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FAMILIAL TRANSITIONAL CELL CARCINOMA AMONG THE POPULATION OF ICELAND

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ABSTRACT

Purpose: Several case reports have described familial aggregation of transitional cell carcinoma of the urinary tract but to our knowledge only 1 epidemiological study specifically addressed the issue of familial bladder cancer. We evaluated the extent of familial aggregation of transitional cell carcinoma among the population of Iceland.

Materials and Methods: The first to third degree relatives of 190 patients with bladder, ureter or renal pelvis transitional cell carcinoma diagnosed between 1983 and 1992 in Iceland were identified through the Icelandic Cancer Family Resource. The records of these 12,328 relatives were subsequently linked to the 1965 to 1994 cancer registry. The observed occurrence of transitional cell carcinoma of the urinary tract was compared to the expected occurrence based on age, gender and calendar specific incidence rates. Observed-to-expected ratios and 95% confidence intervals were calculated.

Results: In 41 of the 190 pedigrees at least 1 relative had transitional cell carcinoma of the urinary tract. Of the probands 38 had only 1 and 3 had 2 affected relatives. The prevalence of family history of transitional cell carcinoma was 3% in first degree and 10% in first or second degree relatives. The risk of transitional cell carcinoma among all relatives was slightly elevated (observed-to-expected ratio 1.24, 95% confidence interval 0.90 to 1.67). The observed-to-expected ratio was greater among second and third degree relatives than among first degree relatives.

Conclusions: The risk of transitional cell carcinoma among relatives of patients is somewhat increased. However, the greater risk for more distant relatives argues against the existence of a hereditary subtype of bladder transitional cell carcinoma, at least in the founder population of Iceland.

Key Words: carcinoma, transitional cell; bladder neoplasms; family

The last decade has shown an increasing interest in inherited forms of common malignancies, which has led to the identification of tumor suppressor genes in breast and ovarian cancer, melanoma and renal cell cancer, and to the discovery of mismatch repair genes in colon cancer. Transitional cell carcinoma of the urinary tract is the fourth most frequent type of cancer among white men. Numerous case reports have described families with transitional cell carcinoma, some of which are convincing for mendelian inheritance. Recently, a germline chromosomal abnormality was found in a bladder cancer kindred. Furthermore, it has been shown that the risk of upper urinary tract but not bladder transitional cell carcinoma is increased more than 10-fold in families with hereditary nonpolyposis colon cancer. Nevertheless, to our knowledge only 1 epidemiological study to date has specifically addressed the issue of familial bladder cancer. In that study, the risk of bladder cancer for first degree relatives of patients was increased by a factor of 2.

Iceland is a small northern Atlantic island with a population of approximately 300,000. The Icelandic Cancer Society has kept a nationwide cancer registry since 1955. The primary source of the registry is the department of pathology of the University of Iceland, which covers the entire country regarding histopathological diagnoses of human material. For this study patients were selected from the registry if they met various criteria, including newly diagnosed transitional cell carcinoma (ICD-O morphologic codes 8120 to 8130) of the bladder, ureter or renal pelvis (ICD-7 site codes 180 and 181) between 1983 and 1992, age at diagnosis 70 years or younger, patient born in Iceland and tumor extending into or beyond the lamina propria or carcinoma in situ (stage pTa papillary carcinomas are not registered in Iceland).

A family tree was constructed for all probands. The necessary information was obtained from existing records of the Genetical Committee of the University of Iceland or from reported genealogies. A standard approach was used for construction of the pedigree. The grandparents of the probands were identified and all descendents of the grandparents were identified insofar as they were related to the proband in the first, second or third degree. Through this routine pedigrees were constructed with all first, second and third degree relatives of the proband except for the great grandparents and
FAMILIAL TRANSITIONAL CELL CANCER IN ICELAND

1.27

25

0.40-1.54

44

9.45

0.35-2.10

No.

13

0.96

1.24

35.37

1,635

1.38

10

0.84

0.90-1.67

4,648

19.70

tervals were calculated using Byar's approximation of the

linking the unique personal identification codes with the

the siblings of the grandparents. Family data of select sets of

years were stratified by gender, 5-year age category and

istry it was not possible to stratify the analyses based on

including persons related by marriage, were identified by cross-

source.8

whichever came first. Subsequently, the observed person-

intestinal cell carcinoma, death, the end of 1994 or age 90 years,

recurrence rates. Finally, observed-to-expected ratios of transi-

cellular carcinoma with corresponding 95% confidence in-

tervals were calculated using Byar's approximation of the

exact Poisson test.9 Since information on tumor stage and

carcinoma when 35 were expected (observed-to-expected ra-

mated that we would reach a power of 99% to detect a 2-fold

the results from the folio wup study in New York,6 we esti-

Overall, 44 relatives were diagnosed with transitional cell carci

,families related to another proband in the third degree.

RESULTS

Of 145 male and 45 female probands who met the inclusion

criteria, 11 (6%) were diagnosed with upper urinary tract

carcinoma only. After construction of the pedigrees it appeared that 5 probands were related in the third degree to another proband. The pedigrees of these 5 probands were excluded from the analyses only when the risk of transitional cell carcinoma for third degree relatives was evaluated. None of the pedigrees met the Amsterdam criteria for the diagnosis of hereditary nonpolyposis colon cancer.11

There were 12,328 relatives (an average of 65 per proband) and 3,730 persons related by marriage identified through the Icelandic Cancer Family Resource. In 38 pedigrees 1 relative was related to another proband in the third degree. The pedigrees of these 5 probands were excluded from the analyses only when the risk of transitional cell carcinoma for third degree relatives was evaluated. None of the pedigrees met the Amsterdam criteria for the diagnosis of hereditary nonpolyposis colon cancer.11

Of first-degree relatives of 190 Icelandic probands with disease

<table>
<thead>
<tr>
<th>Degree</th>
<th>No. Observed</th>
<th>No. Expected</th>
<th>Observed-to-Expected Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>1,635</td>
<td>6</td>
<td>6.22</td>
<td>0.96</td>
</tr>
<tr>
<td>Second</td>
<td>4,648</td>
<td>13</td>
<td>9.45</td>
<td>1.38</td>
</tr>
<tr>
<td>Third*</td>
<td>6,045</td>
<td>25</td>
<td>19.70</td>
<td>1.27</td>
</tr>
<tr>
<td>First-Third</td>
<td>12,328</td>
<td>44</td>
<td>163.77</td>
<td>1.24</td>
</tr>
<tr>
<td>Married-in-laws</td>
<td>3,730</td>
<td>10</td>
<td>11.94</td>
<td>0.84</td>
</tr>
</tbody>
</table>

* Five pedigrees were excluded from this analysis because the probands were related to another proband in the third degree.

DISCUSSION

The study of inherited forms of cancer may result in specific knowledge of the pathogenesis of inherited and sporadic variants of the disease. Therefore, much attention has been given to hereditary subtypes of the common malignancies, such as breast cancer, colon cancer, melanoma and renal cell carcinoma. In all of these malignancies specific genes have already been identified. In addition, the existence of inherited forms of prostate cancer and lung cancer has been suggested by segregation analyses.12,13

The evidence for the existence of familial transitional cell carcinoma from epidemiological studies conducted to date is far from consistent,2 probably due at least partly to the fact that almost all studies evaluated familial clustering of bladder carcinoma as 1 of many hypotheses. Most of these studies used an ill-defined definition of family history. The largest study of bladder cancer is a population based study of 2,992 patients and 5,792 controls conducted in 1978 (the United States National Bladder Cancer Study).14 Of bladder cancer patients 6% versus 4% of the controls had a first degree relative with cancer of the urinary tract. The odds ratio adjusted for race, sex, smoking and age was calculated to be 1.5 (95% confidence interval 1.2 to 1.8). This risk appeared to be somewhat greater in persons younger than 45 years (odds ratio 2.7, 95% confidence interval 0.8 to 2.9) and in female patients (odds ratio 1.6, 95% confidence interval 1.1 to 2.7).

The evidence for the existence of familial transitional cell carcinoma was not different (59.4 and 63.5 years, respectively). Likewise, the probands with a first degree relative were not younger than those with a more distant relative with transitional cell carcinoma. Compared to other Icelanders the first degree relatives of transitional cell carcinoma patients did not appear to have an increased risk of cancer (see table). An increased risk, although not statistically significant, was found for more distant relatives. Overall, 44 relatives were diagnosed with transitional cell carcinoma when 35 were expected (observed-to-expected ra...
In that situation no adjustment can be made for the total number of relatives, age, sex, smoking status and age at diagnosis of the relatives. Kramer et al. collected demographic data and cigarette smoking status on all first degree relatives of 319 male bladder cancer patients diagnosed in New York and 319 neighborhood controls. The 2 cohorts of relatives were then associated with the New York State tumor registry to obtain valid data on cancer occurrence. A total of 14 cases of bladder cancer was found among 1,619 relatives of patients and 7 were found among the 1,773 relatives of controls (observed-to-expected ratio 1.9, 90% confidence interval 1.1 to 2.7). Goldgar et al. estimated familial risk ratios from the Utah population data base by identifying all cases of cancer in first degree relatives of cancer patients. The observed values were compared to those expected based on cohort specific internal rates calculated from 400,000 relatives of all individuals in the Utah population data base known to have died in Utah. A total of 48 bladder cancers was observed in the 1,452 first degree relatives of bladder cancer patients when only 31 were expected (relative risk 1.5, 95% confidence interval 1.0 to 2.2). Among relatives of probands with early age bladder cancer (younger than 60 years) the relative risk was 5.1 (95% confidence interval 1.0 to 12.5).

We used a comparable approach to that of the New York and Utah studies. Pedigree information and data on cancer occurrence in the pedigrees were collected from existing records. The family members were not asked about the structure of the family or cancer in the family, which leaves recall bias impossible. It appeared that the prevalence of family history of transitional cell carcinoma was greater (10% in first or second degree relatives) than reported in the literature (2 to 8%), which indicates some degree of misclassification of family history in the epidemiological studies conducted until now. On the other hand, familial clustering is not as strong as previously reported. The risk of transitional cell carcinoma among relatives of patients with the disease was increased by approximately 25% although this increase was not statistically significant. Since we were not able to adjust for the effects of environmental factors, such as smoking behavior and occupation, the increased risk we observed for third degree relatives would favor a genetic cause of this familial clustering. After all, familial aggregation of environmental factors is not likely to exist beyond the first or second degree. On the other hand, the findings that the risk of transitional cell carcinoma is not increased in first degree relatives as well as that patients with a relative with transitional cell carcinoma are not younger than those without such a relative strongly argues against an inherited subtype of transitional cell carcinoma. These findings are in contradiction with all of the case reports and particularly with the studies of Kramer and Goldgar et al. The explanation for this discrepancy is not clear. Possibly our study was hampered by small numbers. Although our study included the entire country of Iceland during 3 decades only 6 cases of transitional cell carcinoma were expected among first degree relatives. Whereas the power of the study was sufficient to detect clustering in all relatives it was not sufficient to detect clustering in first degree relatives only.

Another possible explanation is that familial transitional cell carcinoma may be underrepresented in the founder population of Iceland. The original settlers of Iceland in the latter part of the ninth and the beginning of the tenth centuries were mainly from Norway with some minor admixture from southern Sweden, Denmark and the British isles. After Iceland was fully settled little immigration occurred from outside. If these settlers did not carry certain susceptibility genes the existence of hereditary subtypes of diseases may remain undetected. Thus, the advantage of the unique infrastructure of Iceland regarding data collection for genetic epidemiological studies may be overruled by the characteristics of its population. Therefore, further research in different populations will be necessary.

REFERENCES