Trends and risk factors of cutaneous melanoma in Europe

Trends en risicofactoren voor het melanoom van de huid in Europa

Esther de Vries

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Voor Linda

Als ik de Aarde ga verwarmen
Laat ik haar leven in mijn armen
Van sterren weefde ik het verre, aan het Noorderlicht
Maar soms ben ik kokend als lood
Ik ben het leven en de dood
In vuur en liefde, in alle pijn
En kind, ik troost je, kijk omhoog
Vandaag span ik mijn regenboog, die is alleen voor jou

(Lennaert Nijgh; Pastorale)

Contents

Chapter 1

Introduction

Introduction

In the past century, skin cancer has become a large but 'silent' epidemic in white Caucasian populations all over the world. The group of skin cancers can be divided into three main types of skin cancer: cutaneous malignant melanomas (melanoma, 10% of skin cancers), squamous cell carcinomas (SCC, 10% of skin cancers) and basal cell carcinomas (BCC, 80% of skin cancers). Squamous and basal cell carcinomas together comprise the majority of the 'non-melanoma skin cancers' (NMSC). As NMSC are rarely fatal, in contrast to melanoma, which can be very aggressive, reports on skin cancer usually focus on melanoma. However, NMSC constitute a substantial part of the total number of new cancer cases, though their numbers are usually difficult to define as most cancer registries do not routinely register them. In the Eindhoven cancer registry, one of the few cancer registries collecting information on basal cell carcinoma, all skin cancer types have been registered since 1955, and in the period 1993-1997 new primary BCC accounted for 17%, SCC for 3% and melanoma for 2% of the total number of incident cancers [1].

Since the 1970s many publications have appeared on the rapidly increasing trends in melanoma, initially only in mortality, later also for incidence rates. These publications each applied their own choice of patient population and standardisation methods [2-11]. In the 1990s, there was a lack, particularly for incidence, of systematic and formal analysis of international melanoma trends and age-specific trend analyses. Moreover, incidence and mortality rates were often presented separately, covering different populations and/or non overlapping time periods. Only very limited information was available on trends in non-melanoma skin cancers and most information on NMSC came from Australia [12-17]. Within Europe, in the 1990s, there were significant differences in survival of melanoma and in the ratio of incidence to mortality rates.

Observations from descriptive epidemiology (geographical patterns, ethnic variation, risks in migrants, anatomical distribution, socio-economic status and occupation [18-28]) suggested an important role of exposure to sunlight in skin cancer development. This role was most straightforward in the case of squamous cell carcinoma but markedly less so in basal cell carcinoma and in particular, melanoma, as has recently been presented graphically by Armstrong et al (figure 1) [29].
Non-melanoma skin cancers are positively correlated with measurements of cumulative sun damage and a history of keratoses. Squamous cell carcinoma is mainly caused by the accumulation of large doses of chronic sun exposure. Basal cell carcinomas seem influenced by both chronic and intermittent sun exposure patterns. Melanomas (not including lentigo maligna melanomas) are most strongly influenced by intermittent exposure to ultraviolet radiation. The intermittent sun exposure hypothesis was formulated for melanoma in the 1980s, based on the following findings: (a) melanoma occurrence is associated with sunburns; (b) melanoma does not follow an anatomical distribution concurring with sites of sun exposure, unlike squamous cell carcinoma, which does;

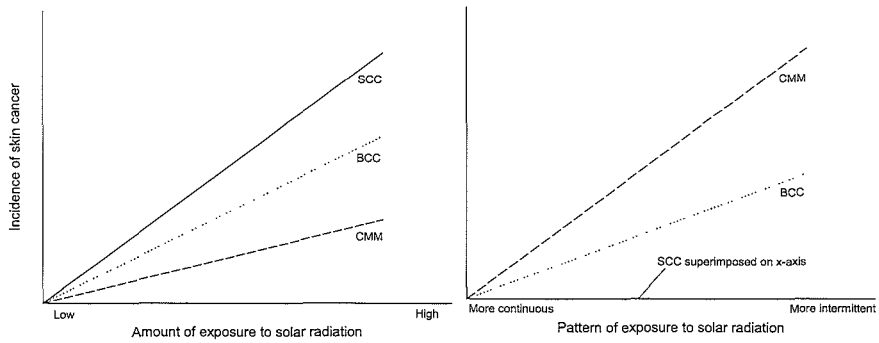

Figure 1: Illustration of hypothesis regarding independence of amount and pattern of exposure to solar radiation and determining risk of BCC, SCC and melanoma (CMM). From [29].

(c) indoor workers are at a greater risk of developing a melanoma than outdoor workers; (d) vacations in sunnier areas than the place of residence is a common risk factor for melanoma in Europeans.

The ultraviolet component of sunlight (mainly UV-A and UV-B) is responsible for changes in cells ultimately leading to skin cancer [30, 31].
Based on this knowledge it was concluded that limiting the population's amount of exposure to ultraviolet radiation could prevent further increases in skin cancer incidence. Moreover, as there is no effective treatment for metastasised melanomas, the only way to improve the prognosis of melanoma patients is to detect melanomas in early stages. Focussing on early detection is therefore of key importance in the battle against melanoma mortality. In the 1970s, primary and secondary prevention campaigns were organised in Australia, later followed by Scotland and certain Northern and Central European countries [32-37]. If these prevention efforts have been effective, rates of melanoma incidence and mortality will have presently stabilised or even decreased, thereby making a renewed effort in describing the historical and actuarial skin cancer epidemic in the Netherlands and throughout Europe desirable.

During the 1980s, use of sunbeds became popular in north-western Europe. The effect of exposure to ultraviolet (UV) radiation emitted from sunbeds had been studied in several case-control studies. However, these studies suffered from methodological and practical problems such as confounding by sun exposure, socially desirable answers, a (too) short period between exposure and outcome, limited sample sizes, etc. Nevertheless, the effects of ultraviolet radiation from artificial sources, such as sunbeds, were assumed to be similar to those of the sun, depending on the ratio of UV-A and UV-B and therefore potentially contributing to the increases in skin cancer incidence. A case-control study, of adequate size and to be executed in 6 European countries, was designed, to study the effect of sunbeds on melanoma risk, by experts experienced in the field of melanoma epidemiology.

In this thesis we have attempted to describe the skin cancer epidemic in the Netherlands and the melanoma epidemic in Europe, allowing comparisons between countries and regions within Europe. We also present some of the results of the large, international case-control study investigating the association between sunbed use and melanoma risk.

The main questions addressed in this thesis are:

1. **What were the trends in melanoma incidence and mortality rates in the Netherlands and throughout Europe, and are there indications that they may start to level off?**
2. **Are these trends comparable with those of other skin cancers?**
3. **What explanations for the trends are suggested by the observed patterns in melanoma incidence and mortality?**
4. **Did the use of sunbeds contribute to the increases in melanoma incidence?**

Chapters 2 and 4 of this thesis are based on routinely collected cancer registry data. In chapter 2 trends in incidence and mortality and the expected future burden of skin cancer (up to 2015) in the Netherlands are explored. We examined whether the observed, apparently decreasing melanoma mortality rates in cohorts born after 1955 continued [11] and described the melanoma epidemic more in-depth. Patterns in melanoma incidence and mortality across Europe are presented, according to sex, age and country.

In **chapter 3** we analysed determinants of melanoma incidence such as season, latitude and sunbed use. Over the last decades, the use of sunbeds has become increasingly popular in Europe. In **chapter 3** risks associated with sunbed use, determinants of melanoma risk and determinants of sunbed use are analysed, using the case-control approach. In addition, the perception by melanoma patients themselves about the causes of their melanoma was studied. We were initially interested in the latter, to better understand the patients' perspective. When starting the analysis of the case-control data, however, indications of underreporting of sun-exposure by the melanoma cases arose. The patients' opinion supported the suggestion of underreporting.

In **chapter 4** we explored possible reasons for the increases in melanoma incidence and stabilisations in mortality rates. We also explored the large differences in incidence/mortality ratios and survival rates across Europe, looking at the distribution of known prognostic factors for melanoma across Europe.

In **chapter 5** we made a summary of the trends in and current knowledge about melanoma and explored reasons for the observed trends throughout Europe.

Lastly, in **chapter 6**, a summary of the results is given and the four research questions are answered. Limitations of the data used and methodological aspects are discussed and the results interpreted. Finally, scenarios for the future burden of skin cancer in the Netherlands and suggestions for future public health action and research are discussed.

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Chapter 2

Variation in disease frequency in time and place in the Netherlands and Europe

Chapter 2.1

Rising trends in the incidence of and mortality from cutaneous melanoma in the Netherlands: a northwest to southeast gradient?

Reprinted from European Journal of Cancer 39(10): Vries E. de, Schouten L.J., Visser O., Eggermont A.M.M., Coebergh J.W.W., Working Group of Regional Cancer Registries: Rising trends in the incidence of and mortality from cutaneous melanoma in the Netherlands: a northwest to southeast gradient? Pages 1439-1446.

Summary

The aim of this study was to determine characteristics of the trends in incidence of and mortality from cutaneous malignant melanoma in The Netherlands. We used incidence data from the Netherlands Cancer Registry since 1989 and the causes of death registry of Statistics Netherlands since 1950. Data were age-adjusted and age-specific rates were calculated. Age-period-cohort modelling was applied to the mortality data. Between 1989 and 1998, age-adjusted incidence rates increased, mainly among those aged 45 years and older. Incidence rates were highest in the north-west and lowest in the south-east. Mortality rates increased in all age-categories, but more so among males than females. For women, an age-period model fitted the data, with decreasing relative risks after 1972. Age-period-cohort models were needed for males. The most likely explanation for the higher incidence is increasing intermittent over-exposure to ultraviolet (UV) radiation. The regional differences in melanoma incidence rates would correspond with host characteristics opportunities for and recreational exposure. Melanomas were detected at earlier stages in females, possibly explaining the flattening out of the female mortality rates.

Introduction

Over the last decades, increasing trends in the incidence of and mortality from cutaneous malignant melanoma (hereafter called melanoma) have been observed for all Caucasian populations, although mortality rates have begun to stabilise in middle-aged individuals in some populations [1-5]. The main environmental risk factor for melanoma is exposure to ultraviolet (UV) radiation, especially intermittent exposure at a young age (relative risk 1.4–4.3) [6, 7]. Prosperity and secularisation have increased in The Netherlands in the past century [8]. This probably resulted in increased intermittent exposure to UV radiation due to more sunbathing, which may have influenced the incidence rates for melanoma in The Netherlands.
The major host factor related to melanoma risk is skin type: people with a fair complexion who burn easily (skin types 1–2) have a 2- to 3-fold greater risk of developing malignant melanoma than those who tan easily (skin types 3–4) [9]. Most people in The Netherlands have skin types 2–3 [10].
We analysed the incidence (also according to anatomical site) and mortality rates for cutaneous melanoma in The Netherlands in the time periods of 1989–1998 and 1950–1999, respectively to determine trends. Birth cohort effects on mortality were investigated, for people born since 1900, to see whether the previously observed flattening of the mortality rates in people born after the 1950 in The Netherlands continues [2].

Patients and methods

Data
Data according to anatomical site, histological type and region were obtained from the population-based Netherlands Cancer Registry [11]. The cancer registry receives lists of newly diagnosed cases on a regular basis from all pathology departments in the country. In addition, lists of hospitalised cancer patients are provided by the medical records departments of the hospitals. Following this notification, the medical records of newly diagnosed patients (and tumours) are collected and the necessary information is abstracted from the medical records by trained tumour registrars from the cancer registry. Data are checked for duplicate records. Records are assumed to be complete since 1989 [12, 13]. Statistics Netherlands (CBS) provided mortality data (according to the International Classification of Diseases (ICD) codes) for the period of 1950–1999. Regional mortality data were available since 1969 (region north consisting of the provinces Friesland, Groningen, Drente; region west: North and South Holland, Zeeland, Utrecht; region south: Northern Brabant and Limburg and region east: Overijssel, Gelderland, Flevoland [13-15]).The Netherlands are situated between 50.5 and 53.3° latitude and have a relatively large coastal area (North Sea coast) in the western and northern parts of the country. Annual incidence rates were computed per 100,000 person-years for each sex and calculated as 3-year moving means. Age-specific mortality rates were calculated per 100,000 person-years and per 5-year birth cohorts since 1900.

Analysis

Age-adjustment was performed by direct standardization according to the European Standard Population (European Standardised Rates (ESR)). Trends in both incidence and mortality were estimated by calculating the Estimated Annual Percentage Change (EAPC). The EAPC was calculated by fitting a regression line to the natural logarithm of the rates using calendar year as a regressor variable, i.e. $y = mx + b$ where y = ln(rate) and x = calendar year. Then the EAPC=100*(e^m-1). Testing the hypothesis is equal to zero is equivalent to testing the hypothesis that the slope of the line in the above equation is equal to zero. The latter hypothesis was tested using the t-distribution of $m/SE(m)$, while the number of degrees of freedom was equal to the number of calendar years minus two. The standard error of m, i.e. $SE(m)$, was obtained from the fit of the regression line. This calculation assumed that the rates increased or decreased at a constant rate over the entire period, although the accuracy of this assumption has not been tested. Tests for regional differences in ESR were performed. The Netherlands were divided into four regions: west, north, east, south. Poisson models using period of registration as a continuous variable and region as a categorical variable were constructed using STATA software, using the equation: $y = N \times e^{\alpha region + \beta period}$.

Likelihood ratio tests were performed for the models with only period of registration ($y = N \times e^{\alpha+\beta period}$) versus the model which included region ($y = N \times e^{\alpha region+\beta period}$), to see if the variable region contributed significantly to the observed rates. Non-parametric tests for trend from north to south using the Cuzick adaptation of the Wilcoxon rank sumtest were performed using the nptrend option in the STATA software [16]. The trend was calculated for the order: north, west, east, south. Differences in the stage distribution according to the TNM criteria by gender were calculated with a Pearson $\chi 2$ test. Age-period-cohort analyses were performed on the mortality data for 1958–1997, using EUROCIM software [17]. This software works according to the Clayton and Schifflers methods [18, 19].

Table 1: Age-specific incidence (unstandardised, per 10^5 person-years) 1989-1997 of various histological subtypes and anatomical sites of melanoma according to different age categories, 1989-'97

	Males		Females	
Type of melanoma	35-64 yrs	≥ 65 yrs	35-64 yrs	≥ 65 yrs
LMM	0.3	1.8	0.3	1.7
SSM	6.9	7.1	10.8	8.2
NM	2.4	5.0	2.5	4.4
ALM	0.1	0.3	0.1	0.3
Other	5.1	10.1	6.7	9.5
Anatomical site				
Head/neck	1.7	8.0	1.5	5.8
Trunk	7.5	8.0	5.5	2.8
Arms	2.4	3.7	4.1	5.7
Legs	2.5	3.4	8.7	8.9

(LMM: lentigo maligna melanoma, SSM: superficial spreading melanoma, NM: nodular melanoma, ALM: acrolentiginous melanoma, Other: other and not specified melanomas)

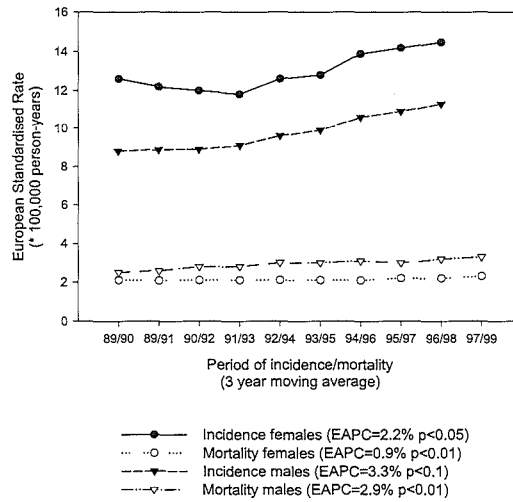

Figure 1: Incidence and mortality of cutaneous malignant melanoma, 3-year moving average, European Standardised Rates (*10^5 person-years), with Estimated Annual Percentage Change (EAPC).fig.

Results

Overall incidence and mortality data

Between 1989 and 1998, a total of 18,383 melanoma cases were diagnosed in The Netherlands (7,502 males and 10,881 females). The average population size of the Netherlands in this period was 15,255,745. Between 1950 and 1999, 10,854 melanoma deaths (5,678 males and 5,176 females) were recorded by Statistics Netherlands. The total population size of The Netherlands increased from 10,113,741 inhabitants in 1950 to 15,760,225 in 1999. Between 1989 and 1998, the age-adjusted incidence rates for melanoma increased from 9.5 to 11.5 per 100,000 person-years for males (EAPC 3.3%, P=0.006) and from 13.3 to 14.8 per 100,000 person-years for females (ESR) (EAPC 2.2%, P=0.004) (fig. 1). Overall age-adjusted mortality rates remained largely unchanged for females at ±2.2 per 105 person-years (EAPC 0.9%, P<0.004). In contrast, male melanoma mortality rates increased markedly from 2.5 to 3.1 per 105 person-years (EAPC 2.9%, P=0.001) (fig. 1). Age-specific incidence rose in absolute terms mainly in those over age 45; mortality rates increased in all age categories for both sexes in the period of 1950–1999 (figs. 2 and 3).

Incidence according to localisation and histological subtype

For males, melanomas occurred predominantly on the trunk, for females on the legs. Melanomas on the head and neck area were more common among older people. Other subtypes of melanoma were encountered more often in patients aged 65 years or older (table 1).

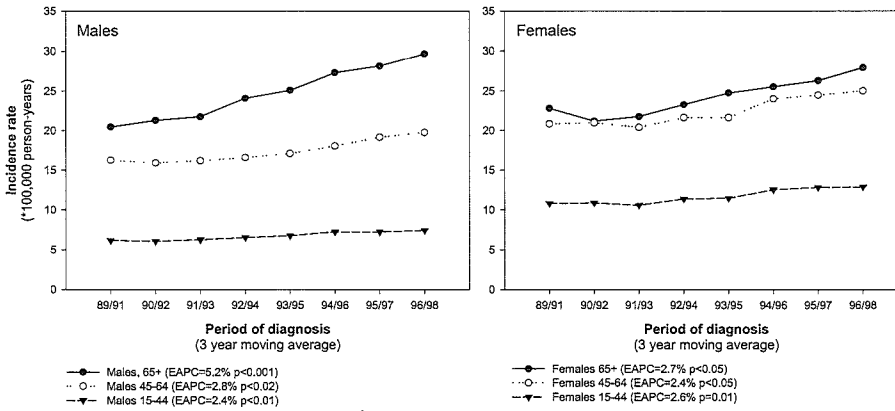

Fig 2. Age-specific incidence rates (*10^5 person-years) for cutaneous malignant melanoma, according to gender, 3-year moving average, with Estimated Annual Percentage Change (EAPC).

Most superficial spreading melanomas (SSM) and nodular melanomas (NM) occurred on the trunk of males and the legs of females (table 2). Analyses by stage revealed that melanomas in women were detected in more favourable stages than in men (table 3).

Regional differences

The estimated annual percentages change according to region did not differ significantly, but the incidence rates were higher in the north and west than in the south and east (fig. 4). Table 4 shows the outcome of the Poisson models including population as an explanatory categorical variable. For both sexes, the likelihood ratio comparing this model with the model containing only period as an explanatory variable was highly significant (males: χ^2 (df=3)=87.07, P<0.0001; females: χ^2 (df=3)=64.79, p<0.0001).

Tests for trend revealed a north to south gradient for both sexes (males Z=-3.23, p<0.01; females Z=-2.98, p<0.01). In the northern and western regions of the Netherlands, rates were higher than in the east and south (table 4).

Since 1969, the mortality rates have not differed notably between regions, although they were consistently higher in the west and slightly lower in the south (data not shown).

Age-period-cohort analysis of mortality data

Age-period-cohort analyses resulted in an age-period-drift model as the best fitting model for female mortality data, with a decrease in relative risks after 1972 (age-period-drift model: deviance=129.23, degrees of freedom (df)=119, p=0.25). For males, an age-period-cohort model was needed to describe the data adequately (age-period-cohort model: deviance=113.70, df=96, p=0.10).

Identifiability problems, inherent in age-period-cohort models, precluded a concise assessment of the cohort and period of changes in mortality rates among males [18].

Table 2: Incidence (ESR per 10^5 person-years) of various histological subtypes of melanoma according to anatomical site and gender, 1989-1997

Type of	Head/neck		Trunk		Arms		Legs		Other and overlapping	
melanoma	Males ESR (%)	Females ESR (%)	Males ESR (%)	Females ESR (%)	Males ESR (%)	Females ESR (%)	Males ESR (%)	Females ESR (%)	Males ESR (%)	Females ESR (%)
LMM	0.2 (12.8)	0.2 (15.5)	0.0* (1.0)	0.0* (0.7)	0.0* (1.3)	0.0* (1.7)	0.0* (1.3)	0.1 (1.2)	0.0* (0.5)	0.0* (0.8)
SSM	0.5 (30.6)	0.5 (34.5)	2.2 (52.2)	1.8 (59.0)	0.7 (48.1)	1.4 (50.0)	0.7 (44.2)	2.8 (50.5)	0.0* (3.4)	0.0* (7.6)
NM	0.3 (18.8)	0.2 (15.4)	0.7 (17.4)	0.4 (12.1)	0.3 (20.2)	0.4 (15.7)	0.3 (17.1)	0.7 (14.1)	0.0* (2.3)	0.0* (2.0)
ALM	- (-)	0.0* (0.1)	0.0* (-)	- (0.0*)	0.0* (0.9)	0.0* (0.8)	0.1 (2.9)	0.1 (1.6)	- (-)	- (-)
Other	0.7 (37.8)	0.5 (34.5)	1.4 (29.4)	0.9 (28.2)	0.4 (29.5)	0.9 (31.8)	0.6 (34.5)	1.8 (32.6)	0.6 (93.3)	0.4 (89.6)
Total	1.7 (100)	1.3 (100)	4.4 (100)	3.1 (100)	1.5 (100)	2.7 (100)	1.6 (100)	5.4 (100)	0.6 (100)	0.5 (100)

(LMM: lentigo maligna melanoma, SSM: superficial spreading melanoma, NM: nodular melanoma, ALM: acrolentiginous melanoma, Other: other and not specified melanomas)

* ESR smaller than 0.05

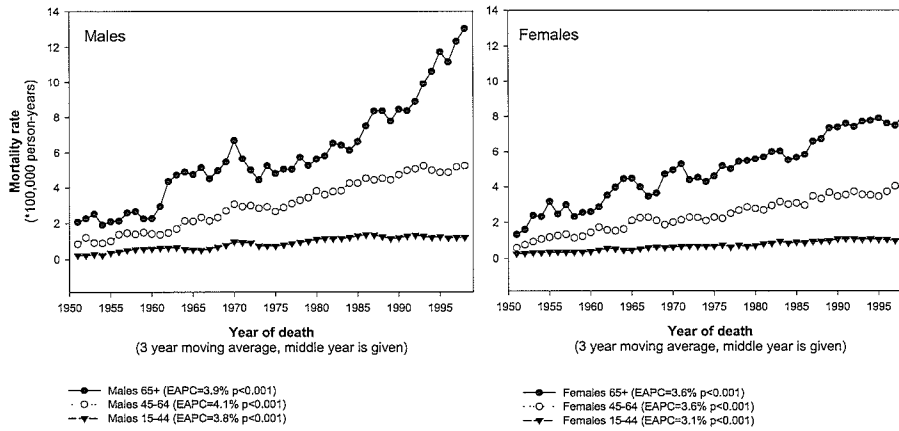

Figure 3: Age-specific mortality rates (*10^5 person-years) for cutaneous malignant melanoma, according to gender, 3 year moving average, with Estimated Annual Percentage Change (EAPC).

Discussion

Incidence and mortality

As in most fair-skinned populations [1, 20, 21], age-adjusted incidence rates for cutaneous melanoma have continued to rise in The Netherlands since 1989, the first year of the National Cancer Registry (NCR). The increase was exhibited by both sexes and all age categories. Incidence rates for three regions of The Netherlands (the province of Friesland and the cities The Hague and Rotterdam) in the period 1960–1962 were much lower (1.7 per 100,000 person-years for males, 2.6 per 100,000 for females), although these data are probably incomplete [22].

Table 3: Stage distribution by sex for melanomas diagnosed in the period 1989-1998

	T1 (%)	T2 (%)	T3 (%)	T4 (%)
Males	22.5	28.5	35.2	13.9
Females	21.7	35.3	33.4	9.6
Pearson χ^2	2711.75 (df=3), p<0.001			

T1: Breslow thickness ≤0.75 mm and/or invasion of papillary dermis (Clark level II); T2: Breslow thickness >0.75, ≤1.50 mm and/or invasion of papillary-reticular dermal interface (Clark level III); T3: Breslow thickness >1.50, ≤4.00 mm and/or invasion of reticular dermis (Clark level IV); T4: Breslow thickness >4.00 and/or invasion of subcutaneous tissue and/or satellite(s) within 2 cm of primary tumour (Clark level V). Percentages are based on numbers of known T-stage. The proportion of unknown stages (Tx) is equally distributed for males and females (5.5% for males, and 5.0% for females)

Table 4: Results of the Poisson regression model for regional differences. Model: $y = N \times e^{\alpha_{region} + \beta_{period}}$

variable		Males coefficient	p-value	Females coefficient	p-value
Period		0.033	<0.001	0.022	<0.001
Region*	West	-0.150	<0.001	-0.062	0.053
	East	-0.146	<0.001	-0.167	<0.001
	South	-0.272	<0.001	-0.161	<0.001
Constant		-75.484		-53.392	
Test for trend		Z=-3.23	<0.01	Z=-2.98	<0.01

* Region north is reference value

Data from the Eindhoven Cancer Registry, which registers newly diagnosed cancers in southeast Netherlands, show that in the period 1958–1997, age-standardised incidence rates for melanoma rose from 1.6 to 13.1 per 100,000 person-years for males and from 0.9 to 15.9 per 100,000 person-years for females (ESR) [23].

Experience with the 'freckles bus', a beach screening campaign performed in the midwestern part of the country in 1989, showed that publicity about the risks of sunbathing and skin cancer led to an increase in the number of consultations for skin cancer among general practitioners and dermatologists [24]. The increase in the incidence of melanoma can largely be explained by an increased detection of SSM, and an increased population awareness since the 1980s [25]. In the 1960s, general practitioners (GPs) saw, on average, 1 melanoma patient every 10 years, but this has since become more frequent: approximately 1 melanoma patient every 3 years. Heightened awareness among GPs is therefore also likely.

Since the 1950s, more and more Dutch people have gone regularly to the mountains in Europe for walking and skiing and to southern Europe for summer holidays. These activities result in increasing intermittent sun exposure, possibly causing the rising incidence rates [26]. Subtropical holidays became more popular only in the 1990s. The prevalence of sunbed use in The Netherlands is high, in a sample of 501 people who

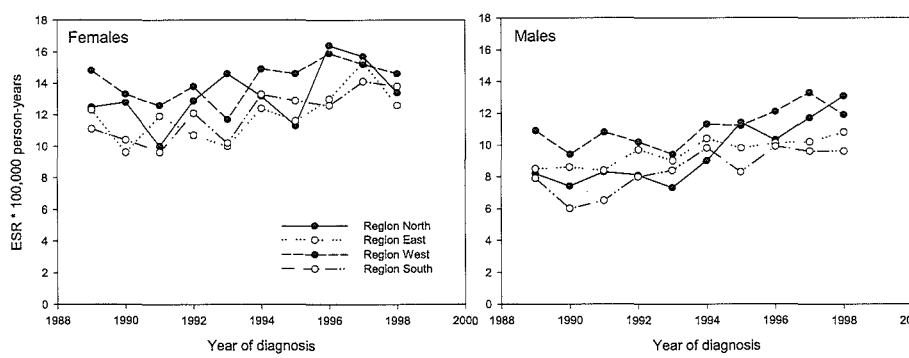

Figure 4: Regional variation in melanoma incidence rates (*10^5 person-years) (European Standardised Rates (ESR)).

participated in a telephone interview, 33% used sunbeds or sun-lamps [27]. Incorrect sunbed use could increase incidence rates of melanoma in the future, although investigations have not yet provided consistent evidence on the relationship between the use of UV-lamps and the development of cutaneous melanoma [28].
In contrast to the incidence rates, melanoma mortality rates appeared to have stabilised for females in the period 1989–1999. As elsewhere, this is likely due to an increased detection of thinner, superficial spreading melanomas, with a relatively good prognosis [29]. From our analyses by stage, it is also clear that the stage distribution was more favourable for women than for men. However, for middle-aged and older men, mortality rates for melanoma continued to increase. Older people, particularly males, seem less observant with regard to changes in moles or other aspects of their skin. Most melanomas on older males are quite thick and occur on the trunk, often on the back, where they are not as quickly detected as melanomas on other parts of the body [30, 31]. Mortality rates for males were similar to those in Belgium [4], where it rose from 2.5 to 3 per 100,000 person-years in the period 1989–1992. Female mortality, however, dropped in Belgium, while it has stabilised in The Netherlands. Mortality rates in Sweden have levelled off for both sexes since the mid-1980s, with a downward trend for women who died in the period 1987–1996 [26].

Incidence by localisation and histological subtype
Most melanomas occurred on the trunk (males) and legs (females). As elsewhere, this is most likely due to different clothing and sun-exposure habits in the past [21, 32, 33].
Melanomas on commonly exposed body parts (head and neck region) occurred more often in older age categories (both male and female). However, melanomas on the trunk, legs and other less intermittently exposed body sites occur in both the younger and older age categories. This points to a different aetiological pathway for these tumours. In other studies, melanomas on the head and neck region and the hands were found to be predominantly of the lentigo maligna (LMM) type, whereas SSM occurred predominantly on the trunk and upper and lower limbs [21, 34, 35]. Chronic exposure to UV-radiation seems to cause predominantly LMM, whereas intermittent exposure causes more SSM [36]. Increases have been seen mainly in the SSM type [25].

Regional differences
Incidence rates were highest in the western and northern parts of the country. According to the Royal Dutch Meteorological Institute, cities near the coast in the northern and western parts of the country had approximately 10% more sun-hours (1536–1581 h annually compared with 1377–1476 h in other parts of the country) [37]. In the west, there is a long coast with many beaches and lakes and it is traditionally the most prosperous part of the country. The north is rural, but also has a coast and many lakes, where many aquatic sports are practised. The south and east do not have any coastline and are more rural. The northwest to southeast gradient also has a religious gradient (from mainly Protestant to mainly Catholic), which carries with it many social characteristics [38]. The decline in the western region after 1989 could be due to a higher incidence caused by the freckle bus campaign in 1988 [24]. In western Australia, SSM was associated with frequent boating and fishing (Odds Ratios 1.03–

2.72) [39], activities which can be practised more easily in the western and northern regions of The Netherlands. Although incidence differed between regions, this did not appear to affect the mortality rates.

Cohort effects
Female mortality flattened off after 1972. Male mortality needed age-period-cohort models to describe the data adequately, making it hard to interpret the exact findings because of identifability problems [18]. Earlier analyses of Dutch mortality data also needed age-period- cohort models. With the assumption of a mathematical function for the mortality rates in relation to age, results indicated that time period effects increased up to 1970, and birth cohort effects increased from 1900 to 1955 [2]. In Australia, the Nordic Countries and the United States of America (USA), age-cohort models were found, starting with a decrease among females from generations born just before World War II. In the United Kingdom (UK) and Canada, the rates have been flattening for those born since 1945–1950. In France and Italy, where the increase started much later, steep increases in mortality rates for melanoma were observed without a major change in this trend as yet [3, 4]. Period effects were not found in other countries. They represent influences which affect the mortality rates in all age groups simultaneously. In The Netherlands, these changes took place in the early 1970s, long before any prevention or awareness campaigns were organised.
Factors that could have caused the period effects are (a) changes in the ICD classifcations, (b) changes in histopathological criteria, (c) increasing exposure of all age groups to an aetiological factor with a short latency period or (d) improved death certification. There were no relevant changes in the ICD codes for cutaneous melanoma. Changes in histopathological criteria may have occurred, most likely being the inclusion as melanoma of lesions that were formerly not investigated or were coded as benign. This would influence incidence rates, but not mortality, because these lesions have a very good prognosis. UV-radiation is the best known risk factor, but it has a latency period of at least 10, and more likely 20, years. Another aetiological factor with a short latency period may exist, but there are no clues as yet to any such short-latency risk factors for melanoma. The most plausible factor that may have caused the period effects are changes in death certification. There are no data available to determine the extent to which improvements in death certification may have contributed to the trends in melanoma mortality in The Netherlands.

Conclusions
Incidence rates and male mortality rates for melanoma were still rising in The Netherlands in the period 1989–1998, but female mortality rates started to stabilise; this was confirmed in an age-period-cohort analysis of mortality data. The regional differences in melanoma incidence rates correspond with host characteristics and opportunities for recreational exposure. The most likely cause of the rising incidence rates in our country is the increasing intermittent exposure to UV radiation in the past. Melanomas were detected at an early stage among females, possibly explaining the stabilising mortality rate for this group. Consequently, marked awareness remains necessary.

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Chapter 2.2

Rapid and continuous increases in incidence rates of basal cell carcinoma in the southeast Netherlands since 1973

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Summary

The objective of this study was to determine characteristics of the trends in incidence of basal cell carcinoma (BCC) in the Netherlands. We used incidence data of basal cell carcinoma from the Eindhoven Cancer Registry (Comprehensive Cancer Centre South) in the south of the Netherlands from 1973-2000. Data were age-adjusted and age-specific rates were calculated. Joinpoint and age-period-birth cohort modelling were applied.

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

Introduction

Over the last decades, increasing trends in the incidence of basal cell carcinoma (BCC) have been observed for Caucasian populations, with a decreasing average age of onset [1-4]. An analysis of the nature of trends in incidence of BCC by age, period and birth cohort in the Netherlands can clarify to what extent the behaviours (sun-exposure-related) are birth-cohort related.
It has been estimated that more than one-third of all cancers in the USA are NMSC [5], and that in Australia, which has the highest rate of skin cancer in the world, the estimated incidence in 1985 was twice that for all other cancers combined [6]. Rates in Europe are generally lower, albeit unknown in most areas: in the south-eastern parts of the Netherlands BCCs accounted for 17% of all cancer cases in both males and females (calculated from Coebergh et al, 2001 [7]).
We analysed incidence rates for primary BCC in the southeast of the Netherlands in the periods 1973-2000, by sex, site and age. To determine trends, we further investigated variations by birth cohort and period.

Materials & Methods

Data
Data on incident primary BCC cases, according to anatomical site, were obtained from the population-based Eindhoven Cancer Registry [7]. The Eindhoven cancer registry serves more than 12 general hospitals that are served by 6 pathologic laboratories, all participating in the nationwide PALGA network, that also notifies the regional cancer registries. The cancer registry receives lists of newly diagnosed cases on a regular basis from the pathology departments, including cases whose material was sent in by general practitioners. In addition, the medical records departments of the hospitals provide lists of outpatients and hospitalised cancer patients. Following this notification, the medical records of newly diagnosed patients (and tumours), often only available from the outpatient departments, are collected and trained tumour registrars from the cancer registry abstract the necessary information. Data are checked for duplicate records. Records are assumed to be complete.
Only first primary BCC were registered.
During the study period 1973 to 2000, the population size of the Eindhoven cancer registry catchment region increased from 592,000 to 2,100,000, mainly due to an expansion of the registry area [7].
Annual incidence rates were computed per 100,000 person-years for each sex and calculated as 3-year moving means.

Analysis
Age-adjustment was performed by direct standardisation according to the European Standard Population (European Standardised Rates (ESR)). Cumulative incidence rates were calculated as the sum of the age-specific incidence rates for ages 0-74, multiplied with the width of the age-groups (5 years). Cumulative risks were calculated from the cumulative rates as follows: Cumulative risk=100 * (1-exp (-cumulative rate/100)).

Trends in incidence were estimated by calculating the Estimated Annual Percentage Change (EAPC) using STATA 7 software. The EAPC was calculated by fitting a regression line to the natural logarithm of the rates using calendar year as a regressor variable, i.e. $y = mx + b$ where $y = ln(rate)$ and x = calendar year. Then the $EAPC=100 * (e^m - 1)$. This calculation assumes that the rates increased or decreased at a constant rate over the entire period.
Joinpoint analyses were performed to discern significant changes in the trend and, if present, when they occurred [8]. Linear line segments are connected on a log scale to identify changes in trend data in terms of the annual rates of change in fixed periods of time [8], although cross-sectional cancer rates generally do not change abruptly. The software used for these analyses was the Joinpoint Regression Program, version 2.6 of the National Cancer Institute. Age, drift, period and birth cohort effects were investigated using the age-period-cohort modelling as described by Clayton and Schifflers, using STATA 7 software [9]. "Drift" is a term which was introduced by Clayton and Schifflers to describe models for which age-period and age-cohort parameters fit the data equally well. The model implies the same linear change in the logarithm of the rates over time in each age group. Such a model thus serves as an estimate of the rate of change of a regular trend [9]. Included age groups were those between 25 and 74 years of age. Five-year periods were chosen from 1976-1980 until 1996-2000.

Results

Overall incidence data
Between 1973 and 2000, a total of 23,511 primary BCC cases were diagnosed in the Eindhoven Cancer Registry region (11,865 males and 11,646 females).
The age-specific incidence curves illustrate the high incidence rates of BCC, even at relatively young ages (figure 1). Seventy-seven percent of all BCC material that was analysed in the pathology lab was sent by dermatologists, 8% by general surgeons, 8% by plastic surgeons, 3% by general practitioners and 4% by other specialists.

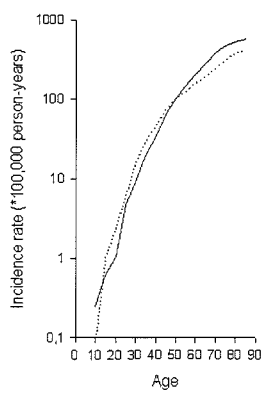

Figure 1. Age-specific incidence curve for BCC (*10^5 person-years), solid line=males, dashed line=females

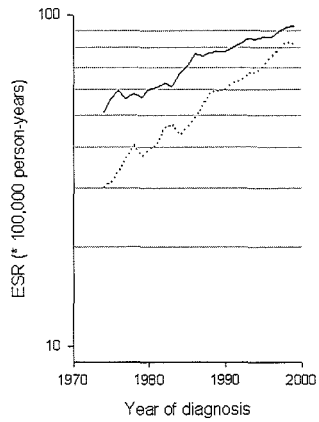

Figure 2. Incidence of BCC, 3 year moving average, European Standardised Rates (ESR)(*10^5 person-years). Solid line=males, dashed line=females.

Between 1973 and 2000 the age-adjusted incidence rates for BCC (European Standard Population) increased from 40 to 92 per 100,000 person-years for males and from 34 to 79 per 100,000 person-years for females, with an estimated annual percentage change (EAPC) of 2.4% for males and 3.9% for females (table 1, figure 2).

In the period 1973-2000, cumulative incidence risk before the age of 75 increased from 3.1% to 7.3% in males and from 2.5% to 6.2% in females. Age-specific incidence rose amongst all age groups in both sexes, especially in young women (EAPC 5.7%) (table 1, figure A available on-line). Rates in young females became higher, and increased more rapidly than in young males; rates in the middle-aged (50-69) were about equal for both sexes, but in older males incidence remained higher than in females.

Table 1: Overall, age- and site-specific incidence of BCC (per 10^5 person-years) by sex, 1973-2000

	Males		Females	
	EAPC[a] (95% CI)	Incidence[b]	EAPC[a] (95% CI)	Incidence[b]
All ages	2.4 (2.2-2.5)	93	3.9 (3.7-4.1)	82
25-49	2.2 (1.9-2.4)	33	5.7 (5.4-6.0)	45
50-69	2.4 (2.3-2.6)	204	4.5 (4.4-4.6)	191
70+	2.4 (2.3-2.4)	522	2.2 (2.2-2.3)	340
Head/neck	1.7 (1.6-1.8)	71	2.9 (2.8-3.1)	57
Trunk	5.7 (5.4-6.0)	15.4	7.7 (7.4-8.1)	15.7
Arms	4.6 (4.1-5.1)	5.5	7.7 (7.1-8.3)	6.0
Legs	6.9 (6.1-7.7)	3.8	7.9 (7.3-8.5)	4.6
Other and overlapping	0.91 (0.91-0.95)	0.2	0.97 (0.96-0.98)	0.4

[a]: Estimated Annual Percentage Change with 95% confidence interval (CI)
[b]: Incidence: Age-standardised incidence rates per 100,000 person-years for the period 1998-2000

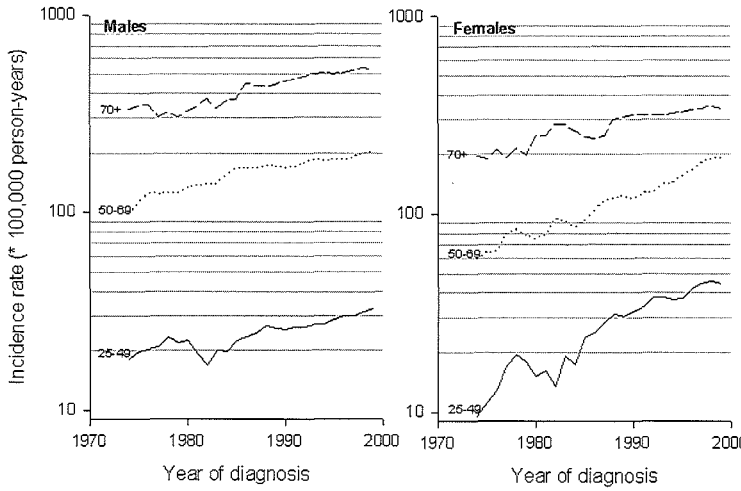

Figure A. Age-specific incidence rates (*10^5 person-years) for BCC, according to sex, 3 year moving average

Incidence by site

BCCs occurred predominantly in the head and neck region in both sexes, followed by the trunk and the limbs, with higher rates on the limbs for females than for males. Increases in rates were seen at all sites, with smallest increases in the head and neck region, and most notable increases on the trunk and in females (table 1, figure B available on-line). The proportion of BCC in the head and neck region decreased over time for both sexes, especially in the younger age group, whereas the proportion on the trunk, arms and legs increased significantly in this age group. The strongest proportional increases were seen on the trunk in young males and females (table A available on-line).

Joinpoint analyses

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

Age-period-cohort analysis of incidence data

Age-period-cohort analyses resulted in an age-drift model that was the most parsimonious model for males, while an age-drift-cohort model fitted the data adequately for females (table B available on-line). Relative risks in females decreased from the earliest birth cohorts, born in the beginning of the 20th century, until those cohorts born in 1921, then levelled off and started increasing again, up until the most recent birth cohorts (figure 3).

Table A: Body site distribution of BCC by period, age group and sex

Period	35-64 years Head and neck		Trunk		Arms		Legs		Other	
Males	%	N	%	N	%	N	%	N	%	N
1976-1980	87	269	8	26	4	11	1	3	1	2
1981-1985	82	318	13	52	4	14	1	3	0	0
1986-1990	77	696	14	126	6	54	2	16	1	10
1991-1995	76	1270	17	288	5	76	2	33	0	2
1996-2000	70	1459	20	416	7	144	3	69	0	5
Females										
1976-1980	85	173	9	18	2	4	2	4	2	5
1981-1985	80	210	11	29	3	8	5	12	1	3
1986-1990	73	584	16	130	5	38	4	35	2	14
1991-1995	69	1093	18	290	6	96	7	106	0	5
1996-2000	63	1422	23	518	7	153	6	143	0	7

Period	65+ years Head and neck		Trunk		Arms		Legs		Other	
Males	%	N	%	N	%	N	%	N	%	N
1976-1980	88	261	5	14	2	7	3	8	2	6
1981-1985	85	328	9	36	3	13	1	5	1	5
1986-1990	85	856	9	92	4	36	1	11	1	9
1991-1995	85	1676	8	151	4	83	2	46	0	5
1996-2000	80	1873	12	280	4	95	3	73	0	7
Females										
1976-1980	85	223	8	22	3	7	2	6	1	3
1981-1985	86	341	7	28	3	10	4	17	0	1
1986-1990	84	836	7	73	3	33	4	39	2	17
1991-1995	85	1659	7	134	3	58	5	106	0	4
1996-2000	81	1946	8	195	4	104	6	137	0	7

Discussion

BCC is the most common malignant tumour in persons with a pale skin in the Netherlands. Even though its incidence rates are currently already very high, increases in incidence of several percents per year are observed. There are no indications of flattening or recession of this trend, in contrast with incidence rates of cutaneous melanomas, which are flattening off in the young age groups in the Netherlands, like in other northern European countries [10, 11]. Increases in BCC were most rapid in young females, in whom incidence rates are currently higher than in males, especially on the trunk and limbs [12].

In other parts of Europe, reported (world standardised) incidence rates of BCC per 100,000 person-years varied markedly (table 2). It must be noted however, that some of these observations were made about a decade ago, and if rates had increased in the same speed as in the Netherlands, the incidence rates would currently be substantially higher.

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

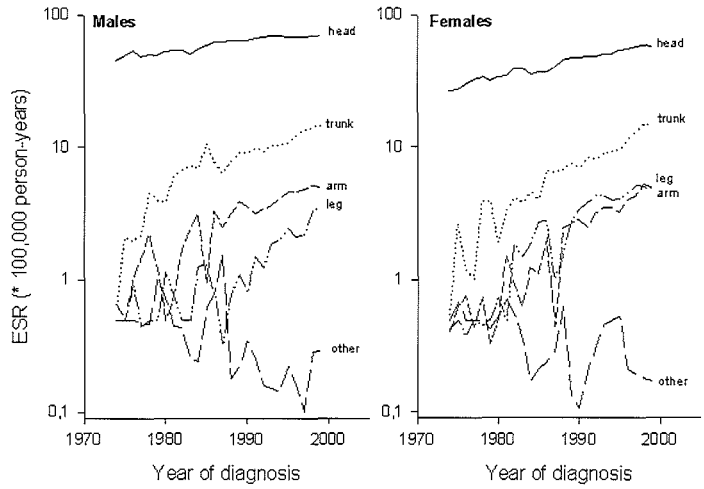

Figure B. Site-specific incidence of BCC, according to sex, 3 year moving average, with EAPC (head=head and neck, trunk=trunk, arm=arms and shoulders, leg=legs and hips, other=other cutaneous and not specified)

Moreover, this registry-based study in the southeastern part of the Netherlands may have been hampered by the usual difficulties, such as incomplete registration and inadequate histological verification, especially if BCCs would be excised by general practitioners. There are several reasons, however, why we believe that the vast majority of BCCs are reported to the cancer registry, and the registration of primary BCCs is very good: our good contacts with dermatologists and pathologists which are supported by the nationwide computerized PALGA-archive, and the fact that most general practitioners do not excise (suspected) BCC's (in our study about 3%) [13]. Moreover, in the cases where general practitioners excise the BCC, the pathologists receive the specimens for examination and the BCC will be reported to the cancer registry.

Ultraviolet radiation is the most important environmental risk factor for the development of BCC, especially in those with a sun-sensitive skin type, although the mechanism is still unclear. A particular amount of sun exposure delivered in infrequent, probably intense 'bursts' may increase the risk of BCC more than a similar dose delivered evenly spread over the same total period of time [14, 15]. This hypothesis matches with our data. BCCs increasingly appear on sites, mainly the trunk, that are not continuously exposed to the sun when outdoors.

The increased incidence rates are most likely caused by changes in sunbathing behaviour in the young and middle-aged, which has changed markedly during the twentieth century. Especially, after the Second World War, more leisure time became

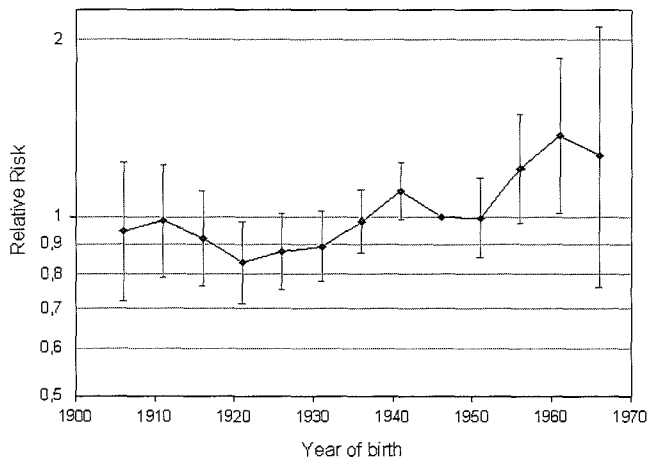

Figure 3: Cohort effects in females from age-cohort-drift model. Relative risk by birth cohort (reference cohort: 1946)

available for outdoor activities and for holidays in the sun, wherebye since the 1980's holidays to the (sub) tropics became affordable for many. Clothes changed allowing larger parts of the skin to be exposed, especially on the beaches. These changes were strongest in young females, and resulted in increasing exposure of the usually covered body sites (trunk, arms, legs) to ultraviolet radiation.

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

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

The two most important histological subtypes of BCC are nodular and superficial BCC, possibly with different aetiological mechanisms. Superficial BCC occurs in younger patients, more often in females than in males, and on the trunk and extremities.
Nodular BCC occurs significantly more often in males and in the head and neck region. Superficial BCC (on the trunk) appear to be related to intermittent sun exposure, whereas the nodular BCC (on the face and neck) appear to be related more to chronic sun exposure [12].

Table 2: Reported age standardised incidence rates (world standard population, per 100,000 person-years) and increases in rates in western Europe

Registry	Year	Males	Females	Increase
Finland [16]	1991-1995	49	45	240% (1966/'70 vs 1991/'95)
Hull, U.K. [4]	1991	116*	104*	335% (1978/'91)
Vaud, Switzerland [3]	1991-1992	69	62	144% (males 1976/'80 vs 1991/'92) 182% (females 1976/'80 vs 1991/'92)
Wales [2]	1998	128	105	15% (1988/'98)
Schleswig-Holstein. Germany [17]	1998-2001	54	44	-
Eindhoven, the Netherlands	1998-2000	63	58	185% (males 1973/'75 vs 1998-2000) 286% (females)

* Crude rate

Table B: Goodness-of-fit statistics of the age-period-cohort analysis (25-74 year old)

Model	Males			Females		
	GOF[a] χ^2	df[b]	P	GOF χ^2	Df	p
Age	169.2	40	0.00	541.6	40	0.00
Age+drift	36.5	39	0.58	64.1	39	0.01
Age+drift+period	32.9	36	0.62	54.3	36	0.03
Age+drift+cohort	21.9	27	0.74	30.9	27	0.27
Age+drift+period+cohort	20.1	24	0.69	19.6	24	0.72

[a]: GOF: Goodness-of-fit statistic, a p value smaller than 0.05 indicates a lack of fit of the model with the data. The best fitting, most parsimonious model has a p-value > 0.05 and the lowest number of variables (i.e. the highest number of degrees of freedom).
[b]: df: degrees of freedom

Based on our observations of an increase in BCC, most marked in young females, mainly on the trunk and extremities, with a decrease in the proportion of BCC in the head and neck region, especially in the young and middle-aged, we hypothesize that the increases have been mainly in superficial BCC. An increase in intermittent (mostly recreational) sun exposure and decrease in chronic (mostly occupational) sun exposure is likely as well. The proportional increase of nodular BCC observed in a university-hospital based study in the western part of the country with time, and in all body regions, does not contradict the above, because there may have been specific referral of these patients to the university hospital where the study was conducted [12].

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

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Chapter 2.3

Predictions of skin cancer incidence in the Netherlands up to 2015

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Summary

Background & Aims: Skin cancer is an important, growing public health problem among white Caucasians, causing a heavy burden on dermatologists and general practitioners. The aim of this study was to predict the future incidence of skin cancer in the Netherlands up to 2015.
Methods: Expected numbers of skin cancer cases in the Netherlands up to 2015 were calculated by trend modelling of observed rates for melanoma and squamous cell carcinoma (SCC) between 1989 and 2000 obtained from the Netherlands Cancer Registry and for basal cell carcinoma (BCC) obtained from the Eindhoven Cancer Registry; these rates were then multiplied by the predicted age distributions. Incidence rates were fitted to 4 different models, and predictions were based on the best fitting model.
Results: An increase of 80% in the total number of skin cancer patients is expected in the Netherlands: from 20,654 in 2000 to 37,342 in 2015. The total number of melanoma cases is expected to increase by 139%, with the largest increase for males (males aged 35-64: 111%, males aged ≥65: 139%); numbers of patients with SCC will increase overall by 80%, mainly among older males and females (increases 79%) and females aged 35-64 (increase of 93%). The number of cases of BCC will increase by 78%, with the largest increase for those aged 15-64 (males 66% increase, females 94% increase), especially for sites other than the head and neck. The contribution of demographic changes (ageing effect) was largest for males with BCC and SCC (35 to 44%).
Conclusions: If incidence rates for skin cancers in the Netherlands will continue to increase and population growth and ageing remain unabated, a rise in annual demand for care of more than 5% could occur, putting a heavy burden on general practitioners and dermatologists. In the absence of marked changes in current UV-exposure, these increases will probably continue after 2015.

Introduction

In fair-skinned Caucasian populations, skin cancer has become a large health problem. In past decades, skin cancer incidence rates have steadily increased [1-3], leading to a growing demand for health care services to inspect suspected lesions and treat patients.
The majority of skin cancers are carcinomas, also referred to as non-melanoma skin cancers (NMSC), comprising basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Basal cell carcinoma can be a burden for patients and the health care system in terms of (often disfiguring) operations and health care, but is rarely lethal. About 80% of BCC are in the head and neck area. Squamous cell carcinoma can sometimes be fatal for immune compromised patients but this occurs in less than 1 in 50 new cases [4].
Melanoma skin cancers are far less frequent than NMSC but are responsible for the majority of skin cancer deaths. When diagnosed at an early stage melanoma can easily be excised and cured. Advanced melanoma, however, is very difficult to treat and often fatal.
To determine past trends in the skin cancer epidemic and to predict future incidence rates, numbers of new patients, and demand for health care related to skin cancer, we performed trend analyses over the period 1989-2000 using the Netherlands cancer registry and extrapolated these trends up to the year 2015.
The Eindhoven Cancer registry is one of the few cancer registries that records data on BCC [5]; rates for first primaries are reliable, because of consistent histological verification.

Data and methods

Data
The basis for the predictions was data on new melanomas and SCC diagnosed in the Netherlands in the period 1989-2000 and new BCC diagnosed in the area of the Eindhoven Cancer Registry in the same period, population data for the same period and forecasts of the size and structure of the population in the future (CBS demographic prognoses 2002).
Both the national [1] cancer registry and the Eindhoven cancer registry are based on ascertainment by pathological laboratories. The Netherlands Cancer Registry is assumed to be complete since 1989, the Eindhoven Cancer Registry since 1970, both with a changing population at-risk in later years. In the year 2000, the Netherlands had 7,846,317 male and 8,017,633 female inhabitants and the Eindhoven Cancer Registry region had 1,055,061 male and 1,056,972 female inhabitants. Only first primary BCC, SCC and melanomas were used for this analysis [5, 6]. Only invasive SCC and melanomas were used for the predictions in this study, *in situ* lesions were excluded.
The new cancer cases were grouped into 18 five-year age groups (0-4, 5-9, ..., 80-84, 85+ years) and body site distribution for each sex.

Predictions

The predicted numbers of skin cancer cases in the Netherlands in 2005, 2010 and 2015 were estimated by first predicting the incidence rates on the basis of observed rates for 1989-2000, according to the methods described by Hakulinen and Dyba [7, 8], and then multiplying these rates by the population forecast for these periods, derived from Statistics Netherlands.

Four models of incidence rates as a function of population and time were made, the model fit statistics were compared and the best-fit models were chosen.

The analysed models were:

$$EM_{it} = \alpha_i + \beta_i * t \quad (1)$$

$$EM_{it} = \alpha_i * (1 + \beta * t) \quad (2)$$

$$EM_{it} = \exp(\alpha_i + \beta * t) \quad (3)$$

$$EM_{it} = \exp(\alpha_i + \beta_i * t) \quad (4)$$

where $EM_{it} = c_{it} / n_{it}$ is the expected value of the incidence in age group i and period t, n_{it} is the number of person-years, c_{it} the number of cases and α_i, β and β_i are unknown parameters. The period t can be regarded as a surrogate variable for the changes in the collective impact of various carcinogens to which a population was exposed at a particular point in time. Here, all models are written as a function of calendar time t. Substitution of the year of birth of a cohort for t in these models would yield identical models and predictions. As long as the focus is trend extrapolation, the non-identifiability problem in age-period-cohort models does not cause further complications [8].

Model 1 assumes linear changes over time (β_i *t) and a basic age-specific incidence, α_i at t=0 (1989). Model 2, being a special case of model 1, can be considered as a linear model with constraints (i.e. with a single age-independent proportionality coefficient β). This model assumes proportional effects for different age groups; the age-specific absolute change in incidence is proportional to the corresponding age-specific baseline rate. Therefore within the period of prediction this model retains the age-pattern of incidence rates existing in the data. Age-specific predictions can therefore be made with greater accuracy.

Model 3 is based on the assumption of the same fractional rise for all age groups, being an exponential change with time (exp[β *t]). Model 4 specifies different fractional changes for different age-groups [7, 8].

All models are adjusted for possible over-dispersion and prediction intervals were calculated [8]. Prediction intervals consist of (a) the confidence interval for the expected value of the observation itself, which depends on the fit of the model plus (b) the variance of the expected incidence given by the parameter values and the year of prediction [7].

Age groups were 15-34, 35-64, 65+ years and all ages. Analyses according to body site were only performed for BCC; it was not possible to study or predict trends by body site for SCC and melanoma due to the small numbers. All incidence rates were calculated per 100,000 person-years. For comparison with other countries, the rates were adjusted for age according to the European Standard Population [9]. This adjustment eliminates the effect on rates of changes in age distribution.

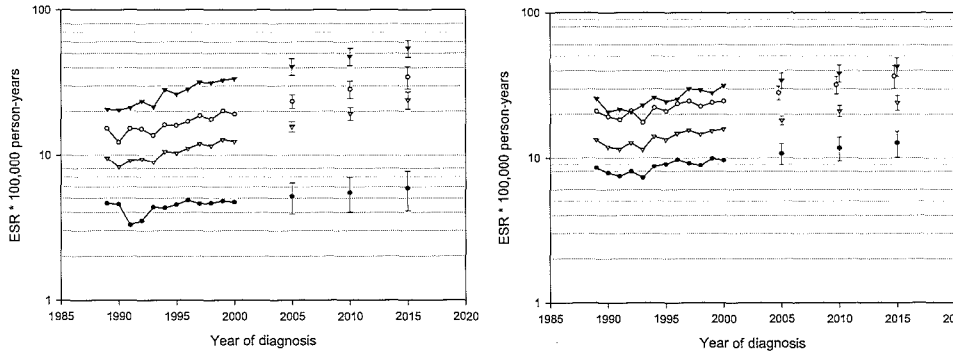

Figure 1: Observed and predicted (extrapolated) age-standardised incidence of cutaneous malignant melanoma with 95% prediction intervals: (1a) males, (1b) females. (●: aged 15-34 years, O: aged 35-64 years, ▼: aged 65 and over, ▽: all ages)

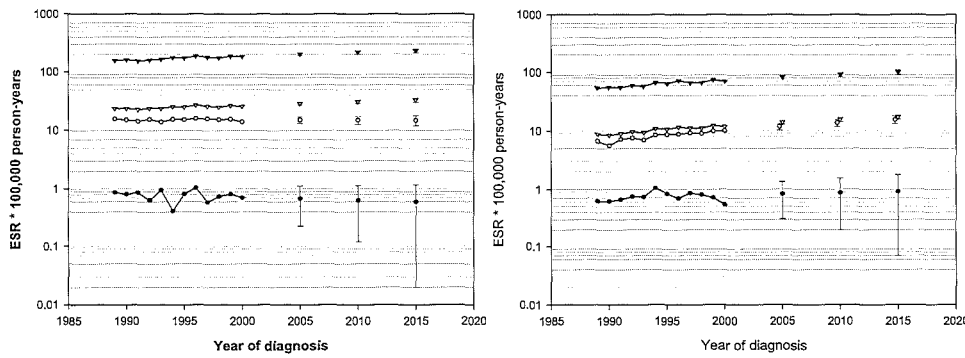

Figure 2: Observed and predicted (extrapolated) age-standardised incidence of squamous cell carcinoma with 95% prediction intervals: (1a) males, (1b) females. (●: aged 15-34 years, O: aged 35-64 years, ▼: aged 65 and over, ▽: all ages)

Incidence rates were converted into expected numbers for the Netherlands by using population forecasts up to 2015 from CBS. Age-specific incidence rates were multiplied by the predicted sizes of the age groups to calculate expected numbers of new patients. The increase in numbers was calculated relative to the numbers found for the year 2000.

To distinguish between changes in expected numbers of new patients due to an increase in rates and those due to demographic changes we calculated (1) expected numbers using the rates for 2000 applied to the predicted population, and (2) using the observed population in 2000 applied to the predicted incidence rates. The percentage change in these numbers relative to those of 2000 was calculated.

Results

The difference in predicted rates and numbers between the selected models and the other 3 models was generally small, except when one of the other models showed a lack of fit to the observed data.
Skin cancer incidence rates have increased markedly and will continue to do so. In 2000, BCC was by far the most common type of skin cancer, with about 92 cases per 100,000 person-years among males and around 79 cases per 100,000 person-years among females in the Netherlands. SCC and melanoma were detected less frequently: around 25 and 12 cases per 100,000 person-years for males and 12 and 16 cases per 100,000 person-years for females, respectively (table 1a, b).

Melanoma
Melanoma incidence rates have increased rapidly in the past 12 years and are expected to keep on doing so in the future (table 1, fig 1ab). The absolute total number of new cases is expected to be more than 4,800 in 2015, compared to around 2,400 in 2000.
The number of patients with a cutaneous melanoma is expected to increase considerably for both sexes (238% and 171% increase for males and females in 2015 compared to 2000, respectively) (table 1). Increasing incidence rates rather than demographic changes are mainly responsible for these increases (table 2).

SCC
Incidence rates of SCC have increased markedly in the past 12 years, especially for the older age groups, and are expected to continue to do so in the future (figure 2a and b, table 1). For 2015 the predicted age-standardised incidence rates are 33 per 100,000 for males and 17 for females, with the highest rates for the older age groups (table 1, figure 2ab); this would translate into more than 6,000 new cases annually in the Netherlands in 2015, compared to around 3,400 new cases per year in 2000 (table 1).
The future number of SCC patients is affected more by demographic changes among males and by changing incidence rates for females (table 2).

BCC
Incidence rates for first primary BCC have increased rapidly in the past decades and are expected to keep rising (figure 3ab, table 1). Presently incidence rates are the highest for males, especially in the oldest age-categories (438 per 100,000 person-years), but the younger females are expected to catch up with them (table 1, figure 3ab).
Incidence rates are expected to increase fairly rapidly in the youngest age groups (15-34 years) since the numbers will probably double by 2015 (table 1, figure 3ab). For 2015 the predicted annual incidence rates are 122 per 100,000 males and 119 for females; this would imply more than 26,000 new cases of first primary BCC in the Netherlands annually, compared to around 15,000 in 2000 (table 1).

Table 1a: Predicted incidence rates and 95% prediction intervals of skin cancer by age, sex and type of skin cancer up to 2015.

	Age	Model[a]	2000	2005	2010	2015
	Years		Observed	Expected (95% PI)	Expected (95% PI)	Expected (95% PI)
Melanoma						
Males	15-34	2	4.7	5.2 (3.9-6.4)	5.5 (4.0-7.0)	5.9 (4.1-7.7)
	35-64	4	19.1	23.5 (21.0-26.1)	28.5 (24.6-32.4)	34.6 (28.6-40.7)
	65+	2	33.7	40.9 (35.6-46.2)	47.7 (41.4-54.0)	54.4 (47.0-61.8)
	All	4	12.4	15.7 (14.4-17.0)	19.3 (17.3-21.4)	24.0 (20.7-27.3)
Females	15-34	2	9.6	10.7 (8.9-12.5)	11.7 (9.5-13.9)	12.7 (10.1-15.2)
	35-64	4	24.6	28.1 (25.1-31.0)	32.0 (27.6-36.4)	36.7 (30.2-43.2)
	65+	2	31.5	34.3 (30.1-38.5)	38.4 (33.4-43.5)	42.6 (36.7-48.5)
	All	4	15.7	18.1 (16.8-19.4)	21.1 (19.2-23.0)	24.1 (21.3-26.8)
Squamous Cell Carcinoma						
Males	15-34	3	0.7	0.7 (0.2-1.1)	0.6 (0.1-1.2)	0.6 (0.0-1.2)
	35-64	2	13.9	14.9 (13.0-16.8)	14.8 (12.5-17.1)	14.7 (11.9-17.6)
	65+	1	182.5	200.3(187.9-212.8)	214.6 (199.6-229.6)	228.9 (210.9-247.0)
	All	4	25.4	28.4 (26.8-30.1)	30.5 (28.3-32.7)	32.8 (29.9-35.7)
Females	15-34	3	0.5	0.8 (0.3-1.4)	0.9 (0.2-1.6)	0.9 (0.1-1.8)
	35-64	2	10.0	11.8 (10.3-13.4)	13.6 (11.7-15.4)	15.3 (13.1-17.6)
	65+	1	70.3	82.3 (76.0-88.5)	91.2 (83.6-98.7)	100.1 (91.1-109.1)
	All	1	11.7	13.8 (12.9-14.7)	15.5 (14.3-16.6)	17.1 (15.8-18.5)
Basal Cell Carcinoma*						
Males	15-34	3	3.2	5.8 (2.9-8.6)	6.6 (2.1-11.1)	7.5 (0.8-14.2)
	35-64	2	110	117.2(107.4-127.0)	127.6 (114.0-141.1)	137.9 (120.5-155.4)
	65+	2	438	489.7(449.0-530.3)	518.0 (461.2-574.8)	546.4 (472.8-619.9)
	All	3	91.7	102.7 (96.0-109.5)	112.01 (101.7-122.4)	122.3 (107.5-137.0)
Females	15-34	3	13.6	15.8 (10.1-21.6)	22.7 (10.5-34.5)	32.7 (10.5-54.9)
	35-64	2	111	138.1(130.3-145.8)	147.3 (140.2-154.5)	177.8 (165.5-190.2)
	65+	4	289	341.3(308.8-373.8)	375.0 (323.9-426.2)	414.5 (338.8-490.2)
	All	1	78.9	95.7 (90.6-100.8)	107.4 (100.4-114.4)	119.1 (110.1-128.1)

ESR: European Standardised Incidence Rates per 100,000 person-years,
* Not nationwide available, based on rates from Eindhoven
[a] Model used for the predictions. Numbers refer to the numbers of the model as described in the methods section.

Analyses according to subsite revealed the head and neck area to be the most common site for first primary BCC, although a marked increase was not observed for this site. Rates for the trunk, arms and legs have been increasing rapidly. In 2000, observed rates for the trunk were slightly higher among males but on the basis of current trends, women are expected to exhibit higher rates than males in 2015 (figure 4ab).
In 2015, rates for first primary BCC are expected to have more than doubled compared with 2000 for both sexes, and the numbers will be almost double (males: 181%, females 175%) (table 1). The increases in numbers are influences more by increasing incidence rates than by demographic changes (table 2), while the combination of the two may cause very marked increases.

Table 1b: Observed and expected annual number of newly diagnosed skin cancers and 95% prediction intervals, 2000-2015

	Age	2000	2005		2010		2015	
		Observed	Nr (95% PI)	%	Nr (95% PI)	%	Nr (95% PI)	%
Melanoma								
Males	15-34	115	113 (86-139)	99	113 (82-143)	99	124 (87-161)	109
	35-64	598	807 (721-894)	135	1036 (892-1179)	173	1263 (1039-1488)	211
	65+	297	396 (345-447)	133	522 (453-590)	176	709 (613-806)	239
	All	1012	1369 (1256-1482)	135	1811 (1618-2005)	179	2413 (2076-2749)	238
Females	15-34	223	229 (191-267)	103	235 (191-279)	105	264 (210-317)	118
	35-64	769	943 (844-1042)	123	1129 (974-1284)	147	1294 (1063-1525)	168
	65+	409	458 (403-513)	112	541 (471-611)	132	672 (579-764)	164
	All	1406	1673 (1554-1792)	119	1996 (1817-2174)	142	2400 (2130-2671)	171
Squamous cell carcinoma								
Males	15-34	16	15 (5-24)	92	13 (2-24)	82	13 (0-25)	79
	35-64	415	503 (440-566)	121	560 (474-647)	135	557 (450-664)	134
	65+	1590	1958 (1839-2077)	123	2393 (2228-2558)	151	2972 (2742-3203)	187
	All	2021	2513 (2368-2657)	124	3071 (2852-3289)	152	3756 (3424-4088)	186
Females	15-34	13	18 (7-29)	136	18 (4-31)	135	19 (2-37)	147
	35-64	295	394 (342-445)	133	498 (429-566)	169	568 (484-652)	193
	65+	1054	1297 (1203-1391)	123	1510 (1389-1631)	143	1772 (1617-1928)	168
	All	1362	1699 (1591-1806)	125	2018 (1878-2157)	148	2349 (2172-2526)	172
Basal cell carcinoma								
Males	15-34	82*	129 (66-192)	157	134 (42-227)	163	157 (17-298)	191
	35-64	3337*	3980 (3648-4313)	119	4727 (4225-5228)	142	5110 (4463-5757)	153
	65+	3880*	4787 (4390-5183)	123	5064 (4509-5618)	131	5341 (4623-6059)	138
	All	7300*	9038 (8445-9630)	124	10940 (9930-11951)	150	13186 (11598-14774)	181
Females	15-34	322*	351 (224-478)	109	458 (221-696)	142	676 (216-1135)	210
	35-64	3358*	4617 (4358-4876)	137	5328 (5068-5588)	159	6474 (6025-6923)	193
	65+	3873*	3330 (3016-3644)	86	3652 (3161-4143)	94	4028 (3306-4749)	104
	All	7553*	9677 (9158-10196)	128	11392 (10628-12156)	151	13238 (12198-14279)	175

Numbers: Annual number of newly diagnosed tumours in the Netherlands
%: total percentage change in numbers compared to the final observed period (2000) (100%: no change: <100% decrease in numbers, >100% increase in numbers)
* Not nationwide available, numbers calculated based on age-specific rates (in 5 year age categories) from Eindhoven times the national population size in 2000 in 5-year age categories
95% P.I. = 95% prediction interval

Discussion

Skin cancer is one of the most common cancers in white Caucasian populations. Rates have increased markedly and are expected to keep rising, with the largest absolute increase in the most common type of skin cancer, BCC. Of special concern are the rates for young people, especially females, which are increasing rapidly for melanoma and BCC. Patterns of observed and expected age-specific incidence differed greatly among the types of skin cancer studied. The observed patterns, with increases in melanoma and BCC, for intermittently exposed body sites would suggest that intermittent UV-exposure was the main cause of the rising skin cancer rates in the last decades.
The mean age at diagnosis of these tumours is lower for BCC and melanoma than for SCC. Therefore, expected demographic changes will have a larger impact on the numbers of new SCC cases in the future than on BCC and melanoma. Increases in incidence rates will lead to marked increases in expected numbers of BCC and melanoma patients in the future.
The reliability of our estimates depends on many factors: (a) random variation of the predicted rates, which can be derived from the prediction interval around the estimates, and (b) potential changes in UV-exposure whether related to changes in behaviour or not, resulting in altered UV-exposure patterns in the population. In the period studied they may not yet be affected by the thinning of the ozone layer. Recently, a report studying the effect of changes in the ozone layer, including potential skin cancer rates, was released [10]. Scenario studies of skin cancer that took into account the restrictions set in the Montreal Protocol predicted an expected 21% increase in numbers of skin cancer patients by 2050 compared to 2002; with the Copenhagen amendments the projected incidence of all skin cancers will increase by 7.5% by 2050, compared to an expected increase of 35% with no restrictions [10]. These projections, however, do not take into account patterns in the observed past incidence rates, nor were they adjusted for future changes in demography. Increases in incidence rates were based only on the expected increase in ambient UV-radiation.
Rates for melanoma are expected to increase for all age groups, but more markedly among the young. This would be in contrast to a previous study investigating trends in incidence and mortality of melanoma across Europe, which seemed to indicate a levelling off of incidence and mortality rates in northern and, to a lesser extent western Europe, especially for the young age groups [1].
When our results are compared to the predicted changes in melanoma incidence in the Nordic countries, the pattern for the Netherlands is most similar to that of Denmark. In the other Nordic countries overall rates seem to stabilise or decrease and expected numbers for the young will decrease instead of increase [11]. We did not have information on the mean thickness of melanomas. On the basis of observations from other studies we expect the patterns to be similar to those in high-incidence regions, such as Australia, the United States and northwestern Europe, where the number of thin melanomas seems to be increasing, while the number of thick melanomas remains stable [12-15]. This caused the mean thickness of the melanomas to decrease over time, which is usually accompanied by improvements in survival.

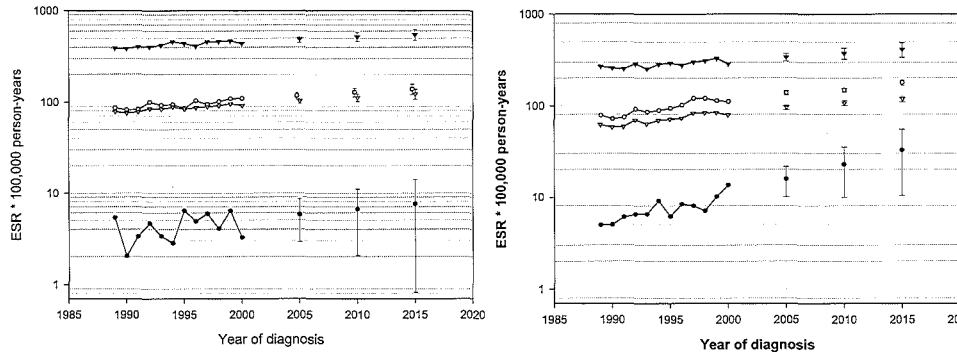

Figure 3: Observed and predicted (extrapolated) age-standardised incidence of basal cell carcinoma with 95% prediction intervals: (1a) males, (1b) females. (●: aged 15-34 years, O: aged 35-64 years, ▼: aged 65 and over, ▽: all ages)

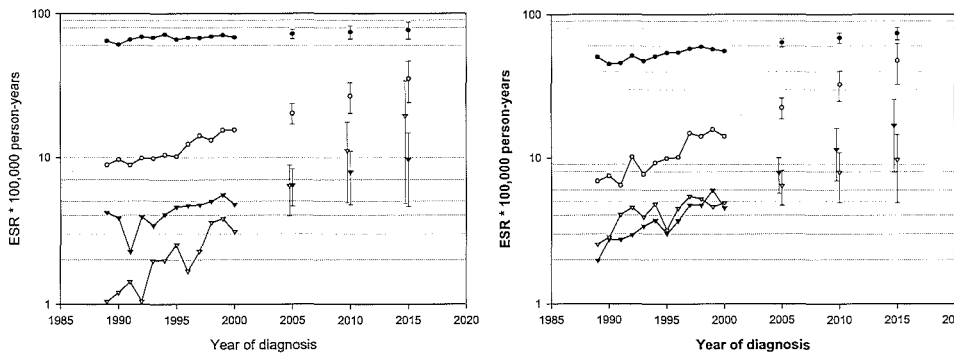

Figure 4: Observed and predicted (extrapolated) age-standardised incidence of site-specific basal cell carcinoma with 95% prediction intervals: (1a) males, (1b) females. (●: head and neck, O: trunk, ▼: arms, ▽: legs)

SCC is commonly thought to be associated with cumulative chronic sun exposure, which supports the observation that rates are highest in the oldest age groups [16, 17]. However, a marked increase was observed in females aged 35-64, pointing to a possible increase in sun exposure in this cohort. Whereas intermittent sun exposure has been increasing over the past few decades (holidays and leisure time), probably causing the increases in melanoma and BCC, chronic sun exposure presumably did not, due to less work outdoors. Rates for SCC have been increasing, albeit not as steeply as BCC and melanoma, whereas two decades ago, the increase in the rates for BCC and SCC were comparable [18]. Many in-situ lesions of SCC (keratoses) are treated and hence do not progress to invasive SCC. The incidence of in-situ SCC might be increasing more, but since it was not registered it cannot be assessed.

Basal cell carcinoma was by far the most common type of skin cancer, with rapidly increasing expected rates for both sexes, especially young females.
Differential changes will also occur in the distribution according to subsite; the majority of BCCs will still occur in the head and neck region, but BCCs on other body sites, such as the trunk, arms and legs, will increase faster than those in the chronically exposed head and neck region, possibly due to intermittent exposure to ultraviolet radiation. As in other studies , remarkable expected increases were found for BCCs on the trunk and legs [18-20], especially for women, probably due to the increasing popularity of sunbathing and wearing bikinis or even monokinis since the 1960's.
Presently, dermatologists in the Eindhoven area have already observed an increasing number of young female patients with many signs of solar damage and BCCs on the trunk (personal communication) [21]. In other parts of the world, similar patterns have been reported, with very moderate increases in the head and neck region and substantial increases for both sexes on the trunk and lower limbs [18].
The largest increases in incidence rates were found for BCC and melanoma, both of which have been associated with intermittent over-exposure to UV radiation [16, 22, 23]. Moreover, the increases in BCC incidence were found mainly for the intermittently exposed body-sites: trunk, arms and legs [18, 20]. Rates for SCC and BCCs in the head and neck area, which are associated with chronic UV exposure, have not increased substantially [18, 20].

Policy implications
It is clear that the predicted rates and the numbers of newly diagnosed patients with various skin cancers should keep activities for primary prevention and early detection high on the public health and clinical agenda in the Netherlands. They will increase the burden on general practitioners, dermatologists and to a lesser extent also (plastic) surgeons [24].

Table 2: Percentage change in annual numbers of new cases of skin cancer compared to the final observed data (2000) due to changes in rates and demography

	Melanoma		Squamous cell carcinoma		Basal cell carcinoma	
	Rates (%)	Demography (%)	Rates (%)	Demography (%)	Rates (%)	Demography (%)
Reference						
2000	100	100	100	100	100	100
Males						
2005	126	108	111	113	112	111
2010	154	115	119	127	122	123
2015	191	122	128	144	133	135
Females						
2005	114	104	117	107	120	107
2010	132	108	130	114	133	113
2015	154	112	144	120	146	120

Demography: % change in numbers of cases compared to the final observation period (2000) due to demographic projections: projected population numbers are applied to the rates of 2000 (100%: no change: <100% decrease in numbers, >100% increase in numbers). *Rates*: % increase in numbers of cases compared to the final observation period (2000) due to changes in incidence rates: projected rates are applied to the population in 2000 (100%: no change: <100% decrease in numbers, >100% increase in numbers)

Pathologists will also see an increase in work load, depending on the capacity of GPs and dermatologists to differentiate between skin lesions. Assuming that for each new case another 20 to 50 patients at increased risk will visit the GP or dermatologist, the demand for detection will increase quite markedly: for a GP this is estimated to increase from one to two patients per day. GP's and dermatologists will have to find ways to deal with this patient demand, which is supposed to double in the next decade. Unfortunately, these care providers are becoming increasingly scarce due to the combination of restrictions of the numbers of medical students since the mid 1980's (up to 2002), together with the feminisation of medical care providers. Therefore, scenarios are being developed to discuss options for increasing the efficiency of preventive care. Such options include training and employing nurse practitioners or other practitioners, in fact developing new types of preventive service. Teledermatology has the potential to improve the service, but will not make practice more efficient.

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Chapter 2.4

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.

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Summary

We analyzed time trends in incidence of and mortality from malignant cutaneous melanoma in European populations since 1953. Data were extracted from the EUROCIM database of incidence data from 165 cancer registries. Mortality data were derived from the WHO database. During the 1990s, incidence rates were by far highest in northern and western Europe, whereas mortality was higher in males in eastern and southern Europe. Melanoma rates have been rising steadily, albeit with substantial geographic variation. In northern Europe, a deceleration in these trends occurred recently in persons aged under 70. Joinpoint analyses indicated that changes in these trends took place in the early 1980s. In western Europe, mortality rates have also recently leveled off (estimated annual percentage change (EAPC) from −13.6% (n.s.) to 3.3%), whereas in eastern and southern Europe both incidence and mortality rates are still increasing (incidence EAPCs 2.3–8.9%, mortality EAPCs −1.8% (n.s.) to 7.2%). Models including the effects of age, period and birth cohort were required to adequately describe the rising incidence trends in most European populations, with a few exceptions. Time trends in mortality were adequately summarized on fitting either an age-cohort model (with the leveling off of rates starting in birth cohorts between 1930 and 1940) or an age-period-cohort model. The most plausible explanations for the deceleration or decline in the incidence and mortality trends in recent years in northern (and to a lesser extent western) Europe are earlier detection and more frequent excision of pigmented lesions and a growing public awareness of the dangers of excessive sunbathing.

Introduction

In recent decades, cutaneous melanoma (melanoma) incidence and mortality rates have been steadily and markedly increasing in many European countries, particularly among Caucasian populations[1-3]. Most melanomas are thought to be caused by intermittent (not chronic) exposure to UV radiation[1, 4-6], especially during childhood, though exposure in adulthood certainly also plays a part[7, 8]. In older people, melanomas appear to be more related to chronic exposure. This is suggested by the body site distribution of melanomas in the elderly, with more melanomas on chronically exposed body sites[9, 10]. Also, in the elderly, melanomas are more often of the lentigo maligna or acral lentiginous type, both of which are related to chronic exposure to UV radiation[11]. The rises in melanoma incidence and mortality are often attributed to a variety of behavioral changes in lifestyle in European populations, resulting in increasing intermittent exposure to UV radiation: increasing outdoor recreational activities and desire to tan as well as holidays spent in (sub)tropical climates or at high altitudes[6, 12]. However, there is evidence that in several countries trends in melanoma mortality rates are stabilizing or even decreasing[2]. From age-period-cohort analyses of mortality data, it is known that in countries with high melanoma incidence mortality rates increased starting from birth cohorts around 1880 (Australia, the Nordic countries, United States)[13-15] and stabilized in cohorts born around 1940–1950, when UV awareness was still low. There is a paucity of published data on incidence trends, particularly in European populations, however. Here, we describe temporal patterns in melanoma incidence and mortality in Europe based on data from 211,557 new melanoma patients recorded in 63 cancer registries during the period 1953–1998 and 148,485 deaths from melanoma abstracted from the WHO mortality database.

Materials and methods

Incidence and mortality data were extracted from the EUROCIM database [16]. The incidence data in EUROCIM originate from the European Network of Cancer Registries, comprising 165 registries,16 of which 63 qualified for this trend analysis. Registries that were included in *Cancer Incidence in 5 Continents* [17], had 9 years or more of incidence registration and were of sufficient size to not give strongly fluctuating estimations qualified for inclusion in our study. For each population, the longest available period of registration was used where possible, varying from 9 to 44 years of observation (table 1). Data used to describe incidence patterns were based either on countrywide registration systems (Denmark, Estonia, Finland, Norway, Sweden, England and Wales, Scotland, the Netherlands, Croatia, Slovenia, Czech Republic, Slovakia and Poland) or on registries that covered only part of the national population (Switzerland, Spain, Italy and France) (table 1). Exclusion criteria for incidence data included small populations at risk (*e.g.,* Iceland and Germany, only registries in Hamburg and Saarland cover >10 years), resulting in fluctuating rates and an insufficiently extended period of registration to examine trends. In 1996, there were 15,228 incident melanoma cases in the included countries (6,729 males, 8,499 females). For mortality data, nationwide data sets were available from the WHO Mortality Databank. Data from the same

Table 1: Description of the registry populations and trend estimations: incidence and mortality

INCIDENCE	Period	ASR[1]	ASR[1]	Pop.	Male/female	25-49	50-69	70+
25+	of registry	Start	end	Size[2] ($x10^6$)	Ratio cases	EAPC (95% CI)	EAPC (95% CI)	EAPC (95% CI)
Males								
North								
Denmark	1978-1996	12.9	20.6	1.79	0.7	2.5 (1.7-3.2)	3.9 (3.4-4.4)	5.9 (5.4-6.3)
England & Wales	1971-1997	2.6	10.6	17.29	0.6	5.2 (4.5-5.8)	6.8 (6.3-7.3)	7.0 (6.6-7.4)
Estonia	1968-1997	2.4	17.5	0.43	0.6	2.6 (1.8-3.3)	3.6 (3.2-4.0)	4.6 (4.3-4.9)
Finland	1953-1997	2.3	20.6	1.69	0.9	3.7 (3.5-4.0)	4.6 (4.4-4.8)	4.9 (4.8-5.1)
Norway	1953-1997	3.0	30.7	1.53	0.8	3.9 (3.7-4.1)	6.0 (5.8-6.1)	5.5 (5.4-5.6)
Scotland	1960-1997	2.2	15.6	1.66	0.6	5.8 (5.3-6.2)	6.7 (6.4-7.0)	5.1 (4.9-5.3)
Sweden	1960-1998	4.3	24.7	2.98	0.9	3.0 (2.7-3.3)	4.6 (4.4-4.8)	5.6 (5.5-5.8)
West								
France[3]	1982-1996	6.3	12.3	2.01	0.7	5.8 (4.2-7.3)	5.1 (4.0-6.1)	8.6 (7.7-9.5)
Netherlands	1989-1997	14.0	17.9	5.61	0.7	2.7(-0.1-5.5)	4.2 (2.1-6.3)	9.5 (7.6-11.5)
Switzerland[3]	1983-1996	15.1	27.6	1.84	0.9	1.1(-0.1-2.3)	4.0 (3.3-4.7)	6.2 (5.7-6.7)
East								
Czech Republic	1985-1997	10.2	15.6	3.21	0.9	2.2(0.4-4.0)	3.7 (2.7-4.7)	7.0 (6.2-7.9)
Slovakia	1968-1997	1.2	10.5	1.56	0.8	5.3 (4.6-5.9)	6.8 (6.4-7.2)	9.2 (8.8-9.6)
Poland[3]	1987-1997	4.1	5.8	1.76	0.7	2.0(-1.6-5.7)	4.3 (2.1-6.5)	3.9 (2.1-5.8)
South								
Italy[3]	1985-1997	8.0	15.0	1.72	0.8	3.4 (1.5-5.3)	4.8 (3.7-6.0)	6.7 (5.6-7.8)
Slovenia	1983-1997	6.4	14.7	0.63	0.8	7.9 (6.3-9.6)	3.3 (2.4-4.3)	9.8 (8.9-10.7)
Spain[3]	1985-1997	5.0	7.8	1.73	0.7	6.0 (3.2-9.0)	5.7 (3.9-7.6)	4.2 (2.8-5.5)
Females								
North								
Denmark	1978-1996	17.2	23.3	1.89		3.0 (2.4-3.6)	3.3 (2.8-3.7)	3.8 (3.3-4.3)
England & Wales	1971-1997	3	19.0	18.56		4.1 (3.6-4.6)	4.7 (4.3-5.1)	5.4 (5.0-5.7)
Estonia	1968-1997	2.5	11.5	0.54		4.1 (3.5-4.7)	4.5 (4.1-4.9)	6.4 (6.0-6.8)
Finland	1953-1997	2.6	14.2	1.85		3.4 (3.1-3.6)	3.9 (3.7-4.1)	4.0 (3.8-4.2)
Norway	1953-1997	2.4	31.1	1.61		4.3 (4.1-4.5)	6.1 (5.9-6.2)	4.4 (4.3-4.5)
Scotland	1960-1997	4.8	14.3	1.85		5.2 (4.8-5.5)	5.4 (5.1-5.7)	4.9 (4.7-5.1)
Sweden	1960-1998	5.4	23.4	3.15		3.4 (3.1-3.6)	3.9 (3.7-4.1)	4.0 (3.8-4.1)
West								
France[3]	1982-1996	8.4	13.9	2.10		5.0 (3.8-6.2)	4.7 (3.8-5.6)	3.5 (2.7-4.3)
Netherlands	1989-1997	19.4	22.5	5.88		2.9 (0.7-5.1)	3.2 (1.3-5.1)	7.3 (5.4-9.3)
Switzerland[3]	1983-1996	21	10.4	1.95		1.3 (0.3-2.3)	0.4 (-0.3-1.2)	2.7 (2.0-3.3)
East								
Czech Republic	1985-1997	8.7	16.1	3.58		5.2 (3.6-6.8)	4.1 (3.0-5.2)	5.5 (4.5-6.4)
Slovakia	1968-1997	3.9	10.6	1.75		4.5 (3.9-5.0)	5.2 (4.8-5.6)	4.8 (4.4-5.2)
Poland[3]	1987-1997	6.2	5.5	1.90		2.2(-0.8-5.3)	5.8 (3.6-8.0)	5.6 (3.6-7.6)
South								
Italy[3]	1985-1997	8.3	14.3	1.85		6.1 (4.5-7.8)	4.9 (3.7-6.2)	3.0 (1.8-4.1)
Slovenia	1983-1997	7.2	13.3	0.71		3.1 (1.8-4.4)	6.0 (4.9-7.0)	4.8 (3.8-5.7)
Spain[3]	1985-1997	5.4	22.8	1.78		4.8 (2.5-7.0)	5.0 (3.3-6.7)	4.7(3.4-6.0)

countries as for incidence were used, except for Estonia and Slovakia because their mortality statistics covered only a very short period or were considered unreliable.
For France, the first years of registration were omitted (1958–1968) because of coding problems during the transition from ICD-7 to ICD-8. In 1994, there were 6,846 melanoma deaths in the included countries (3,521 males, 3,325 females). Only invasive cutaneous melanomas were included in the analyses (ICD-7 190, ICD-8 172, ICD-9 172, ICD-10 C43). Because age-specific rates in many populations were subject to substantial annual variation, 3-year averages of the rates were graphed for 3 age categories, 25–49, 50–69 and 70+, for each sex. Differences in susceptibility, subsite of the melanoma and exposure were expected among these groups. All data presented, except those in figure 1, are for people aged 25 and older. The estimated annual percentage change (EAPC) was calculated for all populations.

Table 1 (continued): Description of the registry populations and trend estimations: incidence and mortality

MORTALITY	Period	ASR[1]	ASR[1]	Pop	Male/female	25-49	50-69	70+
25+	of registry	Start	end	Size[2] (*10[6])	ratio deaths	EAPC (95% CI)	EAPC (95% CI)	EAPC (95% CI)
Males								
North								
Denmark	1958-1996	2.7	6.0	1.79	1.2	1.2 (0.7-1.7)	3.3 (3.0-3.6)	3.1 (2.9-3.4)
England & Wales	1958-1997	0.9	3.8	17.29	0.8	2.3 (1.7-3.0)	3.8 (3.4-4.3)	4.2 (3.9-4.5)
Finland	1958-1996	1.3	4.3	1.68	1.2	1.0 (0.5-1.6)	2.4 (2.1-2.8)	3.2 (3.0-3.5)
Norway	1958-1996	1.9	7.3	1.51	1.4	1.3 (0.8-1.7)	3.9 (3.6-4.2)	3.7 (3.5-3.9)
Scotland	1968-1997	1.7	4.2	1.66	0.9	2.3 (1.3-3.3)	3.2 (2.6-3.9)	3.5 (3.1-4.0)
Sweden	1958-1996	2.2	5.4	2.96	1.1	0.2 (-0.3-0.7)	2.8 (2.5-3.1)	3.4 (3.1-3.6)
West								
France	1969-1997	1.1	3.2	18.69	1.0	3.3 (2.0-4.6)	4.6 (3.8-5.4)	5.0 (4.4-5.5)
Netherlands	1958-1997	1.3	4.9	5.27	1.1	2.6 (2.1-3.2)	3.2 (2.9-3.6)	2.7 (2.4-2.9)
Switzerland	1958-1994	2.2	4.8	2.35	1.2	0.4 (-0.1-1.0)	2.4 (2.1-2.7)	4.7 (4.4-4.9)
East								
Czech republic	1986-1997	6.0	5.7	3.21	1.3	1.6 (-0.4-3.7)	3.3 (2.2-4.5)	7.0 (6.1-7.9)
Poland	1961-1996	0.4	2.5	11.26	0.9	4.8 (4.0-5.7)	6.0 (5.5-6.5)	5.7 (5.3-6.2)
South								
Italy	1958-1996	0.6	3.1	19.55	1.1	3.1 (2.3-3.9)	5.0 (4.5-5.5)	6.3 (5.9-6.6)
Slovenia	1985-1997	5.2	4.9	0.63	1.0	3.0 (-0.1-6.1)	0.0(-1.5-1.5)	5.3 (4.1-6.5)
Spain	1958-1997	0.03	2.3	12.86	1.4	8.5 (7.2-9.8)	8.9 (8.0-9.7)	7.5 (7.0-8.0)
Females								
North								
Denmark	1958-1996	2.1	3.4	1.89		0.0 (-0.4-0.5)	2.4 (2.0-2.7)	2.2 (1.9-2.5)
England & Wales	1958-1997	1.3	3.1	18.56		0.9 (0.3-1.5)	2.9 (2.5-3.3)	3.7 (3.3-4.0)
Finland	1958-1996	1.5	2.1	1.85		0.1 (-0.6-0.7)	1.6 (1.2-2.1)	2.1 (1.8-2.4)
Norway	1958-1996	1.4	4.7	1.60		1.5 (1.0-2.0)	3.3 (2.9-3.7)	2.6 (2.4-2.9)
Scotland	1968-1997	2.3	2.2	1.85		0.4 (-0.5-1.4)	0.9 (0.3-1.6)	0.8 (0.3-1.2)
Sweden	1958-1996	2.0	3.0	3.14		1.0 (0.4-1.6)	0.0 (1.7-2.5)	2.1 (1.8-2.3)
West								
France	1969-1997	0.9	2.4	20.61		2.6 (1.2-4.0)	4.0 (3.1-4.9)	4.2 (3.6-4.8)
Netherlands	1958-1997	1.4	3.4	5.54		2.3 (1.9-2.9)	2.6 (2.2-3.1)	1.9 (1.6-2.2)
Switzerland	1958-1994	0.9	3.0	2.55		0.7 (0.1-35.2)	2.6 (2.1-3.0)	3.2 (2.9-3.5)
East								
Czech republic	1986-1997	3.1	3.2	3.58		4.7 (2.9-6.4)	3.9 (2.7-5.2)	4.7 (3.6-5.8)
Poland	1961-1996	0.3	2.0	12.63		4.6 (3.8-5.5)	5.0 (4.4-5.6)	4.4 (4.0-4.8)
South								
Italy	1958-1996	0.5	2.2	21.60		3.1 (2.2-4.0)	4.3 (3.7-4.9)	5.3 (4.9-5.8)
Slovenia	1985-1997	4.2	4.2	0.71		3.7 (0.6-6.9)	4.4 (2.4-6.5)	4.5 (3.4-6.2)
Spain	1958-1997	0.02	1.8	14.03		7.9 (6.5-9.4)	8.8 (7.8-9.9)	7.7 (7.2-8.3)

There may be differences in population size between incidence and mortality data, due to the different original sources of these databases. In those countries where only regional incidence data were available, the population sizes on which the incidence data are based may be much smaller than those used for the mortality data.

[1] European Standard Population per 100,000 person-years, in population >=25 years of age, [2] At the end of the registration period, [3] Covering only part of the country: France: Bas-Rhin, Calvados, Doubs, Isere, Somme and Tarn; Switzerland: Geneva, Basel, Neuchatel, St Gall-Appenzell, Zürich; Spain: Navarra, Catalonia, Granada; Italy: Lombardy, Parma, Ragusa, Florence, Turin; Poland: Lower Silesia, Krakow City.

EAPCs were calculated by fitting a regression line to the natural logarithm of the rates using calendar year as a regressor variable, *i.e.*, $y = b + mx$, where y = ln(rate) and x = calendar year. The EAPC is then estimated as $100 * (e^m - 1)$. Testing that the EAPC is 0% is equivalent to testing the null hypothesis that the slope of the line in the above equation is equal to 0. This was tested by comparing m/SE(m) with a t-distribution on $k - 2$ degrees of freedom, where k is the length of the period. The standard error of m, SE(m), was obtained from the fit of the regression line. The calculation assumed that the logarithm of the rates changed at a constant rate over the entire period.

Joinpoint analyses were performed to discern significant changes in the trend and, if present, when they occurred[18]. In joinpoint analyses, linear line segments are connected on a log scale to identify changes in trend data in terms of the annual rates of change in fixed periods of time[18], though cross-sectional cancer rates generally do not change abruptly. In populations where joinpoint analyses revealed changes in time trends by age category, age-period-cohort analyses were performed to jointly examine the influence of longitudinal and cross-sectional changes[19, 20].

Results

Geographic variations

The incidence of melanoma in Europe was highest in the northern European countries, especially in Scandinavia (table 1, fig. 1), where age-standardized rates (European standard population) as high as 20.7 per 100,000 person-years were found in the latest 3 years of observation (1995–1997) in Norwegian women of all ages (fig. 1). Incidence rates were lowest in southern and eastern Europe for both males and females, with rates between 5 and 10 per 100,000 person-years. The incidence/mortality ratios vary considerably, from <2 in males for low-incidence countries like Spain and Italy to >4 in the high-incidence areas in northern Europe and Switzerland (fig. 1). Incidence rates were usually higher in women than in men; hence, the sex ratio (M/F) was less than 1 for all countries.

Mortality rates differed much less within Europe (varying from 1.5 to 5.2 per 100,000 person-years). Mortality rates were lower in women than in men. Compared to the incidence in the 1990s, mortality rates were highest in southern and eastern Europe and lowest in northern and western Europe.

Temporal variations

Melanoma incidence and mortality rates rose in all countries included in the study (table 1, fig. 2a,b). In northern Europe, increases were most pronounced; incidence rates increased about 10-fold in the period 1953–1997 in Norwegians aged 25 and older (3.0-30.7 in males and even more in females, 2.4-31.1); the rise in Finnish men (2.3–20.6) was also considerable (table 1).

In the early years of registration, the strongest increases in incidence were seen in northern Europe, followed by western Europe and, in the later years, by southern and eastern Europe. Mortality rates increased as well but much less steeply than incidence rates; they appeared to reach a plateau, especially in the high-incidence countries. Inspection of 3-year averages by age group showed that the increase in incidence rates has leveled off, especially in younger age groups, in many northern European countries in both sexes (males in Denmark, Norway, Sweden, Finland, England and Wales; females in Norway, Sweden, Finland, England and Wales), Switzerland, Czech Republic (males) and Slovakia (males). Mortality rates exhibited weaker increases than incidence rates (*e.g.,* EAPC 0.1% (n.s.) in Finnish females of 25–49 years). The difference between incidence and mortality was most obvious in the younger age groups in northern and western European countries (table 1, fig. 2a,b). Among older men and women in all countries, incidence and mortality rates were still increasing.

European populations. Also, northern European populations may have been exposed to more intermittent exposures due to differences in sun behavior and faraway holiday experiences. *(ii)* Increases in the amount of ambient UV irradiance would be consistent with the increases in incidence of melanomas and other skin cancers, but such changes occurred only after the start of the upward trends of skin cancer and are of lower magnitude than the observed increases in incidence[6].

Increasing amounts of UV radiation would be expected to affect melanoma incidence rates only after a delay of about 20 years, due to the long latency period of UV radiation for the induction of melanoma[27, 28]. *(iii)* Increased ascertainment[19] of suspected lesions could have contributed to the increases in incidence. Since the mid-1980s, many primary and secondary prevention campaigns have been organized, raising the level of awareness of skin cancer in both professional health-care workers and the general population, resulting in higher rates of detection of melanomas. Some registries have reported increased detection of pigmented lesions following prevention campaigns. There are clear trends toward thinner lesions in some populations, indicating earlier if not increased ascertainment [6, 22, 23, 29, 30]. One would expect the effect to be a temporary increase in incidence, however. Changes in coding and registration practices are less likely to have contributed to the increases[6]. It is known that in some registries up to 23% of melanoma cases are not registered[31]. It is not known if this underregistration is constant in time. If this were the case, the trends would remain the same. If, however, this underregistration is not constant in time, it may influence trend estimations. Changes in pathologic diagnostic criteria could also influence melanoma incidence rates. This is not very likely to have happened; in a large study investigating this hypothesis, only very small shifts in diagnostic categories were found[32]. With respect to mortality from melanoma, a moderation of increases and even decreases has been observed in several European countries[2, 33] and melanoma survival rates have improved in the last decades[23, 33-37]. This improvement in survival is most probably related to increasingly early detection of melanomas and resection of suspected pigmented lesions. One of the main prognostic factors is the Breslow thickness, which has been recorded by some registries since the 1980s. In some European countries, decreases in the mean or median melanoma thickness have been observed [22, 23, 30, 35, 36, 38]. There have been no major changes in treatment methods for melanoma patients recently, except for smaller excision margins[39]. Despite their lower incidence of melanoma, men exhibit higher mortality rates than women in most countries. Melanomas in men present more often on the trunk[23, 37, 40], which has a poorer prognosis[41, 42]. In a British study, it was found that men have less knowledge about appropriate preventive measures, present with the disease at later stages and respond less to public health education processes[43]. An age-period or age-cohort model failed to explain trends in incidence in most countries, except in Finnish females, where an age-period model fitted. In the other populations, age-period-cohort-models were needed, which, due to identifiability problems, are very difficult to interpret[19]. Germany was not included in these analyses, but previous analyses on data from Saarland and Hamburg showed that an age-period-cohort model was needed to describe the data in Saarland, whereas in Hamburg an age-drift model fitted the data[3]. Age-cohort models were sometimes sufficient to describe changes in mortality rates,

with the major decline in rates occurring in generations born in the 1930s, as was observed previously in Europe, the United States and Australia[13-15]. Survival following diagnosis of melanoma, adjusted for prognostic factors, is generally less favorable for men than for women, as has been observed before in Europe, Australia and the United States[23, 35, 37, 44]. In our study, melanoma mortality rates for men were up to twice those for women (table 1). The difference in melanoma incidence between intermediate incidence (France, Italy, Spain) and high-incidence (Scandinavia) populations is decreasing. This is due to a stabilization and sometimes even a decrease in incidence and mortality in the young age groups in northern Europe in recent years,

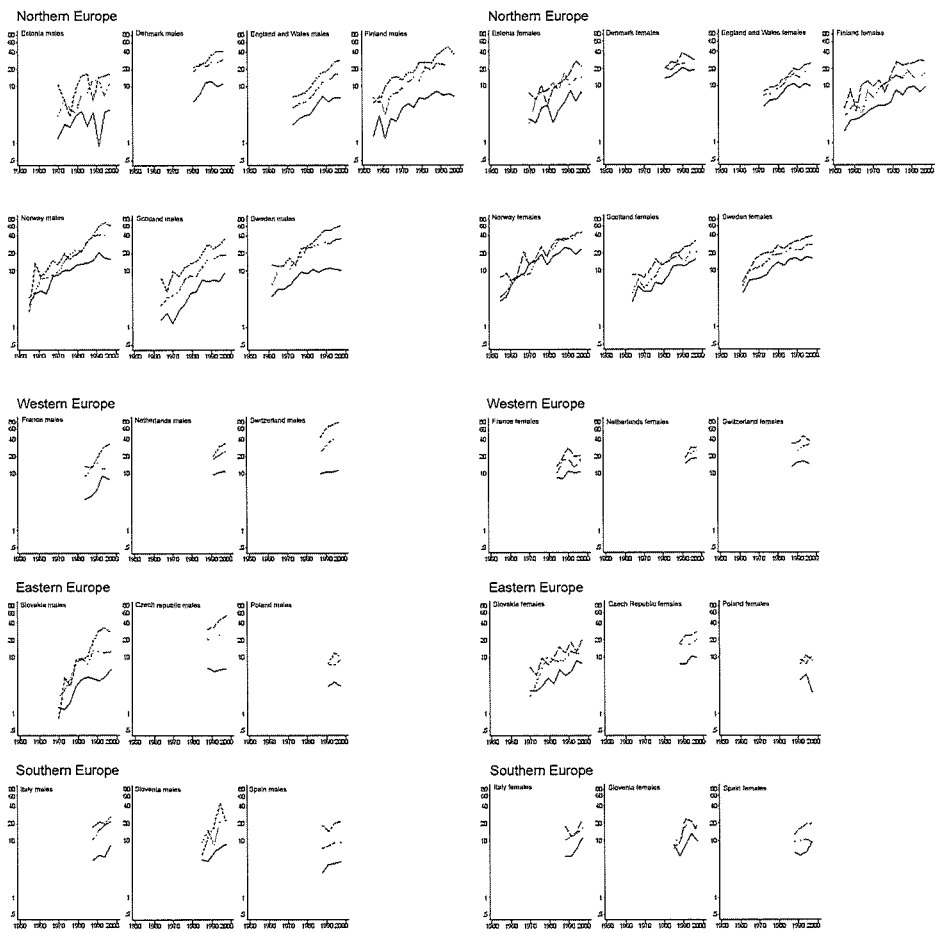

Figure 2a. Three-year averages of age-specific melanoma incidence trends in Europe per 100,000 person-years. Solid lines, 25-49 years old; dotted lines, 50-69 years old; dashed lines, 70+ years old.

whereas rates are still increasing steeply in southern Europe. Severi *et al.*[13] found the highest rates of increased mortality in countries like France, Italy and the former Czechoslovakia, with increases being most marked in older age groups and in men. Møller *et al.*[45] predicted that melanoma incidence trends would stabilize or decrease in most of the Nordic countries up to the year 2020, which is in line with the flattening off of incidence rates in young age groups in these countries observed in our study. This flattening off of rates would be expected to result in stabilizing or decreasing future incidence trends. The plateau, or even decreases, in the trends in young people in

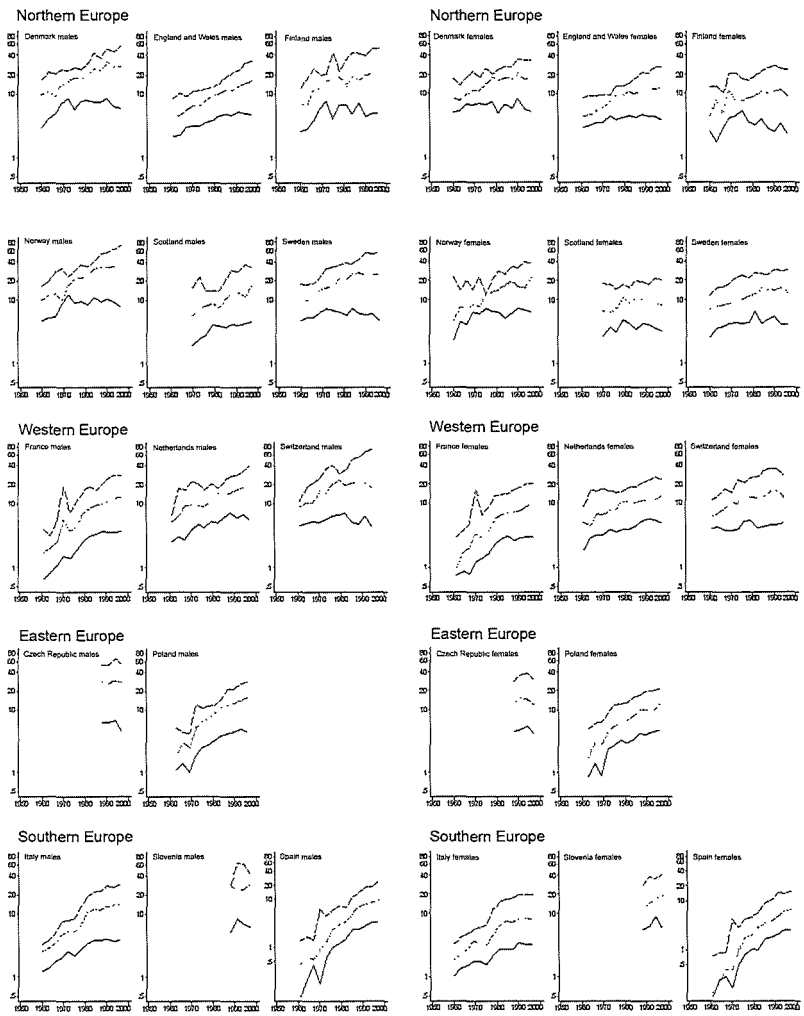

Figure 2b. Three-year averages of age-specific melanoma mortality trends in Europe per 100,000 person-years. No mortality data were available for Estonia and Slovakia. Solid lines, 25-49 years old; dotted lines, 50-69 years old; dashed lines, 70+ years old.

northern and western Europe are more distinct in mortality rates than in incidence rates. This may be due to early detection of lesions since this would moderate mortality but not incidence trends. The youngest age groups are more likely to be influenced by the public health campaigns that have been conducted in the northern and western European countries[46-48]. The moderation in mortality trends would appear to be cohort-related if prevention campaigns were more effective in young people. However, most of the detected lesions are probably thin melanomas. In general, melanomas with a Breslow thickness of <1 mm have a very good prognosis with a low incidence of metastasis[35, 42]. If the increase in incidence is mainly caused by detection of these very thin melanomas, many of them might have never progressed to metastatic disease and, hence, would never appear in the mortality statistics. The observation of higher incidence/mortality ratios in high incidence countries compared to low-incidence countries is in line with an effect of awareness campaigns in the high-incidence countries, where melanomas would be discovered at earlier stages and therefore survival is expected to be better. We observed changes in the trends around 1980 or later, when the first awareness and prevention campaigns concerning skin cancer were launched in some northern and western European countries[49].

For changes in incidence rates due to diminished exposure to UV radiation, a much longer time frame appears to be needed. The induction period for UV radiation to cause melanoma is estimated to be at least 10 years[50] but may be nearer 20 years. Therefore, changes in sunbathing habits can be expected to result in changes in incidence rates only in the future. If indeed childhood is the main period in which exposure to UV radiation is harmful, then changes in sun exposure would have the most impact when children whose outdoor habits were changed enter the malignant melanoma risk ages. Another explanation for the decrease or stabilization of the rather high incidence rates in the north could be that rates cannot increase any further. Populations in the northern European countries may have reached almost maximal levels of risk, with a constant proportion of susceptible people in the population. The northern European countries have a high socioeconomic status, where even people in the lower socioeconomic groups can afford sunbathing. As a result, sunbathing habits may have started earlier in northern Europe compared to other countries. Despite the overwhelming evidence for UV radiation and host factors like nevi and skin type being involved in melanoma risk, the etiology of melanoma at a personal level remains an enigma. A variety of host factors and behaviors are important in determining actual melanoma risk or progression to invasive disease. If exposure to UV radiation at young ages (<20 years) is really the main behavioral risk factor, changing behavioral patterns at adult ages would hardly affect melanoma incidence rates. However, if sunrelated behavior would influence melanoma risk at all ages[8], period effects would be expected from successful campaigns. In older people, more melanomas are found on the chronically exposed body parts, like the head and neck[9] and are often of the acral lentiginous or lentigo maligna type[11]. These observations suggest that in older melanoma patients other risk factors may be involved. In conclusion, the epidemiology of cutaneous melanoma in Europe has markedly changed in the last 50 years, with rising trends first emerging in Scandinavia and the United Kingdom, then spreading to western, southern and eastern Europe, each with a time interval of about 10 years.

The recent favorable changes in trends in countries with very high melanoma incidence, like the United States, Australia and, as observed here, the Nordic countries, suggest that the epidemic must be combated by increased awareness of both UV exposure and early detection of suspected lesions. In these analyses, information on changes in histologic type, body site distribution and thickness of melanomas was available in only some registries. A look at time trends in these factors would provide more insight into the causes and patterns of melanoma incidence and mortality.

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Annex Table A1: Results of joinpoint analyses for incidence data

Region Europe	Country	Age	Males Nr of jp	Yr of Jp (CI)	EAPC (%)	95% CI	Females Nr of jp	Yr of jp (CI)	EAPC (%)	95% CI
East	Cz	25-49	0		2.9	(1.5 ; 4.2)	0		5.3	(3.1 ; 7.5)
		50-69	3	1988 ('87-'89)	10.2		0		3.1	(3.1 ; 5.9)
				1991 ('90-'92)	-1.4					
				1995 ('93-'95)	7.2					
					-4.3					
		70+	0		7.4	(5.7 ; 9.1)	0		5.2	(3.7 ; 6.6)
	Sk	25-49	1	1981 (77-"84)	11.8	(7.5 ; 16.2)	0		4.2	(3.3 ; 5.0)
					2.5	(0.9 ; 4.1)				
		50-69	1	1982 ('77-'88)	16.3	(11.4 ; 21.5)	1	1979 ('75-'84)	10.3	(5.4 ; 15.4)
					2.3	(0.3 ; 4.3)			3.3	(1.9 ; 4.7)
		70+	0		7.9	(6.3 ; 9.5)	0		4.7	(3.5 ; 5.8)
North	Dk	25-49	0		2.3	(1.1 ; 3.5)	0		3.0	(2.2 ; 3.9)
		50-69	0		3.8	(2.9 ; 4.7)	0		3.0	(2.2 ; 3.9)
		70+	0		5.6	(4.5 ; 6.7)	0		3.4	(2.2 ; 4.6)
	E&W	25-49	0		3.6	(1.8 ; 5.4)	0		2.6	(1.3 ; 3.9)
		50-69	1	1987 ('83-'91)	9.0	(7.0 ; 11.1)	1	1988 ('86-'90)	6.5	(5.3 ; 7.6)
					3.8	(2.0 ; 5.7)			1.8	(0.3 ; 3.3)
		70+	0		6.8	(5.9 ; 7.6)	0		5.3	(4.6 ; 5.9)
	Est	25-49	0		2.4	(0.9 ; 4.0)	0		4.1	(2.8 ; 5.5)
		50-69	0		3.4	(2.0 ; 4.9)	0		4.5	(3.3 ; 5.8)
		70+	0		4.7	(2.9 ; 6.5)	0		6.1	(4.6 ; 7.7)
	Fin	25-49	1	1987 ('85-'90)	4.9	(4.3 ; 5.5)	1	1982 ('78-'89)	4.5	(3.6 ; 5.5)
					-1.4	(-3.4 ; 0.8)			1.1	(-0.5 ; 2.7)
		50-69	1	1986 ('81-'90)	5.6	(4.9 ; 6.4)	1	1983 ('75-'88)	5.4	(4.5 ; 6.4)
					1.3	(-0.6 ; 3.1)			0.6	(-1.0 ; 2.2)
		70+	0		4.8	(4.1 ; 5.4)	0		3.9	(3.4 ; 4.4)
	N	25-49	2	1968 ('62-'75)	8.3	(5.9 ; 10.8)	1	1976 ('72-'79)	8.1	(6.5 ; 9.5)
				1991 ('89-'94)	3.8	(2.7 ; 4.1)			1.7	(0.8 ; 2.5)
					-3.1	(-6.8 ; 0.8)				
		50-69	1	1989 ('87-'92)	6.9	(6.2 ; 7.5)	1	1984 ('81-'88)	7.9	(7.1 ; 8.7)
					0.8	(-2.1 ; 3.8)			2.4	(1.1 ; 3.8)
		70+	1	1979 ('68-'87)	4.1	(2.6 ; 5.6)	0		4.1	(3.6 ; 4.7)
					6.6	(5.4 ; 7.8)				
	Sco	25-49	0		5.5	(4.9 ; 6.1)	0		4.9	(4.4 ; 5.5)
		50-69	0		6.6	(6.1 ; 7.2)	2	1976 ('71-'88)	5.1	(2.6 ; 7.7)
								1979 ('77-'93)	20.2	(-22.0 ; 85.2)
									3.0	(1.9 ; 4.1)
		70+	1	1968 ('63-'73)	-3.9	(-11.7 ; 4.5)	0		4.9	(4.4 ; 5.4)
					5.9	(5.1 ; 6.7)				
	S	25-49	1	1988 ('82-'91)	4.0	(3.5 ; 4.6)	1	1990 ('77-'92)	4.2	(3.6 ; 4.8)
					-0.7	(-2.5 ; 1.1)			-1.2	(-4.0 ; 1.7)

Annex Table A1 (continued): Results of joinpoint analyses for incidence data

Region Europe	Country	Age	Males Nr of Jp	Yr of Jp (CI)	EAPC (%)	95% CI	Females Nr of jp	Yr of jp (CI)	EAPC (%)	95% CI
	S	25-49	1	1988 ('82-'91)	4.0	(3.5 ; 4.6)	1	1990 ('77-'92)	4.2	(3.6 ; 4.8)
					-0.7	(-2.5 ; 1.1)			-1.2	(-4.0 ; 1.7)
		50-69	1	1984 ('81-'88)	6.9	(6.2 ; 7.7)	1	1979 ('76-'86)	6.6	(5.6 ; 7.7)
					1.3	(0.4 ; 2.3)			2.2	(1.6 ; 2.9)
		70+	2	1974 ('65-'88)	3.4	(0.9 ; 6.0)	0		3.9	(3.5 ; 4.3)
				1990 ('82-'93)	7.4	(6.1 ; 8.8)				
					2.4	(0.3 ; 4.7)				
West	F	25-49	0		5.5	(3.1 ; 8.0)	0		5.2	(3.2 ; 7.3)
		50-69	0		4.7	(1.9 ; 7.7)	0		4.6	(2.3 ; 7.1)
		70+	0		8.0	(5.8 ; 10.2)	0		2.9	(0.5 ; 5.3)
	NI	25-49	0		2.3	(0.5 ; 4.0)	0		2.9	(1.2 ; 4.6)
		50-69	0		4.1	(1.3 ; 6.9)	0		2.4	(-0.9 ; 5.7)
		70+	0		10.0	(7.6 ; 12.0)	0		6.7	(2.8 ; 10.7)
	CH	25-49	0		1.6	(-0.3 ; 3.6)	0		0.8	(-0.7 ; 2.4)
		50-69	0		3.5	(1.0 ; 6.0)	0		0.8	(-0.6 ; 2.2)
		70+	0		6.0	(3.6 ; 8.4)	0		3.1	(1.5 ; 4.8)
South	It	25-49	0		4.2	(1.8 ; 6.6)	0		5.7	(2.3 ; 9.2)
		50-69	0		4.9	(3.2 ; 6.5)	0		5.0	(3.3 ; 6.6)
		70+	0		6.5	(4.1 ; 8.9)	0		3.2	(0.6 ; 5.9)
	Slo	25-49	0		8.3	(6.1 ; 10.6)	0		3.9	(1.1 ; 6.8)
		50-69	0		4.2	(1.2 ; 7.3)	0		5.8	(3.8 ; 7.8)
		70+	0		8.9	(4.5 ; 13.5)	0		4.4	(0.4 ; 8.5)
	E	25-49	0		5.3	(3.2 ; 7.5)	0		6.0	(2.6 ; 9.5)
		50-69	0		6.3	(4.3 ; 8.3)	0		5.5	(2.0 ; 9.1)
		70+	0		3.9	(1.0 ; 6.9)	0		4.2	(1.8 ; 6.6)

Annex Table A2: Results of joinpoint analyses for mortality data

Region Europe	Country	Age	Males Nr of jp	Yr of jp (CI)	EAPC (%)	95% CI	Females Nr of jp	Yr of jp (CI)	EAPC (%)	95% CI
East	Cr	25-49	0		0.9	(-4.0 ; 6.0)	0		1.9	(-2.4 ; 6.5)
		50-69	0		2.7	(-0.1 ; 5.5)	0		1.2	(-2.3 ; 4.7)
		70+	0		5.6	(0.8 ; 10.5)	0		2.6	(-2.3 ; 7.7)
	Cz	25-49	0		-1.8	(-6.4 ; 3.0)	0		-0.1	(-4.2 ; 4.1)
		50-69	0		-0.1	(-2.3 ; 2.2)	0		-0.4	(-3.2 ; 2.5)
		70+	0		2.2	(-0.2 ; 4.7)	1	1990 ('89 ; '94)	16.8	(4.8 ; 30.2)
									-5.4	(-9.3 ; -1.4)
	Pl	25-49	0		4.2	(3.5 ; 4.9)	1	1970 ('61-'76)	13.3	(2.1 ; 25.6)
									2.9	(2.0 ; 3.8)
		50-69	1	1972 ('64-'80)	13.0	(7.2 ; 19.2)	1	1964 ('62-'69)	58.2	(8.8 ; 130.0)
					4.2	(3.4 ; 5.0)			3.9	(3.4 ; 4.5)
		70+	0		5.3	(4.6 ; 6.0)	0		4.0	(3.3 ; 4.6)
North	Dk	25-49	1	1968 ('64-'73)	10.4	(2.6 ; 18.8)	0		0.0	(-0.9 ; 0.8)
					-0.4	(-1.5 ; 0.8)				
		50-69	1	1990 ('84-'93)	3.9	(3.1 ; 4.7)	1	1977 ('72-'92)	4.7	(2.8 ; 6.7)
					-3.9	(-10.6 ; 3.3)			0.6	(-0.9 ; 2.0)
		70+	0		3.4	(2.6 ; 4.2)	0		2.2	(1.5 ; 2.8)
	E&W	25-49	1	1985 ('79-'94)	3.0	(2.4 ; 3.7)	1	1987 ('77-'92)	1.3	(0.8 ; 1.8)
					-0.4	(-2.0 ; 1.2)			-2.2	(-4.3 ; -0.2)
		50-69	0		3.9	(3.6 ; 4.2)	1	1979 ('74-'83)	4.7	(3.9 ; 5.5)
									1.5	(0.7 ; 2.2)
		70+	1	1979 ('74-'86)	3.1	(1.9 ; 4.3)	1	1970 ('65-'76)	1.3	(-1.2 ; 3.8)
					5.6	(4.8 ; 6.4)			4.4	(3.9 ; 4.8)
	Fin	25-49	1	1970 ('64-'74)	8.3	(1.1 ; 16.0)	1	1972 ('66-'76)	5.5	(0.9 ; 10.4)
					-0.9	(-2.4 ; 0.8)			-2.4	(-4.1 ; -0.8)
		50-69	1	1970 ('64-'77)	8.9	(3.0 ; 15.2)	0		1.4	(0.6 ; 2.3)
					1.1	(-0.3 ; 2.2)				
		70+	0		3.1	(2.3 ; 3.9)	0		1.9	(1.1 ; 2.7)
	N	25-49	1	1970 ('66-'74)	7.6	(2.0 ; 13.4)	0		1.2	(0.3 ; 2.1)
					-0.6	(-1.9 ; 0.6)				
		50-69	1	1994 ('80-'94)	4.2	(3.5 ; 4.9)	0		3.5	(2.7 ; 4.2)
					-18.9	(-48.4 ; 27.6)				
		70+	0		3.9	(3.0 ; 4.7)	0		2.8	(2.1 ; 3.6)
	Sco	25-49	0		2.0	(0.9 ; 3.2)	0		-0.4	(-1.6 ; 0.8)
		50-69	0		3.2	(2.1 ; 4.3)	0		1.1	(-0.1 ; 2.4)
		70+	0		3.5	(2.0 ; 4.9)	0		1.2	(0.1 ; 2.2)
	S	25-49	1	1994 ('67-'94)	0.3	(-0.4 ; 0.9)	0		0.8	(0.0 ; 1.5)
					-31.2	(-65.2 ; 36.1)				
		50-69	1	1986 ('81-'89)	4.0	(3.3 ; 4.7)	1	1993 ('81-'94)	2.5	(2.1 ; 3.0)
					-1.5	(-3.8 ; 0.8)			-11.8	(-25.9 ; 4.9)
		70+	0		3.4	(2.9 ; 3.9)	0		2.1	(1.6 ; 2.7)

Annex Table A2 (continued): Results of joinpoint analyses for mortality data

Region Europe	Country	Age	Males Nr of jp	Yr of jp (CI)	EAPC (%)	95% CI	Females Nr of Jp	Yr of jp (CI)	EAPC (%)	95% CI
West	F	25-49	1	1984 ('78-'88)	6.3	(4.6; 8.1)	1	1980 ('77-'85)	8.2	(4.6; 11.8)
					0.7	(-0.8; 2.2)			0.7	(-0.6; 1.9)
		50-69	2	1973 ('71-'77)	-6.7	(-14.6; 1.9)	1	1979 ('76-'83)	8.4	(6.8; 10.0)
				1979 ('77-'83)	14.2	(8.2; 20.6)			2.8	(1.8; 3.8)
					3.3	(2.7; 3.8)				
		70+	1	1990 ('76-'95)	6.1	(4.7; 7.4)	2	1973 ('71-'76)	-10.1	(-21.9; 3.4)
					1.7	(-2.4; 5.9)		1977 ('75-'81)	21.7	(-1.1; 49.8)
									3.3	(2.5; 4.1)
	Nl	25-49	0		2.1	(0.3; 3.9)	0		1.9	(0.2; 3.6)
		50-69	0		3.1	(2.6; 3.6)	1	1979 ('70-'84)	4.2	(2.8; 5.6)
									1.3	(0.2; 2.5)
		70+	0		2.8	(2.0; 3.6)	0		2.0	(1.4; 2.6)
	CH	25-49	0		0.4	(-0.5; 1.3)	0		0.6	(-0.1; 1.3)
		50-69	1	1978 ('74-'81)	5.4	(3.6; 7.3)	1	1991 ('60-'92)	3.0	(2.2; 3.9)
					-1.1	(-2.9; 0.7)			-13.6	(-3.8; 12.7)
		70+	2	1976 ('70-'78)	8.2	(5.4; 11.0)	1	1989 ('84-'92)	4.1	(3.1; 5.1)
				1979 ('76-'82)	-10.0	(-48.5;57.1)			-5.0	(-13.0; 3.8)
					6.3	(4.5; 8.2)				
South	I	25-49	0		3.6	(1.8; 5.5)	0		3.1	(4.1; 4.7)
		50-69	2	1978 ('72-'80)	5.7	(4.3; 7.1)	3	1970 ('62-'73)	6.8	(4.0 ; 9.6)
				1981 ('79-'83)	16.1	(-12.1;53.4)		1973 ('71-'77)	-9.5	(-38.8;33.6)
					1.5	(0.1; 2.5)		1981 ('79-'84)	12.5	(7.9; 17.2)
									1.0	(0.0; 1.9)
		70+	1	1982 ('80-'86)	8.6	(7.3; 9.9)	1	1984 ('79-'91)	7.7	(6.3; 9.0)
					3.1	(1.9; 4.4)			1.5	(-0.4; 3.4)
	Slo	25-49	0		2.6	(-3.3; 8.7)	0		4.0	(-2.9; 11.3)
		50-69	0		0.8	(-3.0; 4.6)	0		3.3	(-1.1; 7.3)
		70+	0		4.5	(-5.1; 14.9)	0		3.8	(-0.7; 8.5)
	E	25-49	1	1984 ('80-'88)	11.4	(9.0; 13.9)	1	1979 ('72-'83)	11.9	(8.6; 15.3)
					3.0	(0.7; 5.3)			5.1	(3.5; 6.7)
		50-69	1	1990 ('86-'93)	10.2	(9.1; 11.4)	1	1976 ('74-'81)	18.0	(14.0; 22.2)
					1.2	(-2.5; 5.1)			6.1	(5.3; 7.0)
		70+	0		7.2	(6.4; 7.9)	1	1989 ('86-'93)	9.2	(7.8; 10.7)
									2.1	(-1.2; 5.5)

jp= joinpoint; CH=Switzerland, Cro=Croatia, Cz=Czech Republic, Dk= Denmark, E=Spain, E&W=England and Wales, Est=Estonia, F=France, Fin=Finland, I=Italy, N=Norway, Nl=Netherlands, Pl=Poland, S=Sweden, Sco=Scotland, Slo=Slovenia, Sk=Slovakia

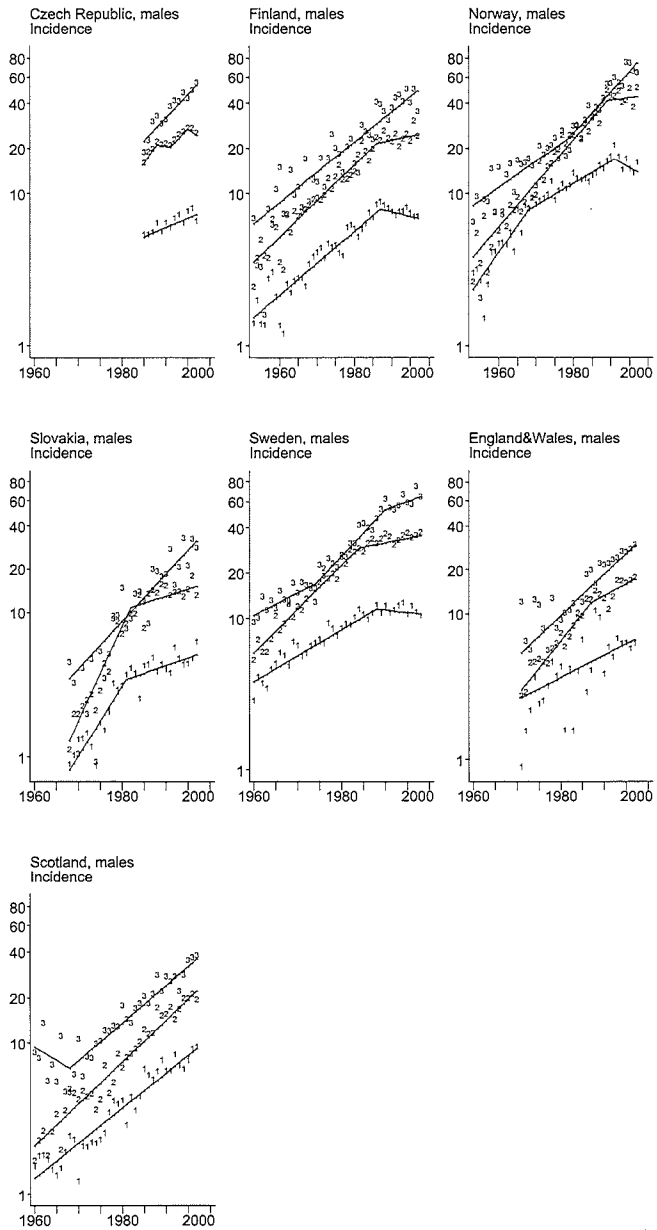
Annex Table B: Goodness of fit (deviance) of the fitted models.

Incidence 25-74	Age-period-drift	Age-cohort drift	Age-period-cohort
Sweden males	292.2	65.9	37.6*
	df=54, p<0.001	df=45, p=0.023	df=40, p=0.580
Sweden females	65.9	88.8	32.5*
	df=54, p=0.129	df=45, p<0.001	df=40, p=0.793
Norway males	292.4	107.8	57.3*
	df=72, p<0.001	df=63, p<0.001	df=56, p= 0.427
Norway females	203.6	183.4	57.0*
	df=72, p<0.001	df=63, p<0.001	df=56, p=0.439
Finland males	88.6	80.8	39.7*
	df=72, p=0.089	df=63, p=0.065	df=56, p=0.951
Slovakia females	48.8	47.7*	35.1
	df=45, p=0.320	df=36, p=0.09	df=32, p=0.330
Slovakia males	69.2	94.1	23.1*
	df=45, p=0.010	df=36, p=0.00	df=32, p=0.870
Finland females	75.5*	103.3	54.7
	df=72, p=0.367	df=63, p=0.001	df=56, p=0.523
England and Wales males	135.9	84.9	42.7
	df=36, p<0.001	df=27, p<0.001	df=24, p=0.011
England and Wales females	429.2	341.9	155.5
	df=36, p<0.001	df=27, p<0.001	df=24, p<0.001

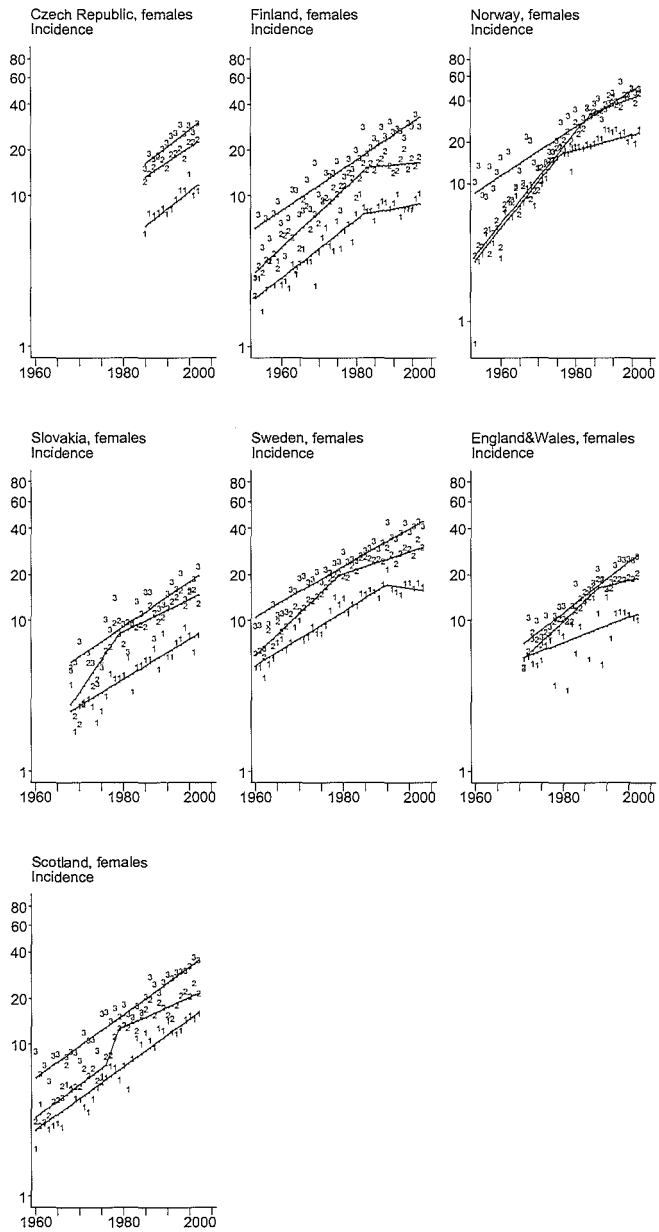
* Best fitting model

Mortality 25-74	Age-period-drift	Age-cohort drift	Age-period-cohort
Sweden males	158.5	60.4*	50.1
	df=54, p<0.001	df=45, p= 0.062	df=40, p=0.132
Sweden females	69.0	57.5	43.6*
	df=54, p=0.082	df=45, p=0.101	df=40, p=0.321
Norway males	115.4	45.9*	37.0
	df=54, p<0.001	df=45, p= 0.436	df=40, p= 0.606
Norway females	90.4	39.4*	36.5
	df=54, p=0.001	df=45, p=0.709	df=40, p=0.627
Finland males	70.4	59.8	42.8*
	df=54, p=0.066	df=45, p=0.068	df=40, p=0.353
Finland females	73.6	58.9	46.4*
	df=54, p=0.039	df=45, p= 0.080	df=40, p=0.226
England and Wales males	237.7	61.0*	55.0
	df=63, p<0.001	df=54, p=0.240	df=48, p= 0.226
England and Wales females	361.6	75.6	63.2*
	df=63, p<0.001	df=54, p= 0.028	df=48, p=0.070

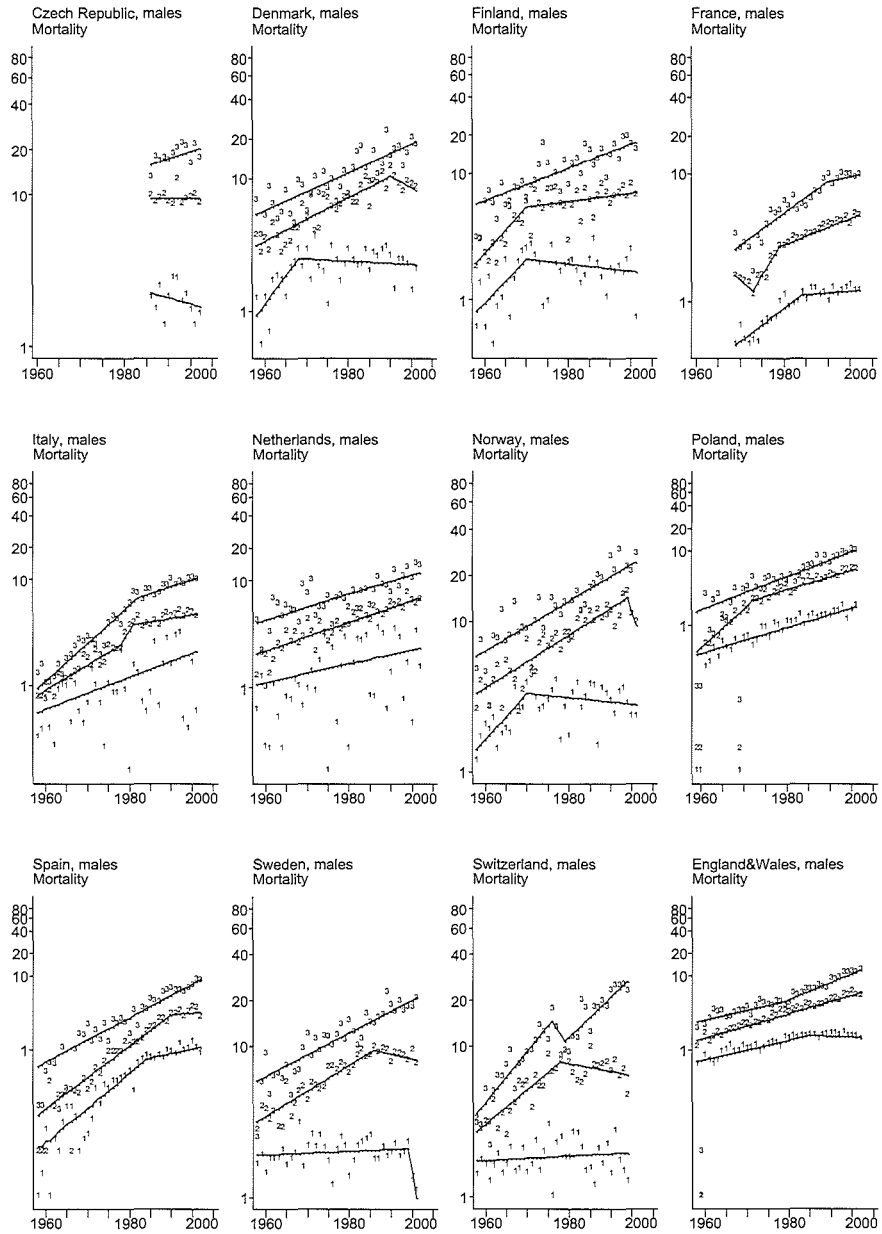
* Best fitting model



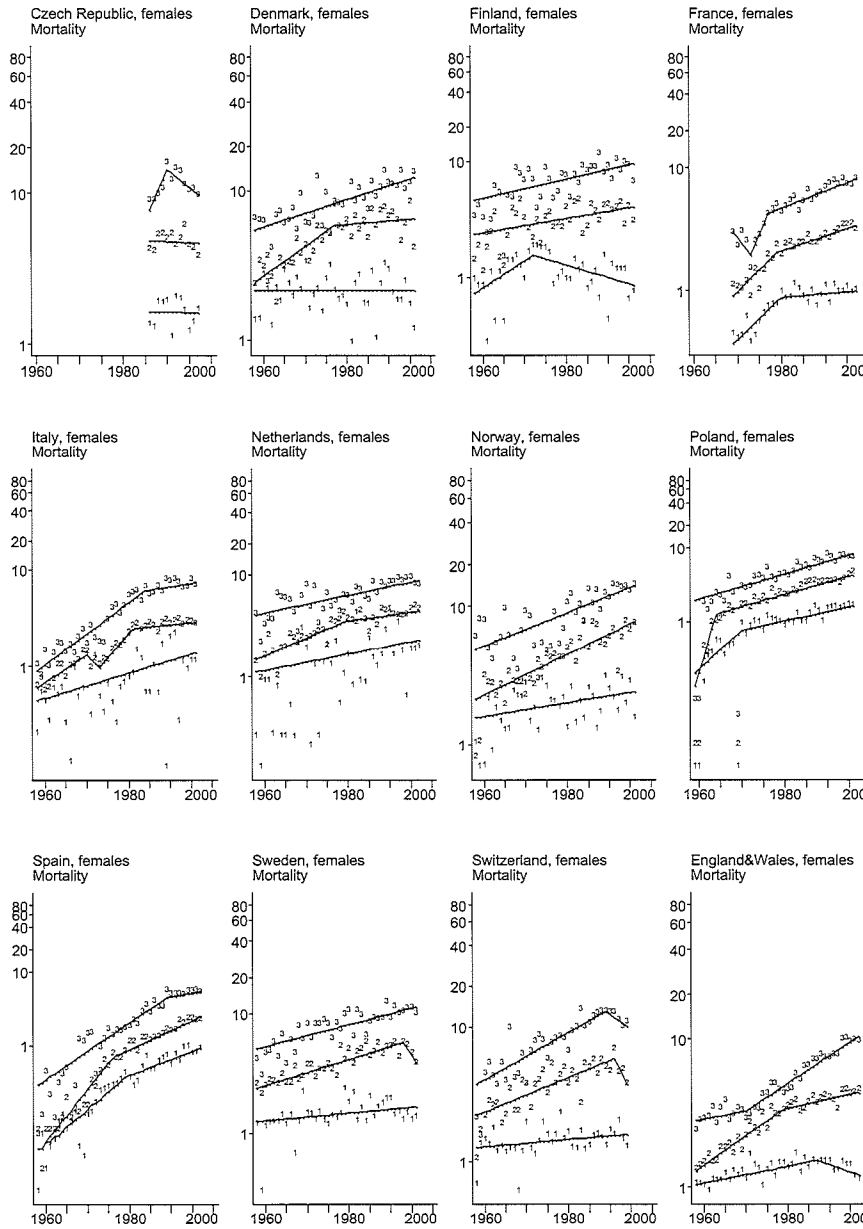
Annex Figure A: Joinpoint models of incidence data
1= 25-49 years, 2=50-69 years, 3=70+ years



Annex Figure A (continued): Joinpoint models of incidence data
1= 25-49 years, 2=50-69 years, 3=70+ years



Annex Figure B: Joinpoint models of mortality data
1= 25-49 years, 2=50-69 years, 3=70+ years



Annex Figure B (continued): Joinpoint models of mortality data
1= 25-49 years, 2=50-69 years, 3=70+ years

Chapter 3

Determinants of melanoma incidence

Chapter 3.1

Seasonal variation in the occurrence of cutaneous melanoma in Europe: influence of latitude. An analysis using the EUROCARE group of registries.

Reprinted from European Journal of Cancer: M. Boniol*, E. de Vries*, J.W.W. Coebergh, J.F. Doré and the EUROCARE Working group. Seasonal variation in the occurrence of cutaneous melanoma in Europe: influence of latitude. An analysis using the EUROCARE group of registries. Paper in press.

* Both authors contributed equally to this manuscript

Summary

Objective: To analyse seasonal variations in melanoma incidence in Europe.
Methods: Data from 28,117 cutaneous melanoma cases reported during the 1978-1993 period to the EUROCARE group of registries were analyzed.
Results: There is a clear summer peak in incidence in western countries (summer to winter ratio: 1.31 $p<0.0001$ Nam's test), which was not observed in central Europe (summer to winter ratio: 1.06 $p = 0.0699$). The amplitude of seasonality is higher for females (summer to winter ratio = 1.38, 95% CI (1.31 - 1.44)) than for males (summer to winter ratio = 1.21 95% CI (1.14 - 1.29)), it is also higher for upper and lower limbs (1.44 and 1.46 respectively) than for head and neck or trunk (1.09 and 1.20 respectively). The amplitude of seasonality also varies with latitude and increases with time: in a linear regression adjusting for age, sex and anatomical localisation, the date of diagnosis was significantly closer to summer solstice with decreasing latitude ($p = 0.0005$) and for more recent year of diagnosis ($p = 0.0123$).
Conclusions: The effect of latitude on the amplitude of the seasonal variation in melanoma incidence in Europe may be an indicator of the role of UVB exposure. Furthermore, an increase in intentional sun exposure could lead to an increase in melanoma promotion and thus to an increase in amplitude of seasonal variation.

Introduction

The incidence of cutaneous melanoma is increasing steadily, doubling every ten to fifteen years [1]. An intriguing phenomenon is the existence of a seasonal variation in melanoma incidence with a summer peak [2-10]. This seasonality trend has been found in different parts of the world in registries and cancer surveys for cutaneous melanoma but was never observed for ocular melanoma [4, 11].

Some authors suggested that this increase of the incidence in summer could derive from an over-diagnosis due to the efficacy of seasonal public campaigns and from a better awareness of the population or a better ability to detect a skin lesion when less clothes are worn during summer time [6, 10]. However, in the same way as the observation of a higher incidence of cutaneous melanoma, but not that of ocular melanoma [12], in southern latitudes [13-15] led to attribute a role in melanoma development to solar ultraviolet radiation, the seasonal variation in incidence of cutaneous melanoma could also be due to a late promotion effect mediated by ultraviolet radiation [2, 6, 9].
Should the summer excess in the occurrence of cutaneous melanoma result from an increased ascertainment due to screening or higher awareness, then one would expect to observe melanomas diagnosed at an earlier stage. Moreover, this increased ascertainment in summer months should be evidenced by an increase in the number of melanomas diagnosed on non-exposed body sites (such as the trunk). By contrast, if seasonal variation results from a late promotion effect, then one could think of a boosting of the last steps of melanoma progression leading to melanomas with a clinically more aggressive phenotype.

The significant seasonal variation in cutaneous melanoma incidence was observed for invasive melanomas, but not for in situ melanomas, which is in line with a late promotion effect [9]. Should the seasonal variation in melanoma incidence be the result of over-diagnosis in summer, we should also observe a similar seasonal variation in pre-invasive forms of melanoma.
An effect of solar ultraviolet radiation on the seasonal variation in melanoma incidence was suspected based on the existence of a difference in the amplitude of seasonality according to latitude in the United States of America, where the ratio of the number of summer cases to winter cases was higher in south than in the north.

In Europe, the cancer registries participating in EUROCARE cover a large scale of latitudes in western and central Europe [16]. In an analysis of melanoma characteristics in Europe we observed higher incidence and lower Breslow thickness in western than in Eastern Europe [17]. Using data from the same registries, we analysed the seasonal variation in melanoma incidence, the amplitude of seasonality according to the latitude and the characteristics of this seasonality according to host factors. We investigated the hypothesis of the existence of a difference in tumour progression stage according to the season of diagnosis and explored in a multivariate analysis whether the period of diagnosis is stable with time.

Materials and methods

Data from the EUROCARE database were used for this analysis [16]. EUROCARE consists of routine population-based cancer registry incidence data and follow-up of 5 years. After exclusion of the Rotterdam registry (only one year of recording), data from 20 registries in 12 countries were used for this analysis. In some countries the whole population was covered (Estonia, Slovenia, Slovakia, Sweden), in others, only regional registry data were available (France, Switzerland, the Netherlands, Poland, Spain, Italy, United Kingdom). The available data from the EUROCARE group were for the period 1978-1993. However, some registries began to include observations in the EUROCARE project after 1978. Only invasive melanomas and cases with histological confirmation of the melanomas were included. In total 28,117 cases were included in the analyses, 22,659 from western Europe and 5,458 from Eastern Europe. In the database both the ICD-9 and the ICD-O-2 coding were used. When these codes did not match, we used the ICD-9 code, because this had been used before [16]. Misclassifications due to these coding problems are not expected to be related to season in any way.
Data analysis was performed using SAS software (SAS v8.2 , SAS Institute Inc., Cary, NC, USA). Tests for seasonal variation in incidence were performed according to Nam's method [18], the ratio summer to winter used months of June, July and August for summer and December, January and February for winter.
The latitude chosen for each registry was of the city where the registry is situated to avoid a bias due to different catchments sizes. We used the Pearson correlation test to assess the correlation between latitude of registry and amplitude of the seasonality. Since Breslow's tumour thickness does not follow a normal distribution, we used the Kruskall-Wallis test to compare tumour thickness according to season of diagnosis. Forty-nine percent of the observations were excluded in the analysis on Breslow thickness due to missing values or non-reliable Breslow entry in the database (e.g. Breslow greater than 23mm).
To analyse the independent effect of the different parameters in a multivariate analysis, we used the contribution of each case on the seasonality. This contribution was expressed as the distance in days between the date of diagnosis and the summer solstice (June 21st). Hence, each case was given an individual value for its period of diagnosis: the smaller the distance, the more this case contributed to seasonality. We analysed in a generalised linear model the effects of the latitude of the registry and of year of diagnosis on this distance between date of diagnosis and summer solstice, adjusting for age, sex and anatomical localisation.

Results

Table 1 shows that for most of western European registries, a significant seasonal variation existed in melanoma incidence for the period 1978-1992, the summer to winter ratios varying from 1.1 (Stockholm) to 1.75 (Tarn). Two registries reported a limited number of cases or reporting cases over a shorter period of time. By contrast, there was no such seasonal variation in the central European registries, except for Slovakia. Figure 1 shows the number of cases diagnosed in central and western Europe

by month of diagnosis, and indicates that the incidence of cutaneous melanoma peaks in June/July in western Europe.
The amplitude of seasonal variation in melanoma incidence appeared to vary with the latitude of the registry (table 1): it was higher for southern countries than for northern countries. Despite the small number of points available to calculate a relation between amplitude of the seasonality and latitude of the registry, the correlation is nearly significant: R = -0.4, p = 0.07 Pearson's test (figure 2).

To evaluate an eventual effect of the season of diagnosis on the severity of the disease, we analysed Breslow's tumour thickness according to season of diagnosis in western Europe (table 2). The analysis used only the 11,598 melanoma cases for which Breslow thickness was available. Melanomas diagnosed in winter were thicker

Table 1. Registries in EUROCARE: number of melanoma cases and amplitude of seasonality

Registry	Period	N	Latitude (degree)	Summer to winter ratio	P (Nam-test)
Western Europe		22659	-	1.31	<0.0001
Eastanglia (U.K.)	1978-1992	2207	52.13	1.5	<0.0001
Eindhoven (Netherlands)	1978-1992	894	51.26	1.2	0.0281
Geneva (Switzerland)	1983-1991	449	46.12	1.34	0.0141
Granada (Spain)	1987-1992	175	37.1	1.38	0.0682
Lombardy (Italy)	1978-1992	649	45.28	1.45	0.0004
Lund (Sweden)	1991-1992	526	55.42	1.51	0.0005
Oxford (U.K.)	1978-1993	2644	51.44	1.16	0.0043
Saarland (Germany)	1978-1992	1080	49.14	1.33	0.0005
Stockholm (Sweden)	1978-1991	3102	59.3	1.1	0.0252
Tarn (France)	1982-1992	265	44.01	1.75	0.0007
Turin (Itlaly)	1985-1991	469	45.03	1.26	0.0384
Tuscany (Italy)	1985-1989	392	43.46	1.34	0.0199
Yorkshire (U.K.)	1978-1992	2892	53.58	1.25	<0.0001
Wessex (U.K.)	1978-1992	2734	51.04	1.55	<0.0001
Westmidlands (U.K.)	1978-1992	4181	52.29	1.34	<0.0001
Central Europe		5458	-	1.06	0.0699
Cracow (Poland)	1978-1992	332	50.04	0.92	0.699
Estonia	1978-1992	876	59	0.84	0.9682
Slovakia	1978-1990	2709	48.4	1.14	0.0097
Slovenia	1983-1992	1061	46.03	1.12	0.0957
Warsaw (Poland)	1987-1992	480	52.16	1.06	0.3328

than in summer (mean = 2.15 mm and 2.03 mm respectively, and median = 1.5 mm and 1.5 mm respectively, p = 0.0027 Kruskal-Wallis test), but this was mainly due to a higher proportion of a few thick melanomas (>3 mm) diagnosed in winter whereas the proportion of thin melanomas (<0.5 mm) remained stable throughout all seasons.

By contrast, in central Europe, where no seasonal variation was evidenced, no difference in Breslow's tumour thickness according to the season of diagnosis was observed (data not shown). Since there was a high proportion of missing values for Breslow thickness, we tested the seasonal variation of melanoma according to the presence or absence of information for Breslow thickness. No differences were observed in frequencies of melanoma by month of diagnosis between cases with thickness information and cases without information in western registries (p=0.58 χ^2-test) or in eastern registries (p=0.60 χ^2-test).

We further investigated the association between the main host characteristics (age, sex, anatomical localisation of the tumour) and season of diagnosis of melanoma. Age was not associated with season of diagnosis (data not shown). However, the amplitude of seasonal variation varied with sex and the anatomical localisation of the tumour (table 3). We observed only limited seasonality for head and neck melanomas, but an important seasonal variation for melanomas on the extremities and trunk. We also observed a difference between men and women: the amplitude was significantly greater for women than for men (the confidence intervals of summer to winter ratios did not overlap). This difference between males and females could not be attributed to a confounding effect of anatomical localisation, since in a stratified analysis the amplitude was always greater or equal in females compared to males, independent of the anatomical site under study (data not shown).

We used a generalised linear model to study the predictors of the distance in days between the date of diagnosis and the summer solstice (June 21) in western Europe. This model also included the latitude of the registry and the year of diagnosis, and was adjusted for age, sex, and anatomical localisation of the tumour. Confirming the crude correlation between latitude of the registry and amplitude of seasonal variation (figure 2), we found that latitude influenced the distance to solstice (t = -3.51, p = 0.0005): the more southern the domicile of a case, the closer was the date of diagnosis to the summer solstice.

Table 2 . Breslow's tumor thickness (mm) of melanoma cases in EUROCARE study for the period 1978-1993 according to season of diagnosis.

Season	N	Mean	Median	1st quartile	3rd quartile
Winter (December, January, February)	2430	2.15	1.5	0.7	2.7
Spring (March - May)	2817	2.03	1.3	0.7	2.5
Summer (June - August)	3242	2.03	1.5	0.7	2.5
Autumn (September - November)	3109	2.04	1.3	0.7	2.5

p = 0.0027 (Kruskall Wallis test, chi²=14.16)

Table 3 . Amplitude of seasonality in melanoma incidence according to anatomical localisation and sex

		Summer to winter ratio (95% CI)	
		Western Europe	Central Europe
Anatomical localisation			
	Head and neck	1.09* (0.99-1.20)	1.07 (0.88-1.31)
	Trunk	1.20** (1.12-1.29)	0.99 (0.87-1.12)
	Upper limb	1.44** (1.32-1.58)	1.04 (0.85-1.27)
	Lower limb	1.46** (1.38-1.56)	1.12 (0.97-1.28)
	Other/unspecified	1.43* (1.03-1.99)	1.28 (0.92-1.78)
Sex			
	Male	1.21** (1.14-1.29)	1.05 (0.94-1.18)
	Female	1.38** (1.31-1.44)	1.06 (0.96-1.17)

* $p<0.05$, ** $p<0.01$
amplitude is the ratio of melanomas diagnosed in summer to melanomas diagnosed in winter; the 95%CI is derived from Nam's test for seasonality

In addition, the year of diagnosis was also related to this distance ($t = 2.50$, $p = 0.0123$), melanomas diagnosed in recent years being closer to summer solstice. The period of diagnosis of cutaneous melanoma was thus not stable over time and a significant linear increase was exhibited in the amplitude of the seasonal variation over successive years in western Europe.

Discussion

Our study, using the registries participating in this sub-study in the EUROCARE project, confirmed the presence of seasonal variation with a summer peak in the incidence of cutaneous melanoma in Europe, as already described in different parts of the world including some European countries. Interestingly, a significant seasonal variation was evidenced in all but one western European registry, whereas this appeared in only two of the five registries from central Europe, and with a much smaller amplitude and significance. One of the differences between western and central Europe is more late diagnosis of melanoma in the latter which was demonstrated in the same registries [17]. This delay in diagnosis in central Europe may have led to a smoothing of the seasonal variation, rendering it undetectable.
In western countries, where a seasonal variation in melanoma incidence existed, seasonality of melanoma incidence was also influenced by latitude which in turn affected the distance to solstice, both correlations being of borderline significance. The amplitude of seasonality in melanoma diagnosis was greater in states closer to the Equator [2]. This study could be the first demonstration of a direct link between seasonality of melanoma diagnosis and latitude of residence. This observation is in line with the hypothesis of a role of ultraviolet radiation as a promoting factor of the growth of melanoma during the late stages of development of the disease.

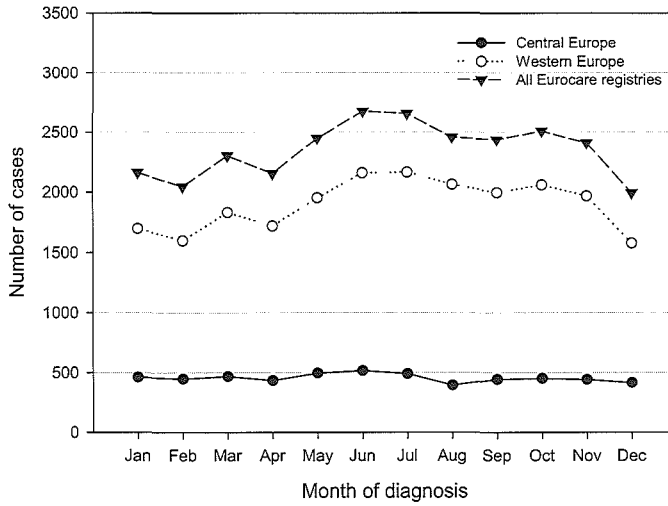


Figure 1. Number of cases by month of diagnosis

However, we did not observe that melanoma would be diagnosed in a more advanced stage (as determined with Breslow's tumour thickness) in summer than in winter. On the contrary, we found a reverse association, which actually resulted from a few thick melanomas in the winter category; the clinical difference according to season was not relevant (no difference for the mean neither for the median).
One could suggest that this result is in line with the hypothesis of melanomas diagnosed in summer being at an earlier stage due to an overdiagnosis during this period. But the result itself is questionable since we had to exclude 49% of observations. Some registries did not record Breslow's thickness, but for those who normally recorded thickness, the exclusions due to missing values for Breslow's thickness were not randomly distributed: Missing values occurred more frequently for registries of central and southern Europe, with increasing age at diagnosis and for women. Furthermore, the distribution of the Breslow's thickness in the remaining observations was far from a linear one as we found some highly repeated values (1, 1.5, 2) in our dataset. These problems illustrate the heterogeneity in data collection and coding across registries; 5 out of 21 registries did not register Breslow's tumour thickness. There is no reasons why the distribution of Breslow's thickness would not be linear when the diagnostic process is homogeneous [19].

In the United States [6], the amplitude of seasonal variation was higher for women than for men. This difference could result from a better skin awareness of women resulting in an increase in the number of melanomas diagnosed in summer for women. But, as women are more willing to get a tan and tend to sunbathe more than men, this difference in amplitude could also be due to a promoting effect of UV exposure greater for women than for men.

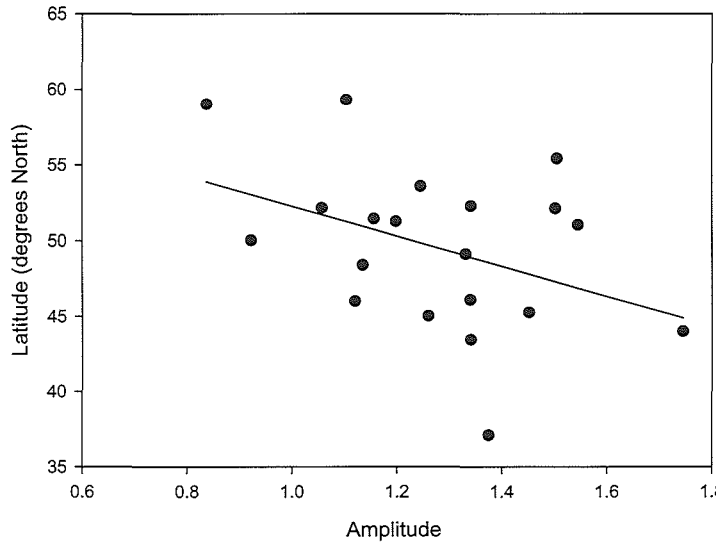


Figure 2: Amplitude of the seasonal variation (ratio of number of cases summer to winter) of cutaneous melanoma according to latitude in EUROCARE.

The existence of seasonal variations in melanoma incidence has also been attributed to seasonal variations in clothing habits. And indeed, our observation that the amplitude of seasonality was greater for melanomas on the extremities than for head and neck melanomas could result from seasonal variations in clothing habits. However, if seasonality of incidence of cutaneous melanoma could stem from variations in clothing habits, then we would expect to observe a seasonal variation of even greater amplitude for melanomas developing on usually non-exposed body sites (such as the trunk). But the amplitude of the seasonal variation is lower for the trunk than for the extremities. The difference in amplitude of seasonality between different body sites could reveal some body sites actually to be more sensitive to a promoting effect of recent exposure.

The observed increases in amplitude of seasonality in melanoma incidence with a more recent year of diagnosis may reveal that melanomas are more and more frequently diagnosed close to the summer solstice. The important increases in the incidence of cutaneous melanoma during the past half century has been mainly attributed to a continuous temporal change in sun exposure habits, but this does not preclude a promotion effect on the late stages of melanoma development.
Most secondary prevention campaigns have only been implemented in northern and western Europe in the late eighties, but in the following decade they did not materialize and hence they are unlikely to have affected the amplitude of the seasonal variation back to the period used in our analysis. The continuous temporal change of the amplitude of the seasonal variation is then more in line with a promoting effect of UV

exposure and could be related to changes in behaviour with an increased intentional sun exposure, not to mention the possible increases in global UV irradiation.
The association between latitude and amplitude of the seasonal variation in melanoma incidence is also more in line with this hypothesis. In Europe with its north to south gradient of intentional sun exposure (northern inhabitants having more willingness to get a tan in spite of their pale complexion), recent exposure to UV light could have a promoting effect on the development of melanoma.
Biological studies confirm the existence of a short term effect of UV irradiation for promoting growth of naevi or melanoma. After a short period (14 days) of intense exposure, naevi components change and some of them acquired dysplastic features [20].
The existence of a seasonal variation of DNA damages in peripheral blood lymphocytes measured by comet assay showed the rapid deleterious effect of recent solar exposure [21]. UVB irradiation of melanoma cell lines triggered metastatic ability [22].
Finally, the association between seasonal variation in melanoma incidence and decreasing latitude of residency would add further support to the involvement of exposure to UVB in melanoma occurrence and progression, which is currently supported by biological and epidemiological data [23, 24]. UVB radiation appears to be a better candidate than UVA to have such a promotion effect since the increases in proportion of UVB in solar radiation with decreasing latitude are more pronounced than that of UVA [25, 26].
Our study pointed to the possible influence of recent exposure as a promoting factor for melanoma development, as was suspected by the observed seasonal variation of incidence. However, the observation of higher amplitude of seasonality for women and for extremities could also indicate a role of better ascertainment in summer (due to less clothing worn or sensitising to harmless visible effects of solar exposure) which leads to a rise in melanoma excisions in summer. The two possible hypotheses to explain seasonal variation of melanoma incidence could coexist and explain the different characteristics of seasonality we evidenced in our study.
The analysis of seasonality of melanoma incidence in Europe may help in gaining insight into mechanisms of melanoma development in relation with UV exposure, and the influence of latitude may indicate a role of exposure to UVB.

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Chapter 3.2

A multicentre epidemiological study on sunbed use and cutaneous melanoma in Europe

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A multicentre epidemiological study on sunbed use and cutaneous melanoma in Europe.

Summary

Objectives: To assess the association between sunbed use and cutaneous melanoma in a population aged less than 50 years.
Methods: From April 1999 until July 2001, a case-control design compared sunbed use and sun exposure in 622 melanoma cases and 649 controls who were interviewed in Belgium, France, The Netherlands, Sweden and the UK. All cases and controls were aged 18 to 49 years.
Results: Fifty-six percent of cases ever used sunbeds compared to 52% of controls. A significant difference in prevalence of sunbed use was found amongst the 5 European countries with the highest prevalence in countries of northern Europe. The adjusted melanoma risk associated with ever sunbed use was 0.86 (95% CI: 0.67-1.09). Fourteen percent of cases and the same percentage of controls used sunbeds for more than 35 hours. No association was found between sunbed use and melanoma, even for subjects who reported highest levels of sunbed use in terms of cumulative hours of exposure. Lag time between first exposure to sunbeds and time of study was also not associated with an increased risk of melanoma. The adjusted odds ratio for melanoma associated with the mean number of weeks spent in sunny climates after the age of 14 years was 1.12 (95% CI 0.88-1.43) and the adjusted odds ratio for melanoma associated with any sunburn after the age of 14 years was 1.11 (95% CI 0.86-1.43). There are however strong indications that these odds ratios are influenced by recall and selection biases.
Discussion: Sunbed use was not found to be associated with an increased melanoma risk in this large European study and no dose response was observed. Sun exposure was also not significantly associated with melanoma in the population studied. Sunbed use has become increasingly prevalent over the last 20 years and this study has shown that this is particularly relevant for northern European countries. Because of a potential long lag time and the rise in sunbed use in recent years, the full impact of sunbed exposure on melanoma and non-melanoma skin cancers may not become apparent for many years. Recall bias may also have affected the results as widespread public health campaigns have improved knowledge regarding the risk of ultraviolet radiation and skin cancers.

Introduction

The fashion of using sunbeds to acquire a tan is now widespread among fair skinned populations, particularly in northern European countries where the levels of natural ultraviolet radiation is low. Many case-control and latitude studies have shown that exposure to the sun is recognised as the major environmental risk factor for cutaneous melanoma [1, 2]. Ultraviolet radiation (UVR) is deemed to represent the part of the solar spectrum involved in the genesis of melanoma. Therefore, it has been suggested that sunbed use could also contribute to melanoma incidence in Caucasian populations as UVA is thought to be relevant for the pathogenesis of melanoma.
In the absence of a valid animal model for human melanoma, epidemiological studies are required to provide evidence of an association between sunbed use and melanoma. Six epidemiological case-control studies explored the relationship between exposure to sunbeds and cutaneous melanoma [3-7]. Results have been conflicting and two reviews have concluded that these studies did not provide conclusive evidence for an association between sunbed use and cutaneous melanoma [3, 8]. Most of these studies included melanoma patients of all ages although sunbed use is especially prevalent in younger age groups. The objective of this study was to investigate whether sunbed use represents a risk factor for cutaneous melanoma in Europe in individuals aged less than 50 years of age. One prospective cohort study did find a convincing association between exposure to sunbeds and melanoma risk [9].

Methods

A multi-centre case-control study was carried out in Sweden, the Netherlands, United Kingdom, Belgium and France between December 1998 and July 2001. In all participating institutions, the study protocol was cleared by a local Ethical Committee.

The group of cases
Consecutive melanoma cases aged 18 to 49 years with histologically proven first primary cutaneous melanoma were recruited for the study. Melanoma cases were flagged up via dermatologists, pathologists, plastic surgeons, oncologists and melanoma databases. Exclusion criteria were as follows: (a) if the patient had a lentigo malignant melanoma or in-situ melanoma or a secondary melanoma or if the melanoma was not their first primary, (b) unable to respond, or to understand the questionnaire (e.g., too sick or mentally impaired), (c) non Caucasian.
The recruitment of cases varied between countries and the methods for each country is presented below:
For Sweden: Most cases were seen at the Karolinska Institute in Stockholm. Because of lower than expected numbers of cases diagnosed at the Karolinska Institute, cases were also recruited at the hospital of Uppsala, where because of long distances, some interviews were done by telephone. For cases recruited in the Uppsala area who were unable to attend the hospital, naevus counts were not performed.
For The Netherlands: 35% of cases originated from an a tertiary reference centre (the Daniel den Hoed Cancer Center in Rotterdam) and the remaining 65% were recruited

through general hospitals of South Netherlands where the recruitment of cases was monitored using the cancer registry of the South of the Netherlands [10].
For the United Kingdom: cases were recruited via dermatologists, oncologists and pathologists located in the Greater London area.
For Belgium: cases were recruited from Oncology and Surgery clinics in a teaching hospital in Brussels (Jules Bordet Institute, Brussels) as well as a from a large dermatology clinic in another teaching hospital in Brussels (the Erasmus Academic Hospital).
For France: cases were recruited from several dermatology clinics and cancer hospitals throughout France (Burgundy, Lille, Thionville, Paris and Bordeaux).

Selection criteria for controls
In each country, controls were recruited to match age and gender of the cases. Age groups for frequency matching purpose were 18 to 29, 30 to 39 and 40 to 49 years old. Exclusion criteria for controls were (a) a history of skin cancer, (b) subjects unable to directly respond to questionnaires and (c) non Caucasian.

The recruitment of controls followed three procedures:
(*i*) random selection of controls from population registries, (*ii*) recruitment from general practices which matched the geographical areas of the controls; and (*iii*) door-to-door search ("neighbourhood controls"). The latter method was successfully used in a previous study of melanoma in Belgium, France and Germany [6, 11].
Recruitment of controls was done as follows for each country:
For Sweden: Controls were derived from a random sample of population registries. A letter was sent to potential controls asking for participation. In the Uppsala area, because of long distances, some interviews were done by telephone and naevus counts could not be performed for a subset of controls.
For The Netherlands: Most controls were derived from GP practices which matched the geographical area of the cases. Additionally, an advertisement in a regional newspaper resulted in the recruitment of 25 further controls.
For the United Kingdom: the controls were derived from lists of patients attending GPs within the Greater London area which matched the geographical area of the cases.
Belgium and France: Search for controls was done using the door-to-door search.

Interviews
Professional interviewers conducted all the interviews in all countries. They were trained in order to provide a standard application of the questionnaires and to minimize interview bias. Interviewers applied the questionnaires in the same manner to both cases and controls, and whenever possible, interviews had to take place at home.
Blinding of the case or control status was not possible as the melanoma excision was visible when examining the skin and details were collected regarding the location and date of diagnosis of the tumour.

Questionnaires
Standard questionnaires were devised using past experiences of epidemiological studies of melanoma in Europe [5, 6, 12]. The questionnaires were also tested before the start of the study in a subset of cases and controls in Belgium and France. Questionnaires were translated for each country and tested before use.

Sunbed use was first recorded as "ever used sunbeds in a lifetime" and was divided in two age groups (before 15 years of age and 15 years of age or over). Cases and controls were then asked to recollect each episode of sunbed exposure in terms of type of device used for each episode. Twelve photographs were shown to assist subjects in the selection of sunbed devices. These pictures comprised mercury lamps which were popular in northern Europe in the forties and fifties. Several pictures also showed various portable ultraviolet units which generally displayed three to six short fluorescent lamps of only high-pressure UVA lamps for tanning of the face only. Several tanning units for the whole body were also showed: medium size horizontal sunbeds with 8 to 12 fluorescent lamps installed on a single panel unit or large horizontal double-panel UV units comprising more than 12 fluorescent lamps with or without high-pressure UVA lamps for the face or high pressure units for the whole body as well as vertical units.
For each episode the following was also recorded: location of use (gym, beauty parlour, hairdresser, hospital or home), numbers of sessions, numbers of minutes for each session and the year of start and year of end for each episode. Potential side effects of sunbed use such as redness, itching or severe sunburn was also demanded.

Statistical analysis
The statistical analysis followed standard procedures for analysis of case-control data, using odds ratio as estimates of the relative risk. All analysis were done using unconditional logistic regression methods. 95% confidence intervals (95% CI) were derived from these models [13]. When not specified, adjustment of melanoma risk was done for age, sex, skin phototype (4 groups) [14], sunburns before and after the age of 15, hair colour (3 categories) and the average number of holiday weeks spent in sunny areas after the age of 15 years. All p values were two-sided. When the data had a non-Gaussian distribution, descriptive statistics used the median and the interquartile range.

Results

628 melanoma cases and 650 controls were recruited for the study. Six cases and one control were excluded from the analysis because they did not meet the inclusion criteria. Hence, the analyses are based on 622 cases and 649 controls.
The mean age of the cases varied between countries from 37.8 years in France to 39.4 years in the UK. In all countries, the male to female ratio was less than 1.
The most frequent histological subtype was superficial spreading melanoma (76%) followed by nodular melanoma (15%). The mean Breslow thickness was 1.46 mm (median: 0.90 mm).

Table 1. Characteristics of cases (n=622) and controls (n=649) included in the study.

		Cases N (%)	Controls N (%)	Crude OR (95% CI)	Adj. OR** (95% CI)
Age	Mean (years)	39	38	1.01 (1.00-1.02)	1.02 (1.00-1.03)
	Standard deviation	8.9	9.0		
Sex	Female (ref)	394 (63)	425 (65)	1.00	1.00
	Male	228 (37)	224 (35)	1.10 (0.87-1.38)	1.20 (0.94-1.52)
Skin phototype	IV (good tanner) (ref)	65 (10)	127 (20)	1.00	1.00
	III	205 (33)	281 (43)	1.42 (1.00-2.02)	1.26 (0.88-1.82)
	II	252 (41)	177 (27)	2.78 (1.95-3.97)	2.22 (1.51-3.28)
	I (never tan)	100 (16)	64 (10)	3.05 (1.98-4.71)	2.36 (1.49-3.74)
Haircolour *	Dark (ref)	131 (21)	193 (30)	1.00	1.00
	Medium	295 (47)	338 (52)	1.29 (0.98-1.69)	1.21 (0.92-1.60)
	Red or blond	196 (32)	118 (18)	2.45 (1.78-3.36)	1.97 (1.40-2.76)
Sunburn < 15 years	No (ref)	324 (52)	395 (61)	1.00	1.00
	Yes	298 (48)	254 (39)	1.43 (1.14-1.79)	1.12 (0.88-1.43)
Sunburn > 14 years	No (ref)	184 (30)	244 (38)	1.00	1.00
	Yes	438 (70)	405 (62)	1.43 (1.13-1.81)	1.11 (0.86-1.43)
Family history of melanoma	No (ref)	567 (91)	613 (94)	1.00	1.00
	Yes	55 (9)	36 (6)	1.65 (1.07-2.55)	1.49 (0.95-2.34)

*dark (black or dark brown), medium (clear brown or auburn), red or blond (red or blond)
** Calculated from a logistic model including all variables in the table.

Fair skin and fair hair were more frequent amongst cases (table 1). Sunburn history during childhood and adulthood was associated with an increased melanoma risk, but the association disappeared after adjustment for skin type and hair colour. A family history of melanoma yielded an odds ratio for melanoma of 1.49 (95% CI 0.95-2.34). 52% of cases and 56% of controls reported at least one sunbed use after the age of 14 (table 2). The odds ratio for melanoma associated with ever use of sunbeds was 0.89 (95% CI 0.70-1.14). There was a sharp north to south gradient in the prevalence of sunbed use: in Sweden 86% of controls ever used sunbed compared to 19% in France. The risk of melanoma did not vary significantly by country. A trend was observed with a lower risk of melanoma associated with sunbed use in countries with a high prevalence of sunbed use such as Sweden and higher risk for countries with low prevalence of sunbed use such as France, but this trend did not reach statistical significance.

Table 2. Ever sunbed use after 14 years old and risk of cutaneous melanoma. Cases n=622, controls n=649

Country	Sunbed use ≥ 14 years	Cases N (%)	Controls N (%)	Crude OR (95% CI)	Adj. OR * (95% CI)
Sweden	No	18 (21%)	13 (14%)	1.00 (ref.)	1.00 (ref.)
	Yes	73 (79%)	81 (86%)	0.61 (0.28-1.32)	0.60 (0.25-1.44)
The Netherlands	No	40 (27%)	35 (21%)	1.00 (ref.)	1.00 (ref.)
	Yes	108 (73%)	134 (79%)	0.73 (0.44-1.22)	0.88 (0.50-1.55)
UK	No	83 (52%)	74 (46%)	1.00 (ref.)	1.00 (ref.)
	Yes	76 (48%)	87 (54%)	0.78 (0.50-1.21)	0.87 (0.53-1.41)
Belgium	No	23 (43%)	23 (43%)	1.00 (ref.)	1.00 (ref.)
	Yes	31 (57%)	30 (56%)	1.03 (0.48-2.22)	0.75 (0.30-1.89)
France	No	133 (78%)	141 (81%)	1.00 (ref.)	1.00 (ref.)
	Yes	37 (22%)	31 (19%)	1.21 (0.72-2.05)	1.07 (0.60-1.90)
All	No	297 (48%)	286 (44%)	1.00 (ref.)	1.00 (ref.)
	Yes	325 (52%)	363 (56%)	0.86 (0.69-1.08)	0.86 (0.67-1.09)

*Adjusted for age, sex, skin phototype, haircolour, sunburn before and after 15 years old, and the mean number of holiday weeks per year in sunny areas after 15 years old.

Sunbed use for tanning purposes was reported by 198 cases (32%) and 229 controls (35%) (Adjusted odds ratio: 0.85; 95% CI: 0.65-1.12). Sunbed use for a reason other than to get a tan was reported by 127 (20%) cases and 134 (21%) controls (Adjusted melanoma risk: 0.86; 95% CI: 0.64-1.17).

Fifty-two cases (8%) and 42 (7%) controls reported at least one exposure to sunbeds before the age of 15 (table 3). Exposure before the age of 15 was most prevalent in Sweden and the Netherlands. Sunbed used in childhood was not associated with an increased melanoma risk.

Cumulative sunbed use (hours for exposure) was calculated for each subject from birth to interview. Fourteen percent of cases and 14% of controls reported a cumulative sunbed use of 35 hours or more. No dose dependent relationship was found between hours of exposure and melanoma risk (table 3). Of note is that the proportions of cases and control subjects in each strata of cumulative sunbed use follow a similar pattern in both case and control groups.

Time since first used sunbed was also calculated. More than 14% of cases and controls had their first sunbed use at least nineteen years before the interview. The time lag between first sunbed use and melanoma diagnosis was not associated with melanoma. Reporting of itching, redness or severe sunburn following sunbed use was not associated with increased melanoma risk (table 3).

Table 3. Lifetime sunbed use and risk of cutaneous melanoma.

	Cases (n=622)	Controls (n=649)	Crude OR (95% CI)	Adjusted OR * (95% CI)
Sunbed use during life				
Never sunbed use (referent)	284 (46%)	272 (42%)	1.00	1.00
Only <15 years of age	13 (2%)	13 (2%)	0.96 (0.44-2.10)	1.04 (0.44-2.42)
Only >15 years of age	286 (46%)	335 (52%)	0.82 (0.65-1.03)	0.88 (0.67-1.17)
Before and after 15 years	39 (6%)	29 (4%)	1.29 (0.77-2.14)	1.55 (0.88-2.75)
Cumulative lifetime sunbed use (in hours) (1)				
<2	68 (11%)	83 (13%)	0.78 (0.55-1.13)	0.78 (0.52-1.15)
2-9.9	99 (16%)	91 (14%)	1.04 (0.75-1.45)	1.12 (0.77-1.62)
10-34.9	72 (12%)	93 (14%)	0.74 (0.52-1.05)	0.84 (0.55-1.28)
35+	80 (13%)	90 (14%)	0.85 (0.60-1.20)	1.10 (0.71-1.69)
Time (in years) between first sunbed use and interviews (2)				
<8	69 (11%)	92 (14%)	0.72 (0.50-1.02)	0.79 (0.53-1.18)
8 to 12.9	81 (13%)	89 (13%)	0.87 (0.62-1.23)	0.93 (0.63-1.39)
13 to 19.9	88 (14%)	97 (15%)	0.87 (0.62-1.21)	0.90 (0.61-1.33)
19+	97 (16%)	95 (15%)	0.98 (0.70-1.36)	1.07 (0.72-1.58)
Skin reaction after sunbed use				
No reaction	208 (33%)	249 (38%)	0.80 (0.62-1.02)	0.91 (0.67-1.22)
Ever Itching (3)	24 (4%)	29 (4%)	0.79 (0.45-1.40)	0.80 (0.43-1.47)
Ever Simple redness (4)	72 (12%)	70 (11%)	0.98 (0.68-1.42)	0.94 (0.61-1.43)
Ever Painful sunburn	34 (5%)	29 (4%)	1.12 (0.67-1.89)	1.13 (0.64-1.99)

* Adjusted for age, sex, skin phototype. hair colour, sunburn history before and after 15 years old, and mean number of holiday weeks each year in sunny areas after 15 years old
(1) Data could not be calculated for 19 cases and 20 controls.
(2) Data could not be calculated for 3 cases and 4 controls.
(3) But never redness or sunburn.
(4) But never sunburn.

As for the prevalence of sunbed use, numbers of hours of exposure and lag time since first use increased from south to north (data not shown). Analyses by country did not reveal any patterns of sunbed exposure associated with melanoma risk but numbers were small when countries were examined separately. An analysis restricted to subjects with skin type I or II, or red/blond hair did not affect the results either.

In controls aged 15 years or over, 38% used sunbeds at home compared to 27% and 14% in tanning parlours and beauty institutes respectively. The remaining 17%, 3% and 1% were exposed in gym, workplaces and hospitals respectively. Most controls used sunbeds at one location and rarely at two different locations (table 4). Use of sunbed at home was more common amongst Dutch controls: more than 70% compared to 48% in the UK, 24% in France, 23% in Sweden, and 20% in Belgium. The location of sunbed use did not affect the results in terms of melanoma risk (table 4).

Table 4. Characteristics of sunbed use.

	Cases (n=622) N (%)	Controls (n=622) N (%)	Crude OR (95% CI)	Adjusted OR * (95% CI)
Never used sunbeds during lifetime	284 (46)	272 (42)	1.00 (ref.)	1.00 (ref.)
Place of sunbed use ≥ 15 years old				
Use only < 15 years old	13 (2)	13 (2)	0.96 (0.44-2.10)	0.87 (0.38-1.96)
Only at home	126 (20)	145 (22)	0.83 (0.62-1.11)	0.85 (0.62-1.15)
Only outside home	170 (27)	188 (29)	0.87 (0.66-1.13)	0.85 (0.64-1.14)
Both at home and outside	5 (1)	2 (1)	2.39 (0.46-12.4)	3.14 (0.59-16.8)
No place specified	24 (4)	29 (4)	0.79 (0.45-1.40)	0.75 (0.41-1.34)
Type of sunbed machine during lifetime				
Only small and medium size UV units	94 (15)	103 (16)	0.87 (0.63-1.21)	0.89 (0.64-1.26)
Only large double-panel UV units	141 (23)	157 (24)	0.86 (0.65-1.14)	0.82 (0.61-1.11)
Small, medium and large size UV units	84 (13)	97 (15)	0.83 (0.59-1.16)	0.86 (0.60-1.23)
Type of machine not known/not reported	19 (3)	20 (3)	0.91 (0.48-1.74)	0.78 (0.40-1.53)
Cumulative duration of use of small and medium size UV units during lifetime				
1 to 179 minutes	66 (11)	62 (10)	1.02 (0.69-1.50)	0.98 (0.65-1.46)
180 to 1199 minutes	56 (9)	59 (9)	0.91 (0.61-1.36)	0.90 (0.59-1.37)
≥ 1200 minutes	56 (9)	79 (12)	0.68 (0.46-0.99)	0.78 (0.52-1.16)
Cumulative duration of use of large size UV units during lifetime				
1 to 159 minutes	67 (11)	90 (14)	0.71 (0.50-1.02)	0.69 (0.47-1.00)
160 to 719 minutes	77 (12)	80 (12)	0.92 (0.62-1.31)	0.90 (0.62-1.32)
≥ 720 minutes	81 (13)	84 (13)	0.92 (0.65-1.31)	0.95 (0.65-1.37)

* adjusted for age, sex, skin phototype, haircolour, sunburn history before and after 15 years and the mean number of holiday weeks in sunny areas after 15 years.

Type of sunbed devices differed significantly between exposure which took place at home and exposure outside the home (such as beauty parlours or gyms). When sunbed use took place at home, small or medium size UV units were used by 85% of controls. In contrast, when exposure took place outside the home, large double-panel UV units were used by 88% of controls. The type of devices used did not affect melanoma risk: 178 cases (29%) and 200 controls (31%) used small and medium size UV units whilst 225 cases (36%) and 254 controls (39%) used large size, double-panel UV units . Table 4 shows that a large proportion of the exposure to sunbeds happened with small or medium devices at home where more than 10% of cases and controls accumulated over 20 hours compared to 12 hours for large size double panel UV units. No association was found between melanoma occurrence and the cumulative duration of exposure since birth to small, medium or to large size UV units (table 4).
Use of large size, double-panel UV units (generally outside the home) was the predominant type of sunbed use in Sweden, with cumulative exposure using these types of devices far exceeding exposure seen in other countries (table 5).

Table 5. Lifetime cumulative duration (in minutes) of sunbed use in subjects who ever used sunbeds.

Country	Cases		Controls	
	Median	Interquartile range	Median	Interquartile range
Sweden				
Small and medium size UV units	175	32.5-775	175	30-750
Large, double-panel, UV units	1010	352-2715	1200	450-3750
The Netherlands				
Small and medium size UV units	793	180-4410	1720	360-4235
Large, double-panel, UV units	410	158-950	300	120-900
United Kingdom				
Small and medium size UV units	200	30-520	150	40-520
Large, double-panel, UV units	233	83-780	120	45-360
Belgium				
Small and medium size UV units	110	70-860	600	200-2000
Large, double-panel, UV units	300	100-675	413	200-1040
France				
Small and medium size UV units	60	55-300	53	40-100
Large, double-panel, UV units	150	60-300	150	70-200
Five countries				
Small and medium size UV units	320	75-1920	600 *	100-2400
Large, double-panel, UV units	360	125-1150	300 **	100-1100

Wilcoxon rank sums test for the difference between cases and controls: * $p = 0.217$;** $p = 0.222$.

In contrast, in the Netherlands, the small and medium size UV units usually used at home were the predominant mode of exposure.

To assess the melanoma risk associated with sun exposure, we asked about the mean number of holiday weeks spent after 15 years old in sunny areas, and whether the interviewee engaged in sunbathing activities during holidays in sunny areas. A negative association was found between melanoma and sunbathing activities: 376 (60%) cases reported sunbathing activities during holidays, for 443 (68%) controls, yielding an adjusted melanoma risk of 0.81 (95% CI: 0.63-1.04). When sunbathing activities were combined with the number of holiday weeks in sunny areas, the latter sun exposure indicator was significantly associated with melanoma when subjects did not report sunbathing activities (table 6, upper panel). But when subjects reported sunbathing activities, the melanoma risk associated with 2 or ≥3 holiday weeks in sunny areas decreased. This pattern of 'disappearance' of the melanoma risk when adding the reported sunbathing behaviour to the models was also observed when the reported ever/never use of sunbeds were added to the model with holiday weeks in sunny areas (table 6, lower panel): the melanoma risk associated with holiday weeks in sunny areas was systematically lower when subjects reported ever use of sunbeds.

Discussion

The study reported here confirmed the expected associations between melanoma and fair skin, positive family history and duration of holidays in sunny areas but did not find a significant association between sunbed use and melanoma risk. Another interesting finding was that the prevalence of sunbed exposure in cases and controls in our study were the highest ever reported.

Table 6. Holidays after 15 years old, sunbathing, sunbed use and melanoma risk.

Mean holiday weeks each year after 15 years old	Ever sunbathing	Cases (n = 622)	Controls (n = 649)	Adjusted melanoma risk* (95% CI)
0-1	Never	56 (9%)	72 (11%)	1.00 (ref.)
0-1	Ever	62 (10%)	69 (11%)	1.20 (0.72-2.00)
2	Never	92 (15%)	69 (11%)	1.71 (1.06-2.78)
2	Ever	158 (25%)	158 (24%)	1.38 (0.90-2.13)
3+	Never	98 (16%)	65 (10%)	1.79 (1.10-2.90)
3+	Ever	156 (25%)	216 (33%)	1.07 (0.70-1.63)
	Ever sunbed use			
0-1	Never	54 (9%)	63 (10%)	1.00 (ref.)
0-1	Ever	64 (10%)	78 (12%)	0.84 (0.50-1.40)
2	Never	110 (18%)	96 (15%)	1.29 (0.81-2.07)
2	Ever	140 (23%)	131 (20%)	1.18 (0.75-1.87)
3+	Never	120 (19%)	113 (17%)	1.17 (0.74-1.86)
3+	Ever	134 (22%)	168 (26%)	0.94 (0.60-1.49)

* Adjusted for age, sex, skin phototype, haircolor, sunburn before and after 15 years old.

The cumulative use of sunbed was very high with 14% of subjects using sunbeds for more than 35 hours. Typical annual programme proposed by many tanning parlours comprises 12 to 20 sessions of 20 minutes, i.e., 4 to 6 hours per year. Thus, a cumulative exposure of 35 hours corresponds to "UVA-tanning" programmes repeated over 6 to 9 years. Previous studies have reported similar high prevalence of sunbed use in young adults in countries like Sweden and the Netherlands [15]. The pronounced north to south gradient in the prevalence of sunbed use observed in the study reported here has previously been reported by other groups [6]. Our study also found a significant proportion of subjects who used sunbeds before the age of 15.
Before discussing these results further, limitations of this study need to be briefly discussed. A more detailed discussion of the possible biases in this study is given in chapter 3.3 of this thesis.

Within a multi-centre case-control study in five European countries, it proved difficult to implement a uniform method in terms of recruitment of cases and controls. When a population-based cancer registry was not available, recruitment of cases was done from oncology/dermatology and plastic surgery clinics as well as pathology departments. Cancer centres tended to recruit more advanced melanoma cases, while patients from other clinics had thinner lesions. However, histological subtypes of melanoma, mean thickness and male to female ratio reflected population based data in all countries so it is unlikely that this has affected the results.

The number of weeks of holidays in sunny areas and melanoma were related. However, there was no risk associated with reported sunbathing habits, in contrast with previous findings in Europe [11, 16, 17]. In the 1992-93 study in Belgium, Germany and France [6, 11], sunbathing activities further increased the melanoma risk associated with increasing numbers of weeks of holidays in sunny areas. In the present study, sunbathing activities diminished the increased risk associated with weeks of holidays in sunny areas. Results on sunbed use and weeks of holidays in sunny areas showed a

similar pattern. This suggests that cases and controls may give accurate figures for the number of weeks abroad but underestimate their sunbathing activities as they are aware that this is risk behaviour. The way the sunbathing data was collected may also have been too crude with a "yes"/"no" answer and this may have given rise to underestimates of the true pattern of exposure whilst on holidays.

A sub-study based on 69 Dutch participants of this case-control study also suggests that recall bias may have been an issue. A survey explored the perceived "causes" of melanoma and found that a substantial proportion of cases denied that their melanoma could be related to sun exposure. This may be explained by a feeling of guilt over a "at risk" behaviour which is nowadays well known to the public. It is therefore possible that melanoma cases tended to underscore their sunbathing and, possibly, sunbed use [18].

For the last 15 years, primary prevention campaigns have put a considerable emphasis on dangers of sun exposure, and on putative hazards associated with sunbed use. Prevention campaigns warning about the risk of sunbed use and regulations concerning the commercial exploitation of sunbeds started in the late eighties in Sweden. In contrast, in France, prevention campaigns discouraging sunbed use only became common in the late nineties. When our study was started, controversy raged in the UK about the safety of sunbeds, and several countries, including Belgium, France and the UK were introducing or reviewing regulations on the installation and public use of artificial tanning devices. In the Netherlands the Ethical Committee, that usually focuses on experimental research, compelled the local study coordinator to inform both cases and controls on actual objectives of the study, before interviews could be conducted. This may also have affected recall in both cases and controls.

Several studies have shown that sun exposure and sunbathing may be protective especially in good tanners and the explanation may be that chronic sun exposure may confer some protection against melanoma [19]. But the interpretation of these studies is not straightforward as it is possible that these results may also be affected by recall bias with cases underscoring their true exposure as they are now fully informed of the risk attached to sun exposure. In a study of melanoma in twins, Cockburn and co-workers [20] showed that recall bias was influenced by prior knowledge that sunbathing was a risk factor for melanoma. In Sweden, Boldeman et al reported on possible underreporting of sunbed use and sunbed-induced sunburns [15]. Behavioural scientists have showed that reported sun exposure and sun protection habits rarely corresponded to actual behaviours [21, 22]. It is clear that the collection of sun and sunbed exposure data over a lifetime is a difficult task.

Extensive information of the public on hazards of sun exposure and sunbed use may also have biased the recruitment of controls who may have been keener to take part in a skin cancer study looking at risk factors if they were concerned about their behaviour and potential risk. As an indicator of the plausibility of biased selection of control subjects in the study reported here study, 14% of controls in Sweden had never used sunbeds, while a survey done in 1999 in the same area of Stockholm in subjects of the

same age showed that 30% of subjects had never used sunbeds [15]. In Lund, an area in the south of Sweden, 40% of control subjects 18-60 years old had never used sunbeds in the period 1995 to 1997 [23]. In the Netherlands, a telephone population-based survey done by the Netherlands Cancer Society in the year 2000 showed that about 37% of people 18 to 49 years of age used sunbeds [24]. It therefore appears that the prevalence of sunbed use in controls was particularly high in the study reported here and this raises the possibility that cases and controls who came forward may have had higher sunbed exposure than population average. The potential denial in cases who under-reported their true exposure and the recruitment of controls who were very keen to take part as they may have been regular sunbed users may have led to an under-estimation of risk.

In our study, sunbed use and sun exposure did not seem to be significantly associated with melanoma risk. Several, but not all, other case-control studies and one prospective cohort study investigating this association, found an increased risk of melanoma associated with sunbed use [5, 6, 9, 23, 25].
Exposure to UV radiation has been related to several other negative effects such as sun damage, dysplastic skin lesions, non-melanoma skin cancers and other skin and non-skin disorders, which confer significant morbidity and health costs [26]. The possibility of chronic UVA exposure having effects on cutaneous immune responses may also have implications for HPV virus carriage and skin cancers [27-29]. Furthermore, exposure to regular UVA may also affect circulating cells which may also have implications for non skin disorders.

In conclusion, sunbed and sun exposure were not found to be significant risk factors for melanoma in the populations studied in five European countries. However, the results may have been substantially affected by recall bias towards less exposure in cases and self selection of exposed controls. One could argue that if a risk of melanoma exists with sunbed use it is not likely to be large. Our data, even considering all the potential biases, showed that sunbed use became quite prevalent in young adults and even children. Therefore, we cannot exclude significant repercussions in 20 years time in terms of skin and non-skin disorders. The true risk of sunbed use for melanoma may need to be re-evaluated in 10 years time to assess exposure to sunbeds especially as this is now affecting younger age groups.

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Chapter 3.3

Good general knowledge of risk factors might pose a problem for case-control studies: the example of sunbed use and melanoma.

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Case-control studies have several advantages over other types of analytical epidemiological studies, especially when studying a relatively rare disease: they can generally be performed in a much shorter time period than cohort studies, do not require such a large sample size as cohort studies and are therefore cheaper. Despite their usefulness and wide applicability, case-control studies have limitations and biases might occur [1, 2]. First, in case-control studies the information on risk factors is collected from cases after their diagnosis and this might pose serious biases in self-reported past exposures. It is generally thought that greater effort on the part of cases to remember past exposures, knowledge about risk factors for the disease, or tendency for changes in behaviour following diagnosis or treatment influence the accuracy of reporting among cases ("recall bias"). This can lead to what is referred to as "differential misclassification" and, finally, to biased estimates of risk. Second, participation rates in case-control studies are frequently low and often lower in controls than cases. Bias can arise because the reasons why cases and controls choose (or refuse) to take part in a study may be related to exposures of interest.

In general, biases can occur in case-control studies of all types of disease but they are more likely to occur when there has been a great deal of public information about the relation between potential or established risk factors and the disease. This is particularly relevant for melanoma because people are more and more aware of the hazards associated with sun exposure. Using a case-control study of melanoma in twins and asking melanoma cases and their co-twins to quantify their own exposures and asking both twins which twin had the greater exposure, researchers found evidence of bias in reports of sunbathing in childhood and adulthood and possibly of freckling in childhood [3]. More evidence that case-control status influences reporting of risk factors came from a study conducted in the cohort of the Nurse's Health Study. The ability to tan reported by women diagnosed of melanoma was lower than that reported by the same women before the diagnosis [4].

We present here the problems encountered in a case-control study assessing the association between sunbed exposure and melanoma risk in Europe. In order to study the effects of sunbeds on melanoma risk, one must correct for important confounders, such as skin type and exposure to natural sunlight, as well as protective measures taken before the diagnosis. We described the problems encountered in this study and the implications it might have for studying known risk factors in a well-informed population.

The case-control study was performed in Sweden, the Netherlands, the United Kingdom, Germany, Belgium and France, collecting data from 622 melanoma cases and 649 controls eligible for analysis, aged between 18 and 50 years. Trained interviewers interviewed both cases and controls and performed a naevus count on both arms. The recruitment of cases was through hospitals or population based cancer registries. Controls were either randomly selected from population registries, selected from lists of patients attending GP practices, selected through door-to-door searches or recruited through an advertisement in a local newspaper. In the Netherlands the local ethics committee requested that participants be informed about the purpose of the study, including giving information about the risks of sun exposure for melanoma. During the interview, using a standardised questionnaire, respondents were asked about sunbathing habits and sunbed use. Demographic data as well as data on skin type, eye and hair colour and freckles were also collected. The questions about sunbed use over a lifetime were aided by showing two coloured charts with 12 pictures of sunbed and sunlamp devices commonly used in Europe since the 1950s. The German cases and controls were excluded from our analyses because of protocol violations with respect to methods of case selection and choice of interviewer. Details of the study are described in chapter 3.2 of this thesis.

We observed large differences in prevalence of sunbed use in both cases and controls in the various participating countries, with considerable differences in the odds ratio (OR) estimates per country. With increasing prevalence of sunbed use, the OR associated with sunbed use decreased. The overall adjusted odds ratio for melanoma with ever versus never sunbed use was smaller than one (not significant) (Table 1).

Table 1. Sunbed use after the age of 14 years and risk of melanoma

Country	Sunbed use < 14 yr	Cases (n=622)	%	Controls (N=649)	%	Crude OR	95% CI	Adj. OR*	95% CI
Sweden	No	18	21%	13	14%	1		1	
	Yes	73	79%	81	86%	0.61	(0.28-1.32)	0.60	(0.25-1.44)
Netherlands	No	40	27%	35	21%	1		1	
	Yes	108	73%	134	79%	0.73	(0.44-1.22)	0.88	(0.50-1.55)
United Kingdom	No	83	52%	74	46%	1		1	
	Yes	76	48%	87	54%	0.78	(0.50-1.21)	0.87	(0.53-1.41)
Belgium	No	23	43%	23	43%	1		1	
	Yes	31	57%	30	56%	1.03	(0.48-2.22)	0.75	(0.30-1.89)
France	No	133	78%	141	81%	1		1	
	Yes	37	22%	31	19%	1.21	(0.72-2.05)	1.07	(0.60-1.90)
All countries	No	297	48%	286	44%	1		1	
	Yes	325	52%	363	56%	0.86	(0.69-1.08)	0.86	(0.67-1.09)

* Adjusted for age, sex, phototype, haircolour, number of sunburns before and after 14 years of age and the mean number of weeks of holidays in sunnary areas after the age of 14.

Before adjusting for sun exposure, we investigated the association between reported sun exposure and melanoma risk. Instead of the usual positive association we observed a *negative* association between sun exposure and melanoma risk. The adjusted OR for ever versus never sunbathing and melanoma was 0.84 (95% CI: 0.65-1.09) (table 2). This is not in agreement with published data: in a meta-analysis of 20 case-control studies on intermittent sun exposure and melanoma risk the summary OR for intermittent sun exposure was 1.87 (95% CI 1.67 – 2.09) [5]. For other, non-intentional sun exposure variables a positive association with melanoma was found. For example, the adjusted melanoma risk increased with more than one week of holiday in sunny areas after 15 years of age (OR 1.2 (95% CI 0.9-0.1.7)), which is in line with the observations of a recent prospective cohort study, where the OR was 1.44 (95 % CI 0.89-2.34) [6]. The association with reported skin phototype (adjusted OR for skin type I vs skin type IV: 2.4, 95% CI 1.5-3.7) and interviewer-determined hair colour (adjusted OR red or blond vs brown/black 2.0 (95% CI 1.4-2.8) were also confirmed in our study. Numerous epidemiological studies in similar Caucasian populations have found that sunbathing activities increase the risk of melanoma, especially in case of intermittent exposures and in younger age groups [5, 6].

The observed "protective" effect on melanoma associated with sunbathing in our study raised the hypothesis that to some extent, our findings could be attributable to the underreporting of sunbathing by melanoma cases.

In most studies on melanoma protection habits, like avoiding the sun and wearing hats or t-shirts, these are associated with relative risks for melanoma lower than one.

Table 2: Sun exposure and sun protection habits in cases and controls and melanoma risk.

		Cases (%)	Controls (%)	Adj. OR[a]	IC 95%	Other studies (reference)
Sunbathing	No	39	31	1.00		
	Yes	61	69	0.84	(0.65; 1.09)	1.87 (1.67; 2.09) [5]*
Sunbathing in hot hours	Never	46	41	1.00		
	Rarely	9	8	0.68	(0.39 ; 1.19)	
	Sometimes	23	21	0.63	(0.39; 1.02)	
	Often	21	29	0.90	(0.56; 1.46)	
Holidays to sunny areas	< 1 week/year	14	12	1.00		
	≥ 1 week/year	86	88	1.21	(0.85; 1.74)	1.44 (0.89; 2.34) [6]
Sunscreen use	Never/rarely	38	39	1.00		
	Sometimes-often	62	61	1.20	(0.94; 1.54)	1.8, (1.1; 2.9) [7]
T-shirt wearing	Never	5	3	1.00		
	Rarely	5	7	1.83	(0.86; 3.88)	
	Sometimes	16	16	1.73	(0.89; 3.38)	
	Often	27	24	1.67	(0.88; 3.17)	
	Always	48	51	2.11	(1.13; 3.94)	
Hat wearing	Never	47	49	1.00		
	Rarely	15	14	0.91	(0.64; 1.28)	
	Sometimes	19	17	0.89	(0.64; 1.23)	
	Often	14	12	0.88	(0.61; 1.27)	
	Always	5	7	1.64	(0.99; 2.74)	

[a]Adjusted for age, sex, haircolour, skin phototype, country and sunbathing (yes vs no)

*In this study [5], a summary OR for sun exposure was given based on 20 studies

We therefore hypothesised that if sunbathing was underreported, sun protection behaviour would be over-reported. Therefore, we investigated the OR associated with protective behaviours. Always wearing a t-shirt was significantly associated with an elevated risk of melanoma, and wearing a hat was also associated with an increased melanoma risk (borderline significance). Although using sunscreens has previously been shown to protect against melanoma [7-11], the fact that using hats and wearing t-shirts was a risk factor was unexpected and has never been shown before in case-control studies.
In this study, numbers of naevi on the arms were also measured, by a trained interviewer. Naevus counts have been positively correlated with high levels of sun exposure in many Caucasian populations [10, 12-14]. We therefore checked this established association between sun exposure and naevus count separately in our cases and controls. The positive association between sun exposure before the age of 15 and naevus count was confirmed in controls in our study for reported episodes of sunburn during childhood. For reported sunburns in cases before and after the age of 14, and for reported sunburns in controls after the age of 14, the association was weaker and not significantly increased. However, reported sunbathing in adulthood appeared *inversely* related to naevus counts in cases, albeit not significantly. The more the reported sunbathing took place during the warmest hours of the day, the stronger the negative association with naevus count (table 3). This negative association was stronger in cases than controls.

A substudy was performed in the Netherlands [15] assessing cases' knowledge about melanoma risk factors. The results showed that 56% of the melanoma cases did not believe that their melanoma had anything to do with sun exposure and it is therefore possible that they underreported their true exposure. This is despite the information provided on sun exposure and melanoma in the information sheet given to the participants before the interview as well as the regular media campaigns on melanoma and sun exposure in the Netherlands.

Table 3: Naevus count on the arms according to sunburn experiences and intentional intermittent sun exposure in cases and controls*

Variable		Cases		Controls	
		%**	95 % CI	%	95% CI
Sunburns <15	Never	Ref		Ref	
	≥ 1 time	4.3	(-3.1 ; 10.7)	8.2	(0.89 ; 14.4)
Sunburns ≥15	Never	Ref		Ref	
	≥ 1 time	2.3	(-6.4 ; 9.6)	2.2	(-7.0 ; 9.8)
Sunbathing during warm hours	Never sunbathing	Ref		Ref	
	Sunbathing, but never or rarely during warm hours	-4.6	(-18.0 ; 5.7)	0.18	(-12.4 ; 9.9)
	Sunbathing sometimes, regularly or often during warm hours	-6.5	(-17.2 ; 2.1)	-3.3	(-14.9 ; 5.9)

* Poisson regression model with over-dispersion parameter, adjusted for country, age, sex, haircolour, phototype and the variables in the table
** Percentage increase in number of naevi relative to the reference category. Percentage calculated according to the Poisson regression model with the formula log(estimation+1)

These observations led us to speculate that certain cases may have denied that they could have been 'responsible' for their melanomas and therefore underreported their intentional sun exposure, and, most likely, their sunbed exposure as well. If feeling guilty about their behaviour may have occurred, one would expect the cases with a more serious diagnosis, i.e. with a thicker melanoma, to have stronger underreporting of exposure. To test this hypothesis, we estimated the OR for reported sunbed use as a function of the most important prognostic factor for melanoma, the Breslow thickness.
We constructed a graphical representation of the estimated melanoma risk associated with sunbeds as a function of Breslow thickness, adjusted for age and sex. In order to do this, the OR for cases had to be estimated repeatedly, in the different classes of thickness compared to the complete group of controls. Cases were ordered according to reported Breslow thickness. The first 200 cases (Cases 1-200, i.e. those with the thinnest Breslow thicknesses) were compared to the complete group of controls and the OR was calculated. Subsequently, cases number 2-201 were analysed in the same way, afterwards cases 3-202, etc. This method resulted in a representation of the OR for sunbed use and melanoma risk as a function of the 'moving average' of Breslow thickness. As no Breslow thickness was available for the Belgian cases, we excluded them as well as Belgian controls from this analysis, which was conducted on 568 cases and 578 controls. With increasing Breslow thickness, the reported melanoma risk associated with sunbed use decreased, and even reached significance in very thick melanomas (with a Breslow thickness greater than 2.5 mm) (figure 1). This analysis was repeated, but stratified for reported duration of sunbed use (more versus less than ten hours). The results are given in figure 2. As Breslow thickness increases, the associated risk of melanoma with sunbeds decreased the most in those with a long duration of sunbed use.

In our study ever sunbed use in controls varied from 19% in France up to 86% in Sweden. This high prevalence of sunbed use in controls in our study (table 1) was compared to those in other recent case control studies: 59% of controls used sunbeds in Sweden [16] and 26% in the United Kingdom [17] although these studies included older cases and controls which may have created lower prevalence as sunbed use significantly decreases with age. We were keen to investigate whether self-selection of controls had occurred, introducing bias in the odds ratio estimates.

In countries where many health campaigns for skin cancers have been organised and melanoma incidence is high (Sweden, Netherlands, England), the knowledge of the normal population regarding potential melanoma risk factors including sunbeds is likely to be high [2].
Eligible controls who used sunbeds were probably more likely to accept the invitation to participate in a melanoma study than those who did not use sunbeds and this may have created a selection bias. This selective participation amongst controls who were sunbed users might be due to a feeling of 'guilt' or 'worry' about their habits. The inclusion of controls who were more likely to use sunbeds would therefore dilute the true risk of sunbed use in melanoma.

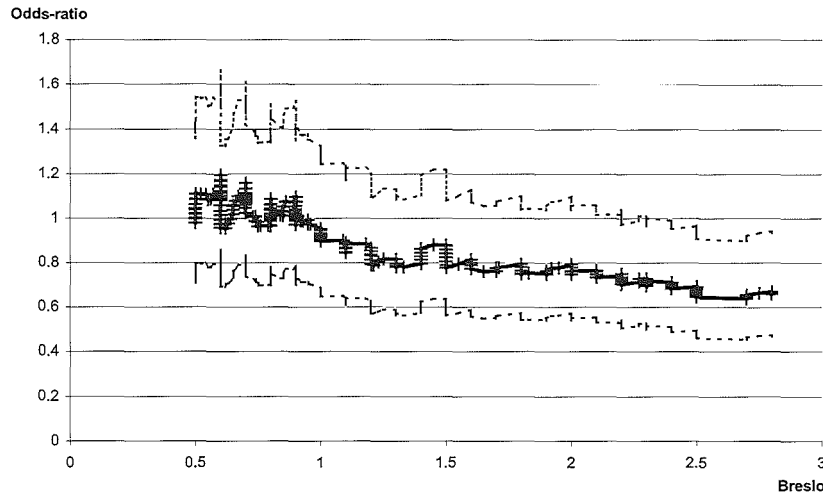

Figure 1. Risk of melanoma (with 95% confidence interval) associated with sunbed use as a function of Breslow thickness, adjusted for age and sex.

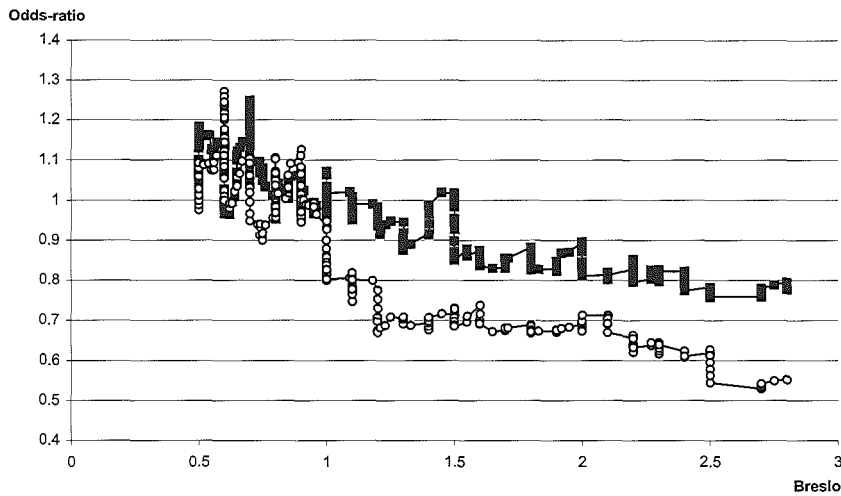

Figure 2: Risk of melanoma (with 95% confidence interval) associated with reported duration of sunbed use (Less than 10 hours vs more than 10 hours) as a function of Breslow thickness, adjusted for age and sex. (Squares: less than 10 hours sunbed use, circles, more than 10 hours sunbed use).

Our results suggest that both melanoma cases and controls in this study underreported their sun exposure, but this was more severe in cases. Our data is also possibly affected by the need to provide 'socially desirable answers' amongst cases and controls, but especially amongst cases. A reason for their underreporting may be a 'search for explanations that are beyond their control', thereby avoiding blaming themselves for their serious disease. This is in line with earlier studies performed amongst patients of serious illnesses [15, 18].

Whilst we cannot rule out the possibility that sunbed use is not a risk factor for melanoma and may even be protective, the indications for potential biases in recruitment and recall make it impossible to rely on risk estimates derived from our analyses. The data presented here highlight the need to be aware of potential recall and selection biases when studying an exposure for a disease in a well educated and informed population.

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Chapter 3.4

Determinants of sunbed use: an EEC multi-centre study

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Ultraviolet radiation (UVR) is the main environmental factor linked to melanoma, mainly in Caucasian populations. UVA was until the early 1990s thought to be a "safer" UV radiation in terms of skin cancer risk compared to UV-B but more recent work in vivo and in vitro in humans and animals has shown that this is not the case and that UVA can induce melanoma [1-6]. Although UV-B is responsible for most of the production of dimers in DNA which reflects the damage caused at the cellular level, UVA also causes significant DNA damage via free radicals [3]. The main source of ultraviolet radiation on earth is that from the sun, containing both UV-A and UV-B radiation, but sunbeds, emitting mainly high quantities of UV-A, and recently increasing amounts of UV-B, are becoming more and more prevalent. Therefore, many epidemiological studies have attempted to investigate the role of sunbed exposure in melanoma, reviewed by Young [7]. Whilst a few studies found a weak association between melanoma and sunbed exposure many others did not confirm this. The issues raised when reviewing these studies are low power, poor recall, recall bias and sun exposure acting as a major confounder. We encountered similar problems in our study, described in chapter 3.2 and 3.3 and decided to investigate which factors were associated with sunbed use in order to better understand the characteristics of sunbed users and the problems encountered when adjusting for sun exposure measures.

Our study was performed in Sweden, the Netherlands, the United Kingdom, Belgium and France, collecting data from in total 579 cases and 622 controls eligible for analysis, aged between 18 and 50 years, who were all interviewed, preferably at home, by a trained interviewer. The recruitment of cases was through hospitals or populations based cancer registries. Controls were either randomly selected from population registries, selected from lists of patients attending GP practices, selected through door-to-door searches or recruited through an advertisement in a local newspaper.

Table 1: Reported sunbed use after the age of 15 in the various participating countries

Country	Sunbed use				Mean number of hours	Mean age at start use
	Yes	%	No	%	(95% CI)	
Sweden	158	88	22	12	15.5 (11.5-20.8)	19
Netherlands	245	78	68	22	17.2 (13.7-21.8)	24
UK	169	54	145	46	3.5 (2.6-4.6)	22
Belgium	54	66	28	34	6.2 (4.0-9.6)	26
France	68	21	262	79	2.2 (1.6-3.0)	27
Total	694		525		8.8 (7.6-10.2)	23

During the interview, using a standardised questionnaire, respondents were asked about sunbathing habits and sunbed use, as well as about more general characteristics such as skin type, eye colour, age, occupational status, etc. The questions about sunbed use were aided by the showing two coloured charts with 12 pictures of sunbed and sunlamp devices commonly encountered in Europe since the 1950s. More details of the study are described in chapter 3.2 of this thesis. Because we had strong indications for underreporting of sun exposure and self-selection among controls (chapter 3.3), the risks associated to sunbed use from our study are most likely biased.

In this substudy we wanted to study which factors were associated with reported sunbed use after the age of 15 and duration of sunbed use, irrespective of case or control status. Mean duration of exposure to sunbeds in hours was calculated multiplying the number of sessions per person times the reported duration of a session in minutes. As this number was not normally distributed, a log-transformation was applied. Chi-squared statistics were used to determine if differences in reported sunbed behaviour were statistically significant.

Logistic regression modelling was used to predict sunbed use based on our data.

Great variation was observed in terms of sunbed use across Europe with the highest use seen in Sweden and the Netherlands and the lowest in France (table 1). In all countries sunbed use was higher in women (results not shown). Swedes started using sunbeds at young ages (mean age at start use: 19).

Table 2 shows a comparison in host characteristics and sunbathing behaviour for those who reported sunbed use compared to those who did not. The mean age of sunbed users was 37.5 years and non-users 37.8 years.

Table 2: Characteristics of those who use sunbeds after 15 years of age compared with those who did not

Variable		Sunbed use						Mean nr of hours
		Yes	%	No	%	Value of Z / χ^2 (df)	P-value	(95% CI)
Total		694		525				mean 8.8 hr (7.6-10.2)
Age (mean)		37.5		37.8		Z=0.73	0.47	
Sex	Males	200	46	233	54	χ^2=31.6 (1)	<0.0001	7.3 (5.5-9.8)
	Females	494	63	292	37			9.4 (7.9-11.2)
Phototype	Always burn	72	46	85	54	χ^2=25.8 (3)	<0.0001	5.1 (3.4-7.8)
	Often burn	233	56	183	44			6.4 (4.9-8.4)
	Sometimes burn	303	65	164	35			12.0 (9.6-14.8)
	Never burn	86	48	93	52			10.1 (6.6-15.6)
Haircolour	Red	38	55	31	45	χ^2=15.3 (3)	0.0016	8.3 (4.6-15.1)
	Blonde	157	66	81	34			8.7 (6.4-11.7)
	Light brown	185	60	123	40			12.3 (9.2-16.4)
	Black/brown	314	52	290	48			7.3 (5.8-9.1)
Eye colour	Blue	362	63	217	37	χ^2=31.21 (2)	<0.0001	10.6 (8.7-13.0)
	Green	148	62	89	38			7.2 (5.3-9.8)
	Brown/black	184	46	219	54			7.0 (6.6-9.5)
Sunbathing	Never	195	37	329	63	χ^2=165.5 (3)	<0.0001	4.0 (3.0-5.4)
	Rarely	69	63	40	37			8.4 (5.6-12.5)
	Sometimes	175	65	96	35			8.8 (6.5-11.8)
	Often	255	81	60	19			15.7 (12.6-19.7)
Sunscreen Use	Always	237	61	153	39	χ^2=53.0 (4)	<0.0001	10.2 (8.0-13.0)
	Often	224	64	126	36			8.5 (6.6-10.9)
	Sometimes	150	56	118	44			6.4 (4.5-9.0)
	Rarely	63	52	59	48			13.8 (8.2-23.4)
	Never	20	23	68	77			5.5 (2.6-11.4)

Females used sunbeds significantly more often and longer than males (63% vs 46% and 9.4 vs 7.3 hours respectively) and a higher percentage of people with light hair and / or eye colour reported sunbed use compared to those with black or brown hair and/or eyes.
The different phototypes showed only moderate differences in prevalence of sunbed use, but the mean number of hours of sunbed use was much lower in those with sun-sensitive skin. Sunbathing during hot hours and sunscreen use were positively associated with sunbed use: the more reported sunbathing and sunscreen use, the higher the prevalence of sunbed use. More reported sunbathing during hot hours was positively correlated to the mean duration of exposure.

After adjusting for all other variables, only sex, country, sunbathing and sunscreen use were significantly associated with risk of sunbed use in a multivariate logistic regression analysis, summarized in table 3. Women are twice as likely to use sunbeds than males, those who never sunbathe are 3 times less likely to report sunbed use and those who always use sunscreens are 3 times more likely to report sunbed use, the Swedes have a 20 fold increased prevalence of sunbed use.

This sub-study looking at the prevalence of sunbed use across Europe is one of the largest collecting more than 1000 subjects. The results of the case-control analysis have been reported in chapter 3.2 of this thesis. We found that high percentages of people with a sun-sensitive skin used sunbeds. The duration of sunbed use in this group was limited compared to those with a less sensitive skin.

Table 3: Logistic regression results: multivariate analysis. (N=1219, Ever sunbed use after 15= 694, never 525)

Variable		Odds ratio	95% CI
Age		0.99	(0.97-1.01)
Sex	Female	2.07	(1.52-2.80)
	Male	1	(ref)
Phototype	Always burn	0.90	(0.51-1.57)
	Often burn	0.91	(0.57-1.46)
	Sometimes burn	1.17	(0.74-1.84)
	Never burn	1	(ref)
Haircolour	Red	0.86	(0.46-1.60)
	Blonde	1.45	(0.97-2.18)
	Light brown	1.13	(0.79-1.62)
	Brown/Black	1	(ref)
Eye colour	Blue	1.00	(0.71-1.42)
	Green	1.23	(0.81-1.87)
	Brown/black	1	(ref)
Sunbathing	Never	0.27	(0.18-0.40)
	Rarely	0.53	(0.30-0.93)
	Sometimes	0.49	(0.32-0.75)
	Always	1	(ref)
Sunscreen use	Always	3.49	(1.82-6.69)
	Often	3.99	(2.06-7.73)
	Sometimes	2.70	(1.38-5.28)
	Rarely	2.19	(1.05-4.58)
	Never	1	(ref)
Country	Sweden	21.71	(11.99-39.31)
	Netherlands	11.90	(7.81-18.13)
	UK	3.95	(2.66-5.85)
	Belgium	7.34	(4.15-12.99)
	France	1	(ref)

People who regularly used sunscreens tended to use sunbeds more often than those who did not. They might use the sunscreens to be able to stay in the sun longer, elongating their exposure time in order to get a deeper tan. The apparent harmful effects of sunscreen use might operate through this mechanism [8-11].
The fact that those who sunbathe more report have a higher and longer reported sunbed use has been found before [12]. It is illustrative of the difficulties of analysing the risk for melanoma associated with sunbed use. Sunbathing and sun protection habits are strongly correlated to sunbed use. Since one always has to adjust for sunbathing and sun protection habits when studying the risk of melanoma, this phenomenon makes it difficult to prove a causal relationship between sunbed use and melanoma risk, if it exists.

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Chapter 3.5

Patients' perception of the cause of their melanoma differs from that of epidemiologists

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SIR, Exposure to sunlight is considered the major environmental cause of melanoma [1]. In Europe, 80% of melanomas may have been caused by ultraviolet (UV) radiation; the significance of intermittent periods of intensive exposure to UV radiation as a child, sometimes reflected by a history of sunburns during childhood, seems unequivocal [2, 3]. We report here on patient perception of the cause of melanoma, based on 69 Dutch patients, aged 19–50 years, who were diagnosed with melanoma in 1998–2000 and participated in a European study on sunbed use and melanoma risk. Before the interview, they received a leaflet stating that exposure to UV radiation is an important risk factor for melanoma. During a face-to-face interview, they answered questions regarding sunbathing habits since their youth, including sunbed use. At the end of the interview, they were asked about their perception of the cause of their melanoma. Sixty-three (91%) of patients responded, 25 males and 38 females, with a median age of 39 (19–50) years. Their answers are listed in table 1, according to sunburn experience, skin type, anatomical site and level of education, respectively. One-third of the respondents mentioned exposure to the sun as a possible cause of their melanoma; 12 of 63 (19%) were quite certain that exposure to the sun was the cause of their melanoma, seven (11%) blamed sunbed use and 10 more (16%) did not exclude the possibility that exposure to UV radiation was the cause of their melanoma (Table 1). Males attributed their melanoma directly to the sun or sunbeds more often (32%) than females (22%).

Patients who were more susceptible to the sun (fair-skinned, blue eyes, blond hair) and had been sunburned frequently during childhood and adulthood were more likely to hold UV radiation responsible for their melanoma. Of those with skin type 1 and 2, 42% attributed their melanoma directly to the sun or sunbeds, whereas 43% of those with skin type 3 and 4 assumed the opposite, with an odds ratio of 3.3 (0.9-12.1). Comparing patients with a high level of education and patients with a lower level of education, 60% vs. 40%, respectively, mentioned UV radiation as a possible cause of their melanoma. Only two of five patients with melanomas on the most exposed areas of the body (head and neck) blamed exposure to the sun for their melanomas. In the category 'other', one patient mentioned the Chernobyl incident and two patients mentioned swimming in polluted water as a cause. The latter received a lot of attention in the media after it was listed as a risk factor for melanoma in a 1994 Dutch study [4].

Four people assumed that they had a greater risk of developing melanomas because a relative had had (skin) cancer: a father with non-melanoma skin cancer, a grandmother with melanoma, two relatives with cancer of unknown type. Patient perception of the cause of their melanoma did not correlate with the reported number of sessions on sunbeds, tanning habits, or wearing protective clothing when in the sun. Although most scientists, health educators and physicians assume that melanomas are usually caused by exposure to the sun, only one-third of patients say that such exposure could have caused their melanomas; only in the group with a higher level of education was this percentage higher (60%). Most patients who blamed exposure to the sun for their melanoma had a sun-sensitive skin (skin type 1 and 2) and had suffered more sunburns, during both childhood and adulthood. In an earlier case–control study cancer patients held less firm convictions about causative factors in the aetiology of cancer than did non-cancer patients and cancer patients listed 'God's will' and 'Inherited' more often as one of the top four causes of cancer [5]. How can this discrepancy between real risks and risk perception be explained? Patients may not like the idea that their behaviour could have caused the melanoma. By endorsing other explanations that are beyond their control, they avoid blaming themselves. However, patients who easily get sunburnt were more familiar with the harmful effects of the sun and more likely to mention the sun as a risk factor. People with a less sensitive skin type may be less familiar with the adverse effects of UV radiation and therefore assume that exposure to the sun is harmless, despite the fact that the dangers of exposure to the sun have been reported extensively in the media.

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Table 1: Patients' perception of the causes of their melanoma (%) according to different sunburn experience, skin type, anatomical site of the melanoma and levels of education

		Sunburn experience				Skin type[a]		Anatomical site of primary melanoma				Educational level	
		≤ 14 years		>14 years									
	All	Yes	No	Yes	No	1&2	3&4	Head and neck	Trunk	Limbs	Buttocks / genital area	Low / Medium[b]	High[c]
n	63	18	44	25	37	33	30	5	17	38	3	43	20
	%	%	%	%	%	%	%	%	%	%	%	%	%
Sun-related causes:													
Sun & sunbed	30	44	20	40	19	42	17	40	41	26		28	35
No idea, possibly sun/sunbeds	16	17	16	32	8	15	17		6	24		12	25
Non sun-related causes:													
No idea, but *not* sun	33	11	43	24	41	24	43	40	29	34	33	37	20
Sensitive skin	8	11	7	8	8	15		20	6	5	33	9	5
Rubbing/damaging skin	8	11	7	8	8	9	7			13		9	5
Stress	10	17	7	4	14	6	13	20	12	5	33	9	10
Inherited risk	6	11	5	4	8	6	7		12	5		5	10
Other	5		7	12	8		10		18			2	10

[a] Skin type 1&2: burn easily, do not tan well, skin type 3&4: burn moderately, tan well. [b] Vocational training or less: 58% had phototype 1&2 and 42% had phototype 3&4. [c] College/university: 60% had phototype 1&2 and 40% had phototype 3&4

Chapter 4

Variation in prognostic factors

Chapter 4.1

Lower incidence rates but thicker melanomas in eastern Europe before 1992: a comparison with Western Europe

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Summary

The objective of this study was to investigate the epidemiology of melanoma across Europe with regard to Breslow thickness and body-site distribution. Incidence data from Cancer Incidence in 5 Continents and the EUROCARE-melanoma database were used: 28,117 melanoma cases from 20 cancer registries in 12 European countries, diagnosed between 1978 and 1992. Regression analysis and general linear modelling were used to analyse the data. Melanomas in eastern Europe were on average 1.4 mm thicker ($p<0.05$) than in Western Europe and appeared more often on the trunk. From 1978 to 1992, their Breslow thickness had decreased in western but not eastern Europe. There was a latitude gradient in incidence, with highest rates in southern regions in eastern Europe and an inverse gradient in western Europe, with highest rates in the north. Mortality:incidence ratios were less favourable in southern parts across Europe, especially in eastern Europe. If eastern European populations copy the sunbathing behaviour of the west it is likely that in the near future a higher melanoma incidence can be expected there.

Introduction

Incidence and mortality rates for melanoma have been increasing in all Caucasian populations in recent years [1-3]. Incidence rates and increases therein are, however, far from identical in the different populations. Within Europe, incidence rates show a marked north:south gradient, with the highest (but flattening) rates in northern Europe but rapidly increasing rates in southern and eastern Europe [4]. These trends can partly be explained by differences in susceptibility and (recreational) exposure to sunlight between the different populations, but many causes remain to be explored.
A distinct political division existed within Europe up to the early 1990s (the closed and the open societies), which was reflected in different social systems, prosperity and health behaviour; these factors may have affected recreational habits and immune status, both of which are related to melanoma. In this study, we have investigated differences in incidence, mortality:incidence (M:I) ratios and characteristics at the date of diagnosis (thickness, body site and age distribution) for melanoma across Europe (north to south and east to west) in the 1980s by latitude and longitude.

Materials and methods

Data
Data from several population-based cancer registries were used. The incidence data and M:I ratios for the 26 European cancer registries presented in fig. 1 were derived from Cancer Incidence in 5 Continents, covering the period 1988–92 [5]. Patient-specific data were taken from a specially composed melanoma subset of the EUROCARE database [6]. This database consists of survival data derived from population-based cancer registries, was set up to explain differences in relative survival across Europe [7], and contained information on age, sex, date of diagnosis, survival status and date of death, site, Breslow thickness [8] and morphology. Data on incident melanoma cases diagnosed between 1978 and 1992, derived from 20 cancer registries across Europe, were included in this EUROCARE-melanoma database. Only the malignant melanomas and cases with histological confirmation were included. From the EUROCARE database we included 28,117 cases in the analyses, 5458 from eastern Europe (registries from Estonia, Poland, Slovakia and Slovenia) and 22,659 from western Europe (registries from the United Kingdom, The Netherlands, Sweden, Italy, France, Spain, Switzerland and Germany). The latitude and longitude of all registries were entered in the database, based on the location of the city in which the registry is situated, to avoid a bias due to differences in catchment size per registry. The latitude of the town of the registry was used as a proxy for the latitude of the city of residence of the patient. This method could have caused some distortion but is not expected to have biased our results substantially, especially as most registries covered only a limited range of latitudes.
Anatomical localisation was registered according to the International Classification of Diseases (ICD) as: head-and-neck area, trunk, upper limb, lower limb, other and unspecified. Data on histology were registered according to the ICD and grouped into

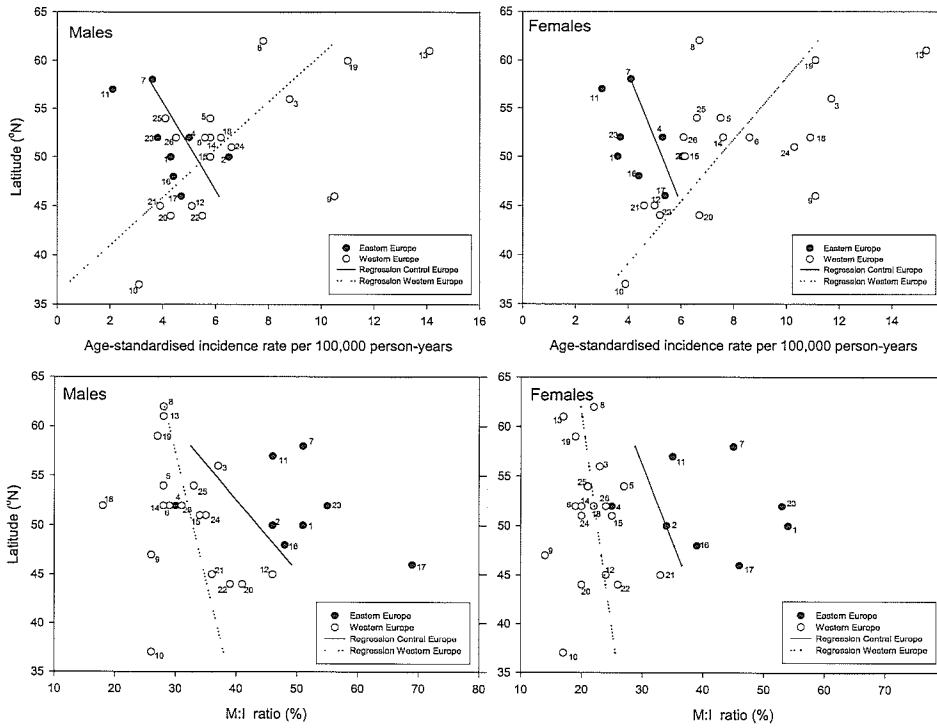

Figure 1 (a) Age-standardised incidence rate (world standard population) of cutaneous malignant melanoma per 100,000 person-years by latitude, weighed by population size of the registry (b) Mortality: Incidence ratios of cutaneous malignant melanoma (%) by latitude, weighed by population size of the registry..

Males
East: Incidence= -0.22*latitude + 16.30 (p<0.001)
West: Incidence= 0.41*latitude – 14.71 (p<0.001)

Females:
East: Incidence= -0.15*latitude + 12.75 (p<0.001)
West: Incidence= 0.31*latitude – 8.27 (p<0.001)

Males
East: M:I = -1.39*latitude + 112.92 (p<0.001)
West: M:I = -0.39*latitude + 52.37 (p<0.001)

Females
East: M:I = -0.64*latitude + 65.95 (p<0.001)
West: M:I = -0.23*latitude + 34.00 (p<0.001)

Registries and their population size (per 1000)
1: Cracow (748), 2: Czech Republic (10342), 3: Denmark (n=5145), 4: Eastern Germany (n=16648), 5: East Anglia (n=2062), 6: Eindhoven (n=936), 7: Estonia (n=1562), 8: Finland (4981), 9: Geneva (382), 10: Granada (788), 11: Latvia (2654), 12: Lombardy (793), 13: Norway (4245), 14: Oxford (2545), 15: Saarland (1067), 16: Slovakia (5298), 17: Slovenia (1999), 18: Southern Ireland (532), 19: Sweden (8558), 20: Tarn (346), 21: Turin (996), 22: Tuscany (1168), 23: Warsaw (1625), 24: Wessex (2966), 25: Yorkshire (3658), 26: West Midlands (5219)

four categories: superficial spreading melanoma (SSM), nodular melanoma (NM), other types of melanoma (other) and melanomas not otherwise specified (NOS).

Analyses

Linear-regression analysis was performed on age standardised incidence rates and M:I ratios, weighted for the population size of the registry. For analysis of body-site distribution, cases were divided into those younger than 50 years (n=10,962) and those 50 years and older (n=17,155). Data on anatomical site were missing for one case only. χ^2 statistics were calculated for differences amongst groups. For the analysis of the Breslow thickness, only the invasive melanomas and cases with histological confirmation and a known Breslow thickness were included. As not all cancer registries collected information on Breslow thickness (Slovakia, Tarn, West Midlands and Yorkshire did not have these data and the proportion of missing values varied elsewhere), there were 15,402 cases with no suitable data on Breslow thickness (8600 from the registries without any information on Breslow thickness; 6802 from the other registries (i.e. 35% of the cases from registries with information on Breslow thickness; 59% missing in eastern Europe versus 31% missing in western Europe)). After exclusions, 12 715 cases were included in the analyses of Breslow thickness, 1117 in eastern Europe and 11 598 in western Europe. As Breslow thickness was not normally distributed, we used a log transformation to calculate the mean Breslow thickness. The log(Breslow+1) was used to avoid negative effects of thickness values between 0 and 1 mm. In a generalised linear model we analysed the effects of age, year of diagnosis, sex, latitude and site on the log(Breslow+1) for eastern compared with western Europe.

Results

The incidence of melanoma in eastern Europe was similar to that of southern countries in western Europe, but lower than in more northern countries there, many of which are on the same latitude as the eastern European countries. Age-standardised incidence rates exhibited a north:south gradient in eastern Europe, but a south:north gradient in western Europe (fig. 1a). M:I ratios were higher in the south of both regions than in the north, and in eastern as compared with western Europe, indicating a higher mortality relative to incidence (fig. 1b). The characteristics of the melanoma patients of each contributing registry are presented in table 1. The age distributions were similar across Europe, but the female:male ratios in the incidence rates were higher in western than eastern Europe. The following differences emerged in the mean Breslow thickness between eastern and western Europe, and in the distribution according to body site of the primary melanomas and their histology (tables 1, 2ab). Melanomas in eastern Europe were on average 1.38 mm (95% CI 1.33; 1.43) thicker than those in western Europe and seemed to be less often SSM (table 1). Melanomas on the trunk were relatively more common in eastern Europe, in all ages and both sexes (37% of all melanomas in eastern Europe versus 26% in western Europe). The frequency of melanoma on the limbs was lower in eastern Europe, but similar for both regions at other body sites.

Table 1: Characteristics of the population of melanoma patients of each registry, data from the EUROCARE-melanoma database (in alphabetical order of country, incidence refers to the period 1988-1992, mean age and Breslow thickness refer to the period 1978-1992)

		N	Mean age (yrs) (sd)	Incidence[a] Male	Incidence[a] Female	Latitude	Longitude	Histology[b] SSM n (%)	NM n (%)	Other n (%)	NOS n (%)	Breslow thickness N	Breslow thickness Mean	Breslow thickness 95% CI[c]
Central Europe		5458	54.9 (15.9)									1117	2.96	(2.82;3.11)
Estonia		876	56.0 (16.1)	3.6	4.1	59.0° N	24.5° E	0 (0)	2 (0.2)	694 (79)	180 (21)	169	3.44	(3.04;3.88)
Poland	Cracow	332	53.7 (15.0)	4.3	3.6	50.0° N	19.6° E	1 (0)	89 (27)	5 (2)	237 (71)	183	3.26	(2.96;3.58)
	Warsaw	480	55.0 (14.9)	3.8	3.7	52.2° N	20.6° E	16 (3)	51 (11)	135 (28)	278 (58)	118	3.88	(3.36;4.46)
Slovakia		2709	54.7 (16.0)	4.4	4.4	48.4° N	17.1° E	422 (16)	960 (35)	300 (11)	1027 (38)	0	-	-
Slovenia		1061	54.8 (15.9)	4.7	5.4	46.0° N	14.5° E	102 (10)	194 (18)	154 (15)	611 (58)	647	2.63	(2.46;2.80)
Western Europe		22659	55.5 (17.2)									11598	1.59	(1.56;1.61)
France	Tarn	265	58.9 (18.2)	4.3	6.7	44.0° N	2.2° E	111 (42)	39 (15)	39 (15)	76 (29)	0	-	-
Germany	Saarland	1080	55.5 (16.3)	5.8	6.1	49.1° N	9.4° E	326 (30)	154 (14)	181 (17)	419 (39)	411	1.44	(1.32;1.56)
Italy	Lombardy	649	55.5 (16.5)	5.1	5.0	45.3° N	8.6° E	185 (29)	157 (24)	94 (14)	213 (33)	276	2.14	(1.93;2.37)
	Turin	469	59.0 (15.1)	3.9	4.6	45.0° N	7.6° E	203 (43)	53 (11)	59 (13)	154 (33)	247	1.71	(1.53;1.91)
	Tuscany	392	57.3 (16.0)	5.5	5.2	43.5° N	11.2° E	201 (51)	74 (19)	40 (10)	77 (20)	283	1.86	(1.69;2.04)
Netherlands	Eindhoven	894	49.8 (16.9)	5.6	8.6	51.3° N	5.3° E	260 (29)	61 (7)	43 (5)	530 (59)	672	1.32	(1.24;1.41)
Spain	Granada	175	53.9 (16.5)	3.1	3.9	37.1° N	2.5° W	76 (43)	42 (24)	50 (29)	7 (4)	144	2.02	(1.73;2.35)
Sweden	Lund[d]	526	60.0 (16.4)	11.0	11.1	55.4° N	13.4° E	226 (43)	79 (15)	34 (6)	187 (36)	482	1.26	(1.16;1.37)
	Stockholm[d]	3102	55.8 (17.4)	11.0	11.1	59.3° N	17.6° E	0	0	0	3102 (100)	3044	1.27	(1.23;1.32)
Switzerland	Geneva	449	56.1 (17.5)	10.5	11.1	46.1° N	6.1° E	206 (46)	106 (24)	39 (9)	98 (22)	408	1.09	(0.99;1.19)
Un. Kingdom	East Anglia	2207	56.4 (17.2)	5.8	7.5	52.1° N	0.3° E	577 (26)	228 (10)	217 (10)	1185 (54)	951	2.56	(2.51;2.61)
	Oxford	2644	53.2 (17.0)	5.8	7.6	51.4° N	1.2° W	474 (18)	311 (12)	155 (6)	1704 (64)	1355	1.62	(1.54;1.70)
	Wessex	2734	56.1 (17.6)	6.6	10.3	51.0° N	1.2° W	699 (26)	402 (15)	264 (10)	1369 (50)	0	-	-
	West Midlands	4181	55.1 (17.4)	4.5	6.1	52.3° N	1.6° W	1042 (25)	788 (19)	554 (13)	1797 (43)	3325	1.75	(1.70;1.80)
	Yorkshire	2892	56.2 (17.3)	4.1	6.6	53.6° N	1.1° W	725 (25)	418 (14)	310 (11)	1439 (50)	0	-	-

[a] Age-standardised incidence data per 100,000 person-years from Cancer Incidence in 5 Continents, World Standard Population [5]

[b] SSM: superficial spreading melanoma, NM: nodular melanoma, Other: other, specified type of melanoma; NOS: unspecified histological type of melanoma

[c] 95% CI: 95% confidence interval

[d] Only national incidence data available

Table 2a: Number of incident cases of cutaneous melanoma by body site, males

	Males						Females					
	Aged <50		Aged ≥ 50		All ages		Aged <50		Aged ≥ 50		All ages	
	West (%)	East (%)	West (%)	East (%)	West (%)	East (%)	West (%)	East (%)	West (%)	East (%)	West (%)	East (%)
Head and neck	360 (11)	76 (9)	1222 (22)	233 (16)	1582 (18)	309 (13)	367 (6.5)	105 (9)	1560 (19)	355 (19)	1927 (14)	460 (15)
Trunk	1449 (45)	453 (56)	2275 (40)	776 (52)	3724 (42)	1229 (53)	1227 (22)	399 (32)	954 (12)	383 (20)	2181 (16)	782 (25)
Upper limb	573 (18)	96 (12)	875 (16)	174 (12)	1448 (16)	270 (12)	1008 (18)	185 (15)	1422 (18)	281 (15)	2430 (18)	466 (15)
Lower limb	653 (20)	120 (15)	914 (16)	226 (15)	1567 (18)	346 (15)	2781 (49)	495 (40)	3738 (46)	819 (43)	6519 (47)	1314 (42)
Other	14 (0.4)	7 (0.9)	27 (0.5)	4 (0.3)	41 (0.5)	11 (0.5)	44 (0.8)	12 (1.0)	60 (0.7)	12 (0.6)	104 (0.8)	24 (0.8)
NOS	183 (5.7)	62 (7.6)	328 (5.8)	80 (5.4)	511 (5.8)	142 (6.2)	251 (4.4)	41 (3.3)	373 (4.6)	64 (3.3)	624 (4.5)	105 (3.3)
Total (100%)	3232	814	5641	1493	8873	2307	5678	1237	8107	1914	13785	3151
	χ^2 :48.5, df=5, p<0.001¶		χ^2 :73.1, df=5, p<0.001¶		χ^2 :107.6, df=5, p<0.001¶		χ^2 :80.3, df=5, p<0.001¶		χ^2 :96.3, df=5, p<0.001¶		χ^2 :157.3, df=5, p<0.001¶	

¶: χ^2 testing the null hypothesis that the body site distribution is equal in Western and Eastern Europe.

In all age groups, most melanomas were found on intermittently exposed body sites (trunk, upper limbs and lower limbs). In older people there were more melanomas on the head and neck, and relatively fewer on the trunk, than in younger people (table 2). The difference between the younger and older age groups was the most pronounced in western European females: in the under-50 year group only 6.4% of cases had a melanoma on the head and neck, compared with 19% in the group 50 years and older. In eastern Europe, the differences between younger and older age groups were similar, but less pronounced.

In eastern Europe melanomas were slightly thicker in the north than in the south, especially in males and females under 50 years of age; in western Europe no difference was observed in mean thickness between the north and the south, or in any subgroup. Thicker melanomas occurred in patients 550 years old in western Europe; males had thicker melanomas than females within the same region and age group except for those under the age of 50 years in eastern Europe (table 3). The Breslow thickness was less for females, for those at younger ages, for those living at higher latitudes (i.e. more northerly) in western Europe and having a trunk melanoma, whereas this fact pertained to living at lower latitudes (more southerly) in eastern

Table 3: Mean Breslow thickness1 (and 95% confidence interval) by region and age.

	Aged < 50		Aged ≥ 50	
	North[2]	South[2]	North	South
Males				
Eastern Europe	3.47 (2.84;4.20)	2.26 (1.92;2.65)	4.10 (3.63;4.62)	3.40 (2.99;3.84)
Western Europe	1.48 (1.42;1.55)	1.51 (1.33;1.70)	1.87 (1.82;1.94)	2.01 (1.84;2.21)
Females				
Eastern Europe	3.36 (2.91;3.86)	2.33 (2.03;2.67)	3.14 (2.80;3.51)	2.52 (2.26;2.81)
Western Europe	1.22 (1.18;1.25)	1.24 (1.13;1.36)	1.72 (1.67;1.77)	1.68 (1.54;1.83)

[1] Mean Breslow thickness was computed using a log-transformation
[2] North: >=49.1° N , South <49.1° N

Table 4: Size and direction of the effect (t-values) of the multivariate models to predict the log of (Breslow thickness+1).

		Western Europe t-value# (n=11,598)	Central Europe t-value# (n=1,117)
Age (continuous)		23.83**	4.75**
Year of diagnosis		-3.22*	0.48
Latitude		-14.00**	4.43**
Sex[1]		-10.81**	-3.56*
Site	Trunk (ref)		
	Head and neck	1.54	0.16
	Upper limb	0.84	1.44
	Lower limb	4.92**	0.82
	Other	2.66*	0.42
R^2 (%explained variance)		7.4	5.5

t-value: testing the hypothesis of the coefficient being zero: a negative number indicates a 'protective' effect with increasing values (per unit) of the variable, a positive number a 'increase in risk', * $p < 0.05$, ** $p < 0.0001$, [1] male is reference category, [2] west=reference category

Europe (table 4). The likelihood of having a thicker melanoma decreased with increasing year of diagnosis only in the west. Divergent latitude effects on Breslow thickness were found (table 4). The highest risk of a thick melanoma was at a high latitude (north) in eastern Europe, whereas in western Europe the highest risk was at a low latitude (south). The risk of a thick melanoma was similar for all sites in eastern Europe and highest for the lower limbs in the west. Cases with an unknown Breslow thickness were most often of unknown histology (55% of cases in western Europe; 44% in eastern Europe), making it impossible to make any firm statement about the real histological distribution. There was a tendency for relatively more NM in eastern Europe and more SSM in the west (table 5).

Discussion

We analysed population-based cancer registry data from a total of 28,117 incident melanoma cases in Europe during the period 1978–1992. Differences in the characteristics of melanoma emerged between people from eastern and western Europe, people older and younger than 50 years, and between males and females. On analysing the trends in incidence and mortality of cutaneous malignant melanoma in eastern and western Europe, a striking difference in pattern was observed. In eastern Europe there was a south:north gradient in incidence, with the highest rates in the south. In western Europe, this correlation was inverted, with more melanomas in the north. In other continents, melanoma rates in Caucasian populations are generally highest in regions closest to the Equator [9].

Table 5: Histological subtype of cases with missing information on Breslow thickness

	SSM	NM	other	NOS
Eastern Europe	2385 (22%)	1365 (12%)	1277 (12%)	6034 (55%)
Western Europe	441 (10%)	1039 (24%)	987 (23%)	1874 (44%)

SSM: superficial spreading melanoma, NM: nodular melanoma, Other: other, specified type of melanoma; NOS: unspecified histological type of melanoma

The inverse gradient in the west of Europe has been observed before [10] and has been attributed to differences in skin type, with very light-skinned people in northern Europe and populations with much more pigmentation in the south. Our findings confirm the inverse association with latitude for western, but not eastern, Europe, although the skin-type distribution from north to south in eastern Europe is probably similar to that in western Europe. It is therefore unlikely that the observed differences could be due to differences in skin phototype. The difference between the north of eastern Europe and the north of western Europe is most likely due to differences between the people of the two regions in their opportunities for intermittent sunlight exposure during foreign holidays and recreational activities. Populations in north-west Europe became very prosperous during the 1960s and could afford to go on holidays to sunny areas. M:I ratios were higher in eastern Europe and in the southern parts of western Europe, indicating a worse survival in these areas. The M:I ratio was low in north-west Europe, where incidence rates are high; this is probably related to improved survival in this region due to detection at favourable stages.

The regression lines for eastern Europe (fig. 1b) were shifted to the left compared to the observed M:I ratios of the relevant registries, due to the weighing by registry size. The two largest registries, Eastern Germany (population: 16,648,000) and Czech Republic (population: 10,342,000), exhibited a relatively low M:I ratio compared to the other eastern European countries. In eastern Europe, relatively more melanomas were found on the trunk, especially in females. The frequency on the limbs was lower in eastern Europe; frequencies on the other body sites were similar for eastern and western Europe. We compared the body-site distribution of melanomas in the two age categories. In people of 50 years and older, relatively more melanomas occurred in the head and neck area than in the younger age group, in which melanomas were more prevalent on the trunk (both regions) and the lower limb (western Europe). It is generally believed that intermittent sun exposure has a greater potential for producing melanoma than continuous exposure, although at older ages melanoma is more common on body sites with continuous sun exposure [11]. Head-and-neck melanomas are thought to be affected by chronic exposure to ultraviolet light, in contrast to melanomas on the trunk, upper and lower limbs, where intermittent sun exposure is thought to be the risk factor.

Melanomas in eastern Europe were on average much thicker than those diagnosed in western Europe (mean difference 1.38 mm) and appeared relatively more often on the trunk. A difference of this magnitude results in substantial differences in survival rates [6]. Moreover, SSM, which is generally associated with thin lesions and a good prognosis, seemed to be more prevalent in western Europe, although firm statements about the histological distribution are not possible. Predictors of a thick melanoma differed between eastern and western Europe. Age and male sex were associated with thicker melanomas in both regions. In eastern Europe, the highest risk of a thick melanoma was for those living in the north; in western Europe this was the case for those living in the south. Breslow thickness had decreased over time only in western Europe. Awareness of the risks of suspected skin lesions may have been associated with a decline in Breslow thickness in western Europe. Since the early 1980s increasing attention has been paid in north-west Europe to informing the population about the

risks of sunbathing, the need to inspect the skin for suspect lesions, and the early detection of melanoma [12-18]. These campaigns were aimed both at preventing melanoma development and increasing the proportion of cases detected at early, favourable stages of the disease. A greater awareness is also expected in areas of high incidence, such as north-west Europe. To the best of our knowledge, few or no prevention and awareness campaigns have been organised in southern and eastern Europe and the incidence in these regions is relatively low, which probably explains why melanomas diagnosed in later years in western Europe were on average thinner, and people living at lower latitudes had a higher risk of having a thick melanoma. southern European populations exhibited lower incidence rates than those in the north, but the lesions were on average thicker. By contrast, people living in the north of eastern Europe were at higher risk of developing thick melanomas, corresponding with the overall melanoma risk, most probably due to their lighter skin type, and the lack of prevention or awareness campaigns. This could also explain why Breslow thickness had not decreased over time in eastern Europe. In the period 1978–1992, melanomas in eastern Europe generally had less favourable characteristics in terms of Breslow thickness and body-site distribution than those in western Europe, possibly explaining differences in survival between these regions. Host characteristics such as skin type will have had a similar distribution in both regions, making it unlikely that skin type could account for the observed differences between eastern and western Europe. The difference in Breslow thickness may also be due to a delay in diagnosis in eastern Europe, because of suboptimal functioning of the dermatological services.
Alternatively, there might be an 'over'-diagnosis of thin melanomas in western Europe, causing a decrease in the average and median Breslow thickness. Several studies have found a marked increase in the incidence of thin melanomas with stable rates of thick melanomas in western European countries [19-21]. Moreover, these increases were not accompanied by similar increases in mortality. These observations have suggested the existence of two types of melanoma, possibly with different epidemiological features: thin (mainly SSM) and thick (mainly NM) melanomas [22]. Some of the thin melanomas might be clinically harmless and are not likely to cause death if untreated [19]. This possibility would explain why mortality rates are stabilising in many western European countries and M:I ratios are favourable, while incidence rates are still increasing [4].
If they indeed exist, these thin, harmless melanomas may be diagnosed more often than before in western European countries due to prevention campaigns, which are usually preceded by an increased awareness in the population, and possibly there has been an increase in some unknown aetiological risk factor. The lower median Breslow thickness in western Europe might be due to large increases in the number of these thin, relatively harmless melanomas (often of SSM type), while the number of thick melanomas (often NM) remains stable.

To summarise, in the period 1978–1992, eastern European populations had a low incidence of melanoma and high M:I rates. The Breslow thickness did not decrease over time as was the case in western Europe. If eastern European populations are adopting a western European lifestyle, with more opportunities for intermittent sun exposure, this will most likely be reflected in increasing incidence rates for melanoma,

as has been happening in western Europe in the past decades. If these increases are not accompanied by decreases in case-fatality rates, this will result in large numbers of deaths from melanoma in eastern Europe. Action must be taken for the secondary prevention of (more and thinner) melanomas in eastern Europe in order to detect them at early stages and improve survival.

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Appendix
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Chapter 4.2

Monitoring stage-specific trends in melanoma incidence across Europe reveals the need for more complete information on diagnostic characteristics.

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Summary

Aim: Cutaneous malignant melanoma has been characterised by rapid and steady increases in incidence and mortality in white populations. Some reports mentioned declining trends in the mean thickness of these tumours, but other studies suggested a stable incidence of thick melanomas. The aim of this study was to describe the stage distribution of melanomas across Europe, with particular reference to temporal trends.
Methods: Twenty-three cancer registries provided data sets containing information on stage and histology, 21 of which were used for a general description and nine for trends analyses.
Results: Despite a preponderance of missing data, interesting patterns emerged: a less favourable stage distribution in populations with relatively low incidence, but high case-fatality rates, and a favourable trend in stage and histology distribution over time, including a shift from later to earlier stages in recent years.
Early detection campaigns raising awareness for thin lesions can potentially improve melanoma survival rates. Monitoring of stage-specific trends in melanoma incidence can assess the impact of such interventions. This paper demonstrates the potential utility of high quality, timely cancer registry data in pursuing such public health objectives and addresses the need for more complete information on diagnostic features of melanoma patients. This will allow more informative evaluations of preventive strategies.

Introduction

In a previous study, exploring time trends in cutaneous malignant melanoma (melanoma) incidence and mortality across Europe, we observed that the patterns of incidence of, and mortality from melanoma have changed in the last 50 years, with rising trends first emerging in Scandinavia and the UK, then spreading to western, southern and eastern Europe, each with an approximate delay of one decade. In populations with high melanoma incidence (mainly Northern European countries), the mortality rates were not much higher than in those with relatively low incidence. It was hypothesized that this is an effect of awareness and early detection. Increased recognition of suspected lesions could have contributed to the increases in incidence without causing increases in mortality [1].

Since the mid-1980s, primary and secondary prevention campaigns have been organised in north-western Europe, raising the level of awareness of skin cancer in both professional health care workers and the general population. They have probably resulted in higher rates of detection of melanomas at earlier stages and trends towards thinner lesions were observed in European cancer registries [2-9].

This would imply more favourable prognostic indicators: an earlier stage, a more favourable histology (more superficial spreading melanomas (SSM), fewer nodular melanomas (NM)), and higher detection rates of lesions on body sites that are more difficult to inspect, such as the trunk, mainly the back.

Methods

Registries

Cancer registries, members of the European Network of Cancer Registries (ENCR), were asked to provide a temporal data series containing information on the stage (TNM stage, Breslow thickness, Clarke stage and/or registry-specific stage) and/or histology distribution of all melanoma of the skin registrations diagnosed in their catchment populations for a subsequent analysis of patterns in melanoma incidence across Europe. Twenty-three registries responded positively, of which 21 were included in our analyses. The inclusion criterion for the cross-sectional inventory of melanoma characteristics across Europe was to have sufficient information on stage (i.e., <50% cases with missing stage information (Tx)). Data from two of the 23 registries were not included in our analyses because they had limited data on stage (more than 50% missing in recent years).

The data series of nine registries was of sufficient duration to warrant an analysis of trends in melanoma features, registries with <10 years of observation (n=5) were excluded. To lessen the possibility of erroneous interpretation registries with <100 melanoma cases per year (n=6), and <50% of cases with stage information (n=2) were also excluded.

We also compared our incidence data with corresponding survival statistics derived from published data on the registries/countries concerned [10, 11].

Data

Only invasive melanomas were included in the analyses. All records were checked for mismatches between histology and topography codes. Where doubts existed about the validity of the data, the case was excluded (n=222 (0.3%)).

Stratification by stage was based on the T classification that divides melanoma patients into 5 groups, described in table 1. Data coded according to the TNM classification, Breslow thickness, Clark level of invasion, and/or registry-specific coding systems were all recoded into this classification. Where several classification variables were available, information from each source was used to determine the stage. If thickness and level of invasion did not coincide with the T classification, the more 'severe' code was used (e.g. if the Breslow thickness was low, but Clark level indicated invasive melanomas, the latter was used to determine the stage).

Table 1: The T classification

Stage	Breslow tumour thickness	Clarke level of invasion	T (TNM)
T1	≤ 0.75 mm	II	T1
T2	> 0.75 mm but ≤ 0.75 mm	III	T2
T3	>1.50 mm but ≤ 4.0 mm	IV	T3
T4	> 4 mm	V	T4
Tx	Missing	Missing	Missing

Analysis

Age-standardised incidence rates per 100,000 person-years were calculated using the European standard population by stage, histology, and body site. Due to small numbers, and the random variation thereby generated, it was not feasible to stratify further by age. We tried using log-linear approaches, modelling incidence rates with age, stage and period as main effects, testing the effects of interaction between these three variables for each registry, by sex. As the models generated offered little further insight into the rather complex temporal variations observed, we decided not to present the results of these analyses in this publication. Thus we present here the trends according to these clinical features, using three-year aggregates to allow some smoothing of the rates.

Results

Data on 36,253 male and 47,703 female cutaneous malignant melanoma cases were included in the study. The characteristics by registry for the latest 3 years of observation are listed in table 2. Percentages of Tx varied between 0 and 60%, median age at diagnosis between 51 and 68 years. The highest incidence rates were found in Switzerland, Czech Republic and the Netherlands in males and in Switzerland, the Netherlands and Italy/Northern Ireland in females. Women had more favourable features than men, being younger (median age 56 in women versus 59 in men), having fewer stage T4 melanomas (7.7% versus 11.0%, $p<0.0001$) and nodular melanomas (13.8% versus 16.2%, $p<0.0001$) than males.

Table 2a: Characteristics by registry in the last 3 years of the respective registration periods*: males

Registry	period	EASR[1]	N	Median Age + range[2]	5 yr rel. surv. [3]	Stage T1 n (%)	T2 n (%)	T3 n (%)	T4 n (%)	Tx n (%)
Canary Islands	1995-1997	5,1	87	62 47;72		6 (7)	16 (18)	25 (29)	15 (17)	25 (29)
Malta	2000-2002	8,8	51	60 50;71		11 (22)	7 (13)	10 (20)	2 (4)	21 (41)
Navarra	1997-1999	8,5	76	60 47.5;73	73.4	9 (12)	20 (26)	24 (32)	6 (8)	17 (22)
Rioja	1995-1997	4,8	29	62.5 36;74	73.4	7 (24)	8 (28)	11 (38)	2 (7)	1 (3)
Tuscany	1997-1999	11,1	232	56 42;71	71.7	78 (34)	26 (11)	49 (21)	16 (7)	63 (27)
Turin	1996-1998	11,1	182	59 48;70	71.7	45 (25)	79 (43)	20 (11)	6 (3)	32 (18)
Slovenia	1998-2000	11,1	336	59 45;71	60.6	62 (18)	119 (35)	90 (27)	32 (10)	33 (10)
Ticino	2000-2002	21,8	88	63 52.5;74.5	83.0	18 (21)	27 (31)	27 (31)	8 (9)	8 (9)
St Gall-Appenzell	1997-1999	20,9	160	60 50;70	83.0	25 (16)	48 (30)	41 (26)	17 (11)	29 (18)
Saarland	1998-2000	9,8	177	60 46;69	77.4	57 (32)	28 (16)	27 (15)	15 (8)	50 (28)
Cracow	1997-1999	5,8	62	65 54;69	55.8	12 (19)	16 (26)	15 (24)	16 (26)	3 (5)
Czech Republic	1998-2000	13,0	1937	62 50;71	60.3	726 (37)	380 (20)	410 (21)	237 (12)	177 (9)
Flanders	1997-1999	5,3	508	59 46;70		69 (14)	79 (16)	103 (20)	50 (10)	207 (41)
East Anglia	1998-2000	9,1	406	60 50;70	74.0	210 (52)	109 (27)	63 (16)	12 (3)	12 (3)
Netherlands	1996-1998	12,0	2815	54 42;67	79.2	450 (16)	424 (15)	595 (21)	321 (11)	1025 (36)
Münster	1999-2001	9,5	398	61 45;70	77.4	87 (22)	109 (27)	106 (27)	25 (6)	71 (18)
Bremen	1999-2000	8,8	70	63 55;74	77.4	22 (31)	6 (9)	12 (17)	6 (9)	24 (34)
Northern Ireland	1999-2001	9,4	221	60 44;72	53.5	36 (16)	45 (20)	83 (38)	15 (7)	42 (19)
Latvia	2000-2002	3,9	127	62 48;72		41 (32)	53 (42)	19 (15)	7 (6)	7 (6)
Stockholm	2000-2002	10,8	322	57 44;73	84.6	137 (43)	104 (32)	61 (19)	20 (6)	0
Thames	1998-2000	7,9	1651	62 48;74	74.0	250 (15)	312 (19)	389 (24)	265 (16)	435 (26)

* Except Bremen: only 2 years of observation
[1] EASR: European Age Standardised Rates per 100,000 person-years;
[2] Range= interquartile range;
[3] Relative survival: national (not regional) data based on Eurocare III (cases diagnosed between 1990-1994) are given [11], except for Northern Ireland [10];

Table 2a: (continued)

Registry	Histology					Site					
	NM N (%)	SSM N (%)	LMM N (%)	Other N (%)	NOS[4] N (%)	H&N[5] N (%)	Trunk N (%)	Arm N (%)	Leg N (%)	Other N (%)	NOS[4] N (%)
Canary Islands	19 (22)	15 (17)	3 (3)	10 (11)	40 (46)	11 (13)	22 (25)	13 (15)	14 (16)	12 (14)	15 (17)
Malta	9 (18)	26 (51)	2 (4)	3 (6)	11 (22)	9 (18)	25 (49)	6 (12)	7 (14)		4 (8)
Navarra	19 (25)	30 (39)	6 (8)	9 (12)	12 (16)	18 (24)	38 (50)	7 (9)	11 (14)		2 (3)
Rioja	3 (10)	1 (3)	2 (7)	1 (3)	22 (76)	4 (14)	4 (14)	3 (10)	15 (52)		3 (10)
Tuscany	22 (9)	130 (56)	7 (3)	24 (10)	49 (21)	23 (10)	118 (51)	27 (12)	37 (16)	1 (0,4)	26 (11)
Turin	10 (5)	140 (77)	7 (4)	1 (1)	24 (13)	18 (10)	96 (53)	28 (15)	28 (15)	1 (0,6)	11 (6)
Slovenia	61 (18)	57 (17)	12 (4)	26 (8)	180 (54)	45 (13)	193 (57)	40 (12)	45 (13)		13 (4)
Ticino	12 (13)	48 (55)	2 (2)	6 (7)	20 (23)	11 (13)	41 (47)	16 (18)	17 (19)	1 (1)	2 (2)
St Gall-Appenzell	25 (16)	90 (56)	14 (9)	5 (3)	26 (16)	36 (23)	64 (40)	39 (24)	21 (13)		
Saarland	29 (16)	66 (37)	5 (3)	11 (6)	66 (37)	26 (15)	66 (37)	33 (19)	26 (15)		26 (15)
Cracow	1 (1)		1 (2)		58 (97)	8 (13)	34 (55)		12 (19)		9 (13)
Czech Republic	564 (29)	482 (25)		849 (44)[6]	42 (2)	231 (12)	1087 (56)	292 (15)	204 (11)	8 (0,4)	115 (6)
Flanders	51 (10)	128 (25)	14 (3)	18 (4)	297 (58)	81 (16)	114 (22)	49 (10)	70 (14)		194 (38)
East Anglia					406 (100)	92 (23)	156 (38)	87 (21)	58 (14)		13 (3)
Netherlands	484 (17)	1305 (46)	199 (7)	132 (5)	695 (25)	543 (19)	1214 (43)	466 (17)	439 (16)	2 (0,1)	151 (5)
Münster	31 (8)	175 (44)	43 (11)	10 (3)	139 (35)	61 (15)	110 (28)	61 (15)	59 (15)		107 (27)
Bremen	22 (31)	24 (34)	4 (6)	6 (9)	14 (20)	11 (16)	36 (51)	9 (13)	9 (13)		5 (7)
Northern Ireland	42 (19)	82 (37)	26 (12)	9 (4)	62 (28)	58 (26)	70 (32)	35 (15)	33 (15)		25 (11)
Latvia					127 (100)	24 (19)	71 (56)	12 (9)	18 (14)	1 (0,8)	1 (0,8)
Stockholm	32 (10)	213 (66)	23 (7)	8 (2)	46 (14)						
Thames	178 (11)	250 (15)	47 (3)	49 (3)	1127 (68)	310 (19)	608 (37)	282 (17)	251 (15)	13 (0,8)	187 (11)

[4] Not otherwise specified
[5] Head and neck;
[6] Including LMM, not separately registered

Table 2b: Characteristics by registry in the last 3 years of the respective registration periods*: females

Registry	period	EASR[1]	N	Median Age + range[2]	5 yr rel. survival[3]	Stage T1 n (%)	T2 n (%)	T3 n (%)	T4 n (%)	Tx n (%)
Canary Islands	1995-1997	5,8	116	60.5 44-72		19 (16)	29 (25)	29 (25)	11 (9)	28 (24)
Malta	2000-2002	6,6	43	55 45-70		14 (33)	6 (14)	5 (12)	1 (2)	17 (40)
Navarra	1997-1999	6.7	64	58.5 46-73	89.6	14 (22)	16 (25)	10 (16)	4 (6)	20 (31)
Rioja	1995-1997	4,2	25	62.5 36-74	89.6	1 (4)	6 (24)	10 (40)	8 (32)	0
Tuscany	1997-1999	12,3	289	56 42-71	82.8	94 (33)	58 (20)	55 (19)	18 (6)	64 (22)
Turin	1996-1998	11,4	208	58 43-70	82.8	54 (26)	84 (40)	22 (11)	5 (2)	43 (21)
Slovenia	1998-2000	10,2	376	59 45-71	70.1	57 (15)	131 (35)	115 (31)	43 (11)	30 (8)
Ticino	2000-2002	18,1	110	56 42-72	91.4	29 (26)	41 (37)	24 (22)	7 (6)	9 (8)
St Gall-Appenzell	1997-1999	19,3	176	55 40-75	91.4	21 (18)	44 (25)	39 (22)	14 (8)	47 (27)
Saarland	1998-2000	7,5	158	60 44-72	89.6	46 (29)	30 (19)	22 (14)	10 (6)	50 (32)
Cracow	1997-1999	6,1	85	57 42-69	58.8	18 (21)	25 (29)	32 (38)	9 (11)	1 (1)
Czech Republic	1998-2000	11,1	2036	58 46-72	77.9	843 (41)	452 (22)	402 (20)	183 (9)	150 (7)
Flanders	1997-1999	8,1	849	56 42-70		140 (16)	157 (18)	143 (17)	35 (4)	374 (44)
East Anglia	1998-2000	9,3	452	55 45-70	85.8	295 (65)	94 (21)	47 (10)	5 (1)	11 (2)
Netherlands	1996-1998	15,2	3924	51 39-67	88.5	846 (22)	692 (18)	672 (17)	267 (7)	1447 (37)
Münster	1999-2001	11,1	504	51.5 35-68	89.6	124 (25)	155 (31)	132 (26)	18 (4)	75 (15)
Bremen	1999-2000	11,8	101	58 43-72	89.6	28 (28)	21 (21)	10 (10)	4 (4)	38 (38)
Northern Ireland	1999-2001	12,3	340	58 39-72.5	53.5	49 (14)	67 (20)	143 (42)	23 (7)	58 (17)
Latvia	2000-2002	5,6	275	64 52-75		84 (31)	105 (38)	54 (20)	24 (9)	8 (3)
Stockholm	2000-2002	10,3	335	61 48-72	91.4	127 (38)	90 (27)	81 (24)	37 (11)	0
Thames	1998-2000	8,9	2182	60 44-75	85.8	411 (19)	508 (23)	386 (18)	246 (11)	631 (29)

* Except Bremen: only 2 years of observation

[1] EASR: European Age Standardised Rates per 100,000 person-years;

[2] Range= interquartile range;

[3] Relative survival: national (not regional) data based on Eurocare III (cases diagnosed between 1990- 1994) are given [11], except for Northern Ireland [10];

Table 2b: (continued)

Registry	Histology					Site					
	NM	SSM	LMM	Other	NOS[4]	H&N[5]	Trunk	Arm	Leg	Other	NOS[4]
	N	N	N	N	N	N	N	N	N	N	N
	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Canary	21	23	2	18	52	13	16	27	32	4	24
Islands	(18)	(20)	(2)	(16)	(45)	(11)	(14)	(23)	(28)	(3)	(21)
Malta	12	16	1	2	12	1	13	10	16		3
	(28)	(37)	(2)	(5)	(28)	(2)	(30)	(23)	(37)		(7)
Navarra	14	25	4	8	13	11	13	13	25		2
	(22)	(39)	(6)	(13)	(20)	(17)	(20)	(20)	(39)		(3)
Rioja	11		3	1	10	4	8	5	5		3
	(44)		(12)	(4)	(40)	(16)	(32)	(20)	(20)		(12)
Tuscany	15	173	6	36	59	21	82	27	134	1	24
	(5)	(60)	(2)	(12)	(20)	(7)	(28)	(9)	(46)	(0,4)	(8)
Turin	28	128	13	7	32	19	51	26	91	1	20
	(13)	(62)	(6)	(3)	(15)	(9)	(25)	(13)	(44)	(0,5)	(10)
Slovenia	63	64	25	44	180	66	113	53	132		12
	(17)	(17)	(7)	(12)	(48)	(18)	(30)	(14)	(35)		(3)
Ticino	11	68	2	4	25	15	25	21	43	2	3
	(10)	(62)	(2)	(4)	(23)	(14)	(23)	(19)	(39)	(2)	(4)
St Gall-	20	96	22	6	32	48	25	46	57		
Appenzell	(11)	(55)	(13)	(3)	(18)	(27)	(14)	(26)	(32)		
Saarland	19	60	17	11	51	24	30	26	55		23
	(12)	(38)	(11)	(7)	(32)	(15)	(19)	(16)	(35)		(15)
Cracow			5		80	17	33	3	27		5
			(6)		(94)	(20)	(39)	(4)	(32)		(6)
Czech	538	601		864	33	298	638	383	622	6	89
Republic	(26)	(30)		(42)[6]	(2)	(15)	(31)	(19)	(31)	(0,3)	(4)
Flanders	65	250	27	22	485	86	93	72	224	1	373
	(8)	(29)	(3)	(3)	(57)	(10)	(11)	(8)	(26)	(0.1)	(44)
East Anglia					452	55	81	82	224		10
					(100)	(12)	(18)	(18)	(50)		(2)
Netherlands	517	2015	251	171	970	529	966	801	1484	1	143
	(13)	(51)	(6)	(4)	(24)	(13)	(25)	(20)	(38)	(0)	(4)
Münster	41	244	43	7	169	55	98	73	185		93
	(8)	(48)	(9)	(2)	(34)	(11)	(19)	(14)	(37)		(18)
Bremen	26	46	5	4	20	11	23	22	39		6
	(26)	(46)	(5)	(4)	(20)	(11)	(23)	(22)	(39)		(6)
Northern	57	159	24	11	89	55	43	68	135		39
Ireland	(17)	(47)	(7)	(3)	(26)	(16)	(13)	(20)	(40)		(11)
Latvia					275	48	66	52	102	1	6
					(100)	(17)	(24)	(19)	(37)	(0,4)	(2)
Stockholm	57	201	23	7	47						
	(17)	(61)	(7)	(2)	(14)						
Thames	213	426	67	45	1431	296	340	410	914	9	213
	(10)	(20)	(3)	(2)	(66)	(14)	(16)	(19)	(42)	(0,4)	(10)

[4] Not otherwise specified
[5] Head and neck;
[6] Including LMM, not separately registered

Age-adjusted incidence rates increased over time in Slovenia, the Czech Republic, Latvia, Münster, the Netherlands, East Anglia (males) and Northern Ireland (males) and stabilised in Thames, Stockholm, East Anglia (females) and Northern Ireland (females). In northern Europe (countries north of Switzerland), females had higher rates than males; in southern Europe incidence rates were similar for both sexes, or higher in males (table 2a and 2b).

The stage distribution varied substantially across registries, although there were large numbers of unknown stage (Tx). However, of the known stages, the distribution varied from predominantly T1/T2, with few T3/T4 melanomas (Bremen, Czech Republic, East Anglia, Latvia, Malta (females), Saarland, Stockholm, Torino), to a more or less equal distribution of T1-T3 with a lower T4 (Flanders (females), Malta (males), Münster, Netherlands (females), Slovenia (males), St Gall Appenzell (females), Ticino, Tuscany). A high percentage of T3/T4 was found in males in Flanders, the Netherlands, St Gall Appenzell and Ticino, in Slovenian females, and in both sexes in the Canary Islands, Cracow, Navarra, Northern Ireland, Rioja and Thames (table 2a and 2b).

In the period 1995-2000, cases with a T4 melanoma at diagnosis were older than cases with other known stages (table 3). Across the participating cancer registries, advanced stage melanomas were seen more frequently in males and were often NM. The thinner melanomas, predominantly SSM, were found more frequently in females (table 3).

As data on histology and body site were largely missing for stage Tx it is impossible to make any definite statements on prevailing histological subtype or body site among the missing stages. Over the whole period, cases with missing information on stage were slightly older (median age 60 (IQ range 45-72)) than those with information on stage (median age 56 (43-69)). The sex distribution was similar, 58% females in Tx versus 56% females in the other T. Amongst the Tx there were less NM (7% versus 19%) and SSM (16% versus 34%) and more melanomas with unspecified or other histology (77% versus 47%), of which they were more often LMM (6% versus 3%). Cases with Tx often did not have a specified topography (20% in Tx versus 3% in known T), occurred more often in the head and neck region (18% versus 15%) and less often on the trunk (21% versus 34%), upper and lower limbs (40% versus 48%) than known T.

The most prevalent observed histological type was SSM, but NM was equally frequent as or even more frequent than SSM in Czech Republic, Slovenia, Thames (males) and Bremen (males). In most registries, males had more NM than females.

The prevailing body sites of melanoma cases in Europe in females were the lower limbs (legs and hips) and the trunk in males. However, in Malta, Rioja, the Czech Republic, Cracow and Slovenia, trunk melanomas were quite common in females (≥30% of melanomas).

Table 3: Characteristics of different stages of melanomas, all registries, 1995-2000

		T1	T2	T3	T4	Tx	All (total)
Total n		9446	7730	7477	3395	8550	36598
Age	median age (IQ range)	53 (41-66)	54 (42-67)	61 (47-73)	66 (52-76)	60 (46-73)	58 (44-71)
Sex	Males	3880 (41%)	3256 (42%)	3580 (48%)	1782 (53%)	3665 (43%)	16163 (44%)
	Females	5566 (59%)	4474 (58%)	3897 (52%)	1613 (48%)	4885 (57%)	20435 (56%)
Histology	NM	565 (6%)	947 (12%)	2298 (31%)	1260 (37%)	664 (8%)	5734 (16%)
	SSM	4339 (46%)	3167 (41%)	1840 (25%)	357 (11%)	2088 (24%)	11791 (32%)
	NOS+other	4542 (48%)	3616 (47%)	3339 (45%)	1778 (52%)	5798 (68%)	19073 (52%)
	(NOS*	2644 (28%)	2474 (32%)	2262 (30%)	1205 (36%)	4381 (51%)	12966 (35%)
	(LMM*	362 (4%)	215 (3%)	178 (2%)	48 (1%)	629 (7%)	1432 (4%)
Site	Head and neck	1203 (13%)	857 (11%)	1097 (15%)	578 (17%)	1544 (18%)	5279 (18%)
	Trunk	3261 (35%)	2546 (33%)	2304 (31%)	992 (29%)	1831 (21%)	10934 (30%)
	Arm & shoulder	1682 (18%)	1346 (17%)	1233 (16%)	499 (15%)	1214 (14%)	5974 (16%)
	Leg& hip	2332 (25%)	2192 (28%)	2166 (29%)	847 (25%)	2012 (24%)	9549 (26%)
	Other	12 (0.1%)	10 (0.1%)	19 (0.3%)	14 (0,4%)	52 (0.6%)	107 (0,3%)
	NOS	956 (10%)	779 (10%)	658 (9%)	465 (14%)	1897 (22%)	4755 (13%)

* Based on all registries except Czech Republic which has only information based on NM, SSM and other'

Trends

The proportion of Tx was relatively stable over time in a few registries, and trends could be cautiously interpreted: in the Czech Republic, the main increases have been in T1/T2 and in females, T4 have been decreasing. In Slovenia, Northern Ireland (females) and Thames (males), rates have been increasing in all stages except Tx. In Stockholm, increases were mainly in T1 until 1990, after which overall and stage-specific rates started to decline (figure 1 a-c). The stage distribution at diagnosis improved, with a stable incidence of advanced stage melanomas and an increase in early stage melanomas. Incidence rates of NM were stable over time in males and decreased in females, whereas rates of LMM increased sharply in females. Trends of SSM followed the pattern of the general increases in melanoma incidence in this period, increasing up to 1990, afterwards levelling off.

In the Thames and East Anglia registries, data are more difficult to interpret due to pervasive changes in trends in Tx melanomas, especially in East Anglia. At the end of the observed period the stage distribution in East Anglia seems quite favourable, with a large proportion of early stage melanomas, and few stage T4 melanomas in both males and females. In Thames, the numbers of cases with Tx were very high, making interpretation difficult. The strongest increases seem to have been in T1, with more moderate increases in T4 in females, with equal increases in all stages in males. The trends by histology in this cancer registry were mainly in SSM in females, with equal trends in NM and SSM in males. In most registries, trends by stage were more difficult (or impossible) to interpret due to considerable changes in the trends in Tx. Incidence rates of SSM were increasing strongest over time, trends of NM were levelling off in the Czech Republic, Münster, the Netherlands, Stockholm and Thames. Trends were generally upward for all body sites, with slightly steeper increases in melanomas of the trunk in both males and females in most registries (table 2a and 2b, figures A-F).

Discussion

We found differences in the features of melanoma across European cancer registry areas in terms of stage and histology, being slightly more favourable in northern and western European populations relative to those in southern and eastern Europe. Furthermore, more than 30% of the melanomas in females occurred on the trunk in Southern and eastern European cancer registries, a body site associated with unfavourable prognosis, whereas this percentage was between 10 and 20% in most other European registry areas. Such a phenomenon has been observed in eastern European women in the period 1978-1992 [12].

Historically, the highest observed melanoma incidence rates in Europe were found in the Nordic countries. In our data, however, incidence rates in Stockholm are high, but no longer amongst the three highest incidence rates, which were found in Switzerland, Czech Republic and the Netherlands in males and Switzerland, the Netherlands and Italy/Northern Ireland in females. This might be due to the fact that the rates have been stabilising in Stockholm, but are still increasing in other countries.

Early detection campaigns were expected to result in a (temporary) increase in melanoma incidence, with increases mainly in thin and SSM melanomas, later followed by a decrease in incidence rates. In Australia, where campaigns started earlier than in Europe, shifts towards thinner lesions and more SSM melanomas and less NM melanomas have been observed over time, accompanying improvements in melanoma survival [13]. The first prevention and early detection campaigns were organized in Europe in the late 1970s and mid 1980s, in Scandinavia [3] and the United Kingdom [14, 15]. Therefore, effects of these campaigns would be expected to appear earliest in these countries. In the Stockholm data, observations are in line with the expectations: an increase in incidence up to 1990, mainly in T1, followed by a levelling off and decrease of rates, with improving stage and histology distribution at diagnosis.

In the Netherlands and Germany, campaigns started in the late 1980s but screening effects were not observed: all stages of melanoma increased, with a relatively low number of T4 melanomas compared to T1-T3 and Tx and many SSM compared to NM. As we do not have trend data before 1989, it is difficult to say what the situation looked like before the introduction of the prevention campaigns. The decrease in the number of NM in the Netherlands and Münster could be an indication of increasingly favourable histology at diagnosis. One study looked at the effect of a preventive campaign carried out in 1989 in the coastal area of western Netherlands and observed a temporary increase in the incidence of mainly thin melanomas after the campaign [16].

To our knowledge, skin cancer prevention/awareness campaigns have not been organized in the 1980s and early 1990s in Latvia, Poland, Slovenia, and Northern Ireland. In Italy there were some local campaigns, of which one, organised in the Florence area, seems to have been successful in reducing mortality rates, especially amongst males [17].

For some countries, no survival data were available (Canary Islands, Flanders, Latvia, Malta).
Three out of four countries with a reported lower survival than the European average (Italy, Northern Ireland, Poland, Slovenia) showed a less favourable histology (Slovenia) or stage distribution (Cracow, Northern Ireland). Other registries with a seemingly unfavourable stage distribution however, reported good national survival rates (Netherlands males, St Gall Appenzell (Switzerland) males) [11]. This might be partly due to the large percentage of missing stages (26% Tx in St Gall Appenzell, 37% in the Netherlands); if they are predominantly early stages the stage distribution would in reality be a lot better than it appears to be from our data.

In countries where awareness campaigns were organised around the 1980s (Czech Republic, Germany, the Netherlands, Sweden, and the UK), the stage distribution became generally quite favourable: more T1 and T2 melanomas and relatively few T4 melanomas compared with the other known stages. However, Latvia demonstrates the same pattern, despite the absence of organised campaigns. Moreover, rates in Latvia were flat, showing no indications of rising incidence rates. A higher awareness of the disease appropriated to higher incidence is not a likely explanation for the trends in Latvia, given its incidence rates are relatively low. An alternative explanation is that after the collapse of the Soviet Union, more patients go to private hospitals, causing under-registration of melanoma cases.

Quality of the data
The quality of the cancer registries involved in this study varies. Details can be found in the latest volume of CI5 [18], which did not include data from Bremen, Münster and Rioja. The data from Bremen were not included in CI5 (generally covering 1993-97) as the years of registration submitted are for a later period (1999-2000), the data for the Münster cancer registry were not submitted for CI5. Rioja was not included in CI5 because at the time of compiling CI5 the population data for the relevant period were not yet available (J. Ferlay, personal communication).
Despite registries' concerted efforts to get complete registration, some degree of underregistration is almost inevitable [19-22]. Thin melanomas were probably more likely to be underreported in registries without pathology-based registration, causing underestimation of the number of stage 1 melanomas in this study.
The interpretation of the types of histology is hampered by the fact that one registry only delivered data coded as NM, SSM and 'other' whilst the other registries gave the codes by ICD (ICD-9, ICD-10 or ICD-O) and are therefore more detailed. The specification of the 'other' category (table 3) is therefore based only on the registries that contributed the full ICD coding for histology.

The problem of missing data
The interpretation of our data is hampered by the large number of cases with missing information on stage, histology and/or body site distribution. Earlier reports of the features of melanoma patients in European populations have been written [3-8, 23]. In one such study [8], data with missing information on stage, concerning 20% of the

cases, were excluded from the analyses. It is likely that their absence has incurred biases in the results.
Stang et al [5] decided to take the trends in unknown stages into account and interpreted their data with more caution. In other publications the percentage of missing information on Breslow thickness was not given [6, 7], but in one of them, 16% of data on Clarke level were missing [6]. Data on stage or Breslow thickness at diagnosis in South Wales and Stockholm seemed to be complete [3, 4].

Implications
Judging from the high percentages of stage T3 and T4 at time of diagnosis, much can still be gained by improving the early diagnosis of melanoma. The recent levelling off of rates in the high incidence countries are indicative of improving prospects in the future, particularly if observed changes in the stage at diagnosis result in a continual process towards thinner lesions.
As melanoma features are less favourable in southern and eastern European countries and in males, prevention campaigns targeted at specific populations can potentially improve melanoma survival rates substantially. The degree of early detection in the general population can be measured by the cancer registry thus indicating the room for improvement in the thickness distribution [24]. It is therefore important to monitor the stage-specific trends in melanoma at regional, national and European level. This paper demonstrates the potential utility of high quality, timely cancer registry data in pursuing these public health objectives, but more fundamentally, addresses the urgent need for more complete information on diagnostic characteristics of melanoma patients. Such a development will then allow more informative evaluation of strategies aimed at prevention and early diagnosis of melanomas.

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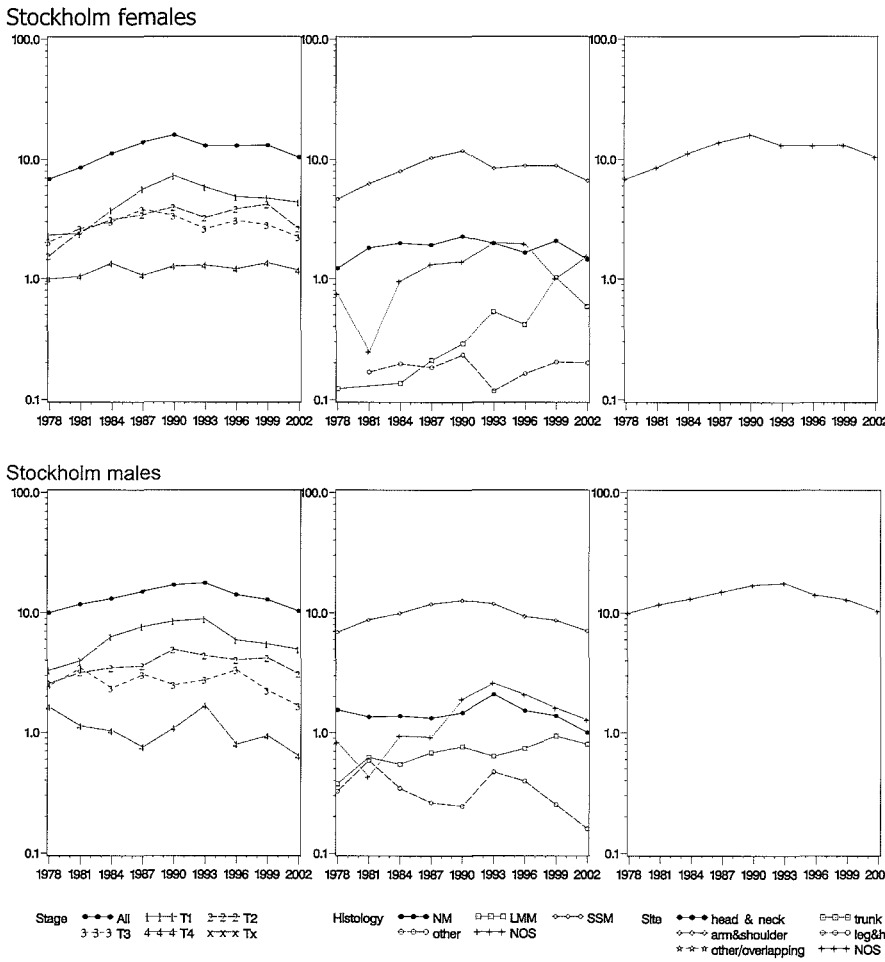
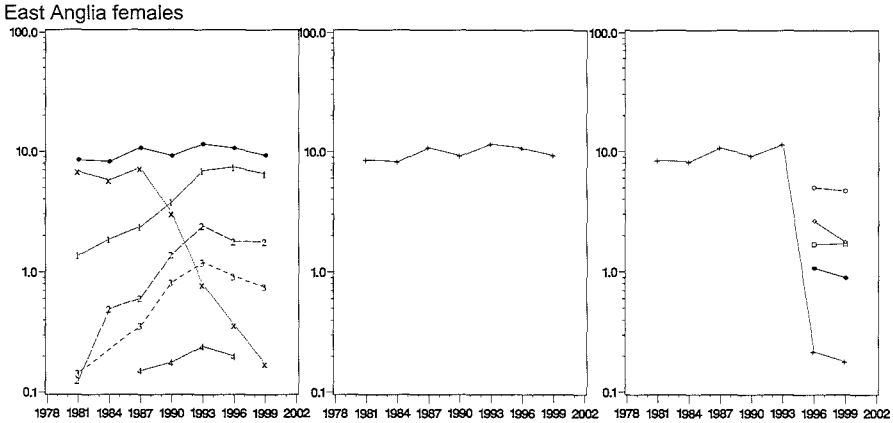


Figure 1a: Trends by stage, histology and site in Stockholm

East Anglia females



East Anglia males

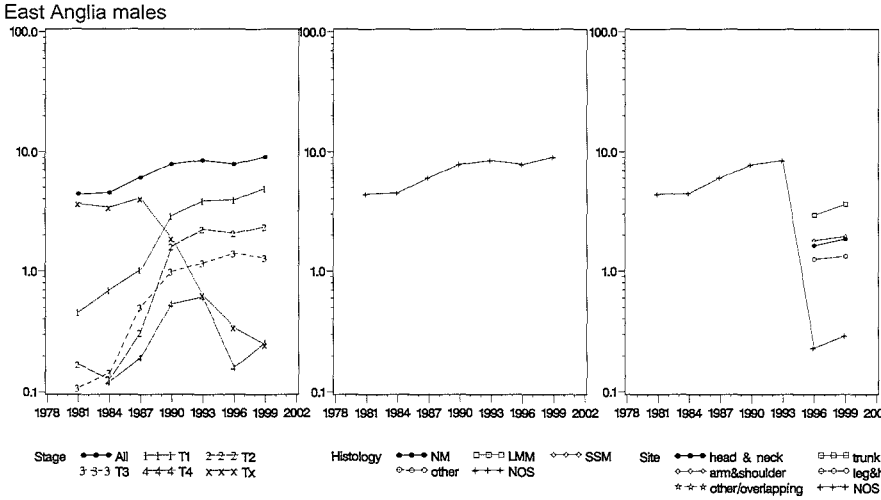
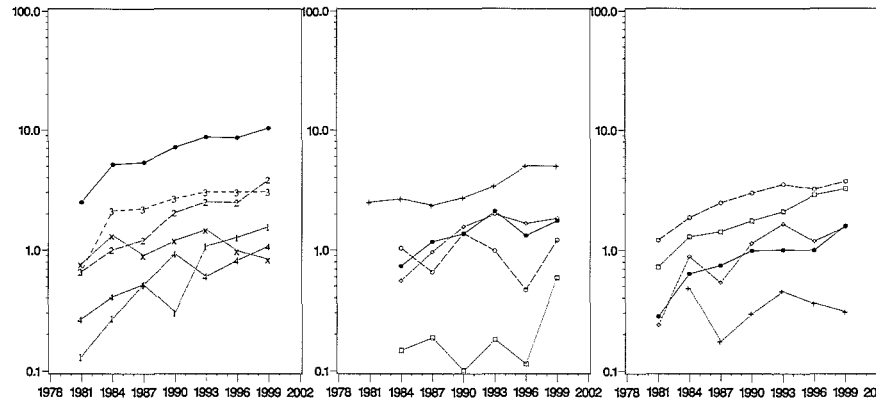
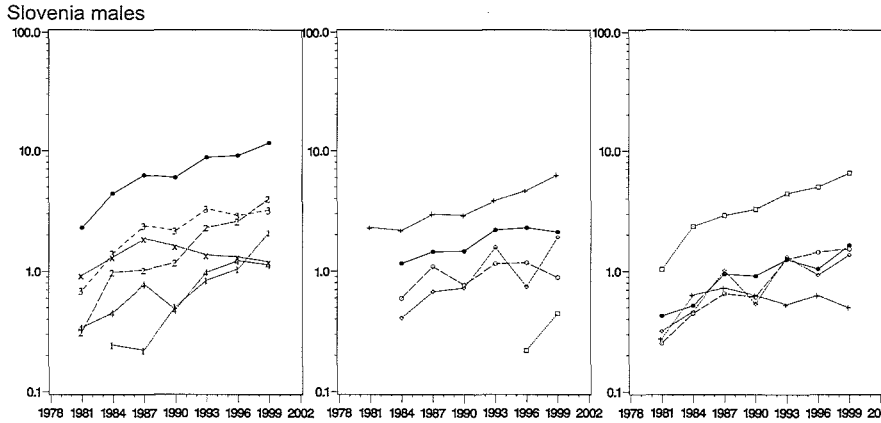


Figure 1b: Trends by stage, histology and site in East Anglia

Slovenia females



Slovenia males



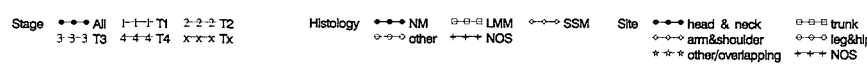
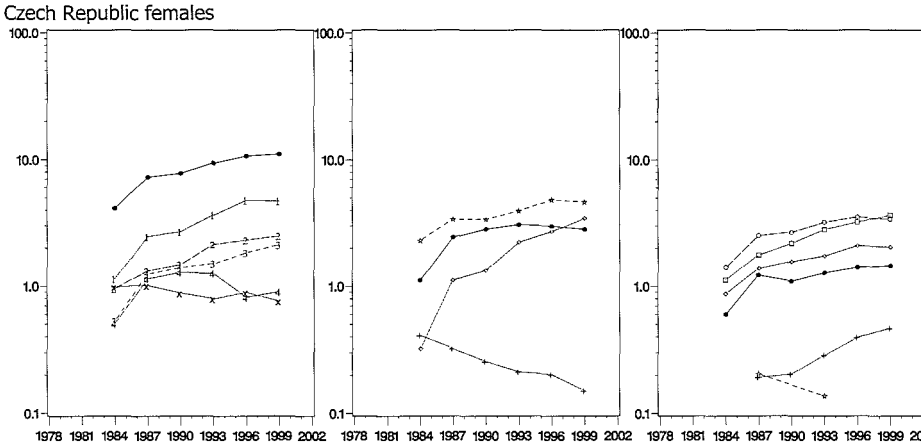
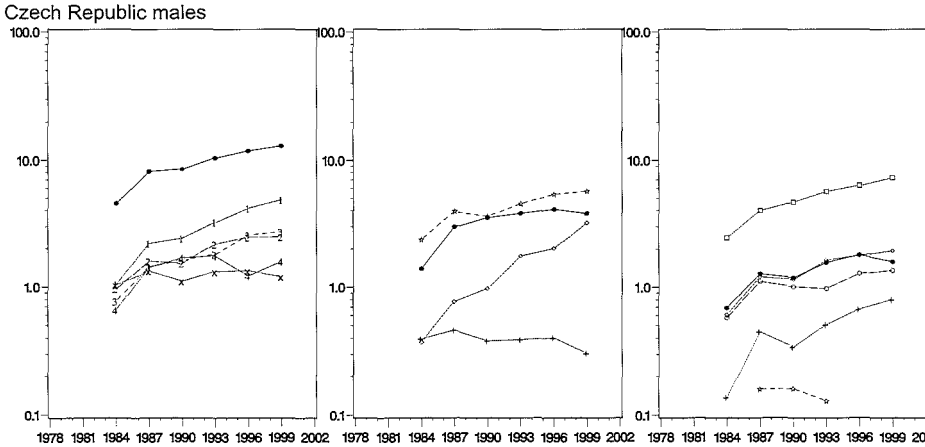


Figure 1c: Trends by stage, histology and site in Slovenia

Czech Republic females



Czech Republic males



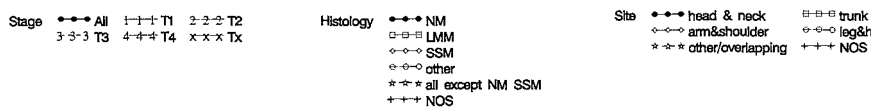


Figure A: Trends by stage, histology and site in Czech Republic

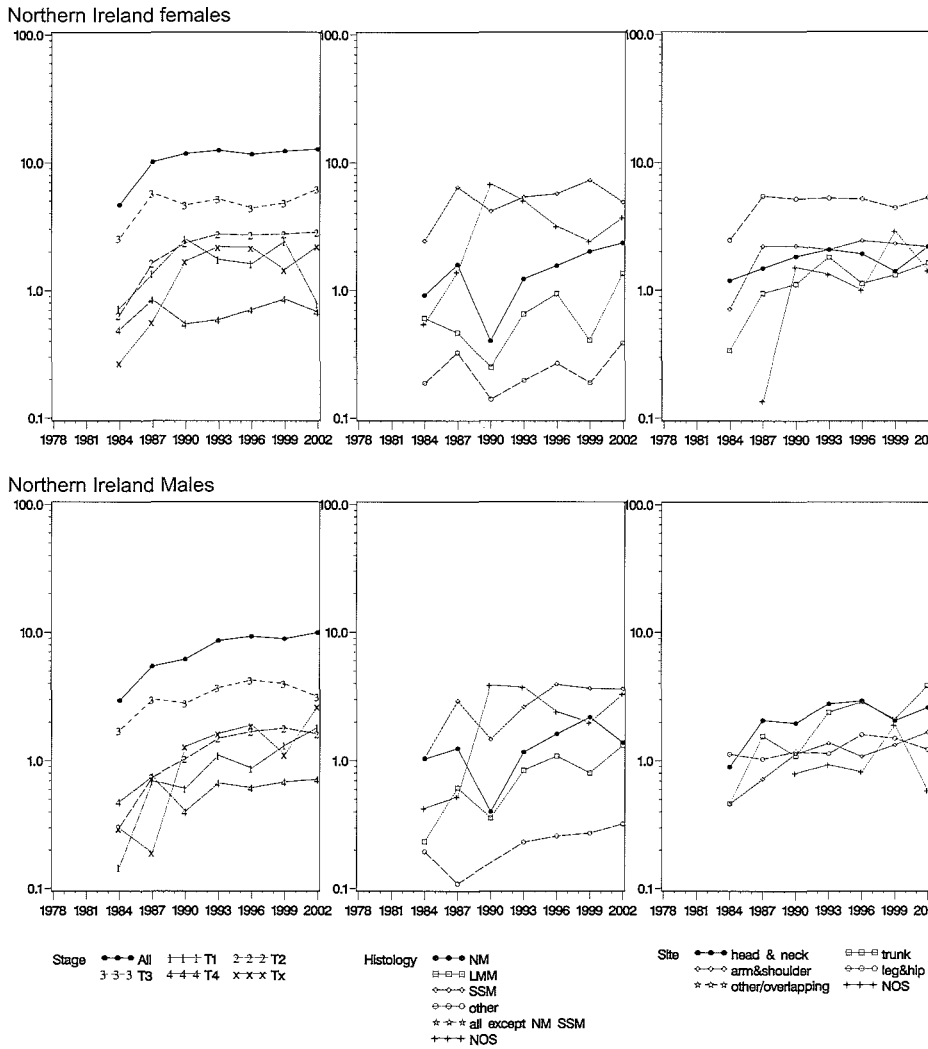
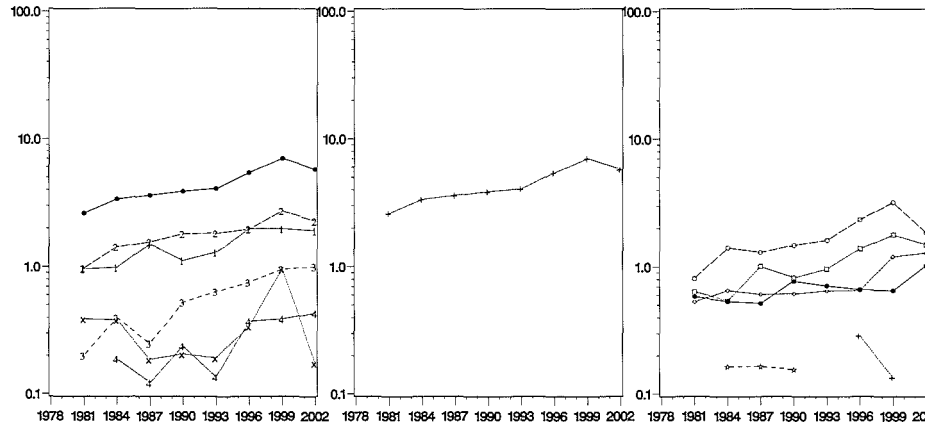
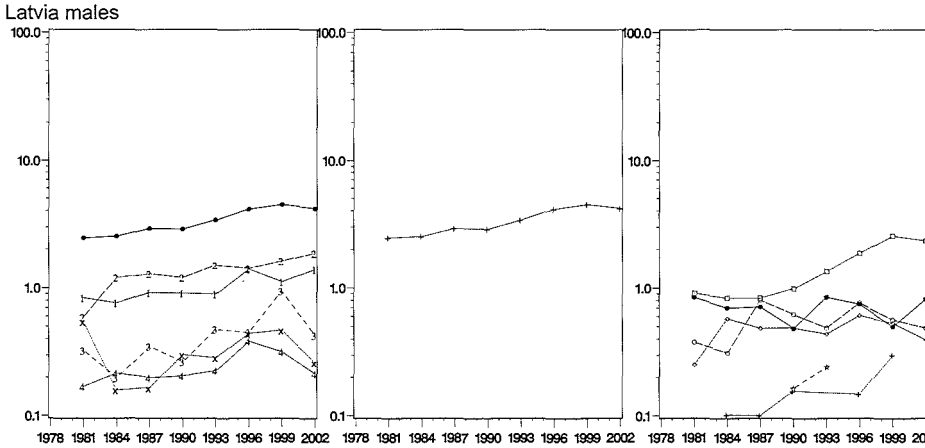


Figure B: Trends by stage, histology and site in Northern Ireland

Latvia females



Latvia males



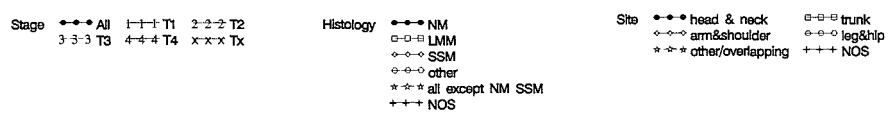


Figure C: Trends by stage, histology and site in Latvia

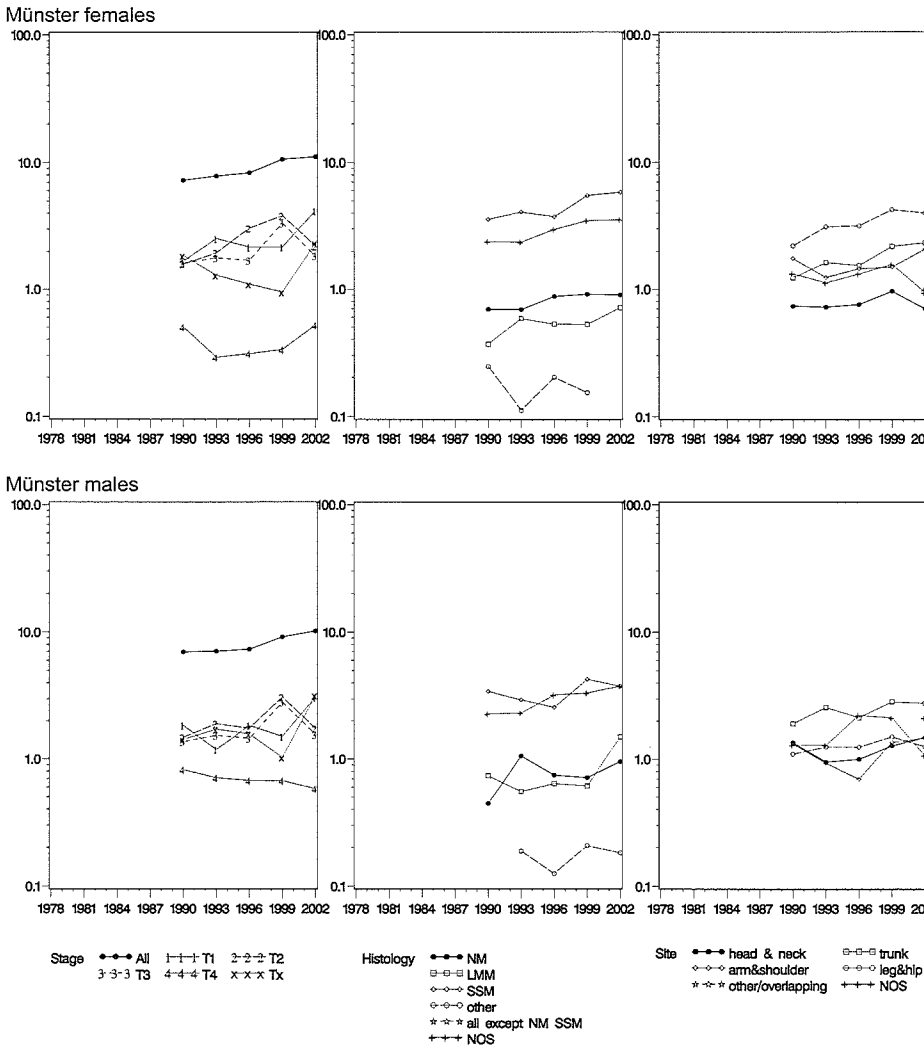
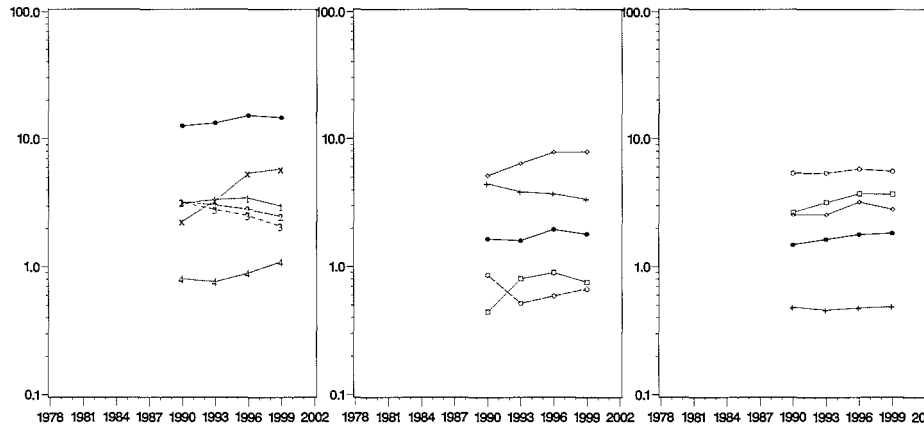
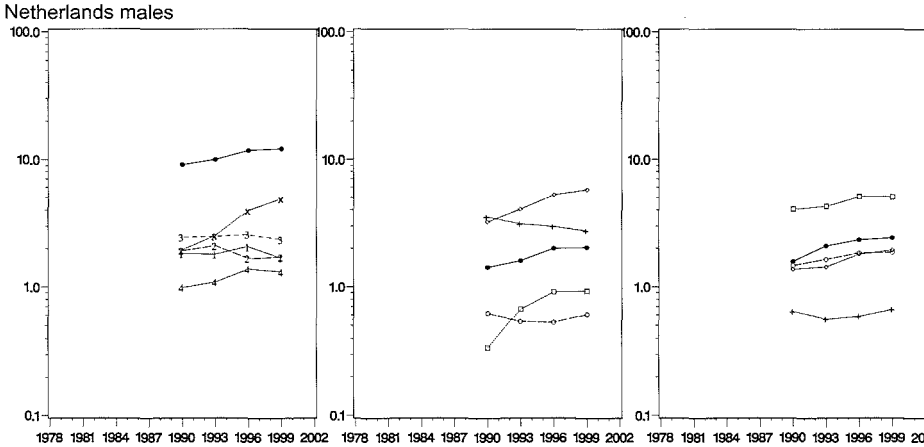


Figure D: Trends by stage, histology and site in Münster

Netherlands females



Netherlands males



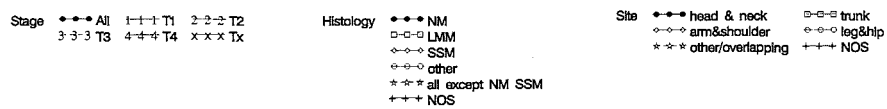


Figure E: Trends by stage, histology and site in the Netherlands

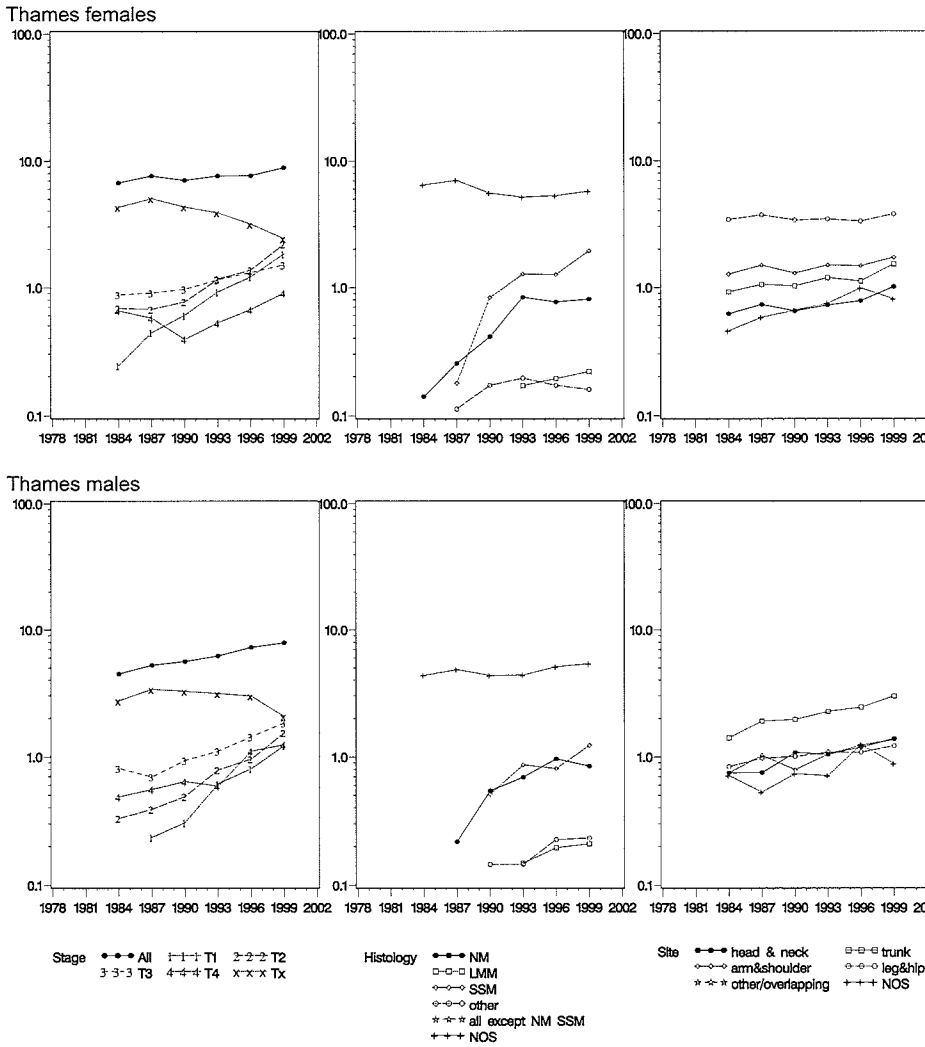


Figure F: Trends by stage, histology and site in Thames

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Chapter 5

Cutaneous malignant melanoma in Europe

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Summary

Cutaneous malignant melanoma is on the rise in fair skinned societies. Both its incidence and mortality rates have been increasing in Europe over the past decades, the latter seem to stabilise in Scandinavia. The main cause of melanoma is intermittent exposure to ultraviolet radiation, especially in combination with endogenous factors like skin type and genetic predisposition. Evidence on an association between sunbed use and melanoma is inconclusive, but seems to point to a slightly increased risk associated with sunbed use. Within Europe, considerable variation in patterns of melanoma incidence and mortality existed. In this paper, we discuss the possible explanations for the observed trends and options for primary and secondary prevention. Early detection seems the most promising way to combat the relatively poor survival rates in southern and eastern Europe.

Introduction: descriptive epidemiology

Cutaneous malignant melanoma (melanoma) is less common than the familiar basal and squamous cell tumours of the skin, but much more fatal. It is mainly a disease of white people, but people with a more pigmented skin can also develop melanomas. It develops by the malignant transformation of melanocytes. In Europe it is the 17th most commonly diagnosed cancer in males and 8th most common in females [1]. In 2000, approximately 26,100 males and 33,300 females were diagnosed with melanoma in Europe, and around 8,300 males and 7,600 females died of their disease [1]. In the Netherlands, which has a relatively high incidence compared with European standards, the cumulative incidence rate before the age of 75 in the year 2000 was 1% in males and 1.25% in females. Melanoma is one of the most important cancers in terms of 'years of potential life lost per death' as it is diagnosed in relatively young people [2-4] (Fig. 1). In the United States, a person dying of melanoma would die about 17 years before the age of 65 years [2], in Denmark 14-15 years and in Belgium 6-8 years [3, 4].

Ultraviolet Radiation

In white populations, exposure to ultraviolet radiatio (UVR) is the main cause of all common skin cancers, including melanoma [5]. It can induce skin cancers by three mechanisms: it directly damages DNA leading to mutations; it produces activated oxygen molecules that in turn damage DNA and other cellular structures; and it leads to a localized immuno-suppression, thus blocking the body's natural anti-cancer defences [6, 7].

Risk factors for melanoma

Intermittent exposure to UVR is the major environmental risk factor for melanoma, especially in combination with endogenous factors (skin types I and II, immune deficient status, genetic predisposition)[5]. Patients with genetic abnormalities like *Xeroderma Pigmentosum* are at a 1000-fold increased risk [8]. If melanoma runs in the family, the relative risk of developing another skin cancer is 2-3 [9] and familary forms of melanoma (familial atypical multiple mole syndrome) have been discovered [8].

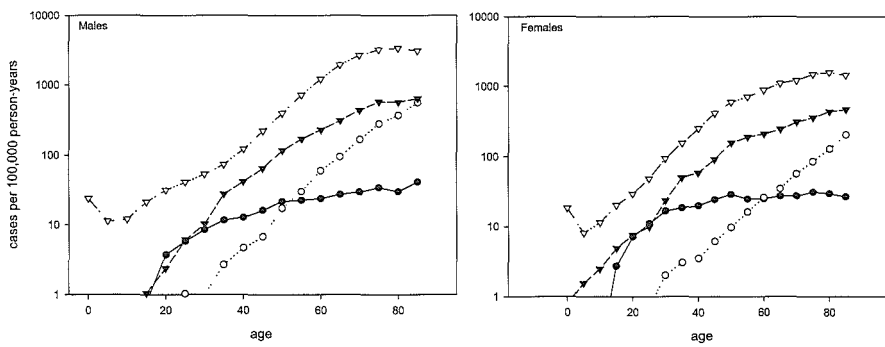

Figure 1: Age-specific incidence of skin cancer. All data are based on the Netherlands data 1996-1998, except basal cell carcinoma (BCC), based on the Eindhoven Cancer Registry Area 1996-1998. (filled circles: melanomas; open circles: squamous cell carcinomas; filled triangle: BCC 1996-1998; open triangle: all tumours except skin)

Table 1: Associations between exposure patterns and melanoma features

Host and tumour feature		Size of relative risk of melanoma related to:	
		Intermittent exposure	Chronic exposure
Age at diagnosis	Young	+++	+
	Old	+	+++
Histology	Superficial spreading	+++	+
	Nodular	++	+
	Lentigo Maligna	+	+++
Subsite	Head and neck	+	+++
	Trunk	+++	+
	Extremities	+++	+

The association between UVR and melanoma is ambiguous, with differences in risks associated with the dose, the way it is delivered (intermittent vs chronic exposures) and critical time periods (table 1).

UVR can be subdivided into UV-A, UV-B and UV-C. Their effects are summarised in table 2. UVR is absorbed by the skin, but does not penetrate it. The majority of mainly UV-B (and in special conditions also UV-C, which normally does not penetrate to the surface of the Earth) is absorbed in the epidermis by various molecules such as keratins and DNA, in which UVR can suppress immune reactions, induce tolerance to antigens, upregulate gene expression and induce mutations [6]. Without repair of the damage, mutations in the DNA can eventually result in the formation of tumours [7]. These changes in the molecules are often harmful, but the damaged molecules can usually be replaced by normal molecules.
Various mechanisms exist to repair DNA that was damaged by UVR, for example the nucleotide excision repair mechanisms (NER). Damage in stem cells or extracellular structures can accumulate and have negative effects, such as elastosis, premature ageing of the skin, wrinkling, cataract and skin cancer [7].
Intermittent exposure to UVR in white people, especially during childhood, has been postulated to be the main risk factor for the development of melanomas. UVR increases the risks of developing skin cancer, mainly in susceptible people (skin type 1-2 and tendency to freckle, with many naevi). For all skin cancers, skin phototype is an important determinant of risk; people who easily get sunburned, have a higher risk of developing skin cancer in comparison with those who tan easily and do not burn (table 3) [10, 11].

Table 2: Features of different types of UV-radiation

	UV-A	UV-B	UV-C
Wavelength (nm)	315-400	280-315	100-280
Penetrates to earth surface	++++	++	-
Induces sunburn	++	+++	+
Induces pigmentation	++	+++	-
Induces thickening of epidermis	-	+++	+
Skin aging (elastosis, keratosis)	++	+++	+
Stimulates vitamin D_3 synthesis	+++	+++	-
Carcinogenic	++ [12-14]	+++	+

+: weak effect, ++ moderate effect, +++ strong effect, UV : ultraviolet

Table 3: Crude and adjusted relative risks of developing melanoma for selected risk factors [10]

Risk factor		RR Males (95% CI)		RR Females (95% CI)	
		Crude	Adjusted*	Crude	Adjusted*
Skin type	3-4	1		1.0	
	2	1.2 (0.6-2.5)	4.9 (0.7-36)	1.2 (0.8-1.8)	1.5 (0.7-3.3)
	1	1.4 (0.8-2.5)	7.3 (1.1, 48)	1.1 (0.7-1.7)	1.3 (0.6-2.9)
Severe sunburn	0	1		1	
	1-2	3.0 (1.8-5.0)	2.8 (1.3-5.6)	1.9 (1.3-2.8)	1.5 (1.0-2.4)
	3+	9.2 (3.4-25)	7.6 (1.8-32)	3.6 (1.7-7.7)	2.3 (0.9-5.6)
Total naevi	<20	1		1	
	≥20	10 (3.6-28)	13.9 (2.7-71)	6.6 (3.4-13)	6.7 (2.9-15)
Freckling tendency	None	1		1	
	some	3.8 (1.9-7.6)	4.4 (1.5-13)	2.9 (1.8-4.6)	3.1 (1.7-5.6)

* Adjusted for total naevi, atypical naevi, freckling tendency, severe sunburn, tropical residence, ultraviolet use, skin type [10].

Melanoma in non-Caucasians

Melanoma is uncommon in negroid people (table 4), Asians and Middle- and South-American populations, probably due to a better protection of the skin by a larger amount of pigment in the skin and possibly different ('wiser') sun-exposure patterns. In many African and Asian societies it is considered beautiful to have a light skin and people try to avoid sun-exposure.

UVR is considered a less important risk factor for skin cancer in coloured people. In non-whites melanomas appear more often on the non-pigmented areas of the skin [15], are often of the acral lentiginous melanoma type and appear at the palms of hands, soles of the feet and under the nails [16, 17]. A common problem in non-Caucasian populations is that pigmented lesions in the skin are often more difficult to notice and therefore melanomas are often detected at late stages, hence the high case-fatality rates [16, 17].

Ultraviolet radiation from sunbed use (risks and behaviour)

The increased use of sunbeds, emitting significant amounts of UV-A and/or UV-B radiation, is of concern, especially since a substantial proportion of young people use sunbeds [24]. Although the risks of melanoma associated with sunbed use have not been unequivocally established, it is likely that the effects on the skin are equal for all sources of UVR. Studies of the risk of sunlamp use for the development of skin cancer, have suffered from methodological and practical problems of varying kind (table 5).

However, all studies on this topic since 1990 point to an increased risk associated with sunbed use, although most studies did not find significant effects. Moreover, sunbed use has become widespread only relatively recently and it might take a longer time to see the effects of sunbed use on skin cancer risk (table 6).

Table 4: Age-standardised incidence rates per 100,000 person-years in the SEER registry (USA) 18

SEER REGISTRY (from CI-5)	ASR (world) males	ASR (world) females
Blacks	1.00	0.5
Whites	15.4	11.6

SEER= surveillance, epidemiology and end-results

Table 5: problems in interpretation of the association between sunbed use and melanoma risk

Strong confounding of sunbed use with sun exposure
Lack of objective measures for sun exposure to adjust for confounding
Recall bias in recalling lifetime sun- and sunbed exposure in cases and controls [14, 19-23]
Type of sunbed use
Reliable information on frequency and duration of sunbed use

Prognostic indicators

Melanoma thickness, body site, histological type of the melanoma, gender of the patient and ulceration are important indicators of patient prognosis (table 7). By far the most important prognostic indicator of melanoma survival is thickness. Generally, older patients do less well than younger patients with the same tumour thickness even after correcting for age, and females do better than males. Superficial spreading melanomas generally have a better prognosis compared with other histological subtypes, because they usually have a thin Breslow thickness [25].

Geographical variation in melanoma incidence and mortality in Europe

Melanoma has shown a rapid rate of secular increase in incidence for white populations, whereas in pigmented people its incidence remained rather stable. Generally, melanoma incidence rates in white populations increase with proximity to the Equator [26] but in western Europe the inverse pattern is observed, with the highest incidence rates noted in the north [27], (figures 2, 3).

Exceptions are the mountainous countries of Switzerland and Austria, which exhibit high incidence rates compared with the countries surrounding them [18, 29, 30]. Within the Nordic countries, melanoma incidence displayed a north-to-south gradient, as would be expected (fig. 2) [31, 32].

However, in eastern Europe the highest incidence rates were observed in the south [33]. Age standardised incidence rates per 100,000 person-years varied from around three in Spain, Belarus and Poland to around 14 in Norway and parts of Switzerland [18]. The higher incidence rates in northern Europe were usually attributed to the lighter skin type of the northern European populations compared with the Mediterranean populations and their relative affluence, enabling them to go on holidays to southern Europe during summer and expose themselves intensively and intermittently to amounts of sun their skin is not used to [26].

Table 6: European studies on the association between melanoma risk and sunbed use published since 1990, only studies that adjusted at least for an indicator of sun exposure and phototype and give an estimate of the adjusted risk are included.

Authors	Country, year	Cases	Controls	Adjusted RR/OR
Garbe [28]	Germany 1993	856	705	RR: 1.5 (0.9-2.4)
Autier [19]	Germany, France, Belgium 1994	420	447	OR: 2.1 (0.84-5.4)
Westerdahl [22]	Sweden 1994	400	640	OR: 1.3 (0.9-1.8)
Westerdahl [23]	Sweden 2000	567	913	OR: 1.8 (1.2-2.7)
Bataille [20]	United Kingdom 2004	413	416	OR: 1.2 (0.84-1.7)

Table 7: Prognostic indicators for melanoma

Prognostic factor	Most favourable when:
Breslow thickness	Thin (<1.51 mm)
Histology	Superficial spreading melanoma
Age	Young
Sex	Female
Ulceration	Absent
Mitotic Activity Index	Low

Trends in incidence and mortality

Since the 1970s there have been reports of 'alarming' increases, initially in melanoma mortality [34], closely followed by reports on melanoma incidence [31]. These reports observed a doubling in the melanoma rates every 10 to 20 years (annual increments between 3% and 7%) in populations of European origin for both genders [4]. Generally, the incidence rates increased markedly for the intermittently exposed body sites (trunk, legs, etc.) whereas increases on the face and neck were moderate. In males, the largest increases were found on the trunk and in females on the legs and arms [35-43].

In northern Europe, where incidence rates became very high during the 1980s, the rates seem to be levelling off since the mid-1990s, especially in younger age groups [27, 41, 42, 44-47]. In contrast, in southern and eastern Europe rates are now increasing steeply in all age categories [27, 45, 47].

Over the last decades, increases in incidence have mainly been observed for thin melanomas, whereas the rate of thick melanomas seems to be relatively stable [48, 49]. This increase in the number of thin melanomas is mainly observed in countries with high incidence rates, where increases in rates are mainly seen in the superficial spreading type [41, 50-54]. In countries with lower incidence rates, increases are generally more evenly spread across thickness categories.

Survival is related to the stage distribution of melanomas at diagnosis. This is generally good in countries with high incidence rates, whereas survival rates are rather poor in the lower incidence countries (figure 4) [33, 41, 42, 55].

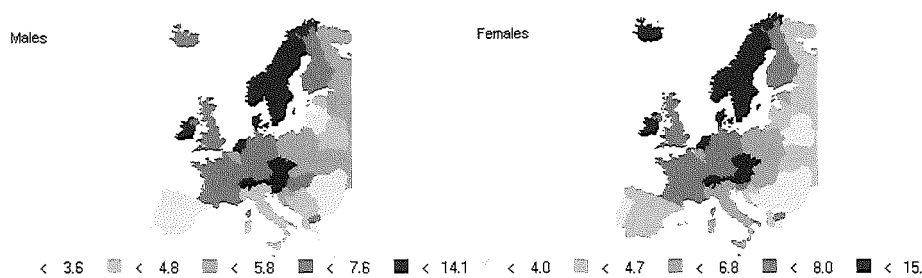

Figure 2: incidence of melanoma in Europe (source: Globocan)

Although incidence rates of melanoma vary greatly within Europe, mortality rates show less variation. Currently, mortality rates are levelling off in many populations with high melanoma incidence rates, such as Australia, the United States, and countries in north-western Europe (Scandinavian countries, United Kingdom, the Netherlands, Germany, Switzerland) [27, 29, 30, 46, 47, 56]. In some countries, a levelling off of incidence rates is now also observed, starting in the young age groups [27]. Awareness usually starts in the younger age groups.

Age-period-cohort analysis

Evidence is accumulating that in several populations (USA, Australia, New Zealand, Sweden, the Netherlands, Germany) the increasing mortality rates have started to level off, starting with birth cohorts from the 1930s/1940s [44, 56-62]. In other countries, generally those with lower incidence rates (Italy, Spain, southern Europe) there was no sign of a downwards trend, at least up until the 1990s [45, 63, 64].

Explanation of trends – are the increases real or partly due to an artefact?

The strong increases in melanoma incidence and mortality over the last decades also indicate the growing problem of the burden of skin cancer prevalence on the health-care system, even though many patients are truly cured. To assess the causes of these trends, whether they are real or artificial and if rising incidence rates can be prevented, is therefore important [49] (Table 8).

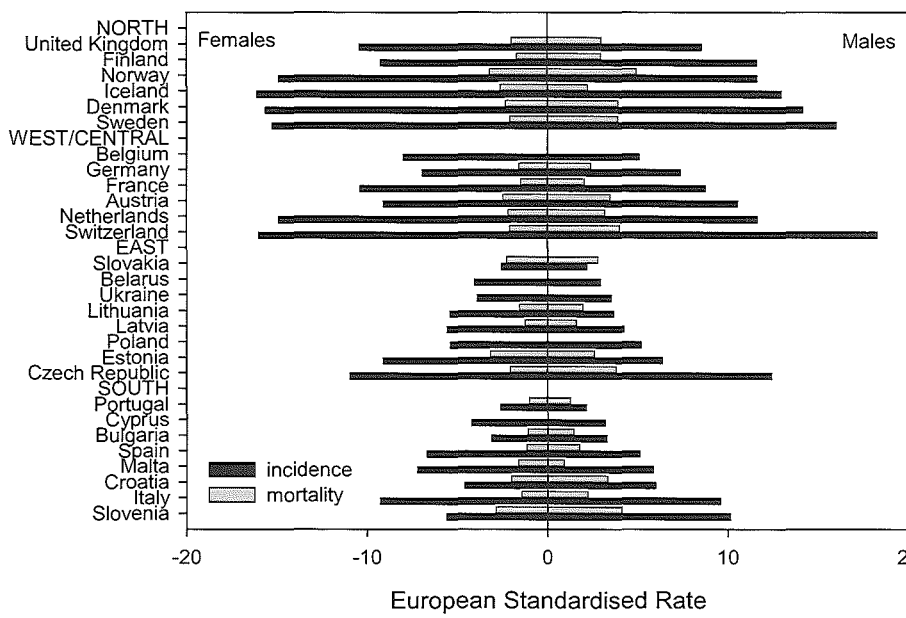

Figure 3: incidence and mortality of melanoma in Europe. Rates are given for 1996-1998 except for Austria, Belarus, Latvia, Lithuania, Norway, Portugal, Slovakia (1995-1997) and Cyprus (1998-1999). Source: EUROCIM

Completeness of registration

In many registries, the completeness of melanoma registration will have improved over time. However, there are still indications that melanoma is underreported in several cancer registries [65-67]. Underreporting is more likely for out-patients and in cases where the pathological laboratories do not report cases to the cancer registry. This concerns mainly the thin, early stage melanomas [66]. However, the marked increases in melanoma incidence have also been observed in countries which are known to have a nearly complete pathology-based registration of melanoma cases, such as in the Netherlands, Scotland, Finland and Sweden [41, 53, 66]. Therefore, improvements in the completeness of registration are unlikely to explain the marked increases observed in the last decades.

Increased awareness / Early detection

Increased awareness of the population in general and of the medical profession seems a more plausible reason for the increases, observed in melanoma incidence. Increased awareness of the population and/or early detection campaigns have urged more people to go and see the doctor when they have a skin lesion, thereby improving detection of (mainly thin) melanomas. This would result in an increase in the incidence of thin melanomas, and after a while, a decrease in numbers of thick melanomas, as melanomas would be detected in early stages, before they developed to advanced disease [49]. This increase in melanoma incidence should however be temporary, as the time of diagnosis is only brought forward, without a real increase in incidence; without the early detection the melanomas could be detected at later stages (lead-time bias). However, there has been no such temporary increase: in some countries, melanoma incidence rates increased in all age groups since the 1960s until at least the end of the 1980s and in some cases, into the 21st century [27]. In the case of melanoma, the effect of increased awareness could take a long time, starting mainly in the young and higher socio-economic classes, slowly spreading to the middle-aged, elderly and lower socio-economic groups.

Moreover, inspecting the relative survival curves, the early detection of melanomas would be expected to translate in decreasing mortality rates after some 5-7 years. However, melanoma mortality rates have also been increasing, albeit more slowly than the incidence rates. While the proportion and number of thin melanomas has increased, the number of thick melanomas has remained stable or slightly increased, instead of decreasing [48, 49].

However, this might be age-dependent. In the Eindhoven cancer registry, large increases in the rates of thin melanomas (<1.5 mm) were observed in the young, with decreasing rates of thick melanomas, whereas in the elderly (aged 60 years and older), there were no major changes in thickness distribution [69].

There is no other explanation for the relatively low mortality rates in countries with high melanoma incidence rates than a higher awareness of melanoma in these populations. This means that most melanomas are diagnosed in early, treatable stages.

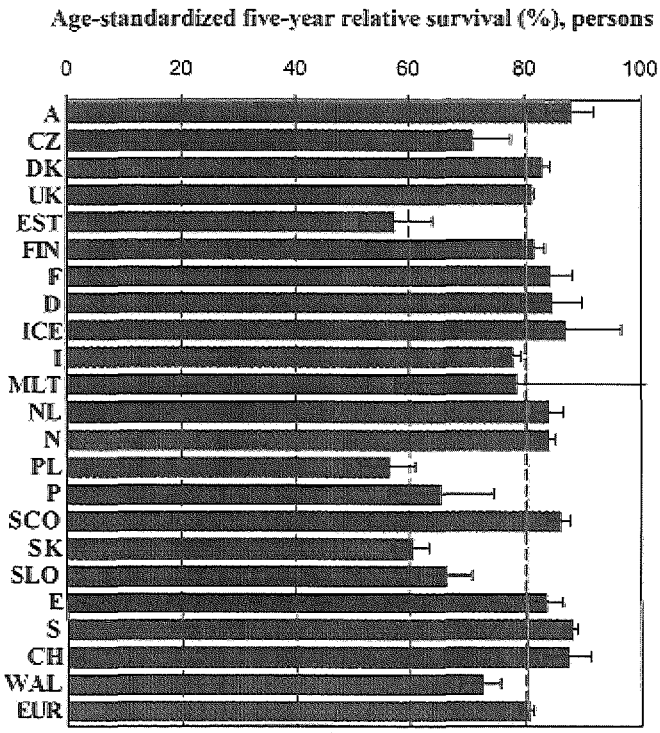

Figure 4: Age-standardised five-year relative survival of melanoma of skin in Europe in adults diagnosed between 1990-1994. Figure taken from [68]. (A =Austria, CZ = Czech Republic, DK = Denmark, UK = United Kingdom, EST = Estonia, FIN = Finland, F = France, D = Germany, ICE= Iceland, I=Italy, MLT = Malta, NL = The Netherlands, N = Norway, PL = Poland, P = Portugal, SCO = Scotland, SK = Slovakia, SLO = Slovenia, E = Spain, S = Sweden, CH = Switzerland, WAL = Wales, EUR = Total for Europe)

Changes in diagnostic criteria

Increased concerns about the melanoma problem in the medical field should urge medical doctors to more carefully inspect suspected lesions. Some lesions that were previously regarded as benign might, due to a more careful inspection, be regarded as melanoma. This theory has been tested by several groups, but there seems to be little evidence for changes in histological criteria as the cause for the rises in melanoma incidence [70, 71]. Furthermore, the observation of birth cohort effects [44, 56-62] makes it unlikely that a systematic improvement in death certification would have accounted for the rises in melanoma mortality rates, as this would translate into period effects.

The proportion of thin melanomas has increased over recent decades [41, 48, 49, 54].

Assessment of malignancy of pigmented lesions is based on microscopically-observed characteristics. This malignancy criterion is used for all melanomas, both thick and thin, and is used to predict the biological behaviour of the disease. In other words, an untreated malignant lesion would eventually kill the patient. For the thick melanomas this prediction of malignant behaviour seems to hold true: In Scotland, 5-year survival was 47% and 55% for men and women with tumours thicker than 3.5 mm, whereas this was 93% and 97% for those with tumours thinner than 1.5 mm [41]. The assumption of malignancy has been debated for thin melanomas; it was hypothesized that a non-metastasising form of melanoma might explain recent observations of increasing trends of thin melanomas with a better survival in South-Australia [72], and the stable numbers of thick melanomas despite a growing number of thin melanomas [49]. However, the increased awareness of melanoma risk in the population could also lead to the overdiagnosis of thin lesions, with similar clinical and histological characteristics as malignant melanoma, but with a benign biology.
Changes in melanoma biology have also been proposed to explain the trends: if UVR acts as a promotor in melanoma, then a decrease in UV-exposure could lead to a slower progression of the lesions [73]. Thin melanomas more recently diagnosed in New South Wales seem to progress at a slower rate than expected based on past trends [72].
Considering the above, the increasing incidence rates may partly be caused by early detection and the diagnosis of clinically insignificant melanomas [49]; however, the largest part of the increases in melanoma incidence and mortality rates is assumed to be real.

Causes of the real increases in melanoma rates

The 'real' increases in melanoma rates are most commonly attributed to changes in lifestyle with increasing intermittent exposure to ultraviolet (UV) radiation, due to the popularity of sunbathing and tanning since the late 19th century. Before the Industrial Revolution wealthy people had a pale skin: they worked or stayed indoors, lower classes were mainly outdoors. During the industrialisation of society (1750-1800),

Table 8: Schematic presentation of possible determinants of the changes in trends and the associated expected and actual observations

Cause of 'increase'	Hypothetical observations	Actual observations
Completeness of registration improved either or not by increasing involvement of pathology labs	More outpatient diagnoses	increases also observed in near-complete registries with link to pathology
Increased awareness / early detection	Temporary increase	often not observed
	Improved stage at diagnosis	often observed
	Decreasing mortality	small increases and some decreases
Changes in diagnostic criteria	Changing practises	not observed
	Period effects for changes	birth cohort effects
Increased intermittent sun exposure in the past		
in behaviour, fashion	Generation (birth cohort) effects	Birth cohort effects were observed in mortality
in environment (e.g. ozon)	Period effects	Period effects were observed
charterflights		

machines appeared, and the working classes started working indoors in the factories. Only the rich had the time and money to afford recreational outdoor life, such as going to the beach, sports, walking in the mountains, skiing and sailing, and having a tan became the symbol of having money and being healthy. By the early 1920s, daily exposure to sunlight was also advised as a cure for many diseases (acne, rickets, tuberculosis), especially for children. By the 1930s a suntan had become a symbol for wealth and health. Swimwear changed, with shoulder straps, which could be lowered to keep an even tan. During the 1960s the bikini, and later monokini, appeared, allowing women's bodies close to total exposure.
Since the 1950s holidays to sunny destinations and charter flights (first to Mediterranean regions, from the 1980s also to the (sub)tropical countries) became popular, and could be afforded by an increasing number of people.
In the 1940s, suntan lotion was introduced, originally designed to help in getting a tan, not to protect against the sun. In the 1950s first suspicions of sunlight as a cause of melanoma arose [74]. In the 1960s indoor tanning, mainly in winter, became possible through the use of sun lamps. Throughout the 1970s and 1980s, reports of increasing incidence and mortality rates of melanoma were reported [75-77], while the fashion press suggested that suntans make you look healthier and feel younger. The use of sunbeds became increasingly popular during the 1980s. Tanning saloons boomed and sunbeds became available for use at home. Moreover, in Germany in the 1970s the 'Körpercultur' and nudism became popular, exposing the whole body to the sun. Tanning became increasingly popular, despite a growing body of scientific evidence that tanning not only leads to early aging of the skin, but also causes skin cancer [31, 74]. Awareness of the link between UV-exposure and skin cancer grew slowly – especially when people started to worry about damage to the ozone layer in the early 1980s.
Although today we know the risks of sun-exposure, a tanned skin remains desirable, beaches are crowded, sales figures of self-tanning lotions and sunbeds are high and cheap flights to sunny destinations in (sub)tropical areas are widely available and consumed.

Given an induction time of some 20-40 years between exposure and melanoma occurrence, the increasing popularity of sunbathing and getting a tan in the past is in accordance with the currently continuing increases of melanoma incidence mainly on the trunk in males and on the legs in women [39, 78-83].

Another explanation for the increases is the depletion of the ozone layer, which protects the earth's surface against UV-radiation by filtering out a large part of the UVR from the sunlight before it reaches the earths' surface.

Table 9: The excess number of skin cancers under the Vienna protocol: scenario's of ozone depletion in the years 2050 and 2100 in a population of 160 million in north-western Europe (including Belgium, the Netherlands, Luxembourg, Denmark, Germany and Great Britain)[88].

	Extra cases of skin cancer per year	
Ozone depletion Scenario	In 2050	in 2100
No restrictions	55 680 (+35%)	550 000 (+315%)
Montreal Protocol	36 960 (+21%)	170 000 (+95%)
Copenhagen amendments	14 240 (+7.5%)	4 000 (+2%)

Chemical substances released in the earth's atmosphere are slowly breaking down the ozone layer, increasing the amount of UVR that reaches the earth's surface and likely increasing the risk of skin cancer. Estimates indicate that skin cancer incidence rates could increase dramatically by the end of this century compared to the situation around 2000 [84] (table 9).

Vaccination during childhood against tuberculosis with the Bacille Calmette-Guérin (BCG) vaccine or against smallpox with the vaccinia vaccine, or having experienced one or more infectious diseases may decrease the risk of developing melanomas (odds ratios between 0.29 and 0.44) [85-87]. Part of the increases in melanoma incidence could be due to the abolishment of this type of vaccination in Europe.

Stabilisations

Recent stabilisations in melanoma mortality rates (in some cases followed by incidence rates) are reported in high-incidence countries, such as Australia, USA, Sweden, Norway and Germany [4, 27, 37, 42, 47]. Only the mortality rates levelled off initially, starting in the late 1970s, with increasing incidence rates. This was most likely because of an improved patient survival [41, 42, 55] due to earlier detection, as there were no major improvements in systemic melanoma treatments. Melanoma incidence rates were also levelling off (Denmark, the Netherlands, Switzerland and the United Kingdom) or even decreasing (Finland, Norway, Sweden) in the young age groups, starting in the 1980s [27]. Furthermore, the mean and median stage or thickness at diagnosis is decreasing [41, 48, 49, 54, 55] with an increasing registration of thin, superficial spreading melanomas.

Changes in the biology of the melanoma with less aggressive lesions could also be consistent with a continuing rise in melanoma incidence with a moderation or stabilisation in the mortality rates.

Primary and secondary prevention

The fashion of tanning has contributed substantially to the increases in skin cancer incidence. However, undoubtedly incidence rates may have increased due to the greater awareness of people of the risks of sunbathing and their growing knowledge about the need to inspect the skin for suspected lesions. In the late 1970s and the 1980s projects were initiated to increase awareness (Starting in Australia, followed by Scotland, Scandinavia, and other European countries) which increased detection of skin cancers, often in more favourable stages than they used to be [89-92]. These campaigns seemed to be most effective in young females, whereas males were more difficult to reach [93].

Primary prevention

If melanomas and other skin tumours develop mainly due to excessive intermittent exposure to UVR in susceptible people then limiting exposure to UVR should prevent skin cancer. The question is whether a high-risk approach is sufficient (only preventing skin cancer in the high-risk groups) or whether a mass-campaign should be organised. Moreover, since UVR also exerts positive effects on human health [94-98], one cannot

advise plain avoidance of exposure, especially in moderate climates like north-western Europe. However, if having a tan would no longer be considered healthy and beautiful, people could change their patterns of sun exposure, possibly resulting in decreasing skin cancer incidence rates.
In the prevention of melanoma it seems particularly meaningful to prevent multiple erythemas during childhood, convincing parents and caretakers not to let children stay too long in the sun. For these purposes, mass media campaigns would be most effective, since the general attitude of the population towards sunbathing and having a tan needs to be adapted before behavioural changes might be induced.

Protection against UV radiation
Given the positive and negative effects of UV radiation, balanced messages should inform people about 'safe' ways to be in the sun. There are several ways to protect your skin against the harmful effects of UV-radiation: natural protection (tanning), avoiding the sun, clothes/hats, sunscreens.

Natural protection
Tanning is a protection mechanism of the skin. Absorbing layers are thickened and pigmented and mechanisms to clear away or repair the damage are stimulated (renewing proteins, repairing DNA, replacing dead or damaged cells). The extra pigment and thickening of the epidermis serve to protect the underlying cells of the skin against UVR, rendering the skin less sensitive to sunburns. This protection disappears after a couple of weeks of limited exposure.
A slow adaptation of the skin to the sun is important in protecting against UV radiation, both in the sun and in sunbeds, allowing the skin to thicken and form pigmentation as protective mechanisms. Sunbed manufacturers have developed schemes for the use of sunbeds.

Clothes and seeking shade
Wearing clothes and hats when outside or seeking the shade decreases the amount of exposure to UVR drastically, although not completely. Fabrics let fractions of UVR through, depending on their texture and UVR often gets reflected, for example by sand or snow, making UVR exposure in shadows possible.

Sunscreen use and self-tanning lotions
Most sunscreens in use consist of a combination of organic substances that absorb both UVA and UVB. Sunscreens with zinc oxide or titanium dioxide protect the skin mainly by reflecting UVR.
The sun protection factor (SPF) is determined with an artificial light-source and applying 2 mg of product per m^2. In practise people usually use insufficient amounts of the product to realise the protection they envisage. Reasons for this are ignorance, aesthetic unattractiveness (so much lotion will make you look white), and the high costs of sunscreens. Protection by sunscreens is also lower than the indicated SPF at high altitude and with a lot of wind and transpiration.

A group of experts of the International Agency for Research on Cancer has investigated the preventive effects of sunscreen use on the development of skin cancer: the use of protective cream could indeed prevent erythema and squamous cell carcinoma after *non-intensive* sun-exposure. Its protective effect for basal cell carcinoma and melanoma, however, is not yet determined, as it is difficult to study due to the long latency period. There is even evidence that the use of sunscreens may paradoxically increase the risk of melanoma development by increases sunbathing-time. Out of the 15 case-control studies examined by the group of experts, only 3 resulted in a significantly reduced risk of melanoma with relative risks between 0.2 and 0.6, the others observed no significant effect (4 studies) or an increased risk (8 studies, RR between 1.7 and 3.5) [99].
More sunscreen is needed in areas closer to the equator or highup in the mountains, in summer, and during the warmest hours of the day.

Quick- and self-tanning lotions
There is no connection between skin cancer and the use of quick-tanning substances, except for products containing bergamot oil, which have a carcinogenic effect and this product is currently banned [100]. Self-tanning substances, which give the skin a brown colour without sun exposure colorize the corned layer of the skin, but do not stimulate melanin production. Many of these substances contain β-carotene. Elevated risks of the use of these products have not been demonstrated to date.

Secondary prevention
Early detection of skin tumours seems useful, as a relatively simple surgical treatment in early stages dramatically improves the prognosis of patients and an effective treatment for metastases is not yet available. Early detection aims at reducing 'patient delay', limiting mutilation and preventing death. Early stage melanoma is recognised by patients and their partners and by dermatologists, general practitioners and doctors doing physical examinations on their patients.
One can distinguish between screening of persons with an increased risk of melanoma because of a familial vulnerability, with increased risk of melanoma because of skin type and skin damage, and screening of the general population.
Regular screening of the total population for melanoma does not seem useful and is not propagated in any country in the world. The advantages gained are small, because the incidence of melanoma is low, and melanomas are already diagnosed at favourable stages, especially in women and young males. The chance that screening will result in a more positive stage is small. Moreover, every screen interval (in other tumours usually 2-5 years) would be too long for the category of fast growing aggressive melanomas.
However, it seems likely that people with a familiar risk of developing melanomas (those with familiar or sporadic dysplastic naevus syndrom, *Xeroderma Pigmentosum* and large congenital naevi, representing about 10% of all melanoma patients) can benefit from regular check-ups. Screening in these populations and regular checks (every 6-12 months) leads to earlier detection [101].

Heightened alertness is desirable in groups of people with a combination of risk factors, indicating increased risk of developing melanomas (a sum of having light skin, blond or red hair, freckles, family history of skin cancer, multiple dysplastic naevi, men aged 50 years and older, history of severe sunburns in childhood).
Initiatives for screening, even if only directed at high-risk groups, increase the awareness in the general population. This effect may be more important than the direct effects of screening itself.

Future perspectives

In many countries where incidence is high and where awareness and (secondary) prevention campaigns have often been organised, moderations in the increases of melanoma mortality rates are observed within a few years, followed by moderations in melanoma incidence in younger age groups after more than 10 years, corresponding with the observed birth cohort effects in the mortality rates [27, 44, 46, 47, 56-62]. If these trends persist, and efforts to improve awareness and increase early detection of melanomas are maintained and/or initiated, a decrease in the overall melanoma mortality rates can be expected. However, melanoma incidence rates in the elderly, mainly in males, remain high and survival rates for this group are worse than average.
If the hypothesis that many of the newly diagnosed thin melanomas are of a benign biology holds true, some of the increases in melanomas might turn out to have been artificial.
If a more prudent attitude towards sun exposure and having a tanned skin can be achieved, incidence rates of melanoma can really be expected to decrease, as in Europe between 54 and 80% of melanomas are assumed to be caused by intermittent sun exposure [5].
Without measures to prevent the ozone layer from further breakdown and more prudent recreational and sunbathing behaviour and clothing styles, skin cancer incidence rates will keep increasing rapidly.

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Chapter 6

Interpretation and discussion of results

Chapter 6

Interpretation and discussion of results

The studies presented in this thesis illustrate the increasing problem of skin cancer in European societies and the complexities of examining the relationship between exposure to ultraviolet radiation and skin cancer.

Short summary of results pertaining to the general research questions of this thesis

Question 1: What were the trends in melanoma incidence and mortality rates in the Netherlands and throughout Europe and are there indications that they may start to level off?

Incidence rates of melanoma have been increasing in the Netherlands and throughout Europe. Rates increased most prominently in the older age categories but in the young (aged 25-49) the annual percentages of increase were also considerable. In the Netherlands, age-standardised mortality rates increased particularly in the group of elderly males.
In eastern Europe incidence rates were increasing with proximity to the equator, as was also observed in Australia and the USA. An inverse pattern was observed in western Europe, with the highest rates in the north. Pertaining to the geographic variation within Europe, incidence rates were very high in north-western Europe and Switzerland, however, in young age groups mortality and incidence rates were levelling off in some of these countries. In southern and eastern Europe incidence rates were lower but increasing markedly in all age categories.
Contrary to prior expectations, mortality rates throughout Europe, in generations born after 1945 do not seem to stabilise. Whereas there were large differences in incidence rates across Europe, mortality rates were more comparable.
Trends in the Netherlands concur with those of north-western Europe, lagging about 10 years behind those of Scandinavian countries. This would imply an expected stabilisation of incidence rates in the young over the coming decades, whereas predicted future incidence rates are expected to continue to rise in all age groups. As in other countries, melanoma mortality rates in elderly males are worrying, as they continue to increase rapidly.

Question 2: Are these trends comparable with those of other skin cancers?

Incidence rates for basal cell carcinoma in the southeast of the Netherlands increased rapidly and the main increases were seen for young females and on the trunk and extremities, as is the case for melanoma. BCC now occurs more frequently on intermittently exposed body sites, whereas it was previously a tumour most commonly observed in the head and neck region. This has strong similarities with the characteristics of the melanoma trends, where relative tumour densities are highest in the head and neck region, but observed increases were most prominent on intermittently exposed body sites [1] (table 1).
Whereas BCCs and melanoma started appearing with increased frequency in young age groups, increases in squamous cell carcinomas were mainly observed in older age categories. These observations support the hypothesis that the increases in BCC and melanoma are related to intermittent sun exposure, as opposed to those in squamous cell carcinoma which is related to chronic sun exposure [2-5].

Table 1: comparisons in melanoma, BCC and SCC trends over the last decade according to subsite [6, 7]

	Melanoma	BCC	SCC
Total	+++	+++	+
Head and neck	+/-	+/-	++
Upper limbs	+	++	+/-
Lower limbs	+	++	+/-
Trunk	++	++	+/-

+++: strong increase, ++: moderate increase, +: increase, +/-: little or no increase

Question 3: What explanations for the trends are suggested by the observed patterns in melanoma incidence and mortality?

The marked increases in incidence and mortality of melanoma, observed in all Caucasian populations world-wide, are most likely due to a combination of increased (recreational) sun exposure and a heightened awareness of the need to inspect the skin for suspect lesions. Differences or changes in histopathological criteria for melanoma or an improved registration are unlikely to be the cause of the increases in incidence rates and the observed differences within Europe. The high incidence rates of melanoma in north-western Europe are accompanied by relatively low mortality rates, largely comparable to those in the lower incidence regions in Europe. This is an indication for an earlier stage at diagnosis in the high incidence countries, most likely due to an increased awareness amongst the general population and health care providers of suspect lesions. Detection and treatment of very early stage melanomas results in low case-fatality rates. In regions with high incidence rates but relatively low mortality rates, high proportions of the new melanomas were, as expected, in the early stages, whereas many of the diagnosed melanomas were in an advanced stage in regions with lower incidence but high case-fatality rates.

Melanomas diagnosed in eastern Europe, where survival rates are relatively low, had on average a higher Breslow thickness and appeared more often on the trunk, explaining the high case-fatality rates.

Question 4: Did the use of sunbeds contribute to the increases in melanoma incidence?

It impossible to draw any firm conclusions regarding this question based on our analyses. This is due to a strongly suspected differential recall bias in both cases and controls, combined with self-selection amongst controls. We encountered specific problems in this case-control study, such as the suspected differential recall bias and self-selection of controls. The investigation of an association between sunbed use and melanoma risk is aggravated by the aforementioned problems, as well as by random recall bias and the strong correlation between sunbed use and indicators and predictors of sun exposure. This causes any effect from sunbed use to strongly diminish after correcting for sunbathing.
As a recent levelling off of trends in melanoma incidence rates in young men and women has been observed in regions which have a very high and increasing reported prevalence of sunbed use amongst young people, it does not seem likely that the increasing use of sunbeds has substantially contributed to the observed increases in melanoma incidence.

Limitations of the studies

Population based data
The studies presented in chapters 2 and 4 are entirely based on population based data collected by cancer registries. Population based databases have the advantage that there is no risk of selection bias but the information they contain is limited. As all data are routinely collected, individual exposure data are seldom available. In the European data there was no information on ethnic origin. The data used in our analyses were almost certainly complete and reliably registered. A correction was made for double counts of the same tumour, which might otherwise have greatly influenced incidence rates, particularly in cases where secondary tumours are common, such as in the case of basal cell carcinoma. Due to the linkage with the national pathology registry (Pathologisch Anatomisch Landelijk Geautomatiseerd Archief (PALGA)), all tumours in the Dutch Cancer Registry have a known histology and even patients not admitted to hospital for skin cancer, were registered.
In chapter 4, we used databases that contain specifically collected information about stage, histology and body site. Unfortunately, despite the registries' attempts to collect this extra information, many data were still missing. In order to monitor time trends in skin cancer characteristics as indicator of improved early detection, it is essential to have an (almost) complete data collection about stage, histology and body site. It is therefore highly important to collect information on these variables.

Predictions

The methods used to predict the results in chapter 2.3 have proved to be accurate in validation studies performed with Scandinavian data. However, there are many possible fallacies in these models. The models are relatively arbitrary and exposure data could not be used as input. We do not know exactly how exposure to ultraviolet radiation has changed over the last decades or how this would precisely influence the subsequent skin cancer incidence rates, but we do know that the amount of UV-radiation reaching the earth's surface is increasing due to the breakdown of the ozone layer. Moreover, sunbathing behaviour has become increasingly popular over the past decades. The effects of the so-called 'hole' in the ozone layer are most likely not yet perceptible but may become visible in the near future. However, if international agreements (the Montreal Protocol Amendments) are kept, maximum increases of approximately 10% are expected around the year 2060. This 10% increase will be difficult to ascertain due to standard fluctuations in incidence rates. Therefore, the predicted incidence rates of skin cancer until 2015 as presented in chapter 2.3 are likely to be marginally underestimated.

Case-control study

In chapter 3 we presented the results of a large, international case-control study designed to investigate the risk of subsequent melanoma development as a result of sunbed use. As already explained in chapter 1, investigating this risk is challenging. The study suffered from biases and other methodological problems although it was designed by investigators with substantial experience of case-control studies in melanoma research and although attention was paid in order to circumvent certain problems encountered by other groups studying the same topic. Most people use sunbeds to get a tan and getting a tan is related to skin cancer. This being the case, one of the Vandenbroucke criteria for 'convincing outcomes in observational research' has not been met, namely that 'observational research should be restricted to questions where the exposure allocation is unrelated to the outcome' [8]. Therefore it is questionable whether an observational study can give convincing evidence as to the issue whether sunbed use conveys a risk of developing skin cancer [8].

One unexpected problem was the apparent underreporting of sun exposure by cases. We were able to use naevus count as an indicator of sun exposure as the number of naevi on the arms both of cases and controls was assessed by the interviewer and naevus count and sun exposure have repeatedly been reported to be positively correlated. The strongest indication of the underreporting of sunbathing habits was perceptible in the inverse relationship between interviewer-determined number of naevi and self-reported sunbathing habits. As was expected, an increased number of naevi was positively related to melanoma risk (<20 vs ≥ 20 naevi: OR 3.0). This underreporting probably occurred as a result of the large amount of attention paid to skin cancer prevention programmes in recent years. In the future, this issue may pose problems in all studies designed to investigate risks of melanoma that are based on self-reported measures of sun exposure. The general population and specifically skin cancer patients, are well aware of the risks of excessive amounts of sun exposure. This may have led to a conscious or subconscious underreporting of sun exposure in

respondents wanting to give socially desirable answers. Cases may underreport because they do not want to accept responsibility for their melanoma. This was illustrated by the fact that there seemed to be a stronger underreporting of sunbed use amongst patients with a thicker melanoma. Apart from underreporting, apparent self-selection of controls also poses a problem. Of the eligible controls, those who used sunbeds seem to have been more interested in participation, whereas those who did not sunbathe or use sunbeds may have been less interested in participating. Despite attempts to form a representative control group, this apparent self-selection seems to have resulted in an unusually high percentage of sunbed users amongst this group. The combination of underreporting and self-selection has made it impossible to draw any conclusions regarding the risk of developing melanoma associated with sunbed exposure.
Apart from the specific problems encountered in this case-control study, the investigation of an association between sunbed use and the risk of skin cancer is aggravated by the strong correlation between sunbed use and indicators and predictors of sun exposure. This causes any effect from sunbed use to diminish after correcting for sunbathing.
Taking into account all the evidence from the recently published cohort- [9] and case-control studies [10-16] and indications of UVA carcinogenity [17-22], it seems likely that exposure to ultraviolet radiation from sunbeds results in an increased risk of skin cancer. This risk, however, does not appear to be very high, because in Scandinavian countries, where the prevalence of sunbed use is high, incidence rates in young and middle aged women are levelling off.

Interpretation of the results

The observed increases in incidence and mortality rates of melanoma are most likely due to an increased exposure to ultraviolet radiation as a result of increasing (recreational) time spent outdoors in sunny areas or high up in the mountains.
The assumption that the worldwide increases in skin cancer incidence can already be attributed to the depletion of the ozone layer is questionable as most cases observed in trend studies were already in their thirties or older when the depletion of the ozone layer began to be perceptible and childhood is the period in which UV-exposure brings the highest risk of developing melanoma later in life.
In chapter 5, various explanations for the observed patterns in incidence and mortality rates are discussed in further detail. The pattern of high melanoma incidence in the north and low incidence in the south of western Europe is likely due to the gradient in the combination of wealth and skin type from north to south. The wealthiest, sun-sensitive populations live in the north and the less affluent but darker skinned populations live in the south. The former could also afford to go on holidays to (sub)tropical areas, although their skin-type was not adapted to the kind of exposures they encountered in these regions. Southern populations spent their holidays largely in areas with similar or lower UV-levels compared to those of their own country. Also, they most likely had different patterns of behaviour, such as taking a siesta, limiting their exposure to the sun.

In eastern Europe there was no such wealth-gradient, resulting in the incidence following the expected patterns with highest rates in the south.
The disadvantageous melanoma survival that was observed in southern and eastern Europe could be due to later stages at diagnosis or faster growing melanomas. The latter is possibly a result of a promoting effect of recent UV-exposure on melanoma progression [23]. If sun exposure were to have such an effect, more melanomas would be detected in summer and a worse survival would be expected for southern European populations. We found an increased incidence of melanoma in summer months, possibly caused by such a promoting effect but which could also be due to a better visibility of the skin because of other clothing habits. Melanomas detected in the summer were on average thinner than those detected in winter, which would contradict the hypothesis of a short-term progressive effect of UV-exposure and would favour the explanation of different clothing habits.

In Australia, the United States and certain European countries, reports on stabilising trends in melanoma mortality rates appeared and in some of these countries, incidence also was observed to be levelling off [24-29].
For mortality rates these stabilisations could be due to an increase in early detection as well as an improvement in survival and cure probabilities. An alternative explanation for the stagnation of mortality rates with increasing incidence rates would be Burtons hypothesis of the existence of a thin, non-metastasising form of melanoma which histologically shows malignant features [30].
The stabilisations in incidence rates might be due to effective primary prevention campaigns, although this does not seem to be the most likely explanation. Effects on incidence from primary prevention campaigns is not to be expected until at least 20-30 years after introduction. That time has not yet passed as the first big prevention campaigns were started in approximately 1980 in Australia [31], with campaigns in north-western Europe following later [28]. It is also possible that the complete susceptible population has been maximally exposed, making it impossible for the rates to increase any further, as may be the case in Scandinavia and Australia.

Basal cell carcinoma
Traditionally, basal cell carcinomas were thought to be related to the cumulative amount of UV exposure during life, as was indicated by the high percentage of BCCs occurring in the head and neck region. However, evidence is being accumulated that BCC, like melanoma, is related to sun exposure on non-working days, mainly amongst sun-sensitive subjects. Increases in first primary BCC are mainly seen on the trunk and increasingly in young females [2, 3, 32-35]. Estimates of dose-response curves indicate that beyond a certain level of sun exposure risk of first primary BCC does not increase further [3, 32]. These observations indicate a role for intermittent sun exposure for the risk of BCC. The mechanisms for BCC aetiology through UV-exposure might be similar to those of melanoma: melanin in the upper layers of the skin protects against damage in the stem cells. BCCs could easily develop on the intermittently exposed body sites with increasing intermittent exposure on the trunk, such as is the case with sunbathing and sunbed use.

The Eindhoven Cancer Registry at the Comprehensive Cancer Centre South is unique in its collection of information on first primary BCC. This information has made it possible to study this very common, yet seldom studied, skin tumour. Relative risks of first primary BCC by cohort were increasing in women born after 1956, whereas stabilisations seemed to occur in women born during the 1940s. Due to the large numbers, it is easier to analyse more recent cohorts of BCC patients than of melanoma patients.
Melanoma mortality rates have been observed to be stabilising in cohorts born around the 1940s [26, 27, 36-42] and therefore both melanoma incidence and mortality were expected to be levelling off in generations born after 1950. The observations in the BCC group, combined with the concept that BCC and melanoma have a common risk factor, namely intermittent sun exposure, could indicate that melanoma rates may not remain stable in birth cohorts from ca 1940, contrary to the expectations of many [26, 27, 36-42]. Instead, incidence rates might be starting to increase again in cohorts born in the 1950s. If these rises in incidence are accompanied by an early detection and treatment, mortality rates may remain stable.
For melanoma in the Netherlands, the observation by Nelemans et al [37] of a levelling off of mortality rates in cohorts born from 1955 does not seem to hold true.

Clues for aetiology: A contribution to the intermittent exposure hypothesis and the hypothesis of a divergent pathway for the development of melanoma

In this thesis, we made several observations supporting the 'intermittent sun exposure hypothesis': (a) trends by body site distribution: whereas most melanomas and basal cell carcinomas are found on the head and neck area, increases in incidence are found mainly on the intermittently exposed trunk and extremities; (b) the strong increases of skin cancer over the past decades, first observed in northern Europe, are in accordance with sunbathing, outdoor recreation and (sub)tropical holiday destinations becoming more popular. These were first available for affluent people/societies, later for the majority of the population.

The observation that at young ages melanomas appear mainly on intermittently exposed body sites, whereas at an older ages they appear more often on chronically exposed skin, supports the hypothesis of a divergent pathway for the development of melanoma [1, 43, 44]. This hypothesis states that there are two divergent pathways for the development of melanoma after a UV induced transformation of melanocytes. One is associated with melanocyte proliferation (related to melanomas on the trunk and other intermittently exposed body sites) and the other is associated with chronic exposure to sunlight (related to melanomas on the head and neck area) [43, 44].

Public Health implications of trends: A growing discrepancy between supply and demand of care for skin cancer in the Netherlands.

Based on the observations from our analyses in this thesis, a considerable increase in skin cancer incidence in north-western Europe is expected in the coming decade as a result of epidemiological (2-4% per year) and demographic changes (1-3% per year). In the Netherlands, the annual increase in number of new skin cancer patients or people with a strong suspicion of skin cancer, was estimated to be in total approximately 4% per year: from 20,000 new skin cancer cases around the year 2000 to approximately 37,000 cases by 2015.
Prevalence of melanoma is increasing because of (a.) increases in incidence, (b.) an increase in the early detection of suspected lesions because of an increased awareness in both the general population and the medical field and (c.) improving survival. The following data from the southeast Netherlands illustrate this problem: in 2002 the 20-year prevalence of melanoma (i.e. the number of people per 100,000 who were diagnosed with melanoma within 20 years prior to the date of report) in this region doubled in comparison with that of 1990: from 41 to 102 per 100,000 males and from 77 to 171 per 100,000 females. This means an average age-adjusted increase of 7-8% per year. In absolute numbers the increase was 159% in males and 124% in females (almost 12% annually in males and 10% in females).
This implies substantial implications for costs: In Stockholm, Sweden, the estimated annual discounted cost-of-illness due to skin cancer was approximately 162 million Swedish kronor (approximately 16,2 million US dollars) for a population of 1.8 million inhabitants [45]. Adapted to the situation in the Netherlands (approximately 16 million inhabitants), there being a slightly higher incidence of melanoma in the Netherlands than in Stockholm, these costs would currently be around 150 million US dollars per year.

Heightening the degree of awareness of skin cancer in the general population remains important in lowering mortality and would eventually prevent new cases by changing behaviour. However, an increased awareness will result in an increased demand for care for people with suspect lesions and/or diagnosed tumours. This care is comprised of informative education, early detection, differential diagnostics of suspected skin lesions, surveillance of patients in who had a skin tumour removed and care for those with an increased risk of developing skin cancer. Complicated procedures such as the increasingly popular Mohs surgery add to the workload of pathologists and surgeons [46]. Medical specialists confronted with this preventative care are mainly GPs and dermatologists with plastic-, general- and oncologic surgeons contributing as well. Usually, there is a peak in the demand for skin cancer care in spring and early summer. This is due to the combination of increased visibility of the skin because of changes in clothing habits as well as the launching of (new) campaigns focussing on skin cancer and skin care, both by commercial and official cancer prevention organisations. Without changes in policy, the demand for preventative and excision oriented care may more than double within the next 10 years.

The quality of the care delivered is depends on a sufficient supply of care, which is currently determined mainly by the supply of dermatologists and general practitioners (GPs).

In the Netherlands, a satisfactory provision of medical services is becoming increasingly problematic because of the shortages in the number of:
- general practitioners: currently 5% and within 10 years possibly 25% of the Dutch population will be without a GP, this threatens early detection and treatment of skin cancer;
- dermatologists: according to estimates of the manpower agency, the insufficient numbers of dermatologists amounts to approximately one full time unit per hospital, (not including a general decrease in demand); dermatologists also have to deal with increases in other problems such as diabetes, allergies, arterial and venous insufficiencies in the legs;
- (Plastic) surgeons will have an increasingly limited amount of time to treat skin cancer patients.

In countries such as Germany and Belgium the number of these types of medical specialists more than doubles that of the Netherlands. The combination of the three aforementioned shortages is worrying and requires unconventional measures. One could think of introducing qualified assistants, such as skin therapists, nurse practitioners and/or trained assistants in the dermatology clinics.

In the southern and eastern parts of Europe, melanoma incidence rates are still increasing rapidly and given the economic developments in eastern Europe they may even accelerate. Survival in these regions is lower than in north-western Europe, probably due to a delayed diagnosis. Therefore, primary and secondary prevention of melanoma will be of big importance in these regions. Strategies to improve the general knowledge of and attitudes towards sunbathing and to detect melanomas in early stages can be adopted from north-western Europe, where they seem to have been relatively successful. Without extra care for prevention of skin cancer, we can expect large increases in both skin cancer incidence and mortality in these parts of Europe.

Prevention

The increases in skin cancer incidence rates pose a challenge for public health measures. Designing and implementing prevention activities, both primary and secondary, will remain important in combating the skin cancer epidemic.
When educating the public about the risks of sunbathing people should, however, not be discouraged altogether from spending time outdoors in the sun, especially in regions with moderate climates such as north-western Europe. The disadvantages related to overexposure to ultraviolet radiation should be in balance with the benefits of being outdoors, such as physical activity, which is important in combating, amongst other things, obesity and heart disease. A growing amount of evidence is being found for ultraviolet radiation having a protective function against the development of several

cancers, such as cancers of the prostate, breast and colon [47-53]. It has also been associated with a lower occurrence of (auto-immune) diseases such as multiple sclerosis, insulin-dependent diabetes mellitus, rheumatoid arthritis, rickets, muscle weakness, osteomalacia, secondary hyperparathyroidism and hypertension [47-55]. Odds ratio and relative risk estimates for these diseases vary approximately between 1.5 and 5 for the lowest versus highest exposure categories of sunlight exposure and/or serum vitamin D levels. The possible benefits of UVR exposure for human health should therefore be assessed along with its adverse effects [55].

How to change behaviour?

Primary prevention of skin cancer usually aims to reduce the amount of exposure to UV-radiation by (a) limiting sun-seeking activities such as sunbathing and using sunbeds; (b) having people protect themselves against the sun by several methods such as using sunscreen, wearing protective clothes and hats, seeking the shade, and limiting the time outdoors at the warmest time of day. The most commonly used protection against the sun in Europe is sunscreen [56, 57], which is in fact not the best method of protection, as it increases the time spent in the sun without getting sunburnt but most likely does not fully protect against skin cancer [58-62].

People usually assume that knowledge is the most important determinant of behaviour and therefore think that people will 'improve' their behaviour if they have the correct knowledge. This assumption is wrong: knowledge is only one of the many determinants of attitude, which in turn is only one of 3 determinants of behavioural intention. Several studies have concluded that although the public awareness of skin cancer is increasing, such awareness is usually not translated into behavioural changes [56, 63-68].

According to the Theory of Planned Behaviour [69], behavioural intentions are influenced by (a) peoples beliefs about a behaviour and thoughts about the consequences of that behaviour (attitude), (b) beliefs about the normative expectations of others and motivation to comply with these norms (perceived subjective norm) and (c) perception about the presence of factors that may facilitate or impede performance of the behaviour and the perceived power of these factors (control beliefs) (figure 1). In this model it becomes clear that just giving people information will not be enough to achieve behavioural changes.

The *background variables* are mainly demographic and cultural factors, some of which are associated with sunbathing habits, such as gender and latitude. These are important determinants of sunbathing behaviour but are not (easily) changed and therefore not useful for interventions. However, the targeting of specific risk groups in prevention campaigns could be improved.

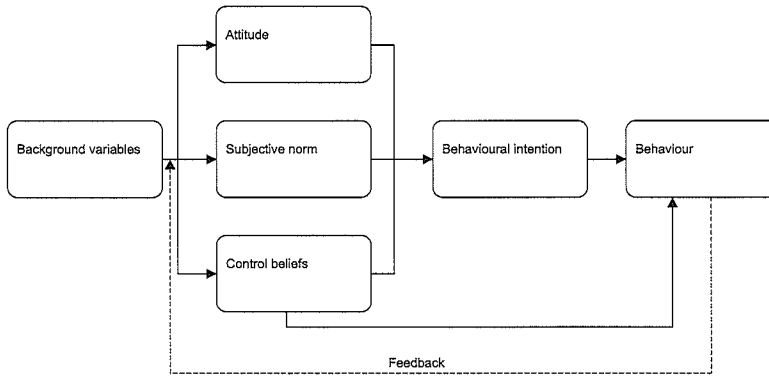

Figure 1. Schematic representation of the Model of Planned Behaviour [69].

Attitudes are formed based on earlier learning experiences, such as experiences of sunburn, positive reactions on having a tan, knowing people with skin cancer, knowing about the ageing effect the sun has on the skin, etc. The perceived pros and cons fall into four categories: health beliefs, appearance beliefs, emotional beliefs and beliefs about alternative behaviours.
If someone thinks that a disadvantage of sunbathing is to have an increased risk of skin cancer, but does not think that this is a large disadvantage (health beliefs), it will have little effect on his/her attitude. Moreover, if that person thinks that the advantage of sunbathing is the development of a tan, that a tan is a symbol of health and wealth and perceives this as very important (appearance beliefs) and also feels relaxed during sunbathing (emotional beliefs), the perceived advantages of the behaviour will outweigh the disadvantages.

The degree of influence of the positive effects of sunbathing on appearance should not be underestimated. One study, for example, showed that even people with a high hereditary risk of skin cancer stated 'attractiveness' as the most important reason for sunbathing [70].

Health and appearance beliefs can be influenced by interventions. For example, in order to make the health beliefs 'weigh' more in the evaluation of pros and cons, primary prevention campaigns could, apart from informing people about the risks of skin cancer, also pay attention to the ageing effects on the skin of UV-exposure (health and appearance). Conveying the message that limiting sun exposure will prevent premature wrinkling may be more effective than discussing the risk of skin cancer when it comes to changing peoples' attitudes towards sunbathing and sun protection. Appearance beliefs may be changed as well by, for example, working on the 'subjective norm' as is discussed below. Emotional beliefs, in contrast, are more difficult to address, as they are based on experiences, such as the fact that people feel relaxed when they are in the sun.

The *subjective norm*, the perceived expectation of important other people, is another goal for health educators. If someone perceives that 'important others' have a negative attitude towards sunbathing and a positive attitude towards sun protection, that person may be more inclined to copy this behaviour. Therefore, if prevention campaigns manage to have the desired behaviours promoted by the fashion and movies industries and/or important others, such as celebrities, this might be more effective than conveying information on the risks of skin cancer. Having a suntan is still a symbol of health and wealth in western societies. Changing this positive image into a negative one will be difficult, but most likely very effective. If caregivers can be convinced of the importance of protecting their children against over-exposure to the sun and their place as role models for their children, it may pay off in two ways. Firstly, the sun-protection habits of the caregivers protect their children and themselves and secondly, influence their children's future behaviour.

Control beliefs are the perceptions about the presence of factors that may facilitate or impede performance of the behaviour and the perceived power of these factors. In these beliefs, several aspects can be distinguished: (a) perceived control is a person's belief about the degree to which health risk can be reduced, (b) the perceived efficacy is the belief about the degree to which some specific preventive action will be effective in reducing the risk and (c) someone's (perceived) self-efficacy is the belief about one's capabilities to perform a specific preventive action.
In the case of skin cancer control the perceived control is the degree to which someone thinks skin cancer is preventable. The perceived efficacy is the degree to which that person thinks that a particular protective measure, for example using sunscreen, helps to prevent skin cancer. The (perceived) self-efficacy is the degree to which that person can apply the preventive measure (remembers to use sunscreen on the right moment, bring enough sunscreen to re-apply it, etc.). Intervention campaigns could be aimed at convincing people about the effectiveness of the desired protective behaviour, decreasing the barriers for sun protection and increasing those for sun exposure. A study in four kibbutzim in Israel indicated that beliefs about sun tanning and sun exposure habits (barriers) were good predictors of the likelihood to engage in protective behaviour in young age-groups (15-29 years). In older age groups the best predictors are the value of health and appearance [71]. These findings illustrate the importance of tailoring preventive measures to specific age groups.

From the Model of Planned Behaviour it can be deducted that people are more apt to process information correctly when the message is better suited to considerations that are relevant to them. This will increase the chance of effective behavioural change. Through new developments in satellite technology, adequate information on expected UV-levels in different regions (up to city-level) can be gathered and local UV-predictions made for up to 5 days in advance. These UV predictions can be translated into recommendations for protection for people with different skin phototypes and living in different geographical areas.

Currently this kind of information is only available on the internet in the Netherlands, (http://www.knmi.nl/voorl/weer/zonkracht.html) but its potential utility would be much more effective if it were to be presented along with the daily weather forecasts.

An additional problem in changing people's sunbathing behaviour is that the advantages of limiting sun exposure (less skin damage, lower risk of skin cancer) are mainly long-term effects, whereas the advantages of sunbathing are perceived at a short term (increased perceived attractiveness, fewer skin problems such as acne). Short-term effects are more powerful in motivating people's behaviour. Moreover, most people have personally experienced the positive effects of the sun, whereas only relatively few people know people with skin cancer. In an Australian study, men with a high level of negative experiences with skin cancer were more likely to adequately protect themselves from the sun [72]. Sun protection behaviour seems to be more related to personal experience concerning skin cancer, than to the knowledge of the risks of sun exposure [72, 73].

Primary prevention: the target group

Preventing sunburns and high exposure to ultraviolet radiation before the age of 20 may be one of the potentially most effective primary preventive measures, as both the very common basal cell carcinomas and the very aggressive melanomas seem to be particularly associated to exposure throughout childhood and teenage years.

One could debate as to whether limiting exposure to ultraviolet radiation in adulthood would be important in preventing incidence if an individual has been heavily exposed during childhood, as this is considered the most important exogenous determinant for melanoma risk. If the hypothesis of a divergent pathway for the development of skin cancer holds true, the cumulative amount of exposure will be a risk factor for melanoma at older ages on the sun-exposed body sites. If ultraviolet exposure has a short-term progressing effect on melanoma cells, exposure in adulthood will result in poorer prognosis for the melanoma patient. In addition, sun exposure at all ages contributes to the cumulative amount of exposure and therefore the risk of squamous cell carcinoma and basal cell carcinoma and melanoma in the head and neck region. Therefore it must be recommended to limit sun exposure at all ages.

Some groups would like to see stricter rules governing solariums. However, this is unlikely to be effective in the Netherlands, as a large percentage of people who use sunbeds do so at home.

Effective campaigns

The most famous campaign for the primary prevention of skin cancer, the 'Slip! Slap! Slop!' SunSmart campaign, has successfully been conducted in Australia. The program aims to 'change personal and institutional attitudes and behaviours through environmental and organisational change and control over existing disease, and to reduce the incidence and mortality of skin cancer' [31]. It has been running for over 20 years and incorporates mass media work, sponsorship of sporting events, resource development and organisation, professional education, advocacy of policy development as well as having a strong research and evaluation component.

It has been successful in changing attitudes (e.g. a drop from 69% (in 1988) to 35% (in 1998) of respondents that agree that 'friends think a suntan is a good idea' and from 51% to 20% for those agreeing that 'I feel more healthy with a suntan'), as well as changing knowledge and behaviour (50% reduction in people getting sunburnt from 1988 to 1998). Structural and organisational changes (schools making the wearing of a hat for children playing outside compulsory, creating playgrounds and swimming pools with a lot of shade, adapting the weather forecasts, etc.) have also been accomplished. Targeting special activities or settings is another approach to encourage protection from the sun. In Australia and Hawaii, campaigns that actively involved the staff of outdoor recreation sites were successful. The use of shade and protective clothing increased in both adults and children [74, 75]. However, primary prevention campaigns in Australia and the southern states of the United States have to deal with completely different circumstances compared to those in (northern) Europe. Skin cancer incidence rates in Australia are extremely high, almost every person knows somebody with skin cancer, also the amount of solar radiation is much higher than in (northern) Europe, where the fact that sun exposure also brings benefits to our health [47-55] and overall feeling of well-being conflicts with preventive messages. In northern Europe people 'miss' the sun, mainly in winter and some populations have very high rates of depression, partly due to the lack of sunlight [76]. It is difficult finding a balance between risk of skin cancer and protection against these other diseases. Still very little is known about the efficacy of primary prevention campaigns in Europe [56, 57, 64, 77].

Early detection

As melanoma is a highly malignant tumour with fast increasing incidence rates, it remains important to make an effort to detect melanomas at an early, treatable stage when excision can provide a cure. Regular screening of the complete Dutch population for melanoma does not seem useful, as the incidence of melanoma is relatively low and the stage of melanomas at diagnosis is already quite positive (mainly in women and young males) [78]. Chances of screening reaching even more positive stages are small, particularly as there seems to be a lower uptake in the group of males and people from deprived areas for screening [79, 80]. These are exactly the groups where improvements in stages at diagnosis could be made. Therefore, strategies to improve skin self-awareness as opposed to screening should be developed and evaluated.

The increases in incidence rates in melanoma are especially worrying for the group of middle aged and elderly males, as their mortality rates are still increasing rapidly. Fourty-four percent of all melanoma deaths in the Netherlands in the year 2000 (total melanoma deaths was 470) occurred in males aged 50 and older. The differences in survival between males and females might be explained by a female advantage due to female steroids, which seem to influence melanoma progression [81]. Another explanation for these differences is the increased awareness of naevi and early signs of melanoma among women [82] and the lower attentiveness of men to their bodies. The combination of these characteristics makes women seek medical advice at an earlier stage of the disease. Partners may play an important role in early detection of suspected lesions of the skin. Early detection campaigns should therefore be paying extra attention to reach the group of elderly (single) males.

In the regions with high mortality:incidence ratios (mainly in southern and eastern Europe) general awareness of characteristics of melanoma should be raised to help people recognise suspected lesions and improve the stage at diagnosis.
Median thickness of melanomas in eastern Europe was very high, leaving ample opportunities for early detection. The focus should be on skin self-examination and alertness to suspicious lesions. In a US study, people were taught by nurse and using a photo book how to do skin self-examination. This seemed to be effective at increasing patient adherence [83]. This method could be applied to high-risk groups, such as people with a family history of skin cancer, with a light, sun-sensitive skin, and/or having dysplastic naevi.

Recommendations for future research

For future research into skin cancer development and prevention, it is important to obtain better insight in the aetiologic processes leading to the various types of skin cancer. Findings from stem cell, immunological, molecular and genetic research should be merged into the mechanisms of disease. Better insight into the effects of ultraviolet radiation on human health and its specific mechanisms – both positive and negative – may help in treating various diseases and can be used as a basis for integrated prevention campaigns.
Groups of patients with thick and thin melanomas could be compared to study determinants of melanoma thickness.

Some of the questions related to preventative messages that are currently unanswered are: Is it beneficial for people who have been heavily exposed in childhood to limit their sun exposure in adulthood? Does recent sun exposure alter prognosis of melanoma? Which is the precise group of people who should be extra careful in the sun? What are the adequate protection measures against UV-radiation? Is sunscreen effective in protecting against the various forms of skin cancer? What are the risk factors for melanoma other than exposure to UV-radiation?
The challenge when it comes to prevention campaigns will be to discourage over-exposure to ultraviolet radiation without discouraging sun exposure completely, as exposure to UV-radiation also has positive effects, which should not be overlooked. For Caucasians, exposure of the hands and face during outdoor activities appears to be sufficient for this purpose. More information on the sun prevention campaigns executed in Europe, including information on their (in)effectiveness, should become available. More insight into the determinants of different types of sunbathing and sun protection behaviour should be attained. This would help to tailor intervention campaigns, facilitate international cooperation and would avoid repeating ineffective efforts to reduce sun-exposure of the population.

To monitor the effects of population based primary or secondary prevention campaigns, one can use population based cancer registry data with the condition that they are of sufficient quality and collect information on relevant prognostic indicators such as stage, thickness, ulceration and histologic subtype.

Pathologists should therefore carefully document these data. If more patient-specific data can be easily linked to registries' databases of skin cancer patients, unselected patient groups could be studied in more depth.

Epidemiological studies of skin cancer risk should no longer solely depend on self-reported measures of sun exposure, but should also have some indication of sun-induced UV-damage. Several of these methods, based on skin reflection and measures of solar damage are now becoming available, but their potential use, based on validity and reliability, still needs to be sufficiently assessed.

Age and site specific trends could give a better insight into the theory of the divergent pathways for melanoma. For example, in a group of patients with head and neck melanomas, one could examine if there are more signs of chronic UV-damage to the skin as well as whether squamous cell carcinomas are more common as a secondary tumour compared to the group of patients with melanomas on the trunk. If the hypothesis holds true, trunk melanomas should be more common than head and neck melanomas in naevus-prone people.
Regarding basal cell carcinoma, accumulating evidence points to similarities between basal cell carcinoma and melanoma in terms of aetiological factors. As basal cell carcinoma is a much more common tumour than melanoma, it might be worthwhile to make more of an effort to study basal cell carcinomas, including collecting information on primary BCC by cancer registries and designing cohort-studies to prospectively study the risk of BCC in certain exposed groups. Ideally, one would design a randomised controlled trial to study the effect of sunbed use, but this would be ethically unacceptable. Therefore, one is left only with the possibility to study the effects of sunbed use in observational studies. This might be done prospectively for basal cell carcinoma instead of melanoma, as the incidence rates of BCC are substantially higher and increasing, particularly in the group of young females, the most important group of sunbed users.

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Summary

This thesis presents studies on different aspects of the epidemiology of melanoma: variations in disease frequency in time and place, determinants of melanoma incidence and variation in prognostic factors.

In chapter 2 we presented the developments in melanoma incidence and mortality in the Netherlands and Europe. In the Netherlands we observed marked increases in incidence rates (2-3% per year), specifically in people older than 45 years of age. Age-standardised mortality rates increased only modestly amongst females (1% per year), but more substantially in males (3%). Age-specific mortality rates increased markedly with increasing age, especially in males. We observed a north-west to south-east gradient in melanoma incidence rates within the Netherlands, with higher rates in the northwest. This gradient corresponded with gradients in skin- and haircolour and opportunities for recreational activity and shares characteristics with patterns throughout Europe.
Considering the geographic variation within Europe, incidence rates were very high in north-western Europe (age-standardised rates (ASR) up to 31 in Norway) and mountainous areas of Switzerland (ASR 25), but mortality and incidence rates were levelling off in young age groups in some of the aforementioned countries. In other regions, incidence rates were lower but increasing markedly for all age categories. Whereas incidence rates in most fair-skinned populations increase with further proximity to the equator (as was also observed in eastern Europe), an inverse pattern was observed in western Europe.
The high incidence rates in melanoma in north-western Europe were accompanied by relatively low mortality rates, largely comparable to those in the lower incidence regions in Europe. The high survival rates in north-western Europe are most likely due to early detection of melanomas. The increases in incidence rates in melanoma were worrying for primarily the group of elderly males, as their mortality rates are still increasing.
In chapter 2.2 we discussed the trends in the southeast of the Netherlands in incidence rates of first primary basal cell carcinoma (BCC), which shares many features with melanoma. This area of the Netherlands is one of the few regions in the world where information on this common skin tumour is routinely registered by the cancer registry (IKZ). The rates increased rapidly with 2-4% per year and the main increases were noticed in the group of young females with an annual increase of almost 6%. Relative risks of BCC by cohort were increasing in women born after 1956, whereas a stabilisation of this risk seemed to occur in women born in the 1940s.
Incidence rates of melanoma, BCC and squamous cell carcinoma have been and are predicted to continue increasing in the Netherlands. Interestingly, the increased rates of melanoma and BCC are already observed in the young age groups. The total number of skin cancer patients with a first primary is expected to increase from around 20,000 new cases in the year 2000 to around 37,000 cases in 2015. Although, apart from

melanoma, the majority of skin cancer is hardly ever fatal, the increasing number of patients places a heavy burden on the health care system, particularly when complicated (surgical) procedures, such as Mohs' surgery, are required.

In chapter 3 we presented evidence on the existence of a seasonal pattern of melanoma incidence in western Europe, which was stronger at higher latitude (i.e. more north). The highest incidence rates for melanoma were in summer. This can have several reasons; different clothing habits in summer increase the visibility of the skin and therefore facilitate the detection of skin lesions, alternatively, exposure to ultraviolet radiation may promote melanoma progression in the short term. In eastern Europe no seasonal patterns were observed, possibly due to delays in diagnosis, as illustrated by the high mean Breslow thickness of melanomas detected in eastern Europe.
We also studied the relation between sunbed use and melanoma risk in a large, international case-control study. Unfortunately, the study suffered from biases and other methodological problems, hampering any firm conclusions to the main study question: is sunbed use an independent risk factor for the development of melanoma?
An unexpected problem was the apparent underreporting of sun exposure by cases, as was illustrated by the negative association between reported sun exposure and melanoma risk and naevus count, the positive association between reported protective behaviours and melanoma risk, and the high percentage of cases denying that sun exposure could have caused their melanoma. Self-selection of controls may also have complicated this study. Apart from the specific problems encountered in this case-control study, the investigation of an association between sunbed use and melanoma risk is aggravated by the strong correlation between sunbed use and indicators and predictors of sun exposure.

In chapter 4 we described the differences in body site and histologic type distribution in different age categories of melanoma patients in the Netherlands. For those under 65 years of age, superficial spreading melanoma (SSM) was the prevalent histologic subtype, occurring predominantly on the trunk in males and the arms and legs in females. For those 65 and older, SSM was also the prevailing histological subtype, but nodular melanomas and lentigo maligna melanomas were much more common in this age group. Melanomas in this age group appeared substantially more often in the head and neck region. Similar differences in body site distribution were found elsewhere in Europe. Unfortunately, histological subtype is not sufficiently recorded by many cancer registries in Europe.

We used cancer registry data to analyse trends in prognostic factors, which are an indication of the effectiveness of early detection campaigns. We investigated several prognostic indicators, such as stage, histologic subtype and body site of the melanomas but due to large numbers of missing values it was practically impossible to draw firm conclusions regarding changes in these variables over time. However, there was a regional variation, with high proportions of new cancer cases in early stage in regions (in north-western Europe) with low mortality rates in comparison with their incidence

rates, such as Stockholm and East Anglia. This was the opposite case in the southern and eastern regions which had high mortality rates in comparison to incidence, such as Rioja, Cracow and Navarra.
Melanomas in eastern Europe presented more often on the trunk and had a higher mean thickness compared to those in the west (mean difference 1.4 mm), explaining the lower survival of melanoma in eastern Europe.
Increases over time in BCC were mainly seen on the trunk and extremities. Whereas BCC used to be a tumour most commonly found in the head and neck region, they are now becoming more common on the intermittently exposed body sites. This has strong similarities with trends in melanoma incidence, which showed the strongest increases on intermittently exposed body sites. Cancer registry data can be very useful in monitoring these kind of trends and we think more cancer registries should register data on BCC to get more insight into the skin cancer epidemic.
The collection of data on site, histology and stage of melanomas is far from complete in many European cancer registries. In order to monitor trends, evaluate the effects of early detection activities and investigate opportunities for improvements in early detection, the completeness of registration needs to be improved in the near future.

In chapter 5 and chapter 6 (the general discussion) we concluded that the most likely cause of the increases in melanoma incidence and mortality is the increased intermittent exposure to ultraviolet radiation which has been ongoing in the 20th century, due to the positive image of having a tan, increased leisure time, changing recreational habits and the increasing availability of affordable flights to (sub)tropical destinations. The strong observed and predicted increases in skin cancer incidence will result in an increased demand of at least 4% per year for preventative and diagnostic care by medical specialists, mostly general practitioners and dermatologists. However, the current and expected future shortages in the number of dermatologists and general practitioners will limit the quality of preventative care that can be given.

Primary prevention of melanoma remains of crucial importance, but is aggravated by the fact that sunlight has both positive and negative health effects. Moreover, in north-western Europe the amount of sunlight is limited and few young people have been directly confronted with skin cancer, making them less receptive to prevention messages. Having a tanned skin is still a symbol of health and wealth in western societies. Changing this positive image of having a tan into a negative one will most likely be very effective for primary prevention. Early detection activities should focus on the middle aged and elderly, especially males, as mortality rates in this group are still relatively high.
More research is needed to unravel the complicated associations between sun exposure and skin cancer risk. The use of good quality cancer registry data can help in monitoring the effects of primary or secondary prevention campaigns.

Samenvatting

In dit proefschrift worden verscheidene aspecten van de epidemiologie van het melanoom van de huid (melanoom) beschreven: variaties in ziektefrequentie in tijd en plaats, determinanten van de incidentie van melanoom en variatie in prognostische factoren.

In hoofdstuk 2 beschreven we de ontwikkelingen in incidentie en mortaliteit van melanoom in Nederland en Europa. In Nederland zagen we opvallende toenames in incidentie rates (2-3% per jaar), met name bij mensen van 45 jaar en ouder. De voor leeftijd gestandaardiseerde mortaliteit nam weinig toe bij vrouwen (1% per jaar), bij mannen was de toename sterker (3%). Leeftijdsspecifieke sterftecijfers namen sterk toe met leeftijd, met name bij mannen. Er was een gradiënt in incidentie van noordwest naar het zuidoost Nederland, met de hoogste rates in het Noordwesten. Deze gradiënt kwam overeen met gradiënten in huids- en haarkleur en recreatieve mogelijkheden.
Incidentie rates in Noordwest Europa waren hoog (voor leeftijd gestandaardiseerde rates (ASR) tot 31 in Noorwegen) en het hooggelegen Zwitserland (ASR 25), maar rates in mortaliteit en incidentie vlakten af in de jongere leeftijdscategorieën in enkele van deze landen. In andere Europese regio's waren de incidentierates lager maar namen snel toe in alle leeftijdsgroepen. Terwijl de incidentie rates in de meeste blanke populaties toenemen naarmate men dichter bij de evenaar komt, zoals ook in Oost Europa het geval was, werd een omgekeerd patroon gezien in West Europa.

De hoge incidentie rates voor melanoom in Noordwest Europa gingen samen met relatief lage rates in mortaliteit, grotendeels vergelijkbaar met die in Europese regio's met een lagere incidentie. De gunstige overleving in Noordwest Europa hangt waarschijnlijk samen met vroege ontdekking van melanomen. De toenames in incidentie van het melanoom waren vooral zorgwekkend voor de groep oudere mannen, waar de rates in mortaliteit nog steeds sterk toenamen.

In hoofdstuk 2.2 presenteerden we trends in de incidentie rates van het basaalcelcarcinoom (BCC) in Zuidoost Nederland. Deze regio is een van de weinige gebieden ter wereld waar informatie over deze tumoren wordt verzameld door de kankerregistratie (IKZ). De kenmerken van BCC hebben veel overeenkomsten met die van het melanoom. De rates namen snel toe met 2 tot 4% per jaar. De belangrijkste toenames werden waargenomen bij jonge vrouwen met toenames van bijna 6% per jaar.
Relatieve risico's naar geboortecohort namen toe bij vrouwen die geboren werden na 1956, terwijl er een afvlakking leek te zijn bij vrouwen die eerder, in de jaren 1940, werden geboren.
Incidentie rates van melanoom, BCC en plaveiselcelcarcinoom in Nederland zijn toegenomen, en zullen blijven toenemen, zoals duidelijk werd in hoofdstuk 2.3.

Toenames in het aantal melanoom- en BCC-patiënten worden ook verwacht in de jonge leeftijdsgroepen. Het totale aantal huidkankerpatiënten met een eerste primaire tumor neemt naar verwachting toe van ongeveer 20.000 nieuwe gevallen in het jaar 2000 tot zo'n 37.000 in het jaar 2015.
Het toenemende aantal nieuwe huidkankerpatiënten plaatst een zware druk op de gezondheidszorg, zelfs al is de grote meerderheid van de huidkankers niet dodelijk. Steeds vaker worden ingewikkelde (chirurgische) procedures toegepast, zoals Mohs micrografische chirurgie, wat nog een grotere druk op de zorg tot gevolg heeft.

In hoofdstuk 3.1 bevestigden we het bestaan van een seizoensgebonden patroon van incidentie van het melanoom in West Europa, waarbij de meeste melanomen in de zomer werden gediagnosticeerd. Dit patroon was sterker in gebieden met een hogere breedtegraad (in het Noorden). De piek in de zomer kan verschillende oorzaken hebben. Andere kleedgewoontes in de zomer maken een groter deel van de huid zichtbaar. Daardoor worden afwijkende plekjes op de huid makkelijker ontdekt. Ook zou blootstelling aan ultraviolette straling op de korte termijn de progressie van melanoom kunnen stimuleren.
In Oost Europa werd geen seizoensgebonden patroon in incidentie waargenomen. Dit zou verklaard kunnen worden door vertragingen in de diagnose, geïllustreerd door de hoge gemiddelde Breslow dikte van melanomen die in Oost Europa gediagnosticeerd werden.

We bestudeerden ook het verband tussen het gebruik van zonnebanken en de kans op het krijgen van een melanoom in een groot, internationaal, patiënt-controle onderzoek (hoofdstuk 3.2-3.5). Helaas had de studie te lijden onder biasen en andere methodologische problemen, die het trekken van conclusies over de belangrijkste onderzoeksvraag, namelijk of het gebruik van zonnebanken de kans op het krijgen van een melanoom vergroot, onmogelijk maakte.

Er was een sterk vermoeden van onderrapportage van blootstelling aan de zon door zowel patiënten als controles. Dit vermoeden werd veroorzaakt door (a) de negatieve associatie tussen gerapporteerde blootstelling aan de zon en de kans op melanoom en het aantal moedervlekken op de armen, (b) de positieve associatie tussen gerapporteerd beschermend gedrag en de kans op melanoom en (c) het hoge percentage van patiënten dat ontkende dat blootstelling aan de zon een bijdrage zou hebben kunnen leveren aan hun melanoom.
Zelfselectie van controles kan ook een rol hebben gespeeld in deze studie. Naast de specifieke problemen die we in deze studie tegen kwamen, wordt het onderzoek naar het verband tussen zonnebankgebruik en de kans op melanoom bemoeilijkt door de sterke correlatie tussen zonnebank gebruik en indicatoren van zongedrag.

In hoofdstuk 2.1 beschreven we de verschillen in verspreiding van melanoom naar lichaamsdeel en histologisch type in verschillende leeftijdsgroepen van melanoompatiënten in Nederland. In patiënten jonger dan 65 jaar was superficieel verspreidend melanoom (SSM) het meest prevalente histologische type, dat met name

voorkwam op de romp bij mannen en op de armen en benen bij vrouwen. Bij patiënten van 65 jaar of ouder was SSM ook het meest voorkomende histologische type, maar nodulaire melanomen en lentigo maligne melanomen werden ook veelvuldig geobserveerd. In deze leeftijdsgroep kwamen melanomen veel vaker in de hoofd-hals regio voor dan bij de jongere patiënten. Vergelijkbare verschillen in lichaamsverdeling werden elders in Europa gevonden (hoofdstuk 4).

We gebruikten data van de kankerregistratie om prognostische factoren te analyseren. Trends in deze factoren kunnen een indicatie van de effectiviteit van campagnes voor vroege opsporing geven. We analyseerden meerdere indicatoren, zoals stadium, histologisch subtype en anatomische lokalisatie van het melanoom. Helaas was het vaak onmogelijk om conclusies over de trends te trekken doordat er veel gegevens ontbraken.
Er werd echter wel een patroon van geografische variatie ontdekt, met hoge proporties van nieuwe gevallen van kanker in de vroege stadia in regio's met lage mortaliteit vergeleken met de incidentie (in Noordwest Europa, bijvoorbeeld Stockholm en East Anglia). Dit patroon was omgekeerd in het Zuiden en Oosten van Europa, waar de mortaliteit hoog was ten opzichte van de incidentie (bijvoorbeeld in Rioja, Cracow en Navarra).
Melanomen in Oost Europa kwamen het meest voor op de romp en waren gemiddeld dikker in vergelijking met melanomen in West Europa (gemiddeld verschil 1.4 mm), wat ook de lagere overleving van het melanoom in Oost Europa verklaart.
Toenames in BCC met de tijd werden vooral gezien op de romp, armen en benen. Terwijl BCC een tumor was die meestal in het hoofd-halsgebied voorkwam, werden de toenames in BCC vooral waargenomen op de onderbroken blootgestelde lichaamsdelen. Dit vertoont sterke overeenkomsten met de kenmerken van de trends in het melanoom, waar de toenames het sterkst waren op de onderbroken blootgestelde lichaamsdelen.

Gegevens van kankerregistraties zijn zeer bruikbaar voor het bestuderen van dit soort trends. Meer kankerregistraties zouden gegevens over BCC moeten verzamelen om een beter inzicht in de huidkankerepidemie te krijgen. De gegevens van lichaamsdeel, histologie en stadium van melanomen is echter verre van compleet in veel kankerregistraties in Europa. Om trends te volgen, vroege detectie activiteiten te evalueren en te onderzoeken waar de mogelijkheden voor vroege detectie liggen, zal de registratie van deze gegevens in de nabije toekomst sterk verbeterd moeten worden.

In hoofdstuk 5 en de algemene discussie (hoofdstuk 6) kwamen we tot de conclusie dat de meest aannemelijke oorzaak van de toenames in de incidentie van het melanoom de toegenomen intermitterende blootstelling aan ultraviolette straling is. Dit type blootstelling nam sterk toe in de 20e eeuw door toenames in het aantal vrije dagen, veranderende recreatiepatronen, en de toegenomen aanwezigheid van betaalbare vluchten naar (sub)tropische gebieden.

De sterke geobserveerde en voorspelde toenames in de incidentie van huidkanker zullen uitmonden in een toenemende vraag naar preventieve en diagnostische zorg door medisch specialisten, met name dermatologen, van zo'n 4% per jaar. De huidige en verwachte toekomstige tekorten in het aantal huisartsen en dermatologen zal de kwaliteit van de zorg echter beperken.

Primaire preventie van het melanoom (door het beperken van excessieve blootstelling aan ultraviolette straling) blijft van cruciaal belang, maar wordt bemoeilijkt door het feit dat zonlicht zowel positieve als negatieve (gezondheids) effecten heeft. Bovendien is in Noordwest Europa de hoeveelheid zonlicht beperkt en zijn maar weinig jonge mensen ooit direct geconfronteerd met huidkanker, wat ervoor zorgt dat ze minder gevoelig zijn voor preventieve boodschappen. Het hebben van een gebruinde huid is nog steeds een symbool van gezondheid en welvaart in Westerse maatschappijen. Het veranderen van dit positieve imago van het hebben van een bruine huid in een negatief imago zal waarschijnlijk een zeer effectieve primaire preventie boodschap zijn. Campagnes voor vroege opsporing zouden zich vooral moeten richten op mannen van middelbare en oudere leeftijd, aangezien de mortaliteit in deze groep nog steeds hoog is.
Er is meer onderzoek nodig om de complexe associaties tussen blootstelling aan de zon en de kans op huidkanker te verhelderen. Kankerregistratiedata van goede kwaliteit kunnen helpen bij het analyseren van primaire en secundaire preventie campagnes.

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Curriculum Vitae

Esther de Vries was born on July 26th, 1977 in Amersfoort, the Netherlands. After graduating from secondary school in 1995 she started studying Biology at the University of Utrecht. She also spent one year at the University of Maastricht, where she completed the Epidemiology programme of the faculty of Health Sciences. In August 2000 she was awarded her degree in Biology, specialising in endocrinology, health education and epidemiology. In September 2000 she started her PhD project on the epidemiology of melanoma at the Department of Public Health in the Erasmus MC in Rotterdam and in the Comprehensive Cancer Centre South (IKZ) that also includes the Eindhoven Cancer Registry. She was registered as Epidemiologist A with the Netherlands Epidemiological Society (VvE) in 2001 and received the degree of Master of Science in Epidemiology from the Netherlands Institute of Health Sciences (n i h e s) in 2003.

She has been a member of the Epidemiology of Melanoma (EpiMel) group of the European Organisation for Research and Treatment of Cancer (EORTC-MG) in Brussels, Belgium since 2000.
In the spring of 2002 and autumn of 2003, she was invited to work at the Unit of Descriptive Epidemiology of the International Agency for Research on Cancer, World Health Organisation (IARC, WHO) in Lyon, France. At IARC, she investigated patterns of melanoma incidence and mortality based on data from 165 cancer registries throughout Europe. She was also assistant-teacher of statistics during the 'Summer School on cancer registration and applications in epidemiology' and wrote a Cancer Fact Sheet on melanoma for the European Network of Cancer Registries (ENCR).
Between 2000 and 2004, whilst working at the Department of Public Health of Erasmus MC, she focussed her research activities on skin cancer epidemiology. She also supervised MSc students during the research and writing phases of their Masters-projects. Since November 2003 she has been a member of the seminar committee of the Department of Public Health and has also been involved in the organisation committee for the annual congress (WEON) of the Netherlands Epidemiological Society (VvE), held in Rotterdam.
She has been involved in several projects of the Cancer Watch Committee of the Dutch Cancer Society: she wrote the report 'Ultraviolet Radiation and Skin Cancer' in 2001 and 2002 on behalf of the expert committee 'Sunbathing and Skin cancer'; in 2003 and 2004 she contributed to the report 'Cancer in the Netherlands; trends, prognoses and implications for health care' on behalf of the expert committee 'Prevalence'.

On September 1st, 2004 she started her job as a post-doc researcher at the department of Public Health in Rotterdam within the framework of the collaboration with the IKZ. Her activities include teaching, analysing and interpreting cancer registry data. She is currently preparing a study on the positive health effects of ultraviolet radiation, incorporating the study of secondary tumours and co-morbidity in cancer patients. She is also involved in developing proposals on cancer prevention for the European Community 6th Framework Programme.

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