Familial Risks in *in Situ* Cancers from the Family-Cancer Database

Kari Hemminki* and Pauli Vahtinen

Department of Biosciences at Novum, Karolinska Institute, 141 57 Huddinge, Sweden

Abstract

The Swedish Family-Cancer Database was used to analyze relationships between parents and offspring with *in situ* cancers and between *in situ* cancers in one generation and invasive cancer in the other generation. A total of 130,000 *in situ* cancers and close to 400,000 invasive cancers were included from 1959 to 1994. The data on family relationships and cancers came from registered sources and should be free from bias. The offsprings' familial relative risks (FRRs) were calculated for concordant and discordant parent-child cancer sites. The most common male *in situ* site was skin (both melanoma and precancerous epithelial lesion), whereas cervix, breast, and skin were common female sites. Increased FRRs were observed for concordant sites: colon, breast, cervix, skin (melanoma), and, in males, precancerous epithelial lesions. The findings were consistent when *in situ* cancer-invasive cancer and *in situ* cancer-*invasive* cancer relationships were explored. FRRs were higher for *in situ* colon cancer and melanoma than the respective estimates in invasive cancers, and for the remaining sites, they were equal or somewhat lower. At discordant sites, increased FRRs of *in situ* cancers were observed for female breast and melanoma and, at many sites, implicated in tobacco and human papilloma virus carcinogenesis, together with cervix. Family histories of *in situ* cancers deserve clinical attention.

Introduction

Noninvasive (*in situ*) cancers are becoming more common at many sites due to intensified screening programs and clinical diagnostic methods. Noninvasive cancers have a tendency to progress to invasive cancer; therefore, treatment of *in situ* cancers is thought to prevent metastasis of the disease. Etiological data on *in situ* cancers are scanty, but the assumption is that the risk factors are similar to those of invasive cancers. For breast cancer, this has been addressed in analytical epidemiological studies. Established risk factors of breast cancer were found to increase the risk of breast cancer *in situ*, but probably more for the ductal than for the lobular form (1–3). In all these studies, family history was found to be a risk factor: risk of developing ductal breast cancer *in situ* was ~2.5-fold in women whose first-degree relatives had a breast cancer (2, 3). In lobular cancer *in situ*, the familial risk was confined to those diagnosed before the age of 50 years (1).

The Swedish Cancer Registry has recorded cancers since 1958, but for *in situ* cancers, reporting improved around 1970. All these cancers are included in the nationwide Swedish Family-Cancer Database, by far the largest database ever used for the study of familial cancer. It offers unique possibilities for reliable estimation of familial risks because all the data on family relationships and cancers were obtained from registered sources of complete coverage. This database has previously been used to study familial relationships in invasive cancers (4–9). Here, we investigated familial relationships in noninvasive and invasive cancers at single sites and across sites. FRRs were calculated for offspring with *in situ* cancer when their parents had similar or different cancers.

Subjects and Methods

The Swedish Family-Cancer Database includes all persons born in Sweden in 1941 with their biological parents, totaling over 6 million individuals (4–7). Since the previous studies, the database has been enhanced with information on those who have died since 1960, making it practically complete for studies on adult cancer (8). Cancers, including *in situ* cancers, were retrieved from the nationwide Swedish Cancer Registry from 1958 to 1994 (10). A four-digit diagnostic code according to the 7th Revision of the International Classification of Diseases was used. Offspring were diagnosed for their first primary cancer in the nation-wide Family-Cancer Database, manuscript in preparation.

*in situ* cancers were selected for analysis if there were at least 70 sex-specific cases in the offspring, limiting the number of sites considered to 7. These sites were also of primary interest in the *in situ*-invasive cancer comparisons. However,

Received 4/20/98; revised 6/23/98; accepted 7/14/98.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

The work was supported by The Swedish Council for Planning and Coordination of Research, The Stockholm County Council, The Cancer Fund, and The King Gustaf V Jubilee Fund.

* To whom requests for reprints should be addressed, at Center for Nutrition and Toxicology Novum, 141 57 Huddinge, Sweden. Phone: 46-8-6089243; Fax: 46-8-6081501; E-mail: Kari.Hemminki@cn.tki.se.

1 K. Hemminki and P. Vahtinen. Familial risks in common cancer analyzed from the nation-wide Family-Cancer Database, manuscript in preparation.

2 The abbreviations used are: FRR, familial relative risk; CI, confidence interval.

References


2. The abbreviations used are: FRR, familial relative risk; CI, confidence interval.
invasive lung and oral cancers were additionally included because of large number of cases and associations to \textit{in situ} cancers. FRRs were calculated for cancer in offspring, by considering concordant and discordant parental sites, using the indirect method of age standardization (11). CIs were calculated assuming Poisson distribution (11). Offspring were analyzed independent of the family structure, but it was controlled so that multiple-case families did not change the results. For melanoma, there was a single family of the total of 40 in which the parent had an invasive melanoma and two siblings had \textit{in situ} melanoma. No adjustments were made for the observation periods or for multiple comparisons. The latter problem was assessed by considering the uniformity of the sex-specific results (father-son, son-father, father-daughter, and so on) for \textit{in situ} cancer and \textit{in situ}-invasive cancer analysis.

**Results**

The Swedish Cancer Registry was started in 1958, and invasive cancers were recorded from then on. \textit{In situ} cancers were under-reported in the beginning, but after national mass screening for cervical cancer in the 1960s, reporting increased first for \textit{cervix} cancer by the end of the 1960s and for other \textit{in situ} cancer in the 1970s. The Family-Cancer Database contained 1.31 million fathers and mothers who had 1.91 million sons and 1.86 million daughters. Fathers had 170,000 primary and 8,300 \textit{in situ} cancers; mothers had 160,000 primary and 57,000 \textit{in situ} cancers. Sons had 18,000 primary and 990 \textit{in situ} cancers; daughters had 31,000 primary and 64,000 \textit{in situ} cancers. The most common primary and \textit{in situ} cancers are shown in Table 1. Parental cancers distributed as did all cancers in Sweden, with prostate and breast cancers dominating. The most frequent paternal \textit{in situ} cancers were skin, rectum, and melanoma, and the most frequent maternal \textit{in situ} cancers were cervix, skin, and breast. Common \textit{in situ} cancers among sons were melanoma, skin, and rectum; among daughters, they were cervix, breast, and ovary. The mean diagnostic ages of males with \textit{in situ} cancers were higher than those with invasive cancer: 67 and 65 years for fathers and 38 and 35 years for sons, respectively. This is due to the relatively high diagnostic age for \textit{in situ} skin cancer. For females, the reverse was the case, the mean diagnostic ages of those with \textit{in situ} and invasive cancer being 42 and 60 years for mothers and 31 and 37 years for daughters, respectively. These data were greatly influenced by cervical cancer in \textit{in situ}.  

\textbf{In Situ-in Situ.} There were a few concordant \textit{in situ} cancers in fathers and sons. For skin, there were five pairs, giving an FRR of 3.6 (95% CI, 1.2–8.6). Concordant melanoma also showed a high FRR of 8.7, but with only two pairs only (95% CI, 1.0–34.7). Fathers and daughters had an increased risk for concordant melanoma (FRR = 8.4; \textit{n} = 4; 95% CI, 2.4–22.4) and discordant skin melanoma (FRR = 2.4; \textit{n} = 9; 95% CI, 1.1–4.6). Moreover, in fathers and daughters, concordant colon cancer \textit{in situ} showed a high FRR of 42 with two pairs (95% CI, 4.9–167).

\textit{FRRs} of \textit{in situ} cancers in daughters whose mothers had \textit{in situ} cancers are shown in Table 2. Almost all of the pairs of sites with a significant increase involved cervix. Maternal \textit{in situ} cervix cancer associated significantly with rectal, cervical, and other female genital cancers in daughters. For breast-breast and breast-melanoma, FRRs were 1.5 (95% CI, 0.3–4.6) and 3.3 (95% CI, 1.1–7.9), respectively. As concordant sites, ovarian and skin cancers showed increased FRRs of borderline statistical significance. No concordant pairs of colon cancer were found. For mothers and sons, there were no statistically significant associations, but cervix-rectum was close (FRR = 2.4; \textit{n} = 5; 95% CI, 0.8–5.8), and some increase was also noted for breast-melanoma (FRR = 2.4; \textit{n} = 2; 95% CI, 0.3–9.8). There were one concordant pair of colon cancer \textit{in situ}.

\textbf{Offspring in Situ-Parent Cancer.} Sex-specific FRRs were calculated for \textit{in situ} cancer in offspring by parental cancer (Table 3).
In situ cancer in sons by father's cancer was significantly increased for two specific sites only, both of which were concordant: melanoma (FRR = 4.4) and skin (FRR = 3.1). Some increases were also observed in colon-colon and colon-rectum pairs, but the FRRs of 1.9–2.7 failed to reach statistical significance due to small numbers of pairs. Daughters' in situ cancers by fathers' cancer showed high FRRs, particularly for colon-colon, colon-rectum, and rectum-colon, whereas there were no cases for rectum-rectum. Melanoma risk was significantly increased as a concordant site. Additionally, cervix in situ in combination with oral and lung cancer in father had increased FRRs.

Sons' in situ cancer by maternal cancer showed significant increases in FRRs for two concordant sites, colon and melanoma (Table 3). In situ cancer in daughters by maternal cancer showed significant increases at many sites (Table 3). Concordant sites of significant familial risk were colon, breast, cervix, and skin (melanoma). Discordant sites of increased FRRs were oral-cervix, lung-cervix, and cervix-rectum.

Offspring Cancer-Parent in Situ. There were relatively few cases when familial risks of cancer in offspring were analyzed by parental cancer in situ. Thus, the results in Table 4 are presented for sons and daughters combined. The FRR of cancer was increased in offspring by paternal cancer in situ at two concordant sites, colon, and skin (melanoma), and at one discordant pair of sites, rectum-oral. Similar analysis by maternal cancer in situ resulted in a significant increase at two concordant sites, cervix and skin (melanoma), and between skin cancer and melanoma.

**Table 3** FRR of cancer in situ in offspring by parental cancer

<table>
<thead>
<tr>
<th>Parental cancer</th>
<th>Offspring in situ</th>
<th>Father-Son FRR n</th>
<th>95% CI</th>
<th>Father-Daughter FRR n</th>
<th>95% CI</th>
<th>Mother-Son FRR n</th>
<th>95% CI</th>
<th>Mother-Daughter FRR n</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Cervix</td>
<td>1.2 458</td>
<td>1.1–1.3*</td>
<td>1.4 139</td>
<td>1.2–1.6*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>Colon</td>
<td>2.1 2</td>
<td>0.2–8.4</td>
<td>6.5 6</td>
<td>2.5–14.5*</td>
<td>10.1 9</td>
<td>4.7–19.3*</td>
<td>8.0 7</td>
<td>3.3–6.8*</td>
</tr>
<tr>
<td>Colon</td>
<td>Rectum</td>
<td>2.7 4</td>
<td>0.7–7.1</td>
<td>3.8 4</td>
<td>1.1–10.0*</td>
<td>2.8 4</td>
<td>0.8–7.4</td>
<td>3.1 3</td>
<td>0.7–9.6</td>
</tr>
<tr>
<td>Rectum</td>
<td>Colon</td>
<td>0</td>
<td></td>
<td>10.8 7</td>
<td>4.5–22.7*</td>
<td>0</td>
<td></td>
<td>2.2 1</td>
<td>0.0–15.6</td>
</tr>
<tr>
<td>Rectum</td>
<td>Rectum</td>
<td>1.9 2</td>
<td>0.2–7.5</td>
<td>0</td>
<td></td>
<td>1.4 1</td>
<td>0.0–9.6</td>
<td>2.0 1</td>
<td>0.0–14.2</td>
</tr>
<tr>
<td>Lung</td>
<td>Cervix</td>
<td>1.2 1355</td>
<td>1.2–1.3*</td>
<td>1.4 534</td>
<td>1.3–1.5*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>Breast</td>
<td>0</td>
<td></td>
<td>1.8 93</td>
<td>1.5–2.2*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>Ovary</td>
<td>0.8 29</td>
<td>0.6–1.2</td>
<td>5.5 4</td>
<td>1.5–14.6*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervix</td>
<td>Rectum</td>
<td>0</td>
<td></td>
<td>0.8 7</td>
<td>0.3–1.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervix</td>
<td>Cervix</td>
<td>1.6 942</td>
<td>1.5–1.7*</td>
<td>1.5 19</td>
<td>0.9–2.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>Breast</td>
<td>1.5 19</td>
<td>0.9–2.4</td>
<td>1.5 19</td>
<td>0.9–2.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>Ovary</td>
<td>0.8 7</td>
<td>0.3–1.7</td>
<td>0.8 7</td>
<td>0.3–1.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>Melanoma</td>
<td>4.4 8</td>
<td>1.9–8.8*</td>
<td>3.2 11</td>
<td>1.6–5.7*</td>
<td>5.7 10</td>
<td>2.8–10.6*</td>
<td>3.4 11</td>
<td>1.7–6.1*</td>
</tr>
<tr>
<td>Skin</td>
<td>Skin</td>
<td>3.1 6</td>
<td>1.2–6.8*</td>
<td>2.3 5</td>
<td>0.8–5.6</td>
<td>2.2 2</td>
<td>0.3–8.6</td>
<td>1.8 2</td>
<td>0.2–7.4</td>
</tr>
</tbody>
</table>

* 95% CI does not include 1.0.

**Table 4** FRR of cancer in offspring by parental cancer in situ

<table>
<thead>
<tr>
<th>Parental in situ</th>
<th>Offspring cancer</th>
<th>Father-Offspring FRR n</th>
<th>95% CI</th>
<th>Mother-Offspring FRR n</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>Colon</td>
<td>4.0 5</td>
<td>1.3–9.6*</td>
<td>1.9 2</td>
<td>0.2–7.6</td>
</tr>
<tr>
<td>Colon</td>
<td>Rectum</td>
<td>3.4 2</td>
<td>0.4–13.8</td>
<td>4.0 2</td>
<td>0.5–16.2</td>
</tr>
<tr>
<td>Rectum</td>
<td>Oral</td>
<td>5.0 5</td>
<td>1.7–12.0*</td>
<td>1.2 1</td>
<td>0.0–8.7</td>
</tr>
<tr>
<td>Rectum</td>
<td>Colon</td>
<td>0.9 2</td>
<td>0.1–3.7</td>
<td>2.3 4</td>
<td>0.7–6.2</td>
</tr>
<tr>
<td>Rectum</td>
<td>Rectum</td>
<td>1.9 2</td>
<td>0.2–7.7</td>
<td>1.2 1</td>
<td>0.0–8.7</td>
</tr>
<tr>
<td>Breast</td>
<td>Breast</td>
<td>1.4 26</td>
<td>1.0–2.1*</td>
<td>1.4 26</td>
<td>1.0–2.1*</td>
</tr>
<tr>
<td>Cervix</td>
<td>Cervix</td>
<td>1.7 127</td>
<td>1.4–2.0*</td>
<td>1.7 127</td>
<td>1.4–2.0*</td>
</tr>
<tr>
<td>Ovary</td>
<td>Ovary</td>
<td>3.0 5</td>
<td>1.0–7.2</td>
<td>3.0 5</td>
<td>1.0–7.2</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Melanoma</td>
<td>3.4 11</td>
<td>1.7–6.1*</td>
<td>3.6 14</td>
<td>2.0–6.0*</td>
</tr>
<tr>
<td>Skin</td>
<td>Melanoma</td>
<td>1.4 37</td>
<td>1.0–1.9</td>
<td>1.6 41</td>
<td>1.1–2.1*</td>
</tr>
<tr>
<td>Skin</td>
<td>Skin</td>
<td>1.1 4</td>
<td>0.3–2.9</td>
<td>1.9 7</td>
<td>0.8–3.9</td>
</tr>
</tbody>
</table>

* 95% CI does not include 1.0.

**Discussion**

It is generally accepted that reliable quantitative estimates on familial risks in cancer are necessary for clinical decisions, family counseling, diagnostic programs, and health education. Furthermore, they increase the understanding of cancer etiology and provide rationale for gene identification (12, 13). However, such data on noninvasive cancers are very limited. Noninvasive cancers may progress to invasive cancers, and they are usually treated with such concerns in mind. Understanding familial relationships in noninvasive cancers should be just as important as understanding these relationships in invasive cancer (14–17); this information should help those who must deal with the increasing numbers of in situ cancers, both in clinical medicine and in health policy.

Here, we used the nationwide Family-Cancer Database, in which all data are coming from registered sources and should be unbiased. However, concerns in families in which many members have had disease may lead to more frequent screening and earlier detection of cancer. This cannot be excluded, but 97% of the diagnoses are morphologically verified in the Swedish Cancer Registry by methods including histological and cytological analyses (10). Here, we proceeded in two stages, first by looking at familial risks in noninvasive cancers only, and then combining invasive cancer in offspring to noninvasive cancer in parents and vice versa. In the first stage (analysis of in situ cancers only), the relatively small number of cases was limiting, partially due to underregistration of in situ cancers in...
the early follow-up period. Despite small numbers, familial risks were noted for colon, melanoma, and skin, which will be discussed later. Cervix showed an FRR of 1.8, almost as high as that we observed previously for invasive cervical cancer (FRR = 2.0). A number of other familial associations were observed with cervix, including rectum (and anus) and other female genital organs. These were observed among mother-daughter pairs but with similar indications in other relevant parent-child pairs. Involvement of human papilloma virus in all these sites is well known (18). However, whether the explanation to the observed familial susceptibility would be a vertical infection by human papilloma virus or other agents; inherited immunodeficiency toward such infection; common lifestyles, such as high risk for sexually transmitted infections; or any combination of these cannot be determined. In any case, cervical cancer appears to involve a certain lifestyle in which tobacco smoking is common, based on the present dataset. Cervical cancer in situ-lung cancer was a common familial relationship, according to Table 3. Moreover, both mothers and daughters, who had invasive cervical cancer as the first primary cancer, had an excess of lung cancer as a second primary, suggesting excessive smoking in the families.  

In situ breast cancer In situ melanoma combination showed the highest familial risk (FRR = 3.3) when the mother had in situ breast cancer and the daughter had in situ melanoma. This is unlikely to be artifactual. Over 10 different sex-specific comparisons were carried out in this study on invasive and in situ cancers between breast and melanoma and melanoma and breast, and all but one showed FRRs exceeding unity but not higher than 1.4. In an independent study from this database, an interaction of invasive breast cancer and melanoma was observed (7). When both parents had these malignancies, the offspring were at a large risk for both breast cancer and melanoma.

In the second stage, the comparison of in situ cancer with invasive cancer showed consistent familial effects for the following concordant sites: colon, breast, cervix, skin (melanoma), and skin squamous cell. There were increased risks for rectum and ovary, but these failed to reach statistical significance. Quantitatively, the risk estimates for colon ranged extensively in different comparisons, from 1.9 to 10.1 (Tables 3 and 4). However, in all these comparisons, the 95% CIs overlapped, and the variation may not have any biological meaning. The mean FRR (FRR = 6.4) was clearly higher than that observed for familial invasive colon cancer in this database (FRR = 2.0) or in other sources in which register-based information is used (14, 17). This suggests that the familial proportion is higher in the registered noninvasive colon cancers than in invasive colon cancers and may relate to colonic polyps being risk factors of colon cancer. The two risk estimates on breast cancer, 1.4 and 1.8, are somewhat lower than those observed for invasive breast cancer in this Database (FRR = 1.9; Ref. 8) and in other register-based sources (14–16). The estimate on in situ breast cancer from Table 2 (both mother and daughters presenting in situ cancer) was 1.5. We cannot distinguish noninvasive ductal from lobular breast cancer in this database, but assuming that most in situ cancers are ductal, our familial risk estimates are lower than those found for ductal cancer in interview studies (2, 3).

The six different FRRs for melanoma in Tables 3 and 4 were surprisingly uniform, giving a mean FRR of 4.0. This is higher than that found for invasive melanoma in this (FRR = 2.7) and the Utah Database (FRR = 2.1; Ref. 14). This is most likely an indication of higher diagnostic intensity for in situ disease with a positive family history and presentation of multiple nevi. For the invasive squamous cell carcinoma of skin, familial risk has only been noted for males in this database (FRR = 3.9). Here, the only significant familial effects were also observed for males only. The FRR was 3.5 when both the father and the son had in situ skin cancer and 3.1 when the son’s in situ cancer occurred in combination with the father’s invasive skin cancer.

In summary, there was a clear familial component in in situ cancers of colon, breast, cervix, and skin for melanoma and precancerous epithelial lesions (in situ squamous cell carcinoma). These were observed both in comparing in situ cancers in parents and offspring and in comparing in situ cancers and invasive cancer in the two generations. Familial risks were higher in in situ cancers of colon and skin (melanoma) and equal or somewhat lower at the remaining sites as compared to familial risks of the respective invasive cancers. Family histories of in situ cancers should deserve a clinical consideration that is equal to that of invasive cancers.

References
Familial risks in in situ cancers from the Family-Cancer Database.

K Hemminki and P Vaittinen


Updated version  Access the most recent version of this article at:
http://cebp.aacrjournals.org/content/7/10/865

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.