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Original Paper

Familial Testicular Cancer in a Single-centre Population*

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Familial occurrence of testicular cancer suggests a genetic predisposition to the disease. A genetic susceptibility may also be reflected by the occurrence of bilateral testicular neoplasms and the high rates of urogenital developmental anomalies in families prone to testicular cancer. In this study, the proportion of familial testicular cancer cases was analysed retrospectively in a single-centre population of 693 testicular cancer patients treated between 1977 and 1997 and the relative risk (RR) for first-degree relatives of patients was estimated. In addition, the existence of bilateral testicular neoplasms and urogenital developmental anomalies in familial testicular cancer patients was evaluated. 24 of the 693 patients (3.5%) had a first-degree relative with testicular cancer. These 24 cases belonged to 17 families; in 7 of these 17 families both affected first-degree family members were part of the study population of 693 patients. Consequently, the 693 studied patients belonged to a total of 686 families. Thus, the actual proportion of familial testicular cancer was 2.5% (17 of 686 families). The familial cases consisted of 11 brother pairs, including 2 pairs of identical twins and 1 pair which also had two affected cousins, and 6 father–son pairs (in total 36 cases, 12 treated elsewhere). Estimates of the RR to first-degree relatives showed a 9- to 13-fold increased RR to brothers ($P < 0.001$) and a 2-fold increased RR to fathers (P = non-significant (n.s)) of testicular cancer patients. Among the 36 patients with familial testicular cancer, 2 (5.6%) had bilateral testicular cancer, 4 (11.1%) had undescended testis, 3 (8.3%) had inguinal hernia, and 1 (2.8%) showed renal hypoplasia. The present data on familial occurrence of testicular cancer may lend support to a role of genetic factors in the aetiology of testicular cancer. © **1999 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

UNDESCENDED TESTES (UDT) and an antecedent contralateral testicular neoplasm are well-known risk factors for the development of testicular cancer. A number of other predisposing factors such as inguinal hernia, atrophic testes, infertility, mumps orchitis, occupational exposure to polyvinyl chloride, and *in utero* exposure to oestrogens have been less consistently correlated with testicular cancer [1–4]. Recently, increasing attention has been paid to family history of testicular cancer as a potential risk factor in the aetiology of testicular malignancies. Numerous families with two or more first-degree relatives diagnosed with testicular cancer have been reported [5–16]. The prevalence of familial testicular cancer in these studies varies between 1.0 and 2.8% [6, 8, 10, 12–16]. Moreover, brothers of testicular cancer patients appear to have a 3- to 12-fold increased relative risk (RR) of developing a testicular neoplasm themselves [6, 10, 12, 14, 15]. The RR to fathers of testicular cancer patients is less pronounced and varies between 2 and 4 [12, 14]. The increased RR to brothers is higher than found for most other cancers and it is difficult to explain the magnitude of this risk elevation by shared environmental factors

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alone [17–20]. In general, familial occurrence of testicular cancer and an increased risk for male first-degree relatives of developing the same disease may be caused by shared environmental factors, genetic factors, or both. A genetic susceptibility to testicular cancer is emphasised by the occurrence of a second primary testicular neoplasm in 1–6% of all testicular cancer cases, which is higher than expected by chance alone [21–26]. In addition, higher rates of urogenital developmental anomalies such as UDT and inguinal hernia have been reported in families prone to testicular cancer which may also reflect a genetic predisposition to the disease [6, 16]. Several candidate genes that may play a role in testicular cancer development have been proposed [27–29].

In the present study, the proportion of familial testicular cancer in a single-centre population in the past two decades was analysed and the RR for first-degree male relatives of testicular cancer patients of developing a testicular malignancy themselves was estimated. In addition, the existence of bilateral testicular neoplasms and urogenital developmental anomalies in familial testicular cancer cases was evaluated and the possible role of genetic factors in the aetiology of testicular cancer is discussed.

PATIENTS AND METHODS

In the period January 1977 to December 1997, 693 patients with testicular cancer were treated at the Groningen University Hospital (GUH), The Netherlands. Of these patients, 540 were diagnosed with a non-seminomatous and 153 with a seminomatous testicular germ cell tumour. The difference between the total number of non-seminomas and seminomas is due to different referral patterns. Traditionally all patients diagnosed with a non-seminoma within a defined area of the comprehensive cancer centre in the northern part of The Netherlands (CCNN) (2.1 million inhabitants) are referred to the GUH for further management after having been hemi-orchidectomised at the local hospital. In contrast, the majority of patients diagnosed with a seminoma are referred to one of the three radiation facilities within the CCNN area (including the GUH) for radiation treatment. Patients with seminoma who have a positive family history of testicular cancer are not selectively referred to the GUH. The medical records of all 693 patients were reviewed for the presence of a family history of testicular cancer at diagnosis or during follow-up. The proportion of familial testicular cancer, defined as the presence of at least two affected first-degree relatives within one family, was analysed. When both affected first-degree members of a family belonged to the study population, adjustment was made for double ascertainment of these families.

Patients with familial testicular cancer were studied in detail and the following data were collected: age at diagnosis, histology, stage of disease, treatment and follow-up. Furthermore, information was obtained about the occurrence of bilateral testicular cancer and a history of UDT or other urogenital developmental anomalies. For affected family members not treated at the GUH, the diagnosis of testicular cancer was confirmed by collecting data from medical records in the hospitals where the treatment took place.

Differences in age at diagnosis between familial and non-familial testicular cancer cases were analysed by means of the Mann–Whitney U-test.

In addition to the proportion of familial testicular cancer, the RR was calculated to estimate the risk of testicular cancer associated with a first-degree relative having testicular cancer. Because insufficient data were available on the number of brothers and the vital status of first-degree relatives of testicular cancer cases, RRs were calculated using estimates of the mean number of brothers, and all first-degree relatives were considered to be alive at the time of analysis. The mean number of brothers of testicular cancer cases was estimated to be 0.50 and 0.75. These estimates were mainly based on the mean number of siblings per family in The Netherlands. In the 1980s and 1990s this mean number of siblings varied between 1.75 and 2.5 [30]. After adjustment for the number of mothers without sons and the number of probands without brothers, this mean number of siblings per family corresponded to an estimated figure for the mean number of brothers of testicular cancer cases somewhere between 0.50 and 0.75. Furthermore, all fathers and half of the brothers expected to develop testicular cancer were considered to have been diagnosed with the disease before the proband developed a testicular neoplasm.

The incidence rate for testicular cancer among the male population in the northern part of The Netherlands between 1989 and 1993 was 4.49 per 100 000 [31] and the overall death rate among the male population was 9 per 1000 [32]. Accurate incidence rates for testicular cancer were not available for the period before 1989. The figures for incidence and death rate were used to obtain the number of testicular cancer cases expected assuming a stable prevalence of the disease. RRs were calculated as the ratio of observed to expected numbers of testicular cancer. The precision of the RR estimates was assessed by calculating 95% confidence intervals assuming a Poisson distribution of the observed testicular cancer events.

RESULTS

24 of 693 patients (3.5%) had a first-degree relative with testicular cancer. These 24 familial cases belonged to 17 families, i.e. in 7 of these 17 families the affected first-degree family members were part of the study population of 693 patients. Consequently, these 693 patients belonged to a total of 686 families. Since this study deals with the proportion of affected families rather than the proportion of affected patients, the actual proportion of familial testicular cancer was 2.5% (17 of 686 families). The familial testicular cancer cases consisted of 11 brother pairs, including 2 pairs of identical twins and 1 pair which also had 2 affected cousins, and 6 father–son pairs. This results in a total number of 36 familial cases in the 17 affected families (Table 1). In 9 of 12 familial cases not treated at the GUH, diagnosis of testicular cancer was confirmed by information obtained from other hospitals. In 3 cases treated elsewhere, data on testicular cancer were irretrievable due to death of these patients in the past.

18 of 36 patients had non-seminoma as the primary tumour, 15 had seminoma, and for 3 deceased patients, the histology was unknown. Both bilateral cases had 2 seminomatous tumours. In 10 families with known histology, the cases involved had concordant histological types, the remaining 4 families with known tumour types showed discordant histology of testicular tumours.

The median age at initial diagnosis was 31.1 (range 19.0–70.7) years in 36 familial cases, and 30.8 (range 14.8–75.1) years in 669 patients without a family history of testicular cancer ($P = 0.50$). Age at presentation was also calculated separately for each histological type. For non-seminomas, the

Table 1. *Characteristics of familial testicular cancer cases (with an affected first-degree relative)*

	Proband					Relative with testicular cancer					
Family No.	Age at onset (year)	Histology	Stage	Outcome	Notes	Relative	Age at onset (year)	Histology	Stage	Outcome	Notes
1	33	NS	I	NED	—	MZ twin*	27	NS	II	NED	—
2	25	NS	II	NED	UDT	MZ twin	36	Sem	I	NED	Consanguinity father's parents (cousins)
3	29	NS	I	NED	—	Brother*	33	NS	I	NED	Inguinal hernia
4	25	NS	II	NED	—	Brother*	24	NS	I	NED	UDT
5	26	NS	II	NED	—	Brother*	29	Sem	II	DOD	—
6	25	NS	II	NED	—	Brother*	26	NS	IV	DOD	—
7	29	NS	IV	NED	—	Brother*	37	Sem	II	DOD	—
						Son of father's brother	38	NS	II	NED	—
						Son of mother's brother*	29	Sem	I	NED	Bilateral TC
8	36	Sem	I	NED	Bilateral TC	Brother*	54	Sem	I	NED	—
9	25	NS	II	NED	UDT	Brother	36	NS	II	NED	—
10	25	NS	II	NED	Inguinal hernia	Brother	26	NS	III	NED	Inguinal hernia
11	63	Sem	II	NED	—	Brother	21	Unknown	Unknown	DOD	—
12	33	NS	I	NED	—	Father	35	Sem	I	NED	—
13	41	Sem	I	NED	—	Father	19	Unknown	Unknown	DNED	—
14	60	Sem	I	NED	Hypoplastic kidney	Father	71	Sem	I	DNED	—
15	29	NS	III	NED	UDT	Father	41	Unknown	Unknown	DOD	—
16	42	Sem	I	NED	—	Father	47	Sem	I	NED	—
17	27	Sem	I	NED	—	Father	38	Sem	I	NED	—

NS, non-seminoma; Sem, seminoma; UDT, undescended testis; TC, testicular cancer; MZ, monozygotic; NED, no evidence of disease; DOD, died of disease; DNED, died, no evidence of disease. *Patients also treated at the Groningen University Hospital and part of the study population ($n = 693$).

median age at diagnosis was 26.8 (range 24.0–38.4) years in familial cases ($n = 18$) and 29.0 (range 14.8–74.2) years in non-familial cases ($n = 525$) ($P > 0.50$). For seminomas, the median age was 38.1 (range 27.3–70.7) years in familial cases ($n = 15$) and 40.6 (range 18.0–75.1) years in non-familial cases ($n = 144$) ($P > 0.50$).

Among the 36 patients with familial testicular cancer, 2 patients (5.6%) had bilateral testicular cancer and 4 patients (11.1%) had a history of UDT. In addition, 3 patients (8.3%) had a history of inguinal hernia and 1 patient (2.8%) with a left-sided testicular tumour showed hypoplasia of the left kidney.

In addition to the previously described 24 patients who had affected first-degree relatives, 15 other testicular cancer patients (2.2%) in our study population had a second- or third-degree relative with testicular cancer. These 15 patients belonged to 12 families (1.7%; 12 of 690) with a total number of 24 familial cases (9 cases treated elsewhere). Among these 24 patients with an affected second- or third-degree relative, 3 patients (12.5%) had bilateral testicular cancer, 4 patients (16.7%) had a history of UDT, and 1 patient (4.2%) had a history of inguinal hernia. One patient (4.2%) with antecedent UDT and a right-sided testicular tumour also demonstrated agenesia of the right kidney.

The RRs for testicular cancer in male first-degree relatives of testicular cancer cases are listed in Table 2.

DISCUSSION

Familial occurrence of testicular cancer is a well recognised but rare event. The present study is one of the largest studies analysing the proportion of familial testicular cancer and the association of this event with urogenital developmental anomalies and bilateral testicular cancer in a single-centre population. The actual proportion of familial testicular cancer of 2.5% in the current series is consistent with other studies, reporting familial clustering of the disease with affected first-degree relatives in 1.0–2.8% of cases [6, 8, 10, 12–16].

The proportion of familial testicular cancer in this series may have been influenced by the retrospective nature of the

Table 2. *Relative risks for testicular cancer in male first-degree relatives of testicular cancer patients*

Relative	Observed No. with testicular cancer	Expected No. with testicular cancer	RR	(95% CI)	*P*
Fathers	6	3.43	1.75	(0.64–3.81)	n.s.
Brothers*					
0.50	11	0.86	12.74	(6.38–22.64	<0.001
0.75	11	1.29	8.54	(4.27–15.24)	<0.001

n.s., not significant; RR, relative risk; CI, confidence interval. *Estimated mean number of brothers for a proband.

study. The proportion found could be slightly lower than the actual proportion of familial testicular cancer determined in a prospective study, in which data on family history of testicular cancer are recorded systematically in all patients. However, the figure for familial testicular cancer in the present retrospective series may be somewhat higher than in a prospective study because cases studied retrospectively are exposed much longer to the risk of having a relative with testicular cancer [15]. These relatives may not only develop a testicular neoplasm in the time before the cases from the present series were diagnosed, but also during the follow-up period of these cases.

In a recently reported large multicentric prospective study on familial testicular cancer by Dieckmann and Pichlmeier, the prevalence of familial testicular cancer with an affected first-degree relative was found to be 1.1% [15], which is not distinctively different from figures in the current and other retrospective studies [6, 8, 10, 12–14, 16]. In the present series, the histological diagnosis of family members treated for testicular cancer at other institutions was verified in the majority of cases. Ascertainment of histology in affected relatives most likely ensures a high reliability of the present data on familial aggregation of the disease.

According to risk estimates in the current study, brothers of testicular cancer cases appeared to have a 9- to 13-fold increased risk of developing a testicular neoplasm. The RR to fathers was only slightly increased. The finding that the increased familial risk was more pronounced between brothers than between fathers and sons is consistent with most previous studies. In these previous studies the magnitude of the RR elevation in brothers ranges from 3 to 12 [6, 10, 12, 14, 15]. It must be noted that the risk estimates in the current series were based on several assumptions with respect to the mean number of brothers and the vital status of male first-degree relatives of testicular cancer cases. These assumptions may inevitably have an impact on the reliability of the present data. However, because all first-degree relatives were considered to be alive at the time of analysis, the estimate of the expected incidence of testicular cancer in relatives is probably higher than the true expected incidence. Consequently, the RRs in the present study, calculated as the ratio of observed to expected numbers of testicular cancer, are most likely to represent minimum figures. The estimated risks to brothers, however, had wide confidence intervals, a finding also reported in most other studies. The current risk estimates for relatives of cases also have to be judged with some reserve as they were based on the mean number of siblings per family in the normal population. The fertility rate in families with testicular cancer, however, is most likely to be lower than in the normal population.

A significant proportion of men with testicular cancer have impaired spermatogenesis at diagnosis, i.e. before treatment, and infertility may represent a risk factor for the development of a testicular neoplasm [2, 33]. In addition, infertility may be caused by treatment for malignant disease. This treatment-induced infertility may result from retrograde ejaculation after retroperitoneal lymph node dissection or as a result of toxic effects of chemotherapy or radiotherapy on the germ cells of the remaining testis [34, 35]. The effect of treatment on fertility was probably more significant in the earlier years of the study, especially for non-seminomas. Nerve-sparing surgery, reduced toxicity of chemotherapy and improvements in radiotherapy have decreased the treatment-induced infertility rate in recent years [34, 36]. However, both pre-existent and treatment-induced infertility have affected the ability of testicular cancer cases in the parent generation to reproduce and, consequently, have influenced the mean number of male relatives at risk of developing a testicular neoplasm. The poorer survival in earlier years, in particular of non-seminomas, has also influenced the ability of cases to reproduce. Thus, reduced fertility of testicular cancer cases and higher mortality in former generations certainly had an effect on the familial occurrence of testicular cancer and the RR to male relatives. Therefore, the use of normal population data have to be judged with caution. Nevertheless, it seems clear that the risk to brothers of testicular cancer cases of developing the same disease is definitely increased. This risk is certainly higher than the RR to first-degree relatives in most common cancers, which usually varies between 2 and 3 [10, 18, 19]. RRs to siblings of cases exceeding a factor of 3 without implying some form of genetic susceptibility can only be due to shared environmental risk factors that are extremely potent [17]. Since such potent environmental risk factors have not been identified for testicular cancer so far, the magnitude of the RR to siblings of testicular cancer cases strongly suggests the involvement of genetic factors in the aetiology of testicular cancer [12]

For several cancers, including testicular cancer, age at diagnosis has been reported to be younger in familial cases compared with age at diagnosis of the same cancer in non-familial or sporadic cases [37]. This observation is in accordance with Knudson's two-hit model for tumorigenesis in patients with a familial predisposition to a certain cancer [38]. In the present series, the younger age in familial cases is not confirmed by comparison of all familial and all non-familial cases without considering histology. However, separate analysis of seminomas and non-seminomas showed a slight although not significant younger age at diagnosis in familial cases compared with non-familial cases for both histological subgroups. The lack of difference in age at diagnosis between all familial and all non-familial cases might partially be explained by the higher proportion of seminomas among familial cases with known histology (45%, 15 of 33) compared with the proportion of seminomas among non-familial cases (22%, 144 of 669). Because seminomas are commonly diagnosed at an older age than non-seminomas, the over-representation of seminomas among familial cases has resulted in a higher median age in the group of all familial cases compared with the group of all non-familial cases. This over-representation of seminomas in the familial group may have been influenced by the higher survival and better fertility after treatment of seminomas, mainly in former generations.

A higher proportion of bilateral disease in familial cases as compared with sporadic cases has been reported for cancer in paired organs (breast, eye, kidney), and underlines a genetic susceptibility to the disease [10, 15, 39]. In the current study, the occurrence of bilateral testicular cancer in 6% of familial cases with affected first-degree relatives is not different from the prevalence of bilateral tumours reported in 1–6% of general testicular cancer cases in the literature [21–26]. These data in the literature include an earlier series from the GUH which demonstrated the presence of bilateral testicular cancer in 3% of 365 general testicular cancer cases [25]. All of these 365 cases are also included in the current series in which they form more than half of the total study population. Thus, the proportion of bilateral testicular cancer in familial cases in the

present series seems not distinctively different from that reported previously in general cases at the same institution. In the current series, however, bilateral involvement of the testes was additionally present in 13% of familial cases with affected second- or third-degree relatives. It must be noted that bias in the ascertainment of second- and third-degree relatives with bilateral testicular cancer may have occurred as such cases with a notable history are more likely to be reported than cases without bilateral involvement. Consequently, the data on bilateral testicular cancer in second- and third-degree relatives have to be judged with some reserve.

In the current series, UDT and inguinal hernias were present in 11% and 8% of familial cases with affected first-degree relatives, respectively. In an earlier study at the same institution in the 1970s, a history of UDT and inguinal hernia has been reported in 5.2% and 3.4% of 230 general testicular cancer cases, respectively [40]. Although the proportions of both UDT and inguinal hernia seem to be slightly higher in the current familial cases compared with a historical group of general cases treated at the same institution, the figures in the current familial cases are not different from those reported in non-familial cases in the literature [1, 2]. However, in the present study UDT was additionally found in 17% of testicular cancer cases with affected second- or third-degree relatives, suggesting an association between UDT and familial occurrence of testicular cancer. As mentioned previously for bilateral testicular cancer, bias in ascertainment due to over-reporting of second- and third-degree relatives with UDT also may have occurred. Tollerud and colleagues reported a high prevalence of urogenital developmental anomalies, including UDT and inguinal hernias, in familial testicular cancer cases and their first-degree relatives. They suggested a relationship between urogenital maldevelopment and predisposition to testicular neoplasia. In addition, they proposed a mechanism in which abnormal migration of embryonic tissue results in an increased risk of developing testicular cancer, possibly influenced by hormones [6]. However, genetic factors could also account for the high frequency of urogenital developmental anomalies in families prone to testicular cancer.

In conclusion, the proportion of familial testicular cancer in a single-centre population was 2.5%. Brothers of testicular cancer cases had a minimum 9-fold increased RR of developing a testicular neoplasm. The findings in the present study may lend support to the involvement of genetic factors in the aetiology of testicular cancer, but also do not exclude a possible influence of shared environmental factors operating *in utero* such as exposure to maternal oestrogens. Further research is indicated to clarify the molecular genetic basis of testicular cancer and to identify potential susceptibility genes playing a role in the aetiology of the disease.

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