Aus der

Universitäts-Hautklinik Tübingen

Incidence of cutaneous melanoma with past and present trends until 2033 in Germany and Denmark. Impact of UVR exposure and demographic changes

Inaugural-Dissertation
zur Erlangung des Doktorgrades
der Humanwissenschaften

der Medizinischen Fakultät
der Eberhard Karls Universität
zu Tübingen

vorgelegt von

Keim, Ulrike

2020

Dekan:	Professor Dr. B. Pichler
1. Berichterstatter:	Professor Dr. C. Garbe
2. Berichterstatter:	Professor Dr. A. Kelava

Tag der Disputation: 07.05.2020

For Adele

Table of Contents

List of Tables

List of Figures

Abbreviations

AAPC	Average annual percentage change
AIDS	Acquired Immune Deficiency Syndrome
AIHW	Australian Institute of Health and Welfare
ALM	Acral lentiginous melanoma
APC	Annual percentage change
APC	Age-period-cohort
ASIR	Age-standardized incidence rates
AU	Australia
BCC	Basal cell carcinoma
Bc-l2	B-cell lymphoma 2
B-RAF	B-rapidly accelerated fibrosarcoma
C	Cytidine
CCRD	Center for Cancer Registry Data
CDK4	Cyclin-dependent kinase 4
CDKN2	Cyclin-dependent kinase inhibitor 2
CI	Confidence interval
CI5	Cancer Incidence in Five Continents
CIR	Crude incidence rates
CM	Cutaneous melanoma
CPD	Cyclobutane Pyrimidine Dimers
D	Denmark
DCO	Death Certificate Only
DNA	Deoxyribonucleic Acid
EAPC	Estimated annual percentage change
ECIS	European Cancer Information System
F	Finland
GCO	Global Cancer Observatory
HDI	Human Development Index
I	Iceland
IARC	International Agency for Research on Cancer
ICD	International Statistical Classification of Diseases and Related Health Problems
IR	Incidence rate

MC1R	Melanocortin-1 Receptor
MM	Malignant melanoma
N	Norway
NA	Not applicable
NCI	National Cancer Institute
NMSC	Non-melanoma skin cancer
NSW	New South Wales
NZ	New Zealand
OR	Odds Ratio
p.a.	per annum
PAF	Population attributable fraction
QLD	Queensland
RKI	Robert Koch-Institute
RR	Relative Risk
S	Sweden
SCC	Squamous cell carcinoma
SEER	Surveillance, Epidemiology and End Results
T	Thymidine
UK	United Kingdom
UN	United Nations
US	United States
UV	Ultraviolet
UVR	Ultraviolet radiation
WHO	World Health Organization
XP	Xeroderma pigmentosum
yrs	years

1 Introduction

1.1 Background

Cutaneous melanoma (CM), is a malignant tumor of the skin, which originates from pigment producing cells, the melanocytes by neoplastic transformation (Gilchrest et al., 1999, Owens and Watt, 2003). It has developed from a rather rare tumor in the past to a tumor with growing medical importance. The incidence of CM has steadily increased over the past 50 years, predominantly in fair-skinned populations (Erdmann et al., 2013, Garbe and Leiter, 2009, Nikolaou and Stratigos, 2014). According to global estimates for 2012, there were over 230,000 new cases of melanoma, of which 100,000 occurred within Europe, and an estimated 55,000 related deaths. Melanoma burden is highest in Australia and New Zealand, where incidence rates (IR) are between 40 and 60 cases/100,000 per year, followed by North America and Northern Europe with rates over 20 cases/100,000 per year (Ferlay et al., 2015, Greinert et al., 2015, Karimkhani et al., 2017).

The major causal risk factor for melanoma development is exposure to ultraviolet radiation (UVR), (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 1992). About 80% of diagnosed melanoma are found on body sites exposed to intermittent UVR. Changes in lifestyle, namely from sun avoidance to sun-seeking behavior, have largely contributed to the steep increase in incidence of CM observed over the past decades (de Vries et al., 2003, Garbe and Leiter, 2009). In most European countries, melanoma rates continue to rise, particularly in higher age groups. First signs of stabilization or declining rates, however have been reported from younger birth cohorts in Australia/New Zealand, North America, and in Scandinavia (Arnold et al., 2014, Erdmann et al., 2013, Whiteman et al., 2016). These more favorable trends are attributed to primary prevention campaigns aimed to reduce harmful UVR exposure. In contrast to other malignant diseases, which develop predominantly at an advanced age (i.e. the sixth or seventh decade of life), melanoma can also occur at a younger age (median age at diagnosis is 55 years).

Nevertheless, as with other tumors, the risk of being diagnosed with melanoma increases with age. The highest incidence rates are recorded in men and women aged 65 years or older (Garbe and Leiter, 2009, Robert Koch Institut Berlin, 2017).

Since the early 1970s, increased life expectancy and low birth rates have caused a phenomenon known as demographic aging. It is characterized by a significant shift in the age distribution in the population towards an increased proportion of older people (Christensen et al., 2009). Both, high incidence rates among older cohorts and their growing presence in the population, imply an ongoing increase of melanoma for the foreseeable future.

The predicted increase in melanoma burden represents a major challenge for future health care provision and indicates the need for targeted melanoma control measures. Health care officials need detailed information about the expected disease burden in order to set research priorities and to plan the allocation of limited resources for core elements of cancer control. These include: primary prevention, screening and early diagnosis, treatment, rehabilitation and palliative care. An understanding of the forces that might affect future trends is essential in translating cancer predictions to decision making processes. Main determinants of cancer development are exposure to risk factors (in melanoma mainly UVR exposure) and demographic changes (population size and age distribution). In order to achieve effective melanoma control, it is crucial to estimate the number of new melanoma cases due to changes in exposure to UVR and demographics (Bashir and Esteve, 2000, Bray and Moller, 2006).

The following literature review (chapters 1.2-1.4) has a dual purpose. First, it will provide insights into the epidemiology of melanoma (chapter 1.2) with a focus on incidence trends and the role of UVR exposure in the pathogenesis of melanoma. Another part (chapter 1.3) will be devoted to demographic changes, in particular, the phenomenon of demographic aging and its impact on public health care systems in the future. Chapter 1.4 summarizes recent scientific research on future melanoma burden attributed to UVR exposure and

demographic changes. Secondly, this literature review aims to identify gaps in research in order to position the present project within its field.

1.2 Epidemiology of cutaneous melanoma

Since the early 1970s, incidence rates, and to a lesser extent also mortality rates, of melanoma have steadily increased (Arnold et al., 2014, de Vries and Coebergh, 2004, Erdmann et al., 2013, Forsea et al., 2012, Leiter et al., 2014, Nikolaou and Stratigos, 2014). While mortality rates remained roughly stable or declined since the 1990s (Autier et al., 2015, Barbaric et al., 2016, de Vries et al., 2003, Severi et al., 2000), melanoma incidence continued to rise. Although accounting for less than 5% of all skin cancers, melanoma is the major cause of death from skin cancer (Garbe and Leiter, 2009). Given steep increases in incidence and high risk of mortality, this type of skin cancer poses an enormous burden on society and public health. As the main focus of the present project was to investigate melanoma incidence trends over time and the impact of UVR exposure and demographic changes, mortality trends of melanoma will not be covered in this project.

1.2.1 Incidence trends

Geographical variations

The frequency of the occurrence of cutaneous melanoma is closely related with the constitutive color of the skin and the geographical region (de Vries et al., 2003, Leiter et al., 2014). It occurs nearly exclusively in white populations (of European origin). In dark pigmented populations such as Africa, Asia and partly Southern and Eastern Europe, the incidence of malignant melanoma (MM) is relatively low. Overall, the lifetime risk of developing melanoma is about 2.4% in Caucasians, 0.1% in Blacks, and 0.5% in Hispanics (de Vries and Coebergh, 2004, Erdmann et al., 2013, Gloster and Neal, 2006).

The highest age-standardized incidence rates (ASIR) for 2012 in both males and females were reported from Australia and New Zealand (about 35/100,000 per year; according to the World Standard Population), where incidence rates tend to be two to three times higher than anywhere else in the world. The second highest rates were found in North America, followed by Northern and

Western Europe (rates over 10/100,000 per year in both sexes). Very low incidence rates (below 0.5/100,000 per year in both sexes) were estimated for South-Eastern Asia and South-Central Asia (Ferlay et al., 2015), Table 1.

Incidence rates within Europe show great variation. Generally, melanoma incidence increases with proximity to the equator ('latitude gradient'). In Western Europe, however the inverse pattern is observed, with 3- to 6-fold higher incidence rates in Northern countries (i.e. Scandinavia) than in Southern Europe (de Vries et al., 2004, de Vries and Coebergh, 2004). Exceptions are Switzerland and the Netherlands which exhibit high incidence rates about 20/100,000 per year (also age-standardized according to the World Standard Population) compared with the surrounding countries. The lowest incidence rates in Europe were found in the Mediterranean and Eastern countries (4-8/100,000 per year) which are less than half of that of Western Europe (12-20/100,000 per year). Darker skin type (type III-IV according to Fitzpatrick) in the Mediterranean populations and different attitudes to recreational activities are responsible for this Nord-South gradient (de Vries et al., 2004, Erdmann et al., 2013, Garbe and Leiter, 2009, Nikolaou and Stratigos, 2014).

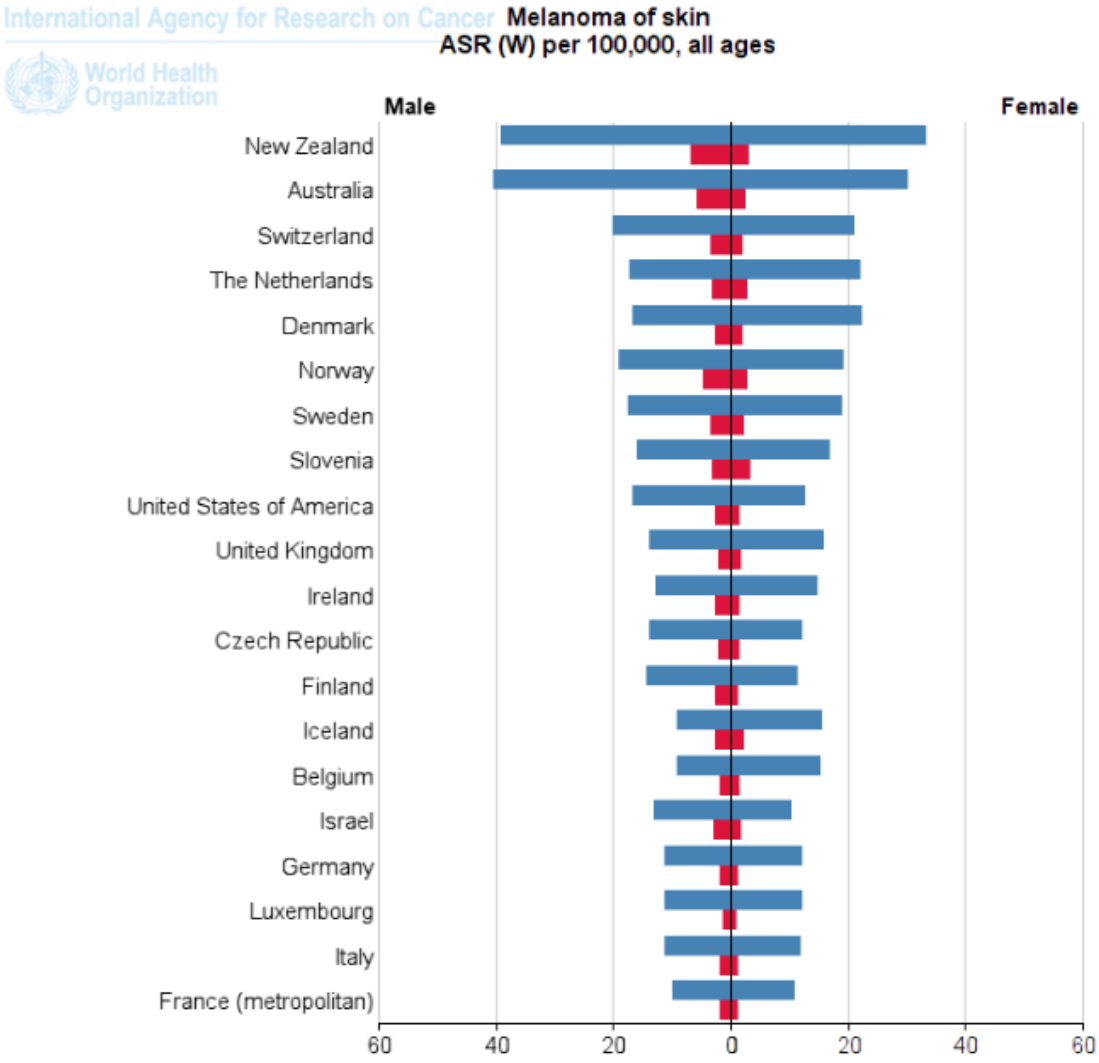
Table 1 and Figure 1 provide an overview about global melanoma incidence rates for 2012.

Table 1: Age-standardized, crude incidence rates and cumulative risk for selected regions in 2012, both sexes.

Population	ASIR[1]	CIR[2]	Cumulative Risk[3]
Australia/New Zealand	35.1	53.8	3.75
Northern America	13.8	21.3	1.50
Europe	8.6	13.5	0.89
Northern Europe	14.6	23.2	1.51
Denmark	19.2	28.5	1.91
Norway	18.8	30.4	2.02
Sweden	18.0	30.7	1.90
Western Europe	12.1	19.7	1.24
Germany	11.4	20.6	1.20
The Netherlands	19.4	28.7	1.95
Switzerland	20.3	32.1	2.05
Southern Europe	8.1	12.2	0.81
Central and Eastern Europe	4.5	7.0	0.49
Africa	1.1	0.6	0.13
Asia	0.5	0.5	0.05

[1] ASIR: Age-standardized incidence rates (Segi World Standard Population) per 100,000
[2] CIR: Crude incidence rates per 100,000
[3] Cumulative risk [0-74 years] (in %)

Source: Globocan 2012 (IARC, 2012)



Source: Globocan 2012 (IARC, 2012)

Figure 1: Age-standardized incidence rates (World Standard Population) from 20 populations with the highest incidence rates of melanoma worldwide for 2012.

Temporal trends

The incidence of CM has steadily increased in fair-skinned populations over the past 50 years. The annual increase varied between different populations, but has been estimated to be 3-7% (Arnold et al., 2014, de Vries and Coebergh, 2004, Leiter and Garbe, 2008).

Steep increases were mainly reported from industrial countries with Caucasian populations (Northern America, Northern Europe, Australia and New Zealand) (Aitken et al., 2018, Fuglede et al., 2011, Glazer et al., 2016, Helvind et al., 2015, Holman et al., 2018, Richardson et al., 2008, Whiteman et al., 2008), whereas in populations with greater pigmentation (Asia and Africa) melanoma incidence has remained largely unchanged (Erdmann et al., 2013, Ferlay et al., 2015). Rising incidence rates were observed across all age groups, most obvious however in subjects older than 60 years (Jemal et al., 2011, MacKie et al., 2009). 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 UVR, have largely contributed to the observed increase in melanoma incidence in the past (de Vries et al., 2003, Eggermont et al., 2014, Erdmann et al., 2013). 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 United States of declining incidence rates within younger birth cohorts (Aitken et al., 2018, Arnold et al., 2014, Bulliard et al., 1999, de Vries et al., 2003, Erdmann et al., 2013, Hall et al., 1999, Iannacone et al., 2015, Richardson et al., 2008, Watson et al., 2016, Whiteman et al., 2016).

The following section describes global melanoma incidence trends of different populations with different susceptibility to melanoma due to their geographical location and genetic predisposition.

Global data were assembled from the Cancer Incidence in Five Continents (CI5), Volume I-XI (IARC, 2018), as well as from the online database Globocan 2012 (IARC, 2012), both released from the International Agency for Research on Cancer (IARC). To increase the time period of data (the last year of

diagnosis available in Volume XI is 2012), melanoma incidence rates were additionally obtained from national population-based cancer registries of Autralia (AIHW, 2018), the United States (SEER, 2018) and Europe (ECIS, 2018). Melanoma incidence data for Scandinavian countries were sourced from the NORDCAN data base (NORDCAN, 2018).

In order to compare global melanoma trends, incidence rates are age-standardized according to the World Standard Population (Segi) and are expressed as incidence per 100,000 persons per year.

Australia

Between 1982 and 2014, age-standardized incidence rates increased for men and women by +70% from 20.6/100,000 per year (20.8 for males and 20.7 for females) to 34.9/100,000 per year (41.0 for males and 29.4 for females). During the observation period, the melanoma incidence went through three different phases characterized as rapid increase (+6.9% p.a.) at the beginning (1982-1987), a moderate increase (+1.7% p.a.) until 2005 (with a peak in 2005 at 36.8/100,000 per year), and declining rates (-0.7% p.a.) thereafter (AIHW, 2018, IARC, 2012, Whiteman et al., 2016).

Uniformly, increasing trends of incidence were seen across all age groups. The highest increase in melanoma rates without signs of stabilization or leveling off was observed in older men and women (≥65 years), while declining rates were reported for younger age groups (-1.2% p.a. for men and -1.8% p.a. for women) from the end of the 1990s onwards, especially for those aged 25-44 years (Whiteman et al., 2016),

United States (White population)

In US whites, age-standardized incidence rates increased between 1975 and 2012 by +135% for females (from 7.3 to 17.1/100,000 per year) and by +176% for males (from 7.9 to 21.8/100,000 per year), respectively. Strong increases (+3.4% p.a.) for both sexes were seen between 1975 and 2007, followed by slower increases thereafter. From the 2000s onwards, rates in US males aged 25-44 years appear rather stable (+0.1% p.a.), whereas rates in older men and

in US Caucasian women, irrespective of age, continued to rise (Glazer et al., 2016, Holman et al., 2018, IARC, 2012, SEER, 2018, Weir et al., 2011).

Europe

Incidence trends in Europe are greatly varying. In all European countries incidence rates of CM have steadily increased since the 1950s. Between 1990-2007 incidence rates have risen by an average of +3.8% p.a. for women and by +4.2% for men (Arnold et al., 2014).

The strongest increases were observed in Northern Europe, followed by Western and later also in Eastern and Southern Europe (de Vries et al., 2003, Greinert et al., 2015). While a deceleration in the trends could be observed in some Western and more notably in Northern European countries from the 1990s onwards, rates continue to climb in other regions of Europe, particularly in Southern and Eastern Europe (Arnold et al., 2014, de Vries et al., 2003, Erdmann et al., 2013, Forsea et al., 2012).

Northern Europe (Norway, Sweden, Finland, Denmark and Iceland)

Scandinavia has the longest period of cancer registration. Each of the Nordic countries has a population-based cancer registry. The Danish Registry is the oldest and was founded in 1942. The Norwegian, Finnish and Icelandic registries were founded in 1952-1954 and the Swedish Registry in 1958 (Engholm et al., 2010, Gjerstorff, 2011, Moller et al., 2002).

While melanoma incidence rates were low in the 1950s/1960s (in the range between 1 and 3 cases/100,000 per year), incidence rates grew rapidly over the last 5-6 decades. Of all Northern European countries, the highest incidence rates for 2013 were reported from Denmark, ranging between 21 and 28 cases/100,000 per year for men and women, respectively. Incidence rates between 8 (Iceland), 14 (Finland) and ≥20 cases/100,000 per year (Sweden and Norway) were observed in the other Scandinavian countries.

The greatest increase in incidence between 1990 and 2008 was observed for men in Iceland (+6.1% p.a.), and was most pronounced in higher age groups (70+ years: +13.7% p.a.). While incidence rates slightly increased in the youngest age group (25-44 years) in Finland (men:+1.5% p.a., women: +1.9%

p.a.) and in Icelandic men (+3.1% p.a.), between 1990 and 2008, it significantly decreased in Norwegian males (-2.8% p.a.) and remained rather stable in Norwegian females (-0.7% p.a.) and Swedish males (+0.5% p.a.) and females (+0.9% p.a.). Incidence rates in Icelandic females aged 25-44 years increased initially (1992-2001: +13.5% p.a.) and then declined (2001-2008: -7.3% p.a.). Over the entire period (1990-2008) an overall increase of +6.8% p.a. has been estimated. In more recent years (2008-2013), however, reversing trends with slightly increasing incidence rates were observed among young women (25-44 years) in Norway and more pronounced in Sweden, rates among Icelandic women continued to decline. Between 1990 and 2007 melanoma incidence rates in Denmark increased uniformly across all age groups. While among men, the highest increase was observed in the age group ≥70 years (+4.0% pea), the strongest increases were seen among women younger than 45 years (+2.5% p.a.) (Arnold et al., 2014, NORDPRED, 2016, Whiteman et al., 2016).

Western Europe (The Netherlands, Switzerland)

In the Netherlands, age-standardized incidence rates have continuously increased between 1990 and 2013. While incidence rates of melanoma were less than 10 cases per 100,000 in 1990, melanoma rates grew up to around 20 cases per 100,000 in 2013 for both sexes. Between 1990 and 2007, the annual increase ranged between +3.5% p.a. (females) and +4.2% p.a. (males), respectively (Arnold et al., 2014, de Vries et al., 2005, ECIS, 2018, Holterhues et al., 2013).

Similar trends were observed for Switzerland. For men and women, age-standardized incidence rates doubled from 10 cases per 100,000 in 1990 to around 20 cases per 100,000 in 2013, corresponding to an annual increase of about +3%. For men, a minor deceleration in the trend was observed from 1995 onwards, however this was not statistically significant.

In both countries, trends of increasing melanoma rates were observed across all age groups. In the Netherlands, the strongest increase in incidence (+5-6% p.a.) was found in the highest age group (70+ years), while in Switzerland men and women aged between 25 and 44 years experienced the largest increases (approximately +3% p.a.) (Arnold et al., 2014, ECIS, 2018).

Eastern Europe (Czech Republic, Slovakia)

Since 1990, the incidence of melanoma has increased significantly in both countries, across all ages. Incidence rates in the Czech Republic have risen for both sexes from 7-8 cases per 100,000 in 1990 to around 13 cases per 100,000 in 2013 and were higher than reported rates in Slovakia, where the rates increased from 4-5 cases per 100,000 in 1990 to 8-10 cases per 100,000 in 2013. Slovakia recorded a stronger increase between 1997 and 2004 (+7.1% p.a.) after initially a moderate growth (1990-1997: +2.7% p.a.), while rates in the Czech Republic continued to evenly increase throughout the observation period (Arnold et al., 2014, ECIS, 2018)

Southern Europe (Portugal Slovenia)

In Southern Europe, the lowest melanoma incidence rates have been reported from the cancer registry of Northern Portugal. During the study period (1996-2010), melanoma incidence rates rised for men and women from 1-2 cases/100,000 per year to around 5 cases/100,000 per year. Significantly higher incidence rates, climbing from 5 cases/100,000 in 1990 to 15 cases/100,000 in 2012 were observed in Slovenia. Increasing rates of melanoma were seen in all age groups, the greatest increases occurred in the oldest age group (70+ years). For both countries, the estimated annual increase ranged between +5% p.a. (females) and +6% p.a. (males) (Arnold et al., 2014, ECIS, 2018).

Asia and South America

Melanoma incidence rates in Asian (<1 cases/100,000 per year) and South American countries (2-4 cases/100,000 per year) are low, and in contrast to other countries rather stable over time. An exception is Israel, where incidence rates between 9 (females) and 11 (males) cases per 100,000 have been reported for the period 2000-2002. As in other countries, incidence rates have largely stabilized since the mid-1990s (Erdmann et al., 2013, IARC, 2012, 2018).

Clinical epidemiology (Sex and age distribution)

The male/female ratio of melanoma varies among different countries. A male predominance has been recorded in countries with a high melanoma incidence, such as Australia, New Zealand and the United States (Geller et al., 2002, Marks, 2002). Conversely, melanoma incidence is higher among females in lower-incidence countries (i.e. Scotland or Great Britain) (Erdmann et al., 2013, MacKie et al., 2002). Increases in melanoma incidence among men however have changed the predominance of women in high-latitude, lower-incidence populations, resulting in a more balanced male/female ratio (Garbe and Leiter, 2009). Up to age 50, melanoma is more common in females, while melanoma incidence beyond this age is higher in males than in females (Erdmann et al., 2013, Nikolaou and Stratigos, 2014).

Melanoma is diagnosed at a median age of 55, which is earlier than other skin cancers are diagnosed (Robert Koch Institut Berlin, 2017). It affects a disproportionally large number of young adults and is one of the most common cancers diagnosed among adolescents and young adults (Baade et al., 2011, Lange et al., 2007, Watson et al., 2016). The risk of developing melanoma increases with age. In most high-risk populations (i.e. Australia, New Zealand, Northern Europe) incidence rates peak at the seventh and eighth decades of life, with rates ranging between 50 cases/100,000 per year in females and 100 cases/100,000 per year in males (MacKie et al., 2002, Robert Koch Institut Berlin, 2017).

1.2.2 Risk factor: Ultraviolet radiation

The role of sunlight in the pathogenesis of melanoma

The malignant melanoma is a malignant tumor originating from pigment producing cells, the melanocytes by neoplastic transformation (Gilchrest et al., 1999, Jhappan et al., 2003). It mainly occurs on the skin, rarely on mucous membranes and other organs. Its predominant location on the outer skin makes it particularly susceptible to damaging UVR. In white-skinned populations, intermittent sun exposure has been identified as the main risk factor for melanoma. Eighty percent of melanomas develop on anatomical sites exposed

to intermittent sun exposure (i.e. trunks or legs) (de Vries and Coebergh, 2004, Elwood and Jopson, 1997, Garbe and Leiter, 2009).

UVR is part of the electromagnetic spectrum with wavelengths 100–400 nm; it is emitted by the sun and by artificial sources (e.g. sunbeds). This wavelength band has been further subdivided into three wavelength regions: UVC (100–280 nm), UVB (280–315 nm) and UVA (315–400 nm). The UV components to reaching the earth's surface consist of about 95% UVA and only 5% UVB. Solar UVC is absorbed by the stratospheric ozone layer and hardly reaches the earth's surface (Greinert et al., 2015).

The role of UVR as a leading environmental cause of melanoma is supported by a series of epidemiological evidence, including a high prevalence of melanoma in populations that migrated from a low to a high ambient UVR environment, a higher incidence in fair-skinned compared with darker-skinned individuals, and a latitude-dependent rise in melanoma incidence among white populations with proximity to the equator (Garbe and Leiter, 2009, Nikolaou and Stratigos, 2014). Case-control studies on the risk for melanoma development have also shown that the risk for CM was associated with the number of melanocytic nevi and the occurrence of sunburns in childhood, both elevating the risk for melanoma development (de Vries and Coebergh, 2004, Leiter and Garbe, 2008, Whiteman et al., 2001).

The epidemiological evidence implicating the causal role of UVR in the pathogenesis of melanocytic nevi and melanoma is confirmed by biological studies. The damaging effect of UVR on the skin can be caused by three different mechanisms. It directly damages DNA leading to mutations, it produces activated oxygen molecules which in turn damage DNA and other cellular structures, and it leads to a localized immuno-suppression that blocks the body’s natural anti-cancer defence (de Vries and Coebergh, 2004, Ichihashi et al., 2003). UVR exposure during childhood seems to be the main factor to induce mutations in the melanocytic system associated with an increased induction of melanocytic nevi and later on an increased risk for the development of malignant melanoma (Garbe and Leiter, 2009, Whiteman et al., 2001). Whether nevi, especially clinically atypical nevi, are precursors for melanoma

however remains a matter of debate. Pathology-based studies have found that only 20 to 30% of melanoma contain nevus cells, suggesting a direct transformation of a nevus into melanoma. The majority of melanomas (70-80%), arise de novo, with no associated nevus (Cymerman et al., 2016, Haenssle et al., 2016, Shain et al., 2015).

Moreover, several clinical and epidemiological features give rise to question a straightforward dose relationship between melanoma risk and UVR exposure. Anatomical site distribution of CM does not correspond to body areas of greatest UVR exposure. Only 10-15% of CMs are found on continuously exposed sites, like the head or the neck, while the majority of melanomas are localized on less frequently exposed body sites (i.e. trunk and limbs). In contrast to non-melanoma skin cancer (NMSC), melanoma already occurs in younger years of life, where it can be assumed that the highest cumulative sun exposure has not yet been reached. Finally, an increased risk of melanoma after high cumulative sun exposure in adulthood and after sunburns during this time could not be found in most case-control studies (Garbe and Leiter, 2009, Nikolaou and Stratigos, 2014). This suggests a more complex association between melanoma and UVR, supporting the hypothesis that melanomas may arise through different causal pathways (Siskind et al., 2005, Whiteman et al., 2006, Whiteman et al., 2003). Different case-control studies have shown melanomas developing at different body sites are associated with distinct patterns and amount of sun exposure. Intermittent sun exposure and sunburns in childhood were strong predictors of melanoma occurring on less frequently exposed body sites, whereas chronic patterns of exposure were more likely to be associated with melanomas localized on continuously exposed sites. Both, patterns of sun exposure and anatomical location of melanocytic nevi seem to play a central role in the suggested pathways (Caini et al., 2009, Chang et al., 2009a, Green, 1992, Olsen et al., 2009). Green et al. proposed the theory of a site-dependent susceptibility of melanocytes to malignant transformation. People with a low propensity for melanocytic proliferation and low numbers of nevi require chronic sun exposure to initiate melanocytes to malignant transformation, thus this occurs on continually exposed body sites, while people with a high propensity

for melanocytic proliferation and a high number of nevi, will tend to develop melanomas on intermittently and less frequently exposed sites (Green, 1992). The theory of different pathways has been strengthened by observations that BRAF gene mutations are more likely in melanoma of younger subjects with larger numbers of nevi, exposed to intermittent UVR than in melanomas localized on continually sun-exposed sites of older patients with few nevi (Greinert et al., 2015, Poynter et al., 2006, Thomas et al., 2007).

The population attributable fraction (PAF)

Rationale and calculation

The population attributable fraction (PAF) provides a valuable appraisal of the impact of a risk factor in cancer causation (Parkin et al., 2011b). It quantifies the proportion and the numbers of cancer cases that can be attributed to a risk factor and that could potentially be avoided by complete elimination of the causative factor. It is helpful in prioritizing cancer control strategies and for the evaluation of the potential impact of interventions seeking to reduce exposure to a risk factor (Shield et al., 2016).

Risk assessment studies require evidence of a causal relationship between a risk factor and disease. Meanwhile there is sufficient epidemiological and biological evidence for the causal role of UVR exposure in melanoma development. In 1992, the International Agency for Research on Cancer (IARC) declared that UVR was carcinogenic to humans (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 1992). The subsequent IARC monograph from 2009 confirmed ‘There is sufficient evidence that UVR causes CM as well as keratinocyte cancers (squamous cell carcinoma (SCC) and basal cell carcinoma (BCC))’ (El Ghissassi et al., 2009, IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012).

The population attributable fraction is estimated by comparing the observed incidence rates in an ‘exposed‘ population with those of an ‘unexposed‘ reference population, and attributing the differences in incidence rates to corresponding differences in exposure to the risk factor between reference and study population (Armstrong and Kricker, 1993, de Vries et al., 2017). Defining an unexposed reference population is challenging because

there are no unexposed populations (all human are to a certain degree exposed to UVR). As solution, Parkin et al. proposed to apply incidence rates from a 'minimal exposed population' as approximation for the incidence rates in an 'unexposed' population (Parkin et al., 2011b). More details referring the calculation of the PAF and the selection of the reference population are provided in chapter 2.2.4.

Global estimates

The proportion of melanoma cases caused by UVR 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 (Armstrong and Kricker, 1993, Arnold et al., 2018a, de Vries et al., 2017, Lucas et al., 2008, Olsen et al., 2015). Most recent estimates for 2012, revealed that around 168,000 cases of melanoma were attributed to excess exposure to UVR, representing 75.7% of all melanoma cases worldwide (Arnold et al., 2018a). 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 UVR-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 UVR 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 UVR. Similarly high values were also estimated for the White US population, with a PAF ranging between 85-92% in females and between 94-96% in males (Armstrong and Kricker, 1993, Arnold et al., 2018a, Islami et al., 2018). 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 (78%) European countries (Armstrong and Kricker, 1993, Arnold et al., 2018a, Arnold et al., 2018b, Parkin et al., 2011a, Parkin et al., 2011b, Winther et al., 1997). Figure 2 displays the estimated PAFs for different countries.

Table 2 provides an overview of studies estimating the proportion of melanoma cases attributable to UVR for different regions, using different reference populations to calculate the PAF%.

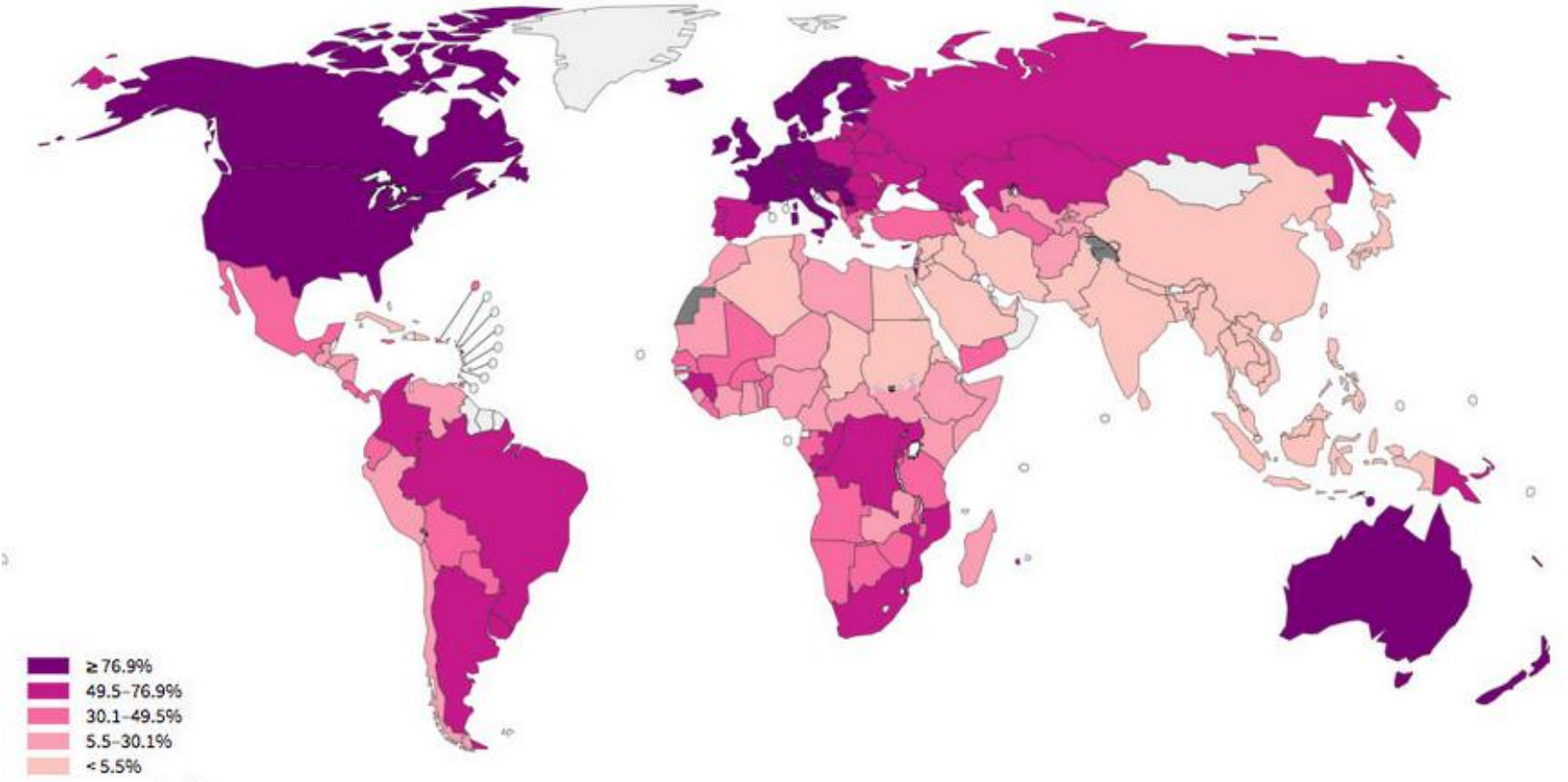


Figure 2: Population attributable fraction (PAF%) of melanoma cases worldwide in 2012, among men and women all ages (30+ yrs), attributable to UVR exposure, by country.

Source: Global Cancer Observatory GCO (IARC, 2012)

Table 2: Estimates of the proportion of melanomas due to UVR (PAF%) calculated for different countries based on different reference populations.

Author, Publication year	Country/Study population I_T	Time period	Reference population I_0	Estimates for PAF%		Method for estimation/ comments
			Population/Anatomical Site	**Males**	**Females**	
Armstrong & Kricker (1993)	Caucasians (QLD/Australia)	1983/1987	Unexposed body site (scalp or buttocks)	97% (94-99%)	96% (93-99%)	PAF% = $[(I_T - I_0) / I_T] \times 100$ I_T : IR study population I_0 : IR reference population estimated weighted average IRs for unexposed sites: I_0 =1.1 per 100,000/year
Armstrong & Kricker (1993)	Caucasians (US Whites)	1983/1987	Black US population	96% (96-96%)	92% (91-92%)	Calculation see above
Armstrong & Kricker (1993)	Caucasians (Native-born Australians)	1990	Immigrants to Australia	Males and females: 68% (64-72%)		Calculation see above
Armstrong & Kricker (1993)	Caucasians (NSW/Australia)	1983/1987	Residents of England/Wales	89% (89-89%)	79% (79-79%)	Calculation see above
Armstrong & Kricker (1993)	Global	1985	Black US population	Males and females: 65%		Calculation see above
Armstrong & Kricker (1993)	Oceania (Australia, New Zealand)	1985	Black US population	Males and females: 94%		Calculation see above

Continued on next page

Author, Publication year	Country/Study population I_T	Time period	Reference population I_0	Estimates for PAF%		Method for estimation/ comments
			Population/Anatomical Site	Males	Females	
Armstrong & Kricker (1993)	North America	1985	Black US population	Males and females: 90%		PAF% = $[(I_T - I_0) / I_T] \times 100$
Armstrong & Kricker (1993)	Central/South America	1985	Black US population	Males and females: 64%		Calculation see above
Armstrong & Kricker (1993)	Europe (without UDSSR)	1985	Black US population	Males and females: 80%		Calculation see above
Armstrong & Kricker (1993)	England/Wales	1985	Black US population	Males and females: 83%		Calculation see above
Armstrong & Kricker (1993)	Nordic Countries (Denmark, Finland)	1985	Black US population	Males and females: Denmark: 94% Finland: 92%		Calculation see above
Armstrong & Kricker (1993)	Asia	1985	Black US population	Males and females: 8%		Calculation see above
Armstrong & Kricker (1993)	Africa	1985	Black US population	Males and females: 3%		Calculation see above

Continued on next page

Author, Publication year	Country/Study population I_T	Time period	Reference population I_0	Estimates for PAF%		Method for estimation/ comments
			Population/Anatomical Site	**Males**	**Females**	
Winther et al. (1997)	Nordic countries: Denmark (D) Finland (F) Iceland (I) Norway (N) Sweden (S)	1980	Unexposed body site (scalp or buttocks)	all: 88% D: 85% F: 80% I: 75% N: 90% S: 90%	all: 90% D: 91% F: 83% I: 80% N: 93% S: 91%	PAF% = $[(I_T - I_0) / I_T] \times 100$
Winther et al. (1997)	Nordic countries (all)	1980	Danish Cohort (1940)	83%	87%	Calculation see above
Winther et al. (1997)	Nordic countries: Denmark (D) Finland (F) Iceland (I) Norway (N) Sweden (S)	1990	Unexposed body site (scalp or buttocks)	all: 93% D: 92% F: 88% I: 80% N: 94% S: 94%	all: 94% D: 94% F: 88% I: 90% N: 95% S: 94%	Calculation see above
Winther et al. (1997)	Nordic countries: Denmark (D) Finland (F) Iceland (I) Norway (N) Sweden (S)	2000	Unexposed body site (scalp or buttocks)	all: 94% D: 93% F: 93% I: 85% N: 95% S: 95%	all: 95% D: 95% F: 93% I: 92% N: 96% S: 95%	Calculation see above
Parkin et al. (2011a/b)	United Kingdom	2010	South Thames Cohort (1903)	89.8%	82.4%	Calculation see above

Continued on next page

Author, Publication year	Country/Study population I_T	Time period	Reference population I_0	Estimates for PAF%		Method for estimation/ comments
			Population/Anatomical Site	**Males**	**Females**	
Olsen et al. (2015)	Australia	2010	UK population (2009/2011) or South Thames Cohort (1903)	69.6% 97%	54.3% 92%	PAF% = $[(I_T – I_0) / I_T] \times 100$
De Vries et al. (2017)	Columbia/Cali	2008/2012	Cali Cohort (1903) South Thames Cohort (1903)	0% (0%*) 62% (77%*) *adjusted for ALM	25% (34%*) 19% (26%*) *adjusted for ALM	Additional: adjustment for not UVR related MMs (ALM): I_A PAF% = $[(I_T – I_A) - (I_0 – I_A)]/(I_T – I_A)$ I_T : IR study population I_0 : IR reference population| I_A : IR (ALM) I_0 : IR reference population
Arnold et al. (2018)	France	2015	South Thames Cohort (1903) French Cohort (1980)	88.6% 82.0%	78.5% 68.2%	PAF% = $[(I_T – I_0) / I_T] \times 100$

Continued on next page

Author, Publication year	Country/Study population I_T	Time period	Reference population I_0	Estimates for PAF%		Method for estimation/ comments
			Population/Anatomical Site	**Males**	**Females**	
Arnold et al. (2018)	Global	2012	South Thames Cohort (1903)	81.3%	69.4%	PAF% = $[(I_T - I_0) / I_T] \times 100$
	Oceania (AU/NZ)			97.4%	93.7%	
	North America			94.1%	84.4%	
	Latin America & Caribbean			65.5%	29.1%	
	Northern Europe			92.3%	86.8%	
	Western Europe			90.1%	82.6%	
	Southern Europe			84.1%	72.8%	
	Eastern Europe			77.7%	60.4%	
	South Africa			83.4%	61.6%	
	Middle East & Northern Africa			60.1%	35.0%	
	Sub Saharan Africa			40.4%	36.1%	
	South Central Asia			11.6%	5.4%	
	South East Asia			5.0%	0.3%	
	East Asia			1.7%	0%	
	HDI very high			91.0%	81.4%	
	HDI high			66.8%	43.9%	
	HDI medium			11.1%	9.1%	
	HDI low			34.9%	33.0%	

Continued on next page

Author, Publication year	Country/Study population I_T	Time period	Reference population I_0	Estimates for PAF%		Method for estimation/ comments
			Population/Anatomical Site	**Males**	**Females**	
Arnold et al. (2018)	Global	2012	3 African cancer registries (Harare/Zimbabwe; Uganda/ Kyadondo; Malawi/Blantyre)	78.4%	56.4%	PAF% = $[(I_T - I_0) / I_T] \times 100$
	Oceania (AU/NZ)			96.6%	89.1%	
	North America			92.5%	72.7%	
	Latin America & Caribbean			55.4%	15.0%	
	Northern Europe			90.5%	77.0%	
	Western Europe			87.9%	70.0%	
	Southern Europe			80.8%	55.1%	
	Eastern Europe			71.4%	33.4%	
	South Africa			76.1%	34.7%	
	Middle East & Northern Africa			52.0%	23.2%	
	Sub Saharan Africa			28.2%	13.3%	
	South Central Asia			9.3%	2.6%	
	South East Asia			0.6%	0.3%	
	East Asia			0.2%	0.1%	
	HDI very high			89.0%	69.4%	
	HDI high			58.1%	21.7%	
	HDI medium			9.1%	5.0%	
	HDI low			24.4%	12.6%	
Islami et al. (2018)	US Whites	2014	US Blacks (2010-2014)	96.0%	93.7%	Calculation see above

Abbreviations: HDI: Human development index, ALM: acral lentiginous melanoma

1.2.3 Other risk factors

In addition to UVR exposure, genetic predisposition and individual host risk factors are also causally linked to melanoma development.

Genetic risk factors

Heritable factors play an important role in melanoma predisposition. A family history of melanoma is associated with a 2-fold increased risk of melanoma. Around 5-12% of patients with melanoma have a family history of CM in one or more first-degree relatives. A large proportion of these patients (30-40%) have inherited mutations in highly penetrant susceptibility genes which are associated with a significantly increased risk of melanoma. Constitutional mutations have been identified in two melanoma susceptibility genes: CDKN2 and CDK4, which play an important role in cell-cycle control (de Vries and Coebergh, 2004, Eggermont et al., 2014, Gandini et al., 2005c, MacKie et al., 2009, Nikolaou and Stratigos, 2014, Olsen et al., 2010c).

Further high- and low risk melanoma genes have been identified, whose variants are linked to phenotypic traits (i.e. red hair, freckling, and sun sensitivity). Among the low-penetrance genes, the strongest association was found for the melanocortin 1 receptor gene (MC1R) (Eggermont et al., 2014, MacKie et al., 2009, Raimondi et al., 2008). A loss in MC1R functions induced by single nucleotide polymorphisms, cause a shift of photoprotective eumelanin to pheomelanin, resulting in red hair, pale skin and freckles. A pooled meta-analysis of different MC1R variants showed a relative risk (RR) of 2.44 (95% CI: 1.72-3.45) for CM in patients carrying the ‘red hair variants‘ compared with a RR of 1.1 (95% CI: 1.1-1.51) for those with ‘non-red hair’ MC1R variants (Williams et al., 2011).

Further hereditary disorders associated with an increased risk of melanoma development, are the dysplastic nevus syndrome, also known as familial atypical multiple-mole melanoma syndrome (Azoury and Lange, 2014, Greene et al., 1985, Rigel et al., 1988) and xeroderma pigmentosum (XP) (Cleaver, 2005, de Vries and Coebergh, 2004, Paszkowska-Szczur et al., 2013).

Phenotypic risk factors

The major constitutional risk factors for melanoma include fair pigmentation, poor tanning ability, multiple nevi, clinically atypical or dysplastic nevi and freckling (Davies et al., 2015, Gandini et al., 2005b, Nikolaou and Stratigos, 2014). A majority of observational studies reported a significant increased risk for melanoma development in patients with multiple or clinically atypical nevi (Chang et al., 2009b, Gandini et al., 2005a, Gandini et al., 2016, Goldstein and Tucker, 2013, MacKie et al., 2009, Olsen et al., 2010a). A meta-analysis has shown a gradual increased risk of melanoma, proportional to the number of common or dysplastic nevi (Gandini et al., 2005a). The relative risk for patients with one dysplastic nevi was 1.45 (95% CI: 1.31-1.60), increased to 3.03 (95% CI: 2.23-4.06) for patients with three dysplastic nevi and were highest for those with five dysplastic nevi (RR=6.36; 95% CI: 3.80-10.33). Patients with a high number of common nevi (>100) showed a 7-fold increased (RR=6.89; 95% CI: 4.63-10.25) risk for melanoma compared with those with low numbers (0-15) of common nevi. A 60% higher risk (RR=1.62: 95% CI 1.44-1.81) for melanoma was reported for individuals having 'fair eye color' (including blue, green and hazel eye color) compared to individuals with 'dark eye color' (Gandini et al., 2005c). With respect to hair color, the RR for melanoma for 'light hair color' (blond, red, and light brown) was 1.87 (95% CI: 1.63-1.95) compared with 'medium dark, brown hair color'. The strongest association (RR=3.64; 95% CI: 2.56-5.37) was found in individuals with red hair color (Gandini et al., 2005c). In a pooled analysis of 15 case-control studies (Olsen et al., 2010b) the RR for melanoma was 1.66 (95% CI: 1.36-2.01) for individuals with skin type I/II compared to subjects with skin type III/IV.

Further risk factors

Artificial ultraviolet radiation exposure: tanning beds

Indoor tanning is an artificial source of intermittent UVR, emitting significant amounts of UVA and/or UVB radiation (de Vries and Coebergh, 2004, Young, 2004). It became popular in the early 1980s among white populations, particularly in the Northern countries and, since then, a substantial proportion of young people use sunbeds (Nikolaou and Stratigos, 2014, Young, 2004). To

date, there is strong evidence that sunbed users are at an increased risk for melanoma development, even after adjustment for outdoor sun exposure (Boniol et al., 2012, Gandini S. et al., 2011, Gandini et al., 2014, Veierod et al., 2010, Westerdahl et al., 2000). The risk increases with the number of sunbed sessions and with initial usage at a young age (Boniol et al., 2012). Findings from a meta-analyses, including 27 studies, showed an overall summary relative risk of 1.20 (95% CI: 1.08-1.34) of melanoma development in ‘ever users‘ of sunbeds and a 1.8% increase of risk for each additional session of sunbed use per year. First use of sunbeds before age 35 years was associated with a summary relative risk of 1.87 (95% CI: 1.41-2.48) (Boniol et al., 2012).

A substantial burden of melanoma can be attributed to artificial UVR. It has been estimated that 5.4% of all new melanoma cases (7% in females), diagnosed every year in European countries, could be attributed to sunbed use (Zhang et al., 2012).

Additional risk factors, increasing the risk for melanoma, include a personal history of skin cancer or other malignancies (Abern et al., 2013, Li et al., 2013), immunosuppression related to organ transplantation (Krynitz et al., 2013, Mudigonda et al., 2013), lympho-proliferative diseases or human immunodeficiency virus infection/AIDS (Eggermont et al., 2014, van Leeuwen et al., 2010).

Other possible associations or factors influencing melanoma risk have been discussed, evidence for a causal relationship with risk of melanoma however remains inconclusive. One study, reviewing long-term use of an immunotherapy with tumor necrosis factor α, reported a 4-fold (OR=3.94) increased risk in patients with inflammatory bowel disease (Long et al., 2012). A potential protective effect of nonsteroidal anti-inflammatory drug use (RR=0.87; 95% CI=0.80-0.95), with regard to developing melanoma has been described (Johannesdottir et al., 2012). There have been no conclusive data so far on the role of female sex hormones (Gandini Sara et al., 2011), the influence of overweight (Sergentanis et al., 2013), or levels of vitamin D (Asgari et al., 2009) in the risk of melanoma carcinogenesis. An association between Parkinson's

disease and an increased risk of melanoma is also controversially discussed (Liu et al., 2011, Olsen et al., 2006, Pan et al., 2011).

1.3 Demographic trends

1.3.1 Demographic aging

Demographic aging is a global phenomenon, occurring primarily in developed countries, most advanced in European countries and in East Asia (Christensen et al., 2009). It describes a process, which is characterized by a shift in the age structure of a population towards an increased proportion of older people and at the same time a sharp decline in younger people (Nowossadeck et al., 2013, Peters et al., 2010, Pritzkuleit et al., 2010).

The age structure of a population is mainly determined by changes in birth rates and life expectancy. Data from Germany are used to illustrate these changes (Grünheid and Sulak, 2016, Statistisches Bundesamt Wiesbaden, 2016).

Low birth rates

In order for one generation to remain numerically stable, a constant birth rate of 2.1 children per woman is required. However, if this falls below the so-called replacement level of 2.1, which is necessary for a generation to replace itself in terms of numbers, this will lead to a decline in the population, especially the younger generation (Pritzkuleit et al., 2010, Statistisches Bundesamt Wiesbaden, 2015a, 2015b).

Between 1955 and 1970, the birth rate was between 2 and 2.5 children per woman. For more than four decades now, the birth rate has been far below the level of 2.1 children per woman. This value was attained in the territory of the Federal Republic of Germany for the last time in 1969 (in the German Democratic Republic in 1971). Since then, the birth rates have been consistently lower. In 2008, the average number of children per woman was 1.38 children (Pritzkuleit et al., 2010). Forecasts by the Federal Statistical Office assume that there will be a constant birth rate for Germany, so that an average number of 1.4 children per woman will continue to be assumed in the future (Statistisches Bundesamt Wiesbaden, 2015a, 2015b).

Life expectancy

In the last 40 years, the life expectancy of female newborns has risen by 9.3 years (from 74.1 years in 1971/1973 to 83.4 years in 2013/2015) and that of male newborns by more than 10 years (from 67.6 years to 78.4 years for the same time period). The gap between the life expectancy of female and male newborn babies, which had been widening since the mid-20th century, has therefore been closing slowly since the 1980s (Nowossadeck, 2012, Peters et al., 2010). The Federal Statistical Office estimates that the average life expectancy in Germany in 2050 is 88.0 years for women and 83.5 years for men (Statistisches Bundesamt Wiesbaden, 2015a, 2015b). But not only the life expectancy at birth has increased, but also the long distance life expectancy, i. e. the life expectancy that a person still has at a certain age. 65-year-old men today have on average an additional 17.7 years of life to expect and women 20.9 years; these are 5.7 and 6.0 years, respectively more than in 1970. Both, rising life expectancy at birth and at long distance life expectancy will increase the number and proportion of elderly people in the population (Peters et al., 2010, Pritzkuleit et al., 2010).

Special features of the current age structure ('Baby boomer generation')

Large changes in the birth rate over a short period of time have a particular influence on the current age structure of a population. After the two world wars, which contributed to great cuts in the age structure due to large numbers of war victims and sharply declining birth rates, the birth rates rose sharply again in the 1960s. The generation born between 1955 and 1970, also known as 'baby boomer generation', is the most populated age group at present. By 2025, this cohort will be 65 years and older, having an increased risk of age-related diseases, such as tumors or other chronic diseases (Nowossadeck, 2012, Pritzkuleit et al., 2010).

Net migration

In contrast to low birth rates, continuously rising life expectancy and cohort-specific peculiarities ('baby boomer generation'), migration from abroad,

especially by younger migrants, may attenuate the process of demographic aging that has been observed (Nowossadeck, 2012).

1.3.2 Demographic aging and its impact on health care systems

Demographic changes and the aging population will lead to two major changes that health care systems will have to account for in the future (Haberland et al., 2006, Nowossadeck, 2012). The aging population will both increase the number of diseases for which the risk increases with age (such as cancers and chronic diseases) and change the age structure of patients towards a higher proportion of older patients. Further, multimorbidity will increase in importance, as will the number of patients requiring geriatric care. The resources, both, financial (direct costs of transport, infrastructure) and human resources (medical and nursing staff) needed for patient care are expected to increase in the future. The situation becomes worse when the declining employment potential is considered. As a result of the aging population, there will be more people who need to be cared for by the health care system, and fewer people to take care of them (Bray and Moller, 2006, Noethern, 2011, Nowossadeck, 2012).

1.3.3 Demographic trends in Germany and in Denmark

Germany

In Germany, the process of demographic aging already began in the 1970s, and will continue in the coming years. This process is predicted to accelerate from 2025 onwards and continue until around 2040 (Nowossadeck, 2012). Population forecasts, based on the 13th coordinated population projection, assume that by 2060, the total German population will shrink by -16.3% from 80.8 million (2013) to 68.7 million inhabitants (in case of weaker immigration - variant 1) and to 73.1 million inhabitants (in case of stronger immigration - variant 2), respectively (Statistisches Bundesamt Wiesbaden, 2015a, 2015b). Particularly sharp declines in population are expected in the working age citizens. The number of 20- to 64- year-olds (2013: 49 million) will fall sharply from 2020 onwards and, depending on the size of net immigration, will be around 34 (-30%) and 38 million (-23%), by 2060. Their proportion in the total population will fall from 61% in 2013 to around 51-52% in 2060. Similarly, the

young population under 20 years of age will decrease from 15 million to 11 (-26%) and 12 million (-18%) in 2060, suggesting that their proportion of the total population will decrease to 18% and 16%, respectively. On the other hand, by 2060, the number of people aged 65 years and over will rise to 22-23 million. While one in five people currently belongs to this age group (2013: 21%), by 2060 it is estimated to become one in three (2060: 32-33%). Four out of ten people aged 65 and over will even be 80 years and older, so that their proportion of the total population will increase from the current 5% (2013: 4.4 million) to 12% or 13% in 2060 (9 million) (Statistisches Bundesamt Wiesbaden, 2015a, 2015b).

Denmark

In contrast to population forecasts for Germany, recent projections released from the Statistics Denmark (Statistics Denmark, 2018b), assume that by 2060, the total Danish population will rise by +4.4% from 5.0 million (2013) to 5.2 million inhabitants in 2060. Strong increases are expected for people aged 65 years and over. Their number (2013: 956,200) will rise to around 1.3 million by 2060 (+39%), so that their proportion in the total population will increase from 19.1% in 2013 to 25.4% in 2060. Even stronger increases (+115%) are expected for the elderly (80+ yrs). Their proportion will rise from 4.5% (224,320) in 2013 to 11% (572,430) in 2060. On the other hand, a decline of -7.5% is expected for people aged between 20 and 64 years. Their numbers will fall from currently 2.84 million (57% of the total population) to around 2.63 million (50.5%) in 2060. Other trends are proposed for the young population (<20 years). In contrast to population forecasts for Germany, their number will increase by +5.2% from 1.19 million (2013) to 1.26 million (2060). Their proportion within the total population however will remain almost stable (23.9% in 2013 vs. 24.1% in 2060) (Statistics Denmark, 2018b).

Observed and projected demographic trends for both countries for three time points (1960, 2010 and 2060) are displayed in Figure 3 (United Nations, 2017).

Figure 3: Observed and projected demographic trends in Germany and Denmark for three time points (1960, 2010 and 2060).

Source: United Nations (UN), Population Division (United Nations, 2017)

1.4 Future perspectives - Impact of UVR exposure and demographics

Incidence predictions, including the forces that might affect future trends (exposure to UVR and demographic changes), play a key role in cancer control programs. They assist health care providers in planning the best possible allocation of limited resources for effective cancer control.

In this chapter, the results of different studies on the future incidence development of melanoma will be presented, in particular those that have also investigated the impact of UVR (risk exposure) and demographic changes on future trends. Incidence predictions are naturally subject to great uncertainty and depend largely on the method and their underlying assumptions (Bray and Moller, 2006, Moller et al., 2002). For this reason, estimates presented in this chapter will be focused on one study in Australia, which mostly resembled the approach of the present study to predict future incidence rates for Germany and Denmark.

The Australian study projected melanoma incidence rates and numbers of cases for six susceptible populations from Australia/New Zealand, the United States and Europe at the same time. Incidence predictions were all based on the same method and the same assumptions, using identical time periods for observation and future periods (Whiteman et al., 2016). By applying modified age-period-cohort models, melanoma incidence rates were projected for four 5-year time periods from 2012/2016 through 2027/2031, based on observed rates between 1982/1986 and 2007/2011.

Results of this study are summarized in Table 3. The information provided in this chapter is supplemented by results from other studies, which have applied the same prediction method (Guy et al., 2015, Mistry et al., 2011, Moller et al., 2002, Moller et al., 2007, Weir et al., 2015).

Australia and New Zealand

Age-standardized incidence rates (US Standard Population 2000) in Australia have already peaked in 2002/2006 (49/100,000 per year) and are projected to continue declining until 2027/2031 (41/100,000 per year). The proposed decline is primarily anticipated for younger age groups (<60 years), whereas rates in

the elderly (>80 years) are expected to continue to increase. At the same time, the numbers of melanoma cases have steadily increased since 1982/1986 and are believed to continue on this trajectory. Between 1982/1986 and 2027/2031, the number of Australians diagnosed with melanoma is expected to rise by +291% from around 4,100 cases to 16,075. Almost equal proportions of the suggested increase will be attributed to changes in UVR exposure (49%) and to changes in demographics (51%) (Whiteman et al., 2016).

Similar trends are expected for New Zealand. Age-standardized incidence rates will peak in 2012/2016 (51/100,000 per year), and then decline slowly thereafter. Incidence rates in persons >80 years will continue to rise, while younger age groups (<60 years) can expect further declines. The numbers of melanoma cases is expected to rise by +363% from about 720 per year in 1982/1986 to 3,300 per year in 2027/2031. Two-thirds (67%) of the projected increase will be due to changes in UVR exposure and only one-third (33%) due to changes in population growth and aging (Whiteman et al., 2016).

In both countries, crude incidence rates (CIR) are projected to continue to rise, signs of stabilization or leveling off in increase might not be expected for the foreseeable future.

United States

Projections suggest that age-standardized incidence rates in US Caucasians will continue to rise at least until 2022/2026 (32/100,000 per year), followed by a slight decline thereafter. An ongoing increase was supposed for the crude incidence rates. Melanoma rates for subjects younger than 60 years are projected to stabilize in 2017/2021, whereas no signs of stabilization or leveling off in increase will be expected for the elderly (>80 years). The numbers of melanoma patients will rise from about 25,000 per year in 1982/1986 to more than 116,000 per year in 2027/2031 (corresponding to a relative increase of +368%). 79% of the predicted increase will be attributed to increasing exposure to UVR (Whiteman et al., 2016).

Similar trends for white males and females in the US were reported by Guy et al. (Guy et al., 2015). Based on observed incidence rates between 1982 and 2011, sourced from the National Program of Cancer Registries and the

Surveillance, Epidemiology, and End Results (SEER) program, this study projected melanoma incidence rates and numbers of cases through 2030. Age-standardized incidence rates (US Standard Population, 2000) are projected to rise at least until 2020, followed by a stabilization thereafter. From 2020 onwards, incidence rates will peak at around 40/100,000 per year in men and between 25 and 30/100,000 per year in females. A steady increase is projected for the numbers of melanoma cases. By 2030, more than 100,000 US males and females are expected to be diagnosed with melanoma.

Another approach to predict future melanoma incidence rates for Caucasians in the US was made by Weir at al. (Weir et al., 2015). Melanoma incidence rates have continuously increased since 1975 and are expected to keep so in future. Until 2020, age-standardized incidence rates (US Standard Population, 2000) will climb up to 30/100,000 per year for women and 40/100,000 per year for men, respectively. Signs of a leveling off or stabilization might be visible in later periods.

United Kingdom

An ongoing increase in age-standardized incidence rates is also projected for the UK. By 2022/2026, incidence rates will peak at around 25/100,000 per year for both, men and women, followed by a possible stabilization (Whiteman et al., 2016). First signs of stabilization or even declining melanoma rates are projected for subjects younger than 60 years from 2026 onwards, while incidence rates in the elderly (80+ years) will continue to rise. No leveling off is expected for the crude rates. Strong increases are suggested for the numbers of patients diagnosed with melanoma, which are expected to rise by +585% from 3,275 cases per year in 1982/1986 to almost 22,500 per year in 2027/2031. Most of the increase (around 90%) in numbers of persons diagnosed with melanoma will be attributable to increasing UVR exposure, rather than to population growth or aging (Whiteman et al., 2016).

Same conclusion are drawn by Moller at al., who estimated future burden of cancer in England up to the year 2020 (Moller et al., 2007). Incidence projections for melanoma suggest an ongoing increase of age-standardized rates until 2020. Thereafter, future rates will reach a plateau with around 20

cases/100,000 per year for males and females. Particularly strong increases are supposed for the absolute numbers of melanoma cases, climbing from 2,630 in 2001 to 4,940 (+88%) in 2020 for males and from 3,380 to 5,600 (+66%) for females, respectively. As in the Whiteman study, for both sexes more than three thirds (66% for males and 75% for females) of the corresponding increase in melanoma cases will be due to changes in risk (Moller et al., 2007).

In a more recent study, Mistry et al. conducted a study on incidence predictions for different types of cancer in the UK up to the year 2030, including melanoma (Mistry et al., 2011). While for several sites, such as stomach, bladder or larynx, age-standardized incidence rates are projected to decrease, age-standardized incidence rates for other sites are expected to increase at rates of 1% or more annually. Melanoma is one of the tumor entities that is expected to show the greatest increase in the coming years (around +1.8% p.a. between 1984 and 2030). Incidence rates will reach more than 20 cases/100,000 per year (22.3 for females and 23.4 for males, respectively) in 2030. Like other studies, age-specific incidence rates will further rise for persons aged 75 years or older, while a leveling off can be expected for younger age groups (Mistry et al., 2011).

Scandinavia (Norway, Sweden)

Incidence predictions performed by Whiteman et al. are restricted to two Scandinavian countries, Norway and Sweden. In both countries, age-standardized incidence rates are projected to peak at around 36/100,000 per year from 2022/2026 onwards. An ongoing increase in incidence rates is estimated for the age group >80 years, while incidence rates in subjects younger than 60 years are projected to stabilize from 2022/2026 onwards. No leveling off of incidence is expected for the crude rates and for the numbers of persons diagnosed with melanoma. In Norway the numbers of melanoma will rise by +333% from 619 cases in 1982/1986 to 2,683 in 2027/2031 and in Sweden by +388% from 1,081 to 5,270. In both countries, more than 80% of the increase will be attributable to increasing UVR exposure (Whiteman et al., 2016).

Incidence predictions for all Nordic countries (Sweden, Norway, Finland, Denmark and Iceland) were already carried out by Moller et al. in the early 2000s (Moller et al., 2007). Based on observed incidence data, future melanoma rates were projected up to the years 2018/2022. Age-standardized incidence rates (World Standard Population) among males in Denmark, Finland, Norway and Sweden were predicted to peak in 2008/2012, whereas the future rates for females did not display a similar downward trend. The largest increases between 1993/1997 and 2018/2022 were estimated for females in Denmark (+36%) and in Iceland (+40%), while only the half of the projected growth was suggested for males (Denmark: +16% and Iceland: +19%). An ongoing increase without any signs of leveling off was proposed for crude incidence rates and for the absolute numbers of melanoma diagnoses. When apportioning the increase in melanoma cases into contribution from changes in risk and changes in demographics, the proportion attributable to changes in risk was particularly high among females. This was evident in Iceland and more notably in Denmark, where about 70% and 75% of the proposed increase in melanoma cases were attributable to changes in UVR exposure (Moller et al., 2002).

Three major findings can be retrieved from the Australian study, supported by trends proposed from other studies: (1) Age-standardized incidence rates will initially rise, but are expected to stabilize or even decline (in Australia already visible since 2005) in future time periods. Signs of stabilizing or even declining rates will be particularly expected for age groups younger than 60 years, while rates in the elderly (>80 years) are projected to continue rising for the next two or three decades; (2) No declines in crude rates and absolute numbers of melanoma cases are anticipated for the foreseeable future, because of high incidence rates in age groups >60 years and demographic aging in the population; (3) In European countries the expected increase in melanoma cases will mainly be attributed to increasing exposure to UVR rather than to demographic changes.

Table 3: Future melanoma incidence trends - Impact of changes in UVR exposure and demographics

Author, Publication year	Country	Time period		Projected incidence trends		Change in the numbers of melanoma cases			Prediction method/ comments
		baseline	(last) projected	ASIR/CIR	Age-specific IR	% total (↑)	% due to UVR exposure	% due to demographics	
Whitemann et al., 2016	Australia	1982/1986	2027/2031	**ASIRs:** peak in 2005, further ↓ **CIRs:** further ↑ (no →/↓)	**<60 yrs:** peak in 2002/2006 further ↓ **≥80 yrs:** further ↑ (no →/↓)	100%	49%	**51**%	APC model (Moller et al.) ↑ in MM cases attributed to changes in demographics +↑ in risk
Whitemann et al., 2016	New Zealand	1982/1986	2027/2031	**ASIRs:** peak in 2012/2016, then ↓ **CIRs:** further ↑ (no →/↓)	**<60 yrs:** peak in 2002/2006 further ↓ **≥80 yrs:** further ↑ (no →/↓)	100%	**67%**	33%	APC model (Moller et al.) ↑ in MM cases mainly attributed to ↑ in risk rather than demographics
Whitemann et al., 2016	Norway	1982/1986	2027/2031	**ASIRs:** peak in 2022/2026, then slight ↓ **CIRs:** further ↑ (no →/↓)	**<60 yrs:** peak in 2022/2026 then ↓ **≥80 yrs:** further ↑ (no →/↓)	100%	**81%**	19%	APC model (Moller et al.) ↑ in MM cases mainly attributed to ↑ in risk rather than demographics

Continued on next page

Author, Publication year	Country	Time period		Projected incidence trends		Change in the numbers of melanoma cases			Prediction method/ comments
		baseline	(last) projected	ASIR/CIR	Age-specific IR	% total (↑)	% due to UVR exposure	% due to demographics	
Whitemann et al., 2016	Sweden	1982/1986	2027/2031	**ASIRs:** after 2022/2026: → **CIRs:** further ↑ (no →/↓)	**<60 yrs:** from 2022/2026 onwards: → **≥80 yrs:** further ↑ (no →/↓)	100%	**89%**	11%	APC model (Moller et al.) ↑ in MM cases mainly attributed to ↑ in risk rather than demographics
Whitemann et al., 2016	US Whites	1982/1986	2027/2031	**ASIRs:** from 2022/2026 onwards: →/↓ **CIRs:** further ↑ (no →/↓)	**<60 yrs:** from 2021 onwards: → **≥80 yrs:** further ↑ (no →/↓)	100%	**79%**	21%	APC model (Moller et al.) ↑ in MM cases mainly attributed to ↑ in risk rather than demographics
Whitemann et al., 2016	UK	1982/1986	2027/2031	**ASIRs:** from 2022/2026 onwards: → **CIRs:** further ↑ (no →/↓)	**<60 yrs:** from 2022/2026 onwards: → **≥80 yrs:** further ↑ (no →/↓)	100%	**93%**	7%	APC model (Moller et al.) ↑ in MM cases mainly attributed to ↑ in risk rather than demographics

1.5 Summary and research question

Increasing exposure to UVR, the major environmental risk factor for melanoma has largely contributed to the steep increase in the incidence of melanoma, which has been observed in many parts of the world, particularly among white-skinned populations since the mid-1950s (Arnold et al., 2014, de Vries et al., 2003, de Vries and Coebergh, 2004, Erdmann et al., 2013, Forsea et al., 2012, Garbe and Leiter, 2009, Nikolaou and Stratigos, 2014). Although melanoma also affects younger age groups, it is diagnosed more often in elderly people (Hoejberg et al., 2016). While incidence rates continue to rise in most European countries, more favorable trends with stabilizising or even declining rates among younger birth cohorts have been observed in Australia/New Zealand, Northern America and in some Northern European countries in recent years. (Coory et al., 2006, de Vries et al., 2003, Erdmann et al., 2013, Fuglede et al., 2011, Holman et al., 2018, Moller et al., 2002, Weir et al., 2011). Still increasing rates among men and women aged 60 years or older, coupled with demographic aging, imply an ongoing increase of melanoma incidence in the future. The expected growing burden of melanoma poses major challenges for future health care systems. Estimating the future burden of melanoma and the forces that might affect future trends, are necessary for setting heath care priorities and to achieve effective melanoma control.

While much effort has been done so far to analyze past and present trends of melanoma incidence (Arnold et al., 2014, de Vries et al., 2003, Erdmann et al., 2013, Garbe and Leiter, 2009, Nikolaou and Stratigos, 2014), there are only a few studies that have attempted to estimate future melanoma burden attributable to changes in UVR exposure and demographics (Moller et al., 2002, Moller et al., 2007, Weir et al., 2015, Whiteman et al., 2016). A comprehensive study in this field has been conducted in Australia (chapter 1.4). This study analyzed recent trends and estimated future melanoma burden in six susceptible populations of mainly European heritage with different patterns of UVR exposure (Australia, New Zealand, US Whites, and populations of the UK, Sweden, and Norway) and varying approaches for melanoma control (Whiteman et al., 2016).

Another study predicting future melanoma burden in all Nordic countries, including Denmark, has been carried out by Moller et al. in the early 2000s (Moller et al., 2002). Based on observed incidence rates (1958-1997), the researchers predicted future melanoma trends up to the year 2020 and apportioned the expected increases in melanoma cases into contribution from changes in population risk (UVR exposure) and population size and age distribution.

Growing melanoma burden in future can also be assumed for Germany and in particular for Denmark, where melanoma incidence rates are currently the second highest in Europe (31.5 per 100,000/year, European Standard Population, WHO 1976), (ECIS, 2018). In both countries, melanoma incidence rates have steeply increased in the past and unlike other countries, there have been no signs of a leveling off so far, neither in Germany (Garbe et al., 2018, Leiter and Garbe, 2008), nor in Denmark (Bay et al., 2015, Helvind et al., 2015). For both populations, there are no recent studies investigating melanoma incidence trends attributable to changes in UVR exposure and demographics. The only studies that could be identified for Germany were those published by Prizkuleit and Quante. However, these studies only examined demographic aspects and did not analyse the effects of changes in risk behaviour (UVR exposure) on the development of melanoma incidence (Pritzkuleit et al., 2010, Quante et al., 2016). For Demark, the study carried out by Moller et al. at the beginning of the 2000s has not been updated since then (Moller et al., 2002).

The present research project sought to address these gaps and raised the question: to what extent have previous trends in melanoma incidence in Germany and Denmark been influenced by UVR exposure and demographic changes and what impact will they have on future trends? Denmark was chosen as a further country, because it has the longest cancer registration in Europe that allows for long-term incidence trend analyses, based on high-quality data with a high degree of completeness (Engholm et al., 2010, Gjerstorff, 2011).

1.6 Aims and objectives

Aim

The aim of the present research project was to investigate the impact of changes in sun exposure and demographics on past and present melanoma burden in Germany (1995-2013) and in Denmark (1943-2013) and to project incidence rates and numbers of melanoma cases according to these changes for the period 2014-2033.

Objectives

1. To describe observed (1995-2013, Germany and 1943-2013, Denmark) and to estimate future (2014-2033) age-standardized, crude and age-specific incidence rates of melanoma, and to identify significant changes in trends, stratified by sex.
2. To describe observed (1995-2013, Germany and 1980-2013, Denmark) and to estimate future (2014-2033) numbers of melanoma cases, and to calculate the relative change from baseline (1995/1998, Germany and 1980/1983, Denmark), stratified by age (<40 yrs, 40-59 yrs, 60-79 yrs, and 80+ yrs) and sex.
3. To estimate the change in the total numbers of new melanoma cases from baseline (1995/1998, Germany and 1980/1983, Denmark) attributable to changes in UVR exposure and to changes in demographics.
4. To estimate the number and proportion of melanoma cases attributed to UVR exposure at baseline (1995/1998, Germany and 1980/1983, Denmark) and in the further course (1999/2003-2029/2033, Germany and 1984/1988-2029/2033, Denmark), stratified by sex.
5. To estimate the number and proportion of melanoma cases attributed to demographic changes at baseline (1995/1998, Germany and 1980/1983, Denmark) and in the further course (1999/2003-2029/2033, Germany and 1984/1988-2029/2033, Denmark), stratified by sex.

2 Materials and Methods

This chapter is divided into four sections. The first two sections provide general information of the data used in the analyses (2.1) and of the basic statistical concepts (2.2). Country-specific details on data source and parameters included in the models are provided in section 2.3 for Germany, and in section 2.4 for Denmark, respectively.

2.1 Data

2.1.1 Data Source

Trend analyses were based on observed incidence rates of CM (ICD-10 code: C43), which were retrieved by database query from population-based cancer registries covering the periods 1995-2013 for Germany, and 1943-2013 for Denmark (Engholm et al., 2010, Robert Koch Institut Berlin, 2016), respectively. Historical and projected population data (1980-2033) were obtained from national statistics agencies from Germany (Statistisches Bundesamt Wiesbaden, 2015a, 2015b) and Denmark (Statistics Denmark, 2018b).

2.1.2 Measures

The present analyses were based on different measures of disease burden, including incidence rates (age-standardized, crude and age-specific rates) as well as absolute numbers of melanoma cases. This was done in order to separately investigate the impact of changes in population risk (UVR exposure) and demographics (population size and age structure) on melanoma burden.

Age-standardized incidence rates are usually used to describe epidemiological trends. They approximate the population's risk of being diagnosed with cancer and are useful to compare cancer burden between populations with different age structure or to compare rates over time within a population. Age-standardized rates however do not fully convey the extent of cancer burden, because they remove the effect of demographic aging in a population. To overcome this shortcoming, crude rates, accounting for the additional effect of an aging population, were additionally analyzed. In order to fully describe

demographic effects, including changes in population size, all investigations were extended by calculating absolute numbers of melanoma cases.

Table 4 provides an overview of measures of disease burden used to describe temporal trends of melanoma incidence attributed to changes in UVR exposure and demographics (population size and age distribution).

Table 4: Measures of disease burden and changes in UVR exposure and demographics

Measure	Epidemiological trends UVR exposure	Demographic trends Population age	Demographic trends Population size
ASIR or age-specific IRs	x		
CIR	x	x	
Number of melanoma cases	x	x	x

ASIR: Age-standardized incidence rate, CIR: Crude incidence rate, IR: incidence rate

Age-standardized incidence rates were standardized using the European Standard Population (WHO, 1976). Age-specific rates were grouped into four age groups (<40 yrs, 40-59 yrs, 50-79 yrs, and 80+ yrs). All rates were reported as 100,000 per year and stratified by sex.

2.2 Statistical analyses

2.2.1 Incidence trends (Joinpoint Regression)

Regression analysis is a widely applied technique to model time trends in incidence and mortality in epidemiological studies. (Kim et al., 2000). Regression analysis provides valuable information for health authorities and physicians to develop cancer control strategies and to answer the following questions:

(1) What is the average change in incidence rates per calendar year?

(2) Is there a constant trend over time or are there any significant changes (in direction and/or magnitude) in trends?

Thus, in modeling trends over time, it is important to be able to detect when statistically significant changes in trends occur. Joinpoint analysis is usually

used to detect these change points (joinpoints) and to determine the trends between joinpoints (Kim et al., 2000, Kim et al., 2004, Kim et al., 2009).

Joinpoint Regression model

A joinpoint regression model, also known as piecewise or segmented regression, describes changing trends over successive segments of time and the amount of change within each segment. Trends are characterized by joined linear segments; a joinpoint is created where two segments meet, representing a statistically significant change in trend. The model assumes continuity at the joinpoints. For each time segment, the annual percentage change (EAPC) and its 95% confidence intervals (CI) were estimated by fitting linear regression lines to the natural logarithm of the incidence rates (dependent variable) using calendar year as independent regressor variable. To summarize the trend in incidence for the entire period of observation, the average annual percentage rate change (AAPC) is calculated as a weighted average of the EAPCs of each joinpoint segment, with the weights equal to the lengths of the EAPC intervals (Clegg et al., 2009).

The joinpoint regression model has the same underlying assumptions as single regression models (homogeneous error variance, independent observations and normally distributed error term). When analyzing time trends, however, the assumption of independence and constant variance is usually not valid. Joinpoint regression models may incorporate estimated variance at each point (i.e. when the response variables are age-standardized rates) or use a Poisson model of variation (i.e. when the response variables are rates or counts), allowing for two kinds of probabilistic models: Normal and Poisson (Kim et al., 2000).

Model fitting

Joinpoint regression takes trend data (e.g. cancer rates) and fits the simplest joinpoint model, that the data allow. The minimum and the maximum number of joinpoints are selected by the user. The program starts with the minimum number of joinpoints (i.e. 0 joinpoints, which is a straight line) and tests whether

adding further joinpoints (up to the maximum number) would significantly improve the fit and must be added to the model.

The default value for the maximum number of joinpoints depends on the number of observed data points (at least seven data points should be observed in order to consider allowing a joinpoint) and is based on two pre-set rules (Kim et al., 2009):

- To reduce model over-fitting, there should be at least four observations between two joinpoints.
- To keep joinpoints from being placed too close to the end points, there should be at least three observations from a joinpoint to either end of the data.

These algorithmic recommendations lead to the following default maximum number of joinpoints, Table 5:

Table 5: Number of observed data points and recommended maximum number of joinpoints

Number of data points	Max. number of Joinpoints (Default)
0-6	0
7-11	1
12-16	2
17-21	3
22-26	4
27+	5

The next step in the modeling process involves the search for the localization of the joinpoints. Two different methods may be applied to determine the best fit of each model:

- The *Grid Search Method* (default setting) tests a discrete number of locations, allowing the joinpoints only to occur exactly at the observations. To find a better fit, the 'number of joinpoints to place between adjacent observed x values' can be set >0 (maximum=9) (Lerman, 1980).
- The *Hudson's Method* does a continuous fitting between observed values to find the best fit (Hudson, 1966). The method provides the best

fit, but is computationally more intensive than the Grid Search Method. A maximum of four joinpoints are allowed when continuous fitting is applied.

The last step is to find the final model, i.e. with the optimal number of joinpoints, and the optimal locations of related joinpoints. Stepwise selection procedures based on hypothesis testing are a common approach to determine the optimal model. All of the resulting combinations of possible trend lines are sequentially compared using a series of Monte Carlo permutation tests, with Bonferoni correction for multiple testing. The option with the fewest joinpoints that provide the best fit to the observed data is chosen as final model (Kim et al., 2000).

The analysis of time trends has been carried out with the Joinpoint Regression Program (Version 4.3.1.0), a statistical software package developed by the Statistical Research and Applications Branch of the National Cancer Institute (NCI) in the United States (National Cancer Institute, 2016).

2.2.2 Incidence predictions (Age-Period-Cohort Model)

Historically, generalized linear regression models have widely been used to predict future incidence rates (Holford, 1983). The rates are modeled as a function of age, calendar period and birth cohort, assuming that the number of incident cases in a specific age group and period is a random variable with a Poisson distribution (Moller et al., 2002, Osmond, 1985).

The classical age-period-cohort model can be written as:

$$R_{ap} = \exp (A_a + D*p + P_p + C_c),$$

where R_{ap} is the incidence rate in age group a and in calendar period p, A_a is the age component for age group a, D is the common drift parameter accounting for the linear component of the trend in period p and cohort c, P_p is the non-linear period component of period p and C_c is the non-linear cohort component of cohort c.

However, two disadvantages may arise from the above described model:

(1) The multiplicative relationship between the rate and the covariates in the standard Poisson regression model produces predictions in which the rates may grow exponentially with time.
(2) A constant drift parameter over a long period of time may not be appropriate, as it can be assumed that more distant periods are less directly affected by current trends than previous periods.

To improve model accuracy, two modifications have therefore been implemented into the classical age-period-cohort model (Moller et al., 2002):

(1) To level off the exponential growth in the multiplicative model, a power link function was used instead of the log link.
(2) To allow for a dampening of the impact of current trends in future time periods, a gradual reduction in the drift parameter of 25%, 50% and 75% in the second, third and fourth 5-year prediction period, respectively was used.

An empirical evaluation has shown that both modifications improved the predictions (Moller et al., 2003). The modified age-period-cohort model has therefore been used for the present predictions:

$$R_{ap} = (A_a + D*p + P_p + C_c)^5,$$

where $R_{ap,}$ A_a, P_p and C_c are defined as in the multiplicative model.

Incidence predictions are based on observed number of cancer cases, observed population figures and on forecasts of population size and age structure. Cancer cases and population data are aggregated into 5-year time periods and 5-year age groups (0-4, to 85+), stratified by sex. Incidence rates are projected for 5-year time periods.

The first age group for which the number of cases exceeds 20 in each of the 5-year observation periods will be included in the regression model. Projections for age groups below this limit are based on average rates in the last 10 years. The number of periods used in the prediction base will be determined by the goodness-of-fit test (5% level).

In order to prevent the projected trend from being influenced by older, less relevant trends, the trends of crude rates were analyzed. When crude rates displayed a significant curvature in the prediction base, the trend in the last 10 years instead of the average change over the entire period was used as drift component D to be projected (Moller et al., 2002).

Incidence predictions were carried out with NORDPRED, a software package in R, available at https://www.kreftregisteret.no/en/Research/Projects/Nordpred/ (NORDPRED, 2016).

2.2.3 Number of new melanomas attributed to changes in UVR exposure and demographics

The numbers of new melanoma cases (2014-2033) were predicted by multiplying the projected incidence rates (chapter 2.2.2) according to sex and 5-year age group (0-4, 5-9,…., 80-84, 85+) by the corresponding population forecasts. The total number of projected melanomas is the sum of melanoma cases in each age group. Observed melanoma cases (Denmark: 1984-2013; Germany: 1999-2015) were sourced directly from the cancer registry databases (NORDCAN, 2018, Robert Koch Institut Berlin, 2016).

The changes in the annual numbers of melanoma cases between baseline and future time periods are influenced both by changes in the risk for cancer (i.e. increase in UVR exposure) and by changes in demographics (population size and age structure). The number of cancer cases can be described as N_{RAS}, with cancer risk ‘R’, population age distribution ‘A’ and population size ‘S’ (Moller et al., 2002), Figure 4:

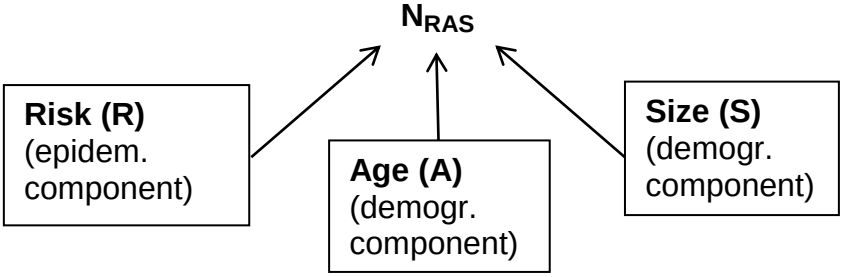


Figure 4: Number of cancer N_{RAS} and their components risk, population age and size

‘R’, ‘A’ and ‘S’ are levels for the observed/baseline period (B) or for future periods (F). N_{BBB} is then the observed number of cases at baseline, when present rates are applied to present population size and age structure. Similarly, N_{FFF} is the predicted number of cases in future, based on projected incidence rates and population forecasts (size and age distribution).

$N_{FFF} - N_{BBB}$ is the total change in the annual number of cases between baseline and future periods and according to Engeland et al. this change can be divided into two components (Engeland et al., 1993):

(1) Changes due to increased risk of being diagnosed with cancer (changes of age-standardized or age-specific incidence rates): $\triangle_{Risk}$

(2) Changes due to demographic variations (population size and age): $\triangle_{Population}$

$$\triangle_{Total} = N_{FFF} - N_{BBB} = (N_{FFF} - N_{BFF}) + (N_{BFF} - N_{BBB})$$
$$= \triangle_{Risk} + \triangle_{Population},$$

N_{BFF} is the expected number of new melanoma cases in future, applying baseline rates (B) to future population size (F) and age structure (F). The number of new cancer cases attributed to change in risk ($\triangle_{Risk}$) is therefore the difference between the number of cases in the future using the predicted (N_{FFF}) or observed (N_{BFF}) rates, while the change due to population structure ($\triangle_{Population}$) is the difference between the number of cases obtained when baseline rates are applied to baseline (N_{BBB}) or future age distribution and population size (N_{BFF}).

To evaluate the impact of demographic aging, the population component ($\triangle_{Population}$) can be divided into two sub-components, changes due to age distribution ($\triangle_{Age}$) and changes due to population size ($\triangle_{Size}$):

$$\triangle_{Population} = \triangle_{Age} + \triangle_{Size} \quad \text{(absolute change) or}$$

$$\triangle_{Population}/N_{BBB} = \triangle_{Age}/N_{BBB} + \triangle_{Size}/N_{BBB} \quad \text{(relative change)}$$

The relative change in the number of new cases due to population size ($\triangle_{Size}/N_{BBB}$) is equal to the relative increase or decrease in population size. The relative change due to age structure is therefore given by:

$$\triangle_{Age}/N_{BBB} = \triangle_{Population}/N_{BBB} - \triangle_{Size}/N_{BBB}$$

$$\triangle_{Age}/N_{BBB} = (N_{BFF} - N_{BBB})/N_{BBB} - \triangle_{Size}/N_{BBB}$$

The supplementary tables (S1 and S3) illustrate how the calculations were carried out in detail.

2.2.4 Proportions of melanoma attributable to UVR exposure (background level)

This chapter describes the method used to estimate the population attributable fraction (PAF%) of melanoma cases that can be attributed to high background levels of UVR (the so-called ‘baseline risk’ for CM).

The traditional approach to estimate the population attributable fraction, using population prevalence of exposure as compared to prevalence in unexposed populations, cannot be applied as there are neither unexposed populations nor reliable exposure data (Arnold et al., 2018a, de Vries et al., 2017, Winther et al., 1997).

Therefore an approach proposed by Parkin et al. was used which compares currently observed melanoma incidence rates in the study population with those of a ‘minimal-exposed’ or ‘low-incidence’ reference population (as approximation of an ‘unexposed’ population) (Parkin et al., 2011b).

The difference in rates or numbers of cases is then attributed to corresponding differences in solar UVR exposure between the study and the reference population.

The PAF% is calculated according to the following formula:

$$PAF\% = (I_S - I_R)/I_S,$$

where I_S is the observed incidence of melanoma in the study population and I_R is the incidence in the reference population.

To get the numbers of melanoma cases that would have been expected with a theoretical-minimum-exposure distribution, age-specific incidence rates of the reference population I_R are multiplied by the age- and sex-specific population sizes of the study population. The expected numbers of melanoma cases N_E are then compared with the observed numbers of the study population N_O and the PAF% is calculated as follows:

$$PAF\% = (N_O - N_E)/N_O$$

The supplementary tables (S2 and S4) illustrate how the calculations for Germany and Denmark have been carried out in detail.

To approximate incidence rates for an 'unexposed population' a series of different low-risk populations, selected according to time, geography/genetic susceptibility or anatomical site, has been described (Armstrong and Kricker, 1993, Parkin et al., 2011b, Winther et al., 1997). Table 6 provides an overview of commonly used reference populations and their selection criteria.

Table 6: Characteristics of commonly used reference populations

Criteria	Reference population	Melanoma IRs	Rationale	Author (Year)
Time	South Thames birth cohort from 1903 (UK)	1.0-1.9/100,000/yr	Historical cohort which is minimally exposed to UVR due to cultural habits (clothing style, recreational activities); Long series of high quality data, included in the 'Cancer Incidence in Five Continents (CI5)	Parkin et al (2005)
	Danish Cohort from 1940s		See above	Winther et al (1997)
Geography	Ethnically similar population living in areas of low UV irradiance (i.e. Wales/England)	3.4-5.9/100,000/yr (in 1983-1988)	Populations, less exposed to UVR, living in areas of low solar irradiance compared to study population (exposed to high solar irradiance); Commonly used to estimate the PAF% for the Australian population having their ancestry in low solar areas (i.e. UK)	Armstrong et al (1993)
	Migration from an area of low to high solar irradiance during adulthood	-	Population living in an area of lower risk for melanoma during childhood (time of highest risk for melanoma); Commonly used to estimate the PAF% for native-born Australians, living in an area of high solar irradiance	Armstrong et al (1993)
Genetics	Non-Caucasian, darker-skinned populations, i.e US Blacks	0.5-0.9/100,000/yr (in 1983-1987)	Dark-pigmented populations, less susceptible to UVR; lesions occurring on sites (plantar surfaces of feet/hands) which are unlikely to be related to UVR	Armstrong et al (1993)
	African populations (i.e. Uganda, Zimbabwe, Malawi)	1.1-3.8/100,000/yr (in 2003-2007)	See above	Arnold et al (2018)
Anatomical site	Unexposed body sites (scalp or buttocks)	Weighted average: 1.1/100,000/yr	Occurrence of melanoma on non-sun exposed sites, melanoma is unlikely to be related to UVR	Armstrong et al (1993)

2.3 Germany: Data and statistical analyses

2.3.1 Data

Cancer registry data

Incidence data of CM, covering the period 1995-2013, were obtained from the Robert Koch-Institute (RKI) in Berlin, which collects data on cancer diseases from all 16 population-based cancer registries in Germany (Robert Koch Institut Berlin, 2016). Within the Robert Koch-Institute, the Centre for Cancer Registry Data (CCRD) is responsible for pooling and quality assurance of the data, including checks for completeness and plausibility. Based on these data, the CCRD regularly estimates and analyses the number of new cancer cases that occur each year.

Initial cancer registration in Germany is based on notifications from hospitals, practicing physicians as well as reports from pathology departments. Case ascertainment is supplemented by death certificates only (DCO-cases) provided by health authorities. In 11 federal states (Saarland, Hamburg, Bremen, Schleswig-Holstein, Lower Saxony, Bavaria, Brandenburg, Mecklenburg-Vorpommern, Saxony, Thuringia, and for the government district of Muenster (North Rhine Westphalia)), the estimated coverage rate was over 90% for the year 2012. Reliable data on new cancer cases are therefore available for a population of around 55 million inhabitants (~70% of the entire German population). According to estimates from the Robert Koch-Institute, only 2% of melanoma cases, reported to the CCRD between 2012 and 2013, were notified by death certificate only (DCO). Both, high coverage rate and low proportion of DCO cases are indicators for the high quality of the data (Robert Koch Institut Berlin, 2016).

Population data

Historical (1995-2013) and forecast (2014-2033) population size and structure, stratified by sex and 5-year age intervals (0-4, 5-9, …, 85+), were retrieved from the Federal Statistical Office in Germany (Statistisches Bundesamt Wiesbaden, 2015a, 2016). Population forecasts were based on data of the 13th coordinated population projection, which was released in April 2015 and which consists of

eight different variants. For the present analyses, variant 4 (G1-L2-W2) was chosen, assuming a birth rate of 1.4 children per women, life expectancy at birth in 2060 of 86.7 years for men and 90.4 years for women, as well as net migration of 200,000 individuals per year (Statistisches Bundesamt Wiesbaden, 2015b).

The observation period covered the years 1995-2013, the first four years (1995-1998) were defined as baseline period with which subsequent rates and melanoma cases were compared. Incidence projections were performed for a time period of 20 years from 2014 until 2033. Except of the baseline period, all measures are given as 5-year average rates or numbers (1999/2003, 2004/2008,…..2024/2028, 2029/2033).

2.3.2 Statistical analyses and parameter setting

Joinpoint regression (Observed incidence trends)

To determine whether incidence rates changed significantly during the period of observed data (1995-2013), the estimated annual percentage change (EAPC) with 95% confidence intervals was calculated using joinpoint regression (Kim et al., 2000). Trend analyses were performed for age-standardized, crude and age-specific incidence rates, separately for men and women.

Joinpoint regression models are sensitive to parameter setting. In order to be able to compare geographical and temporal incidence trends of melanoma, a number of parameters have been predefined. For the analyses of age-standardized incidence rates, constant error variance was assumed, while a Poisson model with heteroscedastic error option was chosen for the analyses of crude and age-specific incidence rates. Permutation testing with an overall significance level of 0.05 and a Grid Search algorithm was used to define the final regression model. Details on parameter selection and model fitting are given in Table 7.

Table 7: Joinpoint regression analyses - parameter setting (for males and females)

Parameter	ASIR	CIR/ age-specific IRs
Model (linear vs. log-linear)	Log-linear	Log-linear
Data distribution of dependent variable (Normal vs. Poisson)	Normal	Poisson
Variance (constant vs. non-constant)	constant	non-constant
Number of joinpoints (min; max)	0; 3	0; 3
Minimum numbers of observations from a joinpoint to either end of the data	4	4
Minimum numbers of observations between 2 joinpoints	4	4
Searching method (Grid or Hudson)	Grid	Grid
Model selection method:	Permutation	Permutation
Number of permutations	n=4499	n=4499
Overall significance level	0.05	0.05

Age-Period-Cohort Model (Projected incidence trends)

Modified age-period-cohort models with a power link function were used to project incidence rates for four 5-year time periods from 2014/2018 through to 2029/2033. The calculations were based on new cancer cases, diagnosed between 1999 and 2013, on population numbers for 1999-2013 and forecasts of population size and age structure for 2014-2033. Incident cancer cases were aggregated into 5-year periods (from 1999/2003 through to 2009/2013) and 5-year age groups (0-4, to 85+) by sex (Moller et al., 2002).

For both, males and females, the first age group for which the number of melanoma exceeded 20 in each 5-year observation period, and which was therefore included in the regression model, was the age group 15-19 years. As crude rates showed a significant departure from the linear trend for both sexes in the prediction base, only the trend in last 10 years was used as a drift component to be projected. Incidence predictions were performed for age-

standardized, crude and age-specific incidence rates, separately for men and women. Final parameter setting is given in Table 8.

Table 8: Age-period-cohort models – parameter setting (for males and females)

Parameter	Value
Number of 5-yr. periods used in estimate (prediction base)	3
Prediction base	1999-2003; 2004-2008; 2009-2013
Number of 5-yr. periods predicted	4
Projected periods	2014-2018; 2019-2023; 2024-2028; 2029-2033
Trend used in predictions (cuttrend)	0; 0.25; 0.5; 0.75
Link function	Power
P-value for goodness of fit	NA*
Used trend (average or recent)	Recent
P-value for recent	<0.001 (both sexes)
First age group estimated (lower age limit)	15-19 yrs (both sexes)

* NA: not applicable as the prediction base is fixed on the minimum of three required 5-year time intervals

Numbers of new melanoma attributed to changes in risk and demographics

The number of melanoma cases between 1999/2003 and 2029/2033 were compared with the number of melanomas diagnosed at baseline period (1995/1998). The total change in the annual number of melanoma ($\triangle_{Total}$) was divided into two components: changes in UVR exposure (population risk) and changes in demographics (population size and age distribution) (Engeland et al., 1993, Moller et al., 2002):

$$\triangle_{Total} = N_{FFF} - N_{BBB} = (N_{FFF} - N_{BFF}) + (N_{BFF} - N_{BBB})$$
$$= \triangle_{Risk} + \triangle_{Population}$$

The risk component ($\triangle_{Risk}$) is calculated as the difference between the numbers of melanoma cases in 1999/2003-2029/2033 using incidence rates of 1999/2003-2029/2033 (N_{FFF}) and baseline rates of 1995/1998 (N_{BFF}). The demographic component ($\triangle_{Population}$) is the difference of melanoma cases obtained when baseline rates (1995/1998) are applied to population size and age structure of 1995/1998 (N_{BBB}) or to population data of 1999/2003-2029/2033 (N_{BFF}).

A detailed description of the calculations is given in the supplementary tables (Table S1).

Proportions of melanoma attributable to UVR exposure (background level)

The population attributable fractions and the numbers of melanoma cases due to UVR at baseline (1995/1998) were estimated as the proportional difference between observed melanoma cases in 1995/1998 by 5-year age groups (0-4 yrs, ..., 85+ yrs) and sex and the expected number of cases applying incidence rates from a historical Danish cohort (1943/1947) (IARC, 2018). This cohort was chosen as reference population given its minimal exposure to UVR, living in an era when clothing styles almost completely covered the skin. 5-year averages of the age-standardized incidences rates (European Standard population, WHO 1976) in 1943/1947 were 1.3/100,000 per year for males and 1.5/100,000 per year for females, respectively. Incidence data from this cohort have been included in the 'Cancer Incidence in Five Continents (CI5)' (IARC, 2018), an indicator of high quality data having high comparability, completeness and validity. Supplementary table (Table S2) describes the details of the calculations.

2.4 Denmark: Data and statistical analyses

2.4.1 Data

Cancer registry data

Melanoma incidence data for Denmark (1943-2013) were sourced from the NORDCAN database (NORDCAN, 2018). The NORDCAN database includes detailed information and results on cancer incidence, mortality and prevalence in each of the Nordic countries over five and more decades (Engholm et al., 2010). The data originates from the national cancer registries and causes of death registries in Denmark, Finland, Iceland, Norway, Sweden, and the Faroe Island.

The Danish Cancer Registry is the oldest, founded in 1942 (Gjerstorff, 2011). First complete year of cancer registration exists since 1943. In Denmark, cancer is reported from multiple sources, including public hospitals, private clinicians/dentists, inpatient hospital registries and pathological laboratories, supplemented by death certificates. Only 0.3% of all cancer cases between 2009 and 2013 were notified by death certificate only (DCO cases). As cancer notification has become mandatory in all of the Nordic countries, close to 100% coverage of incident cases has been reported in each of the Nordic cancer registries (Engholm et al., 2010, Larsen et al., 2009, Storm et al., 1997, Teppo et al., 1994). Each of the five Nordic cancer registries has been included in the Cancer Incidence in Five Continents (CI5), indicating to have high quality data.

Population data

In contrast to the melanoma data, which are recorded since the mid-1940s, population data are not available until 1980. Historical (1980-2013) and forecast (2014-2033) population size and structure, stratified by sex and 5-year age intervals (0-4, 5-9, …, 85+), were obtained from the Statistics Denmark (Statistics Denmark, 2018b). Population projections for Denmark include only one scenario for future developments, assuming a birth rate of 1.9 children per women, life expectancy at birth of 87.1 years for men and 89.5 years for women in 2060, as well as net migration of 45,000 individuals per year (Statistics Denmark, 2018a).

1980 is the first year for which both cancer and population data are available. The years 1980-1983 were defined as baseline period. Subsequent time periods were divided into 5-year intervals (1984/1988, 1989/1993,…., 2024/2028, 2029/2033). Rates and numbers of melanoma cases are presented as 5-year averages.

2.4.2 Statistical analyses and parameter setting

Joinpoint regression (Observed incidence trends)

Joinpoint regression models (Kim et al., 2000) were used to analyze incidence trends between 1980 and 2013. Changes in trends were quantified by calculating the estimated annual percentage change (EAPC) and its 95% confidence intervals. Trend analyses were performed for age-standardized, crude and age-specific incidence rates, and were stratified by sex.

For the analyses of age-standardized incidence rates, constant error variance was assumed, while a Poisson model with heteroscedastic error option was chosen for the analyses of crude and age-specific incidence rates. Permutation testing with an overall significance level of 0.05 and a Grid Search algorithm was used to define the final regression model. Details on parameter selection and model fitting are given in Table 9.

Table 9: Joinpoint regression analyses - parameter setting (for males and females)

Parameter	ASIR	CIR	Age-specific IRs
Model (linear vs. log-linear)	Log-linear	Log-linear	Log-linear
Data distribution of dependent variable (Normal vs. Poisson)	Normal	Poisson	Poisson
Variance (constant vs. non-constant)	constant	non-constant	non-constant
Number of joinpoints (min; max)	0; 5	0; 5	0; 3
Minimum numbers of observations from a joinpoint to either end of the data	5	5	5
Minimum numbers of observations between 2 joinpoints	5	5	5
Searching method (Grid or Hudson)	Grid	Grid	Grid
Model selection method:	Permutation	Permutation	Permutation
Number of permutations	n=4499	n=4499	n=4499
Overall significance level	0.05	0.05	0.05

Age-Period-Cohort Model (Projected incidence trends)

Modified age-period-cohort models were used to project incidence rates from 2014/2018 through to 2029/2033 (Moller et al., 2002). Incidence predictions were based on melanoma cases, diagnosed between 1984 and 2013, on population data covering the same time period, and on forecasts of population size and age structure for 2014 until 2033. Incident cases of CM were aggregated into 5-year periods (from 1984/1988 through to 2009/2013) and 5-year age groups (0-4, to 85+) by sex.

For both, males and females, the first age group for which the number of melanoma exceeded 20 in each 5-year observation period, and which was therefore included in the regression model, was the age group 20-24 years. The predictions were based on the last three observation periods (1999/2003-2009/2013) for males and on the last six observation periods (1984/1988-

2009/2013) for females, as determined by the goodness-of-fit test (5% level). As crude rates for females showed a significant departure from the linear trend in the prediction base, only the trend in last 10 years was used as drift component to be projected. For males, the average linear trend over the entire period of observation was used as drift component. Incidence predictions were performed for age-standardized, crude and age-specific incidence rates, stratified by sex. Final parameter setting is given in Table 10.

Table 10: Age-period-cohort models - parameter setting (for males and females)

Parameter	Males	Females
Number of 5-yr. periods used in estimate (prediction base)	3	6
Prediction base	1999-2003; 2004-2008 2009-2013	1984-1988; 1989-1993; 1994-1998; 1999-2003; 2004-2008; 2009-2013
Number of 5-yr. periods predicted	4	4
Projected periods	2014-2018; 2019-2023; 2024- 2028; 2029-2033	2014-2018; 2019-2023; 2024- 2028; 2029-2033
Trend used in predictions (cuttrend)	0; 0.25; 0.5; 0.75	0; 0.25; 0.5; 0.75
Link function	Power	Power
P-value for goodness of fit	0.0941	0.4686
Used trend (average or recent)	Average	Recent
P-value for recent	0.1389	< 0.001
First age group estimated (lower age limit)	20-24 yrs	20-24 yrs

Numbers of new melanoma attributed to changes in UVR exposure and demographics

The number of observed (1984/1988-2009/2013) and projected (2014/2018-2029/2033) melanoma cases were compared with the number of melanomas diagnosed at baseline period (1980/1983). The total change in the annual number of melanoma ($\triangle_{Total}$) was divided into changes due to UVR exposure and into changes due to population structure (size and age distribution) (Engeland et al., 1993, Moller et al., 2002):

$$\triangle_{Total} = N_{FFF} - N_{BBB} = (N_{FFF} - N_{BFF}) + (N_{BFF} - N_{BBB})$$
$$= \triangle_{Risk} + \triangle_{Population}$$

Changes due to risk ($\triangle_{Risk}$) are calculated as the difference between the number of melanoma cases in 1984/1988-2029/2033 using incidence rates of 1984/1988-2029/2033 (N_{FFF}) and baseline rates of 1980/1983 (N_{BFF}). Changes due to population ($\triangle_{Population}$) is the difference of melanoma cases obtained when baseline rates (1980/1983) are applied to population size and age structure of 1980/1983 (N_{BBB}) or to population data of 1984/1988-2029/2033 (N_{BFF}).

A detailed description of the calculations is given in the supplementary tables (S3).

Proportions of melanoma attributable to UVR exposure (background level)

To calculate the numbers and proportion of melanoma cases attributed to UVR at baseline (1980/1983), the same reference population (Danish cohort from 1943/1947) was chosen as for Germany (IARC, 2018). Details of the calculations are provided in supplementary table S4.

3 Results

3.1 Germany

3.1.1 Trends in incidence rates

The results of the Joinpoint regression analysis with estimates of the annual percentage change of observed incidence trends (1995-2013) are summarized and illustrated in Table 12 and in Figure 5, 6 and 7. Projected incidence rates for 2014/2018 until 2029/2033, based on age-period-cohort models, are presented in Table 11 and Figure 8, 9 and 10.

Age-standardized and crude incidence rates

For both sexes, age-standardized incidence rates have almost doubled during the observation period. In men, they climbed by +95.0% from 10.1/100,000 per year in 1995/1998 to 19.7/100,000 per year in 2009/2013, with an average annual increase of +4.4% (95% CI=2.8; 6.1), Figure 5a. Similar increases were observed for females, rising by +96.0% from 9.9/100,000 per year in 1995/1998 to 19.4/100,000 per year in 2009/2013, with an average annual increase of +4.3% (95% CI=1.3; 7.4), Figure 5b. Steepest increases of +11.1% p.a. for both, males and females, were observed between 2006 and 2009, followed by a leveling off in increase thereafter.

The increase in incidence was more pronounced in crude incidence rates. In men, CIRs have risen by +145% from 11.0 in 1995/1998 to 26.9/100,000 per year in 2009/2013, which corresponds to an annual increase of +6.0% (95% CI=4.4; 7.6), Figure 6a. For the same time period, CIRs increased by +111% in females, climbing from 12.1 in 1995/1998 to 25.5/100,000 per year in 2009/2013, with an annual increase of +4.9% (95% CI=2.7; 7.1), Figure 6b. Again, the strongest increases of +13.2% p.a. for males and of +11.7% p.a. for females, respectively, were observed between 2006 and 2009.

Projections, based on age-period-cohort models, suggest further increases in incidence for the next 20 years. In men, ASIRs will rise from 19.7/100,000 per year in 2009/2013 to 29.9/100,000 per year in 2029/2033, with first signs of stabilization from the mid-2020s onwards. In females, ASIRs will climb from

19.4 in 2009/2013 up to 33.6/100,000 per year in 2029/2033, Figure 8a/b, Table 11.

Even higher increases are projected for CIRs. In contrast to ASIRs, no stabilization or leveling off in increase is expected to occur in both sexes. In 2029/2033, CIRs will reach 50.1/100,000 per year in men and 47.3/100,000 per year in women, Figure 9a/b, Table 11.

Age-specific incidence rates

IRs of melanoma increased exponentially with age. Melanoma was rare in adults younger than 40, with IRs of 3.0/100,000 per year for males and of 5.0/100,000 per year for females in 1995/1998. IRs peaked in the elderly (80+ yrs) with IRs of about 30.0 for females and 45.0/100,000 per year for males, respectively, Figure 7a/b, Table 11. Until age 60, melanoma was more common in females than in males (apart from one exception for the age group 40-59 yrs), while the opposite was true for age groups ≥60 years. At the end of the observation period (2009/2013), IRs in men aged 80+ years were almost 90% higher compared to females of same age (89.3/100,000 per year vs. 47.4/100,000 per year), Figure 7a/b, Table 11.

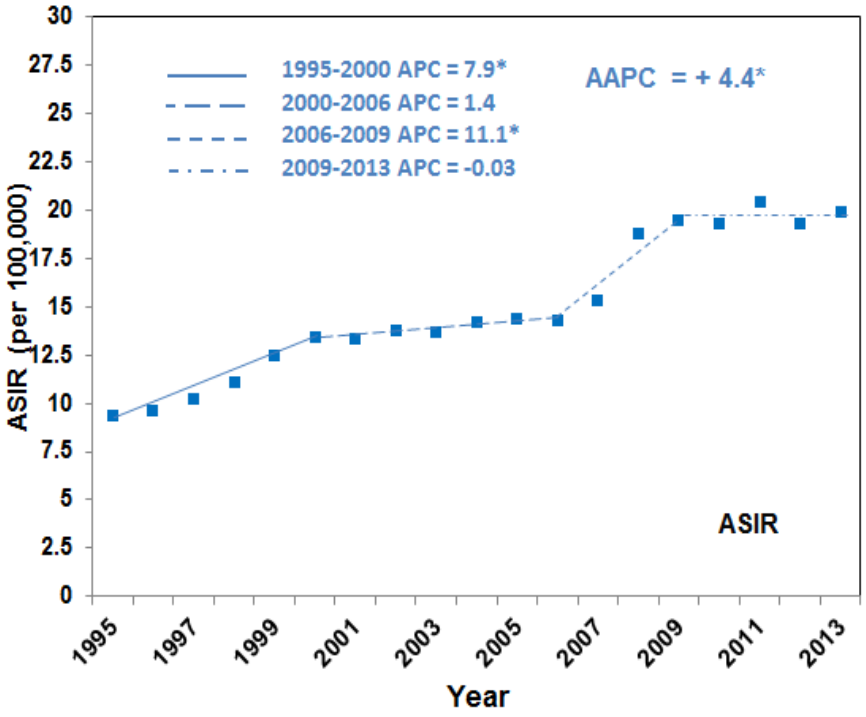
Between 1995/1998 and 2009/2013 melanoma incidence rates increased in all age groups, most obvious in age groups ≥60 years, Table 11, Figure 7a/b. The steepest increase in incidence was observed in the age group 60-79 years, with an average annual increase of +6.2% (95% CI=3.3; 9.2) for males and of +4.8% (95% CI=2.8; 6.8) for females, Table 12, Figure 7a/b. Lower, but also significant increases, ranging between +3.1% p.a. (0-39 yrs) and +4.3% p.a. (80+ yrs) for males and between +3.4% p.a. (80+ yrs) and +4.2% p.a. (40-59 yrs) for females, respectively, were found in the other age groups.

Within the observation period, trends varied across the age groups. Strong increases in incidence were found between 2005/2006 and 2009. Among men, the annual increases ranged between +9.6% (0-39 yrs) and +13.4% (60-79 yrs) and in women between +9.1% (60-79 yrs) and +10.8% (40-59 yrs). Slightly declining incidence rates in the following time period were found for younger age groups. From 2009 onwards, melanoma incidence decreased by -4.4% p.a.

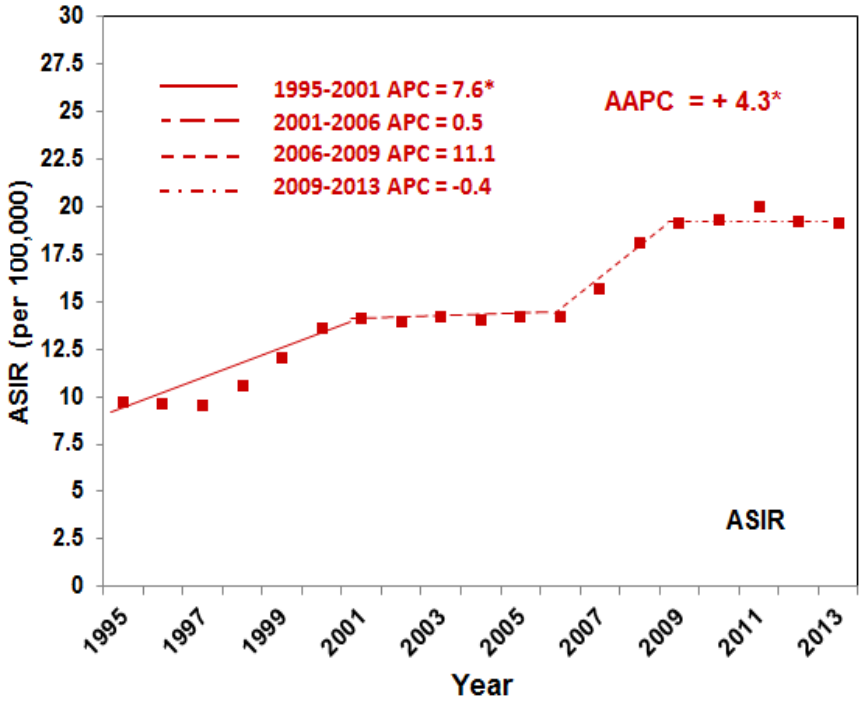
for men (0-39 yrs) and by -3.3% p.a. for women (0-39 yrs), however this was not statistically significant, Table 12.

Trends of increasing incidence rates are anticipated for all age groups in future. Strong and persistent increasing rates are projected for age groups ≥60 years, while for younger age groups first signs of a leveling-off in increase or even declining incidence rates are expected from the mid-2020s onwards, Figure 10a/b, Table 11. For men aged 80+ years, IRs will double from 89.3/100,000 per year in 2009/2013 to almost 180/100,000 per year in 2029/2033. Lower increases are suggested for men between 60 and 79 years of age, rising from 69.2/100,000 per year in 2009/2013 to 102.2/100,000 per year in 2029/2033. For women, the highest increase is projected for the age group 60-79 years. IRs will climb by +82% from 41.7 in 2009/2013 up to 75.8/100,000 per year in 2029/2033. An increase of about +70%, rising from 47.4 in 2009/2013 to 80.1/100,000 per year in 2029/2033, is anticipated for elderly (80+ yrs) women, Figure 10a/b, Table 11. For men and women aged 40-59 years, IRs are predicted to continue to rise at least until the mid-2020s. Incidence rates will peak in 2024/2028 (men: 36.1/100,000 per year and women: 53.5/100,000 per year), thereafter a decline in IRs is expected to occur, Figure 10a/b, Table 11. Trends of increasing IRs are also expected for the youngest age group (<40 yrs), with first signs of stabilization from 2024/2028 onwards. In men, IRs will rise about +65% from 4.6 in 2009/2013 to 7.6/100,000 per year in 2029/2033 and in women by +55% from 9.4 in 2009/2013 to 14.6/100,000 per year in 2029/2033.

(a)



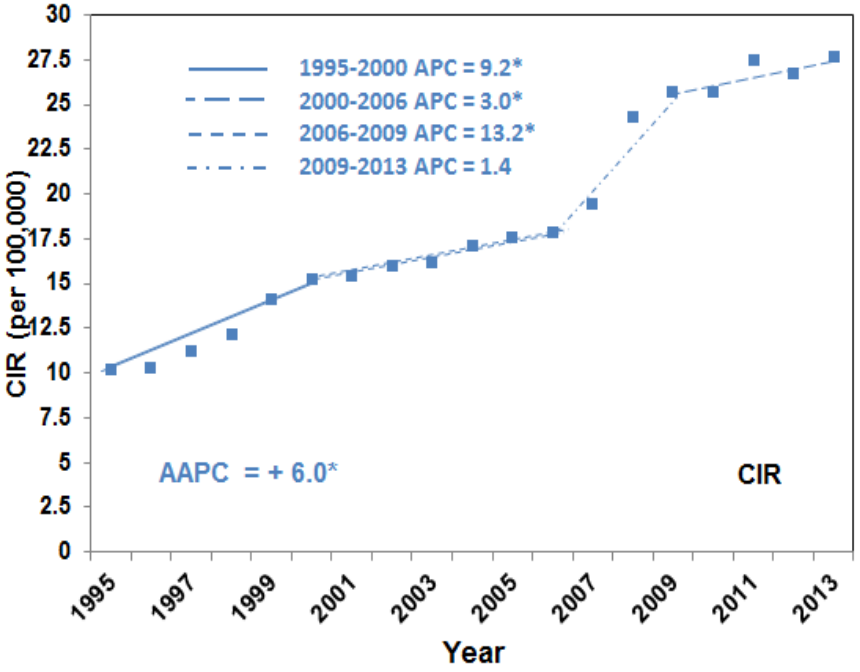
(b)



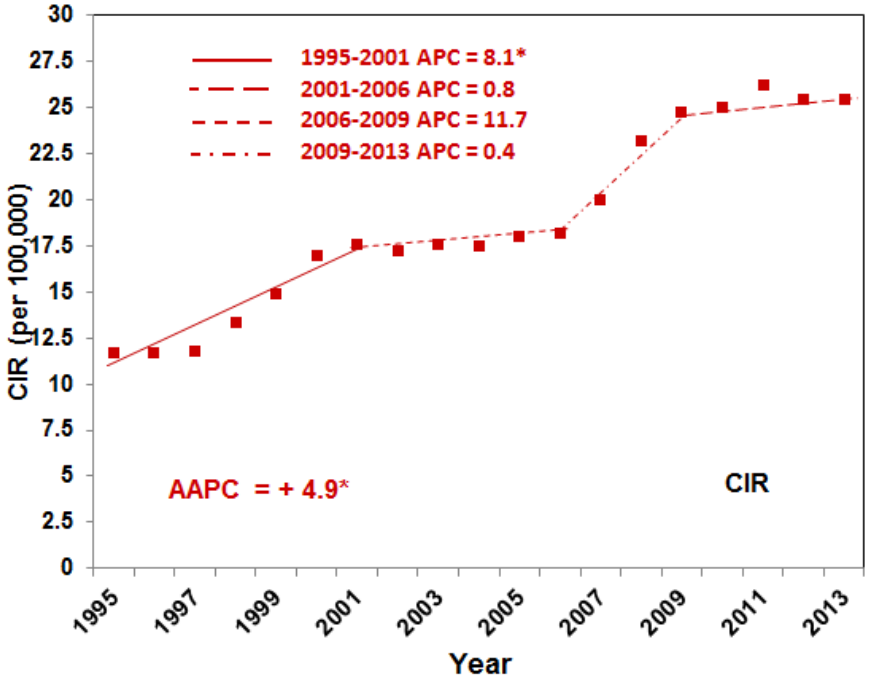
Abbreviations: APC, annual percentage change: AAPC, average annual percentage change
* APC, AAPC are significantly different from zero at α=0.05

Figure 5: Trends of age-standardized incidence rates (European Standard Population, WHO 1976) of cutaneous melanoma, Germany (1995-2013): (a) Males; (b) Females.

(a)



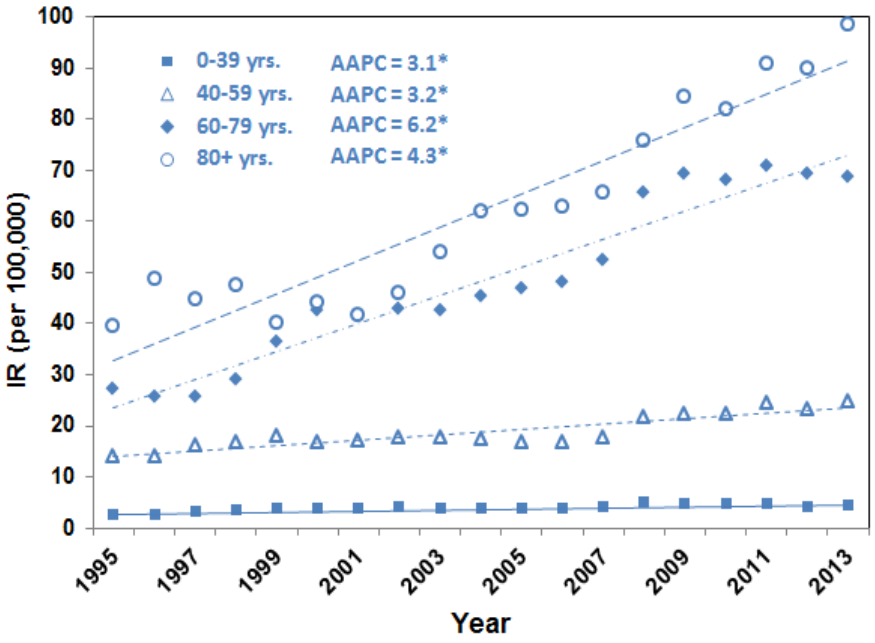
(b)



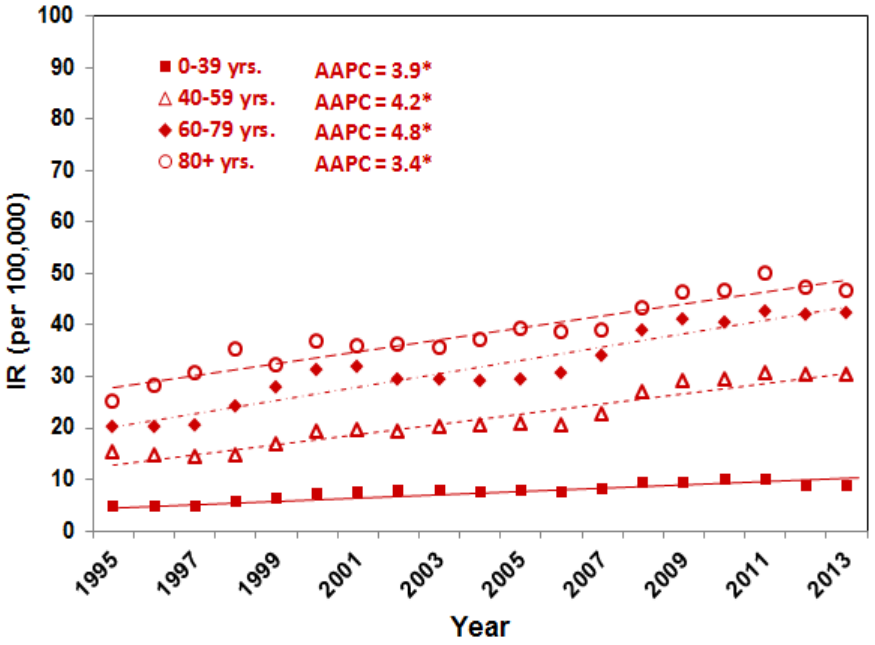
Abbreviations: APC, annual percentage change: AAPC, average annual percentage change
* APC, AAPC are significantly different from zero at α=0.05

Figure 6: Trends of crude incidence rates of cutaneous melanoma, Germany (1995-2013): (a) Males; (b) Females.

(a)



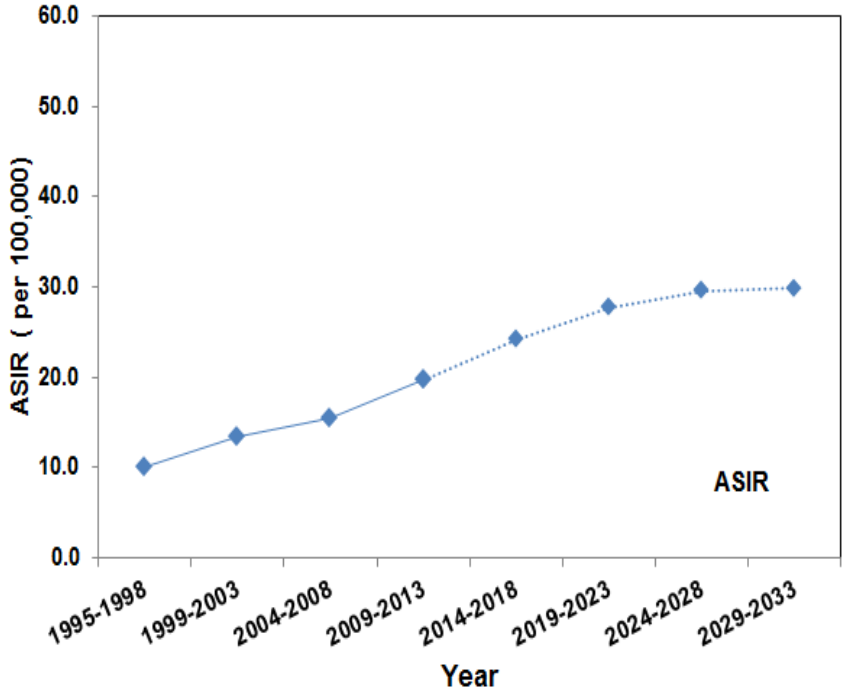
(b)



Abbreviations: APC, annual percentage change: AAPC, average annual percentage change
* APC, AAPC are significantly different from zero at α=0.05

Figure 7: Trends of age-specific incidence rates of cutaneous melanoma, Germany (1995-2013): (a) Males; (b) Females.

(a)



(b)

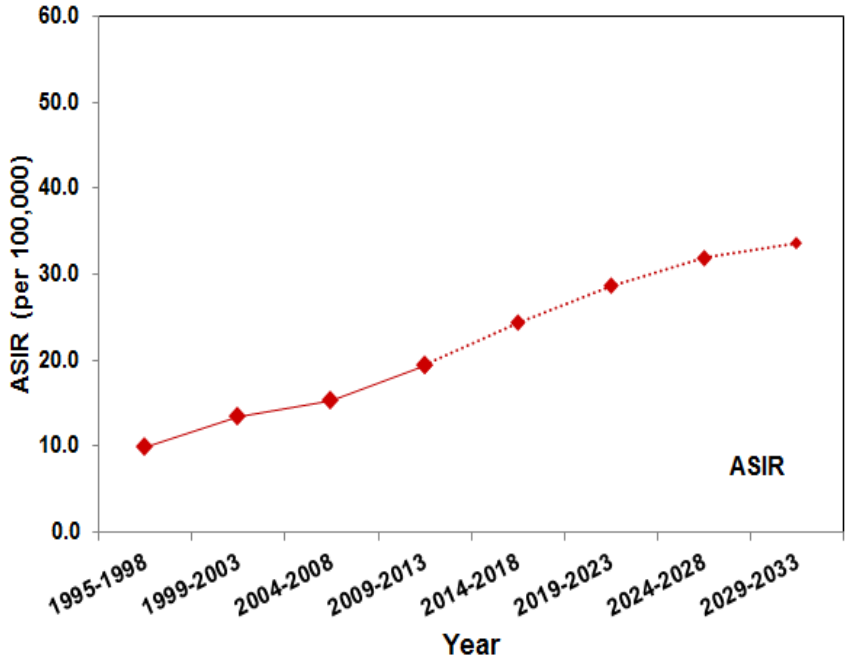
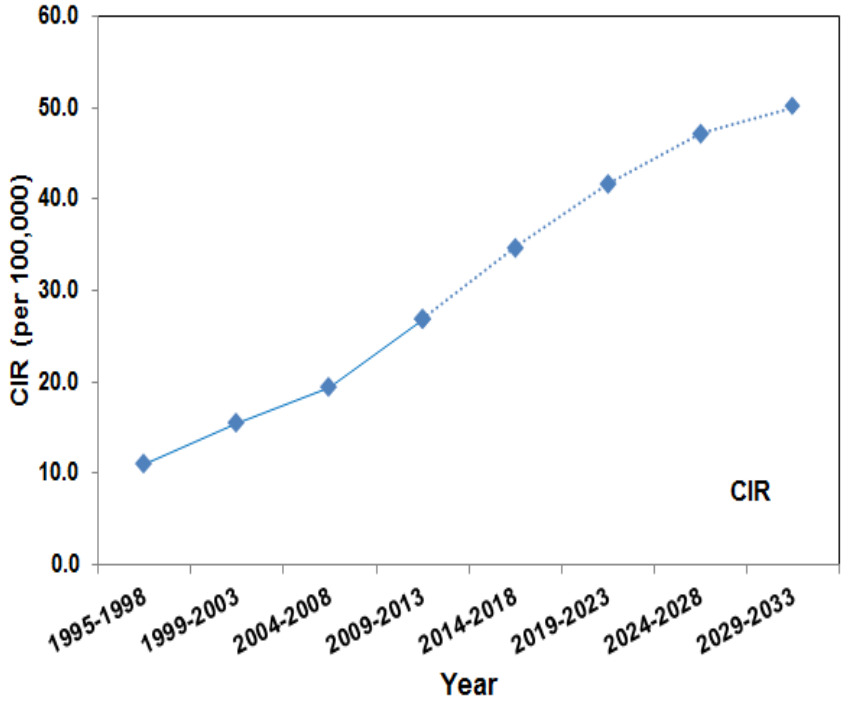


Figure 8: Projections of age-standardized incidence rates of cutaneous melanoma, Germany (2014/2018-2029/2033): (a) Males; (b) Females

(a)



(b)

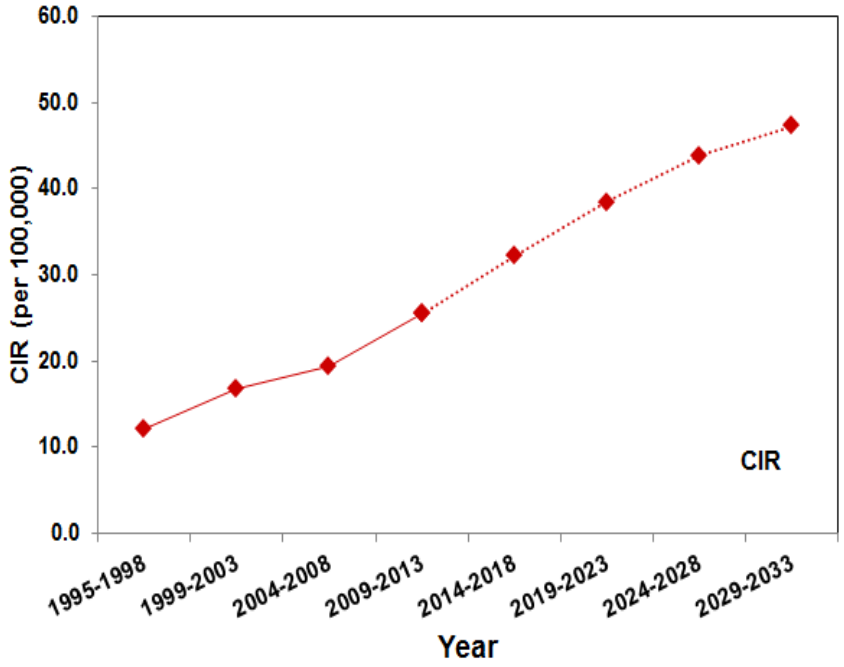
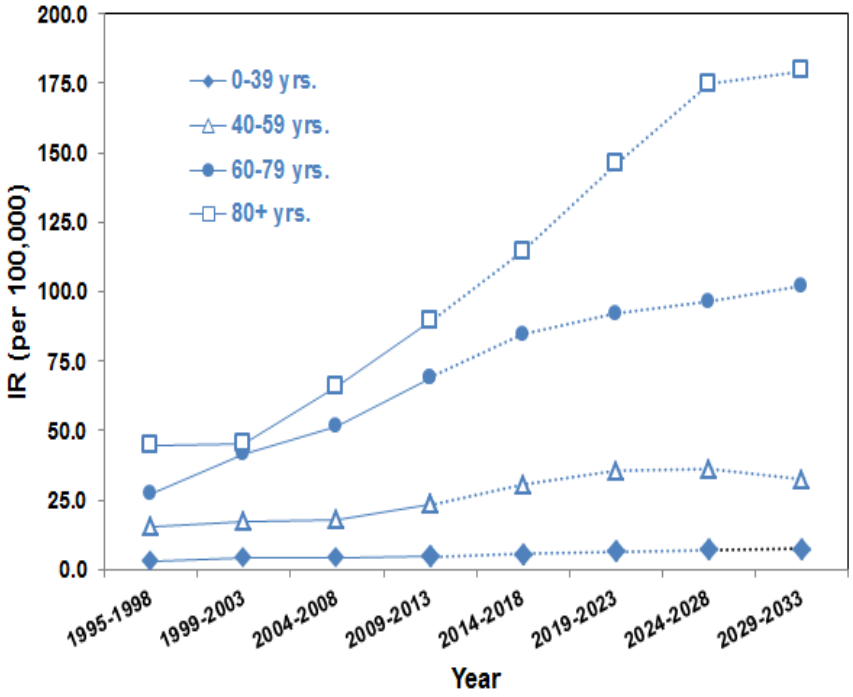


Figure 9: Projections of crude incidence rates of cutaneous melanoma, Germany (2014/2018-2029/2033): (a) Males; (b) Females

(a)



(b)

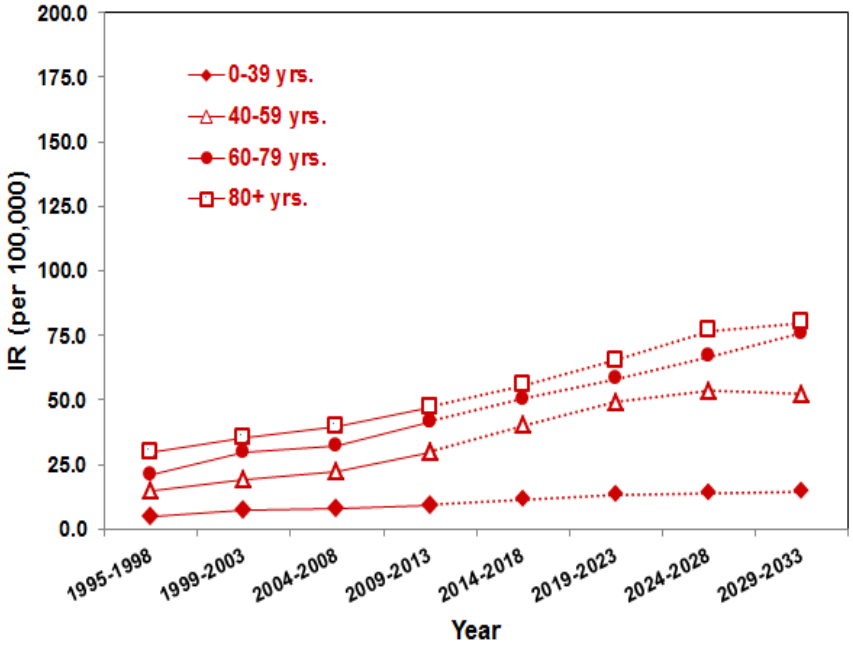


Figure 10: Projections of age-specific incidence rates of cutaneous melanoma, Germany (2014/2018-2029/2033): (a) Males; (b) Females

Table 11: Observed (1995/1998-2009/2013) and projected (2014/2018-2029/2033) age-standardized, crude and age-specific incidence rates of cutaneous melanoma by sex, Germany*

	Observed Data				Projected Data**			
	1995-1998	**1999-2003**	**2004-2008**	**2009-2013**	**2014-2018**	**2019-2023**	**2024-2028**	**2029-2033**
Males								
ASIR	10.1	13.4	15.4	19.7	24.2	27.7	29.6	29.9
CIR	11.0	15.4	19.3	26.9	34.7	41.7	47.2	50.1
0-39 yrs	3.0	4.0	4.1	4.6	5.6	6.7	7.2	7.6
40-59 yrs	15.3	17.5	18.1	23.3	30.5	35.4	36.1	32.5
60-79 yrs	27.0	41.3	51.6	69.2	84.8	92.2	96.6	102.2
80+ yrs	45.0	45.5	66.1	89.3	114.5	145.9	174.9	179.4
Females								
ASIR	9.9	13.5	15.2	19.4	24.4	28.7	31.9	33.6
CIR	12.1	16.8	19.4	25.5	32.2	38.5	43.9	47.3
0-39 yrs	5.0	7.5	8.1	9.4	11.6	13.4	14.2	14.6
40-59 yrs	14.8	19.0	22.3	29.9	40.3	49.1	53.5	52.2
60-79 yrs	21.3	30.0	32.5	41.7	50.5	58.3	67.0	75.8
80+ yrs	29.6	35.3	39.5	47.4	55.6	65.5	76.9	80.1

Abbreviations: ASIR, age-standardized incidence rate (European Standard Population, WHO 1976); CIR, crude incidence rate

* All rates are expressed as number per 100,000 per year

** Based on age-period-cohort models (Moller et al, 2002)

Table 12: Trends and annual percentage change of age-standardized, crude and age-specific incidence rates of cutaneous melanoma by sex, Germany (1995-2013)**

	Line segment 1		Line segment 2		Line segment 3		Line segment 4			
	Year	APC	Year	APC	Year	APC	Year	APC	Year	AAPC (95% CI)
Males										
ASIR	1995-2000	7.92*	2000-2006	1.42	2006-2009	11.13*	2009-2013	-0.03	1995-2013	4.4* (2.8; 6.1)
CIR	1995-2000	9.23*	2000-2006	3.03*	2006-2009	13.17*	2009-2013	1.38	1995-2013	6.0*(4.4; 7.6)
0-39 yrs	1995-1999	12.92*	1999-2006	-0.48	2006-2009	9.62	2009-2013	-4.36	1995-2013	3.1* (1.6; 5.7)
40-59 yrs	1995-1999	6.23*	1999-2006	-0.84	2006-2009	10.38	2009-2013	2.20	1995-2013	3.2* (1.3; 5.2)
60-79 yrs	1995-2000	11.23*	2000-2006	3.37	2006-2009	13.35	2009-2013	-0.48	1995-2013	6.2* (3.3; 9.2)
80+ yrs	1995-2000	-1.31	2000-2013	6.58*					1995-2013	4.3* (2.5; 6.2)
Females										
ASIR	1995-2001	7.60*	2001-2006	0.49	2006-2009	11.11	2009-2013	-0.37	1995-2013	4.3* (1.3; 7.4)
CIR	1995-2001	8.10*	2001-2006	0.79	2006-2009	11.72	2009-2013	0.38	1995-2013	4.9* (2.7; 7.1)
0-39 yrs	1995-2001	9.88*	2001-2006	-0.34	2006-2009	9.52	2009-2013	-3.31	1995-2013	3.9* (1.1; 6.8)
40-59 yrs	1995-2006	3.47*	2006-2009	10.82	2009-2013	1.24			1995-2013	4.2* (1.8; 6.6)
60-79 yrs	1995-2000	10.93*	2000-2005	-0.97	2005-2009	9.06*	2009-2013	0.65	1995-2013	4.8* (2.8; 6.8)
80+ yrs	1995-1998	9.89*	1998-2007	1.51*	2007-2010	7.63	2010-2013	-0.97	1995-2013	3.4* (1.9; 5.0)

Abbreviations: ASIR, age-standardized incidence rate (European Standard Population, WHO 1976); CIR, crude incidence rate

* Annual percentage change (APC) and average annual percentage change (AAPC) are significantly different from zero at α=0.05

** All rates are expressed as number per 100,000 per year

3.1.2 Trends in incident melanoma cases

Observed (1995/1998-2009/2013) and projected (2014/2018-2029/2033) numbers of melanoma cases, which were calculated by applying projected incidence rates to population forecasts, are summarized in Table 13. The percentage change from baseline (1995/1998) by age group is illustrated in Figure 11a/b.

Trends in the total population

For both sexes, the number of persons diagnosed with melanoma increased between 1995/1998 and 2009/2013, for males from 4,372 to 10,567 cases p.a. (+141.7%) and for females from 5,085 to 10,475 cases p.a. (+106%), respectively, Table 13. During the forecast period (2014/2018-2029/2033), an ongoing increase is expected. The number of melanoma cases will climb up to 20,161 new melanoma cases p.a. for males (+361.1% from 1995/1998-2029/2033) and up to 19,397 new cases p.a. in females (+281.5% from 1995/1998-2029/2033), respectively, Table 13.

Trends by age group

Between 1995/1998 and 2009/2013, the number of melanoma cases increased in all age groups. For males, the largest increase was observed in the age groups ≥60 years (60-79 yrs: +235.5%; 80+ yrs: +228.6%). For females, the strongest increases were found in the age groups 40-59 years (+132.2%) and 60-79 years (+116.7%), Table 13, Figure 11a/b.

For the next 20 years, a further increase in melanoma cases is expected for all age groups. The largest increase is projected for subjects aged ≥60 years, particularly for males. In men ≥80 years, the number of melanoma cases will almost quadruple from 1,239 cases p.a. in 2009/2013 to 4,676 cases p.a. in 2029/2033. Relative to baseline period (1995/1998), the number of melanoma cases will rise by +1,140.4% (80+ yrs), while only about half of the increase (+549.3%) is expected for men aged 60-79 years, climbing from 1,660 cases p.a. in 1995/1998 to 10,778 cases p.a. in 2029/2033. A doubling of melanoma cases is also proposed for young and middle-aged men, with relative increases

ranging between +92.2% (0-39 yrs) and +105.1% (40-59 yrs), Table 13, Figure 11a.

For women, a further doubling in melanoma cases is projected for age groups ≥60 years, climbing from 3,809 cases p.a. in 2009/2013 to 8,616 cases p.a. in 2029/2033 (60-79 yrs) and from 1,354 cases p.a. to 3,201 cases p.a. for women aged ≥80 years. In contrast to men, both age groups (60-79 yrs: +390.1% and ≥80 yrs: +366.7%) are expected to experience the largest increase relative to baseline period (1995/1998). Lower increases, but still higher than for men, are proposed for women aged <60 years, ranging between +115.9% (<40 yrs) and +233.2% (40-59 yrs), Table 13, Figure 11b.

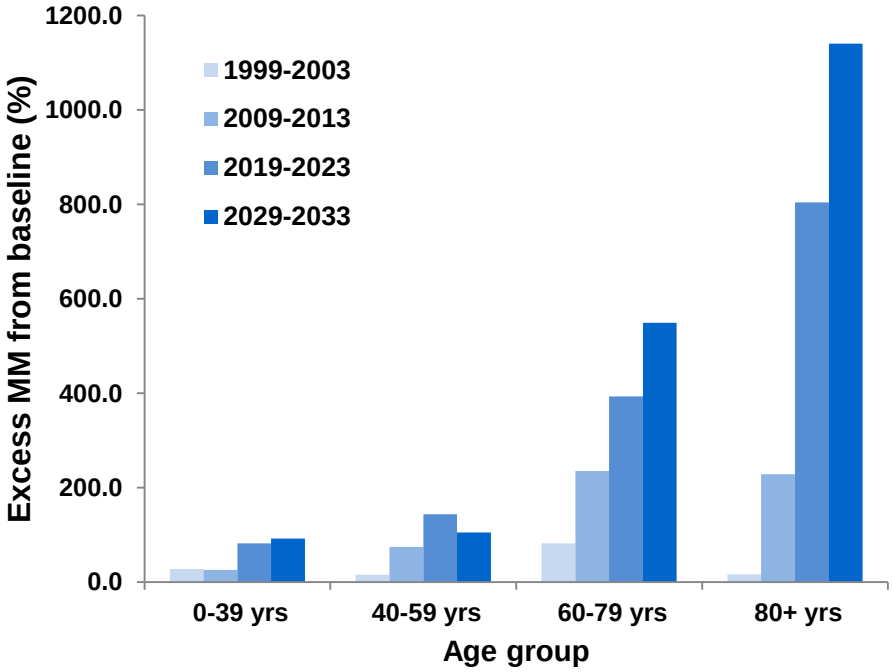
While the increase in the 60+ age groups is expected to continue at least until 2029/2033, a leveling off or even a decline is to be expected for younger age groups from 2020 onwards, Table 13, Figure 11a/b. For men aged 40-59 years, the peak will be reached in 2019/2023 (+143.9%), after which an attenuation of the growth can be expected. First signs of stabilization are also becoming apparent for the age group <40 years from 2024/2028 onwards, with relative increases of around 90%, Table 13, Figure 11a. Similar trends are projected for young (<40 yrs) and middle-aged (40-59 yrs) women. The peak will be reached in 2024/2028, ranging between +119.4% (<40 yrs) and +253.6% (40-59 yrs), followed by a leveling-off in increase thereafter, Table 13, Figure 11b.

Table 13: Number of melanoma cases and percentage change from baseline (1995/1998) by age and sex, Germany (1999/2003-2029/2033)

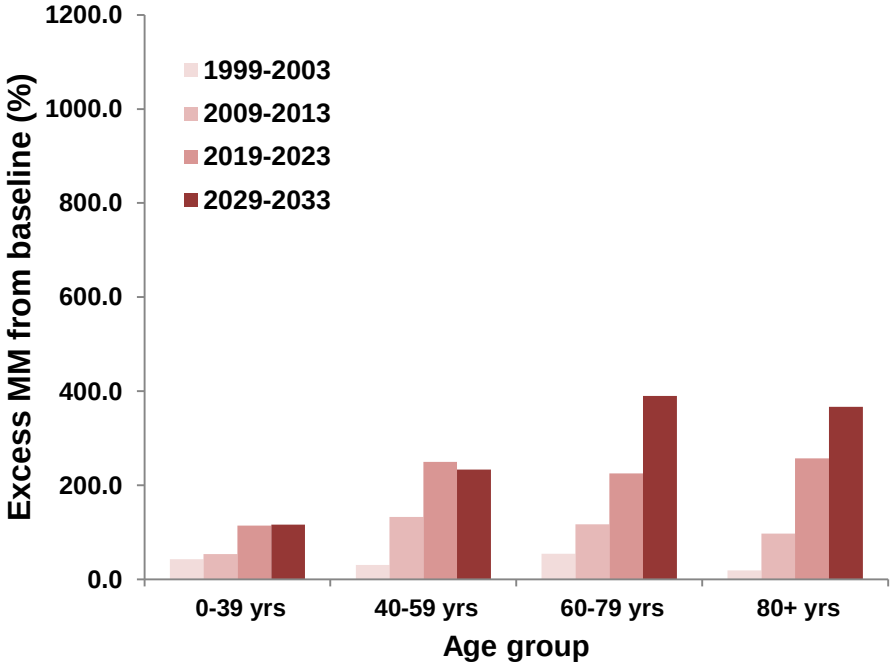
	Observed Data						Projected Data*							
	1995-1998	1999-2003		2004-2008		2009-2013		2014-2018		2019-2023		2024-2028		2029-2033	
Males															
Total	4372	6188	(+41.5%)	7760	(+77.5%)	10567	(+141.7%)	13905	(+218.0%)	16893	(+286.4%)	19054	(+335.8%)	20161	(+361.1%)
0-39 yrs	646	825	(+27.7%)	785	(+21.5%)	812	(+25.7%)	988	(+52.9%)	1178	(+82.3%)	1238	(+91.6%)	1242	(+92.2%)
40-59 yrs	1689	1957	(+15.9%)	2218	(+31.3%)	2946	(+74.4%)	3734	(+121.1%)	4119	(+143.9%)	3936	(+133.0%)	3465	(+105.1%)
60-79 yrs	1660	3021	(+82.0%)	4040	(+143.4%)	5570	(+235.5%)	7126	(+329.3%)	8188	(+393.2%)	9640	(+480.7%)	10778	(+549.3%)
80+ yrs	377	385	(+2.1%)	717	(+90.2%)	1239	(+228.6%)	2057	(+445.6%)	3408	(+804.2%)	4240	(+1024.7%)	4676	(+1140.4%)
Females															
Total	5085	7097	(+39.6%)	8146	(+60.2%)	10475	(+106.0%)	13341	(+162.4%)	15987	(+214.4%)	18134	(+256.6%)	19397	(+281.5%)
0-39 yrs	1040	1482	(+42.5%)	1488	(+43.1%)	1594	(+53.3%)	1954	(+87.9%)	2227	(+114.1%)	2282	(+119.4%)	2245	(+115.9%)
40-59 yrs	1601	2087	(+30.4%)	2671	(+66.8%)	3718	(+132.2%)	4854	(+203.2%)	5599	(+249.7%)	5661	(+253.6%)	5335	(+233.2%)
60-79 yrs	1758	2710	(+54.1%)	2937	(+67.1%)	3809	(+116.7%)	4779	(+171.8%)	5711	(+224.9%)	7262	(+313.1%)	8616	(+390.1%)
80+ yrs	686	818	(+19.2%)	1050	(+53.1%)	1354	(+97.4%)	1754	(+155.7%)	2450	(+257.1%)	2929	(+327.0%)	3201	(+366.7%)

* based on age-period-cohort models (Moller et al., 2002)

(a)



(b)



Abbreviation: MM, malignant melanoma

Figure 11: Relative change of melanoma cases from baseline (1995/1998) by age group and sex, Germany (1999/2003-2029/2033): (a) Males, (b) Females

3.1.3 Shift in the age distribution of melanoma patients

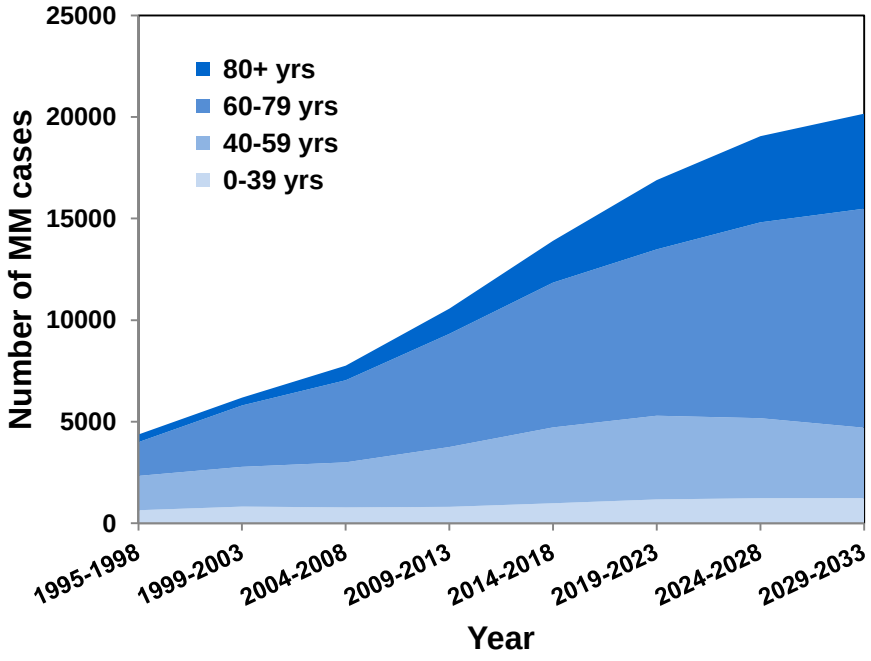
The percentage change in the age distribution of melanoma patients between 1995/1998 and 2029/2033 towards higher proportions of older patients is graphically shown in Figure 13a/b. Corresponding estimates for the absolute numbers of melanoma cases are illustrated in Figure 12a/b.

At the beginning of the observation period (1995/1998), for both sexes the proportion of melanoma patients was almost equally distributed across the age groups (<60 yrs vs. ≥60 yrs), with slightly higher percentages for subjects younger than 60 years (males: 53.4%; females: 51.9%). In the further course a trend towards higher proportion of older patients was observed, which will continue into future, Figure 12 and 13.

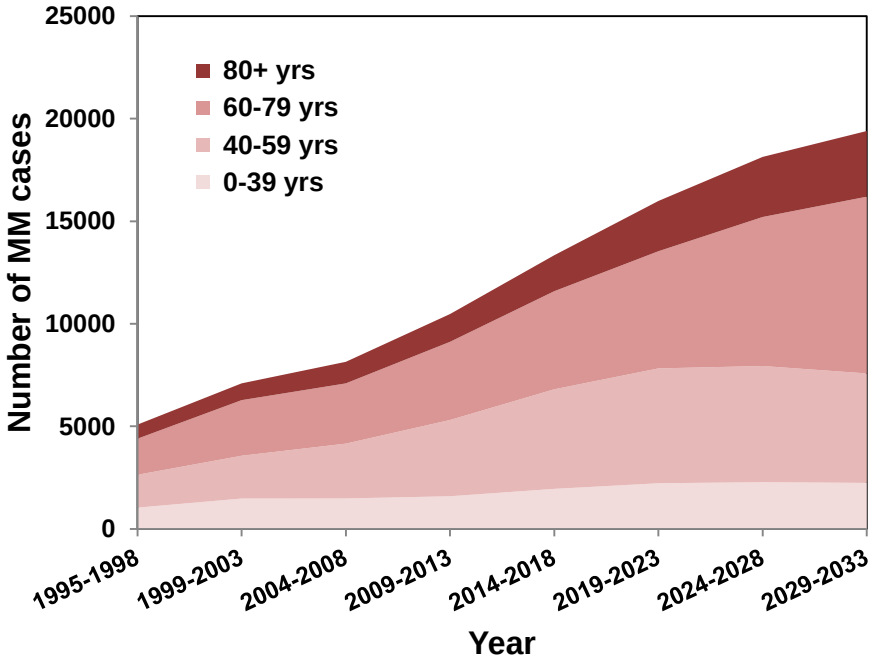
Particularly, men are expected to see a significant increase in the proportion of people diagnosed with melanoma in the age groups ≥60 years. While less than half of the melanoma patients (46.6%) were ≥60 years in the mid-1990s, their proportion grew up to 64.4% in 2009/2013, with a sharp rise in the age group 60-79 years (from 38.0% in 1995/1998 to 52.7% in 2009/2013). A further significant increase is expected by 2029/2033. 76.7% of male melanoma patients will then be 60 years and older, almost a quarter (23.2%) even 80 years and older, Figure 12a and 13a. At the same time, the proportion of melanoma patients aged ≤60 years will significantly decrease from 53.4% in 1995/1998 to less than a quarter (22.3%) in 2029/2033, with equal contribution of both age groups (<40 yrs and 40-59 yrs). For women, the situation will be somewhat different. The proportion of female patients aged ≥60 years will remain fairly constant until 2014/2018 (1995/98: 48.1% and 2014/18: 49.0%). From 2019/2023 onwards, a shift in the age structure will also become apparent among females. The proportion of women with melanoma in the over 60-year-olds will rise from 51.1% in 2019/2023 to 60.9% in 2029/2033, mainly attributable to a high increase in the age group 60-79 years (from 35.7% to 44.4%), Figure 12b and 13b. Simultaneously decreasing proportions of young patients, especially in the youngest age group (<40 years), where the proportion will be reduced by almost half from 20.4% in 1995/1998 to 11.6% in 2029/2033,

will lead to a shift in the age ratio (≥60 years vs. <60 years) from 48.1%:51.9% to 60.9%:39.1%.

(a)



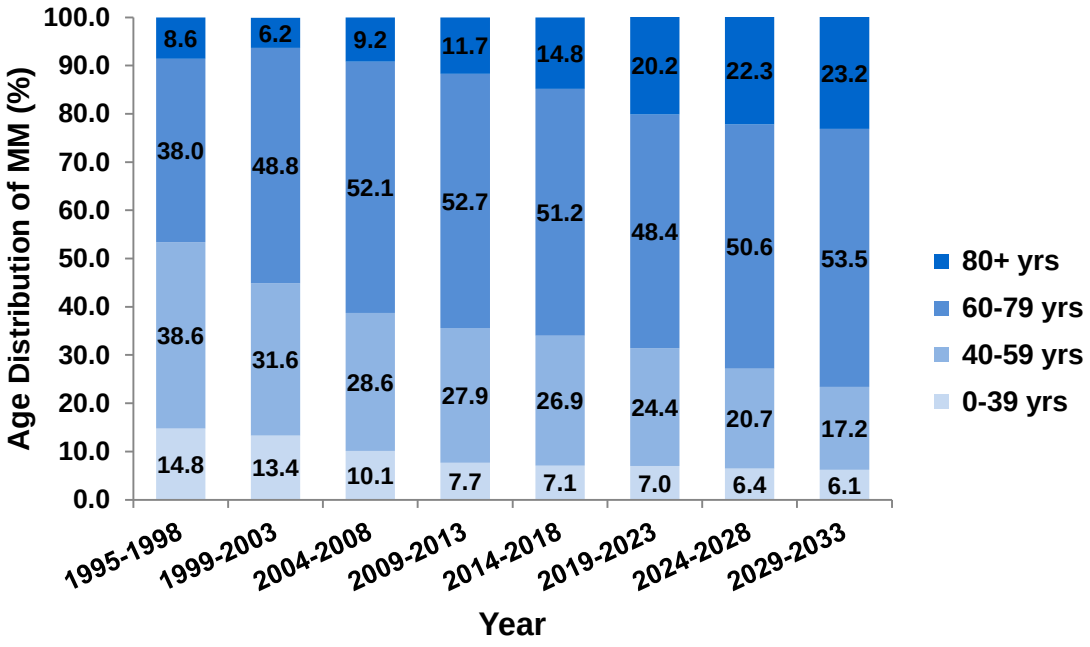
(b)



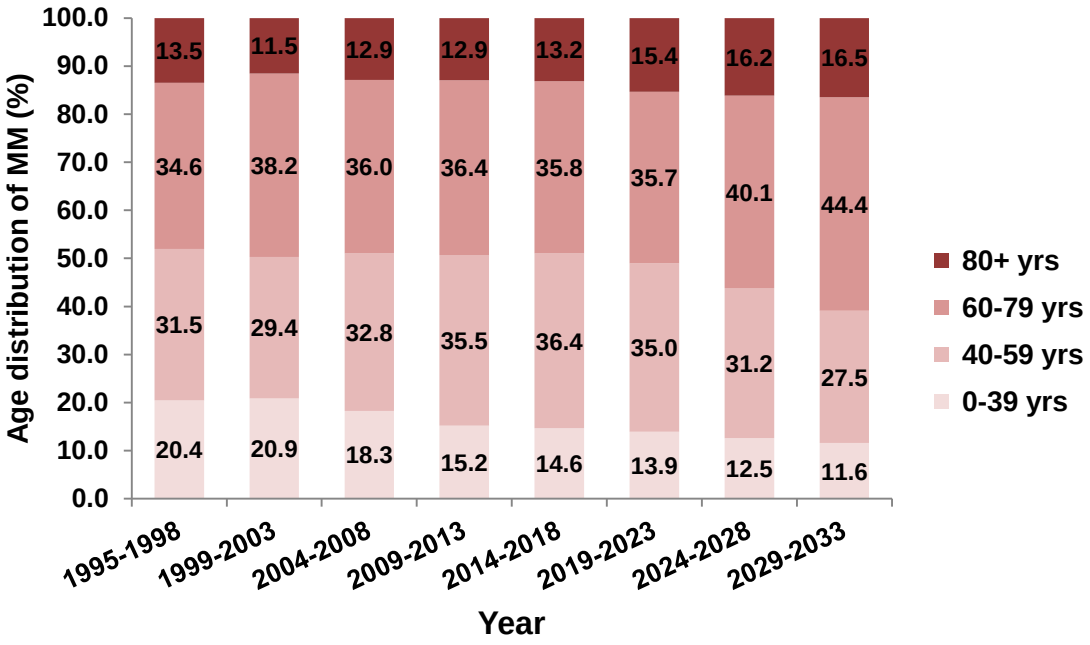
Abbreviation: MM, malignant melanoma

Figure 12: Number of melanoma cases by age group and sex, Germany (1995/1998-2029/2033): (a) Males, (b) Females

(a)



(b)



Abbreviation: MM, malignant melanoma

Figure 13: Age distribution (%) of melanoma cases by sex, Germany (1995/1998-2029/2033): (a) Males, (b) Females

3.1.4 Numbers of new melanoma attributed to changes in UVR exposure and demographics

The excess numbers of observed (1999/2003-2009/2013) and projected (2014/2018-2029/2033) melanoma cases compared to baseline (1995/1998), which were estimated according to the method described by Moller et. al., are summarized in Table 14a/b and graphically illustrated in Figure 14a/b.

Since 1995/1998, the number of melanoma cases has steadily increased in both sexes. In 2009/2013, 6,195 additional melanoma cases were diagnosed among men, representing a total increase of +141.7% (123.5% due to changes in risk and 18.2% due to changes in population structure), Table 14a, Figure 14a. Among women, the corresponding increase was +106% (98.4% due to changes in risk and 7.6% due to changes in population structure), with 5,390 additional melanoma cases in 2009/2013, Table 14b, Figure 14b. Most of the increase in new melanoma diagnoses was attributed to changes in age-specific melanoma risk rather than in population size and aging, most evident among females (92.8% for females and 87.2% for males), Table 14a/b.

For the foreseeable future, the numbers of melanomas diagnosed will continue to rise. Compared to baseline period, almost 15,800 additional melanoma cases are expected to be diagnosed in men in 2029/2033, which corresponds to a relative increase of +361.1% (+322.5% due to changes in risk and +38.6% due to changes in population structure), Table 14a, Figure 14a. For women, 14,312 additional melanoma cases are expected by 2029/2033, an increase of +281.5% (+267% due to changes in risk and +14.5% due to changes in population structure) compared to baseline period, Table 14b, Figure 14b. Again, increasing risk (+89.3% for men and +94.8% for women) rather than changes in population size and age distribution are responsible for the expected increase.

Observed and projected trends differed only slightly between men and women. However, the increase in melanoma due to changes in risk was higher in women than in men (90.7-94.9% in women vs. 83.2-89.3% in men). The opposite applies to the demographic component, which was on average two times higher for men than for women (10.7-16.8% in men vs. 5.1-9.3% in women), Table 14a/b.

Due to only small changes in population size expected between 1995/1998 and 2029/2033 (between -0.7% and +1.3% for men between -2.5% and +0.2% for women), changes in demographics will be mainly attributed to changes in the age structure and less to changes in population size.

Table 14a: Excess number of melanoma cases (1999/2003-2029/2033) attributed to changes in UVR exposure and demographics (population size and age distribution) from baseline (1995/1998), Germany, Males

	Observed Data				Projected Data*			
	1995-1998 (baseline)	**1999-2003**	**2004-2008**	**2009-2013**	**2014-2018**	**2019-2023**	**2024-2028**	**2029-2033**
MM cases	4372	6188	7760	10567	13905	16893	19054	20161
Population	39944028	40244576	40290666	39676775	4,093800	40463800	40407400	40206400
Excess MM (total):		1816 (100.0%)	3388 (100.0%)	6195 (100.0%)	9533 (100.0%)	12521 (100.0%)	14682 (100.0%)	15789 (100.0%)
due to UVR exposure		1574 (86.7%)	2819 (83.2%)	5400 (87.2%)	8437 (88.5%)	11098 (88.6%)	13115 (89.3%)	14102 (89.3%)
due to demographics		242 (13.3%)	569 (16.8%)	795 (12.8%)	1096 (11.5%)	1423 (11.4%)	1567 (10.7%)	1687 (10.7%)
(size)		33 (1.8%)	39 (1.2%)	-31 (-0.5%)	18 (0.2%)	56 (0.4%)	52 (0.4%)	28 (0.2%)
(age)		209 (11.5%)	530 (15.6%)	826 (13.3%)	1078 (11.3%)	1367 (11.0%)	1515 (10.3%)	1659 (10.5%)
Population change from baseline	-	0.8%	0.9%	-0.7%	0.4%	1.3%	1.2%	0.7%
Excess MM from baseline (total)	-	41.5%	77.5%	141.7%	218.0%	286.4%	335.8%	361.1%
due to risk		36.0%	64.5%	123.5%	193.0%	253.8%	300.0%	322.5%
due to population		5.5%	13.0%	18.2%	25.0%	32.6%	35.8%	38.6%
(size)		0.75%	0.9%	-0.7%	0.4%	1.3%	1.2%	0.7%
(age)		4.75%	12.1%	18.9%	24.6%	31.3%	34.6%	37.9%

Abbreviation: MM, malignant melanoma
* based on age-period-cohort models (Moller et al., 2002)

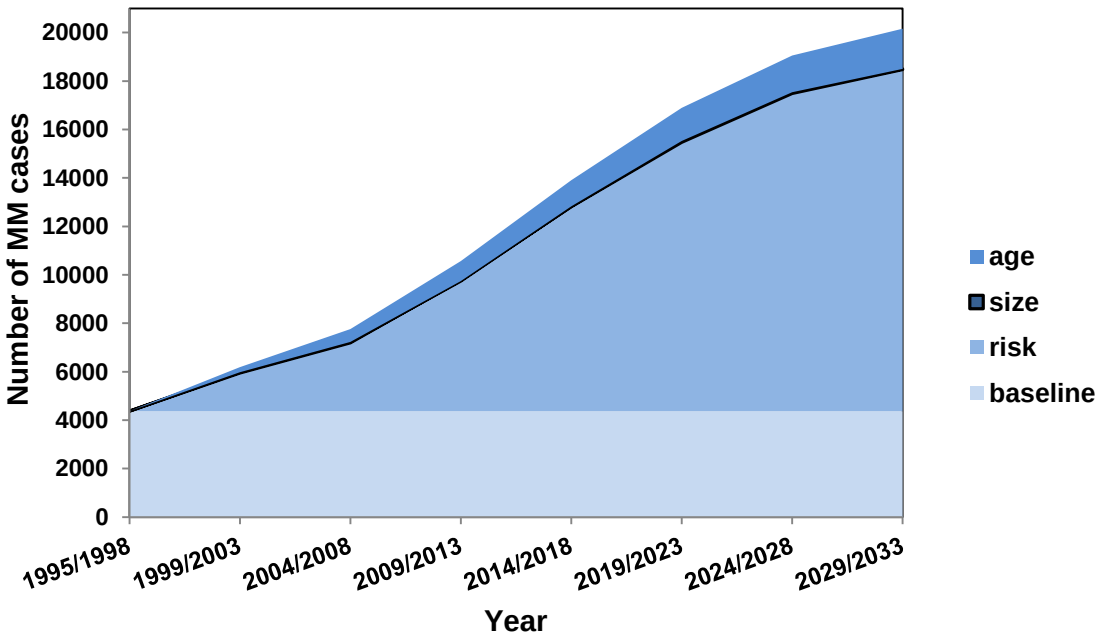
Table 14b: Excess number of melanoma cases (1999/2003-2029/2033) attributed to changes in UVR exposure and demographics (population size and age distribution) from baseline (1995/1998), Germany, Females

	Observed Data				Projected Data*			
	1995-1998 (baseline)	**1999-2003**	**2004-2008**	**2009-2013**	**2014-2018**	**2019-2023**	**2024-2028**	**2029-2033**
MM cases	5085	7097	8146	10475	13341	15987	18134	19397
Population	42036985	42141759	42004123	41357818	41450400	41529800	41318800	40977400
Excess MM (total):	-	2012 (100.0%)	3061 (100.0%)	5390 (100.0%)	8256 (100.0%)	10902 (100.0%)	13049 (100.0%)	14312 (100.0%)
due to UVR exposure		1902 (94.5%)	2775 (90.7%)	5004 (92.8%)	7748 (93.8%)	10273 (94.2%)	12387 (94.9%)	13572 (94.8%)
due to demographics		110 (5.5%)	286 (9.3%)	386 (7.2%)	508 (6.2%)	629 (5.8%)	662 (5.1%)	740 (5.2%)
(size)		12 (0.6%)	-4 (-0.1%)	-82 (-1.5%)	-72 (-0.9%)	-62 (-0.6%)	-86 (-0.6%)	-127 (-0.9%)
(age)		98 (4.9%)	290 (9.4%)	468 (8.7%)	580 (7.1%)	691 (6.4%)	748 (5.7%)	867 (6.1%)
Population change from baseline	-	0.2%	-0.1%	-1.6%	-1.4%	-1.2%	-1.7%	-2.5%
Excess MM from baseline (total)	-	39.6%	60.2%	106.0%	162.4%	214.4%	256.6%	281.5%
due to risk		37.4%	54.6%	98.4%	152.4%	202.0%	243.6%	267.0%
due to population		2.2%	5.6%	7.6%	10.0%	12.4%	13.0%	14.5%
(size)		0.25%	-0.08%	-1.6%	-1.4%	-1.2%	-1.7%	-2.5%
(age)		1.95%	5.68%	9.2%	11.4%	13.6%	14.7%	17.0%

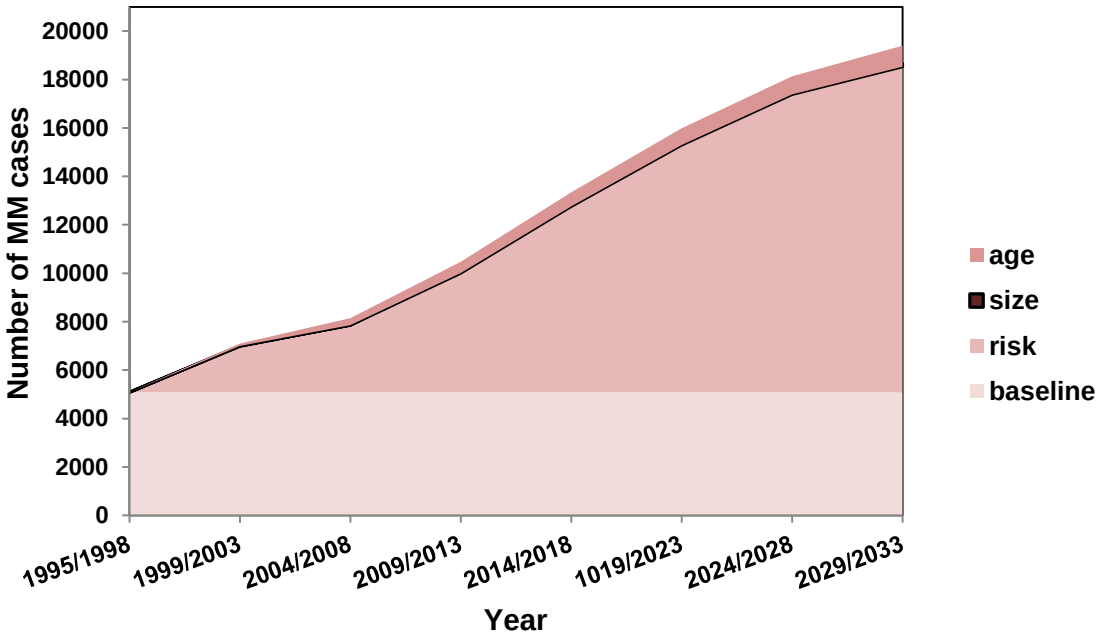
Abbreviation: MM, malignant melanoma

* based on age-period-cohort models (Moller et al., 2002)

(a)



(b)



Abbreviation: MM, malignant melanoma

Figure 14: Number of excess melanoma cases from baseline (1995/1998), attributed to changes in population risk and demographics, Germany (1999/2003-2029/2033): (a) Males, (b) Females

3.1.5 Proportions of melanoma attributable to UVR exposure (background level)

Table 15 shows the number and proportion of melanoma cases attributable to UVR by 5-year age groups and sex at baseline (1995/1998), which were calculated by comparing the observed numbers of melanoma (1995/1998) in the German population with those of a historical Danish cohort from 1943/1947.

An estimated 8,106 (3,816 in males and 4,290 in females) melanoma cases p.a. were attributable to ambient UVR exposure, representing 85.7% of all melanomas diagnosed in 1995/1998. The proportion attributable fraction (PAF%) was higher in men (3,816 attributable cases; 87.3% of all melanomas) than in women (4,290; 84.4%).

The situation is different when age is taken into account. In age groups younger than 40 years the proportion of melanoma caused by UVR is higher in women (86.3%) than in men (80.2%). In age groups >40 years the opposite is true, with larger proportions of UVR-induced melanoma among men compared to women (40-59 yrs: 89% (men) vs. 84.5% (women) and for 60+ yrs: 88.1% (men) vs. 83.4% (women), respectively). In women, a trend towards increasing proportions of UVR-induced melanoma with decreasing age is apparent (60+ yrs: PAF%=83.4%, 40-59 yrs: PAF%=84.5% and for <40 yrs: PAF%=86.3%).

Table 15: Number and proportion of melanoma cases attributed to UVR at baseline (1995/1998) by age and sex, Germany

	Males				Females			
Age (years)	**Expected cases***	**Observed cases**	**Excess cases**	**PAF% (UVR)**	**Expected cases***	**Observed cases**	**Excess cases**	**PAF% (UVR)**
0-4	2	0	-2		4	0	-4	
5-9	5	0	-5		2	0	-2	
10-14	7	1	-6		11	0	-11	
15-19	0	18	18	100.0	0	27	27	100.0
20--24	5	52	47	90.4	22	98	76	77.6
25-29	26	122	96	78.7	30	281	251	89.3
30-34	52	205	153	74.6	24	343	319	93.0
35-39	31	248	217	87.5	49	291	242	83.2
40-44	42	282	240	85.1	35	330	295	89.4
45-49	57	312	255	81.7	48	402	354	88.1
50-54	31	405	374	92.3	44	397	353	88.9
55-59	56	690	634	91.9	121	472	351	74.4
60-64	47	577	530	91.9	52	451	399	88.5
65-69	44	526	482	91.6	73	441	368	83.4
70-74	62	350	288	82.3	116	494	378	76.5
75-79	50	207	157	75.8	40	372	332	89.2
80-84	27	214	187	87.4	67	382	315	82.5
85+	12	163	151	92.6	57	304	247	81.3
Total	**556**	**4372**	**3816**	**87.3**	**795**	**5085**	**4290**	**84.4**

Abbreviations: UVR, ultraviolet radiation, PAF, population attributable fraction

* Incidence rates of a historical Danish cohort (1943/1947) were used as reference population

3.1.6 Proportions of melanoma attributable to UVR exposure and demographics at baseline and in the further course

The numbers and fraction of melanoma cases attributable to UVR and demographics at baseline (1995/1998), and in the further course (1999/2003-2029/2033) are summarized in Table 16a/b. Figure 15a/b illustrate the increase in melanoma cases between baseline and future periods that can be attributed to changes in risk and demographics.

For both sexes, the numbers and proportions of melanomas caused by UVR have increased between 1995/1998 and 2009/2013 and are projected to keep on doing so in future. At baseline, higher proportions of UVR-induced melanomas were observed among males (87.3% in men vs. 84.4% in women), while the opposite is expected for later periods. Among women, the proportion of UVR attributable melanoma will strongly increase, so that by 2029/2033 about 92% of all diagnosed melanoma cases will be attributable to high exposure to UVR, Table 16b, Figure 15b; smaller proportions (89%) are proposed for men, Table 16a, Figure 15a. Reverse patterns are expected for the proportion of melanoma cases attributable to demographic changes, particularly among women. While at the beginning a considerable proportion (>15%) of melanoma diagnosis could be attributed to demographics, their proportion will be reduced by a half from 15.6% in 1995/1998 to 7.9% in 2029/2033. Similar trends, although to a lesser extent, are supposed for males, where demographic changes will count for ≥11% of all melanoma cases over the entire period (1995/1998-2029/2033).

Table 16a: Number and proportion of melanoma cases attributed to UVR and demographic changes at baseline (1995/1998) and following time periods (1999/2003-2029/33), Germany, Males

Time Period	Number of cases	Changes in cases (from baseline)**			Number of cases attributed to		Population attributable fraction (PAF%)	
		overall	due to change in UVR	due to change in demographics	UVR	demographics	UVR	demographics
1995/1998 (baseline)*	4372	-	-	-	3816	556	87.3%	12.7%
1999/2003	6188	1816	1574	242	5390	798	87.1%	12.9%
2004/2008	7760	3388	2819	569	6635	1125	85.5%	14.5%
2009/2013	10567	6195	5400	795	9216	1351	87.2%	12.8%
2014/2018	13905	9533	8437	1096	12253	1652	88.1%	11.9%
2019/2023	16893	12521	11098	1423	14914	1979	88.3%	11.7%
2024/2028	19054	14682	13115	1567	16931	2123	88.9%	11.1%
2029/2033	20161	15789	14102	1687	17918	2243	88.9%	11.1%

Abbreviation: UVR, ultraviolet radiation

* The number of melanoma cases attributable to population risk and demographics at baseline (1995/1998) is given in Table 15

** The excess number of melanoma cases attributed to changes in population risk (UVR) and demographics (population size and age distribution) in following time periods (1999/2003-2029/2033) is given in Table 14a

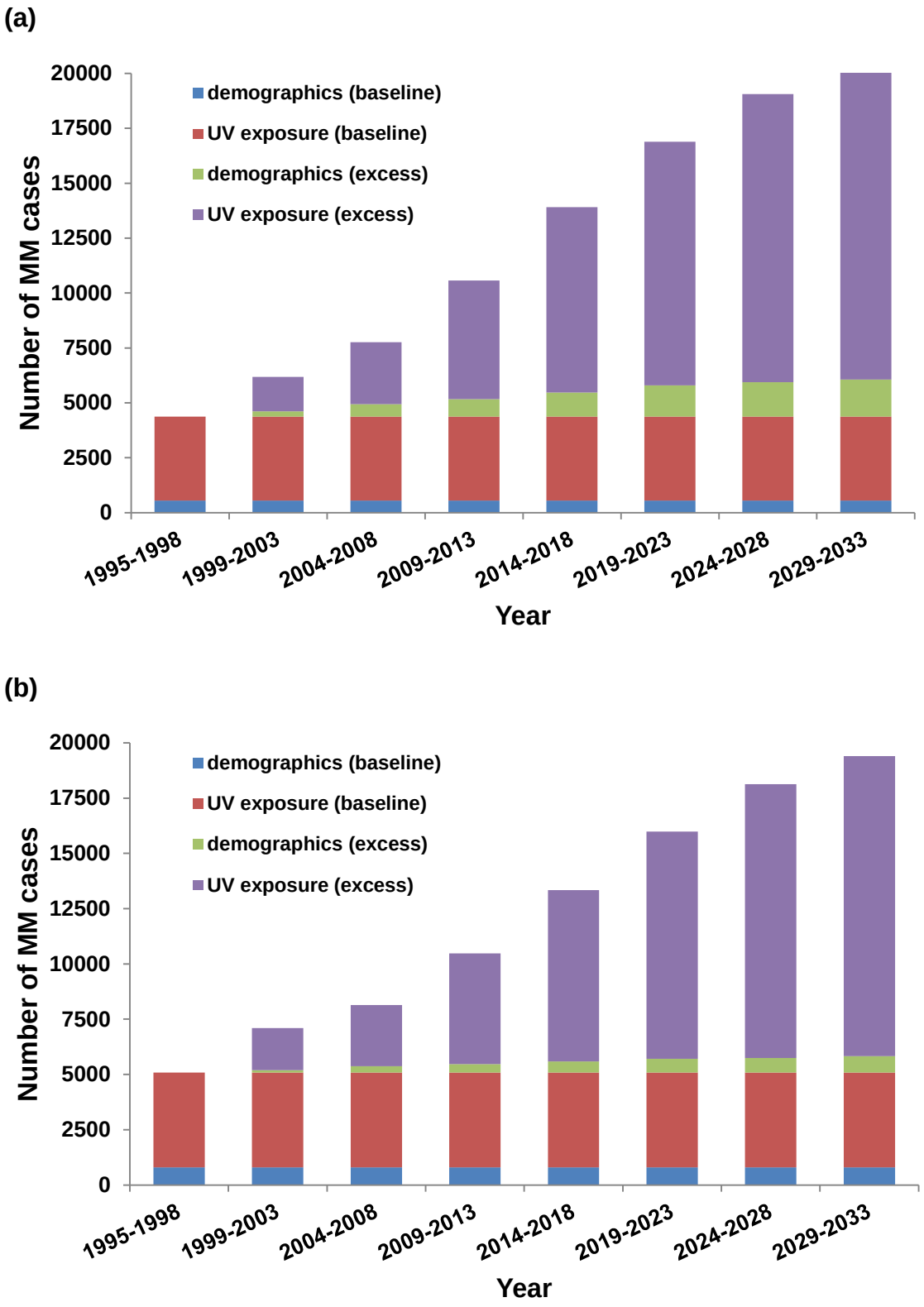
Table 16b: Number and proportion of melanoma cases attributed to UVR and demographic changes at baseline (1995/1998) and following time periods (1999/2003-2029/33), Germany, Females

Time Period	Number of cases	Changes in cases (from baseline)**			Number of cases attributed to		Population attributable fraction (PAF%)	
		overall	due to change in UVR	due to change in demographics	UVR	demographics	UVR	demographics
1995/1998 (baseline)*	5085	-	-	-	4290	795	84.4%	15.6%
1999/2003	7097	2012	1902	110	6192	905	87.2%	12.8%
2004/2008	8146	3061	2775	286	7065	1081	86.7%	13.3%
2009/2013	10475	5390	5004	386	9294	1181	88.7%	11.3%
2014/2018	13341	8256	7748	508	12038	1303	90.2%	9.8%
2019/2023	15987	10902	10273	629	14563	1424	91.1%	8.9%
2024/2028	18134	13049	12387	662	16677	1457	92.0%	8.0%
2029/2033	19397	14312	13572	740	17862	1535	92.1%	7.9%

Abbreviation: UVR, ultraviolet radiation

* The number of melanoma cases attributable to population risk and demographics at baseline (1995/1998) is given in Table 15

** The excess number of melanoma cases attributed to changes in population risk (UVR) and demographics (population size and age distribution) in following time periods (1999/2003-2029/2033) is given in Table 14b



Abbreviation: MM, malignant melanoma

Figure 15: Baseline (1995/1998) and excess number of melanoma cases (1999/2003-2029/2033) attributed to changes in UV exposure and demographics by sex, Germany: (a) Males, (b) Females

3.2 Denmark

3.2.1 Trends in incidence rates

The results of the Joinpoint regression analysis for observed incidence trends and incidence predictions, based on age-period-cohort models, are summarized in Table 17a/b and in Table 18.

Age-standardized and crude incidence rates

Between 1979/1983 and 2009/2013, age-standardized incidence rates have tripled in both sexes. For males, they climbed from 8.6/100,000 per year in 1979/1983 to 29.8/100,000 per year in 2009/2013, with an average annual increase of +3.9% (95% CI=2.9, 4.9), Table 17a and 18. In females, ASIRs increased by an average of +3.9% p.a. (95% CI=3.3, 4.5), from 11.3/100,000 per year in 1979/1983 to 34.3/100,000 per year in 2009/2013, Table 17b and 18. For males, steepest increases (+8.5% p.a.) were observed between 2004 and 2009, followed by a leveling off in increase thereafter (+1.9% p.a.). For women, age-standardized incidence rates have been rising steadily since 2002 (+6.1% p.a.), without any signs of leveling off. Over the entire period (1944/1948-2009/2013), ASIRs displayed an increase of +4.7% p.a. (95% CI=4.6, 4.9) for males, and by +4.6% p.a. (95% CI=4.6, 4.9) for females, Figure 19a/b.

Stronger increases in incidence were observed for crude incidence rates, particularly among males. In men, CIRs have risen from 8.4 in 1979/1983 to 35.6/100,000 per year in 2009/2013, corresponding to an average annual increase of +4.6% (95% CI=3.8, 5.4), Table 17a and 18. In women, CIRs increased from 11.8 in 1979/1983 to 40.1/100,000 per year in 2009/2013, corresponding to an average annual increase of +4.1% (95% CI=3.6, 4.7), Table 17b and 18. For males the strongest increase in CIRs was found between 2004 and 2009 (+9.7% p.a.), followed by a slower increase thereafter (+2.9% p.a.). A continuous increase of CIRs by +6.1% p. a. from 2002 onwards was observed for females. Over a decade of 7 years (1944/1948-2009/2013), the estimated average annual increase in CIRs was +5.3% (95% CI=5.1, 5.4) for males, and +5.1% (95% CI=4.8, 5.3) for females, Figure 20a/b.

Until the mid-1970s (females) and the mid-1980s (males), respectively, ASIRs were generally higher than CIRs, in the following periods the crude rates exceeded the age-standardized rates, Table 17a/b.

Ongoing increases in age-standardized incidence rates until 2029/2033 are projected for both sexes, somewhat stronger growth can be expected among women. For men, ASIRs will rise from 29.8/100,000 per year in 2009/2013 to 53.6/100,000 per year in 2029/2033 (+80%) and for women from 34.3/100,000 per year to 74.6/100,000 per year (+117%), Figure 22a/b, Table 17a/b.

Higher increases are projected for CIRs, with slightly stronger increases among men. CIRs will climb by +122% from 35.6/100,000 per year in 2009/2013 up to 79.1/100,000 per year in 2029/2033 in men, and by +120% from 40.1 in 2009/2013 up to 88.3/100,000 per year in 2029/2033 in women, Figure 23a/b, Table 17a/b.

While changes in crude and age-standardized incidence rates (CIRs: +122% vs. ASIRs: +80%) vary widely among men, the difference among women is rather small (CIRs: +120% vs. ASIRs: +117%). On the other hand, changes in ASIRs are much stronger among women (+117%) than among men (+80%).

Age-specific incidence rates

Age-specific incidence rates increased with age and were generally highest in the elderly (>80 years), most evident among males, Table 17a/b. At start of the registration period (1944/1948), melanoma incidence was very rare in young adults (<40 years), with IRs of less than 1.0/100,000 per year for both sexes. IRs peaked in the elderly (80+ yrs) with IRs of about 5.4 for females and 6.0/100,000 per year for males, respectively. In the age groups <60 years, melanoma was more common in females, while IRs in the elderly (80+ yrs) were generally higher in males. In 1944/1948 the difference in IRs between men and women aged 80+ years was rather small, in the further course however IRs differed significantly and were almost 60% higher in men than in women (2009/2013: 138.2/100,000 per year vs. 87.4/100,000 per year), Table 17a/b.

Between 1980 and 2013, the average annual increase in melanoma incidence was highest in men and women aged ≥60 years. IRs increased by an average of +5.7% p.a. (95% CI=4.4; 7.1) and of +4.1% p.a. (95% CI=2.7; 5.6) for males

and females aged 80+ years. The corresponding increase was +5.1% p.a. (95% CI=3.7; 6.4) and +3.8% p.a. (95% CI=3.1; 4.4) for men and women in the age group 60-79 years, Figure 18a/b, Table 18. Significant increases in melanoma incidence were also observed in younger age groups, where the average increases ranged between +2.9% p.a. (0-39 yrs) and +3.1% p.a. (40-59 yrs) for males and between +3.3% p.a. (40-59 yrs) and +3.7% p.a. (0-39 yrs) for females, respectively Table 18.

Changes in trends between 1980 and 2013, varied across the age groups. For both sexes, melanoma incidence in the age group <40 years, transitioned through three distinct phases, characterized by a modest increase in the first period (males: 1980-2004, APC=+2.3% and females: 1980-2002: APC=+3.4%), followed by steeper increases (males: 2004-2009, APC=+13.4% and females: 2002-2008: APC=+11.0%), and a decline in the last interval, however without being statistically significant (males: 2009-2013, APC=-5.5% and females: 2008-2013: APC=-2.9%), Table 18. No signs of declining incidence rates were found for men and women in the age groups ≥40 years. Trends in these age groups were characterized by moderate increases at the beginning and an acceleration of the increase thereafter. The strongest increase was observed for males aged 60-79 years (2002-2006, APC=+12.6%), followed by a slower increase in more recent years (2006-2013, APC=+4.4%), Table 18.

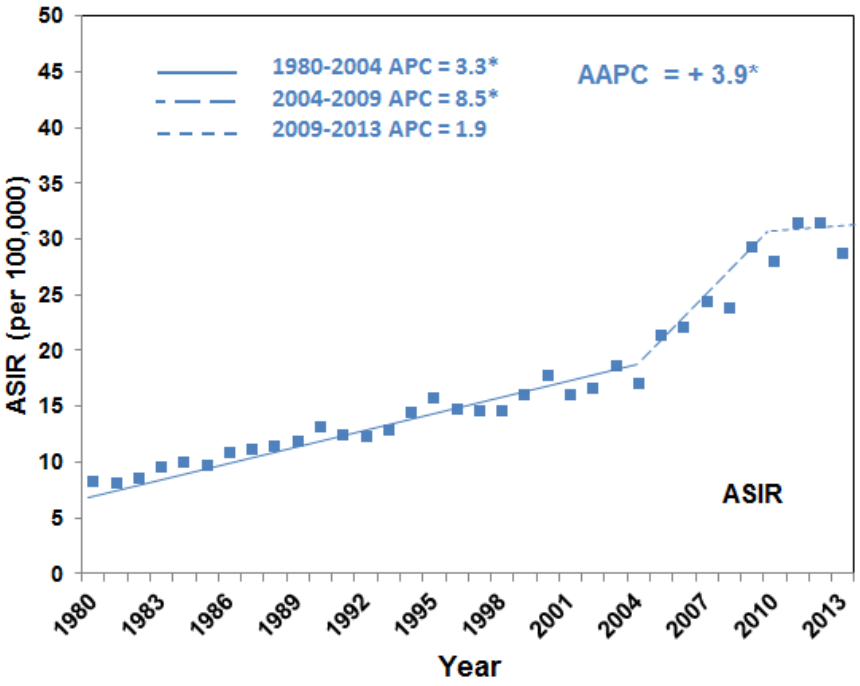
Over the entire period of observation (1944/1948-2009/2013), uniformly increasing incidence rates have been seen in all age groups, Table 17a/b, Figure 21a/b. Among men, the steepest increase was found in age groups >60 years, rising by an average of +5.2% p.a. (95% CI=5.0, 5.5) for those aged 60-79 years, and of +5.4% p.a. (95% CI=4.5, 6.2) for the elderly (80+ yrs), respectively, Figure 21a. Similarly high increases (+6.0% p.a., 95% CI=4.7, 7.2) were also found in women aged 80+ years and even in women under 40 years (+5.1% p.a., 95% CI=4.8, 5.3), Figure 21b.

Trends of increasing incidence rates are anticipated for all age groups, Table 17a/b, Figure 24a/b. Among men, the strongest increase is expected for the age group 80+ years, IRs will increase by +126% from 138.2/100,000 per year in 2009/2013 to 312.0/100,000 per year in 2029/2033. For men aged 60-79 years,

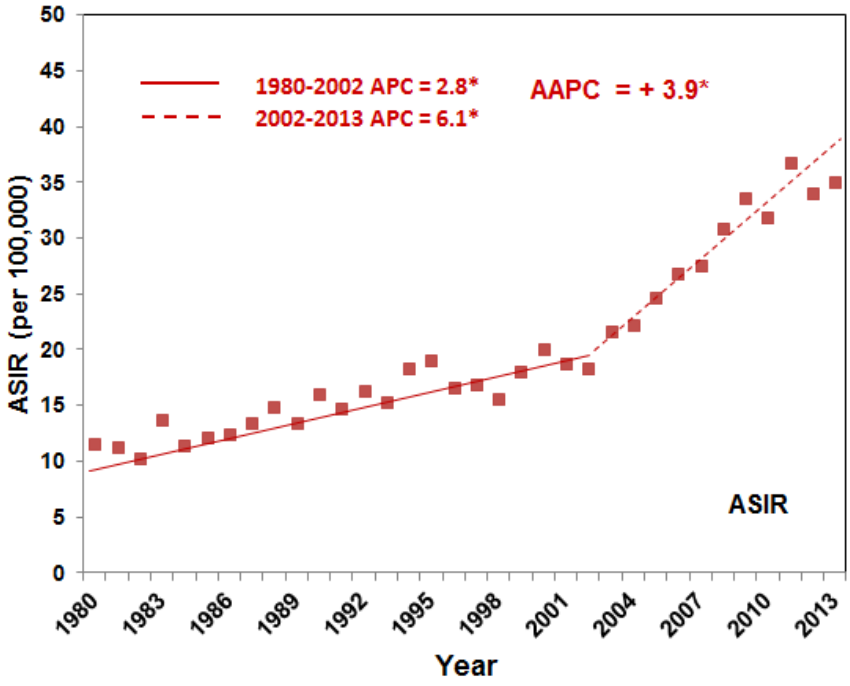
IRs will rise from 89.9/100,000 per year in 2009/2013 to 142.3/100,000 per year in 2029/2033. Steep increases in melanoma incidence rates are also projected for young men (<60 years). IRs will rise from 8.1/100,000 per year in 2009/2013 to 17.4/100,000 per year in 2029/2033 for men aged <40 years and from 37.0/100,000 per year to 70.9/100,000 per year for those between 40 and 59 years of age. A leveling off in increase is not expected for the foreseeable future, Table 17a, Figure 24a.

Steadily increasing IRs without any signs of stabilization or leveling off in increase, are also supposed for women of all age groups. In contrast to the male population, the strongest growth in incidence is expected for age groups <60 years, rising by +125% from 17.0/100,000 per year in 2009/2013 to 38.3/100,000 per years in 2029/2033 in the age group <40 years and by +138% from 52.0/100,000 per year in 2009/2013 to 123.8/100,000 per year in 2029/2033 for women aged 40-59 years, Table 17b, Figure 24b. Moderate increases until 2029/2033, ranging between +74% (80+ yrs) and +81% (60-70 yrs), are expected for women in higher age groups. While the difference in IRs between men and women will be rather small in the age group 60-79 years (142.4 in men vs. 120.7/100,000 per year in women), IRs in elderly men (80+ yrs) are estimated to be twice as high (312.0/100,000 per year) as in women of same age (151.9/100,000 per year) in 2029/2033, Table 17a/b, Figure 24a/b. For age groups <60 years, higher incidence rates are proposed for women, with significant differences in the age group <40 years (38.3/100,000 per year in women vs. 17.4/100,000 per year in men).

(a)



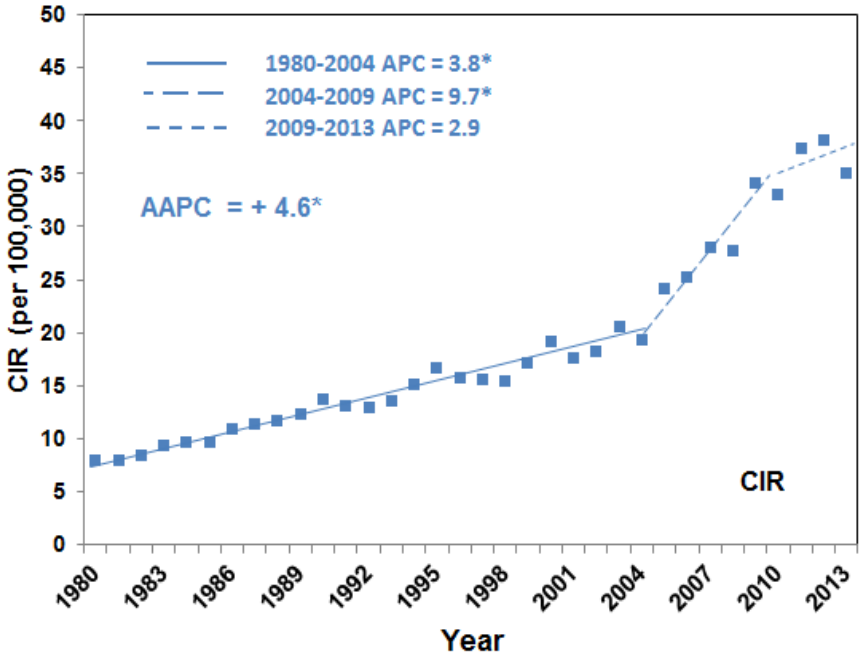
(b)



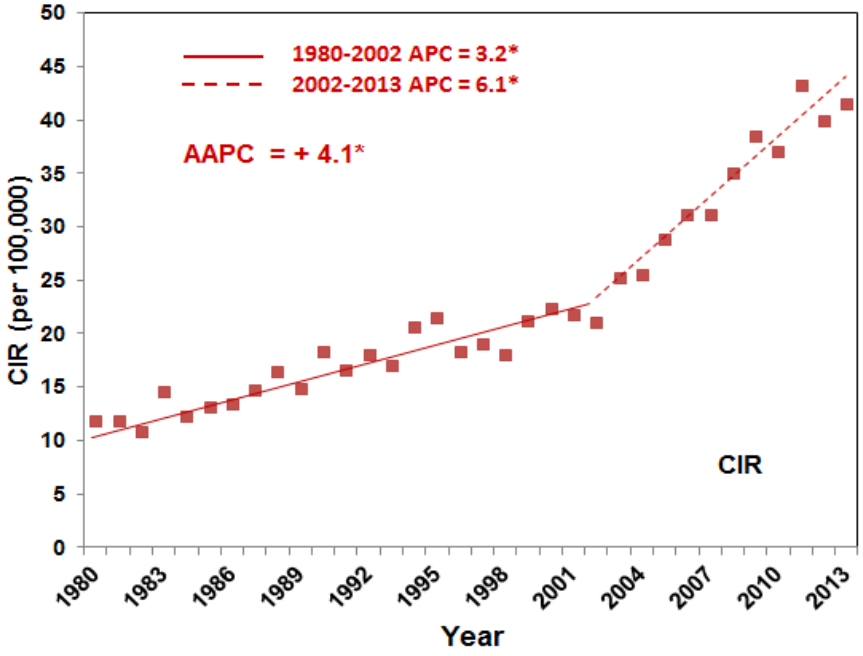
Abbreviations: APC, annual percentage change: AAPC, average annual percentage change
* APC, AAPC are significantly different from zero at α=0.05

Figure 16: Trends of age-standardized incidence rates (European Standard Population, WHO 1976) of cutaneous melanoma, Denmark (1980-2013): (a) Males; (b) Females.

(a)



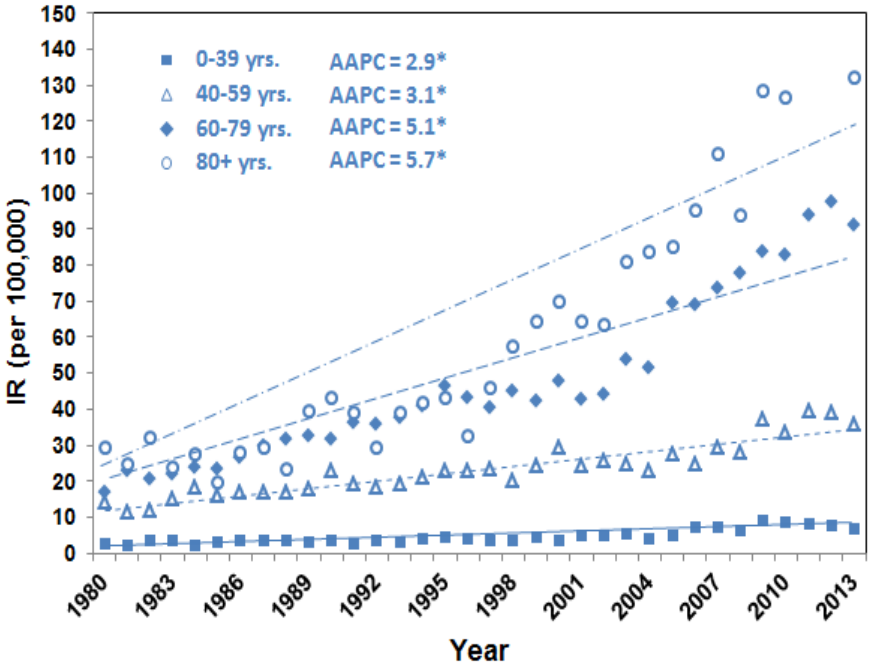
(b)



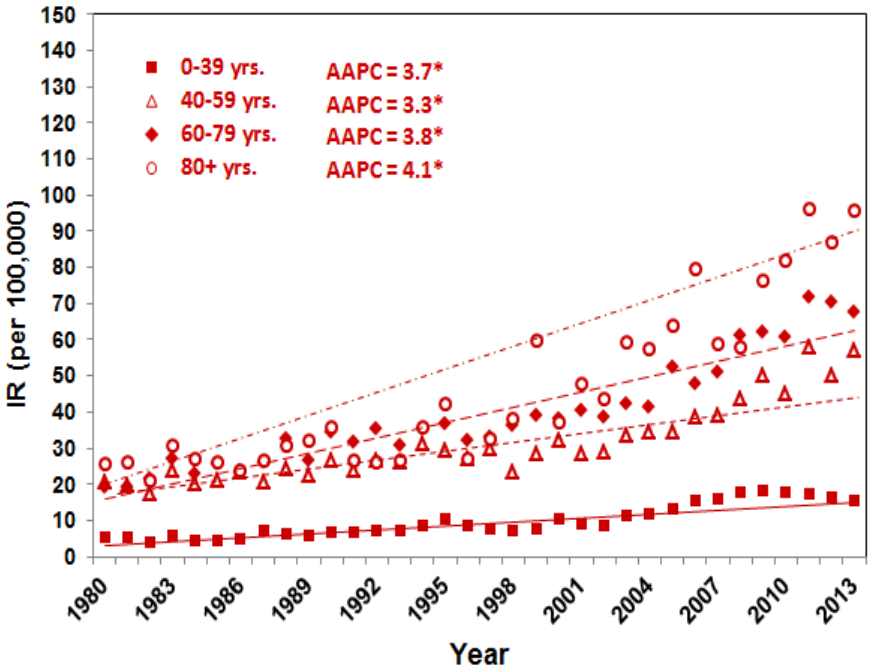
Abbreviations: APC, annual percentage change: AAPC, average annual percentage change
* APC, AAPC are significantly different from zero at α=0.05

Figure 17: Trends of crude incidence rates of cutaneous melanoma, Denmark (1980-2013): (a) Males, (b) Females.

(a)



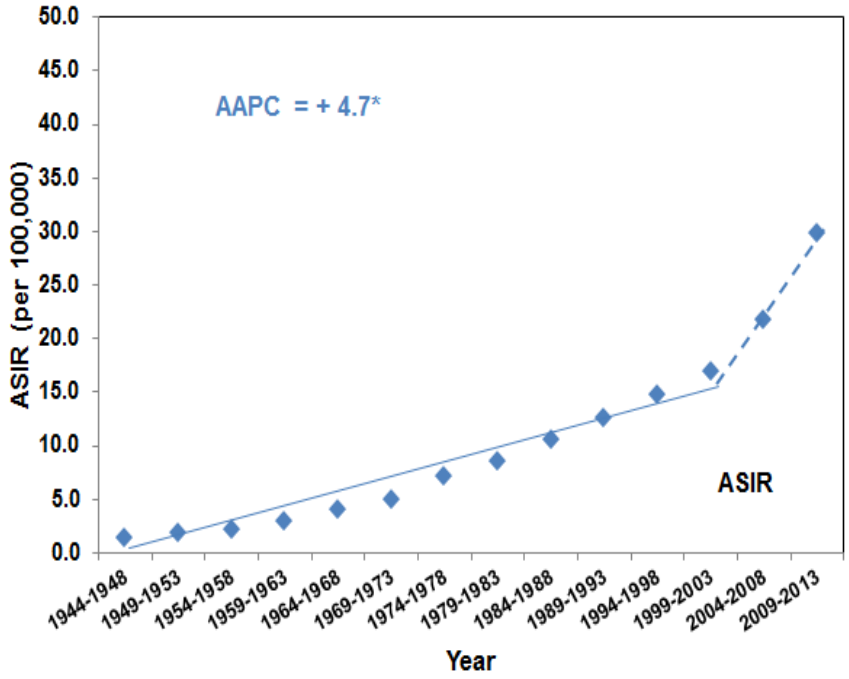
(b)



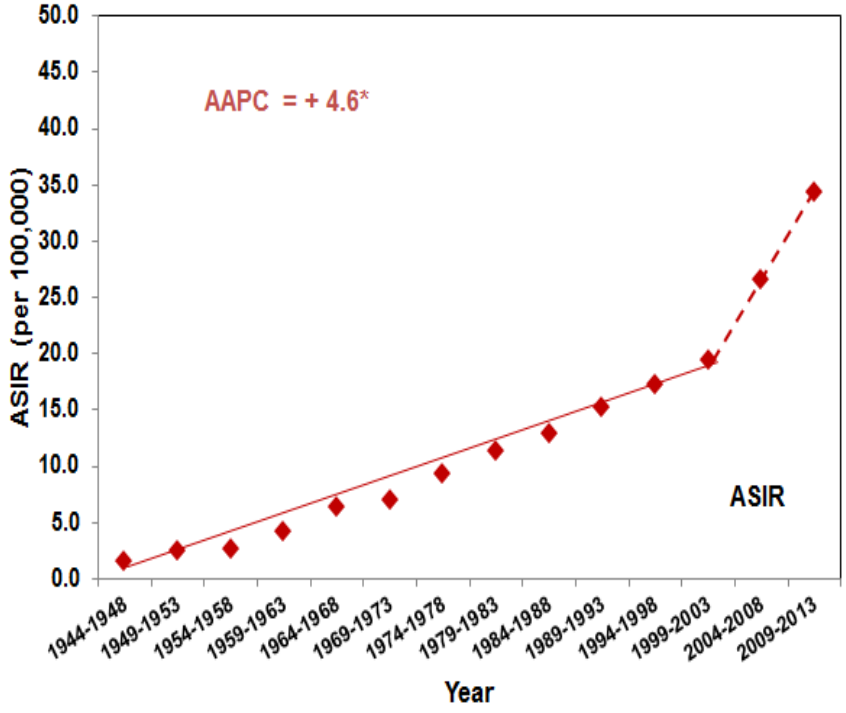
Abbreviations: APC, annual percentage change: AAPC, average annual percentage change
* APC, AAPC are significantly different from zero at α=0.05

Figure 18: Trends of age-specific incidence rates of cutaneous melanoma, Denmark (1980-2013): (a) Males; (b) Females.

(a)



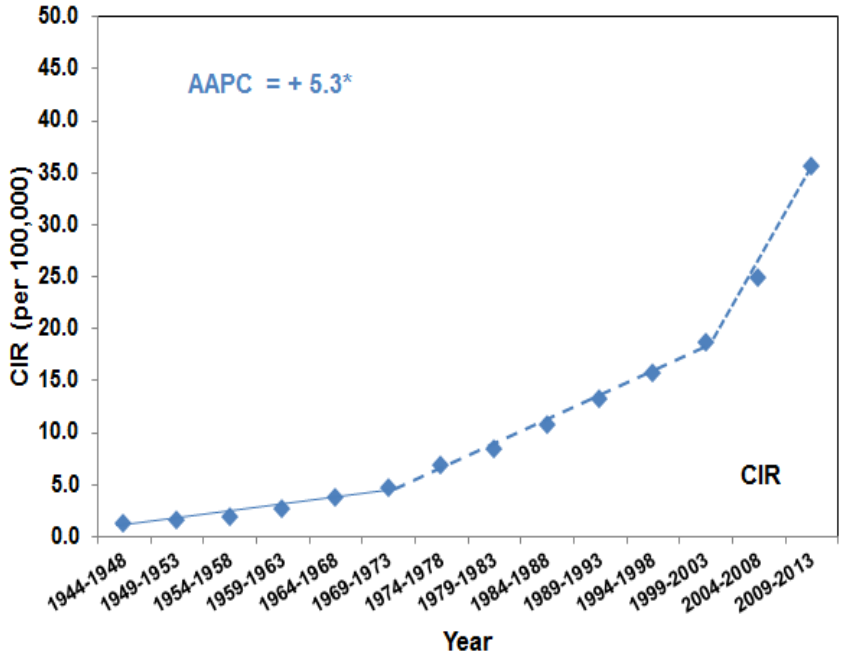
(b)



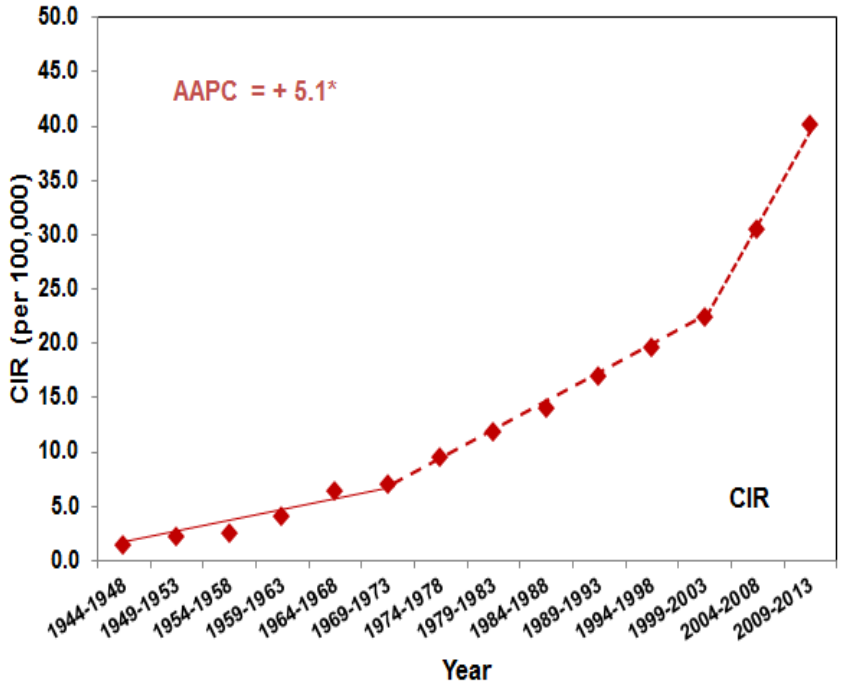
Abbreviations: APC, annual percentage change: AAPC, average annual percentage change
* APC, AAPC are significantly different from zero at α=0.05

Figure 19: Trends of age-standardized incidence rates (European Standard Population, WHO 1976) of cutaneous melanoma, Denmark (1944-2013): (a) Males; (b) Females.

(a)



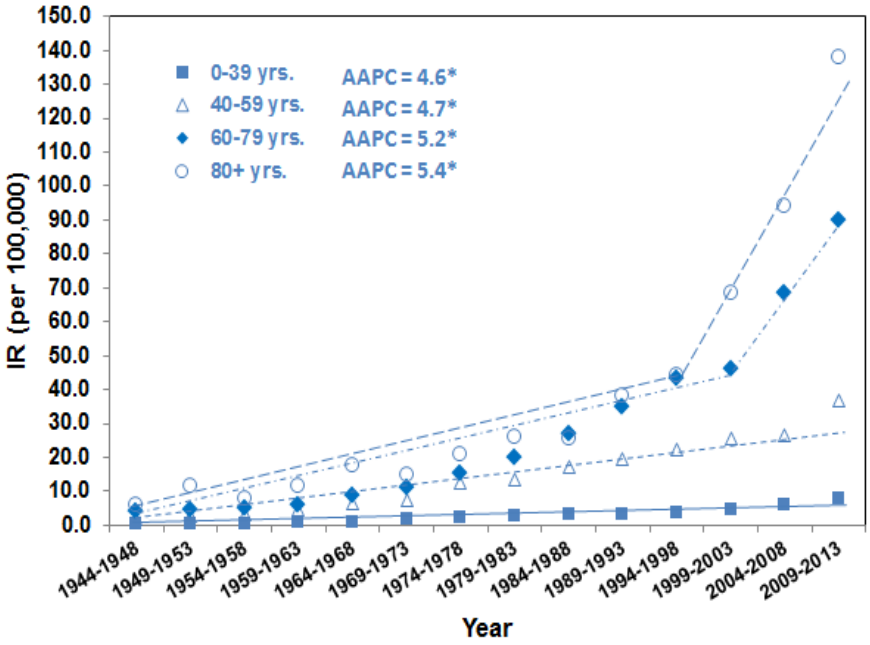
(b)



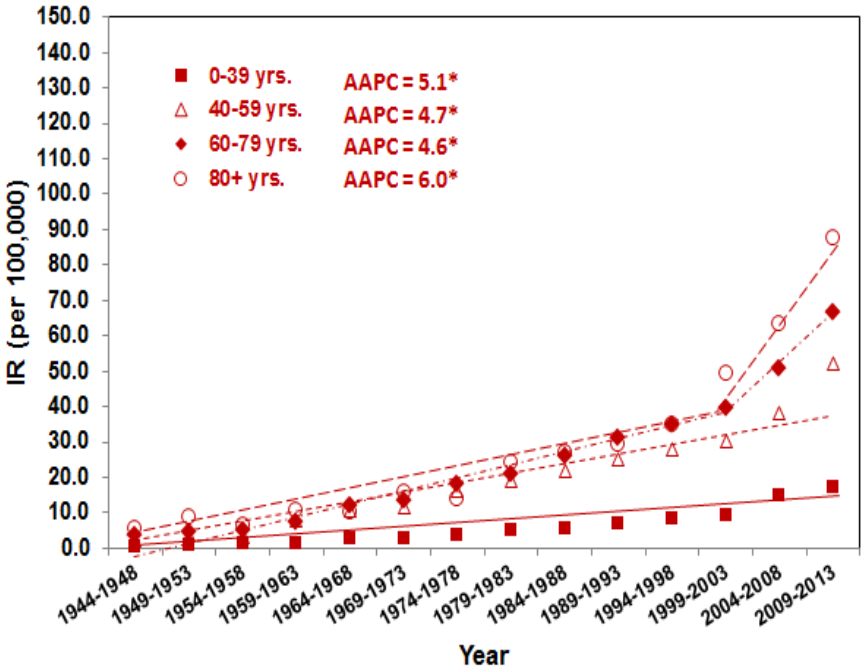
Abbreviations: APC, annual percentage change: AAPC, average annual percentage change
* APC, AAPC are significantly different from zero at α=0.05

Figure 20: Trends of crude incidence rates of cutaneous melanoma, Denmark (1944-2013): (a) Males; (b) Females.

(a)



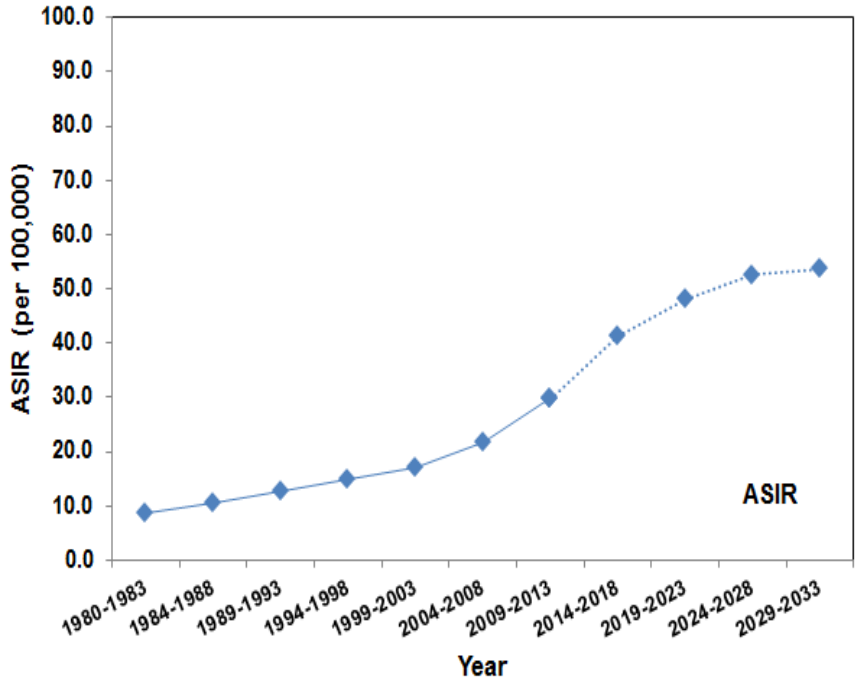
(b)



Abbreviations: APC, annual percentage change: AAPC, average annual percentage change
* APC, AAPC are significantly different from zero at α=0.05

Figure 21: Trends of age-specific incidence rates of cutaneous melanoma, Denmark (1944-2013): (a) Males; (b) Females.

(a)



(b)

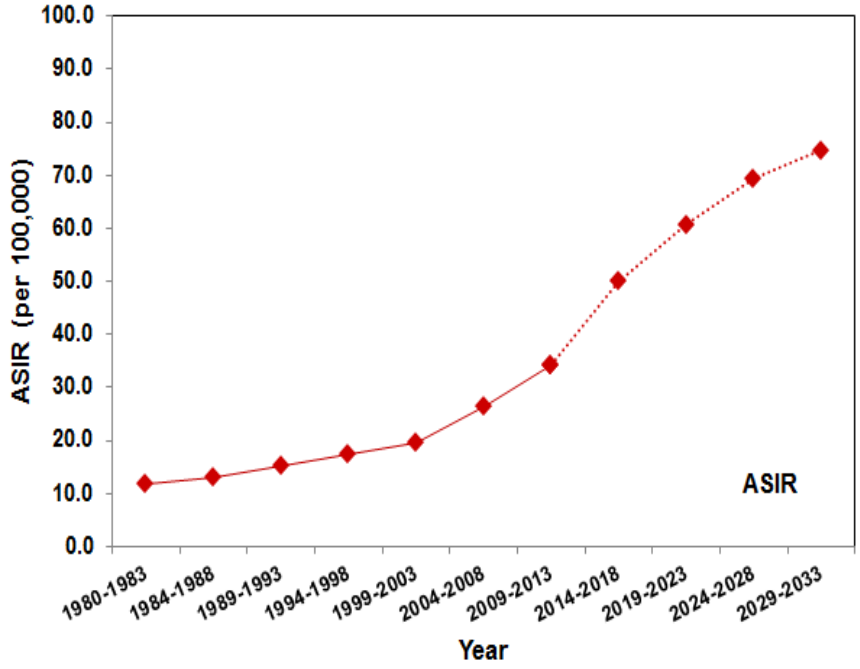
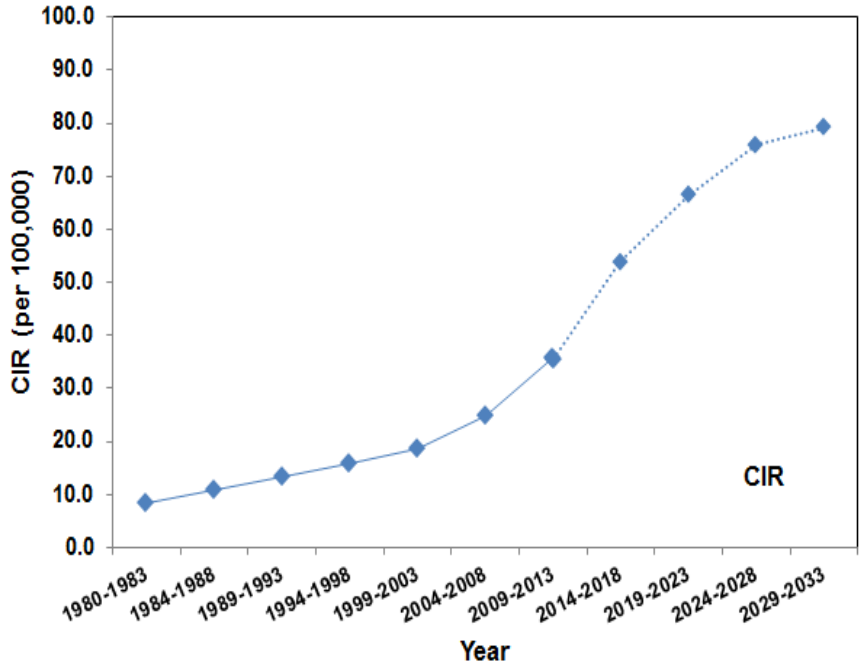


Figure 22: Projections of age-standardized incidence rates (European Standard Population, WHO 1976) of cutaneous melanoma, Denmark (2014/2018-2029/2033): (a) Males; (b) Females.

(a)



(b)

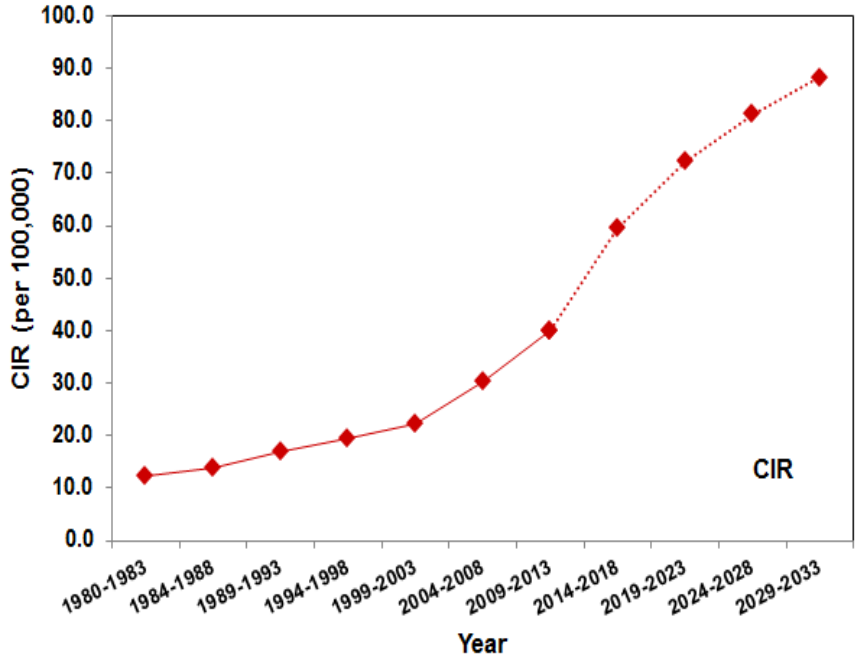
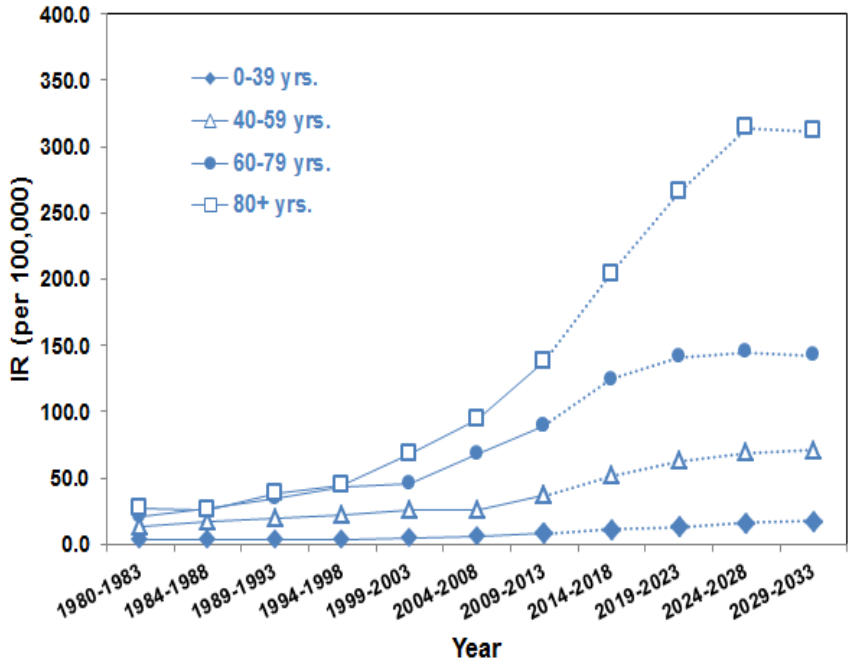


Figure 23: Projections of crude incidence rates of cutaneous melanoma, Denmark (2014/2018-2029/2033): (a) Males; (b) Females.

(a)



(b)

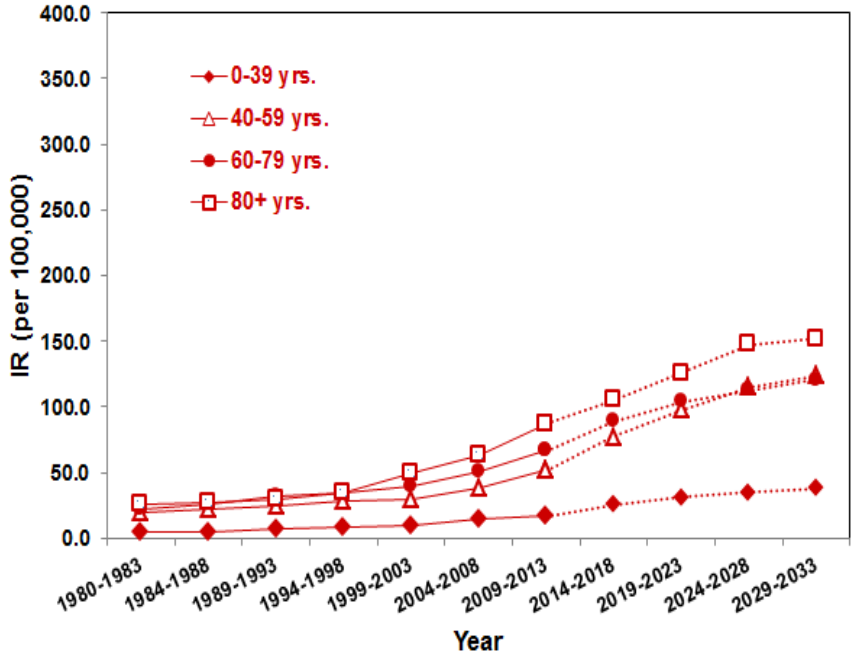


Figure 24: Projections of age-specific incidence rates of cutaneous melanoma, Denmark (2014/2018-2029/2033): (a) Males; (b) Females.

Table 17a: Observed (1944/1948-2009/2013) and projected (2014/2018-2029/2033) age-standardized, crude and age-specific incidence rates of cutaneous melanoma, Denmark, Males*

Time period	ASIR	CIR	Age-specific IRs			
			0-39 yrs	40-59 yrs	60-79 yrs	80+ yrs
Observed Data						
1944-1948	1.4	1.2	0.4	1.6	4.3	6.0
1949-1953	1.9	1.6	0.5	2.7	4.4	11.6
1954-1958	2.1	1.9	0.6	3.4	4.9	8.1
1959-1963	2.9	2.6	0.9	4.4	5.9	11.6
1964-1968	4.1	3.7	1.1	6.3	8.9	17.8
1969-1973	4.9	4.6	1.6	7.5	11.0	15.0
1974-1978	7.2	6.8	2.2	12.7	15.3	20.9
1979-1983	8.6	8.4	2.9	13.6	19.8	26.0
1984-1988	10.6	10.7	3.1	17.0	27.0	25.6
1989-1993	12.6	13.2	3.3	19.5	34.7	38.0
1994-1998	14.8	15.7	3.9	22.1	43.2	44.1
1999-2003	17.0	18.6	4.6	25.6	46.3	68.7
2004-2008	21.7	24.9	5.9	26.5	68.7	94.0
2009-2013	29.8	35.6	8.1	37.0	89.9	138.2
Projected Data**						
2014-2018	41.3	53.8	11.1	51.9	124.4	204.1
2019-2023	48.1	66.5	13.5	63.2	141.2	265.7
2024-2028	52.6	75.9	16.1	69.2	145.0	314.0
2029-2033	53.6	79.1	17.4	70.9	142.3	312.0

Abbreviations: ASIR, age-standardized incidence rate (European Standard Population, WHO 1976); CIR, crude incidence rate; IR, incidence rate

* All rates are expressed as number per 100,000 per year

** Based on age-period-cohort models (Moller et al, 2002)

Table 17b: Observed (1944/1948-2009/2013) and projected (2014/2018-2029/2033) age-standardized, crude and age-specific incidence rates of cutaneous melanoma, Denmark, Females*

Time period	ASIR	CIR	Age-specific IRs			
			0-39 yrs	40-59 yrs	60-79 yrs	80+ yrs
Observed Data						
1944-1948	1.6	1.4	0.6	2.2	3.6	5.4
1949-1953	2.4	2.2	1.0	3.5	4.6	8.7
1954-1958	2.6	2.4	1.3	3.4	5.1	6.3
1959-1963	4.2	4.1	1.4	7.7	7.4	10.5
1964-1968	6.4	6.3	2.6	10.5	12.2	10.3
1969-1973	7.0	6.9	2.6	11.7	13.4	15.7
1974-1978	9.3	9.4	3.7	16.3	18.0	14.0
1979-1983	11.3	11.8	5.1	19.1	20.9	24.0
1984-1988	12.9	14.0	5.4	21.9	26.1	26.9
1989-1993	15.2	17.0	6.8	25.1	31.7	29.5
1994-1998	17.3	19.5	8.4	28.0	34.7	35.1
1999-2003	19.4	22.4	9.5	30.3	39.7	49.5
2004-2008	26.5	30.4	14.9	38.1	50.9	63.6
2009-2013	34.3	40.1	17.0	52.0	66.6	87.4
Projected Data**						
2014-2018	49.9	59.5	25.9	77.5	89.1	105.1
2019-2023	60.7	72.3	31.2	97.9	103.9	125.8
2024-2028	69.4	81.3	34.7	115.0	112.8	147.5
2029-2033	74.6	88.3	38.3	123.8	120.7	151.9

Abbreviations: ASIR, age-standardized incidence rate (European Standard Population, WHO 1976); CIR, crude incidence rate; IR, incidence rate

* All rates are expressed as number per 100,000 per year

** Based on age-period-cohort models (Moller et al, 2002)

Table 18: Trends and annual percentage change of age-standardized, crude and age-specific incidence rates of cutaneous melanoma by sex, Denmark (1980-2013)**

	Line segment 1		Line segment 2		Line segment 3		Line segment 4			
	Year	APC	Year	APC	Year	APC	Year	APC	Year	AAPC (95% CI)
Males										
ASIR	1980-2004	3.34*	2004-2009	8.49*	2009-2013	1.90			1980-2013	3.9* (2.9; 4.9)
CIR	1980-2004	3.84*	2004-2009	9.74*	2009-2013	2.93			1980-2013	4.6* (3.8; 5.4)
0-39 yrs	1980-2004	2.31*	2004-2009	13.41*	2009-2013	-5.48			1980-2013	2.9* (1.8: 5.1)
40-59 yrs	1980-2013	3.06*							1980-2013	3.1* (2.7; 3.5)
60-79 yrs	1980-1995	5.64*	1995-2002	0.42	2002-2006	12.57*	2006-2013	4.38*	1980-2013	5.1* (3.7; 6.4)
80+ yrs	1980-1993	3.26*	1993-2013	7.36*					1980-2013	5.7* (4.4; 7.1)
Females										
ASIR	1980-2002	2.76*	2002-2013	6.11*					1980-2013	3.9* (3.3; 4.5)
CIR	1980-2002	3.17*	2002-2013	6.06*					1980-2013	4.1* (3.6; 4.7)
0-39 yrs	1980-2002	3.39*	2002-2008	10.97*	2008-2013	-2.85			1980-2013	3.7* (2.3; 5.2)
40-59 yrs	1980-2002	1.98*	2002-2013	5.85*					1980-2013	3.3* (2.6; 3.9)
60-79 yrs	1980-2003	3.00*	2003-2013	5.52*					1980-2013	3.8* (3.1; 4.4)
80+ yrs	1980-1993	1.55	1993-2013	5.86*					1980-2013	4.1* (2.7; 5.6)

Abbreviations: ASIR, age-standardized incidence rate (European Standard Population, WHO 1976); CIR, crude incidence rate

* Annual percentage change (APC) and average annual percentage change (AAPC) are significantly different from zero at α=0.05

** All rates are expressed as number per 100,000 per year

3.2.2 Trends in incident melanoma cases

The numbers of observed (1980/1983) and projected (2014/2018-2029/2033) melanoma cases are provided in Table 19a/b. The percentage change from baseline (1980/1983) by age group is illustrated in Figure 25a/b.

Trends in the total population

For both sexes, the number of persons diagnosed with melanoma increased between 1980/1983 and 2009/2013, for males from 214 to 981 cases p.a. (+358.4%), Table 19a and for females from 318 to 1,124 cases p.a. (+253.5%), respectively, Table 19b. During the forecast period (2014/2018-2029/2033), an ongoing increase is expected. The number of melanoma cases will rise to 2,015 new cases p.a. for males (+841.6% from 1980/1983-2029/2033) and to 2,484 new melanomas p.a. for females (+681.1% from 1980/1983-2029/2033).

Trends by age group

Between 1980/1983 and 2009/2013, the number of melanoma cases increased in all age groups. The growth increased with age and was highest in the age groups ≥60 years. The increase ranged between +148.9% (<40 years) and +666.7% (80+ years) in males and between +211% (<40 years) and +396.2% (80+ years) in females, respectively, Table 19a/b, Figure 25a/b.

Until 2019/2023, a further increase in melanoma cases is expected for all age groups and both sexes. Again, the largest increase is projected for subjects aged ≥60 years, particularly among males. For men ≥80 years, the number of melanoma cases will rise from 115 cases p.a. in 2009/2013 to 559 cases p.a. in 2029/2033. Relative to baseline (1980/1983), this corresponds to an increase of +3,626.7%, while only a quarter of that (+952.5%) is expected for men aged 60-79 years, climbing from 80 cases p.a. in 1980/1983 up to 842 cases p.a. in 2029/2033. For women, corresponding estimates are +635% (60-79 yrs) and +1,711.5% (80+ yrs), respectively, Table 19a/b, Figure 25a/b.

Significant increases in incidence are also projected for subjects aged <60 years, particularly for women. For women younger than 40 years, the number of melanoma cases will increase by +553.4% from 73 cases p.a. in 1980/1983 up to 477 cases p.a. in 2029/2033. A lower increase is expected for men

(+366.7%), rising from 45 melanoma cases p.a. in 1980/1983 to 210 cases p.a. in 2029/2033. An ongoing increase in the number of melanoma cases is also supposed for middle-aged women (40-59 yrs), climbing by +571.6% from 116 cases p.a. in 1980/1983 to 779 cases p.a. in 2029/2033. For men aged 40-59 years, a leveling off in increase might be seen from the 2020s onwards. The increase in melanoma cases will peak in 2019/2023 (+470.3%), followed by slightly lower increases (+458.1% and +445.9%) thereafter, Table 19a. First signs of stabilization might also become apparent among men aged 60-79 years from 2024/2028 onwards (with relative increases of +953.8% compared to baseline). No leveling off in increase, however, might be seen in the youngest age group (<40 years), neither for women nor for men, Table 19a/b, Figure 25a/b.

Table 19a: Number of melanoma cases and percentage change from baseline (1980/1983) by age and sex, Denmark, Males, (1984/1988 – 2029/2033)

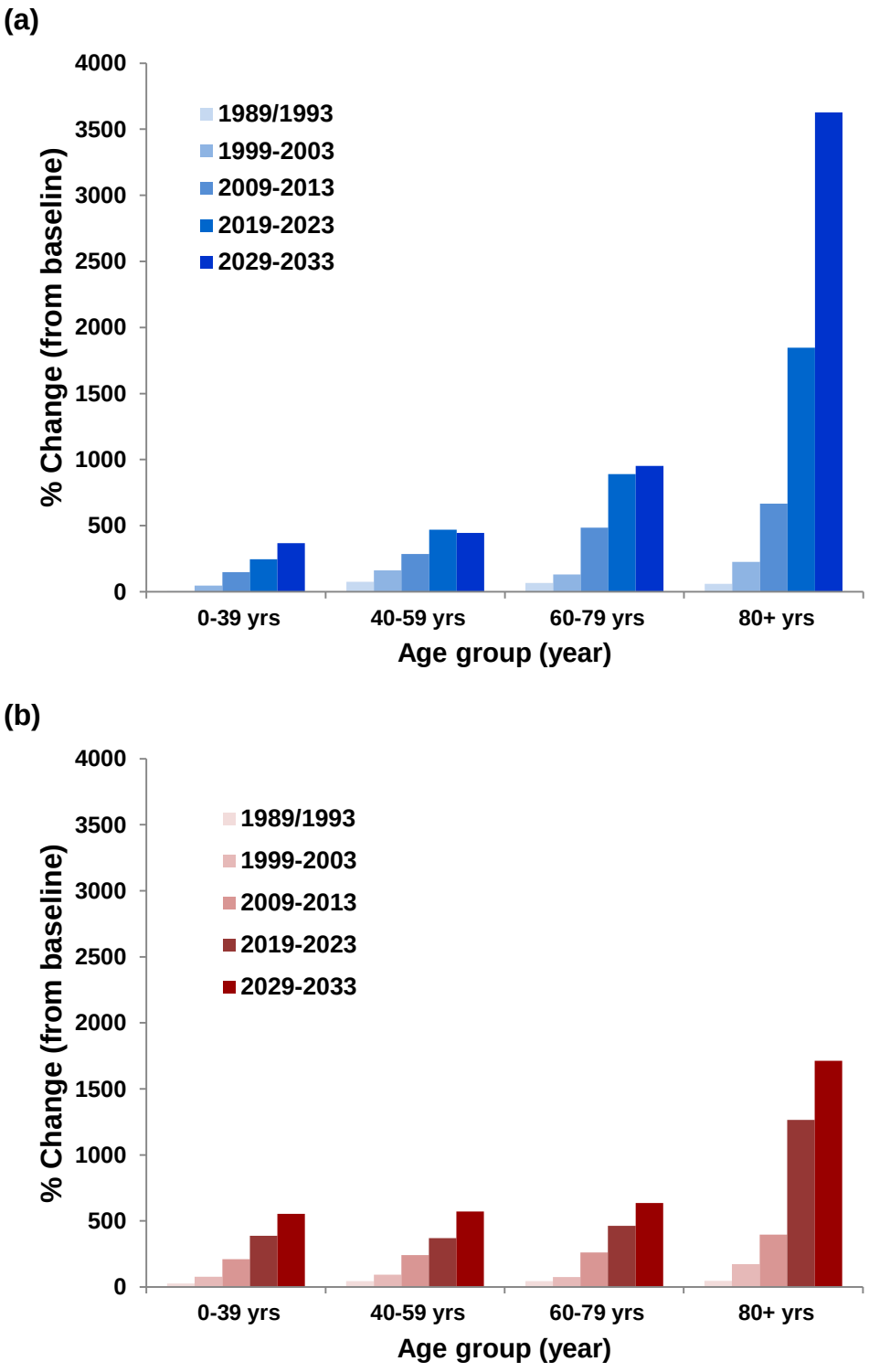
	1980-1983 (baseline)	Observed Data									
		1984-1988		1989-1993		1994-1998		1999-2003		2004-2008	
Total	214	271	(+26.6%)	334	(+56.1%)	408	(+90.7%)	492	(+129.9%)	671	(+213.6%)
0-39 yrs	45	46	(+2.2%)	47	(+4.4%)	55	(+22.2%)	66	(+46.7%)	82	(+82.2%)
40-59 yrs	74	104	(+40.5%)	130	(+75.7%)	159	(+114.9%)	193	(+160.8%)	203	(+174.3%)
60-79 yrs	80	106	(+32.5%)	133	(+66.3%)	164	(+105.0%)	184	(+130.0%)	314	(+292.5%)
80+ yrs	15	15	(+0.0%)	24	(+60.0%)	30	(+100.0%)	49	(+226.7%)	72	(+380.0%)
	1980-1983 (baseline)	**Projected Data***									
		2009-2013		**2014-2018**		**2019-2023**		**2024-2028**		**2029-2033**	
Total	214	981	(+358.4%)	1335	(+523.8%)	1663	(+677.1%)	1907	(+791.1%)	2015	(+841.6%)
0-39 yrs	45	112	(+148.9%)	130	(+188.9%)	156	(+246.7%)	191	(+324.4%)	210	(+366.7%)
40-59 yrs	74	286	(+286.5%)	359	(+385.1%)	422	(+470.3%)	413	(+458.1%)	404	(+445.9%)
60-79 yrs	80	468	(+485.0%)	662	(+727.5%)	793	(+891.3%)	843	(+953.8%)	842	(+952.5%)
80+ yrs	15	115	(+666.7%)	184	(+1126.7%)	292	(+1846.7%)	460	(+2966.7%)	559	(+3626.7%)

*based on age-period-cohort models (Moller et al., 2002)

Table 19b: Number of melanoma cases and percentage change from baseline (1980/1983) by age and sex, Denmark, Females, (1984/1988 – 2029/2033)

	1980-1983 (baseline)	Observed Data									
		1984-1988		1989-1993		1994-1998		1999-2003		2004-2008	
Total	318	364	(+14.5%)	444	(+39.6%)	518	(+62.9%)	605	(+90.3%)	835	(+162.6%)
0-39 yrs	73	75	(+2.7%)	92	(+26.0%)	115	(+57.5%)	129	(+76.7%)	200	(+174.0%)
40-59 yrs	116	133	(+14.7%)	166	(+43.1%)	197	(+69.8%)	224	(+93.1%)	287	(+147.4%)
60-79 yrs	103	125	(+21.4%)	148	(+43.7%)	158	(+53.4%)	181	(+75.7%)	255	(+147.6%)
80+ yrs	26	31	(+19.2%)	38	(+46.2%)	48	(+84.6%)	71	(+173.1%)	93	(+257.7%)
	1980-1983 (baseline)	**Projected Data***									
		2009-2013		**2014-2018**		**2019-2023**		**2024-2028**		**2029-2033**	
Total	318	1124	(+253.5%)	1509	(+374.5%)	1835	(+477.0%)	2102	(+561.0%)	2484	(+681.1%)
0-39 yrs	73	227	(+211.0%)	288	(+294.5%)	356	(+387.7%)	410	(+461.6%)	477	(+553.4%)
40-59 yrs	116	396	(+241.4%)	521	(+349.1%)	544	(+369.0%)	654	(+463.8%)	779	(+571.6%)
60-79 yrs	103	372	(+261.2%)	514	(+399.0%)	580	(+463.1%)	628	(+509.7%)	757	(+635.0%)
80+ yrs	26	129	(+396.2%)	186	(+615.4%)	355	(+1265.4%)	410	(+1476.9%)	471	(+1711.5%)

* based on age-period-cohort models (Moller et al., 2002)



Abbreviation: MM, malignant melanoma

Figure 25: Relative change of melanoma cases from baseline (1980/1983) by age group and sex, Denmark (1989/1993 – 2029/2033): (a) Males, (b) Females

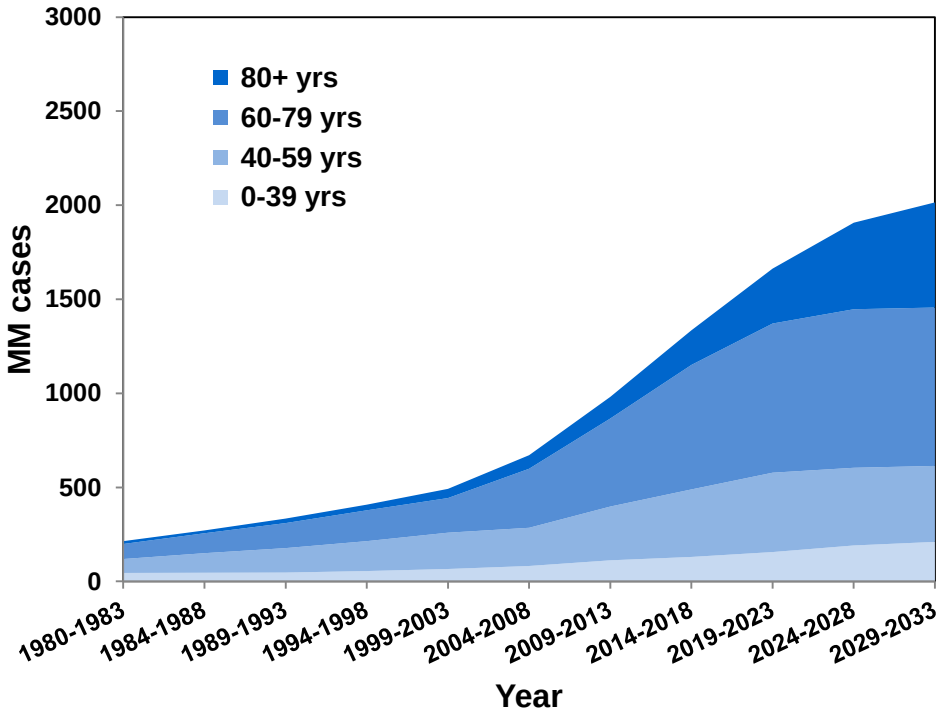
3.2.3 Shift in the age distribution of melanoma patients

Relative and absolute changes in the age distribution of melanoma patients between baseline (1980/1983) and following periods (1984/1988-2029/2033) are shown in Figure 26a/b, and in Figure 27a/b.

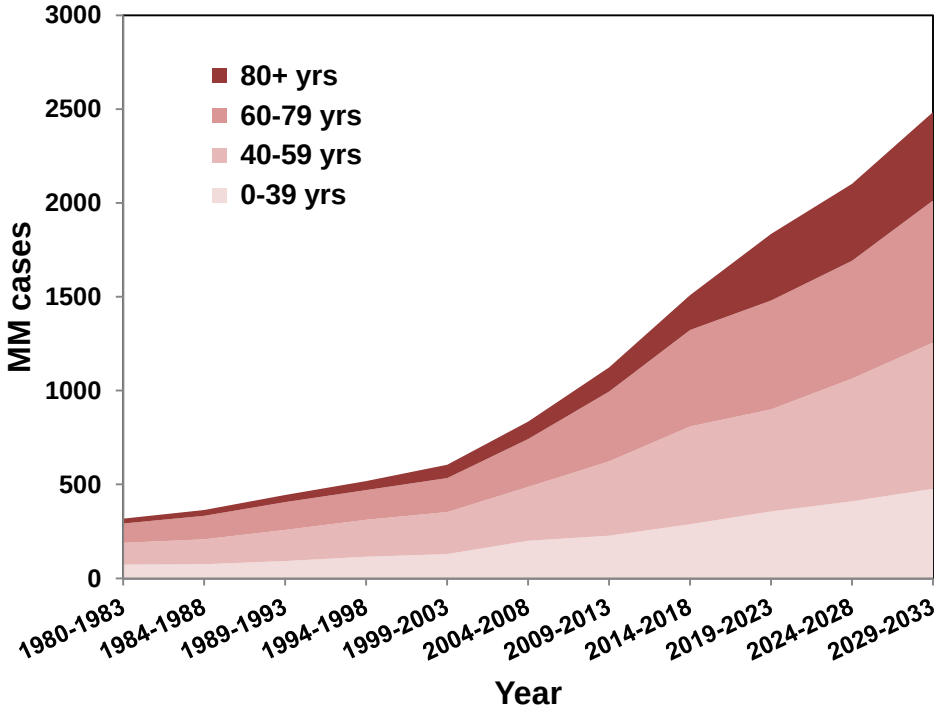
Both, males and females are expected to see a shift in the age distribution of melanoma patients towards an increasing proportion of older patients (≥60 years), most obvious among males, Figure 26a and 27a. Between 1980/1983 and 2029/2033, the proportion of male melanoma patients aged 60 years and older is expected to increase from 44.4% to 69.5%, Figure 27a. The growth in this age group will mainly be attributed to strong increases in the elderly (80+ yrs), climbing from 7.0% in 1980/1983 to 27.7% in 2029/2033. On the other hand, steeply decreasing numbers of melanoma patients aged 40-59 years (from 34.6% in 1980/1983 to 20.1% in 2029/2033) will lead to a significant decline of male melanoma patients younger than 60 years (from 55.6% in 1980/1983 to 30.5% in 2029/2033), Figure 26a and 27a.

Similar trends, although to a lesser extent, are projected for women. The proportion of melanoma patients aged ≥60 years will rise from 40.6% in 1980/1983 to 49.5% in 2029/2033, Figure 26b and 27b. As in men, a large proportion of the projected increase will be due to strong increases among elderly patients (≥80 years), climbing from 8.2% in 1980/1983 up to 19.0% in 2029/2033. At the same time, the proportion of younger patients (<60 years) will decrease from 59.4% in 1980/1983 to 50.5% in 2029/2033, Figure 26b and 27b.

(a)

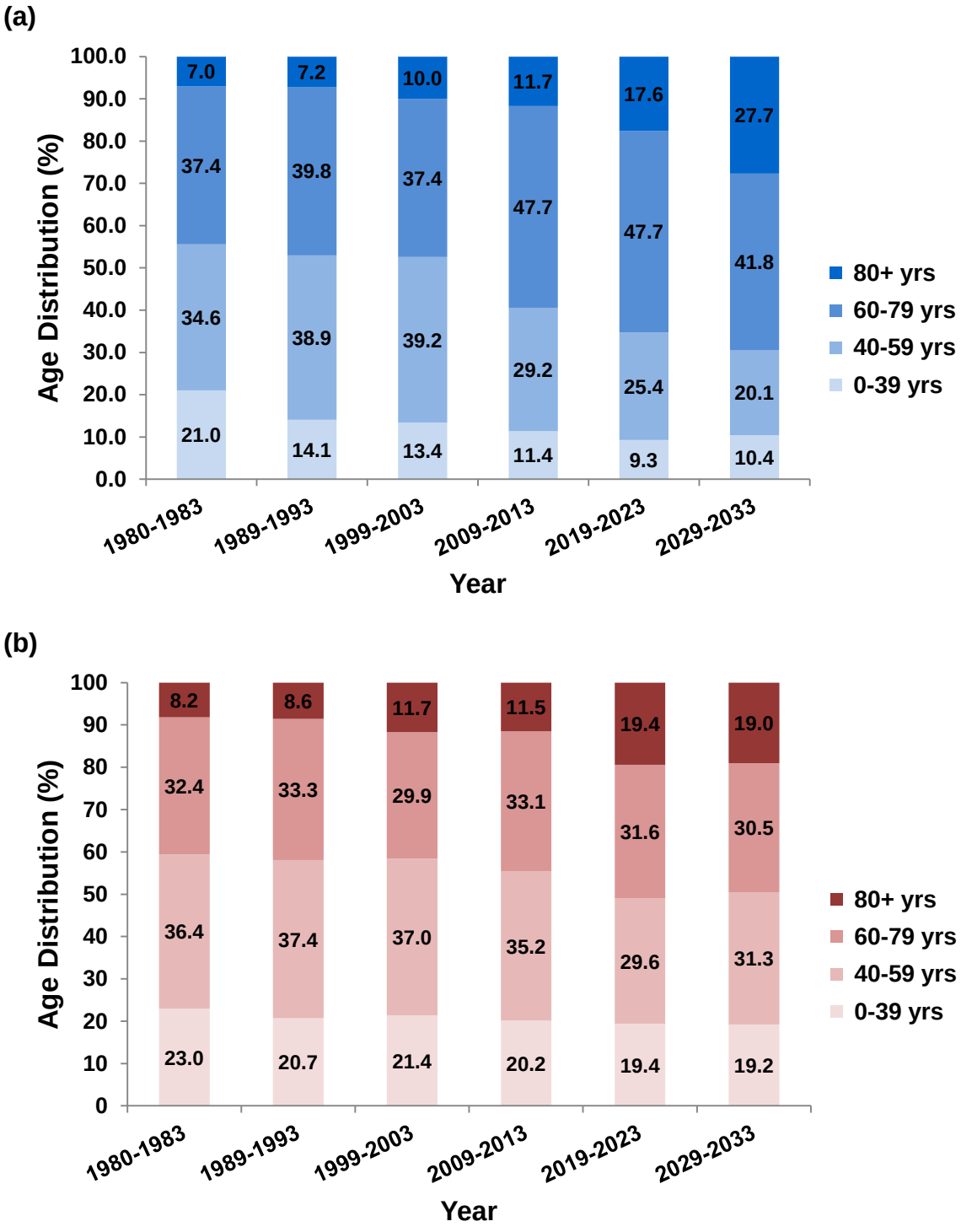


(b)



Abbreviation: MM, malignant melanoma

Figure 26: Number of melanoma cases by age group and sex, Denmark (1980/1983-2029/2033): (a) Males, (b) Females



Abbreviation: MM, malignant melanoma

Figure 27: Age distribution (%) of melanoma cases by sex, Denmark (1980/1983-2029/2033): (a) Males, (b) Females

3.2.4 Numbers of new melanoma attributed to changes in UVR exposure and demographics

Results of the estimated increase in melanoma patients attributed to changes in risk and demographics between baseline and future periods, applying the method developed by Moller et al., are given in Table 20a/b and in Figure 28a/b.

Increasing numbers of melanoma cases since 1980/1983 have been observed in both sexes. For men, 767 additional melanoma cases were diagnosed in 2009/2013 compared to baseline, representing a total increase of +358.4% (+338.3% due to changes in risk and +20.1% due to changes in population structure), Table 20a, Figure 28a. For women, 806 additional melanoma cases were diagnosed in 2009/2013, which corresponds to an increase of +253.5% (+239.7% due to changes in risk and +13.8% due to changes in population structure), Table 20b, Figure 28b. For both sexes, the increase in melanoma cases was mainly attributed to changes in age-specific melanoma risk rather than in population size and aging (+94.4% for males and +94.5% for females), Table 20a/b, Figure 28a/b.

The observed trends are proposed to continue for the next 20 years. Until 2029/2033, 1,801 new melanoma cases will be diagnosed among men, which corresponds to a relative increase of +841.6% (+803.3% due to changes in risk and +38.3% due to changes in population structure). Among women, 2,166 additional melanomas are expected by 2029/2033, representing an increase of +681.1% (+666% due to changes in risk and +21.1% due to changes in population structure) compared to baseline. Again, most of the expected increase in numbers of persons diagnosed with melanoma will be attributable to increasing risk (+95.4% for men and +96.9% for women) rather than to changes in population size and age distribution, Table 20a/b, Figure 28a/b.

For both sexes, the number and proportion of additional melanoma cases diagnosed since baseline due to changes in UVR exposure has increased and is expected to increase in the future, most evident in women. For women, the proportion of new melanomas caused by UVR exposure will increase from 76.1% in 1984/1988 to 96.9% in 2029/2033, for men from 89.5% to 95.4%. The

large difference between men and women, observed in 1984/1988 will narrow in future periods.

Table 20a: Excess number of melanoma cases (1984/1988-2029/2033) attributed to changes in population risk and population structure (size and age distribution) from baseline (1980/1983), Denmark, Males

	Observed Data						
	1980-1983 (baseline)	**1984-1988**	**1989-1993**	**1994-1998**	**1999-2003**	**2004-2008**	**2009-2013**
MM cases	214	271	334	408	492	671	981
Population	2447534	2431364	2420545	2432443	2442834	2454078	2473777
Excess MM (total):	-	57 (100.0%)	120 (100.0%)	194 (100.0%)	278 (100.0%)	457 (100.0%)	767 (100.0%)
due to UVR exposure		51 (89.5%)	109 (90.8%)	177 (91.2%)	253 (91.0%)	424 (92.8%)	724 (94.4%)
due to demographics		6 (10.5%)	11 (9.2%)	17 (8.8%)	25 (9.0%)	33 (7.2%)	43 (5.6%)
(size)		-1 (-1.8%)	-3 (-2.5%)	-1 (-0.5%)	0 (0.0%)	1 (0.2%)	2 (0.3%)
(age)		7 (12.3%)	14 (11.7%)	18 (9.3%)	25 (9.0%)	32 (7.0%)	41(5.3%)
Population change from baseline	-	-0.66%	-1.10%	-0.62%	-0.19%	0.27%	1.07%
Excess MM from baseline (total)	-	26.6%	56.1%	90.7%	129.9%	213.6%	358.4%
due to risk		23.8%	51.0%	82.7%	118.2%	198.2%	338.3%
due to population		2.8%	5.1%	8.0%	11.7%	15.4%	20.1%
(size)		-0.47%	-1.4%	-0.47%	0.0%	0.5%	1.0%
(age)		3.27%	6.5%	8.47%	11.7%	14.9%	19.1%

Continued on next page

	Projected Data*				
	1980-1983 (baseline)	**2014-2018**	**2019-2023**	**2024-2028**	**2029-2033**
MM cases	214	1335	1663	1907	2015
Population	2447534	2482496	2500379	2524712	2548540
Excess MM (total):	-	1121 (100.0%)	1449 (100.0%)	1693 (100.0%)	1801 (100.0%)
due to UVR exposure		1067 (95.2%)	1385 (95.6%)	1621 (95.7%)	1719 (95.4%)
due to demographics		54 (4.8%)	64 (4.4%)	72 (4.3%)	82 (4.6%)
(size)		3 (0.3%)	5 (0.3%)	7 (0.4%)	9 (0.5%)
(age)		51 (4.5%)	59 (4.1%)	65 (3.9%)	73 (4.1%)
Population change from baseline	-	1.43%	2.16%	3.15%	4.13%
Excess MM from baseline (total)	-	523.8%	677.1%	791.1%	841.6%
due to risk		498.6%	647.2%	757.5%	803.3%
due to population		25.2%	29.9%	33.6%	38.3%
(size)		1.4%	2.3%	3.2%	4.2%
(age)		23.8%	27.6%	30.4%	34.1%

Abbreviation: MM, malignant melanoma
* based on age-period-cohort models (Moller et al., 2002)

Table 20b: Excess number of melanoma cases (1984/1988-2029/2033) attributed to changes in population risk and population structure (size and age distribution) from baseline (1980/1983), Denmark, Females

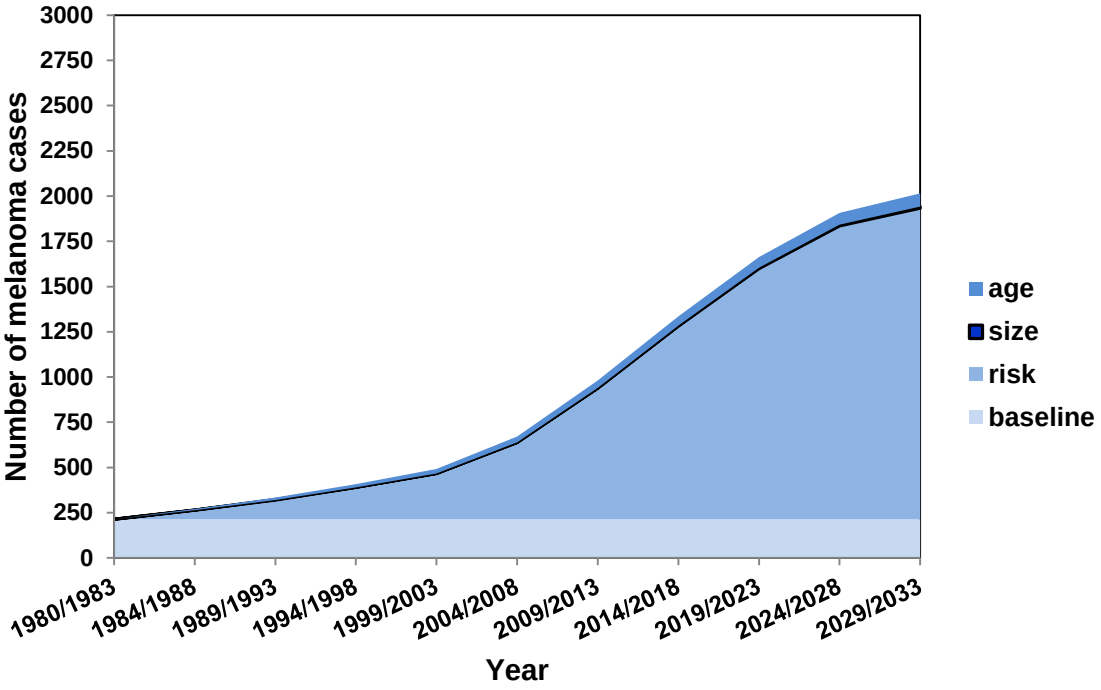
	Observed Data						
	1980-1983 (baseline)	**1984-1988**	**1989-1993**	**1994-1998**	**1999-2003**	**2004-2008**	**2009-2013**
MM cases	318	364	444	518	605	835	1124
Population	2507109	2502238	2494392	2499785	2501366	2503949	2514913
Excess MM (total):	-	46 (100.0%)	126 (100.0%)	200 (100.0%)	287 (100.0%)	517 (100.0%)	806 (100.0%)
due to UVR exposure		35 (76.1%)	105 (83.3%)	172 (86.0%)	253 (88.2%)	478 (92.5%)	762 (94.5%)
due to demographics		11 (23.9%)	21 (16.7%)	28 (14.0%)	34 (11.8%)	39 (7.5%)	44 (5.5%)
(size)		-1 (-2.2%)	-2 (-1.6%)	-1 (-0.5%)	-1 (-0.4%)	0 (0.0%)	1 (0.1%)
(age)		12 (26.1%)	23 (18.3%)	29 (14.5%)	35 (12.2%)	39 (7.5%)	43(5.4%)
Population change from baseline	-	-0.19%	-0.51%	-0.29%	-0.23%	-0.13%	0.31%
Excess MM from baseline (total)	-	14.5%	39.6%	62.9%	90.3%	162.6%	253.5%
due to risk		11.0%	33.0%	54.1%	79.6%	150.3%	239.7%
due to population		3.5%	6.6%	8.8%	10.7%	12.3%	13.8%
(size)		-0.3%	-0.6%	-0.3%	-0.3%	0.0%	0.3%
(age)		3.8%	7.2%	9.1%	11.0%	12.3%	13.5%

Continued on next page

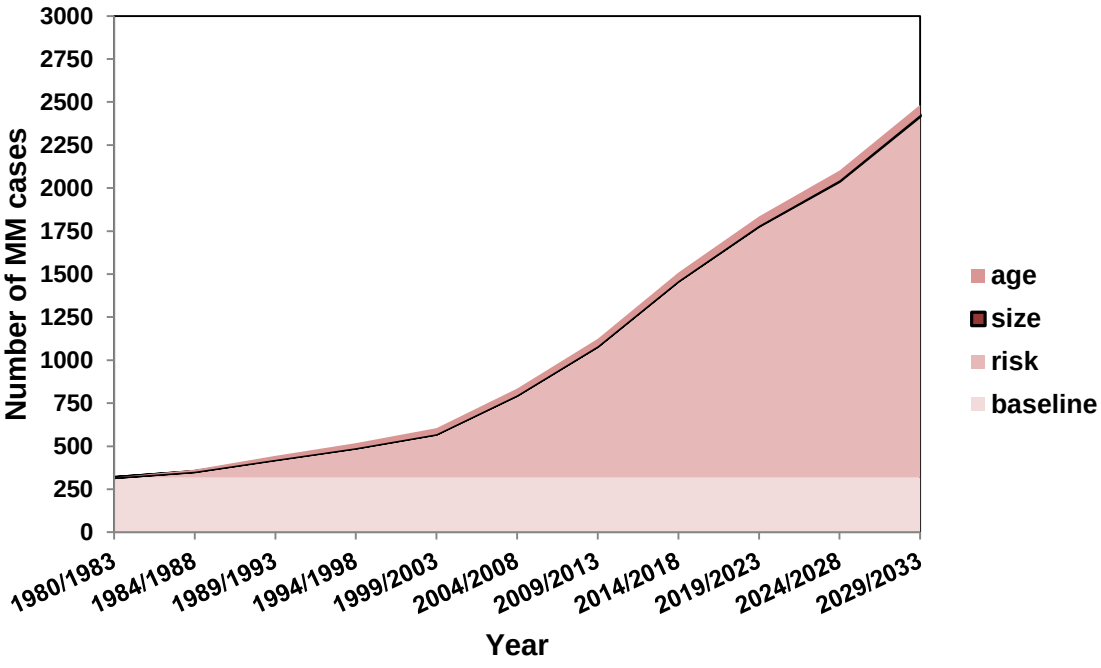
	Projected Data*				
	1980-1983 (baseline)	**2014-2018**	**2019-2023**	**2024-2028**	**2029-2033**
MM cases	318	1509	1835	2102	2484
Population	2507109	2517344	2530835	2552927	2574121
Excess MM (total):	-	1191 (100.0%)	1517 (100.0%)	1784(100.0%)	2166 (100.0%)
due to UVR exposure		1141 (95.8%)	1460 (96.2%)	1721 (96.5%)	2099 (96.9%)
due to demographics		50 (4.2%)	57 (3.8%)	63 (3.5%)	67 (3.1%)
(size)		1 (0.1%)	3 (0.2%)	6 (0.3%)	8 (0.4%)
(age)		49 (4.1%)	54 (3.6%)	57 (3.2%)	59 (2.7%)
Population change from baseline	-	0.41%	0.94%	1.83%	2.67%
Excess MM from baseline (total)	-	374.5%	477.0%	561.0%	681.1%
due to risk		358.8%	459.1%	541.2%	660.0%
due to population		15.7%	17.9%	19.8%	21.1%
(size)		0.3%	0.9%	1.9%	2.5%
(age)		15.4%	17.0%	17.9%	18.6%

Abbreviation: MM, malignant melanoma
* based on age-period-cohort models (Moller et al., 2002)

(a)



(b)



Abbreviation: MM, malignant melanoma

Figure 28: Number of excess melanoma cases from baseline (1980/1983), attributed to changes in population risk and demographics, Denmark (1984/1988-2029/2033): (a) Males, (b) Females

3.2.5 Proportions of melanoma attributable to UVR exposure (background level)

The number and proportion of melanoma cases caused by sun exposure at baseline, using incidence rates of a historical Danish cohort from 1943/1947 as reference population, are summarized in Table 21.

At baseline, an estimated 458 melanoma cases p.a. (182 in males and 276 in females) were attributable to ambient UVR exposure, representing 86.1% of all melanomas diagnosed in 1980/1983. The proportion attributable fraction (PAF%) was slightly higher in women (276 attributable cases; 86.8% of all melanomas) than in men (182; 85%) This trend is visible in all age groups (PAF% in females vs. PAF% in males: <40 yrs: 87.7% vs. 84.4%, 40-59 yrs: 88.8% vs. 87.8% and for 60 +yrs: 84.5% vs. 83.2%), Table 21.

Table 21: Number and proportion of melanoma cases attributed to UVR exposure at baseline (1980/1983) by age and sex, Denmark

	Males				Females			
Age (years)	**Expected cases***	**Observed cases**	**Excess cases**	**PAF% (UVR)**	**Expected cases***	**Observed cases**	**Excess cases**	**PAF% (UVR)**
0-4	0	0	0		0	0	0	
5-9	0	0	0		0	0	0	
10-14	1	1	0	0.0	1	0	-1	
15-19	0	1	1	100.0	0	4	4	100.0
20--24	0	4	4	100.0	2	6	4	66.7
25-29	1	8	7	87.5	2	14	12	85.7
30-34	3	12	9	75.0	1	21	20	95.2
35-39	2	19	17	89.5	3	28	25	89.3
40-44	2	16	14	87.5	2	28	26	92.9
45-49	3	16	13	81.3	2	29	27	93.1
50-54	2	20	18	90.0	3	28	25	89.3
55-59	2	22	20	90.9	6	31	25	80.6
60-64	2	22	20	90.9	3	29	26	89.7
65-69	3	23	20	87.0	4	25	21	84.0
70-74	4	21	17	81.0	6	28	22	78.6
75-79	4	14	10	71.4	2	21	19	90.5
80-84	2	6	4	66.7	3	15	12	80.0
85+	1	9	8	88.9	2	11	9	81.8
Total	**32**	**214**	**182**	**85.0**	**42**	**318**	**276**	**86.8**

Abbreviations: UVR, ultraviolet radiation; PAF, population attributable fraction

* Incidence rates of a historical Danish cohort (1943/1947) were used as reference population

3.2.6 Proportions of melanoma attributable to UVR exposure and demographics at baseline and in the further course

Table 22a/b and Figure 29a/b show the estimated numbers and proportions of melanomas that can be attributed to UVR exposure and demographics at baseline (1980/1983) and in the further course (1984/1988-2029/2033).

Trends of increasing numbers and proportions of melanomas caused by UVR exposure have been observed in both sexes. At baseline (1980/1983), the proportion of melanomas caused by UVR exposure was slightly higher in women (86.8%) than in men (85%). Projections indicate an ongoing increase of UVR-induced melanoma cases. By 2029/2033 up to 95% (94.3% in men and 95.6% in women) of all diagnosed melanoma cases are expected to be caused by high ambient levels of UVR exposure. At the same time, the proportion of melanomas attributable to demographic changes is expected to decline, in males from 15% in 1980/1983 to 5.7% in 2029/2023, and in females by a third from 13.2% to 4.4%.Table 22a/b.

Table 22a: Number and proportion of melanoma cases attributed to UVR and demographic changes at baseline (1980/1983) and following time periods (1984/1988-2029/33), Denmark, Males

Time Period	Number of cases	Changes in cases (from baseline)**			Number of cases attributed to		Population attributable fraction (PAF%)	
		overall	due to change in UVR	due to change in demographics	UVR	demographics	UVR	demographics
1980/1983 (baseline)*	214	-	-	-	182	32	85.0%	15.0%
1984/1988	271	57	51	6	233	38	86.0%	14.0%
1989/1993	334	120	109	11	291	43	87.1%	12.9%
1994/1998	408	194	177	17	359	49	88.0%	12.0%
1999/2003	492	278	253	25	435	57	88.4%	11.6%
2004/2008	671	457	424	33	606	65	90.3%	9.7%
2009/2013	981	767	724	43	906	75	92.4%	7.6%
2014/2018	1335	1121	1067	54	1249	86	93.6%	6.4%
2019/2023	1663	1449	1385	64	1567	96	94.2%	5.8%
2024/2028	1907	1693	1621	72	1803	104	94.5%	5.5%
2029/2033	2015	1801	1719	82	1901	114	94.3%	5.7%

Abbreviation: UVR, ultraviolet radiation

* The number of melanoma cases attributable to UVR exposure and demographics at baseline (1980/1983) is given in Table 21

** The excess number of melanoma cases attributed to changes in population risk (UVR) and demographics (population size and age distribution) in following time periods (1984/1989-2029/2033) is given in Table 20a

Table 22b: Number and proportion of melanoma cases attributed to UVR and demographic changes at baseline (1980/1983) and following time periods (1984/1988-2029/33), Denmark, Females

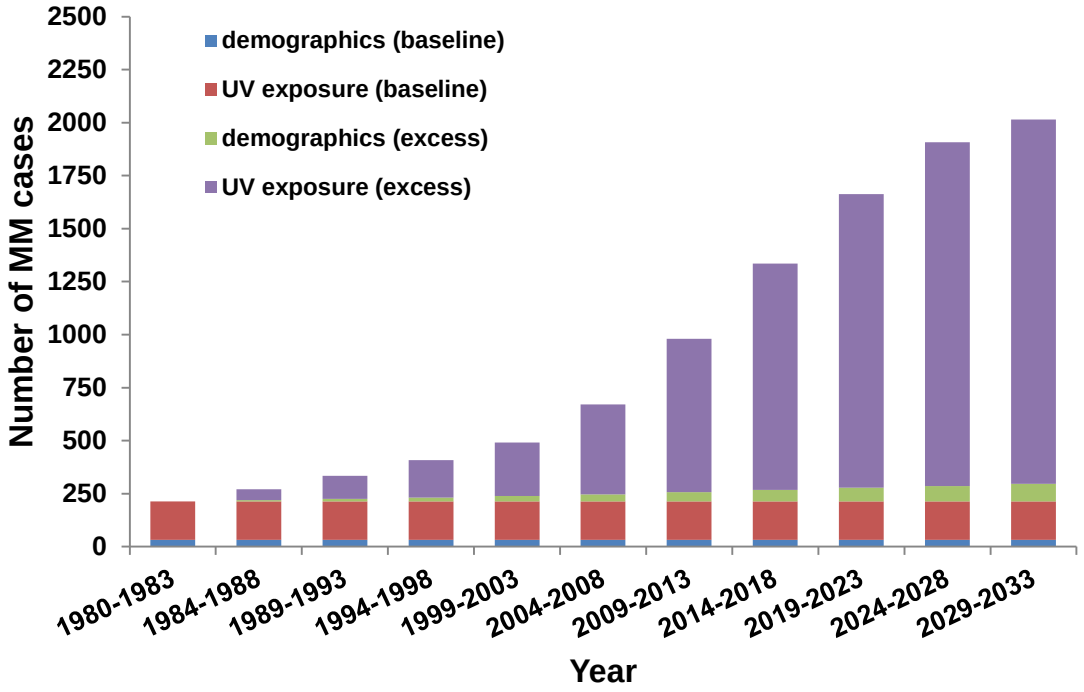
Time Period	Number of cases	Changes in cases (from baseline)**			Number of cases attributed to		Population attributable fraction (PAF%)	
		overall	due to change in UVR	due to change in demographics	UVR	demographics	UVR	demographics
1980/1983 (baseline)*	318	-	-	-	276	42	86.8%	13.2%
1984/1988	364	46	35	11	311	53	85.4%	14.6%
1989/1993	444	126	105	21	381	63	85.8%	14.2%
1994/1998	518	200	172	28	448	70	86.5%	13.5%
1999/2003	605	287	253	34	529	76	87.4%	12.6%
2004/2008	835	517	478	39	754	81	90.3%	9.7%
2009/2013	1124	806	762	44	1038	86	92.3%	7.7%
2014/2018	1509	1191	1141	50	1417	92	93.9%	6.1%
2019/2023	1835	1517	1460	57	1736	99	94.6%	5.4%
2024/2028	2102	1784	1721	63	1997	105	95.0%	5.0%
2029/2033	2484	2166	2099	67	2375	109	95.6%	4.4%

Abbreviation: UVR, ultraviolet radiation

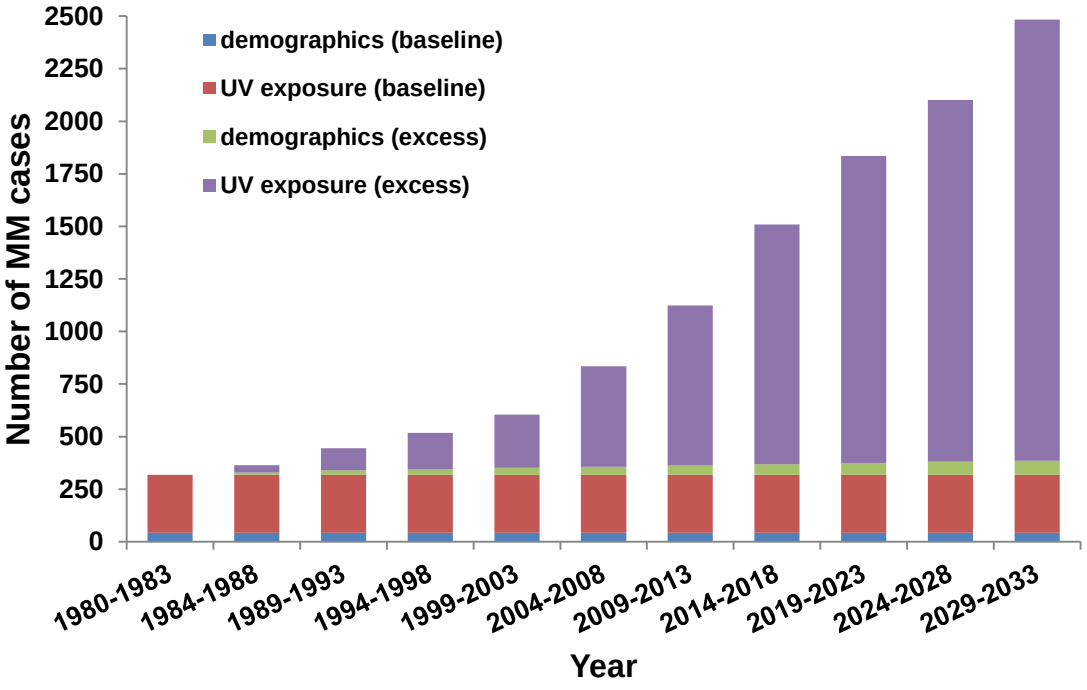
* The number of melanoma cases attributable to UVR exposure and demographics at baseline (1980/1983) is given in Table 21

** The excess number of melanoma cases attributed to changes in population risk (UVR) and demographics (population size and age distribution) in following time periods (1984/1988-2029/2033) is given in Table 20b

(a)



(b)



Abbreviation: MM, malignant melanoma

Figure 29: Baseline and excess number of melanoma cases attributed to changes in UV exposure and demographics by sex, Denmark (1980/1983-2029/2033): (a) Males, (b) Females

4 Discussion

The aim of the present research project was to investigate the impact of changes in UVR exposure and demographics on past and present incidence trends of cutaneous melanoma in Germany and Denmark and to estimate the future melanoma burden according to these changes.

For this purpose, melanoma incidence data were extracted from population-based cancer registries in Germany and Denmark. Data for Germany were obtained from the Center for Cancer Registry Data at the Robert Koch-Institute in Berlin (Robert Koch Institut Berlin, 2016), which describes the incidence of melanoma for entire Germany from 1995 to 2013. Data for Denmark, covering the period from 1943 to 2013, were sourced from the Danish Cancer Registry, which is part of the NORDCAN database (NORDCAN, 2018).

Joinpoint regression analysis was used to identify significant changes in incidence rates over the observation period. Based on observed incidence data, age-period-cohort models were applied to predict future incidence rates from 2014 through 2033. Analyses were carried out for age-standardized, crude and age-specific incidence rates, as well as for absolute numbers of melanoma cases. Age-standardized incidence rates were used to describe changes in UVR exposure over time (risk component), and crude rates were analyzed to account for the additional impact of age (demographic component) on observed and projected incidence trends. Absolute numbers of melanoma cases were calculated to quantify the proportion of melanoma cases attributable to changes in UVR exposure and demographics.

Observed incidence trends

In Germany, age-standardized incidence rates displayed an increase between 1995/1998 and 2009/2013 for both sexes. Specifically, an increase from 10.1 to 19.7/100,000 per year was observed for men and an increase from 9.9 to 19.4/100,000 per year was observed for women. This corresponds to an average annual increase of +4.4% for men and of +4.3% for women. A particularly strong increase in incidence rates (+11% p.a. for men and women) was seen between 2006 and 2009, which has largely been attributed to the

introduction of skin cancer screening and the resulting increase in diagnoses (Breitbart et al., 2012, Waldmann et al., 2012). In the years after 2009, this increase has leveled off for both sexes.

In Denmark, the age-standardized incidence rates for men increased from 1.4/100,000 per year in 1944/1948 to 29.8/100,000 per year in 2009/2013 and for women from 1.6 /100,000 per year to 34.3/100,000 per year. During this time period, the average annual increase was estimated at +4.6% for women and +4.7% for men. Between 1950 and 1970, incidence rates in Denmark increased slightly. From the 1970s onwards the increase becomes somewhat steeper. Particularly strong increases can be observed from the 2000s onwards.

In both countries, the increase in melanoma incidence was more pronounced in crude incidence rates, most notably among men. In Germany. the crude rates rose by an average of +4.9% p.a. for women and of +6.0% p.a. for men between 1995/1998 and 2009/2013, and in Denmark by an average of +5.1% p.a. (women) and +5.3% p.a. (men) between 1944/1948 and 2009/2013.

The overall incidence trends observed in this study are largely consistent with those reported from other countries with predominantly fair-skinned populations. The reported annual increase varied between different populations but has been estimated to be between 3-7% (de Vries et al., 2003, Erdmann et al., 2013, Garbe and Leiter, 2009). Between 1990 and 2007, incidence rates in Europe increased by an average of +3.8% pea for women and by an average of +4.2% p.a. for men (Arnold et al., 2014).

Long-term trends are reported from Scandinavia, where cancer registration has already been established since the early 1940s. Osterlind et al. was one of the first researchers who described incidence trends in Denmark (Osterlind et al., 1988a, Osterlind et al., 1988b). Between 1943 and 1982, a five- to six-fold increase in age-standardized incidence rates was reported for both sexes. During this period, incidence rates in females were consistently higher than in males. This increase continued in the following years (Bay et al., 2015, Fuglede et al., 2011, Helvind et al., 2015). Between 1985 and 2012, incidence rates increased by an average of +4.5% p.a. for men and by an average of +4.3% p.a. for women, reaching rates of 29.5 and 31.7/100,000 per year in 2012,

respectively. An even stronger increase was observed from 2004 onwards (Bay et al., 2015), which was also seen in the present study.

The general trend towards increasing melanoma incidence rates is largely due to changes in lifestyle and social behavior, involving an increasing amount of UVR exposure. Since the middle of the 20th century, a new ideal of beauty has developed which embodied tanned skin as a symbol of health and prosperity, resulting in a radical change from sun avoidance to sun-seeking behavior. Increasing number of holidays spent in (sub)tropical, sunny locations, more outdoor leisure activities or changes in fashion that favour less clothing, have led to an increasing amount of sun exposure (de Vries and Coebergh, 2004, Erdmann et al., 2013). Since the 1960s, the use of artificial sources of UVR (i.e. tanning beds, sun lamps) became increasingly popular, particularly in Northern European countries, which also contributed to an increase in UVR exposure (Bataille et al., 2005, Gandini S. et al., 2011, Hery et al., 2010).

In the present study, increasing incidence rates of melanoma were seen across all age groups. In both countries, the strongest increase was observed in the age groups ≥60 years, most obvious in men. In Germany, between 1995/1998 and 2009/2013, incidence rates in the elderly (80+ years) increased by an average of +4.3% p.a. for men and by an average of 3.4% p.a. for women. Even higher were the increases for those aged 60-79 years, incidence rates increased by +6.2% p.a. among men and by +4.8% p.a. among women. Steeply rising incidence rates were also found for younger age groups, especially for females, where the estimated annual increase ranged between +3.9% (<40 years) and +4.2% (40-59 years), respectively.

In Denmark, the strongest rise in incidence between 1944/1948 and 2009/2013 was also found for subjects aged ≥60 years, ranging between +5.2-5.4% pea for men and between +4.6-6.0% p.a. for women, respectively. Remarkable increases were also observed in younger age groups (<60 years). This was most pronounced among young women (<40 years: +5.1% pea), but was also apparent among men (+4.6% p.a.).

Strong increases in incidence rates in older age groups (≥60 years) is an ubiquitous observation that is frequently reported (Arnold et al., 2014, Bay et al.,

2015, Fuglede et al., 2011, Hoejberg et al., 2016). Declining rates, as already observed in Australia, New Zealand (Baade et al., 2011, Iannacone et al., 2015), North America (Gaudette and Gao, 1998) or in some Northern European countries (Arnold et al., 2014, de Vries et al., 2003, Erdmann et al., 2013), among younger cohorts, as result of successful primary prevention (de Haas et al., 2010, Iannacone and Green, 2014, Montague et al., 2001), are not discernible in Germany and Denmark.

Still rising incidence rates in younger age groups, most notably among women, have also been reported from other countries, such as the Netherlands (de Vries et al., 2005), England, Slovenia (Erdmann et al., 2013), the US (Weir et al., 2011), and from Denmark (Bay et al., 2015, Fuglede et al., 2011, Helvind et al., 2015). Findings from different European studies indicate that the increase among young people might be in part attributable to an increasing number of thin melanomas (Downing et al., 2006, MacKie et al., 2007, Montella et al., 2009). Especially women are known to participate more often in screenings programs, that in turn may lead to earlier diagnosis, and thus to higher proportions of thin and less invasive melanoma. Nevertheless, increasing proportions of melanomas located on body sites (i.e.trunk or the limbs), that are subject to intermittent sun exposure (Bataille et al., 2005, Bradford et al., 2010, Hery et al., 2010), and rapidly growing proportions of superficially spreading melanoma, are indications for a true increase in melanoma incidence due to increasing sun exposure (Anderson et al., 2009, de Vries and Coebergh, 2004, Holterhues et al., 2010, MacKie et al., 2007). Frequent use of artificial sources of UVR (i.e. tanning beds), known to be very popular among young Scandinavian women (Gandini S. et al., 2011, Hery et al., 2010), might also have contributed to rising incidence rates in these cohorts.

Trends towards stabilization of melanoma incidence in Denmark since 2011, in particular for those younger than 40 years, have currently been reported from a study investigating incidence trends in eight susceptible population groups between 1982 and 2015 (Olsen et al., 2018). The authors however stated, that it is still too early to say whether the current melanoma incidence trends in Denmark will be sustained over time.

Projected incidence trends

Future incidence trends have been calculated for both countries from 2014/2018 until 2029/2033. Incidence predictions are usually based on extrapolation of past trends in three time-related variables, age, period and cohort (Bray and Moller, 2006, Moller et al., 2002) and their continuation into future. The statistical model that is most commonly used in incidence predictions is the age-period-cohort model, in which period and cohort effects are proxies for events such as risk factors, which often cannot be measured directly. Age, the third component included in the model, is the most important time-related variable that influences risk of cancer.

In the present analyses, a modified age-period-cohort model with a power link function was used. Assuming that current trends have less impact on later prediction periods, the model allowed for a gradual reduction (0% in the first, 25% in the second, 50% in the third and 75% in the fourth prediction period) of the drift parameter in later periods. As incidence trends showed a significant deviation from the linear trend in more recent periods for males and females in Germany and for females in Denmark, only the trend of the last 10 years was used as drift component to be projected, while for Danish males the average trend over the entire period of observation was used.

Incidence projections for Germany suggest a further increase in age-standardized incidence, signs of a slight leveling off can be expected for males from the mid-2020s onwards. By 2029/2033, the age-standardized incidence rates will rise to a 29.9 in men and to 33.6 /100,000 per year in women. A steeper increase, without any signs of a leveling off is projected for the crude incidence rates. By 2029/2033, crude incidence rates are expected to reach values of 50.1/100,000 per year for men and of 47.4/100,000 per year for women. The predicted increase will initially affect all age groups. Continuously increasing rates are expected for age groups ≥60 years, while men and women younger than 60 years might see a leveling off or even a decrease in incidence rates from 2024/2028 onwards.

Higher incidence increases are expected in Denmark. By 2029/2033, age-standardized incidence rates will increase to 53.6/100,000 per year for men and

to 74.6/100,000 per year for women. Even steeper increases are expected for the crude incidence rates, reaching values of 79.1/100,000 per year for men and of 88.3/100,000 per year for women. A flattening off is not to be expected in the foreseeable future. Rising incidence rates are proposed for all age groups. In contrast to Germany, there are no signs of a leveling off in younger cohorts, neither for men, nor for women.

The projected ongoing increase in crude incidence rates in Germany and Denmark is largely caused by high incidence rates among the elderly and and their growing representation in the population (Statistics Denmark, 2018b, Statistisches Bundesamt Wiesbaden, 2016).

In both countries, incidence rates for age groups ≥60 years will continue to rise. Different trends are supposed for younger cohorts (<60 years). In Germany, it seems likely that screening and prevention campaigns (Breitbart et al., 2012, Waldmann et al., 2012) might cause changes in risk behavior, particularly among younger cohorts, that might be reflected in stable or even declining incidence rates from the mid-2020s onwards. In Denmark, incidence rates in younger cohorts are expected to increase further, signs of stabilization are not to be expected until 2029/2033. Although a large skin cancer prevention campaign, called ‘Reduce your sun’, was introduced about the same time (in 2007) as in Germany, this does not seem to have a significant effect in the near future. The proportion of sunbed user could be reduced by 50% since 2007 (from 22% to 11% in 2012), but using artificial sources of UVR, particularly among young women, is still very common in Denmark (Bay et al., 2015). During the summer of 2010, 41% of the Danish population, reported at least one episode of sunburn, among children and young adults (15-19 years) even 73% were sunburned (Helvind et al., 2015). Prevention campaigns to reduce UVR exposure do not yet appear to be fully implemented, thus more favorable projections for younger cohorts in Denmark are not to be expected in the foreseeable future.

The predicted incidence trends for Germany and Denmark broadly parallel others. (Guy et al., 2015, Mistry et al., 2011, Moller et al., 2002, Weir et al., 2015, Whiteman et al., 2016). The most comprehensive study predicting future

melanoma incidence rates and which most closely resembled the own approach, was carried out by Whiteman et al. (Whiteman et al., 2016). This study predicted incidence rates and numbers of melanoma for six susceptible populations with different patterns of UVR exposure and varying approaches for melanoma control from 2012/2016 until 2027/2031: Australia, New Zealand, the US (Whites), the UK, and for two Scandinavian countries (Norway and Sweden). Except of Australia and New Zealand, where age-standardized incidence rates have already peaked in 2005 or predicted to peak in near future (2012/2016), age-standardized rates in the US and in all European countries are expected to rise at least until 2022/2026, followed by stabilizing or even declining rates thereafter. Age-standardized incidence rates will peak at 25/100,000 per year in the UK, at 32/100,000 per year in the US population, and at around 36/100,000 per year in the Scandinavian countries (Norway and Sweden). However, for all populations, no declines are anticipated in crude incidence rates and for subjects aged 60 years or older in the foreseeable future. Incidence rates among younger cohorts (<60 years) in Australia and New Zealand have already peaked in 2002/2006 and then declined. Similar trends are not to be expected until 2021 for the US and until 2026 for Europe (UK, Norway and Sweden).

In Norway and Sweden, campaigns to reduce the burden of melanoma were already established in the 1990s (Nilsen et al., 2011, Nilsen et al., 2008). They appear to be showing the first signs of success in the near future (Whiteman et al., 2016) or have already done so (de Vries et al., 2003, Erdmann et al., 2013). In Denmark, the first large skin cancer prevention program was not launched until 2007 (Koster et al., 2011). This might explain the expected ongoing increase among younger people in Denmark.

Impact of changes in exposure to UVR on melanoma incidence trends

Exposure to UVR is a well-established risk factor for melanoma development (Gandini et al., 2005b, Gilchrest et al., 1999). In 2009, the IARC confirmed that there is sufficient evidence that solar radiation causes CM, SCC, and BCC, and declared UVR as carcinogenic for humans (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012) .

The mechanisms by which UVR causes cutaneous melanoma are well understood. The main intracellular target for UVR is DNA (Gilchrest et al., 1999). Ultraviolet B radiation is responsible for the formation of the principal DNA lesions, cyclobutane pyrimidine dimers (CPD) and pyrimidine (6-4) pyrimidone photoproducts (Freeman et al., 1989, Mitchell et al., 1991), whose incorrect repair leads to base mutations of cytidine to thymidine (C>T or CC>TT), which are considered as 'UV signature mutations' (Matsumura and Ananthaswamy, 2002). Ultraviolet A radiation causes oxidative DNA damage that is also potentially mutagenic, or it leads to immunosuppression that prevents the immunologic rejection of nascent ultraviolet induced skin cancers (Ichihashi et al., 2003).

UVR exposure during childhood seems to be the main factor to induce mutations in the melanocytic system associated with an increased induction of melanocytic nevi and later on an increased risk for the development of malignant melanoma (Leiter and Garbe, 2008, Whiteman et al., 2001). A longitudinal study of 1,232 German children (2-7 years of age) has shown that higher numbers of incident nevi were associated with host factors like light skin complexion (skin Type II vs. IV, $p=0.022$) and freckling of the face ($p<0.001$), with environmental factors like intermittent-high sun exposure during holidays ($p<0.001$) and chronic-moderate ultraviolet radiation at home ($p=0.007$), and with sunburns ($p=0.005$) (Bauer et al., 2005). Whether nevi, especially clinically atypical nevi, are precursors for melanoma however remains a matter of debate. Pathology-based studies have found that only 20-30% of melanoma contain nevus cells, suggesting a direct transformation of a nevus into melanoma. The majority of melanomas (70-80%), arise de novo, with no

associated nevus (Cymerman et al., 2016, Haenssle et al., 2016, Shain et al., 2015).

Quantifying the numbers and proportion of melanoma cases attributable to UVR exposure and which could be prevented by reducing UVR exposure plays an important role in cancer control planning.

The central research question of the present project was ‘How many cases of melanoma are caused by UVR exposure?’ This question addressed two different aspects. First, the proportion of melanoma cases that can be attributed to high background levels of UVR in the population, the so-called ‘baseline risk’, and second the increase of melanoma cases attributable to changes in risk behavior, namely increase in UVR exposure, over time.

In a first step, an approach described in previous studies (Parkin et al., 2011a) was used to calculate the population attributable fraction and numbers of melanoma cases due to ambient UVR (at baseline). For this purpose, observed melanoma incidence rates at baseline were compared with those of a ‘minimally-exposed’ or low-incidence reference population, attributing differences in melanoma cases to corresponding differences in UVR exposure between the reference and study population.

In the literature, there are a series of different reference populations described. Detailed information of commonly used reference populations, including their criteria for selection is given in the method section (2.2.4). Frequently used reference populations are, for example, historical cohorts that are believed to have been minimally exposed to the sun, or dark skinned populations whose risk of melanoma is naturally lower. Melanoma incidence rates for these reference populations are usually in the range between 1-5 cases per 100,000/year.

In the present analysis the incidence rates from a historical Danish cohort of the years 1943-1947 was used as reference population. In this period the (age-standardized) incidence rates were 1.3/100,000 for men and 1.5/100,000 per year for women.

For Germany, the proportion of UVR-induced melanomas at baseline (1995/1998) was estimated at 84.4% for women and at 87.3% for men. In

Denmark, the proportion of melanomas diagnosed at baseline (1980/1983) was slightly higher in women (86.8%) compared to men (85%). Estimates for the PAF, retrieved from this study, are in line with those published from other studies (Armstrong and Kricker, 1993, Arnold et al., 2018a, Olsen et al., 1997, Winther et al., 1997). The estimated PAFs for white-skinned Caucasian populations were between 80% and 90%, depending on the reference population used to calculate the PAF.

First estimates for the global melanoma burden caused by UVR was provided by Armstrong and Kricker in the early 1980s (Armstrong and Kricker, 1993). To calculate the PAF, they compared rates of melanoma in US Blacks (for 1985) with incidence rates of 24 standard regions of the world. Although the estimates varied by region, they concluded that approximately 65% of all melanomas worldwide have been caused by UVR. The highest proportion of melanomas attributable to UVR were found in Oceania (94%) and North America (90%). Similar high proportions (92-94%) were also calculated for the Scandinavian countries (Finland and Denmark) and Switzerland. Lower proportions were estimated for South and Eastern Europe, ranging between 78% and 87%. Very low proportions of melanoma attributable to UVR, in the range between 3-8%, were described for Africa and Asia (Armstrong and Kricker, 1993).

A higher PAF for the global burden of melanoma due to UVR was described by Arnold et al. in a recent study from 2018. Using the Birth Cohort of 1903 from the UK, he estimated that globally around 168,000 new melanoma cases diagnosed in 2012 were attributable to excess UVR, corresponding to a population attributable fraction of 76%. The proportion of melanoma cases attributable to UVR exposure varied widely across regions, ranging between less than 1% to 96%, with the lowest and highest PAF observed in East Asia and Oceania, respectively. PAFs between 80% and 90% were also estimated for Europe and North America. Within Europe, the values for the PAF showed great variation. The highest PAFs were reported from the Northern (90%) and Western (86%) European countries, lower PAFs were estimated for South (78%) and East (68%) Europe (Arnold et al., 2018a).

First efforts to estimate the melanoma burden attributable to UVR for the Scandinavian countries, have been made by Winther et al. at the end of the 1990s. Following the suggestion of Armstrong and Kricker, they used the incidence rates of melanoma on parts of the body usually not exposed to the sun (i.e. scalp/buttocks) as estimates for an 'unexposed' population and compared these rates with observed (1980-1990) and projected (2000) incidence rates of melanoma for the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden). In 1980 the proportion of melanoma caused by UVR for all Nordic countries together, was estimated at 88% for men, and at 90% for women. Higher proportions (94% for men and 95% for women) were assumed for the year 2000. In Denmark, exposure to UVR accounted for 85% of all diagnosed melanomas among men and for 91% among women in 1980. Corresponding estimates for the year 2000, ranged between 93% for men and 95% for women (Winther et al., 1997).

In a further analysis, Winther et al. have chosen a similar approach as in the present research project. They used incidence rates of malignant melanoma of a Danish cohort from 1940 as an estimate for the incidence rates of melanoma of an 'unexposed' reference population and compared these with incidence rates observed in all Nordic countries together for 1980. Using the latter approach, he found a PAF of 83% for men and of 87% for women, which are close to those found by applying the approach suggested by Armstrong and Kricker (Armstrong and Kricker, 1993).

The second part of the research question on the effects of UVR on melanoma incidence trends was devoted to the increase in melanoma cases due to changes in UVR exposure after the baseline period. For this purpose, current or projected melanoma incidence rates were compared with those that would be expected when the population would have been exposed to ambient levels of UVR experienced by the study population at baseline. The difference in observed/projected and expected number of melanoma cases were then be attributed to changes in UVR exposure. Calculations were based on the method described by Moller et al. in the early 2000s (Moller et al., 2002).

For the estimation in Germany, the period between 1995 to 1998 was defined as baseline period, the following time periods (1999/2003-2029/2033) were considered in 5-year time intervals. During this period, between 83% and 95% of new melanomas were caused by an increase in UVR exposure. This was most evident among women, where between 91% and 95% of all newly diagnosed melanoma cases were attributable to increasing UVR exposure. Slightly lower were the estimates for men, ranging between 83-89%.

In Denmark, the period 1980-1983 was defined as baseline and the increase, following baseline period, was also analyzed in 5-year periods up to 2029/2033. For men, the increase caused by UVR was between 90% and 96%, and for women between 76% and 97%.

These findings are consistent with estimates published by Whiteman et al. (Whiteman et al., 2016). He estimated the numbers and proportion of newly diagnosed melanoma cases attributable to changes in risk and demographics for six populations between 1987/1991 and 2027/2031, using the years 1982-1986 as baseline period. Within the European countries, the highest increase due to UVR was calculated for the United Kingdom (around 92%), somewhat lower were the corresponding estimates for the Scandinavian countries, ranging between 76-87% for Norway and between 79-89% for Sweden, respectively. In the white US population, the increase in melanoma caused by UVR was estimated to range between 73-81%. In Australia and New Zealand, successfully implemented prevention programs could reduce the proportion of new melanoma cases attributable to UVR from 72% in 1987/1991 to 49% in 2027/2031 and from 76% to 67%, respectively.

Finally, to illustrate temporal trends of the melanoma burden attributable to UVR in Germany and Denmark, the population attributable fraction of melanomas due to UVR at baseline and their increase in the further course were summarized, Tables 16a/b and Tables 22a/b. In Germany, the proportion of melanoma attributable to UVR is proposed to increase from 87% in 1995/1998 to 89% in 2029/2033 in men and from 84% to 92% in women. In Denmark, the PAFs for males will rise from 85% in 1980/1983 to 94% in 2029/2033 and in females from 87% to 96%, respectively.

Impact of demographic changes on melanoma incidence trends

Age plays an important role in the pathogenesis of melanoma. Although occurring at an earlier age (median age at diagnosis is 55 years) than most other malignant tumors, the risk of being diagnosed with melanoma increases with age (Garbe and Leiter, 2009, Robert Koch Institut Berlin, 2017). Aging characterizes the cumulative exposure of the body to carcinogens over time, and the accumulation of series of mutations that are necessary for unregulated cell proliferation that leads to cancer. Further, it influences the host response to injury and there is an age associated decrease in the capacity to repair DNA and to remove UVR-induced photoproducts from UVR-irradiated skin, resulting in an increase in the rate of mutations (Goukassian et al., 2000, Moriwaki et al., 1996).

In most western countries life expectancy has significantly increased over the last decades. In 1950 life expectancy in Germany was 64 years for men and 68.5 years for women, in Denmark life expectancy was 68 years for men and 70 years for women. For 2010, life expectancy in both countries was 77 years for men and about 82 years for women. Increasing life expectancy and declining birth rates, have caused a significant shift in the age distribution of the population towards higher proportions of older people. In Germany, in 1995/1998 the proportion of the people older than 60 years was 18% for men and 25% for women. Until 2029/2033 their proportion will rise to 33% for men and to 38% for women. In Denmark, in 1980/1983 the proportion of the those aged >60 years was 18% for men and 22% for women, by 2029/2033 the proportion will rise to 30% for men and to 34% for women (Statistics Denmark, 2018b, Statistisches Bundesamt Wiesbaden, 2015b, 2016).

The second research question was devoted to the impact of demographic changes on past, present and future incidence rates of melanoma in Germany and Denmark.

The influence of age on the increase in the incidence of melanoma becomes most apparent when comparing the percentage increase in crude incidence rates, which accounts for the additional effect of demographic aging, with the corresponding increase in the age-standardized incidence rates. For this

purpose, the percentage increase between baseline rates (Germany: 1995/1998 and Denmark: 1979/1983) and end of observation (2009/2013) was determined for crude and age-standardized incidence rates.

In Germany, between 1995/1998 and 2009/2013 the crude incidence rates increased by +145% for men and by +111% for women. Age-standardized rates increased in the same period by +95% for men and by +96% for women, respectively. In Denmark, the increase in crude incidence rates between 1979/1983 and 2009/2013 was about +324% in men and about +240% in women. In the same period, age-standardized incidence rates have risen by +247% among men and by +204% among women. The additional effect of age incorporated in the crude incidence rates explain their stronger relative increase (between baseline and end of observation) compared to those observed in age-standardized rates.

To gain more insight into the melanoma burden across different age groups, the relative increase in numbers of melanomas between baseline and subsequent periods has been calculated for four different age groups (<40 yrs, 40-59 yrs, 60-79 yrs, and 80+ yrs).

In both countries, the strongest increase until 2029/2033 will be seen for patients aged ≥60 years, particularly among elderly (80+ years) men. In Germany, the number of melanoma cases in this age group will rise by +1,140%, significantly lower (around +100%) will be the increase in men younger than 60 years. Among females, the proposed increase will be less pronounced, ranging between +116% in the age group <40 years and +390% for the age group 60-79 years. The same trends are anticipated for Denmark for the time period between 1980/1983 and 2029/2033. In this period, the expected number of melanoma cases in men will rise by +367% for those younger than 40 years and by +3,630% for the elderly (80+ years). In women, the steepest growth will also be seen in the age group 80+ years (+1,710%), significantly rising numbers of melanoma cases however are also expected for young and middle-aged women, ranging between +550% (<40 years) and +572% (40-59 years).

The sharp increases in the age groups ≥60 years will lead to a significant shift in the age structure of melanoma patients in future, most notably among men. In Germany, the proportion of melanoma patients aged ≥60 years will increase from 47% in 1995/1998 to 77% in 2029/2033 in men, and from 48% to 61% in women. In Denmark, their proportion will rise from 44% in 1980/1983 to 70% for men and from 41% to 50% for women.

To quantify the impact of demographic changes on melanoma incidence trends, the increase in the number and proportion of melanoma cases attributable to changes in population structure (changes in age distribution and size) have been calculated. For this purpose, the number of melanoma cases observed at baseline were compared with those that one would expect when baseline rates would be applied to future population size and age distribution. The difference between expected and observed melanoma cases were then be attributed to demographic changes. Calculations were based on the method described by Moller et al. (Moller et al., 2002).

For Germany, the years 1995-1998 were defined as baseline period. The following time periods between 1999/2003 and 2029/2033 were considered in 5-year periods. In men, demographic changes accounted for 11-17% of the increase in melanoma cases between 1999/2003 and 2029/2033, and in women for 5-9%, Tables 14a/b.

In Denmark, the period 1980-1983 was defined as baseline and the increase, following baseline period, was also analyzed in 5-year periods up to 2029/2033. Among men, 4-11% of all newly diagnosed melanoma cases between 1984/1988 and 2029/2033 could be attributed to demographic changes. Among women, the increase in melanoma cases caused by demographic aging, significantly decreased from 24% in 1984/1988 to 3% in 2029/2033, Tables 20a/b.

Similar results were reported by Whiteman et al. (Whiteman et al., 2016). In Europe, demographic changes accounted for 8-24% of the observed or projected increase in melanoma cases between 1987/1991 and 2027/2031 (UK: 8%, Sweden: 11-21%, Norway: 13-24%). Slightly higher proportions were estimated for the US (19-27%). Exceptions were Oceania. In New Zealand,

demographic changes contributed to 33% and in Australia to 51% of all newly diagnosed melanoma cases between 1987/1991 and 2027/2031.

These findings suggest that demographic changes have less impact on melanoma incidence trends than UVR exposure. The impact of demographic changes on cancer incidence trends depends largely on the age at tumor diagnosis. In general, the higher the median age of onset, the stronger the influence of demographic changes on incidence trends. Unlike epithelial skin tumors (BCC and SCC), which predominantly occur at an advanced age, melanoma can already be diagnosed early in life (Leiter et al., 2014, Weir et al., 2011). This relationship is well illustrated in a study from the Netherlands (de Vries et al., 2005). This study investigated the incidence trends of three different types of skin cancer with different disease ages (CM, BCC, SCC) and estimated the contribution of risk and demographic changes to the increase in incidence. While demographic changes accounted for 51% of the expected increase in BCC and for 61% in SCC incidence, only 17% of the projected increase in melanoma incidence could be attributed to demographic changes.

The different age at which melanomas and epithelial tumors are diagnosed, results from different responses of melanocytes and keratinocytes to damaging UVR (Gilchrest et al., 1999). After sun exposure, the severely damaged keratinocytes undergo apoptosis, leaving the less damaged keratinocytes to upregulate their DNA-repair capacity and to undergo nearly perfect repair (Norris et al., 1997, Polakowska et al., 1994). The skin tans, providing protective melanin to surrounding keratinocytes. Frequent subsequent exposure to UVR within the SOS-response period will enhance the increases in repair capacity and melanin content, and minimizing, but not eliminating the cumulative mutational damage in the keratinocytes. In contrast, first high dose of UVR will cause substantial damage to melanocytes, but no apoptosis. Their high content of anti-apoptotic proteins (i.e. Bcl-2) prevents them from apoptosis (Rodriguez-Villanueva et al., 1995). The melanocytes will survive and accumulate UVR-induced DNA mutations, so that even in childhood or adolescence melanomas can develop (Gilchrest et al., 1999).

Finally, the numbers and proportion of melanoma caused by demographic aging at baseline and in the further course were summarized, Tables 16a/b and Tables 22a/b. In Germany for the time period 1995/1998-2029/2033, the proportion of melanoma cases attributable to demographic changes ranged between 11-15% among men and between 8-16% among women, Tables 16a/b. In Denmark, demographic changes accounted for 6-15% of all melanomas diagnosed between 1980/1983 and 2029/2033 among men, and for 4-13% among women, Tables 22a/b.

In both countries, most of the increase (≥80%) in the numbers of persons diagnosed with melanoma were attributable to increasing UVR exposure rather than to demographic aging (<20%).

Outlook

Incidence predictions suggest an ongoing increase of melanoma incidence rates at least until the mid 2020s. In Germany, first signs of a leveling off in increase can be expected from 2024/2028 onwards among men. In Denmark, a further strong increase is anticipated for both sexes. The expected increase will initially be noticeable in all age groups. In Germany, the increase in younger age groups (<60 years) is expected to level off from the mid-2020s onwards. In both populations, a strong increase is expected in the older age groups (60+ years) without any signs of stabilization. The long latency period from exposure to carcinogenic risk factors (such as UVR) and clinical presentation (20-30 years) may explain the ongoing increase in incidence for those aged 60+ years. This increase reflects a part of the population who have already accumulated enough amounts of UVR during their life time, which is necessary for malignant transformation.

Incidence predictions for a longer period (≥20 years) are difficult, as they would need to incorporate any changes in risk behavior (reduced exposure to UVR) into their calculations. In most European countries and in the US, however, prevention campaigns aimed to combat skin cancer, do not yet appear to be universally effective. They show only modest improvements in attitudes and behavior regarding tanning, sunburn, use of protective clothing or sunscreen so

far (de Haas et al., 2010, Ettridge et al., 2011, Health and Human, 2014, Lazovich et al., 2012, Montague et al., 2001). Surveys of European young in recent years revealed that many Europeans go on holidays in sunny destinations with the expressed aim of sunbathing and getting a tanned skin. Among vacationers returning from their holidays, a relatively high proportion reported sunburn, indicating frequent intermittent sun exposure. Moreover, there seems to exist a widespread misconception about how to protect the skin from sun exposure. While sunscreen products were frequently used, wearing protective clothing and seeking for shade were less practiced (Petersen et al., 2013, Petersen et al., 2015, Reinau et al., 2014). Even if prevention campaigns will lead to behavioral changes in some population groups, the time span between changes in risk behavior and their reflection on declining incidence rates is long. Therefore we may not see the full impact of primary measures in the near future.

Nevertheless, examples from Australia and New Zealand have shown that sun protection campaigns can be successful if they last long enough and are widely spread in the population (Erdmann et al., 2013, Whiteman et al., 2016). In both countries, first skin cancer prevention programs, including children and adolescents as an important target group, have been introduced in the early 1980s (Iannacone and Green, 2014, Montague et al., 2001). These programs involved a number of important sun protection measures such as wearing hats and sun protective clothing, using sunscreen, minimizing the time children spend outdoors during peak hours or providing shadow zones (Ettridge et al., 2011, Montague et al., 2001). As a result, a flattening of incidence growth is already becoming apparent in Australia and New Zealand, most notably among younger cohorts (Iannacone and Green, 2014, Iannacone et al., 2015, Whiteman et al., 2016).

Similar trends are not discernible neither in Germany nor in Denmark. For this reason, it seems to be likely that the incidence of melanoma in both countries will continue to rise for the foreseeable future, and probably beyond 2030. To combat UVR-induced melanoma burden, we should learn from the public health campaigns in Australia and New Zealand geared toward reducing UVR

exposure. In Germany and Denmark continuing efforts to promote skin cancer prevention and risk modification are needed. Only a more prudent attitude towards tanned skin and a sustainable change in UVR exposure might result in more promising trends after 2030s.

Strengths and limitations:

This study is the first to quantify the melanoma burden due to changes in UVR exposure and demographics in Germany by calculating the corresponding population attributable fractions (PAF). Previous estimates for Denmark, carried out by Winther et al. in 1997 (Winther et al., 1997), have been updated using the most recent incidence data for melanoma. To estimate the melanoma burden due to UVR, melanoma incidence data from a historical Danish cohort (1943/1947), was used as reference population. This has the advantage that both the study and reference population represent identical ethnic groups with the same genetic risk for melanoma. This minimizes any bias resulting from confounders unrelated to UVR.

Main strengths of the present study are the comprehensive nature with detailed data analyses based on high quality data from two population-based cancer registries (Engholm et al., 2010, Robert Koch Institut Berlin, 2016). A high completeness in the data can be assumed for both Germany and Denmark. The coverage rate in Denmark is close to 100% due to mandatory cancer notification. In Germany, the coverage rate was 90% in 11 federal states for the year 2012. Less than 2% of the melanoma cases, reported to the registries, were notified by death certificate only (DCO). Both, high coverage rate and low proportion of cases reported by DCO, guarantee a high quality of the data. Cancer incidence data for Denmark are provided over a long period of time. In Scandinavia, cancer registration began in the early 1940s, so that melanoma incidence data for Denmark have been available since 1943, covering a period of seven decades (Engholm et al., 2010, Gjerstorff, 2011).

Incidence trend analyses have been preformed for a series of different measures, including age-standardized and crude incidence rates as well as absolute numbers of melanoma cases. This has allowed to analyze incidence trends from both epidemiological (impact of UVR as the main risk factor for

melanoma) and demographic (impact of population aging) perspectives. The impact of risk exposure was assessed by applying age-standardized incidence rates. Crude incidence rates and absolute numbers of melanoma cases were used to account for the impact of aging on incidence trends.

The present study has several limitations. First, as for every statistical model, joinpoint regression relies on some assumptions (Kim et al., 2000), whose violation may result in biased estimates. Linear regression, used to fit the data, assume a linear relationship between the outcome variable (incidence rates) and the considered time variable. Further, different parameter settings may lead to differences in model selection (location and number of joinpoints), producing different incidence trends. Second, incidence predictions always carry some uncertainty with them. They are a mathematical extrapolation of past trends assuming that the same trend will continue into the future, and are intended to illustrate future changes that might be expected to occur if the assumptions were to apply over the prediction period. Projections do not attempt to allow for future changes in detection methods (such as the introduction of new screening programs) or changes in risk factors beyond the base years of the model which may affect future cancer incidence rates (Bray and Moller, 2006). Present incidence predictions are based on a modified age-period-cohort model, which was developed by Moller et al. (Moller et al., 2002). This model has been tested and validated in the Nordic countries, in Canada, in the UK and other countries, and a series of conditions that lead to the most accurate predictions has been applied (Mistry et al., 2011, Moller et al., 2002, Nowatzki et al., 2011). Supposing that future cancer incidence cannot continue to rise exponentially, the assumption of unchanged trends was modified by attenuating the drift component of the changes in rates by 25%, 50% and 75% for the second, third and fourth projection period. Further, it was assumed that future incidence rates are more likely to be influenced by recent than historical trends. Thus, when joinpoint analyses have shown a significant change in crude incidence rates in the most recently time period, the trend in the last 10 years was used as drift component D to be projected, instead of the average trend of the whole period. The estimates here were presented without standard errors or confidence

intervals, as these would be extremely low due to the large population. The uncertainty associated with incidence predictions concerns the unquantifiable bias when trends in incidence rates behave differently from the underlying assumptions about past rates. Third, forecasted population data used to calculate the absolute numbers of expected melanoma cases in future, are by their nature predictions themselves, based on forecasted birth/death rates and on assumptions about future immigration and emigration levels. Thus, any bias caused by population forecasts cannot completely be ruled out. Fourth, UVR is emitted naturally from the sun, but can also emerge from artificial sources of UVR (i.e. tanning beds or sun lamps), which has also been causally linked to increasing risk for melanoma (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012). The present analysis did not calculate the PAF associated with artificial sources of UVR. Findings from different studies and systematic reviews/meta-analyses suggested that the PAF for this association is negligible on population level, ranging between 2.6% for Australia and 9.4% for Europe (Arnold et al., 2018b, Gandini et al., 2014, Wehner et al., 2014). In some high-risk countries such as the U.S. or Northern and Western Europe, however, where the prevalence of indoor tanning in young adults has been increasing, exposure to tanning devices may account for up to 10-15% of all diagnosed melanoma cases (Boniol et al., 2012). This should not be disregarded when quantifying the melanoma burden caused by UVR. In addition, as most sunbed users have also a tendency to show greater exposure to natural sunlight (Grange et al., 2015), it is difficult to disentangle the melanoma burden caused by artificial UVR exposure from that of natural sunlight. Finally, underreporting of melanoma diagnosis to cancer registries might be a further limitation of the present analyses. A comprehensive cancer registration in Germany does not exist until 2011. Although the majority of registries now have a coverage rate of ≥90% and can thus be considered almost complete, there were still some registries in 2012 with a lower coverage rate for which the incidence rates had to be estimated on the basis of the complete registries. A certain degree of underreporting cannot be excluded also for Denmark, especially in the early 1940s. But this shortcoming may be

compensated by overreporting and increasing detection of thin melanoma, related to screening or improved diagnostics.

The literature review revealed a lack of research investigating the impact of UVR exposure and demographic changes on previous and future melanoma incidence trends in Germany and Denmark.

This study observed trends of increasing melanoma incidence in Germany (1995-2013) and Denmark (1943-2013). Rising incidence rates were obvious in all age groups, most pronounced in men and women aged 60 years or older. In both countries, overall melanoma incidence is destined to increase for the next two decades (2014-2033). In Germany, rates appear to stabilizise or to decline among young men and women (<60 yrs) from the mid-2020s onwards. Strongly rising incidence rates in older people and their growing representation in the population will further increase the burden of melanoma in the future. Nevertheless, the proportion of melanomas attributable to demographic changes is rather small (PAF≤15%). Melanoma seems to be less influenced by demographic aging than other malignant skin tumors, such as BCC or SCC, due to its earlier age of onset. UVR remains the most important causal risk factor for melanoma and is responsible for the majority of melanomas diagnosed in the past or in the future (PAF: 85-96%).

In conclusion, this study provides further evidence for the predominant role of UVR exposure in the causation of melanoma. Although demographic change will continue to push forward the future burden of melanoma, it will play a rather subordinate role. Since UVR is a modifiable risk factor, a large number of melanoma cases could in principle be prevented by eliminating or reducing the causative factor. This harbors a high potential for primary skin cancer prevention. Key interventions must include educational campaigns that promote an enhanced awareness for melanoma and emphasize the importance of changing the behavior to reduce the exposure to UVR. As childhood and adolescence is the most critical window for melanoma development, younger cohorts are an important target group for primary melanoma prevention. Since the increase in melanoma incidence in older populations is likely be caused by previous sun exposure, primary prevention seems to be less effective in this

group. In order to counter the effects of an aging population, efforts in secondary prevention (screening and early detection) should therefore be continued and targeted at people over 60 years of age.

5 Summary

Background:

The incidence of cutaneous melanoma (CM) has steadily increased over the past 50 years in predominantly fair-skinned populations. The observed increase is largely attributed to increasing risk exposure (UV radiation) and to demographic changes. While rates in Northern America and Oceania seem to have leveled off in recent years, particularly in younger cohorts, melanoma rates in most European countries continue to rise. The continual increase in incidence rates in higher age groups and their growing presence in the population will lead to a further sharp increase in the number of melanoma cases in the future. Estimating melanoma incidence trends and identifying the main forces (risk exposure and demographic changes) that might drive these trends are crucial for targeted cancer control measures aimed to reduce future melanoma burden.

Objectives:

To investigate the impact of UVR exposure and demographic changes on past/present incidence trends of CM and to estimate the future melanoma burden according to these changes for Germany and Denmark.

Material and Methods:

Melanoma incidence data (ICD-10, C43) for Germany (1995-2013) and Denmark (1943-2013) were retrieved from the Center for Cancer Registry Data (CCRD) at the Robert Koch-Institute and from the NORDCAN database. Historical (1980-2013) and projected population data (2014-2033) were sourced from national statistics agencies. Incidence trends (Germany: 1995-2013; Denmark: 1944-2013 and 1980-2013) were analyzed using joinpoint regression and quantified by calculating the estimated annual percentage change (EAPC) and its 95% confidence intervals. The number of future melanoma cases and incidence rates (2014/2018-2029/2033) were projected using modified age-period-cohort models. The increase in the number of melanoma cases was apportioned into contribution from change in population risk (UVR exposure) and changes in population size and age structure (demographic component).

The numbers of melanomas attributable to high ambient levels of UV radiation at baseline (Germany: 1995/1998; Denmark: 1980/1983) were calculated by comparing baseline incidence rates (IRs) with those of a historical Danish cohort (1943/1947), minimally exposed to UVR. The analyses were carried out for age-standardized (ASIR) (European Standard Population, WHO 1976), crude (CIR) and age-specific (<40 yrs, 40-59 yrs, 60-79 yrs, 80+ yrs) incidence rates, recorded as 100,000 persons per year and stratified by sex.

Results:

The incidence of CM in Germany and Denmark has steadily increased during the past and will continue to do so for the foreseeable future. Between 1995/1998 and 2009/2013, the ASIRs in Germany almost doubled to 19.7/100,000 for men and to 19.4/100,000 for women. In Denmark, ASIRs increased for both sexes from less than 2 cases per 100,000 in 1944/1948 to 29.8 for men and to 34.3/100,000 per year for women in 2009/2013. IRs increased in all age groups. Sharp increases were noted for those aged 60+, particularly among men. Until 2029/2033, ASIRs in Germany will climb to ≥30 cases/100,000 (men: 29.9; women: 33.6). ASIRs in men will probably stabilize from 2024/2028 onwards. In Denmark, the ASIRs will reach 53.6 cases for males and 74.6 cases/100,000 for females. Stronger increases, without a leveling off, are expected for the CIRs and for those aged 60+ yrs, particularly for men. While IRs in people under 60 will stabilize or decline from the mid 2020s onwards in Germany, IRs in age groups ≤60 yrs will continue to rise in Denmark. Steeply rising IRs in higher age groups and population aging will significantly increase the number of melanoma cases in future. Until 2029/2033, their number will reach about 40,000 (men: 20,161; women: 19,397) in Germany and about 4,500 (men: 2,015; women: 2,484) in Denmark. Strong increases among those aged 60+ yrs, most evident among men (80+ yrs: Germany, 1995/1998-2029/2033: +1,140%; Denmark, 1980/1983-2029/2033: +3,627%) will change the age distribution of melanoma patients towards higher proportion of old and very old patients. In Germany, the number of patients aged 60+ yrs will rise from less than 50% (for both sexes) in 1995/1998 to 77% for men and to 61% for women in 2029/2033. In Denmark, their proportion will

increase to around 70% for males and to 50% for females. Nevertheless, the contribution of demographic aging to the increase in melanoma cases at population level will be rather small (5-11% for men and about 5% for women for the period 2009/2013-2029/2033). In both populations, most of the increase in number of melanoma cases will be attributable to increasing UVR exposure, particularly among women (Germany: 90-95%, Denmark: 76-97%). Overall, including the number of melanomas attributable to high ambient UVR level at baseline, the population attributable fraction (PAF) of melanomas caused by UVR exposure in Germany will range between 84-92% for women and between 87-89% for men. Corresponding estimates for Denmark are: 85-96% (women) and 85-95% (men).

Conclusion:

In both populations, melanoma burden will increase in future. Most of the expected increase (80-97%) in melanoma diagnoses will be attributable to increasing exposure to UVR rather than to demographic aging. Since UVR is the only known modifiable risk factor for melanoma, a large number of melanoma cases could be prevented by reducing exposure to UVR. In order to steam the future melanoma burden, primary prevention should remain the cornerstone of melanoma control efforts. To counter the effects of an aging population, secondary prevention will be another important component for future melanoma control.

Zusammenfassung

Hintergrund:

Die Inzidenz des kutanen Melanoms hat in den letzten 50 Jahren stetig zugenommen, insbesondere in hellhäutigen Populationen. Der beobachtete Anstieg ist weitgehend auf die zunehmende Risikoexposition (UV-Strahlung) und den demografischen Wandel zurückzuführen. Während sich die Raten in Nordamerika und Ozeanien in den letzten Jahren, insbesondere in jüngeren Kohorten, offenbar stabilisiert haben, steigen die Melanomraten in den meisten europäischen Ländern weiter an. Der kontinuierliche Anstieg der Inzidenzraten in höheren Altersgruppen und deren wachsende Präsenz in der Bevölkerung wird die Zahl der Melanomfälle in Zukunft deutlich erhöhen. Eine Abschätzungen zukünftiger Inzidenztrends, insbesondere wie stark diese Entwicklungen von der Sonnenexposition und dem demografischen Wandel getrieben werden, sind für gezielte Kontrollmaßnahmen zur Verringerung der Melanombelastung von entschiedender Bedeutung.

Zielsetzung:

Untersuchungen zur Auswirkungen von UV Exposition und demografischem Wandels auf vergangene/gegenwärtige Inzidenztrends des kutanen Melanoms und Abschätzung wie stark diese Faktoren die zukünftige Melanombelastung in Deutschland und Dänemark beeinflussen werden.

Material und Methoden:

Melanom-Inzidenzdaten (ICD-10, C43) für Deutschland (1995-2013) und Dänemark (1943-2013) wurden aus dem Zentrum für Krebsregisterdaten (ZfKD) des Robert Koch-Instituts sowie aus der NORDCAN-Datenbank extrahiert. Historische (1980-2013) und projizierte Bevölkerungsdaten (2014-2033) wurden von den nationalen statistischen Bundesämtern bezogen. Die Inzidenztrends (Deutschland: 1995-2013; Dänemark: 1944-2013 und 1980-2013) wurden mittels Joinpoint-Regression analysiert und quantifiziert, indem die geschätzte jährliche prozentuale Veränderung (EAPC) und ihre 95% Konfidenzintervalle berechnet wurden.

Die Anzahl der zukünftigen Melanomfälle und Inzidenzraten (2014/2018-2029/2033) wurden mit Hilfe modifizierter Alter-Perioden-Kohorten-Modelle prognostiziert. Der Anstieg der Melanomfälle wurde in zwei Anteile unterteilt: (1) Veränderungen im Risikoverhalten der Bevölkerung (erhöhte UV Exposition), (2) demografischer Wandel. Um die Anzahl der Melanome zu bestimmen, die auf die geografisch bedingte UV Strahlung zurückzuführen ist, wurden die Inzidenzraten zu Beobachtungsbeginn (Deutschland: 1995/1998; Dänemark: 1980/1983) mit denen einer historischen Kohorte aus Dänemark (1943/1947) verglichen, die einer minimalen Sonnenexposition ausgesetzt war. Die Analysen wurden für altersstandardisierte (ASIR) (Europäische Standardbevölkerung, WHO 1976), rohe (CIR) und altersspezifische (<40 Jahre, 40-59 Jahre, 60-79 Jahre, 80+ Jahre) Inzidenzraten durchgeführt, die als 100.000 Personen pro Jahr erfasst und nach Geschlecht geschichtet wurden.

Ergebnisse:

In Deutschland und in Dänemark sind die Inzidenzraten des kutanen Melanoms in den vergangenen Jahren stetig angestiegen. Dieser Anstieg wird sich in den nächsten Jahren weiter fortsetzen. Zwischen 1995/1998 und 2009/2013 haben sich die alterstandardisierten Inzidenzraten in Deutschland nahezu verdoppelt, bei Männern auf 19,7/100.000 und bei Frauen auf 19,4/100.000. In Dänemark stiegen die ASIRs für beide Geschlechter von weniger als 2 Fällen pro 100.000 in den Jahren 1944/1948 auf 29,8 für Männer und auf 34,3/100.000 für Frauen in den Jahren 2009/2013. Die Inzidenzraten sind in allen Altersgruppen gestiegen. Starke Zuwächse wurden bei Personen über 60 Jahre verzeichnet, insbesondere bei den Männern. Bis 2029/2033 werden in Deutschland die ASIRs auf ≥30 Fälle/100.000 (Männer: 29,9; Frauen: 33,6) ansteigen. Bei den Männern ist ab 2024/2028 mit einer Stabilisierung der ASIRs zu rechnen. In Dänemark werden die ASIRs 53,6 bei den Männern und 74,6 Fälle/100.000 bei den Frauen erreichen. Stärkere Anstiege, ohne Anzeichen einer Abflachung, werden für die rohen Raten, sowie für die Inzidenzraten bei den ≥60-Jährigen erwartet, insbesondere bei den Männer. Während sich die IRs in Deutschland bei den unter 60-Jährigen ab Mitte der 2020er Jahre stabilisieren oder sogar zurückgehen werden, werden diese in Dänemark (in den Altersgruppen ≤60

Jahre) weiter ansteigen. Stark zunehmende IRs in höheren Altersgruppen und ihr wachsender Anteil in der Bevölkerung werden zu einem deutlichen Anstieg der Melanomfälle in Zukunft führen. Bis 2029/2033 wird die Anzahl der Melanomfälle in Deutschland auf ca. 40.000 (Männer: 20.161; Frauen: 19.397) und in Dänemark auf ca. 4.500 (Männer: 2.015; Frauen: 2.484) steigen. Starke Zunahmen bei den über 60-Jährigen, am deutlichsten bei den Männern (80+ Jahre: Deutschland, 1995/1998-2029/2033: +1.140%; Dänemark, 1980/1983-2029/2033: +3.627%) wird die Altersstruktur der Melanompatienten verschieben und den Anteil an alten und sehr alten Patienten deutlich erhöhen. In Deutschland wird die Anzahl der Patienten ≥60 Jahre von weniger als 50% (für beide Geschlechter) in den Jahren 1995/1998 auf 77% für Männer und auf 61% für Frauen in den Jahren 2029/2033 ansteigen. In Dänemark wird sich ihr Anteil auf rund 70% für Männern und auf 50% für Frauen erhöhen. Dennoch ist der Anteil der demografischen Alterung am Anstieg der Melanomerkrankungen auf Bevölkerungsebene eher gering sein (5-11% für Männer und etwa 5% für Frauen im Zeitraum 2009/2013-2029/2033). In beiden Bevölkerungen wird der Hauptanteil des Melanomanstiegs auf zunehmende UV-Exposition zurückzuführen sein, insbesondere bei den Frauen (Deutschland: 90-95%, Dänemark: 76-97%). Insgesamt, einschließlich der durch die geografische Lage bedingten UV Strahlung, wird der Anteil an Melanomen, der durch Sonnenexposition verursacht wird, in Deutschland zwischen 84-92% bei den Frauen und zwischen 87-89% bei den Männern liegen. Die entsprechenden Schätzungen für Dänemark liegen bei 85-96% (Frauen) bzw. bei 85-95% (Männer).

Schlussfolgerung:

In beiden Populationen wird die Melanombelastung in Zukunft zunehmen. Der größte Anteil des zu erwartenden Anstiegs (80-97%) wird auf zunehmende Sonnenexposition zurückzuführen sein und nur zu einem geringen Anteil auf die demografische Alterung. Da UV Strahlung der einzige bekannte modifizierbare Risikofaktor für das Melanom ist, könnte eine große Anzahl an Melanomfällen durch eine geringere UV-Exposition verhindert werden. Um die zukünftige

Melanombelastung zu begrenzen, sollte die Primärprävention der Eckpfeiler der Melanomkontrolle bleiben. Um den Auswirkungen einer alternden Bevölkerung entgegenzuwirken, wird die Sekundärprävention ein weiterer wichtiger Bestandteil der zukünftigen Melanomkontrolle sein.

6 List of references

Abern MR, Tsivian M, Coogan CL, Kaufman HL, Polascik TJ. Characteristics of patients diagnosed with both melanoma and renal cell cancer. Cancer Causes Control 2013;24(11):1925-33.

AIHW. AIHW Australian Institute of Health and Welfare: Cancer Incidence Data, available at: https://www.aihw.gov.au/reports/; 2018 [accessed 20 March 2018].

Aitken JF, Youlden DR, Baade PD, Soyer HP, Green AC, Smithers BM. Generational shift in melanoma incidence and mortality in Queensland, Australia, 1995-2014. Int J Cancer 2018;142(8):1528-35.

Anderson WF, Pfeiffer RM, Tucker MA, Rosenberg PS. Divergent cancer pathways for early-onset and late-onset cutaneous malignant melanoma. Cancer 2009;115(18):4176-85.

Armstrong BK, Kricker A. How much melanoma is caused by sun exposure? Melanoma Res 1993;3(6):395-401.

Arnold M, de Vries E, Whiteman DC, Jemal A, Bray F, Parkin DM, et al. Global burden of cutaneous melanoma attributable to ultraviolet radiation in 2012. Int J Cancer 2018a.

Arnold M, Holterhues C, Hollestein LM, Coebergh JW, Nijsten T, Pukkala E, et al. Trends in incidence and predictions of cutaneous melanoma across Europe up to 2015. J Eur Acad Dermatol Venereol 2014;28(9):1170-8.

Arnold M, Kvaskoff M, Thuret A, Guenel P, Bray F, Soerjomataram I. Cutaneous melanoma in France in 2015 attributable to solar ultraviolet radiation and the use of sunbeds. J Eur Acad Dermatol Venereol 2018b.

Asgari MM, Maruti SS, Kushi LH, White E. A cohort study of vitamin D intake and melanoma risk. J Invest Dermatol 2009;129(7):1675-80.

Autier P, Koechlin A, Boniol M. The forthcoming inexorable decline of cutaneous melanoma mortality in light-skinned populations. Eur J Cancer 2015;51(7):869-78.

Azoury SC, Lange JR. Epidemiology, risk factors, prevention, and early detection of melanoma. Surg Clin North Am 2014;94(5):945-62, vii.

Baade PD, Green AC, Smithers BM, Aitken JF. Trends in melanoma incidence among children: possible influence of sun-protection programs. Expert Rev Anticancer Ther 2011;11(5):661-4.

Barbaric J, Sekerija M, Agius D, Coza D, Dimitrova N, Demetriou A, et al. Disparities in melanoma incidence and mortality in South-Eastern Europe: Increasing incidence and divergent mortality patterns. Is progress around the corner? Eur J Cancer 2016;55:47-55.

Bashir S, Esteve J. Analysing the difference due to risk and demographic factors for incidence or mortality. Int J Epidemiol 2000;29(5):878-84.

Bataille V, Boniol M, De Vries E, Severi G, Brandberg Y, Sasieni P, et al. A multicentre epidemiological study on sunbed use and cutaneous melanoma in Europe. Eur J Cancer 2005;41(14):2141-9.

Bauer J, Buttner P, Wiecker TS, Luther H, Garbe C. Risk factors of incident melanocytic nevi: a longitudinal study in a cohort of 1,232 young German children. Int J Cancer 2005;115(1):121-6.

Bay C, Kejs AM, Storm HH, Engholm G. Incidence and survival in patients with cutaneous melanoma by morphology, anatomical site and TNM stage: a Danish Population-based Register Study 1989-2011. Cancer Epidemiol 2015;39(1):1-7.

Boniol M, Autier P, Boyle P, Gandini S. Cutaneous melanoma attributable to sunbed use: systematic review and meta-analysis. BMJ 2012;345:e4757.

Bradford PT, Anderson WF, Purdue MP, Goldstein AM, Tucker MA. Rising melanoma incidence rates of the trunk among younger women in the United States. Cancer Epidemiol Biomarkers Prev 2010;19(9):2401-6.

Bray F, Moller B. Predicting the future burden of cancer. Nat Rev Cancer 2006;6(1):63-74.

Breitbart EW, Waldmann A, Nolte S, Capellaro M, Greinert R, Volkmer B, et al. Systematic skin cancer screening in Northern Germany. J Am Acad Dermatol 2012;66(2):201-11.

Bulliard JL, Cox B, Semenciw R. Trends by anatomic site in the incidence of cutaneous malignant melanoma in Canada, 1969-93. Cancer Causes Control 1999;10(5):407-16.

Caini S, Gandini S, Sera F, Raimondi S, Fargnoli MC, Boniol M, et al. Meta-analysis of risk factors for cutaneous melanoma according to anatomical site and clinico-pathological variant. Eur J Cancer 2009;45(17):3054-63.

Chang YM, Barrett JH, Bishop DT, Armstrong BK, Bataille V, Bergman W, et al. Sun exposure and melanoma risk at different latitudes: a pooled analysis of 5700 cases and 7216 controls. Int J Epidemiol 2009a;38(3):814-30.

Chang YM, Newton-Bishop JA, Bishop DT, Armstrong BK, Bataille V, Bergman W, et al. A pooled analysis of melanocytic nevus phenotype and the risk of cutaneous melanoma at different latitudes. Int J Cancer 2009b;124(2):420-8.

Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. Lancet 2009;374(9696):1196-208.

Cleaver JE. Cancer in xeroderma pigmentosum and related disorders of DNA repair. Nat Rev Cancer 2005;5(7):564-73.

Clegg LX, Hankey BF, Tiwari R, Feuer EJ, Edwards BK. Estimating average annual per cent change in trend analysis. Stat Med 2009;28(29):3670-82.

Coory M, Baade P, Aitken J, Smithers M, McLeod GR, Ring I. Trends for in situ and invasive melanoma in Queensland, Australia, 1982-2002. Cancer Causes Control 2006;17(1):21-7.

Cymerman RM, Shao Y, Wang K, Zhang Y, Murzaku EC, Penn LA, et al. De Novo vs Nevus-Associated Melanomas: Differences in Associations With Prognostic Indicators and Survival. J Natl Cancer Inst 2016;108(10).

Davies JR, Chang YM, Bishop DT, Armstrong BK, Bataille V, Bergman W, et al. Development and validation of a melanoma risk score based on pooled data from 16 case-control studies. Cancer Epidemiol Biomarkers Prev 2015;24(5):817-24.

de Haas ER, Nijsten T, de Vries E. Population education in preventing skin cancer: from childhood to adulthood. J Drugs Dermatol 2010;9(2):112-6.

de Vries E, Amador JR, Rincon CJ, Uribe C, Parkin DM. Cutaneous melanoma attributable to solar radiation in Cali, Colombia. Int J Cancer 2017;140(9):2070-4.

de Vries E, Boniol M, Dore JF, Coebergh JW. Lower incidence rates but thicker melanomas in Eastern Europe before 1992: a comparison with Western Europe. Eur J Cancer 2004;40(7):1045-52.

de Vries E, Bray FI, Coebergh JW, Parkin DM. Changing epidemiology of malignant cutaneous melanoma in Europe 1953-1997: rising trends in incidence and mortality but recent stabilizations in western Europe and decreases in Scandinavia. Int J Cancer 2003;107(1):119-26.

de Vries E, Coebergh JW. Cutaneous malignant melanoma in Europe. Eur J Cancer 2004;40(16):2355-66.

de Vries E, van de Poll-Franse LV, Louwman WJ, de Gruijl FR, Coebergh JW. Predictions of skin cancer incidence in the Netherlands up to 2015. Br J Dermatol 2005;152(3):481-8.

Downing A, Newton-Bishop JA, Forman D. Recent trends in cutaneous malignant melanoma in the Yorkshire region of England; incidence, mortality and survival in relation to stage of disease, 1993-2003. Br J Cancer 2006;95(1):91-5.

ECIS. ECIS-European Cancer Information System. Data explorer. Incidence and mortality statistics, available at: https://ecis.jrc.ec.europa.eu/; 2018 [accessed 27 May 2018].

Eggermont AM, Spatz A, Robert C. Cutaneous melanoma. Lancet 2014;383(9919):816-27.

El Ghissassi F, Baan R, Straif K, Grosse Y, Secretan B, Bouvard V, et al. A review of human carcinogens--part D: radiation. Lancet Oncol 2009;10(8):751-2.

Elwood JM, Jopson J. Melanoma and sun exposure: an overview of published studies. Int J Cancer 1997;73(2):198-203.

Engeland A, Haldorsen T, Tretli S, Hakulinen T, Horte LG, Luostarinen T, et al. Prediction of cancer incidence in the Nordic countries up to the years 2000 and 2010. A collaborative study of the five Nordic Cancer Registries. APMIS Suppl 1993;38:1-124.

Engholm G, Ferlay J, Christensen N, Bray F, Gjerstorff ML, Klint A, et al. NORDCAN--a Nordic tool for cancer information, planning, quality control and research. Acta Oncol 2010;49(5):725-36.

Erdmann F, Lortet-Tieulent J, Schuz J, Zeeb H, Greinert R, Breitbart EW, et al. International trends in the incidence of malignant melanoma 1953-2008--are recent generations at higher or lower risk? Int J Cancer 2013;132(2):385-400.

Ettridge KA, Bowden JA, Rayner JM, Wilson CJ. The relationship between sun protection policy and associated practices in a national sample of early childhood services in Australia. Health Educ Res 2011;26(1):53-62.

Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136(5):E359-86.

Forsea AM, Del Marmol V, de Vries E, Bailey EE, Geller AC. Melanoma incidence and mortality in Europe: new estimates, persistent disparities. Br J Dermatol 2012;167(5):1124-30.

Freeman SE, Hacham H, Gange RW, Maytum DJ, Sutherland JC, Sutherland BM. Wavelength dependence of pyrimidine dimer formation in DNA of human skin irradiated in situ with ultraviolet light. Proc Natl Acad Sci U S A 1989;86(14):5605-9.

Fuglede NB, Brinck-Claussen UO, Deltour I, Boesen EH, Dalton SO, Johansen C. Incidence of cutaneous malignant melanoma in Denmark, 1978-2007. Br J Dermatol 2011;165(2):349-53.

Gandini S, Autier P, Boniol M. Reviews on sun exposure and artificial light and melanoma. Prog Biophys Mol Biol 2011;107(3):362-6.

Gandini S, Iodice S, Koomen E, Pietro AD, Sera F, Caini S. Hormonal and reproductive factors in relation to melanoma in women: Current review and meta-analysis. Eur J Cancer 2011;47(17):2607-17.

Gandini S, Sera F, Cattaruzza MS, Pasquini P, Abeni D, Boyle P, et al. Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. Eur J Cancer 2005a;41(1):28-44.

Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer 2005b;41(1):45-60.

Gandini S, Sera F, Cattaruzza MS, Pasquini P, Zanetti R, Masini C, et al. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. Eur J Cancer 2005c;41(14):2040-59.

Gandini S, Stanganelli I, Magi S, Mazzoni L, Medri M, Agnoletti V, et al. Melanoma attributable to sunbed use and tan seeking behaviours: an Italian survey. Eur J Dermatol 2014;24(1):35-40.

Gandini S, Stanganelli I, Palli D, De Giorgi V, Masala G, Caini S. Atopic dermatitis, naevi count and skin cancer risk: A meta-analysis. J Dermatol Sci 2016;84(2):137-43.

Garbe C, Keim U, Eigentler TK, Amaral T, Katalinic A, Holleczek B, et al. Time trends in incidence and mortality of cutaneous melanoma in Germany. J Eur Acad Dermatol Venereol 2018.

Garbe C, Leiter U. Melanoma epidemiology and trends. Clin Dermatol 2009;27(1):3-9.

Gaudette LA, Gao RN. Changing trends in melanoma incidence and mortality. Health Rep 1998;10(2):29-41 (Eng); 33-46 (Fre).

Geller AC, Miller DR, Annas GD, Demierre MF, Gilchrest BA, Koh HK. Melanoma incidence and mortality among US whites, 1969-1999. JAMA 2002;288(14):1719-20.

Gilchrest BA, Eller MS, Geller AC, Yaar M. The pathogenesis of melanoma induced by ultraviolet radiation. N Engl J Med 1999;340(17):1341-8.

Gjerstorff ML. The Danish Cancer Registry. Scand J Public Health 2011;39(7 Suppl):42-5.

Glazer AM, Winkelmann RR, Farberg AS, Rigel DS. Analysis of Trends in US Melanoma Incidence and Mortality. JAMA dermatology 2016.

Gloster HM, Jr., Neal K. Skin cancer in skin of color. J Am Acad Dermatol 2006;55(5):741-60; quiz 61-4.

Goldstein AM, Tucker MA. Dysplastic Nevi and Melanoma. Cancer Epidemiology Biomarkers & Prevention 2013;22(4):528-32.

Goukassian D, Gad F, Yaar M, Eller MS, Nehal US, Gilchrest BA. Mechanisms and implications of the age-associated decrease in DNA repair capacity. FASEB J 2000;14(10):1325-34.

Grange F, Mortier L, Crine A, Robert C, Sassolas B, Lebbe C, et al. Prevalence of sunbed use, and characteristics and knowledge of sunbed users: results from the French population-based Edifice Melanoma survey. J Eur Acad Dermatol Venereol 2015;29 Suppl 2:23-30.

Green A. A theory of site distribution of melanomas: Queensland, Australia. Cancer Causes Control 1992;3(6):513-6.

Greene MH, Clark WH, Jr., Tucker MA, Kraemer KH, Elder DE, Fraser MC. High risk of malignant melanoma in melanoma-prone families with dysplastic nevi. Ann Intern Med 1985;102(4):458-65.

Greinert R, de Vries E, Erdmann F, Espina C, Auvinen A, Kesminiene A, et al. European Code against Cancer 4th Edition: Ultraviolet radiation and cancer. Cancer Epidemiol 2015;39 Suppl 1:S75-83.

Grünheid E, Sulak H. Bevölkerungsentwicklung 2016: Daten, Fakten, Trends zum demografischen Wandel. Bundesinstitut für Bevölkerungsforschung, Wiesbaden (2016) 2016.

Guy GP, Jr., Thomas CC, Thompson T, Watson M, Massetti GM, Richardson LC. Vital signs: melanoma incidence and mortality trends and projections - United States, 1982-2030. MMWR Morb Mortal Wkly Rep 2015;64(21):591-6.

Haberland J, Bertz J, Gorsch B, Dolle R, Kurth BM. [Future cancer incidents in Germany]. Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz 2006;49(5):459-67.

Haenssle HA, Mograby N, Ngassa A, Buhl T, Emmert S, Schon MP, et al. Association of Patient Risk Factors and Frequency of Nevus-Associated Cutaneous Melanomas. JAMA dermatology 2016;152(3):291-8.

Hall HI, Miller DR, Rogers JD, Bewerse B. Update on the incidence and mortality from melanoma in the United States. J Am Acad Dermatol 1999;40(1):35-42.

Health USDo, Human S. Reports of the Surgeon General. The Surgeon General's Call to Action to Prevent Skin Cancer. Washington (DC): Office of the Surgeon General (US); 2014.

Helvind NM, Holmich LR, Smith S, Glud M, Andersen KK, Dalton SO, et al. Incidence of In Situ and Invasive Melanoma in Denmark From 1985 Through 2012: A National Database Study of 24,059 Melanoma Cases. JAMA dermatology 2015;151(10):1087-95.

Hery C, Tryggvadottir L, Sigurdsson T, Olafsdottir E, Sigurgeirsson B, Jonasson JG, et al. A melanoma epidemic in Iceland: possible influence of sunbed use. Am J Epidemiol 2010;172(7):762-7.

Hoejberg L, Gad D, Gyldenkerne N, Bastholt L. Trends in melanoma in the elderly in Denmark, 1980-2012. Acta Oncol 2016;55 Suppl 1:52-8.

Holford TR. The estimation of age, period and cohort effects for vital rates. Biometrics 1983;39(2):311-24.

Holman DM, Freeman MB, Shoemaker ML. Trends in Melanoma Incidence Among Non-Hispanic Whites in the United States, 2005 to 2014. JAMA dermatology 2018;154(3):361-2.

Holterhues C, Hollestein LM, Nijsten T, Koomen ER, Nusselder W, de Vries E. Burden of disease due to cutaneous melanoma has increased in the Netherlands since 1991. Br J Dermatol 2013;169(2):389-97.

Holterhues C, Vries E, Louwman MW, Koljenovic S, Nijsten T. Incidence and trends of cutaneous malignancies in the Netherlands, 1989-2005. J Invest Dermatol 2010;130(7):1807-12.

Hudson DJ. Fitting segmented curves whose join points have to be estimated. J Am Stat Assoc 1966;61:1097-129.

Iannacone MR, Green AC. Towards skin cancer prevention and early detection: evolution of skin cancer awareness campaigns in Australia. Melanoma management 2014;1(1):75-84.

Iannacone MR, Youlden DR, Baade PD, Aitken JF, Green AC. Melanoma incidence trends and survival in adolescents and young adults in Queensland, Australia. Int J Cancer 2015;136(3):603-9.

IARC. IARC International Agency for Research on Cancer: Estimated cancer incidence, mortality and prevalence worldwide 2012. Globocan 2012, available at: http://gco.iarc.fr/; 2012 [accessed 15 August 2016].

IARC. IARC International Agency for Research on Cancer. Cancer Incidence in Five Continents, Lyon (France), available at: http://ci5.iarc.fr/CI5I-X; 2018 [accessed 25 July 2018].

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Solar and Ultraviolet Radiation. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Lyon (France): World Health Organisation 1992;55.

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. A review of Human Carcinogens. IARC Monographs Radiation, Lyon (France): World Health Organisation 2012;100D.

Ichihashi M, Ueda M, Budiyanto A, Bito T, Oka M, Fukunaga M, et al. UV-induced skin damage. Toxicology 2003;189(1-2):21-39.

Islami F, Goding Sauer A, Miller KD, Siegel RL, Fedewa SA, Jacobs EJ, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin 2018;68(1):31-54.

Jemal A, Saraiya M, Patel P, Cherala SS, Barnholtz-Sloan J, Kim J, et al. Recent trends in cutaneous melanoma incidence and death rates in the United States, 1992-2006. J Am Acad Dermatol 2011;65(5 Suppl 1):S17-25.e1-3.

Jhappan C, Noonan FP, Merlino G. Ultraviolet radiation and cutaneous malignant melanoma. Oncogene 2003;22(20):3099-112.

Johannesdottir SA, Chang ET, Mehnert F, Schmidt M, Olesen AB, Sorensen HT. Nonsteroidal anti-inflammatory drugs and the risk of skin cancer: a population-based case-control study. Cancer 2012;118(19):4768-76.

Karimkhani C, Green AC, Nijsten T, Weinstock MA, Dellavalle RP, Naghavi M, et al. The Global Burden of Melanoma: Results from Global Burden of Disease Study 2015. Br J Dermatol 2017.

Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000;19(3):335-51.

Kim HJ, Fay MP, Yu B, Barrett MJ, Feuer EJ. Comparability of segmented line regression models. Biometrics 2004;60(4):1005-14.

Kim HJ, Yu B, Feuer EJ. Selecting the number of change points in segmented line regression. Statistica Sinica 2009;19(2):597-609.

Koster B, Thorgaard C, Philip A, Clemmensen H. Sunbed use and campaign initiatives in the Danish population, 2007-2009: a cross-sectional study. J Eur Acad Dermatol Venereol 2011;25(11):1351-5.

Krynitz B, Edgren G, Lindelof B, Baecklund E, Brattstrom C, Wilczek H, et al. Risk of skin cancer and other malignancies in kidney, liver, heart and lung transplant recipients 1970 to 2008--a Swedish population-based study. Int J Cancer 2013;132(6):1429-38.

Lange JR, Palis BE, Chang DC, Soong SJ, Balch CM. Melanoma in children and teenagers: an analysis of patients from the National Cancer Data Base. J Clin Oncol 2007;25(11):1363-8.

Larsen IK, Smastuen M, Johannesen TB, Langmark F, Parkin DM, Bray F, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur J Cancer 2009;45(7):1218-31.

Lazovich D, Choi K, Vogel RI. Time to get serious about skin cancer prevention. Cancer Epidemiol Biomarkers Prev 2012;21(11):1893-901.

Leiter U, Eigentler T, Garbe C. Epidemiology of skin cancer. Adv Exp Med Biol 2014;810:120-40.

Leiter U, Garbe C. Epidemiology of melanoma and nonmelanoma skin cancer--the role of sunlight. Adv Exp Med Biol 2008;624:89-103.

Lerman PM. Fitting segmented regression models by Grid Search. Appl Statistics 1980;29(1):77-84.

Li WQ, Qureshi AA, Ma J, Goldstein AM, Giovannucci EL, Stampfer MJ, et al. Personal history of prostate cancer and increased risk of incident melanoma in the United States. J Clin Oncol 2013;31(35):4394-9.

Liu R, Gao X, Lu Y, Chen H. Meta-analysis of the relationship between Parkinson disease and melanoma. Neurology 2011;76(23):2002-9.

Long MD, Martin CF, Pipkin CA, Herfarth HH, Sandler RS, Kappelman MD. Risk of melanoma and nonmelanoma skin cancer among patients with inflammatory bowel disease. Gastroenterology 2012;143(2):390-9.e1.

Lucas RM, McMichael AJ, Armstrong BK, Smith WT. Estimating the global disease burden due to ultraviolet radiation exposure. Int J Epidemiol 2008;37(3):654-67.

MacKie RM, Bray C, Vestey J, Doherty V, Evans A, Thomson D, et al. Melanoma incidence and mortality in Scotland 1979-2003. Br J Cancer 2007;96(11):1772-7.

MacKie RM, Bray CA, Hole DJ, Morris A, Nicolson M, Evans A, et al. Incidence of and survival from malignant melanoma in Scotland: an epidemiological study. The Lancet 2002;360(9333):587-91.

MacKie RM, Hauschild A, Eggermont AM. Epidemiology of invasive cutaneous melanoma. Ann Oncol 2009;20 Suppl 6:vi1-7.

Marks R. The changing incidence and mortality of melanoma in Australia. Recent Results Cancer Res 2002;160:113-21.

Matsumura Y, Ananthaswamy HN. Molecular mechanisms of photocarcinogenesis. Front Biosci 2002;7:d765-83.

Mistry M, Parkin DM, Ahmad AS, Sasieni P. Cancer incidence in the United Kingdom: projections to the year 2030. Br J Cancer 2011;105(11):1795-803.

Mitchell DL, Jen J, Cleaver JE. Relative induction of cyclobutane dimers and cytosine photohydrates in DNA irradiated in vitro and in vivo with ultraviolet-C and ultraviolet-B light. Photochem Photobiol 1991;54(5):741-6.

Moller B, Fekjaer H, Hakulinen T, Sigvaldason H, Storm HH, Talback M, et al. Prediction of cancer incidence in the Nordic countries: empirical comparison of different approaches. Stat Med 2003;22(17):2751-66.

Moller B, Fekjaer H, Hakulinen T, Tryggvadottir L, Storm HH, Talback M, et al. Prediction of cancer incidence in the Nordic countries up to the year 2020. Eur J Cancer Prev 2002;11 Suppl 1:S1-96.

Moller H, Fairley L, Coupland V, Okello C, Green M, Forman D, et al. The future burden of cancer in England: incidence and numbers of new patients in 2020. Br J Cancer 2007;96(9):1484-8.

Montague M, Borland R, Sinclair C. Slip! Slop! Slap! and SunSmart, 1980-2000: Skin cancer control and 20 years of population-based campaigning. Health Educ Behav 2001;28(3):290-305.

Montella A, Gavin A, Middleton R, Autier P, Boniol M. Cutaneous melanoma mortality starting to change: a study of trends in Northern Ireland. Eur J Cancer 2009;45(13):2360-6.

Moriwaki S, Ray S, Tarone RE, Kraemer KH, Grossman L. The effect of donor age on the processing of UV-damaged DNA by cultured human cells: reduced DNA repair capacity and increased DNA mutability. Mutat Res 1996;364(2):117-23.

Mudigonda T, Levender MM, O'Neill JL, West CE, Pearce DJ, Feldman SR. Incidence, risk factors, and preventative management of skin cancers in organ transplant recipients: a review of single- and multicenter retrospective studies from 2006 to 2010. Dermatol Surg 2013;39(3 Pt 1):345-64.

National Cancer Institute. Joinpoint Regression Program, Version 4.3.1.0 - April 2016; Statistical Methodology and Application Branch, Surveillance Research Program, National Cancer Institute. 2016.

Nikolaou V, Stratigos AJ. Emerging trends in the epidemiology of melanoma. Br J Dermatol 2014;170(1):11-9.

Nilsen LT, Aalerud TN, Hannevik M, Veierod MB. UVB and UVA irradiances from indoor tanning devices. Photochem Photobiol Sci 2011;10(7):1129-36.

Nilsen LT, Hannevik M, Aalerud TN, Johnsen B, Friberg EG, Veierod MB. Trends in UV irradiance of tanning devices in Norway: 1983-2005. Photochem Photobiol 2008;84(5):1100-8.

Noethern M. Hohe Kosten im Gesundheitswesen: Eine Frage des Alters? In: Statistisches Bundesamt (Hrsg) (2011). Wirtschaft und Statistik 07: S 665-675, available at: http://www.destatis.de; 2011 [accessed 18 February 2018].

NORDCAN. NORDCAN Project - Cancer Statistics for the Nordic Countries, availabe at: http://www-dep.iarc.fr/NORDCAN; 2018 [accessed 15 February 2018].

NORDPRED. "A Software for Predicting Trends in Cancer Incidence", available at: https://www.kreftregisteret.no/en/Research/Projects/Nordpred/Nordpred-software/; 2016 [accessed 10 February 2016].

Norris DA, Middleton MH, Whang K, Schleicher M, McGovern T, Bennion SD, et al. Human keratinocytes maintain reversible anti-apoptotic defenses in vivo and in vitro. Apoptosis 1997;2(2):136-48.

Nowatzki J, Moller B, Demers A. Projection of future cancer incidence and new cancer cases in Manitoba, 2006-2025. Chronic Dis Can 2011;31(2):71-8.

Nowossadeck E. Demografische Alterung und Folgen für das Gesundheitswesen. GBE kompakt 2012;3(2).

Nowossadeck E, Haberland J, Kraywinkel K. Die künftige Entwicklung der Erkrankungszahlen von Darmkrebs und Lungenkrebs. Ergebnisse der Berechnung verschiedener Szenarien für das Jahr 2020. Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz 2013;57:10-110.

Olsen CM, Carroll HJ, Whiteman DC. Estimating the attributable fraction for cancer: A meta-analysis of nevi and melanoma. Cancer prevention research (Philadelphia, Pa) 2010a;3(2):233-45.

Olsen CM, Carroll HJ, Whiteman DC. Estimating the attributable fraction for melanoma: a meta-analysis of pigmentary characteristics and freckling. Int J Cancer 2010b;127(10):2430-45.

Olsen CM, Carroll HJ, Whiteman DC. Familial melanoma: a meta-analysis and estimates of attributable fraction. Cancer Epidemiol Biomarkers Prev 2010c;19(1):65-73.

Olsen CM, Green AC, Pandeya N, Whiteman DC. Trends in Melanoma Incidence Rates in Eight Susceptible Populations through 2015. J Invest Dermatol 2018.

Olsen CM, Wilson LF, Green AC, Bain CJ, Fritschi L, Neale RE, et al. Cancers in Australia attributable to exposure to solar ultraviolet radiation and prevented by regular sunscreen use. Aust N Z J Public Health 2015;39(5):471-6.

Olsen CM, Zens MS, Stukel TA, Sacerdote C, Chang YM, Armstrong BK, et al. Nevus density and melanoma risk in women: a pooled analysis to test the divergent pathway hypothesis. Int J Cancer 2009;124(4):937-44.

Olsen JH, Andersen A, Dreyer L, Pukkala E, Tryggvadottir L, Gerhardsson de Verdier M, et al. Summary of avoidable cancers in the Nordic countries. APMIS Suppl 1997;76:141-6.

Olsen JH, Friis S, Frederiksen K. Malignant melanoma and other types of cancer preceding Parkinson disease. Epidemiology 2006;17(5):582-7.

Osmond C. Using age, period and cohort models to estimate future mortality rates. Int J Epidemiol 1985;14(1):124-9.

Osterlind A, Engholm G, Jensen OM. Trends in cutaneous malignant melanoma in Denmark 1943-1982 by anatomic site. APMIS 1988a;96(11):953-63.

Osterlind A, Hou-Jensen K, Moller Jensen O. Incidence of cutaneous malignant melanoma in Denmark 1978-1982. Anatomic site distribution, histologic types, and comparison with non-melanoma skin cancer. Br J Cancer 1988b;58(3):385-91.

Owens DM, Watt FM. Contribution of stem cells and differentiated cells to epidermal tumours. Nat Rev Cancer 2003;3(6):444-51.

Pan T, Li X, Jankovic J. The association between Parkinson's disease and melanoma. Int J Cancer 2011;128(10):2251-60.

Parkin DM, Boyd L, Walker LC. 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. Br J Cancer 2011a;105 Suppl 2:S77-81.

Parkin DM, Mesher D, Sasieni P. 13. Cancers attributable to solar (ultraviolet) radiation exposure in the UK in 2010. Br J Cancer 2011b;105 Suppl 2:S66-9.

Paszkowska-Szczur K, Scott RJ, Serrano-Fernandez P, Mirecka A, Gapska P, Gorski B, et al. Xeroderma pigmentosum genes and melanoma risk. Int J Cancer 2013;133(5):1094-100.

Peters E, Pritzkuleit R, Beske F, Katalinic A. [Demographic change and disease rates: a projection until 2050]. Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz 2010;53(5):417-26.

Petersen B, Thieden E, Philipsen PA, Heydenreich J, Wulf HC, Young AR. Determinants of personal ultraviolet-radiation exposure doses on a sun holiday. Br J Dermatol 2013;168(5):1073-9.

Petersen B, Triguero-Mas M, Maier B, Thieden E, Philipsen PA, Heydenreich J, et al. Sun behaviour and personal UVR exposure among Europeans on short term holidays. J Photochem Photobiol B 2015;151:264-9.

Polakowska RR, Piacentini M, Bartlett R, Goldsmith LA, Haake AR. Apoptosis in human skin development: morphogenesis, periderm, and stem cells. Dev Dyn 1994;199(3):176-88.

Poynter JN, Elder JT, Fullen DR, Nair RP, Soengas MS, Johnson TM, et al. BRAF and NRAS mutations in melanoma and melanocytic nevi. Melanoma Res 2006;16(4):267-73.

Pritzkuleit R, Beske F, Katalinic A. [Demographic change and cancer]. Onkologie 2010;33 Suppl 7:19-24.

Quante AS, Ming C, Rottmann M, Engel J, Boeck S, Heinemann V, et al. Projections of cancer incidence and cancer-related deaths in Germany by 2020 and 2030. Cancer medicine 2016;5(9):2649-56.

Raimondi S, Sera F, Gandini S, Iodice S, Caini S, Maisonneuve P, et al. MC1R variants, melanoma and red hair color phenotype: a meta-analysis. Int J Cancer 2008;122(12):2753-60.

Reinau D, Achermann C, Arnet N, Meier CR, Hatz C, Surber C. Sun protective behaviour of vacationers spending holidays in the tropics and subtropics. Br J Dermatol 2014;171(4):868-74.

Richardson A, Fletcher L, Sneyd M, Cox B, Reeder AI. The incidence and thickness of cutaneous malignant melanoma in New Zealand 1994-2004. N Z Med J 2008;121(1279):18-26.

Rigel DS, Rivers JK, Friedman RJ, Kopf AW. Risk gradient for malignant melanoma in individuals with dysplastic naevi. Lancet 1988;1(8581):352-3.

Robert Koch Institut Berlin. Zentrum für Krebsregisterdaten (ZfKD) am Robert Koch Institut (RKI), Berlin, available at: https://www.krebsdaten.de/Krebs/DE/; 2016 [accessed 20 August 2016].

Robert Koch Institut Berlin. Die Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. (Hrsg) (2017) Krebs in Deustchland 2013/2014, 11. Ausgabe. Berlin. 2017.

Rodriguez-Villanueva J, Colome MI, Brisbay S, McDonnell TJ. The expression and localization of bcl-2 protein in normal skin and in non-melanoma skin cancers. Pathol Res Pract 1995;191(5):391-8.

SEER. Surveillance,, Epidemiology, End Results (SEER) Program: SEER*Stat Database: Incidence-SEER 9 Registries Research Data, available at: http://www.seer.cancer.gov; 2018 [accessed 4 April 2018].

Sergentanis TN, Antoniadis AG, Gogas HJ, Antonopoulos CN, Adami HO, Ekbom A, et al. Obesity and risk of malignant melanoma: a meta-analysis of cohort and case-control studies. Eur J Cancer 2013;49(3):642-57.

Severi G, Giles GG, Robertson C, Boyle P, Autier P. Mortality from cutaneous melanoma: evidence for contrasting trends between populations. Br J Cancer 2000;82(11):1887-91.

Shain AH, Yeh I, Kovalyshyn I, Sriharan A, Talevich E, Gagnon A, et al. The Genetic Evolution of Melanoma from Precursor Lesions. N Engl J Med 2015;373(20):1926-36.

Shield KD, Parkin DM, Whiteman DC, Rehm J, Viallon V, Micallef CM, et al. Population Attributable and Preventable Fractions: Cancer Risk Factor Surveillance, and Cancer Policy Projection. Current epidemiology reports 2016;3(3):201-11.

Siskind V, Whiteman DC, Aitken JF, Martin NG, Green AC. An analysis of risk factors for cutaneous melanoma by anatomical site (Australia). Cancer Causes Control 2005;16(3):193-9.

Statistics Denmark. Documentation of Statistics for Population Projections for Denmark 2018, available at: http://www.dst.dk; 2018a [accessed 20 July 2018].

Statistics Denmark. Population and Population Projections, available at: http://www.statbank.dk; 2018b [accessed 20 March 2018].

Statistisches Bundesamt Wiesbaden. Bevölkerung Deutschlands bis 2060, 13. koordinierte Bevölkerungsvorausberechnung. Statistisches Bundesamt Wiesbaden 2015a.

Statistisches Bundesamt Wiesbaden. Statistisches Bundesamt: Lange Reihen: Bevölkerung nach Altersgruppen, 13. koordinierte Bevölkerungsvorausberechnung: Bevölkerung Deutschlands bis 2060, availabe at: https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Bevoelkerung/Bevoelkerungsvorausberechnung/_inhalt.html?; 2015b [accessed 20 May 2017].

Statistisches Bundesamt Wiesbaden. Fortschreibung des Bevölkerungsstandes und Bevölkerungsvorausberechnungen, available at: https://www-genesis.destatis.de/genesis/online; 2016 [accessed 10 February 2016].

Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry--history, content, quality and use. Dan Med Bull 1997;44(5):535-9.

Teppo L, Pukkala E, Lehtonen M. Data quality and quality control of a population-based cancer registry. Experience in Finland. Acta Oncol 1994;33(4):365-9.

Thomas NE, Edmiston SN, Alexander A, Millikan RC, Groben PA, Hao H, et al. Number of nevi and early-life ambient UV exposure are associated with BRAF-mutant melanoma. Cancer Epidemiol Biomarkers Prev 2007;16(5):991-7.

United Nations. United Nations, Department of Economic and Social Affairs, Population Division. World Population Prospects: The 2017 Revision. , available at: http://www.un.org/en/development/desa/population/theme/trends; 2017 [accessed 31 August 2018].

van Leeuwen MT, Webster AC, McCredie MR, Stewart JH, McDonald SP, Amin J, et al. Effect of reduced immunosuppression after kidney transplant failure on risk of cancer: population based retrospective cohort study. BMJ 2010;340:c570.

Veierod MB, Adami HO, Lund E, Armstrong BK, Weiderpass E. Sun and solarium exposure and melanoma risk: effects of age, pigmentary characteristics, and nevi. Cancer Epidemiol Biomarkers Prev 2010;19(1):111-20.

Waldmann A, Nolte S, Weinstock MA, Breitbart EW, Eisemann N, Geller AC, et al. Skin cancer screening participation and impact on melanoma incidence in Germany--an observational study on incidence trends in regions with and without population-based screening. Br J Cancer 2012;106(5):970-4.

Watson M, Geller AC, Tucker MA, Guy GP, Jr., Weinstock MA. Melanoma burden and recent trends among non-Hispanic whites aged 15-49years, United States. Prev Med 2016;91:294-8.

Wehner MR, Chren MM, Nameth D, Choudhry A, Gaskins M, Nead KT, et al. International prevalence of indoor tanning: a systematic review and meta-analysis. JAMA dermatology 2014;150(4):390-400.

Weir HK, Marrett LD, Cokkinides V, Barnholtz-Sloan J, Patel P, Tai E, et al. Melanoma in adolescents and young adults (ages 15-39 years): United States, 1999-2006. J Am Acad Dermatol 2011;65(5 Suppl 1):S38-49.

Weir HK, Thompson TD, Soman A, Moller B, Leadbetter S. The past, present, and future of cancer incidence in the United States: 1975 through 2020. Cancer 2015;121(11):1827-37.

Westerdahl J, Ingvar C, Masback A, Jonsson N, Olsson H. Risk of cutaneous malignant melanoma in relation to use of sunbeds: further evidence for UV-A carcinogenicity. Br J Cancer 2000;82(9):1593-9.

Whiteman DC, Bray CA, Siskind V, Green AC, Hole DJ, Mackie RM. Changes in the incidence of cutaneous melanoma in the west of Scotland and Queensland, Australia: hope for health promotion? Eur J Cancer Prev 2008;17(3):243-50.

Whiteman DC, Green AC, Olsen CM. The Growing Burden of Invasive Melanoma: Projections of Incidence Rates and Numbers of New Cases in Six Susceptible Populations through 2031. J Invest Dermatol 2016;136(6):1161-71.

Whiteman DC, Stickley M, Watt P, Hughes MC, Davis MB, Green AC. Anatomic site, sun exposure, and risk of cutaneous melanoma. J Clin Oncol 2006;24(19):3172-7.

Whiteman DC, Watt P, Purdie DM, Hughes MC, Hayward NK, Green AC. Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. J Natl Cancer Inst 2003;95(11):806-12.

Whiteman DC, Whiteman CA, Green AC. Childhood sun exposure as a risk factor for melanoma: a systematic review of epidemiologic studies. Cancer Causes Control 2001;12(1):69-82.

Williams PF, Olsen CM, Hayward NK, Whiteman DC. Melanocortin 1 receptor and risk of cutaneous melanoma: a meta-analysis and estimates of population burden. Int J Cancer 2011;129(7):1730-40.

Winther JF, Ulbak K, Dreyer L, Pukkala E, Osterlind A. Avoidable cancers in the Nordic countries. Radiation. APMIS Suppl 1997;76:83-99.

Young AR. Tanning devices--fast track to skin cancer? Pigment Cell Res 2004;17(1):2-9.

Zhang M, Qureshi AA, Geller AC, Frazier L, Hunter DJ, Han J. Use of tanning beds and incidence of skin cancer. J Clin Oncol 2012;30(14):1588-93.

7 Statement of own contribution

The project was carried out at the University Hospital of Dermatology in Tuebingen under the supervision of Prof. Dr. Claus Garbe, Head of the Section for Dermatooncology. The study was designed by myself in collaboration with Prof. Dr. Claus Garbe.

All statistical analyses (incidence trends and predictions, number and proportion of melanomas attributable to changes in UVR exposure and demographics) were performed by myself. I was statistically advised by Prof. Dr. Rainer Muche, Deputy Head of the Institute for Epidemiology and Medical Biometry at the University of Ulm.

The statistical analysis were based on melanoma incidence data, which were extracted from the population-based cancer registries in Germany (Centre for Cancer Registry Data at the Robert Koch-Institute, Berlin) and in Denmark (NORDCAN data base). The research for cancer registry data was done by myself.

All results and the final version of the manuscript were reviewed by Prof Dr. Claus Garbe and Prof. Dr. Rainer Muche.

I assure that, I have written the manuscript by myself and that I have not used any sources other than those I have given.

Tuebingen,

Acknowledgements

Special thanks go to my supervisors, Prof. Dr. Claus Garbe (Principal Advisor) and Prof. Dr. Rainer Muche (Associate Advisor) for their invaluable encouragement, guidance and assistance throughout the duration of my dissertation. I would like to acknowledge and thank both, Claus who inspired me and made the project possible and Rainer for his statistical advice and assistance with the data analysis.

I would like to thank my colleagues of the Department of Dermatooncology for their inspiring conversations.

I am thankful for the encouragement of my family and their support.

Supplementary Tables

Table S1: Excess number of melanoma cases in 1999/2003 compared to baseline (1995/1998) due to UVR exposure and demographic changes (population size and age), Germany (Males)

	MM **baseline**	Population	MM **observed**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1995/1998	1995/1998	**1999/2003**	1999/2003	**1999/2003**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	2046225	0	1982560	0	0	0	0		
5–9	0	2349718	0	2086492	0	0	0	0		
10–14	1	2340545	0	2383616	0	-1	0	-1		
15–19	18	2316669	25	2390970	18	7	7	0		
20–24	52	2336576	61	2405408	54	9	7	2		
25–29	122	3189766	136	2479631	95	14	41	-27		
30–34	205	3748127	289	3269496	179	84	110	-26		
35–39	248	3455911	314	3705341	265	66	49	17		
40–44	282	3007156	375	3370889	317	93	58	35		
45–49	312	2719786	408	2936877	337	96	71	25		
50–54	405	2368182	481	2587641	442	76	39	37		
55–59	690	2954504	693	2360784	551	3	142	-139		
60–64	577	2369859	936	2765154	673	359	263	96		
65–69	526	1841619	819	2096115	599	293	220	73		
70–74	350	1296554	713	1556564	420	363	293	70		
75–79	207	782064	553	1002413	266	346	287	59		
80–84	214	457218	227	499219	234	13	-7	20		
85+	163	363552	158	365405	164	-5	-6	1		
Total (Σ)	**4372**	**39944028**	**6188**	**40244576**	**4614**	**1816**	**1574**	**242**	**33**	**209**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 0.415381097

Population change from baseline* **L = (D-B)/B**: 0.00752424

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S1: Excess number of melanoma cases in 2004/2008 compared to baseline (1995/1998) due to UVR exposure and demographic changes (population size and age), Germany (Males)

	MM **baseline**	Population	MM **observed**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1995/1998	1995/1998	**2004/2008**	2004/2008	**2004/2008**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	2046225	0	1810339	0	0	0	0		
5–9	0	2349718	0	1986194	0	0	0	0		
10–14	1	2340545	1	2096456	0	0	1	-1		
15–19	18	2316669	31	2410381	18	13	13	0		
20–24	52	2336576	84	2473676	56	32	28	4		
25–29	122	3189766	131	2480195	95	9	36	-27		
30–34	205	3748127	194	2487923	136	-11	58	-69		
35–39	248	3455911	344	3240927	232	96	112	-16		
40–44	282	3007156	469	3663265	344	187	125	62		
45–49	312	2719786	493	3320087	381	181	112	69		
50–54	405	2368182	576	2867340	490	171	86	85		
55–59	690	2954504	680	2495360	583	-10	97	-107		
60–64	577	2369859	911	2226415	542	334	369	-35		
65–69	526	1841619	1273	2535596	724	747	549	198		
70–74	350	1296554	1073	1832111	494	723	579	144		
75–79	207	782064	783	1249080	331	576	452	124		
80–84	214	457218	456	703321	330	242	126	116		
85+	163	363552	261	411999	185	98	76	22		
Total (Σ)	**4372**	**39944028**	**7760**	40290666	**4941**	**3388**	**2819**	**569**	**39**	**530**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A** 0,774967122

Population change from baseline* **L = (D-B)/B** 0.008678095

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S1: Excess number of melanoma cases in 2009/2013 compared to baseline (1995/1998) due to UVR exposure and demographic changes (population size and age), Germany (Males)

	MM **baseline**	Population	MM **observed**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1995/1998	1995/1998	**2009/2013**	2009/2013	**2009/2013**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	2046225	1	1744409	0	1	1	0		
5–9	0	2349718	1	1814385	0	1	1	0		
10–14	1	2340545	2	1987934	0	1	2	-1		
15–19	18	2316669	31	2110193	16	13	15	-2		
20–24	52	2336576	85	2468863	56	33	29	4		
25–29	122	3189766	163	2517038	97	41	66	-25		
30–34	205	3748127	210	2452802	135	5	75	-70		
35–39	248	3455911	319	2435647	175	71	144	-73		
40–44	282	3007156	524	3144764	295	242	229	13		
45–49	312	2719786	740	3552334	407	428	333	95		
50–54	405	2368182	806	3205016	548	401	258	143		
55–59	690	2954504	876	2732872	638	186	238	-52		
60–64	577	2369859	1078	2334710	569	501	509	-8		
65–69	526	1841619	1418	2026934	579	892	839	53		
70–74	350	1296554	1809	2231526	601	1459	1208	251		
75–79	207	782064	1265	1498818	397	1058	868	190		
80–84	214	457218	792	886191	416	578	376	202		
85+	163	363552	447	532341	238	284	209	75		
Total (Σ)	**4372**	**39944028**	**10567**	39676775	**5167**	**6195**	**5400**	**795**	**-31**	**826**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 1.41669621

Population change from baseline* **L = (D-B)/B**: -0.00669067

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S1: Excess number of melanoma cases in 2014/2018 compared to baseline (1995/1998) due to UVR exposure and demographic changes (population size and age), Germany (Males)

	MM **baseline**	Population	MM **projected**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1995/1998	1995/1998	**2014/2018**	2014/2018	**2014/2018**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	2046225	1	1794400	0	1	1	0		
5–9	0	2349718	1	1793000	0	1	1	0		
10–14	1	2340545	1	1852800	0	0	1	-1		
15–19	18	2316669	28	2047600	16	10	12	-2		
20–24	52	2336576	120	2295800	52	68	68	0		
25–29	122	3189766	205	2684600	103	83	102	-19		
30–34	205	3748127	302	2657000	146	97	156	-59		
35–39	248	3455911	330	2538600	182	82	148	-66		
40–44	282	3007156	491	2480600	233	209	258	-49		
45–49	312	2719786	852	3135200	359	540	493	47		
50–54	405	2368182	1142	3499800	599	737	543	194		
55–59	690	2954504	1249	3110600	726	559	523	36		
60–64	577	2369859	1374	2591400	631	797	743	54		
65–69	526	1841619	1606	2153600	615	1080	991	89		
70–74	350	1296554	1956	1800600	485	1606	1471	135		
75–79	207	782064	2190	1862000	493	1983	1697	286		
80–84	214	457218	1267	1101200	517	1053	750	303		
85+	163	363552	790	695000	311	627	479	148		
Total (Σ)	**4372**	**39944028**	**13905**	**40093800**	**5468**	**9533**	**8437**	**1096**	**18**	**1078**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 2.180385385

Population change from baseline* **L = (D-B)/B**: 0.00374955

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S1: Excess number of melanoma cases in 2019/2023 compared to baseline (1995/1998) due to UVR exposure and demographic changes (population size and age), Germany (Males)

	MM **baseline**	Population	MM **projected**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1995/1998	1995/1998	**2019/2023**	2019/2023	**2019/2023**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	2046225	1	1832200	0	1	1	0		
5–9	0	2349718	1	1833000	0	1	1	0		
10–14	1	2340545	1	1824000	0	0	1	-1		
15–19	18	2316669	26	1901000	14	8	12	-4		
20–24	52	2336576	149	2195600	49	97	100	-3		
25–29	122	3189766	242	2480000	95	120	147	-27		
30–34	205	3748127	335	2808800	154	130	181	-51		
35–39	248	3455911	423	2739600	196	175	227	-52		
40–44	282	3007156	502	2594600	244	220	258	-38		
45–49	312	2719786	726	2507000	287	414	439	-25		
50–54	405	2368182	1240	3114000	533	835	707	128		
55–59	690	2954504	1651	3420400	799	961	852	109		
60–64	577	2369859	1816	2982200	727	1239	1089	150		
65–69	526	1841619	1972	2421000	692	1446	1280	166		
70–74	350	1296554	2152	1948600	525	1802	1627	175		
75–79	207	782064	2248	1526000	404	2041	1844	197		
80–84	214	457218	2079	1400800	657	1865	1422	443		
85+	163	363552	1329	935000	419	1166	910	256		
Total (Σ)	**4372**	**39944028**	**16893**	**40463800**	**5795**	**12521**	**11098**	**1423**	**56**	**1367**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 2.863768083

Population change from baseline* **L = (D-B)/B**: 0.01301251

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size (Δsize/N_{BBB}): L = (Δsize/N_{BBB})

Table S1: Excess number of melanoma cases in 2024/2028 compared to baseline (1995/1998) due to UVR exposure and demographic changes (population size and age), Germany (Males)

	MM **baseline**	Population	MM **projected**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1995/1998	1995/1998	**2024/2028**	2024/2028	**2024/2028**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	2046225	1	1789800	0	1	1	0		
5–9	0	2349718	1	1858800	0	1	1	0		
10–14	1	2340545	1	1855400	0	0	1	-1		
15–19	18	2316669	26	1861400	14	8	12	-4		
20–24	52	2336576	162	2012200	45	110	117	-7		
25–29	122	3189766	264	2321200	89	142	175	-33		
30–34	205	3748127	354	2556800	140	149	214	-65		
35–39	248	3455911	429	2853800	204	181	225	-44		
40–44	282	3007156	586	2765600	260	304	326	-22		
45–49	312	2719786	690	2599200	298	378	392	-14		
50–54	405	2368182	989	2484200	425	584	564	20		
55–59	690	2954504	1671	3042400	710	981	961	20		
60–64	577	2369859	2248	3287200	801	1671	1447	224		
65–69	526	1841619	2466	2803800	800	1940	1666	274		
70–74	350	1296554	2522	2209600	596	2172	1926	246		
75–79	207	782064	2404	1681800	446	2197	1958	239		
80–84	214	457218	2060	1169600	549	1846	1511	335		
85+	163	363552	2180	1254600	562	2017	1618	399		
Total (Σ)	**4372**	**39944028**	**19054**	**40407400**	**5939**	**14682**	**13115**	**1567**	**52**	**1515**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 3.358003316

Population change from baseline* **L = (D-B)/B**: 0.01160054

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): L = ($\Delta size/N_{BBB}$)

Table S1: Excess number of melanoma cases in 2029/2033 compared to baseline (1995/1998) due to UVR exposure and demographic changes (population size and age), Germany (Males)

	MM **baseline**	Population	MM **projected**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1995/1998	1995/1998	**2029/2033**	2029/2033	**2029/2033**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	2046225	1	1686600	0	1	1	0		
5–9	0	2349718	1	1816200	0	1	1	0		
10–14	1	2340545	1	1881000	0	0	1	-1		
15–19	18	2316669	26	1892600	14	8	12	-4		
20–24	52	2336576	172	1972800	44	120	128	-8		
25–29	122	3189766	262	2137400	82	140	180	-40		
30–34	205	3748127	358	2397800	131	153	227	-74		
35–39	248	3455911	421	2603000	186	173	235	-62		
40–44	282	3007156	557	2880000	271	275	286	-11		
45–49	312	2719786	753	2771000	318	441	435	6		
50–54	405	2368182	891	2579200	441	486	450	36		
55–59	690	2954504	1264	2435000	569	574	695	-121		
60–64	577	2369859	2147	2933600	715	1570	1432	138		
65–69	526	1841619	2896	3107600	888	2370	2008	362		
70–74	350	1296554	3017	2581000	696	2667	2321	346		
75–79	207	782064	2718	1929400	511	2511	2207	304		
80–84	214	457218	2166	1324600	621	1952	1545	407		
85+	163	363552	2510	1277600	572	2347	1938	409		
Total (Σ)	**4372**	**39944028**	**20161**	**40206400**	**6059**	**15789**	**14102**	**1687**	**28**	**1659**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 3.6110904

Population change from baseline* **L = (D-B)/B**: 0.0065685

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S1: Excess number of melanoma cases in 1999/2003 compared to baseline (1995/1998) due to UVR exposure and demographic changes (population size and age), Germany (Females)

	MM **baseline**	Population	MM **observed**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1995/1998	1995/1998	**1999/2003**	1999/2003	**1999/2003**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	1940357	0	1880100	0	0	0	0		
5–9	0	2229795	0	1979934	0	0	0	0		
10–14	0	2219407	1	2261455	0	1	1	0		
15–19	27	2194211	49	2269391	30	22	19	3		
20–24	98	2229393	181	2323644	102	83	79	4		
25–29	281	2988806	241	2377130	223	-40	18	-58		
30–34	343	3488358	480	3090385	304	137	176	-39		
35–39	291	3259618	530	3491994	311	239	219	20		
40–44	330	2894738	514	3221085	367	184	147	37		
45–49	402	2654033	473	2875262	435	71	38	33		
50–54	397	2325116	505	2565661	438	108	67	41		
55–59	472	2960431	595	2369889	378	123	217	-94		
60–64	451	2487954	785	2873584	521	334	264	70		
65–69	441	2155853	607	2333365	477	166	130	36		
70–74	494	2117549	685	2013974	470	191	215	-24		
75–79	372	1612946	633	1863796	430	261	203	58		
80–84	382	1139603	416	1193616	400	34	16	18		
85+	**304**	1138817	402	1157493	309	98	93	5		
Total (Σ)	**5085**	**42036985**	**7097**	**42141759**	**5195**	**2012**	**1902**	**110**	**12**	**98**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 0.395584837

Population change from baseline* **L = (D-B)/B**: 0.00249242

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S1: Excess number of melanoma cases in 2004/2008 compared to baseline (1995/1998) due to UVR exposure and demographic changes (population size and age), Germany (Females)

	MM **baseline**	Population	MM **observed**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1995/1998	1995/1998	**2004/2008**	2004/2008	**2004/2008**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	1940357	0	1718769	0	0	0	0		
5–9	0	2229795	0	1886130	0	0	0	0		
10–14	0	2219407	1	1989451	0	1	1	0		
15–19	27	2194211	49	2291341	28	22	21	1		
20–24	98	2229393	192	2395851	105	94	87	7		
25–29	281	2988806	292	2415280	227	11	65	-54		
30–34	343	3488358	382	2409811	237	39	145	-106		
35–39	291	3259618	572	3095011	276	281	296	-15		
40–44	330	2894738	755	3486394	398	425	357	68		
45–49	402	2654033	676	3209930	486	274	190	84		
50–54	397	2325116	590	2852324	487	193	103	90		
55–59	472	2960431	650	2525157	403	178	247	-69		
60–64	451	2487954	705	2303866	418	254	287	-33		
65–69	441	2155853	897	2763120	565	456	332	124		
70–74	494	2117549	706	2184791	510	212	196	16		
75–79	372	1612946	629	1786038	412	257	217	40		
80–84	382	1139603	574	1480619	497	192	77	115		
85+	**304**	1138817	476	1210240	322	172	154	18		
Total (Σ)	**5085**	**42036985**	**8146**	42004123	**5371**	**3061**	**2775**	**286**	**-4**	**290**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 0.602123998

Population change from baseline* **L = (D-B)/B**: -0.00078175

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S1: Excess number of melanoma cases in 2009/2013 compared to baseline (1995/1998) due to UVR exposure and demographic changes (population size and age), Germany (Females)

	MM **baseline**	Population	MM **observed**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1995/1998	1995/1998	**2009/2013**	2009/2013	**2009/2013**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	1940357	1	1657001	0	1	1	0		
5–9	0	2229795	1	1722468	0	1	1	0		
10–14	0	2219407	1	1886238	0	1	1	0		
15–19	27	2194211	47	2002610	25	20	22	-2		
20–24	98	2229393	220	2364984	104	122	116	6		
25–29	281	2988806	370	2433905	229	89	141	-52		
30–34	343	3488358	419	2406173	237	76	182	-106		
35–39	291	3259618	535	2392650	214	244	321	-77		
40–44	330	2894738	895	3052677	348	565	547	18		
45–49	402	2654033	1053	3443584	521	651	532	119		
50–54	397	2325116	920	3159595	539	523	381	142		
55–59	472	2960431	850	2788334	445	378	405	-27		
60–64	451	2487954	842	2439921	442	391	400	-9		
65–69	441	2155853	954	2195400	449	513	505	8		
70–74	494	2117549	1158	2588211	603	664	555	109		
75–79	372	1612946	855	1952875	451	483	404	79		
80–84	382	1139603	678	1438776	483	296	195	101		
85+	304	1138817	676	1432415	381	372	295	77		
Total (Σ)	**5085**	**42036985**	**10475**	**41357818**	**5471**	**5390**	**5004**	**386**	**-82**	**468**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 1.06008162

Population change from baseline* **L = (D-B)/B**: -0.01615641

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): L = ($\Delta size/N_{BBB}$)

Table S1: Excess number of melanoma cases in 2014/2018 compared to baseline (1995/1998) due to UVR exposure and demographic changes (population size and age), Germany (Females)

	MM **baseline**	Population	MM **projected**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1995/1998	1995/1998	**2014/2018**	2014/2018	**2014/2018**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	1940357	1	1704000	0	1	1	0		
5–9	0	2229795	1	1703600	0	1	1	0		
10–14	0	2219407	1	1757800	0	1	1	0		
15–19	27	2194211	43	1937200	24	16	19	-3		
20–24	98	2229393	266	2173800	95	168	171	-3		
25–29	281	2988806	418	2527800	238	137	180	-43		
30–34	343	3488358	585	2527400	249	242	336	-94		
35–39	291	3259618	639	2466600	220	348	419	-71		
40–44	330	2894738	822	2427800	277	492	545	-53		
45–49	402	2654033	1273	3059400	463	871	810	61		
50–54	397	2325116	1450	3428400	585	1053	865	188		
55–59	472	2960431	1309	3118000	497	837	812	25		
60–64	451	2487954	1124	2717600	493	673	631	42		
65–69	441	2155853	1117	2342200	479	676	638	38		
70–74	494	2117549	1200	2064400	481	706	719	-13		
75–79	372	1612946	1338	2340000	540	966	798	168		
80–84	382	1139603	860	1608800	540	478	320	158		
85+	304	1138817	894	1545600	412	590	482	108		
Total (Σ)	**5085**	**42036985**	**13341**	**41450400**	**5593**	**8256**	**7748**	**508**	**-72**	**580**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 1.623751414

Population change from baseline* **L = (D-B)/B**: -0.013954

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S1: Excess number of melanoma cases in 2019/2023 compared to baseline (1995/1998) due to UVR exposure and demographic changes (population size and age), Germany (Females)

	MM **baseline**	Population	MM **projected**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1995/1998	1995/1998	**2019/2023**	2019/2023	**2019/2023**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	1940357	1	1739200	0	1	1	0		
5–9	0	2229795	1	1741800	0	1	1	0		
10–14	0	2219407	1	1733400	0	1	1	0		
15–19	27	2194211	40	1798200	22	13	18	-5		
20–24	98	2229393	306	2073400	91	208	215	-7		
25–29	281	2988806	458	2317200	218	177	240	-63		
30–34	343	3488358	634	2612600	257	291	377	-86		
35–39	291	3259618	786	2583400	231	495	555	-60		
40–44	330	2894738	943	2504600	286	613	657	-44		
45–49	402	2654033	1104	2449200	371	702	733	-31		
50–54	397	2325116	1635	3054600	521	1238	1114	124		
55–59	472	2960431	1917	3392600	541	1445	1376	69		
60–64	451	2487954	1633	3054000	554	1182	1079	103		
65–69	441	2155853	1399	2625600	537	958	862	96		
70–74	494	2117549	1375	2225200	519	881	856	25		
75–79	372	1612946	1304	1883200	434	932	870	62		
80–84	382	1139603	1337	1958800	657	955	680	275		
85+	304	1138817	1113	1782800	475	809	638	171		
Total (Σ)	**5085**	**42036985**	**15987**	**41529800**	**5714**	**10902**	**10273**	**629**	**-62**	**691**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 2.14414278

Population change from baseline* **L = (D-B)/B**: -0.0120652

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S1: Excess number of melanoma cases in 2024/2028 compared to baseline (1995/1998) due to UVR exposure and demographic changes (population size and age), Germany (Females)

	MM **baseline**	Population	MM **projected**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1995/1998	1995/1998	**2024/2028**	2024/2028	**2024/2028**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	1940357	1	1699000	0	1	1	0		
5–9	0	2229795	1	1765400	0	1	1	0		
10–14	0	2219407	1	1763000	0	1	1	0		
15–19	27	2194211	39	1764400	22	12	17	-5		
20–24	98	2229393	317	1900800	84	219	233	-14		
25–29	281	2988806	483	2171400	204	202	279	-77		
30–34	343	3488358	643	2372000	233	300	410	-110		
35–39	291	3259618	797	2647200	236	506	561	-55		
40–44	330	2894738	1083	2605600	297	753	786	-33		
45–49	402	2654033	1193	2514400	381	791	812	-21		
50–54	397	2325116	1346	2442800	417	949	929	20		
55–59	472	2960431	2039	3021800	482	1567	1557	10		
60–64	451	2487954	2256	3325400	603	1805	1653	152		
65–69	441	2155853	1922	2959000	605	1481	1317	164		
70–74	494	2117549	1642	2505000	584	1148	1058	90		
75–79	372	1612946	1442	2052200	474	1070	968	102		
80–84	382	1139603	1255	1596000	535	873	720	153		
85+	304	1138817	1674	2213400	590	1370	1084	286		
Total (Σ)	**5085**	**42036985**	**18134**	**41318800**	**5747**	**13049**	**12387**	**662**	**-86**	**748**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 2.566248095

Population change from baseline* **L = (D-B)/B**: -0.0170846

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S1: Excess number of melanoma cases in 2029/2033 compared to baseline (1995/1998) due to UVR exposure and demographic changes (population size and age), Germany (Females)

	MM **baseline**	Population	MM **projected**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1995/1998	1995/1998	**2029/2033**	2029/2033	**2029/2033**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	1940357	0	1600600	0	0	0	0		
5–9	0	2229795	1	1725000	0	1	1	0		
10–14	0	2219407	1	1786600	0	1	1	0		
15–19	27	2194211	40	1794000	22	13	18	-5		
20–24	98	2229393	331	1867200	82	233	249	-16		
25–29	281	2988806	470	1997800	188	189	282	-93		
30–34	343	3488358	637	2225800	219	294	418	-124		
35–39	291	3259618	765	2407200	215	474	550	-76		
40–44	330	2894738	1045	2670200	305	715	740	-25		
45–49	402	2654033	1300	2616000	396	898	904	-6		
50–54	397	2325116	1385	2509400	428	988	957	31		
55–59	472	2960431	1605	2421200	386	1133	1219	-86		
60–64	451	2487954	2285	2966800	538	1834	1747	87		
65–69	441	2155853	2525	3231000	661	2084	1864	220		
70–74	494	2117549	2151	2836200	661	1657	1490	167		
75–79	372	1612946	1655	2325400	537	1283	1118	165		
80–84	382	1139603	1351	1772400	595	969	756	213		
85+	304	1138817	1850	2224600	592	1546	1258	288		
Total (Σ)	**5085**	**42036985**	**19397**	**40977400**	**5825**	**14312**	**13572**	**740**	**-127**	**867**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 2.81472049

Population change from baseline* **L = (D-B)/B**: -0.025206

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): L = ($\Delta size/N_{BBB}$)

TableS2: Number and proportion of melanoma cases at baseline (1995/1998) attributable to UVR exposure, applying incidence rates of a historical Danish cohort from 1943/1947 as reference population, Germany (Males)

	IR[1]	Population size[2]	MM expected	MM observed[2]	MM excess	PAF%
	1943/1947	1995/1998	1995/1998	1995/1998	1995/1998	1995/1998
Age (years)	**A**	**B**	**C = (A*B)/100,000**	**D**	**E = D - C**	**F = (E/D) *100**
0–4	0.1	2046225	2	0	-2	
5–9	0.2	2349718	5	0	-5	
10–14	0.3	2340545	7	1	-6	
15–19	0	2316669	0	18	18	100.0
20–24	0.2	2336576	5	52	47	90.4
25–29	0.8	3189766	26	122	96	78.7
30–34	1.4	3748127	52	205	153	74.6
35–39	0.9	3455911	31	248	217	87.5
40–44	1.4	3007156	42	282	240	85.1
45–49	2.1	2719786	57	312	255	81.7
50–54	1.3	2368182	31	405	374	92.3
55–59	1.9	2954504	56	690	634	91.9
60–64	2	2369859	47	577	530	91.9
65–69	2.4	1841619	44	526	482	91.6
70–74	4.8	1296554	62	350	288	82.3
75–79	6.4	782064	50	207	157	75.8
80–84	5.9	457218	27	214	187	87.4
85+	3.3	363552	12	163	151	92.6
Total	1.1	39944028	**556**	**4372**	**3816**	**87.3**

[1] Incidence rates (per 100,000/year) of a historical Danish cohort of 1943/1947 (reference population)

[2] Data refer to German population (males) in 1995/1998

Table S2: Number and proportion of melanoma cases at baseline (1995/1998) attributable to UVR exposure, applying incidence rates of a historical Danish cohort from 1943/1947 as reference population, Germany (Females)

	IR[1]	Population size[2]	MM expected	MM observed[2]	MM excess	PAF%
	1943/1947	1995/1998	1995/1998	1995/1998	1995/1998	1995/1998
Age (years)	**A**	**B**	**C = (A*B)/100,000**	**D**	**E = D - C**	**F = (E/D) *100**
0–4	0.2	1940357	4	0	-4	
5–9	0.1	2229795	2	0	-2	
10–14	0.5	2219407	11	0	-11	
15–19	0	2194211	0	27	27	100.0
20–24	1	2229393	22	98	76	77.6
25–29	1	2988806	30	281	251	89.3
30–34	0.7	3488358	24	343	319	93.0
35–39	1.5	3259618	49	291	242	83.2
40–44	1.2	2894738	35	330	295	89.4
45–49	1.8	2654033	48	402	354	88.1
50–54	1.9	2325116	44	397	353	88.9
55–59	4.1	2960431	121	472	351	74.4
60–64	2.1	2487954	52	451	399	88.5
65–69	3.4	2155853	73	441	368	83.4
70–74	5.5	2117549	116	494	378	76.5
75–79	2.5	1612946	40	372	332	89.2
80–84	5.9	1139603	67	382	315	82.5
85+	5	1138817	57	304	247	81.3
Total	1.4	42036985	**795**	**5085**	**4290**	**84.4**

[1] Incidence rates (per 100,000/year) of a historical Danish cohort of 1943/1947 (reference population)

[2] Data refer to German population (females) in 1995/1998

Table S3: Excess number of melanoma cases in 1984/1988 compared to baseline (1980/1983) due to UVR exposure and demographic changes (population size and age), Denmark (Males)

	MM **baseline**	Population	MM **observed**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1980/1983	1980/1983	**1984/1988**	1984/1988	**1984/1988**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	148385	0	131143	0	0	0	0		
5–9	0	176316	0	151676	0	0	0	0		
10–14	1	189795	1	177519	1	0	0	0		
15–19	1	202622	2	193009	1	1	1	0		
20–24	4	184010	4	198261	5	0	-1	1		
25–29	8	182838	8	181363	8	0	0	0		
30–34	12	194899	12	180898	11	0	1	-1		
35–39	19	192144	19	195794	20	0	-1	1		
40–44	16	148848	26	184592	20	10	6	4		
45–49	16	132933	23	144524	17	7	6	1		
50–54	20	130168	28	128379	20	8	8	0		
55–59	22	133442	27	124526	20	5	7	-2		
60–64	22	124087	31	123209	22	9	9	0		
65–69	23	109607	34	108131	23	11	11	0		
70–74	21	88539	22	89677	21	1	1	0		
75–79	14	57762	19	63218	15	5	4	1		
80–84	6	32225	8	34730	6	2	2	0		
85+	9	18916	7	20715	10	-2	-3	1		
Total (Σ)	**214**	**2447534**	**271**	**2431364**	**220**	**57**	**51**	**6**	**-1**	**7**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 0.26635514

Population change from baseline* **L = (D-B)/B**: -0.00660657

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S3: Excess number of melanoma cases in 1989/1993 compared to baseline (1980/1983) due to UVR exposure and demographic changes (population size and age), Denmark (Males)

	MM **baseline**	Population	MM **observed**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1980/1983	1980/1983	**1989/1993**	1989/1993	**1989/1993**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	148385	0	143166	0	0	0	0		
5–9	0	176316	0	131096	0	0	0	0		
10–14	1	189795	1	151693	1	0	0	0		
15–19	1	202622	2	177630	1	1	1	0		
20–24	4	184010	5	190565	4	1	1	0		
25–29	8	182838	10	194298	8	2	2	0		
30–34	12	194899	10	178414	11	-2	-1	-1		
35–39	19	192144	19	178449	18	0	1	-1		
40–44	16	148848	30	193044	21	14	9	5		
45–49	16	132933	40	181048	21	24	19	5		
50–54	20	130168	31	140225	22	11	9	2		
55–59	22	133442	29	121960	20	7	9	-2		
60–64	22	124087	33	114761	21	11	12	-1		
65–69	23	109607	37	108115	22	14	15	-1		
70–74	21	88539	35	88455	21	14	14	0		
75–79	14	57762	28	65804	16	14	12	2		
80–84	6	32225	15	38915	7	9	8	1		
85+	9	18916	9	22904	11	0	-2	2		
Total (Σ)	**214**	**2447534**	**334**	**2420545**	**225**	**120**	**109**	**11**	**-3**	**14**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 0,560747664

Population change from baseline* **L = (D-B)/B**: -0.01102718

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S3: Excess number of melanoma cases in 1994/1998 compared to baseline (1980/1983) due to UVR exposure and demographic changes (population size and age), Denmark (Males)

	MM **baseline**	Population	MM **observed**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1980/1983	1980/1983	**1994/1998**	1994/1998	**1994/1998**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	148385	0	159951	0	0	0	0		
5–9	0	176316	0	143998	0	0	0	0		
10–14	1	189795	0	131571	1	-1	-1	0		
15–19	1	202622	1	152047	1	0	0	0		
20–24	4	184010	6	176439	4	2	2	0		
25–29	8	182838	10	188067	8	2	2	0		
30–34	12	194899	17	192063	12	5	5	0		
35–39	19	192144	21	176757	18	2	3	-1		
40–44	16	148848	25	176355	19	9	6	3		
45–49	16	132933	38	189833	23	22	15	7		
50–54	20	130168	48	176415	27	28	21	7		
55–59	22	133442	48	134391	22	26	26	0		
60–64	22	124087	43	113192	20	21	23	-2		
65–69	23	109607	42	101646	21	19	21	-2		
70–74	21	88539	43	88804	21	22	22	0		
75–79	14	57762	36	65048	16	22	20	2		
80–84	6	32225	19	40865	7	13	12	1		
85+	9	18916	11	25001	11	2	0	2		
Total (Σ)	**214**	**2447534**	**408**	**2432443**	**231**	**194**	**177**	**17**	**-1**	**18**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 0.906542056

Population change from baseline* **L = (D-B)/B**: -0.00616596

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): L = ($\Delta size/N_{BBB}$)

Table S3: Excess number of melanoma cases in 1999/2003 compared to baseline (1980/1983) due to UVR exposure and demographic changes (population size and age), Denmark (Males)

	MM **baseline**	Population	MM **observed**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1980/1983	1980/1983	**1999/2003**	1999/2003	**1999/2003**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	148385	0	155865	0	0	0	0		
5–9	0	176316	0	160685	0	0	0	0		
10–14	1	189795	0	144339	1	-1	-1	0		
15–19	1	202622	2	131830	1	1	1	0		
20–24	4	184010	5	150608	3	1	2	-1		
25–29	8	182838	13	173340	7	5	6	-1		
30–34	12	194899	22	184988	11	10	11	-1		
35–39	19	192144	24	189874	19	5	5	0		
40–44	16	148848	33	174670	19	17	14	3		
45–49	16	132933	38	173246	21	22	17	5		
50–54	20	130168	55	185017	29	35	26	9		
55–59	22	133442	67	169705	28	45	39	6		
60–64	22	124087	58	126134	23	36	35	1		
65–69	23	109607	45	101547	21	22	24	-2		
70–74	21	88539	45	85194	20	24	25	-1		
75–79	14	57762	36	66787	16	22	20	2		
80–84	6	32225	27	41451	7	21	20	1		
85+	9	18916	22	27554	13	13	9	4		
Total (Σ)	**214**	**2447534**	**492**	**2442834**	**239**	**278**	**253**	**25**	**0**	**25**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 1.299065421

Population change from baseline* **L = (D-B)/B**: -0.00192020

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S3: Excess number of melanoma cases in 2004/2008 compared to baseline (1980/1983) due to UVR exposure and demographic changes (population size and age), Denmark (Males)

	MM **baseline**	Population	MM **observed**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1980/1983	1980/1983	**2004/2008**	2004/2008	**2004/2008**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	148385	0	150628	0	0	0	0		
5–9	0	176316	0	156473	0	0	0	0		
10–14	1	189795	1	160954	1	0	0	0		
15–19	1	202622	3	144636	1	2	2	0		
20–24	4	184010	7	130398	3	3	4	-1		
25–29	8	182838	18	147861	6	10	12	-2		
30–34	12	194899	23	170257	10	11	13	-2		
35–39	19	192144	30	182877	19	11	11	0		
40–44	16	148848	42	187834	20	26	22	4		
45–49	16	132933	39	171868	20	23	19	4		
50–54	20	130168	50	168817	26	30	24	6		
55–59	22	133442	72	178299	29	50	43	7		
60–64	22	124087	99	160280	29	77	70	7		
65–69	23	109607	86	115228	24	63	62	1		
70–74	21	88539	64	87312	21	43	43	0		
75–79	14	57762	65	66406	16	51	49	2		
80–84	6	32225	41	44243	8	35	33	2		
85+	9	18916	31	29706	14	22	17	5		
Total (Σ)	**214**	**2447534**	**671**	**2454078**	**247**	**457**	**424**	**33**	**1**	**32**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 2.135514019

Population change from baseline* **L = (D-B)/B**: 0.002673712

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): L = ($\Delta size/N_{BBB}$)

Table S3: Excess number of melanoma cases in 2009/2013 compared to baseline (1980/1983) due to UVR exposure and demographic changes (population size and age), Denmark (Males)

	MM **baseline**	Population	MM **observed**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1980/1983	1980/1983	**2009/2013**	2009/2013	**2009/2013**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	148385	0	148955	0	0	0	0		
5–9	0	176316	0	151035	0	0	0	0		
10–14	1	189795	1	156877	1	0	0	0		
15–19	1	202622	4	161645	1	3	3	0		
20–24	4	184010	14	143703	3	10	11	-1		
25–29	8	182838	18	128732	5	10	13	-3		
30–34	12	194899	31	146127	9	19	22	-3		
35–39	19	192144	44	168927	17	25	27	-2		
40–44	16	148848	55	181373	20	39	35	4		
45–49	16	132933	72	185610	22	56	50	6		
50–54	20	130168	72	168135	26	52	46	6		
55–59	22	133442	87	163014	27	65	60	5		
60–64	22	124087	122	169326	30	100	92	8		
65–69	23	109607	140	148069	31	117	109	8		
70–74	21	88539	121	101657	24	100	97	3		
75–79	14	57762	85	70574	17	71	68	3		
80–84	6	32225	68	46368	8	62	60	2		
85+	9	18916	47	33650	16	38	31	7		
Total (Σ)	**214**	**2447534**	**981**	**2473777**	**257**	**767**	**724**	**43**	**2**	**41**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 3.584112150

Population change from baseline* **L = (D-B)/B**: 0.010722139

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): L = ($\Delta size/N_{BBB}$)

Table S3: Excess number of melanoma cases in 2014/2018 compared to baseline (1980/1983) due to UVR exposure and demographic changes (population size and age), Denmark (Males)

	MM **baseline**	Population	MM **projected**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1980/1983	1980/1983	**2014/2018**	2014/2018	**2014/2018**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	148385	0	133381	0	0	0	0		
5–9	0	176316	0	149663	0	0	0	0		
10–14	1	189795	1	151422	1	0	0	0		
15–19	1	202622	4	157674	1	3	3	0		
20–24	4	184010	12	160648	3	8	9	-1		
25–29	8	182838	30	141871	6	22	24	-2		
30–34	12	194899	34	127323	8	22	26	-4		
35–39	19	192144	49	145135	15	30	34	-4		
40–44	16	148848	71	167876	18	55	53	2		
45–49	16	132933	82	179605	21	66	61	5		
50–54	20	130168	103	182430	28	83	75	8		
55–59	22	133442	103	163207	27	81	76	5		
60–64	22	124087	127	155582	28	105	99	6		
65–69	23	109607	171	158013	33	148	138	10		
70–74	21	88539	201	133140	32	180	169	11		
75–79	14	57762	163	85449	20	149	143	6		
80–84	6	32225	98	51814	9	92	89	3		
85+	9	18916	86	38264	18	77	68	9		
Total (Σ)	**214**	**2447534**	**1335**	**2482496**	**268**	**1121**	**1067**	**54**	**3**	**51**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 5.238317757

Population change from baseline* **L = (D-B)/B**: 0.01428458

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S3: Excess number of melanoma cases in 2019/2023 compared to baseline (1980/1983) due to UVR exposure and demographic changes (population size and age), Denmark (Males)

	MM **baseline**	Population	MM **projected**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1980/1983	1980/1983	**2019/2023**	2019/2023	**2019/2023**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	148385	0	141392	0	0	0	0		
5–9	0	176316	0	134019	0	0	0	0		
10–14	1	189795	1	150250	1	0	0	0		
15–19	1	202622	4	152332	1	3	3	0		
20–24	4	184010	12	156685	3	8	9	-1		
25–29	8	182838	44	158846	6	36	38	-2		
30–34	12	194899	48	140735	9	36	39	-3		
35–39	19	192144	47	126859	13	28	34	-6		
40–44	16	148848	75	144897	16	59	59	0		
45–49	16	132933	94	167143	20	78	74	4		
50–54	20	130168	115	177681	28	95	87	8		
55–59	22	133442	138	178410	29	116	109	7		
60–64	22	124087	144	157054	28	122	116	6		
65–69	23	109607	169	146401	30	146	139	7		
70–74	21	88539	225	143594	34	204	191	13		
75–79	14	57762	255	114241	27	241	228	13		
80–84	6	32225	174	65245	12	168	162	6		
85+	9	18916	118	44592	21	109	97	12		
Total (Σ)	**214**	**2447534**	**1663**	**2500379**	**278**	**1449**	**1385**	**64**	**5**	**59**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 6.771028037

Population change from baseline* **L = (D-B)/B**: 0.02159096

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S3: Excess number of melanoma cases in 2024/2028 compared to baseline (1980/1983) due to UVR exposure and demographic changes (population size and age), Denmark (Males)

	MM **baseline**	Population	MM **projected**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1980/1983	1980/1983	**2024/2028**	2024/2028	**2024/2028**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	148385	0	156641	0	0	0	0		
5–9	0	176316	0	141750	0	0	0	0		
10–14	1	189795	1	134386	5	0	-4	4		
15–19	1	202622	4	150966	1	3	3	0		
20–24	4	184010	11	151125	3	7	8	-1		
25–29	8	182838	51	154756	6	43	45	-2		
30–34	12	194899	63	157493	9	51	54	-3		
35–39	19	192144	61	140159	14	42	47	-5		
40–44	16	148848	67	126534	13	51	54	-3		
45–49	16	132933	83	144082	17	67	66	1		
50–54	20	130168	120	165251	25	100	95	5		
55–59	22	133442	143	173886	28	121	115	6		
60–64	22	124087	179	172356	31	157	148	9		
65–69	23	109607	179	148962	31	156	148	8		
70–74	21	88539	211	134838	32	190	179	11		
75–79	14	57762	274	125036	29	260	245	15		
80–84	6	32225	262	89520	16	256	246	10		
85+	9	18916	198	56970	26	189	172	17		
Total (Σ)	**214**	**2447534**	**1907**	**2524712**	**286**	**1693**	**1621**	**72**	**7**	**65**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 7.911214953

Population change from baseline* **L = (D-B)/B**: 0.031533050

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S3: Excess number of melanoma cases in 2029/2033 compared to baseline (1980/1983) due to UVR exposure and demographic changes (population size and age), Denmark (Males)

	MM **baseline**	Population	MM **projected**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1980/1983	1980/1983	**2029/2033**	2029/2033	**2029/2033**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	148385	0	163610	0	0	0	0		
5–9	0	176316	0	157023	0	0	0	0		
10–14	1	189795	1	142119	1	0	0	0		
15–19	1	202622	3	135039	1	2	2	0		
20–24	4	184010	11	149799	3	7	8	-1		
25–29	8	182838	54	149307	6	46	48	-2		
30–34	12	194899	67	153499	9	55	58	-3		
35–39	19	192144	74	156921	16	55	58	-3		
40–44	16	148848	80	139897	15	64	65	-1		
45–49	16	132933	76	125960	15	60	61	-1		
50–54	20	130168	109	142605	22	89	87	2		
55–59	22	133442	139	162036	27	117	112	5		
60–64	22	124087	173	168562	30	151	143	8		
65–69	23	109607	210	164635	34	187	176	11		
70–74	21	88539	213	138746	33	192	180	12		
75–79	14	57762	246	119550	29	232	217	15		
80–84	6	32225	271	99586	18	265	253	12		
85+	9	18916	288	79648	37	279	251	28		
Total (Σ)	**214**	**2447534**	**2015**	**2548540**	**296**	**1801**	**1719**	**82**	**9**	**73**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 8.41588785

Population change from baseline* **L = (D-B)/B**: 0.04126840

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): L = ($\Delta size/N_{BBB}$)

Table S3: Excess number of melanoma cases in 1984/1988 compared to baseline (1980/1983) due to UVR exposure and demographic changes (population size and age), Denmark (Females)

	MM **baseline**	Population	MM **observed**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1980/1983	1980/1983	**1984/1988**	1984/1988	**1984/1988**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	141717	0	125489	0	0	0	0		
5–9	0	169304	0	145330	0	0	0	0		
10–14	0	180533	1	170272	0	1	1	0		
15–19	4	193069	4	183150	3	0	1	-1		
20–24	6	175640	7	189334	6	1	1	0		
25–29	14	174270	15	173780	14	1	1	0		
30–34	21	187032	16	173400	19	-5	-3	-2		
35–39	28	184875	32	188519	30	4	2	2		
40–44	28	145700	41	178570	34	13	7	6		
45–49	29	133157	36	142587	31	7	5	2		
50–54	28	132394	26	130068	30	-2	-4	2		
55–59	31	139783	30	129189	29	-1	1	-2		
60–64	29	133824	33	133863	29	4	4	0		
65–69	25	125553	33	124302	24	8	9	-1		
70–74	28	112486	32	113158	28	4	4	0		
75–79	21	85764	27	93546	23	6	4	2		
80–84	15	55269	16	62649	17	1	-1	2		
85+	11	36741	15	45033	12	4	3	1		
Total (Σ)	**318**	**2507109**	**364**	**2502238**	**329**	**46**	**35**	**11**	**-1**	**12**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 0.144654088

Population change from baseline* **L = (D-B)/B**: -0.00194304

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S3: Excess number of melanoma cases in 1989/1993 compared to baseline (1980/1983) due to UVR exposure and demographic changes (population size and age), Denmark (Females)

	MM **baseline**	Population	MM **observed**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1980/1983	1980/1983	**1989/1993**	1989/1993	**1989/1993**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	141717	0	135680	0	0	0	0		
5–9	0	169304	0	125605	0	0	0	0		
10–14	0	180533	0	145421	0	0	0	0		
15–19	4	193069	3	169501	3	-1	0	-1		
20–24	6	175640	14	180841	6	8	8	0		
25–29	14	174270	21	186278	15	7	6	1		
30–34	21	187032	24	171932	19	3	5	-2		
35–39	28	184875	30	172293	27	2	3	-1		
40–44	28	145700	44	187013	36	16	8	8		
45–49	29	133157	50	176259	37	21	13	8		
50–54	28	132394	41	139624	30	13	11	2		
55–59	31	139783	31	125703	28	0	3	-3		
60–64	29	133824	33	122908	29	4	4	0		
65–69	25	125553	39	124371	24	14	15	-1		
70–74	28	112486	44	111366	28	16	16	0		
75–79	21	85764	32	95187	23	11	9	2		
80–84	15	55269	22	70014	19	7	3	4		
85+	11	36741	16	54395	15	5	1	4		
Total (Σ)	**318**	**2507109**	**444**	**2494392**	**339**	**126**	**105**	**21**	**-2**	**23**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 0,396226415

Population change from baseline* **L = (D-B)/B**: -0.00507246

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S3: Excess number of melanoma cases in 1994/1998 compared to baseline (1980/1983) due to UVR exposure and demographic changes (population size and age), Denmark (Females)

	MM **baseline**	Population	MM **observed**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1980/1983	1980/1983	**1994/1998**	1994/1998	**1994/1998**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	141717	0	151754	0	0	0	0		
5–9	0	169304	0	136558	0	0	0	0		
10–14	0	180533	0	126098	0	0	0	0		
15–19	4	193069	3	145254	3	-1	0	-1		
20–24	6	175640	13	168426	6	7	7	0		
25–29	14	174270	31	179117	14	17	17	0		
30–34	21	187032	34	184986	20	13	14	-1		
35–39	28	184875	34	171520	27	6	7	-1		
40–44	28	145700	41	171422	33	13	8	5		
45–49	29	133157	58	185123	40	29	18	11		
50–54	28	132394	56	173202	37	28	19	9		
55–59	31	139783	42	135706	30	11	12	-1		
60–64	29	133824	39	119797	26	10	13	-3		
65–69	25	125553	43	113924	22	18	21	-3		
70–74	28	112486	40	110872	28	12	12	0		
75–79	21	85764	36	93173	23	15	13	2		
80–84	15	55269	28	71041	20	13	8	5		
85+	11	36741	20	61814	17	9	3	6		
Total (Σ)	**318**	**2507109**	**518**	**2499785**	**346**	**200**	**172**	**28**	**-1**	**29**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 0.628930818

Population change from baseline* **L = (D-B)/B**: -0.00292113

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S3: Excess number of melanoma cases in 1999/2003 compared to baseline (1980/1983) due to UVR exposure and demographic changes (population size and age), Denmark (Females)

	MM **baseline**	Population	MM **observed**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1980/1983	1980/1983	**1999/2003**	1999/2003	**1999/2003**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	141717	0	147918	0	0	0	0		
5–9	0	169304	0	152507	0	0	0	0		
10–14	0	180533	1	136936	0	1	1	0		
15–19	4	193069	4	126177	2	0	2	-2		
20–24	6	175640	13	144093	5	7	8	-1		
25–29	14	174270	28	166756	14	14	14	0		
30–34	21	187032	38	177355	20	17	18	-1		
35–39	28	184875	45	184303	29	17	16	1		
40–44	28	145700	48	170635	33	20	15	5		
45–49	29	133157	47	169696	36	18	11	7		
50–54	28	132394	63	182127	39	35	24	11		
55–59	31	139783	66	168904	38	35	28	7		
60–64	29	133824	49	130125	28	20	21	-1		
65–69	25	125553	42	111349	22	17	20	-3		
70–74	28	112486	47	101524	25	19	22	-3		
75–79	21	85764	43	93037	23	22	20	2		
80–84	15	55269	35	70468	19	20	16	4		
85+	11	36741	36	67457	19	25	17	8		
Total (Σ)	**318**	**2507109**	**605**	**2501366**	**352**	**287**	**253**	**34**	**-1**	**35**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 0.902515723

Population change from baseline* **L = (D-B)/B**: -0.0022905

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S3: Excess number of melanoma cases in 2004/2008 compared to baseline (1980/1983) due to UVR exposure and demographic changes (population size and age), Denmark (Females)

	MM **baseline**	Population	MM **observed**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1980/1983	1980/1983	**2004/2008**	2004/2008	**2004/2008**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	141717	0	143729	0	0	0	0		
5–9	0	169304	0	148639	0	0	0	0		
10–14	0	180533	1	152817	0	1	1	0		
15–19	4	193069	5	137161	2	1	3	-2		
20–24	6	175640	24	125114	4	18	20	-2		
25–29	14	174270	43	143049	12	29	31	-2		
30–34	21	187032	56	165160	18	35	38	-3		
35–39	28	184875	71	176755	28	43	43	0		
40–44	28	145700	73	183621	35	45	38	7		
45–49	29	133157	67	169198	36	38	31	7		
50–54	28	132394	67	167113	36	39	31	8		
55–59	31	139783	80	177938	40	49	40	9		
60–64	29	133824	88	162772	36	59	52	7		
65–69	25	125553	70	122644	24	45	46	-1		
70–74	28	112486	51	100482	25	23	26	-3		
75–79	21	85764	46	86072	21	25	25	0		
80–84	15	55269	46	71226	20	31	26	5		
85+	11	36741	47	70458	20	36	27	9		
Total (Σ)	**318**	**2507109**	**835**	**2503949**	**357**	**517**	**478**	**39**	**0**	**39**
	N_{BBB}		N_{FFF}		N_{BFF}	$N_{FF\,F}$ - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 1.625786164

Population change from baseline* **L = (D-B)/B**: -0.00126034

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S3: Excess number of melanoma cases in 2009/2013 compared to baseline (1980/1983) due to UVR exposure and demographic changes (population size and age), Denmark (Females)

	MM **baseline**	Population	MM **observed**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1980/1983	1980/1983	**2009/2013**	2009/2013	**2009/2013**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	141717	0	141334	0	0	0	0		
5–9	0	169304	1	144205	0	1	1	0		
10–14	0	180533	1	149065	0	1	1	0		
15–19	4	193069	8	153494	3	4	5	-1		
20–24	6	175640	29	136743	5	23	24	-1		
25–29	14	174270	44	124589	10	30	34	-4		
30–34	21	187032	61	142343	16	40	45	-5		
35–39	28	184875	83	164971	26	55	57	-2		
40–44	28	145700	105	176489	34	77	71	6		
45–49	29	133157	110	182722	39	81	71	10		
50–54	28	132394	93	167293	36	65	57	8		
55–59	31	139783	88	163643	36	57	52	5		
60–64	29	133824	114	172225	38	85	76	9		
65–69	25	125553	111	154757	30	86	81	5		
70–74	28	112486	82	112920	28	54	54	0		
75–79	21	85764	65	86807	22	44	43	1		
80–84	15	55269	60	67010	18	45	42	3		
85+	11	36741	69	74304	21	58	48	10		
Total (Σ)	**318**	**2507109**	**1124**	**2514913**	**362**	**806**	**762**	**44**	**1**	**43**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 2.53459119

Population change from baseline* **L = (D-B)/B**: 0.003112828

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S3: Excess number of melanoma cases in 2014/2018 compared to baseline (1980/1983) due to UVR exposure and demographic changes (population size and age), Denmark (Females)

	MM **baseline**	Population	MM **projected**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1980/1983	1980/1983	**2014/2018**	2014/2018	**2014/2018**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	141717	0	126507	0	0	0	0		
5–9	0	169304	1	141819	0	1	1	0		
10–14	0	180533	1	144575	0	1	1	0		
15–19	4	193069	6	149750	3	2	3	-1		
20–24	6	175640	30	152725	5	24	25	-1		
25–29	14	174270	70	135585	11	56	59	-3		
30–34	21	187032	78	123807	14	57	64	-7		
35–39	28	184875	102	142113	22	74	80	-6		
40–44	28	145700	127	164723	31	99	96	3		
45–49	29	133157	148	175867	38	119	110	9		
50–54	28	132394	132	181110	39	104	93	11		
55–59	31	139783	114	164449	37	83	77	6		
60–64	29	133824	115	159046	35	86	80	6		
65–69	25	125553	146	164937	32	121	114	7		
70–74	28	112486	142	144610	36	114	106	8		
75–79	21	85764	111	100299	25	90	86	4		
80–84	15	55269	85	69555	19	70	66	4		
85+	11	36741	101	75867	21	90	80	10		
Total (Σ)	**318**	**2507109**	**1509**	**2517344**	**368**	**1191**	**1141**	**50**	**1**	**49**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 3.745283019

Population change from baseline* **L = (D-B)/B**: 0.00408239

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S3: Excess number of melanoma cases in 2019/2023 compared to baseline (1980/1983) due to UVR exposure and demographic changes (population size and age), Denmark (Females)

	MM **baseline**	Population	MM **projected**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1980/1983	1980/1983	**2019/2023**	2019/2023	**2019/2023**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	141717	0	134249	0	0	0	0		
5–9	0	169304	1	127151	0	1	1	0		
10–14	0	180533	1	142362	0	1	1	0		
15–19	4	193069	6	145303	3	2	3	-1		
20–24	6	175640	29	149047	5	23	24	-1		
25–29	14	174270	90	151583	12	76	78	-2		
30–34	21	187032	105	134974	15	84	90	-6		
35–39	28	184875	124	123892	20	96	104	-8		
40–44	28	145700	136	142219	27	108	109	-1		
45–49	29	133157	141	164651	35	112	106	6		
50–54	28	132394	141	174895	38	113	103	10		
55–59	31	139783	126	178911	40	95	86	9		
60–64	29	133824	125	160769	35	96	90	6		
65–69	25	125553	129	153154	30	104	99	5		
70–74	28	112486	154	155073	38	126	116	10		
75–79	21	85764	172	130567	32	151	140	11		
80–84	15	55269	182	82733	23	167	159	8		
85+	11	36741	173	79302	22	162	151	11		
Total (Σ)	**318**	**2507109**	**1835**	**2530835**	**375**	**1517**	**1460**	**57**	**3**	**54**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 4.770440252

Population change from baseline* **L = (D-B)/B**: 0.00946349

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S3: Excess number of melanoma cases in 2024/2028 compared to baseline (1980/1983) due to UVR exposure and demographic changes (population size and age), Denmark (Females)

	MM **baseline**	Population	MM **projected**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1980/1983	1980/1983	**2024/2028**	2024/2028	**2024/2028**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	141717	0	148656	0	0	0	0		
5–9	0	169304	0	134651	0	0	0	0		
10–14	0	180533	1	127479	0	1	1	0		
15–19	4	193069	6	142875	3	2	3	-1		
20–24	6	175640	30	144453	5	24	25	-1		
25–29	14	174270	105	147760	12	91	93	-2		
30–34	21	187032	123	150733	17	102	106	-4		
35–39	28	184875	145	134968	21	117	124	-7		
40–44	28	145700	164	123848	24	136	140	-4		
45–49	29	133157	170	142010	30	141	140	1		
50–54	28	132394	160	163675	35	132	125	7		
55–59	31	139783	160	172850	39	129	121	8		
60–64	29	133824	150	175353	38	121	112	9		
65–69	25	125553	149	155620	30	124	119	5		
70–74	28	112486	151	145107	36	123	115	8		
75–79	21	85764	178	140897	35	157	143	14		
80–84	15	55269	204	109295	30	189	174	15		
85+	11	36741	206	92698	26	195	180	15		
Total (Σ)	**318**	**2507109**	**2102**	**2552927**	**381**	**1784**	**1721**	**63**	**6**	**57**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 5.610062893

Population change from baseline* **L = (D-B)/B**: 0.01827523

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): $L = (\Delta size/N_{BBB})$

Table S3: Excess number of melanoma cases in 2029/2033 compared to baseline (1980/1983) due to UVR exposure and demographic changes (population size and age), Denmark (Females)

	MM **baseline**	Population	MM **projected**	Population	MM **expected**	total change **(MM excess)**	Change due UVR	Change due to pop. (total)	Change due to pop. size	Change due to pop age
	1980/1983	1980/1983	**2029/2033**	2029/2033	**2029/2033**					
Age	**A**	**B**	**C**	**D**	**E = (A/B)*D**	**F = C-A**	**G = C-E**	**H = E-A**	**I = L*N_{BBB}**	**J = H-I**
0–4	0	141717	0	155265	0	0	0	0		
5–9	0	169304	1	149086	0	1	1	0		
10–14	0	180533	1	134979	0	1	1	0		
15–19	4	193069	7	127948	2	3	5	-2		
20–24	6	175640	32	142053	5	26	27	-1		
25–29	14	174270	123	143226	12	109	111	-2		
30–34	21	187032	144	146962	16	123	128	-5		
35–39	28	184875	169	150757	24	141	145	-4		
40–44	28	145700	192	134968	26	164	166	-2		
45–49	29	133157	205	123748	27	176	178	-2		
50–54	28	132394	196	141295	30	168	166	2		
55–59	31	139783	186	162007	36	155	150	5		
60–64	29	133824	198	169784	37	169	161	8		
65–69	25	125553	188	170442	33	163	155	8		
70–74	28	112486	185	148363	37	157	148	9		
75–79	21	85764	186	133011	33	165	153	12		
80–84	15	55269	226	118761	33	211	193	18		
85+	11	36741	245	121465	34	234	211	23		
Total (Σ)	**318**	**2507109**	**2484**	**2574121**	385	**2166**	**2099**	**67**	**8**	**59**
	N_{BBB}		N_{FFF}		N_{BFF}	N_{FFF} - N_{BBB}	N_{FFF} - N_{BFF}	N_{BFF} - N_{BBB}		

Excess melanomas from baseline **K = (C-A)/A**: 6.81132075

Population change from baseline* **L = (D-B)/B**: 0.02672895

* Relative change in pop. size (column L) is equal to relative change in the number of new melanoma cases due to pop. size ($\Delta size/N_{BBB}$): L = ($\Delta size$ N_{BBB})

Table S4: Number and proportion of melanoma cases at baseline (1980/1983) attributable to UVR exposure, applying incidence rates of a historical Danish cohort from 1943/1947 as reference population, Denmark (Males)

	IR[1]	Population size[2]	MM expected	MM observed[2]	MM excess	PAF%
	1943/1947	1980/1983	1980/1983	1980/1983	1980/1983	1980/1983
Age (years)	**A**	**B**	**C = (A*B)/100,000**	**D**	**E = D - C**	**F = (E/D) *100**
0–4	0.1	148385	0	0	0	
5–9	0.2	176316	0	0	0	
10–14	0.3	189795	1	1	0	0.0
15–19	0	202622	0	1	1	100.0
20–24	0.2	184010	0	4	4	100.0
25–29	0.8	182838	1	8	7	87.5
30–34	1.4	194899	3	12	9	75.0
35–39	0.9	192144	2	19	17	89.5
40–44	1.4	148848	2	16	14	87.5
45–49	2.1	132933	3	16	13	81.3
50–54	1.3	130168	2	20	18	90.0
55–59	1.9	133442	2	22	20	90.9
60–64	2	124087	2	22	20	90.9
65–69	2.4	109607	3	23	20	87.0
70–74	4.8	88539	4	21	17	81.0
75–79	6.4	57762	4	14	10	71.4
80–84	5.9	32225	2	6	4	66.7
85+	3.3	18916	1	9	8	88.9
Total	1.1	**2447534**	**32**	**214**	**182**	**85.0**

[1] Incidence rates (per 100,000/year) of a historical Danish cohort of 1943/1947 (reference population)

[2] Data refer to Danish population (males) in 1980/1983

Table S4: Number and proportion of melanoma cases at baseline (1980/1983) attributable to UVR exposure, applying incidence rates of a historical Danish cohort from 1943/1947 as reference population, Denmark (Females)

	IR[1]	**Population size**[2]	**MM expected**	**MM observed**[2]	**MM excess**	**PAF%**
	1943/1947	1980/1983	1980/1983	1980/1983	1980/1983	1980/1983
Age (years)	**A**	**B**	**C = (A*B)/100,000**	**D**	**E = D - C**	**F = (E/D) *100**
0–4	0.2	141717	0	0	0	
5–9	0.1	169304	0	0	0	
10–14	0.5	180533	1	0	-1	
15–19	0	193069	0	4	4	100.0
20–24	1	175640	2	6	4	66.7
25–29	1	174270	2	14	12	85.7
30–34	0.7	187032	1	21	20	95.2
35–39	1.5	184875	3	28	25	89.3
40–44	1.2	145700	2	28	26	92.9
45–49	1.8	133157	2	29	27	93.1
50–54	1.9	132394	3	28	25	89.3
55–59	4.1	139783	6	31	25	80.6
60–64	2.1	133824	3	29	26	89.7
65–69	3.4	125553	4	25	21	84.0
70–74	5.5	112486	6	28	22	78.6
75–79	2.5	85764	2	21	19	90.5
80–84	5.9	55269	3	15	12	80.0
85+	5	36741	2	11	9	81.8
Total	1.4	**2507109**	**42**	**318**	**276**	**86.8**

[1] Incidence rates (per 100,000/year) of a historical Danish cohort of 1943/1947 (reference population)

[2] Data refer to Danish population (females) in 1980/1983