Short Communication

Germ-Cell Testicular Cancer in Offspring of Finnish Immigrants to Sweden

Scott M. Montgomery,[1] Fredrik Granath,[1] Anna Ehlin,[1] Pär Sparén,[2] and Anders Ekbom[1]

[1]Clinical Epidemiology Unit, Department of Medicine, Karolinska Hospital and [2]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

Abstract

Variation in testicular cancer incidence can be used to assist in identification of risks. Finland has a significantly lower germ-cell testicular cancer risk than Sweden. Finns who immigrate to Sweden maintain their lower risk irrespective of age at immigration. We investigated difference in risk between Finland and Sweden by examining germ-cell testicular cancer incidence in males born in Sweden to Finnish immigrant parents. Swedish general population registers were used to identify 11,662 males born in Sweden where both Finnish parents immigrated to Sweden from Finland from 1969 or afterward. All of these offspring were at least 15 years old by final follow-up in 2001. Some six offspring (all diagnosed between ages 20 and 24 years) had a diagnosis of germ-cell testicular cancer. Comparison with the Swedish population rate produced standardized incidence ratios [SIR (95% confidence interval)] of 0.85 (0.31-1.84) for all the men and 1.75 (0.64-3.81) for the 20- to 24-year age group. SIRs calculated using the Finnish population rates produced an overall SIR (95% confidence interval) of 1.11 (0.41-2.41) and 2.95 (1.08-6.42) for the 20- to 24-year age group. Although the substantially reduced risk of testicular cancer previously observed in Finnish immigrant to Sweden was not found, this study had insufficient statistical power to conclude that environmental exposures explain the difference in germ-cell testicular cancer risk between Finland and Sweden. (Cancer Epidemiol Biomarkers Prev 2005;14(1):280–2)

Introduction

Testicular cancer incidence has increased in developed countries throughout the world (1-5), and this is consistent with a causal role for environmental exposures. There is also considerable variation in testicular cancer risk between countries during the same period, suggesting differences in exposure or susceptibility. Although they are neighboring developed countries, the incidence in Finland is less than half of that found in Sweden (6). Young Finnish immigrants to Sweden maintain their lower risk for testicular cancer irrespective of age at immigration (7, 8), indicating that the differences in testicular cancer risk between these countries is not due to disease ascertainment but to true differences in exposure or population susceptibility. This phenomenon could be due to differences in environmental exposures, probably operating in early life perhaps *in utero*, or to differences in genetic susceptibility, as there is evidence that genetic factors may be important in the etiology of testicular cancer (9).

Through the study of male offspring born in Sweden of Finnish parents, it is possible to investigate whether it is a Finnish family origin, implying a role for genetics, or whether it is place of birth, implicating early environmental exposures, which is important in determining the difference in testicular cancer risk between Sweden and Finland. It is possible to identify Finns who immigrated to Sweden since 1969 and their offspring who were born in Sweden using population registers. We examined the risk of testicular cancer in male offspring born in Sweden to Finnish émigré parents. As substantial numbers of Finns migrated to Sweden during this period, there is an opportunity to investigate mechanisms underlying the differences in testicular cancer incidence between these countries. If the offspring of immigrants have lost the lower risk of testicular cancer observed in first-generation immigrants, this indicates that differences in environmental exposures, rather than genetic factors, may explain the difference in risk between Sweden and Finland.

Materials and Methods

All residents in Sweden can be identified through the unique national identity number allocated at birth or immigration (10). The Swedish Emigration Register has recorded immigration to Sweden from Finland since 1969 (11). This and the Multi-Generation Register (12), which links parents and children, were used to identify all male offspring of Finnish immigrants born in Sweden between 1969 and 2001. The study was limited to offspring with *two* parents who were Finnish immigrants. A diagnosis of testicular cancer in offspring was identified through the Swedish Cancer Register, where completeness of reporting for testicular cancer is estimated to be close to 100% (13). The Total Population Register (11) was used to identify members of the cohort with incomplete follow-up due to emigration or death.

The Finnish Cancer Register (13) was used to provide the rates of germ-cell testicular cancer among residents of Finland. This register collects data on all cancer diagnoses mad in Finland with submissions from physicians as well as pathologic, cytologic, and hematologic laboratories and from dentists. The completeness of the Finnish Cancer Register is comparable with the Swedish Register (13), as the Finnish Register is thought to identify >99% of cancer diagnoses.

Received 3/10/04; revised 7/16/04; accepted 7/21/04.

Grant support: Swedish Cancer Foundation project 4566-B01-01XAA.

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Requests for reprints: Scott M. Montgomery, Enheten för klinisk epidemiologi, Karolinska sjukhuset M9:01, SE-171 76 Stockholm, Sweden. Phone: 46-8-51-77-93-25; Fax: 46-8-51-77-93-04. E-mail: Scott.Montgomery@medks.ki.se

The cohort members were followed from their date of birth to the date of diagnosis for testicular cancer, date of death, date of emigration, or end of follow-up (December 31, 2001), whichever came first.

The Karolinska Hospital Ethics Committee approved this study.

Statistical Methods

Standardized incidence ratios (SIR [95% confidence intervals (95% CI)]) for germ-cell testicular cancer were calculated based on both Swedish and Finnish population rates for the same ages and period (14). The rates of germ-cell testicular cancer were obtained from the Swedish and Finnish cancer registers (13). Age adjustment was by the following four age groups: 15 to 19, 20 to 24, 25 to 29, and ≥30 years. Separate SIRs were also calculated for each of the age strata using the Swedish and Finnish rates. Following the incidence distribution of germ-cell testicular cancer, the analysis was restricted to offspring who attained at least age 15 years. SAS statistical software was used to perform this calculation.

Results

A total of 11,662 male offspring born of Finnish immigrant parents who had achieved a minimum age of 15 years by the end of the follow-up period were identified, producing 100,132 person-years at risk. There were 3,242 (27.8%), 3,580 (30.7%), 3,347 (28.7%), and 1,493 (12.8%) men in the 15 to 19, 20 to 24, 25 to 29, and ≥30 years age groups, respectively. A total of six men had a diagnosis of germ-cell testicular cancer, and all of these cancers occurred in the 20- to 24-year age group. There were equal numbers when divided by histologic type (seminoma/nonseminoma). None of the 13,665 male offspring (generating 257,197 person-years at risk) who had not achieved age 15 years by the end of the follow-up period had a diagnosis of germ-cell testicular cancer.

Comparison with Swedish Rates. Based on the Swedish cancer incidence rates, some 7.08 cancers were expected for this population, producing an overall SIR (95% CI) of 0.85 (0.31-1.84). Analysis of the 20- to 24-year age group, where all of the cancers were observed with 3.43 expected, produced a SIR (95% CI) of 1.75 (0.64-3.81). Neither of these SIRs represents a statistically significant association with testicular cancer. None of the other age groups (without events) were associated with a statistically significantly reduced risk of testicular cancer.

Comparison with Finish Rates. When compared with the Finish cancer incidence rates, the total number expected for this age distribution was 5.42, producing an overall SIR (95% CI) of 1.11 (0.41-2.41), indicating a slightly raised risk that did not achieve statistical significance. In the 20- to 24-year age group, where all of the cancers were observed, only 2.03 cancers were expected, producing a statistically significantly raised SIR (95% CI) of 2.95 (1.08-6.42). A statistically significant association was not observed in any of the other age groups.

Discussion

This study did not find evidence of a strong protective effect of Finnish parentage among male offspring born in Sweden based on the Swedish rates of testicular cancer. This is in contrast with the markedly reduced risk observed in a previous study among those *born* in Finland who then immigrated to Sweden, with a SIR (95% CI) of 0.34 (0.21-0.53; ref. 8). In our study, the overall SIR based on Finnish rates was somewhat raised, although this did not achieve statistical significance. The SIR based on Finnish rates for the age stratum where all of the cancers were diagnosed did achieve statistical significance, providing limited evidence of a raised testicular cancer risk compared with men who were born and remained in Finland. Although the study had somewhat limited statistical power, the lack of the previously observed strong protective effect of Finnish origin (8) coupled with some evidence of a higher risk compared with the Finnish population suggests that the difference in testicular cancer risk between Finland and Sweden may not have a solely genetic basis. However, a study with greater statistical power is required to confirm this.

The previous studies of germ-cell testicular cancer risk among males who were born in Finland but immigrated to Sweden found that the reduced risk was independent of both age at immigration and duration of residence in Sweden (7, 8). The most likely explanations for these findings are that a Finnish origin confers hereditary protection or that early life exposures associated with birth in Finland are protective. The results of this study lend some support to the hypothesis that early environmental exposures associated with country of birth may be important in determining germ-cell testicular cancer risk. Several pieces of evidence point to the potential importance of *in utero* exposures in influencing germ-cell testicular cancer risk. Some maternal symptoms and complications during pregnancy, including nausea and bleeding, have been associated with testicular cancer (15-19). Other markers of potential fetal exposures associated (although not always consistently) with testicular cancer include number of previous pregnancies (16, 20-22), birth weight (17, 19, 23), gestational age (15, 17, 23), and twin pregnancies (21). One theory that might explain some of these associations is that fetal exposure to estrogen increases the risk of testicular cancer through mechanisms such as suppressed production of fetal testosterone, androgen receptor expression, and insulin-like factor-III (24). Although this is an attractive theory, some studies did not find evidence that conditions associated with high estrogen levels during pregnancy increase testicular cancer risk in offspring (25). Despite the lack of certainty about the estrogen hypothesis, the *in utero* environment seems to be of importance in determining testicular cancer risk; therefore, maternal exposures before or during pregnancy are likely to exert a significant influence. Fetal exposures may be influenced by some characteristics of the country of residence, including the social milieu that influences maternal lifestyle and behavior.

The possibility that these results are due to a selection effect should be considered as, for example, variation in testicular cancer risk by socioeconomic groups in Finland has been reported (26). There does not seem to be a selection effect operating on Finnish-born migrants to Sweden, as a previous study (likely to include the fathers of this study's subjects) reported a substantial and statistically significant reduced risk of testicular cancer, consistent with the Finnish rates (7, 8). No offspring recorded as being born of two Finnish parents who migrated to Sweden during the study period and where the birth was after date of immigration were excluded from the analysis. The Swedish system of population registration makes systematic failure to identify potential subjects through Finnish mothers remaining unidentified unlikely. However, if some (Finnish) fathers did not remain with mothers until the birth, they might not be recorded as the father, resulting in a failure to identify some offspring. Direct selection among the offspring would have to operate through death or migration from Sweden at an age before testicular cancer developed, thus reducing follow-up time that could be analyzed rather than through their

complete exclusion from the study. There is no evidence that large-scale migration or mortality accounts for the results, as the majority of subjects did not have a truncated follow-up.

The parents of this study's subjects were both immigrants to Sweden from Finland. An advantage of this sample is that any genetic influence associated with Finish origin is less likely to have been diluted by unions between Finns and other nationals. Therefore, the results of this study can more robustly refute a solely genetic mechanism to explain differences in incidence between Nordic countries. As the study was of offspring with two Finnish parents, we could not ascertain if maternal or paternal factors influence testicular cancer risk. We focused on offspring with an attained age of $\geq$15 years, as the incidence of germ-cell testicular cancer begins to emerge at this age; inclusion of younger children would not have improved the precision of the estimate. A disadvantage of this study is its limited statistical power resulting from the number of subjects and the low number of cancers that occurred among them. Therefore, it is possible that a somewhat reduced risk for testicular cancer exists in this population, but our study did not have sufficient power to detect it. The study was too underpowered to investigate variation by histologic type. Although the overall SIR based on Finish rates did not achieve statistical significance, the SIR for the age strata where all the events occurred showed a statistically significantly raised risk, providing some evidence that these men are at higher risk of testicular cancer than those born in Finland. Despite the limited statistical power, Sweden is one of the few countries where this study could be conducted. This is due to the record linkage possibilities, particularly between generations, offered by Swedish population registers coupled with relatively large-scale immigration from a neighboring country with a notably lower testicular cancer risk.

Although the previously observed protective effect of Finnish origin was not found among these men, this study had insufficient statistical power to conclude that men of Finnish origin born in Sweden are at higher testicular cancer risk than those born in Finland. Confirmation of this finding would point to differences in environmental exposures in early life rather than a solely genetic explanation for differences in germ-cell testicular cancer rate between Finland and Sweden, and causes of the increased incidence of testicular cancer should be sought among environmental exposures or lifestyle factors operating through parents before or during pregnancy.

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