Cutaneous melanoma in children and adolescents
and aspects of naevus phenotype in melanoma risk assessment

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To Jan, Linus and Simon with love
"The important thing is not to stop questioning. Curiosity has its own reason for existing"

A. Einstein
ABSTRACT

Cutaneous malignant melanoma (CMM) is one of the most rapidly increasing cancers in the Swedish population. The aetiology of melanoma is a complex interplay between genetics, host characteristics and environmental factors. The host characteristic with the strongest association with CMM is a phenotype with high numbers of common naevi and with dysplastic naevi. The principal environmental factor is sun exposure.

Melanoma risk assessment (paper I)
In a multi-national study including 986 subjects from Sweden, Denmark, the UK, Germany and the Netherlands, the ability of primary care physicians and nurses to identify individuals at increased melanoma risk was assessed. The atypical mole syndrome (AMS) scoring system for melanoma risk was used. The AMS scoring system consists of a five point check list incorporating total body naevus counts, clinically dysplastic naevi and body distribution of naevi. After brief training, the overall agreement in diagnosis between the trained personnel and experienced dermatologists was 94.5% (kappa value 0.70, p<0.05). The study showed that the scoring system successfully can be taught to personnel in primary care.

The naevus phenotype in a population in northern Sweden (paper II)
The naevus phenotype was investigated in a population living in the inland of northern Sweden with a low melanoma incidence. Two hundred and one participants from the community of Storuman were included. The median naevus count was 15 common naevi/individual, and the prevalence of dysplastic naevi was 11%. The median naevus count and prevalence of dysplastic naevi were significantly lower than previously described in populations with higher melanoma incidence and higher ambient ultraviolet exposure in southern Sweden. This geographical variation in naevus phenotype might be explained by differences in levels of sun exposure and in genotype.

Cutaneous malignant melanoma in children and adolescents (papers III–V)
During the years 1973 to 2002, 250 cases of primary CMM in individuals aged 0–19 years were reported to the Swedish Cancer Registry. Histological material was available for review in 87% of the cases registered during the two first decades (1973–1992). The diagnostic accuracy in the reviewed material was 88%.

The melanoma incidence doubled in teenagers between the first decade (1973–1982) and the second (1983–1992). During the third decade (1993–2002) the increasing trend was broken. A decrease in incidence was noted in boys during 1993–1997, and in girls during 1998–2002. In younger children the incidence remained extremely low, only 4 cases in children aged 0–9 years were reported during the studied 30-year period. The trunk was the most common melanoma site in boys, and legs and trunk were the most common sites in girls. Superficial spreading melanoma was the most frequent subtype, followed by nodular melanoma. During the two first decades (1973–1992), the median melanoma thickness decreased from 1.5 to 0.9 mm. The melanoma-specific 5-year survival rate was 93%. The most important prognostic factor was melanoma thickness. The prognosis for thin lesions was excellent, during a median follow up time of 12 years, no tumour less than 0.8 mm was lethal according to the Registry.

The results indicate that CMM in teenagers has many features in common with adult onset melanoma. The study also underlines the importance of not neglecting lesions suspected for malignant change in children and adolescents, as early detection and removal is crucial for the prognosis also in this young age group.
LIST OF ORIGINAL PAPERS

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


V. Karlsson P. and Fredrikson M. Cutaneous malignant melanoma in children and adolescents in Sweden, 1993–2002: the increasing trend is broken. (Submitted to Int J Cancer)
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## ABBREVIATIONS AND SYNONYMS

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<th>Definition</th>
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<tr>
<td>AMS</td>
<td>Atypical mole syndrome</td>
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<tr>
<td>Atypical mole</td>
<td>Dysplastic naevus, atypical naevus</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>Cyclin-dependent kinase inhibitor 2A</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CMM</td>
<td>Cutaneous malignant melanoma/s</td>
</tr>
<tr>
<td>CN</td>
<td>Common naevus/naevi</td>
</tr>
<tr>
<td>DN</td>
<td>Dysplastic naevus/naevi (clinically defined unless otherwise specified), atypical naevus/naevi, atypical mole/s</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>Cutaneous malignant melanoma (unless otherwise specified)</td>
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<tr>
<td>Melanoma</td>
<td>Cutaneous malignant melanoma (unless otherwise specified)</td>
</tr>
<tr>
<td>NM</td>
<td>Nodular melanoma/s</td>
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<tr>
<td>SSM</td>
<td>Superficial spreading melanoma/s</td>
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<tr>
<td>UK</td>
<td>United Kingdom</td>
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<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
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</table>
INTRODUCTION

The melanoma epidemic

Since the middle of the last century cutaneous malignant melanoma (CMM) is one of the most rapidly increasing cancers in fair-skinned populations worldwide. It has become a substantial health burden in the western world, as the disease occurs in comparatively young individuals and widespread disease is associated with high mortality. In Sweden, the age-standardised incidence rate of CMM increased from 4 to 20 per 100,000 between 1960 and 2000. Today CMM represents the seventh and sixth most common cancers in Swedish men and women, respectively. CMM affects close to 2000 individuals and causes 400 deaths annually in Sweden, and the cumulative lifetime melanoma risk is estimated at 1 in 50 at age 85 years.

In parallel to the steep increase in melanoma incidence, there has been a rise in melanoma mortality, albeit at a lower rate. The slower increase in mortality has been attributed to earlier detection and a higher proportion of thin lesions at diagnosis, as there has been no substantial change in melanoma therapy and there is still no cure available for widespread disease.

Recently, although the incidence continues to increase as a whole, more favourable trends have been found among certain subgroups in countries with high- and medium high risks of melanoma. The incidence increase has levelled off, and in some instances the incidence has even started to decrease in the younger and middle-aged populations and in females in Australia, New Zealand, the UK, the US and Canada. Meanwhile, the incidence continues to rise at older ages and in males. Similar trends have been found for melanoma mortality. In Sweden, there was a stabilisation in the melanoma incidence during 1990–1999. During this period, the proportion of cases aged under 50 years decreased, with a corresponding proportional increase in cases aged over 50 years.

Aetiology

The aetiology of malignant melanoma is a complex interplay between genes and environmental factors that is far from completely understood. Solar radiation is the only known environmental factor for melanoma development, evidenced from migration, latitude and case-control studies. The strong influence of sun exposure in melanoma genesis is
illustrated by the five fold higher incidence of CMM in Australia than in the UK \(^1\), although the two populations share a common genetic background.

**Sun exposure and the skin**

The harmful effects of sun exposure on the skin are generally attributed to ultraviolet (UV) radiation. UV radiation has both direct and indirect effects on the skin \(^{14}\). UVB (280-320 nm) radiation is directly absorbed by DNA, which leads to DNA damage and potentially mutagenic changes of the DNA sequence. The role of UVA (320-400 nm) in the aetiology of CMM is controversial, but is suggested by its ability to generate intracellular reactive oxygen species, which potentially are both genotoxic and cytotoxic \(^{14,15}\). UV radiation alters the intercellular regulatory crosstalk between keratinocytes and melanocytes in the skin and influences cell proliferation and apoptosis \(^{14,16}\). In addition, UV radiation has immunosuppressive properties, that indirectly might promote tumour survival \(^{17}\). More recently, the role of epigenetic changes in carcinogenesis have become highlighted \(^{18}\). Free radicals have been implicated in influencing the cell’s extra-genomic regulatory mechanisms \(^{19}\), which makes the future exploration of the relationship between UV-light, epigenetic changes and melanoma of great interest.

The cellular origin of melanoma, the melanocyte, is the skin’s defender against the deleterious effects of UV radiation. Sun protection of the skin is achieved by pigmentation and epidermal thickening. Human pigment exists mainly in two forms: the brown-black eumelanin and red-yellow pheomelanin. Melanin is produced by the melanocytes and distributed in melanosomes to the surrounding keratinocytes as protecting “caps” over the nucleus. Melanin physically protects the nucleus by scattering UV radiation, and, particularly eumelanin, has also the ability to scavenge UV-induced free radicals and reduce reactive oxygen species \(^{14}\). In addition, the process that leads to cell division, the cell cycle, is strictly regulated in order to maintain the cell’s genomic stability. Cell cycle control leads UV-induced DNA damage to cell cycle arrest and subsequent DNA repair or apoptosis \(^{14}\).

Even if the melanocyte is a key cell in the defence against UV radiation, melanocytes are also vulnerable for the UV radiation’s mutagenic effects. UV radiation has been implicated in the initiation, promotion and progression of melanoma genesis \(^{20}\). However, the relationship between sun exposure and melanoma is complex \(^{21}\). Sun exposure, when measured in terms of number of sunburns, time spent on holidays in sunnier climates and sunbathing, is only asso-
associated with a moderately increased risk for melanoma\textsuperscript{22}. Host factors, pigmen-
tary traits and ultimately genetics interact with sun exposure, and possibly other not yet identified environ-
mental factors, on melanoma risk.

HOST FACTORS

Host characteristics conferring an increased melanoma risk are fair complexion, poor tanning
ability and propensity to sunburn, freckles, light or red hair and blue or green eyes\textsuperscript{23, 24}. However, independently of other pigmentary traits, the strongest risk factor for melanoma is a
phenotype with high numbers of common naevi (CN) and with dysplastic, or atypical naevi
(DN)\textsuperscript{25-33}. CN occur during the first decade of life, increase rapidly in numbers during the
second, and peak during the third decade of life. Thereafter CN are supposed to mature,
regress and finally disappear, becoming rare at older ages\textsuperscript{34, 35}. The expression of naevi is
under genetic and environmental control\textsuperscript{36, 37}. Sun exposure particularly during childhood and
adolescence has been shown to promote naevus formation\textsuperscript{38-41}.

Dysplastic naevi (DN, synonyms: atypical naevi, atypical moles) are clinically defined as
large naevi (\(\geq 5\) mm in diameter) with a diffuse or irregular margin, and irregular or mottled
pigmentation\textsuperscript{42}. Histologically, DN are pigmented naevi featuring cytological atypia and
architectural disorder\textsuperscript{43}. In 1984, Clark et al. proposed DN to be the intermediate step
between CN and CMM in a multistep tumour progression model\textsuperscript{35}. DN are markers of
increased melanoma risk\textsuperscript{32}, as well as precursor lesions in a proportion of CMM\textsuperscript{44}.
However, DN are not uncommon in the normal population\textsuperscript{45}, and the vast majority of these
lesions do not progress to CMM. Surprisingly high numbers of CN and a high prevalence of
DN have previously been found in a Swedish population living in a coastal city (Gothenburg) in
southern Sweden\textsuperscript{45}. In Paper II, we investigated the prevalence of CN and DN in a
population with low ambient sun exposure in the inland of northern Sweden.

THE ATYPICAL MOLE SYNDROME (AMS) AND THE AMS PHENOTYPE

Approximately 10 percent of the melanoma cases occur in a familial context\textsuperscript{46}. It was early
recognised that many melanoma families expressed a phenotype characterised by high num-
bers of CN and multiple DN (the BK-mole, FAMMM, DNS or AMS-syndrome), and it was
hypothesised that the increased melanoma risk and aberrant naevus phenotype were both due
to an autosomal inherited dominant gene\textsuperscript{47}. Later on, this phenotype was found not to be
uncommon also in sporadic melanoma cases\textsuperscript{42}. In the UK, a clinical scoring system in order
to identify possible carriers of this gene was made by Julia Newton Bishop and colleagues in 1993 \(^{48}\). The scoring system consists of five components, and incorporates naevus counts, clinically DN, and body distribution of naevi (Table 1). Each component scores 1 point. A person scoring 3 or more points is considered to have the AMS phenotype, which has been associated with an increased risk ratio for melanoma of more than 10 compared with individuals with very few naevi\(^{30}\).

**Table 1. AMS scoring system. The patient is considered to have the AMS phenotype if the total score is 3 or more.**

<table>
<thead>
<tr>
<th>Component</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>100 or more naevi 2 mm or bigger</td>
<td>1 point</td>
</tr>
<tr>
<td>(50 or more if under 20 or over 50 years)</td>
<td></td>
</tr>
<tr>
<td>2 or more dysplastic naevi(^a)</td>
<td>1 point</td>
</tr>
<tr>
<td>1 or more naevi in the anterior scalp</td>
<td>1 point</td>
</tr>
<tr>
<td>1 naevus on the buttocks or 2 or more on the dorsum of the feet</td>
<td>1 point</td>
</tr>
<tr>
<td>1 or more pigmented lesion of the iris</td>
<td>1 point</td>
</tr>
</tbody>
</table>

\(^a\) Defined as naevus 5 mm or more in diameter with an irregular or blurred edge and with irregular or mottled pigmentation

The AMS scoring system was proposed as a useful tool to identify persons at increased melanoma risk in the general population. However, there was concern that the scoring procedure should be too complicated to carry out for non-dermatologists. In Paper I, we explored the possibility to teach this scoring system to nurses and general practitioners, i.e. non-specialist professional health care personnel usually involved in screening procedures for other diseases.

**Genetic alterations and melanoma genesis**

Studies of melanoma kindreds have revealed some germline (inherited) mutations involved in melanoma genesis, although in the majority of cases the underlying genetic changes remain to be elucidated \(^{49}\). High susceptibility genes are associated with a substantially increased lifetime risk for melanoma development, even if the exact magnitude of this increase is difficult to determine \(^{50, 51}\). The risk is modified by environmental levels of sun exposure \(^{51}\) as well as by other genes \(^{52}\). All known high susceptibility genes involve genes coding for proteins involved in the control of the cell cycle \(^{49}\). The most common, found in approximately 20-40\%
of melanoma kindreds, involve the *CDKN2A* gene on chromosome 9p21. The *CDKN2A* gene encodes for the proteins p16 and p14ARF, which both act as tumour suppressors. P16 inhibits cyclin-dependent kinase 4, which leads to inhibition of the cell cycle transition from G1 to S phase via the Rb pathway. Mutated p14ARF protein is less common and usually concomitant with malfunctioning p16. P14 ARF exerts cell cycle control via the p53 pathway. Rare germline mutations involve chromosome 16q24 resulting in increased amounts of cyclin-dependent kinase 4, which acts as an oncogene promoting cell cycle transition from G1 to S phase.

Low susceptibility genes are associated with a moderately increased melanoma risk and are much more common in the general population than high susceptibility genes. The *MC1R* gene is a key determinant for human pigmentation. Variants of this gene are common in white populations, and are associated with diverse pigmentation characteristics such as red hair, freckles and pale skin with low tanning ability and increased risk for skin cancer including malignant melanoma.

Somatic (acquired) genetic alterations commonly found in melanoma tissue are activating mutations in the *BRAF*-gene. *BRAF* is part of an intracellular signalling pathway that normally is activated by extracellular growth stimuli. Activated *BRAF* leads to activated ERK, a key protein involved in several vital cellular mechanisms such as proliferation, differentiation, survival, and cell-to-cell interactions. Among other genetic aberrations found in melanoma tissue are somatic mutations in, again, the *CDKN2A* gene.

**Several roads to melanoma**

Cutaneous malignant melanoma is a heterogeneous disease. There is emerging evidence of divergent pathways leading to melanoma, each involving diverse patterns of sun exposure and genetic changes. The rapidly rising melanoma incidence has been attributed to changes in clothing styles and changing sun habits, indoor work in combination with increased leisure time spent outdoors, and the increased opportunity for people to go abroad on vacation in sunnier climates. With the exception of lentigo malignant melanoma, the cumulative amount of sun exposure has previously not been considered as important in the aetiology of CMM as the pattern of sun exposure. Instead, there has been strong evidence that intermittent exposures are the most harmful with acute, intense bursts of UV radiation on unprotected, untanned skin. However, also chronic UV exposure has been shown to be of importance, but
there seems to be diverse genetic pathways and risk profiles involved in melanoma formation on intermittently versus chronically UV-exposed skin 59.

The highest melanoma density, i.e. the most common body site of melanoma when adjusted for body surface area, has been found on the back in patients aged under 50 years. At older ages, the highest melanoma density has been found on chronically exposed sites, the face and the ears 60. In 1998, Whiteman et al. proposed a “divergent pathway” model for the pathogenesis of CMM 59. In this model, melanocytes are initiated and transformed by sunlight early in life. In naevus-prone individuals, the melanocytes have an increased susceptibility for UV exposure, and due to an intrinsic instability of the melanocyte population, they need little further sun exposure for tumour progression 59. Melanomas with histologic remnants of a naevus have been found to be associated with younger age at onset, a high naevus density, and more frequently with trunk than with head and neck site 61. High naevus counts have also been found to be more predictive of melanoma risk in younger than in older subjects 31. In contrast, in individuals with a low propensity for naevus formation, the transformed melanocytes require continuous sun exposure to progress further into melanomas 59. Melanomas occurring in skin with chronic sun damage (i.e. with signs of severe solar elastosis) are negatively correlated with naevus remnants, but positively associated with solar keratoses, a history of non-melanoma skin cancer, head and neck site and older age at onset 61, 62.

Melanomas associated with chronic sun damage, in contrast to naevus-associated melanomas, have a high frequency of aberrant expression of p53, which often is found in non-melanoma skin cancer and frequently bears signs of UV-induced mutations59. Melanomas from intermittently exposed, but not chronically exposed sites are associated with somatic mutations in the \textit{BRAF} gene 63. \textit{BRAF} mutations are also frequent in CN 64. Recently, a link between \textit{BRAF} mutations and host factors associated with skin pigmentation has been discovered 65. Variants in \textit{MC1R} have been shown to be associated with melanomas with \textit{BRAF} mutations, but not with melanomas related to chronic sun damage, and variant alleles of \textit{MC1R} have been suggested to be an inherited susceptible factor for BRAF-mutant melanoma 65.

\textit{Sun exposure in childhood and melanoma risk}
Several migrations studies have implicated that sun exposure during childhood is of particular importance for future melanoma risk 66, 67, even if sun exposure in adulthood also play a role 68, 69. There is some experimental evidence lending support to these epidemiological findings of a critical period for sun exposure early in life. Hypothetically, the expanding skin surface
during growth, which reasonably contains more proliferating melanocytes than adult skin, is particularly vulnerable for the mutagenic effects of UV radiation. Melanocytes exposed to UV radiation in vitro up-regulate their anti-apoptotic proteins, which promote survival for mutated cells. The chances for transformation increase if the melanocytes are stimulated by growth factors. In human skin transplanted onto severe combined immune deficiency mice, UVB exposure in combination with growth factors, but not UVB alone, has been shown to induce melanoma phenotypes.

Cutaneous malignant melanoma in children and adolescents

Sun exposure in childhood and adolescence is critical for naevus formation, and probably also critical for future melanoma risk. Nevertheless, CMM occurring as early as during childhood or adolescence are rare. Only 1-2% of all CMM is reported in individuals under 20 years of age, and of these the vast majority occur in the second decade of life. Because of its rarity, literature has mainly consisted of case reports and hospital series of CMM in the young, including rare disorders with neonatal CMM transplacentally transferred from mother to child, melanomas arising in giant congenital naevi, and melanomas associated with neurocutaneous melanosis. Other known risk factors associated with early onset melanoma are xeroderma pigmentosum, chemotherapy for childhood cancer, and familial melanoma.

Histopathological challenges

Studies on CMM in childhood have been complicated because of histopathological difficulties in discriminating some benign pigmented lesions from CMM. Spitz’ naevus is a clinically benign tumour, with histological features resembling a malignant melanoma. It is most frequent in children, even if it exists at all ages. The Spitz’ naevus was first described by Sophie Spitz in 1948. Until then, CMM in children were thought to have a much better prognosis than in adults, as many benign lesions had been classified as malignant melanomas. Still, not all tumours subsequently classified as Spitz naevi proved to be biologically benign. A subset of these tumours metastasised with lethal outcome. Even today, the histopathological interpretation of some of these lesions is under debate. There seems to be a continuum of Spitzoid lesions ranging from benign Spitz’ naevi to atypical Spitzoid lesions and Spitzoid malignant melanomas, and it is not always possible to accurately discriminate between biologically benign and malignant lesions. Another histopathological pitfall in diagnosis of CMM in children is benign cellular nodules simulating invasive melanoma in giant congenital naevi. As in adults, the discrimination in children between melanoma and
naevi with severe atypia can be challenging. Uncertainties in the histopathological interpretation have led to over-diagnosis as well as under-diagnosis of CMM particularly in children. When Malec and Lagerlöf made a histological review of all cases of CMM in children younger than 14 years of age reported to the Swedish Cancer Registry during 1959–1971, they found that only 1 of 26 (4%) lesions fulfilled the criteria of a malignant melanoma. A high degree of over-registration in other Scandinavian registries has been reported from that time, as well as from European melanoma centres more recently.

Melanoma incidence in children and adolescents

In 1996, an increasing incidence of CMM in children 14 years or younger was reported in a population-based study from Australia. In addition, the highest ever recorded incidence of CMM in children was found in Queensland, Australia, being approximately ten times higher than in the UK. This prompted us to investigate the incidence and characteristics of CMM in Swedish children and adolescents, based on data from the population-based Swedish Cancer Registry. In order to validate the cancer registry data and to obtain more detailed information on the histological features of these tumours, a majority of the reported tumours underwent a review by pathologists with special interest in this field. The incidence and tumour characteristics of CMM in children and adolescents in Sweden during three decades, between the years 1973 and 2002, are presented in Papers III-V.
PAPER I

Aim of the study

- To study whether it is possible, after brief training, for personnel in primary care to identify individuals with the atypical mole syndrome (AMS) phenotype, the strongest phenotypic risk factor for CMM.

Participants and methods

The study was conducted in five North European countries: the UK, Germany, the Netherlands, Denmark and Sweden. Dermatologists from the participating countries first met in London to learn the AMS scoring system, the five point check list developed to identify individuals at increased melanoma risk described in Introduction (Table 1, page 14). An individual scoring 3 points or more was considered to have the AMS phenotype.

The inter-observer variation between the five dermatologists on 14 patients was studied both before and after a short training session. Subsequently, physicians and/or nurses from primary care in each country were taught the AMS scoring system during a structured one or two half-day sessions by the trained dermatologist.

Consecutive patients 18–50 years of age coming for medical appointments in primary care were asked to participate in the study. The patients were examined independently by both the trained observer and the dermatologist. The agreement between the trained observer and the dermatologist was assessed for each component of the AMS scoring system and for the overall AMS diagnosis.

In Sweden the study was conducted in Linköping, a city with 130,000 inhabitants situated in the inland in the south. Patients were enrolled from three primary care centres. Two primary care nurses, one general practitioner and one military general practitioner participated as non-specialists. Three hundred and twenty-six subjects were offered examination, and 299/326 (92%) accepted to participate. For the 27 subjects declining participation, the reasons were insufficient time in 4 cases, that the study not was appropriate to them in 2 cases and unknown in the remaining cases. In the Netherlands and Denmark, a similar number of subjects were studied. In Germany and the UK the study design was modified because it was believed
that most patients would not like to undress in those countries. In an earlier study, 25 CN or more on the face and arms had been shown to be predictive of the AMS phenotype to 80% \(^{30}\). Instead of a total body examination of all participants in Germany and the UK, the trained observers counted the total numbers of CN on the face and arms as a pre-screening test, and selected only individuals most likely to have AMS for full body examination by the dermatologist. In order to assess the pre-screening test, the dermatologist also repeated the pre-screening test and fully examined every tenth patient who had been screened by the trained observer. As a result, smaller samples, with a higher prevalence of the AMS-phenotype, were examined in Germany and the UK. A total of 986 patients were included in the study (Table 2).

### Table 2. Study base. Distribution of subjects assessed for the AMS score (n=986).

<table>
<thead>
<tr>
<th>No. of participants</th>
<th>Comment</th>
</tr>
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<tbody>
<tr>
<td>Sweden</td>
<td>299</td>
</tr>
<tr>
<td>Denmark</td>
<td>305</td>
</tr>
<tr>
<td>Netherlands</td>
<td>294</td>
</tr>
<tr>
<td>Germany</td>
<td>22</td>
</tr>
<tr>
<td>UK</td>
<td>66</td>
</tr>
</tbody>
</table>

**Statistical analyses**

The ability of the trained observer to recognise each of the five components of the AMS scoring system and the overall AMS diagnosis relative to the dermatologist was expressed in terms of specificity and sensitivity. Kappa statistic was used to adjust for agreement by chance.

**Results**

**Inter-observer variation between dermatologists**

The agreement between the dermatologists on the AMS scores in the 14 patients was found to be good, both before and after the initial training session. The overall AMS diagnosis differed only in 1 of 14 patients between one dermatologist and the remaining four.
**Inter-observer variation between dermatologist and trained observer**

The overall agreement between the dermatologist and the trained observer as to whether the patient fulfilled the criteria for AMS or not was 94.5% (932/986, kappa=0.70, p<0.05). The sensitivity of the trained observer to agree on the AMS diagnosis identified by the dermatologist was 81% (73/90). The specificity of the trained observer to agree on the patient not having the AMS phenotype was 96% (859/896). Regarding the five separate components of the AMS scoring system, the agreement on each component was exact in 67%, but differed not more than on one point in 97% of the cases. The highest agreements were found for the total naevus count (presence of 100 CN or more), and for the presence of 2 or more DN. The lowest agreement was found for the appearance of naevi on the buttocks or feet.

In the study population three CMM were detected, of which two were observed by both the trained observer and the dermatologist.

**Prevalence of the AMS phenotype**

In Sweden, 7% of the study population had 100 or more CN (or 50 or more if under 20 years of age), 6% had 2 or more DN, 17% had 1 or more naevi on the anterior scalp, 49% had 1 naevus on the buttocks or 2 or more on the dorsum of the feet, and 4% had 1 or more pigmented iris lesion. In the Swedish study population the prevalence of the AMS phenotype (score 3 points or more) was 5% (16/299) according to the dermatologist’s score. The prevalence of AMS was higher in the Danish and Dutch study populations (7% and 10% respectively).

The low percentage (7%) of the Swedish study population in Linköping with 100 CN or more (or 50 or more if under 20 years of age) was somewhat surprising. In a previous study from Gothenburg 45 22% of the studied population had 100 CN or more. Gothenburg is a high incidence area for CMM, with a relative incidence rate of 1.3 compared with Linköping and Sweden in general88. To further explore the variation in naevus phenotype between populations from different geographical areas, and with different levels of melanoma incidence in Sweden, we investigated the prevalence of CN and DN in an area with low melanoma incidence in the north of Sweden, Storuman. The naevus phenotype in Storuman is presented in Paper II. A comparison between the three Swedish populations is made in Discussion.
Paper II

Aim of the study

- To study the naevus phenotype in a Swedish population with a low incidence of CMM

Participants and methods

Storuman is a small community with 4,000 inhabitants in the inland in the north of Sweden (latitude 65° N). The incidence of CMM in Storuman is low, the relative rate is 0.3 of the mean incidence in Sweden. The summer is short and cold, and the intensity of the UV light in the area is approximately 30-50% lower than in southern Sweden.

Study base

Two hundred and eighty-two inhabitants of the municipality of Storuman aged 30-50 years were randomly selected from the census file, and invited to participate in the study by letter. One hundred and ninety-one (68%) accepted to be examined. Another 10 subjects, personnel and patients, were asked to participate and enrolled from the general practice where the examinations were performed. A total of 201 individuals participated in the study, 95 men and 106 women. Of the 91 subjects who declined participation, the reasons were insufficient time in 17 cases, 6 thought they had too few naevi, 5 had moved from the area, and in the remaining cases no reason was given.

Naevus counts and questionnaire

The study design was made as similar as possible to previous studies conducted in Gothenburg in order to enable comparisons between the two populations. Full body examination, excluding the genital area, was performed in all 201 subjects. All CN at least 2 mm in diameter were counted. DN were recorded and defined as a naevus at least 5 mm in diameter, with a diffuse or irregular border and a mottled or irregular pigmentation. The number of CN and DN were recorded for body site, defined in 16 different areas as described elsewhere (Table 3). The size of each area was calculated and expressed as a percentage of the total body surface area. The body surface areas were defined according to sun exposure patterns as rarely, chronically or intermittently UV exposed areas (Table 3). Hair- and eye colour and skin type according to Melski were registered. The participants answered a short
questionnaire on heredity of melanoma, ethnicity, occupational and spare-time sun exposure and where in Sweden they had spent their childhood.

All the examinations were performed in springtime, in the beginning of June 1997 and April 1998 by one observer (PK). In order to validate the counting technique, a sample of 48 subjects (24%) was also examined by IR who participated in the previous studies from Gothenburg.

**Statistical analysis**

The results are presented in median instead of mean values because of the positively skewed distribution of the total nevus counts in the study population. The Mann-Whitney U test was used to compare two variables and number of CN/individual. When three variables were compared, the Kruskal-Wallis test was used. Fisher’s exact test was used to compare proportions of individuals with and without DN, and subjects with 100 CN or less. The Chi squared test was used when more than proportions of two categories were compared. Unless otherwise specified, 95% confidence limits (CI) and significance levels (p< 0.05) were used. The numbers of CN in Storuman and Gothenburg were compared using the Chi squared test, with categories of 0-24, 25-49, 50-74, 75-99 and ≥ 100 CN/individual. Agreement between the two observers was estimated using the kappa statistic, with the same categories as above.

**Results**

The median number of CN was 15 per individual (range 0-332) (Figure 1). One or more DN were present in 23/201 (11%) of the subjects. Individuals with at least one DN had a higher median number of CN (median 68 CN) than those without DN (median 14 CN) (p<0.05).

There was no significant age-or gender difference in naevus numbers or prevalence of DN. The inter-observer agreement was strong in the 48 subjects examined by the two observers (PK and IR) (Kappa value 0.79, 95% CI 0.59-0.99, correlation coefficient 0.96).
Table 3.  Site distribution and naevus density of CN in Storuman (n=201)

<table>
<thead>
<tr>
<th>Area a</th>
<th>Sun exposure a</th>
<th>Median no. of CN</th>
<th>Naevus density</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Face</td>
<td>Chronic</td>
<td>1</td>
<td>0.29</td>
</tr>
<tr>
<td>B Scalp</td>
<td>—</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C Arms medial</td>
<td>Rare</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>D Arms, lateral</td>
<td>Intermittent</td>
<td>2</td>
<td>0.40</td>
</tr>
<tr>
<td>E Palms</td>
<td>—</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>F Dorsum of hands</td>
<td>Chronic</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>G Chest</td>
<td>Intermittent</td>
<td>3</td>
<td>0.25</td>
</tr>
<tr>
<td>H Lower abdomen</td>
<td>Rare</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>I Back</td>
<td>Intermittent</td>
<td>5</td>
<td>0.42</td>
</tr>
<tr>
<td>J Buttocks</td>
<td>Rare</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>K Thighs, anterior</td>
<td>Intermittent</td>
<td>1</td>
<td>0.10</td>
</tr>
<tr>
<td>L Lower legs, anterior</td>
<td>Intermittent</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>M Thighs, posterior</td>
<td>Intermittent</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N Lower legs, posterior</td>
<td>Intermittent</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>O Dorsum of feet</td>
<td>Intermittent</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

a As defined in ref 91.
Naevus density: median CN/percentage of body surface area 91.

Figure 1.  Distribution of total body naevus counts in Storuman (n=201)
Site distribution and naevus density

The site distribution of CN is presented in Table 3. Most of the CN were situated on the trunk. Men had a higher proportion of CN on the back than females (median 35% versus 22%, p<0.05), and females had a higher proportion of CN on the legs (median 14% versus 8%, p<0.05).

The highest density of CN, i.e. the highest median number of CN/percentage of body surface area, was found on the back (0.42), the lateral aspects of arms (0.40), the face (0.29) and the chest (0.25). Chronically and intermittently exposed body sites had similar densities of CN, median 0.17 and 0.20 respectively. Rarely exposed sites had the lowest density of CN, median 0.05 CN/percentage of body surface area. Most DN were situated on the back and chest (33/38), and a few were found on the lower abdomen and buttocks (4/38).

Pigmentary traits and questionnaire

Subjects who mainly spent their spare time outdoors had significantly more CN than those who preferred indoor activities (median 18 and 9 respectively, p<0.05). Common outdoors activities were hunting, fishing, snow scooter riding, gardening and open-air life. Thirteen subjects had spent their childhood in southern Sweden. These individuals had a tendency towards higher numbers of CN than those who spent their childhood in northern Sweden (median 44 and 15 respectively, p=0.08). This subgroup also had a higher prevalence of DN (4/13, 31%) than the rest of the study population (16/169, 9%) (p<0.05). No significant differences in prevalence of CN or DN was found with regard to skin type, hair or eye colour, indoor or outdoor work, holidays in sunny climates, burns, use of sun beds, residency abroad 1 year or more in a sunnier climate, ethnicity or melanoma heredity.

Subjects with 100 CN or more

Twelve (12/201, 6%) of the subjects had 100 CN or more. When comparing this group with those having less than 100 CN, they had a substantially higher prevalence of DN (67% versus 9%, p<0.01). At a 90% significance level, a higher proportion of the subjects with at least 100 CN had spent 1 year or more abroad in a sunnier climate (p=0.06) and they had a higher prevalence of light brown/dark blond than dark brown/black hair (p=0.08).
Aims of the study

- To study the incidence of CMM in children and adolescents in Sweden from 1973 through 2002
- To study the histological characteristics of CMM in this young age group
- To study the prognostic factors and clinical outcome of CMM in children and adolescents

Materials and methods

Data on all reported cases of CMM in individuals under 20 years of age during 1973–2002 were obtained from the Swedish Cancer Registry. The Swedish Cancer Registry is a population-based, nation-wide registry of high quality established in 1958. Notification is mandatory by law, and is to be made by both the diagnosing pathologist and clinician. The estimated coverage is close to 100% \(^\text{93}\). The Registry provides data on gender, age at diagnosis, tumour site, number of previously registered malignant tumours, date and cause of death, diagnosing pathology laboratory and reporting clinic. Data on all reported cases during 1973–1992 and during 1993–2002 were obtained from the Registry in 1995 and 2005, respectively. In order to follow the cases as long as possible, additional data on survival in cases reported during 1973–1992 were obtained in 2005.

Pathology reports and histological review

A copy of the original pathology report was requested from the pathology laboratories in question. Histological materials, original slides and/or paraffin blocks, were also provided for the histological review of tumours diagnosed during the two first decades, 1973–1992. Two or three pathologists without knowledge of the original report or clinical outcome independently made a histological review of the tumours.

Statistical analysis

The mean annual incidence rates per million person-years were age-adjusted to the Swedish standard population based on the census of 2000 as a reference population. For comparisons
of incidence between time periods, age groups and gender Poisson regression analysis was used. Comparisons between continuous data were made by the Mann-Whitney U test. Categorical data were compared using the chi squared test. Fisher’s exact test was used for sample sizes less than or equal to five. Survival analysis was made with the Kaplan-Meier method, and the log-rank test was used to compare the survival of different groups. The Cox regression model was used to compare the effects of several variables on survival. P-values less than 0.05 were considered as significant. Only two-sided tests were used.

Results

During 1973–2002, 256 cases of CMM in individuals aged 0–19 years were registered in the Registry. The original pathology report was available for 227/256 (89%) of the reported cases. Tumour material from 154/177 reported cases (87%) during the first two decades (1973–1992) was available for histological review. The distribution of the study sample is presented in Table 4.

Histological review of tumours reported during 1973–1992

One hundred and fifty-four tumours reported during the two first decades (1973–1992) underwent histological review. According to the original pathology reports, 148/154 cases had originally been diagnosed as primary CMM. The remaining 6 cases were correctly diagnosed as benign naevi (4 cases) or melanoma metastases (2 cases). Of the remaining 148 cases, 126 were re-evaluated as primary malignant melanomas. In 4 cases, the opinion differed between the three pathologists: Spitz naevi (2 tumours), dysplastic naevi (2 tumours) or malignant melanoma. These tumours were classified as suspected malignant melanomas. In 18 cases, the tumours were re-evaluated as non-melanoma lesions (Table 5). Thus, the diagnosis malignant melanoma, or suspected malignant melanoma of the skin was confirmed in 130/148 (88%) of the correctly reported, reviewed tumours. There was no difference in diagnostic accuracy between tumours diagnosed in individuals aged 0-14 years as compared with individuals aged 15–19 years (18/20, 90% versus 112/128, 88% respectively). The diagnostic accuracy increased from 85% (39/46) in 1973–1982 to 89% (91/102) in 1983–1992. None of the patients with a tumour reconsidered upon review as a benign lesion, or as suspected malignant melanoma, has been reported dead of the disease to the Registry (median follow-up time 18 years, range 8 to 28 years).
Table 4. Study base. Distribution of reported cases of CMM, available pathology reports and reviewed cases during 1973–2002.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Registered cases</strong></td>
<td>59</td>
<td>118</td>
<td>79</td>
<td>256</td>
</tr>
<tr>
<td><strong>Mis-reported cases</strong></td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td><strong>Reported cases, primary CMM</strong></td>
<td>55</td>
<td>116</td>
<td>79</td>
<td>250</td>
</tr>
<tr>
<td><strong>Original pathology reports</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary CMM</td>
<td>43</td>
<td>100</td>
<td>78</td>
<td>221</td>
</tr>
<tr>
<td>Not available</td>
<td>12</td>
<td>16</td>
<td>1</td>
<td>29</td>
</tr>
<tr>
<td><strong>Re-examined cases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not available material</td>
<td>9</td>
<td>14</td>
<td>–</td>
<td>23</td>
</tr>
<tr>
<td>Re-examined cases</td>
<td>46</td>
<td>102</td>
<td>–</td>
<td>148</td>
</tr>
<tr>
<td><strong>Non-melanoma diagnoses</strong></td>
<td>7</td>
<td>11</td>
<td>–</td>
<td>18</td>
</tr>
<tr>
<td>Suspected CMM</td>
<td>3</td>
<td>1</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>CMM</td>
<td>36</td>
<td>90</td>
<td>–</td>
<td>126</td>
</tr>
<tr>
<td>Invasive CMM</td>
<td>33</td>
<td>88</td>
<td>–</td>
<td>121</td>
</tr>
<tr>
<td>Melanoma in situ</td>
<td>3</td>
<td>2</td>
<td>–</td>
<td>5</td>
</tr>
</tbody>
</table>

* Tumours originally not classified as primary CMM: benign naevi and melanoma metastases.
* Cases originally classified as primary malignant melanomas, and reclassified as non-melanoma lesions upon review (see Table 5).
* Cases in which opinion differed between the three reviewing pathologists as to whether the lesions were malignant melanomas or not (see text for further details).

Table 5. Tumours re-evaluated as non-melanoma lesions in reviewed material (n=18)

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spitz naevi</td>
<td>5</td>
</tr>
<tr>
<td>Dysplastic naevi</td>
<td>5</td>
</tr>
<tr>
<td>Atypical compound naevi</td>
<td>5</td>
</tr>
<tr>
<td>Atypical junction naevus</td>
<td>1</td>
</tr>
<tr>
<td>Compound naevus with a large nodulus in dermis</td>
<td>1</td>
</tr>
<tr>
<td>Non-melanocytic tumour</td>
<td>1</td>
</tr>
</tbody>
</table>
**CMM in children and adolescents during three decades**

Based on the 250 cases of primary CMM reported to the Registry during 1973–2002, the following analysis was made.

**Age and sex distribution**

The disease was extremely uncommon in younger children. At about 12 years, the incidence started to rise sharply with age (Fig. 2). Four (4/250, 2%) cases occurred in children aged 0–9 years. Twenty-nine children (29/250, 12%) were aged 10–14 years, and 217 (217/250, 87%) were aged 15–19 years. There were 101 males and 149 females, rendering a male to female ratio of 0.68. The female predominance was more pronounced at ages 18 and 19 years (Fig. 2).

**Figure 2.** Age and sex distribution of reported cases of CMM in individuals aged 0–19 years, 1973–2002 (n=250).
Melanoma incidence

During the first two decades (1973–1992), the age-standardised incidence rate doubled in individuals aged 0–19 years (Table 6 and Fig. 3). During the third decade (1993–2002), the increasing trend was broken. In boys, the incidence decreased during 1993–1997 compared with 1988–1992 (p<0.05). In girls, the incidence remained high during 1993–1997 and decreased during 1998–2002 (p<0.05) (Fig.3).

Table 6. Number of reported cases and mean annual incidence rates of primary CMM in individuals aged 0–19 years, Sweden 1973–2002.

<table>
<thead>
<tr>
<th>Time period</th>
<th>No.</th>
<th>Crude</th>
<th>ASR</th>
<th>Relative rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1973-1982</td>
<td>55</td>
<td>2.5</td>
<td>2.3</td>
<td>1a</td>
</tr>
<tr>
<td>1983-1992</td>
<td>116</td>
<td>5.5</td>
<td>5.0</td>
<td>2.1 (1.7–2.5)</td>
</tr>
<tr>
<td>1993-2002</td>
<td>79</td>
<td>3.7</td>
<td>3.6</td>
<td>0.74 (0.58–0.92)</td>
</tr>
</tbody>
</table>

a Reference category.

No: Number of reported cases; Crude: Crude incidence rate per million; ASR: Age standardised incidence rate per million (Swedish population 2000)

Figure 3. Age-standardised incidence rate of CMM in individuals aged 0–19 years, 1973–2002 (n=250).
The incidence increased between the first decade (1973–1982) and the second decade (1983–1992) in the age groups 10–14 years (p<0.05) and 15–19 years (p<0.05). During the third decade (1993–2002), there was a decrease in incidence in adolescents aged 15–19 years (p<0.05) and in children aged 10–14 years (p=0.05). The very low incidence in children under 10 years of age remained stable during the study period (Fig. 4).

**Cohort analysis**

When comparing the age-specific incidences by 5-year birth cohorts, the incidence in adolescents aged 15–19 years peaked in boys born between 1968 and 1972, and in girls born between 1973 and 1977 (Fig. 5).

![Boys and Girls Age-Specific Incidence Chart](chart.png)

Figure 5. Age-specific incidence by 5-year birth cohorts, in boys and girls aged 0–9 years, 10–14 years and 15–19 years (n=225).
Melanoma site

The trunk was the most common tumour site in boys, and the lower limb was the most frequent site in girls (Fig. 6). Boys had a higher proportion of melanomas on the trunk (p<0.05) and in the head and neck region (p<0.05) than girls. Girls had a higher proportion of melanomas on the lower (p<0.05) and upper limb (p<0.05) than boys.

![Graph showing site distribution of CMM in boys and girls aged 0–19 years, 1973–2002 (n=250).](image)

**Figure 6.** Site distribution of CMM in boys and girls aged 0–19 years, 1973–2002 (n=250).

Melanoma site over time

During the three decades studied, there were significant changes in incidence for melanomas on the trunk and legs (Fig.7). In boys, the incidence of trunk melanomas increased during 1973–1992 (p<0.05), followed by a decrease in 1993–2002 (p<0.05). In girls, there was a steep rise in incidence of melanomas on the legs during 1973–1992 (p<0.05), followed by a decrease during 1993–2002 (p<0.05). The incidence of trunk melanomas in girls also increased, albeit later in time, peaking during 1993–1997 (p<0.05) followed by a decrease during 1998–2002 (p<0.05). A discrete and non-significant peak of melanomas on the legs was noted in boys during 1988–1992. The incidence of melanomas at other sites than trunk and legs remained fairly constant during the thirty years studied (Fig. 7).
Figure 7. Site distribution of CMM in boys and girls aged 0–19 years over time, 1973–2002 (n=250).
**Histological features of reviewed tumours reported during 1973–1992**

In the reviewed material from the two first decades, 121 of 126 verified primary CMM were invasive melanomas and 5 were melanomas in situ. There were 33 invasive CMM from the first decade, and 88 from the second. The histological features of the reviewed, invasive melanomas are summarised in Tables 7 and 8.

**Table 7. Histological features of 121 invasive CMM, reported in 1973–1992. Reviewed material.**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histogenetic subtype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSM</td>
<td>20</td>
<td>61 %</td>
<td>59</td>
<td>67 %</td>
</tr>
<tr>
<td>NM</td>
<td>11</td>
<td>33 %</td>
<td>23</td>
<td>26 %</td>
</tr>
<tr>
<td>ALM</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3 %</td>
</tr>
<tr>
<td>LMM</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unclassified</td>
<td>2</td>
<td>6 %</td>
<td>3</td>
<td>3 %</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Clark level</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>10</td>
<td>30 %</td>
</tr>
<tr>
<td>III</td>
<td>15</td>
<td>45 %</td>
</tr>
<tr>
<td>IV</td>
<td>8</td>
<td>24 %</td>
</tr>
<tr>
<td>V</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Excludeda</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Precursor lesion</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital naevus</td>
<td>0</td>
</tr>
<tr>
<td>Common naevus</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Ulceration</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SSM</td>
<td>3</td>
</tr>
<tr>
<td>NM</td>
<td>8</td>
</tr>
</tbody>
</table>

*One tumour excluded because of regression, Clark level could not be assessed.
SSM, superficial spreading melanoma; NM, nodular melanoma; ALM, acral lentiginous melanoma; LMM, lentiginous malignant melanoma.
Table 8. Tumour thickness according to Breslow in 121 invasive CMM, reported in 1973–1992. Reviewed material.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Md (range)</td>
<td>No.</td>
</tr>
<tr>
<td>Total</td>
<td>1.5 (0.3–5.0)</td>
<td>32³</td>
</tr>
<tr>
<td>Males</td>
<td>1.7 (0.5–5.0)</td>
<td>16</td>
</tr>
<tr>
<td>Females</td>
<td>1.1 (0.3–5.0)</td>
<td>16</td>
</tr>
<tr>
<td>SSM</td>
<td>0.9 (0.3–4.0)</td>
<td>19</td>
</tr>
<tr>
<td>NM</td>
<td>2.3 (0.8–5.0)</td>
<td>11</td>
</tr>
</tbody>
</table>

³One tumour excluded because of regression, Breslow index could not be assessed.
⁴Three tumours excluded because of regression
Md, median.

The most common histogenetic subtype was SSM (65%), followed by NM (28%). The proportions of SSM and NM did not significantly change between the two decades. The median tumour thickness decreased from 1.5 in the first decade to 0.9 mm in the second (p<0.05). The decrease over time reached statistical significance for girls (p<0.05) but not for boys (p=0.23). In girls, the median thickness of SSM decreased from 1.15 mm to 0.6 mm (p<0.05). The median thickness of NM did not significantly change during the period. An increase of Clark level II tumours, and corresponding decrease in Clark level III tumours were noted but these changes did not reach statistical significance.

NM were thicker than SSM, 2.2 mm versus 0.7 mm (p<0.05). Boys had thicker melanomas than girls, median 1.2 mm versus 0.8 mm (p<0.05). Boys tended to have a higher proportion of NM than girls did, 19/53 (36%) versus 15/68 (22%) respectively (p=0.09). Girls tended to have a higher proportion of SSM than boys did, 49/68 (72%) versus 30/53 (57%) respectively (p=0.08).

Ulceration was more common in thick lesions. The median thickness of ulcerated tumours was 2.3 mm. The proportion of ulcerated tumours decreased from 33% to 13% during the two decades (p<0.05). In 19/113 (17%) of SSM and NM an associated precursor lesion were identified histologically: 14 common naevi and 5 lesions with histological features indicative of a congenital naevus. None of these was a giant congenital naevus.
Histological features of tumours reported during 1993–2002

Data on the histological features of tumours reported during the third decade (1993–2002) were based on the original pathology reports. Twenty-four of 78 (31%) of these tumours were unclassified according to histogenetic subtype, in contrast to 3/88 (3%) in the reviewed material from the previous decade (Table 7). However, in contrast to the reviewed material, the original reports from the previous decades did also contain a high proportion of unclassified lesions (36%). When comparing data from the original reports only, disregarding the review, the distribution of histogenetic subtypes was similar without significant changes between 1993–2002 and 1983–1992. In the original reports from the third decade (1993–2002) SSM was the most common subtype (43/78, 55%), followed by NM (8/78, 10%). The median tumour thickness at diagnosis was 0.8 mm. Boys had a higher proportion of NM than girls, 7/24 (29%) versus 1/55 (2%) respectively (p<0.05), and boys tended to have thicker melanomas at diagnosis than girls (1.2 and 0.75 mm respectively, p=0.09).

CMM in children 14 years or younger

Four cases of CMM were reported in children under 10 years of age at diagnosis. In 1974, there was a 1 year and 4 months old boy diagnosed with a melanoma in a congenital naevus. Ten months later, the child died of the disease. No pathology report or material for histopathological review was available in this case, but the case has been described in a report by others 94. In 1989, a 9-year old girl presented with a SSM on the leg; 0.6 mm thick and Clark level II. An ulcerated melanoma, Clark level V and 3.3 mm thick, occurred in a 9-months old boy in 2002. The girl and the little boy were still alive according to the Registry, 13 years and 7 months after diagnosis respectively. In the fourth reported case, the lesion did not fulfil the histopathological criteria for a malignant melanoma upon review.

Twenty-nine cases occurred in children aged 10–14 years. There was no sex-difference in incidence of CMM in this age group; there were 14 boys and 15 girls. As in the older age group, the trunk was the most common site of melanoma in boys (7/14, 50%), and the lower limb was the most common site in girls (7/15, 47%).

During the third decade (1993–2002) the melanomas were thicker in children aged 0–14 years than in adolescents aged 15–19 years, 2.0 mm versus 0.7 mm respectively (p<0.05). During this period the Clark levels of the tumours were also more advanced in the younger age group,
6/9 (67%) of the tumours invaded to Clark level IV or V as compared with 19/73 (26%) in the older age group (p<0.05). A higher median thickness and a higher proportion of more advanced Clark levels were also found in children aged 0–14 years in the reviewed material from the first two decades (1973–1992), although these differences did not reach statistical significance.

Mortality

Twenty-six of 250 cases reported to the Registry during 1973–2002 died of the disease (follow-up time median 12 years, range 1 month to 29 years). Three patients died of other causes. The melanoma-specific 5-year survival rate was 93%. There was no statistically significant change in mortality during the three decades (Table 9).

Table 9. Melanoma-specific survival rates in individuals aged 0–19 years during 1973–2002.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year</td>
<td>95% (52/55)</td>
<td>93% (108/116)</td>
<td>90% (43/48&lt;sup&gt;a&lt;/sup&gt;)</td>
</tr>
<tr>
<td>10-year</td>
<td>87% (48/55)</td>
<td>91% (105/115&lt;sup&gt;a&lt;/sup&gt;)</td>
<td></td>
</tr>
<tr>
<td>15-year</td>
<td>85% (47/55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-year</td>
<td>83% (45/54&lt;sup&gt;a&lt;/sup&gt;)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> One patient censored, dead of other cause than CMM.

Histological data on 22 of 26 lethal tumours were available; 17 based on reviewed material and 5 based on original reports. Of these 22 lethal tumours, 55% (12/22) was NM and 44% (10/22) was ulcerated. Only one tumour was Clark level II, the rest were levels III–V. The median thickness of the lethal tumours was 1.8 mm (range 0.8 mm to 7.0 mm).

The time from diagnosis to death in lethal cases varied between 10 months to 15 years (median 3 years and 10 months). Boys had a higher mortality rate than girls, 16% (16/101) versus 7% (10/149) respectively (p<0.05). Children under age 15 at diagnosis had a higher mortality rate than adolescents, 21% (7/33) versus 9% (19/217) respectively (p<0.05).
Cox regression analysis of the reviewed tumours, including sex, age, and thickness according to Breslow (per mm increase) showed that the thickness at diagnosis was the most important prognostic factor for survival (p=0.005). When adjusting for melanoma thickness, the difference in mortality between the sexes became statistically insignificant, while age under 15 years at diagnosis persisted as an independent prognostic factor (p=0.028).

In the reviewed sample, three individuals were diagnosed with a minimal deviation melanoma. Two lesions were Clark level III and one Clark level IV, 0.7 mm, 1.26 mm and 7.7 mm at diagnosis respectively. Thirteen, 22 and 14 years after diagnosis none of them have been reported dead to the Registry.

Risk factors

In five cases, a previous malignancy was registered in the Registry; 1 neuroblastoma, 1 epidermoid cancer, 1 malignant fibrous histiocytoma, 1 Hodgkin’s disease and 1 non-Hodgkin lymphoma. One patient had xeroderma pigmentosum. No indication of a CMM arising in a giant congenital naevus was found in our series of reviewed tumours from the first two decades (1973–1992), or according to the original pathology reports on tumours from the third decade (1993–2002). Complete information on hereditary factors, phenotype characteristics of the patients or clinical presentation of the tumours was not available in our material.

In paper III, the incidence of CMM in Swedish children and adolescents during 1973–1992 were based on reviewed and verified CMM. As a consequence, the above mentioned increase in incidence between the first decade (1973–1982) and the second (1983–1992) is less defined than in paper III, as the diagnostic accuracy increased from 85% in the first decade to 89% in the second.
DISCUSSION

Screening for the AMS phenotype

In Paper I, we showed that it is possible, after a brief training, for primary care doctors and nurses to recognise the AMS phenotype, and thus to identify individuals at increased melanoma risk. After one or two half days sessions only, the trained observers obtained results comparable to experienced dermatologists. Furthermore, in the study population two CMM were recognised by the trained observer.

Screening for melanoma in the general population has been discussed, especially in high incidence countries but no nation-wide population screenings have been carried out. In Europe, where the lifetime risk for the disease is comparatively low, a general population screening would not be cost-effective. Preventive work has instead focused on sun avoidance messages and public health campaigns aiming at early detection of melanoma targeting the population as a whole. In addition, a special national program for high risk families for melanoma has been carried out in Sweden since the beginning of the 1990s. Our study showed the feasibility of teaching health care personnel to recognise the AMS phenotype, but the question is whether the AMS scoring system would be adequate enough to identify individuals at increased risk in the general population. There is no doubt that the AMS phenotype is associated with an increased melanoma risk, but the majority of melanoma patients will not express the phenotype. Only 15% of the patients in the British case-control study fulfilled the criteria for the phenotype. Furthermore, the sensitivity of the scoring system decreases with age which could be an effect of the natural history of naevi, disappearing later in life. This might also be due to a higher frequency of melanomas associated with cumulative chronic sun exposure, and not with naevus proneness, later in life in line with the divergent pathway hypothesis. Thus, the AMS-scoring system would identify a subset, but not all individuals at an increased melanoma risk.

The original idea of the scoring system was to identify gene carriers in families with hereditary melanoma in the UK. Later on, the then unidentified melanoma predisposing gene proved to be germline mutations in *CKDN2A* in some of these families. In 2000 Julia Newton Bishop and colleagues published a study on the correlation of the AMS phenotype, gene carrier status and melanoma risk in five British families harbouring the *CDKN2A*
mutation\textsuperscript{99}. They showed that mutant gene-carriers expressed the AMS phenotype to a significantly higher degree than non-carriers, in line with the idea that the \textit{CDKN2A} gene is both naevogenic and involved in melanoma carcinogenesis\textsuperscript{99}. However, there was a large degree of variation in families and between families, and a large overlap between carriers and non-carriers that made the authors conclude that the scoring system was not accurate enough for predicting gene carrier status or melanoma risk. Revision of the scoring system (excluding scalp and iris naevi) increased the sensitivity for carrier status and melanoma risk, but the overlap between carriers and non-carriers remained still too large to allow for appropriate discrimination\textsuperscript{99}. A scoring system with a high degree of both sensitivity and specificity for melanoma risk based on naevus phenotype only might prove to be inadequate. A more multifactorial screening tool for melanoma risk, including phenotypic as well as genotypic variables, as recently outlined by Whiteman and Green\textsuperscript{100} might be a more successful approach in future.

Geographical variation in naevus phenotype in Sweden

As total numbers of CN, and presence of DN both are strong determinants for melanoma risk\textsuperscript{26}, it was of interest to compare the naevus phenotype in Swedish populations from geographical areas with different levels of melanoma incidence (Table 10). Storuman, with a melanoma incidence rate of 0.3 relative to the mean incidence in Sweden, was selected to represent the low melanoma incidence area. Linköping represented the medium-high incidence area, with a relative rate of 1.0\textsuperscript{88}. The data on the naevus phenotype in Linköping was obtained from the study sample in Paper I. To make data from Paper I comparable with the population sample in the Storuman study, only individuals aged 30–50 years in the Linköping population were included in the following comparison. The naevus phenotype in the Gothenburg population has previously been described in detail by Augustsson \textit{et al.}\textsuperscript{91} Gothenburg is a high melanoma incidence area, and the relative incidence rate was 1.3 in comparison with the mean incidence in Sweden at that time\textsuperscript{88}. Gothenburg is a city with 500,000 inhabitants on the west coast in the south of Sweden.

There was a large variation in naevus phenotype between the three studied populations (Table 10 and Fig. 8). The highest naevus counts were found in Gothenburg, the area with the highest melanoma incidence (median 53 CN/individual\textsuperscript{91}). In the medium high incidence area, Linköping, the naevus counts were significantly lower than in Gothenburg (median 23 CN/individual, \textit{p}<0.05). In Storuman, the low incidence area, the naevus counts were
significantly lower than in Linköping (median 15 CN/individual, p<0.05). No difference in prevalence of DN was found between the populations in Linköping and Gothenburg (19% versus 18% \(^91\)). The prevalence of DN was significantly lower in Storuman (11%) than in Linköping and Gothenburg (p<0.05) (Table 10).

Table 10. **Total body nevus counts and prevalence of DN in three populations from different geographical areas in Sweden. Data from Gothenburg obtained from ref \(^91\) with permission from the authors.**

<table>
<thead>
<tr>
<th></th>
<th>Storuman</th>
<th>Linköping</th>
<th>Gothenburg (^91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latitude °N</td>
<td>64.6</td>
<td>58.2</td>
<td>57.4</td>
</tr>
<tr>
<td>Site</td>
<td>inland</td>
<td>inland</td>
<td>coast</td>
</tr>
<tr>
<td>Relative incidence of CMM (^a)</td>
<td>0.3</td>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Number of participants</td>
<td>201</td>
<td>165</td>
<td>310</td>
</tr>
<tr>
<td>Number of CN/individual (median)</td>
<td>15</td>
<td>23</td>
<td>53</td>
</tr>
<tr>
<td>Prevalence of DN</td>
<td>11%</td>
<td>18%</td>
<td>19%</td>
</tr>
</tbody>
</table>

\(^a\)Relative to mean incidence of CMM in Sweden during 1983–1992 \(^88\)

Figure 8. **Distribution of naevus counts in three populations from different geographical areas in Sweden.** \(^1\)Data on the population in Gothenburg from ref \(^91\).
The two populations from Storuman and Gothenburg differed somewhat in their ethnicity, pigmented traits, leisure time and occupational sun exposure. In Storuman 17/201 (8%) reported at least one Saami relative, which is in line with results of studies of genetic markers in the area. Only 5/201 (3%) had at least one parent of non-Scandinavian origin, as compared with 8% in Gothenburg. In Storuman, skin types I and II were more common than in Gothenburg (30% and 8% respectively), as well as dark brown or black hair (45% and 16% respectively). Fewer individuals in Storuman went to sunnier countries on holidays than in Gothenburg (62% versus 89% had spent at least one week on holiday in a sunnier climate), a lower proportion had indoor work (64% versus 76%) and fewer used sunbeds regularly (5% versus 14%).

Interestingly, in spite of much lower total body counts, the naevus density was of the same magnitude at chronically exposed body sites in Storuman and in Gothenburg (Storuman men and women median 0.17 CN/percentage of body surface area, Gothenburg men 0.17, and women 0.33, personal communication). The Storuman population had lower naevus density both at intermittently exposed sites (men 0.23 and women 0.17 in Storuman versus men 0.64 and women 0.61 in Gothenburg) and at rarely exposed sites (0.05 in men and 0.08 in women in Storuman versus men 0.47 and women 0.42 in Gothenburg).

Comparable data regarding the naevus density and distribution of CN over the body surface, other pigmented traits, ethnicity, heredity and factors relating to sun exposure were not available for the population in Linköping, as the study design in Paper I differed from the study design in Paper II and the Gothenburg study.

The comparison between Storuman, Linköping and the previously published data from Gothenburg, shows that there is a large geographical variation in naevus phenotype in Sweden. Up north, where the climate is cold, summer is short and UV-levels low, people have few CN and few have DN. Higher naevus counts and a higher prevalence of DN are found in southern Sweden, with the highest naevus counts recorded on the Swedish west coast. The co-variation in melanoma incidence, with the lowest incidence up north and the highest on the west coast, is well in line with an aetiological role for sun exposure both in melanoma and naevus formation. The difference in naevus density found at intermittently exposed body sites between individuals living in Storuman and Gothenburg, in contrast to a similar density at chronically exposed sites is consistent with the idea that intermittent sun exposure...
is more nevogenic than chronic exposure. Interestingly, there was also a difference in nevus density at rarely exposed body sites. In Storuman, the nevus density was lowest at these sites, in contrast to Gothenburg where the nevus density at rarely exposed sites were higher than at chronically exposed sites. Considering the importance of gene-environment interactions in nevus development, this might be explained by genetic differences between the two populations. Hypothetically, it might also be an effect of some indirect influence from sun exposure, as UV exposure has been shown to induce proliferation of melanocytes not only at exposed but also at covered body sites.

In Storuman, the small subgroup of individuals who had spent their childhood in southern Sweden had a tendency for higher nevus counts (median 44 versus 15, p=0.08) and had a higher prevalence of DN (31% versus 9%, p<0.05) than the rest of the study population. Migration studies have shown similar findings with higher nevus counts in individuals who have spent their childhood in a sunnier climate, or arrived in a sunny environment early in life as opposed to migrants arriving in adulthood. The difference in nevus phenotype between the native-born population and those who had moved into the area as adults is in line with the idea that sun exposure during childhood is of crucial importance for nevus formation. An influence from genetic differences is also possible.

It is interesting to analyse the nevus phenotype in Linköping more in detail. Linköping is geographically situated much closer to Gothenburg than to Storuman. The prevalence of DN was the same as in the Gothenburg population (18% and 19% respectively), but the median nevus count of 23 CN/individual was closer to the median nevus count of 15 in Storuman than the median count of 53 in Gothenburg (Fig. 8). Comparing results from different investigators is always difficult. However, the same definition of nevi and the same counting technique were used in Storuman, Linköping and Gothenburg, and one of the investigators (IR) participated in all three studies. This make us believe that these differences are valid and not an effect of inter-observer bias. It might be argued that the lower nevus counts in Linköping than in Gothenburg are due to a higher UV exposure of the Gothenburg population as the city is situated on the coast, offering more opportunities for leisure time spent swimming, sailing and sunbathing. However, it seems unlikely that this is the only explanation for such a large difference in nevus counts, when the difference is only moderate between Linköping and Storuman. In addition, the studies in Linköping and Storuman were conducted ten years after the study in Gothenburg which might have influenced the results.
When the naevus profile was investigated in Linköping, the regional melanoma incidence in Linköping was similar to the melanoma incidence in Gothenburg ten years earlier\textsuperscript{106, 107}. Thus, diverse naevus phenotypes have been found in Linköping and Gothenburg, in spite of similar melanoma incidences at the time of investigation. The findings suggest that the aetiologies of CN and CMM are in common, but that different genotypes and/or environmental factors might modify the relationship between sun exposure, naevus phenotype and melanoma incidence.

Cutaneous malignant melanoma in children and adolescents

In Papers III–V we showed that the melanoma incidence increased rapidly in Swedish teenagers during 1973–1992, followed by a decline during 1993–2002. The incidence in younger children remained extremely low. The incidence increase was mainly due to an increase in trunk melanomas in boys, and in leg and trunk melanomas in girls. SSM was the most common melanoma subtype, followed by NM. The median thickness of the tumours decreased during the two first decades.

\textit{Histological review}

A histopathological review of the cases reported to the Swedish Cancer Registry was a pre-requisite for the study of the melanoma incidence during 1973–1992, as a high degree of over-reporting of childhood melanomas during 1959–1971 had been shown in a previous study\textsuperscript{82}. A review was the only way to validate the data reported to the Registry. Reassuringly, the histopathological diagnostic accuracy had improved substantially since the previous period. The diagnostic accuracy was 88\% during 1973–1992 and no difference was found between children aged 0–14 years and individuals aged 15–19 years. Still, the diagnostic accuracy in adults have been estimated at 94–95\%\textsuperscript{4, 108}. The lower diagnostic accuracy in children and adolescents might reflect a higher proportion of pigment tumours expressing features in the grey zone between benign and malignant lesions\textsuperscript{80} in this young age group. This might have lead to a higher degree of over-diagnosis, as the risk of over-reporting must be balanced against the risk of under-reporting. The degree of under-diagnosis of CMM during the study period is not possible to estimate, as melanomas classified as naevi not will be reclassified unless they metastasise. Two cases in our material were reported as melanoma metastases without previously reported primaries, which might have been an effect of under-reporting. However, a high degree of under-reporting would have lead to a higher proportion of metastasising melanomas and consequently a higher mortality rate than found in
our study. The 93% 5-year survival rate in our series speaks against a high degree of under-reporting during the studied time period.

The rise and fall in melanoma incidence

Since our first report (Paper III) a rise in melanoma incidence in adolescents has been observed in several other European countries and in the US\textsuperscript{109-113}. The rapid rise in melanoma incidence in teenagers during 1973–1992 in Sweden parallels the incidence increase in adults at that time\textsuperscript{93}. The sex-specific site distribution, with more melanomas on the trunk in boys and on the legs in girls, and the increasing proportion of thin SSM in girls also mirrors the disease in the adult population. This might implicate sun exposure as an aetiological factor for CMM, just as in adults, as early as during adolescence in susceptible individuals. The several fold higher incidence of CMM in Australian than in British children lends further support to this hypothesis\textsuperscript{87}. In addition, in the US an association between residency in areas with high ambient UV exposure and increased risk for teenage melanoma has been found\textsuperscript{113}.

There are two published case-control studies on CMM in children\textsuperscript{114} and adolescents\textsuperscript{115}, both from Queensland, Australia. Both are population-based. No cases of melanomas arising in giant congenital naevi or patients with xeroderma pigmentosum were found. Strong risk factors for both children and adolescents were high counts of CN and presence of many large CN. Other risk factors were inability to tan, heavy facial freckling and melanoma heredity. Interestingly, no difference was found in levels of cumulative sun exposure between cases and controls. This has been interpreted as an effect of a high influence of a genetically determined susceptibility for CMM in these individuals living in a climate with high levels of sun exposure\textsuperscript{114,115}. This genetic susceptibility is of course of great interest for our understanding of the aetiology of CMM in young individuals and for melanoma genesis in general. However, the prevalence of germline \textit{CDKN2A} mutations was found to be very low in both the child and adolescent populations\textsuperscript{115,116}, and the responsible gene(s) for early onset melanoma remains unknown. More lately, the low prevalence of \textit{CDKN2A} mutations in individuals with childhood and teenage melanomas was confirmed in a Swedish study, where only 1 of 51 examined cases was found to have a functional \textit{CDKN2A} mutation\textsuperscript{117}.

In a study by Berg and Lindelöf\textsuperscript{118} the incidence of CMM in children and adolescents during 1958–1992 in Sweden was described. In their study, the high degree of over-reporting of CMM during the 1960s had not been taken into consideration, which inflated their data from
that period. In accordance with our findings, they described an increase in melanoma incidence during 1973–1992, but they reported a higher absolute number of CMM than could be found in the data from the Swedish Cancer Registry. They concluded that the incidence of CMM started to rise in boys at 16 years of age and in girls at 15 years. In contrast, we found that the incidence started to rise at 12 years of age (Fig. 2). Between 1973–1982 and 1983–1992 the increase in melanoma incidence was significant for the age group 15–19 years and 10–14 years (or more exactly, 12–14 years as the incidence remained low in cases 10 and 11 years) (Fig. 4). In fact, the relative incidence increase was even higher for the age group 10–14 years than for the age group 15–19 years (RR 4.7 [95% CI 2.7–7.5] and RR 1.9 [95% CI 1.5–2.3] respectively). The inclusion of non-cutaneous melanomas in their study initially claimed to include malignant melanoma of the skin only was later evident in the dissertation of one of the authors (ref 119, page 296 in paper I, printed words in original article crossed out by hand). The discrepancy in results between their and our studies has probably mainly been due to the inclusion of non-cutaneous melanomas, which have a different age-distribution and affect a higher proportion of younger children, in their material.

If an increase in sun exposure of the young was a reason for the rising melanoma incidence in teenagers during 1973–1992, would the recent decline in incidence reflect a decrease in sun exposure of children and adolescents more recently? The variation in melanoma incidence over time at intermittently exposed sites; trunk and legs, with the largest increase and subsequent decrease for the same sites is consistent with this idea (Fig. 7). Public health campaigns aiming at reducing excessive sun exposure started in Sweden in the mid 1980s. The decline in incidence in adolescent boys was found for the cohort born around 1975 and in adolescent girls for the cohort born around 1980 (Fig. 5). The impact of primary preventive programs should reasonably have been high for younger children, as parents usually are susceptible for health messages regarding children. On the other hand are teenagers in general seen as one of the most difficult groups to influence with public health messages. Nevertheless, there are some indications that this task not is completely impossible. A Swedish study showed a decrease in sunbathing and frequency of sunburn after a simple intervention in subjects 18–37 years of age, and the younger age group changed their attitudes significantly more than the older. Furthermore, the prevalence of regular sun bed use decline to half in adolescents between 1993 and 1999. Changes in sun exposure may also have been influenced by the new era of computers and computer games, leading young people to spend more time indoors than prior generations.
The decrease in melanoma incidence in the younger population in Australia has been considered as related to an increase of immigrants with darker complexions and at a lower risk for melanoma. According to Statistics Sweden, the immigration to Sweden from non-Nordic countries has increased since the 1980s. The proportion of individuals born in a non-Nordic country, aged 0–19 years in 2002 was 14%, and 19% had at least one parent of non-Nordic origin. It seems reasonable to believe that the melanoma incidence in part has been modified by the influx of immigrants with more favourable skin types and at low melanoma risk. Still, it cannot be the sole explanation for the decrease. The non-Nordic immigration had already begun to increase while the melanoma incidence continued to rise in 1983–1992. The magnitude of the immigration increase has been lower than the observed decrease in incidence during 1993–2002, and mere dilution effects due to non-Nordic immigration cannot explain the more pronounced decrease of CMM at intermittently UV-exposed sites. In addition, an effect solely due to immigration would affect the sexes equally, and cannot be the reason for the earlier incidence decrease in time for boys than for girls.

To speculate, a third factor possibly contributing to a decrease in melanoma incidence might be the increasing prevalence of atopic dermatitis in Swedish children. The prevalence of atopic dermatitis among children has been on the rise in northern Europe for decades. The cumulative incidence rate of atopic dermatitis from birth to 7 years of age has been estimated at 15-20% for those born in the 1980s. It has been shown that children and adults with atopic dermatitis have significantly less CN than controls. The biological rationale for this phenomenon is not known. Interestingly, it seems that local factors in the chronically inflamed skin play a critical role, as atopic diseases not involving the skin do not influence naevus numbers. A similar phenomenon has been observed in allogenic bone marrow transplantation patients, where chronic cutaneous graft versus host disease has been found to be associated with decreased numbers of naevi. As numbers of naevi is a major determinant of melanoma risk, individuals with atopic dermatitis would theoretically run a lower risk to develop melanoma. If this is the case needs further investigation.
CMM, puberty and growth

The characteristic age distribution of CMM, with a several-fold higher incidence in the second decade of life than in the first has consistently been found in studies of CMM in the young. A sharp incidence increase beginning at about age 12–13 years has been reported in studies from Australia, the US, and Europe. This is suggestive of an association between CMM and factors involved in the complex process of accelerated growth and development of sexual maturity during puberty. As mentioned in Introduction, some experimental evidence lends support to the idea that the expanding skin surface during growth is at increased risk for mutagenic influences, and melanoma risk has been shown to be positively associated with increasing body surface area. However, female sex hormones have not been shown to influence melanoma risk, and pubertal status does not influence the increase in naevus numbers during adolescence. Growth hormone therapy has been implicated in naevus formation in one study, but this finding has not been confirmed by others. Individuals with acromegaly have an increased general cancer risk, but no demonstrated increased risk of CMM. The exact mechanisms that link changes during puberty to melanoma risk remain to be clarified.

Gender differences in melanoma distribution

Interestingly, trunk melanomas were more frequent in boys, and melanomas on the lower limb in girls. This sex-specific site-distribution has been seen in CMM in adults, and a parallel naevus-distribution has been found in both children and adults. The sex-specific difference in distribution of both CN and CMM have been attributed to different clothing habits of men and women. On the other hand, studies of CN in European children have showed that boys develop more CN on the trunk than girls do, already at 6–7 years of age. The most compelling evidence of an innate sex-specific distribution of naevi was shown in a study of CN in Hutterite children in Canada. The Hutterite’s religious costume covers all body sites except for the face and hands. These sun-protected children demonstrated a sex-specific distribution of CN with more CN on the trunk in boys and on the extremities in girls consistently from 6 to 15 years of age. In 1993, Green proposed that regional differences in the susceptibility of melanocytes for malignant change could explain the site distribution of CMM. If so, this regional susceptibility differs between males and females since early childhood. However, this could not explain the increasing incidence in trunk melanomas in girls during recent years (Fig. 7), a finding that also is seen in Swedish women in whom trunk melanomas have had the most rapid increase in incidence during the 1990s. This would be
more in line with the clothing style hypothesis. If the expanding skin surface during growth is at increased risk for mutagenic influences and melanoma risk is positively associated with increasing body surface one could also speculate that the sex-specific differences in melanoma distribution is related to differences in proportional growth between boys and girls. Hypothetically, if the trunk area proportionally were larger in men than in women, in relation to the total body surface area, and the extremity area proportionally larger in women, this would generate a sex-specific difference in relative area and in relative increase during growth leading to a sex-specific difference in area susceptible for malignant change. Temporal changes would then reflect changes in body proportions over time, such as the increasing frequency of overweight in children and adolescents.

Risk factors for early onset melanoma
One known case of xeroderma pigmentosum was included in our series, and 5 patients were survivors of childhood cancers. Even if these known predisposing conditions only constitute a small percentage of all melanoma cases in this age group, a substantially increased melanoma risk at the individual level is conceivable, as the prevalence of these conditions is very low in the general population. No known case of a CMM arising in a giant congenital naevus has been described from the studied 30-year period. Hereditary status or phenotypic characteristics were not known in our material. A high prevalence of DN and a ten percent frequency of self-reported heredity for CMM have been found in a series of 51 Swedish melanoma cases aged under 20 years, which is consistent with the risk profile for early onset melanoma found in Australia.

Survival rates and prognostic factors
The 5-year melanoma-specific survival rate was 93% in our study. A 93.6% melanoma-specific survival rate in this age group was found in a recent large population-based study from the US. In contrast to the US study, the survival rate in our series did not improve during the study period. It was surprisingly high already during 1973–1982, 95% (or 94% when adjusted for an estimated over-registration) as compared with 82% in the early 1980s in a population-based study of adults in central Sweden. The median thickness and the proportion of more advanced Clark levels were higher in the adult sample, which can explain this difference in mortality between these two groups. During 1993–2002 the survival rate, median thickness and invasion levels were comparable in children and adolescents to those seen in the general Swedish population. The median thickness was even lower in
adolescents than in adults, indicating an early detection of these tumours in teenagers.

The most important prognostic factors for CMM in children and adolescents are melanoma thickness and tumour stage at diagnosis\textsuperscript{85,152-157}. Our results confirm the prognostic significance of tumour thickness at diagnosis. The influence of stage at diagnosis could not be explored, as data on regional or distant metastases at diagnosis were not available from the Registry or the pathology reports. Boys had a higher mortality than girls, consistent with the higher proportion of thicker lesions in boys. The higher proportion of NM in boys than in girls might imply that gender differences influence tumour biology.

Children aged 0–14 years had a higher mortality rate than individuals aged 15–19 years, and young age was found to be an independent risk factor in our multivariate analysis. The missing data on tumour stage at diagnosis make this finding difficult to evaluate; either was the increased mortality risk in this age group an effect of a more advanced stage at presentation or an effect of young age \textit{per se}. Others have found age under 10 years to be associated with an improved survival rate, although small numbers and a selected study-population make these results uncertain\textsuperscript{154}. In our material, the melanomas were thicker in children aged 0–14 years during the third decade (1993–2002). During this period the Clark levels of the tumours were also more advanced in the younger age group. Similar differences, albeit not statistically significant were found in our reviewed material from the first two decades (1973–1992). Any definite conclusions can not be made based on these small samples, but perhaps this might be an indication of a higher proportion of more advanced lesions in the younger age group, becoming more evident when the melanoma incidence declines. Thicker melanomas due to delayed diagnosis might be explained by more uncommon clinical variants of CMM, or by a low awareness of that melanomas do occur in childhood and a reluctance to take skin biopsies from children\textsuperscript{158-161}. Alternatively, it might be an effect of more aggressive and rapidly growing tumours in this age group\textsuperscript{158}. This emphasises the importance of that suspicious lesions should be excised for histopathological evaluation, regardless of the age of the patient. Considering the rarity of the disease in children, and a sometimes unusual clinical presentation, it seems reasonable that there should be a low threshold for referring the patient to experts in the field for examination in order to avoid unnecessary surgery\textsuperscript{159}. Furthermore, larger collaborative studies, with sufficiently long follow-ups, are needed to standardise the histological criteria for the more uncommon variants of CMM and to study their prognosis both in children and adults\textsuperscript{80,160,161}. 
Future directions

The melanoma incidence in adolescents has decreased during the last decade. However, the battle is not won, and the melanoma incidence in teenagers is still higher than in the 1970s. In order to maintain a more favourable trend in melanoma incidence in Swedish adolescents, preventive measures aiming at reducing excessive sun exposure in childhood and adolescence must continue. At the same time, health messages regarding sun exposure and sun avoidance must be balanced. Recent studies indicate that sun exposure may have beneficial effects on certain cancer and autoimmune diseases, perhaps due to the role of UVB radiation in the synthesis of vitamin D in the skin\textsuperscript{162-166}. Further research is important on this issue, in order to clarify the optimal balance between sun-exposure and sun-avoidance. In future more individualised health messages might be needed. Screening methods, including both genetic and phenotypic variables\textsuperscript{100}, might be a future possibility. With such a predictive tool, the idea to teach primary care personnel screening for individuals at increased melanoma risk might become fruitful.
SUMMARY AND CONCLUSIONS

- Physicians and nurses in primary care can successfully be taught to recognise individuals expressing a naevus phenotype associated with an increased melanoma risk. After a brief training during up to two half day sessions, primary health care personnel can obtain results comparable to those of experienced dermatologists

- There are large geographical variations in naevus phenotype in the Swedish population. Low naevus counts and a low prevalence of dysplastic naevi are found in northern Sweden, where melanoma incidence and UV levels are low

- During the 30-year period 1973 to 2002, 250 cases of primary cutaneous malignant melanoma in individuals younger than 20 years of age were reported to the Swedish Cancer Registry

- A histological review of tumours reported to the Registry during the first two decades (1973–1992) showed a diagnostic accuracy of 88%, a substantial improvement compared with the 1960s


- The incidence of cutaneous malignant melanoma remained low in younger children. Only 4 cases were reported in children aged 0–9 years during the 30-year period

- The trunk was the most common melanoma site in boys. In girls, the legs and more lately the trunk were the most common sites. During the first two decades (1973–1992), the largest increases in incidence were found for melanomas on the trunk in boys and on the legs in girls. During the third decade (1993–2002), the decrease in incidence was most pronounced in each sex for the same sites
• SSM was the most frequent subtype of melanoma, followed by NM. The median thickness of SSM in girls decreased from 1.15 mm during the first decade to 0.6 mm in the second decade.

• The 5-year melanoma-specific survival rate was 93%. The most important prognostic factor for survival was melanoma thickness at diagnosis.

• Early detection and removal of thin lesions was associated with an excellent prognosis. No tumour less than 0.8 mm at diagnosis was lethal during a median follow up time of 12 years.

Riskbedömning för malignt melanom (Delarbete I)
I delarbete I undersökte vi om det var möjligt att lära ut en metod för doktorer och sköterskor i primärvården att identifiera individer med en ökad risk för malignt melanom. 986 patienter från fem nordeuropeiska länder deltog i studien. Primärvårdspersonal fick under en till två eftermiddagar lära sig ett poängsystem (the AMS scoring system), som går ut på att värdera en individens ”naevusprofil” baserat på individens totala antal vanliga naevi, fördelningen av vanliga naevi på kroppen, och förekomsten av dysplastiska naevi. Tre poäng eller fler av fem möjliga definerade individer med en förhöjd melanomrisk. Primärvårdspersonalen uppnådde i hög grad samma resultat som hudspecialister när det gällde att avgöra om en individ hade en naevusprofil associerad med förhöjd melanomrisk. Studien visade att det är möjligt att under kort tid lära ut en metod för att identifiera individer med ökad risk för malignt melanom.

Naevusprofil i norra Sverige (Delarbete II)
I delarbete II undersökte vi naevusprofilen i en population med låg förekomst av malignt melanom i norra Sverige. 201 invånare i Storuman i Västerbottens inland undersöktes. Vi fann att befolkningen där hade få vanliga naevi och få dysplastiska naevi, mycket färre än vad man ser i södra Sverige. Resultaten kan förklaras både av skillnader i solexponering och genetiska skillnader, och stödjer hypotesen om att det finns gemensamma orsaker till både malignt melanom och naevi.

Malignt hudmelanom hos barn och ungdomar 1973–2002 (Delarbete III–V)
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