Familial risk in testicular cancer as a clue to a heritable and environmental aetiology

K Hemminki¹,² and X Li*,¹

¹Department of Biosciences at Novum, Karolinska Institute, 141 57 Huddinge, Sweden; ²Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 580, 69120 Heidelberg, Germany

We used the nation-wide Swedish Family-Cancer Database to examine the risk for testicular cancer in offspring through parental and sibling probands. Among 0–68-year-old offspring, 4082 patients had testicular cancer in years 1961–2000, among whom 68 (1.67%) had an affected father/brother. Standardized incidence ratios (SIRs) for familial risk were four-fold when a father and nine-fold when a brother had testicular cancer: Histology-specific risks (for the testicular cancer) were similar for sons of affected fathers, but were higher among brothers for teratoma and seminoma than for mixed histologies. Standardized incidence ratios for either histology depended on the age difference between the brothers: 10.81 when the age difference was less than 5 years compared to 6.69 for a larger age difference. Parental colorectal, pancreatic, lung and breast cancer and non-Hodgkin’s lymphoma and Hodgkin’s disease were associated with seminoma among sons. Seminoma risk was also increased when a sibling had melanoma. Teratoma was associated with parental lung cancer and melanoma. The high familial risk may be the product of shared childhood environment and heritable causes. Familial cases of fraternal pairs with an early-onset teratoma represent a challenge for gene identification.

SUBJECTS AND METHODS

Statistics Sweden maintains a ‘Multigeneration Register’ in which offspring, born in Sweden in 1932 and later, are registered with their parents (as declared at birth) and they are organized as families (Hemminki et al, 2001a). Information on the Database is available at the Nature Genetics website as ‘Supplementary information’ (Hemminki and Granstrom, 2002). The data on families and cancers have a complete coverage, barring some information (Hemminki et al, 2002) and they are organized as families (Hemminki and Li, 2002b; Hemminki et al, 2002). Among the sons of the Danish immigrants, an equally large but opposite change takes place (Hemminki and Li, 2002a).

*Correspondence: Dr X. Li, Department of Biosciences at Novum, Karolinska Institute, 141 57 Huddinge, Sweden; E-mail: xinjun.li@cnt.ki.se

Received 24 October 2003; revised 9 January 2004; accepted 19 January 2004; published online 16 March 2004

Keywords: testicular cancer; seminoma; teratoma; familial risk; genetics; hereditary
The registered site of cancer is as a four-digit diagnostic code based on the 7th revision of the International Classification of Diseases (ICD-7). The following ICD-7 codes were grouped: 'upper aerodigestive tract' cancer codes 161 (larynx) and 140–148 (lip, mouth, pharynx), except for code 142 (salivary glands), 'lymphoma' codes 200, 202 (non-Hodgkin lymphoma), 201 (Hodgkin's disease) and 'leukaemia' codes 204–207 (leukemias), 208 (polycytemia vera) and 209 (myelofibrosis). Rectal cancer, ICD-7 code 154, was subdivided into the anus (squamous cell carcinoma, 154.1) and mucosal rectum (154.0). Basal cell carcinoma of the skin is not registered in the Cancer Registry. Up to 1992, the histology of testicular cancers as in the Cancer Registry (WHO/HS/CANC/24.1 Histology Code) was used, to define seminoma (pathology codes 066) and teratoma (826, also including embryonal tumours). From 1993, ICD-0-2/ICD with histopathological data according to the Systematized Nomenclature of Medicine (SNOMED, http://snomed.org) was used, referred to here as 'SNOMED'.

Standardized incidence ratios (SIRs) were used to measure cancer risks for sons (i.e., offspring) according to the occurrence of cancers in their families. When more than two affected sons were found in any family, they were counted as independent events. Standardized incidence ratios were calculated for sons whose parents or brothers had the same, discordant cancer, that is, using parents or brothers as probands. Follow-up started for each offspring at birth, immigration or January 1, 1961, whichever came latest, and terminated on diagnosis of the first cancer, death, emigration, or the closing date of the study, December 31, 2000.

Parents’ ages were not limited but sons were 0–68 years of age. All tumour incidence rates were based on the data in the Family-Cancer Database, and they were essentially similar to rates in the Swedish Cancer Registry. Rates were standardized to the European population. Standardized incidence ratios were calculated as the ratio of observed (O) to expected (E) number of cases. The expected numbers were calculated from 5-year-age-, sex-, tumour type-, period- (5-year bands), socioeconomic status- (six groups) and residential area- (three groups) specific standard incidence rates for all sons lacking a family history (Esteve et al., 1994). Confidence intervals (95% CI) were calculated assuming a Poisson distribution (Esteve et al., 1994). Risks for siblings were calculated using the cohort method, described elsewhere (Hemminki et al., 2001b).

The kappa statistic was used as the measure of agreement between histologies: (observed number of cases – expected number of cases)/(1 – expected number of cases) (Armitage and Berry, 1994). The kappa can assume values between −1 and 1; 0 shows a complete chance occurrence and −1 or 1 show a completely determined occurrence. Values between 0.40 and 0.60 are considered moderately determined occurrences. A negative kappa value would, in the present context, indicate a determined occurrence of a discordant histology, which is biologically unlikely, so we present only positive values of kappa in this paper.

RESULTS

The Family-Cancer Database, which covered years 1961–2000 from the Swedish Cancer Registry, included 4082 testicular cancers in sons of ages 0–68 years and 3878 fathers with testicular cancer (Table 1). Seminoma accounted for 49.8% and teratoma 48.4% in sons, while in fathers the proportions were 39.1 and 38.2%, respectively. Seminoma showed a 6–8-year later median age of onset than teratoma (35 vs 27 in offspring and 39–33 in fathers). According to the SNOMED histology, covering years 1993–2000, embryonal carcinoma accounted for 14.8% in sons and 10.9% in fathers. The age-specific incidence rates of testicular cancer among sons are shown in Figure 1 according to the SNOMED histology. The peak incidence for teratoma and embryonal carcinoma occurred at ages 20–24 years, and for seminoma showed a peak incidence at 30–34 years.

Table 2 presents risks for the histological types among brothers according to their age difference. Those born less than 5 years apart had higher risks, particularly at ages over 24 years, but below age 25 for the teratoma showed no age difference.

Age- and histology-specific familial risk for testicular cancer was analysed using fathers or brothers as probands (Table 3). The overall SIRs were approximately two-fold higher between brothers (8.58) than between sons and fathers (3.78). The risks were slightly higher for unmixed histologies compared to the mixed histologies for all significant SIRs. Among brothers, the SIR for seminoma was 3.27, compared to 1.27 for all cases (data not shown).

Age-specific familial SIR for seminoma is shown in Figure 2A for sons of fathers and among brothers with testicular cancer; Figure 2B shows the curves for teratoma. The shapes of the curves for teratoma resemble each other independent of proband status, and those for all cases (data not shown).

We analysed using SNOMED histopathology, available only from 1993 (data not shown), that teratoma showed an age peak at 15–29 years in sons of fathers with testicular cancer (N = 3, SIR = 8.48, 95% CI 1.60–25.10). Among brothers, both SNOMED types showed peak SIRs at 30–44 years (seminoma, N = 10,
SIR = 11.74, 95% CI 5.59–21.68; teratoma, N = 5, SIR = 26.16, 95% CI 6.26–61.55). No familial cases were found for embryonal carcinoma.

Table 4 presents associations of testicular cancer with other cancers in families, including mothers and sisters. Both seminoma (1.19) and teratoma (1.13) were increased when parents had any cancer (only associations at discordant sites being considered). For seminoma, a significantly increased risk was found when parents had colorectal, pancreatic, lung and breast cancer and non-Hodgkin’s lymphoma and Hodgkin’s disease. Seminoma was also increased when a sibling (brother or sister) had melanoma. Teratoma was associated with parental lung cancer and melanoma. For testicular cancer as a whole, an increased risk was found when the mother was diagnosed with ‘other uterine tumours’ or the father with nervous system cancer; these uterine tumours included three leiomyosarcomas, two adenocarcinomas, two chorioncarcinomas, two embryonal sarcomas, one stroma cell sarcoma and two unspecified sarcomas. It was also noteworthy that there were three

Figure 1 Age-specific incidence of testicular cancer in offspring according to the SNOMED histology in years 1993–2000.

### Table 2

| Histological types | Age at diagnosis | O | SIR | 95% CI | O | SIR | 95% CI |
|--------------------|------------------|---|-----|--------|---|-----|--------|
| **Seminoma**       |                  |   |     |        |   |     |        |
| 0–24               | 1                | 11.49 | 0.00 | 65.89 | 0 | 6.81 | 3.38 |
| >24                | 14               | 10.62 | 5.79 | 17.87 | 11 | 6.40 | 3.18 |
| All                | 15               | 10.87 | 5.96 | 17.65 | 11 | 6.40 | 3.18 |
| **Teratoma**       |                  |   |     |        |   |     |        |
| 0–24               | 5                | 11.61 | 3.66 | 27.31 | 5 | 10.74 | 3.39 |
| >24                | 9                | 10.18 | 4.61 | 19.41 | 6  | 5.73 | 2.06 |
| All                | 14               | 10.65 | 5.80 | 17.91 | 11 | 7.27 | 3.61 |
| **All types**      |                  |   |     |        |   |     |        |
| 0–24               | 7                | 13.08 | 5.18 | 27.10 | 5 | 8.54 | 2.69 |
| >24                | 23               | 10.27 | 6.50 | 15.44 | 17 | 6.29 | 3.66 |
| All                | 30               | 10.81 | 7.29 | 15.45 | 22 | 6.69 | 4.19 |

Bold type: 95% CI does not include 1.00. O = observed; SIR = standardised incidence ratio; CI = confidence interval.

### Table 3

| Histological types in proband | Age at diagnosis | O | SIR | 95% CI | O | SIR | 95% CI | O | SIR | 95% CI |
|--------------------------------|------------------|---|-----|--------|---|-----|--------|---|-----|--------|
| **Seminoma**                   |                  |   |     |        |   |     |        |   |     |        |
| Paternal proband               |                  |   |     |        |   |     |        |   |     |        |
| Seminoma                       | 0–24             | 0 | 3.42 | 0.87  | 13.69 | 3  | 3.50 | 1.39  | 7  | 4.05 | 1.46 |
| >24                            | 4                | 3.52 | 0.92 | 14.76 | 3  | 3.6  | 0.68  | 10.66 | 7   | 4.05 | 1.46 |
| All                            | 4                | 3.18 | 0.83 | 8.23  | 6  | 4.05 | 1.46  | 8.87  | 10  | 4.05 | 1.46 |
| Teratoma                       | 0–24             | 0 | 3.64 | 1.63  | 25.58 | 3  | 7.2   | 1.36  | 21.32 | 5   | 8.45 | 2.19 |
| >24                            | 2                | 4.01 | 0.38 | 14.76 | 0  | 2.28 | 0.22  | 8.39  | 2   | 2.28 | 0.22 |
| All                            | 2                | 3.61 | 0.34 | 13.27 | 3  | 4.2  | 0.79  | 12.45 | 5   | 8.45 | 2.19 |
| All types                      |                  |   |     |        |   |     |        |   |     |        |
| Paternal proband               |                  |   |     |        |   |     |        |   |     |        |
| Seminoma                       | 0–24             | 0 | 3.53 | 1.27  | 7.73  | 3  | 2.42 | 0.46  | 7.15  | 9   | 3.02 | 1.37 |
| >24                            | 6                | 3.19 | 1.15 | 6.98  | 10  | 4.42 | 2.1   | 8.15  | 16  | 4.42 | 2.1 |
| All                            | 6                | 3.19 | 1.15 | 6.98  | 10  | 4.42 | 2.1   | 8.15  | 16  | 4.42 | 2.1 |
| Fraternal proband              |                  |   |     |        |   |     |        |   |     |        |
| Seminoma                       | 0–24             | 1 | 11.7 | 0    | 67.04 | 3  | 7.79 | 1.47  | 23.07 | 5   | 10.29 | 3.25 |
| >24                            | 15               | 9.65 | 5.38 | 15.95 | 6  | 6.11 | 2.2   | 13.38 | 21  | 8.15 | 3.03 |
| All                            | 16               | 9.75 | 5.56 | 15.88 | 9  | 6.58 | 2.98  | 12.55 | 26  | 8.49 | 5.54 |
| Teratoma                       | 0–24             | 0 | 6.88 | 3.12  | 13.12 | 9  | 9.95 | 4.51  | 18.98 | 18  | 8.02 | 4.74 |
| >24                            | 9                | 6.39 | 2.93 | 12.88 | 16  | 11.50 | 6.55  | 18.71 | 25  | 8.76 | 5.67 |
| All                            | 9                | 6.39 | 2.93 | 12.88 | 16  | 11.50 | 6.55  | 18.71 | 25  | 8.76 | 5.67 |
| All types                      |                  |   |     |        |   |     |        |   |     |        |

Bold type: 95% CI does not include 1.00. O = observed; SIR = standardised incidence ratio; CI = confidence interval.
Testicular cancer
K Hemminki and X Li

Figure 2  Age-specific SIR for histological type of testicular cancer in the offspring of paternal and fraternal probands: (A) seminoma; (B) teratoma. The numbers of cases are shown for each age group. * Shows that the 95% CI for the SIR did not include 1.00.

brothers had seminoma (SIR was 0.31. These are still low values, but the interpretation is difficult because of the relatively small number of cases. The lower kappa values between sons and fathers than between brothers may be due to a more defined disease phenotype within one generation than between two generations.

The higher familial risk for testicular cancer among brothers than father–son pairs may suggest the involvement of a recessive mode of inheritance or an X-linked susceptibility locus in the aetiology of testicular cancer, consistent with the segregation analysis and the gene-mapping findings (Heimdal et al., 1997; Rapley et al., 2000). Such results would point to the importance of the maternal lineage of inheritance and perhaps also maternally exerted environmental factors. The difference in SIR among brothers close in age (10.81) compared to those further apart (6.69) suggests environmental effects. Testicular cancer has been reported as the site with the highest proportion of childhood-shared environmental effects in a family study of all major cancers (Czene et al., 2002). Although both histological types showed the effect of age difference, the risks for early-onset teratoma appeared to be least influenced by the age difference. These results suggest that environmental factors during childhood and adolescence influence the risk of contracting a late-onset testicular cancer (Hemminki et al., 2002; Hemminki and Li, 2002b). Identifying these factors might explain the riddle of increasing incidence trends and also the difference between immigrants and their sons (Hemminki and Li, 2002a). On the other hand, the search for heritable effects should target brother pairs with an early-onset teratoma.

Age-specific familial risks of Figure 2 showed the highest risks for seminoma in the 40 s, for both brothers and son–father pairs. For teratoma, two discrete peaks were noted, particularly among brothers. The early-onset teratoma peak (20 – 24 years) coincided with its peak incidence, but the late-onset peak (35 – 39 years) occurred 15 years later and close to the peak paternal risk of seminoma. Based on the risks by age difference, the younger teratoma component may be the most heritable familial component, whereas the later component of teratoma and seminoma may have a strong environmental origin.

In families of seminoma patients, associations were found with colorectal, pancreatic, lung and breast cancer and non-Hodgkin’s lymphoma and Hodgkin’s disease among parents. Among brothers, there was an association with seminoma and melanoma. Teratoma was associated with parental lung cancer and melanoma. However, no association has been found for primary melanoma or lung cancer following first testicular cancer (Dong et al., 2001). Testicular cancer was associated with mothers’ unusual uterine...
tumours, including chorionepithelioma (SIR = 2.40, 95% CI 1.23–4.20). No oestrogen-related cancer risks were observed in mothers of testicular cancer patients in a Danish study (Kroman et al, 1996). In the 26 families in our study with two sons with testicular cancer, three had mothers with colorectal cancer (SIR = 7.49, 95% CI = 1.41–22.18), of whom two pairs of brothers had seminoma, giving SIR = 1.107 and 95% CI = 1.04–40.71. cFor all types of testicular cancer by father’s nervous system cancer, SIR = 1.50. 95% CI = 1.03–2.10.

In summary, the present study may offer some explanation to the inability in finding susceptibility genes for testicular cancer. The high familial risk may be the product of shared childhood environment and heritable causes and so may be difficult to untangle. Identifying any relevant environmental factors will be challenging but may explain some of the changes in testicular cancer incidence. For gene identification, fraternal pairs with teratoma below age 25 may be particularly useful.

ACKNOWLEDGEMENTS

The Family-Cancer Database was created by linking registers maintained at Statistics Sweden and the Swedish Cancer Registry.
Heimdal K, Olsson H, Tretli S, Flodgren P, Borresen AL, Fossa SD (1996) Familial testicular cancer in Norway and southern Sweden. *Br J Cancer* 73: 964–969

Heimdal K, Olsson H, Tretli S, Fossa SD, Borresen AL, Bishop DT (1997) A segregation analysis of testicular cancer based on Norwegian and Swedish families. *Br J Cancer* 75: 1084–1087

Hemminki K, Czene K (2002) Attributable risks of familial cancer from the Family-Cancer Database. *Cancer Epidemiol Biomarkers Prev* 11: 1638–1644

Hemminki K, Granstrom C (2002) Risk for familial breast cancer increases with age. *Nat Genet* 32: 233

Hemminki K, Li X (2002a) Cancer risks in Nordic immigrants and their offspring in Sweden. *Eur J Cancer* 38: 2428–2434

Hemminki K, Li X (2002b) Cancer risks in second-generation immigrants to Sweden. *Int J Cancer* 99: 229–237

Hemminki K, Li X (2003) Familial risk of cancer by site and histopathology. *Int J Cancer* 103: 105–109

Hemminki K, Mutanen P (2001) Birth order, family size, and the risk of cancer in young and middle-aged adults. *Br J Cancer* 84: 1466–1471

Hemminki K, Li X, Czene K (2002) Cancer risks in first-generation immigrants to Sweden. *Int J Cancer* 99: 218–228

Hemminki K, Li X, Plna K, Granstrom C, Vahttinen P (2001a) The nationwide Swedish Family-Cancer Database: updated structure and familial rates. *Acta Oncol* 40: 772–777

Hemminki K, Vaittinen P, Dong C (2001b) Sibling risks in cancer: clues to recessive or X-linked genes? *Br J Cancer* 84: 388–391

Jacobsen R, Bostofte E, Engholm G, Hansen J, Olsen JH, Skakkebaek NE, Moller H (2000) Risk of testicular cancer in men with abnormal semen characteristics: cohort study. *BMJ* 321: 789–792

Kroman N, Frisch M, Olsen JH, Westergaard T, Melbye M (1996) Oestrogen-related cancer risk in mothers of testicular-cancer patients. *Int J Cancer* 66: 438–440

Kumar V, Cotran R, Robbins S (1997) *Basic Pathology*. Philadelphia: W.B. Saunders

Moller H, Skakkebaek NE (1997) Testicular cancer and cryptorchidism in relation to prenatal factors: case–control studies in Denmark. *Cancer Causes Control* 8: 904–912

Rapley EA, Crockford GP, Teare D, Biggs P, Seal S, Barfoot R, Edwards S, Hamoudi R, Heimdal K, Fossa SD, Tucker K, Donald J, Collins F, Friedlander M, Hogg D, Goss P, Heidenreich A, Ormiston W, Daly PA, Forman D, Oliver TD, Leahy M, Huddart R, Cooper CS, Bodmer JG, Easton DF, Stratton MR, Bishop DT (2000) Localization to Xq27 of a susceptibility gene for testicular germ-cell tumours. *Nat Genet* 24: 197–200

Swerdlow AJ, De Stavola BL, Swanwick MA, Macnochlie NE (1997) Risks of breast and testicular cancers in young adult twins in England and Wales: evidence on prenatal and genetic aetiology. *Lancet* 350: 1723–1728

Westergaard T, Andersen PK, Pedersen JB, Frisch M, Olsen JH, Melbye M (1998) Testicular cancer risk and maternal parity: a population-based cohort study. *Br J Cancer* 77: 1180–1185

Westergaard T, Olsen JH, Frisch M, Kroman N, Nielsen JW, Melbye M (1996) Cancer risk in fathers and brothers of testicular cancer patients in Denmark. A population-based study. *Int J Cancer* 66: 627–631