Drug effects on melanoma
Koomen, E.R.

Chapter 3

Burden of disease in Dutch melanoma patients, 1989-2006

Burden of melanoma

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Abstract

Background: Burden of disease is a concept describing loss of health and death due to diseases and has not been adequately studied for melanoma.

Patients and Methods: Age- and gender-specific incidence data from all patients diagnosed with melanoma between 1989 and 2006 were obtained from the Netherlands Cancer Registry. Mortality numbers were extracted from the Statistics Netherlands database. Life tables with the probability of developing a melanoma were calculated per 5-year period with use of the DevCan software. The standard life expectancy for both men and women per 5-year age group were estimated using DISMOD software. The Years Lost due to Disability (YLD) and Years of Life Lost (YLL) due to melanoma were calculated using these life tables and life expectancies. The disability adjusted life years (DALY), a general measure for the burden of a disease, was estimated by adding YLD and YLL.

Results: The incidence of melanoma almost doubled between 1989 and 2006 (cumulative incidence rate increased from 1.03-1.31% to 2.02-2.11%). The burden of melanoma to society increased rapidly between 1989 and 2006. On average, patients lived 21.6-28.2 years with a melanoma diagnosis. Melanoma resulted in a loss of 17.8-20.1 years per before the age of 95, for those that died of their melanoma.

Conclusion: Melanoma is becoming a great burden to Dutch society. Health care providers may have to adjust their current policy in treating patients with melanoma.

Abbreviations

YLD   Years Lived with Disability; the number of incident cases times the disability weight (0.05) times the average duration of the case until remission or death

AYLD   Average Years Lived with Disability; the YLD divided by the number of incident cases

YLL   Years of Life Lost; the number of deaths times the standard life expectancy at age of death

AYLL   Average Years of Life Lost; the YLL divided by the number of deaths

YLWD   Years Lived with Disease; the number of incident cases times the average duration of the case until remission or death

Introduction

In the past three decades the incidence of melanoma has markedly increased in people of European ancestry. In 2005, melanoma was the 8th most common cancer in males and the 5th most common cancer in females in The Netherlands (a total of 3515 cases among 16.4 million inhabitants) (www.ikcnet.nl). De Vries *et al.* have predicted that by 2015 the number of new cases per year will exceed 4800. [1] Compared with most other malignancies, melanoma affects patients at a younger age and has relatively good survival rates for the majority of patients, which have improved over time due to early detection. [2-5] This implies an increasing number of melanoma survivors who live with a cancer diagnosis and it's social and psychological effects and may utilize health care for medical and psychological reasons related to their melanoma history over a prolonged period of time, which can become a great burden for health care providers.

Usually, the magnitude of a cancer problem is expressed in incidence and mortality rates and numbers. However, the magnitude of the societal problem can also be expressed in a quite different way using Burden of Disease concepts that measure the disease burden for individuals or populations. These burden of disease measures may be used for research purposes, public health campaigns and for the allocation of limited health care resources. The burden of a disease can be estimated by calculating the number of years of life lost (YLL), the number of years of life lived with disease (YLD) and Disability Adjusted Life Years (DALY). [6] These additional measures are of

key importance in estimating the burden of cancer types that occur in young patients and often have a favorable prognosis.

Only a few studies have investigated the burden of melanoma. Brochez and colleagues investigated the burden of melanoma in Belgium, expressed as years of potential life lost and showed that in those terms, melanoma was the second most important cancer of all adult-onset cancers. [7] Melanoma resulted in a loss of 8 years before the age of 65 in males and 6 years in females. In the United States, the burden of melanoma has also been expressed by years of potential life lost and these rates were one of the highest for adult-onset cancers. [8] None of these studies evaluated changes in the burden over time, nor did they include the part of the population aged over 65, which is continuously growing in many European countries and therefore represents a population group which is of increasing importance.

In the Netherlands, the burden of melanoma has never been estimated by YLL, AYLL, YLD or DALYs. Therefore, we estimated the size of the burden of melanoma within the general Dutch society with these four measures using data for 1989-2006 in 4 time periods (1989-1991, 1992-1996, 1997-2001, and 2002-2006).

Patients and methods

Population
Age- and gender-specific data on newly diagnosed patients with melanoma (ICD-0 codes: C44.0-C44.9) were obtained from the Netherlands Cancer Registry, which collects incidence and tumor data on all newly diagnosed cancers in the Netherlands from the regional comprehensive cancer centers since 1989 (i.e., only first melanoma's were used for this study). We used incidence data for 1989 to 2006. Annual data on age and gender of cancer fatalities and population composition were obtained from Statistics Netherlands.

Study design
To estimate the burden of melanoma, we calculated Disability Adjusted Life Years (DALYs) by adding the number of Years of Life Lost (abbreviated YLL) by a person as a consequence of premature death due to melanoma plus the number of years of lived with disability (abbreviated YLD) caused by melanoma by a person . According to Murray *et al.*, one DALY represents the loss of one year of life lived in full health. The sum of these DALYs across the population, or the burden of disease, can be thought of as "a measure of the gap between the current health status and an ideal health

situation in which the entire population lives to an advanced age, free of disease and disability". [9]

Statistical methods

All analyses were performed for 5-year periods (except for period 1989-1991, as data was only available for 18 years) and stratified for gender. The cumulative incidence was calculated per 5-year age group by dividing the number of patients with melanoma by the total population without melanoma and totaling these results. European standardized incidence rates (ESR) were then calculated by multiplying the incidence rates with standard European population data (http://seer.cancer.gov/ stdpopulations/). To calculate the probability of a person being newly diagnosed with a melanoma during the 5-year period we used the life table method, which unlike cumulative incidence data, takes into account that the cause of death of a melanoma patient might not be related to melanoma. Also, this method calculates the probability of being diagnosed with melanoma and dying from it, for people without a history of melanoma. The DevCan software program, which was developed by the National Cancer Institute in the United States, was used to calculate these probabilities. [10] For these calculations the following assumptions were made:

(a) The incidence of melanoma is constant in each 5-year period;

(b) The probability of death not being caused by melanoma is the same for melanoma patients as for people without a history of melanoma;

(c) The data obtained from the Netherlands Cancer Registry and Statistics Netherlands were for 5-year age groups. To raise the accuracy, DevCan divides these age groups into 10 periods of 6 months. In each 6 month age group the incidence and mortality rates increase in 10 equal steps and are constant in each 6 month age group. This leads to an exponential decrease with age in each 6-month age group. The numbers of patients at risk and the probability of being diagnosed with a melanoma can therefore be more accurately calculated;

(d) All melanoma specific mortalities are registered with the Netherlands Cancer Registry.

To estimate YLD, we multiplied the number of incident cases by the average duration a patient lives with melanoma in The Netherlands and a weighing factor, determined by the World Health Organization (WHO), that reflects the impact of melanoma on health related quality of life on a scale from 0 (perfect health) to 1 (dead). Melanoma disease duration was estimated using DISMOD. [11] YLLs were calculated using the appropriate life tables. YLL corresponds to the number of deaths due to melanoma

multiplied by the standard life expectancy in the general population at the age which death occurs as estimated by a standard life table. [6] The average years of life lost (AYLL) were calculated by dividing the YLL by the number of melanoma deaths. DALYs were calculated as the sum of the YLL due to premature mortality in the population and the YLD for incident cases of the health condition (i.e., melanoma). To calculate the actual years a patient lives with their melanoma, the years lived with disease were calculated (YLWD). Therefore, we multiplied the number of melanoma patients with their life expectancy at time of diagnosis.

Results

Incidence and mortality

Between 1989 and 1991, an average of 1603 Dutch people were newly diagnosed with melanoma per year (Table 1A and 1B); this increased to 3171 individuals per year in the period 2002-2006. Of all newly diagnosed melanoma patients, 43.3% was male (ESR 15.9 per 100,000 person-years) and 56.7% was female (ESR 19.5 per 100 000 person-years) (Table 1). Cumulative incidence rates almost doubled in men (1.03% in 1989-1991 to 2.02% in 2002-2006) and increased from 1.31% to 2.13% in the same time period for females.

Age at diagnosis of melanoma increased over time; patients diagnosed in 1989-1991 were predominantly diagnosed at an age of 35-50 years (both males and females) whereas people newly diagnosed with melanoma between 2002-2006 were often older (men: mainly 55-70 years, women: mainly 40-60 years) (Fig. 1).

Mortality slowly increased from 182 to 333 males and 182 to 257 females by 2002-2006. Cumulative mortality rates also doubled up to 0.61 for males and up to 0.40% for females. An increase of melanoma mortality was particularly observed for men aged 55 to 65 and females >75 years.

Probability of being diagnosed with melanoma and to die from it

DevCan produced estimations of the probability for a person to develop a melanoma and the probability of dying from a melanoma in a certain age group (Table 2). In 2006, male newborns had an overall chance of 1 in 62 to develop a melanoma, for female newborn this was 1 in 50. A man of 40 years old had a probability of 1.1% to develop a melanoma before the age of 75 years. For females, this probability was 1.2%. Men were more likely to die of a melanoma; the probability for a 40-year old male to die due to melanoma before the age of 75 was 0.3%. By the age of 65, this

Table 1   Incidence, mortality and burden of disease of Dutch melanoma patients

	Males				Females			
	1989-1991	1992-1996	1997-2001	2002-2006	1989-1991	1992-1996	1997-2001	2002-2006
Number of new melanoma patients	1900	3810	5154	6859	2909	5508	6986	8998
Age standardized incidence rate	8.87	10.08	12.83	15.87	12.25	13.27	15.93	19.53
Cumulative incidence risk	1.02	1.22	1.60	2.00	1.31	1.40	1.71	2.11
Cumulative incidence rate	1.03	1.23	1.61	2.02	1.31	1.41	1.73	2.13
Number of melanoma deaths	546	1072	1335	1664	547	965	1068	1293
Age standardized mortality rate	2.62	2.90	3.37	3.84	2.21	2.20	2.22	2.48
Cumulative mortality risk	0.37	0.44	0.53	0.60	0.30	0.31	0.33	0.39
Cumulative mortality rate	0.37	0.44	0.53	0.60	0.30	0.31	0.33	0.39
YLL	47	51	61	74	54	53	54	63
YLD	10	11	14	18	19	20	25	31
DALYs	57	63	75	92	73	74	79	94
YLWD	199	224	284	368	373	408	495	617
AYLD	1.2	1.1	1.1	1.1	1.5	1.4	1.4	1.4
AYLWD	23.2	22.4	21.6	21.6	29.1	28.8	28.3	28.2
AYLL	19.3	18.2	17.9	17.8	22.4	21.5	20.3	20.1

All numbers except for the number of new melanoma patients are expressed per 100 000 Dutch inhabitants
YLD: years lived with disability; YLWD: years lived with disease; YLL: years of life lost; DALY: disability adjusted life years; AYLD: average years lived with disability; AYLWD: average years lived with disease; AYLL: average years of life lost.

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Figure 1   European standardized incidence rates by age at diagnosis

A: men
B: women
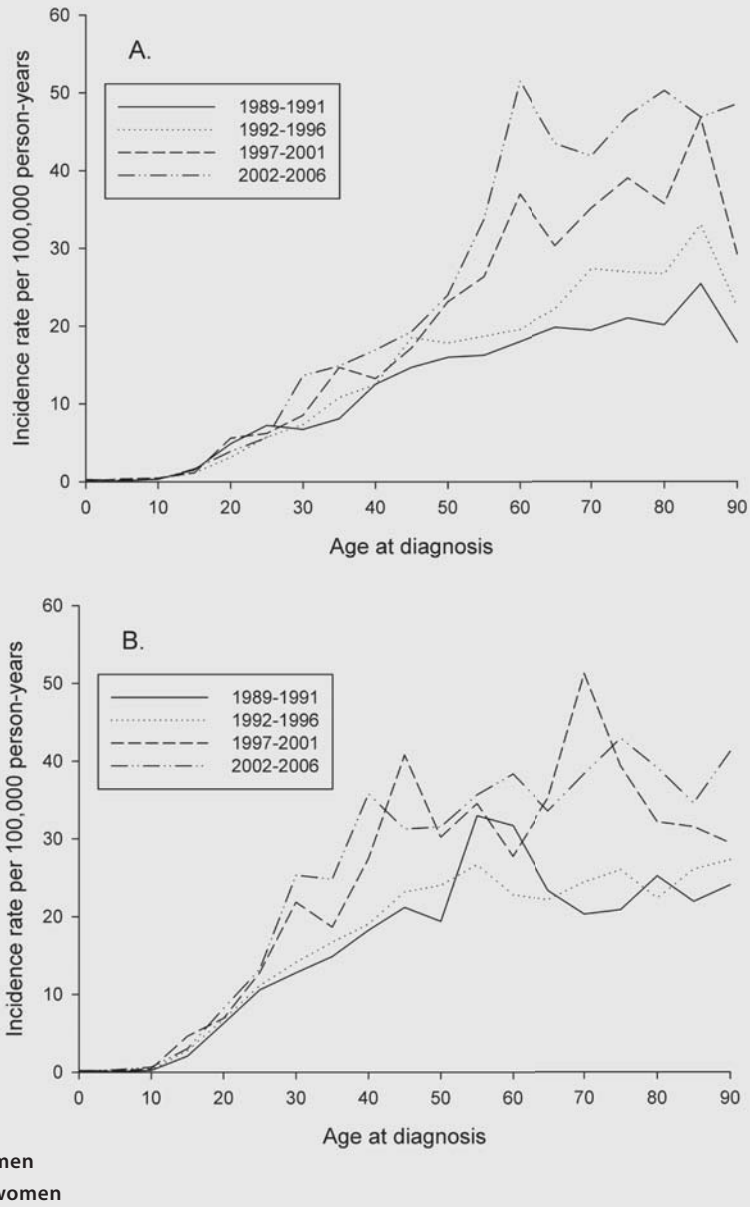
Table 2   Percentage of men and women who develop melanoma by a specific age (Z), given cancer free at current age (Y), 2006

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Men

	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	95+
0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.2	0.3	0.4	0.5	0.7	0.9	1.1	1.3	1.4	1.5	1.6	1.6	1.6
5		0.0	0.0	0.0	0.0	0.1	0.1	0.2	0.3	0.4	0.5	0.7	0.9	1.1	1.3	1.4	1.5	1.6	1.6	1.6
10			0.0	0.0	0.0	0.1	0.1	0.2	0.3	0.4	0.5	0.7	0.9	1.1	1.3	1.4	1.5	1.6	1.6	1.6
15				0.0	0.0	0.1	0.1	0.2	0.3	0.4	0.5	0.7	0.9	1.1	1.3	1.4	1.5	1.6	1.6	1.6
20					0.0	0.1	0.1	0.2	0.3	0.4	0.5	0.7	0.9	1.1	1.3	1.4	1.5	1.6	1.6	1.6
25						0.0	0.1	0.2	0.3	0.4	0.5	0.7	0.9	1.1	1.2	1.4	1.5	1.5	1.6	1.6
30							0.1	0.1	0.2	0.3	0.5	0.6	0.8	1.0	1.2	1.4	1.5	1.5	1.5	1.5
35								0.1	0.2	0.3	0.4	0.6	0.8	1.0	1.2	1.3	1.4	1.5	1.5	1.5
40									0.1	0.2	0.3	0.5	0.7	0.9	1.1	1.2	1.3	1.4	1.4	1.4
45										0.1	0.2	0.4	0.6	0.8	1.0	1.1	1.3	1.3	1.3	1.3
50											0.1	0.3	0.5	0.7	0.9	1.1	1.2	1.2	1.2	1.2
55												0.2	0.4	0.6	0.8	0.9	1.1	1.1	1.1	1.1
60													0.2	0.5	0.6	0.8	0.9	1.0	1.0	1.0
65														0.2	0.4	0.6	0.7	0.8	0.8	0.8
70															0.2	0.4	0.5	0.6	0.6	0.6
75																0.2	0.4	0.5	0.5	0.5
80																	0.2	0.3	0.3	0.4
85																		0.2	0.2	0.2
90																			0.1	0.2
95																				0.3

Women

	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	95+
0	0.0	0.0	0.0	0.0	0.1	0.1	0.2	0.3	0.5	0.7	0.8	1.0	1.2	1.3	1.5	1.7	1.8	1.9	2.0	2.0
5		0.0	0.0	0.0	0.1	0.1	0.2	0.3	0.5	0.7	0.8	1.0	1.2	1.3	1.5	1.7	1.8	1.9	2.0	2.0
10			0.0	0.0	0.1	0.1	0.2	0.3	0.5	0.7	0.8	1.0	1.2	1.3	1.5	1.7	1.8	1.9	2.0	2.0
15				0.0	0.1	0.1	0.2	0.3	0.5	0.7	0.8	1.0	1.2	1.3	1.5	1.7	1.8	1.9	2.0	2.0
20					0.0	0.1	0.2	0.3	0.5	0.6	0.8	1.0	1.2	1.3	1.5	1.7	1.8	1.9	2.0	2.0
25						0.1	0.2	0.3	0.4	0.6	0.8	0.9	1.1	1.3	1.5	1.7	1.8	1.9	1.9	1.9
30							0.1	0.2	0.4	0.5	0.7	0.9	1.1	1.2	1.4	1.6	1.7	1.8	1.9	1.9
35								0.1	0.3	0.4	0.6	0.8	1.0	1.1	1.3	1.5	1.6	1.7	1.8	1.8
40									0.1	0.3	0.5	0.7	0.8	1.0	1.2	1.4	1.5	1.6	1.7	1.7
45										0.2	0.3	0.5	0.7	0.9	1.1	1.3	1.4	1.5	1.5	1.5
50											0.2	0.3	0.5	0.7	0.9	1.1	1.2	1.3	1.4	1.4
55												0.2	0.4	0.6	0.8	1.0	1.1	1.2	1.2	1.2
60													0.2	0.4	0.6	0.8	0.9	1.0	1.1	1.1
65														0.2	0.4	0.6	0.8	0.8	0.9	0.9
70															0.2	0.5	0.6	0.7	0.7	0.7
75																0.2	0.4	0.5	0.6	0.6
80																	0.2	0.3	0.4	0.4
85																		0.2	0.3	0.3
90																			0.2	0.2
95																				0.1

Figure 2 Years Lived with Disease (YLWD) and Average Years Lived
with Disease (AYLWD) by year of diagnosis

YLWD & AYLWD for al melanoma incident cases
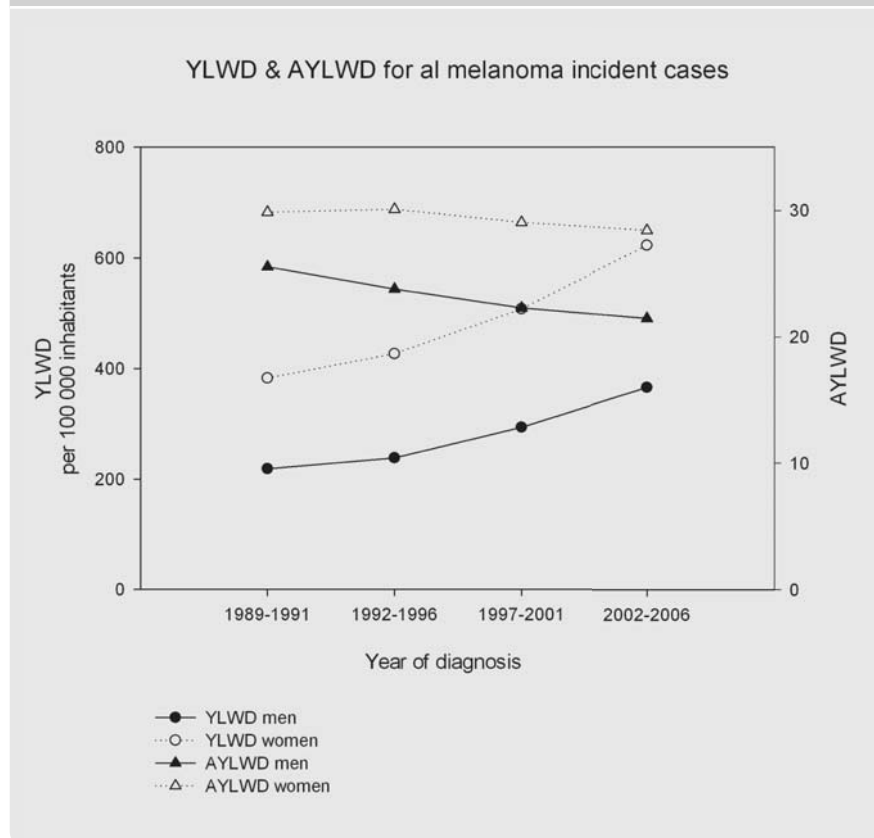
probability had decreased to 0.1%. Corresponding probabilities for females were 0.2%
for a woman aged 40 and 0.1% for women aged 65.

Years Lived with Disability (YLD)

The average number of years that a male melanoma patient lived with melanoma,
adjusted for disability due to melanoma (disability weight: 0.05) decreased from 1.16
years in 1989-1991 to 1.08 years in 2002-2006. Females had a higher AYLD: 1.46 years in
1989-1991 and 1.41 years in 2002-2006 compared to men (Table 1).
In contrast to the slight decreases in AYLD, the total YLD of melanoma in the general
population rapidly increased for both sexes. For men, the YLD increased from 10 to 18

years per 100 000 inhabitants (1989 to 2006) and from 19 (1989-1991) to 31 years (2002-2006) for women.

Years lived with disease (YLWD)

The Average Years Lived with Disease (AYLWD), without adjustments for disability, decreased for both sexes, from 23.2 to 21.6 years for men and 29.1 to 28.2 years for females (Table 1 and Fig. 2). The total years of life with melanoma in the general population has rapidly increased. For men a total of 365.8 life-years lived with melanoma per 100 000 inhabitants in 2002-2006 was estimated compared to 198.7 years in 1989-1991. For women the YLWD rose from 373.3 to 616.9 (Fig. 2).

Figure 3   Years of live lost (YLL) and Average Years of Life Lost (AYLL)
by years of diagnosis
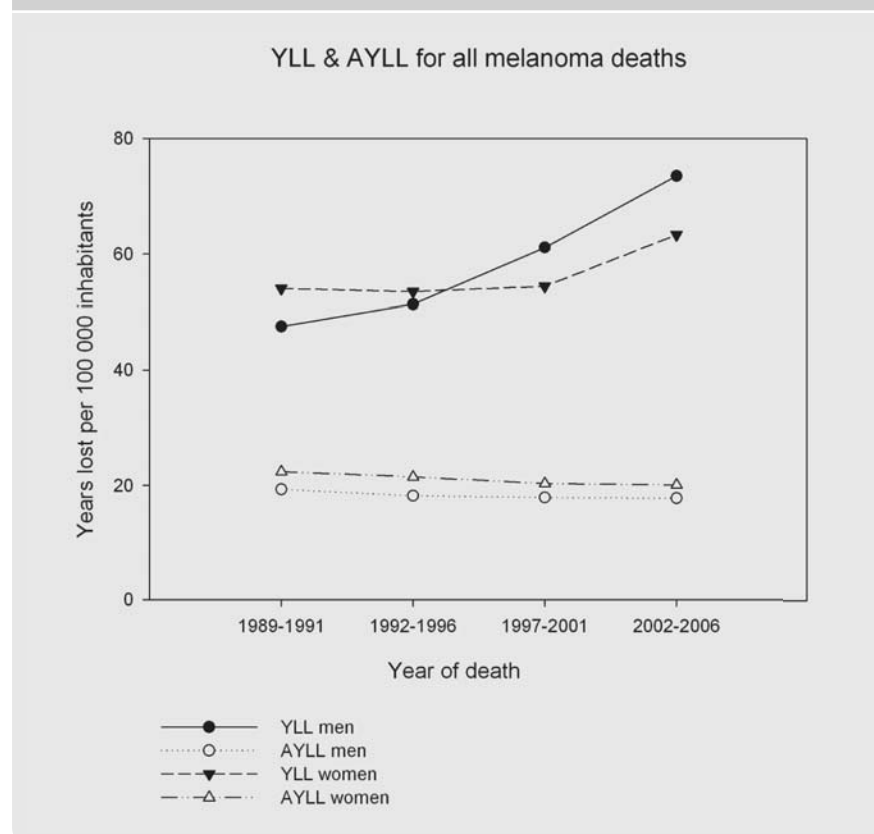
Years of life lost (YLL)

In 1989-1991, a male melanoma patient lost on average 19.3 life-years (AYLL) which decreased to 17.8 years in 2002-2006. For females the AYLL also decreased from 22.4 to 20.1 years. However, the total YLL to melanoma in the Dutch population almost tripled for men and more than doubled for females. In 2002-2006 the total YLL for melanoma for females was 63 years per 100 000 inhabitants (Table 1). Analyses of YLL per 5-year age group showed that the YLL of men aged 50-65 years increased most notably over 1989 to 2006. For women the YLL increased especially for women aged 50 to 80 years and aged 35-39 (data not shown).

Disability Adjusted Life Years (DALY)

The burden of melanoma as estimated by DALYs per 100 000 inhabitants also increased over 1989-2006 (men: 57 to 92 and females: 73 to 94 inhabitants). The increase over 1989-2006 was steeper for men than women, but the increase of the DALYs appeared comparable for both sexes in the 2002-2006.

Discussion

The high YLD and YLLs for melanoma patients emphasize the impact of melanoma on (specialized) health care and the increasing melanoma incidence suggests that this will further rise in the future. YLD and YLWD emphasize the importance of burden-of-disease-concept measures as they estimate the number of years patients might be in need for additional (psychological) care. This is in contrast to incidence rates, which only mark the increasing number of patients that will require treatment and follow-up. The high estimates of the burden of disease concepts also illustrate that there is profit to be gained in the management of melanoma patients and its survivors.

Increases in mortality of melanoma in the Netherlands were modest and much smaller than those observed for incidence; the burden of melanoma in terms of YLL the Netherlands increased considerably between 1989 and 2006 up to an YLL of 20. This high YLL is due to the fact that many patients are middle aged when diagnosed with their first melanoma and that most of those who die of melanoma die fairly soon after the diagnosis. Our results cannot be directly compared to the few other studies looking at burden of disease measure for melanoma, as the other studies used a cut-off value of 65 years. [7, 8] Although a cut-off of value of 65-years to calculate YLL is commonly used for the determination of premature mortality in an occupational

population to assess loss of productivity, analyses unrestricted by age are needed to assess the duration that people are affected by a disease. For this reason, we decided not to use this age cut-off. Moreover, most melanoma patients are diagnosed at an age of 55-65 years and most patients have a 5-10 year survival rate of >90%. [2] Dutch melanoma patients live to be on average 75 years of age, a cut-off value of 65 years would underestimate the YLL with about 10 years.

AYLL is calculated as YLL divided by the number of melanoma deaths. However, if you include all melanoma patients (dead or alive) and not just those who died of melanoma, melanoma was associated with a mean loss of approximately three years of life for an individual melanoma patient between 2002 and 2006. Although the numbers of life years lost per patient and life years lived with disease are slightly decreasing over time, reflecting improving survival and a slightly increasing age at diagnosis on average, the burden of melanoma to society has increased rapidly between 1989 and 2006, mostly due to increases in incidence rates.

The lifetime probability of an individual melanoma patient to die from their melanoma was low, implying that the majority of melanoma patients will live many years after their diagnosis (YLD for males: 18 per 100 000 men and for females: 31 per 100 000 women). The disability weight used in calculating the YLD was 0.05 [12], which is based on the prognosis of melanoma patients. Previous research has shown that more than a third of melanoma patients experience considerable levels of anxiety, mainly during diagnosis and treatment. [13] Moreover, patients' concerns may be very specific (e.g., in relation to UV exposure) and not be fully captured by generic health-related quality of life instruments. For example, a cross-sectional study among more than 500 melanoma survivors up to 10 years of diagnosis showed that most melanoma patients reported less frequent holidays to sunny destination compared to the times before their diagnosis and they also reported more anxiety for the deleterious effect of UV-light on their skin and more use of more protective measures, including practicing less hobbies outside and more protective clothing. Moreover, a proportion of melanoma survivors reported difficulty obtaining a life insurance or mortgage. These findings suggest that the YLD might not fully capture the actual years patients are living with their melanoma and its consequences; the disability weight should probably be raised to capture the true impact of melanoma on quality of life. Therefore, we calculated the Years Lived with Disease (YLWD), not taking the disability weight into account, as well and observed that a melanoma patient on average has to live 20 to 30 years with the impact of melanoma on their daily life.

To our knowledge we are the first to fully report on the burden of disease concepts in melanoma and to estimate the probability of being diagnosed with melanoma for the Dutch population. Dutch females had a probability of 1.6% of developing a melanoma during their lifetime, for males this was 1.2%. Calculating the probability of developing a cancer by estimating the cumulative risk does not take other comorbidities into account, nor the probability of dying from a disease other than melanoma. Therefore we calculated the risk of developing melanoma by the life table method using the DevCan program that calculates the probability of developing a melanoma and the probability of someone dying from it. These calculations were based on a hypothetical cohort and the estimated results of the DevCan analyses were confirmed by a standard life table. A life table makes it possible to answer simple questions of patients pertaining to their survival or the chance of developing a melanoma in the general population in certain age and sex groups. A persons' life time risk of developing a melanoma seemed relatively low, however the Dutch Cancer Society has shown before that this probability almost equals that of the chance for a women to develop ovarian cancer, non-Hodgkin lymphoma or lymphoma. [10]

Conclusion

In conclusion, the burden of melanoma is high and is increasing suggesting a need for adjusting health care policies to cope with this burden. Our research also shows that, even though a disease may be relatively rare and/or has a good prognosis, it can be associated with a great burden to individual patients' and society.

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