Molecular Mechanisms of Basal Cell and Squamous Cell Carcinomas

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Dedication

I dedicate this book to Univ.-Prof. Dr. med. Wolfgang Tilgen, my teacher in dermato-oncology.
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Rapid progress in the understanding of carcinogenesis and pathology of epithelial skin cancer has led to new strategies for the prevention and treatment of these malignancies. The goal of this volume is to comprehensively cover in a highly readable overview our present knowledge of pathogenetic mechanisms and molecular biology of Basal Cell and Squamous Cell Carcinomas. Topics that are discussed in-depth by leading researchers and clinicians range from the newest findings in epidemiology, histology, photobiology, immunology, cytogenetics, and molecular pathology to new concepts for prophylaxis and treatment. Experts in the field as well as health care professionals not intimately involved in these specialized areas are provided with the most significant and timely information related to these topics. It is the aim of this book to summarize essential up-to-date information for clinicians and scientists interested in the biology of Basal Cell and Squamous Cell Carcinomas.

The chapters are written by authors who are experts in their respective research areas, and I am grateful for their willingness to contribute to this book. I would also like to express my thanks to Ron Landes, Cynthia Conomos, Sara Lord and all the other members of the Landes Bioscience staff for their expertise, diligence and patience in helping me complete this work.

Jörg Reichrathy, Prof. Dr. med.
CHAPTER 1

The Epidemiology of Basal Cell and Squamous Cell Carcinoma

Hao Wang and Thomas L. Diepgen*

Abstract

Basal cell and squamous cell carcinoma (nonmelanoma skin cancer = NMSC) are now the most common type of cancer in the Caucasian population, and the incidence of skin cancer has reached epidemic proportions. The highest incidence rates (IR) were reported from population-based studies in Australia with an IR of more than 2% for basal cell carcinoma (BCC) in males (females 1.1%), and 1.3% for squamous cell carcinoma (SCC) (females 0.7%). In this chapter, current epidemiologic data concerning the incidence and its worldwide trends, risk factors, like UV-radiation, ionizing radiation, predisposing host conditions, ageing, smoking, alcohol, diet, medical conditions, occupation, chemical carcinogenes, as well as important aspects of prevention will be discussed.

Incidence of Nonmelanoma Skin Cancer (NMSC)

Nonmelanoma skin cancer (NMSC) represents two types of malignant tumors of the skin: basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). They belong to the most common cancers in the world. Both arise from the epidermal tissue of the skin: SCC from epidermal keratinocytes, and BCC from the basal cells of the epidermis. BCC is more common with a ratio of 4:1 to SCC. Although BCC and SCC can be lethal, they are not associated with significant mortality; nevertheless the associated morbidity and therapeutic costs are an increasing burden to the health care system. Of the top-10 health priorities in the U.S.A. for this decade, NMSC ranks as number eight.

Because of its relatively low mortality, NMSC is not registered in most cancer surveillance systems. The way of reporting to most tumor registries is also not consistent, therefore actual incidence rates are not always easy to estimate from these registries and can more accurately be obtained by population-based studies and surveys. Such studies have mainly been performed in Australia and the U.S.A. Table 1 clearly shows the relatively high incidence rates of NMSC; except for Singapore. These incidence rates are reported from countries or regions which have predominantly a white population. Countries that are closer to the Equator have much higher incidence rates, while incidence rates in males are consistently higher than in females. In all these, mostly white, populations BCC is more common.

The highest rates are reported from Australia, with about twice as many BCC's compared to SCC's. Annual incidences of NMSC in north Queensland reach more than 2000 BCC's per 100,000 for men and more than 1100 BCC's per 100,000 for women. For SCC's the rates for...
men in north Queensland are more than 1300 for men and more than 700 for women per 100,000. Also the U.S.A. has high incidence rates, with considerably more BCC's. Like in Australia, rates are much higher in areas that are closer to the equator. The incidence rate of NMSC, i.e., BCC and SCC combined, in the U.S.A. is estimated to be almost similar to the incidence of all other cancers combined. From the table it becomes clear that the rates in a number of European countries or regions, which tend to be at a higher latitude than Australia and the U.S.A., are substantially lower. However, it might also be possible that the incidence rate of nonmelanoma skin cancer is underestimated in Europe. Two regions in Germany and the nearby Netherlands have per 100,000 an incidence rate of BCC in the order of 43—63 for men, and 32-58 for women. Rates for SCC are in Germany about 11 for men, and about 5 for women. It is interesting to note that the two areas in Switzerland have higher rates than Germany and the Netherlands, probably because these Swiss and Italian regions are further south, i.e., have more sunlight. Incidence rates in Slovakia seem to be relatively low compared to the other European regions. Singapore has a predominantly Chinese, i.e., nonwhite, population, which may explain the low incidence rates.

Differences in notification or detection of cases may account for some of the variability in the incidence rates. Another source of variability may be the different standard populations that were used for the age-standardisation: the US uses its own US standard population, the Netherlands the European standard, while the other studies use the worlds standard population. It is unlikely that these age adjustments account for major differences.

Table 1. Age-standardised incidence rate (per 100,000) at various world locations for men and women

<table>
<thead>
<tr>
<th>Location</th>
<th>Period</th>
<th>Standardization (Age)</th>
<th>Men BCC</th>
<th>Men SCC</th>
<th>Women BCC</th>
<th>Women SCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>Total</td>
<td>1995</td>
<td>world-standard population</td>
<td>1173</td>
<td>600</td>
<td>629</td>
</tr>
<tr>
<td></td>
<td>North Queensland</td>
<td>1997</td>
<td>world-standard population</td>
<td>2058</td>
<td>1332</td>
<td>1195</td>
</tr>
<tr>
<td></td>
<td>U.S.A.</td>
<td>1994</td>
<td>world-standard population</td>
<td>407</td>
<td>81</td>
<td>212</td>
</tr>
<tr>
<td></td>
<td>New Hampshire</td>
<td>1993-1994</td>
<td>United States population</td>
<td>309.9</td>
<td>97.2</td>
<td>165.5</td>
</tr>
<tr>
<td></td>
<td>Northcentral</td>
<td>1998-1999</td>
<td>United States population</td>
<td>930.3</td>
<td>356.2</td>
<td>485.5</td>
</tr>
<tr>
<td></td>
<td>New Mexico</td>
<td>1996</td>
<td>United States population</td>
<td>935.9</td>
<td>270.6</td>
<td>497.1</td>
</tr>
<tr>
<td>Europe</td>
<td>Wales, U.K.</td>
<td>1998</td>
<td>world-standard population</td>
<td>128</td>
<td>25</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>Saarland, Germany</td>
<td>1995-1999</td>
<td>world-standard population</td>
<td>43.7</td>
<td>11.2</td>
<td>31.7</td>
</tr>
<tr>
<td></td>
<td>Schleswig-Holstein</td>
<td>1998-2001</td>
<td>world-standard population</td>
<td>53.6</td>
<td>11.2</td>
<td>44.0</td>
</tr>
<tr>
<td></td>
<td>Vaud, Switzerland</td>
<td>1995-1998</td>
<td>world-standard population</td>
<td>75.1</td>
<td>28.9</td>
<td>66.6</td>
</tr>
<tr>
<td></td>
<td>Neuchatel, Switzerland</td>
<td>1996-1998</td>
<td>world-standard population</td>
<td>78</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trentino, Italy</td>
<td>1992-1997</td>
<td>world-standard population</td>
<td>72.7</td>
<td>23.4</td>
<td>53.9</td>
</tr>
<tr>
<td></td>
<td>Slovakia</td>
<td>1993-1995</td>
<td>world-standard population</td>
<td>38.0</td>
<td>6.7</td>
<td>29.2</td>
</tr>
<tr>
<td>Asia</td>
<td>Chinese Singapore</td>
<td>1993-1997</td>
<td>world-standard population</td>
<td>6.4</td>
<td>3.2</td>
<td>5.8</td>
</tr>
</tbody>
</table>
Trends in Incidence of BCC and SCC

The incidence of NMSC is rising in a number of countries. In addition to differences in incidence rates, there are also differences in the relative rates of change in the incidence of BCC compared to SCC.

The increase of NMSC was obvious in the time span between 1979/80 and 1993/94 in New Hampshire, U.S.A. In particular, the rate of SCC increased considerably: 253% among men and 350% among females. In men and women the rate of BCC increased by more than 80%. These changes were associated with increased exposure to sunlight, with the most prominent increase in incidence occurring among men on the trunk, and among females on the lower limbs. In New Mexico, U.S.A., marked increase in SCC rates were observed over the years between 1977 and 1999. Between 1985 and 1995 incidence rates of NMSC increased in Australia, whereby the increase in incidence of SCC was higher than of BCC. Also very high incidence rates compared to northern parts of the U.S.A. are reported from south-eastern Arizona, U.S.A., whereby it seems that this high incidence is not increasing further. Especially the incidence of SCC declined between 1985 and 1996.

Incidence rates for BCC increased steadily among men and women over the years 1976-1998 in the canton Vaud, Switzerland. This region employs a uniform ascertainment system for NMSC. Interestingly, there was a decline in the rates for SCC since 1990, after a levelling off in the late 1980s. In the study in nearby city Neuchatel this pattern was also reported. Downward trends of SCC over the past decades are also observed from Singapore, while the incidence of BCC increased on average by 3% every year over the years 1968 to 1997. A lower increase in the incidence of SCC and rising incidence of BCC is seen in Slovakia, over the year 1978-1995. Age-adjusted incidence rates of BCC have risen in the Netherlands since 1973; this was more pronounced among females. In males, there was a linear increase in rates, also affecting the younger birth cohorts, with indications that this trend will continue.

Increasing risks in white populations are clearly associated with living closer to the equator, which points to exposure to sunlight as a main causal factor. This is supported by the fact that NMSC occurs mainly on sun exposed skin.

Risk Factors

A combination of inherited and constitutional factors, with exposure to environmental factors determines the likelihood NMSC will occur in any individual. Skin colour and the response of the skin to sunlight are constitutional factors. This fact is obvious in Caucasians who have a combination of light skin and blue or blond hair; many of them get a sunburn instead of a tan when they are exposed to direct sunlight. NMSC is uncommon in black populations, Asians and Hispanic.

Ultraviolet Radiation (UVR)

The major environmental cause of BCC and SCC is exposure to sunlight, in particular the UV component of sunlight. Within the spectrum of UV, it is mainly the UVB (wavelengths 280-320 nm) that is carcinogenic, while the UVA spectrum (320-400 nm) is carcinogenic to a lesser extent. Clinical studies and studies in migrants have shown the causal link between sunlight (i.e., UV) and NMSCs. NMSC is much less common in white populations who are permanently resident in high latitude regions, where daily exposure to sunlight is low. Those who migrate early in their life from such regions to lower latitudes increase their exposure levels to sunlight and show a higher risk of developing skin cancer.

However, different profiles of UV exposure are important for BCC and SCC: For BCC the major risk factors are UV exposure during childhood and intense intermittent UV exposure. For SCC the risk factor is the chronic cumulative UV exposure. This was shown in a recent large-scale population study, showing that a very high cumulative UV dose (>145,000 kJ/m² within 6-year (1998-2003)) was associated with a doubling of the total numbers of tumors per person and a significantly increased risk of having SCC. In this study, participants who received very high doses had a BCC/SCC ratio of 2.1.
The face, neck and arms are the most common sites for NMSC, and these sites are the body areas that have the highest exposure to sunlight. Data from Vaud cancer registry show that on the face the incidence rates for SCC are about 120 times higher than on the trunk (which is normally much less exposed to sunlight). For BCC the rates on the face are about 40-50 times higher than on the trunk.

**Factors Affecting UV Radiation**

Changes in the environment and in lifestyle affect the UV radiation that reaches the skin of humans. One major concern is depletion of the ozone layer, because this layer is important in shielding against excess UVB. The ozone layer has decreased by about 2% over the past 20 years. For a 1% decrease in total column atmospheric ozone an increase of 2.7% in NMSC was to be expected. It was estimated that the UV radiation over lifetime due to a 2% decrease in ozone concentration will cause a 6-12% increase in NMSC in an exposed population. White populations living closer to the equator have a higher incidence of NMSC; the incidence of SCC doubles for very 8-10 degrees decline in latitude.

**Artificial UV Radiation**

In white-skinned populations more and more persons, especially young women, are using sun tanning beds, either at home or in tanning-studios. The increased exposure to this kind of artificial UV may increase the risk of NMSC. In a recent study, the risk estimate for any use tanning devices was 2.5 for SCC and 1.5 for BCC.

**Ageing**

With increasing age, there is an increasing cumulative exposure to UV radiation and a reduced capacity to repair DNA damage. This may be a reason of the exponential increase of the risk of NMSC with age. The incidence of SCC increases more rapidly with age than BCC. Among individuals over 75 years old the incidence of BCC was approximately 5 times higher, and the incidence of SCC was approximately 35 times higher compared to individuals 50-55 years of age.

**Smoking**

Smoking and other types of tobacco use are clearly associated with SCC of the lip. In general, SCC is positively related to cigarette smoking in most studies, but not all. The risk of developing SCC by smoking is increased twofold. It is not clear whether there is a link between BCC and smoking: the majority of the large-scale studies (Male Health Professionals Follow-up Study, Nurses Health Study, US Radiological Technologists cohort study) have not detected an association. BCC in young women was associated with past or current history of smoking. Smoking was associated with an increased prevalence of BCCs larger than 1.0 cm in diameter.

**Alcohol**

An association of alcohol consumption and BCC could not be demonstrated in case-control studies. However, three large cohort studies reported a significantly increased risk of BCC with increasing daily alcohol intake: the Male Health Professionals Follow-up Study, Nurses Health Study, US Radiological Technologists cohort study. The relationship between alcohol and SCC has not been specifically investigated.

**Diet**

Dietary factors do not seem to be causally related to the risk of BCC in humans. Experimental studies in mice demonstrated a decreased latent period and increased number of skin tumors when the animals received a diet high in fat or with a high fraction of polyunsaturated fatty acids.