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Platinum Priority – Testis Cancer

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Cancer Risk in Relatives of Testicular Cancer Patients by Histology Type and Age at Diagnosis: A Joint Study from Five Nordic Countries

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Abstract

Background: None of the population-based epidemiologic studies to date has had a large enough sample size to show the familial risk of testicular cancer (TC) by age at diagnosis for patients and their relatives or for rare histologic subtypes.
Objective: To estimate absolute and relative risks of TC in relatives of TC patients by age at diagnosis in patients and their relatives and histological subtypes.
Design, setting, and participants: In a joint population-based cohort study, 97 402 first-degree relatives of 21 254 TC patients who were diagnosed between1955 and 2010 in five European countries were followed for cancer incidence.
Outcome measurements and statistical analysis: Standardized incidence ratios (SIRs) were estimated using histology-, age-, period-, and country-specific incidence rates as references. Lifetime cumulative risks were also calculated.
Results and limitations: The lifetime cumulative risk of TC in brothers of a patient with TC was 2.3%, which represents a fourfold increase in risk (SIR 4.1, 95% confidence interval [CI] 3.6–4.6) compared to the general population. TC in a father increased the risk by up to twofold in his son (95% CI 1.7–2.4; lifetime risk 1.2%) and vice versa. When there were two or more TC patients diagnosed in a family, the lifetime TC risk for relatives was 10–11%. Depending on age at diagnosis, twins had a 9–74% lifetime risk of TC. Family history of most of the histologic subtypes of TC increased the risk of concordant and most discordant subtypes. There was a tendency toward concordant age at diagnosis of TC among relatives.
Conclusions: This study provides clinically relevant age-specific cancer risk estimates for relatives of TC patients. Familial TC patients tended to develop TC at an age close to the age at diagnosis of TC among their relatives, which is a novel finding of this study.
Patient summary: This joint European population study showed that sons and brothers of testicular cancer patients are at higher risk of developing this cancer at an age close to the age at diagnosis of their relatives.

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1. Introduction

Testicular cancer (TC) is one of the most common cancers in young men between the ages of 15 and 44 yr, especially in Nordic countries [1]. Numerous reports have detailed the rapid and general increase in incidence rates in many European countries over the last few decades [2–5]. In spite of substantial heterogeneity in the rates, it has been predicted that the vast majority of European countries will face an increasing TC burden over the next two decades [6].

TC germ cell tumors are broadly separated into two groups, seminomas and nonseminomas, each accounting for approximately 50% of cases [7]. Nonseminoma tumors consist of several different histologic subtypes (embryonal cell carcinoma, yolk sac tumor, choriocarcinoma, and teratoma), each displaying a different stage of embryonic or extra-embryonic differentiation with varying tumor marker profiles. Teratoma, composed of two or more embryonic cell layers, lacks the potential to metastasize but can sometimes transform into a somatic malignancy (ie, sarcoma) and exhibit aggressive behavior [7]. TC histology is an important issue because each subtype has its own distinct clinical behavior and therefore requires a different treatment approach.

Risk factors for developing TC include age, race and ethnicity, and family history. The disease mainly affects young white Caucasian populations [8]. Cryptorchidism, occupational exposure (firefighting and aircraft maintenance), environmental exposure to organochlorine pesticides, disorders of sexual development, in utero hormonal exposure, viral (Epstein-Barr virus, cytomegalovirus, parvovirus B19, and human immunodeficiency virus) infections, subfertility or infertility, testicular carcinoma in situ, and previous history of TC are also potential predisposing factors [9–13].

Family history is a risk factor for which advice and management may bring both medical and psychosocial benefits. However, to provide evidence-based advice, counselors and caregivers along the entire medical referral system chain need to be aware of the true familial risks, particularly for cancers such as TC that are not covered by the current familial risk management guidelines.

A few population-based epidemiologic studies have reported the familial relative risk for histologic subtypes of TC, but none had a large enough sample size to analyze less common histologic subtypes, familial associations between histologic subtypes, or the risk stratified by age in detail [14–17]. In the present study, a pooled set of nationwide family cancer data from five countries in northern Europe with a high degree of comparability and validity [18] was used to systematically and comprehensively quantify the risk of TC in relatives of TC patients by age and histology at diagnosis of patients and their relatives. Such a risk quantification is lacking in the literature because of sample size limitations and the rarity of some histologic subtypes.

2. Patients and methods

Our large data set consisted of pooled population-based family cancer data from five Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden, with unbiased genealogical and high-quality cancer data), representing a total population of nearly 25 million. Sweden is the largest, with a population slightly greater than 9 million. Denmark, Finland, and Norway all have populations around 5 million, while Iceland has approximately 300 000 inhabitants. More than 150 000 incident cancers are diagnosed in the Nordic countries each year, nearly 60 000 cancer deaths are reported, and almost 1.1 million residents alive at the end of 2011 had at least one diagnosis of cancer. In general, differences among the Nordic cancer registries are minor and the pooled data can be used safely for cancer studies [13]. Information on all TC patients in this large data set (n = 21 254) and their first-degree relatives (n = 97 402) was used for this study. The Nordic countries have population-based registers through which any TC patient can be identified with the cancer status (and histologic subtype) in their fathers, brothers, or sons. With the exception of Iceland (with complete genealogical information for all subjects), sibships could only be ascertained in the offspring generation (those with identified fathers). International Classification of Diseases for Oncology version 3 (ICD-O-3) was used to identify histologic subtypes of TC: seminoma (M9061.3, M9062.3, and M9063.3), nonseminomatous germ cell tumor (M9065.3), embryonal carcinoma (M9070.3), yolk sac tumor (M9071.3), choriocarcinoma (M9100.3 and M9101.3), teratoma (M9080.3, M9081.3, M9083.3, and M9084.3), and mixed germ cell tumor (M9085.3). We also studied other rare histologic subtypes, such as Leydig cell (M8650.3), Sertoli cell (M8640.3), sarcomas, and other specified tumors (M8590.3, M8140.3, M8240.3, M8620.3, M9050.3, M9060.3, and M9072.3). However, these did not include any familial cases. Familial TC was defined as two TC patients in a family. The data characteristics for each country are shown in Supplementary Table 1.

2.1. Statistical analyses

Standardized incidence ratios (SIRs) were used to compare the cancer risks for individuals with identified fathers and a family history of cancers in their relatives compared to the risk in their counterparts in the general population. Follow-up was started for fathers of TC cases at the birth of the TC child; for sons and brothers it was started at birth, immigration, or on January 1 of the country-specific registration start year (1955, 1961, 1967, or 1968; Supplementary Table 1), whichever came latest. Follow-up was terminated at the diagnosis year of the first primary cancer, death, emigration, or the country-specific closing date of the study, (December 31, 2008, 2009, or 2010; Supplementary Table 1). SIRs were calculated as the ratio of observed to expected numbers of cases (indirect method of standardization). The age- (5-yr bands), period- (5-yr bands), cancer site-, morphology-, and country-specific incidence rates in the background population provided by the cancer registries were used as the reference groups (strata-specific cancer incidence rate in the background population). The expected numbers were calculated as the strata-specific cancer incidence rate in the background population multiplied by the corresponding person-years value for subjects with a family history of TC in the study population. We calculated 95% confidence intervals (CIs) assuming a Poisson distribution. SAS version 9.3 (SAS Institute, Cary, NC, USA) was used for the data analysis.

The lifetime cumulative risk (assumed to be 0–79 yr based on the average life expectancy in Nordic countries, 78.5 years in 2010) [19] was calculated according to the following formulas: age-specific annual incidence rate = number of cases for each 5-yr age group divided by person-years for that age group (0–4, ..., 75–79 yr); age-specific cumulative rate = 5 × age group–specific annual incidence rate; lifelong cumulative rate = sum of all age-specific cumulative rates; and lifelong cumulative risk = 1 – exp (– lifelong cumulative rate). To avoid bias in cumulative risk calculation towards overestimation due to ignorance of competing causes of death, exact values for person-years from