Original Research

Epidemiology of cutaneous melanoma and keratinocyte cancer in white populations 1943–2036

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Abstract  Objectives: Cutaneous melanoma (CM) and keratinocyte cancer (KC) cause considerable morbidity and mortality. We analysed long-term trends of CM and KC in different white populations.

Material and methods: Age-standardised (European Standard Population 2013) incidence and mortality rates (ASIR, ASMR) of CM were extracted from cancer registries in Denmark, New Zealand and the US SEER-Database. ASIRs of KC were sourced from registries of the German federal states Saarland and Schleswig–Holstein, and from Scotland. Age-period-cohort models were used to project melanoma incidence trends.

Results: In Denmark between 1943 and 2016, melanoma ASIR increased from 1.1 to 46.5 in males, and from 1.0 to 48.5 in females, estimated to reach 60.0 and 73.1 in males and females by 2036. Melanoma mortality in Denmark (1951–2016) increased from 1.4 to 6.7 (males) and 1.2 to 3.7 (females). In New Zealand between 1948 and 2016, ASIR increased from 2.7 to 81.0 (males) and from 3.8 to 54.7 (females), slight declines are estimated by 2036 for both genders. Age-period-cohort models were used to project melanoma incidence trends.

Melanoma mortality increased six-fold in New Zealand males between 1950 and 2016; smaller increases were observed in females. We observed three- to four-fold increases in melanoma

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1. Introduction

High incidence rates of cutaneous melanoma (CM) and keratinocyte cancer (KC) are reported predominantly from white populations, susceptible to damaging effect of UV radiation, the main cause of skin cancer [1]. They rarely occur in dark-skinned populations, e. g. Africans or Asian, who are protected against UV radiation by their pigment [2]. In the period after the Second World War, white populations, especially in Western countries, experienced a sharp increase in the incidence rates of CM and KC [3,4]. First cancer registration, including melanoma began in Connecticut, Denmark and New Zealand, where incidence data were reported since 1935, 1943 and 1948, respectively. This allows analysis of incidence trends over more than seven decades [5,6].

Before 1950, melanoma incidence rates were also very low (<5 cases per 100,000 person-years) in white populations [5,6] and showed a tremendous increase after the Second World War. In some high-risk countries, such as Scandinavia or New Zealand, the incidence rates have increased by a factor of 30–40 over a period of 70 years. The annual increase varied between different populations but has been estimated to be 3–7% [7,8].

Incidence data for KC are scarce. Studies, that have attempted to estimate the burden of KC, have observed similar trends to melanoma with steeply increasing incidence rates [9]. In cancer registries, KC is recorded as non-melanoma skin cancer (NMSC), and this definition includes rare adnexal tumours, Merkel cell carcinomas, cutaneous sarcomas, and lymphomas in addition to basal cell carcinomas and squamous cell carcinomas [10]. However, the proportion of these rare tumours besides KC is less than one percent and is insignificant to the increase in incidence of this cancer entity [11]. Unlike for incidence, however, rare tumours such as Merkel cell carcinoma play a greater role for mortality. Throughout the manuscript, the term KC is used instead of NMSC.

The aim of the present study was to analyse long-term trends in incidence and mortality rates of CM and KC using data from long-standing cancer registries with historical data. For CM, we examined data from registries covering the populations of Denmark, New Zealand and the US. For KC, we used registry data from the German federal states Saarland and Schleswig–Holstein, and from Scotland. No KC registry data were available from America or Oceania.

2. Material and Methods

2.1. Cancer registry and population data

Data on incident cases and deaths of CM (ICD-10: C43) and KC (ICD-10: C44) were retrieved from population-based cancers registries in the United States, New Zealand and from the European countries, Denmark, Germany and Scotland. Historical and forecast population sizes and age structure were obtained from the statistics agencies of each nation.

Melanoma incidence (1943–2016) and mortality (1951–2016) data for Denmark were sourced from the NORDCAN database, which records cancer data for each of the Nordic countries for more than five decades [12]. Historical (1980–2016) and projected (2017–2036) population data were obtained from the Statistics Denmark [13].

For New Zealand, melanoma incidence (1948–2016) and mortality data (1950–2016) were obtained from the New Zealand Cancer Registry [14]. Population estimates and projections were retrieved from Statistics New Zealand [15].

Melanoma data for US whites were sourced from the SEER Program. Incidence data (1975–2016) were extracted from the SEER 9 database, comprising 9 registries, which together represent about 9.4% of the total US population [16]. The population structure for the SEER 9 white population largely resembles that of all US whites. Thus, 9.4% of each age and sex category of the total population, sourced from the US Census Bureau, was used as estimates for the population projections [17]. CM mortality data (1970–2017) were available for the total US Population [16].

Incidence data on KC for Germany were obtained from two epidemiological cancer registries. The Saarland Cancer Registry records KC incidence data between 1970 and 2017, the Cancer Registry in Schleswig–Holstein covers the period 1999–2016 [18,19]. Data on KC for Scotland (1992–2017) were extracted from the Scottish Cancer Registry, which provides separate data for basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) [20].
Incidence rates and mortality rates were age standardised using the New European Standard Population from 2013 and are expressed as number per 100,000 person-years (p.a.), stratified by sex [21].

2.2. Analyses of incidence trends

The average annual percentage of change (AAPC) in observed incidence and mortality rates was calculated using the Joinpoint Regression Program (version 4.8.0.1, National Cancer Institute, Bethesda, MD, USA) [22]. Modified age-period-cohort models with a power-link function were used to predict melanoma incidence rates for four 5-year periods (2017–2021 to 2032–2036). Details of the regression model have previously been described [23]. Briefly, the calculations were based on observed melanoma cases (last year of observation 2016), on population data covering the same period, and population forecasts for 2017 to 2036. Incident cancer cases were aggregated into 5-year periods and 5-year age groups (0–4, to 85+), and stratified by sex. The number of observation periods used in the prediction base was determined by a goodness-of-fit test (5% level). The linear trend parameter was gradually reduced by 25%, 50% and 75% in the second (2022–2026), third (2027–2031) and fourth (2032–2036) prediction period, accounting for the attenuating impact of current trends in future times. Analyses were carried out with NORDPRED, a statistical software package in R [24].

3. Results

3.1. Melanoma incidence trends

In Denmark, ASIRs for men rose from 1.1 in 1943 to 46.5 in 2016 and from 1.0 to 48.5 for women, corresponding to an average annual percentage change of 4.8% for both sexes (Fig. 1A). For men, projected incidence rates peaked between 2027 and 2031 (60.4), and then stabilised. Incidence rates for women are expected to rise to 73.1 by 2032–2036 (Fig. 1B).

In New Zealand, ASIRs increased at around 4.2% p.a. for women, climbing from 3.8 in 1948 to 54.7 in 2016 and at around 5.2% p.a. for men, climbing from 2.7 to 81.0 (Fig. 1C). In 1995, the incidence curve shows a sharp increase with a subsequent decrease in 1996 and 1997. Then, for both women and men, the curve shows a flattening. Since 1994 new regulations codified the manner in which reports were made to the NZ Cancer Registry. Many historic diagnoses were reported to the newly organised registry, which had the effect of showing large increases in all cancers for a couple of years (1995–1996). These are widely regarded as artefacts following implementation of the new legislation. By 2032–2036 rates are projected to fall to 60.4 for men and to 42.7 for women (Fig. 1D).

In the US, we observed three- to four-fold increases in melanoma incidence rates. The SEER data showed an increase in the ASIRs from 11.3 in 1975 to 54.7 in 2016 for men (AAPC = 4.0%) and from 9.5 to 32.8 for women (AAPC = 3.1%) (Fig. 1E). For the next 10–15 years, ASIRs will rise for males to 59.1 and for females to 36.6. Signs of stabilisation (females: 36.2) or a decline (males: 56.1) is to be expected in later years for both sexes (Fig. 1F).

3.2. Melanoma mortality trends

Melanoma mortality rates increased by 1–3% p.a. in all populations. In Denmark, ASMRs rose from 1.4 in 1951 to 6.7 in 2016 for men and from 1.2 to 3.7 for women (Fig. 2A). In New Zealand, ASMRs increased from 2.2 in 1950 to 15.1 in 2016 for men and from 1.4 to 6.0 for women (Fig. 2B). In the US, ASMRs for men increased from 3.1 in 1970 to 6.7 in 2009; and then declined to 5.1 cases in 2017. ASMRs for women remained largely the same (around 2.1 cases) (Fig. 2C).

3.3. KC incidence trends

Stronger increases (2–6% p.a.) were found for KC. In the German federal state of Saarland ASIRs rose from 18.6 in 1970 to 174.1 in 2017 (AAPC = 5.5%) for men and from 17.0 to 147.8 for women (AAPC = 5.7%) (Fig. 3A). In Schleswig–Holstein, ASIRs increased from 204.2 in 1999 to 391.4 in 2016 for men (AAPC = 2.6%) and from 137.2 to 262.9 for women (AAPC = 3.8%) (Fig. 3B). In 2015 and 2016, there was a sharp increase in the incidence of KC, resulting in the highest values of 391 for men and of 262 for women. The possible reason for this development might be the implementation of a new cancer registry law in 2015.

In Scotland, both entities have shown rising incidence rates, with stronger increases for SCC (AAPC = 3.1–4.0%) than for BCC (AAPC = 1.8–2.4%). For the period 1992 to 2017, the ASIRs of SCC increased from 44.5 to 107.2 in men and from 17.2 to 34.8 in women. The ASIRs of BCC increased from 103.2 to 178.3 in men and from 78.1 to 122.7 in women (Fig. 3C).

3.4. KC mortality trends

In Germany, ASMRs for KC first decreased and then stabilised in the last two decades. In the German federal state of Saarland, ASMRs dropped from 2.4 in 1972–1976 to 1.3 in 2012–2016 for men and from 1.1 to 0.5 for women. In Schleswig–Holstein, ASMRs remained nearly stable with 0.53 for 1999–2003 and 0.62 for 2012–2016 for men and with 0.15 and 0.4 for women.
4. Discussion

This study examined incidence trends for CM in the Danish cancer registry over 73 years, in the New Zealand cancer registry over 68 years and in the US SEER database over 41 years. We found substantial increases in CM in all three populations over time, ranging between 3% and 5% p.a. for both sexes. In Denmark and New Zealand with data from the middle decades of the 20th century CM incidence was very low (<5/100,000 p.a.). By the 1970s, CM incidence had climbed to about 10/100,000 p.a. in Denmark and the US, and in New Zealand.
Zealand to about 20/100,000 p.a. By the start of the new millennium, in all three populations, CM incidence had basically doubled (women) or even tripled (men). In subsequent decades rates have continued to rise. It is striking that in the USA and New Zealand significantly higher incidence rates are found in males than in females, whereas in Europe rather a reverse trend is evident. Olsen et al. describe in a comparative analysis that total melanoma incidence in Caucasians was higher in men than women in US individuals, Canada, Australia, and New Zealand, but not in Denmark, the UK, Norway and Sweden [25]. This suggests different UV exposure habits.

However, based on underlying trends by age, birth cohort and time period, we project that rates will likely plateau in the coming decades.

For KC, much less data are available, as KC is not registered by most cancer registries worldwide. In particular, there are no registry data for KC from North America and Oceania. Therefore, the true disease burden of skin cancer remains unclear and is often
underestimated [26]. A number of studies that have attempted to estimate the burden of KC have reported exceptionally high incidence rates of KC for sub-populations within those countries. Five time higher incidence rates of KC have been reported from Queensland, Australia [27].

We analysed population-based data from two registries in Germany and one in Scotland. In Germany, the Saarland Cancer Registry records KC data since 1970. In the five decades between 1970 and 2017, KC incidence increased about 9-fold for both men and women. It is striking that the registered incidence rates for KC in Schleswig-Holstein and Saarland differ greatly with slightly 100 cases more in Schleswig-Holstein than in Saarland. The most likely explanation for this is the degree of pigmentation of the respective populations. While in Northern Germany a Scandinavian skin type (blond and skin types I–II) is more predominant, in Southern Germany many people are brown to black haired and pigmented with skin types III and IV.

The data from Scotland, which only date back to 1992, show a similar picture of markedly rising incidence of KC over recent decades. In 2017, the ratio of SCC to BCC was about 2:3 in men and 1:4 in women.

For melanoma, mortality has also continued to rise over time in all populations, although at a slower pace than incidence, suggesting an increase in thicker melanomas, in addition to thinner, good prognosis tumours.

Skin cancer is mainly caused by UV radiation (UVR) [28]. Historically, rates of sunlight-induced skin cancers were low among populations residing in high-latitude locations, due to the ambient conditions, and the attitudes of modesty that prevailed. At the beginning of the 20th century, the ideal of pallor still existed and people protected themselves from UV radiation to the greatest extent possible. Rising incidence rates suggest that a fundamental change in behaviour took place worldwide around the middle of the 20th century. It was not until after the Second World War that there was a change in perceptions. “Tanning” became a symbol of beauty and health and has become a dominant goal in holidays [29,30]. Sun holidays, preferably by the sea, have become a part of the normal life of broad social strata. One reason for the increase in incidences may also be the earlier diagnosis of CM and KC, since many of these tumours were not diagnosed early in the past. In addition, there is also speculation about possible overdiagnosis, although this cannot be quantified [31].

For both CM and KC, the main intracellular target for UVR is DNA [32]. Ultraviolet B radiation is responsible for the formation of the principal DNA lesions, cyclobutane pyrimidine dimers and pyrimidine (6-4) pyrimidine photoproducts, whose incorrect repair leads to base mutations of cytidine to thymidine (C > T or CC > TT), which are considered as ‘UV signature mutations’ [33,34]. Both CM and KC are caused by UVR, but keratinocytes can go into apoptosis upon UV damage and KC only develop at older ages. Melanocytes, on the other hand, have an apoptosis-protective mechanism and melanomas can occur as early as adolescence because of cumulative mutations [32].

A measure of the number of mutations is the tumour mutation burden (TMB). The highest TMB among all cancers is found in basal cell carcinomas, followed by cutaneous squamous cell carcinomas, cutaneous melanomas and bronchial carcinomas [35,36]. These are tumours triggered by exogenous carcinogens, skin tumours by UVR and bronchial carcinomas by smoking.

Beginning in the early 1980s, numerous prevention campaigns have been introduced in high-risk populations to combat skin cancer. Nevertheless, still rising incidence rates of CM and KC, particularly in Europe and the US, suggest that previous prevention campaigns have not been effective so far. An exception is apparently Australia, where a flattening of the incidence with plateau formation is reported from about 2005 [3]. High incidence rates of skin cancer, especially of melanoma, prompted Australia to start first prevention campaigns in the early 1980s. The prevention campaigns were accompanied by sustainable measures such as the introduction of sun protective clothing for schoolchildren (school uniforms), the installation of sun sails in public places and schoolyards, etc. This could explain the stabilisation of incidence rates in Australia in recent years [37].

Incidence projections for Denmark and the US suggest a further increase in incidence at least until 2025. Thus, melanoma will probably be one of the most common types of cancer in white susceptible populations in future [3,38]. People who will develop skin cancer during this period have already accumulated sufficient amounts of UVR to develop skin cancer. Due to the long latency period of 20–30 years, it is not expected that behavioural changes will lead to a significant decrease in melanoma incidence in the coming years.

The present work has some limitations. There are only a few registries worldwide that have continuously registered CM for more than five decades. Therefore, the trends in incidence rates of CM are exemplary rather than representative. The overall data on KC is very sparse and only a few registries worldwide document KC.

In conclusion, this study confirms the overall observed sharp increase in the incidence rates of CM and KC in white populations in recent decades. Although considerable efforts have been undertaken in many susceptible populations to combat skin cancer, a further increase in melanoma, and most likely also in keratinocyte skin cancer, are to be expected in the near future. In New
Zealand and Australia, however, skin cancer prevention campaigns appear to be showing initial successes in decreasing incidence rate of melanoma.

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Author contributions

CG, UK, SG, TA, AK, BH, PM, LF, UL, DW: conceived, designed, and planned the study. CG, UK, AK, BH: acquired the data. CG, UK, SG, TA, AK, BH, PM, LF, UL, DW: analysed the data. CG, UK, SG, TA, AK, BH, PM, LF, UL, DW: interpreted the data. CG, UK, TA, LF, UL, DW: drafted the manuscript. CG, UK, SG, TA, AK, BH, PM, LF, UL, DW: reviewed the manuscript for important intellectual content. All authors reviewed the interim drafts and the final version of the manuscript and agreed with its content and submission.

Conflict of interest statement

Dr. Garbe reports personal fees from Amgen, grants and personal fees from BMS, personal fees from MSD, grants and personal fees from Neracare, grants and personal fees from Roche, grants and personal fees from Sanofi, outside the submitted work. Dr. Amaral reports grants from Neracare, grants from Novartis, grants from SkylineDx, personal fees and travel support from BMS, travel support from Novartis, personal fees from CeCaVa, outside the submitted work. Dr. Leiter reports personal fees from Roche, Novartis and Sanofi, grants and personal fees from MSD, outside the submitted work. Dr. Whitman reports grants from National Health and Medical Research Council of Australia, personal fees from Pierre-Fabre, outside the submitted work. All remaining authors have declared no conflicts of interest.

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