**Familial Risks for Cervical Tumors in Full and Half Siblings: Etiologic Apportioning**

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**Abstract**

Many studies have shown familial aggregation for cervical cancer, but they have been unable to distinguish between shared environmental and genetic effects. Full and half-siblings were identified from the nationwide Swedish Family-Cancer Database, including invasive and in situ cervical cancers in women up to age 70 years. Half-siblings were defined through a common father or mother. Standardized incidence ratios, adjusted for several variables, were calculated for proband-wise risks between full and half-siblings. The familial risk for full siblings was 1.84, compared with 1.40 for maternal and 1.27 for paternal half-siblings. These data were used to apportion familial risk for cervical tumors in full siblings into a heritable component, accounting for 64%, and an environmental component, accounting for 36% of the total risk. No evidence for gene-environment interactions was found. The intractable difficulty in separating cervical cancer causation will be an obstacle for a successful identification of susceptibility genes.

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**Introduction**

Cervical cancer is the second most common female cancer worldwide, for which the main cause is genital infection with human papilloma virus (1). Viral infection, cellular immortalization, and tumor progression require complex, long-term interactions between the viral and the host genomes, thus leaving scope for individual susceptibility to cervical cancer (2). Familial aggregation for cervical cancer has been observed in most, but not all, studies (3-5), and also the heritability estimates differ extensively (6-8). The main difficulty has been to distinguish shared environmental effects from those of genes. The strongest evidence for heritability was provided by Magnusson and coworkers in a Swedish study comparing risks between full sisters (relative risk, 1.93) and half-sisters (relative risk, 1.45), combined for benign and malignant tumors of the cervix. The finding was attributed to genetic factors by the authors, and it gave almost a perfect fit for additive genetic effects (9). The relative risks for maternal and paternal half-sibling were almost identical, suggesting further that environmental factors shared by family members were not important. Environmental sharing should be stronger for maternal half-siblings, who normally live in the same family, than for paternal half-siblings, who are similar to adoptees with regard to environmental sharing. Heritable effects influence the existence of susceptibility genes, and the above results have further encouraged a large number of candidate gene studies (10-13).

The use of half-siblings in studies assessing heritability is based on the assumption that these are similar to full siblings in environmental factors. However, the parents of half-siblings have divorced, and cervical cancer risks of divorcees are increased in Sweden (14). We thus first investigate the risk for cervical cancer among offspring of divorced parents in Sweden. We then use these data for the adjustment of familial risks for full and half-siblings.

**Subjects and Methods**

Full and half-siblings were identified from the nationwide Swedish Family-Cancer Database, covering invasive and in situ cervical cancers reported to the Swedish Cancer Registry in years 1958 to 2002 (15). Familial risks in invasive and in situ cervical tumors are almost identical (15). Only offspring (born since 1932 and ages 0-70 years) with known parents were included among families with at least two children. Half-siblings were defined through a common father or mother. Standardized incidence ratios (SIR) were calculated as the ratio of observed to expected number of cases using the proband-wise multiple counting method, described elsewhere (16). "Observed" in the tables gives the true number of observed cases. The expected numbers were calculated from 5-year age-, sex-, region-, period-, and socioeconomic status-specific standard incidence rates. An additional adjustment was done for the number of partners, with whom parents of the subjects had had children, classified as the sum of partners. Confidence intervals (95% CI and 99% CI) were calculated assuming a Poisson distribution (17).

**Results**

The SIR of invasive cervical cancer was increased in daughters of parents who had children with more than one partner (Table 1). The SIR was 1.19 for invasive cervical cancer if both parents had had more than one partner. The SIR was >1.20 for all cervical tumors if either parent had had more than one partner. These results were highly significant, pointing to the importance of this variable in the analysis of familial risks.

Familial risk for full siblings was 1.92 for invasive and 1.82 for all cervical tumors (Table 2). The latter figure increased to 1.84 when it was additionally adjusted for the number of partners, with whom the parents of the siblings had had children. The SIRs for half-siblings markedly decreased when...
they were fully adjusted, from 1.64 to 1.31. The SIR was higher for maternal (1.40) than for paternal half-siblings (1.27). We analyzed also the age differences of the various sibling types by counting the number of years between the oldest and the youngest sibling among all siblings in the present families. For full-siblings the mean was 5.6 years, for paternal half-siblings it was 13.0 years, and for maternal half-siblings it was 10.8 years.

**Discussion**

The lower-than-expected familial risks and the difference between paternal and maternal half-siblings in the fully adjusted familial risks for cervical tumors do not support the role for additive genetic effects and call for more complex multifactorial models. Paternal half-siblings would be expected to experience very limited environmental sharing because, first, children of divorced parents usually stay with their mothers and, second, the age difference of half-siblings is large, alienating contacts even if parents and circumstances would allow them. In the present study, the age difference between the oldest and youngest paternal half-siblings was 13 years. Although the present data were adjusted for socioeconomic factors and parental divorce, we cannot exclude the existence of small residual social confounding in the risk estimates.

Based on the above reasoning, the familial risk of 1.27 of paternal half-siblings could be the best estimate of a true heritable effect for 25% of gene sharing, i.e., familial excess of 0.27; 1.27 − 1.00 = 0.27. For full siblings, sharing 50% of their genes, the excess should be then 0.54 (SIR, 1.54). The excess familial risk of 0.13 in maternal half-siblings compared with paternal ones is compatible with some level of environmental sharing, which, however, was lower than the calculated excess environmental risk in full siblings (1.84 − 1.54 = 0.30). The small difference between the excess environmental risk between full siblings and maternal half-siblings (0.30 versus 0.13) could be completely accounted for by a higher degree of environmental sharing in full siblings, leaving no appreciable room for gene-environment interactions. Thus, this model apportions the familial risk for cervical tumors in full siblings, with an excess familial risk of 0.84, into a heritable component (0.54% or 64%) and an environmental component (0.30% or 36%). The heritable effects could conceivably be parentally derived genes related to immunologic and other mechanisms governing human papilloma virus infection and malignant transformation. The environmental factors—in this context including anything that is not heritable—could be behavioral patterns regulating the likelihood of exposure to human papilloma virus, health contentiousness, and response to calls for screening (15). The relative high heritable component agrees with theoretical calculations on the scope of environmental influence on familial risk estimates in cancer (18, 19). The data caution about equating familial risks with heritable effects for cancers for which environmental risk factors are known. The environmental component in the familial aggregation of cervical cancer, albeit minor, will interfere with attempts to identify underlying susceptibility genes and it should be considered in the planning of such studies.

**Table 1. Risk for cervical cancer by numbers of partners with whom parents had children**

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Mother 1, father 1</th>
<th>Mother &gt;1, father 1</th>
<th>Mother 1, father &gt;1</th>
<th>Mother &gt;1, father &gt;1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed</td>
<td>SIR (95% CI)</td>
<td>Observed</td>
<td>SIR (95% CI)</td>
<td>Observed</td>
</tr>
<tr>
<td>Invasive</td>
<td>4,114</td>
<td>1.00 (0.97-1.03)</td>
<td>306</td>
<td>1.09 (0.97-1.22)</td>
</tr>
<tr>
<td>Invasive + in situ</td>
<td>74,677</td>
<td>1.00 (0.99-1.01)</td>
<td>6,992</td>
<td>1.24 (1.21-1.27)</td>
</tr>
</tbody>
</table>

**Table 2. SIR for cervical cancer in full and half-siblings according to the Family-Cancer Database**

<table>
<thead>
<tr>
<th>Sibling type</th>
<th>Invasive only</th>
<th>Invasive + in situ</th>
<th>Invasive + in situ (adjusted)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>SIR (95% CI)</td>
<td>Observed</td>
</tr>
<tr>
<td>Full sibling</td>
<td>34</td>
<td>1.92 (1.33-2.68)</td>
<td>8,069</td>
</tr>
<tr>
<td>Paternal half-sibling</td>
<td>2</td>
<td>1.38 (0.13-5.07)</td>
<td>734</td>
</tr>
<tr>
<td>Maternal half-sibling</td>
<td>0</td>
<td>0.67</td>
<td>677</td>
</tr>
<tr>
<td>Any half-sibling</td>
<td>2</td>
<td>0.75 (0.07-2.77)</td>
<td>1,411</td>
</tr>
</tbody>
</table>

**References**

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