CORRESPONDENCE

RE: Familial Cancer Clustering of Urothelial Cancer: A Population-Based Case–Control Study

Kari Hemminki, Hongyao Yu, Otto Hemminki, Jan Sundquist

Martin and coworkers reported data on familial associations of urothelial cancers (n = 7266) with urothelial cancers and with other (discordant) cancers based on the Utah Population Database, asserting novelty in being able to control for smoking and histology (1). Studies with multiple discordant cancers are subject to chance findings, but the authors guarded against these by assessing consistency of the findings between first-degree relatives, second-degree relatives, and cousins. They referred to four previous studies on the same subject but stated that their study had the advantages of focusing on urothelial histology and being conducted on a population with a low frequency of smokers, thus reducing confounding by smoking. The concern about smoking is valid, but one of the previous studies was conducted on the same Utah population (2); the remaining three were done in Sweden, which has historically had the lowest frequency of smokers in Europe, particularly for men (15% since 2000; http://www.pnlee.co.uk/downloads/iss/iss-sweden_111024.pdf) (3–5). Moreover, Supplementary Table 2 from Martin et al. (available online) showed a weak association of urothelial cancers with smoking-related cancer (hazard ratio [HR] = 1.13, 95% confidence interval [CI] = 1.07 to 1.20, among first-degree relatives) compared with familial urothelial cancers (HR = 1.73, 95% CI = 1.50 to 1.99).

The advantage of specifically selecting urothelial cancers is not supported by their own data, which show almost identical hazard ratios for urothelial vs bladder cancer without histologic specification: 1.73 (95% CI = 1.50 to 1.99) vs 1.69 (95% CI = 1.47 to 1.95) in first-degree relatives; 1.35 (95% CI = 1.21 to 1.51) vs 1.35 (95% CI = 1.20 to 1.50) in second-degree relatives; and 1.07 (95% CI = 0.99 to 1.14) vs 1.08 (95% CI = 1.00 to 1.16) in cousins (Supplementary Table 2, available online). This is in fact understandable because more than 90% of bladder cancers are of urothelial type (6). Strangely, Figure 1 confuses the issue about histology. On top 13 724 patients are listed for “all bladder and upper tract cancer patients.” These are then divided into 7266 “urothelial bladder and upper tract patients” and 6462 “nonurothelial upper and lower tract histology” patients. It is not possible that 47% of bladder and upper tract cancer patients have nonurothelial histology, but whether this group includes kidney cancer and patients lacking histology is not stated.

Our previous analyses were based on the Swedish Family-Cancer Database, which we have recently updated to include cancers from 1958 to 2015 (7). It includes 86 058 cancers of the bladder and urinary tract (International Classification of Diseases, version 7, code 181). Of these, 96.7% were bladder cancers, 2.0% were ureter cancers, and the remainder were tumors in other parts of the urinary tract. Among bladder cancer, 98.0% of histology was transitional cell carcinoma. Squamous cell carcinoma, specifically pointed out by Martin and coworkers as a deviant histology, accounted for 1.2% of all bladder cancer.

In Table 1, we show the influence of anatomic location and histology on bladder cancer risk based on the above Swedish data. Familial relative risk for urinary tract cancer (International Classification of Diseases, version 7, code 181) was 1.81 (95% CI = 1.68 to 1.94) when first-degree relatives were diagnosed with urinary tract cancer. The relative risk increased to 1.87 (95% CI = 1.73

<table>
<thead>
<tr>
<th>Cancer risk</th>
<th>Family history</th>
<th>No. of patients</th>
<th>Relative risk (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract</td>
<td>Urinary tract</td>
<td>1245</td>
<td>1.81 (1.68 to 1.94)</td>
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<tr>
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<td>1213</td>
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<td>1154</td>
<td>1.85 (1.72 to 2.00)</td>
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<tr>
<td>Bladder, transitional cell</td>
<td>Bladder, transitional cell</td>
<td>1013</td>
<td>1.87 (1.73 to 2.02)</td>
</tr>
</tbody>
</table>

Table 1. Relative risks for urinary bladder cancer
to 2.02) when bladder anatomy and transitional cell histology were specified both in patients and family members. We conclude that sometimes claims of novelty are just novelty of claims.

**Funding**

Supported by the German Cancer Aid.

**Notes**

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The authors have no conflicts of interest to disclose. The funder had no role in the collection, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication.

**References**