Rapid and Continuous Increases in Incidence Rates of Basal Cell Carcinoma in the Southeast Netherlands Since 1973

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This study is aimed to determine the characteristics of the trends in incidence of basal cell carcinoma (BCC) in the Netherlands. We used incidence data of BCC from the Eindhoven Cancer Registry (Comprehensive Cancer Centre South) in the south of the Netherlands from 1973 to 2000. Data were age-adjusted and age-specific rates were calculated. Joinpoint and age-period-birth cohort modelling were applied. Between 1973 and 2000, age-adjusted incidence rates of BCC increased in both sexes, most markedly among (young) females. Recent increases were most marked on the trunk. The male data fitted age-drift models, suggesting a linear increase in rates over time, not attributable to either period- or cohort effects. In females, age-cohort-drift models described the data adequately, suggesting changes in intermittent UV exposures in subsequent cohorts. Incidence of BCC in the Netherlands is increasing rapidly, especially at body sites that are not chronically exposed to sunlight. The most likely explanation is an increased intermittent overexposure to UV radiation. This could have introduced an equal fractional increase in risk at all ages in all cohorts. There is no indication of an end to this trend in BCC.

Keywords: age-period-cohort models/epidemiology/incidence/registries/trends

Over the last decades, increasing trends in the incidence of basal cell carcinoma (BCC) have been observed for Caucasian populations, with a decreasing average age of onset (Coebergh et al., 1991; Ko et al., 1994; Levi et al., 1995; Holme et al., 2000). An analysis of the nature of trends in incidence of BCC by age, period, and birth cohort in the Netherlands can clarify to what extent the behaviors (sun-exposure-related) are birth cohort related.

It has been estimated that more than one-third of all cancers in the USA are NMSC (Preston and Stern, 1992), and that in Australia, which has the highest rate of skin cancer in the world, the estimated incidence in 1985 was twice that for all other cancers combined (Giles et al., 1998). Rates in Europe are generally lower, albeit unknown in most areas: in the southeastern parts of the Netherlands BCC accounted for 17% of all cancer cases in both males and females (calculated from Coebergh et al., 2001).

We analyzed incidence rates for primary BCC in the Southeast of the Netherlands in the periods 1973–2000, by sex, site, and age. To determine trends, we further investigated variations by birth cohort and period.

Results

Overall incidence data

Between 1973 and 2000, a total of 23,511 primary BCC cases were diagnosed in the Eindhoven Cancer Registry region (11,865 males and 11,646 females).

The age-specific incidence curves illustrate the high incidence rates of BCC, even at relatively young ages (Fig 1). Seventy-seven percent of all BCC material that was analyzed in the pathology lab was sent by dermatologists, 8% by general surgeons, 8% by plastic surgeons, 3% by general practitioners and 4% by other specialists.

Between 1973 and 2000, the age-adjusted incidence rates for BCC (European Standard Population) increased from 40 to 92 per 100,000 person-years for males and from 34 to 79 per 100,000 person-years for females, with an estimated annual percentage change (EAPC) of 2.4% for males and 3.9% for females (Table I, Fig 2). In the period 1973–2000, cumulative incidence risk before the age of 75 increased from 3.1% to 7.3% in males and from 2.5% to 6.2% in females. Age-specific incidence rose amongst all age groups in both sexes, especially in young women (EAPC 5.7%) (Table I, Fig S1 available online). Rates in young females became higher, and increased more rapidly than in young males; rates in the middle-aged (50–69) were about equal for both sexes, but in older males incidence remained higher than in females.

Incidence by site

BCC occurred predominantly in the head and neck region in both sexes, followed by the trunk and the limbs, with higher rates on the limbs for females than for males. Increases in rates were seen at all sites, with smallest increases in the head and neck region, and most notable increases on the trunk and in females (Table I, Fig S2 available online).

Abbreviations: APC, age period cohort; BCC, basal cell carcinoma; EAPC, estimated annual percentage change; ESR, European standardized rate
The proportion of BCC in the head and neck region decreased over time for both sexes, especially in the younger age group, whereas the proportion on the trunk, arms, and legs increased significantly in this age group. The strongest proportional increases were seen on the trunk in young males and females (Table S1 available online).

**Joinpoint analyses** No changes in the linear trends were observed in the joinpoint analyses (results not shown), implying that no changes in the linear trend, such as signs of levelling off or sudden increases in rates, were detected.

### Table I. Overall, age- and site-specific incidence of basal cell carcinoma (per 10^5 person-years) by sex, 1973–2000

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EAPC a (95% CI)</td>
<td>Incidence b</td>
</tr>
<tr>
<td>All ages</td>
<td>2.4 (2.2–2.5)</td>
<td>93</td>
</tr>
<tr>
<td>25–49</td>
<td>2.2 (1.9–2.4)</td>
<td>33</td>
</tr>
<tr>
<td>50–69</td>
<td>2.4 (2.3–2.6)</td>
<td>204</td>
</tr>
<tr>
<td>70+</td>
<td>2.4 (2.3–2.4)</td>
<td>522</td>
</tr>
<tr>
<td>Head/neck</td>
<td>1.7 (1.6–1.8)</td>
<td>71</td>
</tr>
<tr>
<td>Trunk</td>
<td>5.7 (5.4–6.0)</td>
<td>15.4</td>
</tr>
<tr>
<td>Arms</td>
<td>4.6 (4.1–5.1)</td>
<td>5.5</td>
</tr>
<tr>
<td>Legs</td>
<td>6.9 (6.1–7.7)</td>
<td>3.8</td>
</tr>
<tr>
<td>Other and overlapping</td>
<td>0.91 (0.91–0.95)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

a Estimated annual percentage change with 95% confidence interval (CI).

b Incidence: Age-standardised incidence rates per 100,000 person-years for the period 1998–2000.
Age-period-cohort analysis of incidence data. Age-period-cohort analyses resulted in an age-drift model that was the most parsimonious model for males, while an age-drift-cohort model fitted the data adequately for females (Table S2 available online). Relative risks in females decreased from the earliest birth cohorts, born in the beginning of the 20th century, until those cohorts born in 1921, then levelled off and started increasing again, up until the most recent birth cohorts (Fig 3).

Discussion

BCC is the most common malignant tumor in persons with a pale skin in the Netherlands. Even though its incidence rates are currently already very high, increases in incidence of several percents per year are observed. There are no indications of flattening or recession of this trend, in contrast with incidence rates of cutaneous melanomas, which are flattening off in the young age groups in the Netherlands, like in other Northern European countries (de Vries et al., 2003a, b). Increases in BCC were most rapid in young females, in whom incidence rates are currently higher than in males, especially on the trunk and limbs (Bastiaens et al., 1999).

In other parts of Europe, reported (world standardized) incidence rates of BCC per 100,000 person-years varied markedly (Table II). It must be noted, however, that some of these observations were made about a decade ago, and if rates had increased in the same speed as in the Netherlands, the incidence rates would currently be substantially higher.

Trend analyses of incidence are of course sensitive to changes in the detection by increased awareness of patients and the availability of medical attention. Due to a higher awareness amongst health care professionals and the general population, detection and registration rates may have improved. We observed, however, different changes by age group, subsite, and sex, which would be evidence against artifactual rises of the rates.

Moreover, this registry-based study in the southeastern part of the Netherlands may have been hampered by the usual difficulties, such as incomplete registration and inadequate histological verification, especially if BCC would be excised by general practitioners. There are several reasons, however, why we believe that the vast majority of BCC are reported to the cancer registry, and the registration of primary BCC is very good: our good contacts with dermatologists and pathologists which are supported by the nationwide computerized PALGA archive, and the fact that most general practitioners do not excise (suspected) BCC (in our study about 3%) (Eulderink, 1994). Moreover, in the cases where general practitioners excise the BCC, the pathologists receive the specimens for examination and the BCC will be reported to the cancer registry.

Table II. Reported age standardized incidence rates (world standard population, per 100,000 person-years) and increases in rates in Western Europe

<table>
<thead>
<tr>
<th>Registry</th>
<th>Year</th>
<th>Males</th>
<th>Females</th>
<th>Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hull, UK</td>
<td>1991</td>
<td>116(^a)</td>
<td>104(^a)</td>
<td>335% (1978/1991)</td>
</tr>
<tr>
<td>(Ko et al, 1994)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Holme et al, 2000)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schleswig-Holstein, Germany</td>
<td>1998–2001</td>
<td>54</td>
<td>44</td>
<td>–</td>
</tr>
<tr>
<td>(Katalinic et al, 2003)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

\(^a\)Crude rate.
Ultraviolet radiation is the most important environmental risk factor for the development of BCC, especially in those with a sun-sensitive skin type, although the mechanism is still unclear. A particular amount of sun exposure delivered in infrequent, probably intense “bursts” may increase the risk of BCC more than a similar dose delivered evenly spread over the same total period of time (Kricker et al, 1995a, b). This hypothesis matches with our data. BCC increasingly appear on sites, mainly the trunk, that are not continuously exposed to the sun when outdoors.

The increased incidence rates are most likely caused by changes in sunbathing behavior in the young and middle-aged, which has changed markedly during the twentieth century. Especially, after the Second World War, more leisure time became available for outdoor activities and for holidays in the sun, whereby since the 1980s holidays to the (sub) tropics became affordable for many. Clothes changed allowing larger parts of the skin to be exposed, especially on the beaches. These changes were strongest in young females, and resulted in increasing exposure of the usually covered body sites (trunk, arms, legs) to ultraviolet radiation.

Traditionally, BCC were more commonly seen in older patients, usually males, and presented on the chronically exposed skin, such as the head and neck area. Based on our results, we expect that the “typical” BCC patients in northwestern Europe are becoming younger, more often female, and increasingly with affected sites other than the head and neck area, i.e., more commonly the trunk.

BCC incidence rates in women exhibited a cohort-effect, with still increasing rates in younger birth cohorts, which implies a behavioral risk factor, probably sun exposure, with an increasing influence over successive generations. As this effect is not discernable in the trend in men, it appears that the trend in men is mainly attributable to “drift”, possibly caused by intermittent overexposure to solar UV radiation, which increased more gradually over time in a broad age range.

The two most important histological subtypes of BCC are nodular and superficial BCC, possibly with different etiological mechanisms. Superficial BCC occurs in younger patients, more often in females than in males, and on the trunk and extremities. Nodular BCC occurs significantly more often in males and in the head and neck region. Superficial BCC (on the trunk) appear to be related to intermittent sun exposure, whereas the nodular BCC (on the face and neck) appear to be related more to chronic sun exposure (Bastiaens et al, 1998). Based on our observations of an increase in BCC, most marked in young females, mainly on the trunk and extremities, with a decrease in the proportion of BCC in the head and neck region, especially in the young and middle-aged, we hypothesize that the increases have been mainly in superficial BCC. An increase in intermittent (mostly recreational) sun exposure and decrease in chronic (mostly occupational) sun exposure is likely as well. The proportional increase of nodular BCC observed in a university-hospital-based study in the western part of the country with time, and in all body regions, does not contradict the above, because there may have been specific referral of these patients to the university hospital where the study was conducted (Bastiaens et al, 1998).

In conclusion, the most likely explanation for the increasing incidence rate of BCC, especially at body sites that are not chronically exposed to sunlight is increased intermittent overexposure to UV radiation. This could have introduced an equal fractional increase in risk at all ages in all cohorts. In contrast to trends in melanoma incidence, there is no indication of an end to this trend in BCC.

Materials and Methods

Data

Data on incident primary BCC cases, according to anatomical site, were obtained from the population-based Eindhoven Cancer Registry (Coebergh et al, 2001). The Eindhoven cancer registry serves more than 12 general hospitals that are served by six pathologic laboratories, all participating in the nationwide PAL-GA network, which also notifies the regional cancer registries. The cancer registry receives lists of newly diagnosed cases on a regular basis from the pathology departments, including cases whose material was sent in by general practitioners. In addition, the medical records departments of the hospitals provide lists of outpatients and hospitalized cancer patients. Following this notification, the medical records of newly diagnosed patients (and tumors), often only available from the outpatient departments, are collected and trained tumor registrars from the cancer registry abstract the necessary information. Data are checked for duplicate records. Records are assumed to be complete. Only first primary BCC were registered.

During the study period 1973–2000, the population size of the Eindhoven cancer registry catchment region increased from 592,000 to 2,100,000, mainly due to an expansion of the registry area (Coebergh et al, 2001).

Annual incidence rates were computed per 100,000 person-years for each sex and calculated as 3-y moving means.

Analysis

Age adjustment was performed by direct standardization according to the European Standard Population (European standardized rates (ESR)). Cumulative incidence rates were calculated as the sum of the age-specific incidence rates for ages 0–74, multiplied with the width of the age groups (5 y). Cumulative risks were calculated from the cumulative rates as follows:

Cumulative risk = 100 × (1 − exp (−cumulative rate/100)).

Trends in incidence were estimated by calculating the estimated annual percentage change (EAPC) using STATA 7 software (STATA Corporation, College Station, Texas). The EAPC was calculated by fitting a regression line to the natural logarithm of the rates using calendar year as a regressor variable, i.e., $y = \beta_0 + \beta_1x$ where $y = \ln(\text{rate})$ and $x = \text{calendar year}$. Then the EAPC = $100 \times (e^{\beta_1} − 1)$. This calculation assumes that the rates increased or decreased at a constant rate over the entire period.

Joinpoint analyses were performed to discern significant changes in the trend and, if present, when they occurred (Kim et al, 2000). Linear line segments are connected on a log scale to identify changes in trend data in terms of the annual rates of change in fixed periods of time (Kim et al, 2000), although cross-sectional cancer rates generally do not change abruptly. The software used for these analyses was the Joinpoint Regression Program, version 2.6 of the National Cancer Institute.

Age, drift, period, and birth cohort effects were investigated using the age-period-cohort modelling as described by Clayton and Schifflers, using STATA 7 software (Clayton and Schifflers, 1987). “Drift” is a term, which was introduced by Clayton and Schifflers to describe models for which age-period and age-cohort parameters fit the data equally well. The model implies the same linear change in the logarithm of the rates over time in each age group. Such a model thus serves as an estimate of the rate of change of a regular trend (Clayton and Schifflers, 1987). Included
We would like to thank the registry team of the Eindhoven Cancer Registry, without whom the collection of the data on incident basal cell carcinoma patients would not have been possible. This work was supported by the EORTC melanoma group and the Dutch Cancer Society (KWF kankerbestrijding) in Amsterdam.

**Supplementary Material**

The following material is available from http://www.blackwellpublishing.com/products/journals/suppmat/JID/JID23306/JID23306sm.htm

**Figure S1.** Age-specific incidence rates (10^5 person-years) for basal cell carcinoma, according to sex, 3 y moving average.

**Figure S2.** Site-specific incidence of basal cell carcinoma, according to sex, 3 y moving average, with EAPC (head, head and neck; trunk, trunk; arm, arms and shoulders; leg, legs and hips; other, other cutaneous and not specified).

**Table S1.** Body site distribution of basal cell carcinoma by period, age, and sex.

**Table S2.** Goodness-of-fit statistics of the age-period-cohort analysis (25–74 year old)

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