Original Article

Trends of cutaneous melanoma in the Netherlands: increasing incidence rates among all Breslow thickness categories and rising mortality rates since 1989

L.M. Hollestein [1], S.A.W. van den Akker [2], T. Nijsten [1], H.E. Karim-Kos [2], J.W. Coebergh [2]

E. de Vries [1,2].

[1]Department of Dermatology, Erasmus MC, Rotterdam, The Netherlands

[2]Department of Public Health, Erasmus MC, Rotterdam, The Netherlands

Corresponding author:

E. de Vries, PhD

Department of Public Health and department of Dermatology, Erasmus MC

PO Box 2040, 3000 CA Rotterdam, The Netherlands

Tel: +31 10 407 77 30; Fax: +31 10 463 84 75

Email: e.devries@erasmusmc.nl

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Abstract

Background: It has been debated that the epidemic of melanoma is largely due to overdiagnosis, since increases in incidence were mainly among thin melanomas and mortality rates remained stable. Our objective was to examine this controversy in the Netherlands.

Patients and Methods: Information on newly diagnosed melanoma patients was obtained from the Netherlands Cancer Registry (NCR). European Standardised Rates (ESR) and Estimated Annual Percentage Change (EAPC) were calculated for the period 1989-2008. Cohort-based, period-based and multivariate survival analyses were performed.

Results: The incidence rate of melanoma increased with 4.1% (95% CI: 3.6-4.5) annually. Incidence rates of both thin melanomas (≤ 1mm) and thick melanomas (> 4 mm) increased since 1989. Mortality rates increased mainly in older patients (>65 years). Ten-year relative survival of males improved significantly from 70% in 1989-1993 to 77% in 2004-2008 ($p < 0.001$) and for females the 10-year relative survival increased from 85% to 88% ($p < 0.01$). Recently diagnosed patients had a better prognosis even after adjusting for all known prognostic factors.

Conclusion: Since incidence of melanomas among all Breslow thickness categories increased as well as the mortality rates, the melanoma epidemic in the Netherlands seems to be real and not only due to overdiagnosis.

Introduction

Worldwide, almost 200,000 patients are diagnosed with cutaneous melanoma (melanoma) each year [1]. Incidence rates are increasing in all countries, except in Australia and Canada [2]. Although, incidence rates in Australia remain very high. In the Netherlands the incidence of melanoma increased since 1989, the first year of the National Cancer Registry. Incidence, mortality and survival of cutaneous melanoma in the Netherlands were described by de Vries et al. up to 1998 [3]. Ten years of additional data have become available since these analyses. Incidence of all cutaneous malignancies in the Netherlands have recently been described by Holterhues et al., indicating that melanoma incidence has almost doubled in 2005 compared to 1989 [4]. As melanoma incidence rates are rising in many countries, it is debated if this increase represents a real melanoma epidemic or that this might have been caused by increased awareness leading to potential overdiagnosis. Overdiagnosis in melanoma could be the results of diagnostic drift, which reclassified what were previously found to be benign melanocytic nevi as truly malignant melanomas [5-7]. We hypothesized that there is a real increase in melanoma incidence and that, therefore, there is a real increase in thin and thick melanomas as well as melanoma related mortality. To examine this controversy in the Netherlands, incidence rates together with mortality rates and survival of melanoma patients were examined to better understand the recent trends of melanoma in the general Dutch population.

Methods

Data collection

Population-based data from the nationwide Netherlands Cancer Registry (NCR), which started in 1989 and is maintained and hosted by the Comprehensive Cancer Centres, were used [8]. The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA). Additional sources are the

national registry of hospital discharge, which accounts up to 8% of new cases, haematology departments and radiotherapy institutions. Information on patient characteristics like sex, date of birth, and tumour characteristics such as date of diagnosis, subsite (International Classification of Diseases for Oncology (ICD-O-3) [9] histology, stage (Tumour Lymph Node Metastasis (TNM) classification) [10] are obtained routinely from the medical records. The quality of the data is high, due to thorough training of the administrators and computerised consistency checks at regional and national levels. Completeness is estimated to be at least 95%. Follow-up of vital status of all patients was calculated as the time from diagnosis to death or to the 1st of February 2010. The information on vital status was initially obtained from municipal registries and from 1995 onwards from the nationwide population registries network. These registries provide virtually complete coverage of all deceased Dutch citizens.

For the present study, all patients with invasive primary cutaneous melanoma (C43) diagnosed in the period 1989-2008 in the Netherlands were included (n=45,919). Age was divided in three groups (0-44, 45-64, ≥65years). The study period was divided in four categories: 1989-1993, 1994-1998, 1999-2003, and 2004-2008 to study trends. TNM was determined postoperative. Clinical stage was used in cases where postoperative stage was unknown. Tumour localisation was categorised into anatomical subsites: head and neck (C43.0, C43.1, C43.2, C43.3, C43.4), trunk (C43.5), arms (C43.6), legs (C43.7), and other (C43.8, C43.9). For the period 1989-1994 only survival data of five regional cancer registries was available, which are representative for the whole of the Netherlands. Patients younger than 15 years and older than 95 years were excluded from the survival analysis, as well as cases diagnosed by autopsy.

Mortality data for the period 1989-2009 was obtained from Statistics Netherlands.

Statistical analyses

Annual incidence and mortality rates for the period 1989-2008 were calculated per 100,000 person-years, using the annual mid-year population size as obtained from Statistics Netherlands. Rates were age-standardised to the European standard population (European Standardised Rates (ESR)). Changes were evaluated by calculating the estimated annual percentage change (EAPC) and the corresponding 95% confidence interval (CI). To calculate this, a regression line was fitted to the natural logarithm of the rates, using the calendar year as regressor variable (i.e. $y=ax + b$ where $y = \ln(\text{rate})$ and x = calendar year, then $EAPC = 100 * (e^{a-1})$). Incidence rates were also calculated per sex, age group, histological subtype, bodysite and stage.

Due to changes in staging of melanoma over time, time trends were tested by comparing nodular status (N) and metastatic status (M) of the TNM of which the definition remained unchanged over time. Breslow thickness was used to test for trends in melanoma thickness over time, because classification of tumour thickness (T of TNM) changed over time. Time trends in melanoma thickness were calculated for the period 1994-2008, because Breslow thickness was routinely registered since 1994.

Traditional cohort-based 10-year relative survival analysis was used for the period 1989-1998 which represents the survival of patients diagnosed during 1989-1998. Since follow-up was available until January 2010 period-based 10-year relative survival analysis was used for the most recent period 1999-2008, which gives the most up-to-date estimates for this period [11]. Multivariate relative survival analyses, using Poisson regression modeling, were carried out to estimate relative excess risk (RER) of dying adjusted for follow-up interval [12]. Two multivariate models were fit; a model without Breslow thickness, covering the whole period (1989-2008) and a model with Breslow thickness, excluding the first time period (1989-1993). SAS software (SAS system 9.2, SAS Institute, Cary, NC) was used to perform the statistical analyses. P-values were two-sided and considered significant if $p< 0.05$.

Results

The average population size of the Netherlands between 1989 and 2008 was 15.7 million. During this 20-year period 19,393 males and 26,526 females were diagnosed with melanoma. Between 1989 and 2009 5,840 males and 4,769 females died due to melanoma.

Trends in incidence

The age-standardised incidence (ESR per 100,000 person-years) increased from 11.3 in 1989 to 21.7 in 2008 (EAPC 4.1, 95% CI: 3.6-4.5) [Figure 1]. In table 1 ESR are provided per 100,000 person-years for four 5-years periods by sex, age, histopathologic subtype, bodysite, nodular status, metastatic status and Breslow thickness. For both sexes the highest incidence rates were observed in patients older than 65 years. Superficial Spreading Melanoma (SSM) was the most commonly diagnosed subtype in males and females and the incidence of this subtype increased more rapidly than the incidence of other subtypes (EAPC 7.6, 95% CI: 7.1-8.2 and 6.5, 95%CI: 6.0-7.0 for males and females, respectively). The trunk was the most commonly affected body site in males and the legs were the most commonly affected body site in females.

The incidence of melanoma in each of the 4 Breslow thickness categories increased significantly in the study period. Thin melanomas (<= 1mm) increased each year with 7.0% and 6.1% for males and females, respectively. Thick melanomas (>4 mm) increased as well, with an annual increase of 5.3% for males and 6.5% for females. Thick melanomas increased with approximately the same rate as thin melanomas in females. In contrast to Breslow thickness and nodal involvement, the presence of systemic metastasis did not increase significantly between 1989 and 2008.

Trends in survival

Over time, a small increase in relative survival was observed for both sexes [Table 2, Figure 2]. The 10-year relative survival for males increased significantly from 70% in the period 1989-1993 to 77% in the period 2004-2008 ($p < 0.001$). In the same period, the 10-year relative survival for females increased significantly from 85% to 88% ($p < 0.01$). The relative excess risk (RER) of dying decreased significantly over time for males and females [Table 2]. Relative survival improved significantly in more recent periods of diagnosis, also after adjusting for age, histological subtype, bodysite, nodular status, metastatic status and Breslow thickness. Relative excess risks showed the expected patterns for all mentioned covariates [Table 2].

Since Breslow thickness has not been routinely registered during the period 89-93, this first period was not included in multivariate analyses. A multivariate model without Breslow thickness was fit over all four time periods, using the period 89-93 as a reference, showing decreasing RER of dying for the more recent periods [data not shown].

Trends in mortality

The absolute number of annual deaths due to melanoma increased from 337 in 1989 to 794 in 2009. The age-standardised mortality rate due to melanoma increased from 2.2 per 100,000 person years in 1989 to 3.9 per 100,000 person years in 2009 (EAPC 2.3, 95% CI: 2.0-2.6) [Figure 1]. Mortality rates in younger patients (0-44 year) remained stable over the years [Figure 3]. A significant increase in mortality was observed in patients aged 45 to 64 years. The steepest increase in mortality was observed in males and females older than 65 years (EAPC 4.1, 95% CI: 3.1-5.0 and 2.2, 95% CI: 1.4-3.0, respectively).

Discussion

The aim of our study was to assess concordance in time in trends of incidence, mortality and survival of cutaneous melanoma in the Dutch general population. The findings of this study

suggest that the melanoma incidence is truly rising and is not solely depending on increased diagnosis, because melanoma incidence among all Breslow categories increased as well as melanoma mortality.

Trends in incidence

An overall increase in incidence rate was observed, which is in line with results from many countries [2, 13-15]. However, in Australia and Canada incidence rates have been observed to be stabilizing or even decreasing in younger individuals [16-17], possibly as result of successful health care campaigns in avoiding sun exposure [17]. In most countries the increase in incidence rate is primarily due to an increase of thin melanomas while the incidence rate of thick melanomas is no longer increasing [18-19]. It has been debated that this epidemiologic pattern indicates early diagnosis due to improved awareness and possibly overdiagnosis by pathologists rather than a real increase in the disease.

We observed an increase in thin as well as thick (>4 mm) melanomas. In females, the thick melanomas increased annually with the same percentage as thin melanomas. Similar results are reported in England and the USA among older patients (>65 years)[13, 15]. The observed increase over the whole spectrum of all stages of melanoma is an argument in favor of a real increase in incidence of disease [7]. Alternative explanations would include a more conservative approach of the pathologists or improvements in the cancer registry practices. The more conservative pathologist explanation would mainly result in increases in the thin melanomas. It is possible that the cancer registry has improved over time, resulting in a larger proportion of melanomas of all thicknesses appearing in the cancer registry. Indeed, in a study verifying data from 3 regional Dutch cancer registries from 1990 it was found that the completeness of skin malignancies (excluding basal cell carcinomas) was 92.9% [20]. However, the proportion of cases not being included in the database would largely depend on histopathology diagnosis, and presumably most of the 7.1% of ‘missed’ cases would be

squamous cell carcinomas. Moreover, an increase in completeness of the registry above the 92.9% is unlikely to result in EAPCs as strong as observed among all thickness categories in our study.

Although awareness of potential harmful effects of sun exposure has increased in the Netherlands in recent years [21], incidence rates of melanoma have not stabilized and are expected to rise even further [22]. Incidence rates were increasing most steeply in older patients (>65 years). Due to unawareness of potential harmful effects of sunlight in their younger years, these older patients could have accumulated high amounts of sun exposure and high number of sunburns during their (adolescent) lifetime. Prevention campaigns started at the end of the eighties, when the Dutch cancer society (KWF) started campaigns at the Dutch and Spanish beaches to increase awareness of risk factors for skin cancer among these high risk populations [personal communication][21].

The largest incidence rates and mortality rates were observed in older patients. Therefore, future secondary prevention campaigns should aim to increase awareness in this high risk group. Although it might be difficult to reach specific subgroup of patients, targeted secondary prevention campaigns may be possible [23].

Trends in survival

The survival of Dutch melanoma patients has been described for three geographic regions in the Netherlands [24-25], showing that survival rates of females were significantly better and independent of patient's demographics and classical melanoma characteristics. We observed an increase in 10-year relative survival for both sexes over time. In most European countries, the 5-year relative survival improved as well, with a relative increase varying from 1 to 30% [26]. In the observed time period no major improvements in the treatment of melanoma have been introduced. The improvements in relative survival may partly have been caused by increased awareness and earlier detection, which artificially prolongs survival time leading to

a lead time bias in the analysis [27]. Our multivariate survival analyses were adjusted for follow-up time of each patient to correct for lead time bias as much as possible. Observed changes in distribution of melanoma thickness, histological subtype and other prognostic factors could have caused the change in survival. Multivariate analysis on survival showed that period of diagnosis decreased relative survival, independent of changes in distribution of all known prognostic factors over time. This result might be caused by the introduction of the sentinel lymph node procedure for melanoma patients in 1992, although the effect on survival is still unclear and under evaluation [28]. Another possibility is that dermatologist and pathologists in more recent periods became more cautious and classified slightly atypical pigmented lesions more often as malignant melanomas [7]. This diagnostic drift leads to a bias of prolonged survival times in the more recent periods.

It is expected that survival may improve even further in the future, particularly for advanced disease, because new promising therapies are currently tested in clinical trials [29]. These therapies include B-RAF inhibitors and cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) inhibitors. B-RAF is part of the mitogen-activated protein kinase (MAPK) pathway and is mutated in approximately 60% of all melanomas [30]. Increased expression of CTLA-4 downregulates the immune response [31]. By inhibiting CTLA-4 the naturally occurring immune responses to tumor cells can be enhanced. Recently a phase III trial on ipilimumab was published, showing improved overall survival in patients with metastatic melanoma [32].

Trends in mortality

We observed increased mortality rates, which is in contrast with findings in most other countries, where mortality rates remain stable over the years [14-15, 33]. As melanoma thickness is a strong predictor for disease progression, the observed increase in thick melanomas could have been the cause of the increased mortality rates [34-36]. In other

European countries, like England, France, Italy, Sweden and Poland, mortality rates increased as well [26, 37]. In our data mortality rates did not increase as rapidly as incidence rates, which could have been caused by the improved survival of melanoma patients. Incidence rates of patients diagnosed with metastatic melanomas did not increase over time, but mortality rates did increase during the study period and do not seem to stabilize [Figure 3]. This indicates that a subgroup of melanomas without distant metastasis at diagnosis metastasize over time leading to death.

Increased incidence rates accompanied by increased mortality rates suggest a true increase in the amount of melanomas, rather then a potential overdiagnosis [6-7, 38]. We therefore state that the observed increase in incidence reflects a real increase of melanoma patients in the Netherlands, rather than an artifact which have been caused by diagnostic drift.

Conclusion

We observed increased incidence rates of melanoma in the Netherlands since 1989. This was due to the increase of thin as well as thick melanomas, which is a worrying trend as melanoma thickness is a strong predictor for prognosis [34-36]. The increase in incidence was accompanied by an increase in mortality. Survival improved over time independent of the distribution of all known prognostic factors. This pattern points at a real melanoma epidemic in the Netherlands. To improve survival and decrease incidence and mortality rates in the future, efforts should be made to increase primary and secondary prevention of melanoma. Primary prevention campaigns should aim at parents to protect their children from sunburns in childhood and adolescence. Secondary prevention campaigns should include older and male patients to increase awareness of melanoma.

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Figure Legends

Figure 1: Three-year moving averages of age standardised incidence rates and mortality rates (ESR) of melanoma in the Netherlands, 1989-2008.

Figure 2. Ten-year relative survival of melanoma in the Netherland by period of diagnosis and sex, 1989-2008

Figure 3: Three-year moving averages of age standardised mortality rates (ESR) of melanoma by age of males (**A**) and females (**B**) in the Netherlands, 1989-2008.

Table 1. Age standardised incidence rates (ESR) of melanoma in the Netherlands, 1989-2008

	Males						Females					
	N[a]	1989-1993	1994-1998	1999-2003	2004-2008	EAPC (95% CI)	N[a]	1989-1993	1994-1998	1999-2003	2004-2008	EAPC (95% CI)
Incidence												
Overall	**21306**	**9.0**	**11.3**	**13.8**	**17.9**	**4.54 (4.01-4.97)**	**28889**	**12.2**	**14.6**	**17.2**	**21.5**	**3.72 (3.22-4.22)**
Age												
0-44	5758	2.6	3.0	3.4	4.1	2.80 (2.33-3.28)	10057	4.6	5.3	6.3	7.6	3.36 (2.78-3.94)
45-64	9152	4.0	5.0	6.3	8.1	4.62 (4.02-5.22)	10846	5.2	6.3	7.4	9.2	3.73 (3.14-4.32)
≥65	6396	2.3	3.2	4.2	5.7	5.98 (5.53-6.44)	7986	2.4	3.0	3.5	4.7	4.33 (3.64-5.02)
Subtype												
SSM	10924	3.4	5.3	7.0	10.6	7.64 (7.05-8.22)	16388	5.4	7.9	10.3	14.3	6.50 (6.01-6.98)
NM	3434	1.5	2.0	2.4	2.5	3.65 (2.84-4.47)	3626	1.6	1.9	2.1	2.2	2.08 (1.27-2.89)
ALM	153	0.1	0.1	0.1	0.1	6.95 (2.77-11.13)	256	0.1	0.1	0.1	0.2	6.42 (3.67-9.16)
LMM	652	0.3	0.4	0.4	0.5	4.43 (2.54-6.32)	944	0.3	0.4	0.5	0.6	5.74 (4.37-7.11)
Other	6143	3.8	3.5	3.8	4.2	0.52 (-0.24-1.29)	7675	4.8	4.2	4.2	4.2	-0.95 (-1.67- -0.23)
Bodysite												
Trunk	9815	4.1	5.0	6.3	8.5	4.95 (4.47-5.43)	7326	2.8	3.7	4.6	6.0	5.23 (4.80-5.65)
Head/Neck	3465	1.5	1.9	2.4	2.7	3.77 (2.89-4.66)	3219	1.3	1.5	1.7	2.0	2.95 (2.43-3.47)
Legs	3406	1.5	1.9	2.2	2.8	3.98 (3.20-4.77)	11306	5.2	5.8	6.9	8.1	2.98 (2.31-3.66)
Arms	3455	1.3	1.8	2.2	3.0	5.40 (4.57-6.22)	6112	2.5	3.0	3.5	4.7	4.09 (3.27-4.90)
Other	1165	0.6	0.6	0.8	0.9	2.69 (1.67-3.71)	926	0.5	0.5	0.5	0.6	1.59 (0.35-2.83)
Breslow thickness[b]												
<= 1 mm	7162		3.9	5.2	7.8	7.01 (6.10-7.92)	11960		6.5	9.0	11.9	6.14 (5.35-6.92)
1.01-2 mm	3686		1.9	3.0	3.8	6.81 (5.56-8.06)	4873		2.5	3.7	4.7	6.16 (5.41-6.91)
2.01-4 mm	2805		1.5	2.3	2.8	6.19 (4.82-7.56)	2769		1.4	2.0	2.4	5.37 (3.92-6.83)
>4 mm	1909		1.1	1.6	1.9	5.26 (4.05-6.47)	1547		0.7	1.0	1.2	6.51 (5.12-7.89)

Unknown	2490		2.9	1.7	1.6	-5.13	(-7.55- -2.72)	2857		3.5	1.5	1.3	-8.23 (-11.5- -4.96)
Nodular status													
TNM-N0/X	19710	8.6	10.6	12.6	16.3	4.22	(3.77-4.67)	27672	12.0	14.1	16.3	20.4	3.46 (2.95-3.97)
TNM-N1+	1596	0.4	0.7	1.2	1.5	9.12	(7.60-10.64)	1217	0.2	0.4	0.9	1.1	11.53 (9.78-13.28)
Metastatic status													
TNM-M0/X	21036	8.8	11.1	13.6	17.7	4.59	(4.16-5.03)	28695	12.1	14.4	17.2	21.4	3.74 (3.23-4.26)
TNM-M1+	270	0.1	0.2	0.2	0.1	0.10	(-2.09-2.29)	194	0.1	0.1	0.1	0.1	0.88 (-1.78-3.54)

[a] values may not add up to 100% of all melanomas due to missing values.
[b] Breslow thickness was routinely registered since 1994.

Table 2. Multivariate relative survival analysis of melanoma in the Netherlands, 1989-2008

	Males				Females			
	Univariate[a]		Multivariate[a,b]		Univariate[a]		Multivariate[a,b]	
	RER	95% CI	RER	95% CI	RER	95% CI	RER	95% CI
Period of diagnosis								
1989-1993	1				1			
1994-1998	0.88	(0.79- 0.98)	1		0.84	(0.74- 0.96)	1	
1999-2003	0.81	(0.72- 0.90)	0.90	(0.82- 0.99)	0.75	(0.65- 0.85)	0.92	(0.82- 1.03)
2004-2008	0.69	(0.62- 0.78)	0.83	(0.75- 0.92)	0.69	(0.59- 0.80)	0.88	(0.77- 1.00)
Age								
00-44	1		1		1		1	
44-64	1.27	(1.16- 1.38)	1.25	(1.14- 1.38)	1.41	(1.27- 1.56)	1.29	(1.15- 1.45)
65+	1.83	(1.66- 2.02)	1.61	(1.45- 1.79)	2.55	(2.27- 2.86)	1.78	(1.57- 2.03)
Subtype								
SSM	1		1		1		1	
NM	4.45	(4.01- 4.93)	1.30	(1.17- 1.46)	6.01	(5.24- 6.89)	1.42	(1.23- 1.64)
ALM	3.50	(2.38- 5.15)	1.37	(0.90- 2.09)	5.64	(3.91- 8.13)	2.61	(1.81- 3.76)
LMM	0.35	(0.15- 0.85)	0.27	(0.11- 0.70)	0.77	(0.38- 1.55)	0.16	(0.03- 0.77)
Other	4.10	(3.73- 4.51)	1.40	(1.26- 1.56)	5.13	(4.54- 5.81)	1.51	(1.33- 1.73)
Bodysite								
Trunc	1		1		1		1	.
Head/Neck	1.22	(1.09- 1.36)	0.98	(0.87- 1.11)	0.980	(0.83- 1.16)	0.84	(0.71- 1.00)
Legs	0.99	(0.89- 1.11)	0.82	(0.73- 0.93)	0.53	(0.47- 0.61)	0.54	(0.48- 0.61)
Arms	0.70	(0.61- 0.80)	0.70	(0.61- 0.80)	0.52	(0.44- 0.61)	0.47	(0.40- 0.56)
Other	7.46	(6.78- 8.20)	4.07	(3.54- 4.68)	9.26	(8.20- 10.46)	4.32	(3.59- 5.20)
Breslow thickness								
<= 1 mm	1		1		1		1	
1.01-2 mm	7.19	(5.35- 9.67)	5.26	(4.08- 6.78)	7.44	(5.45- 10.15)	5.54	(4.21- 7.28)

2.01-4 mm	20.43	(15.39- 27.12)	11.39	(8.88- 14.61)	21.06	(15.57- 28.48)	10.87	(8.25- 14.32)
>4 mm	36.40	(27.43- 48.29)	17.15	(13.32- 22.09)	54.73	(40.60- 73.79)	21.53	(16.25- 28.53)
Unknown	29.93	(22.58- 39.66)	10.20	(7.92- 13.14)	25.20	(18.69- 33.98)	8.68	(6.56- 11.49)
Nodular status								
TNM-N0/X	1		1		1		1	
TNM-N1+	4.70	(4.32- 5.11)	2.32	(2.10- 2.56)	7.77	(6.97- 8.67)	2.87	(2.53- 3.26)
Metastatic status								
TNM-M0/X	1		1		1		1	
TNM-M1	17.25	(15.01- 19.81)	7.00	(5.95- 8.23)	31.26	(26.31- 37.13)	7.31	(5.97- 8.96)

[a]The analysis is adjusted for follow-up time
[b]The first period could not be included in the multivariate model, because Breslow thickness was not routinely registered before 1994

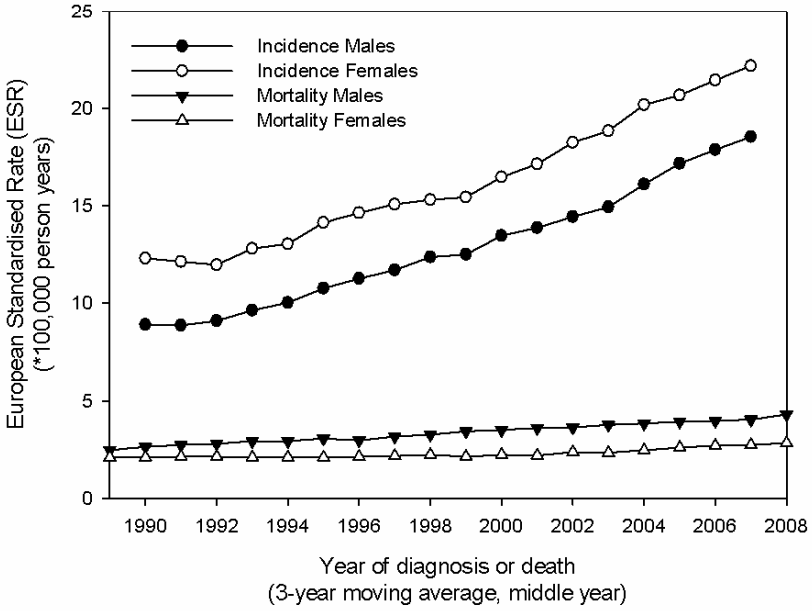

Figure 1: Three-year moving averages of age standardised incidence rates and mortality rates (ESR) of melanoma in the Netherlands, 1989-2008.

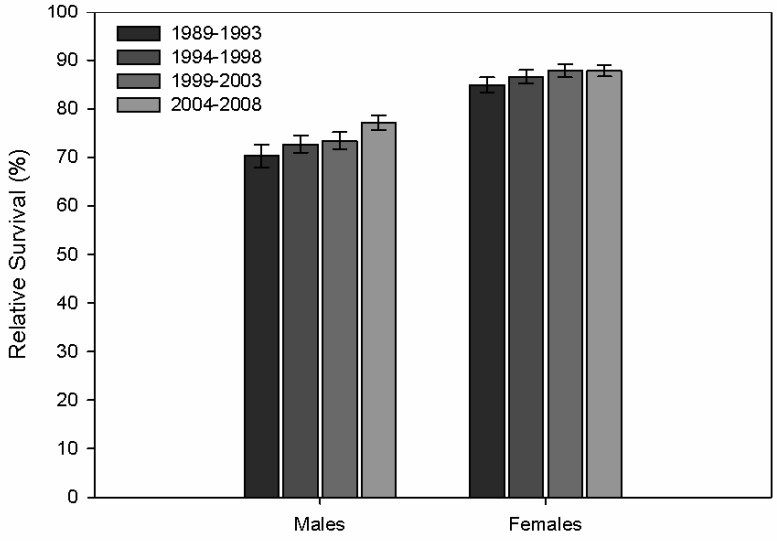

Figure 2. Ten-year relative survival of melanoma in the Netherland by period of diagnosis and sex, 1989-2008

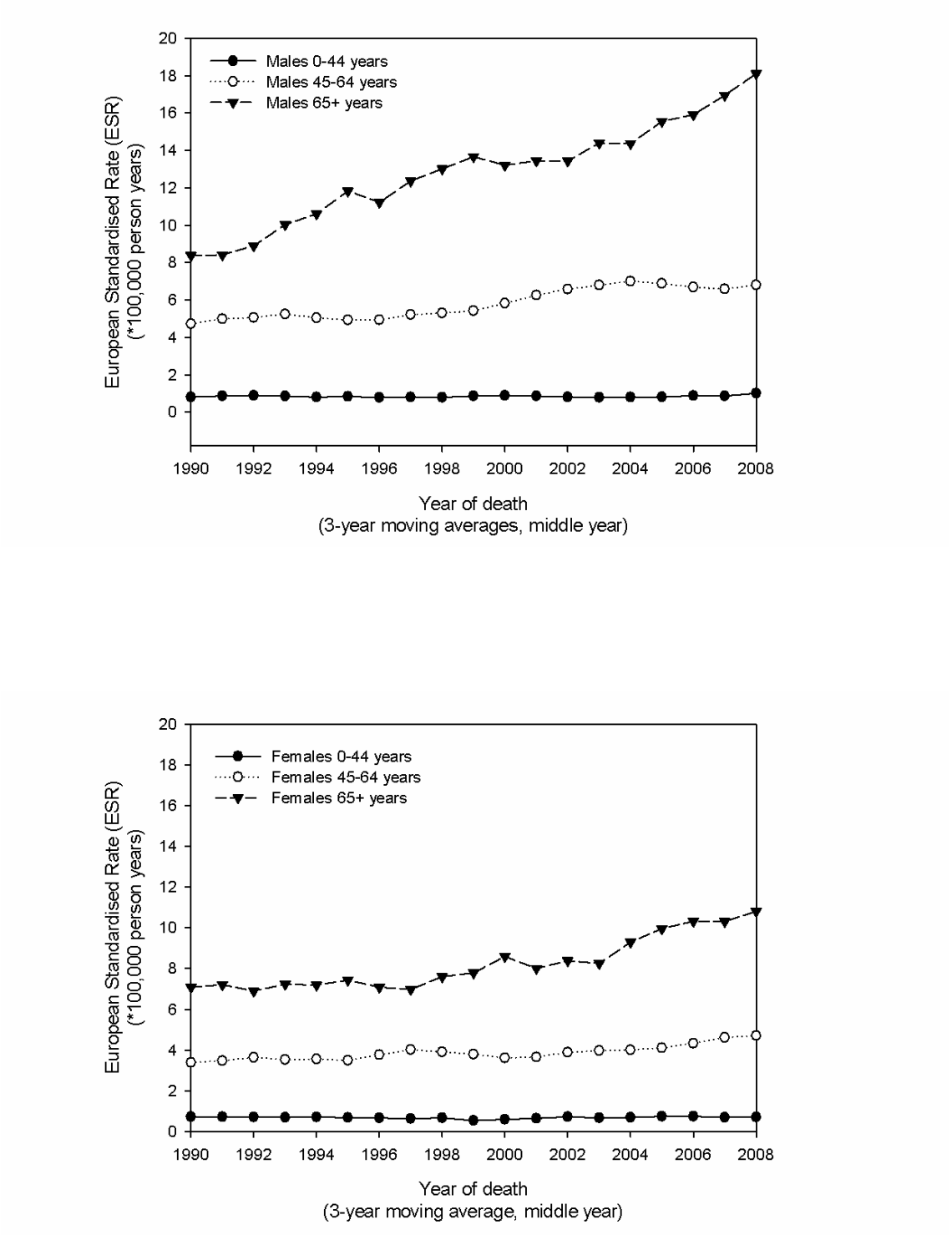

Figure 3: Three-year moving averages of age standardised mortality rates (ESR) of melanoma by age of males (**A**) and females (**B**) in the Netherlands, 1989-2008.