Cutaneous distribution of melanoma and sun exposure in Switzerland: aetiological considerations

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Abstract

The relation between detailed cutaneous distribution of melanoma and indicators of sun exposure patterns has scantily been explored in moderately sun-sensitive populations. The precise site of 1,658 primary malignant melanomas, registered between 1995 and 2002 in Switzerland, were retrieved and clinically validated. Relative melanoma density (RMD) was computed by the ratio of observed to expected number of melanomas allowing for body site surface areas, and further adjusted for site-specific melanocyte density. 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: (1) an unexpectedly high RMD for the face in women (5.6 versus 3.7 in men), (2) the absence of a male predominance for melanomas on the ears, and (3) 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 paralleled general indicators of sun exposure and behaviour, except for the hand (RMD=0.2). RMD increased with (cumulative) site sun exposure, but a few notable exceptions support the impact of intermittent exposure in melanoma risk.

Introduction

The anatomical body site of cutaneous melanoma is of importance because (1) it is an independent prognostic factor [1], (2) site-specific trends may be indicative of some impact of early detection and preventive measures, and (3) mostly, it is one of the best surrogates for assessing the pattern of sun exposure (chronic versus intermittent) and generating aetiological hypotheses [2, 3].

However, the uneven distribution of melanoma on the body cannot be explained by differences in sun exposure alone [4]. Melanocytes, the cells of origin for melanoma and which are unequally distributed on the skin surface [5], might differ in their response to UV insults and susceptibility to malignant transformation according to anatomical region. Emerging evidence suggests that melanomas at different body sites might arise through distinct causal pathways [6-8].

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 [9-11] and relative skin surface areas used for adjustment varied across studies.

Based on 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 [12-14], 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. More extensive analysis and discussion of results from this dataset have been published elsewhere [15].

Material and Methods

This study considered all primary malignant cutaneous melanomas, newly diagnosed between 1995 and 2002 in 6 Swiss cantons covered by a cancer registry (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 [16]. 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 [16, 17].

The SMS provided the detailed anatomical site of 1,287 melanomas (90% of the 1,428 questionnaires issued), for which démographic, epidemiological and clinical data were obtained by linkage with the cancer registries files. No statistically significant difference was observed between returned and unreturned questionnaires in the distribution of the main variables (body site, age, sex). In Ticino, details on the body site are routinely recorded in a comparable manner to that applied in the SMS [15]. The site distribution of melanoma did not differ materially across registries, thus analyses were performed for all registries combined.

After exclusion of 33 lesions arising in unspecified, multiple or contiguous sites, and 25 melanomas whose site was insufficiently detailed (7 trunk NOS, 12 upper limbs NOS, 6 lower limbs NOS), this study included 1,658 melanomas (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 (5 out of 9 centres) satisfactorily included geographical, socio-economical and lifestyle factors associated with melanoma [16].

Division of the human body took into account (1) sun exposure and clothing patterns, (2) anatomical regions for which the percent body surface areas were already measured or estimated and, (3) current coding practices and coding systems used by cancer registries. 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. 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 [18]) for 18 sites.

Anatomical sites were also aggregated for each sex into 4 categories of sun exposure [9], based on clothing preferences of Swiss people at the relevant time period. RMD were calculated by type of sun exposure and broad age group. Concomitant adjustment for anatomical differences in melanocyte density [5] and surface area was computed by combining both sets of weights (details available from the authors). Chi-square tests were performed 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 melanomas 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 3-fold in women as compared to 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 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 melanomas (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 for 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.

Tab. 1. *Number of cases and relative melanoma density (RMD) in Switzerland according to sex and 18 body sites*

Body site	No. cases		RMD		
	Men	Women	Men	Women	
Ear	13	19	3.26	4.29	ns[1]
Nose	5	8	3.14	4.51	ns
Cheek, jaw	27	79	2.61	6.86	**
Other parts of face	41	38	5.72	4.77	ns
Face, total[2]	86	144	3.72	5.60	**
Scalp	18	4	0.61	0.12	**
Neck	25	16	1.31	0.75	ns
Chest	81	39	1.02	0.44	**
Abdomen, flank	44	30	0.92	0.56	*
Back	202	102	2.53	1.15	**
Buttocks	23	20	0.58	0.45	ns
Perineum, groin, peri/anal areas	3	4	0.38	0.45	ns
Shoulder	84	59	3.51	2.22	**
Upper arm	60	75	1.51	1.69	ns
Forearm, wrist	36	49	0.75	0.92	ns
Hand (incl. fingers)	6	9	0.15	0.20	ns
Hip, thigh	57	106	0.38	0.63	**
Leg, calf, ankle	40	178	0.36	1.44	**
Foot (incl. toes)	23	35	0.41	0.56	ns

[1] P-value for the statistical comparison of RMD between men and women at this specific site; * $p<0.05$ ** $p<0.01$; ns: not significant.

[2] Ear, nose, cheek, jaw, and other or unspecified parts of face combined.
RMD, relative melanoma density

While about 70% of melanomas 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% vs 45.6%, $p<0.001$). Lesions on usually covered sites were more frequent in males than females (17.8% vs 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 3-fold difference between least and most exposed body sites.

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 50-64 age group (RMD=2.1).

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

Tab. 2. *Relative melanoma density (RMD), with and without correction for density of melanocytes, by sex and estimated gender-specific sun exposure in Switzerland*

Estimated sun exposure[1]	No. cases		RMD		RMD (corrected for melanocyte density)	
	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

[1] See Bulliard et al. [15] for details of site exposure classification.

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. However, the global pattern of increasing density of tumours with increasing (estimated) sun exposure persisted after this adjustment.
Since the age distribution of melanoma cases varies across body sites, RMD were computed separately for 3 age brackets (0-49, 50-64, 65+) by sex, site and estimated sun exposure (data not shown; [15]). 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

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 [9, 19]. Melanomas of the hand comprised a particularly heterogenous group (2 palmar, 5 dorsum and 8 fingers' lesions) of varied morphological types which could be related to different aetiological pathways [20].

Being a relative 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 melanomas 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 3 to 6-fold male to female ratio in density of melanoma on the ears and often a higher RMD for the face in men than women [9-11, 21]. 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 [22].

The distribution of lesions on the upper limbs is of particular interest because (1) everyday clothing habits translate into an increasing (cumulative) sun exposure with increasing distance from the trunk, and (2) the exposure shifts from high intensity and intermittency (shoulder) to chronicity (hand). The gradually increasing density from the hand to the shoulder (apart for 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. Several factors may explain why some of our results differ from earlier studies. The specific role of recent, differential incidence trends by body site [23, 24] or of some specificities inherent to the Swiss population (high socio-economical status and fraction of indoor office workers, type and setting of outdoor pursuits) cannot, however, be quantified with this dataset.

Elwood and Gallagher [9] 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 an 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. Results could support such an effect (RMD converged towards one, especially for chronically exposed sites). However, the large differences in RMD which subsisted after controlling for melanocyte density indicate that the probability of epidermal melanocytes to become cancerous varies with the type (or site) of exposure. Hence, these descriptive data lend support to a site-specific aetiology for melanoma, one related to chronic exposure and the other to melanocyte instability.

In conclusion, the advent of detailed body site coding systems, compatible with the standard 4-site classification (head, trunk, upper and lower limbs) 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 [17]. In fact, historical codes, grouping for instance hand and shoulder under upper limb, 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.

Acknowledgements

This study was supported by a research grant from the Swiss Cancer League (KFS-00925-09-1999) and performed during the tenure (by JLB) of a Fellowship from the Swiss National Science Foundation (Nr. 32-63130.00). Practitioners are gratefully acknowledged for taking the time to complete the questionnaires. We are indebted to the staff of the cancer registries of Neuchâtel, St-Gall/Appenzell, Vaud, Wallis and Ticino for their valuable collaboration.

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