Epidemiology of Skin Cancer: Update 2019

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Abstract

Melanoma and keratinocyte skin cancer (KSC) are the most common types of cancer in White-skinned populations. Both tumor entities showed increasing incidence rates worldwide but stable or decreasing mortality rates. Rising incidence rates of cutaneous melanoma (CM) and KSC are largely attributed to increasing exposure to ultraviolet (UV) radiation, the main causal risk factor for skin cancer.

Incidence rates of KSC, comprising of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are much higher than that of melanoma. BCC development is mainly the cause of an intensive UV exposure in childhood and adolescence, while SCC development is related to chronic, cumulative UV exposure over decades. Although mortality is relatively low, KSC is an increasing problem for health care services causing significant morbidity.

Cutaneous melanoma is rapidly increasing in White populations, with an estimated annual increase of around 3–7% over the past decades. In contrast to SCC, melanoma risk is associated with intermittent and chronic exposure to sunlight. The frequency of its occurrence is closely associated with the constitutive color of the skin and the geographical zone. Changes in outdoor activities and exposure to sunlight during the past 70 years are an important factor for the increasing incidence of melanoma. Mortality rates of melanoma show stabilization in the USA, Australia, and in European countries. In the USA even dropping numbers of death cases were recently reported, probably reflecting efficacy of the new systemic treatments.

Among younger cohorts in some populations (e.g., Australia and New Zealand,), stabilizing or declining incidence rates of CM are observed, potentially caused by primary prevention campaigns aimed at reducing UV exposure. In contrast, incidence rates of CM are still rising in most European countries and in the USA. Ongoing trends towards thinner melanoma are largely ascribed to earlier detection.

Keywords

Keratinocyte skin cancer · Melanoma · Increasing incidence · Decreasing or stable mortality · Chronic or intermittent sunlight exposure

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Introduction

Skin cancers are currently the most frequent solid cancers in White populations, while they are rare in African and Asian populations because these populations have effective pigment protection. The main forms are melanoma, originating from pigment cells of the skin, and basal cell carcinoma and squamous cell carcinoma, originating from keratinocytes. All skin cancers in White populations are caused in 90–95% by UV radiation and are therefore considered to be predominantly caused by population attributable factors [1]. This means that skin cancers could be avoided as far as possible by changing the behavior and avoiding UV exposure.

The important role of UV radiation in the development of skin cancer is also reflected in the mutation patterns of these tumors. The investigation of tumor mutational burden in 27 different tumors showed the following picture: the lowest tumor mutational burden was found in hematological and pediatric tumors, and the highest tumor mutational burden was found in lung cancer and melanoma [2]. These are characteristically caused by exogenous carcinogens such as cigarette smoke and UV radiation. The mutation pattern in melanoma with C-T transitions in about 90% of all mutations is also characteristic for UV-induced mutations. Further studies on skin tumors showed that the mutation load in squamous cell carcinoma of the skin is even significantly higher than in melanomas. In squamous cell carcinoma, 61 mutations/Mb were found, in melanoma just 13/Mb [3].

Incidence and mortality of melanoma are well documented in many registers worldwide. Observed cases are recorded in cancer registries, and estimates based on these data are made for new cancer cases or deaths. The estimates are made in advance and are therefore more up-to-date than the cases observed. The American Cancer Society's Department of Epidemiology and Surveillance Research has been making such case number estimates since 1970 and has reported reliable estimates on melanoma since 1975. The data for the USA are summarized in Table 6.1 for the period 1975–2019 [4–16]. During this period, the number of melanoma cases increased more than tenfold and deaths doubled between 1975 and 2016. While the number of new cases continued to increase and even doubled between 2000 and 2019, the number of deaths showed an interesting development: from 2016 to 2019, there was a significant decrease in the number of deaths. In 2019, 2900 fewer patients died from melanoma than in 2016. Most likely because of the efficacy of the new targeted therapies and the new immunotherapies, probably a certain percentage of patients with metastatic melanoma are currently being cured.

The incidence of keratinocyte skin cancer is much higher than that of melanoma, but keratinocyte skin cancer has a very low mortality rate. This is the reason why keratinocyte is hardly recorded by cancer registries worldwide. In the USA, there is no cancer registry data on keratinocyte skin cancer. In order to collect data on keratinocyte skin cancer, evaluations of health insurance data were carried out. It turned out that 2–3,000,000 procedures for the treatment of keratinocyte were billed annually [17]. In Germany, keratinocyte skin cancer is recorded by several cancer registries in different federal states. Here it was shown that the incidence of keratinocyte skin cancer is about ten times higher than that of melanoma. For 2010, 25 cases of melanoma and 250 cases of keratinocyte skin cancer per 100,000 inhabitants per year were registered in Germany [18, 19]. About 80% of keratinocyte skin cancers are basal cell carcinomas, and about 20% are squamous cell carcinomas.

The purpose of this review is to provide an overview of the data available worldwide on the epidemiology of melanoma and skin cancer. The causal role of UV exposure in the development of melanomas and skin cancer will be addressed in particular. Trends of increases in incidence and mortality are analyzed. Particular attention will be paid to detecting the onset of plateau formation or even a decrease in incidence.

Table 6.1 Annual estimates of new melanoma cases and deaths by the American Cancer Society's Department of Epidemiology and Surveillance Research for the USA from 1975 to 2019

Year	Estimated new cancer cases	Estimated cancer deaths
1975	9000	5000
1980	14,100	4600
1985	22,000	5500
1990	27,600	6300
1995	34,100	7200
2000	47,700	7700
2005	59,580	7770
2010	68,130	8700
2015	73,870	9940
2016	76,380	10,130
2017	87,110	9730
2018	91,270	9320
2019	96,480	7230

Keratinocyte Skin Cancer

Incidence of Keratinocyte Skin Cancer

Keratinocyte skin cancer (KSC) is by far the most frequent cancer in White populations, and numerous studies have shown that incidence rates of KSC are increasing worldwide [20–25]. KSC generally occurs in persons older than 50 years, and in this age group, its incidence is increasing rapidly. In the USA the estimated case numbers of KSC is more than 1000.000 per year of which roughly 20–30% are SCC and 70–80% are BCC [26]. In the White population in the USA, Canada, and Australia, a mean annual increase of KSC of 3–8% was observed since 1960 [20, 26–28]. Few studies found nearly 50-fold differences in the incidence of basal cell carcinoma (BCC) and 100-fold differences in squamous cell carcinoma (SCC) between Caucasian populations in Northern Europe and Australia [20, 29]. Within Australia there is a marked North to South gradient with the most extreme incidence rates of KSC recorded in Queensland [30]. Age-standardized incidence rates (ASIR) of KSC, reported by a 3-year study (2011–2014), were 3105/100,000/year for men and 2296/100,000/year for women [30]. This study also showed that within the 3-year study period, 47% of the patients suffered from multiple KSC which strongly correlated with higher ages. Age-specific incidence increased from 26/100,000/year among 20–24-year-old people and reached rates of more than 6000/100,000/year among those aged 80–84.

In Germany, the age-standardized incidence rate of KSC was reported to be 113.2/100,000/year in men and 85.1/100,000/year in women in 2014 (European Standard Population ESP) [31]. Between 2007 and 2014, the estimated annual percentage change (EAPC) of the age-standardized incidence rate of keratinocyte skin cancer was 3.6% among men and 5.2% among women [32]. The KSC incidence rates in Germany corresponded well with data from Denmark (126.5/100,000/year for males and 124,8/100,000/year for females in 2012) (Fig. 6.1e) [33].

Increasing incidence rates of BCC and SCC have been reported in several European countries. A study from the Scottish cancer registry over a period of 12 years revealed an annual increase of 1.4–3.5% [25]. The Danish cancer registry also evaluated the incidence rates of BCC and SCC over a period of 30 years, and the incidence rates have risen between 3.1 and 4.6% per year [24]. Finally, a German study, including data from 11 cancer registries over a period of 13 years, reported an annual increase of 3.3–11.6% for BCC and SCC [23]. In the German Federal State of Saarland between 1970 and 2016, the KSC age-standardized incidence rates

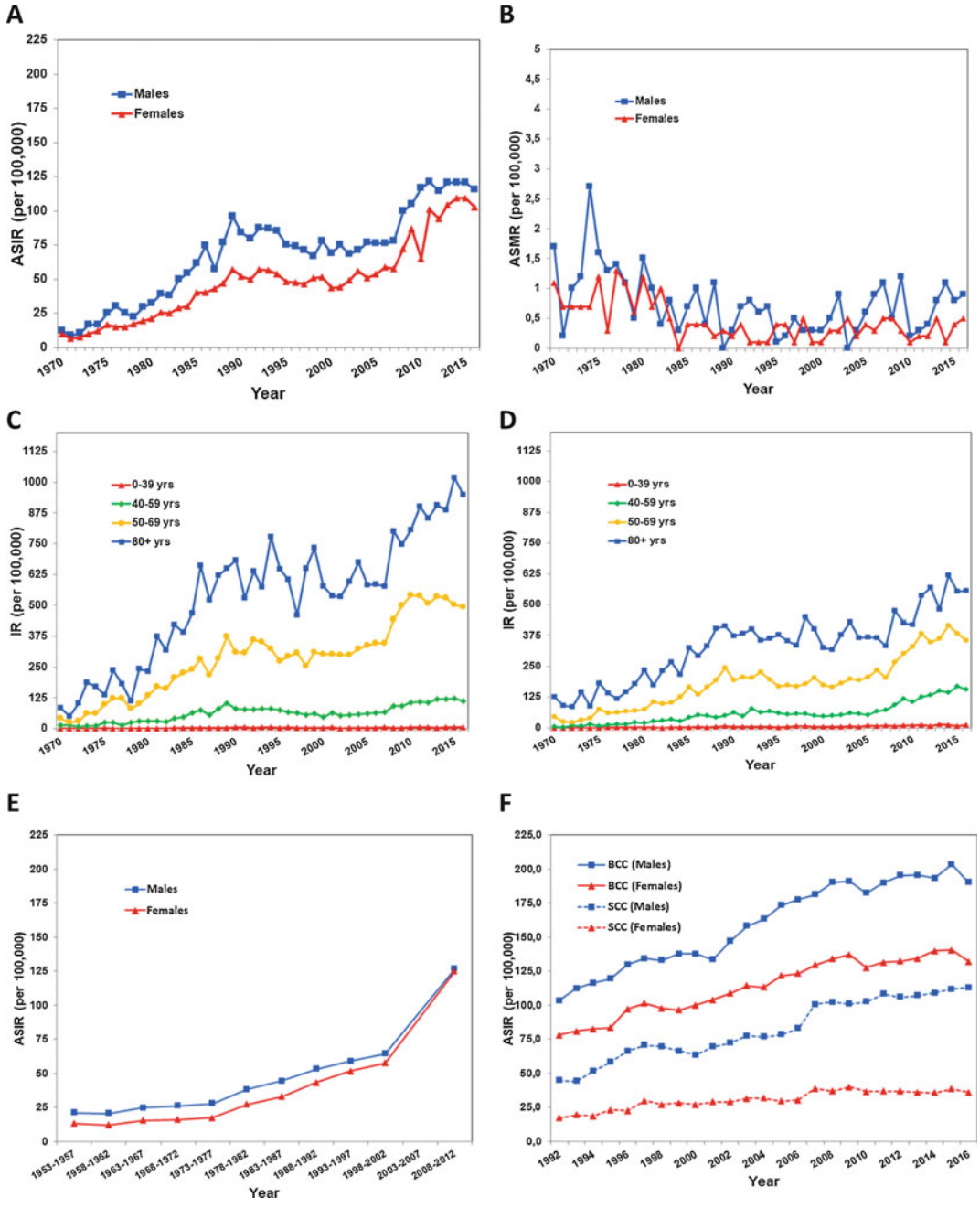

Fig. 6.1 Incidence and mortality rates of keratinocyte skin cancer in Germany (Saarland), Scotland, and Denmark. (**a**) Age-standardized (European Standard Population) incidence rates (ASIR) of keratinocyte skin cancer in Saarland 1970–2016. (**b**) Age-standardized (European Standard Population) mortality rates (ASMR) of keratinocyte skin cancer in Saarland 1970–2016. (**c**) Age-specific incidence rates (IR) of keratinocyte skin cancer in Saarland 1970–2016 (males). (**d**) Age-specific incidence rates (IR) of keratinocyte skin cancer in Saarland 1970–2016 (females). (**e**) Age-standardized (World Standard Population) incidence rates (ASIR) of keratinocyte skin cancer in Denmark 1953–2012**.** (**f**) Age-standardized (European Standard Population) incidence rates (ASIR) of keratinocyte skin cancer in Scotland 1992–2016, separately for SCC and BCC

increased from 12.0 to 115.6/100,000/year in males and from 9.7 to 102.7/100,000/year in females (Fig. 6.1a) [34]. Age-specific incidence rates continuously increased between 1970 and 2016. Throughout the entire period, the highest incidence rates were observed in persons 80 years and older. In this age group, incidence rates increased from 85.3 in 1970 to 950.1/100,000/year in 2016 in males and from 126.8 to 554.5/100,000/year in females. In the same period, considerably lower incidence rates were observed in the youngest age group (40 years and younger). Between 1970 and 2016, the incidence rates increased for both sexes from less than 0.01 to 6.4/100,000/year in males and to 11.1/100,000/year in females (Fig. 6.1c, d).

These incidence rates may be underestimated as only the first keratinocyte tumor is registered in many registries. To overcome this problem, a cohort study from the UK, assessing the first BCC and SCC per patient per annum for the period 2013–2015, identified 51% additional tumors, leading to threefold higher incidence rates [35]. In this time period, the mean annual percentage increase was 5% for both BCC and SCC.

Basal Cell Carcinoma

Basal cell carcinoma is worldwide the most frequent cancer in fair-skinned people and occurs more frequently than SCC. It is more commonly found in men than in women. In a cohort study from the UK, BCC incidence in 2013–2015 was 352/100,000/year for men and 219/100,000/year for women [35] (Table 6.2), which is clearly higher than the incidence rate found in Germany. Here, an incidence rate for BCC was reported with 113.8/100,000/year in men and 102.5/100,000/year in women [21], similar to rates found in Scotland 2016 (190.1/100,000/year for men and 132/100,000/year for women) [36] (Table 6.2, Fig. 6.1f). According to estimates from the Robert Koch Institute, in 2014 about 43,863 men and 44,257 women were diagnosed with BCC for the first time [37]**.** Compared to Northern European countries as Scotland or Germany, incidence rates were found to be three- to tenfold higher in the USA and 10- to 20-fold higher in Australia. In Australia highest yearly age-standardized incidence rates were found dependent on the latitude, in Queensland for BCC with 1538/100,000/year for men and 1191/100,000/year for women [30] (Table 6.2).

Squamous Cell Carcinoma

Squamous cell carcinoma is mostly associated with an older age (mean age 70 years at diagnosis), especially in males, who are about twice frequently affected. About 80% of cases occur in people aged 60 years and above [28, 38]. Highest incidence rates were found in Australia. In Queensland, incidence rates in 2011–2014 accounted for 573/100,000/year in men and for 371/100,000/year in women [30] (Table 6.2). In the USA, incidence rates were lower, 207.5/100,000/year for men and 128.8/100,000/year for women [26] (Table 6.2). In the UK the estimated annual percentage change was 6% in the 3-year period from 2013 to 2015. Incidence rates for cutaneous SCC were 111/100,000/year in men and 42/100,000/year in women [35] (Table 6.2). According to estimates from the Robert Koch Institute, in 2014 about 29,300 men and 20,100 women in Germany were diagnosed with SCC for the first time [37]**.** The incidence of SCC in Germany has increased fourfold in the last 30 years [21, 23].

Decrease of Mortality in Keratinocyte Skin Cancer

Compared to the incidence, the mortality of KSC is quite low. The age-adjusted US mortality rate for KSC from 1969 to 2000 was 0.69/100,000/year; the rate among men was twice higher than among women. Overall, SCC and BCC death rates have declined [39]. According to the Rhode Island study, decreasing SCC mortality rates for men and women have been observed when comparing two time periods (1979–1987 and 1988–2000) [40, 41]. Also, the BCC

Table 6.2 Incidence rate of basal cell carcinoma and squamous cell carcinoma in Europe (Germany/Federal State of Schleswig-Holstein [21], Scotland [36], UK [35]), the USA (Minnesota) [26], and Australia (Queensland) [30]

	Incidence rates per 100,000 inhabitants and year	
	Basal cell carcinoma	Squamous cell carcinoma
Germany 2008–2010		
Men	113.8	30.0
Women	102.5	15.6
Scotland 2016		
Men	190.1	113.0
Women	132.0	35.8
US Minnesota 2000–2010		
Men	360	207.5
Women	292.9	128.8
Australia Queensland 2011–2014		
Men	1538	573
Women	1191	371
UK 2013–2015[a]		
Men	352	111
Women	219	42

Incidence rates per 100,000 inhabitants and year, age-standardized for the European Standard Population 1976, US Standard Population 2000 and for the Australian Standard Population

[a]Calculated for the first BCC and the first SCC per patient per year

mortality rate for the current period was estimated at 0.05 compared with 0.10 for the earlier period. In Europe, similarly, a decrease of mortality rates was found [42]. In the Netherlands, SCC mortality rates decreased by −1.9% (95% CI: −3.1% to −0.7%) from 1989 to 2008 annually [43]. A meta-analysis from Wehner et al. [44] compared rates from four countries, Germany [45], Denmark [46], the USA [47], and the Netherlands [43]. For BCC all studies showed similar outcomes with a standard mortality rate reaching from 0.87 to 0.97. For SCC the rates were higher, reaching 1.17 in Germany, 1.3 in Denmark, 1.25 in the USA, and 1.27 in the Netherlands. Therefore, patients with SCC had a 25% increased risk of all-cause mortality compared to the general population. Mortality rates from 1970 to 2016 in western Germany (the Federal State of Saarland) revealed a continuous decrease since the 1970s. In men, the age-standardized mortality rate (European Standard Population) decreased from 1.7/100,000/year in 1970 to 0.9/100,000/year in 2016, and in women this rate decreased from 1.1/100,000/year to 0.5/100.000/year for the same period [34] (Fig. 6.1b).

Clinical Epidemiology of KSC

Keratinocyte skin cancers constitute more than one-third of all cancers in the USA, and the standardized ratio of BCC to SCC is roughly 4:1.2 [48]. Recent studies however reported a more balanced overall BCC/SCC incidence ratio of 1.4:1, which equalized as age increases, reaching 1.1:1 in age groups older than 60 years [49, 50].

KSC generally occurs in persons older than 50 years, and in this age group, its incidence is increasing rapidly, patients with SCC were generally older at the time of diagnosis [28, 51, 52]. The anatomic pattern of increase in BCC and SCC incidence was consistent with an effect of higher sunlight exposure. Over 80% of KSC occur on sun-exposed body sites. For KSC the highest body site-specific incidence rates were found for lip, orbit, nasolabial and ear, nose, cheek, and the dorsum of the hands [53]. In 2008 Brantsch et al. [54] showed that tumor thickness is an independent prognostic factor in SCC. Key prognostic factors for metastasis were increased tumor thickness (hazard ratio HR 4.79), immunosuppression (HR 4.32), localization at the

ear (HR 3.61), and increased horizontal size (HR 2.22). The risk of local recurrence depended on increased tumor thickness (HR 6.03) and desmoplasia (HR 16.11) [54].

Sun Exposure and Keratinocyte Skin Cancer

Sun exposure has since long been regarded to be the major environmental risk factor for nonmelanoma skin cancer [55, 56]. Lifelong cumulative sun exposure has been postulated to be a causal factor for SCC [55], while mixed effects of intermittent and cumulative sun exposure have been discussed as being causal for BCC [56]. A dose-response curve for sun exposure and BCC could be reported by several authors [56].

There is strong evidence to suggest that the role of UV radiation in the development of skin cancer is multifold: [1] it causes mutations in cellular DNA that might ultimately lead to unrestrained growth and tumor formation, (and [2]) it induces a state of relative cutaneous immunesuppression that might prevent tumor rejection and [3] might allow the persistent infection with human papilloma viruses (HPV) as shown in immunosuppression patients [57]. Most UV-induced damage to the cellular DNA is repaired; however, mutations may occur as a result of base mispairing of the cellular DNA. The genes involved in the repair process are also potential UV targets. p53 is a nucleoprotein encoded by a tumor suppressor gene. Mutations of the tumor suppressor gene p53 are implicated in the genesis of a wide variety of human neoplasia including KSC [58]. These mutations were reported to be present in 50% to 90% of SCC [58] and approximately 55% of BCC including very small lesions [59]. A second tumor suppressor gene, the gene for the patched (PTCH) protein in the epidermal growth-stimulating Hedgehog pathway, the human gene homolog of the Drosophila segment polarity gene patched, has also been shown to be mutated in more than 90% of sporadic BCC, in patients with Gorlin-Goltz syndrome, and with xeroderma pigmentosum [60–62]. Furthermore, it has been reported that the observed point mutations both in the PTCH and the p53 genes were predominantly UV-specific transitions [61, 63]. These results provide the first genetic evidence that UV radiation is the principal causal factor for KSC. So far, mutations in the PTCH gene seem to be specific for BCC transformation, apart from SCC in patients with a history of multiple BCC [63].

Recently, some studies report on occupational risk factors for the development of KSC. Occupational exposure to tar, mineral oils, and infrared radiation has also been identified as causative agents for KSC. Now, there is consistent epidemiological evidence for a positive association between occupational UV light exposure and an increased risk of SCC and BCC [64, 65]. In Germany, KSC has been defined as an industrial disease in outdoor workers [66, 67].

A systematic review and meta-analysis published in 2011 demonstrated that working people with many years of outdoor employment have a significantly higher risk of SCC compared to people who work indoors [64]. In addition, the causal relationship between UV radiation and the development of cutaneous SCC carcinoma and actinic keratoses is established from a pathophysiological, experimental, and epidemiological point of view.

Melanoma

Increase of Melanoma Incidence in White Populations

The incidence of cutaneous melanoma (CM) has steadily increased over the past 70 years [28, 68–73]. Steep increases were mainly reported from industrial countries with Caucasian populations (Northern America [74–76], Northern Europe [77, 78], and Australia and New Zealand [79–81]), whereas in populations with greater pigmentation (Asia and Africa), melanoma incidence has remained largely unchanged [69, 82]. A variety of behavioral changes in lifestyle (i.e., increased outdoor recreational activities, desire to tan, more frequent holidays spent in tropical climates), associated with increasing exposure to

UV radiation, have largely contributed to the observed increase in melanoma incidence in the past [68, 69, 83, 84]. The highest incidence rates were reported from Australia and New Zealand. In Australia, the age-standardized incidence rates (WHO standard population, Segi) in 2014 were 41/100,000/year for men and 29.4/100,000/year for women [85].

In the USA, the age-standardized incidence rates (US Standard Population, 2000) increased between 1975 and 2015 from 9.4 to 39.3/100,000/year for men and from 8.2 to 27.2/100,000/year for women (Fig. 6.2a) [86].

Incidence rates within Europe show great variation [69, 72, 87]. The highest incidence rates have been reported from North and West Europe, where age-standardized melanoma incidence rates (European Standard Population, 1976) for 2018 ranged between 23 and 25/100,000/year for both sexes. The lowest incidence rates in Europe were found in the Mediterranean and Eastern countries (7–12/100,000/year), which are less than half of that of Western and Northern Europe [82, 88].

In all European countries, incidence rates of CM have steadily increased since the 1950s. During the period 1990–2007, incidence rates have risen by an average of +3.8% p.a. for women and by +4.2% for men [73]. The strongest increases were observed in Northern Europe, followed by Western and later also in Eastern and Southern Europe [69].

Long-term incidence trends are reported from the Scandinavian countries, where first cancer registration had already begun in the 1940s [89, 90]. The Danish Cancer Registry recorded melanoma patients from 1943 to 2015. Age-standardized incidence rates (European Standard Population, 1976) increased from 0.9/100,000/year for men and 0.8/100,000/year for women in 1943 to 29.4/100,000/year for men and 36.8/100,000/year for women in 2015 (Fig. 6.2c) [91].

In Germany, melanoma incidence data since the 1970s are recorded in the Federal State of Saarland. For men, age-standardized incidence rates (European Standard Population) increased from 2.3/100,000/year in 1970 to 12.0/100,000/year in 2016 and in women from 2.4/100,000/year to 11.4/100,000/year, respectively (Fig. 6.2e). While incidence rates of melanoma continue to rise in most European countries (i.e., in Southern and Eastern Europe), particularly in higher age groups, there have been recent reports from several Northern and Western European countries, Australia, New Zealand, Canada, and the USA of declining incidence rates among younger birth cohorts [69, 79, 81].

Stabilization of Mortality Rates

Mortality from CM has been increasing until the late 1980s in young- and middle-aged populations from most European countries [70, 83, 92] as well as from North America, Australia, and New Zealand [5, 74, 79, 93]. Mortality rates peaked in 1988–1990. Thereafter, mortality trends developed differently. Mortality rates were still rising in several European countries (e.g., Southeastern Europe), particularly for middle-aged and old patients, whereas trends of stabilization or decline were visible among younger cohorts [18, 83, 94–98]. The favorable mortality trends are largely the result of changing patterns of sunshine exposure and sunburn in younger generations as well as to a better and earlier diagnosis of CM [18, 79, 92, 95, 99, 100]. Additionally, a trend towards thinner and less invasive melanomas in both Central Europe and Queensland was observed in the last three decades [101–103].

Age-standardized mortality rates are available for the USA from 1975 onwards. Between 1975 and 2015, the age-standardized mortality rate for men increased from 2.9/100,000/year to 4.1/100,000/year and remained largely the same for women (1.7–1.8/100,000/year) (Fig. 6.2b). Mortality rates have been recorded in Denmark from 1950 to 2015. During this period, mortality rates among men increased from 1.2/100,000/year to 4.0/100,000/year with peaks of up to 4.7/100,000/year in-between. For women, the age-standardized mortality rate increased from 0.9/100,000/year to 2.3/100,000/year with peaks around the 1990s from 3.5/100,000/year

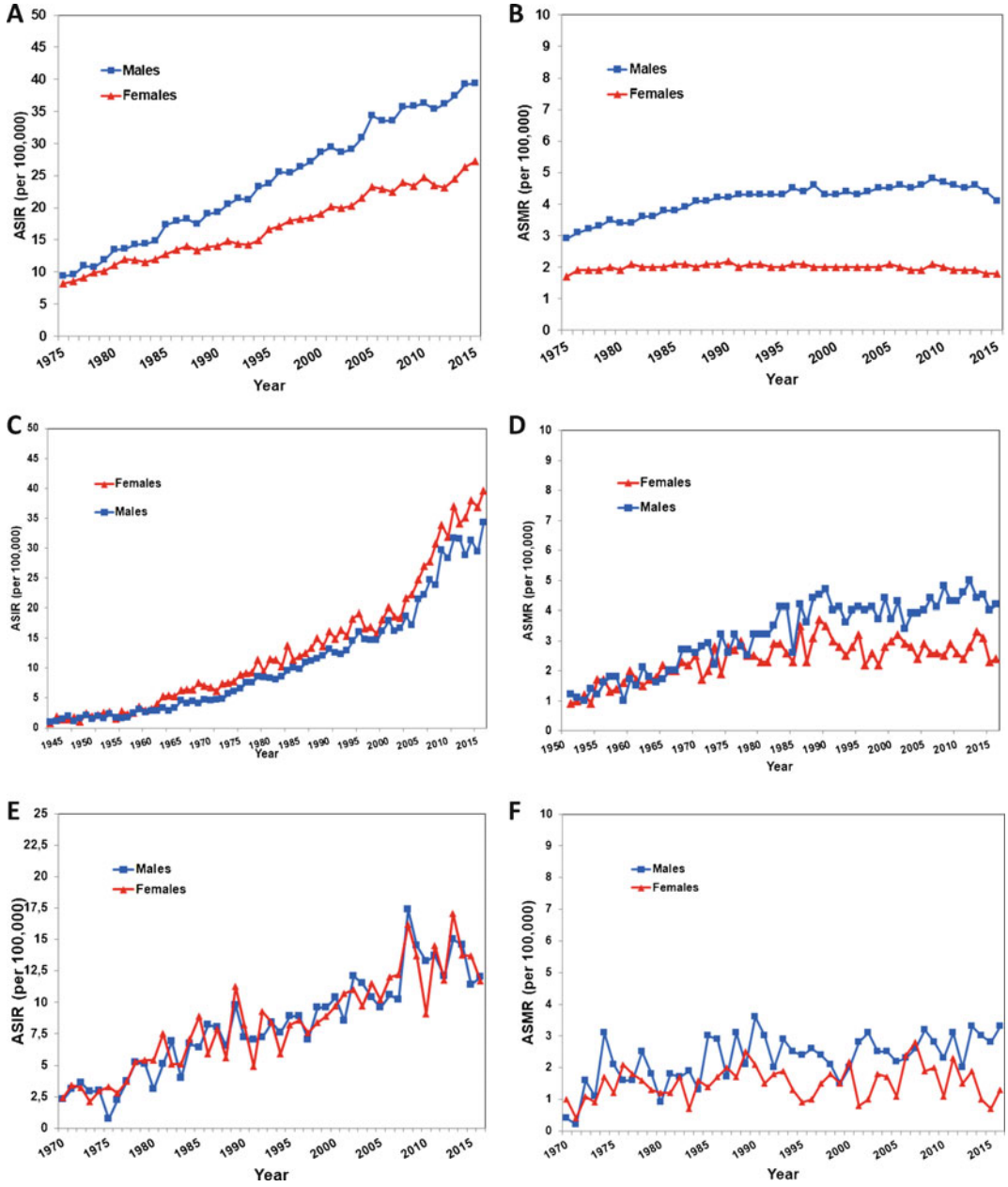

Fig. 6.2 Incidence and mortality rates of melanoma in the USA (SEER 9) and in Denmark. (**a**) Age-standardized (US Standard Population, 2000) incidence rates of melanoma in the USA 1975–2015. (**b**) Age-standardized (US Standard Population, 2000) mortality rates of melanoma in the USA 1975–2015. (**c**) Age-standardized (European Standard Population, 1976) incidence rates of melanoma in Denmark 1943–2015. (**d**) Age-standardized (European Standard Population, 1976) mortality rates of melanoma in Denmark 1943–2015. (**e**) Age-standardized (European Standard Population, 1976) incidence rates of melanoma in Germany (Saarland) 1970–2016. (**f**) Age-standardized (European Standard Population, 1976) mortality rates of melanoma in Germany (Saarland) 1970–2016

(Fig. 6.2d). In the German Federal State of Saarland, age-standardized mortality rates for men rose from 0.4/100,000/year in 1970 to 3.3/100,000/year in 2016, with peaks around 1990 of 3.6/100,000/year, while mortality rates for women only slightly increased from 1.0/100,000/year to 1.3/100,000/year, with peaks of 2.5/100,000/year in 1989 and of 2.8/100,000/year in 2007 (Fig. 6.2f).

Clinical Epidemiology

Incidence trends of melanoma including clinical and histopathological characteristics are based on data from the Central Malignant Melanoma Registry (CMMR). The CMMR is the largest clinical-based melanoma registry worldwide, which was founded in 1983 by the German Dermatological Society [104, 105].

Over the last four decades, the CMMR developed into a large multicenter project, recording data retro- and prospectively from patients diagnosed with CM in more than 70 dermatological centers in Germany (including data from the former Federal Republic of Germany and the former German Democratic Republic), Austria, and the Switzerland. Between 1983 and 2018, a total of 130,600 cases with CM were registered.

Compared to the 1970s where almost 2/3 of CM patients were women (63.5%), equalization in both sexes (51% women and 49% men) was visible in the 1990s in Germany.

In most countries, incidence rates of CM are similar in men and women. Exceptions, with a higher incidence in men, are observed from several high-risk countries (e.g., Australia, New Zealand, and the US Whites) [99, 106]. Higher rates among women are found in countries with lower CM incidence (e.g., Great Britain) [69, 107].

Anatomic Site

The anatomic site varies according to gender. In men most of the tumors are localized on the trunk, and in women the preferred site is lower extremities (Table 6.3). In men 52% of CM are localized at the trunk, thereof 37% at the back, followed by the lower leg (17%). In women 37% of CM are localized at the lower extremity, with 18% at the lower leg, followed by the trunk (27%). CM localized at the head and neck region are nearly equivalent in both sexes [104, 108].

The site-specific incidence of melanoma varies according to age. The incidence of melanoma localized on the trunk and on the lower extremity decreases in higher ages, whereas a significant increase of melanoma localized in head and neck areas was found in older patients [109, 110]. Nearly 80% of melanoma in age groups of 80 and more years were found in head and neck areas. Melanomas developing at different body sites are associated with distinct patterns of sun exposure. Melanomas of the head and neck are associated with chronic patterns of sun exposure, whereas trunk melanomas are associated with intermittent patterns of sun exposure, supporting the hypothesis that melanomas may arise through divergent causal pathways [110–112].

Histological Subtype

The most frequent histological subtype is superficial spreading melanoma which covers nearly 50% of all CM followed by nodular melanoma (16% of all CM), lentigo maligna melanoma (10% of CM), and acrolentiginous melanoma (4% of CM).

Different age distributions are found for the respective histological subtypes. The peak for superficial spreading melanomas is found in patients of 55 to 59 years, for nodular and acrolentiginous melanomas in patients of 65 to 69 years, and in lentigo maligna melanoma in patients of 70 to 74 years.

Tumor Thickness

The tumor thickness is the most important prognostic factor in primary melanoma [101, 113]. In Germany there is an ongoing trend towards thinner melanoma since the 1980s with stabilization from the mid-1990s onwards [114]. For men, the median tumor thickness decreased from 1.61 mm in 1982 to 0.91 mm in 2018 and in women from 1.44 mm to 0.90 mm, respectively (Fig. 6.3).

Table 6.3 Anatomic sites of CM in the CMMR, according to gender. The median age is given at the time point of diagnosis

Anatomic site	Men		Women	
	%	Median age	%	Median age
Face	8.7%	68	9.7%	71
Scalp	7.0%	67	2.6%	64
Neck	2.7%	60	1.8%	57
Anterior trunk	15.3%	58	8.0%	47
Posterior trunk	36.5%	59	18.6%	51
Genital region	0.2%	63	0.5%	64
Upper extremity	11.6%	61	19.4%	60
Lower extremity	16.5%	56	37.0%	54
Others	1.6%	63	2.4%	66

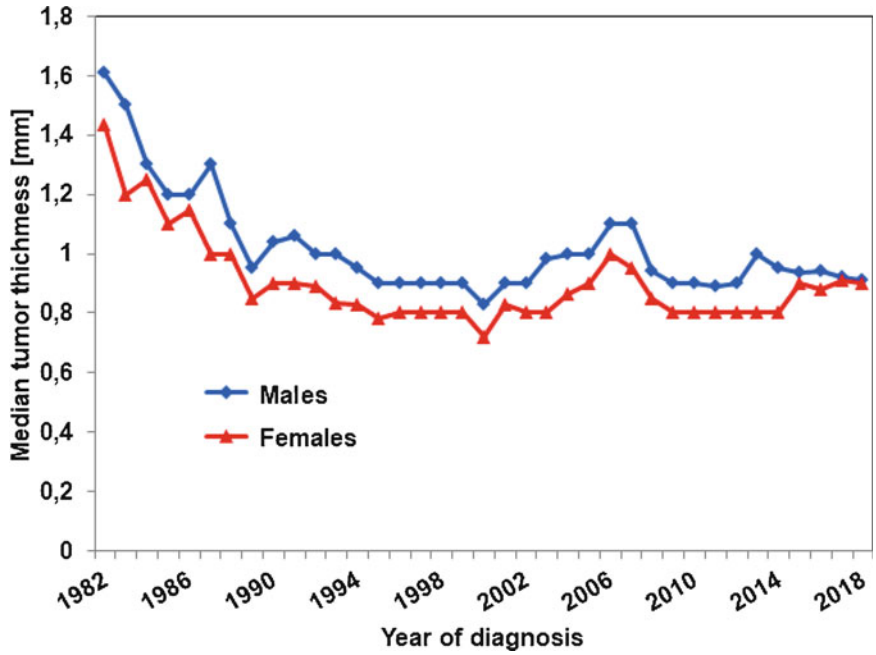

Fig. 6.3 Median tumor thickness of melanoma, recorded in the CMMR (1982–2018), by sex

The tumor thickness at the time point of primary diagnosis is also age dependent. Generally there is a significant decrease of melanoma with a tumor thickness of 1.0 mm or less in higher ages and is less than 50% at the age of 70. In contrast the proportion of thick melanoma increases significantly and reaches 22% at the age of 80 years in both genders.

An analysis of the prognosis of 19,693 patients with primary CM considering tumor thickness was performed based on data recorded by the CMMR since 2000.

In patients with a tumor thickness of 0.8 mm or less, 10-year melanoma-specific survival rates were 97%; for those with a tumor thickness between 0.8 and 1.0 mm, 10-year survival was 90% and decreased to 87% in patients with a tumor thickness of >1.0 to 2.0 mm and to 76% in patients with a tumor thickness of >2.0–4,0 mm. Ten-year survival rates were lowest (58%) in patients with a tumor thickness of more than 4 mm (Fig. 6.4).

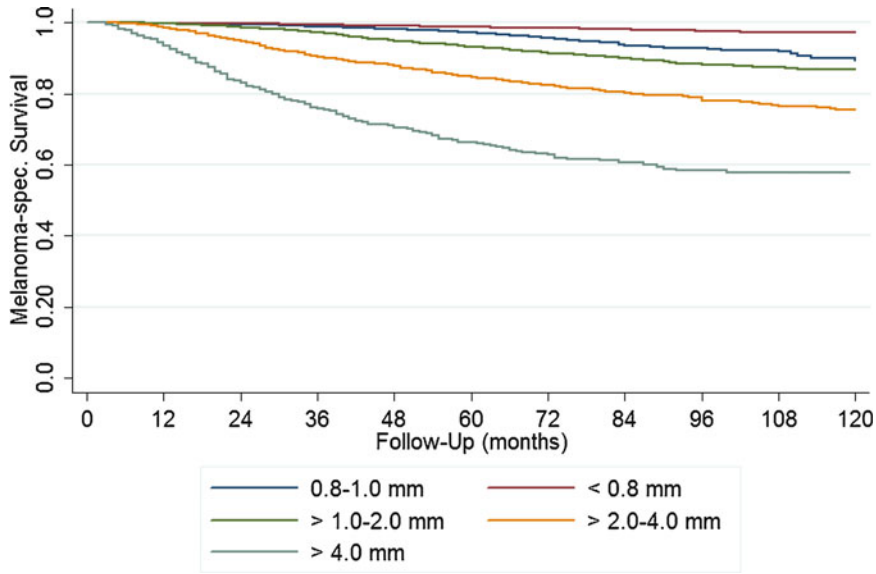

Fig. 6.4 Melanoma-specific survival, according to tumor thickness groups. (AJCC 2017)

Sun Exposure and Melanoma

Population Attributable Fraction: UV Radiation and Melanoma

A series of epidemiological and biological studies have provided sufficient evidence for the causal role of UV exposure in melanoma development [115, 116].

The population attributable fraction (PAF) quantifies the proportion and the numbers of melanoma cases that can be attributed to exposure to UV radiation and that could potentially be avoided by complete elimination of sun exposure. It is helpful in prioritizing melanoma control strategies and for the evaluation of the potential impact of interventions seeking to reduce exposure to UV.

The population attributable fraction is estimated by comparing the observed incidence rates in an "exposed" population with those of a "minimal-exposed" or "low-incidence" reference population (as approximation of an "unexposed" population). The differences in incidence rates are then attributed to corresponding differences in exposure to UV between reference and study population [1, 117].

Population Attributable Fraction: Global Estimates

The proportion of melanoma cases caused by UV exposure varies greatly across different regions, ranging from less than 1% to ≥95%, with the lowest and highest PAF observed in East Asia and Oceania [118, 119]. Most recent estimates for 2012 revealed that around 168,000 cases of melanoma were attributed to excess exposure to UV radiation, representing 75.7% of all melanoma cases worldwide. The burden was higher in men (81.3% attributable cases) than in women (69.4% attributable cases). The vast majority (around 89%, 149,340 of 168,000 cases) of UV-attributable melanoma cases occurred in countries with a very high Human Development Index (HDI), where 86.6% of all melanoma cases (91% among men and 81.4% among women) were due to high UV exposure. This was most pronounced in Australia and New Zealand, where 97.4% of all melanomas in men and 93.4% in women, respectively, were attributable to UV radiation [120]. Similarly high values were estimated for the White US population, with a PAF ranging between 85 and 92% in females and between 94 and 96% in males [1, 121]. Within Europe, the proportion of melanomas attributed to

excess sun exposure shows a great variation. The highest values for the PAF were reported from Northern (90–95%) and Western Europe (86%); lower PAFs were estimated for Eastern (68%) and Southern European countries (78%) [117, 118, 122, 123].

Conclusion

Melanoma and keratinocyte skin cancer (KSC) are now the most common types of cancer in White populations. Both tumor entities show an increasing incidence rate worldwide. The rising incidence rates are predominantly caused by increased exposure to UV radiation. An intensive UV exposure in childhood and adolescence was causative for the development of basal cell carcinoma (BCC), whereas for the etiology of SCC a chronic UV exposure in the earlier decades was accused. Melanoma risk seems to be associated with intermittent and also chronic UV exposure. Although a stabilization of CM incidence rates are observed in younger cohorts in Australia and New Zealand, the impact of primary prevention measures on incidence rates of melanoma is unlikely to be seen in the near future, and rather increasing incidence rates to 40–50/100,000/year should be expected in Europe and in the USA in the next decades.

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