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# Trends in Incidence of Cutaneous Malignant Melanoma in a Swedish Population 1976–1994

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The incidence of cutaneous malignant melanoma has been increasing in Sweden for several decades. In the Stockholm–Gotland area educational activities for healthcare professionals were started in the late 1970s and public primary and secondary prevention campaigns were initiated in the mid-1980s. Melanoma incidence trends have been studied in Sweden, with special reference to trends in the Stockholm–Gotland area where these prevention campaigns were first started. During 1976–1994 the average annual increase of age-standardized incidence in the Stockholm–Gotland area was about 5%, the increase being associated mainly with thin tumors and melanoma in situ. During the 1990s, the incidence among males leveled off. In contrast, no such shift in trend was observed among females, or among males or females residing outside the Stockholm–Gotland area. The campaigns may have contributed to a trend towards earlier diagnosis but there is still no clear effect of the primary prevention efforts.

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According to the Swedish Cancer Registry, the incidence of cutaneous malignant melanoma is continuously rising, with an annual increase in age-standardized incidence of about 3% during the past 20 years (1). A similar pattern has been observed in many other western countries (2–4). An increasing awareness in the general population about the potential significance of pigmented skin lesions may have contributed to the increasing incidence (5). However, this upward trend has been accompanied by an increase in mortality, which indicates that there is, in fact, a true increase in the underlying onset rate of the disease. Recently, a stabilization of and even a decline in melanoma mortality have been reported from some countries (3, 6–9).

The increase in incidence mainly concerns patients with thin melanomas, but an increase in the number of patients with thicker lesions has also been reported (2–5, 10). Population-based cancer registries—such as the Swedish Cancer Registry—often lack detailed information as well as histopathologic classification of the tumors (11, 12). When secular trends in tumor characteristics were investigated in samples from the Swedish Cancer Registry, it was found that the results were inconsistent (13, 14).

In the Stockholm–Gotland area (including Stockholm, population 1.9 million and Gotland, population 58000) educational activities concerning the need for early diagnosis of malignant melanoma were started as early as the late 1970s. A regional collaboration was initiated in 1976 between clinicians and pathologists involved in the primary diagnosis of pigmented skin lesions. One of the aims of this collaboration was to improve treatment results by implementing treatment practice guidelines issued by the Swedish Melanoma Study Group concerning primary diagnosis, treatment and follow-up of patients with cutaneous malignant melanoma. Educational campaigns aimed at primary and secondary prevention were started in the mid-1980s. These campaigns included lectures, information booklets and videotapes targeting clinicians, nurses and other health professionals in the primary healthcare system, the school health system and hospital staff in all the major regional hospitals. A pigmented skin lesion clinic was initiated where preventive strategies for high-risk individuals were developed. The campaigns also included public information through television, radio, newspapers and magazines. Free-of-charge screening activities were offered repeatedly in some of the dermatologic and oncologic clinics in the region (15).

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The intervention did not have an experimental design and the program was not coordinated. Many of the activities had a gradual onset. No evaluation of the coverage of the target group or changes in practice was undertaken. Although an exact starting date cannot be defined, the campaigns in Stockholm–Gotland were initiated on average a few years earlier than similar activities in the rest of Sweden. In 1990 the Swedish Cancer Society initiated a nation-wide melanoma prevention campaign including free-of-charge skin examinations (16).

This study is focused mainly on the population of the Stockholm–Gotland area. During the period 1976 through 1994 detailed clinical and histopathologic data were prospectively collected on more than 5000 cases of cutaneous malignant melanoma. These cases constituted about 98% of all new melanoma cases reported to the Swedish Cancer Registry from the area. The purpose was to analyze the incidence trends by selected clinical and histopathologic parameters in order to assess putative effects of the interventional activities mentioned.

## MATERIAL AND METHODS

Since 1958, all patients diagnosed with cancer must be reported to the Swedish Cancer Registry by the acting clinician as well as the pathologist/cytologist involved in the case. The coverage of diagnosed cancer cases in the Registry has been estimated at about 96% (17). Registration and coding is done according to internationally accepted rules (International Classification of Diseases, Injuries and Causes of Death, ICD). The information on each case in the registry includes age, gender, tumor site, histopathologic type and date of diagnosis. Each case is identified by a personal identification number, which is unique to all persons living in Sweden. Multiple primary tumors occurring in one individual are recorded as separate cases in the incidence statistics. Since the middle of the 1970s all primary cancer registration in Sweden has been carried out at the six regional Oncologic Centers which each year supply processed and computerized data to the National Cancer Registry which compiles the national incidence statistics.

Age-standardized total incidence rates of invasive, cutaneous melanoma—with the 1970 Swedish population as reference—for Sweden, excluding the Stockholm–Gotland area, as well as for the Stockholm–Gotland area for the period 1970–1996 were obtained from the National Cancer Registry.

In 1976 the Swedish Melanoma Study Group issued treatment practice guidelines for patients with cutaneous malignant melanoma. As a part of a regional collaboration, all melanoma patients residing in Stockholm–Gotland at the time of diagnosis, were to be recorded in a database kept at the regional tumor registry. Patients with melanoma in situ (preinvasive, non-metastasizing melanoma) were also included. One institution was responsible for the review of all histopathologic slides. The clinical follow-up of all cases took place at two institutions. The database comprised extensive information about the clinical characteristics of each case, the surgical treatment and histopathologic classification of the tumor, as well as follow-up information.

From January 1976 to December 1994 a total of 5377 cases of cutaneous melanoma were reported to the Cancer Registry from the Stockholm–Gotland area. However, in 88 cases (2%), the melanoma diagnosis could not be confirmed because pathology slides were unavailable. These cases were excluded from the melanoma database, which thus included 5289 cases.

An experienced pathologist reviewed all the pathology slides. The tumors were classified according to histopathologic type (18), tumor thickness (19), level of invasion (Clark) (18) and presence or absence of late regression (20). Prospective registration of ulceration (21) was not introduced until 1989. Therefore, a second review was done of slides in cases for which information on ulceration was missing. Clinical staging was based on the three-stage system (22, 23). Patients with localized melanoma were classified as stage I, those with regional metastases as stage II and patients with disseminated disease as stage III. Extensive checks of the database were made by one of the authors (E. M-B) to ensure completeness, internal consistency and validity.

The study was approved by the Ethics Review Committee of the Karolinska Institute, Stockholm, Sweden.

### *Statistical methods*

Age-specific incidence rates were calculated by grouping cases by age at diagnosis into the following five categories: $<25$, 25–39, 40–54, 55–69 and $\pm 70$ years. Annual age-standardized incidence rates were calculated using the direct method of standardization (24), with the 1970 Swedish population as the reference. Average annual rates for the calendar periods 1976–1979, 1980–1984, 1985–1989 and 1990–1994 were estimated. All data on age-specific and age-standardized incidence were expressed as rates per 100 000 person-years.

Secular trends in incidence were summarized using a regression model that relates the logarithm of the yearly standardized (or age-specific) rates to a linear trend term. This log-linear regression model implies a constant annual change.

Since a linear trend term is not sufficient for assessing changes over time, Poisson regression analyses were used to study changes in incidence in more detail and, in particular, to quantify the putative changes in the incidence trends during the 1990s (see Results section). The data were organized into 13 five-year age groups (20–24, 25–29 . . . 80–84) and 4 calendar periods (1976–1979, 1980–1984, 1985–1989, 1990–1994). The effects of period

adjusted for age on the incidence rates were assessed using Poisson regression models (25, 26). The models were estimated by the maximum likelihood methods using the GLIM 4 software package (27). Model goodness-of-fit was assessed by means of the deviance. For models with the deviance close to their degrees of freedom, the fit was considered adequate.

## RESULTS

### *Cancer Registry data*

During the 1990s, the upward trend in incidence of invasive cutaneous melanoma leveled off among males in Stockholm–Gotland (Fig. 1). This observation was confirmed using a Poisson regression analysis. Among females in the Stockholm–Gotland area the upward incidence trend appeared to peak during the early 1990s but this observation was not confirmed in the Poisson regression analyses. The incidence among males and females residing outside of Stockholm–Gotland rose more or less continuously during the entire study period.

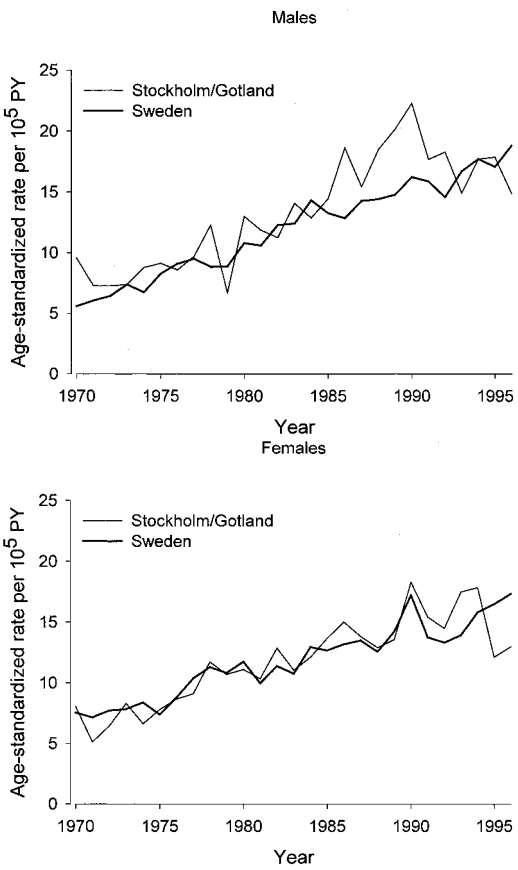


*Fig. 1.* Age-standardized total incidence of invasive, cutaneous melanoma in Sweden during 1970–1996.

### *Melanoma database*

During 1976 through 1994 a total of 5377 cases of cutaneous melanoma, including in situ lesions, were reported to the Cancer Registry from the Stockholm–Gotland area. A review of the histopathologic slides was possible in 5289 cases (98%). The remaining 88 cases (1.6%) were not included in the database since the melanoma diagnosis could not be verified. The mean age of these cases was about 7–8 years higher than that of the others (Table 1). A higher proportion of patients had head-neck melanomas or metastases from an unknown primary melanoma. The registration deficit in the latter group of patients was estimated at about 12%.

### *Incidence trends in Stockholm-Gotland*

An upward incidence trend was observed in both invasive and in situ tumors (Table 2), although the estimated mean annual increase was about twice as large for the in situ tumor cases (9–10%) as that for the invasive tumor cases (4–5%). In contrast to the invasive tumor cases, the upward trend for the in situ cases did not level off during the 1990s (Fig. 2).

An upward trend was observed in all age groups among both males and females (Table 2). In males, the age-specific incidence rates were higher than those in females at ages above 54 years. In contrast, in age groups below 55 years of age, the age-specific incidence rates were higher in females. The leveling of the incidence trend among males during the 1990s concerned ages below 70 years. Among men aged above 70 years the age-specific incidence rates increased during the entire period studied.

The trunk was the predominant tumor site in males, with an almost threefold increase in incidence during 1976–1994 (Table 2). Tumors of the lower extremities showed the highest incidence among females with a more than twofold increase (Fig. 3).

Superficial-spreading melanoma (SSM) showed the highest age-standardized incidence rate among both males and females (Table 2). The observed leveling of the total incidence among males during the 1990s was found to be the result of a trend shift for this particular histogenetic subtype, whereas the incidence for the other types was consistently higher during 1990–1994 than during previous periods. There were relatively few cases of lentigo maligna melanoma (LMM) but there was a statistically significant increase among both males and females.

The median thickness of the tumors decreased from 1.3 mm during 1976–1979 to 0.9 mm during 1990–1994 among males. Among females, the corresponding decrease was from 1.2 mm to 0.7 mm. In males, thin tumors ( $\leq 0.8$ mm) showed the most pronounced increase in incidence during the studied period, although a statistically significant upward trend was estimated for all tumors up to 4.0 mm in thickness (Table 2, Fig. 4). Similarly, there was an

**Table 1**

*Comparison of selected clinical characteristics between cases reported to the Swedish Cancer Registry from the Stockholm–Gotland area from 1976 through 1994, and cases included or not included in the melanoma database during the same period. Estimates of registration deficit in the melanoma database*[a]

| | Total no. in Cancer Registry (%) | Melanoma database | | Registration deficit[a] (%) |
|---|---|---|---|---|
| | | Included (%) | Not included (%) | |
| Mean age (years) | | | | |
| Male | 57.7 | 57.6 | 64.5 | – |
| Female | 54.3 | 54.1 | 62.6 | – |
| Gender | | | | |
| Male | 2 526 (47) | 2 484 (47) | 42 (48) | 1.7 |
| Female | 2 851 (53) | 2 805 (53) | 46 (52) | 1.6 |
| Tumor site | | | | |
| Head-neck | 796 (15) | 772 (15) | 24 (27) | 3.0 |
| Eyelid | 20 | 19 | 1 | 5.0 |
| Ear | 70 | 67 | 3 | 4.3 |
| Face | 564 | 546 | 18 | 3.2 |
| Scalp | 142 | 140 | 2 | 1.4 |
| Trunk | 2 304 (43) | 2 281 (43) | 23 (26) | 1.0 |
| Upper extrem. | 731 (14) | 722 (14) | 9 (10) | 1.2 |
| Lower extrem. | 1 369 (26) | 1 358 (26) | 11 (13) | 0.8 |
| Unspec.[b] | 177 (3) | 156 (3) | 21 (24) | 11.9 |
| Total | 5 377 (100) | 5 289 (100) | 88 (100) | 1.6 |

[a] Defined as the number of cases not included in the database in relation to the total number reported to the Cancer Registry.
[b] Metastasis of unknown primary melanoma (UPM).

increase in thin tumors in females but no statistically significant change was observed in tumors thicker than 2 mm. The leveling total incidence trend for males during the 1990s mostly concerned thin tumors. For tumors $> 4.0$ mm, the incidence among both males and females appeared relatively stable during the period studied.

A statistically significant upward trend was estimated for tumors exhibiting ulceration among males, whereas no significant increase was observed among females (Table 2). In both sexes there were significant, upward trends for tumors exhibiting marked regression.

### *Poisson regression analyses of the Stockholm–Gotland trends*

Regression models were tested for all cases as well as for subsets defined according to invasiveness, tumor site, histogenetic subtype, tumor thickness, and presence/absence of ulceration or regression. The final analysis was restricted to the last three 5-year periods (1980–1994) in order to take goodness-of-fit into consideration. In some of the models including all four time-periods, and especially among men, the model fit could not be considered adequate. When the analysis was restricted to the last three 5-year periods, the model fit was good in practically all subgroup analyses in both sexes and in both age-period models and trend models.

Estimates of the relative risk, based on age-period models, by calendar period (1985–1989, 1990–1994) were calculated with the risk during 1980–1984 set at unity (Table 3). These analyses confirmed a leveling of the total incidence trend among males during the 1990s: the incidence during 1985–1989 as well as that during 1990–1994 was 1.4–1.5 in relation to that during 1980–1984. A continuous upward trend was observed only for some subsets of tumors, such as in situ lesions, upper extremity and lentigo maligna tumors. No leveling of the upward trend for total incidence or the incidence of invasive tumors was observed among females.

## DISCUSSION

In the Stockholm–Gotland area a regional collaboration was initiated in 1976 between clinicians and pathologists involved in the primary diagnosis of pigmented skin lesions. One of the aims of this collaboration was to implement the treatment practice guidelines issued by the Swedish Melanoma Study Group concerning primary diagnosis, treatment and follow-up of patients with cutaneous malignant melanoma. A number of large-scale educational campaigns aimed at primary and secondary prevention of cutaneous malignant melanoma were initiated in the mid-1980s. The rationale for these activities included information from the Swedish Cancer Registry of a rapid increase in the disease as well as reports suggesting that increased public awareness could result in earlier diagnosis and hence a relative increase in cases with thin tumors (28). Moreover, several case-control studies had demonstrated the importance of intermittent sun-exposure with burning in the development of malignant melanoma

**Table 2**

*Cutaneous malignant melanoma in the Stockholm–Gotland region 1976–1994. Total number of new cases and incidence rates by calendar period and gender*

| | Average annual incidence rates per $10^5$ (total number of cases) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Males | | | | Trend[a] | Females | | | | Trend[a] |
| | 1976–1979 | 1980–1984 | 1985–1989 | 1990–1994 | | 1976–1979 | 1980–1984 | 1985–1989 | 1990–1994 | |
| Age-specific rates | | | | | | | | | | |
| <25 years | 1.0 (10) | 0.9 (12) | 1.9 (25) | 1.4 (18) | 2.9 (−2.3; 8.0) | 1.0 (10) | 2.7 (35) | 3.6 (47) | 4.4 (57) | 9.4 (5.1; 13.7) |
| 25–39 years | 7.4 (58) | 6.5 (65) | 9.5 (94) | 10.1 (103) | 2.6 (−0.2; 5.4) | 8.9 (67) | 13.4 (131) | 15.5 (150) | 19.7 (198) | 4.8 (3.0; 6.7) |
| 40–54 years | 14.4 (75) | 16.9 (115) | 24.0 (197) | 23.8 (219) | 3.5 (1.3; 5.8) | 13.1 (69) | 20.5 (138) | 25.3 (201) | 34.0 (309) | 6.0 (4.4; 7.6) |
| 55–69 years | 18.5 (89) | 36.0 (214) | 49.5 (282) | 48.8 (265) | 6.0 (3.7; 8.3) | 21.9 (123) | 23.8 (162) | 31.9 (207) | 34.6 (209) | 3.8 (1.7; 5.8) |
| > 70 years | 23.0 (46) | 42.1 (121) | 61.1 (195) | 79.2 (281) | 8.2 (6.2; 10.3) | 22.1 (79) | 25.6 (129) | 34.8 (194) | 48.3 (290) | 5.4 (3.5; 7.2) |
| Age–standardized rates | | | | | | | | | | |
| Total | 9.7 (278) | 14.7 (527) | 20.9 (793) | 22.3 (886) | 5.4 (3.8; 7.1) | 10.1 (348) | 13.6 (595) | 17.4 (799) | 22.0 (1063) | 5.1 (4.3; 6.0) |
| Head–neck | 1.7 (47) | 2.0 (70) | 2.9 (107) | 3.2 (123) | 4.2 (2.2; 6.2) | 1.6 (57) | 1.5 (79) | 2.6 (130) | 2.9 (159) | 4.6 (2.6; 6.7) |
| Trunk | 5.2 (150) | 8.8 (317) | 12.2 (464) | 13.0 (522) | 5.9 (3.8; 8.1) | 3.1 (103) | 4.1 (174) | 5.3 (234) | 6.8 (317) | 5.7 (4.3; 7.0) |
| Upper extrem. | 0.9 (26) | 1.1 (41) | 2.5 (97) | 3.1 (120) | 8.6 (5.8; 11.4) | 1.4 (48) | 2.0 (89) | 2.9 (143) | 3.2 (158) | 5.3 (2.8; 7.8) |
| Lower extrem. | 1.3 (40) | 2.1 (75) | 2.4 (95) | 2.3 (94) | 3.5 (1.0; 6.0) | 3.8 (129) | 5.6 (240) | 6.1 (273) | 8.7 (412) | 5.1 (3.9; 6.2) |
| Invasive | 8.3 (240) | 11.8 (419) | 17.3 (654) | 17.7 (704) | 5.1 (3.3; 6.8) | 8.8 (303) | 10.6 (467) | 13.8 (633) | 16.4 (802) | 4.2 (3.3; 5.1) |
| In situ | 0.8 (23) | 2.3 (84) | 2.9 (109) | 3.9 (155) | 9.3 (5.5; 13.2) | 1.0 (34) | 2.7 (115) | 3.2 (147) | 5.2 (244) | 10.3 (7.5; 13.0) |
| Unknown primary | 0.6 (15) | 0.7 (24) | 0.8 (30) | 0.7 (27) | 2.1 (−1.1; 5.3) | 0.3 (11) | 0.3 (13) | 0.4 (19) | 0.4 (17) | 0.4 (−3.9; 4.7) |
| SSM[b] | 5.2 (154) | 8.1 (290) | 12.3 (471) | 11.5 (466) | 5.0 (2.7; 7.2) | 6.1 (207) | 8.4 (359) | 10.6 (474) | 11.7 (554) | 4.2 (3.1; 5.4) |
| LMM[c] | 0.2 (5) | 0.1 (4) | 0.3 (10) | 0.8 (30) | 11.5 (6.4; 16.7) | 0.3 (12) | 0.3 (19) | 0.5 (27) | 0.6 (37) | 5.4 (2.4; 8.4) |
| NM | 1.5 (42) | 2.6 (90) | 2.6 (94) | 2.8 (105) | 3.5 (1.1; 5.8) | 1.3 (47) | 0.9 (46) | 1.3 (63) | 1.6 (81) | 1.9 (−0.8; 4.6) |
| UNC/ALM | 1.5 (39) | 1.0 (35) | 2.1 (79) | 2.5 (103) | 7.0 (1.9; 12.1) | 1.1 (38) | 1.0 (43) | 1.4 (69) | 2.5 (129) | 5.9 (2.7; 9.0) |
| ≤0.8 mm | 2.7 (83) | 3.7 (136) | 7.5 (286) | 8.5 (342) | 8.3 (5.8; 10.7) | 3.4 (116) | 4.7 (202) | 7.7 (348) | 9.3 (444) | 7.2 (5.6; 8.9) |
| 0.9–2.0 mm | 2.2 (63) | 3.8 (134) | 4.6 (173) | 4.6 (180) | 4.3 (1.9; 6.7) | 2.7 (90) | 3.2 (140) | 3.7 (169) | 4.5 (210) | 3.2 (1.8; 4.7) |
| 2.1–4.0 mm | 1.7 (47) | 2.4 (86) | 3.2 (123) | 2.7 (106) | 3.5 (0.8; 6.3) | 1.3 (48) | 1.6 (75) | 1.7 (78) | 1.3 (75) | −0.5 (−3.7; 2.6) |
| >4.0 mm | 1.4 (37) | 1.7 (58) | 1.6 (59) | 1.5 (57) | 0.2 (−3.1; 3.5) | 1.2 (44) | 0.8 (41) | 0.6 (31) | 0.9 (53) | −2.0 (−5.5; 1.6) |
| Ulceration: Yes | 2.3 (65) | 3.7 (127) | 4.0 (149) | 3.9 (155) | 2.9 (1.0; 4.8) | 2.2 (78) | 2.2 (100) | 2 (97) | 2.7 (141) | 0.9 (−0.8; 2.7) |
| Regression: Yes | 0.9 (26) | 2.1 (73) | 2.5 (94) | 3.4 (135) | 7.4 (3.9; 10.8) | 0.7 (24) | 1.0 (45) | 1.3 (57) | 1.9 (91) | 7.6 (2.3; 12.9) |

[a] Estimate of annual average percentage change in incidence rates (95% confidence intervals).
[b] SSM = superficial spreading melanoma; LMM = lentigo maligna melanoma; NM = nodular melanoma; ALM = acral lentiginous melanoma; UNC = unclassifiable melanoma.
[c] Estimates of trend based on 2-year moving average.

(29), so public education about sunbathing habits appeared reasonable.

The public campaigns in Stockholm–Gotland and the rest of Sweden were not conducted as controlled experiments, making it difficult in retrospect to assess to what extent their goals were fulfilled. An 18-year observation period is probably too short to observe effects of primary prevention. However, the time-lag between the initiation of the campaigns in the Stockholm area and the rest of Sweden provides an opportunity to distinguish between secondary preventive effects in terms of stage distribution of the campaigns and other secular trends in the population: effects of the campaigns should, theoretically, be first observed in the Stockholm population.

In the current study, we observed a leveling of the upward incidence trend among males in the Stockholm–Gotland area during the 1990s. In contrast to data reported earlier (3, 30, 31), no such shift was observed among females, or in the population residing outside the Stockholm area. In fact, a particularly rapid increase was noted in females under 25 years of age. This observation concurs with recently published data from the Surveillance, Epidemiology, and End Results Program in the United States where an increased birth-cohort risk after 1960 was found among white females (10). The fact that the primary prevention efforts carried out in Sweden to date have not resulted in a consistent decrease in the risk of melanoma may be explained by the hypothesis that it is factors early in life, for instance high levels of UV exposure during childhood and adolescence, that are the main determinants of the risk of melanoma later in life (32). If this hypothesis holds true, effects of primary prevention may well be delayed by several decades.

Secondary prevention through increased knowledge among professionals and the public about melanoma and its precursors, early detection activities among families with dysplastic nevus syndrome and public screening campaigns may have more rapid effects. For instance, the

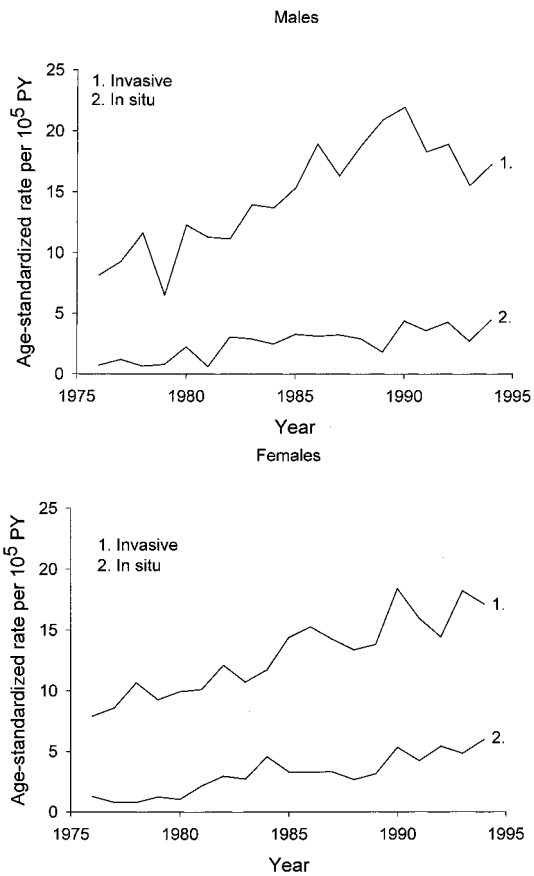


*Fig. 2.* Age-standardized incidence of invasive and in situ cutaneous melanoma for the Stockholm–Gotland area, 1976–1994.

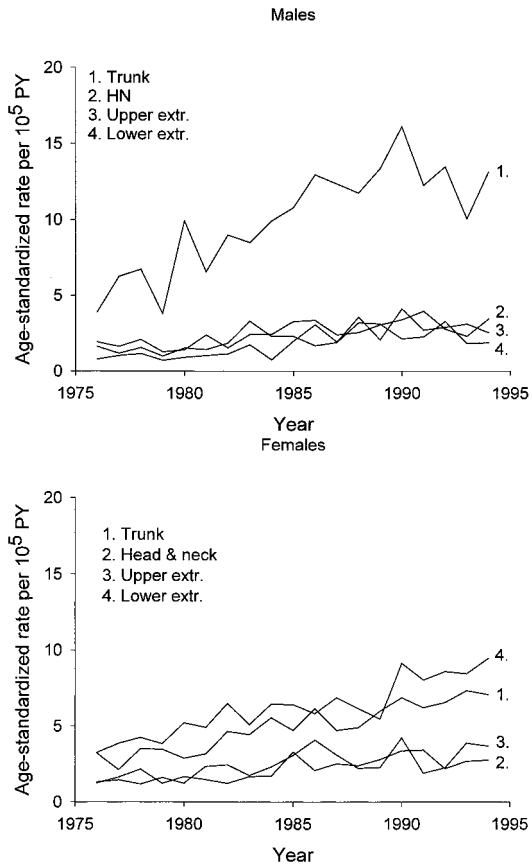


*Fig. 3.* Age-standardized total incidence of cutaneous melanoma for the Stockholm–Gotland area during 1976–1994, by tumor site.

increase in the incidence of melanoma in the Stockholm population mainly concerned thin tumors $\leq$ 0.8 mm and in situ lesions. Moreover, since the mid-1980s there was no increase in tumors >2.0 mm. Similar findings have been reported from other countries with public education campaigns (2, 3).

The temporal trend in incidence among males is interpreted as an increasing trend reaching a plateau. An alternative explanation could be a linear underlying trend with an artefactual peak in the Stockholm–Gotland area, followed by a return to the original slope. The excess peak could be due to over-diagnosis induced by the campaigns.

It was difficult to find models that fitted the observed data during the whole study period. The lack of fit for some of the models could be due to a complex situation. Underlying incidence trends, trends towards earlier diagnosis in the healthcare system and educational campaigns aiming at primary prevention could have different effects in males and females of different ages and during different time-periods.

The more than twofold increase in incidence of cutaneous malignant melanoma during the19-year study period was probably not explained by changes in diagnostic criteria or registration procedures (33, 34). During the entire period, all tumors were reviewed by a few experienced pathologists. Malec et al. found that the melanoma diagnosis was incorrect in about 4% of the melanoma cases reported to the Swedish Cancer Registry (11). Such diagnostic errors probably do not explain the observed time trends since in our material such cases were excluded after review. Registration procedures in the Swedish Cancer Registry have remained the same since the late 1950s. The registration deficit of diagnosed melanoma cases in the Cancer Registry has been estimated at less than 1% (17). In addition, the upward trend in melanoma mortality reported from the Swedish National Cause of Death Registry (35) contradicts an artefactual increase in diagnosed cases.

Concordant with other reports (2, 3, 13, 36) SSM was the predominant tumor type in the Stockholm population, with an average annual increase of about 4–5%. Case-control studies have demonstrated the importance of intermittent sun-exposure with burns especially during childhood for the development of superficial spreading melanoma (SSM) and nodular melanoma (NM) (37, 38). Sun habits in early life also seem to play a role in the development of nevi (39, 40). Melanomas developing from pre-existing

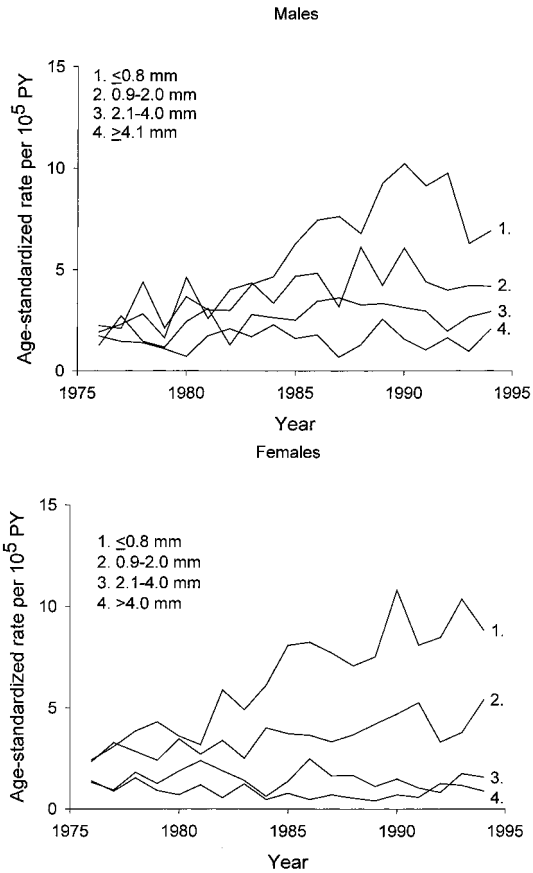


*Fig. 4.* Age-standardized incidence of invasive cutaneous melanoma for the Stockholm–Gotland area during 1976–1994, by tumor thickness.

nevi are typically of the SSM type (41, 42). Consequently, the increase in SSM melanoma may be due to an increasing number of potential precursor lesions.

There have been conflicting observations concerning the incidence trend for nodular melanoma. Some studies have found an increase (3, 13, 36), whereas others have reported a decrease in this type of melanoma (2, 14). In the Stockholm population we observed an upward trend until the mid-1980s among both males and females.

Lentigo maligna melanoma is related to chronic UV exposure (37, 38) and a marked increase in the incidence of lentigo maligna melanoma has been reported from sun-intensive countries (2). The number of cases with lentigo maligna melanoma in our study was small. However, a statistically significant increase in incidence was noted among both males and females.

Temporal trends in the site distribution suggest that the increase in incidence of melanoma may be related to changes in fashion and sun exposure. In accordance with other investigators (3, 12, 36), we found that the predominant tumor site was the lower extremities in females and the trunk in males. Although the total number of cases was small, the most rapid increase was noted for melanomas of the upper extremities among males. A similar increase in tumors of the upper extremities has been described elsewhere (31).

In summary, the educational and screening activities initiated during the late 1970s and 1980s in the Stockholm area may have contributed to a trend towards earlier diagnosis of malignant melanoma since the increase in

**Table 3**

*Cutaneous malignant melanoma in the Stockholm–Gotland region, 1980–1994. Estimates of relative risk and trend using the Poisson regression model*

| | Relative risk (95% confidence interval) | | | | | |
|---|---|---|---|---|---|---|
| | Males | | | Females | | |
| | 1985–1989 | 1990–1994 | Annual change in trend, (%) (95% CI) | 1985–1989 | 1990–1994 | Annual change in trend, (%) (95% CI) |
| Total | 1.4 (1.3; 1.6) | 1.5 (1.3; 1.7) | 3.8 (2.7; 4.9) | 1.3 (1.2; 1.5) | 1.6 (1.5; 1.8) | 5.0 (4.0; 6.1) |
| Head–neck | 1.4 (1.0; 1.9) | 1.4 (1.1; 1.9) | 3.4 (0.4; 6.4) | 1.9 (1.4; 2.6) | 2.1 (1.6; 2.9) | 6.9 (4.0; 9.9) |
| Trunk | 1.4 (1.2; 1.6) | 1.5 (1.3; 1.7) | 3.8 (2.4; 5.3) | 1.3 (1.0; 1.6) | 1.6 (1.3; 1.9) | 4.9 (2.9; 6.8) |
| Upper extrem. | 2.3 (1.6; 3.3) | 2.7 (1.9; 3.9) | 9.0 (5.5; 12.5) | 1.5 (1.2; 2.0) | 1.6 (1.2; 2.1) | 4.6 (2.0; 7.4) |
| Lower extrem. | 1.2 (0.9; 1.6) | 1.1 (0.8; 1.5) | 1.1 (−1.9; 4.2) | 1.1 (0.9; 1.3) | 1.6 (1.3; 1.8) | 4.7 (3.0; 6.5) |
| Invasive | 1.5 (1.3; 1.7) | 1.5 (1.3; 1.7) | 3.5 (2.3; 4.7) | 1.3 (1.2; 1.5) | 1.6 (1.4; 1.8) | 4.5 (3.3; 5.7) |
| In situ | 1.2 (0.9; 1.7) | 1.7 (1.3; 2.2) | 5.6 (2.8; 8.4) | 1.2 (1.0; 1.6) | 2.0 (1.6; 2.5) | 7.3 (4.9; 9.7) |
| SSM | 1.5 (1.3; 1.8) | 1.4 (1.2; 1.7) | 3.3 (1.9; 4.8) | 1.3 (1.1; 1.5) | 1.4 (1.2; 1.6) | 3.4 (2.0; 4.7) |
| LMM[a] | 2.1 (0.7; 6.8) | 4.7 (1.6; 13.7) | 16.9 (6.1; 28.8) | 2.1 (1.0; 4.2) | 2.6 (1.3; 5.3) | 9.2 (2.6; 16.3) |
| NM | 1.0 (0.7; 1.3) | 1.0 (0.8; 1.3) | 0.0 (−2.8; 3.0) | 1.5 (1.0; 2.2) | 1.6 (1.1; 2.4) | 4.6 (0.7; 8.5) |
| UNC/ALM | 2.1 (1.4; 3.2) | 2.6 (1.7; 3.9) | 8.9 (5.0; 12.8) | 1.5 (1.0; 2.2) | 2.6 (1.8; 3.7) | 10.3 (6.5; 14.3) |
| ≤0.8 mm | 2.0 (1.6; 2.5) | 2.2 (1.8; 2.7) | 7.4 (5.4; 9.3) | 1.7 (1.4; 2.0) | 2.0 (1.7; 2.4) | 6.9 (5.2; 8.6) |
| 0.9–2.0 mm | 1.2 (1.0; 1.6) | 1.2 (1.0; 1.6) | 2.0 (−0.3; 4.3) | 1.2 (0.9; 1.5) | 1.4 (1.1; 1.7) | 3.2 (1.0; 5.5) |
| 2.1–4.0 mm | 1.4 (1.0; 1.8) | 1.1 (0.8; 1.4) | 0.5 (−2.3; 3.3) | 1.0 (0.8; 1.4) | 0.9 (0.6; 1.2) | −1.3 (−4.5; 2.1) |
| >4.0 mm[b] | 0.9 (0.6; 1.3) | 0.8 (0.5; 1.1) | −2.7 (−6.3; 1.1) | 0.8 (0.5; 1.3) | 1.0 (0.6; 1.6) | −0.1 (−4.8; 4.9) |
| Ulceration; Yes | 1.1 (0.9; 1.4) | 1.0 (0.8; 1.3) | 0.2 (−2.2; 2.6) | 1.0 (0.7; 1.3) | 1.3 (1.0; 1.7) | 2.6 (−0.2; 5.4) |
| Regression; Yes | 1.2 (0.9; 1.6) | 1.6 (1.2; 2.1) | 4.8 (2.0; 7.7) | 1.2 (0.9; 1.7) | 1.5 (1.1; 2.1) | 4.0 (0.5; 7.5) |

Reference period 1980–1984 (relative risk = 1). The trend variable was assigned the period central values (82, 87 and 92).
[a] Restricted to ages 55–84 years.
[b] Restricted to ages 25–84 years.

incidence during the 1980s and 1990s mainly concerned in situ or thin, invasive tumors. However, there is still no clear effect of the primary prevention efforts, with the possible exception of the male population in Stockholm whose age-standardized incidence appears to have leveled off during the 1990s. Factors early in life, for instance intermittent sunburns during adolescence, are perhaps the main determinants of the risk of melanoma later in life. If this is so, the effects of primary prevention activities may well be delayed by several decades.

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## REFERENCES

1. Cancer incidence in Sweden 1999. Stockholm: The National Board of Health and Welfare. Centre for Epidemiology, 2001.
2. MacLennan R, Green AC, McLeod GR, Martin NG. Increasing incidence of cutaneous melanoma in Queensland, Australia. J Natl Cancer Inst 1992; 84: 1427–32.
3. MacKie RM, Hole D, Hunter JA, et al. Cutaneous malignant melanoma in Scotland: incidence, survival, and mortality, 1979–94. Br Med J 1997; 315: 1117–21.
4. Dennis LK. Analysis of the melanoma epidemic, both apparent and real: data from the 1973 through 1994 surveillance, epidemiology, and end results program registry. Arch Dermatol 1999; 135: 275–80.
5. Burton RC, Coates MS, Hersey P, et al. An analysis of a melanoma epidemic. Int J Cancer 1993; 55: 765–70.
6. La Vecchia C, Lucchini F, Negri E, Levi F. Recent declines in worldwide mortality from cutaneous melanoma in youth and middle age. Int J Cancer 1999; 81: 62–6.
7. Severi G, Giles GG, Robertson C, Boyle P, Autier P. Mortality from cutaneous melanoma: evidence for contrasting trends between populations. Br J Cancer 2000; 82: 1887–91.
8. Giles GG, Armstrong BK, Burton RC, Staples MP, Thursfield VJ. Has mortality from melanoma stopped rising in Australia? Analysis of trends between 1931 and 1994. Br Med J 1996; 312: 1121–5.
9. Cohn-Cedermark G, Mansson-Brahme E, Rutqvist LE, Larsson O, Johansson H, Ringborg U. Trends in mortality from malignant melanoma in Sweden, 1970–1996. Cancer 2000; 89: 348–55.
10. Jemal A, Devesa SS, Hartge P, Tucker MA. Recent trends in cutaneous melanoma incidence among whites in the United States. J Natl Cancer Inst 2001; 93: 678–83.
11. Malec E, Eklund G, Lagerlof B. Re-appraisal of malignant melanoma diagnosis in the Swedish cancer registry. Acta Pathol Microbiol Scand [A] 1977; 85: 707–12.
12. Thorn M, Bergstrom R, Adami HO, Ringborg U. Trends in the incidence of malignant melanoma in Sweden, by anatomic site, 1960–1984. Am J Epidemiol 1990; 132: 1066–77.
13. Thorn M, Ponten F, Bergstrom R, Sparen P, Adami HO. Trends in tumour characteristics and survival of malignant melanoma 1960–84: a population-based study in Sweden. Br J Cancer 1994; 70: 743–8.
14. Masback A, Westerdahl J, Ingvar C, Olsson H, Jonsson N. Cutaneous malignant melanoma in south Sweden 1965, 1975, and 1985. A histopathologic review. Cancer 1994; 73: 1625–30.
15. Ringborg U, Lagerlof B, Broberg M, Mansson-Brahme E, Platz A, Thorn M. Early detection and prevention of cutaneous malignant melanoma: emphasis on Swedish activities. Med Oncol Tumor Pharmacother 1991; 8: 183–7.
16. Ringborg U, Lagerlof B, Beitner H, Molin L, Rorsman H, Swanbeck G. [The Open House campaign for skin examinations resulted in valuable experiences]. Lakartidningen 1992; 89: 1484–5.
17. Mattsson B, Wallgren A. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. Acta Radiol Oncol 1984; 23: 305–13.
18. Clark WH, From L, Bernardino EA, Mihm MC. The histogenesis and biologic behavior of primary human malignant melanomas of the skin. Cancer Res 1969; 29: 705–27.
19. Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. Ann Surg 1970; 172: 902–8.
20. Cochran AJ, Bailly C, Paul E, Remotti F. Melanocytic tumors. A guide to diagnosis. Philadelphia: Lippincott-Raven, 1997: 325–9.
21. McGovern VJ, Cochran AJ, Van der Esch EP, Little JH, MacLennan R. The classification of malignant melanoma, its histological reporting and registration: a revision of the 1972 Sydney classification. Pathology 1986; 18: 12–21.
22. McNeer G, Das Gupta TK. Prognosis in malignant melanoma. Surgery 1964; 56: 512–8.
23. Ringborg U. Cutaneous malignant melanoma.State of the art. MARS. Stockholm: The National Board of Health and Welfare, 2001.
24. Fleiss JL. The standardisation of rates. In: Statistical methods for rates and proportions, 2nd ed. New York: John Wiley and Sons, 1981: 237–55.
25. Clayton D, Schifflers E. Models for temporal variation in cancer rates. I: age-period and age-cohort models. Stat Med 1987; 6: 449–67.
26. Clayton D, Schifflers E. Models for temporal variation in cancer rates. II: age-period-cohort models. Stat Med 1987; 6: 469–81.
27. Francis B, Green M, Payne C. The GLIM system: generalized linear interactive modelling. In: Manual, release, 4th ed. Oxford: Clarendon Press, 1993.
28. MacKie RM. Secondary prevention of cutaneous malignant melanoma. Melanoma Res 1997; 7 (Suppl 2): S151–4.
29. Elwood JM, Jopson J. Melanoma and sun exposure: an overview of published studies. Int J Cancer 1997; 73: 198–203.
30. Bulliard JL, Cox B, Semenciw R. Trends by anatomic site in the incidence of cutaneous malignant melanoma in Canada, 1969–93. Cancer Causes Control 1999; 10: 407–16.
31. Marrett LD, Nguyen HL, Armstrong BK. Trends in the incidence of cutaneous malignant melanoma in New South Wales, 1983–1996. Int J Cancer 2001; 92: 457–62.
32. Whiteman DC, Whiteman CA, Green AC. Childhood sun exposure as a risk factor for melanoma: a systematic review of epidemiologic studies. Cancer Causes Control 2001; 12: 69–82.
33. Philipp R, Hastings A, Briggs J, Sizer J. Are malignant melanoma time trends explained by changes in histopathological criteria for classifying pigmented skin lesions? J Epidemiol Community Health 1988; 42: 14–6.

34. van der Esch EP, Muir CS, Nectoux J, et al. Temporal change in diagnostic criteria as a cause of the increase of malignant melanoma over time is unlikely. Int J Cancer 1991; 47: 483–9.
35. Thorn M, Sparen P, Bergstrom R, Adami HO. Trends in mortality rates from malignant melanoma in Sweden 1953–1987 and forecasts up to 2007. Br J Cancer 1992; 66: 563–7.
36. MacKie R, Hunter JA, Aitchison TC, et al. Cutaneous malignant melanoma, Scotland, 1979–89. Lancet 1992; 339: 971–5.
37. Holman CD, Armstrong BK. Cutaneous malignant melanoma and indicators of total accumulated exposure to the sun: an analysis separating histogenetic types. J Natl Cancer Inst 1984; 73: 75–82.
38. Elwood JM, Gallagher RP, Worth AJ, Wood WS, Pearson JC. Etiological differences between subtypes of cutaneous malignant melanoma: Western Canada Melanoma Study. J Natl Cancer Inst 1987; 78: 37–44.
39. Harrison SL, MacLennan R, Speare R, Wronski I. Sun exposure and melanocytic naevi in young Australian children. Lancet 1994; 344: 1529–32.
40. Autier P, Dore JF, Cattaruzza MS, et al. Sunscreen use, wearing clothes, and number of nevi in 6- to 7-year-old European children. J Natl Cancer Inst 1998; 90: 1873–80.
41. Clark WH, Reimer RR, Greene M, Ainsworth AM, Mastrangelo MJ. Origin of familial malignant melanomas from heritable melanocytic lesions. "The B-K mole syndrome". Arch Dermatol 1978; 114: 732–8.
42. Skender-Kalnenas TM, English DR, Heenan PJ. Benign melanocytic lesions: risk markers or precursors of cutaneous melanoma? J Am Acad Dermatol 1995; 33: 1000–7.