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Familial testicular cancer and second primary cancers in testicular cancer patients by histological type

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Abstract

The Swedish Family-Cancer Database was used to assess familial cancer risks in first-degree relatives and the risks of second primary cancers in testicular cancer patients by the histological type of their testicular cancers. Standardised incidence ratios (SIRs) were employed to estimate cancer risks. Among 4650 patients, 1.3% were familial testicular cancer. Seminomas showed a 10 years later median age of onset than teratomas (30 versus 40 years). The familial risks of testicular cancer were 3.8 for fathers, 8.3 for brothers and 3.9 for sons; they were similar for the two histologies. The fraternal risks were elevated 2- to 2.8-fold for pure histologies compared with the mixed histologies. Significantly increased risks for subsequent cancers were observed in the stomach, pancreas, testis, kidney, bladder, thyroid and connective and lymphatic tissues in the patients. Our data support the contention that genetic predisposition is one of the major contributors to familial and multiple testicular cancers. © 2001 Published by Elsevier Science Ltd.

Keywords: Familial history; Testicular cancer; Seminoma; Teratoma; Second cancer; Follow-up study; First-degree relative

1. Introduction

Testicular cancers are predominantly germ cell tumours of two main histological types, seminomas and teratomas [1]. However, some 60% of germ cell tumours of the testis contain multiple histological types and only 40% contain a single histological type [2]. Despite the fact that testicular cancer accounts for only 1% of all male malignancies, it is the most common solid malignancy affecting males between the ages of 15–35 years. There are marked racial differences in the incidence; for example in USA, the incidence is four times higher among white compared with black men [1]. The incidence of testicular cancer has increased 2 to 4 times in white populations, including Sweden, over the past 40 years [3]. There is some evidence that the increase is a cohort effect [4]. Cryptorchidism, testicular atrophy, infertility and some perinatal factors are the identified risk factors for testicular cancer [5–8]. The risk of seminoma was increased in dizygotic compared with monozygotic twins, which was interpreted as a tumorigenic effect of prenatal oestrogens [9]. Family history of testicular cancer is another well-known risk factor [10–12]. In the Swedish Family-Cancer Database the risk among sons of affected fathers was 4.1, the second highest familial risk among all main cancer sites studied [13]. Based on several *ad hoc* studies, the risk of testicular cancer is higher among brothers than among fathers and sons [14,15]. A segregation analysis favoured a recessive model of inheritance under all assumptions tested for testicular cancer [16]. A candidate locus for testicular cancer of both main histological types was recently mapped on the X chromosome [17]. However, most of these studies have not assessed the effects of the histological type.

In contrast to the pattern for incidence rates, testicular cancer mortality rates are now declining in most populations examined. Testicular cancer has in fact become one of the most curable of all solid tumours [18]. This has led to a raised concern about the long-term side-effects of treatment. However, few population-based studies have been conducted to assess the risks of second primary neoplasms by taking into account histological type of testicular cancer in the patients [19].

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Here, we aimed to examine the familial risks of testicular cancer and risks of second primary cancer in testicular patients according to the histological type of testicular cancer, based on data from the nationwide Swedish Family-Cancer Database. The database includes a population of 9.6 million and is the largest dataset ever used for family studies [20]. As the information about family relationships and cancers, verified pathologically or cytologically, was obtained from registered sources of practically complete coverage lacking recall bias and diagnostic misclassification, the dataset offers unique possibilities for reliable risk estimation.

2. Patients and methods

This study was conducted using the Swedish Family-Cancer Database updated in 1999, formed from the Second Generation Register maintained by Statistics Sweden and linked by the individually unique national registration number to the Swedish Cancer Register at the National Board of Health and Welfare. The Database includes all persons born in Sweden after 1934 with their biological parents, totalling over 9.6 million individuals [20,21]. The Database has a gap among those born between 1935 and 1940 who died before 1997. These individuals lack links to parents in the Database and this probably causes a deficit of some 10 000 cancer cases. The effect is somewhat inflated risk estimates for fatal cancers. All patients with an initial testicular cancer diagnosed between 1 January 1958 and 31 December 1996 and their male first-degree relatives and mothers were retrieved from the Database.

The site of cancer is registered based on a four-digit diagnostic code according to the 7th revision of the International Classification of Diseases (ICD-7). The following ICD-7 codes were pooled: 'upper aerodigestive tract' 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 (polycythemia 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.

The standardised incidence ratio (SIR) was used to estimate cancer risk in the subjects. Each patient was counted individually even in families of two affected brothers. For familial cancer, person-years at risk were accumulated from the date of birth, or 1 January 1958, whichever came first to the date of diagnosis of a first primary cancer, date of death, date of emigration, or 31 December 1996, whichever came first. For second primary cancer, person-years at risk were accumulated for each testicular cancer patient from the date of the first diagnosis and ending with the date of diagnosis of a second primary cancer, date of death, date of emigration, or 31 December 1996, whichever occurred first. SIRs were calculated by dividing observed cases by expected cases derived from site-, sex-, age (5-year age band)-, period (5-year calendar)-, residence (large cities versus the rest)- and occupation (farmer, worker, professional and the rest)-specific rates in the corresponding general population in the Database. Residential area and occupation were considered in analysis to allow for possible treatment-related and socio-economic effects. Confidence intervals (95%CIs) for SIRs were calculated assuming that the cases followed a Poisson distribution [22]. Adjustment for dependence was done in the calculation of 95% confidence intervals (CIs) for risks among brothers [13].

3. Results

Table 1 reports the characteristics of testicular cancer patients by histological type. Among 4650 patients, 51% (2385/4650) were seminoma and 46% (2135/4650) teratoma. Other unspecific type only accounted for 3%. A total of 1.3% (62/4650) were familial testicular cancers. No difference in the age at diagnosis was found between familial and sporadic cases even by histological type. None of 42 patients with multiple testicular cancers had a family history of testicular cancer in first-degree relatives, but multiple testicular cancer cases showed an earlier mean age of onset than sporadic cases, by 8 years for seminomas and 4 years for teratomas. Overall, seminoma showed a 10 years later median age of onset than teratoma (40 versus 30), but had a larger proportion with second primary cancers (8.4% versus 3.4%). Second primary cancers developed an average of 14.3, 12.8 and 5.3 years after the first diagnosis of seminoma, teratoma and other testicular cancers, respectively. The histological type group 'other' was not included in any of the subsequent tables due to the small number of cases.

Table 2 shows familial SIR in men by histological type of testicular cancer in first-degree relatives. The familial risks were very close in sons by father and in fathers by son between both the pure histological types and mixed histologies. Compared with the risk between father–son (3.9) and son–father (3.8), the risk was higher between brothers (8.3), increasing the overall SIR to approximately 2-fold. The fraternal risks were elevated 2- to 2.8-fold for the pure histologies compared with the mixed histologies. The fraternal risk was somewhat higher for seminoma–seminoma (13.1) than for teratoma–teratoma (10.0).

Table 3 presents cancer risks in families of men by histology of testicular cancer. A few sites showed a

Table 1
Characteristics of patients with an initial primary testicular cancer[a]

Characteristics	Histological type			
	Seminoma	Teratoma	Other	Any
No. of patients	2385	2135	130	4650
Familial cases[b]	31	29	2	62
Sporadic cases	2354	2106	128	4588
Multiple cases[c]	19	22	1	42
Person-years of follow-up	28478	21829	1011	51319
Average length of follow-up (years)	11.9	10.2	7.8	11.0
Average age at 1st diagnosis (years)	40	30	41	35
Familial cases	40	28	31	34
Sporadic cases	39	29	41	35
Multiple cases	31	25	32	27
No. of second primary cancers	201	72	7	280[d]
Percent with second cancer (%)	8.4	3.4	5.4	6.0
Average interval between the 1st and 2nd diagnosis (years)	14.3	12.8	5.3	13.7

[a] Person-years at risk for second primary cancer.
[b] Patients had a first-degree relative with testicular cancer.
[c] Both first and second primary cancers were testicular cancers.
[d] One second pancreas cancer had a first-degree relative with testicular cancer.

weak association with seminoma and teratoma, giving a slight increased risk for all cancers (for both, SIR = 1.2, 95% CI: 1.1–1.4). For seminoma, a significantly increased risk was found for pancreatic cancers (SIR = 1.7, 95%CI: 1.0–2.7) and nervous system cancers (SIR = 1.7, 95%CI: 1.1–2.6). For teratoma, no significantly increased risk was found for non-testicular cancers.

Table 4 shows cancer risks in mothers of patients with testicular cancer. A similar analysis was not carried out for sisters or daughters because these have far fewer cancers in the Database. For seminoma and teratoma, cancer risks at most sites in mothers showed a similar pattern (increasing or decreasing), except for rectal, pancreatic cancer and lymphatic tissue. Mothers with a son affected with any testicular cancer were at significantly increased risk for cancer of the lung (1.9), non-endometrium uteri (2.6) and connective tissue (2.5) and melanoma (1.8). It was noteworthy that among 19 mothers with two sons affected with testicular cancer, two had colon adenocarcinoma (SIR = 23.6, 95% CI: 2.1–83.2) and one had rectal adenocarcinoma (SIR = 24.0, 95%CI: 0.0–137) and 16 had no cancer.

Table 2
Risk of testicular cancer by histological type of testicular cancer in first-degree relatives[a]

Familial testicular cancer		Histological type of testicular cancer in men					
		Seminoma		Teratoma		Any	
By family member	Histological type	O	SIR 95% CI	O	SIR 95% CI	O	SIR 95% CI
Father to son	Seminoma	3	3.6 (0.7–10.7)	4	3.4 (0.9–8.8)	7	3.4 (1.4–7.1)
	Teratoma	1	2.7 (0.0–15.7)	3	5.4 (1.0–15.9)	4	4.2 (1.1–11.0)
	Any	4	3.2 (0.8–8.3)	8	4.5 (1.9–8.9)	12	3.9 (2.0–6.8)
Brother	Seminoma	14	13.1 (7.0–24.3)	5	4.7 (1.7–13.3)	20	9.2 (5.4–15.4)
	Teratoma	5	4.7 (1.7–13.3)	12	10.0 (5.1–19.6)	17	7.4 (4.2–12.9)
	Any	20	9.2 (5.5–15.5)	17	7.4 (4.2–13.0)	38	8.3 (5.7–12.2)
Son to father	Seminoma	3	3.4 (0.6–10.2)	1	2.9 (0.0–16.7)	4	3.2 (0.8–8.2)
	Teratoma	4	3.3 (0.9–8.6)	3	5.2 (1.0–15.4)	8	4.3 (1.8–8.6)
	Any	7	3.3 (1.3–6.9)	4	4.3 (1.1–11.1)	12	3.8 (2.0–6.7)
First-degree relative	Seminoma	20	7.2 (4.4–11.2)	10	3.9 (1.8–7.2)	31	5.6 (3.8–8.0)
	Teratoma	10	3.8 (1.8–7.0)	18	7.7 (4.6–12.2)	29	5.7 (3.8–8.2)
	Any	31	5.6 (3.8–8.0)	29	5.8 (3.9–8.3)	62	5.7 (4.4–7.4)

[a] O, observed cases; SIR, standardised incidence ratio; CI, confidence interval.

Table 3
Cancer risks in men by histological type of testicular cancer in first-degree relatives

Site of cancer in men	Histological type of testicular cancer in first-degree relatives					
	Seminoma		Teratoma		Any	
	O	SIR 95% CI	O	SIR 95% CI	O	95% CI
Upper aerodigestive tract	12	1.1 (0.6–1.9)	13	1.3 (0.7–2.2)	25	1.1 (0.7–1.7)
Stomach	18	1.0 (0.6–1.6)	19	1.3 (0.8–2.0)	37	1.1 (0.8–1.5)
Colon	20	1.0 (0.6–1.5)	22	1.2 (0.7–1.8)	42	1.0 (0.7–1.4)
Rectum	19	1.3 (0.8–2.1)	15	1.1 (0.6–1.9)	35	1.2 (0.9–1.7)
Liver	3	0.4 (0.1–1.1)	7	1.0 (0.4–2.1)	10	0.7 (0.3–1.2)
Pancreas	16	1.7 (1.0–2.7)	9	1.0 (0.5–2.0)	25	1.4 (0.9–2.0)
Lung	41	1.3 (0.9–1.8)	33	1.1 (0.8–1.6)	74	1.2 (0.9–1.5)
Prostate	71	1.1 (0.8–1.3)	67	1.1 (0.9–1.5)	138	1.1 (0.9–1.3)
Testis	31	5.6 (3.8–8.0)	29	5.7 (3.8–8.2)	62	5.7 (4.4–7.4)
Kidney	11	0.9 (0.4–1.6)	9	0.8 (0.4–1.5)	20	0.8 (0.5–1.3)
Urinary bladder	21	1.0 (0.6–1.5)	26	1.3 (0.9–1.9)	48	1.1 (0.8–1.5)
Melanoma	10	0.9 (0.4–1.6)	13	1.2 (0.6–2.0)	25	1.1 (0.7–1.6)
Skin	9	0.8 (0.4–1.6)	7	0.7 (0.3–1.5)	16	0.8 (0.4–1.3)
Nervous system	23	1.7 (1.1–2.6)	17	1.3 (0.8–2.2)	40	1.5 (1.1–2.1)
Thyroid	4	2.0 (0.5–5.2)	2	1.1 (0.1–3.9)	6	1.5 (0.5–3.3)
Endocrine	8	1.8 (0.8–3.6)	6	1.4 (0.5–3.1)	14	1.6 (0.9–2.6)
Connective tissue	4	1.4 (0.4–3.7)	1	0.4 (0.0–2.2)	6	1.1 (0.4–2.4)
Lymphoma	19	1.3 (0.8–2.0)	15	1.1 (0.6–1.8)	34	1.2 (0.8–1.7)
Myeloma	3	0.6 (0.1–1.8)	7	1.6 (0.6–3.3)	10	1.1 (0.5–1.9)
Leukaemia	13	1.1 (0.6–1.9)	11	1.0 (0.5–1.9)	24	1.1 (0.7–1.6)
Any cancer	391	1.2 (1.1–1.4)	353	1.2 (1.1–1.4)	753	1.2 (1.1–1.3)

O, observed cases; SIR, standardised incidence ratio; CI, confidence interval.

Table 4
Cancer risks in mothers of testicular cancer patients

Cancer site in mothers	Histological type of testicular cancer in patients					
	Seminoma		Teratoma		Any	
	O	SIR 95% CI	O	SIR 95% CI	O	SIR 95% CI
Upper aerodigestive tract	1	0.4 (0.0–2.1)	2	0.8 (0.1–2.9)	3	0.6 (0.1–1.7)
Stomach	6	0.7 (0.3–1.6)	5	0.7 (0.2–1.7)	11	0.7 (0.4–1.3)
Colon	26	1.4 (0.9–2.1)	19	1.2 (0.7–1.8)	46[a]	1.3 (1.0–1.7)
Rectum	14	1.6 (0.9–2.7)	6	0.7 (0.3–1.6)	19[b]	1.1 (0.7–1.7)
Liver	7	0.8 (0.3–1.7)	7	1.0 (0.4–2.0)	14	0.9 (0.5–1.5)
Pancreas	11	1.6 (0.8–2.8)	5	0.8 (0.3–1.9)	16	1.2 (0.7–1.9)
Lung	16	1.6 (0.9–2.6)	21	2.1 (1.3–3.2)	39	1.9 (1.4–2.6)
Breast	77	1.2 (0.9–1.5)	75	1.1 (0.9–1.4)	158	1.2 (1.0–1.4)
Cervix	11	0.8 (0.4–1.5)	13	0.9 (0.5–1.6)	24	0.9 (0.6–1.3)
Endometrium	13	0.8 (0.4–1.4)	15	1.0 (0.5–1.6)	29	0.9 (0.6–1.3)
Uteri, other	4	2.1 (0.5–5.4)	5	2.6 (0.8–6.0)	10	2.6 (1.2–4.7)
Ovary	16	1.0 (0.6–1.7)	17	1.1 (0.6–1.8)	35	1.1 (0.8–1.6)
Kidney	7	1.0 (0.4–2.0)	5	0.8 (0.2–1.8)	13	0.9 (0.5–1.6)
Urinary bladder	4	0.8 (0.2–2.0)	3	0.6 (0.1–1.9)	7	0.7 (0.3–1.4)
Melanoma	13	1.9 (1.0–3.2)	12	1.5 (0.8–2.7)	26	1.8 (1.1–2.6)
Skin	6	1.2 (0.4–2.6)	5	1.1 (0.4–2.6)	11	1.1 (0.6–2.0)
Nervous system	9	1.0 (0.5–2.0)	9	1.0 (0.5–1.9)	18	1.0 (0.6–1.6)
Thyroid	4	1.3 (0.3–3.3)	3	0.9 (0.2–2.6)	8	1.2 (0.5–2.4)
Endocrine	8	1.2 (0.5–2.4)	12	1.8 (0.9–3.1)	20	1.5 (0.9–2.3)
Connective tissue	4	2.5 (0.7–6.5)	4	2.5 (0.7–6.5)	8	2.5 (1.1–4.9)
Lymphoma	12	1.7 (0.9–2.9)	5	0.7 (0.2–1.7)	17	1.2 (0.7–1.9)
Myeloma	4	1.2 (0.3–3.2)	5	1.8 (0.6–4.1)	9	1.5 (0.7–2.8)
Leukemia	9	1.5 (0.7–2.9)	8	1.5 (0.6–2.9)	17	1.5 (0.9–2.4)
Any cancer	302	1.2 (1.1–1.3)	270	1.1 (1.0–1.2)	588	1.2 (1.1–1.3)

O, observed cases; SIR, standardised incidence ratio; CI, confidence interval.

[a] Two colon cancer-affected mothers had two sons with seminoma, giving a SIR = 23.6, 95% CI: 2.1–83.2.

[b] One rectal cancer-affected mother had one son with seminoma and another with teratoma, giving a SIR = 24.0, 95% CI 0.0–137.

Table 5 reports the risks of second primary cancers following seminomas by follow-up time. The highest risk of second testicular cancer was found within <1 year of follow-up, probably due to the intensive medical surveillance. There was a similar overall risk for second testicular seminoma (11.7) or teratoma (12.3). A significantly elevated overall SIR was found for second primary cancer at colon (1.9), pancreas (3.8), kidney (2.2), urinary bladder (2.4), thyroid (5.4) and lymphatic tissue (2.5). Second gastric and lung cancers showed an increased risk with a borderline significance. Among all these sites except for kidney and lymphatic tissue, a lower SIR was seen in the 1–9-year interval than in the 10–38-year interval.

Table 6 shows the risks for a second cancer after teratoma. The SIRs were very high for second testicular seminoma and teratoma within the first year of follow-up, but the SIRs were similar for the two histological forms throughout the follow-up time. Compared with the 1–9-year interval, the 10–38-year interval showed an increase in the SIRs regardless of testicular cancer histology. At other sites, only second connective tissue cancer showed a significantly increased overall risk ($n=3$, SIR = 6.4, 95% CI: 1.2–19.0) and the larger effect was seen in follow-up period of 1–9 years.

4. Discussion

The early age of onset and high familial risk of testicular cancer suggest that genetic components and childhood exposures, possibly even those occurring *in utero*, may be important aetiological factors for testicular cancer [23,24]. The fact that testicular cancer consists of two major histological subgroups, seminomas and teratomas, with an obvious different age–incidence distribution, suggests that some different risk factors may be involved in the two forms of testicular cancer [25]. An underlying genetic susceptibility may also be expressed as the occurrence of multiple testicular neoplasms and as high rates of urogenital developmental anomalies in patients with testicular cancer [26,27]. Based on these hypotheses, we conducted the present study on histology-specific testicular cancers using Swedish Family-Cancer Database. Cancer cases were obtained from the Swedish Cancer Registry, allowing a long-term follow-up (up to 38 years) for second cancers after an initial testicular cancer.

The overall familial risks of testicular cancer observed in this study were 3.8 for fathers, 8.3 for brothers, 3.9 for sons, respectively. These SIRs are comparable to those reported in the literature, which have been around

Table 5
Risks of second primary cancers following testicular seminomas

Site of second cancer	Follow-up interval (years)							
	<1		1–10		10–38		All	
	O	SIR 95% CI	O	SIR 95% CI	O	SIR 95% CI	O	SIR 95% CI
Upper aerodigestive tract	1	0.7 (0.0–3.7)	3	1.0 (0.2–3.0)	4	0.9 (0.2–2.3)		
Stomach	2	13.0 (1.2–47.7)	1	0.6 (0.0–3.2)	7	2.0 (0.8–4.1)	10	1.8 (0.9–3.4)
Colon	1	5.1 (0.0–29.4)	4	1.6 (0.4–4.1)	11	2.0 (1.0–3.5)	16	1.9 (1.1–3.1)
Rectum			2	1.2 (0.1–4.3)	5	1.2 (0.4–2.9)	7	1.2 (0.5–2.4)
Liver					4	1.9 (0.5–4.9)	4	1.3 (0.3–3.4)
Pancreas			2	1.8 (0.2–6.5)	12	4.9 (2.5–8.6)	14	3.8 (2.1–6.4)
Lung			4	1.0 (0.3–2.7)	15	1.7 (0.9–2.7)	19	1.4 (0.9–2.3)
Prostate	1	1.9 (0.0–10.6)	7	1.1 (0.4–2.3)	17	0.9 (0.5–1.4)	25	0.9 (0.6–1.4)
Testis	11	102 (50.8–183)	5	4.8 (1.5–11.2)	3	6.2 (1.2–18.3)	19	11.6 (7.0–18.1)
Seminoma	5	74.5 (23.5–175)	5	7.3 (2.3–17.2)	3	8.3 (1.6–24.7)	13	11.7 (6.2–20.1)
Teratoma	6	155 (56.0–340)	6	12.3 (4.4–26.9)				
Kidney	3	25.1 (4.7–74.2)	3	1.8 (0.3–5.3)	5	1.6 (0.5–3.7)	11	2.2 (1.1–4.0)
Urinary bladder			3	1.1 (0.2–3.4)	19	3.0 (1.8–4.7)	22	2.4 (1.5–3.7)
Melanoma			1	0.5 (0.0–2.6)	5	1.5 (0.5–3.5)	6	1.0 (0.4–2.3)
Skin	1	9.9 (0.0–56.7)	1	0.8 (0.0–4.7)	3	1.0 (0.2–2.9)	5	1.1 (0.4–2.7)
Nervous system			1	0.5 (0.0–2.9)			1	0.2 (0.0–1.2)
Thyroid	1	39.9 (0.0–228)	1	3.1 (0.0–18.0)	2	5.1 (0.5–18.8)	4	5.4 (1.4–14.1)
Endocrine			1	1.3 (0.0–7.3)	3	2.7 (0.5–8.0)	4	2.0 (0.5–5.3)
Connective tissue			1	2.5 (0.0–14.4)	1	1.7 (0.0–9.8)	2	2.0 (0.2–7.3)
Lymphoma			6	2.9 (1.0–6.3)	8	2.3 (1.0–4.6)	14	2.5 (1.3–4.1)
Myeloma	1	22.2 (0.0–127)			1	0.8 (0.0–4.4)	2	1.0 (0.1–3.8)
Leukaemia	1	9.4 (0.0–54.1)	3	2.2 (0.4–6.6)	1	0.4 (0.0–2.4)	5	1.3 (0.4–3.1)
Any cancer	22	7.3 (4.6–11.0)	49	1.3 (0.9–1.7)	130	1.6 (1.3–1.9)	201	1.6 (1.4–1.9)

O, observed cases; SIR, standardised incidence ratio; CI, confidence interval.

Table 6
Risks of second primary cancers following testicular teratomas

Site of second cancer	Follow-up interval, years							
	<1		1–9		10–38		All	
	O	SIR 95% CI	O	SIR 95% CI	O	SIR 95% CI	0	SIR 95% CI
Upper aerodigestive tract								
Stomach					4	3.5 (0.9–9.1)	4	2.4 (0.6–6.2)
Colon					1	0.5 (0.0–3.1)	1	0.4 (0.0–2.2)
Rectum					3	2.2 (0.4–6.6)	3	1.6 (0.3–4.8)
Liver					1	1.5 (0.0–8.7)	1	1.1 (0.0–6.3)
Pancreas					2	2.5 (0.2–9.1)	2	1.8 (0.2–6.6)
Lung					5	1.7 (0.5–4.1)	5	1.3 (0.4–3.0)
Prostate	1	7.8 (0.0–44.9)	2	1.7 (0.2–6.4)	2	0.4 (0.0–1.4)	5	0.8 (0.2–1.8)
Testis	12	121 (62.3–212)	5	4.5 (1.4–10.6)	5	8.8 (2.8–20.7)	22	12.4 (7.8–18.8)
Seminoma	6	153 (55.2–336)	3	5.2 (1.0–15.5)	3	7.8 (1.5–23.2)	12	12.1 (6.2–21.2)
Teratoma	6	103 (37.3–226)	2	3.9 (0.4–14.3)	2	11.6 (1.1–42.7)	10	13.4 (6.4–24.8)
Kidney			1	2.1 (0.0–11.9)	1	0.9 (0.0–5.0)	2	1.2 (0.1–4.4)
Urinary bladder			1	1.4 (0.0–8.2)	3	1.5 (0.3–4.4)	4	1.4 (0.4–3.7)
Melanoma			1	0.9 (0.0–5.3)	2	1.2 (0.1–4.5)	3	1.1 (0.2–3.2)
Skin			1	2.8 (0.0–16.0)	1	1.0 (0.0–5.8)	2	1.5 (0.1–5.3)
Nervous system					2	1.5 (0.1–5.6)	2	0.8 (0.1–3.0)
Thyroid								
Endocrine					1	1.9 (0.0–10.7)	1	1.1 (0.0–6.1)
Connective tissue			2	10.2 (1.0–37.4)	1	3.9 (0.0–22.6)	3	6.4 (1.2–19.0)
Lymphoma			1	1.0 (0.0–5.8)	4	2.7 (0.7–6.9)	5	2.0 (0.6–4.6)
Myeloma			1	6.3 (0.0–36.1)	1	2.3 (0.0–13.2)	2	3.3 (0.3–12.1)
Leukaemia			1	1.8 (0.0–10.3)	3	3.3 (0.6–9.7)	4	2.6 (0.7–6.8)
Any cancer	13	11.5 (6.1–19.6)	16	1.3 (0.7–2.0)	43	1.5 (1.1–2.0)	72	1.7 (1.3–2.1)

O, observed cases; SIR, standardised incidence ratio; CI, confidence interval.

10 for brothers and between 2 and 5 among fathers and sons [14,15,28]. In young twin brothers, the risk has been as high as 37.5 [9]. This obvious clustering of testicular cancer may be due to the shared risk factors, genetic and probably environmental, among family members. The higher familial risk for testicular cancer among brothers than father-son pairs is consistent with the idea that exposure to risk factors *in utero* may be involved in testicular cancer. An alternative or complementary hypothesis is that there is a recessive mode of inheritance or an X-linked susceptibility locus, explaining the high risk among brothers [13,29]. A further consideration is that the treatment for testicular cancers has markedly improved in the course of this study and many patients in the paternal generation have not survived their disease. Register-based studies have also many truncations in follow-up times, which may lead to unexpected effects.

The novel aspect of the present study was the separation of the histological types of testicular cancer. There was no large difference in familial risks between seminomas and teratomas among father-son pairs. However, there appeared to be a large difference in the familial risk between the pure and mixed histological types among brothers. The risks ranged from 10.0 (teratoma–teratoma) and 13.1 (seminoma–seminoma) for the pure histologies to 4.7 for the mixed histologies.

In families of testicular cancer patients, only seminoma was associated with the risk for other cancers, i.e. pancreatic and nervous system cancers. In mothers of testicular patients, the SIR was increased for lung, non-endometrium uteri and connective tissue cancers, and for melanoma, but no large differences were found for the histological subgroups. No oestrogen-related risks were observed in the mothers of testicular cancer patients in a Danish study [23]. Interestingly, in the nineteen families of our study with two sons affected with testicular cancer, two had mothers with colon adenocarcinomas (SIR = 23.6, 95% CI: 2.1–83.2) and one had a mother with rectal adenocarcinoma (SIR = 24.0, 95% CI: 0.0–137), but none had fathers with testicular cancer. However, there is no previous evidence on the association of testicular cancer and colorectal cancer. Because of multiple testing, some of the associations may be due to chance, in this and the next section.

The increased occurrence of second primary cancers after an initial primary may suggest that the first and the second cancers share environmental, hereditary and immunological factors, although there may also be treatment-induced effects among long-term survivors. It is sometimes impossible to distinguish second tumours as independent primaries; in the case of testicular cancer this may be particularly difficult because histology alone may not be helpful due to common multiple histologies

[2]. The Swedish Cancer Registry has clear instructions about the reporting of multiple primary malignancies and a re-evaluation of 209 multiple primary tumours found 98% of second malignancies to be correctly classified and only 2% were found to be recurrences [30]. The report of a second tumour with a different histology may suggest this is an independent primary cancer. However, because most testicular tumours show multiple histological types [2], some artificial shift in the histological types may take place in the reporting of first and second testicular cancers. Yet, the presentation of contralateral seminomas after teratomas, and *vice versa* is not uncommon in clinical practice [31].

We examined the occurrence of multiple primary cancers in the testis and other sites in testicular cancer patients by the histological type of the initial testicular cancer. For multiple testicular cancers, an overall risk of over 100 was seen within the first year of the initial diagnosis. The high risk is probably due to intensive medical surveillance, as has been observed in many other studies [32–35]. An 11- to 12-fold risk for any second testicular cancer was seen in patients with seminoma or teratoma; there was no difference for the histological types. For other sites, a significantly increased overall SIR was found for subsequent cancers of the colon, pancreas, kidney, urinary bladder, thyroid and lymphatic tissue in seminoma patients and for cancers of the connective tissue in teratoma patients. All these sites were increased in a large international study on long-term survivors of testicular cancer [19]. In this study, acute leukaemia showed the largest excess. In our series leukaemia was increased, particularly after teratoma, but the result was not significant. The SIRs increased over follow-up time at these sites, except for kidney and connective tissue. These data are in agreement with the previous reports suggesting an effect of treatment [19,36], but also leave room for speculation that seminomas may be a part in cancer aggregation. Teratomas showed an approximately 10 year earlier age of onset than seminomas, but only 3.4% of teratomas developed a second cancer, compared with 8.4% of seminomas, indicating some difference between seminomas and teratomas both in clinical management and in aetiology [36].

Knudson developed his two-hit theory on carcinogenesis on paired organs, kidney and eyes. According to the theory, patients who have a familial trait will develop bilateral cancers more frequently and at younger age than sporadic cases [37]. None of the 42 patients with multiple testicular cancers had a family history of testicular cancer in our series. Nor did our data show a difference in the age at diagnosis between familial and sporadic cases even by histological type. This was in accordance with a previous study from Denmark [15]. However, multiple testicular cancer cases showed an earlier mean age of onset than unilateral cases.

In summary, the present study supports the contention that genetic predisposition is one of the major contributors to familial and multiple testicular cancers and the hypothesis that there may be a recessive or X-linked mode of inheritance in the development of some testicular cancers. Although many familial effects and second cancer risks appear to be similar between seminomas and teratomas, the high familial risk among brothers with pure histologies, the patterns of other cancers in affected families, and subsequent cancers in testicular cancer patients suggest subtle differences between the two histologies.

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