Burden of Melanoma

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Introduction

INTRODUCTION

Melanoma is a type of skin cancer that arises from melanocytes. More than 95% of all melanomas occur in the skin, but rarely in the pigmented cells of the eye, meninges or mucosa. This thesis will only regard the invasive cutaneous malignant melanomas.[1]

EPIDEMIOLOGY

The incidence of melanoma has rapidly increased over the past decades and is continuing to do so. In Europe the rate of incidence began to increase in the 1950s in the more affluent Northern European countries due to life style changes such as; more extreme sun behaviour especially in young children, travelling to sunny destination and sun bed use.[2-5] Across western countries the incidence of melanoma increased with minimal 3% annually (4-5% in the Netherlands).

The highest incidence rates for melanoma have been reported for Australia, with an estimated age-standardized rate of 40.2 cases per 100 000 people in 2008.[6] This can be explained by citizens of Australia originating from Irish immigrants with a fair skin (skin type I-II), now being exposed to excessive UV-radiation. Skin cancer is the third most common cancer (excluding basal cell carcinoma) in the Netherlands. It is estimated that one out of six Dutch citizens will develop any type of skin cancer during their life time of which 10% will develop a melanoma. Melanoma is the third most common type of skin cancer in the Netherlands affecting relatively young people (average age of diagnosis around 53 years). In 2006, 1531 men 1949 women were diagnosed with melanoma, with an age standardized rate of 8.5 per 100 000 for men and 11 per 100 000 for women.[2] Incidence rates are increasing with ~4% annually. Therefore, public health campaigns are trying to raise public awareness and are informing people to avoid sunlight during the middle of the day, wear protective clothing (long sleeves, head), use sun cream and parents to protect themselves and especially their children.

In contrast to the continuing rise in melanoma incidence, mortality due to melanoma seems to have stabilized in some countries in the last few years most likely due to increased awareness among patients and physicians resulting in early detection. However, melanoma remains the most deadly type of cutaneous malignancy with approximately 500 deaths in the Netherlands, annually.

CARCINOGENESIS

The exact pathogeneses of cutaneous melanoma is still unknown. Epidemiological studies have shown that sun exposure and genetic predisposition seem to play a role in the development of melanoma.[7]

Exposure of the skin to UV light is a well established risk factor for the development of cutaneous melanoma. DNA damage formation after UV exposure is thought to result in malignant transformation of melanocytes. There is limited information regarding which wave lengths of the UV spectrum are responsible for these effects. The carcinogenic properties of short-wavelength UV light such as UVB have been well known. Because of its wavelength UVB is absorbed in the epidermis which can cause DNA damage in keratinocytes, which subsequently leads to C-T or CC-TT transitions. Also, true generation of oxidative stress and merging with the p53 pathway, UVB may lead to degradation in the DNA.[8]

In recent years however, there have been some indications that UVA might play a role in the development of melanomas as well, as retrospective studies indicate that the use of tanning beds, which mostly contain high dose UVA emitters, increase the risk of melanoma. UVA can deeper penetrate the skin. In contrast to UVB, UVA might play an indirect role in the development of melanoma. It is thought that UVA leads to the production of reactive oxygen species (ROS) that subsequently leads to oxidative damage, single- and doublestrand breaks (SSBs and DSBs). It can cause DNA damage by indirect photosensitizing reactions and produce secondary photoreactions of the existing photoproducts. UVA is also known to induce the photoproduct 8-oxo-7, 8-dihydro-2¢-deoxyguanosine (8oxoG) and CPDs in human skin. Overall, UVA contributes more to the formation of recurrent or hotspot mutations at methylated CpG sites in the mammalian genome than UVB.[8]

RISK FACTORS

It is now widely accepted that increased UV exposure is associated with a higher risk of melanoma. This insight is based on several different epidemiological observations. Epidemiological studies have shown that excessive, intermittent and chronic sun exposure at different age periods affects melanoma development. Especially, short intense periods of sun exposure in early childhood or adolescence, with burning of the skin, appears to be a risk factor for cutaneous melanoma, whereas high levels of cumulative UV exposure has been associated with lentigo maligna melanoma.[9] Chronic UV exposure may be protective of other types of melanoma.[10]

Secondly, people with a fair pigment status (hair, skin, eye colour) are at increased risk.[7] Melanoma rates are also higher at locations with lower latitude, especially among Caucasian immigrants, for example reflecting in the incidence rates of Australia en the US. Equally, naevi (which may be precursors of melanoma) are induced by higher levels of solar exposure.

More importantly, patients with impaired DNA repair of UV induced damage or with polymorphisms in several pigment related genes are at a high risk of developing melanoma. [11] Five to ten percent of all melanomas are in patients with FAMMM (familial atypical multiple mole

melanoma syndrome). In 25-40% of these patients a mutation of the tumor suppressor gene cyclin-dependent kinase inhibitor 2A (CDKN2A) is found, and in a few a mutation in the cyclin dependent kinase 4 (CDK4) gen. Patients with FAMMM have a life time risk of 70% to develop a melanoma.

Also mutations in tumor suppressor genes like c-kit, CDKN2A, p53 and BRAF, have been reported to increase the risk of melanoma. However, it is still unclear, how important mutations of these genes are as a risk factor for melanoma.

CLINICAL EXAMINATION

Early detection of thin melanomas is a key factor in improving survival from melanoma. The clinical diagnosis of cutaneous melanoma continues to be based on a visual inspection of the skin. A history of itching or change in the color, shape, size of a pigmented lesion over time is one of the most sensitive clinical sign for melanoma. These characteristics of melanoma are summarized within the ABCDE-rule of melanoma; wherein the Asymmetry, Border, Color, Diameter and Evolvement of a melanocytic lesion are assessed and scored. Melanomas usually show *asymmetry* in shape with an irregular *border*. Melanomas can have different *colors,* besides different shades of brown or black; red, blue, grey, hypopigmentation and/or depigmentation can be seen as a sign of regression, in up to two thirds of melanomas. About half of these melanomas arise in pre-existing nevus.[12-14] A *diameter* greater than 0.5 cm is also suggestive for a melanoma. Finally, the "E'" is referred to as evolvement of a pigmented lesion over time.

Another accepted concept is the "ugly duckling sign" introduced by Grob and Bonerandi (1998)[15] which indicate that nevi in the same individual tend to resemble one another; a malignant melanoma will then often deviate from the individual's nevus pattern.

Dermatoscopy (i.e., using a magnification of 10X and polarized light) is of great importance in making all these characteristics of a melanoma more distinct, while inspecting a pigmented lesion. It raises the sensitivity to 91% and specificity to 86% of the diagnoses of melanoma in the hands of experienced physicians.[16] With use of the ABCD-rule and dermatoscopy, pigmented lesions are scored with the help of several algorithms (e.g. the rules of Wilhelm Stolz) to make a distinction between a benign, atypical mole or a malignant melanoma. A higher score makes a pigmented lesion more suspect for melanoma.

HISTOLOGY

A diagnostic excision is performed when a lesion is suspect for melanoma. It is important to know if the lesion is in situ or not. An in situ melanoma can be seen as a precursor lesion of

an invasive malignant melanoma. The melanocytes are showing some deformation but they are still within the epidermis. When atypical melanocytes are growing past the epidermal layer (through the basal membrane), into the dermis it becomes an invasive malignant type of melanoma. During this process there are 2 major ways of growth; (1) *radial growth* indicates the initial tendency of a melanoma to grow horizontally within the epidermal and superficial layers. During this phase there is no evidence of angiogenesis. With time, the pattern of growth changes to (2) *vertical growth* phase. The melanoma now grows downward into the deeper dermal layers of the skin as forming a tumor that lacks cellular maturation, without any tendency for the cells to become smaller as they descend into the reticular dermis. During this phase angiogenesis is present.

A pathologist uses Breslow thickness (or Clark level) to express the extent of invasion. These measures are directly correlated to the prognosis of a patient. Microscopic ulceration of the melanoma as well as the mitotic index are also important prognostic factors ([17]; Table 1-2).

There are 4 major types of melanoma; superficial spreading, nodular, lentigo maligna melanoma and acral lentiginous melanoma. Superficial spreading melanoma (SSM) is the most common type of cutaneous melanoma in fair-skinned individuals; approximately 70% of all cutaneous melanomas are superficial spreading. SSM is followed by nodular melanomas (15%), lentigo maligna melanomas (10%) and acral lentinous melanoma (5-10%)

STAGING

Tumor staging of melanoma is an important step for estimating a patients' prognosis and deciding on therapy approach. Following a histological confirmed diagnosis of melanoma a sentinel node procedure can be offered to a patient with a malignant melanoma of a Breslow depth >1.20mm, to detect early lymph node metastases, which may affect a patients cancer stage. It remains controversial whether the sentinel node procedure should be offered to all patients and whether it affects patients' survival. Furthermore, additional image-forming, such as X-ray, CT-scan or PET scan, can be done on indication to detect distant metastases, although one should be aware of the low predicting value. [18]

Next, melanomas can be staged by the AJCC (American Joint Committee on Cancer) classification or TNM classification. (Table 1 and 2) This classification is based on the Breslow depth, lymphnode metastases and whether or not there are distant metastases.[17]

PROGNOSIS

In 2006, 749 people died of skin cancer in the Netherlands, of which 85% died due to melanoma. Next to Breslow thickness, ulceration of the tumor, lymph node metastases and visceral

Table 1: TNM staging categories for cutaneous melanoma according AJCC classification 2009

Classification	Thickness (mm)	Ulceration Status/Mitoses
T		
Tis	NA	NA
T1	≤ 1.00	A: without ulceration and mitosis <1/mm^2 B: with ulceration or mitosis ≥ 1/mm^2
T2	1.01-2.00	A: without ulceration B: with ulceration
T3	2.01-4.00	A: without ulceration B: with ulceration
T4	>4.00	A: without ulceration B: with ulceration
N	**No. of Metastatic Nodes**	**Nodal metastatic Burden**
N0	0	NA
N1	1	a. micrometastases* b: macrometastases¥
N2	2-3	a. micrometastasis* b: macrometastases¥ c: In transit metastases/satellites without metastatic nodes
N3	4+ metastatic nodes, or in transit metastases/satellites with metastatic nodes	
M	**Site**	**Serum LDH**
M0	No distant	NA
M1a	Distant skin, subcutaneous or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases Any distant metastases	Normal Elevated

NA, not applicable: LDH, lactate dehydrogenase. *Micrometastases are diagnosed after sentinel lymph node biopsy. ¥Macrometastases are defines as clinically detectable nodal metastases confirmed pathologically

metastases, the prognosis for men is two times lower than for women. Especially men above the age of 65 have a higher mortality due to melanoma and a significantly lower 5-year survival rate. The 5-year survival rate is 90% for women but only 81% for men. When there are lymphnode metastases the 5-year survival rate drops to 40%. Involvement of lymph nodes and the occurrence of metastases increase the risk of mortality by 9.2 times and 11.2 times, respectively.

TREATMENT

The primary treatment of melanoma is surgery. A re-excision is performed on the primary melanoma site after histological confirmation, with an appropriate margin determined by the Breslow depth (varying between 0.5 and 2 cm). After this procedure only follow-up to detect recurrence of melanomas is indicated.

Table 2: Anatomic stage groupings for cutaneous melanoma according to the AJCC 2009

	Clinical staging				Pathological Staging		
	T	N	M		T	N	M
0	Tis	N0	M0	0	Tis	N0	M0
IA	T1a	N0	M0	IA	T1a	N0	M0
IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N>N0	M0	IIC	T4b	N>N0	M0
III	Any T	N>N0	M0	IIIA	T1-4a	N1a	M0
					T1-4a	N2a	M0
				IIIB	T1-4b	N1a	M0
					T1-4b	N2a	M0
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a	N2c	M0
				IIIC	T1-4b	N1b	M0
					T1-4b	N2b	M0
					T1-4b	N2c	M0
					Any T	N3	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

Clinical staging includes microstaging of the primary melanoma and clinical /radiologic evaluation of metastases. By convection, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.
Pathological staging includes microstaging of the primary melanoma and pathological information about the regional lymph nodes after partiel(i.e. sentinel node biopsy) or complete lymfadenectomy. Pathological stage 0 or stage IA patient are the exception;they do not require pathologic evaluation of their lymph nodes

Effective treatment of metastasized melanoma is quite limited which makes the prognosis of these patients insufficient. The mainstay of patients with distant metastases is systemic therapy. The systemic agents that have been used include chemotherapy (e.g. darcabazine / temozolomide, cisplatin, vindesine/vinblastine, BCNU/fortemustine, and taxol/taxoterel) , immunotherapy (IFN-alpha) and combination of biochemotherapy. Preferably patients are treated as part of well-controlled clinical trials.[19]

New targeted therapies have been introduced with the discovering of tumor suppressor gene mutations. Sorafenib was the first BRAF target therapy to be studied in metastatic melanoma, but has not shown major clinical effects. A more promising BRAF kinase inhibitor is vemurafenib, with response rates over 50% in patients with metastatic melanoma with the BRAF V600E mutation.[20-21] A recent phase 3 study showed a overall survival of 84% in the vemurafenib group compared to 64% in the group treated with dacarbazibe. Response rates were 48% for veramufenib and 5% for dacarbazine.[20]

Ipilimumab blocks cytotoxic T-lymphocyte-associated antigen 4 to enhance an antitumor T-cell reponse. A phase 3 study among HLA-A*0201 positive patients showed a improvement in survival among patients treated with ipilimumab and glycoproteine 100 peptide vaccine (10.0 months) compared to patients receiving only glycoproteine 100 (6.4 months).However severe immune related adverse events occurred in 10-15% of patients treated with ipilimumab.[19]

FOLLOW-UP

The follow-up of patients with a history of melanoma differs across the world and is debated. This is partly due to ever increasing incidence of melanoma, as well as the lack of agreement regarding the reasons for and frequency of follow-up. Reasons for follow-up of melanoma patients include: detection of recurrent melanomas, diagnosis of new potential malignant lesions, reassurance of the patient and/or instructing patients for self-examination of the skin. However, melanoma patients are often not involved in the debate on follow-up. The frequency of follow-up might be limited when patients are capable to detect recurrence of second primary melanomas themselves.

A collaboration of the European Dermatology Forum (EDF), The European Association of Dermato-Oncology (EADO) and the European Organizaztion for Research and Treatment of Cancer (EORTC) have made a guideline for clinicians across Europe. They describe a great variation between different guidelines varying from 2 to 4 times per year for 5 to 10 years.[22-24] In stage I to II melanoma, the intent is to detect early loco-regional recurrence. A follow-up frequency of every 3 months for the first 5 years followed by a follow-up visit once every 6 months for the 6th to 10th year period after diagnosis, is considered adequate. In patients with a thin melanoma (breslowdepth <=1mm) six monthly intervals are considered sufficient. [22] Clinical follow up is standard, but the guideline suggests a possible benefit in additional ultrasonography.[22]

Table 3: Frequency of follow-up according to Dutch melanoma guideline (2005)*

Breslow thickness	Time after diagnosis	Frequency of follow-up
< 1.00 mm	3 months after surgery	One single appointment
> 1.00 mm	Year 1	Once every 3 months
	Year 2	Once every 4 months
	Year 3-5	Once every 6 months
>2.00mm	Year 1	Once every 3 months
	Year 2	Once every 4 months
	Year 3-5	Once every 6 months
	Year 6-10	Annually

* Supplemental tests as indicated

Compared to other melanoma guideline the Dutch melanoma guideline of 2005 is one of the most conservative. The frequency of follow-up, advised by the Dutch melanoma guideline of 2005 is presented in table 3.[18]

AIMS OF THE THESIS

In this thesis we have attempted to describe the incidence of melanoma in the Netherlands and Europe, the impact it has on patients' lives as well as its societal impact. We also describe results of a cross-sectional study on the follow-up of melanoma patients.

The aims of this thesis are:

- To give an overview of the recent trends in epidemiology of melanoma
- To asses patients' perspectives of having been diagnosed with melanoma
- To asses the societal burden of melanoma

To asses the role of melanoma in the skin cancer epidemic in the Netherlands, an overview of all types of skin malignancies and their trends in incidence in the Netherlands is given in chapter 1 based on routinely collected cancer registry data of the Netherland Cancer Registry South. Chapter 2 focuses on melanoma, by describing incidence rates and trend in incidence of melanoma across Europe, based on data provided by several European population-based cancer registries that are member of the European Network of Cancer Registries. In Chapter 3 we reviewed the Health Related Quality of Life of melanoma (HRQoL) patients to get an insight of the impact melanoma can have on a patients' live. This review shows that there was little known on the HRQoL of melanoma patients and only a few studies were population based and in large patient groups. This lead us to initiate a cross-sectional study on HRQoL among 562 Dutch melanoma survivors (chapter 4). Furthermore, we evaluated patient characteristics and follow-up characteristics of melanoma patients, to identify if they could be of influence on their HRQoL.

We investigated whether or not Type D personality is more common among Dutch melanoma patients with worse HRQoL (chapter 5). Type D personality would imply a tendency towards negative affectivity (e.g. worry, irritability, gloom) and social inhibition (e.g. reticence and a lack of self-assurance), which might result in difficulty coping with their diagnosis.

Chapter 6 and 7 describe how patients with melanoma are treated by their physicians and whether or not this is to the patients' satisfaction and/or according to the melanoma guideline. In chapter 8 we tried to quantify the impact of melanoma on society as burden of disease derived from the World Health Organization (WHO) guidelines to assess burden of disease.

A general discussion with current perspectives (chapter 9) concludes this thesis.

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Epidemiology

2

The incidence and trends of cutaneous malignancies in the Netherlands 1989-2005

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ABSTRACT

Epidemiology of rare cutaneous malignancies in the general population is poorly documented. This descriptive study aimed to estimate the incidence and trends of all skin malignancies between 1989 and 2005. Data on skin tumors were extracted from the Netherlands Cancer registry (except for basal cell carcinoma (BCC) data—only available from Comprehensive Cancer Centre South) and categorized according to the International Classification of Diseases for Oncology, third edition, codes. Age-standardized incidence rates (European standardized population rate, ESR) per 100,000 person-years were calculated per year and for the period between 2001 and 2005. Estimated annual percentage changes (EAPCs) were estimated by Poisson regression models. A total of 356,620 skin tumors were diagnosed between 1989 and 2005. Excluding BCC, squamous cell carcinoma (SCC), and melanoma, the remaining skin tumors constituted about 2% of all skin malignancies. The incidence of melanoma showed the steepest increase (EAPC, 4.0%), and ESR was close to that observed for SCC (EAPC, 2.3%) between 2001 and 2005 (17.1 versus 19.6). Hematolymphoid tumors (ESR=0.74) were mainly cutaneous T-cell lymphomas (60.8%). No significant increases in incidence were observed for lymphomas, and appendageal, fibromatous, and myomatous carcinomas during 1989–2005. In addition to keratinocytic cancers and melanoma, there is a wide variety of skin tumors that constitute <2% of all skin malignancies. The incidence of UV-related skin tumors increased significantly and more steeply than did those of other skin malignancies.

INTRODUCTION

Cutaneous malignancies are often categorized in non-melanoma skin cancer (NMSC) and cutaneous melanoma. NMSC is commonly used to address basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), which are keratinocytic cancers, but the category of NMSC comprises a wide variety of skin tumors.

The incidence of skin tumors varies geographically and is relatively well documented for melanoma, SCC and to a lesser extent BCC in different international samples of the general population [1-4]. The frequency of occurrence of the less common cutaneous malignancies such as cutaneous B- and T-cell lymphomas, soft tissue sarcomas (e.g., dermatofibrosarcoma protuberans [DFSP]), sebaceous carcinoma and Merkel cell carcinoma is poorly documented. The studies that mention the incidence rates of these rare skin malignancies are mainly using data from the Surveillance, Epidemiology and End Results (SEER) program, which registers pathology reports of nine areas that cover about 10% of the US population [5-9]. Currently there are over 16.5 million Dutch citizens, of whom the majority is white. The Netherlands Cancer Registry registers all their pathologically confirmed cancers since 1989. According to the Netherlands Cancer registry (www.ikcnet.nl) skin cancers (excluding BCC) rank 4th among the most common cancers in the Netherlands with 9,681 cases in 2007, but mortality is low (European standardized mortality rate = 0.3 per 100,000 person-years).To our knowledge, this is the first population-based study to provide incidence rates for all the major subtypes of skin cancers. Other studies have mainly focused on BCC, NMSC and melanoma [3, 10-13].

The objective of this descriptive epidemiological study is to provide absolute numbers and incidence rates of all skin cancer groups and their trends between 1989 and 2005 in the general Dutch population.

RESULTS

In total an absolute number of 356,620 cutaneous malignancies were registered in the Netherlands Cancer Registry between 1989 and 2005 (including the first primary BCCs from only one registry). The overall European standard population rate (ESR) was 126.31 per 100,000 person-years including the estimated first primary BCC rate for the Dutch population. In men and women, the ESR of cutaneous malignancies (excluding BCC) in 2005 was 52.4 and 39.2 /100.000 person years, respectively. The ESR of all skin tumors but BCC among people aged 60 years or more for 2005 was 27.4 and 16.5 per 100.000 person-years among people younger than 60.

Table 1. European standardized incidence rates for skin cancers in the Netherlands, 1989-2005.

Groups of (invasive) skin tumors*	ICD-O3 codes	Total numbers of tumors (1989-2005)	Median age (25-75 percentile)	Percentage of men	Percentage of total non- BCC skin cancers (1989-2005)+	ESR per 100,000 person-years (2001-2005)
Keratinocytic tumors (Squamous cell carcinomas only)+	8050-8052 8070-8078 8082-8084	57,915	75 (66-82)	62.2	56.5	19.61
Melanocytic tumors	8720; 8721; 8722; 8723; 8730; 8740; 8741; 8742; 8743; 8744; 8745; 8761; 8770; 8771; 8772; 8780	38,647	53 (40-66)	41.5	37.3	17.11
Appendageal tumors	8140; 8143; 8190; 8200; 8230; 8260; 8310; 8390; 8400; 8401; 8402; 8403; 8407; 8408; 8409; 8410; 8413; 8420; 8430; 8480; 8481; 8542	1,258	72 (60-81)	51.0	1.23	0.43
Haematolymphoid tumors	9590; 9591; 9596; 9671; 9673; 9675; 9680; 9684; 9687; 9689; 9690; 9691; 9692; 9693; 9697; 9699; 9700; 9701; 9702; 9705; 9708; 9709; 9714; 9718; 9719; 9731; 9734; 9741; 9754; 9756	2,020	66 (53-76)	57.7	1.97	0.74
Soft tissue tumors	8800; 8801; 8804; 8805; 8810; 8811; 8830; 8832; 8833; 8840; 8850; 8890; 8891; 8894; 8910; 8982; 9120; 9133	1,390	45 (33-65)	54.2	1.36	0.50
Neural tumors	8240; 8246; 8247; 9503; 9540; 9560; 9580	723	76 (68-83)	39.1	0.71	0.29
Other skin tumors	8560; 8562; 8570; 8575; 8980	31	80 (65-87)	54.8	0.03	0.01
Skin tumors NOS	8000; 8001; 8004; 8010; 8011; 8012; 8020; 8021; 8030; 8031; 8032; 8033; 8041	479	74 (64-82)	55.7	0.47	0.12

Abbreviations: BCC, basal cell carcinoma; ESR, European standardized incidence rates; ICD-O3, International Classification of Diseases for Oncology, third edition; NOS, not otherwise specified; WHO, World Health Organization

* Skin cancer groups according World Health Organization (WHO; LeBoit et al, 2006)

+ BCC were excluded because only data on first incident BCC was available from the registry of the Comprehensive Cancer Centre South and not on total numbers of tumors as for other tumor groups (available from all comprehensive registries of the Netherlands Cancer Registry).

Basal cell carcinoma

In the Netherlands, the estimated absolute number of people with a first primary BCC (ICD-O3 morphology codes 8090-8110) that occurred between 1989-2005 was 254,157 (based on an extrapolation of age-specific rates in the Comprehensive Cancer Centre South to the Dutch population), reflecting 70.9% of all skin cancers in the general population of the Netherlands between 1989-2005. Of the BCC patients, 49.1% was male and had a median age of 67 years. In the 5-year-period between 2001-2005, the European standard population rate (ESR) of a first BCC was 87.5 per 100,000 person-years and the estimated annual percentage change (EAPC) was 3.1% (95%CI 3.0-3.2)- between 1989-2005.

Squamous cell carcinoma

The absolute number of SCCs, which is, like BCC, a keratinocytic cancer, was 57,915 in the study period, representing about 16% of skin cancers, including first primary BCCs. The median age was 75 years and 62% of patients with SCC were men. More than half of all non-BCC skin cancers were SCC and its ESR was approximately 20 (Table 1). The age-adjusted EAPC was 2.3% per year and the ESR increased from about 15 to more than 20 between 1989 and 2005 (Figure 1).

Melanoma

In the 16 year study period, 38,647 melanomas were registered, comprising about 11% of all skin malignancies including first primary BCCs (Table 1). The median age of melanoma patients was 53 years and the majority of patients were women (except for desmoplastic melanomas were the majority was male). The ESR of melanoma was 17.1 between 2001-2005, roughly double that of 1989 with an EAPC of 4.0% (95%CI 3.8-4.2).

Of the different histological subtypes of melanoma, superficial spreading melanomas was the most commonly registered (54.1% of all melanomas) with an ESR of more than 10 /100,000 person-years (Table 2). Nodular melanomas comprised 15% of all registered melanomas with an ESR of 2.36. A total of 1,280 lentigo maligna melanomas (3.3% of all melanomas) were diagnosed between 1989 and 2005. Patients with a lentigo maligna melanoma had a median age of 71 years and were 15 to 20 years older than those diagnosed with a nodular or superficial spreading subtype. The ESR of the remaining specific melanoma subtypes ranged between 0.02 and 0.16/100.000 person-years.

Haematolymphoid tumors

A total of 2,020 cutaneous haematolymphoid tumors were diagnosed and confirmed by pathology reports in the Netherlands between 1989 and 2005. In the period 2001-2005, the ESR of these malignancies was 0.74 (Table 1) and the incidence remained stable during the study period, after adjusting for age (Figure 1). Of the haematolymphoid tumors, 60.8% were T-cell and NK-cell lymphomas, 33.4% of B cell origin and the remaining were non specified.

Table 2: European standardized incidence rates for the most common subtypes of skin cancers in the Netherlands, 1989-2005.

Groups of (invasive) skin tumors*	ICDO-3 codes	Total numbers of tumors (1989-2005) percentage within groups	Median age (25-75 percentile)	Percentage of men	ESR per 100,000 person-years (2001-2005)
Melanomas					
M NOS	8720	8,790 (22.7%)	53 (40-67)	41.8	2.91
Nodular M	8721	5,786 (15.0%)	57 (44-71)	48.5	2.36
Superficial spreading M	8743	20,911 (54.1%)	50 (39-62)	39.2	10.55
Lentigo maligna M	8742	1,280 (3.3%)	71 (61-79)	40.9	0.53
Acrolentiginous M	8744	334 (0.9%)	62 (52-74)	38.6	0.16
Desmoplastic M	8745	84 (0.2%)	66 (56-78)	57.1	0.04
M from pre-existing lesion	8740; 8741; 8761; 8780	86 (0.2%)	54 (38-68)	37.2	0.02
Other M	8722; 8723; 8770; 8771; 8772; 8730	1,376 (3.6%)	60 (46-72)	45.8	0.56
Soft tissue tumors					
Fibrosarcomas	8810; 8811; 8830	137 (9.9%)	74 (65-82)	65.7	0.03
Dermatofibrosarcoma protuberans	8832; 8833	1,066 (76.7%)	41 (31-53)	52.2	0.39
Leiomyosarcoma	8890; 8891; 8894; 8910	119 (8.6%)	64 (51-77)	61.3	0.06
Others	8800; 8801; 8804; 8805; 8840; 8850; 8982; 9120; 9133;	68 (4.9%)	77 (66-84)	50.0	0.02
Appendageal tumors					
Sebaceous glands	8410	296 (23.5 %)	74 (63-81)	58.1	0.1
Sweat glands	8400; 8402; 8403; 8407; 8408; 8409	413 (32.8%)	72 (59-82)	48.2	0.15
Extramammary Paget disease	8542	117 (9.3%)	74 (66-82)	57.3	0.04
Others and NOS	8140; 8413; 8143; 8190; 8200; 8230; 8260; 8310; 8390; 8401; 8420; 8430; 8480; 8481	432 (34.3%)	69 (57-80)	47.0	0.14
Neural tumors					
Merkel cell carcinoma	8240;8246;8247	712 (98.5%)	77 (68-83)	38.8	0.29
Other	9503; 9540; 9560; 9580	11 (1.5%)	62 (47-78)	63.6	0.00

Table 2: European standardized incidence rates for the most common subtypes of skin cancers in the Netherlands, 1989-2005. (continued)

Groups of (invasive) skin tumors*	ICDO-3 codes	Total numbers of tumors (1989-2005) percentage within groups	Median age (25-75 percentile)	Percentage of men	ESR per 100,000 person-years (2001-2005)
Haematolymphoid tumors					
B cell lymphomas (L)			69 (54-79)	51.4	0.26
Diffuse large B-cell L	9675; 9680; 9684; 9731; 9734	385 (19.1%)	72 (61-82)	47.3	0.13
Follicular L	9690-9697	136 (6.7%)	62 (52-76)	55.9	0.05
Marginal zone B cell L	9699; 9671	122 (6.0%)	59 (45-73)	57.4	0.07
Other B-cell L	9673; 9687; 9689	17 (0.8%)	66 (29-74)	64.7	0.01
T and NK cell lymphomas (L)			65 (52-74)	61.8	0.43
Mycosis fungoides	9700	742 (36.7%)	64 (53-73)	63.7	0.2
Sézary syndrome	9701	38 (1.9%)	71 (65-79)	50.0	0.01
Primary cutaneous CD30+ T-cell L	9718	97 (4.8%)	59 (46-72)	62.9	0.09
Anaplastic large cell L	9714	48 (2.4%)	58 (42-71)	60.4	0.02
Others	9705; 9708; 9719	16 (0.8%)	69 (56-77)	68.8	0.02
NOS	9702; 9709	293 (14.5%)	66 (50-76)	57.7	0.09
Lymphomas, others and NOS	9590; 9596; 9591; 9741; 9754; 9756	126 (6.2%)	71 (57-80)	50.8	0.05

Abbreviations: ESR, European standardized incidence rates; ICD-O3, international Classification of Diseases for Oncology, third edition; L, lymphoma; NOS, not otherwise specified; M. melanoma; WHO, World Health Organization

* Skin cancer groups according World Health Organization (WHO; LeBoit et al, 2006)

About 60% of the cutaneous T-cell lymphomas (CTCL), were classified as Mycosis Fungoides (with an ESR of 0.20/100,000 person-years), 7.9% were primary CD30+ lymphomas and 3.1% of the patients with CTCL had Sézary syndrome (Table 2). Of the cutaneous the B-cell lymphomas (CBCL), diffuse large and follicular B-cell lymphomas (38.0% and 24.9%, respectively) were the most common subtypes. Patients with CBCL were roughly 5 years older than those with CTCL (median age 64 vs. 69 years). Except for diffuse large BCL and Sezary syndrome, the majority (between 55.9 and 68.8%) of patients were male for each of the subtypes of haematolymphoid tumors.

Other rare skin cancer subtypes

World Health Organization (WHO) groups of cutaneous malignancies that were registered more than 1,000 times in the study period were appendageal and soft tissue tumors (1,258 and 1,390, respectively) with an ESR of more than 0.40 for both subtypes (Tables 1 and 2). In total, 723 neural tumors of the skin were recorded (ESR 0.29). In contrast to the soft tissue tumors, the incidence of appendageal and neural tumors increased significantly with 2.8% and 2.3% annually, respectively, in the 16 year study period (Figure 1).

More than three quarters of the soft tissue tumors of the skin were dermatofibrosarcoma protuberans (DFSP) (1,066 Dutch patients between 1989-2005) with an ESR of 0.39. Almost all neural tumors were Merkel cell carcinomas. About a third of the appendageal tumors were recorded to derive from sweat glands (ESR 0.1) and a quarter from sebaceous glands. Extramammary Paget disease was registered in 117 Dutch people between 1989 and 2005. Appendageal and neural tumors mainly occurred among people aged 70 years or older, whereas the median age at diagnosis of cutaneous sarcomas was 45 years (Table 1). Less than 40% of patients with a Merkel cell carcinoma was male.

Between 1989 and 2005, less than 0.5% of the recorded skin cancers were without a pathology specification and their proportion decreased significantly (-2.1% annually [95%CI -3.9, -0.2]) over time.

DISCUSSION

Among the approximately 15 million Dutch citizens, more than 350,000 skin malignancies have occurred between 1989 and 2005. It was estimated that 1 out of the 6 Dutch citizens will develop a skin tumor in their life time[14]. The keratinocytic skin cancers (BCC and SCC) and melanoma together comprise more than 98% of all skin tumors. The ESR of these three cutaneous malignancies are comparable to these reported previously of the same Dutch population and of other Northern European countries [1, 3, 10], but are substantially lower than in geographic regions such as Australia and parts of the US [15].

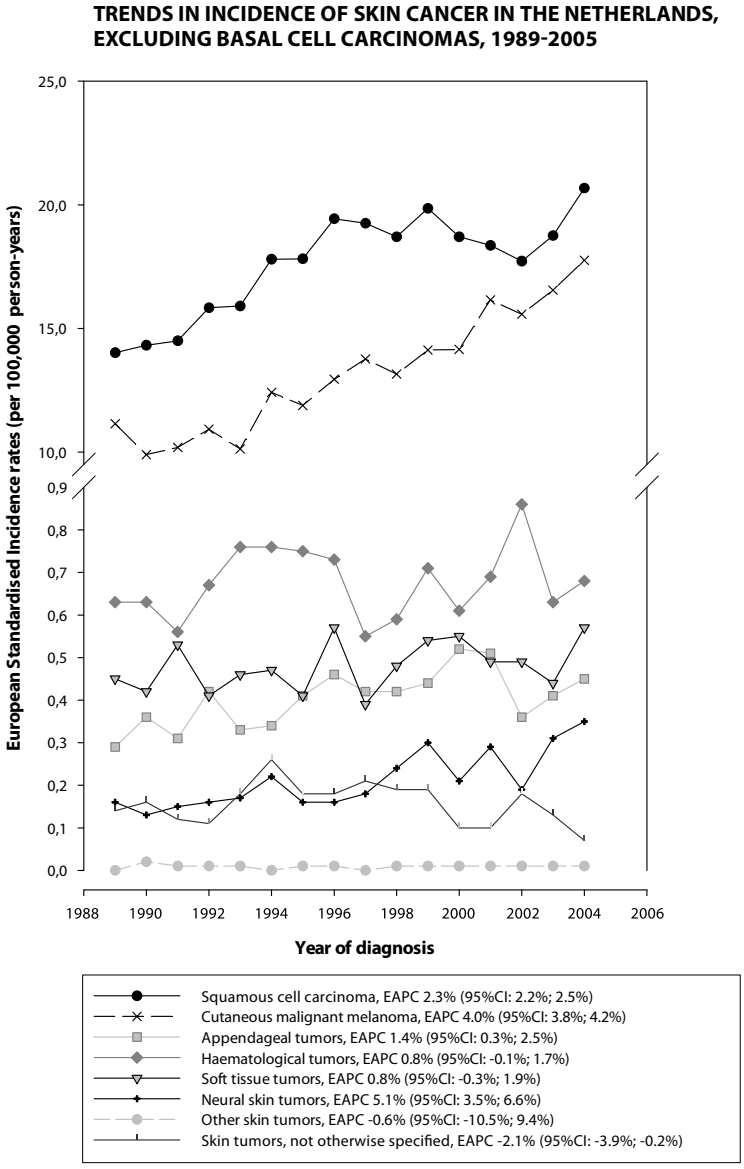

Figure 1. Trends in incidence of skin cancer in the Netherlands, excluding basal cell carcinomas, 1989-2005.

Between 1989 and 2005, the incidence rates of melanoma and SCC steadily increased and almost doubled. Interestingly, the rate of increase of melanoma seemed to accelerate in the last decade and is closing in on the SCC rates. Other UV-related skin cancers such as Merkel cell carcinoma and appendaeal tumors also increased significantly and more rapidly than other non-UV-related tumors such as cutaneous lymphomas and sarcomas. This discrepancy confirms

that changed UV-exposure patterns may be the driving force behind the steep increases of types of cutaneous malignancies that are known to be related to UV exposure. This observation suggests that, besides a potential influence of surveillance and awareness, there must be a true increase in the occurrence of BCC, SCC and melanoma and not just a diagnostic shift [16].

Of the less common skin malignancies, CTCL, CBCL, DFSP, appendageal tumors and Merkel cell carcinoma had the highest incidence rates. Our findings show remarkable similarities to other studies, often from the US using SEER data, despite differences in the distribution of demographic characteristics and geographic locations. The observed ESR of 0.43 for CTCL was in the range of reported incidence rates from Western populations (0.13-0.90 /100,000 inhabitants) [6, 17-18]. In accordance with SEER data, CBCL accounted for just over a third of the cutaneous lymphomas and the observed ESR was very close to the one in a US study [5]. The incidence of DFSP detected in this study (ESR=0.39) and its stability over time is comparable to that documented in four US studies using SEER data [7, 9, 18-19]. Both in our study and in US population-based studies [20-21], the incidence rates of Merkel cell carcinoma were about 0.30 /100,000 inhabitants, with an almost three folds increase over the past two decades which primarily affected elderly people. The Dutch and US incidence of sebaceous carcinoma were comparably low and constant over time (about 0.10/100,000 person-years) [22-23]. In accordance with our findings, the majority of these patients were elderly Whites.

Our study is the first to present a comprehensive overview of the descriptive epidemiology of all WHO skin tumor groups including estimates of specific rare cutaneous malignancies in the same time period and region (except for BCC that was only recorded in the South East of the Netherlands). Moreover, it supplements epidemiologic data on rare skin tumors from the SEER data and provides a European perspective on the occurrence of these malignancies in a general population sample. To minimize misclassification bias, which may have been introduced because of the long study period, the tumors were coded according to the ICD-O3 classification for skin malignancies [24-25] and categorized in WHO skin tumor groups in collaboration with a certified pathologist (Senada Koljenović). Nevertheless, misclassification may have occurred, but the percentage of NOS skin tumors was only 0.47%, which is in concordance with international observations, suggesting that the impact of this bias is limited. Using many sources of information (pathology reports, hospital discharge information, clinical records, etc), the Dutch cancer registries have demonstrated to include most cancers, their records are assumed to be complete since 1989. [26]. Still some underreporting may have occurred as some skin cancers might have been treated without being pathologically confirmed. For some of the skin cancer types, stratified trend analyses were not possible because of the limited number of cases. No information by ethnic background or skin color was available.

In summary, the keratinocytic cancers and melanoma form the overwhelming majority of cutaneous malignancies. The remaining skin tumors constitute about 2% of all malignancies and are predominantly lymphomas, DFSP, appendageal tumors and Merkel cell carcinomas with incidence rates comparable to those observed in the US. The incidence rates of UV-related skin tumors increased significantly and more steeply than those of other, non-UV related, malignancies.

METHODS

In the Netherlands all pathology laboratories are affiliated to the PALGA Foundation, which registers all histopathology and cytopathology reports. The Netherlands Cancer registry, comprising nine Comprehensive Cancer registries, receives weekly reports of PALGA on all pathological confirmed cancers since 1989, covering more than 95% of all cancers in the Netherlands. Using ICD-O3 codes presented in table 1, skin tumors were extracted from the Netherlands Cancer Registry between 1989 and 2005, except for BCCs, which were registered in the Comprehensive Cancer Centre South only. According to the ICD-O3 classification [24-25], skin tumors were grouped in keratinocytic cancers (BCC and SCC excluding in situ lesions), melanomas, appendageal, haematolymphoid, soft tissue, neural tumors and others and non specificied malignancies as suggested by the most recent World Health Organization (WHO) classification of skin tumors [27]. Only invasive lesions were included in the analyses.

The absolute number of newly diagnosed cancers were recorded (and estimated in the case of BCC) for the whole Dutch population. Age-standardized incidence rates were calculated using the European Standard Population (ESR) and expressed per 100,000 person-years for each year between 1989-2005 and for the last five years (2001-2005), separately.

`For the most common malignancies in each of the WHO skin tumor groups, we estimated the annual percentage change (EAPC) in number of incident cases by constructing Poisson regression models with a log-link, modeling the observed number of cases as a function of year of diagnosis, adjusting for age and using the ln(population size) per age group and year as offset variable. The EAPC was calculated with a 95% confidence interval (CI). P-values were two-sided and considered significant if less than 0.05. The analyses were performed using SPSS version 15.0, using generalized linear models.

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Trends in incidence and predictions of cutaneous melanoma across Europe up to 2015

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ABSTRACT

Backgrounds: Melanoma has become a significant health problem in most Caucasian populations. The most recently available data from cancer registries always have a delay of approximately 6 months, but for the sake of validity, often of a few years and they are not always published in easily accessible ways. The 2 main objectives of this study were to determine the incidence and trends in incidence of melanoma and predict incidence rates for 2010 and 2015.

Methods: A retrospective database analyses was performed on data from 30 European Cancer registries that were members of the European Network of Cancer Registries and participated in Cancer Incidence in 5 continents. Predictions were mostly made with use of projection models that were linear in time.

Results: Data was provided by 30 registries of 23 countries in Europe of which most of them had data available from 1990 up to 2006. Overall the incidence of melanoma is rapidly rising and will continue to do so. The incidence among women in Europe was generally higher than men. The highest incidence rates were seen for Scandinavian countries and north-western countries like the UK, Ireland and the Netherlands. The lowest incidence rates were seen for Portugal and Spain, but these estimates were derived from only a few cancer registries. Relatively low incidence rates were also seen for Poland. Poland also had the highest mortality: incidence ratio.

Conclusion: In conclusion, incidence rates of melanoma are expected to continue rising. These trends are worrying in terms of disease burden, and, particularly in eastern European countries, in terms of the number of people that are expected to die due to melanoma.

INTRODUCTION

Cutaneous malignant melanoma (melanoma) represents 4% of skin cancers but is responsible for 80% of skin cancer deaths and all together 1-2% of all cancer deaths [1]. It has become a significant problem in Caucasian populations, with one in 6 persons developing skin cancer in their lifetime, of whom 10% has a melanoma. A recent study predicted that the incidence of melanoma in the Netherlands, will probably become higher than that of squamous cell carcinoma [2]. Through initiatives like the European Network of Cancer Registries (ENCR) it is possible to analyse and publish data from population based cancer registries throughout Europe to identify epidemiologic trends and associated survival for many cancer types [3]. These show that melanoma already has become a significant health care problem across Europe often appearing in the top 10 of most commonly occurring cancers. A study of de Vries et al. showed marked increases in incidence of and mortality from melanoma, but with indications of stabilising trends in some Northern European countries [4]. A study including data mainly from the 1990s showed that stage at diagnosis of melanoma was higher in the former communist countries compared to the northern and western European countries. The most recently available data from cancer registries always have a delay of approximately 6 months, but often of a few years and they are not always published in easily accessible ways, and usually do not contain information on stage at diagnosis. The two main objectives of this study are (1) to determine the recent incidence of melanoma, overall and by sex across Europe and (2) to analyze time trends in incidence and predict incidence rates for 2010 and 2015. Moreover, we inspected mortality:incidence ratios for melanoma across Europe as a proxy for the stage distribution of melanomas across Europe.

METHODS

Data collection

European population-based cancer registries (both National/Regional), members of the European Network of Cancer Registries (ENCR: http://www.encr.com.fr/), and participating in Cancer Incidence in 5 Continents [5-6] were contacted to determine interest in study participation. Those who replied positively and had at least 10 years of data available, with most recent data from 2004 or later were included for the analyses. A retrospective database analysis was performed on data obtained from 30 European Cancer registries.A quality assessment was performed on the participating registries (missing data, collected variables etc). Standard cancer registry procedures and coding rules, described in Cancer Incidence in 5 Continents were applied in all the included registries. The national and regional registries all fulfil the rules regarding patient privacy etc. Cancer Registries record tumour and patient characteristics based on pathological reports or clinical information available. Mortality data was obtained from the mortality database of the World Health Organisation.

Statistical Analysis

The predicted numbers of newly diagnosed cases with melanoma per European country in 2010 and 2015 were estimated by first projecting the incidence rates on the basis of observed rates from 1990 (or first year available after 1990) until the most recently available year (mostly between 2004 and 2007) by 5-year age categories and sex, according to the methods developed by Dyba et al.[7-8], and multiplying these rates in the population forecast for these periods, provided by the cancer registries themselves or derived from Eurostat. For the analysis only invasive melanomas were included.

The method developed by Dyba et al consists of 4 different submodels, 2 out of which are linear in time, and 2 are log-linear in time. Data was fitted to the 4 different models and the best fitting model was used for the projections. Besides the linear component in time trends, age effects observed in the historical data are incorporated in the modeling. The two models for increasing trends and fitted the best for our projections were:

I: $R_{ap}=A_a(1+Dp)$
II: $R_{ap}=A_a+D_ap$

Where R_{ap} = cap /nap is the expected value of incidence in age group *a* and period *p*, *nap* is the number of person years, cap the number of cases. Where A_a is the age-component of age group *a*, *D* is the general drift parameter for all age groups, and D_a is the drift parameter for age group *a*.

The collected data were combined with population-data from the whole population in order to estimate incidence rates when registries covered a non-national, regional catchment area only. Population sizes as reported by Eurostat were used to transform the projected age-specific incidence rates into expected numbers of new cases by age and sex by 2010 and 2015. Both European standardized rates (ESR) and absolute numbers were reported.

Age-specific incidence numbers were divided by the age-specific total population. European standardized rates were then calculated by multiplying the age-specific incidence rates with the standard European population data (http://seer.cancer.gov/stdpopulations/), and expressed per 100,000 person-years. This rate would have been found if the population of a country had the same age-composition (proportion of total population in each five year age class) as a hypothetical European population.

Upon analyzing the data on stage at diagnosis we noted that not all cancer registries documented stage information uniformly and regularly and different staging classifications were used by the various registries (varying from Breslow thickness, Clark level, TNM classification or loco-regional vs. advanced disease). Most registries that did collect information by stage had large proportion of patients with missing information on stage. Therefore, rather than reporting the incomplete stage-distribution we decided to inspected mortality:incidence (M:I) ratios. Mortality data was obtained from the mortality database of the World Health Organisation.

M:I ratios were calculated by dividing age-standardised mortality rates by age-standardised incidence rates. A higher M:I-ratio means that probably more melanoma patients die due to melanoma compared to other countries with lower M:I-ratios.

RESULTS

Data was provided by 23 European countries, of which most of them had data available from 1990 up to 2006. (Table 1) Overall the incidence rates of melanoma have increased markedly and will continue to do so. (Table 2) The difference in predicted rates and numbers between the selected models and the other three models was small (approximately 20-30% by 2015), except when one of the other models showed a lack of fit to the observed data (results not shown). Highest incidence rates were observed in Northern Europe, and lowest in Southern Europe.

Overall mortality rates were higher for men than for women. The highest mortality rates for men were seen in Norway. For women, mortality rates were slightly higher in the Scandinavian countries (except Finland), the Netherlands, Poland and Slovakia.

The highest M:I ratios for both men and women were seen for countries of Eastern Europe, in particular Poland with a M/I ratio of 0.53 for men and 0.43 for women. Northern and Western Europe had relatively low M:I ratios for both men and women. Ireland had the lowest M:I ratio for men (0.16), Scotland and Italy had lowest M:I ratios for women (0.09 and 0.10 respectively). (Fig 1)

Northern Europe (Denmark, England, Estonia, Finland, Iceland, Ireland, Norway, Scotland, Sweden, Wales)

Melanoma incidence rates increased rapidly between 1990 and 2007 in the Northern part of Europe. (Table 2) In this region, Denmark had the highest incidence rates for men and women in 2006, with ESRs of 19.6 for women and 24.0 for men. Estonia had the lowest incidence rates (ESR) in Northern Europe, with 10.8 and 11.2 per 100 000 person-years, form men and women respectively. Except for Estonia, incidence rates are predicted to continue to increase in Northern Europe at least until 2015. The incidence rate for Denmark will increase up to 26.1 per 100 000 person years for men and 29.9 per 100 000 person years for women. Estonia will remain the country in Northern Europe with the lowest incidence rates of 10.7 and 11.3 per 100 000 person-years for men and women respectively. In 2015, 73 men and 114 are expected to be newly diagnosed with malignant melanoma in Estonia. Overall, M:I ratios in Northern Europe were rather low, indicating a good survival and probably favorable stage distribution at diagnosis.(Fig 1)

Table 1: Participating Cancer Registries

Country	Registry	period	Size of registry population	National coverage	Part of Europe
Estonia	Estonian cancer registry	1990-2006	1343314	100%	Northern europe
Finland	Finnish Cancer Registry	1990-2007	5288730	100%	Northern Europe
Germany	Saarland	1990-2006	1046777	1.3%	Western Europe
Iceland	Icelandic Cancer Registry	1990-2008	315459	100%	Northern Europe
Ireland	Ireland	1994-2007	4439750	100%	Northern Europe
Malta	Malta National Cancer Registry	1993-2008	409092	100%	Southern Europe
Poland	Polish Cancer Registry	1999-2007	38115967	100%	Eastern Europe
Portugal	North Region	1996-2005	3280199	31%	Southern Europe
Slovakia	Slovakia	1990-2005	5387285	100%	Eastern Europe
Spain	La Rioja	1993-2005	301084	1%	Southern Europe
Spain	Girona	1980-2007	658984	1.60%	Southern Europe
Spain	Basque country	1990-2004	2110626	5.8%	Southern Europe
Spain	Navarra	1990-2004	607859	1.2%	Southern Europe
Spain	Tarragona	1990-2004	663455	0.3%	Southern Europe
Switzerland	Geneve	1990-2006	443145	2.4%	Western Europe
Switzerland		1990-2008	3531102	100%	Western Europe
UK	UK registries;	1990 - 2006		100%	Northern Europe
UK	England	1990 - 2006	50762945	100%	Northern Europe
UK	N-Ireland	1990 - 2006	4239848	100%	Northern Europe
UK	Wales	1990 - 2007	2979975	100%	Northern Europe
The Netherlands	Netherlands Cancer registry	1989-2007	16381682	100%	Western Eurpe
Slovenia	Slovenia	1990-2007	2019406	100%	Southern Europe
Italy	Modena	1990-2007	677672	1.15%	Southern Europe
Italy	Sondrio	1998-2007	179736	0.3%	Southern Europe
Italy	Umbria	1994-2006	811830	?	Southern Europe
Publically available					
NORDCAN	Norway	1990-2006	4709184	100%	Northern Europe
	Sweden	1990-2006	9148102	100%	Northern Europe
	Iceland	1990-2006	311396	100%	Northern Europe
	Finland	1990-2006	5288730	100%	Northern Europe
	Denmark	1990-2006	5457405	100%	Northern Europe
Scotland		1985-2007	5144200	100%	Northern Europe
Czech republic		1977-2007	10322689	100%	Eastern Europe

Eastern Europe (Czech Republic, Poland, Slovakia)

Of the Eastern European countries data was provided by the cancer registries of Czech Republic, Poland and Slovakia.(Table 1) Czech Republic had the highest incidence rates and Poland the lowest (Table 2). For men the incidence rate in the Czech Republic was 17.8 per 100 000 person years in 2007 and is expected to increase to 19.7 in 2010 and 22.5 per 100 000 person-years by 2015. For women in the Czech Republic this will be 15.8 and 17.8 per 100 000, by 2010 and 2015, respectively. This translates into 1428 men and 1268 women newly diagnosed with melanoma in 2015. The incidence rates for Poland will also increase but might remain the

Table 2: European incidence rates by 2010 en 2015 for men and women

Countries	Incidence rates (ESR per 100,000 person-years)			Projections 2010 (ESR per 100,000 person-years)		Projections 2015 (ESR per 100,000 person-years)		Mortality rates (ESR per 100,000 person-years)			M/I index (ESR per 100,000 person-years)	
	year	men	women	men	women	men	women	year	men	women	men	women
Czech Republic	2007	17.8	15.3	19.7	15.8	22.5	17.8	2007	3.6	1.7	0.2	0.1
Denmark	2006	19.6	24	21.5	24.1	26.1	29.9	2006	4.4	2.6	0.2	0.1
England	2006	14.5	15.7	16.5	19.1	19.7	24.8	2006	3.1	1.9	0.2	0.1
Estonia	2006	10.8	11.2	9.5	10.5	10.7	11.3	2006	3.7	3.6	0.3	0.3
Finland	2007	15.0	12.5	16.8	13.2	19.1	14.7	2007	3.5	1.7	0.2	0.1
Germany	2006	11.2	12.8	14.0	15.3	15.5	18.0	2006	2.4	1.5	0.2	0.1
Iceland	2008	14.7	14.4	14.8	18.8	15.8	17.7	2008	5.0	2.2	0.3	0.2
Ireland	2007	17.1	16	16.7	18.7	19.6	20.7	2007	2.7	2.0	0.2	0.1
Italy	2007	11.5	10.1	12.2	11.1	13.7	12.1	2007	2.4	1.5	0.2	0.1
Malta	2007	8.6	12.1	15.1	23.8	18.3	30.4	2007	1.9	2.2	0.2	0.2
Norway	2007	21.7	21.8	22.1	22.9	23.0	24.2	2007	6.6	3.1	0.3	0.1
Poland	2007	5.7	4.9	6.3	5.4	7.2	5.9	2007	3.0	2.1	0.5	0.4
Portugal	2003	3.3	5	4.6	6.2	5.6	7.1	2003	1.3	1.3	0.4	0.3
Scotland	2007	15.6	19.4	17.0	19.3	19.7	22.1	2007	3.1	1.8	0.2	0.1
Slovakia	2005	10.2	8.8	13.6	12.6	16.1	14.8	2005	4.7	2.6	0.5	0.3
Slovenia	2007	17.9	19.4	19.4	19.8	22.7	23.8	2007	5.8	2.8	0.3	0.1
Spain	2004	8.9	11	10.7	12.7	12.4	14.5	2004	1.8	1.6	0.2	0.1
Sweden	2007	18.8	19.6	19.9	20.3	21.8	22.5	2007	4.4	2.8	0.2	0.1
Switzerland	2006	22.0	20.7	24.7	23.2	26.8	25.3	2006	3.7	2.0	0.2	0.1
The Netherlands	2007	18.2	21.9	20.0	24.0	23.3	27.7	2007	4.1	2.7	0.2	0.1
Wales	2007	15.3	14.4	17.0	17.5	20.5	20.8	2007	3.1	2.1	0.2	0.2

Spain: includes the regions: La Rioja, Basque country, Navarra, Girona and Tarragona. Stage information was only available for Girona, Navarra and La Rioja, making % of advanced disease unreliable.
Italy includes the region of Modena, Umbria and Sondrio
Portugal includes only the Northern region.

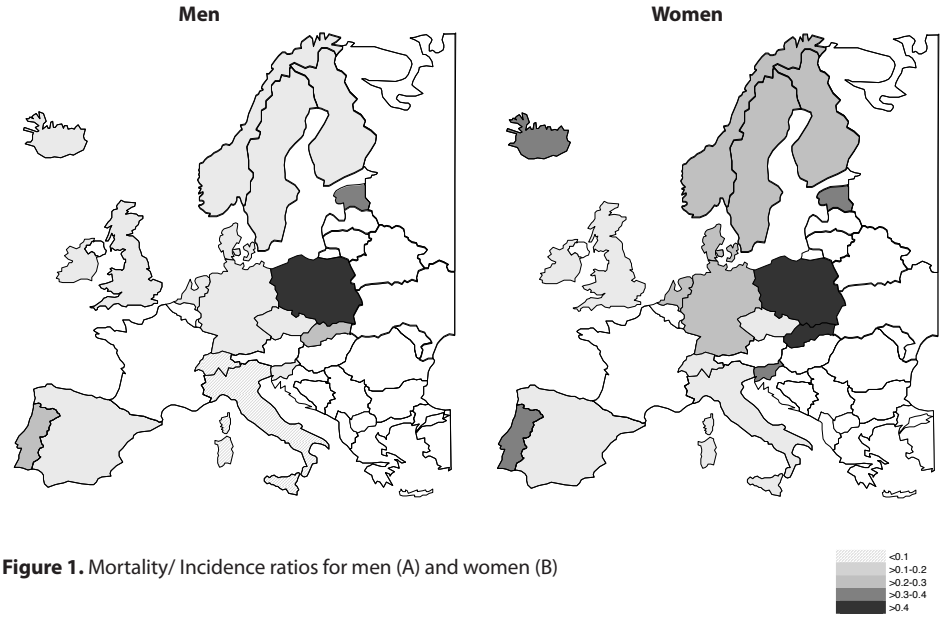

Figure 1. Mortality/ Incidence ratios for men (A) and women (B)

lowest with 7.2 for men and 5.9 for women by 2015. Eastern Europe showed the least favorable M:I ratios, probably indicating a relatively unfavorable stage distribution.(Fig 1)

Southern Europe (Italy, Malta, Portugal, Slovenia, Spain)

Incidence rates for Southern Europe were not available at a national level and provided by separate regional cancer registries and combined and extrapolated to national coverage. Data was provided by cancer registries of 5 South European countries.(Table1) The cancer registry of Northern Portugal reported by far the lowest incidence rates in 2003, with 3.3 per 100 000 for men and 5 per 100 000 for women.(Table 2) The highest rates were seen for Slovenia with ESRs of 17.9 and 19.4 per 100 000 for men and women respectively. These incidence rates are expected to continue to rise to an incidence rate of 22.7 for men and 23.8 per 100 000 for women by 2015, translating into an expected 289 Slovenian men and 314 Slovenian women newly diagnosed with melanoma in 2015. M:I ratios for Southern Europe were generally modest.(Fig 1)

Western Europe (Germany, Switzerland, the Netherlands)

Incidence data for Western Europe (except for Germany) was most complete and this region had, as Northern Europe, the highest incidence rates, all ESRs in this region exceeded 10 per 100 000 person years.(Table 2) Germany had the lowest incidence rates and Switzerland the highest. Incidence rates for all included Western European countries are expected to increase until 2015. Incidence rates for men are expected to be between 15.5 and 26.8 per 100 000 for men by 2015 and between 12.8 and 25.3 for women. Western Europe showed the most favorable M:I ratios. (Fig1)

DISCUSSION

Projections for melanoma incidence per country were made for the years 2010 and 2015, based on the incidence data provided by the participating cancer registries in Europe for the years 1990 up to 2007. Incidence projections were based on series of at least 10 years of data (as of 1997), to make projections more stable. Projections showed that the incidence for melanoma is expected to continue to rise in all countries.

The incidence of malignant melanoma among women in Europe was higher than men for all countries except the Czech Republic, Finland, Ireland, Switzerland, Poland and Slovakia. This higher incidence among females is expected to continue until 2015. The highest incidence rates were seen for the Scandinavian countries and north-western European countries like the UK, Ireland and the Netherlands. The lowest incidence rates were seen for Portugal and Spain. However, data on melanoma incidence were provided by only a few cancer registries in the latter countries, resulting in small percentage coverage of the whole country. Relatively low incidence rates were also seen for Poland.

Stage information would be needed to get a real impression of the stage at diagnosis, indicator of melanoma awareness in the population, detection delay and survival of patients diagnosed with melanoma across Europe. Unfortunately, information on stage was not regularly recorded by most of the cancer registries. For the registries that did have information available on stage for a large proportion of patients, there was no uniformity in the way of recording stage information of melanoma. The way of recording by stage differed from only recording Breslow thickness or Clark level up to only recording the stage of melanoma at diagnosis not specified by TNM-classification. It was therefore impossible to compare the stage distributions between the European countries, neither could we project expected incidence of melanoma by 2010 and/or 2015 by stage. Therefore, to get some impression of the overall survival of melanoma patients per country and a rough idea of the stage distribution, we calculated the mortality-incidence ratio (M:I-ratio). The higher the M:I-ratio the more melanoma patients die due to melanoma. Even though one of the lowest melanoma incidence rates within Europe was found for Poland, it had the highest M:I ratios, indicating that, a large proportion of patients diagnosed with melanoma in Poland will die from melanoma. This is confirmed by a recent study on survival trends of cancers across Europe, reporting one of the lowest survival rates for the cancer registry of Cracow (67.5 in 2000-2004), but also the slowest improvements in survival with 6.1% survival change in the 5-year relative survival between 1990-1994 and 2000-2004 [9]. One of the reasons for this high mortality could be that patients in Poland are likely diagnosed at a more advanced stage, when the treatment for these patients is limited [4]. On the contrary, Norway which had very high incidence rates, had one of the lowest M:I-ratios, although mortality rates were relatively high, probably reflecting favourable stage distribution at diagnosis, possibly

because of high skin cancer awareness in the general population and among physicians. These findings are in line with earlier reports on thicker melanomas occurring in the former communist European countries, and indicate that this unfavourable stage distribution has not yet improved substantially [4].

Several studies have shown that most of the increases in melanoma incidence are due to strong increases in the occurrence of thin melanomas, resulting in better survival for the group of melanoma patients as a whole [10-12]. La Vecchia et al. and Ferlay et al. have shown that it is expected that melanoma-related mortality will be levelling off. The combination of increasing incidence with stabilising mortality indicates strong rises in the number of melanoma survivors.[10-12] However, in some European countries, melanoma incidence rates are rising equally rapidly for the thick melanomas [13], reason for worry as these are the melanomas that are potentially most lethal.

There are several limits to extrapolating incidence rates. The explored time period exceeds several decades, but these projections do not take changes in exposure to risk factors into account such as; the change in UV-radiation due to changes in sun behaviour or changes in the ozone layer. Furthermore these projections are based on former variations in incidence rates since 1990 and a slight stabilization in recent incidence rates will have little effect on the projected rates by 2010 and 2015. Also, potential effects of primary prevention are not considered. Since 2007, men and women aged 35 or older are entitled for skin cancer screening every two years in some countries (e.g. Germany). This might result in even higher incidence rates, but could also have a primary and secondary prevention effect, as patients repeatedly will be reminded of the development, and risk factors of melanoma.

We used the M:I ratio as measure of 'severity' of melanoma, but this measure is more frequently used as a quality indicator for cancer registries [14]. The M:I ratio is indeed not only influenced by the real incidence and mortality but also but the quality of the cancer registry: if many incident cancers are missed and many death-certificate-only cases are included, the M:I ratio will be much higher then when these melanomas would have been picked up at the moment of diagnosis. This might have influenced M:I ratios in our study as well, particularly in situations when melanomas would be diagnosed in private clinics, making it more difficult for the cancer registry to pick them up. However, most included cancer registries were of good quality [6], making the alternative interpretation of M:I ratio as a measure of severity also possible. It should also be noted that an increase in incidence of advanced stages of melanoma can only result in an increase of mortality after a few years. This can lead to a relatively low M:I ratio, as mortality runs behind time. However, this is unlikely to be the case for melanoma, as mortality from melanoma has been mostly stable for the past ten years. [3]

Although unfortunately not all European cancer registries participated in this study, results are comparable to that of previously reported incidence rates [10, 13, 15-21].

Especially for Italy and Germany, only a few of the cancer registries participated, either because, of the inclusion criteria or because they did not respond to our request to participate.

However, there have been some reports on incidence rates of (other regions in) these countries. Crocetti et al, evaluated melanoma incidence and trends in incidence in the area of the Tuscany Cancer Registry (active in the provinces of Florence and Prato; 1,160,000 residents in 2001) between 1987 and 2001. A total of 1977 malignant melanomas were diagnosed in this time period (incidence rate of 15.9 per 100,000 for 1997 to 2001). Incidence rates increased in all age-groups and time periods, with a mean annual increase of 6.4%. Predicted standardized incidence rate for 2002-2006 was 19.2 per 100,000.[17]

The Cancer Registry of Schleswig-Holstein is one of the largest cancer registries in Germany, with 3500 registering institutions, covering a population of 2,8 million inhabitants. Between 1998 and 2001, 1784 malignant melanomas were diagnosed, with an incidence rate of 12.3 per 100,000 men and 14.8 per 100,000 women,[22] which is slightly higher than the observations from the cancer registry of Saarland

Another limitation of this study is related to demographic projections that are dependent on population movements; especially immigration and could effect the projections in incidence and mortality of melanoma.

Our findings show that incidence rates are expected to continue rising, contrary to earlier findings that seemed to indicate a plateauing of incidence rates among the younger populations, at least in Scandinavia [16, 19, 21].

These trends are worrying in terms of disease burden and costs, and, particularly in the Eastern European countries, in terms of the number of people that expected to die of a melanoma. Mainly in countries where incidence is still modest, caution is warranted as rates are increasing and melanomas seem to be detected in relatively late stages causing M:I ratios to be rather high. A combination of primary prevention of melanoma and effective early detection and treatment remains of high importance.

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Patients perspectives of having been diagnosed with melanoma

4

A systematic review of health-related quality of life in cutaneous melanoma

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ABSTRACT

Melanoma can be considered an emerging chronic disease that may considerably affect patients' lives. The authors systematically reviewed the available literature on health-related quality of life (HRQOL) and melanoma. Of reviews and the selected studies, reference lists were hand-searched. The quality of the eligible studies was appraised based on 14 previously published criteria. Of the 158 abstracts, 44 articles were appraised, resulting in 13 selected studies written in English (published between 2001 and 2008). Most studies assessed patients from specialised centres with varying, but relatively advanced, disease stages. The most commonly used instruments were the SF-36 and EORTC QLQ-C30. Recently, a melanoma-specific HRQOL questionnaire [FACT-Melanoma (FACT-M)] was introduced for clinical trial purposes. It showed that approximately one-third of melanoma patients experienced considerable levels of distress, mostly at the time of diagnosis and following treatment. Systemic therapies affected HRQOL negatively in the short term, but to a lesser extent in the long term. Health status and patients' psychological characteristics are associated with higher levels of HRQOL impairment. The authors found that the impact of melanoma on patients' HRQOL is comparable to that of other cancers. Accurately assessing HRQOL impairment in melanoma patients is pivotal, as it may affect disease management, including therapy and additional counselling, future preventive behaviour and perhaps even prognosis.

INTRODUCTION

The incidence of cutaneous melanoma has increased dramatically in the western world in the last few decades (4% for women and 5% for men, annually) [1]. Despite this rise in incidence, the mortality rate seems to be levelling off due to earlier diagnosis [2-3]. Approximately 70% of melanoma patients have a Breslow thickness of less than 1.5 mm, with a 5-year survival rate of 95%. When lymph nodes are involved, the survival rate drops to 20% to 40% [1]. Melanoma affects relatively young and middle-aged people. Patients with melanoma are more at risk of developing a new primary melanoma (1.2% to 8.2%), and their-first degree relatives have a twofold higher risk of developing melanoma [4]. Despite tremendous efforts, melanoma treatment has not changed substantially; in most cases it comprises surgery with or without (sentinel) lymph node resection. A small group of patients with metastasised disease receive chemotherapy and/or interferon therapy (often in clinical trial settings).

About 80% of patients will survive melanoma [1, 3] but remain at-risk for disease progression for many years, for which there is no successful therapy. Therefore, melanoma can be considered a chronic, life-threatening disease. Additionally, patients are aware that UV exposure is an important risk factor for the development of melanoma, which may affect their lifestyles as well as social and professional activities [5].

Altogether, these observations suggest that melanoma may have a considerable impact on patients` lives, including their health-related quality of life (HRQOL), which the World Health Organization (WHO) defines as "an individuals' perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards and concerns. This broad ranging concept is in a complex way affected by the persons' physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment." Because in approximately 75% of patients local surgical excision is an adequate therapy, HRQOL impairment is predominantly determined by psychological aspects and, to a lesser extent, by (long-term) therapy-induced events, as is often observed in other cancers. The psychosocial issues facing patients with an early stage, highly curable disease such as melanoma differ from other types of cancer with profound loco regional effects or distant metastases. Although more than 85% of melanoma patients rated follow-up surveillance to be worthwhile, they also indicated that little attention had been paid to the patients' well-being during surveillance [6].

The objective of this review is to evaluate, summarize, and discuss the available literature concerning HRQOL in patients with cutaneous melanoma.

METHODS

Systematic searches were conducted in PubMed, MEDLINE, and The Cochrane Library with the assistance of a medical librarian. The search algorithm of MeSH used terms was the following: (cutaneous OR skin) AND melanoma AND (quality of life OR life) AND (health status OR health status indicators OR survival analysis OR health-related OR health) NOT "non-melanoma." Restrictions were not placed on publication dates or language. Several inclusion and exclusion criteria were used (Figure 1). The quality of the eligible studies was assessed using criteria for assessing the methodological quality of studies in HRQOL published previously (Table 1) [7]**.** In brief, these criteria focus on the methodological aspects of HRQOL studies, e.g., whether inclusion and exclusion criteria are well-formulated, whether responders and non-responders are reported, and whether socio-demographics of the responders are known and the score range is between 0 and 14. The criteria are quite strict; if a certain criterion is not explicitly mentioned, the default is 0.

Results

Included studies

Of the 158 abstracts extracted from PubMed, 114 were excluded primarily because they did not focus on HRQOL; 44 full articles were reviewed, but only 13 were eligible for this review (Figure 1). The articles were all in English and published between 2001 and 2008.

Quality of included studies

The included studies varied in quality according to the quality criteria used (Table 1) [7]. The scores of the eligible studies ranged between 8 and 12 out of a maximum of 14 (67% and 86%, respectively) (Table 3).

Study design and population

Of the 13 studies that assessed HRQOL in melanoma patients, 7 were cohort studies, 5 were clinical trials, and one was a cross-sectional population-based study. Three studies investigated the effects of therapy such as surgery, interferon, or vaccination on patients' HRQOL. Of the 10 prospective studies, 8 had a study duration of 4 months or less. Only two studies followed patients for more than 2 years after melanoma diagnosis. Six studies were conducted in the United States, of which 3 included patients from specialized melanoma clinics. The remaining European studies most often included patients from tertiary oncology departments. One randomized clinical trial from the United Kingdom and one cross-sectional study from the United States were both population-based. The study size varied between 10 and 674 patients. Five of 13 studies included less than 100 patients (of which 2 had less than 50 patients), and 4 studies had more than 250 patients. The tumour stages varied, but most studies focused on localized disease, and only a few focused on metastasised melanoma (Table 3).

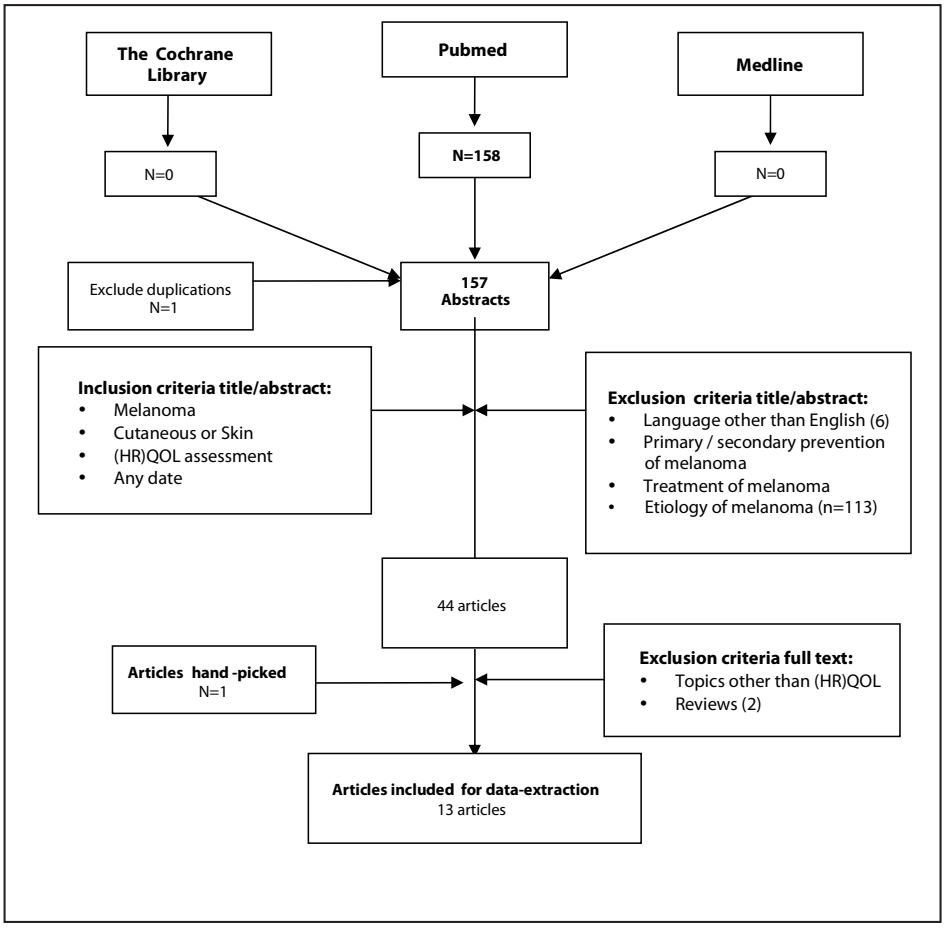

Figure 1. Flow-chart of the systematic search

HRQOL measures

A total of 20 different instruments were used in the 13 studies; 7 measured HRQOL, of which 5 were generic instruments, one was cancer-specific, and one was melanoma-specific (Tables 2 and 3). The most frequently used generic and cancer-specific HRQOL tools were the SF-36 (5/13) and EORTC QLQ-C30 (6/13), respectively. In 3 studies, a combination of generic and cancer-specific tools was used. In 2 studies, health utilities (HALex and EQ-5D) were used as a measure of HRQOL, and in one study a melanoma-specific (FACT-M) tool was used. Recently, the FACT-M questionnaire was proposed as "a reliable and valid instrument for patients with melanoma that can be used for the assessment of QOL in clinical trials" [8-9].

Table 1: List of 14 criteria assessing the methodological quality of HRQOL studies of melanoma patients.

A.	Socio-demographic and medical data are described (e.g. age, race, employment status, educational status, tumor stage at diagnosis etc.)
B.	Inclusion and /or exclusion criteria are formulated
C.	The process of data collection is described (e.g. interview or self-report etc.)
D.	The type of cancer is described
E.	The results are compared between two groups or more (e.g. health population, groups with different cancer treatment or age, comparison with time at diagnosis etc.)
F.	Mean or median and range or standard deviation of time since diagnosis or treatment is given
G.	Participation and response rates for patient groups have to be described and have to be > 75%
H.	Information is presented about patient/disease characteristics of respondents and non-respondents or if there is no selective response
I.	A standardized of valid QOL questionnaire is used
J.	Results are described not only for QOL but also for the physical, psychological and social domains
K.	Mean, median, standard deviations or percentages are reported for the most important outcome measures
L.	An attempt is made to find a set of determinants with the highest prognostic value
M.	Patient signed an informed consent form before study participation
N.	The degree of selection of the patient sample is described

In addition to HRQOL, all included studies reported on other psychological and social constructs, such as social support and personality structure, but these instruments were beyond the scope of this review.

HRQOL impairment in melanoma

The results of the different studies suggested that there are three distinct periods of HRQOL impact during the melanoma experience: diagnosis, treatment, and follow-up [10-11]. The immediate period following diagnosis (i.e., acute survival phase) was often associated with high levels of HRQOL impairment [12-13]. Patients reported more pain, less energy, and more interference of stressors (physical and emotional) on social activities. Importantly, patients also gave worse evaluations of overall personal health. Acute survival is followed by extended survival, which is dominated more by fears of recurrence and less by the physical limitations the cancer or its associated therapies create [10]. In the follow-up phase, psychological distress can interfere with screening recommendations and preventive behaviours [11].

A recent study showed that prior to the definite diagnosis of melanoma, patients reported an excellent HRQOL. During the diagnostic process, however, insomnia increased, while emotional functioning and global health status deteriorated, as measured by standard anxiety scales (HADS, STAI-SFF) and the EORTC QLQ-C30 for patients ultimately diagnosed with melanoma [12].

In a surgical randomized clinical trial (RCT) of high-risk melanoma patients, patients with a 3-cm excision margin had significantly poorer mental and physical functioning (SF-36) compared to those with a 1-cm excision margin [14]. After 3 to 6 months, the difference in HRQOL impact

Table 2. Health related quality of life (HRQOL) instruments used in eligible studies.

Instrument	Type	Goals	Domains / subscales
Brief Symptom Inventory (BSI)	Generic	Measure of emotional distress	Nine clinical scales and three summary scales. Global severity index (GSI): sensitive measure of overall distress.
Chronic Strains Survey (CSS)	Generic	Measure of persistent stressful conditions	Items concerning the existence and perceived burden of economical and social difficulties, strains in work life, alcohol or drug abuse, other chronic diseases, etc.
EuroQol Group (EQ-5D)	Generic	A 5-dimensional health state classification	Five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.
Health and Activities Limitation Index (HALex)	Generic	Provides a HRQOL utility score	A single numerical value for the health state based on patients' perceived health status in conjunction with any activity limitation they might experience. 0=near death state to 1=perfect health with no limitations. Previously validated against a large population of subjects.
Short Form-36 (SF-36)	Generic	Assesses health functioning; often used as a general measure of HRQOL	Eight subscales: physical functioning, vitality, social functioning, general health, bodily pain, physical role, emotional role, and mental health. Two component summary scales: Physical and mental component summary scales (PCS and MCS).
European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30)	Cancer -specific	Assesses the HRQOL of cancer patients participating in international clinical trials	Five functional scales: physical (PF), role (RF), cognitive (CF), emotional (EF) and social (SF) Three symptom scales: fatigue (FA), pain (PA), nausea and vomiting (NV) A global health status / QOL scale (QL) Six single items assessing additional symptoms commonly reported by cancer patients: dyspnoea (DY), loss of appetite (AP), insomnia (SL), constipation (CO), diarrhoea (DI) A single-item on the perceived financial impact of the disease (FI).
Functional Assessment of Cancer Therapy - Melanoma (FACT-M)	Melanoma-specific	Assesses the HRQOL of melanoma patients participating in clinical trials	Fact-G items (general) questions. Melanoma specific sub-scale: 24-items encompassing three HRQOL domains: physical, emotional, and social well-being.
Cassileth Scar Questionnaire	Therapy-specific	Investigates patients' opinion on the size and cosmetic implications of their excisions	12 items, each scored from 1 to 4 (minimum to maximum negative cosmetic impact). The questionnaire also contains outline drawings of the human body on which patients are asked to indicate the size, shape, and location of their scar [16].

Table 3. Summary of eligible and reviewed studies on melanoma and health related quality of life (HRQOL) impairment.

Country Year [Ref]	Research type	Study population	Pts	HRQOL instrument	Conclusions	Quality score (range 0-14)
U.S.A. 2008 [9]	Cohort Prospective 12 months	M.D. Anderson Cancer Center Patients recruited with new melanoma or within the first three years of follow-up	225	FACT EORTC QLQ, POMS MCSDS	Reliable QOL questionnaire for patients with melanoma in clinical trials	9
*Europe 2004 [15]	Randomized Prospective 2 months	Centres throughout Europe Patients with non-ocular melanoma, with or without brain metastases Phase III study comparing fotemustine (F) and dacarbazine (D) (one in each of the patients arms) Metastasized disease	229 (112F, 117D)	EORTC QLQ-C30	"No significant difference in QOL between two groups. The general tendency in the selected QOL dimensions was degradation over time in both arms."	10
Finland 2007 [22]	Cohort Prospective 3-4 months after diagnosis	Oncology Clinic of Tampere University Hospital, Finland Patients with cutaneous melanoma with localized disease. Included patients with Clarke II, II of IV Breslow 0.20 mm-7.00mm. Excluded patients with *in situ* melanoma, Clark V and orbital melanoma	59	WOC, SSF, AX, LES, CSS, RSCL, DEPS	"Women tend to have slightly more psychological symptoms (P=0.085). Patients reported self-perceived QOL as quite good to good."	8
U.K. 2006 [16]	Randomised Prospective 60 months	Weston Park Teaching Hospital, Sheffield Melanoma patients, all stages	674	EORTC QLQ-C30, EQ5D	"Patients in observational group had significantly higher mean QOL than interferon patients."	8

Table 3. Summary of eligible and reviewed studies on melanoma and health related quality of life (HRQOL) impairment. (continued)

Country Year [Ref]	Research type	Study population	Pts	HRQOL instrument	Conclusions	Quality score (range 0-14)
Poland 2005 [17]	Controlled trial Prospective minimum of 56 days after surgery	Department of Soft Tissue and Bone Cancer, Institute of Oncology, Warsaw Two equal groups of 110 patients after radical surgery for melanoma. One group received supplementary IFN-α-2b therapy. Stage unclearly mentioned	220	EORTC QLQ-C30	"The IFN-α-2b significantly affected the emotional, social and physical health of the patients. In spite of adverse effects of treatment, patients scored their QOL as good."	10
Finland 2005 [19]	Cohort Prospective 3 months after diagnosis	Oncology Clinic of Tampere University Hospital Patients with melanoma and breast cancer patients Localized disease, newly diagnosed	175 (Melanoma 72)	WOC, SFSS, AX, LES, RSCL, DEPS, EORTC-QLQ (breast cancer module)	"QOL of newly diagnosed cancer patients is highly associated with psychosocial factors. Non-cancer life stresses seem to be very important in the QOL in newly diagnosed cancer patients. Adjuvant treatment may compromise supportive psychosocial factors that enhance QOL in cancer."	9
U.K. 2006 [12]	Cohort Prospective 6 months	Pigmented Lesion Clinic Malignant and non-malignant skin lesions, all stages	195 (Melanoma 10)	EORTC QLQ-C30 HAD STAI-SSF	"QOL pre-diagnosis was excellent. Emotional functioning, insomnia and global health status deteriorated throughout diagnostic process for patients with malignant melanoma."	12
U.S.A. 2004 [20]	Cohort Prospective 9 months	Multidisciplinary Melanoma Clinic Melanoma patients with stages I - III	351	MOC, BSI, SF-36, WOC, STAI	The healthy cluster reported a significantly higher HRQOL than the unhealthy clusters when confronted with melanoma.	11

Table 3. Summary of eligible and reviewed studies on melanoma and health related quality of life (HRQOL) impairment. (continued)

Country Year [Ref]	Research type	Study population	Pts	HRQOL instrument	Conclusions	Quality score (range 0-14)
U.S.A 2003 [21]	Cohort Prospective 3 months	Anderson Cancer Centre, Houston Population with metatstatic renal cell carcinoma or metastatic melanoma. Phase I/b trial for trial vaccination	53 (Melanoma 24)	ISEL, IES, BSI, SF 36	"The results suggest that social support buffers the negative association between intrusive thoughts / avoidance and psychological adjustment. Overall the results are consistent with a social-cognitive processing model of post-trauma reactions among cancer patients."	10
U.S.A. 2003 [18]	Randomised Prospective 6 months	Melanoma Clinic Melanoma patients with stages I – III	48	BSI SF-36 STAI	"Distress significantly reduced after 4 CBI sessions, with an increase in HRQOL in patients with medium-high distress."	10
U.S.A. 2003 [13]	Cross-sectional Retrospective	Population-based study Patients with melanoma, breast, colon or lung cancer <1 year, 1-5 years and > 5 years, stage unknown	692 (Melanoma = 92)	HALex	"Health utility score lowest directly after treatment and improve over time. Long term (> 5 years) survivors have the highest score."	9
U.S.A. 2001 [11]	Cohort	Multidisciplinary Melanoma Clinic Melanoma patients with stages I - III	287	BSI SF-36 WOC STAI	"A significant minority of patients are distressed and rely heavily on non-beneficial coping strategies."	10

*France, Germany, Norway, Hungary, Spain, Slovakia, Austria

Abbreviations: AX, Anger Expression Scale; BSI, Brief Symptom Inventory; CSS, Chronic Strains Survey; DEPS, Depression Anxiety Scale; EQ-5D, EuroQol group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer; FACT-M, Functional Assessment of Cancer Therapy - Melanoma; HAD, Hospital Anxiety and Depression; HALex, Health and Activities Limitation Index; IES, Impact of Event Scale; ISEL, Interpersonal Support Evaluation List; LES, Life Experience Survey; MCSDS, Marlowe-Crowne Social Desirability Scale, POMS, Profile of Mood States; PAIS-SR, Psychosocial Adjustment of Illness Scale - Self Report; RSCL, Rotterdam Symptom Checklist; SF-36, Short Form-36; SFSS, Structural-Functional Social Support Scale; SSF, Social Support Survey; STAI, State Trait Anxiety Inventory; WOC, Ways of Coping.

between these two patient groups was no longer significant, except for a persisting poor scar perception in the 3-cm excision group. Predictors of poor scar perception were younger age, female gender, a 3-cm excision margin, and poor physical and mental health post surgery. Additionally, patients with a 3-cm margin had more complications, a longer hospital stay, more skin grafts, and a greater physical impairment.

Three clinical trials assessed the effect of chemotherapeutics and/or interferon therapy on patients' HRQOL [15-17]. Patients who received interferon therapy scored significantly lower on their HRQOL in terms of functioning and symptoms compared to the (placebo) control group. The EORTC QLQ-C30 instrument showed that patients had significantly worse mean scores in role functioning (RF), emotional functioning (EM), cognitive functioning (CF), social functioning (SF), and global health status compared to patients in a placebo group [16]. Although systemic drugs (e.g., interferon) decreased patients' HRQOL during treatment, the overall gain in HRQOL was favourable in some patients, especially those with a poor prognosis [17].

In one study, cognitive behavioural intervention significantly decreased distress (i.e., BSI and STAI scores) in patients with medium to high baseline levels of distress [18].

Predictors of HRQOL impairment

Several studies have demonstrated that overall health is the most important predictor of melanoma's impact on HRQOL [9, 19-20]. Patients with poor health are significantly more likely to report higher levels of HRQOL impairment or lower levels of health utility than healthier patients. Patients who report poor physical health have a comparable impact to those with poor psychological health, and those who experienced both reported the lowest HRQOL scores [9, 19]. Not only is global health a predictor of HRQOL, it also deteriorates after the diagnosis of melanoma due to an increase in insomnia and pain [9, 12, 20].

In addition to health status, several psychological factors such as non-cancer life stresses, wishful thinking, and maladaptive coping styles were important determinants of melanoma's level of impact on HRQOL [11]. In patients with metastasised melanoma, low levels of social support were significantly associated with greater psychological distress and poorer mental HRQOL. Additionally, low social support decreased the likelihood of HRQOL adjustment one month after treatment [21].

No studies have investigated the HRQOL across gender, age, and all tumour stages, except in a surgical RCT in which older individuals were significantly more likely to report lower levels of physical functioning, as is expected [14]. Women reported significantly higher levels of anxiety than men surrounding the diagnosis [12].

DISCUSSION

About one third of patients with melanoma have reported clinically significant levels of distress, which is in accordance with findings in other cancers. Distress was highest around the time of diagnosis and immediately post–treatment, and decreased over time [12-14]. Although increased levels of HRQOL impairment is associated with poor recovery and an increase in morbidity and maybe even disease progression [6, 8-13, 18-19, 22], relatively few studies have investigated HRQOL in melanoma patients. The reviewed studies focused mainly on populations from specialized (melanoma or cancer) centers that received additional therapy during short periods of time. The impact of melanoma on individuals from the general population who have survived this skin cancer for many years is not well documented.

Although the SF-36 is the most widely accepted generic HRQOL tool, its psychometric properties have not been tested in melanoma patients. A generic instrument allows for comparability between melanoma patients, other diseases and cancers, and the general population, as normative data exists for many countries. As generic instruments may not be very sensitive in detecting effects that are associated with specific diseases (e.g., sun avoidance behaviour in melanoma patients affects social functioning), the combination of a generic and specific HRQOL instrument is most informative [23].

FACT-M, which is a melanoma-specific HRQOL instrument that focuses on physical domains and was designed for clinical trial settings, has recently been validated in 273 melanoma patients and showed to be reliable, responsive, and have a good construct and convergent validity [8-9]. Because the majority of patients diagnosed with melanoma will most likely experience few limitations in their physical functioning and be much more affected mentally, the content of the FACT-M seems especially appropriate for patients with advanced melanomas and less for those from the general population. Fear of recurrence and changed lifestyles, due to UV avoidance, are likely to be important HRQOL domains that are not fully assessed in any of the available HRQOL instruments, which suggests a lack of content validity. Altogether, the selection of an appropriate HRQOL instrument remains a trade-off between the psychometric properties of the instrument, the study population, and the research objectives of the study [23].

The reported effects of systemic treatment (e.g., interferon) on HRQOL may depend on the treated patient population. Patients who agree to participate in a clinical trial and/or receive therapy may be more motivated and optimistic, and thus are more likely to report benefit and endure more drug-induced toxicity compared to those not receiving systemic treatment. The latter issue is confirmed by the fact that some patients on interferon therapy, which is associated with severe flu-like symptoms, scored their HRQOL during treatment as good [17, 24].

In cancers that are treated with relatively non-aggressive therapies, have relatively good survival rates, and have a high number of years-lived-with-disability, patients' perspectives are very important. In addition to clinical therapy, psychological surveillance after diagnosis and therapy may be needed, especially among patients with poor global health status, those with certain personality structures (e.g., maladaptive coping styles), and those without a social network [11, 21]. Although a pilot study suggested that a psycho-educational intervention might improve survival in melanoma patients, a large Danish RCT demonstrated no increased survival or recurrence-free interval among those who were offered 6 weekly 2-hour sessions of psycho-education compared to the control group [25-26]. In contrast, a few studies have suggested that HRQOL impairment, psychological factors, and personality structure may affect survival rate of melanoma patients [10, 21]. Patients with a "type C" personality (i.e., tending to be cooperative, unassertive, and repress negative emotions through anger-avoidance) may also be less likely to survive melanoma [10, 21].

CONCLUSION

The proportion of patients with melanoma who report high levels of HRQOL impairment is comparable to that observed in other cancers. Optimal measurement of HRQOL in patients with melanoma is challenging because of the fairly unique characteristics of the tumour and its often straightforward treatment. More specific HRQOL measures could assist physicians in identifying patients who are in need of psychological counselling, which may affect treatment, follow-up, and patients' well-being.

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5

Impact of melanoma on patients' lives among 562 survivors: a Dutch population based study

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ABSTRACT

Objective To assess the impact of melanoma on the health-related quality of life of patients from the general population up to 10 years after diagnosis and its determinants.

Design A cross-sectional Dutch population-based postal survey among patients with melanoma for the years 1998 to 2008 using the Eindhoven Cancer Registry.

Main Outcome Measures The 36-Item Short-Form Health Survey (SF-36), Impact of Cancer (IOC) questionnaire and specific melanoma-related questions. The SF-36 scores of the cases were compared with normative data. Multiple linear regression models were used to identify associated factors of SF-36 and IOC scores.

Results The response rate was 80%. The mean age of the 562 respondents was 57.3 years; 62% were female, and 76% had a melanoma with a Breslow thickness of less than 2 mm. The SF-36 component scores of patients with melanoma were similar to those of the normative population. In a multiple linear regression model, stage at diagnosis, female sex, age, and comorbidity were significantly associated ($P < .05$) with the physical and mental component scores. Women were significantly more likely to report higher levels of both positive and negative IOC. Time since diagnosis, tumor stage, and comorbidity were significant predictors of negative IOC scores. Women seemed to adjust their sun behavior more often (54% vs 67%; $P < .001$) than men and were more worried about the deleterious effects of UV radiation (45% vs 66%; $P < .001$).

Conclusion The impact of melanoma seems to be specific and more substantial in women, suggesting that they may need additional care to cope with their melanoma optimally.

INTRODUCTION

Although the prognosis is relatively good for about 80% of patients with melanoma, they remain at risk for disease progression and have an increased risk of developing subsequent melanomas.[1-6] A systematic review on the impact of melanoma on patients' lives that included a variety of psychometric measures suggested that a third of patients with melanoma have reported clinically significant levels of distress.[7] Therefore, melanoma can be considered a chronic life-threatening disease that may affect patients' lives considerably. Because most patients are aware that past sun exposure might have played a role in the development of their melanoma,[8] they are likely to change their lifestyle to minimize UV exposure, which consequently may affect patients' health-related quality of life (HRQoL) as well.

The HRQoL impact of melanoma is not very well documented.[7] Of the 13 eligible studies included in a systematic review, most included a relatively small number of patients who were almost always treated in specialized centers and assessed impact within 2 years after diagnosis. They used a variety of questionnaires assessing patient reported outcomes. Furthermore, a comparison of HRQoL impairment was not made between men and women and between patients with melanoma and the general population and/or other cancer groups.[7] Although the Functional Assessment of Cancer Therapy–Melanoma (FACT-Melanoma) and the Skin Cancer Index have been introduced, neither of them is well suited to measure melanoma-specific HRQoL among the general population of melanoma survivors.[7, 9-11] The FACT-Melanoma was developed for clinical trial purposes that include high-risk patients who have lower survival rates than most patients with melanoma in the general population and who receive additional surgical and/or systemic therapy. The Skin Cancer Index was designed for keratinocytic cancers and not for melanoma.

The objective of this cross-sectional survey was to investigate the impact of melanoma on patients' HRQoL up to 10 years after diagnosis and the association between HRQoL impairment and patient and tumor characteristics. We hypothesized that melanoma survivors would report an impaired HRQoL compared with that of the normative Dutch population and that this impact would diminish over time and differ across sex. A generic and cancer-specific instrument and additional melanoma-specific items were used to evaluate HRQoL and associated factors in a large cohort of (long-term) melanoma survivors from the general Dutch population.

METHODS

Settings and participants

A cross-sectional survey was conducted with the assistance of the Eindhoven Cancer Registry (ECR), Eindhoven, the Netherlands. The ECR records data of patients newly diagnosed as having cancer in the southeast part of the Netherlands,[12] which has a population of about 2.3 million

inhabitants and is served by 18 hospital locations and 2 large radiotherapy institutions. Of the 18 hospitals, 3 large regional hospitals were asked to participate. From the ECR database, all patients diagnosed as having melanoma (*International Classification of Diseases, Oncology,* codes C44.0-C44.9 with morphology codes 8720-8790) from January 1, 1998, to August 1, 2007, in 1 of the 3 hospitals were identified. The time since diagnosis ranged from 6 months to a maximum of 10 years, owing to the fact that there is a 6-month delay before tumors are completely registered in the ECR.

Patients older than 85 years at the time of the survey were excluded because it was expected that they would have difficulty completing a self-administered questionnaire. Deceased patients were excluded by linking the database to the Central Bureau for Genealogy, which collects data on all deceased Dutch citizens or permanent residents via civil municipal registries.

The treating physicians of the 3 hospitals informed their eligible patients by sending a standardized invitation letter and the questionnaire. Patients were reassured that nonparticipation would not have consequences for their follow-up or treatment. By returning a completed questionnaire, patients consented to linkage of the HRQoL data with those of their disease and treatment history as registered in the ECR. Questionnaires were coded for anonymous data collection tracking and linkage with the ECR database. Data were collected from February through May 2008. The medical ethics committee of Catharina Hospital in Eindhoven gave their approval to this study.

Study outcomes

The ECR provided data on melanoma and demographic characteristics of the patients. The questionnaire included a generic and cancer-specific HRQoL instrument (36-Item Short-Form Health Survey [SF-36] and Impact of Cancer [IOC], respectively) and additional questions regarding demographic variables, disease progression, and current comorbidity (adapted from the Charlson comorbidity index).[13-15] For the SF-36, standard scoring procedures of the 8 scales) (ie, Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional subscale, Mental Health) were followed where higher scores indicate better functioning (range, 0-100).[13] Two higher-order component scores for physical (PCS) and mental health (MCS) were also calculated. The IOC was developed by Zebrack et al[15] in 2006 to measure the well-being of long-term cancer survivors and their adjustment to changes. It consists of 41 questions (5-point response scale), 6 domains (ie, physical, psychological, social, existential, meaning of cancer, health worry) with 10 dimensional subscales.[14-15] These 10 subscales are Physical: Health Awareness (4 items); Physical: Body Changes (5 items); Psychological: Positive Self-Evaluation (8 items); Psychological: Negative Self-Evaluation (4 items); Existential: Positive Outlook (3 items); Existential: Negative Outlook (4 items); Social: Life Interferences (3 items); Social: Value of Relationships (2 items); Meaning of Cancer (5 items); and Health Worry (3 items). These subscales were combined to form a higher-order positive or higher-order negative scale (range, 0-5) with higher scores indicating a more positive or negative impact of cancer,

respectively (Table 1). In addition to these pre-existing validated instruments, several melanoma-specific items that assess issues related to treatment, impact on daily life, and follow-up were included (based on expert opinion) because these issues were not covered by the SF-36 or IOC questionnaires (see the subsections titled "Melanoma-Specific Items" and Practical Issues Related to Melanoma" in the "Results" section). Responses were categorized as "less," "the same," "a little bit more," "more," or "a lot more." In the analyses, "more" and "a lot more" were combined. To evaluate the physical symptoms experienced due to melanoma or its treatment, questions regarding pain, itch, swelling, and numbness with a 3-point scale were included.[9] Several items pertained to the extent to which the diagnosis of melanoma affected patients' sun (exposure) behavior (ie, activity in the sun, worry about the effects of the sun on the skin, and sun-protective measures) were included. Furthermore, patients were asked whether applications for health, life, and disability insurance or home mortgage had been hampered because of their melanoma.

Table 1: Domains and subscales of the IOC and their coverage.[a]

Domains and Subscales	Contributes to positive (+) or negative (–) higher order scale of IOC	Number of items (n=40)	Coverage
Physical			
Health awareness	+	4	Concern and care about own health and awareness of physical problems
Body changes	-	5	Upset about negative changes and looks of the body and decreasing energy
Psychological			
Positive self- evaluation	+	8	Personal growth due to the cancer experience
Negative self-evaluation	-	4	Anger and guilt concerning the cancer experience and feeling of aging
Spiritual/Existential			
Positive outlook	+	3	Increased wisdom and spirituality due to cancer experience
Negative outlook	-	4	Worry about future, death and limited time left
Social			
Value of relationships	+	2	Higher value of relationships with family and friends including to other survivors.
Life interference	-	3	Loss of activities or negative interference with life
Meaning of cancer	+	5	Wonder why got cancer, reactions to it and place in life
Health worry	-	3	Worries about reduced health and sensitivity towards physical symptoms as sign of relapse

[a] See Janssen-Heijnen et al.[12]

Statistical analyses

To test for statistical differences, the *t* test and χ^2 test for continuous and categorical variables, respectively, were used. The scores of the SF-36 scales were compared with an age- and sex-matched random normative sample of 1742 Dutch adults from the general population by means of analysis of variance.[13] The age- and sex-matched sample was drawn from a nation-wide sample of the Dutch adults to whom the SF-36 was mailed (2800 households drawn at random from the national telephone registry). Nonresponders were sent reminder letters after 2 months and 3 months following initial mailing. In total, 1771 were returned, representing a 63% response rate, of whom 56% was male.[13] We used Norman's "rule of thumb,"[16] which says that the threshold of discrimination for changes in HRQoL for chronic diseases seems to be approximately half a standard deviation.

Multivariate linear regression analyses were performed to estimate the association between SF-36 and IOC scores and independent variables (expressed as standardized β-coefficients and 95% confidence intervals). Variables were included in the multivariate model if they were significantly associated with the outcome in the univariate analysis and/or were considered a priori to be of clinical relevance. In these models, age and time since diagnosis were entered as continuous variables, tumor stage ranged from I to IV, and presence of comorbidity was binary (yes/no). Four levels of education were used, and marital status was categorized as having a partner vs no partner.

A 2-sided $P < .05$ was considered statistically significant. All statistical analyses were performed using SAS statistical software (version 9.1 for Windows; SAS Institute Inc, Cary, North Carolina).

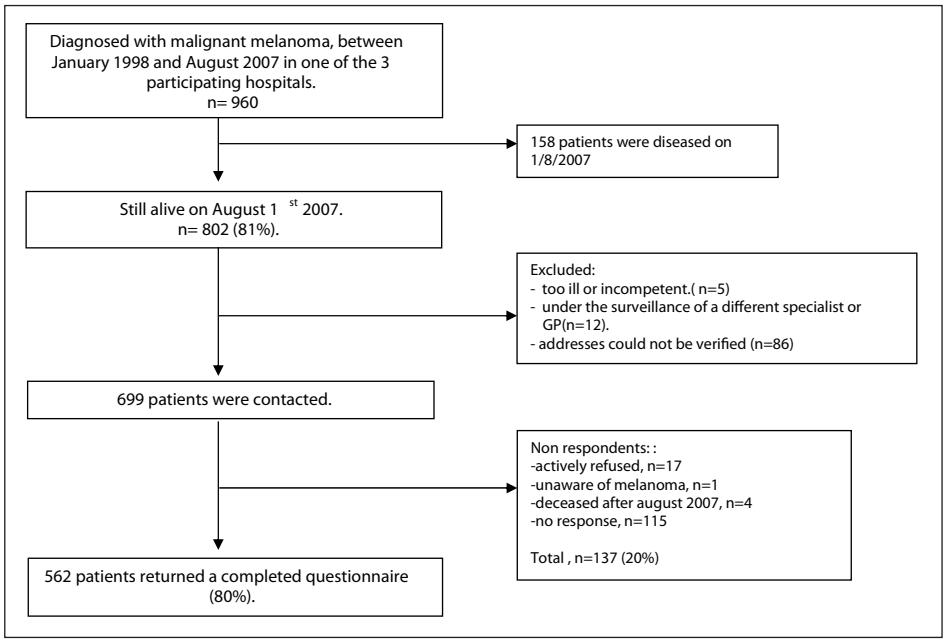

Figure 1. Schematic flow diagram of ascertainment of the study population

RESULTS

Study population

Of the 992 patients diagnosed as having cutaneous melanoma in 1 of 3 hospitals between January 1998 and August 2007, 802 patients were alive on August 1, 2007 (Figure 1). Of these patients, 103 could not be contacted (Figure 1). The remaining 699 survivors received a questionnaire, and 562 responded (80.4% response rate). The distribution of the demographic and melanoma characteristics of the respondents, nonrespondents, and patients with unverifiable addresses were similar with respect to sex, Breslow thickness, stage at diagnosis, and initial treatment (Table 2). Nonrespondents and patients with unverifiable addresses were generally younger ($P < .05$). On average, nonresponders also had longer survival times.

About 70% of patients had been diagnosed as having stage I melanoma, and 49% had a lesion with a Breslow thickness of less than 1 mm (Table 2). Almost all patients underwent

Table 2: Sociodemographic and clinical characteristics of questionnaire respondents , non-respondents and patients with unverifiable addresses.

No. (%)				
Sociodemografic or clinical characteristic	**Respondents**	**Non-respondents**	**Patients with unverifiable addresses**	**P-value**
	N=562	**N=131**	**N=86**	
Age at time of survey, mean (SD), y	57.2 (SD 14.0)	56.4 (SD 15.6)	51.2 (SD 15.0)	0.001
Years since diagnosis, mean (SD)	4.6 (SD 2.6)	5.1 (SD 2.9)	5.3 (SD 2.8)	0.01
Gender				
Male	212 (38)	54 (41)	33 (38)	
Female	350 (62)	77 (59)	53 (62)	0.76
Breslow thickness*				
≤ 1.0 mm	275 (49)	61 (47)	39 (45)	
1.01-2.0 mm	149 (27)	33 (25)	22 (26)	
2.01-4.0 mm	100 (18)	30 (23)	22 (26)	
>4.0 mm	32 (6)	5 (4)	3 (3)	0.64
Stage at diagnosis				
I	400 (71)	87 (66)	56 (65)	
II	108 (19)	32 (24)	22 (26)	
III	42 (8)	8 (6)	6 (7)	0.71
IV	-	-	-	
Treatment				
Surgery	556 (99)	128 (98)	85 (99)	
Sentinal Node	113 (20)	22 (17)	21 (24)	
Lymphadenectomy	27 (5)	7 (5)	4 (5)	
Systemic therapy	3 (0.5)	1 (0.8)	-	
Radiotherapy	3 (0.5)	-	-	
Other	29 (5)	7 (5)	4 (5)	0.81

Note: percentages are rounded off to the nearest whole number

* According to the American Joint Committee on Cancer (AJCC) classification.

local surgical excision, and 20% underwent a sentinel node procedure (SNP). Chemotherapy or radiotherapy was administered in less than 1% of patients. No statistically significant differences were found for Breslow thickness (P = .64) and stage distribution (P = .71) between responders, nonresponders, and patients with unverifiable addresses.

The mean ages at diagnosis and at time of survey of the respondents were 52.6 years and 57.2 years, respectively. Sixty-two percent of respondents were female. Most respondents had at least a high school education, were married, had children, and were employed at time of survey (Table 3). Of all respondents, 35% reported at least 1 other medical condition: hypertension, joint complaints, and/or a history of a malignant disease.

Table 3.: Sociodemographic and clinical characteristics of 562 survivors (respondents).

Characteristic	No. (%)	Characteristic	No. (%)
Age at diagnosis (mean 52.2)		**Marital status**	
≤30	25 (5)	Married	416(74)
30-39	96 (17)	Unmarried or never married	55 (10)
40-49	117 (21)	Divorced	36 (6)
50-59	145 (26)	Widowed	53 (10)
60-69	112 (20)	Partner	464 (85)
70-74	36 (6)	No partner	84 (15)
>80	28 (4)	**Education level**	
Comorbidity		Low(Primary school)	161(29)
Yes	186 (35)	High School	242(43)
No	351 (65)	Medium (Job training etc.)	103(18)
Most frequent co-morbid conditions		Higher education (University etc.)	52(9)
Hypertension	126 (23)	Unknown	4(1)
Arthrosis / Arthritis	111 (21)	Employment	
Malignancy	106 (20)	**Employed**	299 (53)
		Unemployed	245 (44)
		Unemployed (disability)	15 (3)
		Children	
		Yes	462 (83)
		No	97 (17)
		Children at home	183 (39)

Note: percentages are rounded off to the nearest whole number.

36-item short-form health survey

Compared with an age- and sex-matched sample from the general Dutch population, melanoma survivors did not report impaired HRQoL as measured by the SF-36 (Figure 2). Interestingly, patients with melanoma scored statistically significantly higher on PCS and several subscales (Physical Functioning, Role Limitations: Emotional Problems, Mental Health, Bodily Pain, and General Health; data not shown) than the general population, but the mean score differences were less than half a standard deviation suggesting no clinical significant differences, according to Norman's rule of thumb (Figure 2).[16]

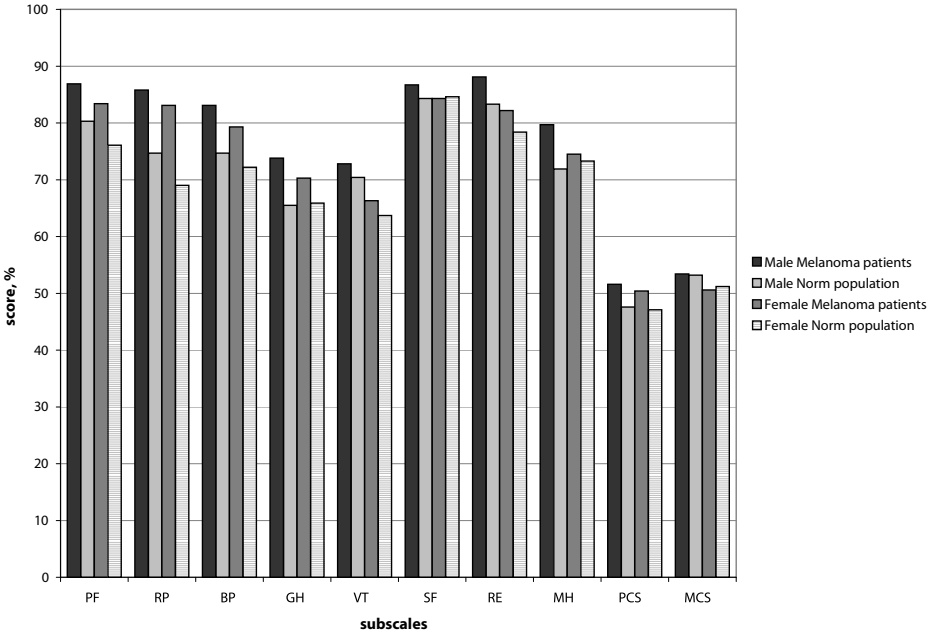

Figure 2. The 36-Item Short-Form Health Survey (SF-36) scores of patients with melanoma compared with normative population. BP indicates Bodily Pain; GH, General Health; MCS, Mental Component Scale; MH, Mental Health; PCS, Physical Component Scale; PF, Physical Functioning; RE, Role Emotional; RP, Role Physical; SF, Social Functioning; and VT, Vitality.

After adjusting for age at time of the survey, years since diagnosis, disease stage, SNP, comorbidity, marital status, and educational level in a multivariate analysis, female sex, older age, tumor stage, and comorbidity were significantly negatively associated with PCS, whereas an SNP was positively associated (Table 4). Female sex and comorbidity were also negatively associated with MCS, whereas having a partner was positively associated with MCS. Women scored significantly lower (indicating higher HRQoL impairment) than men: 1.8 points ($P < .05$) on the PCS and 2.3 points ($P < .05$) on the MCS; however, this was not clinically relevant. In addition, female melanoma survivors reported higher impairment on 5 of 8 subscales (Physical Functioning, Bodily Pain, General Health, Vitality, and Mental Health; data not shown).

Impact of Cancer

To estimate the impact of melanoma on patients' psychological well-being in more detail, the IOC was included[14] (Table 1). The mean scores of patients with melanoma for each subscale of the IOC differed from 2.2 to 3.1. The lowest scores were seen on the subscale Social: Life Interferences, which focuses on cancer- or treatment-related symptoms of the cancer that interferes with a patients' socializing, traveling, or time with family. The highest score of 3.1 was seen on

Table 4: β-coefficients of multiple linear regression analysis: investigating factors associated with SF-36 component scales and IOC Higher order scales.

Characteristic	SF36 components		IOC Higher Order Scales	
	PCS	MCS	Positive Scale	Negative Scale
Sex				
Female vs. male	-1.77*	-2.34*	0.21*	0.24****
Age at time of survey	-0.14****	NS	NS	NS
Time since diagnosis	NS	NS	NS	-0.03**
Stage at diagnosis				
II vs. I	-2.76*	NS	NS	NS
III vs. I	NS	NS	NS	0.24*
IV vs. I	-	-	-	-
SNP	2.34*	NS	NS	NS
Comorbidity	-5.07****	-2.27*	NS	0.16**
Marital Status				
Partner vs. single	NS	4.06**	NS	NS
Education				
High School vs. PS	NS	NS	NS	NS
Medium Edu. vs. PS	NS	NS	NS	NS
Higher Edu. vs. PS	NS	NS	NS	NS

Abbreviations: HRQoL, health-related quality of life; IOC, Impact of Cancer (see table 1); MCS, Mental Component Scale; NS, not significant (P>0.05); PCS, Physical Component Scale; PS, Primary School; SF36, 36- Item Short-Form Health Survey; SNP, sentinel node procedure.

For the SF-36 analysis, positive β-coefficients suggest that characteristics were significantly associated with higher SF-36 scores, suggesting an improved HRQoL.

For the IOC, positive β-coefficients on the positive higher order scale suggest that characteristics were significantly associated with a higher score meaning a higher positive impact of cancer on a patients' perspective.

* < 0.05

** < 0.01

*** < 0.001

**** < 0.0001

the Existential: Positive Outlook subscale, which covers increased wisdom and spirituality due to the cancer experience.

In multivariate analyses, female sex was statistically significantly associated with higher-order positive and negative scales, suggesting that women experience both a more negative and more positive impact of melanoma on their psychological well-being than men (Table 4): compared with men, women scored 0.21 points ($P < .05$) higher on the higher-order positive scale and 0.24 points ($P < .001$) on the higher-order negative scale. Analyses showed that the trends of responses were similar, but that women responded more extremely compared with men (data not shown). On the higher-order negative scale, time since diagnosis was significantly associated with a negative β-coefficient, which implies that for every year further from diagnosis the patient may be less negatively influenced by their cancer. In contrast, more comorbidities and advanced melanoma stage (III vs I) were associated with a higher-order negative IOC score (Table 4).

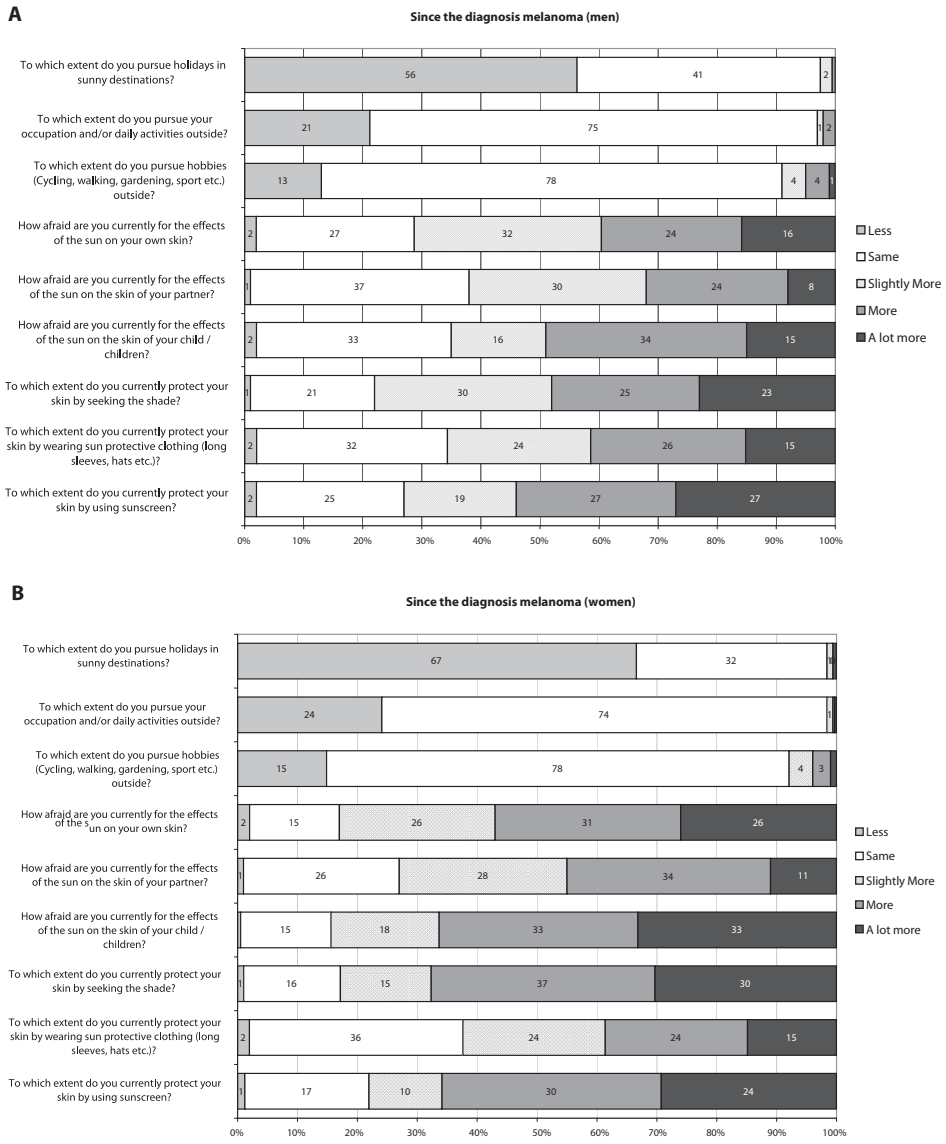

Figure 3. Men's and women's attitudes and behaviors since the diagnosis of melanoma. Responses to melanoma-specific items in men (A) and women (B). Melanoma-specific items questioned melanoma survivors about the extent to which they had changed their sun (exposure) behavior since the diagnosis of melanoma.

Melanoma-specific items

Compared with men, a significant larger proportion of women reported going on vacation to sunny destinations less frequently (67% vs 56%, respectively; $P = .03$). Women were also more worried about the effects of sunlight on their skin (66% vs 45%; $P < .001$) and that of their spouses and children (49% vs 32%; $P < .05$).

Furthermore, female patients reported seeking shade and/or using sunscreen more often than men (67% vs 48%; $P < .001$) (Figure 3). Most men and women reported using sunscreen only in the summer or when the sun shines (83% vs 90%, respectively), with a sun protection factor of 20 to 30 or more (69% vs 72%, respectively). Women were more likely to use sunscreen more times a day than men (25% vs. 64%; $P < .001$).

Compared with men, women experienced more pain (26% vs 11%; $P < .001$), itchiness (26% vs. 21%; $P = .26$), and numbness (29% vs 21%; $P = .10$) of their scars. Swelling of the scar or one of the extremities was reported in approximately 10% of men and women.

Practical issues related to melanoma

Most survivors (94%) stated that their professional situation had not changed after being diagnosed as having melanoma. Five percent of survivors indicated that they had changed jobs, reduced the number of hours worked, had been retrained, or stopped working entirely (including work disability) as a result of their melanoma. Of the 258 patients who attempted to obtain health insurance in the survey period, 5% reported having experienced cancer-related problems in obtaining health insurance. Thirty-five percent (n = 84) reported difficulties obtaining life insurance, 15% (n = 98) reported problems with obtaining a mortgage, and 18% (n = 38) experienced trouble obtaining disability insurance when attempting to obtain one of these.

COMMENT

To our knowledge, this is the first study to investigate SF-36 and IOC scores in a population-based sample of melanoma survivors, showing relatively little impairment of the generic health status and HRQoL. In contrast to our hypothesis, the SF-36 scores were not significantly different compared with the normative SF-36 scores of the general Dutch population. This observation suggests that generic and even cancer-specific HRQoL questionnaires might not be sensitive enough for patients with predominantly low stages of melanoma. More specific, but individual, items showed that several UV-related aspects of patients' lives were affected and that having been diagnosed as having malignant melanoma had practical implications for their daily life (eg, getting a mortgage, health insurance, or life insurance).

Of the studied determinants, female sex was most strongly associated with HRQoL. Also, in the multivariate analyses of SF-36 and IOC scores, older age, comorbidity, and higher tumor stage were significant predictors for lower HRQoL.

We compared the SF-36 scores of patients with melanoma with normative data for the SF-36 obtained from of a nation-wide random sample of Dutch adults (see the "Methods" section), which have been used by several previous studies to compare the SF-36 scores of patients with those of the general population.[17-18] Though not clinically relevant (statistical differences, <0.5 SD),[16] the scores of several SF-36 domains and components were significantly higher among patients with melanoma than those from the general population.[19-20] The finding that patients show far more variability in the response distribution of the individual melanoma-specific items (eg, sun behavior and worry) than in the generic SF-36 may confirm the need to combine generic with disease-specific questionnaires.[19] Although it seems counterintuitive at first and in contrast with our hypothesis, this observation is in accordance with studies investigating other cancers showing that patients who had "survived" a cancer rate their generic HRQoL as similar or even better than those from the general population.[12] Individuals can use various cognitive strategies such as *belief*, *posttraumatic growth,* or *benefit finding* to counteract the negative effect of illness (eg, melanoma) on their well-being.[11] Finding benefit and growth could be viewed as part of the so-called response shift. When diagnosed as having a life-threatening disease, patients may change their internal standard of what constitutes health and HRQoL (recalibration), adjust their priorities (reprioritization), and/or redefine what is important to them (reconceptualization) in face of their condition.[11, 21]

Of the variables studied in multivariate models, female sex was most strongly associated with lower SF-36 scores, higher-order negative and positive IOC scores, and more extreme responses to melanoma-specific items, which is confirmed by previous studies in melanoma and other cancers that show a sex difference in the assessment of HRQoL.[7, 11, 22] In clinical practice, this observation may imply that women need additional care, including follow-up and possibly counseling to optimally cope with their melanoma.[8] However, men might be less aware of general measures of sun protection and need education about these measures after treatment. Besides, other studies that used specific tools to measure anxiety and/or depression suggest that around a third of patients with melanoma suffer substantially.[7] This could be reduced by psychological counseling, which might even lead to better survival.[23] In addition to sex, comorbidity was strongly associated with HRQoL impairment due to melanoma. This association has been observed previously in patients with melanoma,[7] nonmelanoma skin cancers,[22] and solid cancers, suggesting that it remains difficult to differentiate the impact of different diseases. It seems that the impact of skin cancer is lowered by the presence of multiple or severe comorbidities. This observation emphasizes the need to test HRQoL instruments for item bias across the presence of comorbidity because an optimal HRQoL tool should not be influenced by external factors.[19] The finding that older age at time of survey predicted lower scores on the physical scales is most likely explained by the presence of other disabilities and/or an aging effect of the cohort. In the long term, the effect of SNPs was reported as positive on the PCS, which is in agreement with other studies suggesting that additional therapy eventually increased HRQoL in patients with melanoma.[24] The relatively small group of respondents who

had an SNP reported a higher PCS score than those who did not, which is surprising, as surgical complications (eg, lymphoedema and extensive scarring) are likely to impair a patient's well-being. This may suggest that patients who choose to undergo additional or even controversial investigations and/or therapies may differ from those who received local surgical excision only. Although it was initially hypothesized, time since diagnosis did not affect SF-36 scores among melanoma survivors, and the effect of additional years after diagnosis was modest for the negative IOC scale. In other diseases, such as diabetes mellitus, rheumatoid arthritis, non-Hodgkin's lymphoma, and breast cancer, the effect of time since diagnosis on finding benefit or growth is inconsistent.[11, 17] The low adjusted R^2 scores of the multivariate models that assessed predictors of SF-36 and IOC scores suggest that this analysis suffers from residual confounding (ie, multiple HRQoL predictors, such as anxiety, personality type, and coping mechanisms were not included in the analysis).[7, 13-14,25]

Although the effect of melanoma on SF-36 and IOC scores seems to be limited, this cancer may have a profound impact on practical issues of patients' lives and thus affects HRQoL in different domains. A small proportion of individuals experienced difficulties in getting health insurance as a result of their melanoma, but up to a third of the patients experienced difficulty getting life insurance, disability insurance, and/or a mortgage. This type of information is not often assessed in patient populations but seems to be highly relevant in patients who have survived cancer.

This is the largest cross-sectional, population-based study using cancer registry data to investigate the impact of melanoma on patients' HRQoL and other aspects of their lives. Trask and Griffith[22] investigated HRQoL among a large group of patients with melanoma ascertained from a multidisciplinary melanoma clinic. However, compared with our study, the design of their study[22] was very different (eg, selected HRQoL measures, domain-specific tools, including anxiety and depression scales and categorization of patients), making a comparison between the study findings challenging.

A response rate of 80% is very high and in accordance with those of previous studies performed in the southeast part of the Netherlands.[17-18] This high response rate and the fact that respondents and nonrespondents were comparable suggest that selection bias had a minimal effect on the results of this study. Because no specialized melanoma centers were included, the generalizability of our findings is likely to be good. The ECR is a well established cancer registry[12] but does not record recurrence or metastasis from/after melanoma. Consequently, the effect of these events could not be studied separately. No information was available regarding the social economic status (SES) of patients. Higher levels of SES are associated with increased melanoma risk and higher HRQoL.[26-28] As a proxy for SES, educational level was used; three-quarters of the patients had at most a high school degree (Table 2), suggesting a possible overestimation of melanoma on HRQoL.

The SF-36 was used because it is the most commonly used HRQoL instrument and has the advantage of available Dutch norm data, but it is has not been formerly tested in patients with

melanoma.[19] To expand the focus of this study, the IOC, which is a relatively new instrument (and has not been validated in patients with melanoma) and several single items were added. At the time of the survey, the FACT-M, which was intended for the use in clinical trials with a focus on physical limitations, had not yet been validated.[9-10] An indirect comparison of IOC scores suggests that patients' physical and psychological well-being is likely to be less affected by melanoma when compared with breast, prostate, colorectal, or prostate cancer. Patients with melanoma scored lower on all of the positive IOC subscales and higher on only 2 of the negative subscales (body changes and negative self- evaluation)[15] (Table 1).

In conclusion, in a population-based sample of patients who have had malignant melanoma, the impact of melanoma seems to be fairly specific and is not driven by (long-term) treatment effects that affect generic or cancer-specific HRQoL. Therefore, there is need for a melanoma-specific HRQoL instrument that gauges the impact of thin *and* thick melanomas on patients' lives. Female sex and comorbidity were the main predictors of HRQoL impairment in patients with melanoma, but other (psychological) factors are likely to play a role as well and need to be studied in more detail in future studies.

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6

Personality affects health status and impact of cancer among melanoma survivors

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ABSTRACT

Objective We aimed to investigate the prevalence of Type D personality (the conjoint effects of negative affectivity and social inhibition) among melanoma survivors and to obtain insight into its effects on health status, impact of cancer and health care utilisation.

Methods We selected all patients diagnosed with melanoma between 1998 and 2007 from three large regional hospitals in the Netherlands. In total, 699 survivors, alive in January 2008, received a questionnaire including Type D personality scale (DS14), impact of cancer questionnaire (IOC) and SF-36 and 80% responded (n =562).

Results Twenty-two percent of survivors (n = 125) were classified as Type D. They reported a clinically and statistically significant worse general health (57.8 versus 75.6), social functioning (73.1 versus 88.7), mental health (61.7 versus 80.6), more emotional role limitations (67.8 versus 89.4) and less vitality (54.5 versus 72.8) than non-Type D patients. Additionally, they reported a statistically and clinically relevant higher impact of cancer on body changes, negative self-evaluation, negative outlook on life, life interferences and health worry. Furthermore, they were more worried about the influence of the sun on their skin and acted accordingly. No differences were found in health care utilisation.

Conclusions Type D personality has a distinct negative impact on health status in melanoma survivors and is an important factor to screen for in clinical practice. Giving special attention to these patients is important while they are more likely to experience a strong impact of cancer which cannot be explained by socio-demographical or clinical characteristics.

INTRODUCTION

The relationship between personality and cancer has been an important topic of many studies. Major research themes were the association between personality and cancer incidence[1-7] and disease outcomes or mortality.[8-10] However, in these studies personality was defined in a number of different ways and the results were inconclusive. A personality type that has a major impact on cancer incidence, course, disease outcomes and health status has not yet been found.

A distressed personality (Type D) is defined by the combination of two personality traits; the tendency to experience negative emotions (*negative affectivity*) and to inhibit self-expression in social interaction (*social inhibition*).[11] Hence, individuals with a Type D personality are inclined to experience emotional and interpersonal difficulties across time and situations. In the cardiovascular field, the Type D is an important research topic. Type D is recognised as an important determinant for adverse health outcomes, impaired health status and health-related quality of life (HRQoL), several forms of distress (including anxiety, depression and posttraumatic stress) and a decrease in health care utilisation in patients with cardiovascular diseases.[12-18] More recently, similar results have been found in patients with a range of other diseases as well.[19-21] In addition, Type D personality was a prognostic factor for the development of cancer in men with established coronary heart disease, who were free of cancer at baseline.[22]

Although Type D has proven to have much explanatory power to select cardiovascular patients at risk for a low health status, this has not yet been studied in cancer patients. The aim of this study was to determine if melanoma survivors with a Type D personality report a comparable health status, impact of cancer and health care utilisation compared to those without a Type D personality. We hypothesised that Type D patients will report a lower health status, a more negative impact of cancer and a lower health care utilisation compared to those without a Type D personality.

METHODS

Setting and participants

The study was conducted at the Eindhoven Cancer Registry (ECR), which records data on all patients newly diagnosed with cancer in the southern region of the Netherlands.[23] The ECR was used to select all patients diagnosed with melanoma between 1 January 1998 and 1 August 2007 from three large regional hospitals. Melanoma was defined using the ICD-0 codes: C44.0–C44.9 with morphology 8720–8790. Participants older than 85 years of age at the time of survey were excluded, as it was expected that they would have difficulty in completing a self-administered questionnaire without assistance. To avoid including deceased patients, our database was linked with the database of the Central Bureau for Genealogy, which collects data

on all deceased Dutch citizens via the civil municipal registries. Data collection was performed between February and April 2008. Approval for this study was obtained from a local certified Medical Ethics Committee.

Data collection

Medical specialists sent their (former) patients a letter to inform them about the study and a copy of the questionnaire. The letter explained that by returning the completed questionnaire, the patient agreed to participate and consented with linkage of the outcome of the questionnaire with their disease history as registered in the ECR. The patients were reassured that non-participation would not have any consequence for their follow-up care or treatment.

Measures

Patient and tumour characteristics

The ECR routinely collects data on tumour characteristics, including date of diagnosis, histology, clinical stage (tumour-node-metastasis clinical classification[24]), treatment and patient background characteristics including date of birth and comorbidity at the time of diagnosis (a slightly adapted version of the Charlson comorbidity index[25]).

In addition, our patient questionnaire also included questions on sociodemographic data, including marital status, current occupation, educational level, current comorbidity and disease progression (e.g. recurrence, metastasis and new primary tumour).

Type D personality

Type D personality was measured with the 14-item Type D personality scale (DS14).[11] The DS14 is self-administered and takes only a few minutes to complete. The 14 items of this scale are answered on a five-point response scale ranging from 0 (false) to 4 (true). Seven of these items refer to 'Negative Affectivity' or the tendency to experience negative emotions in general (e.g. *I am often down in the dumps*). The remaining seven items refer to the patient's level of 'Social Inhibition' or the tendency to inhibit the expression of emotion in social relationships (e.g. *I am a closed kind of person*). The patients were categorised as Type D using a standardised cut-off score ≥10 on both the negative affectivity and social inhibition subscales, following the protocol as previously established.[11] The DS14 is a valid and reliable scale with Cronbach's α of 0.88/0.86 and a test–retest reliability over a 3-month period of $r = 0.72/0.82$ for the two subscales, respectively.[11]

Health status

The Dutch version of the SF-36 questionnaire was used to assess the health status.[26] It incorporates two composite scales – the Physical Component Scale and the Mental Component Scale[27] – derived from eight domains: physical functioning, role limitations due to physical health

problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems and general mental health.[28] According to standard scoring procedures, the subscales were linearly converted to a 0-100 scale, with higher scores indicating better functioning.

Impact of cancer

The impact of cancer was measured with the impact of cancer questionnaire (IOC). The IOC is a relatively new instrument developed to measure subtle yet important aspects of the cancer survivorship experience that long-term survivors themselves indicate are important.[29] The instrument consists of 41 items covering 10 subscales; health awareness, body changes, positive and negative self-evaluation, positive and negative life outlook, life interferences, value of relationships, meaning of cancer and health worry. Furthermore, these subscales can be used to create two overarching second-order factors inclusive of positive and negative items; the 'higher order positive scale' and 'higher order negative scale'.[30] Internal consistency for these subscales ranged from 0.67 to 0.89. All items are scored on a five-point scale through which respondents indicate their level of agreement. A higher score on a subscale means stronger endorsement of that content area; a high score on a positive scale thus means a higher positive impact of cancer, while a high score on a negative scale means a higher negative impact of cancer. Subscale scores are created by taking the mean of all items in the subscale. While a Dutch version was not available yet, a 'forward–backward' procedure was used to translate the English language version of the IOC into Dutch.

The impact of cancer was also assessed with questions regarding the impact of melanoma on sun behaviour (e.g. activities in the sun) and attitudes towards sun exposure (e.g. worries about the influence of the sun) since diagnosis. The response categories were dichotomised in our analyses into 'less' and 'same or more'.

Health care utilisation

The items concerning health care utilisation included questions on the number of visits to a general practitioner, medical specialist (including those specialists involved in cancer care) and other health care professionals. These questions were asked in a similar way as is done via the annual monitoring of the health care situation of a random sample (n = ±10.000) of the Dutch population by Statistics Netherlands (http://statline.cbs.nl).

This study was done in the Netherlands, where every person has equal access to (specialised) health care. According to the Dutch guidelines, melanoma survivors with a Breslow of <1 mm are followed up once, survivors with a Breslow >1 will be followed up until 5 years after diagnosis and patients with a Breslow >2 will be followed up until 10 years after diagnosis (Dutch national melanoma guidelines; http://www.oncoline.nl).

Statistical analyses

Routinely collected data from the ECR on patient and tumour characteristics enabled us to compare the group of respondents, non-respondents and patients with unverifiable addresses, using *t*-tests for continuous variables and chi-square analyses for categorical variables. Differences between Type D and non-Type D patients in sociodemographic and clinical characteristics, health care utilisation and the impact of melanoma on sun behaviour and attitudes towards sun exposure since diagnosis were also analysed using *t*-tests for continuous variables and chi-square analyses for categorical variables.

Univariate linear regression analyses were carried out to investigate the association of sociodemographic variables (age, gender, marital status, educational level and current occupation) and clinical variables (stage, Breslow, grade, primary treatment, years since diagnosis and comorbidity) with the subscale and component scales of the SF-36 and the subscales of the IOC. We controlled for these variables in the analysis of covariance (ANCOVA), which was used to compare the means of SF-36 and IOC scores between melanoma survivors with and without a Type D personality. We used Norman's 'rule of thumb' that the threshold of discrimination for changes in health status scores for a chronic disease appears to be approximately half a standard deviation.[31]

All statistical test were two-sided and considered significant if $p < 0.05$. All statistical analyses were performed using SAS (version 9.1 for Windows, SAS Institute Inc., Cary, NC).

RESULTS

Patient and tumour characteristics: respondents versus non-respondents

Of the 699 melanoma cancer survivors, 562 (80.4%) returned a completed questionnaire (Fig. 1). A comparison between respondents, non-respondents and patients with unverifiable addresses showed that patients with unverifiable addresses were generally younger ($p < 0.001$) and diagnosed earlier (in years) ($p < 0.01$) compared to respondents and non-respondents. Furthermore, there were no significant differences between respondents, non-respondents and patients with unverifiable addresses regarding gender, Breslow, stage at diagnosis and primary treatment (Table 1).

Patient and tumour characteristics: Type D versus no Type D

Twenty-two percent of melanoma patients in this study were classified as having a Type D personality. There were no statistically significant differences observed between melanoma survivors with and without Type D at the time of the survey in: age, gender, years since diagnosis, Breslow, primary treatment, marital status, educational level, current occupation and disease progression (Table 2). Melanoma survivors with Type D were more likely to report comorbid conditions at the time of questionnaire compared to melanoma survivors without

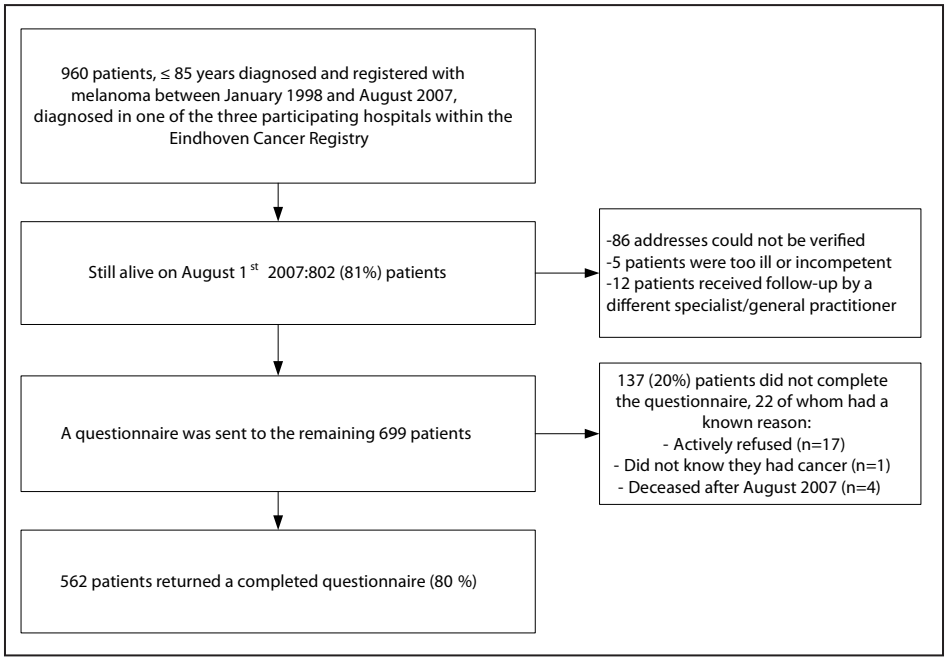

Figure 1. Flow-chart of the data collection process.

Type D ($p < 0.0001$). The most frequently mentioned comorbid conditions among patients with and without Type D were hypertension (24% versus 23%; $p = 0.88$) and arthrosis (30% versus 18%; $p < 0.005$).

Health status

The analysis of covariance revealed that Type D patients reported statistically significant lower scores on all SF-36 scales compared to patients without a Type D personality after adjustment for differences in age at the time of survey, gender, marital status, educational level, Breslow and comorbidity when necessary (Table 3). These differences were considered clinically relevant (>1/2 SD difference) for the subscales general health (57.8 versus 75.6), vitality (54.5 versus 72.8), social functioning (73.1 versus 88.7), role limitations emotional (67.8 versus 89.4), mental health (61.7 versus 80.6) and the mental component summary (43.8 versus 54.0).

Impact of cancer

Analysis of covariance showed that Type D patients reported statistically significant higher scores on all IOC subscales, except for the subscales 'Psychological: Positive Self-Evaluation' ($p = 0.80$) and 'Existential: Positive Outlook' ($p = 0.22$), after adjustment for differences in age at the time of survey, years since diagnosis, gender, marital status, educational level, stage, Breslow, primary therapy and comorbidity when necessary (Table 4). These differences were

Table 1: Demographic and clinical characteristics of questionnaire respondents, non-respondents and patients who were lost to follow-up

	Respondents	Non-respondents	Patients with unverifiable addresses	*p*-Value
	***n* = 562 (%)**	***n* = 137 (%)**	***n* = 86 (%)**	
Mean age (at the time of survey)	57.2 (SD 14.0)	56.4 (SD 15.6)	51.2 (SD 15.0)	0.0013
Mean years since diagnosis	4.6 (SD 2.6)	5.1 (SD 2.9)	5.3 (SD 2.8)	0.0105
Gender				
Male	212 (38)	54 (41)	33 (38)	
Female	350 (62)	77 (59)	53 (62)	0.76
Breslow[a]				
≤1.0 mm	275 (49)	61 (47)	39 (45)	
1.01–2.0 mm	149 (27)	33 (25)	22 (26)	
2.01–4.0 mm	100 (18)	30 (23)	22 (26)	
>4.0 mm	32 (6)	5 (4)	3 (3)	0.64
Stage at diagnosis				
I	400 (71)	87 (66)	56 (65)	
II	108 (19)	32 (24)	22 (26)	
III	42 (8)	8 (6)	6 (7)	
IV	–	–	–	0.71
Treatment				
Surgery	556 (99)	128 (98)	85 (99)	
Sentinal Node	113 (20)	22 (17)	21 (24)	
Lymphadenectomy	27 (5)	7 (5)	4 (5)	
Systemic therapy	3 (0.5)	1 (0.8)	–	
Radiotherapy	3 (0.5)	–	–	
Other	29 (5)	7 (5)	4 (5)	0.81

[a] According to the American Joint Committee on Cancer (AJCC) classification.

Table 2. Sociodemographic and clinical characteristics of melanoma survivors.

	Type D	Non-Type D	*p*-Value[a]
	***n* = 125 (%)**	***n* = 437 (%)**	
Age at the time of survey (mean (SD))	58 (15)	57 (13)	0.24
Age at the time of survey			
≤45 years	29 (23)	93 (21)	
45–54 years	27 (22)	100 (23)	
55–64 years	29 (23)	116 (27)	
≥65 years	40 (32)	128 (29)	0.91
Gender			
Male	39 (31)	173 (40)	
Female	86 (69)	264 (60)	0.07
Years since diagnosis			
<1 years	6 (5)	25 (6)	
1–2	45 (36)	122 (28)	
3–4	28 (22)	121 (28)	
≥5 years	46 (37)	169 (39)	0.18

Table 2. Sociodemographic and clinical characteristics of melanoma survivors. (continued)

	Type D	Non-Type D	*p*-Value[a]
	***n* = 125 (%)**	***n* = 437 (%)**	
Stage at diagnosis			
I	92 (74)	308 (70)	
II	22 (18)	86 (20)	
III	7 (6)	35 (8)	
IV	4 (3)	8 (2)	0.64
Breslow[b]			
≤1.0 mm	64 (51)	211 (48)	
1.01–2.0 mm	34 (27)	115 (26)	
2.01–4.0 mm	19 (15)	81 (19)	
>4.0 mm	5 (4)	27 (6)	0.38
Primary treatment			
Surgery	124 (99)	432 (99)	
Sentinal node	20 (16)	93 (21)	
Lymphadenectomy	3 (2)	24 (5)	
Systemic therapy	0 (0)	3 (1)	
Radiotherapy	1 (1)	2 (0)	
Other	3 (2)	26 (6)	0.50
Comorbidity[c]			
None	47 (38)	196 (45)	
1	41 (33)	132 (30)	
2≥2	37 (30)	109 (25)	<0.0001
Co-morbid conditions (most frequent)			
1. Hypertension	29 (24)	97 (23)	0.88
2. Arthrosis	36 (30)	75 (18)	0.005
Disease progression (self-report)[d]	12 (10)	67 (15)	0.10
Marital status			
Married	89 (71)	327 (75)	
Never married	14 (11)	41 (9)	
Divorced/widowed	22 (18)	67 (15)	0.85
Education level			
Primary school	31 (25)	130 (30)	
Secondary school	54 (43)	188 (43)	
College/university	26 (21)	77 (18)	
Unknown	14 (11)	38 (9)	0.57
Current occupation			
Employed	60 (48)	239 (55)	
Unemployed	65 (52)	195 (45)	0.16

a p-value was adjusted for age at the time of survey, years since diagnosis, gender, marital status, educational level, stage, Breslow, primary therapy and comorbidity at the time of the questionnaire when necessary.

b According to the American Joint Committee on Cancer (AJCC) classification

c Adapted Charlson comorbidity index; assessed by self-report at the time of questionnaire

d Recurrence, metastasis and new primary tumour

Table 3. Health status among melanoma survivors according to Type D personality.

SF-36	Mean (SD)		*p*-Value[a]
	Type D	**Non-Type D**	
	***n* = 125**	***n* = 437**	
Physical functioning	77.8 (26.7)	86.7 (21.0)	<0.0001
Role limitations physical	72.4 (39.3)	87.7 (28.6)	<0.01
Bodily pain	72.1 (27.3)	83.2 (20.4)	<0.0001
General health	57.8 (23.2)	75.6 (20.1)	<0.01[b]
Vitality	54.5 (21.1)	72.8 (17.9)	<0.001[b]
Social functioning	73.1 (24.1)	88.7 (18.2)	<0.0001[b]
Role limitations emotional	67.8 (42.2)	89.4 (26.9)	<0.0001[b]
Mental health	61.7 (19.5)	80.6 (15.0)	<0.0001[b]
Physical component summary	47.8 (10.8)	51.8 (8.4)	<0.01
Mental component summary	43.8 (11.1)	54.0 (7.6)	<0.0001[b]

[a] p-Value was adjusted for age at the time of survey, year since diagnosis, gender, marital status, educational level, stage, Breslow, primary therapy and comorbidity at the time of the questionnaire when necessary.

[b] Clinically relevant difference[31]

also clinically relevant for the subscales body changes, negative self-evaluation, negative life outlooks, life interferences, health worry and higher order negative scale.

Type D patients more often reported fewer holidays to sunny destinations since diagnosis than non-Type D patients (73% versus 66%; $p < 0.01$) (Table 4). In addition, Type D patients reported undertaking less daily activities in the sun (36% versus 20%; $p < 0.001$) and spending less leisure time outdoors (23% versus 11%; $p < 0.0001$). Type D patients were also more worried about the influence of the sun on their skin compared to non-Type D patients (61% versus 48%; $p < 0.01$). No statistically significant differences were found between Type D and non-Type D patients regarding worries about their partner or children's skin (if applicable), seeking shade, wearing protective clothing or using sunscreen.

Health care utilisation

No differences were found between patients with and without Type D in the number of visits to a general practitioner (85% versus 83%; $p = 0.38$) and medical specialist (84% versus 81%; $p = 0.55$) in the past 12 months. Furthermore, melanoma survivors with or without Type D, only sporadically (0–3%) used the following additional care services after cancer treatment: psychologist, social worker, pastoral care, physiotherapist, CAM, oncology nurse and contact with other cancer survivors.

Table 4. The impact of cancer on melanoma survivors according to Type D personality.

	Type D	Non-Type D	*p*-Value
	***n* = 125(%)**	***n* = 437(%)**	
IOC[a,b]			
Physical: health awareness	3.38 (0.91)	2.99 (0.92)	<0.0001
Physical: body changes	2.38 (0.83)	1.84 (0.69)	<0.0001[c]
Psychological: positive self- evaluation	2.76 (0.67)	2.72 (0.76)	0.80
Psychological: negative self-evaluation	2.18 (0.70)	1.72 (0.58)	<0.0001[c]
Existential: positive outlook	3.14 (0.78)	3.06 (0.89)	0.22
Existential: negative outlook	2.86 (0.87)	2.14 (0.83)	<0.0001[c]
Social: life interferences	2.17 (0.78)	1.68 (0.66)	<0.0001[c]
Social: value of relationships	3.02 (0.90)	2.78 (0.93)	<0.02
Meaning of cancer	2.91 (0.72)	2.71 (0.79)	<0.01
Health worry	3.16 (0.95)	2.57 (0.93)	<0.0001[c]
Higher order positive scale	3.04 (0.61)	2.84 (0.70)	<0.01
Higher order negative scale	2.55 (0.66)	1.99 (0.58)	<0.0001[c]
Less activities in the sun (yes)[d]			
Less sun and beach holidays?	88 (73)	255 (66)	<0.01
Less occupation/daily activities?	43 (36)	83 (20)	<0.001
Less leisure time outdoors?	28 (23)	48 (11)	<0.001
Anxiety (yes)[e]			
Own skin?	74 (61)	205 (48)	<0.01
Skin of partner (if applicable)?	43 (37)	118 (29)	0.10
Skin of children (if applicable)?	56 (48)	158 (39)	0.07
Protection (yes)[f]			
Seeking shade	76 (63)	254 (59)	0.49
Protective clothing (e.g. long sleeves and hats)	54 (45)	162 (38)	0.20
Use of sunscreen lotion	79 (65)	279 (65)	0.99

[a] p-value was adjusted for age at the time of survey, years since diagnosis, gender, marital status, educational level, stage, Breslow, primary therapy and comorbidity at the time of the questionnaire when necessary.

[b] a higher score on a subscale means stronger endorsement of that content area; a high score on a positive scale thus means a higher positive impact of cancer, while a high score on a negative scale means a higher negative impact of cancer.

[c] Clinically relevant difference

[d] Compared to the period before your melanoma diagnosis, are you less involved in the following activities in the sun?

[e] Compared to the period before your melanoma diagnosis, are you more worried about the influence of the sun?

[f] Compared to the period before your melanoma diagnosis, do you protect your skin more against the sun?

DISCUSSION

Twenty-two percent of melanoma patients in this study were classified as having a Type D personality. This is within the range of Type D prevalence in the normal population, which ranges from 13% to 24%.[11, 32, 17] Among people with cardiovascular disease, these numbers are more elevated; between 27% and 31%.[12, 14, 33, 34]

Type D patients reported a statistically significant and clinically relevant lower health status measured by the SF-36. Because this is the first study to investigate the effect of Type D on health status among cancer survivors, comparison with other studies is not possible. However, it is known from the literature that the Type D personality construct is associated with a lower health status among cardiovascular patients. For example, Type D was associated with a lower health status pre- and post-cardiac rehabilitation in a study among 368 coronary artery disease patients.[35] In addition, Type D patients were more than twice as likely to report a poor physical health status and were more than five times as likely to report a poor mental health status one year post coronary artery bypass grafting surgery.[36] Also, Type D personality was associated with more than a three to sixfold increased risk of impaired health status in 186 heart transplant recipients 7 years following transplantation.[18]

This is the first study that reports the effect of personality on the impact of cancer, as measured by the impact of cancer questionnaire. Having had melanoma had a greater impact on body changes, negative self-evaluation, negative life outlook, life interferences, health worry and the higher order negative scale of the IOC in Type D patients compared to non-Type Ds. In addition, Type D patients were more worried about the influence of the sun on their skin and were more likely to adjust their life style than non-Type D patients. A higher impact of cancer on Type D patients can possibly be explained by the fact that negative affectivity is one of the main characteristics of Type D, which implies that these patients have the tendency to experience negative emotions in general. This can perhaps also explain why we did not find a difference in the positive IOC subscales (e.g. positive self-evaluation and positive outlook) but did find major differences in the negative ones (e.g. negative self-evaluation and negative outlook). Additionally, negative affectivity might cause Type D patients to estimate their chances of disease progression somewhat higher than non-Type D patients, which causes them to act accordingly by avoiding the sun more frequently. This could be viewed as a positive consequence of having a Type D personality that deserves further research.

A study among heart failure patients found that Type Ds experienced more cardiac symptoms but less often reported these symptoms to their cardiologist compared to non-Type Ds.[13] However, in the current study, no differences were found between those with or without Type D in the number of visits to a general practitioner. This seems plausible because in the Netherlands, almost everyone visits his/her general practitioner at least once a year so differences are hard to find.[37] Furthermore, no differences were found between survivors with and without Type D in the number of visits to a medical specialist. This may be explained by the fact that

there are guidelines on the number of follow-up visits for melanoma patients.[37] In contrast to the study among heart failure patients in which patients should contact the cardiologist or nurse in case symptoms arise. This places the responsibility of making an appointment with the patient, not the cardiologist, and therefore leaves more room for someone's personality to interfere with his or her health care utilisation.

This study has some limitations that should be noted. Although information was present concerning the initial cancer and treatment characteristics of the non-respondents and patients of whom the addresses could not be verified, whether non-respondents declined to participate in the study because of poor health remains unknown. In addition, although Type D personality is a stable construct,[38] the cross-sectional design of our study limits the determination of causal association between Type D personality, health status and impact of cancer as baseline health status and impact of cancer of patients at diagnosis is not known. Therefore, future longitudinal studies with baseline data on Type D personality would be useful in exploring this association between Type D personality and health status, and the subsequent adaptation process to cancer.

Nevertheless, this is the first study that confirms that Type D is not only associated with a lower health status among cardiovascular patients but also plays a major role in cancer patients. One of the strengths of our study, as compared with many previous survivorship studies, is the high response rate that facilitates generalising the results to the larger population of long-term melanoma survivors. In addition, we evaluated a broad spectrum of possible confounding factors, including age at the time of survey, years since diagnosis, gender, marital status, educational level, stage, Breslow, primary therapy and comorbidity at the time of questionnaire. Our results are intriguing and warrant further research with a larger group of melanoma survivors followed over a longer period of time.

Our study provided insight into the role of Type D personality on health status and impact of cancer among melanoma survivors 1/2–10 years after diagnosis. The Type D scale has proven to be a useful screening tool in melanoma survivors to identify subgroups at risk for impaired health status and impact of cancer. Giving special attention to those patients is important while they are more likely to experience a worse health status and stronger impact of cancer than non-Type D patients which can-not be explained by socio-demographical or clinical characteristics. Type D might not just be a personality profile that decreases health status among cardiovascular patients but is more a vulnerability factor for a lower health status in general. So although not the focus of our paper, it demonstrates that personality could play a major role in the clinical care for cancer patients. More research on Type D personality among cancer survivors is therefore warranted.

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7

Melanoma survivors are unsatisfied with received information: A study into characteristics of perceived information disclosure

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MADAM, The incidence of melanoma is rapidly rising which can lead to an increasing burden for health care providers.[1] Information provision is one of the most important aspects of supportive cancer care. Providing information that is congruent with patients' needs may lead to lower levels of distress, better quality of life, improved patient satisfaction and sense of control.[2,3] More disease knowledge can result in informed decision making and can have positive effects on adherence to treatment and follow up, leading to reduced follow-up visits.[1] However, one of the most frequently reported unmet needs by cancer patients is information disclosure.[4] There is a discrepancy between the actual information needs of cancer patients and the perception of health care providers about the needs of cancer patients.[5] Health care providers are often still reluctant to give the full amount of information about cancer and its treatment. Melanoma patients would appreciate especially more information concerning their diagnosis, treatment and skin condition.[6]

We conducted a cross-sectional study to measure the perceived level of, and satisfaction with, information received by melanoma patients.[7] Patients diagnosed with melanoma between 1 January 1998 and 1 August 2007 from three regional hospitals were selected. Melanoma was defined using the ICD-O codes C44.0–C44.9 with morphology 8720–8790. Medical specialists sent their (former) patients a letter to inform them about the study and a questionnaire. The EORTC-QLQ-INFO26 questionnaire was used to evaluate the information received by melanoma patients.[8]

Of the 699 melanoma survivors, 562 (80·4%) returned a completed questionnaire. There were no demographic or clinical differences between respondents and nonrespondents. Demographics and clinical characteristics of participating patients are presented in Table 1.

A large percentage of patients indicated the absence of information about different aspects of melanoma, treatment and aftercare (Table 2).

In multivariate linear regression analysis, none of the patient characteristics was significantly associated with perceived information provision about the *disease*. More information about *medical tests* was associated with shorter time since diagnosis ($\beta = -0{\cdot}10$; $P < 0{\cdot}05$) and a higher stage melanoma ($\beta = 0{\cdot}19$; $P < 0{\cdot}01$). More perceived information provision about *treatment* was significantly independently associated with younger age ($\beta = -0{\cdot}15$; $P < 0{\cdot}05$), higher stage of disease ($\beta = 0{\cdot}20$; $P < 0{\cdot}01$) and higher educational level ($\beta = -0{\cdot}10$; $P < 0{\cdot}05$). Logistic regression analysis showed that satisfaction with information was independently associated with hospital of treatment [odds ratio (OR) = 0·49, 95% confidence interval (CI) 0·32–0·76; $P < 0{\cdot}01$], high educational level (OR = 0·63, 95% CI 0·41–0·99; $P < 0{\cdot}05$) and less frequent use of the internet for additional information (OR = 0·60, 95% CI 0·39–0·92; $P < 0{\cdot}05$).

Patients with a higher disease stage are more likely to undergo more medical tests and/or treatments due to the increased risk of recurrence and metastasis. Therefore these patients might get more attention and information from their health care providers compared with patients with stage I melanoma. Also, the majority of melanoma patients receive most information immediately after diagnosis. After the completion of treatment the contacts of the patients

Table 1. Demographics and clinical characteristics of participating patients (n = 562)

Characteristic	Numbers (%)
Age (years) at time of survey (mean ± SD)	57·2 ± 13·6
Gender, *n* (%)	
Male	212 (38)
Female	350 (62)
Time (years) since incidence (mean ± SD)	4·6 ± 2·6
Stage at diagnosis, *n* (%)	
I	400 (71)
II	108 (19)
III	42 (8)
IV	–
Breslow thickness, *n* (%)	
≤ 1·0 mm	275 (49)
1·01–2·0 mm	149 (27)
2·01–4·0 mm	100 (18)
> 4·0 mm	32 (6)
Treatment, *n* (%)	
Surgery	556 (99)
Sentinal node	113 (20)
Lymphadenectomy	27 (5)
Radiotherapy	3 (0·5)
Systemic therapy	3 (0·5)
Other	29 (5)
Comorbidity, *n* (%)	
None	190 (35)
One	174 (32)
Two or more	174 (32)
Hospital, *n* (%)	
Hospital A	168 (30)
Hospital B	255 (45)
Hospital C	139 (25)
Marital status, *n* (%)	
Married	416 (74)
Never married	55 (10)
Divorced/widowed	89 (16)
Education level, *n* (%)	
Higher education	161 (29)
Intermediate education	242 (43)
Secondary school	103 (19)
Primary school	52 (9)
Current occupation, *n* (%)	
Employed	248 (44)
Unemployed	311 (56)
Socioeconomic status	
Low	80 (15)
Intermediate	220 (40)
High	237 (44)
Institutionalized	6 (1)

Table 1. Demographics and clinical characteristics of participating patients (n = 562) (continued)

Characteristic	Numbers (%)
Follow-up care, *n* (%)	
General practitioner	11 (2)
Dermatologist	452 (81)
Surgeon	138 (25)
Oncologist/internist	48 (9)
Other	12 (2)

Table 2. Perceived information provision characteristics, (n (%))

	Received no information	Received a little information	Received some information	Received a lot of information
Disease				
Diagnosis	47 (9)	309 (56)	154 (28)	41 (7)
Spread of disease	104 (19)	271 (49)	135 (25)	37 (7)
Cause of disease	203 (37)	226 (41)	103 (19)	17 (3)
Under control	76 (14)	258 (47)	164 (30)	48 (9)
Medical tests				
Purpose of test	134 (25)	220 (41)	157 (29)	29 (5)
Course of test	125 (23)	237 (44)	144 (27)	32 (6)
Results of test	74 (14)	237 (44)	188 (35)	38 (7)
Treatment				
Medical treatment	201 (38)	162 (30)	137 (26)	30 (6)
Nonmedical treatment	496 (94)	26 (5)	5 (1)	2 (0)
Expected result	182 (34)	202 (38)	122 (23)	25 (5)
Side-effects	333 (62)	131 (25)	56 (10)	14 (3)
Expected results on disease symptoms	288 (54)	163 (31)	65 (12)	14 (3)
Expected results on social life	423 (80)	84 (16)	18 (3)	7 (1)
Expected results on sexual life	487 (92)	32 (6)	6 (1)	5 (1)
Other services				
Additional help	484 (92)	36 (7)	6 (1)	2 (0)
Rehabilitation	481 (91)	28 (5)	14 (3)	4 (1)
Cope with cancer at home	441 (84)	68 (13)	16 (3)	2 (0)
Psychological assistance	492 (94)	29 (5)	3 (1)	2 (0)
Single items				
Different care locations	472 (91)	38 (7)	9 (2)	3 (0)
Things to do to get better	399 (76)	92 (18)	25 (5)	7 (1)
	Not satisfied	A little satisfied	Quite satisfied	Satisfied
Satisfaction with information	72 (13)	259 (48)	164 (30)	46 (9)
	Not useful	A little useful	Quite useful	Very useful
Usefulness of information	43 (8)	224 (43)	194 (38)	57 (11)
	Yes	No		
Received written information	279 (52)	259 (48)		
Received information on video or CD-ROM	4 (1)	538 (99)		
Wanted more information	135 (25)	402 (75)		
Wanted less information	10 (2)	518 (98)		

with their doctor will diminish,[3] while the information need of the melanoma survivor may still exist. Patients diagnosed and treated shortly before the completion of the questionnaire might have a clearer picture of the information they received and therefore reported to have received more information.

Younger and more highly educated melanoma patients are more likely to be actively involved in decision-making processes and ask more questions. Older patients are reported to be less interested in detailed information and leave the provision of details up to the doctor.[9] Likewise, doctors can be prejudiced against older patients. Furthermore, older and less educated patients may have more difficulties processing and remembering information they receive and may compensate for their reduced cognitive capacity by asking fewer questions to their specialist.[9]

The observed variation in information satisfaction levels between patients treated in different hospitals can be explained by the variation in patient-centred information provision, which is strongly related to information recall and understanding. Our finding that only 25% of the melanoma survivors wanted more information could be explained by the increasing internet use of melanoma patients.[10] When patients are not satisfied with the information received from their health care provider, they will search for additional information on the internet.

Health care providers often have limited time and resources to provide the information that melanoma patients require. With growing evidence that well-informed patients are more satisfied with their care, and do better clinically, efforts are needed to improve the information provision to melanoma patients. Exploration of the patients' personal information needs must lead to a more patient-tailored approach of informing melanoma patients. A good opportunity would be the implementation of a survivorship care plan, which aims at providing a cancer survivor with a summary of their course of treatment, management of late effects, and strategies for health promotion.

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8

Melanoma patients receive more follow-up care than current guideline recommendations: A study of 546 patients from the general Dutch population

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JEADV, accepted

ABSTRACT

Background Follow- up of melanoma patients has been a continuing issue for discussion in the past years partly due to ever increasing incidence of this disease, as well as the lack of agreement regarding the reasons for and frequency of follow- up. Patients' perspectives are often not included in this continuing discussion on follow-up of melanoma patients.

Objective To examine to what extent follow-up is experienced according to the guideline of 2005, by physicians and melanoma patients in a Dutch population from the south-east area of the Netherlands. The patient's perspective and satisfaction over said follow-up shall also be taken into account.

Methods Follow-up among melanoma survivors was investigated and compared with the recommendations of the current Dutch national guideline. All 699 melanoma patients registered at the Eindhoven Cancer Registry (between 1998 and 2008), and treated in 3 regional hospitals, were contacted via postal mail. The survey questioned about treatment, symptoms, impact on daily life and follow-up. Patients with multiple melanomas (n=16) were excluded.

Results Response rate was 80%, 418 patients were still under surveillance for their melanoma. The average time since diagnoses was 4 years, 71% had stage I melanoma. Almost 80% of patients with a Breslow thickness <1mm, reported more frequent follow-up visits than the guideline recommends. Only 5% of the patients wanted to reduce their follow-up frequency. Eighty percent of patients was under supervision of a dermatologist: physical examination, lymph node palpation and/or scar inspection did not regularly occur in 25%, 11% and/or 20%, respectively. These proportions were significantly higher among other specialisms.

Conclusion Follow-up frequency was higher than recommended by the current melanoma guideline in a large group of patients, mainly those with lower Breslow thickness.

INTRODUCTION

Follow-up of melanoma patients has been a continuing issue for discussion in the past years, partly due to ever increasing incidence of this disease, as well as the lack of agreement regarding the reasons for and frequency of follow-up.[1-3] Nowadays, the importance of proper follow-up and first evaluation at diagnosis is raised as new promising targeted therapies are evaluated for the use in melanoma patients.[4] Several possible reasons for completing a follow-up of a melanoma patient include: detection of recurrent melanomas (namely, spreading of the disease), diagnosis of new and potential malignant melanocytic lesions (the risk of developing a new melanoma by a melanoma patient varies between 10 – 30%) and/or reassurance of the patient.[2] The 2005 Dutch melanoma guideline recommends that patients with a thin melanoma (Breslow thickness <1mm, which includes 70% of melanoma patients) return once for a follow-up appointment 1 month after treatment to receive further information. However this is regarded by patients and physicians as insufficient.[5-8] Follow-up occurs more frequently in patients with a melanoma thickness greater than 1.0 mm (13 times in 5 years after diagnosis). Despite the prognostic importance of the Breslow thickness, a discrepancy exists between follow-up in patients with a thick versus those with a thinner melanoma. A small Dutch cross-sectional study consisting of 67 melanoma patients and 25 physicians (both referral and treating physicians), showed that few physicians follow the standard follow-up protocol, and that most of patient follow-up was conducted in order to assuage the fears of the patient.[8] Another study reported that three quarters of patients, in whom a recurrent melanoma was discovered, was actually discovered by the patient.[3] One could therefore view follow-up as unnecessary to detect recurrent melanoma. Based upon this assumption, the number of follow-up appointments could be reduced, provided that the patient receives the proper information regarding the recognition of a recurrent cancer. However, in the same study only 40 percent of patients reported having received this information and most patients reported a preference for a follow-up frequency of every 3 months. They concluded that further research is needed which takes the patient's perspective and preferences regarding follow-up care after being diagnosed with a melanoma into account. [3] The aim of this study is to investigate the current Dutch melanoma guideline, and to examine to what extent follow-up is experienced according to the guideline of 2005, by physicians and 546 melanoma patients in a Dutch population from the south-east area of the Netherlands. The patient's perspective and satisfaction over said follow-up shall also be taken into account.

METHODS

Study Design and Participants

Patients selected for inclusion in this study had been registered by the Eindhoven Cancer Registry and had been diagnosed with melanoma in one of the three participating hospitals between January 1, 1998 and August 1 2007. After cross-checking with the Central Bureau of Genealogy, patients over the age of 85 who were still alive in 2008 were invited by the current treating physician to participate in this cross-sectional study, which examined the impact of melanoma patients' live. Patients diagnosed with multiple melanomas were excluded from this analysis, as follow-up of these patients dependent upon the number of tumors and is therefore difficult to objectify. Permission for participation in this study was obtained by returning an anonymous questionnaire. Patient information was collected between the months of February and May 2008. Permission for completion of this study was granted by the Medical Ethic Committee of the Catherine Hospital, Eindhoven.

Study outcomes

Information regarding melanoma (date of diagnosis, location, histological type, TNM classification, treatment) was obtained via the Eindhoven Cancer Registry. Patient questionnaires included information regarding demographic variables, disease development and treatment, comorbidity, and follow-up. Questions regarding health care usage, such as the number of visits to the family practice physician, specialist, or other medical professionals were also included in the questionnaire. The questions were phrased similarly to questions posed by the Central Bureau of Statistics in the yearly health care census, which is conducted within an independent Dutch study population. The type of specialist who had completed the follow-up (family practice physician, dermatologist, surgeon, plastic surgeon or oncologist) was recorded along with a detailed record of what occurred during the follow-up appointment (e.g. complete disrobement for a total skin inspection, scar inspection and palpation of the lymph nodes). The answers ranged from always, sometimes, to never (the last two responses were combined in the analysis). A follow-up was considered "complete" after a total inspection of the skin, inspection of the scar, and palpation of the lymph nodes had found place, which are the minimal

Table 1: Frequency of follow-up according to Dutch melanoma guideline (2005)*

Breslow tickness	Time after diagnosis	Frequency of follow-up
> 1mm	Year 1	Once every 3 months
	Year 2	Once every 4 months
	Year 3-5	Once every 6 months
>2	Year 1	Once every 3 months
	Year 2	Once every 4 months
	Year 3-5	Once every 6 months
	Year 6-10	Annually

* Supplemental tests as indicated

requirements according to the Melanoma guideline of 1996 and 2005. [5, 9] Follow-ups which occurred more frequently than those recommended in the CBO guideline for Melanoma 2005 (Table 1) were defined as overconsumption [5], representing overuse of healthcare resources.

Statistical Analysis

Significant statistical differences between the distributions of categorical variables were tested using a chi-squared test. A 2-sided p-value <0.05 was defined as statistically significant. All statistical analyses were completed using SPSS (version 15.0)

RESULTS

Study Population

From the 992 patients whom had been diagnosed with melanoma between the dates of January 1998 and August 2007 in one of the three participating hospitals, 81% were still alive per August 1, 2007 (Fig.1). From these 802 patients, 103 were not included in the study due to sickness and according to the advice from their treating physician (n=5), due to treatment via a

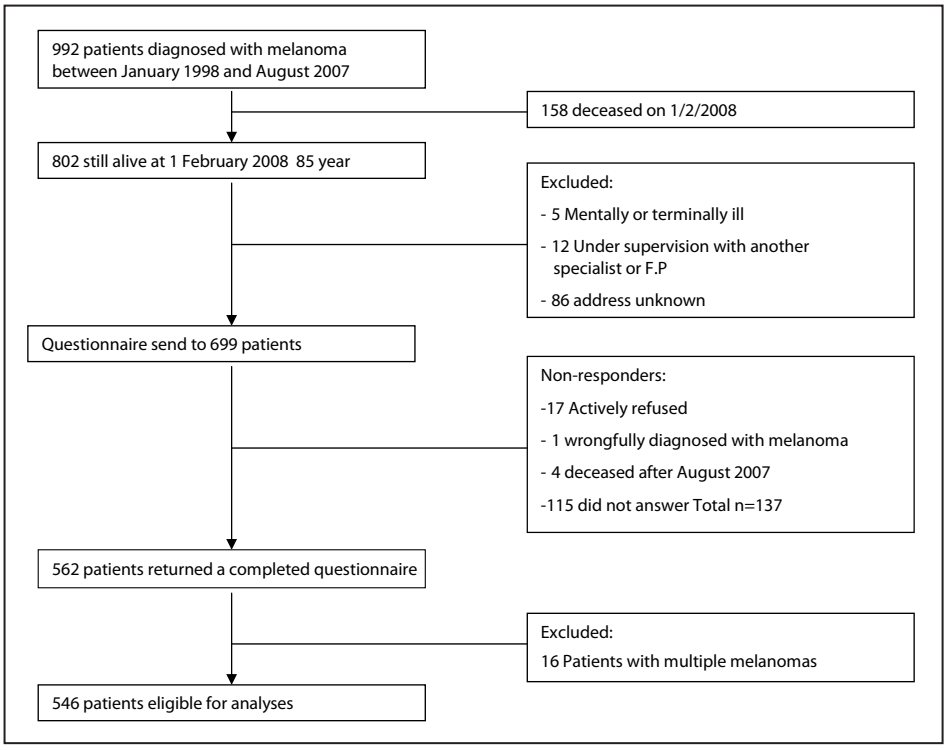

Figure 1 Flow diagram data collection.

different physician (n=12), or due to change in address (n=86). From the original study population, 669 patients remained, of whom 562 completed and returned the questionnaire (80%). Sixteen of these patients developed multiple melanomas. From the non-respondent group, 17 patients actively declined to participate, of whom 4 were deceased after February 2008. One patient was incorrectly registered as having been diagnosed with a melanoma.

The average age of the melanoma patient was 52.2 years at the time of diagnosis and 62% were female (Table 2). From the respondents, 70% had a high school diploma, 74% were married and 52% were employed at the time of the study. From the study population, 34% of patients reported having at least one other additional disease. Past history of hypertension, arthritis/ arthrosis, or cancer was reported by 20% of patients. Seventy one percent of patients had been

Table 2.: Sociodemografic and clinical characteristics of respondents.

Total 562	**%**		**%**
Age at completion of questionnaire		**Stage at time of diagnosis**	
(average 57.2)		Stage I	400 (71)
≤30	25 (5)	Stage II	108 (20)
30-39	96 (17)	Stage III	42 (7)
40-49	117 (21)	Stage IV	-
50-59	145 (26)	Unknown	12 (2)
60-69	112 (20)	**Treatment**	
70-74	36 (6)	Surgery	556 (99)
75-79	26 (5)	Sentinal Node Procedure	113 (20)
≥80	5 (1)	Lymphadenectomy	27 (5)
Age at time of diagnosis		Systemic Therapy	3 (0.5)
(average 52.2)		Radiotherapy	3 (0.5)
≤30	9 (2)	Other	29 (5)
30-39	59 (11)	**Comorbidity**	
40-49	119 (21)	Yes	186 (35)
50-59	123 (22)	No	351 (65)
60-69	143 (25)	**Marriage Status**	
70-74	43 (8)	Married	416 (74)
75-79	47 (8)	Unmarried or never married	55 (10)
≥80	19 (3)	Divorced	36 (6)
Time since diagnosis		Widow/Widower	53 (10)
(average 4.6)		Partner	464 (85)
< 1 year	31 (6)	**Education**	
1 - < 3 year	167 (30)	Elementary School	161 (29)
3 - < 5 year	149 (27)	High School	242 (43)
≥ 5 year	212 (38)	College/ Technical schooling	103 (18)
Breslowthickness at time of diagnosis		Higher Education (university)	52 (9)
≤ 1 mm	275 (49)	**Work**	
1.01-2.0 mm	149 (27)	Employed	299 (53)
2.01-4.0 mm	100 (18)	Unemployed	245 (44)
>4.0 mm	32 (6)	Unemployed(disabled)	15 (3)
Unknown	6 (1)		

NB: percentages are rounded off to whole numbers.

diagnosed with a stage I melanoma and 49% of patients had a Breslow thickness < 1mm (Table 2). Local surgery had been performed on almost all of our patients and 20% had undergone a sentinel node procedure. Other treatments were seldom performed on our patient group.

Follow-up

Of the participants, 77% received follow-up treatment for their melanoma at time of the questionnaire (6 months – 10 year after diagnosis). The 418 patients who were still being followed for their melanoma were on average 4.7 years after diagnosis. Within this group, 6% were <1 year after having been diagnosed, 28% 1– 3 years, 25% 3 – 5 years and 41% 5 – 10 years.

Different physicians

Dermatologists (80%) and plastic surgeons/surgeons (25%) were the most often consulted and involved in follow–up care within our study population. However, the physician who had made the diagnosis of melanoma and/or removed the tumor was not always necessarily involved in follow-up care. Seventy-two percent of patients had their tumors removed by a family practice physician and received follow-up care from a dermatologist. Between 90 and 94% of patients who had had their melanoma removed by a dermatologist also received their follow-up care from this specialist. About half of the melanoma patients who were treated by a plastic surgeon/

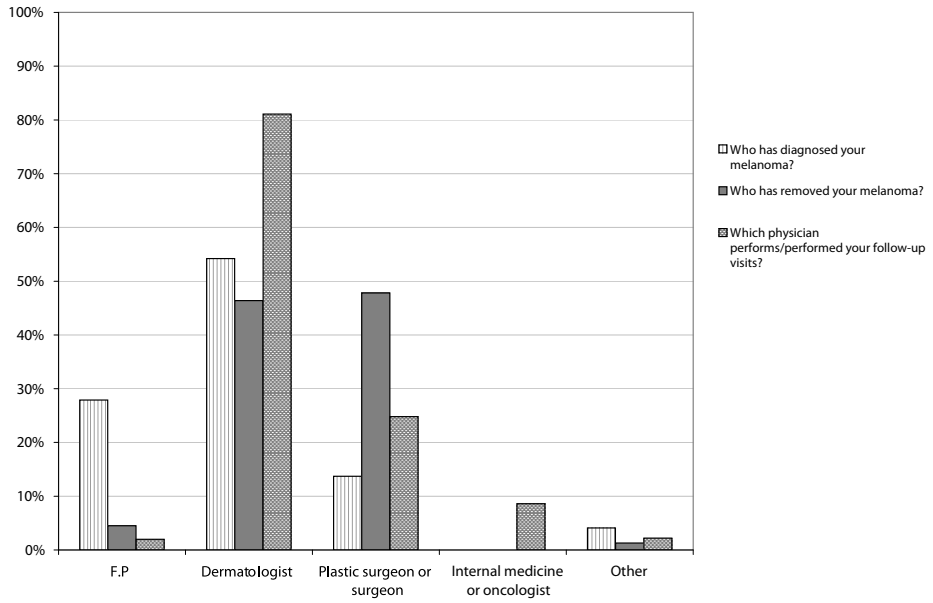

Figure 2: Physicians, who diagnosed, treated and/or performed the follow-up of melanoma patients.

surgeon were being followed- up by this specialist and the other half were being followed- up by a dermatologist (51% and 57% respectively)(Figure 2).

Reported content of follow-up

In order to determine whether a dermatologist actually fulfilled a vital role in the follow-up care of melanoma patients, the patients were divided into 2 groups; group 1 consisted of patients seen by a dermatologist and group 2 consisted of patients who were not seen by a dermatologist. When a dermatologist was involved with the follow-up care of patients, (n=444), 76% of patients reported being required to disrobe for a complete physical inspection, 89% of patients reported that scar inspection occurred and 80% of patients acknowledged that lymph node palpation had taken place. Patients in group 1 (those being seen by a dermatologist) were significantly more often required to undress for a complete physical inspection than those from group 2 who were not seen by a dermatologist (asked to undress 76% vs. 36%, $p<0.0001$). A significant difference was also discovered between the two groups in regards to palpation of the lymph nodes, which also occurred more frequently in patients from group 1 than in patients from group 2 (80% vs. 64%, $p<0.01$). However, despite these significant differences between the two groups of patients, 24% of the 434 patients from group 1 reported sometimes/never being asked to undress, 11% reported that no regular scar inspection took place, and 21% reported that little to no lymph node palpation had been performed. Seventy two percent of patients from group 2 (n=103) were followed up by a plastic surgeon/surgeon. During the follow-up appointments conducted by plastic surgeons/surgeons, 54% of patients reported sometimes/never having been asked to undress in order to complete a full physical examination and 40% of patients reported that lymph node palpation infrequently/never occurred. Furthermore, an additional 17% of patients reported infrequently/never having their scar examined during a follow – up appointment.

Reported satisfaction

Follow-up was rated as good to very good by 83% of patients. Only 3% of patients rated follow-up care as being bad to very bad, of whom 16 of these 17 patients had an incomplete follow-up (no regular skin examination, scar inspection and lymph node palpation). In addition, 23% of patients indicated that they were interested in extra paramedical/medical care after having received treatment for their melanoma (5% family practice visits, 3% physiotherapist, 10 % medical specialist).

Reported follow-up versus guideline recommendations

Within the past year, 40% of melanoma patients had visited a specialist 1 to 2 times regarding concerns about their melanoma and subsequent secondary concerns. Seventeen percent of patients reported visiting a specialist 3-5 times within the past year (Table 3). Eighty percent of patients with a Breslow thickness < 1mm reported to have had more follow-up appointments

Table 3: Heath care usage by participating melanoma patients.

	%
Currently receiving follow-up care (n=556)	
Yes	77
Not anymore	20
Never	2
Number of visits to the F.P in the last 12 mo. due to melanoma (n=545)	
0 times	86
1-2 times	11
3-5 times	3
6-10 times	0
>10 times	0
Number of visits to a specialist in the last 12 mo. due to melanoma (n=547)	
0 times	35
1-2 times	40
3-5 times	17
6-10 times	5
>10 times	2
Appointments made for follow-up care of melanoma (n=553)	
Every 3 mo.	8
Every 4 mo.	8
Every half year	34
1 time per year	29
Every 2 years	1
No definite appointments	21

NB: Patients with multiple melanomas were excluded. Percentages have been rounded off to whole numbers.
F.P. = family practice physician
mo. = months

than the guideline recommends (Figure 3b). In the second year of having being diagnosed, the percentage of excess visits to a specialist decreased, with 39% of patients reporting having visited their physician 2 times instead of 3. The trend continues with 19% of patients having one follow- up appointment instead of two from the third year up until the fifth year. Twenty nine percent of patients with a Breslow thickness > 2mm reported visiting their physician 1 time per year, for six to ten years after having been diagnosed, as recommended by the guideline. The remaining patients with a Breslow thickness >2mm visited their physician more frequently or without a definitive follow-up schema. Almost all melanoma patients (87%) were satisfied with the follow-up plan that they had been given. Only 5% indicated that they preferred fewer follow-up appointments and 7% preferred to be seen more frequently.

As illustrated in table 4, women more frequently attended follow-up visits than men. In addition, patients with a Breslow thickness < 1mm and/or who were under the supervision of a dermatologist were more frequently seen for follow-up appointments than recommended by the guideline. Furthermore, the hospital wherein the follow-up visit took place may also have been an influencing factor.

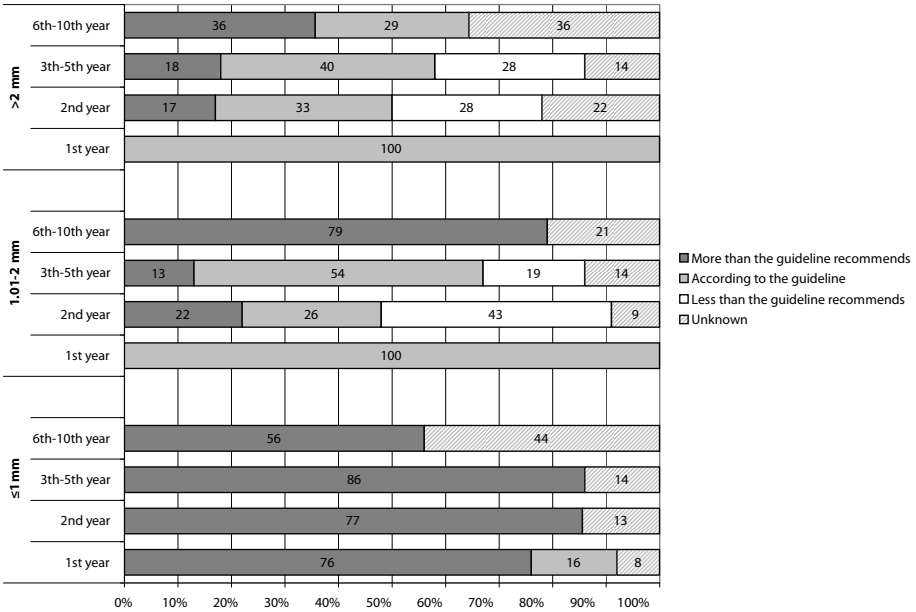

Figure 3: Health care consumption of melanoma patients.

DISCUSSION

In the case of many melanoma patients, the current Dutch guideline has not to been lived up to. A large group of melanoma patients, especially those with a low Breslow thickness, came much more frequently for follow-up appointments than advised by the 2005 guideline.[5]

The current guideline is justifiable on the basis of cost-effectiveness and for the detection of a recurrent or new primary melanoma. However, it does little to take the patient's perspective into consideration.[3, 10-11] Patients were satisfied with the higher frequency of follow-up care that they received and only 5% indicated that they would prefer fewer follow-up appointments. Female patients and/or patients under the supervision of a dermatologist and/or patients with a Breslow thickness <1mm attended follow-up care more frequently than the guideline recommended. The patient's perspective, in addition to that of the treating physician, appears to have an influence on the amount of follow-up care provided. This was earlier demonstrated in a small study of dermatologists and referring physicians who reported scheduling more follow-up visits for their own reassurance.[8] It is very likely that it is difficult for a patient to comprehend that only one follow-up appointment is needed after the removal of a thin melanoma. On the other end of the spectrum are patients with a "thick" melanoma (Breslow thickness >2mm), who must frequently schedule multiple follow-up appointments, despite the fact that this has minimal prognostic value due to the fact that there is no curative treatment for a metastasized melanoma that does not require surgical excision (www.oncoline.nl).[5] In the 1996 guideline

Table 4: Patient characteristics with regard to overconsumption of health care.

	No overconsumption	Overconsumption
	(%)	(%)
Sex		
Woman	59	66
Man	41	34
Age categories		
<50	32	34
50-65	35	39
≥ 65	33	27
Time since diagnosis		
<1 years	4	7
1-3 years	27	34
3-5 years	26	26
>5 years	43	33
Breslowthickness		
<1 mm	21	77
1.01-2 mm	40	13
2.01-4.0mm	27	8
>4 mm	9	2
Unknown	2	0
Follow- up physician*		
F.P.	1	1
Dermatologist	67	90
(Plastic)Surgeon	24	7
Internist/Oncologist	6	2
Other	2	0
Hospital		
1	54	46
2	56	44
3	37	63

* Only patients who received follow-up care by a specified physician.
NB: percentages have been rounded off to whole numbers.
Cat. Age = Categorical age.
F.P. = Family practice physician

follow-up was not indicated according to Breslow thickness.[9] For every Breslow thickness the same frequencies applied, as mentioned in the 2005 guideline (Breslow thickness > 1mm), with a maximum of 10 years. Patients with a Breslow thickness < 1.5mm who were five years after having been diagnosed, were released from the follow-up. In an additional analysis, patients were divided into 3 groups: patients diagnosed according to the 1996 guideline (before 2005), patients diagnosed in 2005, and patients diagnosed after 2005 (a new guideline appeared in 2005). This analysis showed that it appears to be that the frequency of follow-up visits for patients with a Breslow thickness <1mm comply more with the guideline of 1996. There were no definite differences observed among the guidelines for other Breslow thicknesses. It is possible that physicians and patients prefer the older guideline, which advised more follow-up care

for patients with a Breslow thickness <1mm. Yet another explanation could be that patients visit the dermatologist more frequently because of a skin problem other than their melanoma. Additional analysis indicated that 20% of all patients who visited the dermatologist too frequently had a past history of another type of skin tumor.

It is not clear which physicians should perform follow-up care and may depend upon the stage of the melanoma. It is obvious that the dermatologist, possibly with the help of a nurse practitioner or specialized nurse, should play a central role in the follow-up of melanoma patients, primarily due to the nature of the cancer as well as the fact that a great deal of patients are diagnosed within the first stages of the disease. In addition, apparently, a more thorough follow-up occurs when a dermatologist participates in the follow-up care of melanoma patients. However despite these findings, almost a quarter of patients who were seen by a dermatologist reported that they did not receive complete follow-up care, i.e. they were not always given a complete physical examination, nor did scar inspection or lymph node palpation take place. For patients in a later stage of the disease it might be recommendable to be followed-up in a multi-disciplinary setting or should alternate between the care of a surgeon and/or oncologist and dermatologist.[2, 12]

This is one of the largest cross-sectional studies involving melanoma patients within the general population. The response rate of 80% was quite high and corresponded with response rates reported by other studies conducted in the south of the Netherlands.[13-14] However, several limitations to this study must be considered. With a cross-sectional study it is more likely that patients with a stage III or stage IV melanoma are excluded, considering that these patients are often too ill to participate or are deceased. However, this selection primarily includes melanoma patients from general population, from which the majority of patients have been diagnosed with a melanoma with a Breslow thickness of <1mm. Furthermore, these results can be generalized to the rest of melanoma patients in the Netherlands, because none of the patients included had been treated in a university hospital or specialized clinic. One additional limitation of this study is the possibility of recall bias. It is possible that patients who received the diagnosis of melanoma up to 10 years ago were not able to accurately remember and evaluate what level of follow-up care that they had received. However, this possible bias does not apply to the degree of "overconsumption" of health care, as patients were asked to report the frequency of outpatient appointments within the last 12 months. A large number of melanoma patients were diagnosed before the introduction of the current guideline, and it is possible, that in the case of these patients, physicians followed the 1996 guideline instead of that from 2005. This may explain the degree of overconsumption among patients with a melanoma with a relatively low Breslow thickness. Patients experience the most anxiety during diagnosis and treatment. Reducing the amount of follow-up visits might reduce this anxiety. However, a study by Bastiaannet et al on the burden of diagnostic test in 60 patients with lymph node metastases also

showed that patients were more satisfied with follow-up and experiences less burden during diagnostic tests when they were well informed.[15] This suggests an important role of providing patients with accurate information which can prevent additional anxiety during follow-up and improve patient satisfaction with care, wich might lead to reduction in of overconsumption of health care.

Previous studies have shown that social status is of relevance to the incidence of cancer.[16-17] Furthermore it might be of relevance to the coping mechanisms of melanoma patients, which might result in a higher or lower health care need. Table 2 showed that approximately half of the melanoma patients were unemployed and/or had basic education (primairy school or high school) which might mean that these patients have more difficulty with understanding information given by health care providers and might result in difficulty with coping with their disease, which might then lead to higher health care consumption. Unfortunately we did not have enough detailed information to make to accurately evaluate this statement.

In conclusion, our findings indicate that a large group of melanoma patients, particularly those with a low Breslow thickness, more frequently received followed-up care than is advised by the current melanoma guideline. More research is need in order to further investigate why this overconsumption of health care resources occurs, and to discover possible predictors for overconsumption by patients as well as physicians. It is of the utmost importance that the patient's perspective is taken into account when evaluating the follow-up guideline. At this time a prospective study is being conducted in the Netherlands which compares the current guideline with an experimental guideline (less frequently follow-up visits and adjusted for stage of disease), which includes a patients' perspective (www.ikno.nk MELFO study).

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Burden of melanoma

9

Burden of disease in Dutch melanoma patients, 1989-2006

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submitted

ABSTRACT

Background Burden of disease describes loss of health and death due to a disease which has not been adequately studied for melanoma.

Methods Age- and gender-specific incidence data from all patients diagnosed with melanoma in the Netherlands between 1989 and 2006 were obtained from the Netherlands Cancer registry. Mortality numbers and rates 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 of Life lived with 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.

Conclusions 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 of Life lived with Disability	= number of incident cases x disability weight (0.05) x average duration of the disease until remission or death
AYLD	Average Years of Life lived with Disability	= YLD / number of incident cases
YLL	Years of Life Lost	= number of deaths x standard life expectancy at age of death in years
AYLL	Average Years of Life Lost	= YLL / number of deaths
YLM	Years Lived with Melanoma	= number of incident cases x average duration of the disease 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 men and the 5th most common cancer in women 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 its 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 of newly diagnosed cancer patients. However, the magnitude of the societal problem can also be expressed in a quite different way using Burden of Disease measures 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.[6] 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 disability (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 men and 6 years in women. 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).

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 deaths 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 Life 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 new patients with melanoma by the total midyear population and totaling these age-specific results. European standardized incidence rates (ESR) were then calculated by multiplying the age-specific incidence rates with standard European population data (http://seer.cancer.gov/stdpopulations/). The DevCan software program, which was developed by the National Cancer Institute in the United States, was used to calculate the probability of a person being newly diagnosed with a melanoma during the 5-year period by the life table method.[10] The life table method, 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. 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 within 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 Statistics Netherlands and correctly represented by the Comprehensive Cancer Centers.

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] 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 Melanoma were calculated (YLM). 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 annual average of 1603 Dutch citizens was newly diagnosed with melanoma (Table 1); 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 women.

Age at diagnosis of melanoma increased over time. Between 2002 and 2006 melanoma was mainly newly diagnosed in men above the age of 40 and in women above the age of 25 years (Fig. 1).

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

Table 1: Incidence, mortality and burden of disease of Dutch melanoma patients, according to the period of diagnosis

	Men				Women			
	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 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 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
YLM	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
AYLM	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

Source: Netherlands Cancer Registry and Statistics Netherlands

* = per 100 000 Dutch inhabitants

YLD: years lived with disability; YLM: years lived with melanoma; YLL: years of life lost; DALY: disability adjusted life years; AYLD: average years lived with disability; AYLM: average years lived with melanoma; AYLL: average years of life lost.

Probability of being diagnosed with melanoma and to die from it

DevCan produced estimations of the probability for a person to develop a melanoma (Table 2) and the probability of dying from a melanoma in a certain age group. In 2006, male newborns had an overall chance of 1 in 62 to develop a melanoma, for female newborns 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 women, 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 probability had decreased to 0.1%. Corresponding probabilities for women were 0.2% for a woman aged 40 and 0.1% for women aged 65.

Years lived with Melanoma (YLM)

The Average Years Lived with Melanoma (AYLM), 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 women (Table 1 and Fig. 2). The total years of life lived with melanoma in the general population has rapidly increased. For men, a total of 368.0 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 YLM rose from 373.3 to 616.9 (Fig. 2).

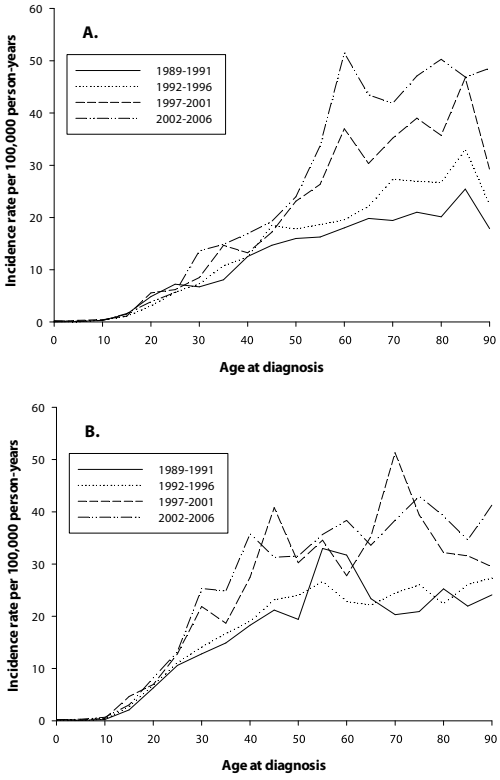

Figure 1. Incidence rates of cutaneous melanoma by age at diagnosis, 1989-2006, per 100,000 person-years.
A: men
B: women

Years of life 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. Women 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 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 among men who died due to their melanoma. For women the AYLL also decreased from 22.4 to 20.1 years. However, the total YLL to melanoma in the Dutch

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

Men

Melanoma free age (years)	Age (years) at diagnosis of melanoma																				
	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

Melanoma free age (years)	Age (years) at diagnosis of melanoma																				
	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

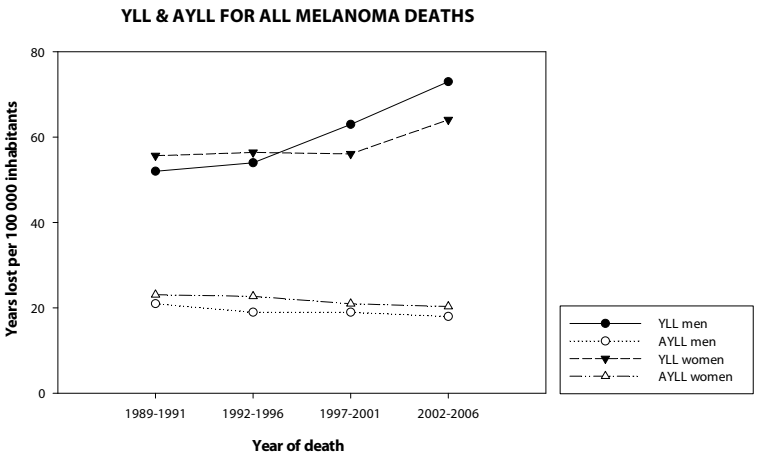

Figure 2. Years Lived with Melanoma (YLM) and Average Years Lived with Melanoma (AYLM) by period of diagnosis.

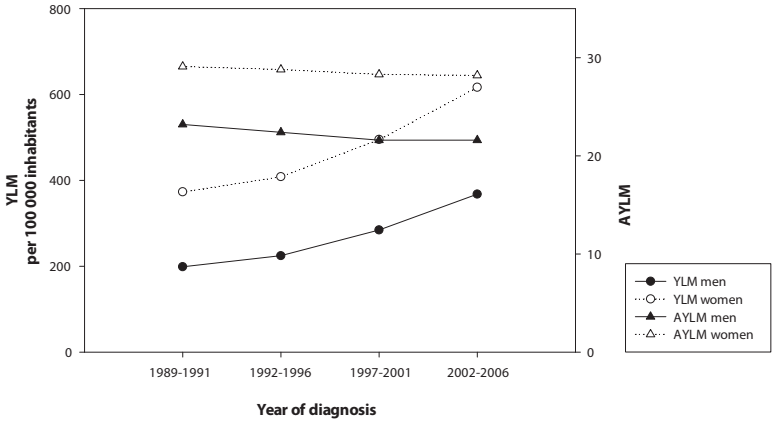

Figure 3. Years of Life Lost (YLL) and Average Years of Life Lost (AYLL) by period of diagnosis.

population almost tripled for men and more than doubled for women during the 18 year time period of our study. In 2002-2006 the total YLL for melanoma for women 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 women: 73 to 94 per 100 000 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 that melanoma has on health care, and the increasing incidence of melanoma suggests that this will further rise in the future. YLD and YLM are important indicators of burden of disease as they estimate the number of years patients might be in need for additional care (including psychological), whereas incidence rates merely indicate a rising trend in the number of patients that will require treatment and follow-up. The high estimates of the burden of disease measures 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. On the other hand, the burden of melanoma in terms of YLL in the Netherlands increased considerably between 1989 and 2006 up to an AYLL of 20. The high YLL is due to the fact that many patients are middle aged when diagnosed with their first melanoma, and most of those who die of melanoma die fairly soon after the diagnosis. Our results cannot be compared directly with the few other studies that have examined the burden of disease measure for melanoma, as those studies used a cut-off value of 65 years.[7-8] Although when calculating YLL, a cut-off of value of 65-years is commonly used to ascertain premature mortality in an occupational population so that loss of productivity can be estimated, in order to be able to assess how long people are affected by a disease, the analysis must be unrestricted by age. It was for this reason that we decided not to use the age cut-off of 65 years. Moreover, the majority of melanoma patients are diagnosed at an age of 55-65 years and thereafter, most patients have a 5-10 year survival rate of >90%.[2] On average, melanoma patients in the Netherlands live to be 75 years of age, which means that adopting a cut-off value of 65 years would result in an YLL being underestimated by about 10 years.

AYLL is calculated as YLL divided by the number of melanoma deaths. However, when all melanoma patients (dead or alive) were included in the calculation, not just those who had died from melanoma, then, on average, between 2002 and 2006, for an individual melanoma patient, melanoma was associated with a mean loss of approximately three years of life . Despite the gradual decline in the numbers of life years lost per patient and life years lived with disease, which is attributable to improving survival and a slightly higher age at diagnosis on

average, the burden of melanoma to society rose sharply between 1989 and 2006, mostly due to increases in incidence rates.

The low lifetime probability of an individual patient to die from his melanoma implies that most melanoma patients will live for many years after their diagnosis (YLD for men: 18 per 100 000 men and for women: 31 per 100 000 women and AYLM ranging from 20-30 years). The disability weight of 0.05 (0 perfect health to 1 death)[12] used when calculating the YLD is based on the prognosis of average melanoma patients. Disability weights for advanced melanoma are higher: 0.75 for metastasized disease and 0.81 for terminal disease. However, the vast majority of patients are not part of these groups. Previous research has shown that over 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 after diagnosis showed that most melanoma patients reported taking holidays to sunny destination less frequent than before their diagnosis, being more anxious about the deleterious effect of UV-light on their skin, and making more use of protective measures, including practicing less hobbies outside and wearing more protective clothing.[14] Moreover, a proportion of melanoma survivors reported difficulty in obtaining a life insurance or a mortgage. These findings suggest that the YLD might not fully capture the actual number of disability-adjusted life years patients live with their melanoma and its consequences; the disability weight should therefore probably be raised, in order to capture the true impact of melanoma on quality of life. It was for this reason that we also calculated the Years Lived with Melanoma (YLM), not taking the disability weight into account.

To our knowledge, we are the first to fully report on the burden of disease measures in melanoma and to estimate the probability for the population of the Netherlands of being diagnosed with melanoma. Dutch women had a probability of 1.9% of developing a melanoma during their lifetime, for men this was 1.6%. The cumulative incidence rates were slightly higher, because these do 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 to estimate the likelihood of a melanoma in the general population, in certain age and sex groups. Though a person's life time risk of developing a melanoma seemed relatively low, the Dutch Cancer Society has shown before that it is almost comparable to the likelihood of a woman developing ovarian cancer, non-Hodgkin lymphoma or lymphoma.[10]

In conclusion, this study has shown that the burden of melanoma in the Netherlands is high and increasing substantially, suggesting a need for health care policies to be adjusted in order to be able 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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10

General discussion

GENERAL DISCUSSION

Epidemiology

The incidence of melanoma has been rapidly rising, (chapter 1) and will continue to rise, at least until 2015 (chapter 2). The highest incidence rates for melanoma were reported for the populations living in Western and Northern Europe, most far away from the equator. It is one of the fastest increasing cancers in terms of incidence in the Western World, almost doubling between 1989 and 2005 in the Netherlands. Cutaneous melanoma might even become more frequent than squamous cell carcinoma, then becoming the most common malignancy after basal cell carcinoma in the Netherlands (chapter 1). [1-2]

The Netherlands cancer registry has an excellent track record in the nationwide registration of cancer incidence (>95% of skin cancers). It is quite unique that one of the eight comprehensive cancer centers in the Netherlands, the Eindhoven Cancer Registry even records the occurrence of newly diagnosed basal cell carcinomas since the early 70's.[1, 3] This wealth of data has led to many important publications on the epidemiology of skin cancer in the Netherlands in the last two decades.[4-7] Unfortunately, skin cancers are not always as well registered with cancer registries across Europe, as they do not all have a national coverage, especially not in the bigger countries of Europe like Germany, France, Poland , Italy and Spain. This leads to difficulties with the generalization of melanoma incidence between different countries, because there can be substantial regional variation, which is even present in a small country like the Netherlands.[8] Furthermore, there is delay of up to 3 years between recording with the cancer registry and publishing incidence numbers. Considering the rising trends in incidence, the most recently reported incidence rates are likely to be an underestimation of the real incidence rates in 2011. Prediction models such as those developed by Dyba et al [9-10], might be used to correct for the registration delay.

In order to estimate the incidence of melanoma one needs to have accurately reported melanoma diagnoses. Yet, some colleagues like G Welch (in the USA) question the existence of a true "melanoma epidemic" in the USA.[11] They state that the increase in melanoma rates is mainly attributable to thin melanomas in most western countries and mainly due to intensive screening by physicians and patients and over-diagnosis by pathologists. Quite a few in situ or thin melanomas would in fact not be true melanomas, and therefore inflate the incidence of melanoma [12]. But one could also say that the increase in thin melanoma is due to an increased awareness and patients' are being diagnosed at an earlier stage, as mortality due to melanoma is stabilizing in some countries. Furthermore, analyses across Europe showed that the incidence of cutaneous melanomas is also increasing in countries that have no screening programmes or well organized health care, thus making it unlikely that the incidence of melanoma has risen just due to intensive screening (chapter 2). Also, trend analyses of cutaneous malignancies showed that the UV related malignancies (including melanoma) increased significantly in contrast to

the non-UV related tumours, suggesting that the incidence rise of melanoma was largely due to excessive UV-exposure is real (Chapter 1).

Mortality rates have stabilized in some countries but seem to be increasing still among people over the age of 65 years.[1] Contrary to observations from many other Western countries, mortality rates are still increasing in the Netherlands. Recently, Hollestein et al. showed that the incidence of melanoma increased among all Breslow categories followed by a rise of melanoma mortality.[1] It is therefore likely that countries with a high mortality/incidence ratio, caused by higher incidence of more advanced stages of melanoma, still have a too low awareness for which there are limited treatment options available.

Patient perspectives of having been diagnosed with melanoma

Health Related Quality of Life

For decades outcome measures such as recurrence and survival have been used to evaluate treatment effects in patients with cancer. However, these traditional outcome measures do not fully capture patients' experiences. Since more and more cancers are treatable, cancer survivors are living longer with their (history of) cancer and the effects of its treatments and adverse events. Patient reported outcomes (PROs) are therefore becoming increasingly important as an addition to clinical outcomes in disease management. This is also true for melanoma patients of whom the majority (>70%) survives their melanoma and may live with this diagnosis, often for several decades (chapter 8). The mean age at diagnosis of melanoma patients is also relatively young (~ 53 years chapter 1) compared to that of other cancers. This, combined with the good prognosis of most melanoma patients implies that a high proportion of patients will live many years with the diagnosis of melanoma and that survivors of melanoma may live with a more or less chronic condition of varying severity that might affect the quality of their lives. Melanoma can have an impact on a patients' psychological well-being through anxiety for recurrence or progression, symptoms due to scarring, and be bothered by practical issues such as obtaining a mortgage of life insurance.

Evaluating PROs among melanoma patients, such as health related quality of life (HRQoL) might give a better impression of the influence a disease has on a patients' physical and physiological well-being.

The HRQoL of cancer patients' depends on many personal factors, such as a person's HRQoL before the cancer diagnosis, their personality (e.g., ability to cope with the disease burden) and a supportive environment. HRQoL impairment has also been reported to be associated with poor recovery, increased morbidity and even disease progression in melanoma patients.[13-14] Improving HRQoL may lead to more satisfied patients and potentially have survival benefit and lead to reduced health care consumption.

Our work on HRQoL of melanoma patients revealed that only since ten years there is an interest in accurately reporting HRQoL of melanoma patients (Chapter 3).[15] Furthermore, the few existing studies were limited by small sample sizes, selected patient populations, short term observations, and were based on patients treated in specialized centers. But the amount of large population-based studies on HRQoL in melanoma patients is slowly rising. We were one of the first to report the HRQoL in long term melanoma survivors (Chapter 4), showing that melanoma can have an impact on patients' up to ten years after diagnosis.[16] Most previous studies had used generic questionnaires only such as the SF-36 and the EORTC-QLQ C30. However, impact of melanoma seems to be fairly specific and is not driven by (long-term) adverse treatment effects that affect generic or cancer-specific HRQoL aspects. It is probably, therefore that several studies showed that HRQoL of melanoma patients, measured with generic questionnaires, seems comparable to that of normative populations [17]. People who survive cancer (or another life changing event) are likely to evaluate HRQoL more positively than those who never had cancer (which is called response shift)[18-19]. In contrast to outcomes from generic questionnaires, long term melanoma survivors reported a relatively large and persistent impact on the *melanoma specific questions* regarding life style changes (related to UV exposure and anxiety of UV exposure), practical issues such as getting insurances, and anxiety for relapse of melanoma. This discrepancy between generic and melanoma-specific items illustrate that reporting HRQoL impairment in melanoma patients suffered from the lack of a standardized melanoma specific HRQoL questionnaire and that the generic measures lack content validity for most melanoma survivors. This might be the reason why HRQoL studies have made use of a variety of different HRQoL questionnaires (Chapter 3). The FACT-M questionnaire was the only questionnaire validated in melanoma patients, but was developed for the use in clinical trials of patients with advanced disease.[20] Therefore, it focuses mainly on physical impairment which is more frequent in patients with advanced stage III or IV melanoma and very limited in patients with lower stages. However, over 70% of melanoma patients will be diagnosed with fairly thin melanoma and therefore have a relatively good prognosis.[1, 21] Moreover, these patients with low stage disease are treated with localized surgery (but increasingly followed by sentinel node exploration) that has few complications and little long term side effects.

In addition to TNM stage of melanoma and melanoma-therapies, other patient characteristics may affect a patients' HRQoL as well. Women report more extreme (positive and negative) impact of cancer on HRQoL than men. Secondly, men are diagnosed at a later age and with higher stages of melanoma; they might thus be less aware of the potential severity of being diagnosed with melanoma. Higher social economic status has also been associated with higher melanoma risk and better HRQoL.[22-23] Having a distressed personality (Type D personality) has a distinctive negative impact on ones' health status as measured by the SF-36 (Chapter 5). The awareness should be raised for these patients with a higher risk for impaired HRQoL as they might need extra care.

Overall, it should be noted that in order to correctly estimate HRQoL of melanoma patients, one should use a melanoma specific HRQoL questionnaire that is also applicable to early stage melanoma cancer patients and survivors, which is currently non-existent in a standardized form for population based use. We have identified gaps in the literature on HRQoL among melanoma patients (chapter 3) and demonstrated that generic HRQoL measures did not reflect the impact of melanoma well. However, we did not introduce a new melanoma specific HRQoL instrument, which is very much needed for daily practice and/or clinical trials. The development of such an instrument would require an evaluation of the various domains of HRQoL (e.g. psychological, physical, daily life) that might be influenced by the melanoma, based on previous studies, but more importantly to evaluate patient and physician's experiences on the impact of melanoma on patients' lives. Furthermore, the questionnaire should be a helpful instrument in daily medical practice, which measures the need of patients for additional care such as psychological support. Currently the Quality of Life Group of the European Organisation for Research and Treatment of Cancer (EORTC) is developing such a questionnaire based on our findings.

Follow-up and information provision

Physicians play an important role in how patients cope with their cancer diagnosis. Patients experience the most distress in the first few months during time of diagnosis and following treatment.[24-26] Patients are confronted with a potentially deadly disease and need to be informed on their treatment options and prognosis, to cope with their disease optimally. Unfortunately, it has been shown that patients are often not satisfied with the information they have received, especially information regarding diagnosis and treatment.[17, 27] A large study by Schlesinger, among 664 disease free melanoma patients found that two third of the patients desired more communication with someone who was involved in the treatment, care and attendance of the patient. Furthermore, more than half of these patients did not feel fully informed about their illness, which is comparable to reports of Dutch melanoma patients found in our study (Chapter 6). These uncertainties on what to expect of their diagnosis as well as of their treatment might result in additional distress among melanoma patients.

According to the Dutch melanoma Study Group guideline, providing patients with information regarding their disease, treatment and prognosis by their physicians, is one of the main reasons of the follow-up of melanoma patients. The Dutch melanoma guideline of 2005 recommends patients with a melanoma with a Breslow depth <1.00mm to have one follow-up visit after treatment to be fully informed about their disease and to receive instructions for self examination of the lymphnodes and skin . Francken et al. showed that patients who are well informed on how to recognize a (new primary) melanoma were more capable to detect recurrences of their melanoma or new primary melanomas.[28-29] This might lead to better survival and even to a reduction in number of follow-up visits needed, suggesting that informing patients properly is worthwhile. Subsequently, this may also lead to less distress.

Optimal delivery of information on a potentially lethal disease to a patient in distress is challenging. In our study more than half of the patients were not satisfied with the information they received on diagnosis and treatment (chapter 6). The communication between patients and their health care providers needs to be improved and structured.[17] A "survivorship care plan" can help to improve patient empowerment and has been introduced for several types of cancer patients to structure the follow-up care of cancer patients and to educate patients on their diagnosis and treatment.[30-31] A survivorship care plan is a personalized document of a patient with cancer, providing the patient with information regarding their diagnosis, treatment and prognosis. It also contains information on patient association groups and contact information of important health organizations. The information implemented in the survivorship care plan is carefully selected by physicians and patients who have considered the information helpful. This type of information provision might help to structure the information provision from physician to patient and it provides the patient with a quick reference-book. A survivorship care plan for melanoma patients and their relatives is likely to improve patients' HRQoL and reduce their distress.

The burden of melanoma on society

Melanoma has an impact on the individual patient (e.g., treatment, survival, and HRQoL) but also places a burden on society in terms of treatment costs, demands on the healthcare system, days of work lost due to treatment, years of life lost, etc. There is a large group of patients being diagnosed at a relatively young age, with a potentially deadly disease that affects one's life for many years. The amount of years living with the disease/diagnosis is increasing as patients are diagnosed at an earlier age and life-expectancy in general is increasing. This increasingly large group of patients will require health care and assistance in coping with their disease. Unfortunately, there is no consensus on how to deal with these patients and how to prevent unnecessary health care consumption as is illustrated by the diversity of follow up regimens (i.e., frequency and duration of follow up ranging from 2 to 4 times per year for 5 to 10 years) in the different national melanoma guidelines across the world.[32-33] The Dutch melanoma guideline is one of the most medically restrained reserved guidelines of Europe with one follow-up visit recommended 3 months after treatment for 70% of melanoma patients (those with stage I disease) and additional X-rays or (ultrasound) scans are made only when considered clinically necessary by the treating physician. Other European countries are used to more frequent follow-up visits and routine X-rays and CT-scans and even PET scans during follow-up. [34-35] Whether or not this difference in follow-up affects melanoma mortality remains unknown, as there is no study available that compares the different approaches of melanoma patients and their disease free survival. However, differences between guidelines with regards to follow-up frequency and contents of the visits are not likely to greatly influence patients' prognosis as survival studies did not show large differences in survival across most European countries.[1, 36-40] It is more likely that in time survival of melanoma patients will be influenced by treatment effects. [41-43] For

now, intense monitoring has the disadvantage of detecting false positive events that need further (invasive) investigations and makes patients unnecessarily worry about the outcome in the absence of a therapeutic consequence. This conservative attitude may change with the introduction of new effective therapies of advanced melanoma.

A large group of our patients (15-30%) reported to experience difficulty obtaining health insurance, life insurance or a mortgage. A few patients also reported to have felt the necessity to change or adapt their working environment (chapter 4), which can cause financial problems for an individual and affects society as well. A study in the United States by Seidler et al[44], assessing the economic burden on melanoma in 1858 people of 65 years and older, based on the SEER-Medicare data (Surveillance, Epidemiology, and End Results) showed that mainly late stage melanoma presented a significant economic burden in the elderly population, resembling the costs of colon cancer.

Mortality due to melanoma mainly occurs in this group of elderly people. In 2008, approximately 50% of people who died from malignant melanoma in the Netherlands were older than 65 years (www.ikcnet.nl). The sample of patients in the study by Seidler et al. accounted for 12% of elderly in the United States. Direct annual costs were estimated to be $ 249 million. Observed life-time costs per-patient were $ 28 210 (during an average survival of 26 months). Costs included: office visits and consultations, imaging by radiology, laboratory tests, visits to the emergency department, hospital stay and treatment costs (surgery, chemotherapy and external radiation). Costs were lower with lower stages. However, the costs made by patients in de US are difficult to compare with health care costs of other countries, as there are great differences in availability of health Insurance. It is for this reason that cost-effectiveness analysis should be done for each country separately.

Francken et al [45] found that only taking a medical history and performing a physical examination seems to be cost effective in patients with localized disease. Instructing patients to detect a recurrence themselves could be cost effective as they might need lesser follow-up visits. In her study patients were diagnosed at an earlier stage which is reducing the melanoma associated costs. However, economic evaluations often included direct medical costs (from an insurers perspective) but did not consider patients' HRQoL (i.e., QALYs were not calculated) making it difficult to construct informed choices based on these studies. It seems obvious that the aforementioned survivorship care plans are of even more interest if the frequency of follow up visits should be (further) reduced as it provides the opportunity to instruct patients on self-examination.

A well known measure of disease burden is QALY (Quality Adjusted Life Years), which includes both the quality and the quantity of years of life lived. In addition to QALY's, the WHO has recommended to use burden of disease expressed by disability adjusted life years (DALY) to

compare the impact of different diseases consistently. DALYs are time-based measures which combine years of life lost due to premature mortality and years of life lost due to time in states of less than full health.[46] Both concepts may be important in the allocation of limited health care resources. An advantage of measuring burden of disease compared to QALY is that DALYs are less influenced by the direct costs related to follow-up and treatments.

For melanoma we have now demonstrated that DALYs for burden of disease for melanoma are comparable with other more common cancers, such as breast cancer and prostate cancer (chapter 8). This is surprising as people in the general population but also physicians are considering cutaneous melanoma as a generally easy to treat disease with relatively good prognoses for most patients.

Estimating the degree of someone's disability in life is extremely difficult but necessary for evaluating the impact of different diseases on society. However, both QALY and DALY use generic QoL questionnaire in assessing the burden of disease. Therefore, a melanoma specific QoL instrument should be considered within weighing the disability factor for calculations of burden of diasease, as additional care to cope with melanoma contributes to the costs.

Currently, the disability weight of a disease in different phases of disease (diagnosis and treatment, preterminal, terminal phase), used for estimating DALYs is established by a group of experts, and weighed against disability caused by other cancers. This is quite strange as different types of cancer have different treatment options, different kind of follow-up and different survival rates. These characteristics of a disease will influence the psychological and physical well-being of a patient quite differently, depending on the type (and stage) of cancer. The experts of the burden of disease project also considered that the disability of a disease decreases immediately when a follow-up period is completed. Most likely this leads to an underestimation of the burden melanoma has on a patients' life. Therefore, we have calculated the years lived with melanoma (YLM), without correction of the disability weight, to get an impression of the actual years that patients live with melanoma. Additionally, we calculated the years of life lived with disability (YLD) with use of the disability weight 0.05 (from time of diagnosis until death). However, the disability weight should be raised considering that the current disability weight does not take HRQoL and influence on daily practice into account.

Future perspectives

With this thesis we have made the following contributions to the current epidemiology and quality of life research on melanoma: We have placed the incidence of melanoma into the perspective of the rising incidence rates of other skin cancers, showing that the incidence of melanoma rises more rapidly than other types of skin cancer. Our study showed that the incidence of all UV-related skin cancers has risen rapidly in the past years, whereas the non-UV related skin cancers exhibited a stable incidence. Trend analyses showed that the incidence of melanoma will continue to rise across different European countries with great differences

in availability of health care and registries between them. This shows that the incidence of melanoma is not just rising because of early detection and better registration or even over-detection as has been suggested previously. There is a need for effective health care campaigns that raise the awareness of the deleterious effects of UV-exposure. It is still of importance that over-exposure to UV-radiation is avoided.

The doubts regarding the existence of a real melanoma epidemic could also be reduced by improving cancer registration in the various areas of the European Union. Upon evaluating the cancer registration data, large variations between registries in coverage, registry of stage and survival data appeared, making it difficult to compare data from different countries in much more depth than age-adjusted incidence data. There is need for uniformity in registration of cancer data, such as registering melanoma incidence ideally according to the AJCC classification.[47] Furthermore, monitoring applied treatments and the occurrence of second primary melanomas would be an indicator of treatment effect and prognosis, which are difficult items to register but would offer a wealth of possibilities for cancer surveillance, particularly now that new treatments for advanced melanoma are expected to be introduced in the short term. Uniformity in registering cancer data would improve the generalizability and is of great importance for the introduction and evaluation of new treatments and follow-up plans. However, this uniformity of intense registration will bring additional costs which might be the reason why cancer registries are restricted in their way of registering new primary melanomas.

The increasing group of melanoma patients that require health care puts a great burden on health care providers. Considering HRQoL and burden of disease for melanoma, the burden that melanoma has on an individual patient as well on society is comparable to those of other more common cancers. The prognosis of most melanoma patients who are diagnosed at an early stage, is relatively good as illustrated by Hollestein et al[1] (relative survival of 77% for men and 88% for women), but still these patients have to deal with their diagnosis and the anxiety of recurrence for many years.[37] Melanoma can be seen as a chronic disease that has a great impact on daily life, as shown by the high number of years lived with disability (YLD) (chapter 8).

We have shown that measuring HRQoL of melanoma patients is diverse and influenced by several patient characteristics (e.g. sex, co-morbidity and personality). Generic QoL instruments seem to be unable to detect the true impact of melanoma on a patients' life. Furthermore, it seems that melanoma can have a long term (up to ten years) influence on a patients' well-being.(chapter 4) Health care providers should be aware that characteristics, such as sex and personality, of their patients could have negative influence on their treatment effects and that these patients might need additional care. They should also be aware that patients are affected by their diagnosis long after they have completed their treatment and/or follow-up and might need additional care. However, we have also detected a lack in communication between health

care providers and melanoma patients.[27] Improving communication might improve HRQoL of melanoma patients in general and allow health care providers notice the need for additional care earlier.[24, 48-49]

Including patients' perspectives in clinical decision making requires the creation of a melanoma specific HRQoL instrument that can be used in the entire spectrum of melanoma patients. This is now even more important because it allows to measure, in addition to using generic measures, the impact of the new and costly therapies for advanced melanoma, that recently appeared to be effective [41-43, 50] Moreover, such a questionnaire could be part of monitoring melanoma patients with or without a survivorship care plan. Increasing patient education on diagnosis, treatment and how to detect recurrence of melanoma by introducing a survivorship care plan is likely to improve patient care and to result in more satisfied patients while not increasing their health care consumption.

There is a tension between minimizing costs and being cost-effective. A restricted melanoma guideline, such as the Dutch melanoma guideline of 2005, is based on the limited available evidence on detecting recurrence of melanoma (i.e., disease progression) and melanoma survival. However, minimal follow-up may also lead to dissatisfaction with care, distress and reduced HRQoL in some melanoma patients. Increasing the frequency of follow up, which is relatively inexpensive, (and to a lesser extent expanding technical investigations during these visits) may result in more satisfied and better informed melanoma patients that are less affected by their melanoma.

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Summary
Samenvatting

Summary

Melanoma is one of the most common but also the most deadly type of skin cancer. It currently affects about 15% of the Caucasian population, and the incidence is increasing annually with 4-5%. The exact pathogenesis of melanoma is still unknown; both UV-exposure and genetic mutations seem to play a role, especially in familial melanoma. Primary treatment of melanoma is surgery, but therapy for metastasized melanoma is limited, leading to a poor prognosis. However >70% of melanoma patients will be diagnosed with a thin melanoma and have to live many years with the consequences of being diagnosed with melanoma. Therefore, it can have a great impact on a patients' quality of life but also on society, as this group of patient who require treatment and after care is rapidly increasing. This thesis describes the epidemiology of melanoma in the Netherlands and in Europe. It also describes patient perspectives on having been diagnosed with melanoma and the impact it has on an individual patient as on society.

EPIDEMIOLOGY

Chapter 2 describes the incidence and trends in incidence of all skin malignancies in the Netherlands between 1989 and 2005, based on data provided by the Netherlands Cancer Registry. A total of 356,620 skin tumors were diagnosed between 1989 and 2005. Excluding basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma, the remaining skin tumors constituted about 2% of all skin malignancies. The incidence of melanoma showed the steepest increase, with incidence rates approaching the European standardized incidence rate of SCC. The incidence of UV-related skin tumors increased significantly and more steeply than did those of other skin malignancies, which is contradicting with assumptions that the incidences are rising due to misdiagnosis and early diagnosis.

Predictions based on data provided by cancer registries across Europe, showed that the incidence of melanoma has risen and is expect to continue to do so until 2015 **(chapter 3)**. The highest incidence rates have been reported for countries in Northern and Western Europe. Estimations of the occurrence of more advanced stages of melanoma by calculating the mortality/incidence ratio showed that advanced stages of melanoma may be more frequent in Eastern European countries. Results showed that melanoma can be seen as a true epidemic across Europe.

PATIENTS' PERSPECTIVES OF HAVING BEEN DIAGNOSED WITH MELANOMA

Chapter 4 describes the findings of a systematic review on the available literature on health-related quality of life (HRQoL) and melanoma. Thirteen studies were selected out of 44 articles.

Studies were written in English and published between 2001 and 2008. Most studies assessed patients from specialised centres with varying, but relatively advanced, disease stages. The most commonly used instruments were the SF-36 and EORTC QLQ-C30. Studies showed that approximately one-third of melanoma patients experienced considerable levels of distress, mostly at the time of diagnosis and following treatment. Systemic therapies affected HRQoL negatively in the short term, but to a lesser extent in the long term. Health status and patients' psychological characteristics were associated with higher levels of HRQoL impairment. Furthermore, the impact of melanoma on patients' HRQoL seems to be comparable to that of other cancers.

In **chapter 5** we describe the findings of our cross-sectional study assessing the impact of melanoma on HRQoL of melanoma survivors from the general population in the south Netherlands. With use of the Eindhoven Cancer Registry, 699 melanoma survivors, diagnosed with melanoma between 1998 and 2008 were invited to participate. Eighty percent op patients were willing to participate. Patients were asked to fill out a postal survey that included the 36-Item Short-Form Health Survey (SF-36), Impact of Cancer (IOC) questionnaire and specific melanoma-related questions. The average age of respondents was 57.3 years, 62% was female and 76% was diagnosed with a thin melanoma (Brelow thickness < 2mm)

The SF-36 component scores of patients with melanoma were similar to those of the normative population. In a multiple linear regression model, stage at diagnosis, female sex, age, and comorbidity were significantly associated (P 0.05) with the physical and mental component scores. Women were significantly more likely to report higher levels of both positive and negative impact of cancer. Time since diagnosis, tumor stage, and comorbidity were significant predictors of negative IOC scores. Women also seemed to have adjusted their sun behaviour more often (54% vs. 67%; P 0.001) than men and were more worried about the deleterious effects of UV radiation (45% vs. 66%; P 0.001). In conclusion, the impact of melanoma seemed to be specific and more substantial in women, suggesting that they may need additional care to cope with their melanoma optimally.

Chapter 6 describes the findings of a cross-sectional study on the prevalence of Type D personality (the conjoint effects of negative affectivity and social inhibition) among melanoma survivors. Furthermore the study aimed to obtain insight into its effects on health status, impact of cancer and health care utilisation. All patients diagnosed with melanoma between 1998 and 2007 from three large regional hospitals in the Netherlands were selected. In total, 699 survivors, alive in January 2008, received a questionnaire including Type D personality scale (DS14), impact of cancer questionnaire (IOC) and SF-36, of whom 80% responded. Twenty-two percent of survivors were classified as having a Type D personality. They reported a clinically and statistically significant worse general health (57.8 vs. 75.6), social functioning (73.1 vs. 88.7), mental health (61.7 vs. 80.6), more emotional role limitations (67.8 vs. 89.4) and less vitality (54.5 vs. 72.8) than non-Type D patients. Additionally, they reported a statistically and clinically relevant higher impact of cancer on body changes, negative self-evaluation, negative outlook

on life, life interferences and health worry. Furthermore, they were more worried about the influence of the sun on their skin and acted accordingly. No differences were found in health care utilisation.

Type D personality seems to have a distinct negative impact on health status in melanoma survivors and might be an important factor to screen for in clinical practice. Giving special attention to these patients is important while they are more likely to experience a strong impact of cancer which cannot be explained by socio-demographical or clinical characteristics.

The perceived level of and satisfaction with received information was investigated in a cross-sectional study among 562 melanoma survivors, with use of the EORTC-QLQ-INFO26 questionnaire **(chapter 7)**. Melanoma survivors indicated that they received no information about different aspects of their disease (9-37%), treatment (38%) and aftercare (84-94%). More than half of the survivors (61%) were not or only a little bit satisfied with the amount of information received; a quarter of the patients indicated that they wanted to receive more information. The amount of information perceived was associated with a higher disease stage, less years since diagnosis, higher educational level and younger age, while satisfaction with information was associated with hospital of treatment, higher educational level and use of the internet.

Several areas of information disclosure are underexposed and a majority of the melanoma survivors is not satisfied with the received information. More patient-tailored information disclosure is needed in order to give every patient the most optimal information. In addition, attention must be paid to patient characteristics that might influence information disclosure. A good opportunity for appropriate information disclosure is the implementation of a survivorship care plan.

In **chapter 8** we discuss patients' perspectives of melanoma patients on follow-up according to the guideline of 2005, in a Dutch population from the south-east area of the Netherlands. The patients' satisfaction over said follow-up was also taken into account. Melanoma survivors were questioned about treatment, symptoms, impact on daily life and follow-up. Sixteen patients with multiple melanomas were excluded as it could influence the reported outcomes. Of 546 respondents, 418 survivors were still under surveillance for their melanoma. The average time since diagnoses was 4 years and 71% had stage I melanoma. Almost 80% of patients with a Breslow thickness <1mm, reported more frequent follow-up visits than recommended by the Dutch melanoma guideline of 2005. Only 5% of the patients wanted to reduce their amount of follow-up visits. Most patients were under supervision of a dermatologist. They reported that physical examination, lymph node palpation and/or scar inspection did not regularly occur in 25%, 11% and/or 20%, respectively. These proportions were significantly higher among other specialisms.

BURDEN OF MELANOMA

Chapter 9 describes the burden of disease in Dutch melanoma patients. Burden of disease describes loss of health and death due to a disease which had not been adequately studied for melanoma.

For this study age- and gender-specific incidence data from all patients diagnosed with melanoma in the Netherlands between 1989 and 2006 were obtained from the Netherlands Cancer registry. Mortality numbers and rates 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 of Life lived with 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.

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.

In **chapter 10** the findings of the studies presented in this thesis are discussed and placed into perspective. The value of registering cancer incidence is discussed and whether or not melanoma can be seen as a true epidemic. The diversity in patient characteristics that seems to influence the HRQoL of melanoma patients, are making it difficult to establish the HRQoL of melanoma patients in population based studies. The need for a melanoma specific questionnaire to capture the impact of melanoma on a patients' live, is pointed out. Also, the satisfaction of melanoma patients with the received follow-up and information on treatment and diagnoses is discussed. The discussion ends with future perspectives that include the development of a melanoma specific questionnaire which can be used in clinical practice and population-based studies. Moreover, the development of a possible survivorship care plan is suggested to improve the communication between melanoma patients and their health care providers.

Samenvatting

Het melanoom is een van de meest voorkomende en een van de meest dodelijke vormen van huidkanker. Ongeveer 15% van de blanke bevolking wordt gediagnosticeerd met een melanoom, deze incidentie stijgt met 4-5% per jaar. De exacte pathogenese van een melanoom is nog steeds onbekend, zowel blootstelling aan UV-straling als genetische mutaties lijken een belangrijke rol te spelen. Chirurgie is eerste keus behandeling, maar de behandeling van het gemetastaseerde melanoom is beperkt, wat leidt tot een slechte prognose. Echter, meer dan 70% van de patiënten wordt gediagnosticeerd met een dun melanoom en zal nog vele jaren met de gevolgen van een melanoom leven. Een melanoom kan dus veel invloed hebben op de kwaliteit van leven van en individuele patiënt, maar ook op de algemene bevolking wanneer deze mensen meer nazorg nodig hebben.

Dit proefschrift beschrijft de epidemiologie van melanoom in Nederland en in Europa. Tevens wordt het perspectief van patiënten gediagnosticeerd met een melanoom belicht en invloed die melanoom heeft op het dagelijks leven van de patiënt als wel op de maatschappij.

EPIDEMIOLOGIE

In **hoofdstuk 2** beschrijven we de incidentie en trends in incidentie van alle maligne huidtumoren in Nederlands gediagnosticeerd van 1989-2005, gebaseerd op data van de Nederlandse Kankerregistratie. In totaal werden 356 620 huidtumoren gediagnosticeerd tussen 1989-2005. De incidentie van zeldzame huidtumoren bedroeg 2%. The incidentie van melanoom toonde de sterkste stijging met incidentie rates die de incidentie rates van het plaveiselcelcarcinoom sterk benaderen. De incidentie van UV- gerelateerde tumoren toonde sterkere toename in incidentie dan andere maligniteiten. Dit spreekt tegen dat de toename in incidentie van huidtumoren veroorzaakt zou worden door verkeerde diagnoses en diagnoses van een vroeg stadium melanoom.

Berekeningen gebaseerd op data aangeleverd door verschillende kankerregistraties in Europa **(hoofdstuk 3)**, laten zien dat de incidentie van melanoom is toegenomen en zal blijven toenemen tot 2015. De hoogste incidentiecijfers werden gezien voor Noord en West-Europa. Schattingen van het voorkomen van gemetastaseerde melanomen door de mortaliteit/ incidentie ratio uit te rekenen, laten zien dat stadium III en IV melanomen mogelijk meer voorkomen in Oost Europese landen.

HET PERSPECTIEF VAN PATIËNTEN OVER GEDIAGNOSTICEERD ZIJN MET EEN MELANOOM

Hoofdstuk 4 beschrijft de beschikbare literatuur over kwaliteit van leven (KvL) van melanoompatiënten. Er werden 13 studies geselecteerd van 44 artikelen. De studies waren geschreven in het Engels en gepubliceerd tussen 2001 en 2008. De meeste studies beschreven resultaten van patiënten van gespecialiseerde klinieken met verschillende, maar relatief vaak vergevorderde stadia van melanoom. The meeste frequent gebruikte vragenlijsten waren de SF-36 en de EORTC QLQ-C30. De studies beschreven dat ongeveer een derde van de melanoompatiënten hoge mate van stress beleven vooral tijdens de periode rondom diagnose en behandeling. Systemische therapieën beïnvloeden KvL voornamelijk negatief op korte termijn, maar minder op lange termijn. Gezondheidsstatus en de psychologische karakteristieken van een patiënt waren geassocieerd met beperkte KvL. Tevens lijkt de invloed van melanoom op KvL van patiënten net zo van invloed te zijn als andere kankers.

In **hoofdstuk 5** wordt een cross-sectionele studie beschreven die de invloed van melanoom op KvL van melanoompatiënten uit de algemene bevolking in het zuiden van Nederland beschreven. Met behulp van het Integraal Kankercentrum Zuid in Eindhoven werden 699 melanoompatiënten, die gediagnosticeerd waren met een melanoom tussen 1998 en 2008 aangeschreven. Tachtig procent van de patiënten was bereidt om mee te werken aan de studie. Patiënten werd gevraagd om een vragenlijst in te vullen die de 36-Item Short-Form Survey (SF-36) en de Impact of Cancer (IOC) vragenlijsten bevatten en een aantal melanoomspecifieke vragen. Patiënten waren gemiddeld 57,3 jaar, 62% was vrouw en 76% was gediagnosticeerd met een dun melanoom (Breslowdikte < 2mm). De SF-36 component scores van melanoompatiënten ware vergelijkbaar met de scores van de normatieve populatie. Ine en multipele lineaire regressie model waren stadium, vrouwelijk geslacht, leeftijd en comorbiditeit significant geassocieerd met de lichamelijke en mentale component scores van de SF-36. Vrouwen rapporteerden significant hogere levels op zowel de negatieve als positieve schalen van de impact of cancer vragenlijst. Tijd sinds diagnose, stadium en comorbiditeit waren significante voorspellers van negatieve invloed van kanker. Vrouwen rapporteerden dat ze vaker hun zongedrag hadden aangepast en meer angst te hebben voor de schadelijke effecten van de zon dan mannen. Een melanoom heeft een specifieke invloed op het leven van een patiënt en lijkt invloed te hebben op vrouwen. Dit suggereert dat zij mogelijk meer behoefte hebben aan nazorg om te kunnen omgaan met de diagnose melanoom.

Hoofdstuk 6 beschrijft de resultaten van een cross-sectionele studie naar de prevalentie van Type D persoonlijkheid (de gelijktijdige aanwezigheid van zowel negatieve affectiviteit en sociale inhibitie) onder melanoompatiënten. Tevens was het doel om meer inzicht te krijgen in de invloed van gezondheidsstatus, invloed van kanker en consumptie van de gezondheidszorg. Alle patiënten gediagnosticeerd met een melanoom tussen 1998 en 2007 in een van de 3 regionale ziekenhuizen in Nederlands werden geselecteerd voor deelname. In totaal, werd

een vragenlijst verstuurd aan 699 overlevenden. Tachtig procent van de patiënten vulden een vragenlijst in die de Type D personality scale (DS14), impact of cancer en SF-36 vragenlijsten bevatten. Tweeëntwintig procent van de overlevenden werden geclassificeerd als het hebben van een Type D persoonlijkheid. Deze patiënten rapporteerden klinisch en statistisch significant slechtere scores op de *general health, social functioning, mental health*, *emotional role limitations* en *vitality* schalen van de SF-36 dan patiënten die geen Type D persoonlijkheid hadden. Verder, rapporteerden zij klinisch en statistisch significant hogere scores op impact of cancer schalen (*body changes, negative self-evaluation, negative outlook on life, life interferences and health worry*). Ook waren zij angstiger voor de schadelijke effecten van UV-licht op hun huid en paste hun zongedrag daarop aan. Er werden geen verschillende gevonden voor gezondheidszorg-consumptie.

Een Type D persoonlijkheid lijkt een negatieve invloed te hebben op gezondheidsstatus in overlevenden van een melanoom en kan mogelijk een belangrijke factor zijn bij de screening in de dagelijke praktijk. Speciale aandacht voor deze patiënten is belangrijk, aangezien een melanoom meer van invloed kan zijn op deze patiënten.

Met behulp van de EORTC-QLQ-INFO26 vragenlijst werd de hoeveelheid informatie verkregen door 562 melanoompatiënten en de tevredenheid met de informatie onderzocht **(hoofdstuk 7)**. Patiënten gaven aan dat zij geen informatie hadden ontvangen betreffende hun ziekte (9-37%), behandeling (38%) en nazorg (84-94%). Meer dan de helft van de patiënten (61%) was niet tot een klein beetje tevreden met de hoeveelheid informatie; een kwart van de patiënten wilden meer informatie. De verkregen hoeveelheid van informatie was geassocieerd met hogere stadia van melanoom, minder jaren sinds diagnose, hoger opleidingsniveau en jongere leeftijd. Tevredenheid met de informatie was geassocieerd met het ziekenhuis die de behandeling uitvoerden, hoger opleidingsniveau en gebruik van internet.

Meerdere gebieden van de informatievoorziening zijn onderbelicht en een meerderheid van melanoompatiënten is ontevreden met de verkregen informatie. Er is behoefte aan meer informatie toegespitst op patiënten om iedere patiënt te voorzien van de meest optimale informatie. Ook dient er aandacht besteed te worden aan de karakteristieken van een patiënt die van invloed kunnen zijn op de behoefte aan informatie. Dit biedt mogelijkheid aan het implementeren van een survivorship care plan.

In **hoofdstuk 8** wordt het perspectief van patiënten in het zuidoosten van Nederland met follow-up volgens de richtlijn van 2005 beschreven. De tevredenheid van patiënten over hun follow-up werd hierbij ook in acht genomen. Melanoompatiënten werd gevraagd naar hun behandeling, symptomen, invloed op dagelijks leven en follow-up. Zestien patiënten met meerdere melanomen werden geexcludeerd, aangezien dit van invloed kon zijn op de follow-up. Van de 546 deelnemers waren 418 patiënten nog steeds onder controle ten tijde van het invullen van de vragenlijst. De gemiddelde tijd sinds diagnose was 4 jaar en 71% had een stadium I melanoom. Bijna 80% van de patiënten met een melanoom met een Breslowdikte <1mm, rapporteerden meer follow-up bezoeken dan geadviseerd in de richtlijn van 2005.

maar 5% van de patiënten wilden het aantal controlebezoeken verminderen. De meeste patiënten waren on controle bij een dermatoloog. Zij rapporteerden dat volledig inspectie van de huid (25%), onderzoek van de lymfeklieren (11%) en/of inspectie van het litteken (20%) niet standaard werd verricht. Deze aantallen waren significant hoger bij andere specialismen.

ZIEKTELAST DOOR MELANOOM

Hoofdstuk 9 beschrijft *burden of disease* in melanoompatiënten. *Burden of disease* beschrijft het verlies van gezondheid en sterfte door een ziekte, dit was nog niet adequaat onderzocht voor melanomen. Voor deze studie werden leeftijd- en geslachtsspecifieke data van alle patiënten gediagnosticeerd met een melanoom tussen 1998 en 2006 verkregen van de Nederlandse Kankerregistratie. Mortaliteitdata werden verkregen van het Bureau van Statistiek. Met behulp van DevCan software werden levenstabellen berekend die de kans op het krijgen van een melanoom vergaven per 5-jaarsinterval. De standaard levensverwachting voor mannen en vrouwen per 5-jaarsleeftijdsgroep werd geschat met behulp van DISMOD software. Het aantal jaren geleefd met een melanoom (YLD) en het aantal jaren verloren door vroege sterfte (YLL) door een melanoom weren berekend met deze levenstabellen en levensverwachtingen. De *disability adjusted life years (DALY)*, een generieke maat voor *burden of diasease,* werd berekend door YLD en YLL bij elkaar op te tellen. De incidentie van melanoom was bijna verdubbeld van 1989 tot 2006 (cumulatieve incidentie rate variërend van 1.03-1.31% to 2.02-2.11%). De invloed van melanoom op de maatschappij berekend als *burden of disease* nam snel toe tussen 1989 en 2006. gemiddeld leefden patiënten 21,6 -28,2 jaar met een diagnose melanoom. Melanoom resulteerden in een verlies van 17,8-20,1 levensjaren voor een leeftijd van 95 jaar, bij mensen die overleden waren door een melanoom.

In **hoofdstuk 10** worden de resultaten van dit proefschrift besproken en in perspectief geplaatst. De waarde van het registerend van de incidentie van kanker wordt besproken en of melanoom gezien kan worden als een epidemie. De diversiteit aan patiëntkarakteristieken die van invloed lijken te zijn op de KvL van patiënt, maken het moeilijk om de KvL van melanoompatiënten in de algemene bevolking vast te stellen. De behoefte voor een melanoom-specifieke vragenlijst die de invloed van een melanoom of het leven van een patiënt kan vaststellen wordt belicht. Ook wordt de tevredenheid van patiënten met de verkregen informatie over hun ziekte en de behandeling besproken. De discussie wordt beëindigd met de perspectieven voor de toekomst met het implementeren van een melanoom-specifieke vragenlijst die gebruikt kan worden voor trials maar ook in de dagelijkse praktijk. Tevens wordt ook mogelijkheid van een survivorship care plan besproken als hulpmiddel om de communicatie tussen patiënten hun behandelaars te verbeteren.

Dankwoord

Dankwoord

En dan nu het hoofdstuk wat voor veel mensen waarschijnlijk het eerste en meteen het laatste hoofdstuk is wat ze van dit proefschrift zullen lezen. Ik neem het deze mensen niet kwalijk, want dat geeft mij wel de gelegenheid om een aantal mensen goed te bedanken. Tijdens een promotietraject leer je vooral hoe belangrijk goede samenwerking en begeleiding is. Ik heb het geluk gehad te mogen profiteren van een samenwerking tussen experts in de epidemiologie en dermatologie, wat goed te zien is aan de lijst met promotoren en copromotoren.

Professor Neumann, ik heb het u niet gemakkelijk gemaakt. Ook na mijn overstap naar de interne geneeskunde heeft u mij altijd het idee geven dat ik welkom ben. Bedankt voor uw geduld en begrip.

Professor Jan Willem Coebergh, het is een eer om een van uw eerste promovendi te zijn net na u "pensioen". Heel erg bedankt voor de altijd kritische beoordeling van mijn manuscripten en kennismaking met experts op het gebied van huidkanker.

Les 1 bij promoveren is, zoek een goede begeleider. Ik had er teveel om uit te kiezen.

Tamar, bedankt voor de goede en vooral gestructureerde begeleiding. Het was fijn om te weten dat je deur altijd open stond voor advies. Je leerde mij nooit de klinische blik uit het oog te verliezen bij onderzoek. Dank je wel.

Lonneke, bij jou is het mede allemaal begonnen. De basis van epidemiologie en statistiek heb ik bij jou geleerd. Dankzij jouw hulp bij de strakke tijdsplanning, hebben Darren en ik een vliegende start kunnen maken met ons afstudeeronderzoek wat de basis is voor dit proefschrift. Ik heb het altijd een enorm fijne samenwerking gevonden.

Esther, je bent mijn paranimf, maar ik vind dat jij zeker ook in het lijstje hoort van copromotoren. Je bent erg belangrijk geweest bij de laatste stukken van dit proefschrift en wanneer Tamar het te druk had was je altijd beschikbaar voor het beantwoorden van vragen, advies en gezelligheid. Zonder jouw begeleiding was dit proefschrift zeker niet tot een goed einde gekomen, dank je wel.

Een promotie gaat pas door, als de kleine commissie ook het proefschrift goedgekeurd heeft. Ik wil daarom de leden van de kleine commissie, Prof.dr. van Busschbach, Prof.dr. Eggermont en Prof.dr. Bergman bedanken voor het kritisch beoordelen van dit proefschrift in een zeer snel tempo.

Minstens zo belangrijk als goede begeleiding, zijn fijne collega's die altijd voor je klaar staan en waarmee je kunt discussiëren over belangrijke en onbelangrijke zaken. Ik wil daarom in het bijzonder mijn kamergenootjes van GK-016 bedanken. Marlies, Suzan, Sophie, Robert en Enes, jullie waren echt enorm fijne collega's. Behulpzaam en altijd in voor een grapje. We hebben vele uren samen doorgebracht in een veel te kleine kamer, maar ik heb nooit behoefte gehad om te gaan verhuizen. Ik kon altijd rekenen op jullie kritische beoordeling van analyses, artikelen en presentaties. Bedankt voor alle gezelligheid en de nodige afleiding.

Tijd is o zo kostbaar bij het afronden van een proefschrift, ik wil daarom mijn opleider Prof. van Saase bedanken om mij in de gelegenheid te stellen dit proefschrift tot een goed einde te brengen, maar zeker ook mijn collega's van de interne geneeskunde die hier alle begrip voor hadden. Bedankt voor jullie steun en belangstelling.

Darren, mijn partner in crime. Vijf maanden, samen in de trein naar Eindhoven, samen ziekenhuizen bezoeken, samen vragenlijsten versturen, samen invoeren, samen analyses doen, samen schrijven, samen achter de computer in de computerzaal of bij het IKZ. Het is een wonder dat we elkaar niet in de haren gevlogen zijn. We waren een goed team. Ik heb genoten van onze samenwerking.

Monique, mijn 2e paranimf(je) en goede vriendin, bedankt voor al je steun, hulp en de nodige afleiding. Heel veel succes met het afronden van je eigen promotie!

Last but not least, mijn ouders en broertje. Bedankt voor jullie altijd luisterend oor, steun en hulp, en dat terwijl jullie vaak geen idee hadden waarvoor het nou was. Hopelijk is het nu iets duidelijker. (Mam, wees gerust er zit ook een Nederlandse samenvatting in dit boekje ;))

List of publications

List of publications

Cornish D, Holterhues C, van de Poll-Franse LV, Coebergh JW, Nijsten T.
A systematic review of health-related quality of life in cutaneous melanoma. Ann Oncol. 2009 Aug;20 Suppl 6:vi51-8.

Holterhues C, Cornish D, van de Poll-Franse LV, Krekels G, Koedijk F, Kuijpers D, et al. Impact of melanoma on patients' lives among 562 survivors: a Dutch population-based study. Arch Dermatol. 2011 Feb;147(2):177-85.

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

Husson O, Holterhues C, Mols F, Nijsten T, van de Poll-Franse LV. Melanoma survivors are dissatisfied with perceived information about their diagnosis, treatment and follow-up care. Br J Dermatol. 2010 Oct;163(4):879-81.

Mols F, Holterhues C, Nijsten T, van de Poll-Franse LV. Personality is associated with health status and impact of cancer among melanoma survivors. Eur J Cancer. 2010 Feb;46(3):573-80.

Holterhues C, Hollestein L, Coeberg JW, Nijsten T, Pukkala E, Holleczek, Truggvadottir L, Comber H, Bento, MJ, Diba, CS, Primic Zakelj M, Izarzugaza MI, Gonzalez JP, Marcos-Gragera, R, Galceran J, Aicua EA, Schaffear R, Pring A, de Vries E. Trends in incidence and predictions of cutaneous melanoma across Europe up to 2015. Submitted

Holterhues C, van de Poll-Franse, de Vries E, Neumann HAM, Nijsten T. Melanoma patients receive more follow–up care than current guideline recommendations: A study of 546 patients from the general Dutch population.
JEADV, accepted

Holterhues C, Nijsten T, Koomen ER, Nusselder W, Karim-Kos HE, de Vries E .
Burden of disease in Dutch melanoma patients, 1989-2006. Submitted

Holterhues C, De Vries E, Nijsten T. De epidemiologie van huidkanker; zorg om de zorg. Nederlands Tijdschrift voor Dermatologie en Venereologie. 2009;19(8).

Curriculum Vitae

Curriculum Vitae

Cynthia Holterhues werd geboren op 19 augustus 1984 in Rotterdam. In 2002 behaalde zij haar VWO diploma aan de OSG De Ring van Putten in Spijkenisse waarna zij begon aan de studie Geneeskunde aan de Erasmus Universiteit te Rotterdam. Na haar reguliere co-schappen verrichtte zij haar afstudeeronderzoek naar " Health-Related Quality of Life of melanomapatients", onder supervisie van Tamar Nijsten en Lonneke van de Poll-Franse. Het afstudeeronderzoek betrof een samenwerking tussen de afdeling Dermatologie van het Erasmus MC in Rotterdam en het Integraal Kankercentrum Zuid, te Eindhoven. De resultaten hiervan bedragen een groot deel van dit proefschrift. Na het afstudeeronderzoek haalde zij haar doctoraalexamen in juli 2008 en vervolgens het artsexamen in november 2008. Aansluitend werkte zij als arts -onderzoeker op de afdeling Dermatologie van het Erasmus MC, waar zij in november 2008 begon aan het huidige proefschrift onder leiding van Tamar Nijsten, Lonneke van de Poll-Franse en Esther de Vries. In januari 2011 werd zij aangenomen voor de opleiding interne geneeskunde van het Erasmus MC, te Rotterdam.

PhD Portfolio Summary

Burden of Melanoma

PhD Portfolio Summary

SUMMARY OF PHD TRAINING AND TEACHING ACTIVITIES

Name PhD student:	Cynthia Holterhues
Erasmus MC Department:	Dermatology
Research School:	NIHES
PhD period:	November 2008 – October 2011
Promotors:	Prof.Dr. H.A.M. Neumann
	Prof. Dr. Coebergh
Supervisor:	Dr. T.E.C. Nijsten
	Dr. L.V. van de Poll-Franse

1. PHD TRAINING	Year	Workload (Hours/ECTS)
General academic skills		
Biomedical English Writing and Communication	2009	4 ECTS
Research skills		
NIHES course: Biostatistics for Clinicians	2009	1 ECTS
EORTC programme: Quality of Life, Symptom Research and Patient Reported Outcomes in Cancer Clinical trials	2009	20 hours
Minicursus Methodologie van patiëntgebonden onderzoek en voorbereiding van subsidieaanvragen	2009	8 hours
Basiscursus regelgeving en organisatie voor klinische onderzoekers (BROK)	2009	8 hours
Presentations		
Holterhues C, Cornish D, van de Poll-Franse LV, Nijsten T. "Impact of melanoma on patients' lives: cross-sectional population based study in the South Netherlands". Presented at the Dermato-Epidemiology Association (IDEA) congress, September 7, 2008, Nothingham.	2008	1 ECTS

Holterhues C, van de Poll-Franse LV, Nijsten T. "Quality of life in melanoma patients". Presented at EGAM meeting, EORTC melanoma group, March 20, 2009, Brussels.	2009	1 ECTS
Holterhues C. "Health care utilisation of melanoma patients in the general population". Presented at the 7th World Congress on Melanoma and 5th congress of the European Association of Dermato-Oncology (EADO), May 16, 2009, Vienna.	2009	1 ECTS
Holterhues C. " Kwaliteit van leven en follow-up van melanoompatiënten". Presented at VIKC Nederlandse Melanoomwerkgroep, November 11, 2009, Utrecht.	2009	1 ECTS
Holterhues C. Kwaliteit van leven van melanoom-patiënten". Presented at "Huidfondsmiddag", Rotterdam, November 18, 2009.	2010	1 ECTS
Holterhues C. "Melanoompatiënten frequenter opgevolgd dat geadviseerd door de richtlijn: een studie onder 546 patiënten uit de algemene bevolking". Presented at the 11de wetenschappelijke jaarvergadering van de Nederlandse Vereniging voor Experimentele Dermatologie, February 5 2010, Lunteren.	2010	1 ECTS
Holterhues C, Nijsten T. " De huidkankerepidemie. Storm in een glas water?". Presented at thema-avond IKW-werkgroep huitumoren, April 12, 2010, Leiden.	2010	1 ECTS
Holterhues C, de Vries E. " Trends in incidence of cutaneous malignant melanoma in Europe: analysis of population based cancer registry data". Presented at 6th EADO congress, June 16, 2010, Athens. (invited speaker)	2010	1 ECTS
Holterhues C, de Vries E, Nijsten T. "Incidence and trends of cutaneous malignancies in the Netherlands, 1989-2005". Presented at the 6th EADO congress, June 16, 2010, Athens.	2010	1 ECTS

International conferences

Dermato-Epidemiology Association (IDEA) congress, September 7, 2008, Nothingham.	2008	1 ECTS
7th World Congress on Melanoma and 5th congress of the European Association of Dermato-Oncology (EADO), May 16, 2009, Vienna.	2009	1 ECTS
EGAM meeting, EORTC melanoma group, March 20, 2009, Brussels.	2009	1 ECTS
6th EADO congress, June 16, 2010, Athens	2010	1 ECTS

Seminars and workshops

PhD day, Erasmus MC	2009	6 hours
Success in research: Learn from the experts	2009	1 hour
Publishing and Acceptance Criteria for Scientific Journals, by Ian Cressie	2009	2 hours
CPO autumn symposium 2009, Cost- Effective Interventions in Health Care: From Evaluation to Application	2009	2.5 hours

Other

"Oncologie is de parel van de Ardennen", Spa, May 30 - June 1, 2010	2010	3 days

Occasional reviewer for:

Archives of Dermato-Venereologica	2009	4 hours
Journal of Investigative Dermatology	2010	4 hours
European Journal of Cancer	2010	4 hours
Journal of the American Academy of Dermatology	2010	4 hours

2. TEACHING ACTIVITIES

Assisting/ supervising junior researchers:

S.C. Flohil, MD, PhD student Dermatology, Erasmus MC Rotterdam 2010. Thesis on basal cell carcinoma

R.J.T. van der Leest, PhD student and resident Dermatology, Erasmus MC Rotterdam, 2010. Thesis on melanoma

Cynthia Holterhues

BURDEN OF MELANOMA