Epidemiological Characteristics of Cutaneous Malignant Melanoma of the Head and Neck

A Population-based Study

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Since cutaneous malignant melanoma (CMM) and melanoma in situ (MIS) of the head and neck have only partially been differentiated from CMM of other anatomic sites, these lesions are classified in detail in this study. Data from 756 patients derived from the population-based register of the Stockholm–Gotland area were analyzed and the findings showed that the incidence of CMM was 3.4 times higher in the face compared to the skin outside the head–neck area and that lentigo maligna melanoma was 74 times and nodular melanoma 2.3 times more common in the face. Mean age at diagnosis was significantly higher for patients with CMM of the head and neck irrespective of histogenetic type. Tumor site within the head and neck related to age at diagnosis. CMM of the head and neck differs from CMM of other locations. Epidemiological data are in agreement with the hypothesis that UV radiation (chronic or intermittent) may give rise to melanomas with various phenotypic traits.

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Cutaneous malignant melanoma (CMM) of the head and neck constitutes a unity of melanomas with characteristics that in some respects are biologically unique. However, the literature contains few population-based studies of invasive CMM (1–3) and melanoma in situ (MIS) (4). Because many of the reports on head and neck CMM originate from retrospective hospital- or multiple-institution databases (5–9), we believe that the thinner, less malignant tumors may have been overlooked thus skewing the epidemiological picture. Therefore, a more thorough analysis of CMM of the head and neck seemed warranted.

The established facts are that the age at diagnosis is higher for patients with CMM of the head and neck than for other cutaneous sites (9, 10). The frequency per unit of skin surface is also higher (9, 11) and the distribution of histogenetic types is distinctive (2, 10, 12–16). Furthermore, the location of the primary tumor on the skin surface has prognostic value. That is, the prognosis is more favorable for patients with CMM of the lower extremities than the trunk (17), and those with scalp, neck and ear CMM have a poorer prognoses than patients with CMM of the face (5, 8, 9, 18). The fact that CMM of different areas of the body varies in some phenotypic characteristics is interesting from an etiological point of view. Intermittent sun exposure is considered the most important environmental risk factor for CMM, but most probably chronic sun exposure may also be a risk factor, at least for the development of subgroups of CMM. The head and neck area is subjected to both chronic and intermittent sun exposure. We therefore aim at a detailed description of CMM of this area by analyzing melanoma patients from a population-based database in the Stockholm–Gotland area.

MATERIAL AND METHODS

The patients studied resided in the Stockholm–Gotland area (latitude 57°N–60°N) in Sweden, an area with a mainly urban population. The mean population per year during the 19-year study period was 1 640 000. In 1976, a care program for patients with CMM was initiated with prospective registration of all new cases with CMM and

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MIS in the Stockholm–Gotland region. Clinicians in Sweden are obliged to report every diagnosis of malignant disease to the Swedish National Cancer Registry (SNCR). Furthermore, pathologists must report separately every malignant diagnosis made on histopathologic or cytological specimens. In 95% of new malignancies SNCR receives a report from *both* the clinician and pathologist or cytologist. This leads to an almost complete registration of malignant tumor diseases in Sweden, in 1978 the skin cancer registration deficit was 0.7% (19). In Sweden, MIS has been reported separately to the SNCR since the start of the registry in 1958. The diagnoses for MIS and CMM are coded according to the World Health Organization's international classification of diseases (ICD) (20).

Patients registered between January 1, 1976 and December 31, 1994 were the subjects of our analyses. A total of 5 136 CMM and MIS cases in 4 964 patients was recorded, of which 771 tumors in 756 patients occurred in the head or neck area. Twelve patients had more than one CMM/MIS in the head–neck region in 1976–1994. Of these, one patient had four primary head–neck CMMs. Only the initially occurring tumor, invasive CMM or MIS, was included in the analyses. The anatomic sites were separated into : face; eyelid and corner of the eye; scalp; auricle-external ear canal, and neck.

All histopathological slides were re-evaluated by a pathologist experienced in identifying and classifying melanocytic lesions. Histogenetic types of CMM were classified according to Clark et al. (21): superficial spreading melanoma (SSM), lentigo maligna melanoma (LMM) and nodular melanoma (NM). Patients diagnosed with a MIS were subgrouped as SSM–MIS and lentigo maligna (LM) (22, 23).

When the melanoma density of CMM and MIS in the head and neck area was compared with that on other skin surfaces, estimates were based on the assumption that the head–neck region as a whole accounts for 9% of the total body surface (24) with the face estimated at 3.5% (25, 26). A density ratio was calculated from the face and the total body density.

The data on incidence are annualized and age-adjusted per 100 000 inhabitants for CMM and MIS, respectively.

STATISTICAL METHODS

Clinical characteristics for continuous variables were compared with the t-test (27), and for a comparison of more than two groups simultaneously the one-way analysis of variance was used (27). Associations between categorical variables were examined using χ^2 tests of independence (28). Direct standardization was used to compute the incidence rate. Age-standardized rates were calculated with weights from the Swedish 1970 census as a standard population (29). Data were processed using SPSS/PC statistical software.

RESULTS

We assessed 5 136 tumors (invasive CMM 4 221, 82% and MIS 915, 18%) of 4 964 patients registered in a database during 1976–1994. The overall proportion of tumors in the head and neck area (771), or patients with tumors (756), compared with the total number of tumors/patients was identical–15%. The proportion of invasive CMM in the head–neck/total skin surface was 12%; 22% of the invasive CMMs of the head and neck were of the LMM type. Of the 756 patients with invasive CMM and MIS of the head and neck, 413 (55.5%) were female and 343 (45.5%) male. Among these, 496 (66%) patients had invasive CMM and 260 (34%) MIS. Female patients were overrepresented for both invasive CMM (52%) and MIS (60%).

At the time of diagnosis, 485/496 patients with CMM had a primary tumor only; none had in-transit or distant metastases at that time. Five patients had satellite metastases (defined as cutaneous metastases within 5 cm of the primary tumor), and 5 patients had regional lymph node metastases. One patient had both a satellite and a regional lymph node metastasis at diagnosis.

Mean age at diagnosis for all patients with invasive CMM and MIS of the head and neck was 66 years (range 15–98 years), compared with 54 years in patients with invasive CMM and MIS of the other skin surfaces of the body ($p < 0.001$). Mean age for men with invasive CMM was 63 years and for women 68 years ($p < 0.001$). A numerical reverse, but not statistically significant, age relationship was observed for patients with MIS (men 69 years, women 66 years).

In Table 1 we compared the mean ages for patients with different histogenetic types of CMM of the head and neck area with those for patients with CMM of other skin surfaces. In all instances the age at diagnosis was higher for CMM located in the head and neck area. When MIS patients were compared, the age at diagnoses differed by 16 years.

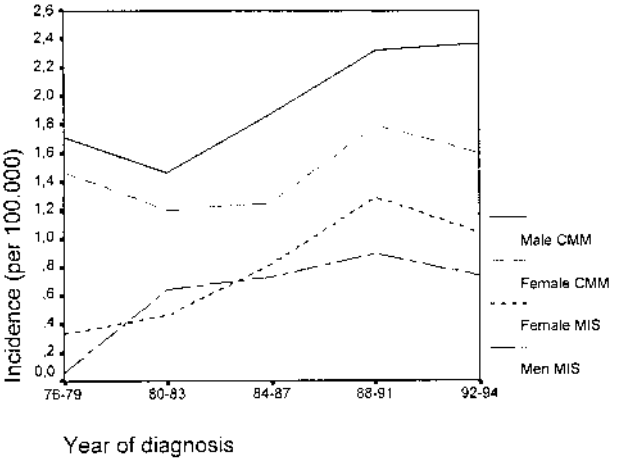

Fig. 1. Age-adjusted incidence for CMM and MIS 1976–1994.

Table 1

Mean age at diagnosis of patients with different histogenetic types of CMM in the head–neck area and other skin areas

	Head–neck area	Total skin except the head–neck area
SSM	59	52
LMM	74	73
NM	68	60
MIS	67	51
All*	66	54

* t-test, $p < 0.001$.

For patients with MIS of the SSM type and invasive SSM, age at diagnosis was the same, 59 years. Patients with LM, on the other hand, were significantly younger than patients with LMM, 70 vs. 76 years ($p = 0.003$).

The distribution of invasive CMM and MIS according to anatomic sites within the head and neck area is presented in Table 2. The face was the predominant site, containing 537/756 (71%) of the tumors. CMM of the face was more frequently observed among female than among male patients (76% vs. 50%). On the other hand, CMM of the auricle-external ear canal, scalp and neck was more frequently observed in male patients (49% vs. 19%). The gender distribution differed significantly ($p < 0.001$) for patients with CMM; 91% of MIS in female patients occur on the face vs. 75% in males ($p < 0.001$). Compared with invasive CMM (64%), MIS produced a higher proportion (85%) of facial tumors in both genders ($p < 0.001$).

The melanoma density of invasive CMM and MIS was then compared for those initiating on the face vs. skin surfaces outside the head–neck area. (Table 3). With the exception of SSM, all other histogenetic types of invasive CMM and MIS predominated in the face. The invasive CMM and MIS groups together were 3.4 times more common in the face compared to skin surfaces outside the head–sneck area. A high ratio was observed for LMM, which was 74 times more common per unit of skin surface in the face. NM was 2.3 times more common in the face.

Table 3

Melanoma density by histogenetic types for facial CMM and MIS compared with on the body skin surface (n = no. of cases)

	Face density a**/n	Body* density a**/n	Density ratio; face/body
Invasive			
SSM	3.5/130	91/2673	1.3
LMM	3.5/93	91/33	74
NM	3.5/41	91/483	2.2
Unclassifiable	3.5/52	91/353	3.8
Total invasive	3.5/316	91/3542	2.3
MIS	3.5/221	91/597	9.6
Total	3.5/537	91/4139	3.4

Total skin surface except the head–neck area.
** Percentage skin area of the whole body surface; face 3.5%, total skin except head/neck 91%.

The distribution of histogenetic types of invasive CMM and MIS between genders is presented in Table 4. For CMM, a χ^2 analysis showed a statistically significant difference among genders ($p < 0.001$) in that 72% of the LMMs were diagnosed in female patients, while 61% of NMs were diagnosed in male patients. Of all cases of MIS, LM was the most abundant (181/260, 70%), whereas 76/260 (29%) were of the SSM type. Although, numerically, more of both MIS types occurred in female patients, χ^2 testing did not find a statistically significant difference between genders ($p = 0.4$).

The age at diagnosis varied considerably among patients with invasive CMM of different anatomical sites within the head and neck area (Table 5). Patients with facial CMM had a mean age of 68 years. Patients with scalp CMM were 10 years younger. When patients with CMM of the face, eyelid and corner of the eye were compared with patients with CMM of the auricle-external ear canal, scalp and neck, a statistically significant difference was recorded, 68 years vs. 60.5 years ($p < 0.001$).

Table 2

Anatomic sites for 496 invasive CMMs and 260 MISs of the head and neck (n = no. of patients)

	Men CMM		Women CMM		Men MIS		Women MIS	
	n	%	n	%	N	%	n	%
1. Face	120	50	196	76	78	75	143	91
2. Eyelid–corner of the eye	3	2	12	5	2	2	1	1
3. Auricle–external ear canal	41	17	13	5	10	10	1	1
4. Neck	60	25	28	11	10	10	8	5
5. Scalp	15	6	8	3	3	3	3	2
Total	239	100	257	100	104	100	156	100

Anatomic sites 1+2 were compared with 3+4+5 by χ^2 test for CMM and MIS, respectively; CMM ($p < 0.001$), MIS ($p < 0.001$).

Table 4

Histogenetic classification of 496 invasive CMMs and 260 MISs of the head and neck related to gender (n = no. of patients)

	Men CMM		Women CMM		Men MIS		Women MIS	
	n	%	n	%	n	%	n	%
SSM	122	51	110	43	30	29	46	29
LMM/LM	30	13	77	30	74	71	107	69
NM	46	19	30	12	–	–	–	–
Unclassifiable	41	17	40	15	–	–	3*	2
Total	239	100	257	100	104	100	156	100

CMM: male and female patients were compared by χ^2 test, $p<0.001$.
MIS: male and female patients were compared by χ^2 test, $p=0.4$ (*not included).

The age-standardized rates for MIS increased among men from 0.19 in 1976 to 1.04 in 1994 and among women from 0.34 to 1.16, respectively. In 1976 the male rate for CMM was 1.98 and in 1994 2.98 while the rate for women showed an increase from 1.1 to 1.62 (see Fig 1).

DISCUSSION

The results from this population-based study of MIS and CMM in Sweden revealed that 12% of the melanoma patients in this database had an invasive CMM in the head and neck area. Previous calculations have varied between 11 and 27% (1, 3, 6, 15, 17, 26, 30–32). Surprisingly, a database in Scotland yielded a 21% proportion of invasive CMM in the country's population (1). Whether the difference between the Scottish and Swedish data reflects true differences in the distribution of CMM on the skin surface or is the result of some registration bias remains to be answered. We found, however, a proportion of LMM within the head and neck of 22%, which is in agreement with a previous study of Swedish melanoma patients (24%) (9) but is a considerably lower figure than that found in the Scottish study (52%) (2). The discrepancies could result from constitutional factors or differing sun exposures.

Reports of the relative proportion of MIS in the head and neck area vary from 2 to 22% (10, 15, 33–36), in contrast to the 32% we found. We consider the data on MIS to be accurate. There has been general agreement that all incidences of MIS should be registered. Furthermore, the same pathologists have diagnosed the tumors during the whole time period. They have also re-evaluated a large proportion of the tumors in the database to ensure that main changes in diagnostic criteria have not occurred. We noted that more females than males had MIS (60%) and invasive CMM (52%), respectively.

Patients tended to be older when diagnosed with CMM in the head and neck area compared with CMM of the total skin surface, and this holds for all histogenetic subtypes. The age difference was greatest for patients with MIS (16 years older) because of the high proportion of LM in the head/neck area. In addition, not only were LMM patients the oldest group but also patients with NM and MIS were older than patients with SSM. Furthermore, the anatomic sites of primary tumors related to age at diagnosis. Thus, patients with scalp and neck CMM were significantly younger ($p=0.05$). It was also shown that patients with MIS of LM type were younger than patients with LMM. The difference indicates that the time required for a LM to progress to an invasive melanoma is probably several years.

Clearly, the density ratio of both invasive CMM and MIS in the face was greater than outside the head/neck area. Overall, the distribution and histogenetic subtypes, as well as age at diagnosis point to important phenotypic characteristics of CMM of the head and neck quite distinct from CMM of other skin sites. Although intermittent sun exposure has been identified as the most important environmental risk factor for CMM (37–42), chronic sun exposure is also an important instigator of LM and LMM (43–45) The fact that NM occurs twice as often on the face as on all other skin surfaces may indicate an association with chronic sun exposure. In fact chronic sun exposure seems to promote all histogenetic subtypes of CMM.

Our data are in accordance with the observation that LMM may be induced mainly by chronic sun exposure. The higher ages for patients with the other histogenetic types of CMM may be explained by a protective role of sun exposure. Evidence for a photoprotection of a natural tan

Table 5

Mean age at diagnoses for 496 patients with invasive CMM of the head and neck by anatomic site (n = no. of patients)

	n	Age
1. Face	316	68
2. Eyelid-corner of the eye	15	66
3. Auricle-external ear canal	54	66
4. Neck	88	58
5. Scalp	23	58
Total	496	66

Age of patients with CMM of anatomic sites 1+2 was compared with age of patients with CMM of anatomic sites 3+4+5 by t-test, $p<0.001$.

has been reported (46–48). If tanning the face were protective, one effect could be that higher accumulated doses of UV radiation would be required to induce facial tumors, thereby delaying the development of CMM in this area. This could also explain the different ages at diagnosis within the head and neck area, with lower ages for patients with CMM of the scalp and neck.

The number of patients was too low to allow a more precise estimation of time trends. As for CMM overall, CMM of the head and neck also increases in incidence over time. The increase is also observed for MIS. Whether there is a leveling-off in CMM incidence after 1990 is a subject for separate analyses of the entire database.

The characteristics of head and neck CMM described here confirm the observations from the Scottish study (1). The high incidence of facial CMM is in accordance with data from numerous reports indicating that sun exposure is the most important environmental risk factor and, probably the cause of most CMMs (37, 40–43). However, how UV radiation causes malignant transformation is not clear. Undoubtedly, the malignant phenotype is dependent on factors such as the total dose and dose rate of UV radiation, both of which may modify its biological effects, and also intermittent versus chronic exposure. Different types of exposure may influence the patterns of mutations in the DNA of melanocytes or nevi cells. Additional constitutional factors may also modify the biological effect of UV radiation: capacity to tan, thickness of the epidermis, DNA repair mechanisms, to mention a few. In a recent study from our laboratory it was shown that CMMs of the head and neck were more likely to contain mutated N-*ras* than melanomas from tissues that had never been exposed to UV-radiation. Moreover, NM to a higher proportion than SSM had N-*ras* activating mutations (49). In order to understand the pathogenesis of CMM, we believe that it is important to identify phenotypic traits of CMM related to different anatomic sites of the tumor. In the next step of the relationships between phenotypic traits, UV-radiation and molecular events will be elucidated.

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