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

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Abstract

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.

Keywords: Melanoma; Cancer registry; Epidemiology; Trends; Incidence; Mortality; Regional

1. 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].

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2. Patients and methods

2.1. 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.

2.2. Analysis

Age-adjustment was performed by direct standardisation 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 $y = \ln(\text{rate})$ 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 $m/\text{SE}m$, while the number of degrees of freedom was equal to the number of calendar years minus two. The standard error of m, i.e. SEm, 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: $y = N \times e^{\alpha_{\text{region}} + \beta_{\text{period}}}$. Likelihood ratio tests were performed for the models with only period of registration ($y = N \times e^{\alpha + \beta_{\text{period}}}$) versus the model which included region ($y = N \times e^{\alpha_{\text{region}} + \beta_{\text{period}}}$), 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 sum-test 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 χ^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].

3. Results

3.1. Overall incidence and mortality data

Between 1989 and 1998, a total of 18 383 melanoma cases were diagnosed in The Netherlands (7502 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 (5678 males and 5176 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 10^5 person-years (EAPC 0.9%, $P < 0.004$). In contrast, male melanoma mortality rates increased markedly from 2.5 to 3.1 per 10^5 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).

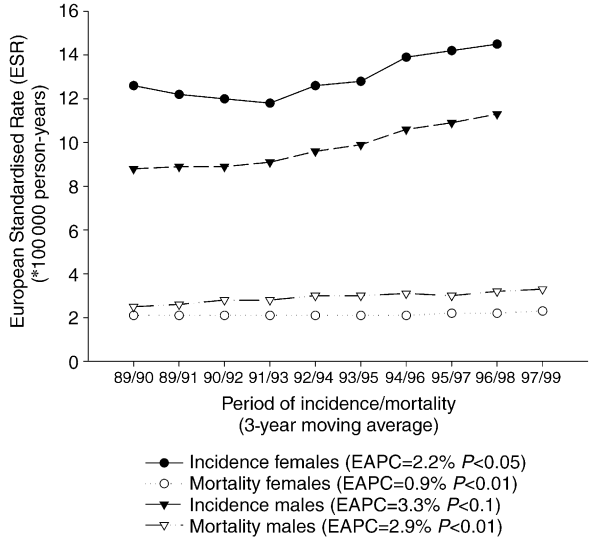

Fig. 1. Incidence and mortality of cutaneous malignant melanoma, 3-year moving average, European Standardised Rates (*10^5 person-years), with Estimated Annual Percentage Change (EAPC).

3.2. 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). 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).

3.3. 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).

3.4. 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].

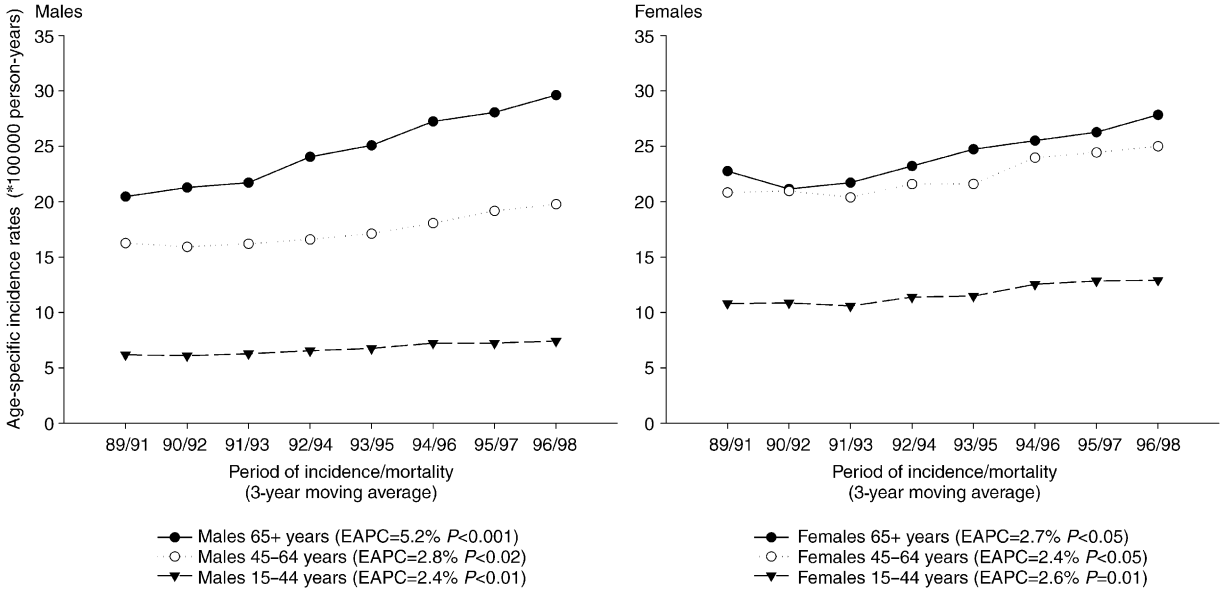

Fig. 2. Age-specific incidence rates (*10^5 person-years) for cutaneous malignant melanoma, according to gender, 3-year moving average, with Estimated Annual Percentage Rate (EAPC).

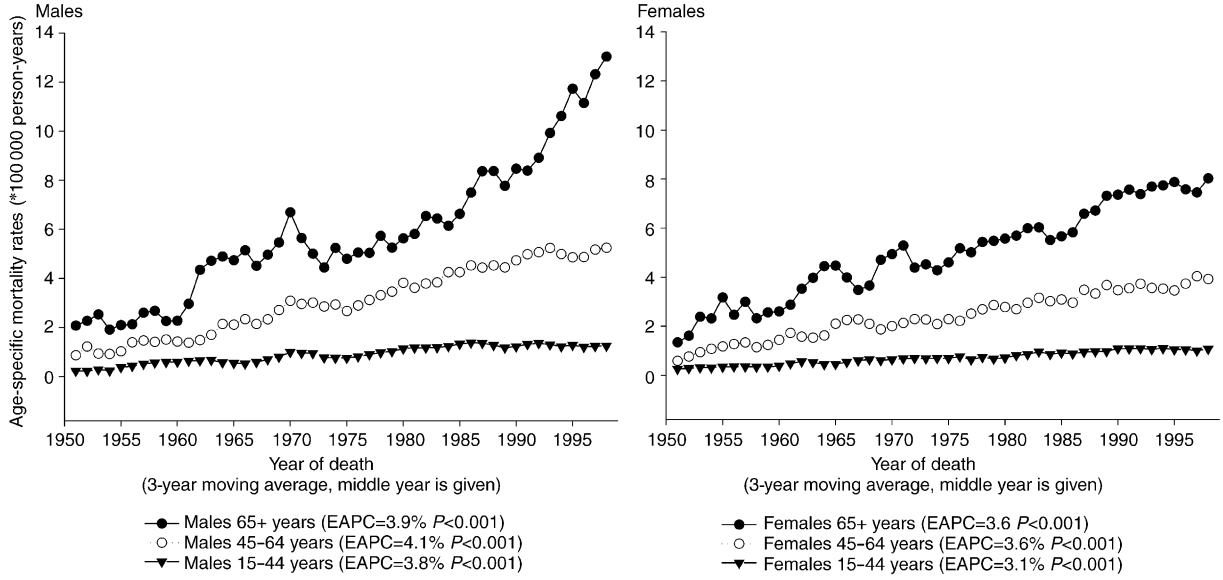

Fig. 3. Age-specific mortality rates (*10^5 person-years) for cutaneous malignant melanoma, according to gender, 3 year moving average, with Estimated Annual Percentage Rate (EAPC).

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

	Males		Females	
	35–64 years	⩾65 years	35–64 years	⩾65 years
Type of melanoma[a]				
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[a]				
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.

[a] Unstandardised incidence rates are given (n/100 000).

4. Discussion

4.1. 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]. 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

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 melanoma	Head/neck		Trunk		Arms		Legs		Other and overlapping	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
	ESR (%)	ESR (%)	ESR (%)	ESR (%)	ESR (%)	ESR (%)	ESR (%)	ESR (%)	ESR (%)	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* (0.9)	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, European Standardised Rate.

* ESR smaller than 0.05.

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 $\leqslant 0.75$ mm and/or invasion of papillary dermis (Clark level II); T2, Breslow thickness > 0.75, $\leqslant 1.50$ mm and/or invasion of papillary–reticular dermal interface (Clark level III); T3, Breslow thickness > 1.50, $\leqslant 4.00$ 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). df, degrees of freedom. 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).

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.

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

Variable	Males		Females	
	Coefficient	P value	Coefficient	P value
Period	0.033	<0.001	0.022	<0.001
Region[a]				
West	−0.150	<0.001	−0.062	0.053
East	−0.146	<0.001	−0.167	<0.001
North	−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

[a] Region North is reference value.

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 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

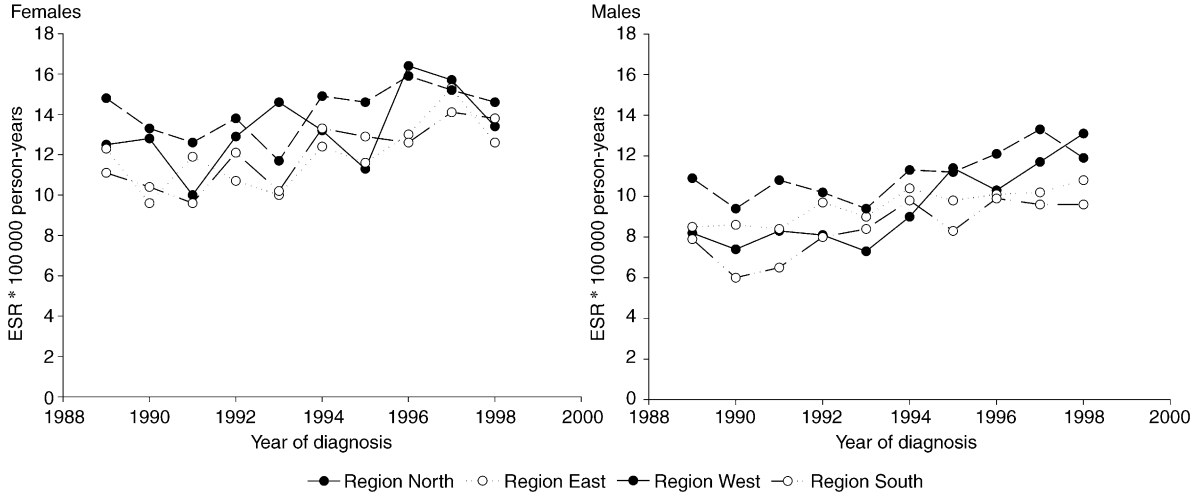

Fig. 4. Regional variation in melanoma incidence rates (*10^5 person-years) (European Standardised Rates (ESR)).

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].

4.2. 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].

4.3. 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.

4.4. 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 identifiability 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 classifications, (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.

5. 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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