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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.¹ Numerous case reports have described families with transitional cell carcinoma,² some of which are convincing for mendelian inheritance.³ Recently, a germline chromosomal abnormality was found in a bladder cancer kindred.⁴ 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.⁵ Nevertheless, to our knowledge only 1 epidemiological study to date has specifically addressed the issue of familial bladder cancer.⁶ 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 250,000. The Icelandic Cancer Society has kept a population based cancer registry since 1955 and has identified relatives of select sets of cancer patients since 1972. This unique infrastructure prompted us to evaluate the

extent of familial clustering of transitional cell carcinoma among this fairly isolated population.

METHODS

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.⁷ For this study patients were selected from the registry if they met various criteria, including newly diagnosed transitional cell carcinoma (ICD-O morphology 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

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the siblings of the grandparents. Family data of select sets of cancer patients have been collected in Iceland since 1972 and are now referred to as the Icelandic Cancer Family Resource.⁸

Cases of transitional cell carcinoma among relatives, including persons related by marriage, were identified by cross-linking the unique personal identification codes with the 1965 to 1994 Icelandic Cancer Registry (until 1965 the registry did not distinguish renal cell cancer from renal pelvic transitional cell carcinoma). To compare the observed with the expected number of cases we first defined the followup of the relatives as the number of person-years from 1965 or age 15 years, whichever came later, until diagnosis of transitional cell carcinoma, death, the end of 1994 or age 90 years, whichever came first. Subsequently, the observed person-years were stratified by gender, 5-year age category and 5-year calendar period. The strata specific total numbers of person-years were multiplied with the Icelandic gender, age and calendar year specific transitional cell carcinoma incidence rates. Finally, observed-to-expected ratios of transitional cell carcinoma with corresponding 95% confidence intervals were calculated using Byar's approximation of the exact Poisson test.⁹ Since information on tumor stage and grade is not readily available from the Icelandic Cancer Registry it was not possible to stratify the analyses based on these characteristics. However, the case reports do not provide any indication that familial transitional cell carcinoma is correlated with a more or less virulent form of transitional cell carcinoma.²

Statistical analysis software was used for computations. For the calculation of strata specific person-years we used the method described by Pearce and Checkoway.¹⁰ Based on the results from the followup study in New York,⁶ we estimated that we would reach a power of 99% to detect a 2-fold increased risk among relatives of 200 cases (α 0.05, 1-sided). For a risk increased by 50% we estimated power to be 73%.

RESULTS

Of 145 male and 45 female probands who met the inclusion criteria, 11 (6%) were diagnosed with upper urinary tract transitional cell 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 diagnosed with transitional cell carcinoma between 1965 and 1994. In 3 pedigrees 2 relatives had transitional cell carcinoma, including a brother-brother and a brother-sister combination. The prevalence of family history of transitional cell carcinoma was 3% in first degree, 10% in first or second degree and 22% in first, second or third degree relatives.

Of all probands 10 (5%) were diagnosed when they were younger than 40 years. Only 1 of them (age 22 years) had a relative with transitional cell carcinoma (second degree, age 72 years). Mean age of probands with and without transitional cell carcinoma in the family was not different (59.4 and 58.5 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-

Observed versus expected cases of transitional cell cancer in relatives of 190 Icelandic probands with disease

Degree	No.	No. Observed	No. Expected	Observed-to-Expected Ratio	95% Confidence Interval
First	1,635	6	6.22	0.96	0.35-2.10
Second	4,648	13	9.45	1.38	0.73-2.35
Third*	6,045	25	19.70	1.27	0.82-1.87
First-Third	12,328	44	35.37	1.24	0.90-1.67
Married in-laws	3,730	10	11.94	0.84	0.40-1.54

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

tio 1.24, 95% confidence interval 0.90 to 1.67). This increased risk seemed to be restricted to male relatives: 36 cases of transitional cell carcinoma were observed versus 26 expected (observed-to-expected ratio 1.36, 95% confidence interval 0.95 to 1.88). Among female relatives 8 cases of transitional cell carcinoma were observed versus 9 expected (observed-to-expected ratio 0.90, 95% confidence interval 0.39 to 1.78). Comparable results were obtained when the risk of bladder cancer instead of the risk of transitional cell carcinoma was evaluated (data not shown).

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 cancer 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 2,982 patients and 5,782 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 1.8, 95% confidence interval 1.1 to 2.7). Since the evaluation of familial cancer was not a major objective of this study, the authors were not able to distinguish bladder cancer from kidney cancer nor were they able to verify the reports on familial cancer occurrence.¹⁴ Piper et al performed a case-control study in young women, the group with a greater than average odds ratio for family history in the aforementioned United States National Bladder Cancer Study.¹⁵ A total of 162 women with bladder cancer 20 to 49 years old was matched to population controls and questioned regarding bladder or kidney cancer (renal cell and transitional cell carcinoma) history in first degree relatives. Of the patients and controls 4 (2.5%) and 1 (0.6%), respectively, reported a positive family history but only 1 patient reported bladder cancer in the father, and 1 reported that a sister had had papillary cancer of the kidney and ureter. The remaining 2 patients and 1 control reported kidney cancer in the father. The major disadvantage of case-control studies that are not initiated to address the issue of familial aggregation is that the exposure (transitional cell carcinoma in the family) is measured by a simple question to the patients and controls.

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.⁶ 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%²), 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 argue 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 Kramer⁶ and Goldgar¹⁶ 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.

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