Trends in tumour characteristics and survival of malignant melanoma 1960–84: a population-based study in Sweden

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Summary In Sweden, improvement in survival rates of patients with cutaneous malignant melanoma has counteracted the increase in incidence to produce a moderate rise in mortality. Our aim was to determine the possible impact of drift in diagnostic criteria, earlier diagnosis and changing biological features of the tumours upon survival. We used a random sample of 528 patients diagnosed between 1960 and 1984 in a strictly defined geographical region. No evidence of drift in diagnostic criteria was found. The proportion of patients with invasion level Clark II increased from 3.2% in 1960–64 to 22.5% in 1980–84. The proportion of thin melanomas (< 0.75 mm) increased from 9.4% to 31.5% and the tumour thickness decreased significantly between each 5 year period of diagnosis. These changes are most likely the results of earlier diagnosis. However, changes in tumour characteristics have occurred, since the proportion of superficially spreading malignant melanoma increased from 35% in 1960–64 to 51% in 1980–84 and the proportion of acral lentiginous melanoma decreased from 11% to 2%. The proportion of nodular melanomas remained fairly constant. The proportion of tumours with lymphocytic reaction did not change, whereas those with histological regression increased slightly. Proportional hazards analyses showed a significantly lower survival in patients diagnosed in 1960–64 but no apparent trend after 1965. This finding remained after adjustment for all studied clinical and histopathological factors which point towards changes in unmeasured biological features of the disease.

Many studies have reported increasing incidence rates of malignant melanoma during the last 30–40 years in countries with white populations (Jensen & Bolander, 1980; Lee, 1985; Hakulinen et al., 1986; Österlind et al., 1986). These trends should be real since so far no apparent changes have been revealed in the histopathological criteria for the diagnosis of malignant melanoma (van der Esch et al., 1991) and the mortality rates have also increased (Holman et al., 1980; Venzon & Moolgavkar, 1984; Thörn et al., 1992). However, the prognosis has improved in recent years, even after adjustment for temporal changes in distributions by sex, age and localisation of the primary tumour (Thörn et al., 1989a).

The reasons for the rising survival rates are incompletely understood, especially since no therapeutic improvements have been established. Putative explanations are, firstly, increased public awareness of malignant melanoma, which may entail diagnosis of more tumours early when they are thin and curable. Secondly, and more speculatively, the biology and natural history of the disease might change over time, e.g. because other aetiologic factors lead to a biologically less malignant phenotype. Studies on tumour progression in malignant melanoma suggest that host defence mechanisms play an important role and that the development of the invasive phenotype involves several steps (Clark et al., 1984). Further, the metastatic capability may also differ between histologically invasive malignant melanomas (Clark et al., 1989).

Our aim was to determine to what extent trends in survival are due mainly to drifts in diagnostic criteria, earlier diagnosis or changes in histopathological features such as histogenetic type or indicators of host defence mechanisms. We studied a sample from a population-based cohort of patients diagnosed between 1960 and 1984 with complete follow-up until 1989.

Patients and methods

The cohort

The Swedish Cancer Registry was created in 1958. All clinicians, pathologists and cytologists must report to the Registry any diagnosis of a malignant disease based on examination of surgically removed tissues or cytological specimens, biopsies or autopsies. Nearly 100% of all cancers are diagnosed by one of these procedures, and in 95% of the cases both the clinician and the pathologist or cytologist notified the Registry (Mattson & Wallgren, 1984).

Our study was done in seven counties in central Sweden with approximately 1.8 million inhabitants. The goal was to draw a random sample of 12 patients from each of 50 subgroups defined by gender, five anatomical locations and five 5-year time periods of diagnosis from 1960 through 1984. The anatomical locations were defined as: eyelid and face; external ear and scalp–neck; trunk; upper extremity; lower extremity. The grouping of histology was based on earlier findings with similar prognoses in these site groups (Thörn et al., 1989b). In total there were 2,093 eligible cases of malignant melanoma at the selected localisations. During the first 5 year period there were 192 eligible cases, during the second period 289 cases, during the third period 391 cases, during the fourth period 543 cases and during the fifth period 678 cases. Because the total number of patients in some subgroups was less than 12 during the earlier periods, there were 570 rather than 600 potentially eligible patients in the sample.

In 42 patients it was not possible to retrieve the original slides or paraffin blocks of the tumours. Thus, 528 (92.6%) of the sampled patients were analysed. Five of them had another cancer erroneously coded as cutaneous malignant melanoma. Further, 24 patients (ten men and 14 women) were excluded because they had tumours classified as ‘not melanoma’ in the histopathological review. These lesions consisted of various benign pigmented tumours and also malignant skin lesions other than melanoma. The trend analyses were based on 499 patients (247 men and 252 women). One patient was excluded from the proportional hazards analysis because of erroneously coded date of death. In ten patients (five men and five women) analysed separately the primary tumour was not known to the patient or to the doctor, most likely because of complete regression of the primary tumour. The multivariate analyses were based on 476 patients with complete information. All patients were followed until 31 December 1989, with respect to date and cause of death, by matching to the National Cause of Death Registry (Statistics Sweden, 1961–91).
Clinical data
We abstracted clinical information from the surgeon’s and the pathologist’s separate reports to the Cancer Registry. The following clinical characteristics were recorded: date of diagnosis, stage of diagnosis, sex, age, anatomical localisation of the primary tumour, date of death and cause of death. Until the end of 1970, the stage of disease was routinely recorded in the clinician’s report as the absence or presence of metastases. In most instances, the location of the metastases was also specified. From 1971 until the end of 1984, we classified the stage of the disease according to the clinical data given by the surgeon on the note of admission to the pathology department or on the clinician’s report to the Registry.

Histopathological data
From the pathology departments – listed on the report to the Cancer Registry – the original slides and paraffin blocks were collected along with the pathologist’s original record of the tumour. All histopathological slides were reviewed by the same pathologist (F.P.). If the original slides were of poor quality or missing, new paraffin sections were prepared. When an original diagnosis of malignant melanoma was changed to a benign diagnosis or to another malignant diagnosis as well as melanomas with unusual morphological features, the paraffin blocks were recut and new slides were examined. Moreover, another pathologist examined the specimens in order to get a second opinion. Whenever a consensus between the two pathologists was obtained, the diagnosis was changed accordingly. In a few cases, immunohisto pathological staining was performed to confirm or reject the diagnosis of malignant melanoma. We evaluated the following histopathological characteristics: histogenetic type, level of invasion, tumour thickness, ulceration, vascular invasion, histological regression, lymphocytic reaction, pre-existing naevoid cell type. A detailed description of the histopathological classification has been reported previously (Thörn et al., 1994).

Analysis
Homogeneity tests were used to test for differences in the distributions of variables between periods of diagnosis. In some cases the data actually used in the tests do not exactly agree with those shown in Table II because categories with small numbers were merged or deleted. A P-value of 5% or lower was considered as significant.

To increase the power of the analyses the trendwise development was modelled using logistic regression models for most of the variables. In addition to variables representing period of diagnosis, these models also included the variables sex, age and location. Two basic sets of models were analysed. In a first analysis, period of diagnosis was included as a continuous variable. Results are reported as odds ratios (OR) with 95% confidence intervals (95% CI) per 5 year period of diagnosis. In a second type of model the variable period of diagnosis was represented by separate dummy variables. OR and 95% CI for the last 5 year period of diagnosis compared with the first one are reported. If the effect of time is basically linear in terms of the log of the odds ratios, the power of the first type of analysis is superior. The purpose of the second type of analysis was to reveal possible non-linear effects. For the continuous variable tumour thickness, standard regression models were used with the dependent variable considered in both original and logarithmic form.

In order to quantify the effect of period of diagnosis on survival alone or while simultaneously adjusting for the effects of other variables, the Cox proportional hazards model was used (Lawless, 1982). Deaths from malignant melanoma, coded in the National Cause of Death Registry (Statistics Sweden, 1961–91) as the underlying cause constituted the only end point in this analysis. Thus, patients were censored at the date of death from other causes, otherwise at 31 December 1989. Survival curves were constructed by the Kaplan – Meier method (Kaplan & Meier, 1958).

Results

Diagnostic criteria
The 24 patients (10 men and 14 women) with tumours classified in the re-examination as ‘not melanoma’ were evenly spread over the study period. Cases classified as melanoma in situ, in the re-examination, increased slightly from 2.2% of the sample in 1960–64 to 6.3% in 1980–84; this difference was not statistically significant.

Trends in prognostic factors
In the area of study the total number of patients with a newly diagnosed malignant melanoma on the selected anatomical sites increased from 192 in 1960–64 to 678 in 1980–84. The stage distribution of the patients by period of diagnosis is displayed in Table I. The proportion of patients with clinically localised disease increased from 82.8% in 1960–64 to 98.2% in 1980–84, whereas patients in stage II decreased proportionally from 15.3% before 1970 to 0.9% during the period 1980–84.

In our stratified sample the proportion of patients with superficially spreading melanoma increased from 35.5% to 51.4% [OR 2.16 (95% CI = 1.15–4.04)] during the study period, whereas no apparent changes were seen for those with lentigo maligna melanoma or nodular melanoma. However, since the incidence of malignant melanoma in the studied population increased, the actual number of patients with lentigo maligna and nodular melanoma should also increase. The proportion of patients with acral lentiginous melanoma decreased from 10.7% to 1.8% [OR 0.15 (0.03–0.72)] and the proportion of those with unclassifiable malignant melanoma decreased from 20.4% to 5.4% [OR 0.17 (0.06–0.48)] (Tables II and III).

The proportion of patients with tumours classified as level of invasion II according to Clark was 3.2% in 1960–64 and 22.5% in 1980–84 [OR 9.12 (2.60–32.0)]; the proportion with level III and IV remained fairly constant, whereas those with level V decreased [OR 0.23 (0.07–0.76)] (Tables II and III).

Tumours ≤0.75 mm increased from 9.4% to 31.5%; those of intermediate thickness (0.76–2.49 mm) largely did not change over time, whereas malignant melanoma of 2.50–3.99 mm decreased during more recent periods. Patients with thick melanomas (≥4.00 mm) constituted a fairly constant proportion up to 1980, but decreased during the last period of diagnosis (Table II). When tumour thickness was analysed

Table I The stage distribution at diagnosis of malignant melanoma in a population-based sample of 499 patients in Sweden, 1960–84, by period of diagnosis

| Stage | 1960–64 | 1965–69 | 1970–74 | 1975–79 | 1980–84 | Total |
|-------|---------|---------|---------|---------|---------|-------|
|       | n %     | n %     | n %     | n %     | n %     |       |
| I     | 77      | 82.8    | 81      | 83.5    | 88      | 94.7  |
| II    | 13      | 14.0    | 16      | 16.5    | 5       | 4.2   |
| III   | 3       | 3.2     | 0       | 0       | 1       | 1.1   |
| All stages | 93 | 100.0 | 97 | 100.0 | 94 | 100.0 |

1, localised disease; II, regional metastases (intransit or lymph nodes); III, distant metastases.
## Table II

The distribution of histopathological characteristics of malignant melanoma in a population-based sample of 499 patients diagnosed in Sweden, 1960–84, by period of diagnosis

| Characteristic                      | 1960–64 | 1965–69 | 1970–74 | 1975–79 | 1980–84 | Total |
|-------------------------------------|---------|---------|---------|---------|---------|-------|
|                                    | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| **Histogenetic type**               |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Superficially spreading melanoma    | 33 | 35.5 | 37 | 38.2 | 45 | 47.9 | 59 | 56.7 | 57 | 51.4 | 231 | 46.3 |  |  |
| Lentigo maligna melanoma           | 5  | 5.4 | 6  | 6.2 | 11 | 11.7 | 5  | 4.8 | 10 | 9.0 | 37 | 7.4  |  |  |
| Nodular melanoma                   | 24 | 25.8 | 33 | 34.0 | 24 | 25.5 | 25 | 24.0 | 29 | 26.1 | 135 | 27.1 |  |  |
| Acral lentigious melanoma          | 10 | 10.7 | 7  | 7.2 | 4  | 4.3 | 6  | 5.8 | 2  | 1.8 | 29 | 5.8  |  |  |
| Melanoma in situ                   | 2  | 2.2 | 4  | 4.1 | 4  | 4.3 | 6  | 5.8 | 7  | 6.3 | 23 | 4.6  |  |  |
| Unclassifiable                     | 19 | 20.4 | 10 | 10.3 | 6  | 6.3 | 3  | 2.9 | 6  | 5.4 | 44 | 8.8  |  |  |
| **All types**                       | 93 | 100 | 97 | 100 | 94 | 100.0 | 104 | 100.0 | 111 | 100.0 | 499 | 100.0 |  |  |
| **Level of invasion (Clark)**      |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| I                                  | 2  | 2.2 | 4  | 4.1 | 4  | 4.2 | 6  | 5.8 | 7  | 6.3 | 23 | 4.6  |  |  |
| II                                 | 3  | 3.2 | 14 | 14.4 | 23 | 24.5 | 16 | 15.4 | 25 | 22.5 | 81 | 16.2 |  |  |
| III                                | 25 | 26.9 | 35 | 36.1 | 30 | 31.9 | 39 | 37.5 | 29 | 26.1 | 158 | 31.7 |  |  |
| IV                                 | 41 | 44.1 | 31 | 32.0 | 28 | 29.8 | 34 | 32.7 | 44 | 39.7 | 178 | 35.7 |  |  |
| V                                  | 12 | 12.9 | 8  | 8.2 | 6  | 6.4 | 7  | 6.7 | 4  | 3.6 | 37 | 7.4  |  |  |
| Unclassifiable                     | 10 | 10.7 | 5  | 5.2 | 3  | 3.2 | 2  | 1.9 | 2  | 1.8 | 22 | 4.4  |  |  |
| **All levels**                      | 93 | 100 | 97 | 100 | 94 | 100.0 | 104 | 100.0 | 111 | 100.0 | 499 | 100.0 |  |  |
| **Invasion of vessels**             |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Absent                             | 41 | 46.1 | 40 | 43.0 | 54 | 58.7 | 59 | 56.7 | 74 | 66.7 | 268 | 54.8 |  |  |
| Present                            | 47 | 52.8 | 52 | 55.9 | 36 | 39.1 | 42 | 40.4 | 37 | 33.3 | 214 | 43.2 |  |  |
| Unclassifiable                     | 1  | 1.1 | 1  | 1.1 | 2  | 2.2 | 3  | 2.9 | 0  | 0  | 7  | 1.4  |  |  |
| **All levels**                      | 89 | 100 | 93 | 100 | 92 | 100.0 | 104 | 100.0 | 111 | 100.0 | 489 | 100.0 |  |  |
| **Regression**                     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Absent                             | 75 | 84.3 | 81 | 87.1 | 80 | 87.0 | 86 | 82.7 | 95 | 85.6 | 417 | 85.3 |  |  |
| Suspect                            | 11 | 12.3 | 10 | 10.8 | 8  | 8.7 | 11 | 10.6 | 13 | 11.7 | 53 | 10.8 |  |  |
| Obvious                            | 3  | 3.4 | 2  | 2.1 | 4  | 4.3 | 3  | 2.7 | 6  | 5.4 | 19 | 3.9  |  |  |
| **All levels**                      | 89 | 100 | 93 | 100 | 92 | 100.0 | 104 | 100.0 | 111 | 100.0 | 489 | 100.0 |  |  |
| **Pre-existing naevus**             |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Absent                             | 82 | 92.1 | 78 | 83.9 | 69 | 75.0 | 82 | 78.9 | 92 | 82.9 | 403 | 82.4 |  |  |
| Present (common)                   | 7  | 7.9 | 9  | 9.7 | 12 | 13.0 | 15 | 14.4 | 13 | 11.7 | 56 | 11.5 |  |  |
| Present (dysplastic)               | 0  | 0  | 6  | 6.4 | 11 | 12.0 | 7  | 6.7 | 6  | 5.4 | 30 | 6.1  |  |  |
| **All levels**                      | 89 | 100 | 93 | 100 | 92 | 100.0 | 104 | 100.0 | 111 | 100.0 | 489 | 100.0 |  |  |
| **Epithelioid cells**               |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Absent                             | 69 | 77.5 | 73 | 78.5 | 76 | 82.6 | 82 | 78.8 | 86 | 77.5 | 386 | 78.9 |  |  |
| Present                            | 20 | 22.5 | 20 | 21.5 | 16 | 17.4 | 22 | 21.2 | 25 | 22.5 | 103 | 21.1 |  |  |
| **All levels**                      | 89 | 100 | 93 | 100 | 92 | 100.0 | 104 | 100.0 | 111 | 100.0 | 489 | 100.0 |  |  |
| **Spindle cells**                  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Absent                             | 62 | 69.7 | 70 | 75.3 | 67 | 72.8 | 87 | 83.7 | 83 | 74.8 | 369 | 75.5 |  |  |
| Present                            | 27 | 30.3 | 23 | 24.7 | 25 | 27.2 | 17 | 16.3 | 28 | 25.2 | 120 | 24.4 |  |  |
| **All levels**                      | 89 | 100 | 93 | 100 | 92 | 100.0 | 104 | 100.0 | 111 | 100.0 | 489 | 100.0 |  |  |

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**Notes:**

- The table includes various histopathological characteristics of malignant melanoma, such as histogenetic type, level of invasion, regression, ulceration, vascular invasion, lymphocytic reaction, pre-existing naevus, epithelioid cells, and spindle cells.

- The data are presented for different periods (1960–64, 1965–69, 1970–74, 1975–79, 1980–84) and also for the total sample.

- The table uses statistical measures such as percentage (%), median, and mean values to illustrate the distribution of these characteristics.

- The significance of these measures is indicated by p-values, where values less than 0.05 are considered statistically significant.

- The table concludes with a section on the distribution of spindle cells, which provides additional information on the characteristics of these cells within the sample.
Table III  Regression models of the trendwise development of histopathological characteristics of malignant melanoma in a population-based sample of 499 patients diagnosed in Sweden, 1960–84, by period of diagnosis. For all variables except tumour thickness model 1 shows the odds ratio (OR) and 95% confidence intervals (95% CI) per 5 year period of diagnosis when period of diagnosis is included as a continuous variable. Model 2 shows OR and 95% CI for the last period (1980–84) compared with the first period (1960–64) when period of diagnosis is represented by separate dummy variables. Both models are adjusted for changes in the distribution by sex, age and localisation of the tumour. For the variable tumour thickness beta parameters are shown.

| Histogenetic type                  | Model 1 OR (95% CI) | Model 2 OR (95% CI) |
|-----------------------------------|---------------------|---------------------|
| Superficially spreading melanoma  | 1.30 (1.13–1.49)    | 2.16 (1.15–4.04)    |
| Lentigo maligna melanoma          | 1.09 (0.85–1.14)    | 2.22 (0.65–7.65)    |
| Nodular melanoma                  | 0.94 (0.82–1.08)    | 0.94 (0.49–1.80)    |
| Acal lentiginous melanoma          | 0.70 (0.53–0.92)    | 0.15 (0.03–0.72)    |
| Unclassifiable                    | 0.59 (0.46–0.76)    | 0.17 (0.06–0.48)    |
| Level of invasion (Clark)         |                     |                     |
| II                                | 1.35 (1.13–1.61)    | 9.12 (2.60–32.0)    |
| III                               | 1.01 (0.88–1.16)    | 0.95 (0.50–1.62)    |
| IV                                | 0.97 (0.85–1.11)    | 0.86 (0.48–1.55)    |
| V                                 | 0.73 (0.56–0.94)    | 0.23 (0.07–0.76)    |
| Ulceration                        |                     |                     |
| Present                           | 0.78 (0.68–0.89)    | 0.40 (0.22–0.73)    |
| Vascular invasion                 |                     |                     |
| Present                           | 1.00 (0.84–1.19)    | 0.83 (0.37–1.85)    |
| Regression                        |                     |                     |
| Present                           | 1.14 (0.99–1.31)    | 1.99 (1.06–3.73)    |
| Lymphocytic reaction              |                     |                     |
| Present                           | 0.94 (0.82–1.08)    | 0.71 (0.39–1.31)    |
| Pre-existing naevus               |                     |                     |
| Present                           | 1.17 (0.98–1.40)    | 2.46 (0.96–6.30)    |
| Spindleoid cells                  |                     |                     |
| Present                           | 1.01 (0.86–1.18)    | 1.00 (0.50–1.98)    |
| Spindle cells                     |                     |                     |
| Present                           | 0.91 (0.78–1.07)    | 0.85 (0.44–1.66)    |
| Tumour thickness                  |                     |                     |
| Original β (95% CI)               | -0.29 (-0.49 to -0.09) | -1.32 (-2.18 to -0.46) |
| Logarithmic β (95% CI)            | -0.134 (-0.205 to -0.063) | -0.60 (-0.91 to -0.29) |

as a continuous variable an average decrease of 0.29 (0.09–0.49) mm per 5 year period was obtained. During the last period tumours on average were 1.32 (0.46–2.18) mm thinner than in 1960–64. Analyses with tumour thickness in logarithmic form produced qualitatively similar results (Table III).

The proportion of patients having ulcerated tumours decreased significantly during the study period from 52.8% to 33.3% [OR 0.40 (0.22–0.73)], whereas the proportion of patients whose tumours showed vascular invasion remained seemingly constant. There was a significant non-linear increase in the proportion of tumours with either slight or severe regression [OR 1.99 (1.06–3.73)]. No apparent change was seen for lymphocytic reaction. The presence of naevus adjacent to the malignant melanoma, either common naevus or dysplastic naevus, occurred more often during recent years [OR 2.46 (0.96–6.30)]. No changes in the specific cell type of the tumours were seen over time (Tables II and III).

Trends in survival

A significant improvement in prognosis took place for patients with malignant melanoma diagnosed from 1965 and onwards compared with patients diagnosed in 1960–64 (Figure 1). The overall corrected 5 year survival rate increased from 54% (95% CI = 42–64%) in 1960–64 to 81% (72–87%) in 1980–84. Similarly, 10 year survival increased from 43% (31–54%) to 77% (68–84%). These trends were further quantified in proportional hazards analyses. A univariate model including period of diagnosis only revealed a significant decrease in relative hazard (RH) for patients diagnosed from 1965 onwards compared with those diagnosed in 1960–64. However, no further significant changes in RH were seen for patients with malignant melanoma diagnosed in 1965–69 compared with those diagnosed during more recent periods. The same pattern with an early significant decrease in RH was found also when adjustments were made for temporal changes in the distribution by gender, age and anatomical site, and also when all studied variables were included in the multivariate model (Table IV).
Table IV Proportional hazards analyses of period of diagnosis as determinant of survival in a population-based sample of 498 patients with malignant melanoma diagnosed in Sweden, 1960–84 and followed until 1989. Relative hazards (with 95% confidence intervals) were estimated from the following models: (a) univariate, (b) multivariate model including sex, age and anatomical site of primary tumour; (c) multivariate model including all variables (476 patients).

| Period of diagnosis | Model 1 | Model 2 | Model 3 |
|---------------------|---------|---------|---------|
| 1960–64             | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| 1965–69             | 0.53 (0.34–0.81) | 0.46 (0.29–0.72) | 0.46 (0.28–0.76) |
| 1970–74             | 0.40 (0.25–0.66) | 0.36 (0.22–0.59) | 0.35 (0.20–0.60) |
| 1975–79             | 0.52 (0.34–0.80) | 0.47 (0.31–0.73) | 0.54 (0.34–0.88) |
| 1980–84             | 0.35 (0.21–0.57) | 0.30 (0.18–0.50) | 0.41 (0.24–0.70) |

Cancer Registry. However, in the present study, misclassification by stage is unlikely since we reviewed all the surgical and pathological reports, which in most cases had information on stage at diagnosis, and if data on stage were missing more detailed Swedish records were collected and checked for stage at diagnosis.

In our study superficially spreading melanoma displayed the largest proportional increase. similar to findings in the combined data from Sydney and Alabama (Balch et al., 1992) and in Scotland (MacKie et al., 1992). In Queensland, however, the proportion of superficially spreading melanoma has remained high (Little et al., 1980). An earlier Swedish study (Thörn et al., 1982) showed among men an increase mainly in the incidence of malignant melanoma located on the trunk, whereas among women tumours located on the extremities and trunk increased. In the present study the increasing superficially spreading melanomas were predominantly also located on the trunk in men and on the trunk or extremities in women (data not shown), as noted also in Scotland (MacKie et al., 1992).

Discussion

The present study was based on a random sample of patients from a defined geographical region with 1.8 million inhabitants, whereas most other studies (Drzewiecki et al., 1990; Balch et al., 1992) evaluated trends in prognostic factors among patients referred to certain hospitals. Further, the same pathologist re-examined all the tumours without prior knowledge of the original pathology report, date of diagnosis or outcome. In total, 42 patients were missing in our random sample. Among the missing patients 31.0% died of malignant melanoma compared with 33.3% in the study sample. The length of follow-up was similar in these two groups. Thus, it is unlikely that the missing patients differed from the studied ones with regard to distribution of prognostic factors. The design of our study needs to be acknowledged when trends are interpreted. Sampling was stratified to optimise power when, for example, survival was analysed separately by gender or site (Thörn et al., 1994). As a consequence, sites where a larger proportion of all tumours occurred will be relatively under-represented in relation to the total when all sampled cases are merged together. Hence, trends confined to – or more pronounced at – these sites will be underestimated in overall analyses.

The main purpose of the study was to shed light on the possible causes of the dramatic increase over time in survival rate among patients with malignant melanoma. In a nationwide analysis based on the Swedish Cancer Registry data we noted a decrease in hazard rate of 64% among men and 71% among women during the period of 1960–82 (Thörn et al., 1989a). Although improvement in treatment can be virtually ruled out as an important cause, several other mechanisms could operate.

Our study offered some possibilities to assess the genuine concern that survival trends in malignant melanoma are confounded by ‘trivial non-biological’ factors such as relaxed histopathological criteria, detection of more borderline lesions owing to increased removal of suspect naevi or improved completeness and specificity in cancer registration; the mechanisms by which these factors would affect survival are less clear though. Like previous studies (Philipp et al., 1987; van der Esch et al., 1991) we found no evidence of drift over time in histopathological criteria for invasive malignant melanoma. Inclusion of melanoma in situ will inflate survival rates since this disease entity entails no excess mortality (Thörn et al., 1994). We have limited power to confirm statistically the evidence of a weak increase in cancer in situ. The proportion of such tumours was too small to explain the overall trends in survival.

The proportion of patients with clinically localised disease in our study increased from approximately 83% in 1960–64 to 98% in 1980–84. similar to the increase in overall incidence of melanoma stage I at the Sydney Melanoma Unit (Balch et al., 1992) and in Queensland, Australia (Little et al., 1980). The observed decrease in metastatic disease at diagnosis from 1970 and onwards partly coincides with the change in recording practices regarding stage in the Swedish
lead time bias in those who ultimately died from the disease. Although difficult to quantify, the magnitude of this effect is likely to be small. The large increase in superficially spreading melanoma, the proportional decrease in acral lentiginous melanoma are probably the early improvement in survival unexplained by studied clinical and histopathological factors point towards changes in unmeasured biological features of the disease.

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