Subsequent Cancers After In Situ and Invasive Squamous Cell Carcinoma of the Skin

Kari Hemminki, MD, PhD; Chuanhui Dong, MD, PhD

Objectives: To compare cancer risks after in situ and invasive squamous cell carcinoma (SCC) of the skin and to determine whether these 2 forms of cancer differ in prognostic significance.

Patients: Subsequent events after in situ and invasive SCC were studied in the Swedish Family-Cancer Database, in which cancer data were obtained from the Swedish Cancer Registry from 1958 to 1996. Among 22,293 patients with in situ SCC, 3,940 had first invasive cancer; among 17,637 patients with invasive SCC, 3,624 had a second occurrence of cancer.

Main Outcome Measure: Standardized incidence ratios (SIRs), ratios of the observed to expected number of cases, served as a measure of relative risk. For overall risks, cases diagnosed within the first year of follow-up were omitted.

Results: The median age of onset was 72 to 73 years for in situ and invasive SCC, respectively. Standardized incidence ratios of all cancers were increased after in situ SCC (men-women, 1.5:1.3) and invasive SCC (men-women, 1.9:1.5). The subsequent occurrences of cancer and their SIRs were similar after in situ and invasive SCC, with skin cancer showing the highest SIR of 6.4:10.0. Among discordant cancers, increased SIRs were recorded for melanoma and a group of malignant neoplasms observed in patients with immunosuppression, including lymphoma and oral cancers. Subsequent cancers in the salivary glands and nasal cavity also showed increased SIRs, particularly after invasive SCC.

Conclusion: Risks of subsequent cancers, including skin cancer, melanoma, and internal cancers, showed similar patterns in patients with in situ and invasive SCC, suggesting that the 2 groups have a similar susceptibility to cancer.

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QUAMOUS CELL carcinoma (SCC) of the skin is the fifth most common cancer among men and the sixth most common cancer among women in Sweden.1 Its putative precancerous precursor lesion, in situ skin cancer (in situ SCC, Bowen disease, squamous intraepithelial neoplasia) is the most common benign/precancerous tumor among men according to data in the Swedish Cancer Registry, while among women, it is second only to in situ cervix cancer.1,2 Basal cell carcinoma is not registered in the Swedish Cancer Registry. The risk factors of in situ SCC remain unestablished, but they may be similar to those of invasive SCC, ie, exposure to UV light and arsenic compounds, immunosuppression, and family history.2,3 Cellular atypia is often equally high among those with in situ SCC and invasive SCC, and many authors indicate that it is difficult to use cytological criteria to define in situ SCC as a benign lesion, in spite of an intact basement membrane in the histological specimens.3,6,7 Even when using molecular markers, such as expression of the P53 gene, in situ and invasive SCC appear indistinguishable.8 Very limited epidemiological data are available to compare in situ and invasive SCC. A relatively small patient population with Bowen disease has been observed for cancers, as discussed recently by Jäger et al.9 By contrast, several studies have been published on a second occurrence of cancer after invasive SCC.10-12

If in situ SCC were merely a precursor lesion of invasive SCC, it would be expected that the 2 forms would be distinguishable across several epidemiological parameters, such as age of onset and spectrum of second malignant neoplasms. Our objective was to determine if indeed there are epidemiological differences between in situ and invasive SCC. We compared the number of malignant neoplasms that occurred after in situ SCC (n=22,293) and invasive SCC (n=17,637) based on data in the nationwide Swedish Family-Cancer Database.
SUBJECTS AND METHODS

The Swedish Family-Cancer Database, updated in 1999, includes data on all persons born in Sweden after 1934, as well as data on their biological parents—a total of 9.6 million individuals.11,12 Occurrences of cancer were retrieved from the nationwide Swedish Cancer Registry from 1938 to 1996. In the 1999 update, the number of invasive cancers in the second generation increased from 50000 to 92000. A 4-digit diagnostic code from the International Classification of Diseases, Seventh Revision (ICD-7), was used; ICD-7 code 191 was used for skin cancer. The persons we included in our study had either in situ SCC as their first in situ cancer or invasive SCC as their first primary invasive cancer. All the reported invasive SCCs are registered with the Swedish Cancer Registry, and no distinction is made between new primary occurrences and recurrences. However, the 4-digit ICD-7 code gives the affected organ, which helps distinguish between new primary occurrences and recurrences. The following ICD-7 codes were pooled: oral cancer, 161 (larynx) and 140 (throat) except for 142 (salivary glands); lymphoma, 200 (non-Hodgkin lymphoma), 201 (Hodgkin disease), and 202 (reticulosclerosis); and leukemia, 204 through 207 (leukemias), 208 (polycythemia vera), and 209 (myelofibrosis). Rectal cancer, ICD-7 code 154, was separated for anus (SCC, 154.1) and mucosal rectum (154.0). Basal cell carcinoma of the skin is not registered in the Swedish Cancer Registry.

Standardized incidence ratios (SIRs) were calculated for second occurrences of cancer after invasive SCC or occurrences of first cancer after in situ SCC as the ratio of observed to expected number of cases. The expected numbers were calculated from age-, sex- and period-standardized rates11,12; 95% confidence intervals were calculated assuming a Poisson distribution.11 P ≤ .05 was considered statistically significant.

Database, which contains data on cancer cases that were reported to the Swedish Cancer Registry from 1958 to 1996. The Swedish Family-Cancer Database has been used in several recent studies characterizing familial relationships in cancer, including in situ and invasive SCC, and our results can be compared with those observed in the family studies.2,13-15

RESULTS

The median age of invasive SCC diagnosis was 72 years for both men and women. Among 11409 male and 6228 female subjects with invasive SCC, 2739 male and 885 female subjects experienced a second occurrence of cancer during the follow-up period. Standardized incidence ratios for subsequent cancers for men after invasive SCC are shown in Table 1 by follow-up intervals. The overall risk was calculated by omitting the first year after invasive SCC (>1 year of follow-up). Cancer sites are shown in this and subsequent tables if the overall SIR was greater than 1.4 (Table 1 or Table 2), or if the SIR was significantly increased. The diagnostic activity was high during the first year of follow-up because the patient was under medical surveillance and a number of second skin cancers and melanomas were diagnosed. The overall SIR was 1.9, and occurrence of a second skin cancer showed the highest SIR of 10.0, even after omission of the cases from the first year of follow-up. Skin cancer was the main contributor to the high overall risk because one third of the occurrences of second cancers were skin cancers. Other sites with increased SIRs were oral cavity, salivary glands, stomach, colon, anus, lung, kidney, skin (melanoma), and connective tissue; there was also an increased SIR for lymphoma.

The overall risk for the occurrence of second cancer after invasive SCC was lower for women (1.5) (Table 2). The second occurrence of skin cancer had an SIR of 9.0. Remarkably high SIRs were also noted for 2 rare cancers, ie, those of the salivary glands and nose, with SIRs of 6.4 and 6.9, respectively.

The median age at which in situ SCC was diagnosed among men was 72 years. We studied the risk of first primary cancer among 11373 men with in situ SCC and found an overall SIR of 1.5 among the 1944 subjects who were affected with primary cancer after the first year of follow-up (Table 3). Invasive SCC showed an SIR of 8.1 and melanoma an SIR of 2.1. Statistically significant increases in SIRs were observed for other malignant neoplasms, including oral and lung cancer and lymphoma. The SIR for cancer of the salivary glands was 2.5, which was of borderline significance. The SIR for invasive SCC was 26.9 within the first year of in situ SCC diagnosis; maximal SIRs were observed for all other cancers that occurred within the first year of follow-up, except for lung cancer, for which the maximal SIR was observed 1 to 4 years after in situ SCC.

The median age at which in situ SCC was diagnosed among women was 73 years. Among the 10920 women with in situ SCC we studied, 1209 experienced primary cancer after the first year of follow-up, with an overall SIR of 1.3 (Table 4). Fewer sites showed significant excess of occurrence compared with men, but rates of occurrence of invasive SCC, melanoma, and lymphoma were comparable. Nasal cancer had an SIR of 11.1 within the first year of follow-up; lung cancer showed no increase. All cancers with a significant increase had the highest SIR during the first year of follow-up, except for lymphoma, for which the maximal SIR was observed 1 to 4 years after in situ SCC.

COMMENT

This is the largest study yet published on in situ SCC, and several conclusions can be drawn. We calculated the overall SIRs in a conservative way by omitting cases from the first year of follow-up. Patients were under intense medical scrutiny during this period, and some cancers were diagnosed earlier than they would have been otherwise. However, all occurrences of invasive SCC were histologically verified in the Swedish Cancer Registry, and the diagnoses were likely to be correct even during the first year of follow-up.

There was a curious uniformity of median diagnostic ages of groups with in situ and invasive SCC (wom-
tests are not used for precursor lesions of skin cancer.

cervical cancer to detect precursor lesions, whereas such
cating a true precursor role for the in situ form of can-
In other words, for cervical cancer, the in situ cancer pre-
situ and invasive forms of breast and cervical cancer.18
then the median age of onset would be expected to be
lower in the former than the latter, as is the case for in

Another intriguing finding was that the pattern of can-
cancers after in situ SCC was similar to that observed after
invasive SCC, and there was consistency among SIRs as
well. The SIRs for skin cancer after in situ SCC was similar to that observed after
invasive SCC, and there was consistency among SIRs as

en with in situ SCC, 73 years; all other groups, 72 years).
If in situ SCC were merely a precursor of invasive SCC,
then the median age of onset would be expected to be
lower in the former than the latter, as is the case for in
invasive forms of breast and cervical cancer.18
In other words, for cervical cancer, the in situ cancer pre-
cedes invasive cancer by approximately 10 years, indi-
cating a true precursor role for the in situ form of can-
When interpreting these findings, one must consider
that the median age of onset was significantly lower in


equipped with in situ SCC, 73 years; all other groups, 72 years).

<table>
<thead>
<tr>
<th>Second Site/ Cancer Type†</th>
<th>Follow-up Interval, y</th>
<th>n</th>
<th>SIR (95% CI)</th>
<th>n</th>
<th>SIR (95% CI)</th>
<th>n</th>
<th>SIR (95% CI)</th>
<th>n</th>
<th>SIR (95% CI)</th>
<th>n</th>
<th>SIR (95% CI)</th>
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<td>2.3 (1.3-3.5)‡</td>
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<td>10.0 (9.4-10.7)‡</td>
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<td>5.0 (2.3-8.8)‡</td>
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<td>2.2 (1.6-2.9)‡</td>
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<td>2.3 (0.5-6.1)</td>
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<td>1.9 (0.7-3.5)</td>
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<td>All second events</td>
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<td>1.8 (1.6-1.9)‡</td>
<td>515</td>
<td>1.6 (1.5-1.7)‡</td>
<td>2420</td>
<td>1.9 (1.8-1.9)‡</td>
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</tbody>
</table>

* n Indicates observed number of cases; CI, confidence interval. Blanks indicate that data were not available.
† Second sites/cancer types were included if the SIR for greater than 1 year in Table 1 or Table 2 was greater than 1.4 or was significantly increased. P ≤ .05 was statistically significant.
‡ The 95% CI did not include 1.0.

<table>
<thead>
<tr>
<th>Second Site/ Cancer Type†</th>
<th>Follow-up Interval, y</th>
<th>n</th>
<th>SIR (95% CI)</th>
<th>n</th>
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<th>n</th>
<th>SIR (95% CI)</th>
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<th>SIR (95% CI)</th>
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<td>2.5 (0.8-5.3)</td>
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<td>Salivary glands</td>
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<td>Stomach</td>
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<td>1.7 (0.0-6.5)</td>
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<td>0.7 (0.0-2.7)</td>
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<td>4.8 (0.0-18.7)</td>
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<td>Nose</td>
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<td>1.0 (0.5-1.8)</td>
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<td>0.9 (0.3-1.8)</td>
<td>10</td>
<td>1.6 (0.7-2.7)</td>
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<tr>
<td>Lung</td>
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<td>Kidney</td>
<td>5-9</td>
<td>2</td>
<td>5.0 (2.1-9.0)‡</td>
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<td>2.6 (1.4-4.2)‡</td>
<td>8</td>
<td>2.4 (1.0-4.4)‡</td>
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<td>2.3 (1.6-3.3)‡</td>
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<tr>
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<td>12.7 (10.7-14.9)‡</td>
<td>62</td>
<td>8.6 (6.6-10.8)‡</td>
<td>33</td>
<td>4.2 (2.9-5.8)‡</td>
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<td>785</td>
<td>1.5 (1.4-1.7)‡</td>
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</table>
Skin cancers are treated successfully by surgery and radiotherapy and, as a consequence, surviving patients are at risk for the occurrence of a second malignant neoplasm. Assuming that the adverse effects of radiotherapy are small (eg, increase in the occurrence of sarcomas of connective tissue after >9 years of follow-up among men only) and that the diagnostic activity for second occurrences of cancer shortly after diagnosis of the first cancer is, as discussed, compensated for by omitting the first year of follow-up, the remaining causes of a second malignant neoplasm are likely to be similar to those of the first cancer (environmental agents and ge-

**Table 3. Standardized Incidence Ratios (SIRs) for Second Event of Cancer After In Situ Squamous Cell Carcinoma of the Skin by Follow-up Interval for Men**

<table>
<thead>
<tr>
<th>Second Site/ Cancer Type†</th>
<th>Follow-up Interval, y</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1</td>
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<td></td>
<td>1-4</td>
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<td></td>
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<td></td>
<td>&gt;9</td>
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<tr>
<td></td>
<td>&gt;1</td>
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<tr>
<td>Oral</td>
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<tr>
<td>Salivary glands</td>
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<td>Stomach</td>
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</tr>
<tr>
<td>Colon</td>
<td></td>
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<tr>
<td>Anus</td>
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<td>Nose</td>
<td></td>
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<td>Lung</td>
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<tr>
<td>Penis</td>
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<td>All second events</td>
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**Table 4. Standardized Incidence Ratios (SIRs) for Second Event of Cancer After In Situ Squamous Cell Carcinoma of the Skin by Follow-up Interval for Women**

<table>
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<td>&gt;9</td>
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<tr>
<td></td>
<td>&gt;1</td>
</tr>
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</table>

* n Indicates observed number of cases; CI, confidence interval. Blanks indicate that data were not available.
† Second sites/cancer types were included if the SIR for greater than 1 year in Table 1 or Table 2 was greater than 1.4 or was significantly increased. P ≤ .05 was statistically significant.
‡ The 95% CI did not include 1.00.
Melanoma is weakly associated with exposure to UV
between invasive SCC and eye melanoma. At most, eye
Epstein-Barr virus. A majority of the world’s popu-
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SCC in one generation and melanoma in another; the
familial relative risks were high for these two malignant
neoplasms. Moreover, we found an association be-
tween invasive SCC and eye melanoma. At most, eye
melanoma is weakly associated with exposure to UV
radiation; data suggest that other shared risk factors
for invasive SCC and melanoma exist (eg, forms of inherited susceptibility). Immunodeficiency has prev-
iously been offered as an explanation for the excess of
lymphomas as a second cancer after invasive SCC. The results of our previous study support this finding
for both in situ and invasive SCC. The increased occur-
rence of cancer of oral and connective tissue may also be a result of immunodeficiency.22
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found that the salivary glands are often the site of the sec-
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In previous studies on second occurrences of can-
cer after invasive SCC, the increase in melanoma has been explained by a common risk factor, UV radia-
tion. Our present results agree with this finding, but
the explanation may be too simple. In a separate analy-
ysis, we have studied familial relationships for invasive
SCC in one generation and melanoma in another; the
familial relative risks were high for these two malignant
neoplasms. Moreover, we found an association be-
tween in situ and invasive SCC, and in situ SCC appears
to be as important a marker for subsequent cancer risk as invasive SCC.

Squamous cell carcinoma (SCC) is the most common
malignant tumor of the skin. Although its incidence has
doubled since the 1950s, the overall mortality has
remained unchanged.1,2 Squamous cell skin cancer
is the most common cancer of the skin, including in situ
(ia. intraepithelial neoplasia) and invasive (beyond the
basal lamina) SCC. In situ SCC can progress to invasive
SCC, which is still a relatively slow-growing tumor.

The sex ratio of invasive SCC is 2 times higher for men, whereas in situ SCC is some-
what more common among women. Taken together, the
findings on familial skin cancer and those of the present
article suggest that there are close etiological links be-
tween in situ and invasive SCC, and in situ SCC appears
to be as important a marker for subsequent cancer risk as invasive SCC.

This unusual aggregation of second occurrences of
cancer in two rare cancer sites led us to review the num-
ber of malignant neoplasms that are associated with the
Epstein-Barr Virus. A majority of the world’s popu-
lation is latently infected with this virus. In addition to
Burkitt lymphoma, the Epstein-Barr virus is associated with non-Hodgkin lymphoma in individuals with
immunosuppression, Hodgkin disease, undifferentiated
nasopharyngeal carcinoma and lymphoepithelial carci-
noma of salivary glands and stomach, and some propor-
tion of gastric adenocarcinomas. The Epstein-
Barr virus may be linked to these forms of cancer be-
cause some individuals with in situ and invasive SCC are
immunocompromised and thus increased risk of ac-
quiring a virally induced disease. The more severe ef-
fects of invasive SCC may signal a higher level of immu-
nosuppression compared with in situ SCC. The involve-
ment of Epstein-Barr virus is speculative; molecu-
lar epidemiological data on viral infection are lack-
ing. However, the hypothesis is consistent with the
present epidemiological data, and it may help solve the enigma of the frequency of occurrence of salivary gland cancer after skin cancer.

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