Magdalena Claeson, MD

EPIDEMIOLOGY OF CUTANEOUS MALIGNANT MELANOMA IN WESTERN SWEDEN

Department of Dermatology and Venereology,
Institute of Clinical Sciences,
Sahlgrenska Academy,
University of Gothenburg

Epidemiology of cutaneous malignant melanoma in Western Sweden

magdalena.claeson@vgregion.se

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"AN OUNCE OF PREVENTION IS WORTH A POUND OF CURE."

– Benjamin Franklin

CONTENTS

ABSTRACT	7
SAMMANFATTNING PÅ SVENSKA	9
LIST OF PAPERS	11
ABBREVIATIONS	13
DEFINITIONS IN SHORT	15
1. INTRODUCTION	17
1.1 EPIDEMIOLOGY OF MELANOMA	17
1.2 CAUSES AND RISK FACTORS	20
1.3 PREVENTION	27
1.4 STAGING AND CLASSIFICATION	35
1.5 PROGNOSIS	39
1.6 MANAGEMENT	40
1.7 HEALTH CARE ECONOMICS AND HEALTH SYSTEMS MANAGEMENT	41
2. AIMS	47
3. METHODS	49
3.1 THE SWEDISH CANCER REGISTRY	49
3.2 THE SWEDISH MELANOMA REGISTRY	49
3.3 THE SWEDISH CAUSE OF DEATH REGISTRY	50
3.4 NATIONELL MILJÖHÄLSOENKÄT 2007 – THE SUN EXPOSURE SURVEY	50
3.5 STUDY DESIGN	51
3.6 ETHICAL CONSIDERATIONS	54
4. RESULTS	57
4.1 STUDY I	57
4.2 STUDY II	57
4.3 STUDY III	58
4.4 STUDY IV	58
5. DISCUSSION & METHODOLOGICAL CONSIDERATIONS	61
5.1 STUDY I	61
5.2 STUDY II	62
5.3 STUDY III	63
5.4 STUDY IV	64
6. CONCLUSIONS	67
7. FUTURE PERSPECTIVES	69
7.1 GEOGRAPHICAL DIFFERENCES IN UVA AND UVB RADIATION LEVELS	69
7.2 MULTIPLE PRIMARY MELANOMAS IN RISK PREDICTION MODELS	69
7.3 PREDICTORS OF MORTALITY FOR THIN MELANOMAS	69
7.4 FURTHER USE OF SYSTEM DYNAMICS	69
8. ACKNOWLEDGEMENTS	73
9. REFERENCES	77
10. PAPERS	91
I. INCIDENCE OF CUTANEOUS MELANOMA IN WESTERN SWEDEN, 1970–2007	
II. MULTIPLE PRIMARY MELANOMAS: A COMMON OCCURRENCE IN WESTERN SWEDEN	
III. LETHAL MELANOMAS: A POPULATION-BASED REGISTRY STUDY IN WESTERN SWEDEN FROM 1990-2014	
IV. MODELLING THE FUTURE: SYSTEM DYNAMICS IN THE CUTANEOUS MALIGNANT MELANOMA CARE PATHWAY	

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ABSTRACT

The incidence of cutaneous malignant melanoma (melanoma) has been rising worldwide for the past decades, causing a major public health problem. The overall aim for this thesis was to study the epidemiology of melanoma in Western Sweden and to suggest secondary preventive interventions.

In study I, data from the Swedish Cancer Registry demonstrated that the melanoma incidence in Western Sweden quadrupled among men and tripled among women between 1970-2007. Coastal areas and the city of Gothenburg showed a higher incidence than inland areas. Analysis of meteorological maps of Western Sweden and a sun exposure survey showed that this could be due to high annual average duration of sunshine and high sun exposure on holidays abroad. In studies II and III, data from the Swedish Melanoma Registry and the Swedish Cause of Death Registry were analysed. Study II showed that, during 1990-2013, 7.4% of all melanoma patients developed multiple primary melanomas. Subsequent melanomas presented with a higher proportion of melanoma in situ. Study III demonstrated that thin melanomas (≤1 mm Breslow) constituted 55.2% of all invasive melanomas and accounted for 14.7% of all melanoma deaths, between 1990-2014. Significantly poorer survival was identified for ulcerated melanomas 0.26-1 mm Breslow and for non-ulcerated melanomas 0.76-1 mm Breslow. In study IV, a system dynamics computer model was developed that projected the number of future melanoma cases. The model compared five plausible future scenarios, showing that after ten years, improved overall secondary prevention would have resulted in a shift towards thinner melanomas.

This thesis concluded that the high incidence of melanoma in Western Sweden justifies a focus on preventive interventions to this area. Patients and physicians need to be alerted about the risk of multiple primary melanomas. The identified subgroup of lethal thin melanomas suggests that these patients may benefit from closer surveillance in follow-up programmes. Lastly, system dynamics modelling proved to be a valuable tool, which can help policymakers select the preventive interventions with the greatest impact.

Keywords: Cutaneous malignant melanoma, Epidemiology, Prevention, Incidence, Mortality, Multiple primary melanomas, Thin melanomas, System dynamics modelling

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SAMMANFATTNING PÅ SVENSKA

MELANOMEPIDEMIOLOGI I VÄSTSVERIGE

Malignt melanom i huden blir allt vanligare i ljushyade befolkningar runt om i världen. Ökningen förklaras delvis av mer UV-exponering i befolkningen, t ex fritidsexponering för sol, förändrade klädvanor, solsemestrar och solarier. Sverige tillhör de länder i världen som har allra högst incidens av melanom. Landet har också en mycket hög kostnad för hudcancervård, i förhållande till befolkningens storlek. Västsverige har sedan länge haft en av de högsta incidenserna av melanom i Sverige. Ökningen av melanom har proportionellt sett varit störst bland de tunna melanomen (≤1 mm Breslowtjocklek). Tunna melanom har i allmänhet en god överlevnadsprognos, men en (oidentifierad) undergrupp av dessa tumörer har ändå potential att orsaka patientens död. Det är också sedan tidigare känt att en del patienter utvecklar flera primära melanom (multipla primära melanom).

Det övergripande syftet med den här avhandlingen var att beskriva melanomepidemiologin i Västsverige, och att föreslå sekundärpreventiva åtgärder. I delarbete I analyserades data från det svenska cancerregistret. Förekomsten av invasiva melanom i Västra Götalandsregionen fyrdubblades bland män och tredubblades bland kvinnor från 1970-2007. Kustkommuner och Göteborg hade en högre incidens än inlandskommuner. Analys av meteorologiska kartor och en solvanestudie från Socialstyrelsen visade att detta kan bero på fler soltimmar/år längs kusten, och på att dessa befolkningar var mer utsatta för solexponering vid semestrar utomlands.

I delarbete II analyserades data från kvalitetsregistret för melanom. Delarbetet visade att 7,4 % av alla melanompatienter i Västra Götalandsregionen utvecklade flera melanom (multipla primära melanom) mellan 1990-2013. Det påföljande melanomet var oftare ett melanom in situ (förstadium) jämfört med det första melanomet. Av de påföljande melanomen diagnostiserades 49 % inom tre år.

I delarbete III kopplades data från kvalitetsregistret för melanom till Socialstyrelsens dödsorsaksregister. Mellan 1990-2014 utgjorde tunna melanom 55.2 % av alla invasiva melanom, och orsakade 14.7% av dödsfallen till följd av melanom i Västra sjukvårdsregionen. En undergrupp med sämre överlevnad för melanom visade sig utgöras av melanom med 0.76-1 mm Breslowtjocklek utan ulceration och melanom med 0.26-1.0 mm Breslowtjocklek med ulceration.

I delarbete IV användes en metod kallad systemdynamik för att bygga en modell för datorsimulering av melanomvårdkedjan. Modellen användes för att illustrera den kraftiga framtida ökningen av antalet melanomfall i Västra Götalandsregionen från 2014-2023. Fem framtida tänkbara scenarion konstruerades, varav vissa inkluderade förebyggande insatser. Modellen visade att förbättrade förebyggande insatser skulle ha givit en förskjutning mot en ökad andel tunna melanom, med bättre prognos.

Sammanfattningsvis har denna avhandling visat att det finns en kraftigt ökande melanomincidens i Västsverige, främst i kustkommuner och i Göteborg. För att kunna minska insjuknandet och dödligheten i melanom är det viktigt att fokusera förebyggande arbete och ekonomiska resurser till dessa områden. En tänkbar sekundärpreventiv insats är att tydligare uppmärksamma patienter och läkare på att det är vanligt att utveckla multipla primära melanom, särskilt inom de första åren efter ursprungsdiagnosen. Vidare bör särskild uppmärksamhet vid behandling och uppföljning riktas mot den undergrupp av tunna melanom som har sämst överlevnad. Slutligen visade sig systemdynamik vara en lämplig metod för att analysera melanomvårdkedjan och för att kunna jämföra olika förebyggande insatser.

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LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Claeson M, Andersson EM, Wallin M, Wastensson G, Wennberg AM, Paoli J, Gonzalez H.** *Incidence of cutaneous melanoma in Western Sweden, 1970-2007.* Melanoma research 2012; 22(5): 392-398.

II. **Claeson M, Holmström P, Hallberg S, Gillstedt M, Gonzalez H, Wennberg AM, Paoli J.** *Multiple primary melanomas: a common occurrence in Western Sweden.* Accepted for publication in Acta Derm Venereol.

III. **Claeson M, Gillstedt M, Whiteman DC, Paoli J.** *Lethal melanomas: a population-based registry study in Western Sweden from 1990-2014.* Submitted.

IV. **Claeson M, Hallberg S, Holmström P, Wennberg AM, Gonzalez H, Paoli J.** *Modelling the future: System dynamics in the cutaneous malignant melanoma care pathway.* Acta Derm Venereol. 2016; 96(2): 181-185.

ABBREVIATIONS

ALM	Acral lentiginous melanoma a.k.a acrolentiginous melanoma
CI	Confidence interval
CMM	Cutaneous malignant melanoma (melanoma)
COX	Cox proportional hazards regression analysis
LMM	Lentigo maligna melanoma
NM	Nodular melanoma
OR	Odds ratio
RR	Relative risk
SD	System dynamics
SSM	Superficial spreading melanoma
UV	Ultraviolet (radiation)

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DEFINITIONS IN SHORT

AJCC staging system	The American Joint Committee on Cancer staging manual for cutaneous malignant melanoma, updated with a seventh edition in 2009.
Breslow thickness	The distance between the upper layer of the epidermis and the deepest point of penetration of a malignant melanoma (measured in millimetres). Named after the pathologist Alexander Breslow.
Clark level	The level of anatomical invasion of a melanoma. Named after the pathologist and dermatologist Wallace H. Clark. Jr.
Fitzpatrick scale	A numerical classification of human skin pigmentation, ranging from type I-VI. Developed by dermatologist Thomas B. Fitzpatrick.
Melanoma incidence rate	The number of new melanomas occurring in a population during a given time period (typically expressed per 100,000 person-years).
Melanoma mortality rate	The number of deaths from melanoma in a population during a given time period (typically expressed per 100,000 person-years).
TNM staging system	The TNM Classification of Malignant Tumours is a cancer staging notation system that describes the stage of a cancer. The system assigns a letter and a number to describe the primary tumour (T), the involvement of lymph nodes (N) and distant metastases (M).

01

INTRO-
DUCTION

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INTRODUCTION

1.1 EPIDEMIOLOGY OF MELANOMA

1.1.1 INCIDENCE

International demographics

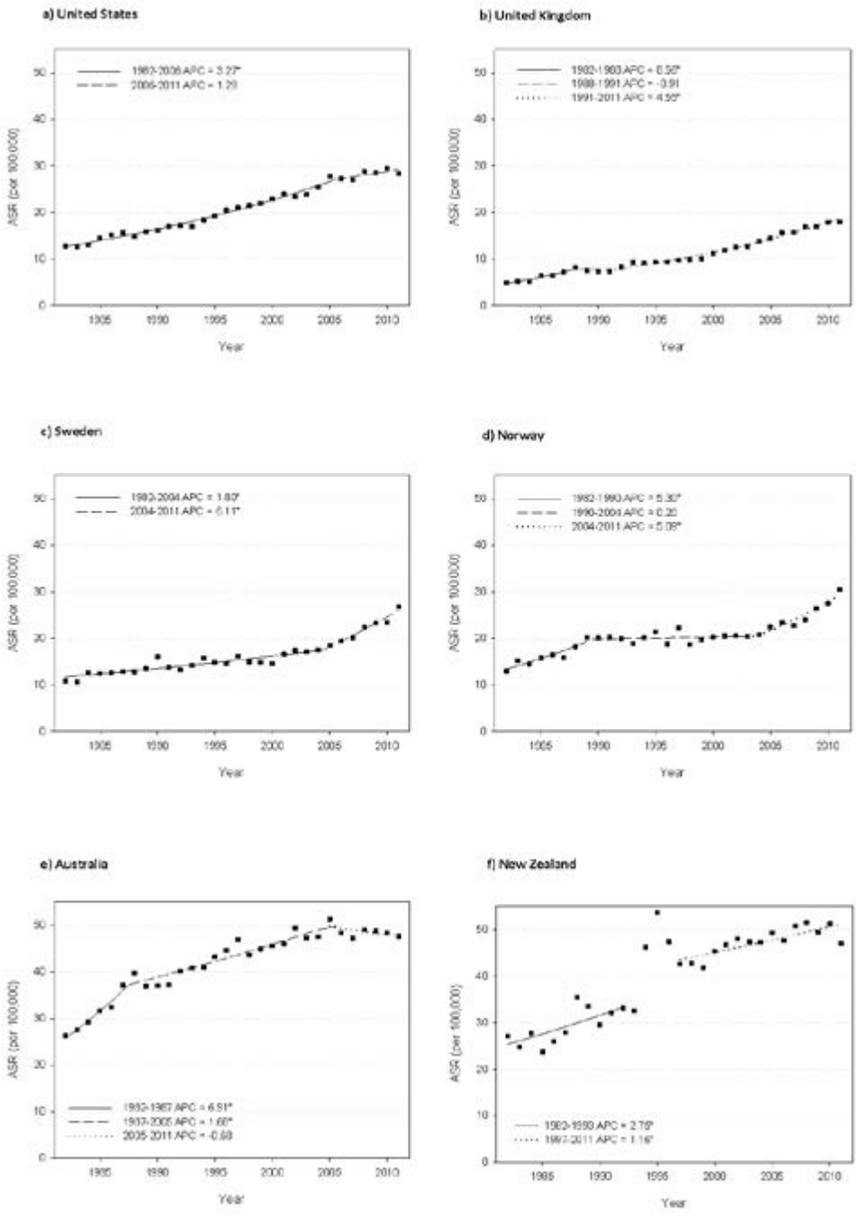
The incidence of cutaneous malignant melanoma (melanoma) has been rising in most fair-skinned populations around the world for the past decades, causing a major public health problem [1, 2]. The highest incidence rates are found in New Zealand and Australia, followed by Switzerland, the Netherlands and the Scandinavian countries of Denmark, Norway and Sweden [3]. The incidence rates of melanoma are approximately twice as high in New Zealand and Australia, as compared to Sweden. In 2012, this was described by the International Agency for Research of Cancer, with incidence rates of around 36 and 35 per 100,000 person-years (World standard population year 2000) for New Zealand and Australia, respectively [3]. The corresponding incidence for Sweden was 18 per 100,000 person-years.

It is well known that melanoma incidence follows a latitude gradient. The latitude affects the sun's angle, and thus the level of UV radiation. As an example of this, high incidence rates are reported in fair-skinned populations living at lower latitudes in the United States, Australia and New Zealand, compared to populations living at higher latitudes in those countries [4]. In Europe, the gradient is not continuous, but decreases with increasing latitude until approximately 50° North, where the countries Belgium and Luxembourg are situated. At this parallel, the incidence reverses and increases in the Netherlands and in Scandinavia [1].

The cause of the steep, worldwide increase of melanoma incidence has been an area of much debate [5]. The increase has been partly attributed to a true increase in melanocytic tumours, due to increased intermittent sun exposure. Outdoor recreational activities, sun-holidays and sunbed use are all examples of intermittent sun exposure. The increasing incidence has also been proposed to be a result of pressure from early detection, leading to overdiagnosis. Improved early detection of melanoma in turn, is perceived as an outcome of improved surveillance techniques and growing awareness of skin cancer in the public [5-7]. Further, the increase has been attributed to diagnostic drift [5].

However, after continuing increases in melanoma rates in fair-skinned populations for decades, recent encouraging studies have shown that Australia is experiencing a decline, with an annual percentage incidence change of -0.68 between the years 2005-2011 [2, 8]. See *Figure 1* for an overview of incidence rates of melanoma for six populations around the world. The age-specific melanoma incidence for persons younger than 60 years of age peaked in Australia between 2002-2006 and then declined.

Figure 1. Age-standardized incidence of melanoma (US standard population year 2000) from 1982-2011 and annual percentage change in six populations. (a) US whites. (b) United Kingdom. (c) Sweden. (d) Norway. (e) Australia. (f) New Zealand. APC, annual percentage change; ASR, age standardized rate.



*The APC is significantly different from zero at α=0.05

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Dermatology, 2016; 136(6), Whiteman DC et al, The Growing Burden of Invasive Melanoma:
Projections of Incidence Rates and Numbers of New Cases in Six Susceptible Populations through 2031, pages 1161-71.
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Swedish demographics

Today, melanoma is the sixth most common type of cancer among men in Sweden, and the fifth most common among women [10]. Of all Swedes, 2.2% of men and 2.1% of women will develop a melanoma before the age of 75 [11]. This can be compared to breast cancer, developing in 10.1% of Swedish women and prostate cancer, developing in 11.8% of Swedish men, before the age of 75. Melanoma, together with other skin cancers (with an exception of basal cell carcinoma), is the fastest increasing type of cancer, representing 17% of the total cancer cases in Sweden [10]. The incidence of melanoma specifically is also rapidly increasing, with an annual percentage increase of over 6%, which is a worrisome trend [12].

In 2014, the incidence rates of melanoma for men and women were 40 and 35 per 100,000 person-years, respectively (Swedish standard population year 2000) [10]. That year, 1,855 men were registered in the Swedish Cancer Registry, having a total of 1,912 melanomas. Correspondingly, 1,813 women were registered having a total of 1,840 melanomas. In addition to the invasive tumours, 3,212 melanomas in situ were registered (1,639 for men, 1,573 for women).

Melanoma incidence varies with age, but melanoma can occur at any age. However, the tumour is excessively uncommon in children. In Sweden, only 69 cases of melanoma were registered in patients <20 years old between 2000-2009. Most of these patients were adolescents, aged 15-19 [13]. In adulthood, melanoma incidence increases with age. In contrary to many other types of cancer, mainly affecting older adults, melanoma is infamous for affecting young and middle-aged persons. Though relatively common in the younger age group, the median age at diagnosis in 2014 was 68 years for men and 63 years for women [14].

Apart from a latitude gradient for the melanoma incidence worldwide, there are also regional north-south geographical differences within Sweden. The incidence level is almost twice as high in the health care regions of Western Sweden and Southern Sweden, as compared to the Northern region [6]. Since decades, Western Sweden has had one of the highest melanoma incidences in the country [13]. The factors contributing to the high incidence in Western Sweden have long been discussed, but no definite answers have been provided. Apart from higher UV radiation levels in Western Sweden compared to Northern Sweden, associating factors like socioeconomic status, genetic mutations specific to the region and high nevus counts in the population have been proposed [15-18].

Future projections for melanoma incidence

Several previous studies have attempted to prognosticate the future number of melanomas for Sweden [2, 19], at around the same time as Study IV of this thesis was published. There is certainly no ease in the melanoma burden projected for Sweden. On the contrary, one study from the Southern Sweden health care region estimates an increase in the number of melanoma cases with 75%, from 645 to 1,129 between the years 2008 and 2022 [19]. Another study estimates a continuous increase of incidence for Sweden as a whole, on-going until at least 2022-2026, taking the ageing population into account [2].

Knowledge of a coming incidence increase is important for several reasons. First, it gives caregivers time to prepare for an increased health care demand. Further, policymakers can allocate resources for preventive strategies to break trends.

Standardization of incidence and mortality rates

The crude incidence rate of melanoma is defined as the number of new cancers occurring in a population during a year. Consequently, the crude mortality rate is defined as the number of deaths from melanoma occurring in a population during a year. However, since populations may differ significantly with respect to characteristics such as age, standardizations of incidence and mortality rates are sometimes used instead of crude rates. The standardizations are used to overcome age differences between populations in different countries or between populations of different time periods. Common standardizations are the World standard population year 2000, the United States standard population year 2000 and the Swedish standard population year 2000. In this thesis, both crude rates and age-standardized rates are used.

1.1.2 MORTALITY

Melanoma is responsible for the vast majority of deaths due to skin cancer. World-wide, more than 55,000 persons were reported to have died from melanoma in the year 2012 [3]. The mortality rates for melanoma have also been rising in many countries for the past decades, but slowly and to a much smaller extent than has incidence rates [2]. The highest mortality rates in the world are found in New Zealand and Australia [3].

In Sweden, the annual percentage change of the mortality rate was low until the mid 1990s (+0.25% for the years 1982-1996), but then slowly started to increase (+1.80% for the years 1996-2011), standardized to the United States population in year 2000 [2]. From 2002 until 2012, the number of women ultimately succumbing to melanoma in Sweden has increased with 48%. The corresponding increase for men was 33% [11]. Although the increase in melanoma deaths has been higher among women during the last years, the overall melanoma mortality is still higher for men than for women. In Sweden, the mortality rates in 2014 were 6.4 for men and 3.9 for women per 100,000 person-years (Swedish standard population year 2000), which corresponded to 292 men and 214 women dying from the disease during that year.

1.2 CAUSES AND RISK FACTORS

This chapter summarizes in short the pathophysiology of melanoma, as well as the main factors increasing the risk of melanoma development. Risk factors have historically been analysed as independent variables, illustrated by the subheadings in the chapter below. However, it is becoming increasingly common to combine risk factors into risk prediction models for skin cancer [20]. Such models will undoubtedly be of importance in the future, both in clinical practice and in public health practice.

1.2.1 PATHOPHYSIOLOGY

Melanoma develops through out-of-control growth of pigment-containing melanocytes in the skin, forming a malignant skin neoplasm. The process is likely to be multifactorial, involving UV light exposure and genetic predisposition, resulting in a build-up of genetic mutations in the melanocyte. Next, activation of growth stimulatory pathways, inactivation of tumour suppressor genes and a defective DNA repair system lead to melanoma cell proliferation. Further in the tumour evolution there is angiogenesis, tumour invasion of the deeper layers of the skin and lack of immune response that causes metastasis [21].

In the lately postulated divergent pathway model it has been hypothesized that melanoma develops through two divergent pathways [22, 23]:

1. In people with low nevus count, cumulative sun exposure causes late-onset melanoma predominantly on the head and neck. Head and neck melanomas are anatomic locations related to patterns of chronic sun damage. The melanoma subtype associated with chronic sun damage is often characterized by initial mutations in the NRAF, NF1, KIT and BRAF^{nonV600E} genes.

2. In people with high nevus count, smaller doses of intermittent sun exposure cause early-onset melanoma predominantly on the trunk and limbs. The trunk and limbs are anatomic locations related to patterns of intermittent sun exposure. This melanoma subtype is often characterized by initial genetic mutations in BRAF^{V600E}.

Previously it was believed that melanomas arise solely within a pre-existing nevus. However, contemporary research shows that only about one of four melanomas develop within a pre-existing lesion [24-26]. Correspondingly, three of four melanomas develop in clinically normal skin ("de novo" melanomas).

1.2.2 UV LIGHT EXPOSURE

UV radiation is separated into UVA (320-400 nm), UVB (290-320 nm) and UVC (100-290 nm). UVC is absorbed by the ozone layer and is therefore not a potential source of radiation on earth. Today, there is consensus about UV light exposure being the major cause of melanoma (see *Figure 2 and 3*) [27]. Since 2009, the World Health Organization classifies UVA, UVB and sunbeds as carcinogenic [28].

Some evidence for UV light exposure being the major cause of melanoma follows below [27, 29-31]:

1. UVA and UVB have been confirmed to cause DNA damage and are involved in melanoma development. However it is still unknown what specific wavelengths that are involved [1].

2. Fair-skinned populations have a higher incidence of melanoma [31].

3. There is an association between sun exposure and the risk of melanoma, with relative risks (RR) increasing for early childhood sunburns (RR=2.24 (95%CI: 1.73-2.89)), sunburns during life (RR=2.08 (95%CI: 1.70-2.55)) and intermittent sun exposure (RR=1.61 (95%CI: 1.31-1.99)) [27].

Also, a recent review has shown that the total UV exposure during life, measured by the objective presence of solar keratoses on the head and neck, is associated with increased risk of melanoma [31].

Figure 2 and 3 (p 20-23). UV light exposure is considered the major cause of melanoma, here exemplified by beach life on sun holidays. Photo: Magdalena Claeson and Unsplash.com

In the Western world, attitudes toward sunbathing have changed during the last centuries. Earlier, avoidance of the sun and a fashion that encouraged a pale white skin was the norm among aristocrats. A suntan, on the other hand, was the mark of a labourer. But in the late 1800s, outdoor recreation activities and sport and tourist organisations started to form. Swimming and sunbathing was perceived as healthy for the body and soul and thus, going to the beach became popular around this period of time [32]. Following this motion, in the 1920s, the famous Parisian fashion designer and businesswoman Coco Chanel made a suntan desirable and a symbol of a privileged life [33]. Much of these attitudes towards a sun-seeking behaviour are dominant also today.

Further, sun holidays have become fashionable during the last half-century, which has increased the level of intermittent sun exposure in fair-skinned populations even more [34, 35]. During the last century, clothing habits have also changed, which probably has had an effect on the melanoma incidence. For instance, a study from Norway has shown that the incidence of melanoma on the breast of younger women increased after the habit of topless sunbathing was introduced in the 1970's [36].

The ozone layer in the stratosphere protects the earth from UV radiation. Depletion of the ozone layer results in more UV radiation from the sun reaching the surface of the earth. As a result of the use of chlorofluorocarbons such as Freon, the total ozone decreased on a global scale in the 1960s and 1970s. However, contrary to public sentiment, the total ozone specifically over Sweden has remained largely unchanged during the last decades [37, 38]. Thus, the increase in skin cancer incidence in Sweden cannot be linked to the ozone layer. Today, the danger of global ozone depletion has hopefully been prevented, with falling Freon levels in the atmosphere.

Sunbeds

Artificial sunbeds (also known as solariums, see *Figure 4*) are devices that can be used to create a cosmetic tan. They emit mostly radiation in the UVA spectrum, but also some UVB radiation [39]. Sunbeds increase the risk of melanoma significantly, with a lifetime exposure to more than 10 tanning sessions resulting in an odds ratio (OR) of 1.34 (95% CI: 1.05-1.71) [40]. Also, first use of a sunbed before the age of 35 has shown to be associated with a RR of 1.87 (95%CI: 1.41-2.48) [41].

Figure 4. Sunbed (also known as solarium) Photo: AdobeStock

There is a north-south gradient with high prevalence of exposure to UV radiation from sunbeds in the populations in northern Europe, compared to southern Europe. A study from 2005, comparing sunbed use in five European countries, showed that participants from Sweden and the Netherlands had the highest cumulative exposure to sunbeds [42]. Further, a survey from the Swedish Radiation Safety Authority from 2008 showed a rate for ever using sunbeds of around 50% among participating Swedes aged 18-24 years [13].

A sharp increase in the incidence of melanoma in Iceland during 1995-2002, resembling a melanoma epidemic, further supports the hypothesis that sunbed use increases the risk of melanoma [43]. The increase in Iceland was higher for melanomas on the trunk among young women, who also had the highest records of sunbed use. The role of sunbeds inducing melanoma was additionally strengthened by the decline in melanoma incidence trends after the Icelandic health authorities introduced a campaign, discouraging sunbed use. The campaign focused on adolescent girls.

1.2.3 GENETICS

Around 8-12% of melanoma patients have a family history of melanoma [44]. It is firmly established that having a relative with melanoma is a risk factor for melanoma. The risk of melanoma development further increases when two first-degree relatives are affected [45]. In Sweden, germline mutations have been found in only 10% of the familial melanoma cases [15, 46]. Germline mutations are constitutional, occur in every cell of the body and can be inherited. The high-risk gene that is best known today is CDKN2A (Cyclin-dependent kinase 2A). This gene is a regulator of cell division and it codes for two different proteins (p16 and p14). Previous research has shown a significantly increased RR of around 60 for developing a melanoma in carriers of CDKN2A mutations [47].

Several somatic mutations are found in the melanoma tumour tissue. Somatic mutations are acquired within a lifetime and are not inherited. The most common somatic mutation found in melanomas is in the BRAF oncogene, occurring in around 50% of melanomas. $BRAF^{V600E}$ mutations are characteristically associated with melanomas on non sun-exposed anatomical locations in younger patients with a high nevus count [48].

Xeroderma pigmentosum is a very rare autosomal recessive disease, occurring in about 2.3 per million live births in Western Europe [49]. The disease is defined by an extreme sensitivity for sun exposure, resulting from a defect in the DNA repair system. One study has shown that Xeroderma pigmentosum patients <29 years of age have a more than 2000-fold increase of melanomas, compared to the general population [50].

1.2.4 SKIN TYPE

Skin types are classified according to the Fitzpatrick scale of human skin pigmentation [51]. The classification measures the response to UV radiation for different types of skin, ranging from skin type I (always burns, never tans) to skin type VI (never burns, deeply pigmented skin). A meta-analysis has shown that people with skin type I and II are at significantly higher risk of melanoma compared to people who do not burn and who tan easily (RR=2.99 (95%CI: 1.75-5.12)) [44]. Skin type is often, but not always, correlated to phenotypic traits as blue or green eye colour, red hair and a tendency to freckle [51]. These phenotypic traits are also signs of constitutional UV-sensitivity, and have been shown to increase the risk of melanoma development in meta-analysis [44].

Melanoma is uncommon in people with darker skin types. For instance, though living in the same country and at the same latitudes, the incidence in the black population in the United States in 2011 was 1 per 100,000 person-years (the United States standard population year 2000), whereas the incidence of non-Hispanic whites was 22 per 100,000 person-years [52]. However, in people of colour, melanomas of the histopathological subtype acral lentiginous melanoma (ALM) are proportionally more common [53]. Unlike other histopathological subtypes, ALMs do not seem to be caused by exposure to UV radiation [54].

1.2.5 MELANOCYTIC NEVI

Although most melanomas develop "de novo", and not in precursor nevi, it cannot be out ruled that genes involved in nevus development are associated

with melanoma formation [24, 25, 55]. It has been established that the number of common melanocytic nevi is a risk factor for the development of melanoma. A high nevus count has also been proposed as an indicator for previous sun exposure [55, 56]. Thus, sun exposure may independently cause both a high nevus count and an increased risk of melanoma development [57]. A review of several studies showed a significantly increased risk for persons with a very high nevus count (101-120 nevi), showing a pooled RR=6.89, in comparison with persons with very few nevi (0-15 nevi) [55]. In conclusion, having a very high number of nevi is considered a strong risk factor for melanoma.

Several studies during the 1990s showed that clinically atypical nevi were associated with higher risk of developing a melanoma [55]. Nevertheless, the clinical criteria for atypical nevi have serious flaws and it seems that the size of nevi and the number of these are probably a better and more objective way of estimating the risk of melanoma [58-60].

Lastly, congenital melanocytic nevi have an increased risk of progression to melanoma, although this is mainly related to congenital nevi of giant size [61, 62].

1.2.6 MULTIPLE PRIMARY MELANOMAS

The risk of developing a subsequent primary melanoma is increased in patients diagnosed with a single primary melanoma. The subsequent primary melanoma occurs separately from the first melanoma, and is not the equivalent of a metastasis. There are numerous risk factors identified for developing multiple primary melanomas, which to a large extent coincide with those for developing a single primary melanoma. Age, fair skin type, family history of melanoma and presence of many or large nevi have all been reported to be important risk factors for multiple primary melanomas [63-65]. It has long been debated whether multiple primary melanomas increase the mortality of melanoma, but recent studies indicate this [66, 67].

Previous studies have shown that a percentage of 0.2-8.6% of patients with single primary melanomas develop multiple primary melanomas [68]. This percentage varies, and one reason for this is that the inclusion or exclusion of melanoma in situ varied between studies. A further reason is that some studies were based in skin cancer clinics, with high-risk patients, and some others were population-based. A third reason to the variation in the proportion of patients with multiple primary melanomas, is the study length, since aging patients are more prone to develop subsequent melanomas. It is not unusual that multiple lesions are detected synchronously with the first melanoma, but detection can also occur during follow-up. Subsequent lesions are most common within the first years of follow-up after diagnosis of the initial melanoma [63, 65, 68-70]. Furthermore, patients who attend regular follow-up have been found to present with thinner melanomas (according to Breslow thickness) than those who did not attend follow-up [71, 72].

In Sweden, during 1990-2008, 2.6% of the patients diagnosed with a single primary melanoma developed one or more subsequent primary melanoma(s) [14]. This percentage increased to 3.2% during the years 2009-2012. Analysing the entire time period from 1990-2014, over 4% of the melanoma patients were registered with multiple primary melanomas. However, the numbers above only included invasive melanoma.

1.2.7 IMMUNOSUPPRESSION

Immunosuppressant medication is obligatory in organ transplant recipients, to prevent organ rejections. However, immunosuppression impairs the capacity of the human immune system to repair cells damaged by UV radiation, which can lead to the development of cancers. It has been estimated that 50% of all organ transplant recipients develop skin cancer [73]. Although immunosuppression is best known to increase the risk of squamous cell carcinoma and basal cell carcinoma, a meta-analysis has also shown a significantly increased risk of melanoma, with a pooled estimated increased risk between 2 and 8 [73]. More so, melanomas in organ transplant recipients have been found to have a thicker depth of invasion according to Breslow and a lower survival compared to non-transplant individuals [73].

1.3 PREVENTION

1.3.1 PRIMARY PREVENTION

Primary prevention is defined as preventing a disease by lowering exposure to risk factors, or by increasing resistance to risk factors. In the case of melanoma, primary prevention is equal to reducing excessive amounts of UV radiation from the sun and from sunbeds. The use of sunscreen is also a form of primary prevention. The goal of primary prevention is to prevent the forming of a melanocytic neoplasm.

Reducing sun exposure

As previously mentioned, there is consensus in the research community about UV radiation as the most important underlying cause of melanoma. Thus, preventive strategies include avoiding excessive sun exposure [27]. But on the other hand, there is no consensus about the exact amount or duration of UV radiation that causes melanoma. Since no consensus has been reached on whether there are UV radiation doses that balance health benefits and unfavourable health effects, it becomes difficult for the public to navigate between mixed messages. One day, media will promote sun protection to prevent skin cancer and the next day the public will be warned about Vitamin D deficiency caused by too little sun exposure [74]. As an example, a recent Swedish study attracted some media attention, suggesting that avoiders of sun exposure showed a reduced life expectancy of 0.6-2.1 years, compared to the study group with the highest sun exposure [75]. This in an interesting idea, suggesting that the positive effects of sun exposure might be mediated by Vitamin D. But the reduced life expectancy may have been due to confounding factors not adjusted for, such as lack of physical activity. This was also acknowledged in the study [76].

In fact, there is sufficient evidence that the sun certainly should not be avoided completely. Humans need Vitamin D, synthesized in the skin upon exposure to UVB radiation. Vitamin D is essential to the immune system and to bone development. Vitamin D deficiency has been associated with increased risk of, among others, common cancers and cardiovascular disease [77]. Thus, a humble attitude to adopt until further research on safe dosages of UV radiation is available would be to be exposed to the sun in moderation. Currently, the guidelines from the Swedish Radiation Safety Authority regarding sun protection is summarized in *Figure 5* [78]:

Figure 5. Sun protection guidelines from the Swedish Radiation Safety Authority

››› PROTECTIVE CLOTHING, A HAT AND SUN GLASSES ARE THE BEST OPTIONS FOR SUN PROTECTION

››› STAY IN THE SHADE IN THE MIDDLE OF THE DAY (11 AM-3 PM)

››› USE SUNSCREEN ON BODY PARTS NOT PROTECTED BY CLOTHING

Effective primary prevention interventions

The influential Community Preventive Services Task Force under the United States Department of Health and Human Services has conducted a systematic review of the effect of community interventions to promote sun protection [79]. There are some examples of settings where sun protection interventions have shown sufficient evidence to be used. These include occupational outdoor settings, outdoor recreational and tourism settings and interventions in childcare centres and in primary and middle schools. Also, sufficient evidence has been found for multicomponent, community-wide campaigns. Such campaigns use a defined name or logo and focus on a specified geographical region. The campaigns work through combining several strategies to increase sun protection behaviour, for instance mass media campaigns, individual directed strategies and policy changes.

The Scandinavian country of Denmark has successfully used multicomponent, community-wide prevention campaigns during the last years. The Danish Sun Safety Campaign has run campaigns like "Flyt hyggen ind i skyggen" and "Lidt skygge skader ikke på ferien" (see *Figure 6*), that used digital dialogue, partnerships with travel agencies, mass media etc. to promote a sun safe behaviour to the Danish

public [80]. Continuous evaluation, including published research studies has also been an important part of the Danish strategy. Denmark has about the same ambient UV radiation levels as Sweden, and may thus be suitable for comparison with Swedish circumstances. However, substantially more economic resources have to be allocated to skin cancer prevention in Sweden to make it possible to set up an organisation similar to the Danish Sun Safety Campaign.

Figure 6. *"Lidt skygge skader ikke på ferien"* – a multicomponent, community-wide campaign set in Denmark in 2012. Copyright permission from the Danish Sun Safety Campaign

Australia is another good example of a country, which has been a forerunner in preventing skin cancer. Primary prevention interventions have been present there since almost forty years, much as a result of the country's high melanoma incidence [3, 81]. One well-coordinated Australian example of a primary preventive intervention is focused on an educational setting, namely primary and middle school-based interventions within the SunSmart programme [82, 83]. The programme has comprehensive coverage in several Australian states, and works through, among others, teaching school children about sun safety, implementing sun safety policies and providing outdoor shade structures. The introduction of a primary prevention programme like "SunSmart" in Swedish child care centres and schools could be a possible way of preventing dangerous sun-related behaviour. No doubted, the programme would have to be adapted to Swedish circumstances regarding for instance ambient UV radiation levels. Further, it would demand vast economic recourses, a huge organization and a long-term commitment. But, the outlook for success of such a programme is very much supported by the above-mentioned research on suitable target groups [79]. Also, several studies have reported on the cost-effectiveness of the "SunSmart" programme, with one study estimating that every dollar invested would give a return of AU$ 2.30 [84, 85]. The problem lies in convincing Swedish policymakers to allocate economic resources for skin cancer prevention right now, although the decreasing morbidity and mortality rates will be first visible after several decades.

The strategic primary prevention activities in Australia, resulting in lower levels of sun exposure in the younger populations, may have contributed partly to the recent stabilization and drop in incidence trends [2]. However, this may not be the entire truth. Another contributing factor that has been proposed is the introduction of information technology. In Australia, as well as in numerous other countries in the world, information technology has lead to more hours spent in front of a computer screen for young people, instead of playing outdoors. Also, the decreasing incidence trends have been suggested to be due to immigration of populations at lower risk of melanoma, due to their darker skin type [86]. Others have argued that the effect of immigration is too small to lead to the observed decrease [87].

Skin cancer awareness

For a lot of Swedes, a suntan still symbolizes a healthy, rich and fashionable lifestyle. The love of the sun among Swedes is a true challenge when trying to promote sun protection behaviours and increase skin cancer awareness. As an example, there is evidence that Swedes are more prone to high-risk sun behaviour in comparison with other countries. In 2010, two international studies on sun protection behaviour and attitudes towards tanning were published [88, 89]. The results of the studies originated from a large web survey, where 8,178 persons from twelve countries around the world participated (Australia, Germany, Israel, Italy, Latvia, the Netherlands, Poland, Slovenia, Spain, Sweden, the UK and the USA). The study showed a lower degree of sun-protection behaviours in Sweden and Latvia compared with all other countries. Participants from Australia reported the highest degree of sun protection. Further, participants from Sweden and Italy reported a high level of intentional tanning, compared to other countries. Attitudes on tanning were assessed using computer-generated photos of people, with varying levels of suntan (see *Figure 7*). When asked to choose among the pictures, Swedes had the highest preferred level of tan, followed by Latvia, the UK and the Netherlands.

Figure 7. Computer-generated photos of people with varying levels of suntan. Swedish participants in a study by Bränström et al. (2010), had the highest preferred level of tan of all participating countries, choosing the bottom left photo [88]

Not only is there consensus in the research community about UV radiation as the major cause of melanoma, there is also widespread knowledge in the Swedish public about this fact. According to a 2005 survey from the Swedish Radiation Safety Authority, 98% of the participating Swedes knew that there is a connection between the UV-rays of the sun and skin cancer [90]. The same authority performed a web survey in 2016, showing that despite knowledge of the harms of the sun, 92% of the participating Swedes stated that they burn in the sun. The reason for sun exposure mentioned in the survey were foremost, with 58% of respondents, that it makes you feel good. Also, 83% still found a suntan attractive [91].

Although a lot of Swedes still burn in the sun and express a high level of preferred tanning, there are also promising results regarding increasing sun protection in the Swedish public. The previously mentioned web survey by the Swedish Radiation Safety Authority also showed that 4 out of 10 respondents spent less time in the sun in 2016, compared to five years before [91]. Another report from the Swedish National Board of Health and Welfare shows that the proportion of 4-year-old and 12-year-old children who are protected from the sun in any way during summertime increased significantly between the years 2003 and 2011 [92]. Moreover, a study from the south of Sweden has showed increased self-reported sun-protective actions among parents of 7-year-old children, between the years of 2002 and 2007. The same study also showed a significantly lower count of the number of nevi per square metre body surface in 2007, compared to in 2002. In this study, the nevi count was used as a proxy for sun exposure [93].

Avoiding sunbeds

Brazil was the first country in the world to outlaw sunbeds for aesthetic use in 2009. This action was trailed by a total ban in Australia in 2016. The ban in Australia followed some years after the highly publicised death of a 26-year-old skin cancer victim called Clare Oliver, who attributed her disease to the use of sunbeds [94, 95]. The death of Clare Oliver started a debate in the media and increased perceptions of the dangers of sunbeds in the Australian population. The media coverage, along with long-standing work from community advocacy groups, eventually led to sunbed legislations [96]. Another illustration of

media attention increasing public awareness was when the American actress Angelina Jolie in 2013 announced that she had had a double mastectomy because of an inherited mutation in the BRCA1 gene. The announcement brought direct focus on inherited risk of breast cancer in the public [97]. To sum up, media attention on a celebrity or on a victim of disease can have a catalytic effect and a large impact on public awareness. If the opportunity presents itself in Sweden in the future, authorities and advocacy groups should try to reinforce the media coverage to increase skin cancer awareness.

Several other jurisdictions have enacted legislation to protect minors from sunbeds, including among others Great Britain, France and Germany [98]. Among the Scandinavian countries, Norway has a ban in place to protect minors, <18 years of age, but this will be fully enforced first in 2017, when an age verification system must be in place at the sunbed facilities [99]. Denmark, on the other hand, does not have a restriction for minors using sunbeds [100]. Despite this, a survey has shown that Denmark has succeeded in decreasing the proportion of sunbed users aged 15-25 from 41% to 14% between 2008 and 2015. The drop in sunbed users aged 15-64 was from 25% to 11 % during the same years. The decreasing sunbed use in the Danish population may be an effect of another multicomponent community-wide campaign by the Danish Sun Safety Campaign: "Sluk solariet" [101].

Already in 2009, the Swedish Radiation Safety Authority recommended regulation of sunbed facilities open to the public, including the prohibition of use for minors [102]. Since 2010, the same authority discourages municipalities from having sunbeds in sports and recreation facilities [78]. As this thesis was being completed, on October 27, 2016, the Swedish government finally announced a ban restricting minors from using sunbeds, to be fully enforced in 2018 [102-104]. After the ban for minors is passed, it would be advisable to keep studying sunbed use to see if the rates are dropping. Previous research has shown that legislation has the potential of reducing a vast number of melanoma deaths [105]. As an example, it was estimated that one in six melanomas in young Australians (18-29 years of age) could be prevented if sunbeds were not available [106]. Most likely, the sunbed ban for minors will have an impact on reducing the number of melanoma deaths also in Sweden. Consequently, a complete sunbed ban for cosmetic use would have an even higher impact.

Sunscreen

Sunscreen is a substance, usually a cream or a lotion, designed to protect from excessive sun exposure. Physical sunscreen works through reflecting and scattering UV radiation and visible light, while chemical sunscreens absorb UV radiation in the skin. Sunscreen can protect both against UVA and UVB radiation, depending on the substance used [107]. There is risk of sunscreens being used to increase sun exposure, so that sunbathers can stay longer in the sun without burning. Also, sunscreens are often used inadequately, with smaller amounts than recommended and too few applications [108].

The use of sunscreen to prevent melanoma has long been controversial [109]. However, the famous Nambour trial, named after a town in Queensland, Australia, has shown that regular use of sunscreen may have protective effects [110]. The study showed a substantial reduction of invasive melanomas for persons using sunscreen, when compared to melanoma in situ. Furthermore, the invasive melanomas in the persons using sunscreen were significantly thinner. There was also a 50% reduction in primary melanomas in sunscreen users, although only reaching borderline significance. Further research in this area is needed.

1.3.2 SECONDARY PREVENTION

Secondary prevention is defined as early detection and treatment of a disease. In the case of melanoma, secondary prevention includes skin self-examination by patients and early detection by physicians (e.g. screening activities). Skin self-examination and early detection by physicians lead to the excision of thinner tumours. Thin tumours have a better prognosis and increased survival rates compared to thicker tumours [111]. Increased survival is the goal for secondary prevention.

Skin self-examination

Fortunately, melanoma is a type of cancer that, in most cases, is easily detectable on the skin surface. Recommending individuals to examine their

own full body skin surface at home, with regular intervals, has proven to be a successful means of reducing melanoma mortality [112]. Thus, skin self-examination is a recommendation that has been widely advised to the public (see *Figure 8*) [113].

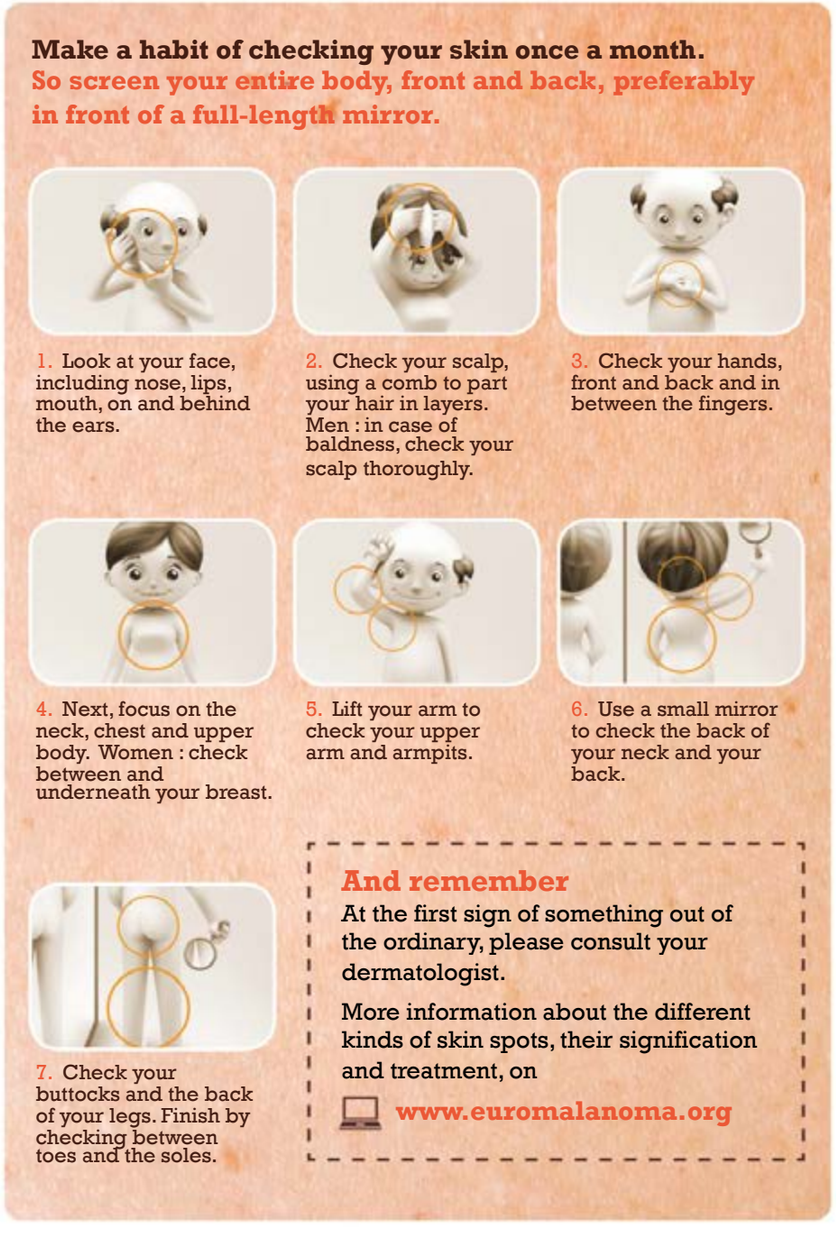


Figure 8. Skin self-examination guidelines, as recommended by the campaign "See it, stop it!" from Euromelanoma.org in 2013. Euromelanoma.org is a European campaign for skin cancer prevention, with the goal to give information to everybody on skin cancer prevention, early detection and treatment. Copyright permission from Euromelanoma.org

The majority of individuals (57% in one study) detect their own melanomas, as opposed to detection by physicians (16%) and spouses (11%) [114]. Women are better at detecting their own melanomas than males (69% versus 47%). Although individuals may be capable of detecting their own melanoma, there is sometimes a delay to seek medical advice. This is commonly referred to as patient's delay, which is defined as the time interval from the appearance of symptoms until the patient seeks medical care. Patient's delay can be caused by a lack of knowledge, fright for the diagnosis, and denial [115]. Patient's delay occurs regardless of the fact that many people are well-aware that early detection may improve the outcome. One study found that in Sweden and Australia, over 90% of melanoma patients had this knowledge [116].

Early detection by physicians (e.g. screening activities)

The time interval from the patient seeking medical care until diagnosis and treatment is known as doctor's delay. One important factor for influencing doctor's delay is lack of knowledge (i.e. low diagnostic accuracy) [116, 117].

Visual, macroscopic examination of a suspicious skin lesion is one way of detecting a melanoma for health care professionals. However, the diagnosis of skin lesions could be further refined using dermoscopy (skin surface microscopy). In a meta-analysis, dermoscopy increased the sensitivity of the diagnostic accuracy of melanoma significantly compared to visual examination. No significant increase in the specificity could be determined [118]. Total body photography combined with digital dermoscopic monitoring is a supportive technique used for high-risk individuals where the entire skin surface is photographed and additional macroscopic and dermoscopic photos are taken of selected lesions and monitored [119, 120]. Digital dermoscopic monitoring, comparing current and previous dermocopic images of melanocytic lesions to detect subtle changes, has proven to be helpful for detecting very early melanomas where specific criteria for melanoma are not yet present [120].

In the era of information technology, another new promising method has appeared to assist in the early detection of melanomas - teledermoscopy referrals. This is defined as attaching dermoscopic photographs to referrals for evaluation by a dermatologist. The use of dermoscopic photographs for triage of referrals has proven to be a useful method for shortening waiting times in the melanoma care pathway [121]. For Western Sweden, the implementation of teledermoscopy referrals is awaited during 2017.

There is money to be saved by channelling resources towards dermatologists examining suspicious skin lesions, instead of general practitioners. The reason for this is that dermatologists have a higher accuracy when diagnosing melanocytic skin lesions [117, 122, 123]. As a result from better diagnostic accuracy, the number of skin lesions needed to excise to detect a melanoma decreases. Lowering the rates of unnecessary excisions of benign skin lesions result in reduced costs [124]. Unfortunately there is a lack of dermatologists in Sweden, resulting in lower access to expert consultations regarding suspicious skin lesions [125]. Moreover, there is a national lack of pathologists, possibly resulting in long delays for pathological reports for excised lesions.

Screening of melanoma can be divided into mass screening of an entire population, opportunistic screening and screening of high-risk populations. Screening is per definition performed on asymptomatic populations.

The principles for mass screening of diseases was developed by Wilson et al. in a publication by the World Health Organization in 1968 [126]. Many, but maybe not all, of the principles that were originally identified, match to the screening of melanoma. First, melanoma is an important and widespread health problem. Second, there is an advantage of early detection of the disease. Also, total body skin examination and dermoscopy are suitable tests for the diagnosis of melanoma, well acceptable to the population. Further, excision is an effective treatment. However, speaking against the introduction of mass screening is the lack of data showing its cost-effectiveness. Moreover, it has to be proven that mass screenings reduce mortality from melanoma, since reducing mortality is the ultimate goal of secondary prevention.

The largest mass screening programme in the world so far was launched in 2008 in Germany, aimed at the entire population >35 years of age. The programme started after initial study data from the state of Schleswig-Holstein showed an instant decline in melanoma mortality rates. However, the decline in mortality was transient and might have been due to awareness effects, selection bias, data artefacts or natural fluctuations of the death rates [127]. In conclusion, there is no sufficient evidence for implementation of mass screening activities of an entire adult population. Consequently, this is also the statement from the Community Preventive Services Task Force under the United States Department of Health and Human Services [128].

Opportunistic screening is understood as screening for melanoma when patients present to a physician for other purposes. For instance, total body skin examination is valuable in patients presenting with localized dermatologic conditions, since this can detect melanomas that would have been otherwise overlooked. In one study, 0.3% of patients seeking for a localized dermatologic condition were found to have a melanoma on covered body parts when screened with total body skin examination. Total body skin examination should be considered in, among others, older patients and in patients consulting for any kind of skin tumour [129]. Opportunistic screening could also be performed together with a routine physical exam by a general practitioner.

Screening of high-risk populations could also be directed towards individuals with a risk factor for melanoma development. There are many examples of this in the literature, including screening of populations with personal or family history of melanoma and populations of men of older age groups [130-133]. Some of these high-risk screening activities favoured from combining several risk factors, which increased the risk of melanoma development among the participants. Screening of high-risk populations has, unlike mass screening, been proven to be cost-effective [84]. Therefore, high-risk population screening is something that could be used more in clinical practice in Sweden. Future screening strategies might also benefit from the use of new information technology [121, 134, 135].

1.4 STAGING AND CLASSIFICATION

1.4.1 STAGING

Worldwide, the American Joint Committee on Cancer (AJCC) staging system is used for cutaneous malignant melanoma (see *Figure 9*) [111]. The AJCC staging system was updated in 2009 and is based on the TNM Classification of malignant tumours. The TNM system describes whether the cancer has spread to the lymph nodes or if it has metastasized, assigning a letter and a number to describe the primary tumour (T), the nodes (N) and metastases (M).

American Joint Committee on Cancer

Melanoma of the Skin Staging 7th EDITION

Definitions

Primary Tumor (T)

- TX Primary tumor cannot be assessed (for example, curettaged or severely regressed melanoma)
- T0 No evidence of primary tumor
- Tis Melanoma in situ
- T1 Melanomas 1.0 mm or less in thickness
- T2 Melanomas 1.01–2.0 mm
- T3 Melanomas 2.01–4.0 mm
- T4 Melanomas more than 4.0 mm

NOTE: a and b subcategories of T are assigned based on ulceration and number of mitoses per mm², as shown below:

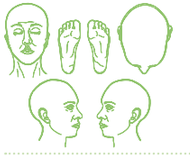
T CLASSIFICATION	THICKNESS (mm)	ULCERATION STATUS/MITOSES
T1	≤1.0	a: w/o ulceration and mitosis <1/mm² b: with ulceration or mitoses ≥1/mm²
T2	1.01–2.0	a: w/o ulceration b: with ulceration
T3	2.01–4.0	a: w/o ulceration b: with ulceration
T4	>4.0	a: w/o ulceration b: with ulceration

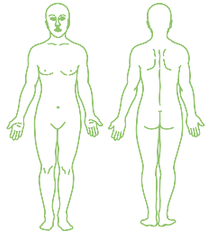
Regional Lymph Nodes (N)

- NX Patients in whom the regional nodes cannot be assessed (for example, previously removed for another reason)
- N0 No regional metastases detected
- N1-3 Regional metastases based upon the number of metastatic nodes and presence or absence of intralymphatic metastases (in transit or satellite metastases)

NOTE: N1–3 and a–c subcategories assigned as shown below:

N CLASSIFICATION	NO. OF METASTATIC NODES	NODAL METASTATIC MASS
N1	1 node	a: micrometastasis[1] b: macrometastasis[2]
N2	2–3 nodes	a: micrometastasis[1] b: macrometastasis[2] c: in transit met(s)/satellite(s) *without* metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) with metastatic node(s)	





Distant Metastatis (M)

- M0 No detectable evidence of distant metastases
- M1a Metastases to skin, subcutaneous, or distant lymph nodes
- M1b Metastases to lung
- M1c Metastases to all other visceral sites or distant metastases to any site combined with an elevated serum LDH

NOTE: Serum LDH is incorporated into the M category as shown below:

M CLASSIFICATION	SITE	SERUM LDH
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

ANATOMIC STAGE/PROGNOSTIC GROUPS

	Clinical Staging[3]			Pathologic Staging[4]			
Stage 0	Tis	N0	M0	0	Tis	N0	M0
Stage IA	T1a	N0	M0	IA	T1a	N0	M0
Stage IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
Stage IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
Stage IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
Stage IIC	T4b	N0	M0	IIC	T4b	N0	M0
Stage III	Any T	≥ N1	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
Stage IV	Any T	Any N	M1	IV	Any T	Any N	M1

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Notes

[1] Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed).

[2] Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

[3] Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

[4] Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic Stage 0 or Stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

Figure 9. The AJCC Melanoma of the skin staging (2009). Copyright permission from the AJCC.

Melanoma in situ (Stage 0)

Melanoma in situ is defined as a melanoma limited to the epidermis, not invading the dermis. The term in situ translates to "in place" in Latin. See *Figure 10* for a photo of a melanoma in situ. Melanoma in situ is classified as Tis histopathologically and as stage 0 clinically.

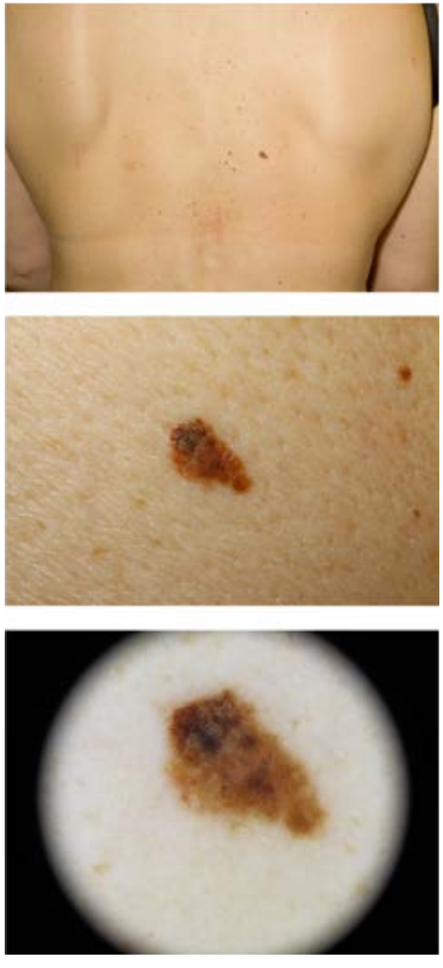


Figure 10. Melanoma in situ on the back of a patient. Photo: John Paoli

Melanoma has been shown to have a radial and a vertical growth phase. First, the tumour grows radially, spreading only in the epidermis. Eventually, if the lesion is not excised, the tumour moves on to a vertical growth phase, invading the deeper layers of the skin – the dermis [136].

Stage I and II (the T-stage)

Stage I and II melanomas are both clinical stages of localized disease, equal to an invasive primary tumour, without signs of lymph node involvement or metastases. The clinical stages I and II will depend on the histopathological T-stage.

The histopathological factors determining the T-stage in localized disease are the Breslow thickness in millimetres (describing the distance between the upper layer of the epidermis and the deepest point of penetration of a malignant melanoma), the presence or absence of epithelium ulceration and the mitotic rate. The absence of ulceration is classified with the letter "a" after the T-stage, whereas the presence of ulceration adds a "b" to the T-stage. The mitotic rate determines how fast-growing the cells in the melanoma are, and is used in the T1 category [137]. The cut-off for defining T1b melanomas (independently of whether there is ulceration or not) is a mitotic rate of ≥1 mitosis/mm^2 [111].

The Breslow thickness divides the melanomas of stage I and II into T-categories: Tis (in situ), T1 (≤1.0 mm), T2 (1.01–2.0 mm), T3 (2.01–4.0 mm) and T4 (>4.0 mm). The Breslow thickness at diagnosis depends on the rate of growth and the time of development of the tumour. Thus, T1a-b and T2a melanomas define a clinical stage I disease whereas T2b, T3a-b and T4a-b melanomas result in a clinical stage II.

In rare cases, when mitotic rate cannot be determined in the histopathological report, the Clark level of anatomic invasion comes into consideration in the staging system. The Clark levels of invasion are defined as follows: level I – melanoma only in the epidermis; level II – invasion into the papillary dermis; level III – expansion into the border between the papillary and the reticular dermis; level IV – invasion into the reticular dermis and level V – invasion into the subcutaneous fat.

Thin melanomas

Within stage I-II, there is a further, commonly used definition of melanomas based solely on the tumour thickness, namely the division into thin, intermediate and thick lesions:

- Thin melanomas have a Breslow thickness of ≤1 mm
- Intermediate-thickness melanomas have a Breslow thickness of 1.01-4 mm
- Thick melanomas have a Breslow thickness of >4 mm

Much of the increase in melanoma incidence in the world is owed to an increase in thin melanomas [2, 138-141]. This is true also for the Swedish melanoma population in recent years, where a shift towards thinner tumours can be seen. During 2007-2011, 50.7% of all melanomas among men and 57.4% among all women in Sweden were thin tumours, compared with 48.4% among men and 57.1% among women during 1997-2001 [141]. During the limited time period of 2002-2006, there was an unexplained tendency in Sweden towards a higher proportion of thick tumours (>4 mm) among women and among older men. However, during 2007-2011, this shifted back towards thinner melanomas.

Not only thin tumours have increased proportionally, but an incidence change of melanoma in situ has also been reported in Sweden. During the years 2009-2013, melanoma in situ rates in men increased from 24 to 32 per 100,000 person-years (Swedish standard population year 2000). Compared to Sweden as a whole, the incidence in men increased from 14 to 24 per 100,000 person-years [14]. Although there has been an increase in the melanoma in situ rates in Sweden, the increase might not be as high as reported. The National Board of Health and Welfare has recently acknowledged the misclassification of dysplastic nevi with severe atypia as melanoma in situ in their publication "Cancer Incidence in Sweden 2014" [10]. This falsely increased the number of newly diagnosed melanoma in situ with as much as 26% in 2014 (unpublished data).

The increasing proportion of thin melanomas has been attributed to a true increase in melanocytic neoplasms, to early detection and to diagnostic drift [5, 138-140, 142]. Melanoma survival is closely connected to tumour thickness, with excellent survival rates reported for thin tumours [111, 143]. However, there have been reports of a difference in survival rate within the group of thin melanomas, with lower rates for tumours ≥0.75 mm [143-145]. The original cut-off in thickness developed by Breslow was >0.75 mm, but since 2002 the cut-off for thin melanomas is 1 mm [111, 137].

Because of the excellent overall survival rates for patients with thin melanomas, these have been somewhat overlooked when investigating the burden of melanoma mortality. Since thin lesions have become so much more common, a recent study from Queensland, Australia has shown that in this population more people die from thin melanomas than from thick lesions (>4 mm) [146]. In that study, between the years 2005-2009, thin melanomas constituted 68% of all melanomas and were attributable to 23% of the melanoma deaths, whereas thick melanomas constituted 3% of all melanomas and accounted for 14% of deaths. Another study from the United States, showed that 26% of all melanoma fatalities were attributable to thin melanomas [147]. Also, thin melanomas have been shown to constitute a large proportion of Years of life with disability and Years of life lost in the disease compared to other melanomas [148]. Altogether, these studies exemplify the need to better identify, already at the time of diagnosis, the subset of patients with thin melanomas that will eventually die from metastasized disease. Consequently, a more detailed prognostic classification of thin tumours is desirable.

If thin melanomas could be classified in more detail according to prognosis, these patients could be monitored closely in follow-up programmes, with imaging techniques or sentinel lymph node biopsies. (See chapter 1.6.1 for a definition of sentinel lymph node biopsies.) And if patients with high-risk melanomas ≤1 mm were monitored more closely, treatment could be offered earlier. Such treatment could include metastasis surgery and the new therapies for metastasized melanoma that have revolutionized the management during the past few years [149]. Specifically, the use of immune checkpoint

inhibitors could be used in an adjuvant setting, despite their toxic side effects, if patients at high risk of death could be identified reliably. Nevertheless, this cannot be proposed to all patients with thin melanomas because of the high costs and the risk of adverse effects.

Stage III (the N-stage)

In stage III, the melanoma has spread beyond the original site in the skin, to satellite metastases, to in transit metastases or to the regional lymph nodes. This is also called regional metastatic disease. In the AJCC 2009, immunohistochemical detection of micrometastases was included, and defined as at least one melanoma marker stained in the tissue (e.g. HMB-45 or Melan-A/MART 1) in cells with malignant morphology [111].

Stage IV (the M-stage)

The definition of stage IV melanoma is that the tumour has metastasized (M-stage) to distant lymph nodes, to other areas of the skin or to internal organs. This is also called distant metastatic disease. Common sites of metastases are the lung, the liver, the brain, the bones, the skin and the gastrointestinal tract [150].

1.4.2 HISTOPATHOLOGICAL SUBTYPE

There are four main histopathological (=histogenetic) types of melanoma; nodular melanoma (NM), superficial spreading melanoma (SSM), lentigo maligna melanoma (LMM) and ALM. Further, there are melanomas of more uncommon histopathological types, such as desmoplastic melanoma, nevoid melanoma, spitzoid melanoma and melanoma arising from a blue nevus [13, 151]. SSM is the most common subtype, followed by NM, LMM and ALM. LMM are commonly found on body areas with chronic sun exposure, as the head and neck. ALM is found on acral body parts (hands, feet and subungual areas) [13].

1.4.3 EXTRACUTANEOUS MELANOMAS

Extracutaneous melanomas are rare tumours that include ocular, mucosal and leptomeningeal melanomas [152]. These tumours develop from melanocytes, which arise from the neural crest during prenatal development. In Sweden, there are around 70-80 new cases of ocular melanomas every year. Mucosal melanomas composed 2.1% of all melanomas in Sweden during the years 1960-2009 [13]. Extracutaneous melanomas have a poorer survival than do cutaneous melanomas [152].

1.5 PROGNOSIS

1.5.1 PROGNOSIS OF LOCALIZED DISEASE

In localized disease (stage I and II), the tumour thickness measured in millimetres according to Breslow, along with the presence of tumour ulceration and the mitotic rate have proven to be the most important prognostic factors [111, 143-145, 153-158]. Also, prognosis has been shown to alter depending on some other factors detailed below.

Breslow thickness

With increasing thickness in the categories T1-T4, there is a substantial decline in the survival of melanoma [111, 143, 144, 153-155, 158]. Comparing data from the patients used to validate the AJCC staging system from 2009 showed that the 10-year survival rate was 92% for T1 melanomas, 80% for T2 melanomas, 63% for T3 melanomas and 50% for T4 melanomas. This is regardless of the presence or absence of tumour ulceration [111].

Ulceration

The presence of tumour ulceration is also an independent prognostic factor, which lowers the survival rate of melanoma [111, 155, 158]. The presence of ulceration in a melanoma of a certain T-category decreases the survival rate as compared to a melanoma of the same T-category without ulceration. In addition, the survival rate of an ulcerated melanoma of a certain T-category closely resembles the prognosis of a melanoma with a one step higher T-category but without ulceration. For example, the 5-year survival rate of a T3b melanoma (68%) is very similar to that of a T4a melanoma (71%) [111].

Mitotic rate

As stated in the subchapter of Staging and classification, mitotic rate was introduced for the first time as an important independent prognostic factor in the AJCC 2009 staging system [111]. Mitotic rates of ≥1 mitosis/mm^2 have shown to correlate significantly with lower survival rates [157, 159]. In one study, a 10-year survival rate of 93% for melanomas with 0 mitosis/mm^2 was reported, whereas a 48% survival rate was found for melanomas with ≥20 mitosis/mm^2 [157].

Clark level

In past times, melanoma staging depended more heavily than today on the Clark level of invasion. However, due to low prognostic value, the AJCC has given the Clark level much less importance as a factor of influence in the current staging system [111]. The Clark level of invasion was replaced by mitotic rate as a primary criterion.

Age & Sex

Older age has shown to be an independent predictor of lower survival [143, 153, 157, 158]. Also, male sex indicates a lower survival of melanoma [143, 153, 154, 156], as previously mentioned in the subchapter of Melanoma mortality.

Anatomic location

Several studies have shown a lowered survival for melanomas located in the head and neck area [143, 154]. Also, one study has reported location on the trunk to be independently associated with lower survival rates [160].

Histopathological subtype

NMs are fast-growing tumours, with vertical growth rates reported in retrospective analyses of 0.33 mm/month, measured in Breslow thickness. This can be compared to the more slow-growing SSMs, with reported growth rates of 0.05 mm/month [161]. A result of fast growth rates is that the tumour rapidly invades deeper layers of the skin, thus having the potential to metastasize earlier. However, multivariate analyses in several studies have also shown that the subtypes NM and ALM are independent prognostic factors of lower survival, regardless of Breslow thickness [143, 154].

1.5.2 PROGNOSIS OF REGIONAL AND DISTANT METASTATIC DISEASE

In regional metastatic disease (stage III), the most important prognostic factors for survival are the number of lymph nodes with metastases, tumour burden at the time of staging (microscopic versus macroscopic), as well as ulceration and thickness of the primary tumour [111].

In distant metastatic disease (stage IV), the site of metastases (nonvisceral, lung, or any other metastatic sites) and elevated serum lactate dehydrogenase (LDH) levels are the prognostic factors used to categorize the melanomas.

1.6 MANAGEMENT

1.6.1 DIAGNOSIS AND MANAGEMENT OF PRIMARY MELANOMAS

When a patient presents with a suspected melanoma, a diagnostic elliptical surgical excision is performed, generally with 2 mm margins. The excision is performed to histopathologically verify the diagnosis, and to confirm the Breslow thickness, the presence or absence of ulceration and the mitotic rate of the tumour. According to the Swedish national guidelines for melanoma management, wide excision with 5 mm margins is recommended for melanoma in situ and lentigo maligna lesions [13]. Surgical margins with 1 cm are recommended for invasive melanomas ≤1.0 mm Breslow and 2 cm margins are recommended for invasive melanomas >1.0 mm Breslow. The margins are clinically measured around the primary tumour or, more commonly, around the scar after a previous diagnostic excision.

A sentinel lymph node biopsy is a procedure in which the sentinel lymph node (the first lymph node to which melanoma cells spread from the primary tumour) is first identified, then removed and later examined to establish if metastatic melanoma cells are present or not. If the sentinel lymph node biopsy is negative, this suggests that the melanoma has not developed the ability to metastasize to the regional lymph nodes. The sentinel lymph node biopsy is a very important prognostic indicator for survival in melanoma patients, but the impact of the sentinel lymph node biopsy on survival rates remains unclear [158, 162]. In Sweden, sentinel lymph node biopsy should be considered in patients with melanomas >1.0 mm Breslow and in patients with melanomas ≤1.0 mm Breslow with ulceration. It can also be discussed in patients with thicker T1 melanomas with mitoses but no ulceration [13]. Following a positive sentinel lymph node biopsy, a complete lymphadenectomy is currently performed.

1.6.2 DIAGNOSIS AND MANAGEMENT OF REGIONAL METASTATIC DISEASE

If palpable lymph nodes are present, fine needle aspiration cytology is recommended to confirm if regional metastatic disease is present. If melanoma metastasis to the regional lymph nodes is confirmed, complete lymphadenectomy should be performed [13].

Regional disease can also present as in transit or satellite metastasis, which can be surgically removed. If in transit or satellite metastases are located to the limbs, isolated limb perfusion is a treatment option [13, 163].

1.6.3 DIAGNOSIS AND MANAGEMENT OF DISTANT METASTATIC DISEASE

When distant metastatic disease is suspected, a PET-scan examination is primarily recommended for staging [13]. Also, serum lactate dehydrogenase and S-100 are analysed, since there are close correlations between the serum concentrations of these markers and tumour load.

During the past few years, several effective treatments for distant metastatic disease have developed [164]. If distant metastasis is present, the primary tumour or biopsy material is analysed for whether a mutation is present in the BRAF oncogene [13]. Today, immune therapy is the first-line treatment, with the exception of a fast-growing tumour with a BRAF mutation [149]. Examples of immune therapy are pembrolizumab, nivolumab and ipilimumab. If the tumour has a BRAF mutation, BRAF-inhibitors as vemurafenib or dabrafenib are used [13, 149]. It is also possible to combine a BRAF-inhibitor with a MEK-inhibitor, e.g. trametinib. Unfortunately, patients develop resistance towards the BRAF- and MEK-inhibitors after some time in treatment. Then, immune therapy may be an option instead.

If brain metastases are present, chemotherapies like dacarbazine or temozolomide are options for treatment. For treatment of smaller brain metastases, stereotactic radiation therapy is an option. Also, palliative radiation therapy can be used for symptomatic metastases on other locations of the body. Further, electrochemotherapy could be chosen for treatment of skin metastases, for example on the trunk [13, 149].

Studies regarding adjuvant therapy with the new melanoma drug therapies are being conducted right now, but no conclusion has been reached yet regarding the effect on overall survival [149]. However, the revolution of new therapies is still very much ongoing, as this thesis is being completed.

1.6.4 FOLLOW-UP

Worldwide, follow-up for melanoma remains an area for debate. A perfect follow-up programme would balance improved survival of the patients with economic costs for the follow-up visits. But at the moment, there is a lack of randomized studies that show an improved survival outcome for patients in follow-up, even if they include examinations as blood test screenings or imaging techniques. Thus, no specific follow-up programme can be supported and consequently, countries and organizations have developed their own programmes [165]. Further research in this area is needed.

In the Swedish national guidelines for melanoma management, follow-up frequency is recommended depending on the staging of the tumour and depending on additional risk factors [13]. As an example, no periodical follow-up is recommended for stage 0 and IA melanomas. Three years of follow-up is recommended for stage IB, II and III melanomas. The risk of developing a subsequent melanoma is disregarded, although multiple primary melanomas are common among melanoma survivors. When introducing the new national guidelines in 2013, Sweden moved towards a considerably lower number of follow-up visits in general [13, 166].

The goals of follow-up are to detect subsequent primary melanomas, to impart knowledge of skin self-examinations and sun protection, to offer reassurance to the patient and to diagnose metastatic disease at an early stage. In localized disease, the inspection and palpation of the surgical scar, palpation of all lymph node regions and inspection of the skin surface characterize follow-up care. In symptom-free patients, further examinations as radiological imaging techniques (CT, MRI or PET-scans), are not required.

1.7 HEALTH CARE ECONOMICS AND HEALTH SYSTEMS MANAGEMENT

1.7.1 COSTS OF SKIN CANCER

The economic impact of melanoma detection, treatment and follow-up on health care is substantial and Sweden is a country with a high cost to population ratio for skin cancer [84, 167]. In 2011, it was estimated that the total economic burden for melanoma in Sweden was over €93 million (*see Table 1*) [168]. Melanoma costs represented over 50% of the total societal cost for skin cancer, and included direct health care costs as well as indirect costs connected to production losses due to morbidity and mortality. However, in 2011 many of the new expensive drug treatments for distant metastatic disease were not in use, and were not included in the analysis [164].

In 2007, the costs for preventive interventions for skin cancer, on a national level in Sweden, were approximated to 18 million SEK [169]. Even though the numbers date a few years back in time, the investments in preventive interventions might not be enough.

Table 1. Cost of skin cancer in Sweden in 2011, in €1,000s (figures in parentheses represent percentage of total cost). Copyright permission from the author, Tinghög and from Acta Dermato-Venereologica [168]

	CMM	NMSC	MIS/CIS	MN	AK	Total
	€/1,000 (%)	€/1,000 (%)	€/1,000 (%)	€/1,000 (%)	€/1,000 (%)	€/1,000 (%)
Direct costs	21,593 (12,2)	39,163 (22)	1,099 (0.6)	21,959 (12.4)	18,393 (10.4)	102,206 (57.5)
Inpatient care	8,803 (5)	6,384 (3.6)	154 (0.1)	199 (0.1)	187 (0.1)	15,727 (8.9)
Outpatient/ primary care	12,789 (7,2)	32,779 (18.4)	945 (0.5)	21,760 (12.3)	18,206 (10.3)	86,479 (48.7)
Indirect costs*	71,783 (40.4)	3,641 (2.1)				75,424 (42.5)
Mortality	64,523 (36.3)	1,682 (1)				66,204 (37.3)
Morbidity	7,260 (4.1)	1,959 (1.1)				9,220 (5.2)
Total costs	93,376 (52.6)	42,804 (24.1)	1,099 (0.6)	21,959 (12.4)	18,393 (10.4)	177,630 (100)

*3 percent discount rate.
CMM: cutaneous malignant melanoma; NMSC: non-melanoma skin cancer; MIS: melanoma in situ; CIS: cancer in situ in the skin; MN: melanocytic naevi; AK: actinic keratosis.

The high burden of melanoma health care costs forces administrations around the world to focus on cost-effectiveness to make the best use of limited resources. System dynamics (further descried in the next chapter) is one of the applicable methods.

1.7.2 SYSTEM DYNAMICS MODELLING

What is system dynamics?

System dynamics is a computerized technique developed to understand the dynamic behaviour of a complex system [170-172]. It uses computer modelling to test alternative strategies and interventions, before they are actually introduced. Computer pioneer Professor Jay Forrester introduced the methodology already in the 1950s in the USA. Since then, it has been applied to economic, ecological and healthcare systems around the world. Industrial managers at the company of General Electric first practiced it, trying to determine the success or failure of a large corporation. In study IV of this thesis, system dynamics modelling was used in another type of complex system - a healthcare setting - more specifically, the melanoma care pathway in Western Sweden.

The complexity of the melanoma care pathway is a result of the multitude of components involved. Below, some of these are mentioned:

Patients
population growth, age of the population, sex, population skin type distribution

Doctors
access to and capability of involved specialists; general practitioners, dermatologists, pathologists, surgeons, oncologists etc.

Other medical resources, which can be unevenly distributed along the care pathway
hospital facilities, access to operation theatres, nurses

Financial resources
the budgets of the involved departments

Information
primary and secondary prevention (for instance information to the public about sun protection and early detection of melanoma)

IT and administrative systems
time-consuming referrals, coordination of the departments involved

Psychological states
tanning habits, skin cancer awareness, patients in denial of the tumour

Biological states
melanoma stages and histopathological subtypes

In complex systems, problems are often characterized by involving several goals and interests that compete for the same resources. Also, long time delays from action to an end-result make it hard to overview the results of an intervention. Further, problems in complex systems are often (erroneously) studied in isolation, instead of applying a "whole system" perspective. In a "whole system", all system components need to work together for success. Thus, the multiple components of the melanoma care pathway make it difficult to forecast the overall

43

results from single actions, for instance shortening waiting times for an appointment to a hospital-based dermatologist.

What kind of problems can be analysed by system dynamics?

To understand this methodology, one has to grasp that system dynamics modelling is something different from standard descriptive statistics that uses p-values and confidence intervals. Instead, system dynamics aims at supplying an approximation to reality that is valuable to its users.

Below is a list of some of the problems that system dynamics modelling is good at capturing; including a notation of the specific problems involved when analysing the melanoma care pathway:

Differences between short and long-term consequences of an action
the value of primary and secondary prevention of melanoma in a long-term perspective

Time delays
doctor's delay and patient's delay, leading to increased tumour thickness

Nonlinear causal relationships
rate of growth of melanomas, propensity to seek healthcare

Complex interactions
cooperation amongst departments, increasing skin cancer incidence leading to a lack of dermatologists

What are the benefits of using system dynamics?

System dynamics is of value when the users of a complex system want to get a deeper comprehension of how it functions. Further, as mentioned above, the methodology is of use to understand long-term consequences of different scenarios - will the future be worse or better? An understanding of future scenarios, before they actually happen, gives the users time to prepare for change and to assemble stronger support.

Moreover, system dynamics can be used to design preventive strategies and for refining guidelines. A well-documented and solid system dynamics model could help policymakers and healthcare stakeholders to choose the most cost-effective preventive intervention. The latter is of great importance to ease pressure on the strained Swedish health system.

02

AIMS

Magdalena Claeson

Epidemiology of cutaneous malignant melanoma in Western Sweden

AIMS

The overall aim of this thesis was to study the epidemiology of melanoma in Western Sweden and to suggest secondary prevention interventions. The specific aims of the studies are detailed below.

- To describe the incidence of melanoma in Western Sweden during 1970–2007, and to study geographical variations in incidence within the region.
- To describe characteristics of multiple primary melanomas (both invasive and in situ) in Western Sweden during 1990-2013.
- To describe characteristics of lethal melanomas in Western Sweden during 1990-2014, with a focus on thin lesions, ≤1 mm Breslow thickness.
- To use system dynamics computer simulations to model future plausible scenarios in the melanoma care pathway, in case of a continued increase in melanoma incidence.

03
METHODS

Magdalena Claeson

Epidemiology of cutaneous malignant melanoma in Western Sweden

METHODS

3.1 THE SWEDISH CANCER REGISTRY

The Swedish Cancer Registry at the National Board of Health and Welfare was founded in 1958 and covers the entire population [173]. The reporting of newly detected cancer cases is compulsory by law for all health care providers. In Sweden, there are six regions for the organization and quality control of cancer healthcare, each with a centre responsible for the prospective registration of tumours. The regional cancer centres collect information about newly registered cases and forward the information to the Swedish Cancer Registry annually, including corrections of previous cases.

The information in the reports include among others:

- patient data (personal identification number, sex, age and place of residence)
- medical data (site of tumour, histopathological subtype, stage, date of diagnosis, reporting hospital and department
- follow-up data (date of death, cause of death, date of migration)

In the Swedish Cancer Registry, invasive lesions, as well as melanoma in situ and lentigo maligna, are all included. The completeness of the data (for all cancers) is very high, with an underreporting of around 4% described in a publication [174].

Data from the Swedish Cancer Registry were used in study I.

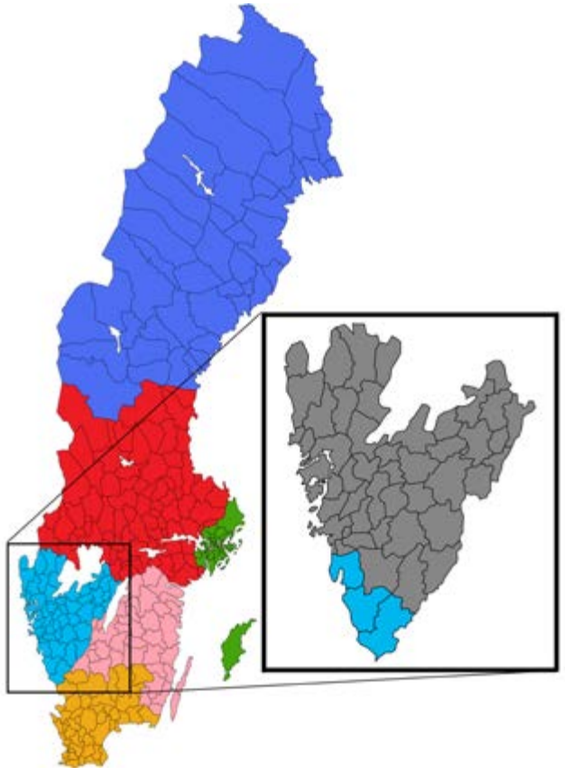
3.2 THE SWEDISH MELANOMA REGISTRY

The Regional Cancer Centre Western Sweden collects the above-mentioned information on new cases of melanoma from the Western Sweden health care region [175]. The data are collected in the Swedish Melanoma Registry, before annual forwarding to the Swedish Cancer Registry at the National Board of Health and Welfare. In the Swedish Melanoma Registry, invasive lesions, as well as melanoma in situ and lentigo maligna, were all included until the month of June 2015. Thereafter, the inclusion of melanoma in situ and lentigo maligna was halted. The coverage of the registry was 99% for invasive melanoma and 92% for melanoma in situ between the years 2009-2013 [176]

The Western Sweden health care region corresponds geographically to the county of Western Sweden and the northern parts of Halland county [175]. This health care region has approximately 1.8 million inhabitants, corresponding to 19% of the national population [177]. Data from the Swedish Melanoma Registry from the population of the Western Sweden health care region were used in study III.

In studies II and IV, only data from the population of the county of Western Sweden were used, which is a part of the Western Sweden health care region. This county has approximately 1.6 million inhabitants, corresponding to 17% of the national population [178]. See *Figure 11* for a map of Sweden and *Figure 12* for a photo of the natural scenery of Western Sweden.

Figure 11. Map of Sweden, divided into six health care regions. In the magnified map of the Western Sweden health care region, the grey area represents the county of Western Sweden [179].



3.3 THE SWEDISH CAUSE OF DEATH REGISTRY

The Swedish Cause of Death Registry collects data since 1961 on the underlying cause of death for all persons registered in Sweden, who died during one calendar year [180]. The collection also includes those who are registered in Sweden, but died outside of the country. The classification is coded according to the international version of the disease classification ICD-10.

3.4 NATIONELL MILJÖ-HÄLSOENKÄT 2007 – THE SUN EXPOSURE SURVEY

Every eight years, the National Board of Health and Welfare conducts a survey concerning adults' environmental health, in collaboration with the Institute of Environmental Medicine at Karolinska Institutet in Stockholm, Sweden. The survey Nationell Miljöhälsoenkät 2007 (NMHE 07) resulted in a report published two years later - Miljöhälsorapport 2009 [181]. The aim of the report was to describe the impact of environmental factors on health in Sweden. Comparison with previous data in the series of surveys (1999, 2007 and 2015) is an important part of the reporting.

In the 2009 survey, the postal questionnaire consisted of 199 environmental health questions, of which six questions were related to sun exposure. These questions considered personal recreational and occupational sun exposure, sun protection behaviour, sunburn episodes, and sunbed use during the previous year. The participants were also asked about their skin type.

Figure 12. Marstrand, Western Sweden. Photo: Cecilia Norman.

3.5 STUDY DESIGN

3.5.1 STUDY I

Subjects

The Swedish Cancer Registry provided data on invasive melanomas for the years 1970-2007, for Sweden as a whole, for the county of Western Sweden, and for three different geographical subareas of Western Sweden.

Design

The Swedish Meteorological and Hydrological Institute provided meteorological maps, showing the annual average duration of sunshine during the years 1961-1990 [17]. The 49 municipalities in Western Sweden were divided into three geographical subareas. Almost all of the municipalities on the coast were classified as having a high annual average

duration of sunshine (1701–1900 h of sun), as well as the larger urban area of Gothenburg, which is also situated on the coast. Almost all of the inland municipalities were classified as having a low average duration of sunshine (≤1700 h of sun).

Data on self-reported sun exposure were obtained from the survey Nationell Miljöhälsoenkät 2007, which included 2,871 participants from Western Sweden [181].

Statistical analysis

The incidence trends in the three different geographical subareas were estimated using ordinary least squares regression on the log-transformed standardized incidence (Swedish standard population year 2000). The regression model included a trend component and indicator variables for the different geographical areas.

Chi-square tests were used to analyse the sun exposure survey, regarding possible differences between the populations of the three geographical areas.

3.5.2 STUDY II

Subjects

Population-based, retrospective data on all invasive and in situ melanomas in the county of Western Sweden, for the years 1990-2013 were extracted from the Swedish Melanoma Registry. Data on patient characteristics, as well as tumour characteristics, were obtained.

Design

Study II analysed the number of multiple primary melanomas and the proportion of patients developing subsequent lesions. Further, the age at diagnosis of patients with multiple primary melanomas was calculated, as well as the Breslow thickness and histopathological subtypes for subsequent tumours. Five-year and ten-year estimates of the probability of developing a subsequent melanoma were calculated. Also, in a univariate Cox proportional hazards model, hazard ratios for developing a subsequent melanoma were analysed.

Time to diagnosis was calculated, defined as the elapsed time from diagnosis of a first melanoma to diagnosis of a subsequent melanoma. Some of the multiple primaries in the registry were detected within a short time period after the first melanoma, indicating that they were both detected within the care pathway of the first melanoma. Therefore, a previously used definition was applied, describing synchronous melanomas as two or more melanomas diagnosed within three months of time [63, 71, 182]. When there were synchronous lesions, we chose the thickest melanoma in the first period of 3 months to be compared with the thickest melanoma in the subsequent period of 3 months.

Statistical analysis

The Wilcoxon rank sum test was used for two-sample comparisons. For paired tests, the Wilcoxon signed rank test was used. The exact binomial test was used as a pairwise sign-test. Fisher's exact test was used to compare proportions. Kaplan-Meier estimates were calculated for the five-year and ten-year probability of developing a subsequent melanoma. Univariate Cox proportional hazards tests were performed to test for dependence between the time from the first to the subsequent melanoma versus sex, age and whether the first melanoma was invasive or in situ. All data were analysed using R version 3.0.3 (The R Foundation for Statistical Computing, Vienna, Austria).

3.5.3 STUDY III

Subjects

Population-based retrospective data on all invasive melanomas in Western Sweden for the years 1990-2014 were extracted from the Swedish Melanoma Registry. Data on patient and tumour characteristics were obtained from the registry.

Design

From the national Swedish Cause of Death Registry, the date and cause of death for all decedents in our cohort until December 31, 2014 were obtained. For the linking between the Cause of Death Registry and the Swedish Melanoma Registry, the Swedish personal identification number was used. Survival time was defined as the time from the date of diagnosis for the first invasive melanoma to the date of melanoma-specific death.

Statistical analysis

Age-standardized incidence rates per 100,000 person-years (the United States standard population year 2000) for invasive melanoma were calculated, as well as crude incidence rates per 100,000 person-years. Also, univariate Kaplan-Meier estimates for 10-year melanoma-specific survival were calculated in 5-year time intervals. A Cox proportional hazards regression model was used to calculate the melanoma-specific survival for different clinicopathological variables. All data were analysed using R version 3.0.3 (The R Foundation for Statistical Computing, Vienna, Austria).

3.5.4 STUDY IV

Subjects

Data extraction from the Swedish Melanoma Registry provided 6,229 cases of invasive melanoma in Western Sweden from 1990 until 2006. This data set was used as a foundation to construct the system dynamics model.

Design

The system dynamics population model was designed exclusively for this study, with the purpose of producing estimates of accumulated melanoma cases for the next 10-year period (2014–2023), and to compare future plausible scenarios. The iThink® computer simulation software (isee Systems Inc., New Hampshire, USA; iseesystems.com) was used.

There are previous examples of collaborative development methods, facilitating effective teamwork involving both medical expertise and system dynamics modellers [12]. The system dynamics model in study IV was developed solely for the melanoma care pathway project, in collaboration with modellers Paul Holmström and Stefan Hallberg. The modellers have long and extensive experience in systems thinking and simulation development, and have worked in healthcare settings as organisational consultants. Holmström and Hallberg are connected to the Centre for Healthcare Improvement, Chalmers University of Technology in Gothenburg, Sweden, which is a research centre for improvement, innovation and transformation of healthcare in Western Sweden.

The model simulates disease progression in a population. In the melanoma care pathway, T-categories specify disease progression. The concept of an ageing chain is used, which means that the condition of the individual depends on the time elapsed since onset of the melanoma. Individuals are grouped at discrete stages of progression, which allows calculation of the number of patients being of a specific T-category over time.

The construction of the system dynamics model is described in detail in the separately published paper "Developing a simulation model for the patient pathway of cutaneous malignant melanoma" [183]. This paper was written by the same authors as study IV, but is not a part of this thesis.

The following numbered list is a summarized overview of the simulation model development.

1. Identify a problematic situation:

The demand for melanoma healthcare in Western Sweden is increasing. What is the number of melanomas that healthcare has to prepare for in ten years from now?

2. Create a hypothesis: What causes the problem?

Increasing melanoma incidence. Doctor's delay and patient's delay.

3. Gather all available evidence:

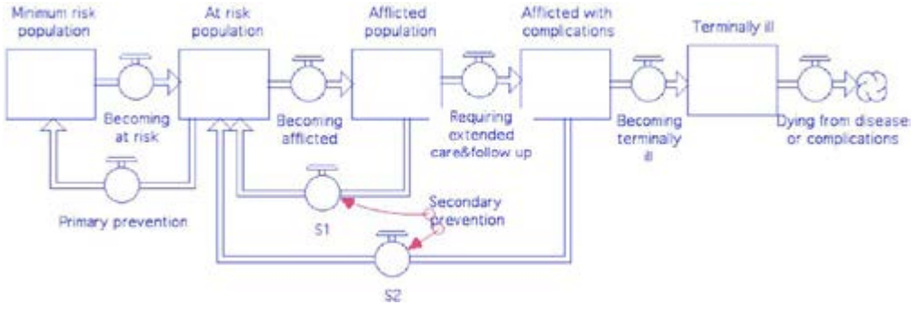
Data were collected regarding the following variables:

- population size [178]
- population growth [184]
- duration for doctor's delay and patient's delay [121]
- data extraction from the Swedish Melanoma – Registry, invasive melanomas 1990-2006
- melanoma incidence rates [185]
- annual percentage increase of incidence [13]
- rate of growth for melanomas of different histopathological subtypes [116, 161, 186]

4. Construct a simulation model:

For an overview of the system dynamics simulation model, see *Figure 13*.

Figure 13. A system dynamics simulation model of melanoma progression –a "stock and flow computer diagram".
Reprinted from Hallberg S, Claeson M et al. Developing a simulation model for the patient pathway of cutaneous malignant melanoma. Operations Research for Health Care. 2015; 6: 23-30. Copyright permission from Elsevier.



5. Define plausible future scenarios for the melanoma care pathway:

All scenarios took the growing population into account, but differed regarding incidence increase and preventive interventions.

- 1. Stable incidence (+8% population growth, no intervention)
- 2. Business-as-usual (+8% population growth, +5.25% incidence increase per year, no intervention)
- 3. Reduced patient's delay (+8% population growth, +5.25% incidence increase per year, -25% patient's delay)
- 4. Reduced doctor's delay (+8% population growth, +5.25% incidence increase per year, -50% doctor's delay)
- 5. Improved overall secondary prevention (+8% population growth, +5.25% incidence increase per year, -25% patient's delay and -50% doctor's delay)

6. Run simulation and compare the outcome of plausible future scenarios:

By sliding knobs and turning dials in the simulation model, data could be altered and different future scenarios for the melanoma care pathway could be compared. For a screenshot of the simulation model interface, see *Figure 14*.

Statistical analysis

No statistical analyses were performed in study IV, since descriptive statistics is not a part of the system dynamics methodology.

3.6 ETHICAL CONSIDERATIONS

Ethical approval from the regional ethics board was obtained for all studies I-IV.

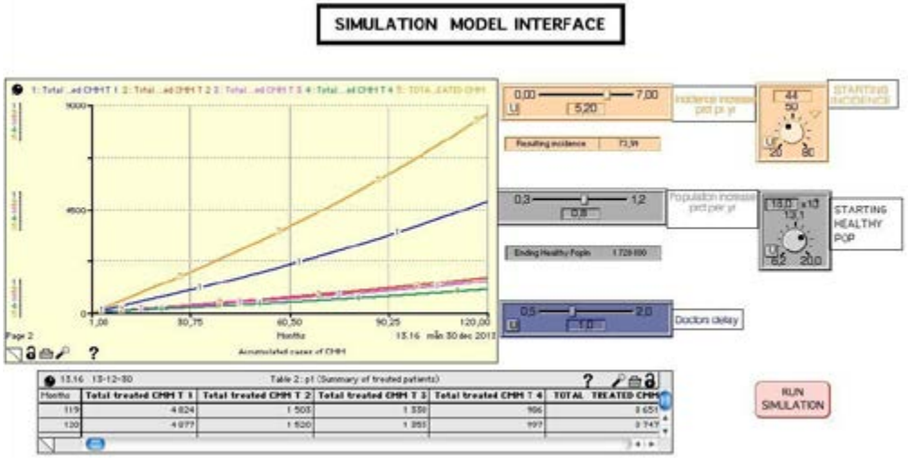


Figure 14. The simulation model interface. Data variables were inserted and could be altered by sliding the knobs and turning the dials. Pushing the button "Run simulation" resulted in an approximation of the accumulated number of melanoma cases for the next ten years, in total and divided by Breslow tumour thickness (T1-T4).

04

RESULTS

Magdalena Claeson

Epidemiology of cutaneous malignant melanoma in Western Sweden

RESULTS

4.1 STUDY I

From 1970-2007, the incidence of melanoma (Swedish standard population year 2000) per 100,000 person-years in Western Sweden increased from 6.8 to 31.1 for men and from 9.1 to 27.1 for women. In Sweden as a whole, the incidence increased from 7.1 to 26.3 for men and from 8.4 to 24.0 for women. The annual percentage change of the incidence in Western Sweden was 3.6% for men (95% CI: 3.2–3.9) and 3.1% for women (95% CI: 2.8–3.5). This can be compared with the increase in Sweden nationwide: 3.6% for men (95% CI: 3.3–3.9) and 2.8% for women (95% CI: 2.5–3.1).

The incidence of melanoma increased in all three geographical areas of Western Sweden, during the period studied. We found a 15.4% (95%CI: 2.3–30.2%, p=0.0199) higher incidence among women in the coastal areas compared with the inland. For men, our results also indicated a 12.7% (95%CI: -1.2 to 28.5%, p=0.075) higher incidence on the coast, but this did not reach statistical significance. The incidence in the city of Gothenburg was also higher than that of the inland areas. It was 34.9% higher for men (95% CI: 18.4–53.7, p<0.0001) and 24.8% higher for women (95% CI: 10.7–40.8, p=0.0004).

The sun exposure survey found differences regarding recreational sun exposure abroad between the three geographical areas. In the areas with the highest incidence of melanoma, the populations reported higher sun exposure on holidays abroad. As an example, in the city of Gothenburg and in the coastal areas, 53% and 50%, respectively, spent 5–6 h/day outdoors during a sun holiday abroad. The corresponding figure was 45% in the inland areas (p=0.0006). Also, the proportion of individuals in the city of Gothenburg and in the coastal areas who spent more than 4 weeks on a sun holiday abroad during the previous year was 6% and 4%, respectively. The corresponding figure for the inland areas was 3% (p=0.0003).

The sun exposure survey also showed differences between the geographical areas regarding occupational sun exposure. In the city of Gothenburg, 24% worked indoors (i.e. spent a maximum of 1 h in the sun during a workday). The corresponding percentage for the inland areas and the coastal areas was 18% and 12%, respectively. Also, 16% of individuals in the inland areas spent 5–6 h outdoors during a workday, whereas only 10% did so in the city of Gothenburg and 12% in the coastal areas (p<0.0001).

4.2 STUDY II

Of all 12,152 patients registered in the Swedish Melanoma Registry between 1990-2013, 11,254 patients only developed a single primary melanoma, whereas 898 patients (486 men, 412 women) developed multiple primaries. Thus, in this population-based cohort in Western Sweden, a proportion of 7.4% of the patients developed multiple tumours.

The median and mean age of the patients with multiple lesions at diagnosis of the first melanoma was 67 and 66 years for men (95% CI 65-67, p<0.001) and 64 and 61 years for women (95% CI 60-63, p<0.001). Most commonly, the patients with multiple primary melanomas developed only two melanomas, (n=729, 81%), although patients with three or four melanomas were not uncommon, corresponding to 126 (14%) and 30 (3%) patients, respectively.

The 10-year estimate for the probability of developing a subsequent melanoma was 5.0% (95% CI 4.4-5.7%). Men showed a higher probability for subsequent lesions than did women, with 10-year estimates of 6.0% (4.9-6.9%) and 4.1% (3.3-5.0%), respectively. Consequently, the Cox proportional

hazards model showed men to be at considerably higher risk of developing a subsequent melanoma compared to females, with a hazard ratio of 1.37 (95% CI 1.15-1.60, p=0.005).

A greater proportion of the subsequent tumours were melanoma in situ lesions (47%) compared to the first melanomas (26%, p<0.0001). Lastly, the median and mean time to diagnosis of the first subsequent melanoma was 38 and 58 months (95% CI, 53-62), respectively.

4.3 STUDY III

During the study period from 1990-2014, 1,287 patients in Western Sweden succumbed to melanoma disease (60.8% men and 39.2% women). The median and mean times to death were 2.9 and 4.1 years, respectively and the median and mean Breslow thickness for all lethal melanomas was 2.9 mm and 4.3 mm (95%CI: 4.0-4.6). During the study period, there was an increase in the incidence (United States standard population year 2000) of thin melanomas from 9.1 (95%CI: 8.5-9.8) to 21.3 (95%CI: 20.4-22.1) per 100,000 person-years.

Thin melanomas (≤1 mm) constituted 55.2% of the total invasive melanomas and accounted for 14.7% (190 patients) of all melanoma deaths. Thick melanomas (>4 mm), on the other hand, constituted 9.7% of all invasive melanomas and accounted for 32.2% (414 patients) of all melanoma deaths.

The overall 10-year melanoma-specific survival for invasive melanomas was 84.5% (95%CI:83.5-85.5), with a survival disadvantage for men with 79.8% (95%CI: 78.2-81.4) against women with 88.8% (95%CI: 87.6-90.0). The survival decreased with age, with the lowest survival in the group of decedents aged over 69 years at diagnosis, with 74.9% (95%CI: 72.6-77.4).

Thin melanomas (≤1 mm) had an overall high survival rate of 96.3% (95%CI: 95.6-97.0). This could be compared to the low survival rate of thick melanomas (>4 mm) of 45.2% (95%CI: 40.5-50.5).

This study sought to further stratify thin melanomas due to prognostic factors. When doing so, we found that the 10-year survival of non-ulcerated tumours 0.76-1 mm and of ulcerated tumours 0.26-1 mm together was 91.9% (95%CI: 90.0-93.9). This survival was significantly poorer than for non-ulcerated tumours ≤0.75 mm, with 98.1% (95%CI: 97.5-98.7) (p<0.0001). There was no patient dying from an ulcerated tumour ≤0.25 mm within the time frame for the survival analysis.

Further, a low 10-year survival rate was noted for melanomas at the "hand, foot and subungual" body sites: 53.9% (95%CI: 44.2-65.7) and at the head and neck body sites: 80.7% (95%CI: 77.3-84.3) In addition to this, the survival for patients with NMs and for patients with ALMs was poor, with 63.0% (95%CI: 60.1-66.0) and 66.7% (95%CI: 57.2-77.7) of the patients surviving after 10 years, respectively.

Moreover, NMs showed an independent and statistically significant decreased survival when compared to SSMs, when controlling for Breslow thickness, ulceration and age group (p=0.013).

4.4 STUDY IV

The results of the system dynamics simulations were presented as the accumulated number of melanoma cases after 10 years in Western Sweden, and the outcome of the five different scenarios were analysed. After 10 years, the business-as-usual scenario would have resulted in 36% more accumulated melanoma cases, compared with the stable incidence scenario. Comparing the number of melanoma cases in the business-as-usual scenario in 2014 (749 cases) compared to in 2023 (1,278 cases) showed a 71% increase.

The improved overall secondary prevention scenario would have resulted in a shift towards thinner tumours, with 10% more cases of category T1 melanomas and 42% less cases of stage T4 melanomas, as compared to the business-as-usual scenario. Also, the improved overall secondary prevention scenario would have resulted in 196 (2%) more cases of CMM during the next 10-year period compared with the business-as-usual scenario. When analysing the simulation outcome of patient's and doctor's delay separately, it was evident that reducing patient's delay would have had the greatest impact on decreasing the number of category T4 melanomas. Comparing with reduced doctor's delay, the reduced patient's delay scenario would have resulted in 26% less cases of category T4 melanomas.

When analysing the scenarios for fast-growing and slow-growing melanomas separately, it was found that improved overall secondary prevention would have had a more substantial impact on reducing the thickness of fast-growing melanomas than it would on the slow-growing melanomas. Thus, improving the secondary prevention of fast-growing melanomas would have reduced the number of category T4 melanomas by 47%, compared with business-as-usual. Improving the secondary prevention of slow-growing melanomas, on the other hand, would only have reduced the number of category T4 melanomas by 3%, compared with the business-as-usual scenario.

Magdalena Claeson

DISCUSSION & METHODOLOGICAL CONSIDERATIONS

5.1 STUDY I

Methodological considerations

The most important limitation of study I can be described in the well-known term "ecological fallacy". Generally, an ecological study design is ideal to find risk factors affecting health in populations that are defined geographically. The great benefit is that a large population can be included, as well as a large number of risk factors. In study I, an alarming increase in melanoma incidence was found in Western Sweden, with an especially high incidence in the city of Gothenburg and in the coastal areas. All data in the study were analysed on a population level, and not on an individual level. The results did show a significant correlation between a high incidence of melanoma and high annual average duration of sunshine, high sun exposure on holidays abroad, as well as with low occupational sun exposure in the three geographical areas. However, according to the theory of ecological fallacy, ecologic correlation does not automatically indicate causation. Some people in the study population may of course have melanomas not related to the studied risk factors.

Also, we could not control for the lifetime geographical mobility of individuals. Data regarding residency in a specific geographical region of Western Sweden were only recorded when the tumour was diagnosed. In other words, some individuals may have spent most of their life in another geographical region.

Nationell miljöhälsoenkät 2007 – the sun exposure survey

Nationwide, over 43,000 participants were selected randomly for the survey Nationell Miljöhälsoenkät 2007, and almost 26,000 participants responded (response rate 59%) [181]. In Western Sweden, 2,871 inhabitants participated (response rate 58%). The response rates differed between the partaking counties, ranging from 55%-69%. The age group of 60-80 years old had the highest response rate (73%). Women had a higher response rate than did men, and the lowest response rate was found in the group of younger men, 18-39 years old (40%). Further, high income and higher education resulted in higher response rates (65% and 68% respectively), as compared to low income and lower education (51% and 54% respectively). A low response rate (41%) was also found in participants born outside of the Nordic countries.

Although the results from the survey are based on a thoroughly developed questionnaire with relatively high response rates overall, it has to be taken into consideration that the difference in response rates between subgroups could have had a minor influence on the study result. The high response rates in participants with high income and higher education may have resulted in an overrepresentation of persons more exposed to UV radiation in the data. In the literature, high socioeconomic status has been linked to an increased risk of melanoma, possibly due to intermittent UV exposure in connection with sun holidays [187, 188]. However, with a deregulated aviation market in Europe, leading to lower air travel costs, the linkage to high socioeconomic status may become weaker in the future [34].

Interestingly enough, there was no difference in population skin type between the three geographical regions in Study I. One might have expected this, due to the relatively high proportion of people with non-Swedish ethnic origin in the city of Gothenburg. This finding might be an effect of the low response rates in survey participants born outside of the Nordic countries.

Non-response bias occurs in statistical surveys if the answers of respondents differ from the potential answers of those who did not answer. In the case of the Nationell Miljöhälsoenkät 2007, an analysis of possible non-response biases was performed. Among a randomly selected subset of 671 non-responders to the postal questionnaire, a short telephone survey was conducted. The analysis yielded no difference in the proportion of responders and non-responders stating their health status as "very good" (23% vs. 24%), when all age groups were included. Unfortunately, the response rates and the non-response bias analysis were only calculated for the entire country of Sweden, and no separate analyses for Western Sweden were available.

Another last concern was the fact that we could not take into account the cumulative sun exposure during life, since the national sun exposure survey only assessed the behaviour in the sun during the previous year.

General discussion

During 1970-2007, the incidence of melanoma in Western Sweden more than quadrupled for men and tripled for women. Within the region, coastal areas and the city of Gothenburg had a higher incidence of melanoma than inland areas. There is consensus today about UV light exposure being the major cause of melanoma, and the findings of study I fit well into this theory. We found that the high incidence of melanoma in coastal areas and in the city of Gothenburg may be connected to UV radiation, because historical meteorological maps demonstrated a higher annual average duration of sunshine here. Other evidence that supports the connection is the high sun exposure on holidays abroad and the low occupational sun exposure in the populations in the coastal areas and in the city of Gothenburg.

There was no sign of a stabilization of the melanoma incidence in Western Sweden during the study period. Instead, the incidence continued to rise dramatically during these decades, mimicking the increase in fair-skinned populations worldwide that was described in the subchapter Epidemiology of melanoma. In comparison with other parts of Sweden, Western Sweden showed the highest melanoma incidence of all counties during the years 2000-2008 [189]. Thus, Western Sweden ought to be a target area when health care stakeholders distribute resources for preventive interventions in the future.

5.2 STUDY II

Methodological considerations

In study II, we analysed multiple primary melanomas in Western Sweden. One concern in the study methodology was the analysis of synchronous melanomas. Whenever a patient had two or more synchronous melanomas within a period of three months, it was decided to analyse the characteristics of the thickest of those tumours, leaving the thinner melanoma(s) out of the analysis. Another way of confronting this problem would have been to analyse the characteristics of the first melanoma detected during that time period. Some previous studies on multiple primary melanomas did not state if the thickest or the first of the synchronous melanomas was analysed. We chose to analyse the thickest tumour, as this tumour was perceived as most likely to have caused the melanoma fatality.

Of concern was also the fact that no data from the Swedish Cause of Death Registry were available for the patients. Thus, no censoring for death or migration could be performed in the 5-year and 10-year Kaplan-Meier estimates for the probability of developing a subsequent melanoma. This may have caused an underestimation of subsequent melanomas, leading to older age groups having inadequately low probabilities of developing subsequent melanomas. Also, the lack of data from the Swedish Cause of Death Registry left us with no possibility to calculate survival rates for patients with multiple primary melanomas.

General discussion

The proportion of patients with multiple primary melanomas in the Western Sweden population was 7.4%. When comparing with previous studies, this percentage has ranged from 0.2%-8.6% depending on the inclusion or exclusion of melanoma in situ, on whether the study was based in a skin cancer clinic or population-based, and on the length of the study period [65, 68]. Since patients with multiple primary melanomas recently have been reported to have lower survival rates than do patients with only a single primary melanoma, this is an important group of high-risk patients to identify [66, 67].

In the Western Sweden population of patients with multiple primary melanomas, a significantly increased proportion of melanoma in situ was found among subsequent melanomas. Further, a trend towards thinner invasive subsequent tumours was observed, but this was not significant (p=0.052). Several previous studies have shown similar results, indicating earlier detection of subsequent tumours [63, 65, 69, 190].

Around half of the subsequent melanomas in Western Sweden were detected within three years time after the initial tumour and the median time to diagnosis of a subsequent melanoma was 3 years and 2 months. Since the longest time-period for follow-up of localized disease is 3 years in the Swedish national guidelines for the management of melanoma, this suggests that many subsequent melanomas will not be detected during the follow-up programmes. Sweden moved towards a considerably lower number of follow-up visits with the introduction of the new national guidelines in 2013 [13]. This will most likely reduce health care costs for follow-up visits of patients with single primary melanomas in the future, but might lead to subsequent melanomas being detected at a later stage.

Finally, men showed a higher hazard of developing multiple primary melanomas. This subgroup could possibly have an increased value of a closer follow-up regimen.

5.3 STUDY III

Methodological considerations

This population-based registry study presented some limitations. One concern was the lack of information in the data set of some specific clinicopathological characteristics that may influence survival; namely the presence of mitosis, the patient phenotype and the patient genotype. Also, data on the Clark level and data on metastatic melanomas with an unknown primary tumour were not available for analysis, which complicated the comparison with other studies on thin melanomas.

Another concern was the time frame of the study, which made a 20-year survival analysis impossible. However, the results showed that 87.7% of the decedents diagnosed between 1990-2004 succumbed to the disease within ten years, so the 10-year survival analysis appeared sufficient.

General discussion

The strength of study III is the population-based approach and the accuracy of the Swedish Melanoma Registry, with a low frequency of missing data. The study repeated some previous findings, confirming low survival rates among the melanoma decedents with the following characteristics: male sex [143, 153, 154], older age [143, 153, 158], increasing tumour thickness [111, 143, 144, 153-155, 158], ulcerated tumours [111, 155, 158], NM subtype [143, 154] and ALM [143, 154] subtype. Further, study III indicated a poor survival for tumours located on the head and neck areas, as well as the "hand, foot and subungual" body sites. Since other studies have only found poorer survival for head and neck tumours [143, 154], these findings should be interpreted cautiously.

Thin melanomas showed to be very common in Western Sweden, constituting 55.2% of the total number of invasive melanomas and contributing to as much as 14.7% of all melanoma deaths. Comparing the results from Western Sweden with a recent study from Queensland, Australia (68% thin melanomas, causing 23% of the melanoma deaths) gave the impression that the "melanoma epidemic" is more immature in Sweden. Thus, the escalating health care costs are to be expected for many years yet [146]. Early detection pressure may also be present in Sweden, as shown by an increasing proportion of thin melanomas [141].

As previously mentioned in the subchapter of Staging and classification, the identification of clinicopathological prognostic factors for lethal thin melanomas remains an important area of research covered by several previous studies [143-145, 153-155, 158, 191, 192]. In study III, we created a prognostic model for thin melanomas, combining two variables - Breslow thickness and ulceration. Significantly poorer survival was identified for ulcerated melanomas with a thickness of 0.26-1 mm and for non-ulcerated melanomas with a thickness of 0.76-1 mm. We therefore suggest the possible future use of our prognostic model in order to include said patients in the follow-up schedules stated in the national guidelines. The use of sentinel lymph node biopsies in such patients may also be considered.

5.4 STUDY IV

Methodological considerations

In the subchapter Health care economics and health systems management, some benefits of using system dynamics modelling were described. However, a drawback of system dynamics is that the model might be perceived as abstract to users not familiar with simulation techniques. A further issue is that the methodology does not use standard descriptive statistics. This might be recognized as odd to non-modellers that are used to depending on statistical significance. However, statistical significance is not an aim of system dynamics. Instead, the aim is to supply an approximation for interpretation of reality that is valuable to the users.

To validate the system dynamics model, we compared simulation data from Western Sweden with corresponding historical data from a subset, i.e. the population of Gothenburg. The error in simulation for the total number of accumulated melanomas was only +3%. We believe this to be a very small and fully acceptable disparity.

Furthermore, no allowance was made for the aging population of Sweden or for increased immigration of people at low risk of melanoma due to their skin type. But the beauty of the system dynamics methodology is the possibility to continually improve the model, as new data and research become available. For instance, if new data on the rate of growth for melanomas would be published, the data used in study IV could simply be exchanged. And if criticisers of the model would point at a factor not taken into consideration at all, this could be included and the model could gradually be updated and perfected.

Most importantly, although the system dynamics model of study IV could show where preventive interventions would have the most impact, the model does not answer the question of how to improve the early detection of melanoma. The improved overall secondary prevention scenario is an ideal envision for the future, but further research has yet to demonstrate how this is best enacted.

General discussion

Numerous influential healthcare organizations practice system dynamics modelling, for example the National Health Service in the United Kingdom and the Centers for Disease Control and Prevention, which is one of the major operators of the U.S. Department of Health and Human Services. Also, there are several examples in the literature of system dynamics modelling used for analysis of preventive interventions [172, 193, 194]. One successful example occurred in New Zealand in 2007, where the long-term effects of smoking cessation interventions over a 50-year period were estimated using a system dynamics model [194]. The results informed a decision by the government to increase funding for smoking cessation by NZ $42 million over 4 years. To the best of our knowledge, system dynamics has not previously been applied to melanoma health care.

A stable incidence of melanoma in Western Sweden is not a very likely scenario, since the last decades have shown steep increases in the incidence trends. A more likely (but unfortunate) envision for the future is the business-as-usual scenario, in which there is an increasing incidence, but no preventive interventions.

Another outcome was that the improved overall secondary prevention scenario would have resulted in 2% more melanomas during ten years, as compared to the business-as-usual scenario. This can be compared with mammography screening, which results in an increased number of early-stage breast cancers detected [195]. The explanation to this is that an improved early detection equals a reduction in time to diagnosis of unknown tumours, and thus more detected tumours. Although the improved overall secondary prevention scenario would have resulted in a slightly increased number of melanomas, this scenario would be the ideal scenario to choose. This is because it resulted in a shift towards thinner melanomas, indicating a better survival prognosis.

The results of study IV suggested a greater importance of reducing patient's delay than reducing doctor's delay, despite the fact that we simulated a 25% reduction in time for patient's delay and a 50% reduction in doctor's delay. This is a consequence of patient's delay consisting of a much longer period of time, leading to a longer growth phase for the melanoma. To reduce patient's delay in the future, skin self-examination could be taught to high-risk individuals [196]. To reduce doctor's delay, technical advances could be used. Examples of technical advances include teledermoscopy referrals, total body photography and sequential digital dermoscopy imaging for follow-up of atypical melanocytic lesions [119, 121, 134]. Access to a dermatologist's expert opinion will also be crucial in the future [197]. Further, the simulation model showed that it would be considerably more important to target fast-growing tumours (i.e. nodular melanomas and acral lentiginous melanomas) for early detection, compared to slow-growing melanomas.

In summary, Western Sweden must prepare for the increasing incidence of melanoma. We believe that lessons learned from the system dynamics model developed in study IV, solely for the melanoma care pathway, could help policymakers when planning preventive interventions.

06

CON-
CLUSIONS

Magdalena Claeson

Epidemiology of cutaneous malignant melanoma in Western Sweden

CONCLUSIONS

Based on the studies presented in this thesis I conclude that:

- There has been an alarming increase in the incidence of melanoma in Western Sweden during 1970–2007, especially in coastal areas and in Gothenburg, suggesting the need for additional preventive measures in these areas.

- Patients, as well as physicians, need to be alerted about the high proportion of melanoma patients who develop subsequent melanomas (7.4%) in Western Sweden, especially during the first years after initial diagnosis.

- Thin melanomas result in a non-negligible proportion (14.7%) of melanoma deaths in the Western Sweden health care region. Thus, more attention should be brought to thin melanomas, in regards to their management and follow-up. Especially non-ulcerated melanomas, 0.76-1 mm and ulcerated melanomas, 0.26-1 mm have a poorer survival compared to other thin melanomas.

- System dynamics is valuable for strategic planning of the melanoma care pathway, helping policymakers to prepare for a continued increase in melanoma incidence and to choose the preventive intervention with the greatest impact.

Magdalena Claeson

FUTURE PERSPECTIVES

This thesis has addressed the epidemiology of cutaneous malignant melanoma in Western Sweden. Further, the thesis has proposed interventions for secondary prevention. In the field of melanoma epidemiology and cancer control, there is a wide range of unanswered questions, which create very appealing opportunities for future research.

7.1 GEOGRAPHICAL DIFFERENCES IN UVA AND UVB RADIATION LEVELS

One development of interest would be to perform studies on the differences in UVA and UVB radiation levels in coastal and inland areas. Findings from such studies may provide additional information regarding the respective roles of UVA and UVB in photocarcinogenesis in these areas.

7.2 MULTIPLE PRIMARY MELANOMAS IN RISK PREDICTION MODELS

This thesis found that as much as 7.4% of the Western Sweden cohort develop multiple primary melanomas. Recently available research has shown patients with multiple primary melanomas to have lower survival rates than patients with single primary melanomas [66, 67]. Thus, it would be of interest to further investigate the possibility to include subsequent melanomas in risk prediction models. Such models could assist physicians making clinical decisions and could even, if substantial evidence is at hand, be included in the follow-up programme of the Swedish national guidelines for the management of melanoma.

7.3 PREDICTORS OF MORTALITY FOR THIN MELANOMAS

Study III of this thesis established that around 15% of all melanoma deaths in Western Sweden occur in patients diagnosed with thin melanomas. This shows that although thin melanomas generally have a very good prognosis, there is a subgroup of these at high risk of causing death. Thus, there is a substantial unmet need for better identification of this large group of patients. If the subgroup of thin melanomas with high risk of death could be identified, these patients could enter follow-up programmes with shorter intervals between examinations. Further, this subgroup could be offered early metastasis surgery, or even adjuvant treatment with one of the new melanoma drug therapies. Therefore, it is in my imminent plans to partake in the next step of a large project trying to further specify the predictors of mortality for thin melanomas. In the thin lethal melanomas project, a case-control study will be designed, aiming at determining whether some carefully chosen clinicopathological factors, somatic mutations and protein markers allow discriminating between lethal and non-lethal thin melanomas.

7.4 FURTHER USE OF SYSTEM DYNAMICS

The simulations in study IV highlight the pending need to allocate resources for melanoma health care in Western Sweden, because of a high projected number of future melanoma cases. With new drug therapies for melanoma developing rapidly, it is all too easy to invest high amounts of money in effective treatment for patients with metastasized disease. However, stakeholders should pause and analyse the most cost-effective strategies already now, in order to make the best use of the limited

economic resources available. System dynamics would be a valuable tool to analyse and compare the cost-effectiveness of the following variables (amongst others):

- A sunbed ban, either partial (for minors) or total
- The introduction of standardized care pathways for melanoma
- Teledermoscopy referrals
- Treatment of metastasized melanoma disease

Further, it would be important to evaluate the simulation model after some time has passed, to see if the approximations were correct and if the model is valid to use. In study IV, it was hypothesized that early detection would have resulted in a shift towards thinner melanomas and thus lower mortality rates. It will be vital to monitor the mortality rates of Western Sweden in the future, to see if early detection has a true effect on the melanoma death rates. This is central, since lowered mortality of melanoma is the goal of early detection and secondary prevention.

System dynamics has already been used in Western Sweden for the simulation of another cancer care pathway, namely lung cancer [198]. In the coming years, we hope for this methodology to be introduced in many more cancer care pathways.

Magdalena Claeson

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09

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Magdalena Claeson

Epidemiology of cutaneous malignant melanoma in Western Sweden

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