Time Trends and Familial Risks in Squamous Cell Carcinoma of the Skin

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Objectives: To study time trends and familial clustering of invasive and in situ squamous cell skin cancers (SCC), with particular reference to sun-exposed and covered sites of the body.

Design: Epidemiologic follow-up study of the whole population.

Setting: The Swedish Family-Cancer Database from the year 2000, to cover individuals born after 1931 with their biological parents, totaling 10.2 million persons.

Patients: Cancer data were obtained from the Swedish Cancer Registry from 1961 through 1998 and included 1907 invasive SCCs in offspring and 12702 and 7167 in fathers and mothers, respectively. The numbers of patients affected by in situ SCC were 2666, 13739, and 13321, respectively.

Main Outcome Measures: Standardized incidence ratios and 95% confidence intervals were calculated for SCC in offspring when parents had SCC. Incidence rates were calculated for the population in the Database.

Results: Incidence trends showed a large increase in reported cases of SCC and particularly of in situ SCC. Among invasive cases, the increase was largest among covered sites. A clear cohort effect was observed particularly for SCC on covered sites. Familial standardized incidence ratios for offspring combining invasive and in situ SCC were 2.25 (95% confidence interval, 1.93-2.59) for concordant exposed sites and 2.60 (95% confidence interval, 1.38-4.20) for concordant covered sites, suggesting no difference between the body parts within the present statistical power.

Conclusions: The higher increase in incidence on covered sites and the strong cohort effect suggest a contribution by intentional tanning. The observed equal increase in the familial effect on exposed and covered sites suggests that familial risk increases proportionately to the background rate.

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SQUAMOUS CELL carcinoma of the skin (SCC; code 191 in the seventh revision of the International Classification of Diseases) was the fourth most common cancer in men and women in Sweden in 1998, with an annual incidence of 30.2/100000 and 14.1/100000, respectively.1 It has been the most rapidly increasing type of cancer in Sweden during the past 20 years;2 the incidence of SCC has increased in many fair-skinned populations, but it has reportedly reached a plateau in the high-incidence area, Arizona.3,4 Intraepidermal SCC (in situ carcinoma or Bowen disease) that has not invaded the basement membrane is the most common benign or precancerous tumor among men in the Swedish Cancer Registry; among women it is second only to in situ cervical cancer. Reporting of in situ cases to the Cancer Registry has increased rapidly, and these outnumber the reported invasive cases in recent years. In situ skin cancer does not appear to be a simple precursor lesion to invasive SCC because the age at onset of both forms is similar; however, the transition between the 2 forms may be rapid, and both lesions may coexist in some specimens.5,9

See also page 876

Cancer statistics show marked sex differences in the incidence of skin cancer by body part, indicative of exposure to solar irradiation. The incidence of skin cancer is about 20 times higher in ears of Swedish men compared with women, whereas in lower limbs the incidence is equal between the sexes.1 The differences remain even when calculated per body surface area.2 Large sex differences have also been observed in Australia.10 In addition to so-
lar irradiation, some other established risk factors for skin cancer, and probably for in situ cancer, are use of tanning devices, family history, fair skin types, arsenic compounds, and immunosuppression.11-14

We have described earlier familial SCC from the nationwide Swedish Family-Cancer Database: standardized incidence ratios (SIRs) to offspring were 2.4 for invasive and 2.8 for in situ SCC.13 In comparisons between the familial cancers at many sites in the Database, the SIR for skin cancer was intermediary, but it exceeded that for breast and colon cancers, for example.15 However, because sun exposure is an established risk factor, it is conceivable that at least part of the familial risk is explained by cumulative exposure to sun, or by an inherited trait of skin type.16 For this study, we used the most recent update of the nationwide Swedish Family-Cancer Database, covering 10.2 million individuals and more than 1.0 million tumors. The Database offers unique possibilities for reliable estimation of familial risks, because the data on family relationships and cancers were obtained from registered sources of practically complete coverage.17 We investigated incidence trends and familial relationships of invasive and in situ SCC particularly on sun-exposed and covered sites to test the hypothesis that the 2 risk factors, genes and environment, would interact.

METHODS

The Swedish Family-Cancer Database, updated in 2000, includes persons born in Sweden after 1931 with their biological parents, totaling more than 10.2 million individuals.18,19 Cancers, including in situ skin cancers (“precancerous epithelial lesions”), were retrieved from the nationwide Swedish Cancer Registry from years 1961 through 1998. A 4-digit diagnostic code according to the seventh revision of the International Classification of Diseases was used. Code 191 was used for skin cancer, but only SCC has been recorded at the Cancer Registry. More than 90% of SCCs have been histologically verified throughout the history of the Swedish Cancer Registry, and in the last decade the percentage has been 100%. Until 1993, the designation “in situ precancerous epithelial lesions” did not distinguish Bowen disease or senile keratosis. Since 1993, a detailed International Classification of Diseases revision O-2 (for oncology) histologic classification has been used, and some 5% of in situ SCCs have been recorded as actinic keratosis. Only the first invasive SCC or in situ cancer in an individual was considered. Sun-exposed sites for male skin cancer included head, neck, and arms, and for women, also legs; all other sites were considered nonexposed.

The incidence rates for SCC in Sweden for the period 1961 through 1998 were calculated for all men and women from the Database. Person-years were accumulated for the living persons in each period. Five-year age-specific and 5-year-period-specific incidence were calculated and standardized according to European standard population. The SIRs were used to measure the cancer risks for offspring according to occurrence of cancers in their parents. Offspring were diagnosed as having their first primary cancer during 1961 through 1998 at ages 0 to 66 years. The age of parents at the time of diagnosis was not limited. The SIRs were calculated as the relative ratio, ie, the ratio between observed and expected number of cases. The expected numbers were calculated from the standard incidence rates specific for tumor site, sex, 5-year age group, period (10-year bands), 3-category region (large cities, south Sweden, middle and north Sweden), and 6-category socioeconomic status (agriculture, worker, blue collar, professional, private, and others) for all offspring.20 Person-years at risk were accumulated for each offspring, beginning with the date of birth or January 1, 1961, and ending with the date of diagnosis of a first primary cancer, date of death, date of emigration, or December 31, 1998. The 95% confidence intervals were calculated with the assumption that the numbers of cancer cases among offspring follow a Poisson distribution.20

RESULTS

This study covered 1907 invasive SCCs in offspring and 12702 and 7167 in fathers and mothers, respectively. The numbers of patients affected by in situ cancer were 2606, 13739, and 13321, respectively. The incidence trends were calculated from the data in the Family-Cancer Database. The changes in annual incidence of invasive SCC are shown in Figure 1 by sun-exposed and nonexposed site. The rates in males increased between 1961 to 1965 and 1996 to 1998 from 5.75/100000 to 14.88/100000 (259%) on sun-exposed sites and from 0.46/100000 to 3.60/100000 (783%) at covered sites. The corresponding rates in females rose from 1.36/100000 to 9.30/100000 (699%) on sun-exposed sites and from 0.08/100000 to 1.26/100000 (1575%) on covered sites. For in situ cancer, the increases were even more dramatic, but most likely depended on increasing reporting of the cases to the Cancer
Registry (Figure 2). In situ rates were highest on sun-exposed sites and almost identical for males and females. For both males and females, the incidence of in situ SCC has surpassed that of invasive SCC.

Skin cancer is a disease of old individuals, and the incidence of invasive cancer increases steeply after age 70 years for men but later for women (Figure 3). The slopes (incidence/age) are quite different for sun-exposed and covered sites. The in situ rates are the same for males and females on exposed sites and are identical to invasive cancer rates in males (Figure 4). At covered sites, rates in males exceeded those in females.

We examined age-incidence relationships in 3 birth cohorts of invasive SCC, those born before 1910, between 1910 and 1930, and after 1930 (Figure 5). There was a modest increase in incidence by birth cohort for SCC on exposed sites for males and females. On covered sites there was a marked increase by birth cohort, particularly among females.

Familial risks were not different for invasive or in situ SCC. SIR for offspring invasive SCC was 2.16 (n=59; 95% confidence interval, 1.69-2.73) when a parent was diagnosed as having invasive SCC, and for in situ SCC it was 2.51 (n = 106; 95% confidence interval, 2.08-3.09) when a parent was diagnosed as having in situ SCC. Familial risks for offspring on sun-exposed and covered sites are analyzed in the Table, combined for invasive and in situ SCC. The number of familial cases was much higher on exposed sites because both offspring and parental body parts were considered. The highest familial risk, 2.60, was for covered sites in offspring and parents, compared with 2.25 for concordant exposed sites. However, none of the SIRs differed significantly from each other. At concordant exposed sites, familial risks were independent of offspring’s age. At other combinations of body parts, the number of cases was too small for conclusions about age dependence. We also examined the possibility of determining familial risks by stratifying parental age, but no familial cases were found for parents diagnosed before 60 years of age when an offspring would have been diagnosed before 50 years of age.

**COMMENT**

The Swedish Family-Cancer Database includes cancers reported to the Swedish Cancer Registry, which has almost complete national coverage and high diagnostic accuracy. In recent years, 100% of skin cancers have been verified histologically, and these include predominantly SCCs because basal cell carcinomas are not recorded. However, it is likely that at least part of the apparent increase in incidence of particularly in situ skin cancers is due to an increasing rate of reporting. Other technical factors may be a change in diagnostic practices and attention regarding skin cancer. To what extent cumulative exposure to solar irradiation has changed during the years is difficult to assess. However, a recent survey of 10000 residents of Stockholm County aged 13 to 50 years showed that more than half of participants had had sunburn within 1 year, almost half had traveled to a sunny resort abroad, and 37% of females and 19% of males used sun beds. Also, our data suggest that intentional exposure to ultraviolet radiation contributes to the increase in the incidence of SCC. The increase in invasive SCC was relatively higher on covered than exposed sites, which could be due to tanning episodes. Further support for the intentional exposure was the marked cohort effect on covered sites.

Heritable cancers caused by a defect in a single gene, such as BRCA1/2 (the gene associated with breast can-
or DNA mismatch repair genes, preferentially affect young individuals, and higher risks of most familial cancers are also found in young age groups. Squamous cell carcinoma does not conform to this pattern, which may indicate that the familial aggregation depends on shared environmental factors or that the heritable factors cause relatively late-onset cancers compared with other cancers. We have attempted to assess the contribution of environmental factors to familial aggregation of cancer by comparing cancer risks between spouses. No spouse correlation was observed for SCC, suggesting that environmental factors are not important.

**Figure 5.** Age-specific incidence of invasive squamous cell skin cancers on sun-exposed and covered body parts in 3 birth cohorts.

**SIRs for Skin Cancer in Offspring by Parental Skin Cancer***

<table>
<thead>
<tr>
<th>Parent (Invasive or In Situ)</th>
<th>Offspring (Invasive or In Situ)</th>
<th>Sun-Exposed Site</th>
<th>Covered Site</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age at Diagnosis, y</td>
<td>O</td>
<td>SIR</td>
</tr>
<tr>
<td>Sun-exposed site</td>
<td>20-29</td>
<td>3</td>
<td>2.38</td>
</tr>
<tr>
<td></td>
<td>30-39</td>
<td>11</td>
<td>2.16</td>
</tr>
<tr>
<td></td>
<td>40-49</td>
<td>47</td>
<td>2.24</td>
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</tr>
<tr>
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<tr>
<td>All</td>
<td>178</td>
<td>2.25</td>
<td>1.93-2.59</td>
</tr>
<tr>
<td>Covered site</td>
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<tr>
<td>All</td>
<td>25</td>
<td>2.28</td>
<td>1.47-3.25</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; O, number of cases observed; SIR, standardized incidence ratio.

*Boldface type indicates that the 95% CI does not include 1.00.
among adults. As SCC is most common at ages greater than 70 years (Figures 3 and 4), the present offspring generation of 0 to 66 years is still young for SCC. Thus, the familial cases were relatively early-onset skin cancers. There was no large difference between the familial risks of invasive and in situ cancers, which was one indication that the in situ form of skin cancer is not a mere precursor lesion of invasive cancer. Another indication was the identical age at onset (Figures 3 and 4). However, the conclusion does not hold if the transition between the 2 forms is rapid or if both lesions coexist in tumors. For tumors where the in situ form is believed to be a precursor lesion, such as cervical cancer, the age at onset of the in situ form is more than a decade earlier.28

One of the aims of the present study was to characterize the relationship between familial and solar-induced risk of SCC. In general, little is known about the interactions of inherited susceptibility, background cancer rates, and environmental factors. A recent international penetrance study on CDKN2A (melanoma susceptibility gene) found a correlation between penetrance of melanoma and its background incidence.27 In an Australian study, familial risk of melanoma did not appear to interact with any of the sun exposure indexes used.28 Our group has shown elsewhere that there were no significant sex effects in familial SCC or most other site-specific cancers.29 The present data show that familial risks were equally high on covered and exposed sites, implying that solar exposure does not interact with the familial risk. Thus, the solar effect is proportionate to the familial and sporadic rate of SCC.

In summary, our data show a large increase in reported cases of SCC, of which in situ cases have increased drastically. Among invasive cases, the increase has been largest among covered sites, which also showed the largest cohort effect, suggesting contribution by intentional tanning. Familial risks of invasive and in situ skin cancers were equally large, and the familial effect was equally high on sun-exposed and covered sites.

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