ACTA ONCOLOGICA

Vol. 29
Fasc. 7

1990

# MALIGNANT MELANOMA IN DENMARK

## Occurrence and risk factors

A. ØSTERLIND

**Abstract**

The age-standardized incidence rate of cutaneous malignant melanoma (CMM) in Denmark increased five- to six-fold between 1943 and 1982. The increase varied by sex and by site, being particularly pronounced for areas of the body normally covered by clothes. A steep increase in risk was revealed for successively younger birth cohorts. Lack of consistency between descriptive epidemiology and indicators for cumulative exposure to sunlight has led to the intermittent exposure hypothesis. Our population-based case-control study, including 474 incident cases of CMM and 926 controls, has further supported this hypothesis and demonstrated that sunbathing is associated with an increased risk of CMM, particularly during childhood and if it leads to sunburning. In addition, the risk of CMM is increased in persons with many pigmented naevi and/or a tendency to freckling. Our study does not support a relationship between CMM and hormonal exposure in women and no association was observed between dietary factors, alcohol intake, tobacco smoking, bathing habits or hair dye use and CMM risk.

*Key words:* Malignant melanoma, epidemiology, incidence, trends, case–control study, risk factors, host factors, sun exposure, Denmark.

Currently, about 600 cases of cutaneous malignant melanoma (CMM) are diagnosed in Denmark every year, 60% of them in females. Like other countries with white populations, Denmark has experienced a dramatic increase in the incidence of and mortality from malignant melanoma over the past few decades. The incidence has increased 5- to 6-fold in both males and females since 1943, when the Danish Cancer Registry started, and an increase in mortality has been observed since 1955, when specific data became available. In contrast to many other malignancies, CMM is common in young adults and the risk has been increasing gradually among successively younger cohorts.

Higher melanoma rates are reported from the Nordic countries than from other European countries (1), perhaps since the fair-skinned, less pigmented Nordic population is more susceptible to melanoma than the more pigmented southern European population. Within the Nordic countries, the incidence is highest in Norway and lowest in Finland and Iceland (2). Furthermore, there is a marked north-south gradient in Norway, Sweden and Finland with the highest incidence in the southern parts of the countries (3–5). This finding may, however, be due to differences in social behaviour relating to sun exposure (3). Boyle & Robertson (6) (in press) have predicted that, failing dramatic intervention, CMM will become one of the most common malignancies in Scotland. Data from the Nordic coutries point in the same direction. In Finland the actual occurrence of skin melanoma in 1980 was compared with that predicted by extrapolation of trends in 1957–1968 and the incidence was found to have increased even more than expected (7).

The case–control study reported by Lancaster & Nelson in 1957 (8) provided evidence that constitutional characteristics such as red or blond hair colour, fair complexion, fine skin texture and blue, grey or green eye colour are related to risk for melanoma. Subsequent case–control studies have supported this suggestion. In 1952, McGovern (9) suggested a relationship between CMM and sun exposure, a relationship which is obviously complex. In most parts of the world, the incidence of melanoma in white populations increases with proximity to the equator, while in Europe the opposite trend is seen (10–12). However, melanoma, in contrast to non-melanoma skin cancers, is

From the Danish Cancer Registry, Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark.

Accepted for publication 6 March 1990.

most commonly not located on the areas of the skin with the highest cumulative sun exposure (13). It has therefore been assumed that intermittent sun exposure may be more important for the melanoma risk than cumulative, chronic sun exposure, especially with regard to superficial spreading melanoma and nodular melanoma (14–17), an assumption which, however, could not be supported in an investigation by Holman et al. (18). There is epidemiological evidence that cumulative, chronic sun exposure is etiologically important in lentigo maligna melanoma, and the role of such exposure is well established for basal cell (BCC) and squamous cell carcinoma (SCC). The contribution of various patterns of sunlight exposure and the interaction between various constitutional and exogenous risk factors thus need further clarification.

Despite its northern location, Denmark has a realtively high incidence of melanoma. Denmark is also a unique place for carrying out epidemiological studies, due to its homogeneous population (with respect to ethnicity, basic education and religion) and its efficient health care system. A high quality, nationwide cancer registry with a long tradition, as well as a central population registry, provide dependable data for population-based studies.

Denmark is located in northern Europe at the 55°–58° latitude in the temperate zone; the climate is coastal. The land area is 43 000 km$^2$ and there is little latitudinal difference in exposure to ultraviolet (UV) light within the country. The number of hours of sunshine is relatively constant, at about 1 600 h/year (Copenhagen), resulting in an average of 4 h of sunlight per day in Denmark, compared to 7 h or more per day in Australia.

We decided to undertake a study of the risk of CMM in Denmark, with the following purposes: 1) to make a detailed description of trends and other incidence characteristics of CMM with particular reference to age, sex, body site, histological type and birth cohort, and to compare these characteristics with those of non-melanoma skin cancers; and 2) to examine (in a case–control study) which factors that are associated with the CMM risk in a northern European population.

## Characteristics of the incidence of cutaneous malignant melanoma in Denmark (1943–1982)

### *Material and Methods*

Population-based cancer registration in Denmark covers a longer time span than for any other country in the world. The material of the Danish Cancer Registry thus provides unique opportunities to evaluate trends and other incidence characteristics for various cancers. Trends in incidence provide important background for evaluating the need for analytical studies and for planning such studies.

The registry data include basic descriptive characteristics, such as sex, age and anatomical site of each melanoma, which are not available elsewhere in detail for such a long time span. Finally, since exposure to UV light is an important risk factor for both melanomas and non-melanoma skin cancers, we compared the different types of skin cancer in order to identify similarities and dissimilarities which might provide aetiological clues (19, 20).

The Danish Cancer Registry was founded in 1942 as the first nationwide programme to register all cases of cancer arising in a defined population. Information on incidence is available from January 1, 1943. The Registry receives notifications mainly from hospital departments and practising specialists; in addition, autopsy reports on cancer patients are received from departments of pathology. Finally, the Cancer Registry annually receives all death certificates from the National Board of Health. A cancer is included in the registry database after verification by the certifying hospital department or general practitioner (21).

The validity and completeness of cancer registration in Denmark have been of high quality throughout its four decades of operation (21–23). The multiple sources of notification of tumours result in a high degree of completeness and accuracy.

Tumour classification throughout the registration period has been made in accordance with the 7th Revision of the International Classification of Diseases (ICD-7) (24). This version distinguishes between malignant melanoma of the skin and non-melanoma skin cancers. Since 1978, all incident cancers have been coded according to ICD-O (25), which includes histology and topography. This classification makes it possible to distinguish between BCC and SCC of the skin and between histological subtypes of melanoma.

All incident cases of CMM since 1943 were selected from the Cancer Registry data to study trends over 1943–1982. Precancerous and in situ lesions were excluded. For comparison of the three main types of skin cancer, all incident cases of non-melanoma skin carcinomas (i.e., BCC and SCC) diagnosed during the 5-year period 1978–1982 were also selected, and variations by age, sex and anatomical site were investigated.

Age-, sex-, subsite- and type-specific rates were calculated as average annual rates per 100 000 males and females, using the Danish population in corresponding calendar years and age groups as denominators. Rates were age-standardized to the world population by the direct method (1). In order to describe time trends in the age-specific incidence rates, we applied statistical models for estimating the separate effects of age, calendar time and birth cohort (26, 27).

### *Results, comments and conclusions*

Malignant melanoma of the skin is a rather rare neoplasm, which in 1985 accounted for 2.2% of all cancers in Denmark (males, 1.8%; females, 2.7%). During the 40-year period 1943–1982, 3 509 male and 5 305 female

patients with CMM were registered. The average annual number of incident cases increased from 59 in 1943–1947 to 476 in 1978–1982. The age-standardized incidence rates showed 5- to 6-fold increases, and reached 6.1 and 8.4 per 100 000 person-years in 1978–1982 for males and females respectively.

*Anatomical sites.* The age-specific incidence curves for melanomas in males and females during 1978–1982 are shown in Fig. 1. Characteristic differences were seen for tumours at different anatomical locations. Thus, the rates of melanomas of the face, scalp and neck increased exponentially with age, similar to that for non-melanoma skin cancers (Figs 1 and 2). There was no discernible sex difference. The rates for melanomas of the trunk, legs and arms in both sexes showed a steep increase, starting in adolescence and continuing to middle age, after which the incidence levelled off. For melanoma of the trunk, a male preponderance was seen at ages 35 and over, while a female preponderance was apparent for melanomas of the legs and of the arms at all ages. The overall age-specific curves (Fig. 2) showed a sharp increase (from 20 to 50 years of age) followed by a more gentle slope after age 50, reflecting the patterns seen for the dominating sites, i.e. trunk and legs. The age-specific incidence curves for BCC and SCC did not show these plateaus. The melanoma subtypes, superficial spreading melanoma and nodular melanoma, showed similar age-specific incidence curves, while lentigo maligna melanoma tended to occur at advanced ages, like non-melanoma skin cancer and melanoma of the face, scalp and neck.

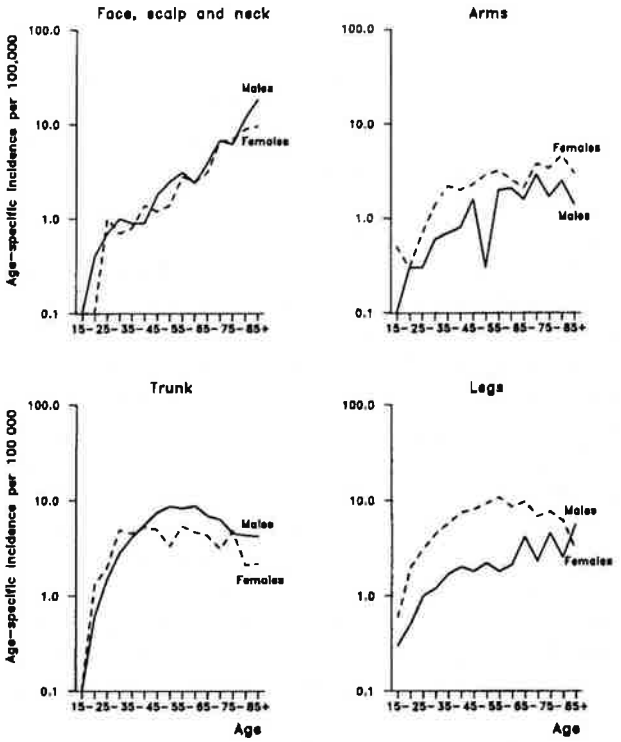


Fig. 1. Age-specific incidence rates of cutaneous malignant melanoma, by sex and anatomical site, in Denmark, 1978–1982. (From (19).) Reproduced by permission of the editor.

Marked differences were observed in the incidences of melanomas at various anatomical locations. In males, the age-standardized incidence rate was highest for melanoma of the trunk, followed by melanoma of the face, scalp and neck, and these rates were higher than those in females. In women, the lower limb and the trunk were most often affected, and the incidence rate for melanoma of the lower limb was more than three times higher in females than in males.

The descriptions of the malignant melanomas in the Danish case–control study allowed a detailed study of their anatomical location. Analysis of these data (derived from incident cases 1982–1985) showed that in males melanomas of the back were most frequent followed by melanomas of the face and of the chest; in females,

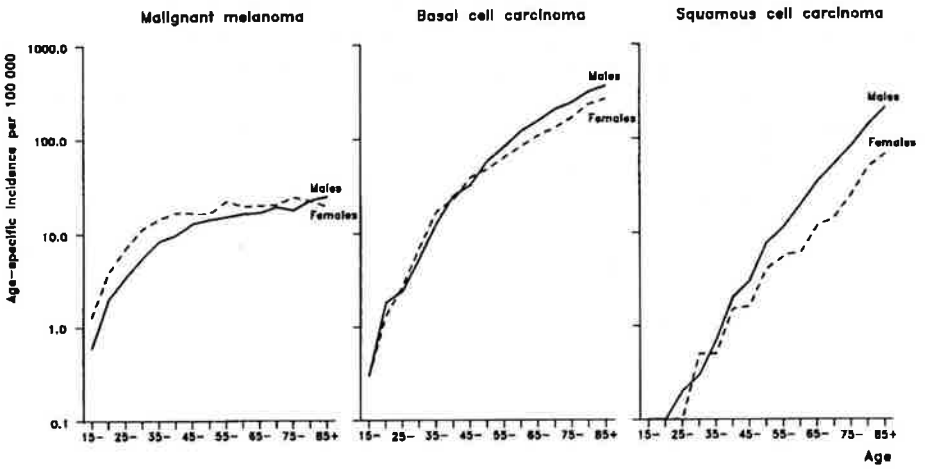


Fig. 2. Age-specific incidence rates of malignant melanoma, basal cell carcinoma and squamous-cell carcinoma of the skin by sex, in Denmark, 1978–1982. (From (19).) Reproduced by permission of the editor.

melanomas of the legs (below the knee) were most common, followed by melanomas of the back and of the face. These data thus confirm that a high proportion of CMM occurs on body sites that are exposed intermittently to UV light. However, the incidence per unit area of skin was also high on the face, which is exposed more continuously to sunlight (16, 28)

The age-standardized rates for non-melanoma skin cancer are, in contrast to melanomas, higher in males than in females. These tumours clearly preponderate at sun-exposed sites, with 80–90% of both BCC and SCC occurring on the face, scalp and neck or on the arms; only 30% of melanomas develop at these sites. While the differences in site distribution between melanoma and non-melanoma skin cancers are obvious, dissimilarities also exist between BCC and SCC. A study of the Danish Cancer Registry showed that during 1978–1982 (19) 73% of SCC developed on the face, scalp or neck and 16% on the upper limb, and the corresponding figures for BCC were 79% and only 2% respectively; 6% of SCC emerged on the trunk, while as many as 16% of BCC occurred at this site. In contrast to what was observed in CMM, there was no major difference in distribution between males and females.

*Time trends.* The age-standardized incidence rate of CMM for males and females increased 5- to 6-fold in the 40-year period 1943–1982. In the period 1955–1982, for which mortality data are available, a doubling in mortality rates was observed. The increase in incidence varied by anatomical site, being particularly pronounced for melanoma of the trunk in both sexes and of the legs in females. A longitudinal examination of the data by birth cohort showed a pattern in which the incidence of melanoma of the trunk in both sexes and of the legs in females increased steeply in successively younger generations of women born later than 1883 and of men later than 1893. In contrast, the rates for melanoma of the face, scalp and neck showed only moderate changes with successive birth cohorts. For melanomas at all sites except for the female leg, a statistical model including age and cohort or age and time adequately described the data (20). Similarly, changes at all sites except the female leg and trunk could be described adequately by the age and drift model (20). The statistical analyses have not elucidated whether the increase in incidence can be attributed to an effect of birth cohort or of time period, but current biological knowledge indicates that it is most plausible to attribute the increasing incidence to a cohort effect.

The increasing trend in incidence seen in the present study is in line with results reported from other Scandinavian countries as well as for most other fair-skinned (Caucasian) populations (2, 29). The increase in incidence varied by sex and by anatomic subsite, and the risk increased in successive birth cohorts, corroborating the results of others (30–32). Our results are also in parallel with those of mortality analyses (33–35). Our data did not indicate a strong effect of time period such as has been reported from Connecticut (36). The cohort effect in Danes corresponds to a four to six times higher risk of developing melanoma in two successive generations (born 25 years apart). The change in risk of trunk melanoma deserves special attention: the incidence of melanomas at this site has always been highest in males but a pronounced increase has occurred in the youngest female cohorts, such that the incidence in young Danish women is now at a similar or even higher level than that in males of the same age (37).

The increase in cohort-specific risks must reflect changes in exposure to one or more important risk factors from generation to generation. The change in exposure has not, moreover, been exactly the same in males and females. The different trends for different anatomical sites indicate a risk factor acting locally on the skin. Exposure to sunlight is thought to be the major aetiological determinant of skin melanoma, and our case–control study clearly points to intermittent, intense exposure to sunlight, especially sunbathing and repeated severe sunburns during childhood, as a risk factor. Changes in sunbathing habits and other recreational activities may reasonably well explain the increased incidences in successive cohorts as well as the differences between males and females.

Our data corroborate the general view that continuous, chronic exposure to the sun is the main risk factor for non-melanoma skin cancer; thus, the tumours tend to occur at advanced ages, to predominate at sun-exposed sites and to occur more frequently in males than in females. In addition, intermittent exposure to the sun may add to the risk of BCC. Our data support the view (14–17) that there is no simple relationship between CMM and cumulative dose of sunlight. The hypothesis that intermittent intense exposure is important in the causation of melanoma is consistent with the time trends and the body site distribution we have observed. The role of intermittent exposure to UV light is suggested by the descriptive data, and confirmation of this hypothesis by analytical data is lacking. Finally, we need a better understanding of the influence of host factors.

## Case–control study of cutaneous malignant melanoma

### *Material and Methods*

The present population-based case–control study in Denmark involving personal interviews with cases and controls in their homes was restricted to eastern Denmark. This part of Denmark is a well defined geographic area consisting of eight municipalities and counties (the municipalities of Copenhagen and Frederiksberg and the counties of Copenhagen, Frederiksborg, Roskilde,

**Table 1**

*Age distribution of melanoma cases and controls among male and female responders*

| Age groups (years) | Males | | Females | |
|---|---|---|---|---|
| | Cases (%) | Controls (%) | Cases (%) | Controls (%) |
| 20–29 | 6 (3.1) | 12 (3.1) | 15 (5.4) | 28 (5.2) |
| 30–39 | 25 (12.9) | 53 (13.6) | 41 (14.6) | 83 (15.5) |
| 40–49 | 38 (19.6) | 85 (21.8) | 75 (26.8) | 149 (27.8) |
| 50–59 | 50 (25.8) | 91 (23.3) | 56 (20.0) | 99 (18.5) |
| 60–69 | 50 (25.8) | 100 (25.6) | 51 (18.2) | 106 (19.8) |
| 70+ | 25 (12.9) | 49 (12.6) | 42 (15.0) | 71 (13.2) |
| Total | 194 | 390 | 280 | 536 |

Vestsjælland, Storstrøm and Bornholm). The inhabitants represent approximately 45% (2.3 million) of the Danish population.

*Cases*

All cases of primary CMM in persons aged 20–79 years who were diagnosed during the period October 1, 1982, to March 31, 1985, and who were residents of eastern Denmark were drawn from the routine notifications in the Danish Cancer Registry. Persons diagnosed with the lentigo maligna melanoma subtype were not included due to their rarity (4% of all melanoma cases) and because their clinical and epidemiological features differ from those of other melanomas; cases reported as preinvasive melanoma were not included. A total of 577 cases were identified, of which 551 were selected on the basis of histopathological criteria. Case ascertainment and data collection were delayed until six months after the first diagnosis, and in fact was not begun until April 1984, i.e. up to 18 months after the first cases were diagnosed. A total of 28 patients died and 6 moved away from eastern Denmark during these delay periods. Permission to contact the ascertained incident cases and to ask for their cooperation in the study was sought from the heads of hospital departments in eastern Denmark from which the melanoma patients had been reported to the Registry; permission was obtained in all but one case. After exclusion of these 35 cases, the case group comprised 516 eligible persons who fulfilled the histopathological criteria of invasive primary skin melanoma. The period of delay between diagnosis and interview was on average 386 days (range 147–1 091 days); 93% of the cases were contacted between 6 and 18 months after diagnosis, and 7% more than 18 months after diagnosis. The age distributions of male and female responders are given in Table 1. The cases were from 20–79 years of age with a mean age at diagnosis of 52 years (men: 53 years; women: 51 years).

The histopathological specimens were reviewed in a standardized manner by one pathologist. Histopathological review was possible for 567 of the 577 melanomas reported. Among the features recorded for each tumour were confirmation or rejection of a diagnosis of primary invasive melanoma, histological subtype, level of invasion according to Clark & Mihm (38) and tumour thickness by the method of Breslow (39) (Table 2). A diagnosis of primary melanoma was rejected for 14 of the 577 cases initially notified as melanoma (mainly metastatic mela-

**Table 2**

*Histopathological characteristics of the 551 incident cases of histologically confirmed melanoma, excluding lentigo maligna melanoma, by sex*

| Characteristic | Males No. (%) | Females No. (%) | Total No. (%) |
|---|---|---|---|
| Histological subtype | | | |
| Superficial spreading melanoma | 153 (65.1) | 206 (65.2) | 359 (65.2) |
| Nodular melanoma | 37 (15.7) | 62 (19.6) | 99 (18.0) |
| Acral lentingenous melanoma | 13 (5.5) | 19 (6.0) | 32 (5.8) |
| Unclassifiable | 25 (10.6) | 26 (8.2) | 51 (9.3) |
| Specimen unavailable | 7 (3.0) | 3 (1.0) | 10 (1.8) |
| Total | 235 | 316 | 551 |
| Level | | | |
| I | 7 (3.4) | 19 (6.6) | 26 (5.3) |
| II | 70 (34.5) | 106 (36.6) | 176 (35.7) |
| III | 71 (35.0) | 74 (25.5) | 145 (29.4) |
| IV | 46 (22.7) | 79 (27.2) | 125 (25.4) |
| V | 9 (4.4) | 12 (4.1) | 21 (4.3) |
| Total classified | 203 | 290 | 493 |
| Unclassifiable | 25 – | 22 – | 47 – |
| Unknown, including unavailable | 7 – | 4 – | 11 – |
| Tumour thickness (mm) | | | |
| <0.75 | 59 (29.8) | 102 (35.5) | 161 (33.2) |
| 0.75–1.49 | 45 (22.7) | 74 (25.8) | 119 (24.5) |
| 1.50–2.99 | 52 (26.3) | 54 (18.8) | 106 (21.9) |
| 3+ | 42 (21.2) | 57 (19.9) | 99 (20.4) |
| Total classified | 198 | 287 | 485 |
| Unclassifiable | 30 – | 25 – | 55 – |
| Unknown, including unavailable | 7 – | 4 – | 11 – |

**Table 3**

*Anatomical site of the 551 incident cases of melanoma, by sex*

| Anatomical site | Males No. (%) | Females No. (%) |
|---|---|---|
| Total No. included | 235 | 316 |
| Broad groups | | |
| Face, scalp and neck | 32 (14) | 22 (7) |
| Trunk | 128 (54) | 85 (27) |
| Upper limb | 24 (10) | 43 (14) |
| Lower limb | 51 (22) | 166 (53) |
| Specific sites | | |
| Face | 9 (4) | 11 (3) |
| Ear | 10 (4) | 2 (1) |
| Scalp and neck | 13 (6) | 9 (3) |
| Chest | 40 (17) | 23 (7) |
| Back | 79 (34) | 50 (16) |
| Abdomen, buttocks and genitalia | 9 (4) | 12 (4) |
| Upper arm | 17 (7) | 28 (9) |
| Forearm and hand | 7 (3) | 15 (5) |
| Thigh | 17 (7) | 57 (18) |
| Leg | 20 (9) | 93 (29) |
| Foot | 14 (6) | 16 (5) |

nomas and naevi); 12 were lentigo maligna melanoma (notified to the Registry as melanoma not otherwise specified (NOS)). These 26 cases were excluded. For the 10 cases for which material was unavailable for review, the original diagnosis was accepted after review of the pathology reports. Thus, the study comprised a total of 551 melanomas in 551 patients.

Information on the specific anatomical location of tumours on the body surface was abstracted from medical records and recorded on a standard form (Table 3).

*Controls*

The controls were a random sample of 1 164 persons drawn in April 1984 from the general population of eastern Denmark. Knowledge of the age and sex distribution of melanoma cases in the area of investigation made it possible to draw age- and sex-stratified controls from the national Central Population Registry. This computerized register was established in 1968 with the purpose of storing commonly used personal data for each inhabitant and acting as source material for the administrative systems in Denmark (40). No individual or additional matching was undertaken. Controls were drawn from the population register at the beginning of the study when data collection was started. They were approached for interview during the subsequent two years; during this period a total of 30 had either died (16), moved from eastern Denmark (9) or moved to an unknown address (5). These 30 ineligible controls were not replaced.

**Table 4**

*Response rate and causes of non-response among melanoma cases and controls in case–control study of malignant melanoma of the skin*

| | Cases No. (%) | Controls No. (%) |
|---|---|---|
| Selected for study | 551[a] | 1164 |
| Ineligible[b] | 35 | 30 |
| Invited to participate (eligible) | 516 | 1134 |
| Completed interview | 474 (91.9) | 926 (81.7) |
| Refused to participate | 27 (5.2) | 168 (14.8) |
| Too ill to participate | 10 (1.9) | 23 (2.0) |
| Contact not achieved | 5 (1.0) | 17 (1.5) |

[a] Histologically confirmed melanomas
[b] Due to delay in ascertainment and data collection, during which subjects either died or emigrated

*Response rate*

An interview was completed for 474 cases (92%) and 926 controls (82%) (Table 4). More controls (15%) than patients (5%) refused to participate, while similar proportions among patients and controls (2%) were unable to participate due to illness. We did not manage to get in touch with 5 patients (1%) and 17 controls (2%). Thus, of the 516 eligible cases and 1 134 eligible controls, interviews were obtained from 474 cases (194 males; 280 females) and 926 controls (390 males; 536 females). The mean ages of case and control responders were similar: 54 years in males and 52 years in females.

*Data collection*

All cases and controls were contacted initially by mail and were asked to participate in a study of the effects of the environment on cancer in general, not mentioning melanoma as the specific disease under study. Within the next few days, patients and controls were contacted by telephone (88%) or by home visit to arrange for an interview. Study subjects who could not be contacted by telephone were considered 'untraceable' after three unsuccessful home visits by an interviewer, at least two of which were undertaken outside normal working hours. The methods used to establish contact with patients and controls were similar in every respect and the trained interviewers were not informed about the subject's case–control status. Patients were interviewed concurrently with controls.

Data were collected by questionnaires administered by the interviewers. An objective assessment of the number of raised pigmented naevi on the arms and of skin, hair and eye colour was performed by the interviewers; the main reason for choosing personal interview over a mailed questionnaire was the importance of an objective assessment of complexion characteristics.

*Interview*

A standardized interview questionnaire was the most important source of the information for the study. Display cards were used to assist the subjects in recognizing drugs and in describing clothing habits. The areas covered in the interview fell into the following groups:

*Demographic factors:* Age, place of residence, type of education, years of education, occupation, job type, marital status; social class was assessed from a scale established by the Danish Institute for Social Research, which takes into account occupation, job type, number of employees and education (41).

*Constitutional factors:* Ethnicity, reaction to sunlight, tendency to freckle, history of naevi and skin cancer, family history of melanoma, height, weight.

*Exposure to UV light:* Recreational, occupational and residential exposure; sunbathing and sunburning; clothing habits; use of sunscreens, soap and detergents; use of sun lamps and sun beds; exposure to fluorescent light.

*Hormonal factors:* Obstetric and gynaecological history, use of oral contraceptives and menopausal replacement therapy.

*Diet, alcohol and other factors:* Usual diet intake questions; coffee, alcohol, tobacco, hair dye use; x-irradiation; skin diseases; bathing habits.

The interview was designed and pretested using volunteer subjects. Supplementary questions were not added during the course of the study. Interviews were performed by four trained interviewers. The majority of interviews took place in the private residence of the persons (94%); the remainder were performed in the workplace or in the interviewers' homes. Interviews were not performed in hospital wards. Information was obtained directly from the cases or controls at all interviews. The time taken to complete an interview was on average 68 min (range 40–149 min). On completion of the interview, subjects were rated according to their interest and cooperation and the apparent reliability of the information they provided. A comparison showed no difference in the distribution of the ratings between the case and the control groups.

*Objective measurements*

The following objective measurements were made by the interviewer after the interview had been completed.

*Skin colour:* Skin colour was measured by direct visual grading of the skin against a ten-step complexion chart designed by Scotto & Fears (42). Measurements were made at three sites: the dorsum of the left hand, a site of continuous sun exposure; the tip of the left shoulder, an intermittently exposed site; and the inner aspect of left upper arm, a site not usually exposed.

*Hair colour:* Natural hair colour was assessed on the back of the head after lifting a tuft of hair, which reflects a 'sample' least affected by the sun, and was graded visually against 20 samples of human hair. Bald persons and those with grey or dyed hair were asked to select the hair sample that would have provided the best colour match with their original hair colour (as adults).

*Eye colour:* Interviewers assessed eye colour by inspection of the left eye and recorded it as blue, brown, grey, green or other.

*Naevus count:* The number of raised, palpable pigmented naevi was counted separately on each arm below the level of the axillae, and the largest diameter of naevi was measured. Naevi, greater or equal to 5 mm in diameter and naevi less than 5 mm in diameter were counted separately. Interviewers counted only naevi that were raised above the skin as determined by direct palpation, in order to avoid confusion with freckles and benign lentigo. Since many junctional naevi can not be palpated, this method of counting yields a conservative number (including mainly compound and intradermal naevi).

*Cutaneous microtopography:* In order to obtain an objective measure of chronic sun exposure, an accurate mould of the skin texture of the dorsum of the left hand was made by use of a fast setting liquid material. The system of grading cutaneous microtopographs described by Beagley & Gibson (43) relates to changes in skin surface texture, which in normal skin, is composed of a series of transverse and diagonal primary lines, which intersect to form quadrilaterals and triangles. Within these primary figures are sets of smaller secondary lines which often meet in the centre of the figure, forming a star configuration. The microtopographs were graded on a six-step scale under blind conditions according to the degree of actinic skin damage as assessed under a dissecting microscope at a magnification of $\times 10$. Microtopographs of adequate quality were obtained for 337 cases and 707 controls.

*Potential sources of bias*

Efforts were taken to reduce selection bias. Thus, it was ascertained that all incident cases had been included that had occurred within a well-defined geographic area in a defined period of time; the controls were selected at random from the same general population. Furthermore, an effort was made to ensure that cooperation was similar in the case and the control groups. However, since 92% of cases and 82% of controls participated, we evaluated whether a case–control difference was introduced by a difference between non-responders and responders (Table 5). Within both case and control groups, non-responders were more often single than responders; non-responding controls were significantly older than responding controls. With regard to place of residence, controls living in Copenhagen were less likely to participate than controls living in other counties. Age and place

**Table 5**

*Percentage distribution of demographic variables among responders and non-responders in case–control study of malignant melanoma of the skin*

| Variable | Responders | | Non-responders | | Difference between responders and non-responders |
|---|---|---|---|---|---|
| | Cases (n = 474) | Controls (n = 926) | Cases (n = 42) | Controls (n = 208) | |
| Age | | | | | |
| 20–29 years | 4.4 | 4.3 | 4.8 | 3.4 | |
| 30–39 years | 13.9 | 14.7 | 16.7 | 6.7 | |
| 40–49 years | 23.9 | 25.3 | 19.0 | 19.8 | Cases: p = 0.60 |
| 50–59 years | 22.4 | 20.5 | 16.7 | 16.8 | Controls: p < 0.0001 |
| 60–69 years | 21.3 | 22.2 | 19.0 | 26.4 | |
| 70+ years | 14.1 | 13.0 | 23.8 | 26.9 | |
| Difference between cases and controls | p = 0.93 | | p = 0.39 | | |
| Marital status | | | | | |
| Unmarried | 8.7 | 9.0 | 14.3 | 19.0 | |
| Married | 74.4 | 70.1 | 52.3 | 46.7 | Cases: p = 0.02 |
| Divorced | 8.6 | 11.2 | 16.7 | 16.7 | Controls: p < 0.0001 |
| Widowed | 8.2 | 9.7 | 16.7 | 17.6 | |
| Difference between cases and controls | p = 0.34 | | p = 0.88 | | |
| County of residence | | | | | |
| København[a] | 20.1 | 18.6 | 21.4 | 26.1 | |
| Frederiksberg[a] | 3.4 | 4.2 | 7.1 | 5.8 | |
| København | 30.3 | 27.5 | 35.8 | 27.5 | Cases: p = 0.76 |
| Frederiksborg | 18.8 | 16.2 | 16.7 | 7.7 | Controls: p = 0.02 |
| Roskilde | 7.5 | 8.4 | 7.1 | 7.3 | |
| Vestsjælland | 9.9 | 12.3 | 4.8 | 12.1 | |
| Storstrøm/Bornholm | 10.0 | 12.8 | 7.1 | 13.5 | |
| Difference between cases and controls | p = 0.31 | | p = 0.31 | | |

[a] Municipality

of residence did not affect the response rate among the cases. No difference between cases and controls within the responding and non-responding groups was found with respect to age, marital status and residence. Data on age and marital status indicate that completion of interview was not influenced by a person's status as a case or a control. The lower response rate among controls probably reflects a lower level of interest in health issues in the general population than in persons who have recently undergone a surgical procedure. It is difficult to assess fully the potential bias introduced by the differences in response rates between cases and controls. Non-participation in survey research is well known to be related to socioeconomic status and life style characteristics, but there is no known or suspected relationship between non-participation and the risk factors examined in this study.

Within the case group, non-responders more often had a nodular or an unclassifiable melanoma, a tumour at level IV or V and very thick lesions (3+ mm) (Table 6). These differences are due to the characteristics of the ineligible cases; eligible non-responders did not differ from responders. No difference was found between responders and non-responders with regard to anatomical site (Table 7).

In order to minimize interviewer bias, the interviewers were kept ignorant of the study hypotheses and were not informed about the subjects's status as a case or control. All study personnel were unaware of the case–control status during the data collection and data processing phase. Even if interviewers discovered the person's case–control status during the interview, it did probably not cause significant observer bias as the questionnaire was standardized, and the interviewers lacked knowledge about the specific hypotheses. Each interviewer interviewed similar proportions of cases and controls and of males and females. Recall bias was minimized by not revealing the specific purpose of the study (in the invitation letter) and by organizing the interview so that questions relating to melanoma and moles were placed towards the end of the interview. It is recognized, however, that patients may be more aware of health-related matters because of their recent diseases. However, the patients were not approached until more than six months

**Table 6**

*Percentage distribution of histopathological variables among 551 incident cases of histologically confirmed melanoma, responders and non-responders*

| Variable | Responders (n = 474) | Non-responders (all) (n = 77) | Difference between responders and non-responders |
|---|---|---|---|
| Histological subtype | | | |
| Superficial spreading melanoma | 68.4 | 54.0 | |
| Nodular melanoma | 16.9 | 27.0 | p = 0.002 |
| Acral lentigenous melanoma | 6.6 | 1.4 | |
| Unclassifiable | 8.1 | 17.6 | |
| Specimen unavailable | (n = 7) | (n = 3) | |
| Level | | | |
| I | 5.6 | 3.3 | |
| II | 37.7 | 21.3 | |
| III | 29.9 | 26.2 | p = 0.004 |
| IV | 23.4 | 39.3 | |
| V | 3.4 | 9.9 | |
| Unclassifiable | (n = 34) | (n = 13) | |
| Unknown, including unavailable | (n = 7) | (n = 4) | |
| Tumour thickness (mm) | | | |
| <0.75 | 35.0 | 20.3 | |
| 0.75–1.49 | 24.7 | 23.8 | p = 0.01 |
| 1.50–2.99 | 22.0 | 20.3 | |
| 3+ | 18.3 | 35.6 | |
| Unclassifiable | (n = 41) | (n = 14) | |
| Unknown, including unavailable | (n = 7) | (n = 4) | |

**Table 7**

*Percentage distribution of anatomical site among 551 incident cases of histologically confirmed melanoma, responders and non-responders, by sex*

| Anatomical site | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | Responders (n = 194) | Non-responders (n = 41) | Difference between responders and non-responders | Responders (n = 280) | Non-responders (n = 36) | Difference between responders and non-responders |
| Face, scalp and neck | 12.4 | 19.5 | | 7.1 | 5.6 | |
| Trunk | 55.7 | 48.8 | p = 0.54 | 26.8 | 27.8 | p = 0.42 |
| Arms | 10.8 | 7.3 | | 12.5 | 22.2 | |
| Legs | 21.1 | 24.4 | | 53.6 | 44.4 | |

after their date of diagnosis to allow for sufficient recovery. By evaluating questions asked about the same subject in different ways, no recall bias has been revealed.

*Data processing and analysis*

The questionnaires were checked for completeness. Some of the variables had to be coded using a standardized set of coding instructions. Crude data arising from interviews, histopathological and clinical data, Central Population Registry data, and administrative data were entered into four separate databases. The interview data were transferred from the questionnaire and were double-keyed after coding. After completion of data entry, the two databases were compared using a program specifically developed for use in the present study, and inconsistencies were printed. The procedure of independent data entry and subsequent comparison was continued until the data in the two databases were identical. The histopathological/clinical and administrative data were entered and checked by a more simple control procedure. After completion of these procedures, all four databases were merged. Data checks were performed for logical errors.

The first stage of analysis involved simple univariate screening by multiple $2 \times 2$ tables and frequency tables to identify major crude associations. Variables consisting of

continuous or multiple levels were usually categorized. The strength of melanoma-exposure associations was measured by the exposure odds ratio, which approximates the relative risk, and 95% confidence intervals were constructed to assess statistical significance. Stratified analysis comprised the next stage, and likely confounding variables were identified during this procedure. Multivariate analysis using a disease probability logistic model was also used to control simultaneously for several confounding variables (44). Tests for trend in the logistic analysis were obtained by categorizing the exposure variable, assigning the score $j-1$ to the $j$th exposure level of the categorical variable, and treating the scored variable as a continuous variable. Differences in risk between subgroups (histological type and anatomical site) were assessed by the method of Thomas et al. (45). Etiological fractions were estimated as described by Cole & MacMahon (46).

### Importance of host factors

The host factors considered in this study were pigmentary constitutional characteristics such as skin colour, hair colour, eye colour, freckling ability, tendency to burn, tanning ability and number of naevi.

Heavily pigmented races and ethnic groups have low incidence and mortality rates of CMM compared with populations of lighter complexion (11, 12), lending support to the assumption that skin pigmentation and dark complexion protect against malignant melanoma.

As early as 1864, Sir James Paget stated that malignant melanoma developed in or under a mole (47). The proportion of melanomas that arise in preexisting naevi and whether melanomas arise in naevi at all are subjects of dispute (48). A relationship between naevi and malignant melanoma has been reported in numerous clinical series, where a substantial proportion (up to 85%) of patients give a history of a longstanding, apparently benign pigmented lesion at the site of the melanoma (49). Histological evidence of an associated benign naevus in contiguity with a malignant melanoma provides more persuasive evidence that melanomas originate in naevi, and naevoid remnants are found in up to 72% of malignant melanomas (49).

In 1952, McGovern (9) suggested that persons with fair skin who do not tan well on exposure to sunlight but who freckle readily seemed to be predisposed to malignant transformation of moles. He also noticed a preponderance of melanomas on sun-exposed parts of the body and drew attention to the importance of sunlight in the aetiology of melanoma.

The first case–control study of CMM was reported from Australia in 1957 by Lancaster & Nelson (8), who focussed on the effects of pigmentary characteristics and sun exposure. The authors found significantly higher proportions of individuals with red or blond hair, fair complexion and blue, grey or green eyes among cases than among controls. Other case–control studies conducted at the same period produced similar results (50, 51), but the results of Beardmore (52) were at variance, possibly because of improper selection of the control group (57% had either keratoses or non-melanoma skin cancer). One study from Norway (53) and one from Scotland (54), showed no difference in pigmentation between cases and controls, but these studies were conducted in homogeneous populations. There was no consistent, significant relationship between melanoma and a tendency to burn on exposure to sunlight in the early studies in which the question had been asked in various ways (Table 8).

These different and inconsistent results may be due to variations in study design, which were not always optimal. Most of the investigations were case–control studies using undefined or unsatisfactorily selected controls, such as patients with other skin cancers or skin diseases. Such patients may have risk factors in common with patients with CMM. These early studies concentrated mainly on the host characteristics, suggested by Lancaster & Nelson (8). Possible associations with benign naevi were not investigated.

The host factors investigated in these studies, and important pigmentary risk factors included in recent case–control studies, are summarized in Table 8. Our investigation was planned in 1982–1983 on the basis of prevailing knowledge and hypothesis and includes pigmentary factors such as hair, skin and eye colour, freckles and reaction to sunlight. Influence of naevi was also included because a syndrome of familial dysplastic naevi and increased risk of melanoma was described by Clark et al. (64), but these distinctive naevi also occur in other individuals (65, 66). Furthermore, we were aware of preliminary data from an Australian case–control study (Holman, personal communication) that indicated a significant influence of an increased number of raised benign naevi. The interviewers in our study, however, were not medical experts, and we therefore found it impossible to apply a set of clinical diagnostic criteria to differentiate between common acquired naevi and dysplastic naevi. Accordingly, we asked the interviewers to count the number of raised (palpable) pigmented naevi on the arms, recognizing that this method possibly excluded most junctional naevi. Completely macular lesions were also excluded because of the difficulty experienced by comparatively untrained observers in distinguishing them from freckles (and benign lentigo). Furthermore, because data collection took place in a non-clinical setting, the naevus count was confined to the arms.

#### *Results, conclusions and comments*

We categorized the host factors into three main groups, representing 1) basic degree of pigmentation, as reflected by skin colour, hair colour and eye colour, which are

**Table 8**

*Case–control studies of cutaneous malignant melanoma[a] (CMM)*

Lancaster & Nelson (8). Cases/controls (C/CC) = 173/173, response rate unknown. Sampling frame: CMM patients treated at large hospitals in Adelaide, Melbourne and Brisbane. Hospital controls with cancers other than skin, matched for sex and age. Age > 14 years. Source of information: interview. Skin, hair, eye colour and skin reaction to sunlight significantly associated with risk.

Pack et al. (50). C/CC = 273/78, response rate unknown. Sampling frame: CMM patients treated at one hospital ('representative group'). Hospital controls with cancer other than CMM, random sample, unmatched. No restrictions. Source of information: 'closely evaluated' by clinical examination. Hair colour and eye colour significantly associated with risk.

Gellin et al. (51). C/CC = 79/1037, response rate unknown. Sampling frame: CMM patients treated at one hospital, histologically proven. Hospital controls with non-tumour skin condition. Age 30–79 years. Source of information: interview and examination recorded on a standardized form. Hair colour, skin colour, and eye colour significantly associated with risk. Skin reaction to sunlight was not associated with risk.

Beardmore (52). C/CC 468/468, response rate unknown. Sampling frame: CMM patients treated at one hospital, histologically proven. Hospital controls including patients with skin cancer matched for sex and age. No restrictions. Source of information: interview. Comments: how hair, skin, and eye colour was evaluated not stated. Hair colour, skin colour, eye colour, and skin reaction to sunlight were not associated with risk.

Klepp & Magnus (53). C/CC = 78/128, response rate unknown. Sampling frame: CMM patients treated at one hospital. Hospital controls with lymphoma, carcinoma or testicular cancer, consecutive, unmatched. Age > 20 years. Patients with advanced disease excluded. Source of information: questionnaire. Hair and eye colour recorded independently by the interviewer and the interviewee. Skin reaction to sunlight and freckling significantly associated with risk, but hair colour and eye colour were not.

Adam et al. (55). C/CC = 111/342, response rate C/CC = 66%/68%. Sampling frame: population-based cases. Population-based controls (randomly selected from general practitioners' lists), matched on age and marital status. Women aged 15–49 years. Source of information: postal questionnaire. Hair colour and skin reaction to sunlight significantly associated with risk, but skin colour was not.

MacKie & Aitchison (54). C/CC = 113/113, response rate unknown. Sampling frame: CMM patients from western Scotland. Hospital controls with conditions not related to skin, matched for sex and age. Age 18–76 years. Lentigo maligna melanoma excluded. Source of information: questionnaire. Hair colour, skin colour, eye colour, and skin reaction to sunlight were not associated with risk.

Beral et al. (56). C/CC = 287/574, response rate C/CC = 77%/unknown. Sampling frame: CMM patients treated at one hospital, histologically proven. Hospital controls, excluding various disease (n = 148). Household sample randomly selected, matched for age and area of residence. Women aged 18–54 years. Source of information: home or hospital interview using a standardized questionnaire. Skin and eye colour and naevi graded by interviewer. Comments: adjusting by stratified analysis. Hair colour, skin colour, and naevi were significantly associated with risk. Freckling and skin reaction to sunlight significant in crude analysis only. Eye colour not associated with risk.

Elwood et al. (57). C/CC = 595/595, response rate C/CC = 83%/unknown. Sampling frame: population-based, pathology slides reviewed. Population controls matched for sex, age, and province. Age 20–79 years. Lentigo maligna melanoma and acral lentigenous melanoma excluded. Source of information: home interview using a standardized questionnaire. Objective (semi-) measurements. Comments: adjustment by use of multiple logistic regression model. Hair colour, skin colour, freckling, acute and chronic sun reaction were significantly associated with risk. Eye colour significant in crude analysis only.

Holman & Armstrong (58). C/CC = 511/511, response rate C/CC = 90%/69%. Sampling frame: population-based, pathology slides reviewed. Population controls, matched for sex, age, and area of residence. Age 10–79 years. Source of information: home interview using a standardized questionnaire. Objective (semi-) measurements and naevi count. Comments: adjustment by use of multiple logistic regression model. Hair colour, acute and chronic sun reaction to sunlight, naevi and family history of melanoma significantly associated with risk. Skin colour and eye colour significant in crude analysis only.

Green et al. (59). C/CC = 183/183, response rate C/CC = 97%/92%. Sampling frame: population-based, histologically proven. Population controls, matched for sex, age, and area of residence. Lentigo maligna melanoma and acral lentigenous melanoma excluded. Source of information: home interview using a standardized questionnaire. Objective (semi-) measurements and naevi count. Comments: adjustment by use of multiple logistic regression model. Hair colour, acute sun reaction, and naevi were significantly associated with risk. Skin colour, eye colour, chronic sun reaction, freckling, and family history of melanoma significant in crude analysis only.

Elwood et al. (60). C/CC = 83/83, response rate C/CC = 74%/92%. Sampling frame: 'population-based?', histologically proven. Hospital controls (in- and outpatients), matched for sex, age, and area of residence. Age > 20 years. Source of information: home interview using a standardized questionnaire. Objective (semi-) measurements and naevi count. Comments: adjustment by use of multiple logistic regression model. Skin reaction to sunlight, freckling, and naevi were significantly associated with risk. Hair colour significant in crude analysis. Eye colour was not associated with risk.

Sorahan & Grimley (61). C/CC = 58/333, response rate C/CC = 64%/60%. Sampling frame: CMM patients treated in two hospitals, no case of lentigo maligna melanoma. Hospital controls excluding skin disease (n = 151). Population controls unmatched. Age 20–70 years. Source of information: postal questionnaire. Comments: adjustment by use of multiple logistic regression model. Naevi significantly associated with risk. Acute sun reaction significant in crude analysis only.

Cristofolini et al. (62). C/CC = 103/205, response rate unknown. Sampling frame: CMM patients treated or controlled at two hospitals. Hospital controls excluding skin tumours. Age 21–80 years. Source of information: interview using a standardized questionnaire. Hair, skin, and eye colour and naevi assessed by dermatologist. Comments: adjustment by use of multiple logistic regression model. Hair colour and family history significantly associated with risk. Skin colour, eye colour, freckling, and naevi not associated with risk.

Østerlind et al. (63). C/CC = 474/926, response rate C/CC = 92%/82%. Sampling frame: population-based, pathology slides reviewed. Population controls, frequency matched on sex and age. Age 20–79 years. Lentigo maligna melanoma excluded. Source of information: home interview using a standardized questionnaire. Objective (semi-) measurements and naevi counts. Comments: adjustment by use of multiple logistic regression model. Hair colour, freckling, and naevi significantly associated with risk. Skin colour, acute and chronic sun reaction, and family history of melanoma significant in crude analysis only. Eye colour not associated with risk.

[a] If one or more of the following variables: hair colour, skin colour, eye colour, skin reaction to sunlight (acute and chronic sun reaction), freckling, naevi, and family history of melanoma is not mentioned means that the variable was not reported/included in the study.

genetically determined, pigmentary, constitutional characteristics; 2) freckling and acute and chronic sun reaction (i.e., tendency to burn and tanning ability respectively), which are general expressions of pigmentary characteristics in response to sunlight; and 3) pigmentation 'disorders' as indicated by the number and size of palpable naevi on the arms and a history of previous excision of benign naevi. This latter factor may indicate a genetic tendency to formation of moles, but it is unknown to what extent environmental factors alone or in combination with genetic predisposition play a role in the occurrence of naevi.

In this study (63), eye colour was not associated with risk of melanoma (Table 9), and our data thus do not corroborate results from early univariate analyses (8, 50, 51). Recent population-based case–control studies, however, have shown that most of the effect of eye colour in the unadjusted analysis is explained by other pigmentary factors (57, 58). The crude relative risk of CMM in our study increased with decreasing pigmentation of skin and hair, a relationship also found in other studies (8, 50, 51, 55–59, 62). Adjustment for the influence of freckling and chronic sun reaction (i.e. tanning ability) reduced the influence of skin colour to a non-significant level, while light hair colour (light brown, fair or blond) remained a significant and independent risk factor. Other case–control studies (57, 58) have found a similar independent influence of the hair colour. It is not clear why hair colour is a stronger risk factor than baseline skin colour (i.e. with no influence of exposure to the sun). Our finding may be due to the fact that the Danish population is very homogeneous with respect to skin colour. Furthermore, our means of assessing skin colour may not have been sensitive enough to distinguish minor differences. Differences in hair colour may be correlated with minor but indiscernible differences in the pigmentation of the skin, suggesting that hair colour could be a marker for baseline skin colour, but there is no current evidence for such a relationship.

The tendency to sunburn reflects an acute reaction to sunlight. Both the crude and adjusted relative risks for CMM increased progressively with the tendency to burn in

**Table 9**

*Relative risk of malignant melanoma of the skin in Denmark, 1982–1985, by skin, hair and eye colour, freckles, and acute and chronic reactions to sunlight*

| Factor | Category | Relative risk, crude [95% confidence interval] | Relative risk, adjusted[a] [95% confidence interval] |
|---|---|---|---|
| Skin colour[b] | Dark | (1.0) | (1.0) |
| | Medium | 1.4 [1.0–1.9] | 1.0 [0.8–1.3] |
| | Light | 1.7 [1.2–2.3] | 1.3 [0.9–1.8] |
| | p-value, trend test | <0.01 | 0.17 |
| Hair colour | Dark-brown/black | (1.0) | (1.0) |
| | Light-brown | 1.5 [1.2–1.9] | 1.5 [1.2–1.9] |
| | Blond/fair | 1.7 [1.0–2.9] | 1.7 [1.0–2.9] |
| | Red | 1.8 [1.1–2.7] | 1.3 [0.8–2.0] |
| | p-value, trend test | <0.001 | 0.04 |
| Eye colour | Brown | (1.0) | (1.0) |
| | Grey/green | 0.9 [0.6–1.2] | 0.7 [0.5–1.1] |
| | Blue | 1.1 [0.8–1.5] | 0.9 [0.9–1.3] |
| | p-value, trend test | 0.33 | 0.96 |
| Freckles | None | (1.0) | (1.0) |
| | Some | 1.5 [1.2–1.9] | 1.5 [1.2–2.0] |
| | Many | 3.0 [2.2–4.1] | 2.9 [2.1–4.1] |
| | p-value, trend test | <0.001 | <0.001 |
| Acute reaction to sunlight | No sunburn | (1.0) | (1.0) |
| | Mild sunburn | 1.3 [1.0–1.6] | 1.1 [0.8–1.4] |
| | Painful sunburn | 1.6 [1.1–2.6] | 1.3 [0.8–2.1] |
| | Blisters | 2.2 [0.9–5.0] | 1.6 [0.7–3.9] |
| | p-value, trend test | <0.001 | 0.16 |
| Chronic reaction to sunlight | Deep tan | (1.0) | (1.0) |
| | Moderate tan | 1.4 [1.1–1.8] | 1.2 [0.9–1.6] |
| | Mild tan | 1.8 [1.3–2.6] | 1.4 [1.0–2.1] |
| | No tan | 2.0 [1.0–3.7] | 1.2 [0.6–2.5] |
| | p-value, trend test | <0.001 | 0.09 |

[a] Estimates were mutually adjusted and adjusted for sex.

[b] Complexion chart sample numbers 1, 2, 3, 4, 5, 6, 7 = dark; 8, 9 = medium; 10 = light (Scotto & Fears, 1978); measured on the inner surface of the left upper arm

the sun (Table 9). This effect became non-significant, however, after controlling for other host characteristics. Similarly, the risk of melanoma decreased with increasing tanning ability but this effect also became unimportant after adjustment for host factors including freckling ability and hair colour. In our study, most of the association between risk of melanoma and tendency to burn easily and tan poorly was due to freckling, a characteristic of pigmentation associated with poor sun tolerance.

The most important and strongest risk factor identified in our study was the number of palpable pigmented naevi counted on the arms. This finding is in agreement with those of other recent case–control studies (58–60). We found a 'dose–response' relationship for both large and small naevi (Table 10). The risk associated with small naevi was not explained by the presence of large naevi. The relative risk related to this variable was unaffected by adjustment for complexion and skin reaction characteristics. Such factors are thus not associated with the probability of naevus development. Our finding implies that as simple a measure as assessing the number of raised naevi on the arms may discriminate subjects with considerably different risks of melanoma.

The number of naevi on the arms has been assessed by slightly different procedures in other case–control studies. Holman & Armstrong (58) and Elwood et al. (60) followed a procedure similar to ours counting only raised pigmented naevi on both arms, while Green et al. (59) counted all pigmented naevi on the left arm. The latter method is more tedious and did not result in a better differentiation of risk groups. Swerdlow et al. (67) counted melanocytic naevi on the entire body and found that the number of naevi on a particular body site was not more specifically predictive of risk of melanoma at that site than of melanoma at other body sites. Counting naevi on the arms, therefore, seems to be both a sensitive and sufficient indicator of the risk related to naevi.

One explanation of these findings is that an increased number of (raised) pigmented naevi may be a surrogate for the presence of dysplastic naevi, which are established precursors of melanoma (68). The diagnosis of a dysplastic naevus is based on histologically proven cytological atypia or dysplasia (69), but morphology, size and location may enable a reasonable clinical identification of these lesions (70).

Freckling, which is an indicator both of the skin's sensitivity to the sun and of sun exposure, was a substantial risk factor (Table 9). This finding is in agreement with other studies (53, 56, 59, 60). The association changed little when adjusted for other pigmentary characteristics.

**Table 10**

*Relative risk of malignant melanoma of the skin in Denmark 1982–1985, by number of raised naevi on arms, history of excision of benign naevi and of affected blood relatives*

| Factor | Category | Relative risk, cruds [95% confidence interval | Relative risk, adjusted[a] [95% confidence interval] |
|---|---|---|---|
| Number of raised naevi on arms, total | None | (1.0) | (1.0) |
| | 1 | 1.5 [1.1–2.1] | 1.4 [1.0–2.0] |
| | 2–4 | 2.3 [1.6–3.1] | 2.2 [1.6–3.1] |
| | 5+ | 5.4 [3.5–8.1] | 5.1 [3.3–7.9] |
| | p-value, trend test | <0.001 | |
| Number of raised naevi on arms, <5 mm (diameter) | None | (1.0) | (1.0) |
| | 1 | 1.6 [1.1–2.2] | 1.6 [1.1–2.3] |
| | 2–4 | 2.5 [1.8–3.4] | 2.3 [1.6–3.3] |
| | 5+ | 5.0 [3.3–7.7] | 4.8 [3.1–7.6] |
| | p-value, trend test | <0.001 | |
| Number of raised naevi on arms, ≥5 mm (diameter) | None | (1.0) | (1.0) |
| | 1 | 1.8 [1.2–2.8] | 1.8 [1.1–2.8] |
| | 2+ | 3.6 [1.8–7.2] | 2.9 [1.4–5.9] |
| | p-value, trend test | <0.001 | |
| Excised benign naevi before melanoma diagnosis | No | (1.0) | (1.0) |
| | Yes | 1.6 [1.1–2.2] | 1.6 [1.1–2.3] |
| Affected blood relatives | No | (1.0) | (1.0) |
| | Yes | 1.7 [1.0–3.1] | 1.5 [0.8–2.9] |

[a] Estimates adjusted for sex, freckles, hair and skin colour. Effect of excised benign naevi and affected blood relatives adjusted for total number of raised naevi.

**Table 11**

*Relative risk (RR) [number of cases; number of controls] of malignant melanoma of the skin in Denmark, 1982–1985, by degree of freckling and by total number of raised naevi on arms. (From (63).) Reproduced by permission of the editor*

| | Total number of raised naevi on arms | | | | RR for freckling (adjusted for number of raised naevi) | Test for trend |
|---|---|---|---|---|---|---|
| | 0 | 1 | 2–4 | 5+ | | |
| Degree of freckling | | | | | | |
| None | (1.0) | 1.7 | 2.5 | 2.9 | (1.0) | |
| | [90; 334] | [30; 65] | [32; 47] | [14; 18] | [166; 464] | |
| Some | 1.5 | 1.8 | 2.7 | 9.1 | 1.4 | |
| | [89; 223] | [29; 61] | [33; 46] | [32; 13] | [183; 343] | $p < 0.001$ |
| Many | 2.5 | 4.8 | 6.1 | 13.9 | 2.7 | |
| | [52; 77] | [18; 14] | [23; 14] | [30; 8] | [123; 113] | |
| RR number of naevi | | | | | | |
| (adjusted for freckling) | (1.0) | 1.5 | 2.2 | 4.6 | | |
| | [231; 634] | [77; 140] | [88; 107] | [76; 39] | | |
| Test for trend | | $p < 0.001$ | | | | |

All RR statistically significantly different from unity

In our study, freckling ability was a more important risk indicator than skin colour, tanning ability or acute reaction to the sun, which are all factors associated with poor tolerance to sun exposure.

Finally, we observed an apparent synergy between the degree of freckling and the number of naevi (Table 11), indicating a joint effect of susceptibility to sun exposure and pigmentary disorders. The two factors affect melanoma development independently, which suggests that they represent separate host characteristics. The identification of strong associations with host factors points to the need for studies into the aetiology of naevi and tendency to freckling if these phenomena are truly causally related to melanoma. Indeed, such studies may hold the key to the understanding of melanoma development. In planning such studies, exogenous factors must also be considered in view of the marked increase in the incidence of melanoma, which cannot be explained by genetic changes.

The finding that individuals with large numbers of naevi and freckling ability are at greatly increased risk of melanoma is, however, of immediate importance. Such individuals could be warned about signs of early melanoma and instructed to avoid risk factors, such as exposure to ultraviolet radiation. Raised naevi on the arms and freckling ability could therefore be simple clinical indicators of increased risk of melanoma. Our results indicate that as much as 48% of melanomas in the population are attributable to the presence of palpable naevi on the arms and of freckles, either alone or in combination.

Concerning the pigmentary factors included in our study there was no significant difference between their association with risk of superficial spreading melanoma and risk of nodular melanoma. This result is in line with the findings of both Elwood et al. (57) and Holman & Armstrong (58).

### Importance of exposure to ultraviolet light

An association between exposure to UV light and risk of CMM has been suspected for many years (9). The carcinogenic effect of UV-B radiation in sunlight has been well established by experimental studies of UV-induced skin cancer in laboratory animals, although melanoma has been produced only in laboratory animals exposed to UV radiation in combination with chemical carcinogens (71–73). The variations in the incidence of CMM both nationally and internationally suggest that exposure to UV light plays an important role in the causation of this cancer. A direct relationship to sun exposure is indicated by such features as an increase in incidence and mortality rates with decreasing latitude and increasing sun exposure in several white populations. There are exceptions to this pattern, since the incidence tends to rise with increasing distance from the equator in Europe, due mainly to the Scandinavian populations. Races and individuals with light pigmentation, and therefore poorly developed natural protection against UV radiation, are more susceptible (providing indirect evidence of an association with UV radiation). Additional evidence is provided by associations with individual level of sun exposure measured for cases and controls in case–control studies, indicating a significant relationship between melanoma and total outdoor exposure (occupational and recreational) (8, 51) although the results are not completely consistent. Neither Lancaster & Nelson (8) nor Klepp & Magnus (53) found a significant relationship between melanoma risk and outdoor occupation.

Epidemiological studies of melanoma suggest that there is no simple dose–response relationship between cumulative exposure to sunlight and risk of CMM. Thus, the distribution of melanomas on the body surface seems to indicate that relatively unexposed sites are affected. This is not the case with regard to lentigo maligna melanoma,

however. An unexpectedly low incidence of melanoma in outdoor workers compared with indoor workers, higher rates in upper socioeconomic groups, and differences in the increases in incidence rates at different anatomical sites have led to the theory that intermittent exposure to the sun may carry a higher risk than continuous, daily exposure. There is also a clear difference between melanomas and other skin cancers in distribution by site, age and sex, suggesting that exposure to UV light plays different roles in the carcinogenesis of these tumours. The risk of non-melanoma skin cancers and of lentigo maligna melanomas thus depends on cumulative sun exposure, while it has been suggested that other types of cutaneous melanoma are related to intermittent and intense bursts of sun exposure as received during recreational outdoor activities, whereas chronic exposure has little effect or may even be protective.

In our case–control study we included questions indicating intermittent sun exposure, such as sunburn, recreational exposures (including sunbathing) and southern European and tropical vacations. Occupational exposure and cutaneous microtopography were included in order to indicate the possible effect of long-term, continuous exposure to the sun.

*Results, comments and conclusions*

We found that the number of severe sunburns in childhood that had caused pain for two days or more was an important risk factor, while severe sunburns later in life were less important (Table 12). Our data revealed a clear dose–response effect, risk of melanoma rising with increasing number of severe sunburn episodes in childhood. The number of sunburns at ages 15–24 years or within the ten years preceding the diagnosis had no significant influence in those who had not been sunburnt at an early age, but the number of study subjects in these groups were small. Our results thus support the hypothesis by Holman et al. (15) that the important time of exposure may be early in life. The fact that sunburns are especially noxious was also found in a Canadian study (75) and in an Australian study (76), while the influence of this factor was not significant in the study by Holman et al. (18). Two earlier studies also showed an association between sunburning and risk of CMM: MacKie & Aitchison (54) reported an elevated risk associated with a history of recent sunburning, and Lew et al. (77) found an increased relative risk associated with vacations at sunny places during childhood.

The risk related to painful sunburns before age 15 increased progressively with the number of raised naevi. Persons who had experienced two to four or five or more severe sunburns in childhood and who had five or more raised naevi on their arms had relative risks for melanoma of 17.6 and 24.4 respectively, compared to those without naevi who had never been sunburnt (Table 13). Although sunburn in childhood may be a risk factor for the development of naevi (78), it is clear that both factors contribute

**Table 12**

*Relative risk of malignant melanoma of the skin in Denmark, 1982–1985, by number of painful sunburns, and by age group (From (74)). Reproduced by permission of the editor*

| Factor | Category | Number of cases | Number of controls | Relative risk, crude [95% confidence interval] | Relative risk, adjusted[a] [95% confidence interval] | Relative risk, adjusted[b] [95% confidence interval] |
|---|---|---|---|---|---|---|
| Number of sunburns before age 15 | Never | 93 | 277 | (1.0) | (1.0) | |
| | 1 | 35 | 80 | 1.3 [0.8–2.1] | 1.2 [0.7–1.9] | |
| | 2–4 | 85 | 121 | 2.1 [1.5–3.0] | 1.0 [1.3–2.9] | |
| | 5+ | 44 | 35 | 3.7 [2.3–6.1] | 2.7 [1.6–4.8] | |
| Trend test, p-value | | | | <0.001 | <0.001 | |
| Number of sunburns during ages 15–24 | Never | 93 | 277 | (1.0) | (1.0) | (1.0) |
| | 1 | 80 (52)[c] | 147 (83) | 1.6 [1.1–2.3] | 1.5 [1.0–2.3] | 1.8 [1.1–2.8] |
| | 2–4 | 73 (27) | 121 (61) | 1.8 [1.2–2.6] | 1.8 [1.2–2.7] | 1.3 [0.8–2.3] |
| | 5+ | 59 (12) | 73 (12) | 2.4 [1.6–3.6] | 1.9 [1.2–3.1] | 1.2 [0.6–2.7] |
| Trend test, p-value | | | | <0.001 | <1.001 | 0.178 |
| Number of sunburns in last 10 years | Never | 93 | 277 | (1.0) | (1.0) | (1.0) |
| | 1 | 29 (12) | 52 (32) | 1.7 [1.0–2.8] | 1.6 [0.9–2.8] | 1.2 [0.5–2.6] |
| | 2–4 | 13 ( 4) | 30 (17) | 1.3 [0.6–2.6] | 1.1 [0.5–2.3] | 0.5 [0.1–1.6] |
| | 5+ | 24 ( 6) | 24 (25) | 3.0 [1.6–5.4] | 3.0 [1.5–5.9] | 2.2 [0.6–7.5] |
| Trend test, p-value | | | | <0.001 | 0.004 | 0.757 |

[a] Estimates adjusted for sex and host factors (i.e., number of raised naevi, freckles, and hair colour): variables in table not mutually adjusted

[b] All persons who sunburned before age 15 were excluded, and estimates were adjusted for sex and host factors.

[c] Numbers in parentheses exclude those sunburned before age 15

**Table 13**

*Relative risk (RR) [number of cases; number of controls] for malignant melanoma of the skin in Denmark, 1982–1985, according to total number of painful sunburns before age 15 and to total number of raised naevi on arms. (From (74).) Reproduced by permission of the editor*

| | Total number of raised naevi on arms | | | | RR for number of sunburns before age 15 (adjusted for total number of raised naevi) [95% confidence interval] |
|---|---|---|---|---|---|
| | 0 | 1 | 2–4 | 5+ | |
| Total number of painful sunburns before age 15 | | | | | |
| Never | (1.0) [36; 195] | 2.4 [17; 38] | 4.1 [28; 37] | 10.8 [12; 6] | (1.0) |
| 1 | 1.7 [17; 53] | 5.4 [10; 10] | 1.5 [3; 11] | 3.6 [4; 6] | 1.2 [0.7–2.1] |
| 2–4 | 2.7 [43; 85] | 3.0 [11; 20] | 8.1 [18; 12] | 17.6 [13; 4] | 2.2 [1.4–3.3] |
| 5+ | 4.7 [19; 22] | 8.1 [9; 6] | 6.5 [6; 5] | 24.4 [9; 2] | 3.5 [2.0–6.2] |
| Trend test, p-value | | | | | <0.001 |
| Total number of raised naevi RR (adjusted for number of sunburns before age 15) [95% confidence interval] | (1.0) | 1.9 [1.2–3.0] | 2.8 [1.9–4.4] | 6.0 [3.1–11.7] | |
| Trend test; $p < 0.001$ | | | | | |

individually to the risk of CMM. Further investigations of the risk of CMM related to dysplastic naevi as opposed to common acquired naevi and of the association between exposure to the sun and the development of naevi may improve our understanding of CMM.

Outdoor recreational activities such as sunbathing and boating, i.e., activities involving the most intense sun exposure, were associated with increased melanoma risk, while activities such as gardening, ball games and hiking, which involve less intense and more regular exposure, were not associated with an increased risk (Table 14). Vacations spent in southern Europe or similar sunny places were a risk factor when the destination was the very sunny resorts (i.e. the beach was the major entertainment). The relative risk associated with this exposure decreased, however, from 1.7 to 1.4 when adjucted for history of sunbathing and sunburning.

Excessive exposure to the sun inevitably results in actinic skin damage, most often on the face, for which site, however, the increase in incidence of CMM has been rather modest. The dorsum of the hand resembles the face with respect of cumulative sun exposure, and the lack of an association between risk of CMM and microtopography at this site thus provides further evidence that cumulative exposure is of limited importance for CMM in Denmark. Holman & Armstrong (79) found a positive relationship between microtopographic changes in the skin (sun-induced skin damage) and risk of melanoma, but this result could be due to the much higher level of exposure to the sun in Australia than in Denmark: 61% of Australians had a microtopography score of 5 or 6 compared to only 9% of the Danes. This finding may also explain the difference in melanoma risk between Australia and Denmark.

Finally, occupational exposure of the skin to sunlight during the summer was not associated with an increased melanoma risk. A low relative risk was thus found both in men with a history of outdoor work during the summer (RR = 0.7) and in men with outdoor work in their most recent occupation (RR = 0.6). Our study, as well as the Canadian case–control study (80), thus indicates that long-term continuous exposure to the sun does not increase, and possibly reduces, the risk of melanoma in males. However, other case–control studies show no consistent pattern of change in melanoma risk related to occupational sun exposure (53, 54, 60).

Exposure to fluorescent light was not a risk factor in our study, nor in others (60, 61, 81, 82): our results do not therefore support the original observation by Beral et al. (83). Sun beds had been used by cases as well as by controls, but the numbers were small and the number of exposures was low, and evaluation of the possible risk or protection related to this new habit is not yet possible.

### Importance of hormonal factors

A number of observations suggest a relationship between hormonal factors, especially oestrogen, in women and the development of cutaneous malignant melanoma. Firstly, a significant level of oestrogen receptors is de-

**Table 14**

*Relative risk of malignant melanoma of the skin in Denmark 1982–1985 by regular participation[a] in different outdoor leisure activities*

| Leisure activity | Category | Relative risk, crude [95% confidence interval] | Relative risk, adjusted [95% confidence interval] |
|---|---|---|---|
| Sunbathing[b] | Never | (1.0) | (1.0) |
| | Ever | 1.8 [1.2–2.5] | 1.6 [1.1–2.4] |
| Boating[b] | Never | (1.0) | (1.0) |
| | Ever | 1.5 [1.1–2.0] | 1.4 [1.0–1.9] |
| Skiing (snow)[b] | Never | (1.0) | (1.0) |
| | Ever | 1.6 [1.2–2.1] | 1.4 [1.0–1.9] |
| Swimming (outdoor)[b] | Never | (1.0) | (1.0) |
| | Ever | 1.3 [1.0–1.6] | 1.1 [0.9–1.5] |
| Gardening[c] | Never | (1.0) | (1.0) |
| | Ever | 1.1 [0.9–1.5] | 1.1 [0.7–1.4] |
| Ball games[c] | Never | (1.0) | (1.0) |
| | Ever | 1.0 [0.7–1.2] | 0.9 [0.7–1.2] |
| Hiking[c] | Never | (1.0) | (1.0) |
| | Ever | 1.0 [0.7–1.4] | 1.0 [0.7–1.4] |
| Horseback riding/ golf[c] | Never | (1.0) | (1.0) |
| | Ever | 0.9 [0.5–1.4] | 0.9 [0.5–1.4] |

[a] On at least 10 occasions in any season.
[b] Estimates adjusted mutually and adjusted for sex and host factors (naevi, freckles, hair colour).
[c] Estimates adjusted for sex, sunbathing and host factors.

tectable in about 40% of male and about 50% of female melanomas (84). Secondly, the age-specific incidence rate of CMM rises more steeply after puberty in females than in males (85); and, thirdly, hyperpigmentation may occur during pregnancy and during topical as well as systemic oestrogen therapy (86).

The result of analytical epidemiological studies have generally not confirmed any consistent influence of hormonal risk factors in CMM. A few studies showed a weak influence of oral contraceptive use (87, 88), but several others did not (55, 89–94). The reproductive characteristics of women have also been examined; late age at first birth was noted as a risk factor (87) and greater number of live births had a protective effect (93). On the basis of these findings, we investigated the possible role of reproductive factors and the use of oral contraceptives and menopausal replacement therapy in 816 female cases and controls included in this study (95).

*Results, comments, and conclusions*

Neither reproductive nor hormonal factors increased the risk of CMM in women. Thus, no association was observed between risk of CMM and age at menarche, duration of menstrual life, age at natural menopause, age at first pregnancy, or number of pregnancies, live births or miscarriges. Neither use of oral contraceptives nor menopausal replacement therapy resulted in an increased risk of melanoma. In our study neither risk of superficial spreading melanoma, nor risk of nodular melanoma was associated with hormonal factors.

Our data add to the increasing body of evidence that reproductive and hormonal factors have no important influence on the development of CMM (55, 89–94, 96). This finding agrees well with the clinically observed insensitivity of CMM to hormonal treatment. The questions asked about hormonal factors were the same as used in a concurrent Danish case–control study of breast cancer, which found an influence of menstrual history, parity and oral contraceptive use (97).

The lack of an association between hormonal factors in women and melanoma and the observation that oestrogen receptor-positive tumours occur in similar proportions in females and males (84) suggest that endocrine characteristics do not play an important role in the difference in incidence rate of CMM between young females and males. Common acquired melanocytic naevi seem to be more prevalent in females than in males (78), but the association

is weak and confounded with age; further investigation of a possible relationship between oestrogens and naevi is required.

### Importance of diet and other factors

Dietary factors are suspected to play a role in the causation of a number of cancers. High intake of food containing retinol or beta-carotene may reduce the risk of cancer in general (98), and high intake of polyunsaturated fat has been suggested to increase the risk of CMM (99–101), and so these two factors were included in our study. Consumption of coffee, tea and alcohol has been suggested as a potential risk factor for CMM, although no consistent results can be derived from available data (102–105)

Since tobacco is a common carcinogen, we also examined smoking habits. Hair dyes were investigated since they may contain carcinogens and have been associated with the occurrence of Hutchinson's melanotic freckle (i.e. lentigo maligna melanoma) (106). Frequent bathing removes the outer layer of the epidermis, which may increase the susceptibility of the skin to UV light (107, 108). Our questionnaire accordingly included questions about these habits.

#### *Results, comments, and conclusions*

The consumption of green vegetables, liver and other dietary items rich in carotene and retinol was very similar in cases and controls. Nor was the risk of melanoma increased in individuals with a high intake of fatty meat, or in a group defined as high fat consumers (by combining quartiles of fatty meat), compared with those who had the lowest intake of fatty meat. The use of margarine and vegetable oil was also similar in the two categories. Our results thus do not corroborate the observation of MacKie et al. (104).

The use of tobacco had no significant influence on the risk of CMM, which is consistent with previous findings (103–105, 110). We found no increased risk of melanoma with consumption of any specific type of alcohol; however, our data, in contrast to those from other studies (103, 105), show a slight protective effect with increasing total alcohol consumption. Coffee drinking did not affect the risk of melanoma, but heavy consumption of tea seemed to increase the risk. Neither coffee nor tea drinking was a significant risk factor in the study by Holman (105). Our data exhibit opposite trends for the influences of coffee and tea intake. The lack of consistency precludes any conclusion with regard to intake of these beverages.

Use of hair dyes had no effect on the risk of melanoma of the head and neck or at any other site. However, lentigo maligna melanoma was not included in our study. Frequency of bathing, type of bathing and type of soap used had no influence on risk of melanoma.

Diet and smoking habits, intake of alcohol and the proportion of dwellings with a bathroom and hot water have changed significantly within the last 50 years. These lifestyle changes have been associated with changes in the incidence of several diseases, including cancers (109). In our study, however, these changes are unlikely to be responsible for the observed 5- to 6-fold increase in incidence rates of CMM.

## Summary and Conclusion

It is rare that a single scientific investigation can prove a causal relationship between an enviromental factor and human disease. Investigations must be repeated in different populations and with different methods to assemble the knowledge needed to establish, with a high degree of certainty, that an association is truly causal. The present study provides additional knowledge about the role of pigmentary constitutional characteristics in the causation of malignant melanoma of the skin, and it supports current theories about the influence of exposure to UV light.

This investigation has resulted in findings that can be useful for the prevention of malignant melanoma, which, in Denmark from 1943–1947 to 1978–1982, showed a 5- to 6-fold increase of the age-standardized incidence rates in both males and females. The increase varied with anatomical site and was most pronounced for body sites normally protected from the sun. A 4- to 6-fold increase in risk was seen relative to the generation born 25 years earlier and it is likely that the observed increasing risk for younger generation will lead to a continued increase of the incidence in the future.

The pattern of melanoma incidence with regard to sex, age and body site distribution differs from that for non-melanoma skin cancers, which are most frequent in men and older age groups and most commonly located on the face, scalp and neck. Our findings are in line with the theory that the cumulative dose of UV light is of limited importance for CMM, while intermittent exposure to UV light may be hazardous for skin that is normally protected against this type of irradiation. The increase in risk from generation to generation is most likely a result of leisure time activities involving outdoor sunbathing, a popular activity since suntanned skin is associated with good health and attractiveness.

The ability to suntan clearly influences the risk of CMM. The results of our case–control study have confirmed the increased risk in relation to fair complexion, especially in persons with freckling ability and with light hair. The protective role of skin pigmentation has been known for a long time, due to the observation of marked differences in the incidence of CMM between light skinned and darker races. Our study shows that even the small differences seen within the Danish population influence the risk of melanoma. The presence of pigmented, palpable

naevi on the arms was the most important risk factor identified in this investigation. The clear increase in risk with increasing number of raised naevi, irrespective of size, indicates that the association is likely to be causal. We found a synergy between the number of raised naevi and freckling ability in the risk of CMM.

The relationship between naevi and melanoma is an important issue for future studies, largely because very little is known about the natural history, distribution and etiology of naevi. The identification of causal factors for naevoid development may have important implications for our understanding of the role of naevi as a precursor lesion. If a major proportion of naevi are due to environmental causes that can be controlled, it may be possible to reduce the incidence of melanoma by preventing the development of naevi.

The importance of intermittent rather than cumulative sun exposure as a cause of skin melanomas has been further clarified by our case–control study. Thus, we observed no increased risk in male outdoor workers, while leisure activities such as sunbathing and boating were associated with increased risk. Sunburn, as an indicator of intermittent sun exposure, seems to have a quantitative influence on melanoma risk, especially if it occurs in childhood. Vacations in sunny resorts had a marginal influence on the risk of CMM, but they may become more important in the future if children are taken to places where intensive exposures give rise to sunburns. Protective sunscreen creams have not been used by our population for a sufficiently long time to enable evaluation of their protective efficacy, and the very short experience with sun beds makes it impossible, at present, to estimate reliably the influence of this type of exposure.

A relationship has been suspected between hormonal and reproductive factors and the risk of CMM, since the number of naevi increases substantially at puberty, and focal increases in pigmentation are seen during pregnancy. Furthermore, CMM does not generally occur at prepuberty. Our investigations do not corroborate the existence of such an association. Age at first pregnancy, number of childbirths, use of oral contraceptives and postmenopausal use of oestrogens did not seem to have influenced the increased incidence of CMM observed.

Changes in diet, smoking habits and alcohol intake have led to increases in the incidence of cancers at a number of sites and have had other adverse impacts on the general health of the population. However, our results indicate that the risk of CMM is uninfluenced by these factors.

Our results point to the possibility of identifying high-risk groups for malignant melanoma of the skin, i.e. individuals with many naevi, many freckles and light hair colour. These individuals may form a target group for counselling and/or intervention. A decrease in the incidence of melanoma would be anticipated if such individuals minimized their exposure to the sun, always avoiding sunburn.

*Request for reprints:* Dr Anne Østerlind, Danish Cancer Registry, Institute of Cancer Epidemiology, Danish Cancer Society, P.O. Box 839, DK-2100 Copenhagen Ø, Denmark.

## REFERENCES

1. Waterhouse J, Muir CS, Shanmugaratnam K, Powell I. eds. Cancer incidence in five continents. Vol. IV (IARC Scientific Publications No. 42), International Agency for Research on Cancer. Lyon, 1982.
2. Magnus K. Incidence of malignant melanoma in the five Nordic countries: significance of solar radiation. Int J Cancer 1977; 20: 477–85.
3. Magnus K. Incidence of malignant melanoma of the skin in Norway, 1955–1970. Variation in time and space and solar radiation. Cancer 1973; 32: 1275–86.
4. Eklund G, Malec E. Sunlight and incidence of cutaneous malignant melanoma effect of latitude and domicile in Sweden. Scand J Plast Reconstr Surg 1978; 12: 231–41.
5. Teppo L, Pakkanen M, Hakulinen T. Sunlight as a risk factor of malignant melanoma of the skin. Cancer 1978; 41: 2018–27.
6. Boyle P, Robertson C. Increase in malignant melanoma incidence in Scotland. Am J Epidemiol (in press).
7. Hakulinen T, Teppo L, Saxen E. Do the predictions for cancer incidence come true? Experience from Finland. Cancer 1986; 57: 2454–8.
8. Lancaster HO, Nelson J. Sunlight as a cause of melanoma: a clinical survey. Med J Aust 1957; 1: 452–6.
9. McGovern VJ. Melanoblastoma. Med J Aust 1952; 1: 85–98.
10. Lancaster HO. Some geographical aspects of the mortality from melanoma in Europeans. Med J Aust 1956; 1: 1082–7.
11. Crombie IK. Variation of melanoma incidence with latitude in North America and Europe. Br J Cancer 1979; 40: 774–81.
12. Jensen OM, Bolander AM. Trends in malignant melanoma of the skin. World Health Stat Q 1980; 33: 2–26.
13. Østerlind A. Malignant melanoma in Denmark 1943–1977. Ugeskr Laeger 1983; 145: 2335–8. (In Danish.)
14. Holman CDJ, Mulroney CD, Armstrong BK. Epidemiology of preinvasive and invasive malignant melanoma in Western Australia. Int J Cancer 1980; 25: 317–23.
15. Holman DCJ, Armstrong BK, Heenan PJ. A theory of the etiology and pathogenesis of human cutaneous malignant melanoma. JNCI 1983: 71: 651–6.
16. Magnus K. Habits of sun exposure and risk of malignant melanoma: an analysis of incidence rates in Norway 1955–1977 by cohort, sex, age and primary tumour site. Cancer 1981; 48: 2329–35.
17. Elwood JM, Hislop TG. Solar radiation in the etiology of cutaneous malignant malanoma in Caucasians. Natl Cancer Inst Monogr 1982; 62: 167–71.
18. Holman CDJ, Armstrong BK, Heenan PJ. Relationship of cutaneous malignant melanoma to individual sunlight-exposure habits. JNCI 1986; 76: 403–14.
19. Østerlind A, Hou-Jensen K, Jensen OM. Incidence of cutaneous malignant melanoma in Denmark 1978–1982. Anatomic site distribution, histologic types, and comparison with non-melanoma skin cancer. Br J Cancer 1988; 58: 385–91.

20. Østerlind A, Engholm G, Jensen OM. Trends in cutaneous malignant melanoma in Denmark 1943–1982, by anatomic subsite. APMIS 1988; 96: 953–63.
21. Jensen OM, Storm HH, Jensen HS. Cancer registration in Denmark and the study of multiple primary cancers, 1943–80. Natl Cancer Inst Monogr 1985; 68: 245–51.
22. Østerlind A, Jensen OM. Evaluation of registration of cancer cases in Denmark in 1977: preliminary evaluation of registration of cancer cases by the Cancer Registry and the National Patient Registry. Ugeskr Laeger 1985; 147: 2485–8. (In Danish).
23. Storm HH. Completeness of cancer registration in Denmark 1943–1966 and efficacy of record linkage procedures. Int J Epidemiol 1988; 17: 44–9.
24. World Health Organization. Manual of the Statistical Classification of Diseases, Injuries and Causes of Death 1955. 7th revision. Geneva, 1957.
25. World Health Organization. International Classification of Diseases for Oncology (ICD-O). First edition. Geneva, 1976.
26. Clayton D, Schifflers E. Models for temporal variation in cancer rates. I: Age-period and age-cohort models. Stat Med 1987; 6: 449–67.
27. Clayton D, Schifflers E. Models for temporal variation in cancer rates. II: The age-period-cohort model. Stat 1987; 6: 469–81.
28. Elwood JM, Gallagher RP. Site distribution of malignant melanoma. Can Med Assoc J 1983; 128: 1400–4.
29. Muir CS, Nectoux J. Time trends: malignant melanoma of the skin. In: Magnus K, ed. Trends in cancer incidence. Causes and practical implications. Washington DC: Hemisphere, 1982: 365–85.
30. Boyle P, Day NE, Magnus K. Mathematical modelling of malignant melanoma trends in Norway, 1953–78. Am J Epidemiol 1983; 118: 887–96.
31. Roush GC, Holford TR, Schymura MH, White C, eds. Cancer risk and incidence trends. The Connecticut perspectice. Washington DC: Hemisphere Publishing, 1987: 203–19.
32. Stevens RG, Moolgavkar SH. Malignant melanoma: dependence of site specific risk on age. Am J Epidemiol 1984; 119: 890–5.
33. Lee JAH, Petersen GR, Stevens RG, Vesanen K. The influence of age, year of birth, and date on mortality from malignant melanoma in the populations of England and Wales, Canada, and the white populations of the United States. Am J Epidemiol 1979; 110: 734–9.
34. Holman CDJ, James IR, Gatley PH, Armstrong BK. An analysis of trends in mortality from malignant melanoma of the skin in Australia. Int J Cancer 1980; 26: 703–9.
35. Venzon DJ, Moolgavkar SH. Cohort analysis of malignant melanoma in five countries. Am J Epidemiol 1984; 119: 62–70.
36. Collins JJ, Devine N. Period and cohort factor in the incidence of malignant melanoma in the state of Connecticut. Environ Health Perspect 1984; 56: 255–9.
37. Østerlind A, Jensen OM. Increasing incidence of trunk melanoma in young Danish women. Br J Cancer 1987; 55: 467.
38. Clark WH, Mihm MC. Lentigo maligna and lentigo-maligna melanoma. Am J Pathol 1969; 55: 39–67.
39. Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. Ann Surg 1970; 172: 902–8.
40. National Centre for Health Statistics. The person number systems of Sweden, Norway, Denmark, and Israel (Vital Health Statistics. Ser. 2-No.84. DHHS Publ. PHS 80-1358), Hyattsville, USA 1980.
41. Enevoldsen B, Michelsen N, Friss-Hashe E, Kamper-Jørgensen F. Social classifications, II. Svalastoga's subdivision according to social status rank and the social grouping employed by the Institute for Social Research. Ugeskr Laeger 1980; 142: 544–50. (In Danish.)
42. Scotto J, Fears TR. Skin cancer epidemiology: research needs. Natl Cancer Inst Monogr 1978; 50: 169–77.
43. Beagley J, Gibson IM. Changes in skin condition in relation to degree of exposure to ultraviolet light. Perth: School of Biology, Western Australian Institute of Technology, 1980.
44. Breslow NE, Day NE. Statistical methods in cancer research, Vol. 1, The analysis of case–control studies (IARC Scientific Publications No. 32), Lyon: International Agency for Research on Cancer, 1980.
45. Thomas DC, Goldberg M, Dewar R, Siemiatycki J. Statistical methods for relating several exposure factors to several diseases in a case–heterogeneity studies. Stat Med 1986; 5: 49–60.
46. Cole P, MacMahon B. Attributable risk percent in case–control studies. B J Prev Soc Med 1971; 25: 242–4.
47. Paget J. Report of a clinical lecture on cases of tumours under moles. Medical Times and Gazette 1864; Jan. 16: 58–9.
48. Ackerman A. An exchange of ideas about dysplastic nevi and malignant melanomas. Part A. Am J Dermatopathol 1985; 7 (suppl): 99–102.
49. Elder DE, Greene MH, Bondi E, Clark WH. Acquired melanocytic nevi and melanoma. The dysplastic nevus syndrome. In: Ackerman A, ed. Pathology of malignant melanoma. New York: Masson Publishing, 1981: 185–215.
50. Pack GT, Davis J, Oppenheim A. The relation of race and complexion to the incidence of moles and melanomas. Ann NY Acad Sci 1963; 100, 719–42.
51. Gellin GA, Kopf AW, Garfinkel L. Malignant melanoma. A controlled study of possibly associated factors. Arch Dermatol 1969; 99: 43–8.
52. Beardmore GL. The epidemiology of malignant melanoma in Australia. In: McCarthy W, ed. Melanoma and skin cancer. Sydney: Government Printer, 1972: 39–64.
53. Klepp O, Magnus K. Some environmental and bodily characteristics of melanoma patients. A case–control study. Int J Cancer 1979; 23: 482–6.
54. MacKie RM, Aitchison T. Severe sunburn and subsequent risk of primary cutaneous malignant melanoma in Scotland. Br J Cancer 1982: 46, 955–60.
55. Adam SA, Sheaves JK, Wright NH, Mosser G, Harris RW, Vessey MP. A case–control study of the possible association between oral contraceptives and malignant melanoma. Br J Cancer 1981; 44: 45–50.
56. Beral V, Evans S, Shaw H, Milton G. Cutaneous factors related to the risk of malignant melanoma. Br J Dermatol 1983; 109: 165–72.
57. Elwood JM, Gallagher RP, Hill GB, Spinelli JJ, Pearson JCG, Threlfall W. Pigmentation and skin reaction to sun as risk factors for cutaneous melanoma: Western Canada Melanoma Study. Br Med J 1984; 288: 99–102.
58. Holman CDJ, Armstrong BK. Pigmentary traits, ethnic origin, benign nevi, and family history as risk factors for cutaneous malignant melanoma. JNCI 1984; 72: 257–66.
59. Green A, MacLennan R, Siskind V. Common acquired naevi and the risk of malignant melanoma. Int J Cancer 1985; 35: 297–300.
60. Elwood JM, Williamson C, Stapleton PJ. Malignant melanoma in relation to moles, pigmentation, and exposure

to fluorescent and other lighting sources. Br J cancer 1986; 53: 65–74.
61. Sorahan T, Grimley RP. The aetiological significance of sunlight and fluorescent lighting in malignant melanoma: a case–control study. Br J Cancer 1986; 52: 765–9.
62. Cristofolini M, Franceschi S, Tasin L, et al. Risk factors for cutaneous malignant melanoma in a northern Italian population. Int J Cancer 1987; 39: 150–4.
63. Østerlind A, Tucker MA, Hou-Jensen K, Stone BJ, Engholm G, Jensen OM. The Danish case–control study of cutaneous malignant melanoma. I. Importance of host factors. Int J Cancer 1988; 42: 200–6.
64. Clark WH Jr, Reimer RR, Greene M, Ainsworth AM, Mastrangelo MJ. Origin of familial melanoma from heritable melanocytic lesions: 'The B-K mole syndrome'. Arch Dermatol 1978; 114: 732–8.
65. Elder DE, Goldman LI, Goldman SC, Greene MH, Clark WH Jr. Dysplastic nevus syndrome: a phenotypic association of sporadic malignant melanoma. Cancer 1980; 46: 1787–94.
66. Nordlund JJ, Kirkwood J, Forget BM, et al. Demographic study of clinically atypical (dysplastic) nevi in patients with melanoma and comparison subjects. Cancer Res 1985; 45: 1855–61.
67. Swerdlow AJ, English J, Mackie RM, et al. Benign melanocytic naevi as a risk factor for malignant melanoma. Br Med J 1986; 292: 1555–9.
68. Roush GC, McKay L, Forget B, Titus L, Kirkwood J. Dependence of total nevi on dysplastic nevi in determining risk for melanoma. Prev Med 1986; 15: 699–700.
69. Greene MH, Clark WH, Tucker MA, et al. Precursor naevi in cutaneous malignant melanoma. A proposed nomenclature. Lancet 1980; 2: 1024.
70. Kelly JW, Crutcher WA, Sagebiel RW. The clinical diagnosis of dysplastic melanocytic nevi—a clinico-pathologic correlation. J Am Acad Dermatol 1986; 14: 1044–52.
71. Vesselinovitch Sd, Mihailovich N, Richter WR. The induction of malignant melanomas in Syrian white hamster by neonatal exposure to urethan. Cancer Res 1970; 30: 2543–7.
72. Clark WH Jr, Min BH, Kligman LH. The developmental biology of induced malignant melanoma in guinea pigs and a comparison with other neoplastic systems. Cancer Res 1976; 36: 4079–91.
73. Kripke ML. Speculations on the role of ultraviolet radiation in the development of malignant melanoma. JNCI 1979; 63: 541–5.
74. Østerlind A, Tucker MA, Stone BJ, Jensen OM. The Danish case–control study of cutaneous malignant melanoma. II. Importance of UV-light exposure. Int J Cancer 1988; 42: 319–24.
75. Elwood JM, Gallagher RP, Davison J, Hill GB. Sunburn, suntan and the risk of cutaneous malignant melanoma. The Western Canada Melanoma Study. Br J Cancer 1985; 51: 543–9.
76. Green A, Siskind V, Bain C, Alexander J. Sunburn and malignant melanoma. Br J Cancer 1985; 51 393–7.
77. Lew RA, Sober AJ, Cook N, Marvell R, Fitzpatrick TB. Sun exposure habits in patients with cutaneous melanoma: a case–control study. J Dermatol Surg Oncol 1983; 9: 981–6.
78. Armstrong BK, De Klerk NH, Holman CDJ. Etiology of common acquired melanocytic nevi: constitutional variables, sun exposure, and diet. JNCI 1986; 77: 329–35.
79. Holman CDJ, Armstrong BK. Cutaneous malignant melanoma and indicators of total accumulated exposure to the sun: an analysis separating histogenic types. JNCI 1984; 73: 75–82.
80. Elwood JM, Gallagher RP, Hill GB, Pearson JCG. Cutaneous melanoma in relation to intermittent and constant sun exposure—The Western Canada Melanoma Study. Int J Cancer 1985; 35: 427–33.
81. English DR, Rouse IL, Xu Z, et al. Cutaneous malignant melanoma and fluorescent lighting. JNCI 1985; 74: 1191–7.
82. Dubin N, Moseson M, Pasternack BS. Epidemiology of malignant melanoma: pigmentary traits, ultraviolet radiation and the identification of high risk populations. In: Gallagher RP, ed. Epidemiology of malignant melanoma. Heidelberg: Springer-Verlag, 1986; 56–75.
83. Beral V, Evans S, Shaw H, Milton G. Malignant melanoma and exposure to fluorescent lighting at work. Lancet 1982; 2: 290–3.
84. Walker MJ, Beattie CW, Patel MK, Ronan SM, Das Gypta TK. Estrogen receptor in malignant melanoma. J Clin Oncol 1987; 5: 1256–61.
85. Østerlind A, Jensen OM. Trends in incidence of malignant melanoma of the skin in Denmark 1943–1982. In: Gallagher RP, ed. Epidemiology of malignant melanoma. Heidelberg: Springer-Verlag, 1986; 8–17.
86. Snell RS, Bischitz PG. The effect of large doses of estrogen and progesterone on melanin pigmentation. J Invest Dermatol 1960; 35: 73–82.
87. Holly EA, Weiss NS, Liff JM. Cutaneous melanoma in relation to exogenous hormones and reproductive factors. JNCI 1983; 70: 827–31.
88. Beral V, Evans S, Shaw H, Milton G. Oral contraceptive use and malignant melanoma in Australia. Br J Cancer 1984; 50: 681–5.
89. Beral V, Ramcharan S, Faris R. Malignant melanoma and oral contraceptive use among women in California. Br J Cancer 1977; 36: 804–9.
90. Bain C, Hennekens CH, Speizer FE, Rosner B, Willett W, Belanger C. Oral contraceptive use and malignant melanoma. JNCI 1982; 68: 537–9.
91. Helmrich SP, Rosenberg L, Kaufman DW, et al. Lack of elevated risk of malignant melanoma in relation to oral contraceptive use. JNCI 1984; 72: 617–20.
92. Holman CDJ, Armstrong BK, Heenan PJ. Cutaneous malignant melanoma in women: exogenous sex hormones and reproductive factors. Br J Cancer 1984; 50: 673–80.
93. Gallagher RP, Elwood JM, Hill GB, Coldman AJ, Threlfall WJ, Spinelli JJ. Reproductive factors, oral contraceptives and risk of malignant melanoma: Western Canada Melanoma Study. Br J Cancer 1985; 52: 901–7.
94. Green A, Bain C. Hormonal factors and melanoma in women. Med J Aust 1985; 142: 446–8.
95. Østerlind A, Tucker MA, Stone BJ, Jensen OM. The Danish case–control study of cutaneous melanoma. III. Hormonal and reproductive factors in women. Int J Cancer 1988e; 42: 821–4.
96. Kay CR. Malignant melanoma and oral contraceptives. Br J Cancer 1981; 44: 479.
97. Ewertz M, Duffy SW. Risk of breast cancer in relation to reproductive factors in Denmark. Br J Cancer 1988; 58: 99–104.
98. Peto R, Doll R, Buckley JD, Sporn MB. Can dietary beta-carotene materially reduce human cancer rates? Nature 1981; 290: 201–8.
99. Pinckney ER. The potential toxicity of excessive polyunsaturates. Am Heart J 1973; 85: 723–6.
100. Goldrick RB, Goodwin RM, Nestel PJ, Davis NC, Poyser

A, Quinlivan NL. Do polyunsaturated fats predispose to malignant melanoma? Med J Aust 1976; 1: 987–9.
101. MacKie BS, Johnson AR, MacKie LE, Fogerty AC, Ferris M, Baxter RI. Dietary polyunsaturated fats and malignant melanoma. Med J Aust 1980; 1: 159–62.
102. Williams RR. Breast and thyroid cancer and malignant melanoma promoted by alcohol-induced pituitary secretion of prolactin, TSH and MSH. Lancet 1976; 1: 996–9.
103. Williams RR, Horm JW. Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the Third National Cancer Survey. JNCI 1977; 58: 525–47.
104. Paffenbarger RS, Wing AL, Hyde RT. Characteristics of youth predictive of adult-onset malignant lymphomas, melanomas and leukemias. JNCI 1978; 60: 89–92.
105. Holman CDJ. Risk factors in the causation of human malignant melanoma of the skin. (Dissertation) Perth: University of Western Australia, 1983.
106. Holman CDJ, Armstrong BK. Hutchinson's melanotic freckle melanoma associated with non-permanent hair dyes. Br J Cancer 1983; 48: 599–601.
107. O'Rourke DA. Excessive washing and melanoma. Med J Aust 1981; 2, 684.
108. MacKie BS. Excessive washing and melanoma. Med J Aust 1981; 1: 258.
109. Østerlind A, Tucker MA, Stone BJ, Jensen OM. The Danish case–control study of cutaneous melanoma. IV. No association with nutritional factors, alcohol, smoking or hair dyes. Int J Cancer 1988: 42: 825–8.
110. Shaw HM, Milton GW. Smoking and the development of metastases from malignant melanoma. Int J Cancer 1981; 28: 153–6.