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Detailed site distribution of melanoma and sunlight exposure: aetiological patterns from a Swiss series

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Background: The relation between detailed cutaneous distribution of melanoma and indicators of sun exposure patterns has scantily been explored in moderately sun-sensitive populations.

Patients and methods: The precise site of 1658 primary malignant melanoma, registered from 1995 to 2002, in Switzerland were retrieved and clinically validated. Relative melanoma density (RMD) was computed by the ratio of observed to expected number of melanoma allowing for body site surface areas, and further adjusted for site-specific melanocyte density.

Results: Sites of highest risks were the face, shoulder and upper arm for both sexes, the back for men, and leg for women. Major features of this series were: (i) an unexpectedly high RMD for the face in women (5.6 versus 3.7 in men), (ii) the absence of a male predominance for melanoma on the ears and (iii) for the upper limbs, a steady gradient of increasing melanoma density with increasing proximity to the trunk, regardless of sex. Age and sex patterns of RMD parallelled general indicators of sun exposure and behaviour, except for the hand (RMD = 0.2).

Conclusion: RMD increased with (cumulative) site sun exposure, but a few notable exceptions support the impact of intermittent exposure in melanoma risk.

Key words: aetiology, anatomical site, melanoma, sun exposure, Switzerland

introduction

The anatomical body site of cutaneous melanoma is of importance because (i) it is an independent prognostic factor [1], (ii) site-specific trends may be indicative of some impact of early detection and preventive measures and (iii) mostly, it is one of the best surrogates for assessing the pattern of sun exposure (chronic versus intermittent) [2–5].

The uneven distribution of melanoma on the body, however, cannot be explained by differences in sun exposure alone [6]. Melanocytes, the cells of origin for melanoma and which are unequally distributed on the skin surface [7], might differ in their response to UV insults and susceptibility to malignant transformation according to anatomical region [3]. Emerging evidence indicates that melanoma at different body sites might arise through distinct causal pathways [8–11].

When comparing the propensity of different sites to produce melanoma, availability of precise site information and consideration of the surface area of body sites are paramount. Most epidemiological series that documented the detailed melanoma site focussed on highly sun-sensitive populations [12–14] and relative skin surface areas used for adjustment varied across studies.

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On the basis of one of the largest detailed population-based series on the cutaneous distribution of melanoma, this study explores the relation between melanoma site and indicators of sun exposure patterns. Data pertain to Switzerland, where quality and completeness of ascertainment for skin cancer is high [15–17], and whose population has a complexion and an environmental UV exposure comparable to most western and central European populations, for which details on melanoma site distribution are sparse. A set of standard skin surface proportions for 18 anatomical regions integrating sun exposure patterns and common coding systems is proposed.

patients and methods

This study considered all primary malignant cutaneous melanoma (ICD-O T: 172.0–172.9, ICD-O M: 8720–8780), newly diagnosed from 1995 to 2002 in six Swiss cantons covered by a cancer registry and for which the detailed anatomical site was available (Neuchâtel, calendar years 1998–2001, n = 126; St-Gallen and both Appenzell 1995–2000, n = 529; Vaud 1999–2001, n = 407; Wallis 1998–2002, n = 225; Ticino 1996–2002, n = 429). For all registries but Ticino, the precise body site was obtained and validated as part of the Swiss Melanoma Study (SMS), which has been described fully elsewhere [18]. Briefly, a one-page questionnaire including a standardised body chart with site delineations was mailed to practitioners (mostly dermatologists) who biopsied the tumour. The diagram showed the anterior and posterior body sides, and the head was presented from front and side (left and right) positions to allow an unequivocal marking of the location of the lesion [18, 19].

The SMS provided the detailed anatomical site of 1287 melanoma (90% of the 1428 questionnaires issued), for which demographic, epidemiological and clinical data were obtained by linkage with the cancer registries files. The sites originally specified and marked on the questionnaire seldom differed (about 5% of discrepant codes), and no statistically significant difference was observed between returned and unreturned questionnaires in the distribution of the main variables (body site, age, sex).

Procedure for melanoma ascertainment in Ticino includes a specific questionnaire filled by the dermatologist. Details on the body site are thereby recorded routinely in a comparable manner [20, 21] to that applied in the SMS, with a small fraction of cases with an unspecified body site (5%). The site distribution of melanoma did not differ materially across registries, thus analyses were carried out for all registries combined.

After exclusion of 33 lesions arising in unspecified, multiple or contiguous sites, and 25 melanoma whose site was insufficiently detailed [seven trunk not otherwise specified (NOS), 12 upper limbs NOS, six lower limbs NOS], this study included 1658 melanoma (89% of all incident cases registered in these cantons over the time period considered). By covering urban, rural and alpine regions, German- and Latin-speaking communities, participating Swiss registries (five out of nine centres) satisfactorily included geographical, socioeconomical and lifestyle factors associated with melanoma [18].

Division of the human body took into account (i) sun exposure and clothing patterns, (ii) anatomical regions for which the percent body surface areas (BSAs) were already measured or estimated [22–24] and (iii) current coding practices and coding systems used by cancer registries [21, 25]. Small areas with few cases were grouped for analyses, that is, supraclavicular area with neck, wrist with forearm, elbow and axilla with upper arm, knee with thigh and ankle with leg/calf (see Appendix). This stratification enables the computation of the relative melanoma density (RMD), that is, the ratio of the observed to the expected number of cases by site, assuming an even distribution of melanoma over the whole body [24]) for 18 sites. For a few sites where proportional BSA were inconsistent across studies on the basis of commonly used sources [12–14], final estimates necessitated some minor adjustment (to ensure proportional surface areas for the head, trunk, upper and lower limbs of respectively 0.09, 0.32, 0.19 and 0.4 of the total body).

Anatomical sites were also aggregated for each sex into four categories of sun exposure [12], on the basis of clothing preferences of Swiss people at the relevant time period, as independently estimated by two of us (JLB and FL, see Appendix). RMD were calculated by type of sun exposure and broad age group. Concomitant adjustment for anatomical differences in melanocyte density [7] and surface area was computed by combining both sets of weights (details available from the authors). Chi-square tests were carried out to investigate associations between categorical variables and *t*-tests used to assess differences between sexes in RMD for any given site.

results

Table 1 presents the ratios of the observed to the expected number of malignant melanoma for 18 anatomical sites. The highest density of tumours occurred on the face, with RMD of 3.7 and 5.6 for males and females, respectively. The density of tumours on the cheek and jaw was three-fold in women as compared with men ($P < 0.00001$), whereas RMD for the ears and the nose indicated a nonsignificant female excess ($P = 0.44$). Reversely, melanoma occurrence was commoner among males than females for the

Table 1. Number of cases and RMD in Switzerland according to sex and 18 body sites

Body site	BSA (%)	Melanocyte density[a]	No. of cases		RMD		
			Men	Women	Men	Women	
Ear	0.5	1400	13	19	3.26	4.29	NS[b]
Nose	0.2	1930	5	8	3.14	4.51	NS
Cheek, jaw	1.3	2310	27	79	2.61	6.86	**
Other parts of face	0.9	1940	41	38	5.72	4.77	NS
Face, total[c]	2.9	2012	86	144	3.72	5.60	**
Scalp	3.7	1220	18	4	0.61	0.12	**
Neck	2.4	1165	25	16	1.31	0.75	NS
Chest	10.0	890	81	39	1.02	0.44	**
Abdomen, flank	6.0	800	44	30	0.92	0.56	*
Back	10.0	930	202	102	2.53	1.15	**
Buttocks	5.0	1260	23	20	0.58	0.45	NS
Perineum, groin, peri/anal areas	1.0	2380	3	4	0.38	0.45	NS
Shoulder	3.0	1210	84	59	3.51	2.22	**
Upper arm	5.0	1210	60	75	1.51	1.69	NS
Forearm, wrist	6.0	1100	36	49	0.75	0.92	NS
Hand (including fingers)	5.0		6	9	0.15	0.20	
Hip, thigh	19.0	1000	57	106	0.38	0.63	**
Leg, calf, ankle	14.0	1510	40	178	0.36	1.44	**
Foot (including toes)	7.0		23	35	0.41	0.56	NS

[a]Expressed in average numbers of melanocyte per square millimetre [7]. Values for ‘other parts of face’, ‘face, total’ and ‘neck’ were obtained by averaging relevant body site estimates. For anatomical sites which included regions with different sun exposure levels, such as the hand and foot (see Appendix), melanocyte density was separately considered for each region. For instance, melanocyte density values used for the foot were 610 (dorsum and heel), 1440 (sole) and 1290 (toes).
[b]*P*-value for the statistical comparison of RMD between men and women at this specific site (see patients and methods).
[c]Ear, nose, cheek, jaw and other or unspecified parts of face combined.
*$P < 0.05$; **$P < 0.01$.
RMD, relative melanoma density; BSA, body surface area, in relative terms; NS, not significant.

scalp and neck areas, as well as the shoulder and most subregions of the trunk. The back was the truncal site with the highest density of melanoma (RMD of 2.5 for men and 1.2 for women). The RMD was remarkably constant for other parts of the trunk for females; this was not so for males. Melanoma density on the upper limb increased in both genders with increasing proximity to the trunk: between the shoulder and the hand, the RMD varied 23-fold for men and 11-fold for women. Apart from the leg in women (RMD = 1.4), the RMD was below unity for anatomical areas of the lower limbs. Males had systematically a lower density of melanoma than females for the lower limbs.

While about 70% of melanoma occurred on intermittently exposed sites (Table 2), lesions were more often associated with a site of low intermittency of sun exposure in men (62.3% in males and 23.9% in females, $P < 0.001$) and of high intermittency in women (8.2% versus 45.6%, $P < 0.001$). Lesions on usually covered sites were more frequent in males than females (17.8% versus 13.1%, $P = 0.008$). For women, the greater the site exposure the denser the occurrence of melanoma. Density of melanoma by category of site exposure was less contrasted for men, with nevertheless a three-fold difference between least and most exposed body sites.

Table 2 also indicates that overall site variations in RMD were only slightly reduced when differences in melanocyte density per unit of skin surface were accounted for. The greatest change occurred for maximally sun-exposed areas with a 50% decrease in RMD for each sex. The global pattern of increasing density of tumours with increasing (estimated) sun exposure, however, persisted after this adjustment.

Since the age distribution of melanoma cases varies across body sites, RMD were computed separately for three age brackets (0–49, 50–64, 65+) by sex, site and estimated sun exposure (Table 3). Under age 50, a raised density of melanoma was observed on the back and the shoulder, and, for women only, on the upper arm. At older ages, density above the unity persisted for these sites in both genders, but the salient feature was the high RMD for the face (5.9 and 11.1 for men and women aged 65 or over). The known predominance of melanoma on the lower limbs in females was most apparent in the 50- to 64-age group (RMD = 2.1). The increase in tumour density with increasing sun exposure became apparent after age 65 for men and from age 50 for women. Sites associated with low and high intermittency of sun exposure showed different patterns of RMD with age, both within and between sexes.

Table 2. RMD, with and without correction for density of melanocytes, by sex and estimated gender-specific sun exposure in Switzerland

Estimated sun exposure[a]	No. of cases		RMD		Adjusted RMD[b]	
	Men	Women	Men	Women	Men	Women
Minimum	140	114	0.50	0.43	0.53	0.46
Low, intermittent	491	208	1.27	0.82	1.28	0.97
High, intermittent	65	397	0.98	1.35	1.01	1.23
Maximum	92	151	1.77	2.63	1.21	1.79

[a]See Appendix for details of site exposure classification.
RMD, relative melanoma density.
[b]Corrected for melanocyte density.

Table 3. Relative melanoma density according to sex, body site and estimated sun exposure

	Men			Women		
	<50 years	50–64 years	65+ years	<50 years	50–64 years	65+ years
Body site[a]						
Face	1.55	2.78	5.92	1.17	4.09	11.14
Scalp and neck	0.59	0.73	1.21	0.35	0.28	0.45
Chest	1.21	1.50	0.86	0.68	0.38	0.25
Abdomen	1.35	1.01	0.56	0.92	0.64	0.15
Back	2.65	2.22	2.70	1.63	0.97	0.80
Buttocks	0.54	0.89	0.37	0.98	0.17	0.12
Shoulder	4.33	3.49	2.97	2.97	2.40	1.33
Upper arm	0.90	2.26	1.35	1.66	1.44	1.91
Forearm	0.45	0.81	0.92	0.92	0.71	1.08
Thigh	0.52	0.36	0.29	0.94	0.71	0.26
Leg	0.54	0.37	0.22	1.10	2.12	1.27
Foot	0.38	0.35	0.48	0.35	0.30	0.97
Estimated sun exposure						
Minimum	0.63	0.54	0.37	0.64	0.33	0.29
Low, intermittent	1.36	1.31	1.17	1.19	0.83	0.45
High, intermittent	0.59	0.83	1.36	1.24	1.56	1.30
Maximum	0.82	1.37	2.71	0.57	1.98	5.16

[a]Sites with <20 melanomas are not presented and head sites were aggregated into face and scalp/neck.

discussion

Results from this large, multicentric study corroborated a dual association of melanoma with sun exposure. Overall, density of melanoma increased with increasing (cumulative) site exposure. A few notable exceptions were the hands and cases below age 50. At younger age, RMD was highest on the intermittently sun-exposed back and shoulder. This supports the apparently greater impact of intermittent exposure in producing melanoma.

From an aetiological point of view, the site distribution generally fitted with the likely sun exposure, particularly in regard to sex differences which matched differences in general clothing patterns and hair cover. Thus, sites of highest risks were the face, the shoulder and the upper arm for both sexes, the back for men and the leg for women. In contrast, the risk of melanoma was lowest for the buttocks, the foot and the perianal, hip and thigh areas for both sexes, as well as for scalp and neck, and the torso for females. The low RMD for the hand (0.2 for each sex), at variance with the high UV exposure of the back of the hand, confirmed observations from other Caucasian populations [12, 26]. Melanomas of the hand comprised a particularly heterogeneous group (two palmar, five dorsum and eight fingers' lesions) of varied morphological types which could be related to different aetiological pathways [27].

Being a relative (rather than absolute) measure, the RMD allows direct comparisons between populations with different melanoma incidence rates. In this respect, our series showed some peculiarities: the density of facial melanoma was unprecedentedly high in women (RMD = 5.6), significantly exceeded that for men (RMD = 3.7) and no male predominance was observed for the ears (RMD of 3.3 and 4.3, respectively). Other Caucasian populations have shown a three to six-fold male to female ratio in density of melanoma on the ears and often a higher RMD for the face in men than women [12–14, 28, 29]. This unexpected finding, given the more frequent use of facial cosmetic and sunscreens by women, did not appear to be explained by substantial differences in histopathological diagnosis or classification of lentigo malignant melanoma (complementary analyses; data not shown). Swiss tend to be sun exposed nearly all year round at altitudes of high UV irradiance. The popularity of mountaineering, hiking and skiing has been postulated to explain the comparatively high density of melanoma of the head in Switzerland and neighbouring Austrian Tyrol [30].

The distribution of lesions on the upper limbs is of particular interest because (i) everyday clothing habits translate into an increasing (cumulative) sun exposure with increasing distance from the trunk and (ii) the exposure shifts from high intensity and intermittency (shoulder) to chronicity (hand). The gradually increasing density from the hand to the shoulder (apart from women aged over 65) may underscore the greater vulnerability to intense exposure of target cells on intermittently exposed sites which are not shielded by permanent or all year round UV-induced facultative pigmentation. To our knowledge, such a steady gradient has not been observed before, but few large series distinguished these four limb sections [31, 32]. Several factors may explain why some of our results differ from earlier studies. The specific role of recent, differential incidence trends by body site [33–36] or of some specificities inherent to the Swiss population (high socioeconomical status and fraction of indoor office workers, type and setting of outdoor pursuits) cannot, however, be quantified with this dataset.

Elwood and Gallagher [12] suggested to consider melanocyte density and other skin features relevant to melanoma development (nevi, amount of pigmentation) in future investigations of the site distribution. The deviation from a uniform body distribution was moderately reduced after accounting for site-specific melanocyte density (Table 2). If the number of melanocytes was essentially determined by the amount of UV exposure, our correction would over-adjust the RMD calculated by category of sun exposure. The convergence of RMD towards one, especially for chronically exposed sites, could support such an effect. The large differences in RMD which subsisted after controlling for melanocyte density, however, indicate that the probability of epidermal melanocytes to become cancerous varies with the type (or site) of exposure [3]. Hence, these descriptive data lend support to a site-specific aetiology for melanoma, one related to chronic exposure and the other to melanocyte instability [8].

The advent of detailed body site coding systems, compatible with the standard four-site classification (head, trunk, upper and lower limbs) [20, 25] and recommended by the European Network of Cancer Registries, should encourage and facilitate the systematic recording of this information with affordable effort by many cancer registries, especially when site information could be obtained on pictorial support [19]. Historical codes, grouping for instance hand and shoulder under upper limb [25], were not designed to allow inference on intensity and intermittency of body site exposure. For example, the age and sex pattern of RMD for the shoulder mirrored that of the back (trunk) rather than that of other upper limb sites, an observation consistent with sunlight exposure of the shoulder.

Constitution and completeness of this series renders selection bias unlikely (melanoma registration is 94%–99% complete in Switzerland; F. Montanaro, Ticino Cancer Registry). Reliability and precision of the site specification in this series, where validation was directly provided by the practitioner who excised the lesion, have been documented [19]. Along with the remarkable consistency in RMD between contiguous sites of apparently similar exposures (chest and abdomen, buttocks and perianal area), we are confident that these results reflect the characteristics of melanoma diagnosed in this moderately sun-sensitive Swiss population.

This study has several limitations. Patterns and duration of sun exposure were inferred from anatomical site and age, respectively. Site grouping by estimated level of sun exposure was arbitrary and could only reflect general patterns of dress. Supine and prone limb sections were not distinguished even though the dorsal part is generally more sun exposed—and afford a more direct, visual inspection—than the ventral part (e.g. the forearm). In absence of sounder data, the adjustment for melanocytic density relied on rather old measures, obtained for some sites from few donors [7].

Our relative BSA estimates for 18 sites integrated as much as possible relevant measures in the most consistent and unified manner. For sites where these estimates could be compared with relative BSA derived from three-dimensional scans of human bodies [37], the concordance was good. Given the heterogeneous estimates of relative BSA applied across epidemiological studies, sometimes derived from the same source of measures, standard values on the basis of anthropometric measurements of a sizable sample of subjects are required. This would provide a sounder basis to interpret differences for small area body sites, such as the ears, for which estimates of the RMD are most sensitive to variation in relative BSA. In the meantime, use of values provided in Table 1 should enhance inter-studies comparisons.

appendix

Likely sun exposure and distribution of 1658 malignant cutaneous melanomas according to sex and detailed body site, Switzerland

Anatomical site	Exposure level[a]	No. of cases	
		Men	Women
Lip	4	2	0
Eyelid	4	4	9
Ear, external auditory canal	4	13	19
Nose	4	5	8
Cheek, jaw	4	27	79
Forehead, eyebrows	4	14	9
Temple	4	16	10
Chin	4	0	5
Face, total[b]	4	86	144
Scalp	2M/1F	18	4
Neck, front	3	9	9
Neck, back	3	16	7
Chest	2M/1F	81	39
Abdomen, flank	1	44	30
Back	2	202	102
Buttocks	1	23	20
Perineum, groin, peri/anal areas	1	3	4
Shoulder	2M/3F	84	59
Axilla, armpit	1	7	1
Upper arm	2M/3F	49	69
Elbow, antecubital space	3	4	5
Forearm, wrist	3	36	49
Back of hand	4	1	4
Palm of hand	1	0	2
Fingers	4	5	3
Hip, thigh	1M/2F	50	87
Knee, popliteal space	1M/2F	7	19
Leg, calf, ankle	2M/3F	40	178
Dorsum of foot, heel	2M/3F	15	11
Sole of foot	1	6	14
Toes	2M/3F	2	10
Total		788	870

[a](1) minimal lifetime exposure, (2) low lifetime, mainly intermittent exposure, (3) high lifetime, mainly intermittent exposure, (4) maximal lifetime (both chronic and intermittent) exposure.

[b]The total includes 10 facial lesions, not otherwise specified.

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