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Familial prostate cancer from the Family-Cancer Database

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Abstract

The aim of this study was to calculate the familial risk for prostate cancer (PC) for different family relationships. PC was studied in the Swedish Family-Cancer Database, updated in 1999 to cover individuals born after 1934 with their biological parents, totalling 9.6 million persons. Cancer data were obtained from the Swedish Cancer Registry from 1958 to 1996 and included 1035 PC cases amongst offspring. 188 families were identified where a father and a son had PC, giving a familial standardised incidence ratio (SIR) of 2.44 (2.10–2.80). The proportion of familial cancers was 18.2% amongst all PC amongst sons. There were only 5 pairs of affected brothers, of which 3 had an affected father. Age of onset modified familial risks modestly; the highest SIR of 4.43 (1.40–9.17) was for sons diagnosed before 50 years of age when the father was diagnosed before 65 years of age. When analysed across sites, an association of PC in one generation and stomach, liver and skin cancer and myeloma in another generation was observed. The link was most consistent for skin cancer. No maternal site was associated with a son's PC, although the SIR of breast cancer was 1.22 (0.95–1.53). No increased risk of malignancy was observed in wives of affected men excluding any shared environmental effect for PC and female cancers.

Keywords: Familial risk; Age of onset; Sibs; Skin cancer; Heritable effect

1. Introduction

Prostate cancer (PC) (code 177 in the 7th revision of the International Classification of Diseases) is the most common male malignancy in developed countries [1]. It is a cancer of old men, the incidence peaking at 80–84 years of age in Sweden [2]. The late age of onset is probably a sign of the lack of strong predisposing factors for most forms of this disease. Indeed, apart from androgenic hormones, family history and ethnic differences no other established risk factors are known. However, the large global differences in incidence suggest a role for environmental factors [1,3–5]. The familial effects, defined as a risk of PC to a first-degree relative of a PC proband, have been consistently observed in epidemiological studies [6–9]. Yet many early case–control studies showed familial risks that exceeded those later observed in cohort studies [8,10], which may be an indication of biases in the case–control studies. The segregation analyses have shown an autosomal dominant mode of inheritance but other evidence from affected brothers in families with unaffected fathers is consistent with an X-linked or recessive mode of inheritance [11]. A recent linkage study on prostate cancer families has provided evidence on genetic heterogeneity. The families with the highest numbers of affected members (5.1/family) and the youngest mean age of onset (64.1 years) showed linkage to chromosome 1 in 30% of cases, whereas the families with the lowest numbers of affected members (3.2/family) and the oldest age of onset (68.2 years) showed linkage to the X chromosome in 15% of cases [11]. Assuming that the former locus is dominant and the latter recessive, the disease would be transmitted from both parents in the former and only from mothers in the latter case. Whether the dominant gene predisposes to cancers other than prostate, and whether the putative recessive gene would carry a risk in heterozygous mothers are emerging epidemiological questions.

We have reported earlier from the nationwide Swedish Family-Cancer Database that PC had a familial risk of 2.3 amongst 14 identified father–son pairs [12,13]. The database offers unique possibilities for reliable estimation of familial risks, because the data on family relationships and cancers were obtained from registered

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sources of practically complete coverage [12,14]. The database covers two generations, parents and offspring. Here we use the 1999 update of the database, covering 9.6 million individuals in a country with a population of 8.8 million. The number of familial cases of PC increased from 14 to 188 father–son pairs when the oldest possible age of sons increased from 54 to 61 years. The familial risk for PC is calculated for different family relationships and for discordant cancers. Furthermore, we consider the possibility of maternal transmission of the disease allele.

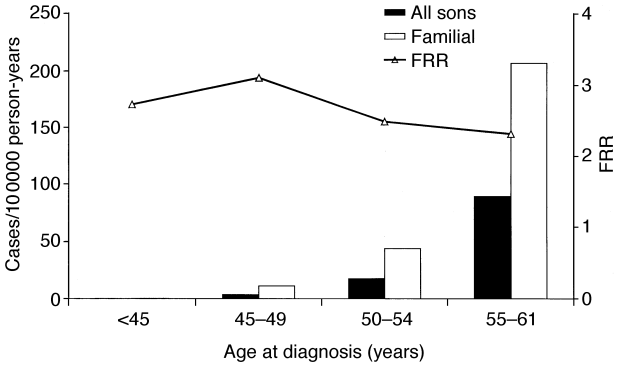

Fig. 1. Incidence of PC in all sons and in those with affected fathers (left scale) and familial relative risk (right scale) by age at diagnosis.

2. Patients and methods

The Swedish Family-Cancer Database, updated in 1999, includes persons born in Sweden after 1934 with their biological parents, totalling over 9.6 million individuals [12,15]. Cancers were retrieved from the nationwide Swedish Cancer Registry from 1958 to 1996. In the 1999 update, the number of invasive cancers in the second generation, 'offspring', increased from 50 000 to 92 000. A 4-digit diagnostic code according to the 7th revision of the International Classification of Diseases (ICD-7) was used. ICD code 177 was used for PC. In most analyses both the first and the second PC were considered combined. The following ICD-7 codes were pooled: 'oral' cancer codes 161 (larynx) and 140–148 (lip, mouth, pharynx), except for code 142 (salivary glands), 'lymphoma' codes 200 (non-Hodgkin's lymphoma), 201 (Hodgkin's disease) and 202 (reticulosis), and 'leukaemia' codes 204–207 (leukaemias), 208 (polycytaemia vera) and 209 (myelofibrosis). Rectal cancer, ICD-7 code 154 was separated for anus (squamous cell carcinoma, 154.1) and mucosal rectum (154.0). Basal cell carcinoma of the skin is not registered in the Cancer Registry.

Age-specific incidence rates in offspring and parents were calculated by the 5-year diagnosis ages. Parents' ages were not limited. Standardised incidence ratios (SIRs) were calculated as the ratio of observed (O) to expected (E) number of cases. The expected numbers were calculated from age- and sex-standardised rates [16]. Confidence intervals (95% CI) were calculated assuming a Poisson distribution [16].

3. Results

In the Database there were 76 447 parents and 1035 offspring with PC; there were 188 affected father–son pairs. Thus 18.2% of affected sons also had an affected father. There were 5 affected pairs of brothers, of whom 3 had an affected father and 2 of these a mother with colon cancer; the third father had additionally a squamous cell skin cancer. Amongst the 2 affected brother pairs whose father was unaffected, the mother of 1 pair had cancer of the nervous system. The dependence of the familial risk of PC on the age of onset is shown in Fig. 1. The incidence rate of familial and all PC increased steeply with age but the familial relative risk (FRR) remained quite stable, at and below 3.0. The modification of sons' SIR for PC by paternal diagnostic age is shown in Table 1. The highest SIR of 4.43 (1.40–9.17) was observed for sons diagnosed before age 50 years when fathers were diagnosed before age 65 years. The lowest SIR was 2.34 (2.00–2.71) in the oldest diagnostic age groups.

The risks of PC in sons associated with any cancer in fathers, and the risks of any cancer in sons associated with fathers' PC are shown in Table 2, by diagnostic age

Table 1
Standardised incident ratio (SIR) for prostate cancer in sons by age at diagnosis

Paternal age at diagnosis of prostate cancer (years)	Son's age at diagnosis (years)								
	< 50			50–61			All ages		
	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
< 65	5	4.43	(1.40–9.17)	19	3.30	(1.98–4.95)	24	3.49	(2.23–5.02)
⩾65	24	2.73	(1.75–3.93)	140	2.29	(1.92–2.68)	164	2.34	(2.00–2.71)
Total	29	2.92	(1.96–4.08)	159	2.37	(2.02–2.76)	188	2.44	(2.10–2.80)

O, Observed cases; CI, confidence interval.

Table 2
Standardised incidence ratio (SIR) for prostate cancer associated with paternal cancer and for cancer associated with paternal prostate cancer

Cancer site	Son's age at diagnosis of prostate cancer associated with paternal cancer (years)						Son's age at diagnosis of cancer associated with paternal prostate cancer (years)					
	< 50			All ages			< 50			All ages		
	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
Stomach	2	0.74	(0.07–2.12)	30	1.29	(0.87–1.80)	45	1.81	(1.32–2.38)	56	1.61	(1.22–2.06)
Colon	1	0.36	(0.00–1.40)	19	0.88	(0.53–1.32)	71	1.17	(0.92–1.46)	93	1.02	(0.82–1.23)
Rectum	0			11	0.79	(0.39–1.32)	33	1.11	(0.76–1.52)	57	1.02	(0.77–1.30)
Liver	1	0.95	(0.00–3.72)	8	0.96	(0.41–1.75)	24	1.66	(1.07–2.40)	29	1.48	(0.99–2.07)
Pancreas	0			11	1.07	(0.53–1.80)	18	1.22	(0.72–1.84)	24	1.12	(0.72–1.61)
Lung	7	1.81	(0.72–3.41)	19	0.68	(0.41–1.02)	53	0.99	(0.74–1.28)	68	0.88	(0.69–1.11)
Breast	0			2	4.89	(0.46–14.00)	4	2.62	(0.68–5.81)	5	1.83	(0.58–3.79)
Prostate	29	2.92	(1.96–4.08)	188	2.44	(2.10–2.80)	29	2.92	(1.96–4.08)	188	2.44	(2.10–2.80)
Testis	0			1	2.43	(0.00–9.54)	142	0.86	(0.72–1.01)	148	0.86	(0.73–1.01)
Kidney	2	1.40	(0.13–4.01)	11	1.06	(0.52–1.77)	45	1.04	(0.76–1.37)	76	1.11	(0.88–1.38)
Urinary bladder	3	1.11	(0.21–2.72)	16	0.81	(0.46–1.25)	65	1.02	(0.79–1.29)	114	1.03	(0.85–1.22)
Melanoma	1	1.46	(0.00–5.73)	6	1.50	(0.54–2.94)	162	0.99	(0.84–1.14)	203	0.95	(0.82–1.08)
Skin	6	3.56	(1.28–6.98)	11	0.84	(0.42–1.41)	49	1.36	(1.01–1.77)	72	1.20	(0.94–1.49)
Nervous system	0			2	0.34	(0.03–0.96)	149	0.90	(0.76–1.05)	171	0.90	(0.77–1.04)
Lymphoma	1	0.81	(0.00–3.18)	6	0.69	(0.25–1.35)	142	0.96	(0.81–1.12)	180	0.98	(0.84–1.13)
Myeloma	0			3	0.61	(0.11–1.48)	22	1.88	(1.17–2.74)	32	1.74	(1.19–2.39)
Leukaemia	2	1.68	(0.16–4.82)	10	1.12	(0.53–1.92)	84	1.02	(0.82–1.26)	100	1.01	(0.82–1.22)
All cancers	57	1.49	(1.13–1.90)	373	1.29	(1.16–1.42)	1403	1.04	(0.99–1.10)	1967	1.07	(1.02–1.12)

O, observed cases; CI, confidence interval.

< 50 years and at any age. The risk of all cancers was increased in most groups and increased SIRs were also observed for prostate cancer in all groups. Sons' risk of PC at age < 50 years was increased for skin cancer (squamous cell carcinoma in the Swedish Cancer Registry) as a paternal site, whereas in the all ages group no increases were observed. When analysis was by paternal PC, stomach, liver, skin cancer and myeloma had an increased SIR at diagnostic ages < 50 years, and SIRs for stomach cancer and myeloma were also increased in the all ages group. It may be worth pointing out that male breast cancer was in excess in both types of

Table 3
Standardised incidence ratio (SIR) for prostate cancer in sons associated with maternal cancer

Cancer site in mother	Age at diagnosis of prostate cancer in sons (years)								
	< 50			50–61			All ages		
	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
Stomach	0			10	0.88	(0.42–1.51)	10	0.79	(0.38–1.36)
Colon	3	1.06	(0.20–2.59)	18	0.84	(0.50–1.27)	21	0.87	(0.54–1.28)
Rectum	1	0.76	(0.00–2.97)	15	1.54	(0.86–2.42)	16	1.45	(0.83–2.25)
Liver	1	0.73	(0.00–2.87)	12	1.11	(0.57–1.82)	13	1.07	(0.57–1.72)
Pancreas	2	1.78	(0.17–5.10)	5	0.57	(0.18–1.19)	7	0.71	(0.28–1.34)
Lung	0			7	0.88	(0.35–1.64)	7	0.76	(0.30–1.42)
Breast	11	1.46	(0.72–2.45)	57	1.18	(0.90–1.51)	68	1.22	(0.95–1.53)
Cervix	1	0.66	(0.00–2.58)	7	0.76	(0.30–1.43)	8	0.74	(0.32–1.35)
Endometrial	3	1.63	(0.31–4.00)	14	1.21	(0.66–1.93)	17	1.27	(0.74–1.94)
Ovary	1	0.56	(0.00–2.20)	16	1.34	(0.77–2.08)	17	1.24	(0.72–1.90)
Kidney	1	0.88	(0.00–3.46)	12	1.46	(0.75–2.40)	13	1.39	(0.74–2.24)
Urinary bladder	2	2.59	(0.24–7.41)	4	0.71	(0.19–1.58)	6	0.94	(0.34–1.84)
Melanoma	0			5	1.22	(0.39–2.53)	5	1.05	(0.33–2.16)
Skin	0			9	1.22	(0.56–2.16)	9	1.09	(0.49–1.92)
Nervous system	1	0.96	(0.00–3.76)	5	0.74	(0.23–1.52)	6	0.77	(0.28–1.50)
Lymphoma	2	1.98	(0.19–5.67)	6	0.84	(0.30–1.65)	8	0.98	(0.42–1.78)
Myeloma	1	2.00	(0.00–7.82)	3	0.82	(0.15–2.01)	4	0.96	(0.25–2.13)
Leukaemia	1	1.14	(0.00–4.48)	9	1.35	(0.61–2.37)	10	1.32	(0.63–2.27)
All cancers	31	0.93	(0.63–1.29)	204	0.88	(0.76–1.01)	235	0.89	(0.78–1.01)

O, observed cases; CI, confidence interval.

analysis, showing a SIR for sons' PC of 4.89 ($n=2$, 0.46–14.00) associated with paternal breast cancer, and a SIR for sons' breast cancer of 1.83 ($n=5$, 0.58–3.79) associated with paternal PC.

An analysis of the SIR for sons' PC associated with maternal cancer showed no significant increases, even for sites that showed increases in the analysis of paternal sites (Table 3). The risks for all cancers were below unity. Maternal breast cancer showed a modest association with sons' PC with a SIR of 1.22 (0.95–1.53). In the group of sons diagnosed at age <50 years there was only one mother diagnosed for breast cancer at age <50 years and the SIR was 1.41 (data not shown).

We wanted to assess shared familial effects that might affect PC in husbands and any cancer in wives. This was done by calculating the cancer risks for wives associated with husbands' PC (Table 4). Data are shown for sites of >100 cancers. The results were surprisingly uniform, all SIRs ranging between 0.80 and 1.05 in the all ages group.

4. Discussion

PC is a disease of old men and the second generation of the Swedish Family-Cancer Database is just entering the critical age of PC. In the present analysis the number of father–son PC pairs has increased 10-fold since the previous analysis up to sons' age of 54 years [12,13]. Even the proportion of familial cases, i.e. affected sons with affected fathers, has increased from 11.5 to 18.2% [13]. However, the familial risk has remained fairly uniform, being currently 2.4 and previously 2.3. The age-specific incidence of PC has increased rapidly towards the older age groups of sons, but the familial relative risks have remained uniform (Fig. 1). When young parental diagnostic age was considered, the familial risk increased to 4.43 (1.40–9.17) (Table 1). These relative risks are among the lowest described in the literature to date [8,10]. However, the data from cohort studies have almost invariably shown lower risks than case-control studies, and the present results agree with the earlier cohort studies. Two of these have been carried out in Sweden and one in Utah [17]. In the Swedish studies, family relationships were established through parish offices, one for men diagnosed for PC between 1958 and 1963 and the other for men diagnosed in southern Sweden [8,9].

The differences between the case–control and cohort studies may reflect biased sampling in the former, also suggested for familial cancer studies at other sites [14,18]. However, PC may be particularly difficult for

Table 4
Standardised incidence ratio (SIR) for cancer in wives associated with husband's prostate cancer

Cancer site in wife	Age at diagnosis (years)											
	<50			50–69			$\geqslant 70$			All ages		
	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
Oral	10	0.71	(0.34–1.23)	83	0.82	(0.66–1.01)	88	0.97	(0.78–1.18)	181	0.88	(0.76–1.01)
Stomach	39	1.25	(0.89–1.68)	251	0.96	(0.84–1.08)	290	0.94	(0.84–1.06)	580	0.96	(0.89–1.04)
Colon	54	0.91	(0.68–1.16)	547	0.91	(0.83–0.98)	755	1.01	(0.94–1.08)	1356	0.96	(0.91–1.01)
Rectum	37	1.24	(0.88–1.68)	293	0.94	(0.84–1.06)	338	1.03	(0.92–1.14)	668	1.00	(0.92–1.08)
Liver	8	0.44	(0.19–0.80)	250	0.93	(0.81–1.04)	348	0.99	(0.89–1.09)	606	0.95	(0.87–1.02)
Pancreas	14	0.92	(0.50–1.47)	195	0.82	(0.71–0.94)	325	1.10	(0.98–1.22)	534	0.97	(0.89–1.05)
Lung	29	0.65	(0.43–0.90)	328	0.78	(0.70–0.86)	255	0.86	(0.76–0.97)	612	0.80	(0.74–0.87)
Breast	573	0.89	(0.82–0.97)	2350	0.94	(0.90–0.98)	1538	1.06	(1.01–1.12)	4461	0.97	(0.94–1.00)
Cervix	227	1.14	(1.00–1.30)	301	0.93	(0.83–1.04)	68	0.63	(0.49–0.79)	596	0.95	(0.87–1.02)
Endometrial	74	1.12	(0.88–1.39)	613	0.95	(0.87–1.02)	305	1.00	(0.89–1.12)	992	0.97	(0.92–1.04)
Ovary	116	1.00	(0.82–1.19)	597	1.01	(0.93–1.09)	301	1.12	(1.00–1.25)	1014	1.04	(0.98–1.10)
Female genital	8	0.80	(0.34–1.44)	57	0.86	(0.65–1.09)	80	0.92	(0.73–1.14)	145	0.89	(0.75–1.04)
Kidney	21	0.82	(0.51–1.21)	267	0.97	(0.86–1.09)	207	0.92	(0.80–1.05)	495	0.95	(0.86–1.03)
Urinary bladder	9	0.59	(0.27–1.05)	172	0.91	(0.78–1.06)	194	0.92	(0.79–1.05)	375	0.90	(0.81–1.00)
Melanoma	59	0.62	(0.47–0.79)	232	0.98	(0.86–1.11)	147	1.00	(0.85–1.17)	438	0.92	(0.83–1.00)
Skin	9	0.69	(0.31–1.22)	122	0.95	(0.79–1.12)	347	1.10	(0.98–1.21)	478	1.04	(0.95–1.14)
Nervous system	72	0.91	(0.71–1.13)	317	0.97	(0.87–1.08)	167	1.01	(0.86–1.17)	556	0.98	(0.90–1.06)
Thyroid	36	0.87	(0.61–1.18)	106	1.05	(0.86–1.26)	61	1.02	(0.78–1.30)	203	1.00	(0.87–1.15)
Endocrine glands	34	0.84	(0.58–1.15)	234	0.92	(0.81–1.04)	155	0.94	(0.80–1.09)	423	0.92	(0.83–1.01)
Connective tissues	15	1.13	(0.63–1.77)	50	0.93	(0.69–1.20)	45	0.97	(0.71–1.28)	110	0.97	(0.80–1.16)
Lymphoma	35	0.87	(0.60–1.18)	215	0.89	(0.77–1.01)	272	1.08	(0.96–1.21)	522	0.98	(0.89–1.06)
Myeloma	9	1.12	(0.51–1.98)	103	0.95	(0.78–1.14)	143	1.13	(0.96–1.33)	255	1.05	(0.93–1.19)
Leukaemia	22	0.74	(0.46–1.08)	194	0.98	(0.85–1.12)	187	0.92	(0.79–1.06)	403	0.94	(0.85–1.03)
All cancers	1587	0.92	(0.88–0.97)	8322	0.93	(0.91–0.95)	7152	1.01	(0.99–1.03)	17061	0.96	(0.95–0.98)

O, observed cases; CI, confidence interval.

the case–control approach because of its late onset. Also, it may be difficult to guard against over-presentation of multi-case families because these are proportionately more frequent in random sampling. Most case–control studies are based on interview data at diagnosis and relatives and the accuracy of reporting may be another concern. In a recent study on prostate cancer reporting bias was studied by comparing the interview data with medical records [19]. Self-reported cases of PC were accurate in 99.8% of cases but breast cancers in other family members were accurate only in 68% of cases; this degree of false reporting would seriously bias risk estimates.

Currently at least four susceptibility loci have been described for PC, three on chromosome 1 and one on the X chromosome, all with penetrance of 50% or more. In addition, a number of polymorphisms with a much lower penetrance have been described [20,21]. In the present population of 188 father–offspring pairs, 3 were from the same families, i.e. included affected brothers. There were only 2 families with affected brothers and an unaffected father. The former pattern fits with a dominant and the latter a recessive mode of inheritance. However, with the relatively young population, penetrance may be incomplete. Thus, the present data are not informative on the possible role of X-linked inheritance as suggested by linkage analysis [11]. In the earlier case–control studies, it has been shown that the number of affected family members influences the risk. It is of interest that in a twin study of cancer, PC showed the highest heritability of 36% amongst all cancers [22]. In twin studies the risk estimates are solely based on comparisons between siblings and would thus cover both recessive and dominant effects. The high heritability in the twin study and the intermediary risk in father–son comparisons would be consistent with the operation of both recessive and dominant effects in PC.

Very few other cancer sites were associated with an increased PC risk in this study. Increased SIRs for PC in fathers and stomach, liver and squamous cell skin cancer and myeloma in sons were observed but only the association with skin cancer emerged consistently when comparing fathers with sons, and sons with fathers. PC is not commonly presented as a second malignancy after squamous cell skin cancer [23,24] and there are no obvious common risk factors for these two cancers. Although both cancers are in excess in immunosuppressed organ transplantation patients, the risks are much higher for squamous cell skin cancer than for PC in these patients. In the present study, PC was in no way associated with typical malignancies of immunosuppressed patients, such as lymphomas [25]. A common property of squamous cell skin cancer and PC is that they have a very high mean age of onset; the highest incidence of skin cancer in Sweden is at ages over 85 years, higher than for PC [2]. Intriguingly, another cancer that is associated with PC, stomach cancer, is also a late onset cancer. Older patients may have a depressed immune function and this may be a cofactor in these cancers that occur later in life [4]. The present study did not confirm associations of PC with cancers of the colon, rectum, breast and lymphatic system observed in Utah and other studies [17]. However, the study is not conclusively negative on breast cancer: mothers of sons with PC had a small excess of breast cancer (SIR 1.22, 0.95–1.53) and there was some indication of male breast cancers, suggesting involvement of *BRCA2* because carriers of *BRCA2* mutations have an excess of prostate cancer [26].

There was no increased risk of malignancy in wives of affected men excluding any shared environmental effect for PC and female cancers. In fact, the SIRs were surprisingly close to unity at all the sites considered. This is an interesting point considering the decades of shared life that the couples have lived. This finding has two implications. Firstly, that prostate cancer may have no environmental risk factors, such as diet, contributing to the development of female cancers [1] and/or heritable factors may contribute to the familial effects observed. These could include the suggested candidate loci on chromosomes 1 and X [11,19–21] and the as yet unidentified commoner genes.

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