigrees, the proband's father was affected (i.e. 5 out of 58 families for which the father was included in the original analysis). It is likely that the predispositions for prostate cancer were inherited through the mother in as many families, and furthermore in some families with no affected brothers, thus making it difficult to find an autosomally dominant pattern in the pedigree. However, our data indicate that the prevalence of hereditary prostate cancer in these families of men with early onset prostate cancer was less than the 40–50% we had expected, based on the calculations made by Carter and associates [11]. A more likely figure would be 20–30%.

There are two possible explanations of this difference: either hereditary prostate cancer is less common in Southern Sweden than in the U.S.A., or hereditary prostate cancer is less likely to be diagnosed at an early age than reported by Carter and associates. Our ongoing prospective epidemiological studies favour the latter explanation, as do data from the study of Smith and associates, in which only 8% of the cases in 91 families with hereditary prostate cancer were diagnosed before the age of 55 years [12].

We conclude that the first-degree relatives of men with early-onset prostate cancer had more than a 3-fold increase in

the risk of developing prostate cancer before the age of 70 years, while their total cancer risk was not increased. This study did not support the assumption that dominantly inherited susceptibility is a major cause of early-onset prostate cancer.

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