Acta Derm Venereol 2001; 81: 268–272

CLINICAL REPORT

Increasing Incidence Rates of Squamous Cell Carcinoma of the Skin in Sweden

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The incidence of squamous cell carcinoma of the skin is increasing world-wide, and in Sweden this tumour is one of the most rapidly increasing malignancies. The aim of this study was to investigate incidence trends of squamous cell carcinoma in Sweden. For the 39,805 tumours registered in the Swedish Cancer Registry 1961–1995, incidence rates were calculated according to gender, age, anatomical site and unit surface area. Multivariate analysis was performed with the age–period–cohort model. Age-standardized incidence rates increased substantially in both men (+425%) and women (+146%) during this period. The highest rates per unit surface area were seen for chronically sun-exposed head–neck sites. Age-specific incidence rates increased in ages ≥ 60 years during the study period. Multivariate analyses showed that age, period and cohort effects in men could best explain the incidence rates, while in women the age–period effects model was adequate. In conclusion, a rapidly increasing incidence trend for squamous cell carcinoma was found, probably explained by increased accumulated sun exposure and increasing incidence among the elderly. ***Key words: ultraviolet; radiation, skin cancer; epidemiology.***

(Accepted April 23, 2001.)

Acta Derm Venereol 2001; 81: 268–272.

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The world-wide incidence rates of skin cancer have increased rapidly during recent decades, especially among the Caucasian population (1). Sunlight is thought to be the strongest environmental risk factor for developing skin cancer. Different exposure habits have been seen for patients with non-melanoma skin cancer [NMSC; squamous cell carcinoma (SCC) and basal cell carcinoma (BCC)] and malignant melanoma. High cumulative chronic sun exposure is probably the most important risk factor for SCC (2), whereas for malignant melanoma intermittent sun exposure and severe burns are considered most important (3). Few studies have been performed on BCC, but the results indicate that the risk for BCC increases with intense ultraviolet (UV) doses delivered intermittently (4).

Data on incident cases of NMSC are seldom recorded routinely in national cancer registries, for several reasons: often no hospitalization is needed, the prognosis is favourable, and not all excised skin cancer specimens are sent for histopathological confirmation. Consequently, population-based studies of patients with NMSC are sparse. BCC is not registered in the Swedish Cancer Registry, whereas SCC has been reported since the beginning in 1958. In Sweden SCC constitutes about 6% of all diagnosed cancers, and among men it was the most rapidly increasing malignant tumour during the 1990s (5).

In the present study the incidence rates of SCC in Sweden from 1961 to 1995 were analysed by gender, age, anatomical site and unit surface area. In addition to age-standardized and age-specific rates, incidence rates per 100,000 unit skin surface area were calculated. For further explanation of the incidence rates, multivariate analysis was performed with age–period–cohort modelling.

MATERIAL AND METHODS

Study population

Data on a total of 39,805 cases (24,890 men and 14,915 women) were collected from the Swedish Cancer Registry with site denoted "NMSC" or "skin (melanoma excluded)", diagnosed between 1 January 1961 and 31 December 1995. Out of the total cases, 25 individuals (19 men and 6 women) were recorded as having 2 tumours simultaneously. It was not possible to distinguish those individuals who developed a subsequent SCC, although this risk is high (standardized incidence ratio 15.6) (6). The diagnoses are coded according to the World Health Organization's International Classification of Diseases; Seventh Revision (7), ICD-7 site 191.1–9. The patients mainly had SCC (92.1% SCC, 6.7% SCC/BBC type mixed, 1.2% other primary malignant tumours of the skin).

Statistical methods

Age-standardized incidence rates of SCC were calculated for men and women annually. The direct method of standardization was used (8), with the world population as a reference. A log-linear regression model, which implies a constant annual percentage change, was used to estimate the temporal trends in the rates. In addition, age-specific incidence rates were estimated as the average rate per year during each 5-year period, starting with 1961–1965 and ending with 1991–1995, using the age groups 0–39, 40–59, 60–79, and ≥ 80 years of age.

The rates per 100,000 unit surface area for a specified site were calculated by dividing the age and site-specified incidence rates of each gender and calendar year by the proportion of the anatomical site area compared with the whole body area (9–11). Thus, for the whole body, rates per 100,000 and per 100,000 unit surface area are identical.

In the multivariate analyses the number of cases was assumed to be Poisson distributed, with a mean that depended multiplicatively on the explanatory variables age, period, cohort and number of person-years. The model was estimated by the maximum likelihood method (12). Submodels, such as a combination of age and period and a combination of age and cohort, were fitted in addition to the full model. The special case when the effects of period or cohort on the logarithmic rates in age–period and age–cohort models were assumed

 ISSN 0001-5555

to be linear was also considered. In that case, it is impossible to separate the period effects from the cohort effects, and the combined linear effect is denoted "drift" (13). The model fit was evaluated in terms of the deviance. By determining the difference in deviance, various models can be compared using the χ^2 distribution. When the deviance is close to the degrees of freedom the model may be considered adequate.

As a measure of the quality of a model M relative to that of the basic age-model A, the following R^2-type measure was used:

$$R^2_M = 1 - [(dev_M/df_M)/(dev_A/df_A)]$$

where dev = deviance and df = degrees of freedom.

For the analysis, 13 5-year age groups (ranging from 20–24 to 80–84 years) and 7 5-year calendar periods (from 1961–1965 to 1991–1995) were defined. A total of 19 9-year overlapping birth cohorts was constructed, starting at 1877–1885 and ending at 1967–1975.

RESULTS

Age-standardized rates

All sites. The age-standardized rates increased among men more than 5-fold from 4.4/100,000 in 1961 to 23.1/100,000 in 1995 and among women from 4.1 to 10.1, respectively (Fig. 1). The average annual percentage increase during the entire length of study was 3.1% [95% confidence interval (CI): 2.7–3.4%] in men and 2.6% (95% CI: 2.2–3.1%) in women. When the average annual percentage increase was calculated in 2 separate time periods, 1961–1980 and 1981–1995, the highest figures were seen during the latter period, for men 4.3% (95% CI: 3.6–5.0%) and for women 4.0% (95% CI: 3.4–4.6%).

Specified sites. The sites analysed were the trunk, upper extremities, lower extremities and head–neck sites (i.e. eyelid, external ear, face, scalp–neck).

In men, for all specified sites there were upward slopes in age-standardized incidence rates in 1981–1995 (Fig. 2*a*). The highest incidence rate was seen for the site head–neck, with an increase during the whole study period from 3.1 to 14.6 (+370%). Incidence rates for specified head–neck sites are shown in Fig. 2*c*; the face and external ears were the subsites with the most elevated rates. The annual percentage increases in incidence rates were highest during 1981–1995, especially for the face (8.1%; 95% CI: 6.8–9.4%), trunk (7.4%; 95% CI: 5.8–8.9%) and upper extremities (5.5%; 95% CI: 4.1–6.8%).

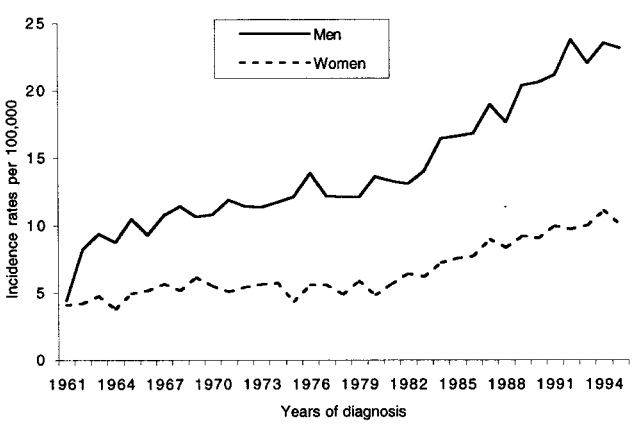

Fig. 1. Age-standardized incidence rates for squamous cell carcinoma (all sites) in men and women.

In women, the age-standardized incidence rates for the site head–neck increased from 2.3/100,000 in 1961 to 5.0/100,000 (+119%) in 1995 (Fig. 2*b*). For specified head–neck sites, SCC of the face rose from 1.7 to 4.2/100,000 (+147%) (Fig. 2*d*). Compared with men, no sharp increase in incidence rates was observed for the locations scalp–neck or external ears. As in men, the annual percentage increases in incidence rates showed the highest figures for time period 1981–1995: head–neck (3.8%; 95% CI: 2.9–4.8%), trunk (7.3%; 95% CI: 4.8–9.8%) and upper extremities (5.5%; 95% CI: 3.1–7.9%).

Age-specific rates

All sites. In men aged 60–79 years incidence rates were increasing slightly, while in men aged 80 years and above there was a dramatic increase with rates close to 400/100,000 (Fig. 3*a*). In women, the age-specific incidence rates rose predominantly from 1981 in ages 60–79 years and for the oldest age group during 1961–1970 and from 1986 onwards (Fig. 3*b*).

Specified sites. In men, for all specified sites (head–neck, trunk, upper and lower extremities) the pattern of age-specific incidence rates was relatively similar; the upward trend in incidence started after 1985 in age groups 60–79 and ≥ 80 years (data not shown). The highest rate per 100,000 was observed for SCC of the head–neck in patients ≥ 80 years: the incidence increased from 107.7 to 293.2/100,000 during 1961–1995. The largest proportional increase, +810% (from 7.0 to 64.0/100,000), was seen for SCC on the scalp–neck in those aged ≥ 80 years.

In women, as in men, increases in age-specific incidence rates after 1985 were observed in ages 60–79 and ≥ 80 years. The only exception to this was SCC of the external ears in the age group ≥ 80 years, which decreased slightly (data not shown).

Incidence rates per 100,000 unit surface area

Site-specific age-standardized incidence rates per 100,000 unit surface area were computed during 1961–1995 (Table I). In both genders, the highest rates were seen for specified head–neck sites. Among men the external ear and eyelid had the highest rates, whereas among women the eyelid and face showed the most elevated rates related to surface area.

Cohort-specific rates

In men, the incidence rates rose mainly in cohorts born between 1897 and 1932, and the highest rate was 325/100,000 in the cohort born 1907–1915 (data not shown). In women, the pattern was similar: rates rose predominantly in cohorts born between 1897 and 1935, and the highest rate was found for birth cohort 1907–1915; the rates were 115/100,000 (data not shown).

Age–period–cohort analyses

Goodness-of-fit statistical tests are shown in Table II. In both men and women, addition of drift, which is a linear effect caused by period and/or cohort, to an age model improved the fit significantly ($p < 0.001$). For both genders, an

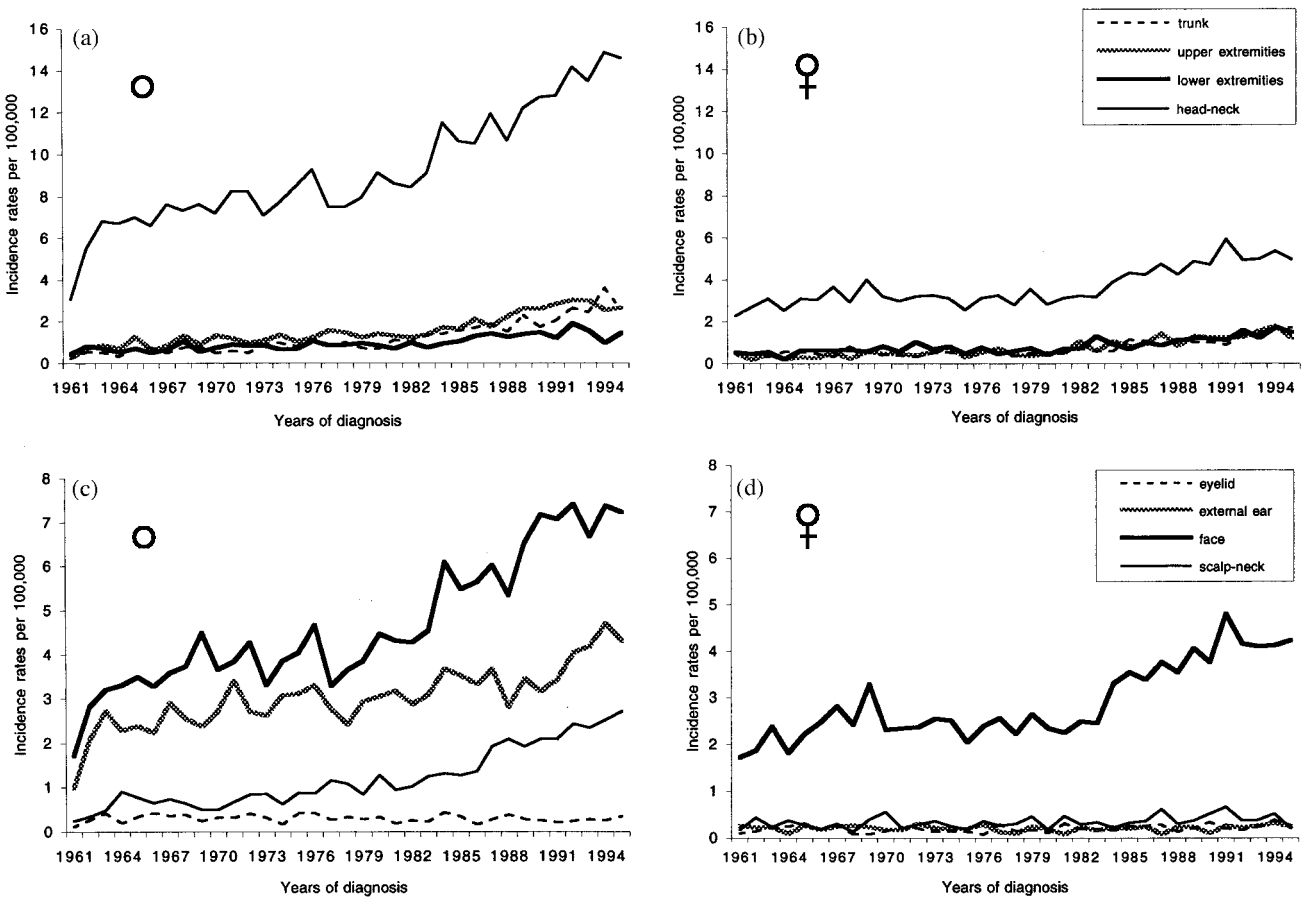

Fig. 2. Age-standardized incidence rates of squamous cell carcinoma for selected anatomical sites (trunk, upper and lower extremities, head–neck) in (*a*) men and (*b*) women, and for specified head–neck sites (eyelids, external ears, face, scalp–neck) in (*c*) men and (*d*) women.

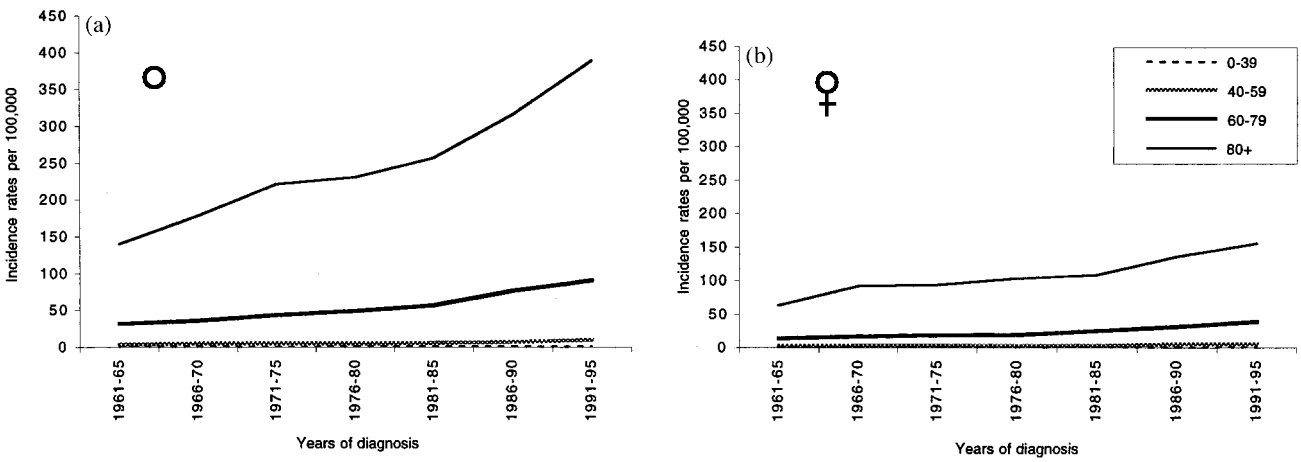

Fig. 3. Age-specific incidence rates of squamous cell carcinoma in (*a*) men and (*b*) women.

age–period model or an age–cohort model – which, in contrast to the age-drift model, allows the period effect or cohort effect to be non-linear – were both significant improvements (all p-values < 0.001) on the age-drift model in explaining the incidence rates of SCC. Further, a significantly improved fit was seen for men in the age–period–cohort model ($p < 0.005$) on both the age–period model and the age–cohort model. Thus, the incidence rates for men were explained by both period effects and cohort effects in addition to age. In women, the age–period–cohort model did not lead to a significant improvement on the age–period effect. Consequently, the age–period model was adequate to explain the incidence rates of SCC for women. This is also supported by the higher explanatory power of the age–period–cohort model in men and age–period model in women shown by the R^2_M-values in Table II.

Table I. *Age-standardized (world) incidence rates of squamous cell carcinoma per unit surface area per 100,000, in Sweden, 1961–1995, by gender and anatomical site*

	Rate per unit surface area per 10^5	
Site	Men	Women
Trunk	3.9	2.3
Upper extremities	8.4	4.0
Lower extremities	2.5	2.2
Head–neck	106.6	42.3
Specified head–neck sites		
Eyelid	306.2	206.5
External ear	624.5	44.3
Face	218.9	135.7
Scalp–neck	20.3	5.7

Table II. *Goodness-of-fit tests of different age-, period and cohort-specific models for incidence of squamous cell carcinoma in men and women in Sweden, 1961–1995; models expressed by the deviance and degrees of freedom (df)*

		Deviance		R^2_M	
Model	df	Men	Women	Men	Women
Age	78	2082.7	945.6	–	–
Age + drift	77	168.8	157.7	0.92	0.83
Age + period	72	120.0[a]	95.1[a]	0.94	0.89
Age + cohort	60	106.1[a]	123.4[a]	0.93	0.83
Age + period + cohort	55	66.4[b]	73.8[c]	0.95	0.89

[a]Significant vs age + drift ($p < 0.001$).
[b]Significant vs age + period and age + cohort ($p < 0.005$).
[c]Not significant vs age + period.
R^2_M: For explanation see Materials and Methods.

DISCUSSION

This large population-based study analysed the incidence trends of SCC in Sweden over a period of 35 years. The incidence rates of SCC increased sharply in both men and women during the whole study period (1961–1995), especially during the second half (1981–1995). The highest figures were found for men with SCC located at head–neck sites, and mostly on the face. The subsites external ear in men and eyelid in women had high rates when site area was taken into account. This study showed that SCC is most common among the elderly and that the age-specific incidence rates increase more over time in these age groups (60–79 and ≥ 80 years). Age–period–cohort effects explained the incidence rates in men, while in women the age–period effects model was adequate. The difference between the genders might be due to the smaller number of female cases, although this is unlikely.

When analysing age-standardized incidence rates, noticeable differences between men and women were found: firstly, the much higher age-standardized incidence rates in general for SCC in men and, secondly, the incidence rate per 100,000 unit surface area indicating that men have marked elevated risks for SCC of the external ears and scalp–neck, whereas women have their highest risk on the eyelids. Explanations for this may include differences in sun-tanning habits, hairstyle, clothing, or indoor and outdoor occupations between the genders (14). Baldness in men leads to a higher dose of UV on the external ears and scalp–neck. The present findings support the hypothesis that almost all SCC occurs on chronically sun-exposed skin. Pearl & Scott reviewed the literature and calculated the relative tumour densities in different incidence studies world-wide (9). This measure gives site densities for each anatomical site, which is important when analysing the correlation between UV exposure and skin cancer. They found an extreme excess of both BCC and SCC on sun-exposed areas, whereas for malignant melanoma a more even distribution over the body was observed. The present results (i.e. continuously rising incidence rates for SCC in general, especially since 1985, higher rates among the elderly, more common in men, most elevated risks for head–neck sites) are consistent with those reported previously for people in Western Europe (11, 15–19) or of European origin (20–22).

Age–period–cohort models are superior to simple descriptive methods. It is possible to test whether a significant improvement is obtained when further factors are included in the model. It can be stated whether the full age–period–cohort model is an improvement on an age–period or an age–cohort model. However, the individual parameters of the full model cannot be identified, thus making the interpretation of the results difficult and limiting the usefulness of the method. In general, changes affecting patients in all ages such as improved diagnostic activities and registration practices should lead to period-based changes in incidence rates. Changes in lifestyle factors or carcinogenic exposures during early life affecting a whole generation should be seen as cohort-based changes. It is unlikely that changes in registration practices or diagnostic activity are major explanations for the increasing trend. A possible explanation could be increased exposure to UV in all age group over the years, although the start of increased UV exposure in most age groups can only be speculated upon. Depletion of the ozone layer in the atmosphere should also result in periodic effects. In Sweden the ozone depletion was greatest during 1980–1990 because of increased air pollution by chlorofluorocarbons, but the thickness of the ozone layer is now stabilizing and it has been predicted that it will slowly increase again.

Several studies of incidence rates and risk factors for SCC have been conducted in Australia. People living in Queensland, which is the tropical and northern part of Australia, are considered to have the highest risk of SCC (22, 23). Exposure to UV radiation, especially UVB (290–320 nm), but also UVA (320–400 nm), is thought to be the most important risk factor (24). UV radiation may also function as an immunosuppressant in the skin with the ability to induce tumours indirectly. Patients treated with long-term immunosuppressive therapy, such as renal transplant recipients, are prone to develop SCC, especially on sun-exposed areas (25). Furthermore, smoking may increase the risk of developing SCC: smoking-related cancers are more common among patients with SCC (6) and recently tobacco smoking was identified as an independent risk factor for SCC (26).

Photoprotection by protective clothing and shelter is the mainstay in skin cancer prevention, but the role of topical sunscreens has been debated. Green et al. recently published a large epidemiological study showing that daily use of topical sunscreens during a 4.5 year period reduced the incidence of SCC but not BCC on chronically sun-exposed sites such as head, neck, arms and hands (27). Thompson et al. showed

that daily use of sunscreens in patients with actinic keratosis reduced the development of further actinic keratosis, though the follow-up period was only 7 months (28).

In conclusion, these data indicate that the incidence of SCC is increasing rapidly, especially in men, on chronically sun-exposed sites and among the elderly. The most likely explanation for this pattern is changed sun-tanning habits leading to a rise in total cumulative sun exposure in individuals. Based on these findings it is important to inform the population about skin cancer and sun-protective behaviour.

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