The incidence of testicular cancer differs remarkably worldwide. Even within rather homogeneous populations like those in the Nordic countries, substantial differences exist. Denmark and Norway have the highest incidences, with rates above 10 cases per 100,000 inhabitants (World Standard Population), whereas the Swedish incidence is about half of this and the Finnish incidence, a quarter of this. The reason for these differences is unknown (1–4).

In the past 30 years, the incidence of testicular cancer has increased in the majority of industrialized countries in North America, Europe, and the Pacific Rim (4–6). The increasing incidence follows a birth cohort pattern (7), implying that lifetime risk is highly dependent on year of birth. Carcinoma in situ found in embryonic testes (7,8) indicates that exposures very early in life can play a role in the development of testicular cancer.

Assessing how the environment affects cancer risk is problematic because of the time lag between exposure and the appearance of cancer. Comparing the risk among first- and second-generation immigrants provides a means to clarify the potential timing of action of environmental factor(s).

The present study was undertaken in Denmark, which, along with Norway, has the highest recorded incidence of testicular cancer in the world. We used a population-based cohort design to study found that Finns who emigrated to Sweden retained the low risk of testicular cancer observed in Finland and further that neither age nor duration of stay in Sweden was associated with their risk (9), and two other studies indicated that testicular cancer incidence among offspring of immigrants to Sweden resembled the testicular cancer incidence observed in the general Swedish population (10,11). However, all of these studies were small.

The testicular cancer risk in first-generation immigrants was lower than that in native-born Danes and reflected that in the countries of origin, whereas the risk in second-generation immigrants was similar to that in natives of Denmark. Together these findings argue for a substantial influence of environmental factors limited to the period early in life, most probably to the period in utero.

**Background** Immigrant studies offer insights into the relative importance of environment and genes in disease etiology. There is considerable variation in testicular cancer incidence worldwide. We investigated testicular cancer risk in first- and second-generation immigrants to Denmark, a high-incidence country, to evaluate the relative influence of genes and environment and the potential timing of action of environmental factor(s).

**Methods** A cohort of 2.1 million men who were born since 1930 and lived in Denmark between 1968 and 2003 was established based on information in the Danish Civil Registration System, which included their immigration histories. Cancer histories were obtained from the Danish Cancer Registry. Testicular cancer risk was estimated as rate ratios (RRs) with 95% confidence intervals (CIs) based on log-linear Poisson regression.

**Results** Overall, 4216 testicular cancer cases occurred during 43 million person-years of follow-up in 2.1 million men. These included 166 cases among 344,444 direct immigrants to Denmark and 13 cases among 56,189 men born in Denmark to immigrant parents. These first- and second-generation immigrants had RRs of testicular cancer of 0.37 (95% CI = 0.31 to 0.43) and 0.88 (95% CI = 0.51 to 1.53), respectively, compared with men born in Denmark of parents born in Denmark. The rate in first-generation immigrants was not modified by age at immigration or duration of stay and reflected that in the country of origin.

**Conclusion** The testicular cancer risk in first-generation immigrants was lower than that in native-born Danes and reflected that in the countries of origin, whereas the risk in second-generation immigrants was similar to that in natives of Denmark. Together these findings argue for a substantial influence of environmental factors limited to the period early in life, most probably to the period in utero.

**J Natl Cancer Inst** 2008;100:41–47
Subjects and Methods

Cohort

The study cohort consisted of all males who lived in Denmark at some time between April 2, 1968, and December 31, 2003, and who were born between January 1, 1930, and December 31, 2003, with a known place of birth. Cohort members were identified in the Danish Civil Registration System, which was established on April 2, 1968, for administrative purposes. The Civil Registration System holds information on birthplace and dates of birth, death, immigration, and emigration of all residents of Denmark since April 2, 1968. For persons born before April 2, 1968, when the Civil Registration System was started, information on birthplace was collected by the Civil Registration System from index cards in municipality registration offices. Unique personal identification numbers allocated to all residents of Denmark by the Civil Registration System are used by all national registries for secure and accurate linkage between registries. Information on testicular cancer status was obtained from the Danish Cancer Registry. The Danish Cancer Registry was established in 1943 and is considered to be close to complete (12).

A first-generation immigrant was defined as a person with a non-Danish birthplace who came to reside in Denmark. Parental birthplace was identified using the parental link in the Civil Registration System. The Civil Registration System contains the identity of parents (if the parent has ever lived in Denmark) for persons born since the beginning of 1950 and is complete for persons born since 1960 (13,14). Persons immigrating without their parents have no parental link in the database and therefore no registration of the parental birthplace. For this reason, for persons born abroad, who had no registration of the parental birthplace, it was assumed that the parents originated from the same country as their child. All other persons with unknown parental birthplace were categorized as having unknown parental birthplace. By this approach, persons born abroad constituted a relatively large proportion of the men with unknown parental birthplace born between 1930 and 1950. Therefore, persons with unknown parental birthplace (to a large degree men born in Denmark between 1930 and 1950) were included as a special category of parental birthplace to obtain more precise estimates of the effects of age and calendar-year in these birth cohorts, but results for this more technical category are not presented. A total of 3286 cases of testicular cancer during 27,231,603 person-years of follow-up occurred in this subgroup of 844,184 men with unknown parental birthplace. Beginning in 1973, persons born in Greenland have been included in the Civil Registration System on equal terms as Danes. As a result, persons who move between Denmark and Greenland are not registered as migrants. Consequently, and because the incidence of testicular cancer is much lower in Greenland than Denmark (15), persons born in Greenland were excluded from the study.

Statistical Analyses

Statistical tests and estimation of rate ratios (RRs) were based on log-linear Poisson regression models with the number of cases as the dependent variable and the logarithm of person-years at risk included as an offset (ie, a parameter in the regression equation with a value that is assumed rather than estimated). Moment-estimation of the dispersions coefficient gave no strong indication of overdispersion (data not shown). Cohort members were followed for testicular cancer from date of birth, date of immigration, first official registration or April 2, 1968, whichever occurred last, until diagnosis of testicular cancer, death, emigration, or December 31, 2003, whichever occurred first. If a person entered and left Denmark multiple times, only the person-years present in Denmark were considered in the study.

All analyses were adjusted for age (1-year categories except the age groups 5–9, 10–14, and >65) and calendar-year (1-year categories). When we compared the testicular cancer risk of second-generation immigrants with that of first-generation immigrants, we adjusted for parental birthplace according to different combinations of parental origins. Adjustment for the parental birthplace effect was performed by including nine variables representing the number of parents (0, 1, and 2) from nine different country groups (Faroe Islands/Iceland, Finland, Norway, Sweden, Northern and Central Europe excluding the Nordic countries [Great Britain, Germany, Austria, Liechtenstein, Luxembourg, Belgium, The Netherlands, Ireland, Poland, Switzerland, Estonia, Latvia, Lithuania, ex-Soviet Union, Russia, Ukraine, Belarus], Southern Europe [Andorra, Monaco, Albania, Bulgaria, France, Greece, Italy, Montenegro, Serbia, Malta, Portugal, Romania, San Marino, Spain, Hungary, Armenia, Azerbaijan, Moldova, Uzbekistan, Kazakhstan, Turkmenistan, Kyrgyzstan, Tajikistan, Georgia, Croatia, Slovenia, Macedonia, ex-Yugoslavia, the Czech Republic, ex-Czechoslovakia], Asia/Pacific and Middle East, the Americas, and Africa). This correction can be interpreted as adjusting for both maternal and paternal birthplace, with the additional assumption that the maternal and the paternal birthplace have equal effects. When we compared the relative risk of testicular cancer for
first-generation immigrants to Denmark by duration of stay and age at immigration, we also adjusted for birthplace of the immigrant, categorized as the parental birthplace. The analyses of age at immigration and duration of stay among men born abroad of Danish parents were investigated by an interaction between age at immigration (before or after 10 years of age) and duration of stay (less or more than 5 years). Tests for homogeneity and trend were performed as likelihood ratio tests. Tests for trend for duration of stay and age at immigration were performed with the variables treated as continuous variables and the median in each category used as the value for the categories. All statistical tests were two-sided.

Results

The cohort included 2,109,459 men who were followed for 43,282,909 person-years. During this time, a total of 4,216 men were diagnosed with testicular cancer.

Table 1 shows the rate ratio of testicular cancer in men living in Denmark according to birthplace and parental birthplace. The referent group was men born in Denmark of parents born in Denmark. Men born outside Denmark of parents born outside Denmark are referred to as first-generation immigrants, whereas men born in Denmark of parents born outside Denmark are referred to as second-generation immigrants. With 166 cases of testicular cancer in 3,444,441 men during 2,681,712 person-years of follow-up, first-generation immigrants had an overall RR of 0.37, 95% confidence interval (CI) = 0.31 to 0.43. With 13 cases of testicular cancer in 56,189 men during 541,775 person-years of follow-up, second-generation immigrants had an overall RR of 0.88 (95% CI = 0.51 to 1.53), statistically significantly different from the risk in first-generation immigrants (  

$P_{\text{homogeneity}} = .002$). The rate ratio in second-generation immigrants was not statistically significantly different from that of second-generation immigrants who had one parent born in Denmark and the other parent born outside Denmark ($P = .70$). The risk in both first- and second-generation immigrants for whom only one parent was born in Denmark did not differ according to whether the parent of Danish origin was the mother or the father (first generation: RR = 1.71 and 1.19, respectively, $P_{\text{homogeneity}} = .42$; second generation: RR = 1.00 and 0.97, respectively, $P_{\text{homogeneity}} = .86$). We found no statistically significant difference in testicular cancer rates in men born of Danish parents in foreign countries relative to men born of Danish parents in Denmark (RR = 1.03 and 1.00, respectively, $P_{\text{homogeneity}} = .92$). It should be noted, however, that parental registration is based on legal parentage and that this group therefore included foreign-adopted men.

The second-generation immigrants for whom both parents were born outside Denmark (13 cases) had 2.48 times the risk of testicular cancer of first-generation immigrants (95% CI = 1.41 to 4.38; Table 1). We stratified this group of men with both parents born abroad into two groups, depending on risk in the country of parental origin. In the stratified analysis, the second-generation immigrants with parents from low-risk countries (7 cases) had a 3.62 times higher risk of testicular cancer compared with the first-generation immigrants with parents from low-risk countries (95% CI = 1.64 to 7.97), whereas the second-generation immigrants with parents from high-risk countries (6 cases) had a statistically nonsignificant 1.86-fold increase in risk (95% CI = 0.81 to 4.24) compared with the first-generation immigrants (Table 1).

The rate ratio of testicular cancer for first-generation immigrants to Denmark of parents born outside Denmark varied considerably by birthplace, reflecting the risk in the country of origin (Table 2). The overall rate ratios in first-generation immigrants from Northern and Central Europe excluding Nordic countries, Southern Europe, Asia/Pacific and Middle East, the Americas, and Africa were 0.67, 0.23, 0.13, 0.62, and 0.11, respectively. These figures were very similar to the risk in their countries of origin: for example, age-standardized (world) incidences relative to the incidence in Denmark were 0.70 for Germany (Saarland), 0.30 for ex-Yugoslavia, 0.07 for India, 0.57 for United States (white), and 0.07 for Algeria (3).

It is possible that an immigrant’s risk for an illness in a new country might be influenced by his age at the time of immigration or the length of his stay. However, the rate ratios of testicular cancer in first-generation immigrants were not associated with age at immigration or duration of stay in Denmark (Table 3).

Table 1. Rate ratio of testicular cancer in men living in Denmark according to birthplace and parental birthplace, 1968–2003

<table>
<thead>
<tr>
<th>Parental birthplace</th>
<th>Risk in parental birthplace†</th>
<th>Birthplace</th>
<th>DK</th>
<th>No. of cases</th>
<th>PYRS</th>
<th>RR$_{PC}$ (95% CI)</th>
<th>FC</th>
<th>No. of cases</th>
<th>PYRS</th>
<th>RR$_{PC}$ (95% CI)</th>
<th>RR$<em>{DK}/$RR$</em>{FC}$ § (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother DK</td>
<td>Father DK</td>
<td></td>
<td>3853</td>
<td>37,883</td>
<td>1 (reference)</td>
<td>23</td>
<td>275</td>
<td>1.03 (0.68 to 1.55)</td>
<td>0.98 (0.65 to 1.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DK</td>
<td>DK</td>
<td></td>
<td>60</td>
<td>825</td>
<td>1.00 (0.77 to 1.29)</td>
<td>9</td>
<td>63</td>
<td>1.71 (0.89 to 3.29)</td>
<td>0.59 (0.29 to 1.20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FC</td>
<td>DK</td>
<td></td>
<td>81</td>
<td>919</td>
<td>0.97 (0.78 to 1.21)</td>
<td>11</td>
<td>95</td>
<td>1.19 (0.66 to 2.15)</td>
<td>0.79 (0.42 to 1.49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FC</td>
<td>FC</td>
<td>All</td>
<td>13</td>
<td>542</td>
<td>0.88 (0.51 to 1.53)</td>
<td>166</td>
<td>2681</td>
<td>0.37 (0.31 to 0.43)</td>
<td>2.48 (1.41 to 4.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>7</td>
<td>478</td>
<td>0.65 (0.31 to 1.36)</td>
<td>59</td>
<td>1887</td>
<td>0.19 (0.14 to 0.24)</td>
<td>3.62 (1.64 to 7.97)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>6</td>
<td>63</td>
<td>1.50 (0.68 to 3.35)</td>
<td>107</td>
<td>795</td>
<td>0.80 (0.66 to 0.97)</td>
<td>1.86 (0.81 to 4.24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* DK = Denmark; FC = foreign country; PYRS = person-years at risk multiplied by 10$^{-4}$; RR = rate ratio; CI = confidence interval.
† The group of men with both parents born abroad was stratified on the testicular cancer risk in their parental country of origin according to Table 2: All (the entire group); Low (one or both parents originate from a low-risk testicular cancer area with a RR $\leq 0.5$); High (none of the parents originate from a testicular cancer area, with a RR $\leq 0.50$).
‡ RR adjusted for age and calendar year.
§ Adjusted for age, calendar year, and birthplace of parents.
**Table 2. Rate ratio of testicular cancer by birthplace in first-generation immigrants to Denmark of parents born outside Denmark compared with men born in Denmark of parents born in Denmark, 1968–2003***

<table>
<thead>
<tr>
<th>Birthplace</th>
<th>No. of cases</th>
<th>PYRS</th>
<th>RR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td>3853</td>
<td>37883</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Outside Denmark</td>
<td>166</td>
<td>2681</td>
<td>0.37 (0.31 to 0.43)</td>
</tr>
<tr>
<td>Nordic countries</td>
<td>51</td>
<td>361</td>
<td>0.87 (0.66 to 1.15)</td>
</tr>
<tr>
<td>excluding Denmark</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faroe Islands</td>
<td>9</td>
<td>77</td>
<td>0.73 (0.38 to 1.41)</td>
</tr>
<tr>
<td>Finland</td>
<td>1</td>
<td>31</td>
<td>0.21 (0.03 to 1.52)</td>
</tr>
<tr>
<td>Iceland</td>
<td>7</td>
<td>48</td>
<td>0.89 (0.42 to 1.87)</td>
</tr>
<tr>
<td>Norway</td>
<td>22</td>
<td>103</td>
<td>1.31 (0.86 to 1.99)</td>
</tr>
<tr>
<td>Sweden</td>
<td>12</td>
<td>101</td>
<td>0.71 (0.40 to 1.25)</td>
</tr>
<tr>
<td>Northern and Central Europe</td>
<td>62</td>
<td>561</td>
<td>0.67 (0.52 to 0.86)</td>
</tr>
<tr>
<td>excluding Nordic countries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>31</td>
<td>231</td>
<td>0.84 (0.59 to 1.20)</td>
</tr>
<tr>
<td>Ireland</td>
<td>3</td>
<td>14</td>
<td>1.11 (0.36 to 3.44)</td>
</tr>
<tr>
<td>Netherlands</td>
<td>4</td>
<td>38</td>
<td>0.62 (0.23 to 1.67)</td>
</tr>
<tr>
<td>Poland</td>
<td>7</td>
<td>72</td>
<td>0.63 (0.30 to 1.32)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>14</td>
<td>137</td>
<td>0.57 (0.34 to 0.97)</td>
</tr>
<tr>
<td>Other†</td>
<td>6</td>
<td>69</td>
<td>0.28 (0.09 to 0.85)</td>
</tr>
<tr>
<td>Southern Europe</td>
<td>14</td>
<td>377</td>
<td>0.23 (0.14 to 0.39)</td>
</tr>
<tr>
<td>Ex-Yugoslavia</td>
<td>9</td>
<td>220</td>
<td>0.27 (0.14 to 0.52)</td>
</tr>
<tr>
<td>France</td>
<td>2</td>
<td>32</td>
<td>0.34 (0.09 to 1.36)</td>
</tr>
<tr>
<td>Other‡</td>
<td>3</td>
<td>124</td>
<td>0.14 (0.05 to 0.44)</td>
</tr>
<tr>
<td>Asia/Pacific and Middle East</td>
<td>23</td>
<td>1051</td>
<td>0.13 (0.09 to 0.20)</td>
</tr>
</tbody>
</table>

* PYRS = person-years at risk multiplied by 10⁻³; RR = rate ratio; CI = confidence interval.
† RRs were adjusted for age and period.
‡ For comparison, the age-standardized (world) incidence compared with Denmark, as reported in Cancer Incidence in Five Continents Vol. VIII, 1993–1997, is as follows: Denmark (reference); Faroe Islands (no record); Iceland (0.59); Norway (0.83); Sweden (0.51); Finland (0.27); Germany, Saarland (0.70); Ireland (0.44); Netherlands (0.47); Poland (0.27); UK (0.52); ex-Yugoslavia (0.30); France (0.47); India (0.07); Canada (0.42); United States, white (0.57). Algeria (0.07).
§ Countries with fewer than two cases. An exception was made for Finland.
∥ Ex-Yugoslavia includes the following countries: Bosnia-Herzegovinia, Croatia, Macedonia, Montenegro, Serbia, and Slovenia.

A similar analysis on age at immigration and duration of stay was performed among men born abroad of Danish parents in an attempt to describe the heterogeneity of the group. Foreign-adopted men would a priori be expected to immigrate in early childhood. A diagnosis of testicular cancer shortly after entering Denmark, however, would suggest immigration due to illness. This subanalysis was only based on 12 cases because we had no information on the date of immigration for 11 of the 23 men born abroad of Danish parents who developed testicular cancer. In this subanalysis, we found that, among men who immigrated at age 10 or older, the testicular cancer rate ratio within the first 5 years following immigration (two cases) was 14.7 (95% CI = 2.07 to 104) times the rate ratio more than 5 years after immigration (2 cases; referent group). Among men who immigrated younger than age 10, the RR within 5 years of immigration (one case) was 1.91 (95% CI = 0.17 to 2.15) compared with reference and more than 5 years after immigration (seven cases) the RR was 0.37 (95% CI = 0.08 to 1.79) compared with the reference group.

**Table 3. Rate ratio of testicular cancer in first-generation immigrants of parents born outside Denmark by duration of stay in Denmark and age at immigration, 1968–2003***

<table>
<thead>
<tr>
<th>Duration of stay, y</th>
<th>No. of cases</th>
<th>PYRS</th>
<th>RR† (95% CI)</th>
<th>P value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>19</td>
<td>248</td>
<td>1.01 (0.57 to 1.78)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>13</td>
<td>184</td>
<td>0.96 (0.50 to 1.22)</td>
<td></td>
</tr>
<tr>
<td>2–4</td>
<td>19</td>
<td>410</td>
<td>0.64 (0.36 to 1.13)</td>
<td></td>
</tr>
<tr>
<td>5–9</td>
<td>33</td>
<td>464</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>10–19</td>
<td>29</td>
<td>467</td>
<td>0.88 (0.53 to 1.45)</td>
<td></td>
</tr>
<tr>
<td>≥20</td>
<td>4</td>
<td>146</td>
<td>0.43 (0.15 to 1.21)</td>
<td></td>
</tr>
<tr>
<td>Unknown§</td>
<td>49</td>
<td>763</td>
<td>0.74 (0.47 to 1.16)</td>
<td></td>
</tr>
</tbody>
</table>

* PYRS = person-years at risk multiplied by 10⁻³; RR = rate ratio; CI = confidence interval.
† Adjusted for age, period, and birthplace.
‡ P_hom = test for homogeneity; P_trend = test for trend. The “unknown” group was not included in the tests.
§ Date of immigration and thus duration of stay and age at immigration was not available for all persons. Consequently, they were treated as a separate category.

**Discussion**

The high incidence of testicular cancer in Denmark could result from genetic and/or environmental factors. We investigated testicular cancer risk in first- and second-generation immigrants as a means to evaluate the impact of the Danish environment on cancer risk and the potential timing of an environmental factor. We found the risk of testicular cancer in first-generation immigrants to remain unchanged by the move to Denmark. The risk in first-generation immigrants was also not modified by age at immigration or duration of residence in Denmark. In contrast, the risk in second-generation immigrants was close to the level observed among Danes in Denmark.

Two previous reports (10, 12) evaluated testicular cancer risk among Finnish immigrants in Sweden. The statistical power in these studies was limited, but a similar pattern was evident. First-generation immigrants maintained the risk of testicular cancer observed in Finland independently of age at immigration and...
duration of residence in Sweden. The risk of testicular cancer in the second-generation Finnish immigrants was close to the risk observed among Swedes in Sweden.

Together, the Swedish (10,12) and now our Danish results lend support to the hypothesis that early environmental exposures associated with country of birth are important in determining testicular cancer risk. The risk of testicular cancer in the first generation of immigrants reflected the risks of testicular cancer in their countries of origin independently of age at immigration and duration of residence. Thus, the overall risk of testicular cancer in the first generation of immigrants was unaffected by environmental factors in their new host country. Given the high incidence of testicular cancer in Denmark, it would be expected, a priori, that the exposure to potential environmental factors of importance for the development of this cancer would be particularly high in this country and, therefore, this setting gives extra credibility to the results. The risk of testicular cancer in second-generation immigrants was more than twice that of first-generation immigrants. Both the first- and second-generation immigrants were born to foreign-born parents, so differences in genetic susceptibility are not likely to explain a doubling of the risk. Instead, we suggest that the increased risk in second-generation immigrants as compared with first-generation immigrants is probably due to the influence of environmental factors. Moreover, although the sample size was small, we found no increased risk in first-generation immigrants who came to Denmark before the age of 10 (Table 3). We conclude, therefore, that the increased risk in second-generation immigrants stems from their birth and early upbringing in Denmark and that the earliest period of life, including in utero, is crucial for an individual’s testicular cancer risk.

When we stratified the group of immigrants with both parents born outside Denmark by the risk in their parental birth country, second-generation immigrants coming from low-risk areas had a nearly fourfold increased risk of testicular cancer compared with first-generation immigrants from low-risk areas. By contrast, second-generation immigrants coming from high-risk areas showed a statistically nonsignificant doubling in risk of testicular cancer compared with first-generation immigrants from these areas (Table 1). Although these analyses were based on very few cases, they raise the possibility that environmental factors present in Denmark may have a smaller influence on the immigrants from high-risk countries than on immigrants from low-risk countries, possibly because the immigrants from high-risk countries have already been affected by some of the same factors in their country of origin.

A number of reports have suggested possible ways in which events during early development might contribute to testicular cancer risk. For example, undescended testis (16), contralateral testicular cancer (17), and familial testicular cancer are established risk factors for testicular cancer (14,18). According to the “estrogen excess theory,” a relative excess of estrogens during early pregnancy may affect the development of the gonads and result in testicular intraepithelial neoplasias, which may develop into testicular cancer (19,20). Factors associated with high gestational estrogen levels, such as being first-born or born to a mother aged 30 years or older, have in some (18,21–29) but not all (18,21,23,25–28,30–33) studies been associated with a relatively higher risk of testicular cancer. The childhood nutrition theory of testicular cancer pathogenesis further holds that premalignant cells that might arise from primordial germ cells following a hormonal imbalance during embryogenesis may undergo further oncogenic transformation by exposure to a high calorie intake during early childhood (18). Adult stature has been used as a surrogate parameter for childhood nutrition, and some studies have reported statistically significant associations between testicular cancer and adult stature (34–39), whereas others have not (32,35,40–44). We did not adjust for any of the mentioned potential confounders in this study because the necessary information was not available for the first-generation immigrants. However, differences in birth weight distribution, perinatal mortality, and adult stature cannot explain the large differences in testicular cancer risk within the Nordic countries because the populations in the Nordic countries historically have had very similar patterns in birth weight, perinatal mortality, and adult stature. The prevalence of undescended testes is higher in Denmark than Finland (45), but the difference does not appear large enough to explain the observed differences in testicular cancer incidence.

The observed differences between Danes and first- and second-generation immigrants could be due to differential misclassification of birthplace. However, such differential misclassification is unlikely because it is mandatory to report information on birthplace for all persons living in Denmark and birthplace has been well recorded for all Danish residents in the Civil Registration System, either at time of birth or time of immigration. Thus, birthplace was registered independently of and before registration of testicular cancer, leaving little possibility for differential misclassification.

The difference in testicular cancer risk in Danes compared with first-generation immigrants could in part be due to a “healthy/unhealthy immigrant effect.” A healthy/unhealthy immigrant effect would cause the risk of testicular cancer according to duration of stay in the new country to be substantially different between the recent and the nonrecent migrants, but this was not observed in the first-generation immigrants of foreign-born parents.

We found that first-generation immigrants of Danish parents had the same risk of testicular cancer as native Danes. A priori such men would be expected to have a lower risk because they had a different early environmental exposure than the native Danes. The fact that the observed risk for this group was not lower than that for native Danes could be used to argue for a genetic risk rather than an environmental risk. However, the estimate is based on a heterogeneous group and should not be used to distinguish between genes and environment. First, the group of first-generation immigrants of Danish parents holds foreign-adopted children because they are registered with their legal parents in the Civil Registration System in the study as born abroad of Danish-born parents instead of to two foreign-born parents. Second, the estimate in the first-generation immigrants of Danish parents could be influenced by a tendency to return to Denmark upon becoming ill. This would cause the risk in the group to be higher than expected. In a subanalysis of the first-generation immigrants of Danish parents, we found that immigrants of Danish parents who came to Denmark before the age of 10 had a low risk whereas immigrants of Danish parents who came to Denmark at the age of 10 or more had a very high risk in the first years after coming to Denmark.
Thus, although this analysis is based on few cases, the risk might be a mixture of a low risk in the foreign-adopted children and high risk in a group of individuals with biological Danish parents, who most likely returned to Denmark for treatment.

Our study has some limitations. Because we were limited to the available data, the study only included a small number of testicular cancers among second-generation immigrants. Thus, although we found the same level of risk in second-generation immigrants as in native Danes, we acknowledge that the confidence limits were wide. However, the study had more than enough power to document that the risk in second-generation immigrants was higher than the level in first-generation immigrants.

Our study had several strengths. It was based on an entire population and a very complete national registration system encompassing more than 43 million person-years of follow-up. Information on cancer outcome was obtained from the Danish Cancer Registry, which contains mandatory national registration of all diagnosis of cancer in Denmark (12). Furthermore, information on immigrant status was obtained before and independent of an eventual diagnosis of testicular cancer limiting the possibility for differential misclassification. Last, since Denmark is a country with an especially high rate of testicular cancer, differences between the rates in Denmark and those in other countries are easier to discern.

In conclusion, our study of the incidence of testicular cancer among immigrants to Denmark suggests that the influence of environmental factor(s) on the development of this cancer is limited to a period early in life. The difference in testicular cancer rates among men born to foreign parents inside Denmark compared with those immigrating to Denmark as children or adults point to the possibility of environmental influences in utero.

References


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