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CUTANEOUS MALIGNANT MELANOMA

ASPECTS ON PROGNOSTIC FACTORS AND TIME-TRENDS IN A SWEDISH POPULATION

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ABSTRACT

One of the aims of this thesis was to assess the possible impact of primary and secondary preventive activities in the population of Stockholm-Gotland with the objective to reduce the incidence and mortality from cutaneous melanoma. Another aim was to investigate whether thin melanomas and hereditary melanomas represent separate biologic entities.

The study base was cases with cutaneous melanoma reported to the Swedish Cancer Registry 1976 – 1994, patients registered in the Stockholm-Gotland Regional Melanoma Registry 1976-1994, individuals reported with malignant melanoma as an underlying cause of death to the Swedish Cause-of-Death Registry 1970-1996, and patients reported to the National Familial Melanoma data base 1987-1994.

The average annual increase of the age-standardised incidence was about 5 % in both genders. The increase mainly concerned thin tumours and melanoma in situ. During the 1990s the incidence in males levelled off. This apparent change in trend was not observed outside the Stockholm-Gotland region. The estimated five-year melanoma-specific survival rate in patients diagnosed with localised cutaneous melanoma increased from 84 % to 92 % during 1976-1994. No time-trend for melanoma-specific survival was observed among patients with regional or distant metastases. The increased survival during 1976-1989 could be fully explained by a trend towards more favourable tumour characteristics. During 1990-1994, screening activities may have contributed to the observed survival improvement. An upward trend in melanoma mortality appeared to level off in the mid 1980s. In females a slight decrease was observed during 1987-1996. The change in trend was most pronounced in the Stockholm-Gotland region. The results indicate that the interventional activities in Stockholm-Gotland may have influenced both melanoma incidence and mortality.

Of patients diagnosed with thin cutaneous melanoma (0.8 mm or less), four percent developed recurrent disease after a median follow-up of 50 months. Anatomic site, tumour thickness, level of invasion and tumour regression were significant prognostic factors. No subgroup of patients could be identified that was without risk of recurrent disease. Thin melanomas did not appear to constitute a separate biologic entity. A family history of melanoma was reported in five percent of patients diagnosed with cutaneous melanoma. Familial melanoma was associated with young age at diagnosis, the presence of dysplastic nevi, multiple melanoma and melanomas detected at an early stage. The prognosis of the familial cases did not differ from that of sporadic melanomas when established prognostic factors were taken into account.

Key words: melanoma, incidence, prognostic factors, survival, mortality, trends, familial, prevention

LIST OF PUBLICATIONS

This thesis is based on the following papers which are referred in the text by their Roman numerals:

I Månsson-Brahme E, Johansson H, Larsson O, Rutqvist LE, Ringborg U:
Trends in incidence of cutaneous malignant melanoma in a Swedish population 1976-1994.
Acta Oncologica 41: 138-46, 2002.

II Månsson-Brahme E, Johansson H, Singnomklao T, Larsson O, Rutqvist LE, Ringborg U:
Time-trends in survival in cutaneous malignant melanoma; a population-based study in Sweden.
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III Cohn-Cedermark G, Månsson-Brahme E, Johansson H, Singnomklao T, Larsson O, Rutqvist LE, Ringborg U:
Trends in mortality from malignant melanoma in Sweden 1970-1996.
Cancer 89: 348-55, 2000.

IV Månsson-Brahme E, Carstensen J, Erhardt K, Lagerlöf B, Ringborg U, Rutqvist LE:
Prognostic factors in thin cutaneous malignant melanoma.
Cancer 73: 2324-32, 1994.

V Månsson-Brahme E, Johansson H, Larsson O, Rutqvist LE, Ringborg U:
Characteristics and survival in familial and non-familial cutaneous melanoma; a population-based study in Sweden.
Manuscript.

CONTENTS

LIST OF ABBREVIATIONS

SSM	Superficial spreading melanoma
NM	Nodular melanoma
LMM	Lentigo maligna melanoma
ALM	Acral lentiginous melanoma
DNS	Dysplastic nevus syndrome
CDKN2A	Cyklin dependent kinase inhibitor 2A (in human)
ICD	International classification of diseases, injuries and deaths
SIR	Standardised incidence rates
UV	Ultraviolet radiation
UVA	Ultraviolet A radiation
UVB	Ultraviolet B radiation
UVC	Ultraviolet C radiation

2 INTRODUCTION

Malignant melanoma of the skin is commonly thought to develop by the transformation of melanocytes (1). These cells are located in the basal layer of the epidermis. They are in contact with surrounding keratinocytes forming a so called epidermal melanin unit . Melanocytes synthesise melanin, a pigment which has a photoprotective function. The amount of melanin produced varies according to the individual's ethnicity, age, anatomic site and stimulating factors such as ultraviolet light and hormones. Melanocytes have a limited capacity to proliferate (2). However, it has been shown, that ultraviolet radiation induces an increased melanocyte population (3, 4). Tanning is the result of melanogenesis in the melanocytes accompanied by transfer of melanin to the adjacent keratinocytes. Strong evidence implicates sunlight as a cause of cutaneous melanoma but the relationship appears complex (5).

Clark et al defined six steps of tumour progression in epidermal melanocytes (6). The first step represents a focal proliferation of melanocytes forming the common, acquired melanocytic nevus, followed by a melanocytic nevus with lentiginous melanocytic hyperplasia (aberrant differentiation). The third step is the development of the dysplastic nevus, a melanocytic nevus with aberrant differentiation and melanocytic nuclear atypia. Further progression involves the radial growth phase of a primary melanoma and later the development of the vertical growth phase. The melanoma cells of the vertical growth phase have the potential to metastasise and metastatic melanoma constitutes the last step of tumour progression.

In Sweden, cutaneous melanoma was a relatively uncommon disease in the 1960s but the incidence has increased rapidly since then (7). In the year 2000, cutaneous melanoma was one of the ten most common malignant tumours in Sweden in both males and females. Almost two out of one hundred individuals will develop the disease during their life-time. Changing sun habits have paralleled or preceded the observed increase in melanoma incidence (8). The upward incidence trend has been accompanied by a less dramatic increase in melanoma mortality (9).

Since the time of Hippocrates, malignant melanoma has been known as a fatal disease (10). However, survival has improved continuously and the five-year survival rate in Sweden today is approximately 80 % (11).

Clinical and histopathologic characteristics are determinants of the prognosis in melanoma. Thickness of the primary tumour is recognised as the most important prognostic factor (12). Cutaneous melanoma is a visible tumour and, therefore, more easily detected in an asymptomatic stage than many other types of cancer. Early detection and treatment may result in improved survival (13).

In order to decrease melanoma incidence and mortality, strategies for both primary and secondary prevention targeting the general population have recently been developed and implemented. Similarly, preventive measures, including education and regular surveillance, targeting individuals at high risk for cutaneous melanoma have been initiated in many countries. The objectives of this thesis included an assessment of the impact of such preventive strategies in a Swedish population.

3 BACKGROUND

DESCRIPTIVE EPIDEMIOLOGY

Cutaneous malignant melanoma affects fair-skinned people of all ages but is rare in children (14). From puberty, the age-specific incidence rises steeply and the mean age at diagnosis in Sweden is 55 years (15). The disease is equally distributed among the sexes but males are more likely to have tumours on the trunk, and females are more likely to have tumours on the legs.

Incidence

The incidence of cutaneous melanoma in most populations of Caucasian origin has been rising for several decades (8, 16). The first reports on increasing incidence of melanoma date from the 1930s in Connecticut, USA, and the 1940s in Denmark (17). During the 1960s through the late 1980s, an annual increase of 3 to 7 % was observed world-wide in fair-skinned populations (18). The highest incidence rates in the world have been reported from Queensland, Australia, and Auckland, New Zealand, with age-standardised incidence rates exceeding 50 per 100,000 person years (calculated using the world standard population) (19, 20). However, there are indications that the incidence rate now is levelling off in some populations (21-25). The increase in incidence has mainly concerned patients with thin melanomas, but an increase of patients with thicker lesions has also been reported (19, 21, 24, 26, 27).

Possible changes in the definition and application of diagnostic criteria for malignancy in pigmented skin lesions as an underlying cause for the observed incidence trends in cutaneous melanoma have been investigated (28, 29). However, there were no indications that temporal trends in incidence could be explained in terms of such changes.

In Scandinavia, the incidence has increased steadily in all countries but rates are lower in Finland and Iceland (30). In Sweden, the average annual increase in incidence rates during 1960 through 1982 was 5.4 % for women and 5.8 % for men (11). The largest increase has been observed for melanoma of the trunk among males. Among females the dominating increase has been for leg melanoma (31). During 1973 through 1992 an increasing incidence was also observed among children and adolescents (32).

According to the Swedish Cancer Registry the incidence of cutaneous malignant melanoma is continuously rising with an average annual increase of the age-standardised incidence of more than 2 % during the last 20 years (33). The increase is less prominent during the last ten years. Similarly, during several decades, a rapid increase in squamous cell carcinoma and basal cell carcinoma has been observed in Sweden (7, 34, 35). In contrast, an upward trend has not been observed for non-cutaneous malignant melanoma. The age-standardised incidence of melanoma of the vulva in Swedish women decreased during 1960 through 1984 by 3 % annually (36). Similarly, the age-standardised incidence in Sweden of uveal melanoma declined significantly among males from 1960 to 1998 (37). Among females, there was a non-significant trend towards a reduced incidence.

In 2000, a total of 1,616 new cases of cutaneous malignant melanoma were reported in Sweden. The age standardised incidence, age adjusted to the Swedish population 2000, was 20 per 100,000 among males and 17 per 100,000 among females (7). Cutaneous melanoma constituted 3.6 % of all cancers in Sweden and it was the eighth most common malignant tumour among males and the ninth among females. The cumulative life-time risk to develop the disease was 1.9 % among males and 1.6 % among females.

Mortality

The upward incidence trend has world-wide been accompanied by an increase in mortality (8). This indicates that there is a true increase in the underlying onset rate of the disease. During 1970 to 1990, the mortality from malignant melanoma in European Community countries increased continuously among both genders (38). Death rates in young adults, aged 20 to 44 years, increased substantially from 1955 to 1989 among males in nine European countries, and among women in eight countries (39). Similar trends were reported from North America and Australia (40).

Recently, a stabilisation and even a decline in melanoma mortality has been reported from several countries (16, 21, 40-43). In Australia, mortality rates in males rose steeply in birth cohorts born before 1930, were stable in cohorts born between 1930 and 1950, and fell in more recent cohorts. The female melanoma mortality showed similar changes but occurred in birth cohorts about five years younger than in males. From 1953 to 1987 the melanoma mortality in Sweden showed an average annual increase of 4.7 % among males and 3.7 % among females (9). However, a deceleration of the

increase started in the 1970s. In an overview of trends in cancer mortality in Europe, a levelling off of the melanoma mortality in Sweden was observed since the mid 1980s (44).

Survival

Survival has changed considerably during the last decades and the five-year relative survival is now around 80% (45, 46). In Sweden, the five-year relative survival rate increased from 50 % in 1960 to approximately 80 % in 1982 (11). Relative survival is defined as the ratio between the observed survival and the expected survival of an age-matched general population.

It has been assumed that early detection and treatment will lead to a decrease in mortality from cutaneous melanoma. The observed increasing incidence in conjunction with a levelling off or even decline in mortality, indicates that early detection may have been effective. An increasing awareness in the general population about the potential significance of pigmented skin lesions may have contributed to the increasing incidence (26). The increase has mainly concerned patients with putatively early detected, thin melanomas, but an increase in the number of patients with thicker lesions has also been reported (19, 24, 26, 27).

RISK FACTORS FOR MELANOMA

Solar ultraviolet(UV) irradiation

The main source of ultraviolet radiation is the sun. UV radiation comprises electromagnetic waves with wave-lengths between 100 and 400 nm. It is divided into three groups: ultraviolet A radiation (UVA) with wave-lengths between 320 and 400 nm, ultraviolet B radiation (UVB) including 280-320 nm, and ultraviolet C radiation (UVC) consisting of wave-lengths shorter than 280 nm. All UV radiation below 290 nm is absorbed in the atmosphere. Approximately 90 % to 95 % of the solar UV radiation energy that reaches the earth is UVA and 5 % to 10 % is UVB (47). UVB is known to cause mutations in oncogenes and tumour suppressor genes. It may also induce and promote development of melanoma as well as other skin tumours (2, 47). UVA causes DNA-damage and is capable of inducing melanoma in certain species of fish and opossums (47). However, the role of UVA in the pathogenesis of melanoma in humans is not clear.

Since melanomas are more common in sun-exposed areas of the skin, McGovern proposed in 1952 that sunlight is an etiologic factor (48). In 1992, the International Agency for Research on Cancer (IARC) declared that there is sufficient evidence that solar irradiation causes melanoma of the skin as well as non-melanocytic skin cancer (49) and that sun exposure appears to be the main environmental cause of melanoma. Variations with latitude in melanoma incidence and mortality have been reported (50). Studies of migration have shown that incidence rates among migrants to high-risk areas exceeded those in the population of the place of origin (8). The risk of disease depended on the age at which the migrants arrived to the high-risk area (51, 52). The concept of a "critical period" of age for the induction of melanoma by ultraviolet irradiation arose from these observations.

The role of sun exposure for melanoma induction is complex. Both the pattern and the amount of exposure appear to be of importance (5). Changing lifestyles such as increased outdoor recreational activities and fashion trends have paralleled the melanoma increase (53, 54). In two recent overviews of published case-control studies, intermittent sun exposure and a history of sun burns was associated with a significantly increased melanoma risk (55, 56). In contrast, a reduced risk was observed for high levels of occupational exposure. High levels of sun exposure during childhood has been found to be a strong determinant of melanoma development, but sun exposure during adult life seems also to play a role (57).

In order to decrease the negative health effects of sun exposure, educational campaigns in many countries have advocated the use of topical sunscreens and other preventive measures. However, the use of sunscreens can increase the duration of intentional sun exposure. Such an extension may increase the risk for melanoma (58-61). Furthermore, individuals with very sun-sensitive skin may be the ones most likely to use sunscreens so an association between sunscreen use and the development of melanoma may only reflect an association between sun-sensitive skin and melanoma risk. A meta-analysis of 11 case-control studies, evaluating the use of topical sunscreen and melanoma risk (62), found no association between sunscreen use and melanoma development. In an evaluation of the cancer-preventive potential of the topical use of sunscreens it was concluded, that sunscreens reduce the risk of sun burn and probably prevent squamous cell carcinoma of the skin (61). However, no conclusion could be drawn about the potential preventive effect on cutaneous melanoma or basal cell carcinoma.

Non-solar ultraviolet irradiation

There is conflicting evidence concerning the use of artificial tanning devices and melanoma risk. Psoralen and UVA (PUVA) have been used in the treatment of psoriasis but studies on the potential association between this treatment and melanoma are conflicting (63, 64). Since the 1950s, home tanning lamps have been used, emitting large proportions of UVB and also UVC. Commercial sun beds, emitting a large proportion of UVA, have been in use since the 1970s. The use of tanning lamps and sun beds have increased the last decades (8). In a Swedish survey in 1999, sun beds were used both among adolescents and adults and were more commonly used by females (65). An increased risk of cutaneous melanoma in relation to the use of tanning devices have been reported but results are inconsistent (66-68).

Host factors

Nevi

Several studies have reported an association between nevi and melanoma. The number of nevi is considered an important risk factor for melanoma development (8, 69-76). The prevalence of nevi shows large geographical and racial differences. The distribution of nevi varies with age, phenotype and gender. In Sweden, the prevalence of common nevi varies with latitude. The prevalence is higher in regions with a high melanoma incidence (77, 78). A relationship between the number of common nevi and the presence of dysplastic nevi has been observed (79). In several reports, dysplastic nevi appeared to be an important marker for melanoma risk and also potential precursors of melanoma (8, 69, 74, 76, 80). Recently, in nevus studies among adult twins, the emergence of nevi seemed to be genetically determined but was modified by age (81, 82).

Several studies indicate an association between sun exposure and nevus formation as well as nevus distribution (76, 83-90). Nevus counts were higher in geographical areas with high levels of sun exposure. Both in children and adults, nevi were more common in body sites that received intermittent UV exposure. Furthermore, the number of nevi was higher among sun sensitive individuals, among those with freckles, and those with a history of sunburns. In addition, in a study among white European children, those who used sunscreens had higher nevus counts than those who used sun protective clothes (91).

Family history

In 1820, Norris reported on a family with two lethal cases of melanoma or "fungoid disease" and the occurrence of many moles in several family members (92). He noted that the melanoma of one patient originated in a mole. Since the study on familial melanoma by Clark et al, published in 1978, the phenomenon of hereditary melanoma has gained increased attention (93). Patients with familial melanoma have been reported to develop melanoma at a younger age, to have thinner tumours, to have higher numbers of nevi, and to frequently develop multiple melanoma compared to sporadic cases of melanoma (94-97). Members of families with multiple cases of cutaneous melanoma and a familial aggregation of dysplastic nevi, the so-called dysplastic nevus syndrome, have a high risk to develop melanoma (98).

Dysplastic nevi are potential precursor lesions for familial melanoma (6, 99) and are important predictors of risk in individuals belonging to melanoma-prone families (80, 100). Clinical practice guidelines including strategies for primary and secondary prevention have been developed for members of high-risk families with dysplastic nevi and cutaneous melanoma (15, 99).

Between 2 and 14 % of cases of cutaneous malignant melanoma have been reported to occur in families with multiple cases of melanoma (94, 95, 101). Genetic factors may be important for the risk to develop melanoma (100, 102). An autosomal dominant mode of inheritance was suggested in the early 1980s (103, 104). This concept is now widely accepted (100, 105). Germline mutations in the gene CDKN2 on chromosome 9p21 have been identified in 8 to 20 % of melanoma-prone families in Europe, Australia and the United States (105, 106). Recently, the Melanoma Genetics Consortium reported that the penetrance of the CDKN2A mutation varied with melanoma population incidence (105). The estimate of CDKN2A mutation penetrance was high in populations with a high melanoma incidence and low in low-incidence populations. The authors suggested that the same factors that influence population rates may also mediate CDKN2A penetrance.

Mutations in the N-ras oncogene are common in melanoma. They have mostly been found in melanomas located in sun exposed areas of the body and are rarely seen in tumours in areas protected from sun exposure (107). These observations indicate an

association between UV radiation and N-ras mutations in chromosome 1p in melanoma. Previously, experimental studies suggested that members of melanoma prone families with dysplastic nevi have an UV hyper-mutability phenotype (108). An increased frequency of N-ras mutations in codon 61 was observed in melanoma metastases from patients with dysplastic nevus syndrome compared to the frequency among patients with non-familial melanoma (109). In a recent study of Swedish kindreds, N-ras mutations were found in 95 % of primary melanomas from patients with CDKN2A germline mutations and a family history of melanoma (M Eskandarpour et al, Manuscript submitted for publication). The mutations were frequently present already in dysplastic nevi and in melanoma in situ. Furthermore, in each individual case the specific N-ras mutation that was present in the primary tumour was also found in the distant metastases. The results indicate, that N-ras mutations in codon 61 may be the result of a hypermutability phenotype associated with familial melanoma in patients with mutations in CDKN2A.

Davies et al recently reported that mutations in the B-raf gene were found in 66 % of melanoma tumours (110). However, the incidence of B-raf mutations in familial melanoma has not yet been determined.

Cutaneous phenotype

Phenotypic traits, including complexion, hair colour, eye colour and freckling have frequently been associated with melanoma risk. (13, 16, 111). A fair complexion, a sun sensitive skin and a tendency to burn have been associated with an elevated risk to develop melanoma. In addition, pigmentary characteristics and sun sensitivity seem to be related to the number of benign nevi and dysplastic nevi (69, 79).

Previous skin tumours

Patients previously treated for invasive melanoma or melanoma in situ have an elevated risk of a second primary melanoma. Multiple melanomas have been reported in 1.3 to 8.2 % of melanoma patients (112-114). In melanoma-prone families, multiple melanomas have been observed in 14 % to 30 % (80, 94, 95, 115, 116). Furthermore, in a study from the Swedish Cancer Registry, patients diagnosed with squamous cell carcinoma of the skin showed a 3-fold risk for a subsequent melanoma (117).

Hormones

Several epidemiological studies have examined the role of sex hormones and melanoma risk (8, 118). There is scant evidence that use of oral contraceptive hormones or menopausal replacement hormones are associated with common nevi or melanoma development. However, pregnant women may experience changes in their nevi during pregnancy. In addition, one study showed an inverse relationship between parity and dysplastic nevi among Swedish women with high nevus counts (79). Furthermore, a Swedish investigation on pregnancy and melanoma development indicated that early childbearing and multiparity may reduce the melanoma risk (119).

Socioeconomic status

An association between social class and the development of melanoma has been reported (16). An increased incidence was observed among individuals with a high level of education and among those with mainly in-door work (120-124). Exposure to sunlight in out-door work does not seem to substantially increase the melanoma risk. The association between social class and melanoma development may be explained in terms of affluent people having more opportunities for recreational, intermittent sun exposure and travels to sunny resorts. Observations that airline pilots have an elevated melanoma risk is considered to support this hypothesis (122, 125, 126). In contrast, in a recent cohort study of Swedish construction workers, there was no increased risk of malignant melanoma, except for tumours of the head and neck in the high exposure group (127). An elevated risk for melanoma of the eye was also found in this group. The incidence is higher among people with a high socio-economic status and the prognosis seems to be better in this group as compared to that among less affluent people (121, 124).

STAGING OF CUTANEOUS MELANOMA

Staging of cancer patients is basic for assessment of prognosis. Clinical staging of cutaneous melanoma in Sweden has been based on the three-stage system (15, 128). According to this system, stage I, localised melanoma, refers to tumours that are confined to the primary site ± satellites within 5 cm of the primary tumour, stage II refers to cases with regional lymph node metastases and/or in-transit metastases, and stage III to cases with disease disseminated beyond the regional lymph nodes.

Internationally, the most commonly used staging system is the American Joint Committee on Cancer (AJCC) classification. This system was recently revised (129-131). Stage I and stage II represents localised melanoma classified according to thickness and the presence or absence of ulceration. Information on level of invasion is only used in tumours 1.0 mm or less. Stage III includes metastases to regional lymph nodes and/or satellites/in transit metastases. Stage IV refers to distant metastases. The revised AJCC classification is intended to be implemented in Sweden.

PROGNOSTIC FACTORS FOR LOCALISED MELANOMA

Clinical factors

Age

Elderly patients often present with thick lesions and have greater mean tumour thickness than younger patients (132, 133). However, even after adjustment for other prognostic factors, old age is significantly related to poor prognosis (12, 134-136).

Gender

Gender is an important prognosticator. After adjusting for other prognostic factors, females have a significantly better prognosis than males (12, 136-138).

Anatomic site

The site of the primary melanoma is also an independent prognostic factor (12, 136-139). Patients with melanomas on the extremities have a better prognosis than patients with melanoma on the trunk. In the head and neck region, patients with face melanomas have a more favourable outcome than patients with melanomas on the scalp and neck.

Histopathological factors

Thickness

Tumour thickness measured in mm according to Breslow (140) is the most important determinant of survival among patients with invasive, localised melanoma (12, 136, 138, 141). In addition, tumour thickness and presence of ulceration have been the most reproducible histologic parameters in cutaneous melanoma (142, 143).

Level of invasion

Level of invasion according to Clark (144) is closely related to tumour thickness. However, in some studies, level of invasion has been found to be an independent prognostic factor (136, 139, 141). In studies of thin melanomas, level of invasion has been shown to be an independent prognostic indicator (145). Consequently, in the

AJCC classification, information on level of invasion is included in the classification of tumours 1.0 mm or less.

Ulceration

Ulceration of the tumour is also related to tumour thickness. However, several studies have demonstrated the independent prognostic significance of ulceration. It is now considered to be the second most important prognosticator after tumour thickness (12, 136, 146).

Regression

Whether signs of regression provide prognostic information remains controversial. Several studies have suggested that in thin melanomas, tumours with regression have an unfavourable prognosis (147-150). In contrast, other investigations have failed to demonstrate any significant influence of regression on melanoma survival (136, 137).

Histogenetic type

In most studies exploring prognostic factors in melanoma the growth pattern has not been found to be an independent prognosticator (136, 139). However, some studies that have used a multivariate approach indicate that the histogenetic type may be of prognostic importance (45, 151-153). Patients with lentigo maligna melanoma often have thin lesions, but after adjustment for tumour thickness patients with lentigo maligna melanoma seem to have a more favourable prognosis (139).

Other factors

It remains unclear whether factors such as inflammatory reaction, mitosis, radial and vertical growth phase provide prognostic information (136, 137, 146). A previous study by Clark et al, indicated a survival rate of 100 % for radial-growth-phase melanomas after a median follow-up time of 150 months (154). However, patients with metastasising radial growth phase tumours have been reported (149, 155, 156). Remnants of a pre-existing nevus in association with the primary melanoma does not seem to be of prognostic value (136) More recently proposed factors, including DNA-ploidy, mean nuclear volume, immuno-histochemical markers, such as Ki-67, serological, and molecular markers may provide prognostic information (146, 157, 158)

TREATMENT AND FOLLOW-UP

A wide excision with a 5 cm free margin and regional lymph node dissection has been the traditional treatment for cutaneous melanoma. This radical operation, often requiring skin grafting, was advocated by Handley in 1907 and was the standard procedure for the ensuing decades (159). In the 1970s it was demonstrated that elective

lymph node dissection did not improve survival (160). Furthermore, large prospective studies have investigated the impact of different surgical margins on recurrence and survival (161-163). No study has so far demonstrated a more favourable outcome for patients operated with more extensive surgery compared to less extensive surgery. However, the optimal surgical margins for melanomas remains controversial (164). In routine practise, there has been a trend toward more narrow surgical margins in recent years.

In 1976 the Swedish Melanoma Group issued treatment practice guidelines for patients with cutaneous malignant melanoma. These guide-lines, including recommendations for surgical treatment, were implemented in the Stockholm-Gotland region (population 1.9 million) already the same year. A regional care program has been updated regularly by the Regional Melanoma Group. In 1997, a document on State of the Art of the treatment of cutaneous melanoma was published by the Swedish Melanoma Group. This document was recently updated (15). Treatment and follow-up recommendations take into account the thickness of the primary tumour.

Patients who develop loco-regional metastases are, typically, treated surgically. Radiation therapy with doses of 5 to 6 Gy per fraction are used for palliation (165). A selected group of patients with loco-regional disease may benefit from isolated limb perfusion (166, 167). The most commonly used cytostatic drug in limb perfusion is melphalan which gives a complete response in up to 50 % of the patients. Patients with disseminated disease have usually received systemic therapy including dacarbazine (DTIC) (168) with a response rate of 15 to 20 %. Temozolomide, with similar effects as DTIC, was recently introduced in the treatment of patients with advanced disease (169, 170). It can be administered orally and penetrates the blood-brain barrier. However, so far no studies on the use of chemotherapy have indicated prolonged survival associated with the treatment in patients with disseminated disease (15).

PREVENTION

Educational campaigns and screening activities have been launched during the last decades throughout the world in an effort to reduce the increase in melanoma incidence and mortality. In the Stockholm-Gotland Region, public campaigns aiming at primary and secondary prevention were started in the mid 1980s (171). These campaigns included educational activities targeting all professionals in the primary health care

system, the school health system as well as hospital staff in all major hospitals. A pigmented skin lesion clinic was initiated where preventive strategies for high-risk individuals were developed. The campaigns also included public information through media and free-of-charge screening activities. Some years later similar activities were initiated also in other Swedish areas. For instance, in 1990 the Swedish Cancer Society initiated a nation-wide melanoma prevention campaign including free-of-charge skin examinations (172). So far, no randomised study on primary or secondary prevention has been done. Possible effects of preventive activities are, therefore, difficult to evaluate.

4 AIMS OF THE THESIS

- To assess the possible impact of the preventive activities in the Stockholm-Gotland region by analysing the incidence, survival and mortality trends of cutaneous melanoma.

- To assess whether the natural time history of the disease, taking into account established prognostic factors, has changed over time.

- To investigate whether thin cutaneous melanoma (0.8 mm or less) constitutes a separate biologic entity of cutaneous melanoma by exploring clinical and histopathologic factors and their influence on survival.

- To determine whether hereditary melanomas have different biologic properties than sporadic melanomas.

5 SUBJECTS AND METHODS

The Stockholm-Gotland Health Region includes Stockholm with a population of approximately 1.9 million and Gotland with a population of about 57,000. This thesis mainly concerns the Stockholm-Gotland region but analyses in paper I and III also comprise national data. The papers are based on information from four registries in which each case is identified by its personal identification number. This number is unique to all persons living in Sweden and permits computerised record linkage.

THE SWEDISH CANCER REGISTRY

Since 1958, patients diagnosed with cancer must be reported to the Swedish Cancer Registry. The cases are reported twice, since the responsible clinician as well as the involved pathologist/cytologist must submit separate reports to the Registry. Approximately 98 % of the cancer cases are morphologically verified. Of the melanoma cases approximately 100 % are verified by a pathologist (7). Cancer diagnoses are not based on death certificate data alone. The reliability of the diagnosis varies with age and type of cancer and may also vary geographically. In 1978, the coverage of diagnosed cancer cases in the Cancer Registry was estimated at about 96% (173). The registration deficit of diagnosed melanoma cases has been estimated at less than 1% (174). A review of a random sample of melanoma cases registered between 1959 and 1968 revealed that the melanoma diagnosis was incorrect in about 4% (175).

Registration procedures in the Swedish Cancer Registry have remained similar since the late 1950s. The information on each case in the Cancer Registry includes age, sex, tumour site, tumour type and date of diagnosis. Registration and coding is done according to internationally accepted rules (International Classification of Diseases, Injuries and Causes of Death, ICD). For the purposes of the current investigations, the diagnosis coded according to the ICD 7th revision was used (176), since it was available for the entire study period. Multiple primary tumours occurring in one individual are recorded as separate cases in the incidence statistics. Since the middle of the 1970s all primary cancer registration in Sweden is done at the six regional Oncologic Centres which each year supply processed and computerised data to the National Cancer Registry which compiles the national incidence statistics. The Regional Oncologic Centre for Stockholm-Gotland was established in 1976.

THE SWEDISH CAUSE OF DEATH REGISTRY

The Swedish Cause of Death Registry prospectively collects information on date and cause of death on all Swedish citizens who die. Statistics on causes of death have been collected in Sweden in some form since 1749. The National Central Bureau of Statistics is responsible for the compilation of the data, and since 1994 The National Board of Health and Welfare is responsible for the yearly publication on causes of death. The underlying cause of death is registered according to the International Classification of Diseases, Injuries and Causes of Death. During 1970 to 1986 registration was done according to the ICD 8th revision, during 1987 to 1996 according to the ICD 9th revision and since 1997 according to ICD 10th revision (177-179).

All deaths in Sweden must be certified by a physician. Until 1980 if a malignant tumour was reported as the underlying or contributory cause of death, the tumour was recorded as the underlying cause of death. In 1981 the registration routines were changed according to recommendations by the World Health Organisation. A cancer diagnosis, mentioned as a contributory cause of death by the certifying physician, was no longer coded as the underlying cause. However, coders at the Registry may change the underlying cause if they consider the reported underlying cause to be an insufficient cause of death. The Registry makes no distinction between deaths caused by cutaneous and non-cutaneous melanoma.

The main source of error in the classification is the reliability of the cause of death certified by the physician (180). The age of the patient may be of importance, since errors of reported underlying cause of death appear to be more frequent among the elderly (181). During the last decades, there has been a secular trend towards a decreased frequency of autopsies in Sweden. In 1970, autopsy was performed in 50 % of all deaths as compared to 15 % in 2000 (180). The decreasing use of autopsy was most marked in people older than 45 years. In 2000, an autopsy was carried out in 20 % of the males and 11 % of the females. Of all cases with malignant melanoma registered as the underlying cause of death, an autopsy was performed in 5.5 % of the males and 6.8 % of the females. These circumstances may have increased mis-classifications in the cause of death statistics.

THE STOCKHOLM-GOTLAND REGIONAL MELANOMA REGISTRY

In 1974 the National Board of Health and Welfare issued recommendations for the planning and organisation of cancer care in Sweden (182). Guidelines for the six oncologic centres were developed to ensure that optimal care was to be available to all cancer patients in the fields of diagnosis, treatment and follow-up. The assignment to the centres was to co-ordinate cancer care. The specific tasks included regional cancer registration, to initiate cancer care programs, to give advice in screening activities, and to be involved in public information. The Oncologic Centre of the Stockholm-Gotland Health Region was established in 1976. During 1978 through 1982 Oncologic Centres were founded in the remaining five health regions.

In 1976 the Swedish Melanoma Study Group issued treatment practice guide-lines for patients with cutaneous malignant melanoma. As part of a regional collaboration, a care program was initiated in the Stockholm-Gotland region. The program included recommendations on referral routines, diagnosis, classification, treatment and follow-up. According to the program, all patients with cutaneous melanoma residing in Stockholm-Gotland at the time of diagnosis were to be recorded in a data base kept at the Oncologic Centre. Patients with melanoma in situ (pre-invasive melanoma) and melanoma of unknown origin were also included. The data base comprises extensive information about the clinical characteristics of each case, the surgical treatment, histopathologic classification of the tumour and follow-up information.

Prospectively collected clinical parameters in the data base includes date of diagnosis, gender, site of the primary tumour, clinical stage of disease, family history of melanoma and other cancers and pigmentation characteristics. Clinical staging is based on the three-stage system (15, 128). Hair colour includes four categories (blonde, light brown, red, dark brown/black) and eye colour five categories (blue, grey, green, brown, mixed). Skin type is categorised according to propensity to burn and tanning ability (type I: always burn, never tan, type II: always burn, sometimes tan, type III: sometimes burn, always tan, type IV: never burn, always tan). Since 1989, a clinical diagnosis (yes, no) of at least one dysplastic nevus (99) at the patient's first clinical examination at the oncologic clinic is prospectively registered in the data base.

During 1976 through 1994, surgical treatment of the primary cutaneous melanoma was excision with at least one cm free margin for tumours with a thickness 0.8 mm or less.

Thicker melanomas were excised with a two to five cm margin, often requiring skin grafting. Occasionally, margins were more narrow due to technical considerations. Elective lymph node dissection was not recommended. In the melanoma data base, the routinely recorded treatment parameters are the date and type of surgical operation as well as the surgical margins.

All histopathologic slides are routinely reviewed by a few experienced pathologists. The tumours are classified according to histopathologic type, tumour thickness, level of invasion (Clark) and presence or absence of late regression. Prospective registration of presence or absence of ulceration was not introduced until 1989. Therefore, a retrospective review was done of slides in cases for whom information on ulceration was missing. Information on the presence of pre-existing nevus in association with the tumour is available for cases registered since 1989.

The clinical follow-up takes place mainly at two institutions. Initially, all patients with localised melanoma were scheduled for regular examinations every third month during five years, and, thereafter, annually up to ten years after primary diagnosis. In 1989 the clinical routines were changed. Patients with in situ melanoma and tumours 0.8 mm or less are only seen at the oncologic clinics once and twice, respectively, after the primary diagnosis. Patients with thicker melanoma are scheduled for a clinical check up four times yearly up to five years. Patients with metastatic disease are typically scheduled for follow-up visits every month. The tumour status is reported to the data base at every visit to the clinic by the responsible physician.

Local recurrence, in-transit metastases, regional lymph node metastases, and disseminated disease is typically verified using cytology, histopathology or diagnostic radiology. A local recurrence is defined as a recurrence in the scar or the transplant. In-transit recurrence is defined as a cutaneous or subcutaneous metastasis between the primary tumour site and the regional lymph nodes. All types of recurrences and date of death are prospectively reported to the data base. Information on cause of death is obtained through linkage to the National Cause of Death Registry.

Extensive checks of the data base to ensure completeness and validity has prospectively been performed by the author (E. M-B). The Melanoma data base is kept at the

Oncologic Centre which enables the registration and quality control to be carried out in collaboration with the Regional Cancer Registry.

THE NATIONAL FAMILIAL MELANOMA DATA BASE

In the mid 1980s, a national program was initiated by the Swedish Melanoma Study Group with the aim to identify and register members of all Swedish families with hereditary melanoma and dysplastic nevus syndrome. In addition, the aim was to develop clinical guidelines for the care of such patients and to implement preventive measures. A national network was organised. Regional, specialised outpatient clinics were established all over the country providing surveillance of patients with pigmented lesions and information on sun protective measures. Hereditary melanoma was defined as the occurrence of cutaneous melanoma (invasive or in situ) in at least two blood relatives. Dysplastic nevus syndrome was defined as the occurrence of clinically diagnosed dysplastic nevi in two blood relatives among hereditary melanoma kindreds (98, 106).

According to the care program for cutaneous melanoma, all newly diagnosed patients with a cutaneous melanoma are questioned about family members diagnosed with the same type of tumour. Starting in 1987, in cases where a family history is obtained, the patient is referred to the specialised out-patient clinic. If the diagnosis of familial melanoma is verified by medical records and histopathologic reports, a pedigree is drawn in collaboration with the proband and the family is given a unique identification number. All family members are offered the opportunity to participate in the prevention program. The relatives living in other parts of the country have the opportunity to be referred to their regional specialised clinic. Data on all family member are reported to the National familial melanoma data base at the Department of Oncology, Karolinska Hospital.

PRIMARY AND SECONDARY PREVENTION IN STOCKHOLM-GOTLAND

Already in the late 1970s, educational activities were started focusing on the need for early diagnosis of malignant melanoma. The regional collaboration initiated in 1976 between clinicians and pathologists involved in the primary diagnosis of pigmented skin lesions included the aim to improve treatment results by implementing practice guide-lines issued by the Swedish Melanoma Study Group. These concerned primary

diagnosis, treatment, and follow-up of patients with cutaneous melanoma. Educational campaigns aimed at primary and secondary prevention were started in the mid 1980s. These campaigns included lectures, information booklets and videotapes targeting clinicians, nurses and other health professionals in the primary health care system, the school health system and hospital staff in all major regional hospitals. A pigmented skin lesion clinic was initiated where preventive strategies for high-risk individuals were developed. The campaigns also included public information through television, radio, newspapers and magazines. Free-of-charge screening activities were offered repeatedly in some of the dermatologic and oncologic clinics in the region(171). The interventional activities in the region started some years earlier than in other parts of the country. In addition, in most other regions the activities were not as comprehensive as in Stockholm-Gotland. In 1990, a nation-wide campaign aiming at primary prevention and early detection of melanoma was conducted by the Swedish Cancer Society (172).

A summary of the study base for the individual papers is displayed in Figure 1.

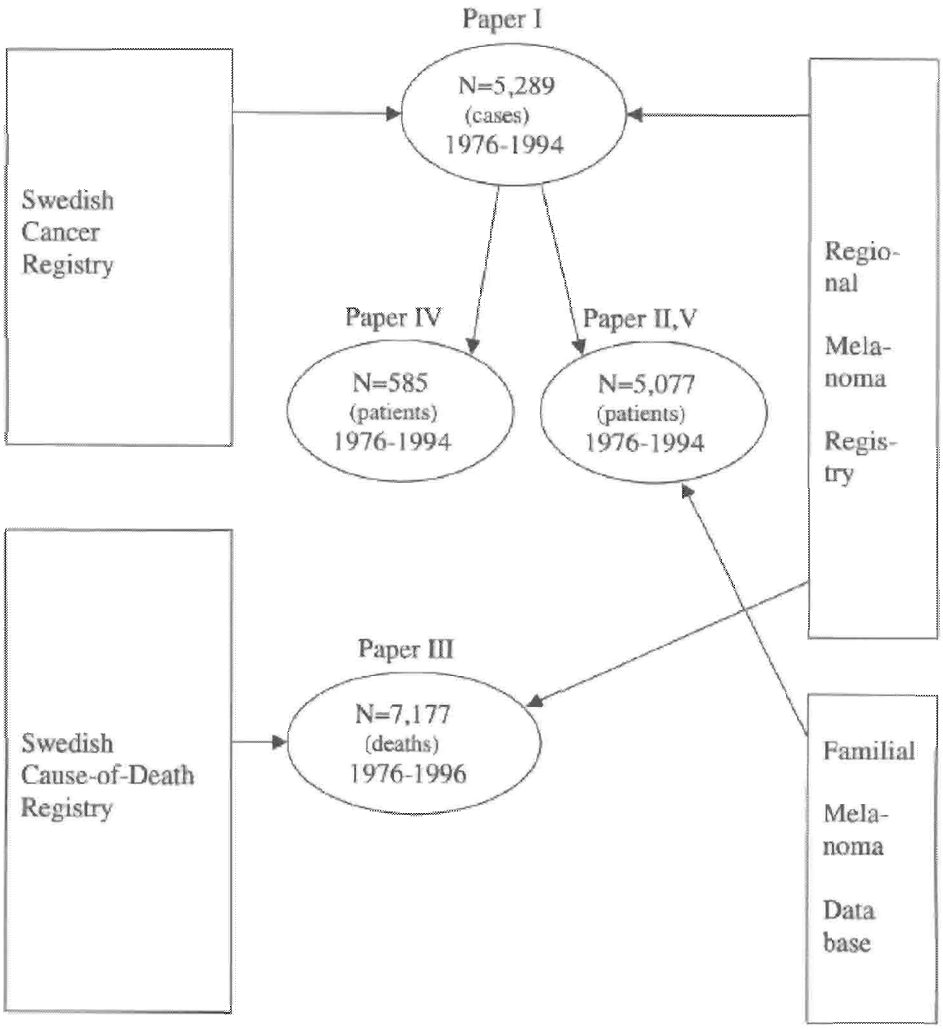

Figure 1. Summary of the study base for the individual papers. Periods of registration in each registry are indicated.

PAPERS I, II AND V

The studies were based on all patients in the Stockholm-Gotland area with a cutaneous malignant melanoma diagnosed during January 1976 through December 1994. Melanoma patients with a diagnosis before 1976 were not included due to lack of clinical and histopathological information. Patients diagnosed after 1994 were not included due to too short follow-up.

During January, 1976 through December, 1994 a total of 5,377 cutaneous melanoma cases were reported from the Stockholm-Gotland area to the Regional Melanoma Registry at the Oncologic Centre. However, in 88 cases (2 %), the melanoma diagnosis could not be confirmed because pathology slides were unavailable. These cases were excluded from the melanoma data base, which thus included 5,289 cases. These cases formed the basis for the study on incidence trends (paper I). Age-standardised, total incidence rates of invasive, cutaneous melanoma using the 1970 Swedish population as reference- for Sweden excluding the Stockholm-Gotland area as well as for the Stockholm-Gotland area for the period 1970-1996 were obtained from the National Cancer Registry.

For the purposes of the studies on prognostic factors and survival trends (paper II) as well as familial melanoma (paper V), patients with their first cutaneous melanoma diagnosed before 1976 were excluded. In cases with multiple synchronous melanomas, the thickest melanoma was registered. Thus, the 5,289 cases included in the regional melanoma registry 1976-1994, corresponded to a total of 5,077 patients. Of these patients, 4,089 presented with a primary invasive cutaneous melanoma. In situ melanoma was diagnosed in 832 patients and 156 patients had primary metastatic disease (unknown primary melanoma). A total of 3,977 patients had invasive cutaneous melanoma clinical stage I (localised melanoma), of whom two were diagnosed at autopsy. These two patients were excluded from the survival analyses. Ninety-five melanoma patients were in stage II (one with a primary in situ tumour) and 18 were in stage III. The common end-date for follow-up was December, 31, 1997. Thirty patients (0.6 %) were lost to follow-up due to emigration.

In paper V, the national data base was matched with the regional melanoma data base using computerised linkage. The self-reported family history in 67 patients in the

regional registry was not possible to verify, probably because the national data base was initiated more than 10 years after the regional data base. The self-reported family history was confirmed in 98 patients out of 165 melanoma patients with family history registered in the regional data base. Information on a positive family history in an additional 102 patients, lacking information on family history in the regional data base, was available from the national data base. Thus, information on a positive family history was available in a total of 267 patients.

PAPER III

The study was based on individuals in Sweden with malignant melanoma reported as the underlying cause of death between 1970 through 1996 in the Swedish Cause of Death Registry (n=7,177). The separation of cutaneous and non-cutaneous melanoma was done by linkage to the Swedish Cancer Registry.

For the Stockholm-Gotland region, the melanoma-related mortality curve was analysed more in depth. Of the 1,298 patients reported in the region 1970-1996 with malignant melanoma as the underlying cause of death, 97 % were verified through linkage to the Regional Cancer Registry. A total of 962 deaths were due to cutaneous melanoma. To study the clinical and histopathologic features in these patients, data in the regional melanoma data base was analysed. Comparisons were made between two time periods, 1983-1985 and 1994-1996, that is, before and after the onset of the educational campaigns launched in the mid 1980s.

PAPER IV

The study was based on 585 patients with a thin cutaneous melanoma (0.8 mm or less) in clinical stage I reported to the Regional Melanoma data base during 1976 to 1986. The registry did not comprise all recently studied putative prognostic factors. Therefore, the prognostic information given by additional characteristics of the tumour was investigated using a case-control technique with individual matching of each patient with recurrent disease with two recurrence-free patients. The matching was done for duration of follow-up, and for clinical and histopathologic factors that were found to be independent predictors for recurrence in a multivariate Cox analysis. The histopathological review of additional tumour parameters was blinded with regard to the original pathology report and clinical outcome.

STATISTICAL METHODS

Annual, age-standardised incidence and mortality rates per 100,000 person-years were calculated using the direct method of standardisation (183) with the 1970 Swedish population as reference (paper I and III).

Secular trends in incidence and mortality rates were evaluated in paper I and III using a regression model that relates the logarithm of the yearly standardised (or age-specific) rates to a linear trend term. This log-linear regression model implies a constant annual change.

Poisson regression analyses were used to study changes in incidence and mortality more in-depth and, in particular, to quantify the putative changes in the incidence trends during the 1990s (paper I). The data were organised into 13 five-year age groups (20-24, 25-29… 80-84) and 4 calendar periods (1976-1979, 1980-84, 1985-89, 1990-94). The effects of period adjusted for age on the incidence rates were assessed using Poisson regression models (184, 185). The effects of age, period and cohort on the mortality rates were also estimated using a Poisson regression model (paper III). This model assumes the number of deaths in subgroups specified by age, period and cohort to be Poisson-distributed.

Poisson regression model parameters were estimated by maximum likelihood methods using the GLIM 4 software package (186). Goodness-of-fit of models and comparisons between nested models were evaluated by means of the deviance. For models with the deviance close to its degrees of freedom, the fit was considered adequate. Change in deviance between two models were assumed to be chi-square distributed with degrees of freedom equal to the difference in the number of parameters in the two models. Models (including age) where the effect of period or cohort on the logarithmic rates were assumed to be linear are denoted "drift-models" (184, 185). In this special case it is impossible to distinguish between period and cohort effects.

Cox's proportional hazards regression models were used in paper II, IV and V for uni- and multivariate analysis of putative prognosticators of the risk of melanoma death in patients with localised (stage I) melanoma. Interactions between different factors in the multivariate models were tested by including product terms (likelihood ratio p-value).

Melanoma-specific survival (paper II and V) was calculated according to Kaplan & Meier. In these calculations deaths preceded by a regional or distant metastasis were defined as melanoma deaths. All other deaths were considered to be unrelated to melanoma and were consequently treated as censored observations. Patients with metachronous multiple melanomas were censored when the second melanoma was diagnosed. Distributional comparisons of melanoma specific survival were made with the log rank test. Two-tailed p-values < 0.05 were considered to be statistically significant.

In the study on thin melanoma (paper IV), all analyses on prognostic factors were done using recurrence as an endpoint. Life table analyses were used to estimate cumulative survival probabilities (187). In the case-control study in the same paper, odds ratios were calculated by conditional regression analysis with maximum likelihood estimates.

The median follow-up time in paper V was calculated using the reverse Kaplan-Meier method (188).

Distributional comparisons of clinical and histopathologic characteristics were done with the chi-square test of independence and multiple logistic regression. Mean age and mean thickness were compared using a two-sample t-test.

The studies were approved by the ethical review committee of the Karolinska Institute, Stockholm, Sweden.

6 RESULTS

PAPER I

During 1976 through 1994 a total of 5,289 cases of cutaneous melanoma, including in situ lesions, were registered in the Stockholm-Gotland Regional Melanoma Registry. The mean age among males was somewhat higher than among females (57.6 years versus 54.1 years) The results of the histopathologic review of the 5,289 cases are summarised in Table 1.

An upward incidence trend was observed both for cases with invasive and in situ tumours although the estimated mean annual increase was about twice as large for the in situ tumour cases (9-10%) as for the invasive tumour cases (4-5%). An upward incidence trend was observed in all age groups among both males and females. In males the age-specific incidence rates were higher than in females at ages above 54 years. In contrast, in age groups below 55 years the age-specific incidence rates were higher in females. During the 1990s the age-standardised total incidence among males levelled off. In contrast, no such trend shift was observed among females The levelling of the incidence trend among males concerned ages below 70 years.

The trunk was the dominating tumour site in males with an almost threefold increase in incidence during 1976-1994. Tumours of the lower extremity showed the highest incidence among females with a more than twofold increase. The increase mainly concerned thin tumours and melanoma in situ whereas the incidence of thick tumours remained stable. The median thickness of the tumours decreased from 1.3 mm during 1976-1979 to 0.9 mm during 1990-1994 among males. Among females the corresponding decrease was from 1.2 mm to 0.7 mm. The levelling total incidence trend for males during the 1990s mostly concerned thin tumours.

Poisson regression models were tested for all cases as well as for subsets defined according to invasiveness, tumour site, histogenetic subtype, tumour thickness, and presence/absence of ulceration or regression. The final analysis was, due to goodness-of-fit considerations, restricted to the last three 5-year periods (1980-1994). These analyses confirmed a levelling of the total incidence trend among males during the 1990s: the incidence during 1985-1989 as well as during 1990-1994 was 1.4-1.5

relative to that during 1980-1984. A continuous upward trend was observed only for some subsets of tumours such as in situ lesions, upper extremity, and lentigo maligna tumours. No levelling of the upward trend for the total incidence or the incidence of invasive tumours was observed among females.

When analysing data from the Swedish Cancer Registry, the incidence among males and females residing outside of Stockholm-Gotland rose more or less continuously during the entire studied period. The analyses of incidence trends in cutaneous melanoma were based on registered data from 1970 to 1994. Information from the Swedish Cancer Registry concerning age-standardised incidence the following six years was recently analysed (Figure 2). These new results indicate, that the levelling of the age-standardised incidence previously observed among males continued during the entire 1990s in the population of Stockholm-Gotland (Figure 3). A similar development appeared to occur in the mid 1990s in the rest of the Swedish population. Furthermore, in females a levelling of the incidence appeared to emerge in the mid 1990s, but the levelling seemed to be most pronounced in the Stockholm-Gotland area (Figure 4).

Table I: Histopathologic characteristics of cases included in the melanoma data base during 1976-1994 by sex.

	Male % (n=2,484)	Female % (n=2,805)	Total % (n=5,289)
Invasive	2,017 (81)	2,205 (79)	4,222 (80)
In situ	371 (15)	540 (19)	911 (17)
Occult primary	96 (3.9)	60 (2.1)	156 (2.9)
Stage[1]			
I (localised)	1,959 (97)	2,160 (98)	4,119 (98)
II (regional met)	44 (2.2)	40 (1.8)	84 (2.0)
III (distant met)	14 (0.7)	5 (0.2)	19 (0.5)
Histogenetic type[1,2]			
SSM	1,381 (68)	1,594 (72)	2,975 (70)
LMM	49 (2.4)	95 (4.3)	144 (3.4)
NM	331 (16)	237 (11)	568 (13)
Unclassifiable/ALM	256 (12.7)	279 (13)	535 (13)
Level of invasion[1]			
II	778 (39)	982 (45)	1,760 (42)
III	701 (35)	679 (31)	1,380 (33)
IV	412 (20)	398 (18)	810 (19)
Thickness[1]			
≤0.8 mm	847 (42)	1,110 (50)	1,957 (46)
0.9-2.0 mm	550 (27)	609 (28)	1,159 (27)
2.1-4.0 mm	362 (18)	276 (13)	638 (15)
>4.0 mm	211 (10)	169 (7.7)	380 (9.0)
Unclassifiable	47 (2.3)	41 (1.9)	88 (2.1)
Ulceration[1]			
Present	496 (25)	416 (19)	912 (22)
Absent	1,273 (63)	1,544 (70)	2,817 (67)
Unclassifiable	248 (12)	245 (11)	493 (12)
Regression[1]			
Present	328 (16)	217 (10)	545 (13)
Absent	1,622 (80)	1,923 (87)	3,545 (84)
Unclassifiable	67 (3.3)	65 (2.9)	132 (3.1)

[1]In situ and occult melanomas are excluded
[2]SSM-superficial malignant melanoma, LMM-lentigo maligna melanoma, NM-nodular malignant melanoma, ALM-acral lentiginous malignant melanoma

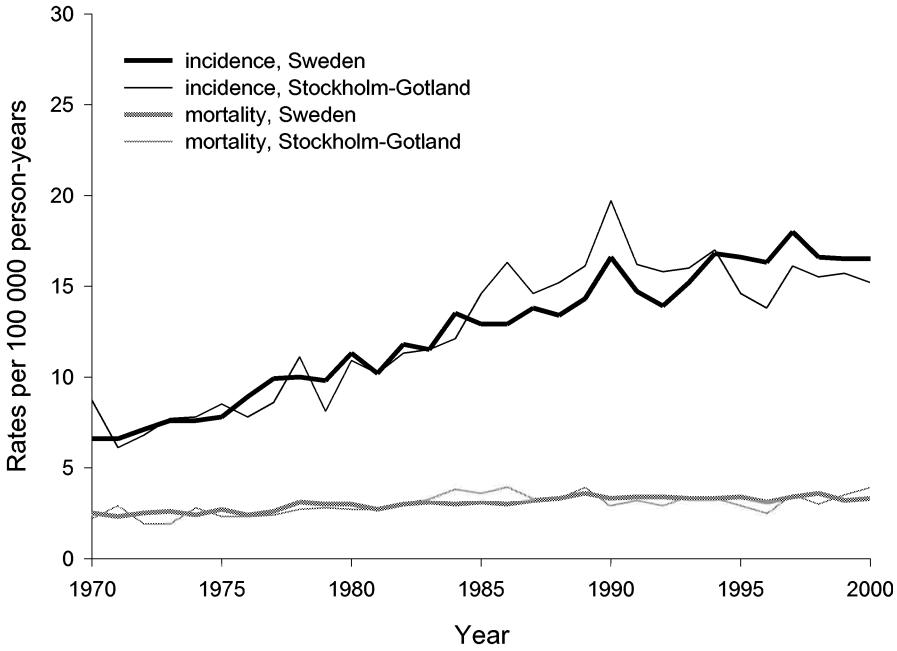

Figure 2. Age-standardised incidence of invasive cutaneous malignant melanoma and mortality from malignant melanoma in Sweden during 1970 to 2000.

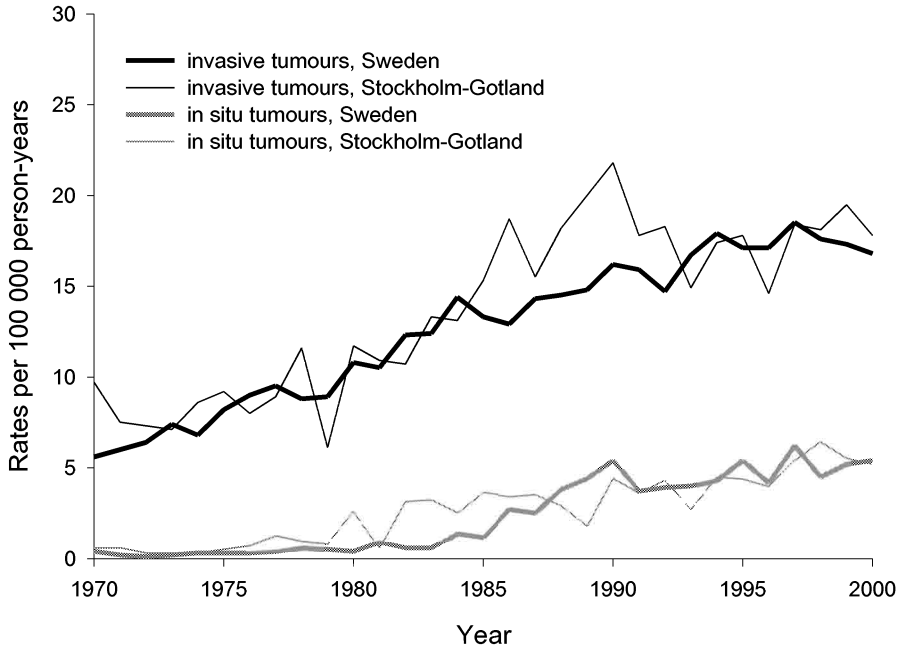

Figure 3. Age-standardised incidence of cutaneous malignant melanoma in males in Sweden during 1970 to 2000.

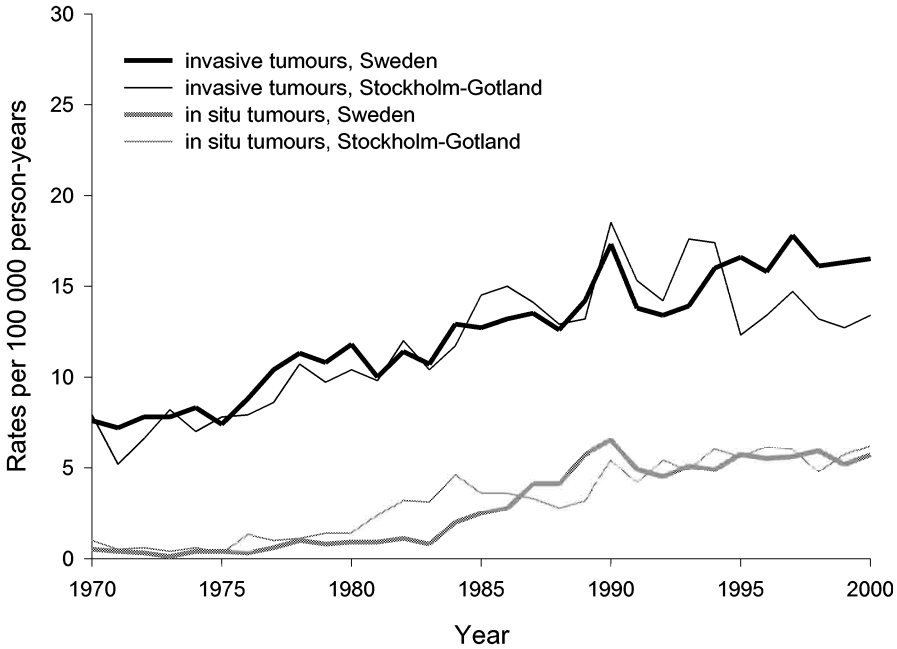

Figure 4. Age-standardised incidence of cutaneous malignant melanoma in females in Sweden during 1970 to 2000.

PAPER II

From 1976 through 1994 the melanoma-specific survival among patients with localised (Stage I) disease increased significantly. The estimated 5-year survival rate was 84 % during 1976-1979, compared to 92 % during 1990-1994 ($p<0.001$). However, no time trend for melanoma-specific survival was observed among patients with regional or distant metastases (Stage II and III).

In the Cox multivariate analyses of prognostic factors among patients with invasive localised melanoma, the following independent prognosticators were identified: tumour thickness, presence of ulceration, age, sex, anatomic site, histogenetic type and period of diagnosis. The presence of late regression was a prognostic indicator in the univariate analysis but the effect disappeared when all other factors were considered. Over time, the prognostic role of thickness and ulceration as well as anatomic site and histogenetic type appeared to decrease whereas the prognostic importance of age and sex was undiminished. When all prognostic factors were taken into consideration the hazard rate ratio of melanoma death was similar for patients who had their melanoma diagnosed the first three calendar periods (1976-1979, 1980-1984, 1985-1989). However, the hazard rate ratio was significantly below unity for patients diagnosed during 1990-1994 (0.7; 95 % CI 0.5 - 0.9). All possible interactions between the studied factors were tested. The only statistically significant interaction was that between period of diagnosis and thickness. However, this interaction did not appear to be the result of a clear time trend. The pattern of the annual hazard rate over time was similar for the first three periods of diagnosis with an increase during the first years followed by decreases after the third year of follow up. Among patients diagnosed during 1990-1994 the pattern was different with a less pronounced early peak.

PAPER III

During 1972-1996, an annual increase in age standardised melanoma-related mortality of 1.8 % (95 % CI 1.3 - 2.2) was observed in males. In females, the corresponding increase was 1.2 % (95 % CI 0.6 - 1.8). In males, the mortality rate increased until the mid 1980s. The estimated annual increase during 1977-1986 was 2.6 % (95 % CI 0.5 - 4.6), whereas during 1987-1996 the mortality was stable. A similar pattern was observed in females, however, during the last ten year period, there was a downward trend, with an estimated annual change of –1.5 % (95 % CI –3.6 - 0.5). The observed

increase in mortality up to the mid 1980s concerned ages above 44 years in both males and females. Since the mid 1980s, the mortality levelled off or decreased at ages 74 years or less. However, in the oldest age group, there was a continuous rise in melanoma mortality throughout the study period. At ages < 45 years a stable or somewhat decreasing mortality was observed. When comparing age specific mortality in the Stockholm-Gotland region with the rest of Sweden, we observed that the mortality rates for females aged > 74 years levelled off since the mid 1980s within the Stockholm-Gotland region. In contrast, a continuous rise in mortality was observed in this age group in other parts of Sweden.

The contribution from non-cutaneous melanoma to the total melanoma-related mortality was approximately 20-25 %. This proportion was relatively stable during the study period. Analyses of the cutaneous melanoma related-mortality trends deviated only slightly from the total melanoma-related mortality. However, during 1987-1996, a significant annual decrease in mortality from cutaneous melanoma of –2.3 % (95 % CI –4.3 - -0.3) was estimated among females. The observed downward trend was most pronounced in the Stockholm-Gotland region as compared to the rest of Sweden. When mortality trends in the Stockholm-Gotland region were analysed with Poisson regression models, the trends were well explained with the age-period model in both males and females. No further improvement was accomplished using the full age-period-cohort model compared to the age-period model. The relative risk of dying from cutaneous melanoma by period, indicated that after the period 1982-1986, there was no further increase in relative risk. In females, the risk decreased to the same level as during 1972-1976 (the reference period). In males, the relative risk reached a plateau at a somewhat higher level than the reference period.

The clinical and histopathologic characteristics of tumours associated with melanoma-related mortality were investigated in the Stockholm-Gotland region. The median survival time from diagnosis to death for 962 patients with cutaneous melanoma was 31.5 months. The median tumour thickness was 2.8 mm. The characteristics of patients with cutaneous melanoma were studied for deaths occurring during 1983-1985 compared to deaths during 1994-1996. No statistically significant difference was found regarding the studied clinical and histopathologic parameters, with the exception of longer median survival in the later period.

The analyses on mortality trends were based on data from 1970 through 1996. Information concerning age-standardised mortality the following four years in Sweden was recently analysed. These new results indicate, that the age-standardised mortality appeared to be fairly stable both among males and females (Figure 2).

PAPER IV

The study was based on 585 patients diagnosed with cutaneous melanoma 0.8 mm or less in Stockholm-Gotland during 1976 to 1986. The median age was 53 years in males and 47 years in females. In males, the trunk was the dominating tumour site and in females the lower extremity. Superficial spreading melanoma was the most frequent histogenetic type of melanoma (90 %). In 391 cases (67 %) the surgical excision was performed with 1-2 cm margin. The remaining patients underwent more extensive surgery.

At a median follow-up time of 50 months (range 8-143 months), recurrent disease developed in 26 patients (4 %). A local recurrence developed in four of the patients (0.7 %) and in-transit metastases in the skin was observed in two patients (0.3 %). In these patients, the median time between primary diagnosis and recurrence was 33 months. Regional lymph node metastases developed in 13 patients (2 %) after a median time of 19 months. Disseminated disease was observed in 15 patients (3 %) after a median time of 41 months. There was no difference in recurrence rate between the patients treated with a narrow excision and those treated with a wider excision.

In the Cox multivariate analyses of putative prognosticators anatomic site, tumour thickness, level of invasion (Clark) and tumour regression were all found to be independent predictors of recurrence free survival. In the case-control study of additional, putative prognostic factors, only grade of inflammatory reaction was found to add significant prognostic information. No subgroup of patients could be identified that was without risk of recurrent disease.

PAPER V

Of the 5,077 patients diagnosed with cutaneous melanoma during 1976 to 1994 in the Stockholm-Gotland area, 267 (5,3 %) had a family history of melanoma. In 181 cases (68 %) first-degree relatives were affected. Melanoma was histopathologically verified in 200 family members (75 %). After exclusion of patients with an unknown primary

tumour, clinical and histopathologic factors in 262 patients with a family history were compared with 4,659 patients without such a history.

Patients with familial melanoma were significantly younger than patients with sporadic melanoma. Their mean age was 48.0 and 55.8 years, respectively. The sex distribution did not differ between the two groups. The proportion of patients reporting a family history during 1976 - 1979 was only 3 % as compared to 6 % during 1990 - 1994. There was no significant difference in regard to eye and hair colour between the groups. Skin type III was the most dominant skin type in both groups but the proportion of type III was larger and the proportion of skin type I and IV was smaller in patients with a family history as compared to non-familial melanoma patients. A larger proportion of patients with familial melanoma presented with at least one dysplastic nevus (72 %) as compared to the non-familial group of patients (58 %). Furthermore, the site of the primary tumour differed significantly between the two groups, patients with a family history of melanoma had more trunk melanomas and less tumours in the head and neck region. Since there appeared to be a complex relationship between anatomic site, mean age and the presence or absence of a dysplastic nevus, a logistic regression analysis was done to compare the distribution of anatomic site among patients with and without family history, taking into account age and dysplastic nevus status. This analysis revealed no significant difference with regard to anatomic site among patients with and without a family history. Patients with familial melanoma had a higher propensity to develop multiple melanomas as compared to patients with non-familial melanoma. The mean tumour thickness was 1.3 mm and 1.8 mm in the familial and non-familial melanoma group, respectively ($p < 0.003$). Ulceration was less common in familial melanoma. A numerically higher proportion of melanomas associated with nevi was found in the familial melanoma group but the difference was not statistically significant.

The median follow-up time in the study was 8.2 years, 7.7 years in patients with a family history and 8.3 years in patients without such a history. In the Cox analyses of putative prognostic factors among patients with invasive localised melanoma, family history of melanoma did not influence prognosis significantly. Nor was the presence of dysplastic nevi or a pre-existing nevus in association with the primary tumour prognostic factors. Eye colour and skin type were prognosticators in the univariate analysis but their effect disappeared after adjustment for the other factors. There was no

statistically significant interaction between any of the studied factors. The overall estimated 5-year melanoma-specific survival rate in patients with a family history of melanoma was 88 % compared to 86 % in patients with no family history. This difference was not statistically significant. The survival among patients with localised (Stage I) disease was 89 % and 88 % in the two groups, respectively.

7 GENERAL DISCUSSION

Cutaneous melanoma constitutes a substantial disease burden for the society. It is one of the ten most common malignant tumours in Australia, New Zeeland, the USA, Canada and Scandinavia (18). In Sweden, cutaneous melanoma constituted 3.6 % of all cancers in the year 2000. It was the eighth most common malignant tumour among males and the ninth among females (7). Additionally, the disease affects both young and old people. A relatively high proportion of premature cancer mortality is due to cutaneous melanoma and the disease causes loss of many potentially productive years of life among young and middle-aged people (189, 190).

The increasing burden caused by cutaneous melanoma in terms of incidence and mortality, together with accumulating evidence concerning the aetiology of melanoma has been the impetus for interventional campaigns in several countries. Public education about ultraviolet radiation as a cause of melanoma started in Australia already in the 1960s (41) followed by campaigns aimed at early detection (191-193). In the Stockholm-Gotland area, an increasing interest in cutaneous melanoma during the 1970s resulted in a regional collaboration and implementation of clinical guide-lines. Large-scale educational campaigns aiming at primary and secondary prevention of cutaneous malignant melanoma were initiated in the mid 1980s. However, no campaigns with an experimental design have so far been conducted.

Valid analyses of trends in incidence and mortality are dependent on access to population based registries. Studies based on hospital based registries may be difficult to interpret due to registration bias. With population based registries, it is important to consider the coverage of the registration and the quality of reported data as well as demographic changes. The Swedish Cancer Registry and the Cause of Death Registry are both population based. They cover almost all new cancer cases and deaths due to cancer in the Swedish population. However, the registries depend on the public's access to health care, diagnostic practices, autopsy frequency, the age structure of the population and registration procedures which may vary over time. In the Stockholm-Gotland region, a melanoma data base was established in 1976. It has a close connection with the Regional Cancer Registry and includes a prospective, detailed registration and follow-up of all new melanoma cases.

The increasing incidence of cutaneous melanoma has often been attributed to changes in lifestyle, such as, increased outdoor recreational activities and fashion trends. However, changes in knowledge, attitudes and behaviour concerning exposure to ultraviolet radiation since the 1970s have been poorly documented. The increase in incidence, estimated at about 5 % annually in the Stockholm-Gotland region during 1976 through 1994, may be related to changes in population exposure to risk factors. The different patterns of the increase according to tumour sites in males and females support this hypothesis. Since childhood exposure may be of importance for the risk of melanoma later in life, it seems reasonable to assume that changes in sun habits preceded the upward incidence trend by several decades.

An increasing awareness of pigmented skin lesions during the study period may have contributed to the increasing incidence. Secondary prevention with increased knowledge among professionals and the general public about melanoma and its precursors, early detection activities among families with dysplastic nevus syndrome and public screening campaigns may have had an impact. We observed an increase in melanoma incidence in the Stockholm-Gotland population that mainly concerned thin tumours ≤ 0.8 mm and in situ lesions. In a study from southern Sweden no significant decrease in tumour thickness was observed during 1965 to 1985 (194). Furthermore, data from the Swedish Cancer Registry indicates that the increase of in situ melanoma started 5-10 years later in Swedish regions outside Stockholm-Gotland (Figure 3, Figure 4). The observed discrepancies may partly be related to the fact that the initiation of care programs and activities aiming at early detection in Stockholm-Gotland started a few years earlier than in the rest of Sweden.

The more than two-fold increase in incidence of cutaneous malignant melanoma during the 19-year study period was probably not explained by changes in diagnostic criteria or registration procedures (28, 29). During the entire period, all tumours were reviewed by a few experienced pathologists. No decrease in thick tumours was observed during the study period and the upward melanoma mortality trend previously reported from the Swedish National Cause of Death Registry (9) contradicts an artefactual increase of diagnosed cases. The increase in the reported proportion of familiar melanoma over time was probably explained by an increasing interest in familiar diseases.

The purpose of early detection and treatment of a potentially lethal disease is to reduce mortality. When analysing age-standardised trends in melanoma mortality during 1970 to 1996 we found, that the mortality rate increased until the mid 1980s. However, during 1987 to 1996 the mortality rate was stable except for the oldest age groups. From 1987 a decreasing mortality was observed among females. The observed changes in mortality may be related to secondary prevention. Since the stabilisation and decrease in mortality mainly affected young people, we have no reason to believe that the observed trends were artefactual. During the study period there have been no major improvements in the treatment of localised or generalised melanoma which could have influenced mortality. Furthermore, a stabilisation and even a decline in melanoma mortality has been reported from several countries where large scale early detection campaigns have been launched (16, 21, 40-43).

Incidence, survival and mortality are related measures. Observed discrepancies between the trends should be artefactual. We found that the increase in incidence was followed by an increase, however less pronounced, in mortality. In the mid 1980s, despite a continuous incidence increase, mortality levelled off. This was correlated to changes in survival. During 1976-1994 melanoma-specific survival in patients with localised invasive melanoma (Stage I) improved and the improvement was most pronounced from the mid 1980s. In contrast, there was no change in survival among patients with regional or disseminated disease. The improved melanoma-specific survival during 1976 to 1989 could be explained by favourable trends in terms of tumour characteristics probably as a result of secondary preventive activities. However, during 1990 to 1994 the survival trend could not be fully explained by the studied prognosticators. It seems reasonable to assume that screening activities introducing lead time bias and length bias sampling during this period contributed to the observed survival improvement.

Underlying incidence trends, trends towards earlier diagnosis in the health care system and educational campaigns aiming at primary prevention could had different effects in males and females in different ages and over time. The activities aiming at early detection appeared to have had an impact on melanoma survival and mortality but the possible effect of the primary prevention efforts has not been clear. However, during 1990 to 1994, the age-standardised incidence appear to have levelled off in the male population in Stockholm-Gotland. No such levelling off was observed among females

during the studied period. However, data from the Swedish Cancer Registry concerning age-standardised incidence the following six years, indicate that the age-standardised incidence among males appeared to have reached a plateau during the 1990s both in the population of Stockholm-Gotland and in the rest of Sweden. Furthermore, a similar trend appeared among females in the mid 1990s but the levelling appeared to be most pronounced in the Stockholm-Gotland area. These observations accord with reports from other populations where the incidence rate also seemed to level off(21-25, 195).

The relationship between the dose and time response between ultraviolet radiation exposure and the development of cutaneous melanoma is complex. UV radiation can act both as an initiator and a promotor of tumour development (2, 196). Sun exposure during childhood has been found to be a strong determinant of melanoma risk, but sun exposure during adult life seems also to play a role. The observation that use of sun beds may increase the risk of cutaneous melanoma in young adults (< 30 years) (67) indicates that the time lag between UV exposure and melanoma development may in some cases be as short as ten years. Theoretically, primary prevention reducing the promotor effect of UV exposure, could result in a relatively rapid decrease of melanoma incidence. Thus, the levelling incidence observed during the 1990s could be related to the public campaigns in the mid 1980s.

Changes in medical practice concerning diagnostic procedures and the frequency of nevus excisions may have affected the incidence trends. An intensified removal of potential precursor lesions, may, theoretically, result in a decreasing number of diagnosed invasive and in situ tumours. An increased knowledge and interest in pigmented lesions may influence people to look for and participate in screening activities (197). This requires, however, a good access to health care (198). During the 1990s, due to economical restraints in the Stockholm-Gotland region, there were large-scale cut-backs in the health care system. The measures taken to improve the health economy may have influenced peoples'access to health care.

Changes in incidence and mortality may be related to population structure. Since the Second World War, Sweden have had immigration from a large number of countries. The proportion of first-generation immigrants have increased from 7 % in 1975 to 11 % in 1994. Today, approximately one million people, constituting 11 % of the Swedish population, are foreign born (199). The proportion of first-generation immigrants in

Sweden varies geographically. In Stockholm-Gotland the proportion is currently 17.6 %. In a study of cancer risks in first-generation immigrants in Sweden, the standardised incidence ratios (SIR) were calculated for melanoma in foreign born immigrants with the Swedish born population as a reference (200). In the foreign born population, the standardised incidence ratio for melanoma was 0.59 (CI 0,59-0,64) among males and 0.64 (CI 0.59-0.69) among females. A potential influence of immigration on the falling melanoma incidence in some population groups in Australia was proposed recently (201). Whether foreign born immigration has influenced melanoma incidence and mortality rates in Sweden merits further investigations.

During the last decades the interest in familial melanoma and dysplastic nevus syndrome has increased. Several genetic mutations have been identified in affected families. The question has arisen if familial melanomas differ from sporadic tumours in terms of clinical and histopathologic characteristics and prognosis. Similarly, thin melanomas, which constitute a rapidly increasing proportion of all melanomas, have become the object of much attention. Papers IV and V focussed on whether thin cutaneous melanoma and hereditary melanoma, respectively, constitute separate biologic entities of cutaneous melanoma. The results indicated that thin cutaneous melanoma appears to represent one end of a continuous, biologic spectrum of cutaneous melanoma. Familial melanoma does not differ from sporadic melanoma in biologic behaviour.

In summary, the public campaigns in Stockholm-Gotland and the rest of Sweden were not conducted as controlled experiments so it is difficult in retrospect to assess to what extent their goals were fulfilled. The observation period may be too short to observe effects of primary prevention. However, the time lag between the initiation of the campaigns in the Stockholm area and the rest of Sweden provides an opportunity to distinguish between secondary preventive effects of the campaigns and other secular trends in the population. Effects of the campaigns should, theoretically, be first observed in the Stockholm population. However, the reasons for the observed changes in melanoma rates are complex and yet not fully understood.

8 CONCLUSIONS

- The educational and screening activities initiated during the late 1970s and 1980s appeared to have resulted in a trend towards earlier diagnosis of cutaneous malignant melanoma, since the increase in incidence during the 1980s and 1990s mainly concerned in situ or thin, invasive tumours (0,8 mm or less) whereas the incidence of thick tumours (>2.0 mm) remained stable. However, no clear effect of the primary prevention efforts was observed during the study period with the possible exception of the male population in the Stockholm area whose age-standardised incidence of invasive, but not in situ, melanoma appear to have levelled off during the 1990s.

- The melanoma-specific survival among patients with localised disease increased significantly during the study period. The estimated 5-year survival rate increased from 84% during 1976-1979 to 92% during 1990-1994 ($p<0.001$). This trend appeared to be most pronounced from the mid 1980s. There was no change in survival among patients with regional or disseminated disease. Tumour thickness, ulceration, age, sex and anatomic site were statistically significant prognosticators for melanoma-specific survival in localised melanoma both during short-term and long-term follow-up. The increased survival of patients with localised melanoma during 1976 to 1989 could be explained by a trend toward more favourable tumour characteristics. During 1990 to 1994 the survival trend could not be fully explained by the studied prognosticators. Screening activities introducing lead time bias and length bias sampling during this period may have contributed to the observed survival improvement.

- Since the mid 1980s, the melanoma mortality in Sweden levelled off with no further increase during the last 10-15 years. In females, a significant decrease of mortality from cutaneous melanoma was observed for the period of 1987-1996, with an estimated annual change of –2.3 %. This trend appeared to be more pronounced in the Stockholm-Gotland region. The mortality among females levelled off or decreased among all age-groups from the mid 1980s in the Stockholm-Gotland region, which was in contrast to the rest of Sweden, where mortality was stable, or increased throughout the studied period. The observed trends coincided with increased preventional activities.

- Among 585 patients treated for thin cutaneous melanoma 0.8 mm or less during 1976 to 1987, recurrent disease developed in only 26 patients (4 %). Anatomic site, tumour thickness, level of invasion and tumour regression were found to be independent prognostic factors. Grade of inflammatory reaction was found to add significant prognostic information. Very thin tumours did recur and no subgroup could be identified that was without risk of recurrent disease. Cutaneous melanoma may present with different forms, but these forms appear to be part of a continuous spectrum rather than distinct biologic entities.

- Familial melanoma was associated with young age at diagnosis, the presence of dysplastic nevi, multiple melanoma, thin melanomas, less ulcerated tumours and melanomas associated with pre-existing nevi. In regard to skin type, the patients with familial melanoma did not constitute a more sun sensitive group as compared to patients with sporadic melanoma. At a median follow-up time of 8.2 years, phenotype and family history did not influence melanoma-specific survival after adjustment for established independent prognostic factors. Thus, the prognosis in patients with familial melanoma did not differ from patients with non-familial melanoma.

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