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REVIEW ARTICLE

Spatial density of primary malignant melanoma in sun-shielded body sites: A potential guide to melanoma genesis

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Abstract

UV radiation is a major factor in melanoma genesis, but non-UV linked factors are also operational, since primary malignant melanomas can emerge in body sites that never see the sun. The scarcity of melanomas in sun-shielded body sites reflects only the *absolute* number of melanomas, not the number of tumours per square unit of the surface in which they emerge. Studies on melanoma density conducted by us and others are here briefly reviewed. The access to reliable numbers along with measurable anatomical areas directed our choice of melanomas at the sun-shielded locations described here. *Melanomas at the body surface*. Calculations of surface areas bearing melanomas relative to the total body surface included sites on the vulva, subungual tissues, volar and palmar skin, and, for comparison melanomas of the face during the same period of time. The density of vulvar melanomas was identical to that in chronically sun-exposed facial skin. Subungual melanomas were almost nine times denser than expected whereas melanomas of palms and soles showed a lower density than expected. *Melanomas beneath the body surface*. The densities of melanomas in the vagina, anal canal and uvea, were calculated separately and compared to the average density of cutaneous melanomas (CMMs) during the same period of time. Melanomas of the anal canal displayed a density almost twice the average for CMMs, whereas the vaginal melanomas were similar in density to CMMs. In contrast, the density of the uveal melanomas was calculated as 50 and 41 times (men and women, respectively) the average density of CMMs. *Conclusion*. The high density of some melanomas in sun-shielded body areas indicates the presence of factors underlying the origins of these tumours that seem to be equivalent in strength to UV radiation and also implies that specific anatomical sites favour the emergence and proliferation of melanomas, independent of UV radiation.

Ultraviolet (UV) radiation is a major factor associated with the genesis of cutaneous malignant melanomas (CMMs) in patients with chronic sun exposure, intermittent exposure or a history of sunburns [1]. However, an equally evident feature is that non-UV linked factors are also operational, since primary malignant melanomas can emerge in body sites that never see the sun. Case studies of melanomas in sun-shielded body sites were published as long as 150 years ago: for example a report of 1857 described melanomas in the anus-rectum [2]. However, such melanomas have been considered merely odd, highly malignant growths. The supposed scarcity of these tumours has made them relatively uninteresting for investigators attempting to establish the source of and treatment for melanomas, an exception being melanomas of the eye. However, this scarcity is deceptive, because it reflects only the absolute number of melanomas at sun-shielded locales, not the tumour density, i.e. the number of tumours per square unit of the surface where they emerge.

Melanomas at sun-shielded body sites

For this brief review, measurements of melanomas' densities were obtained from long-term studies we and others conducted. Sites included were mucosal melanomas of the vulva (example in Figure 1), vagina and the anal canal and, in addition, melanomas of the uvea, of finger and toe nail beds (subungual) and in the palms of hands and soles of feet. The access to reliable numbers along with measurable anatomical areas directed our choice of sun-shielded melanomas brought up in this review. For comparison,

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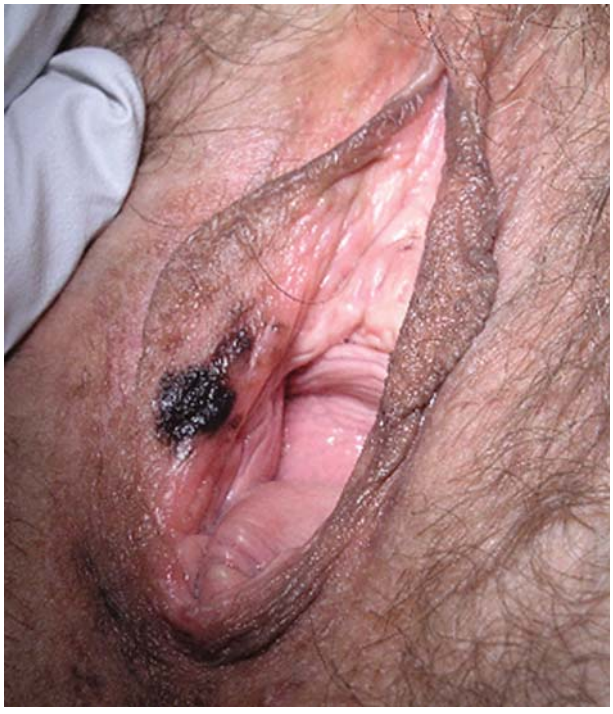

Figure 1. Pigmented vulvar malignant melanoma (mucosal lentiginous type) on the medial part of the right labium minus of a 57-year-old female.

the density of CMMs of chronically sun-exposed facial tissues was reviewed.

The sun-shielded positions of the vulva, vagina, and anal canal are obvious. In contrast, the connection between UV light and the genesis of uveal melanomas is controversial. Epidemiological studies based on latitudinal gradients and outdoor activities [3] have suggested sunlight as a major risk factor. However, recent investigations have found no epidemiological evidence for UV light as a cause of uveal melanomas. For example, in Sweden during 1960–1998, the incidence of uveal melanomas decreased in men and was stable in women, whereas CMMs increased by an average of 6% annually [4]. Furthermore, the age-adjusted incidence of uveal melanomas in USA remained stable during 1973–1997 unlike that of CMMs, which rose [5]. UV light is largely absorbed by the eye lens in adults; that is, transmission of about 75% of UV light (300–400 nm) during early childhood decreases to less than 20% at 80 years of age, as chromatophores derived from tryptophan and other photosensitive molecules continuously accumulate in the lens [6]. Among 18 000 individuals with oculocutaneous albinism type 1–4 no case of uveal melanoma was reported (reviewed in [7]). Again, this argues against UV radiation as a cause of uveal melanoma. A recent meta-analysis based on published compiled physiological, epidemiological, and genetic data concluded that the evidence for UV light-induced uveal melanoma is weak, and inconclusive [8].

Regarding hands and feet, the human nail plate is an efficient sunscreen protecting the subungual tissues from UVB radiation. At UVB wavelengths of 280–315 nm and a nail thickness of 0.25 mm, UV transmission through the nail plate is reportedly less than 25% and virtually 0% at a nail thickness of 0.5 mm [9]. However, the transmission of UVA is somewhat greater ranging from about 25% to slightly more than 50% at a nail thickness of 0.25 mm [9]. Hand palms could be at least partly protected from UV radiation of the sun because of their usual position turned down, away from sunshine, and the soles of feet are usually protected by footwear. Besides, thick epidermis, especially the stratum corneum, should offer protection to both sites.

Spatial density of melanomas at the body surface

The spatial densities described here were calculated from records for all patients with a primary melanoma reported to the (mandatory) Swedish National Cancer Registry [10] or to the Regional Cancer Registry of the Stockholm-Gotland area (part of the National Registry). These records represent different time periods as noted (Tables I and II).

The area of each region of the body surface harbouring melanomas is expressed in percent of the total body surface according to the commonly used method of estimating the extent of burns [11]. However, these regions have been subdivided and recently further subdivided by means of computerised methodology [12]. Calculations of surface areas of the different melanomas relative to body surface include the face [13], subungual tissues, volar and palmar skin [14], and vulva [11,15].

The expected average number of melanomas at each region of the body surface was calculated from the size (percent) of the sub region in question relative to the whole body surface and the number of all CMMs reported during the time period. For example, the vulva is expected to occupy roughly 1% of the body surface [15] and should, accordingly, harbour about 1% of all melanomas at the body surface. A "density ratio," i.e. quotient of observed/expected melanomas for each sub region is, then, computed. As a result, the observed density of vulvar melanomas was significantly higher than expected and tallied with the density of CMMs on chronically sun-exposed facial skin (Table I). This outcome is remarkable, because the face is the densest cutaneous site of melanomas [13]. Also noteworthy is that the vast majority of the vulvar melanomas grew in the glabrous skin ("mucosal membrane") exclusively

Table I. Density of primary malignant melanomas (MMs) at various anatomical sites of the body surface.

Gender	All cutaneous MMs (N)	Regional site	Regional site out of whole body surface (%) [a]	MMs of regional site		Density ratio obs/exp MMs
				observed (N)	expected (N)	
F	18 714[b]	vulva	1	380[b]	187	2.0
F+M	4 221[c]	face	3.5	316[c]	148	2.1
F+M	1 891[d]	subungual	0.1	17[d]	2	8.5
F+M	1 891[d]	palms+soles	4.2	32[d]	79	0.4

All numbers of the Density Ratio are on a significant level (p-value <0.001).
[a]For references and calculations – see text.
[b]Reported to the Swedish Cancer Registry 1960–1998 [10].
[c]Reported to the Stockholm-Gotland Regional Cancer Registry 1976–1994 [10,13].
[d]Reported to the Stockholm-Gotland Regional Cancer Registry 1976–1987 [10,14].

(49%), or extended into the hairy skin of the labium majus (38%) whereas only 13% was found exclusively in the hairy skin [16].

Surprisingly, and for unknown reasons, the observed density of melanomas of the subungual areas exceeded that expected by almost nine times (Table I), even though nails protect subungual tissues from UVB radiation. The hypothesis that UVA radiation, which has a greater degree of transmission through the nails than UVB [9], caused those melanomas cannot be completely excluded, but decisive tests of melanoma genesis by UVA in human skin are pending.

In contrast, the observed density of melanomas of the palms and soles was lower than expected (Table I). The large difference of melanoma density between the subungual tissues and the palms and soles is difficult to explain but favours local factors as the cause.

Spatial density of melanomas beneath the body surface

For melanomas emerging beneath the body surface – in the vagina, anal canal and uvea – different calculations of tumour density were required. The density of each kind of melanoma was calculated separately and then compared with the average density of CMMs during the same period of time. The average body surface has been calculated as 1.9 m^2 for Swedish men and 1.7 m^2 for Swedish women [17].

The vagina is generally regarded as a biological continuum of the vulva, but its surface had to be considered separately here. This surface was recently calculated [18] by means of vinyl polysiloxane casts in 62 adult females and showed a mean of 87.46 cm^2 +\− SD 7.8 cm^2, i.e. a space rather uniform among individual adults. Eighty females with a primary vaginal melanoma were reported in the Swedish series, and their vaginal melanoma densities were computed. In contrast to the vulva, the density of the vaginal melanomas turned out to be similar to the average density of CMMs (Table II).

Fifty-seven percent of the primary ano-rectal melanomas arose exclusively in the anal canal in a Swedish population-based series of 241 males and females surveyed during a 40-year period [19]. The clear-cut definition of the anal canal proposed by Wendell-Smith [20] and by Fenger [21] was employed

Table II. Density of primary malignant melanomas (MM) at various anatomical sites beneath the body surface.

Gender	All cutaneous MMs (N)	Body surface, average (cm^2)[a]	MMs per cm^2 body surface	Regional site	MMs at regional site (N)	Regional site area, average (cm^2)[b]	MMs per cm^2 regional site area	MMs per regional site area/ MMs per body surface	Density ratio MMs at regional site/body surface
M	17 923[c]	19 000	0.94	anal canal	56[c]	38	1.47	1.47/0.94	1.6
F	19 176[c]	17 000	1.13	anal canal	81[c]	38	2.13	2.13/1.13	1.9
F	19 176[d]	17 000	1.13	vagina	80[d]	87	0.92	0.92/1.13	0.8
M	17 090[e]	19 000	0.90	uvea	1542[e]	34	45.35	45.35/0.90	50.4
F	18 334[e]	17 000	1.07	uvea	1455[e]	33	44.10	44.10/1.07	41.2

All numbers are aggregations, thus no statistical uncertainty could be calculated.
[a]According the National Swedish Central Bureau of Statistics (males 1.9 m^2, females 1.7 m^2) [17].
[b]For calculation of site areas – see text.
[c]Reported to the Swedish Cancer Registry 1960–1999 [10,19].
[d]Reported to the Swedish Cancer Registry 1960–1999 [10].
[e]Reported to the Swedish Cancer Registry 1960–1998 [4,10].

here. The density of these tumours has been detailed elsewhere [19]. Briefly, in 137 patients (56 males and 81 females) with a melanoma restricted to the anal canal, the canals' surface was calculated alternatively as 38 cm^2 or 25 cm^2 given that the canal was considered roughly as a cylinder with an average length of 4.2 cm [22] and a diameter of 1.9 cm or 2.9 cm, respectively, depending its "basal" or "strained" situation in normal individuals measured by combined endosonography and manometry [23] (gender differences not reported). The density ratio of anal melanomas/CMMs was 1.6 for males and 1.9 for females, at an anal diameter of 2.9 cm (Table II), but rose to 2.4 and 2.9, respectively, at a diameter of 1.9 cm (not shown in the table). These density ratios could be even higher, since 60 (24%) of the anorectal melanomas grew both in the anal canal and the rectum [19] and so were excluded from the calculations. However, most of these tumours were presumably primary in the anal canal, not in the rectum. Accordingly, the density of anal melanomas was significantly higher than the average density of CMMs during the same period of time (Table II).

In comparing the average density of uveal melanomas per ocular area unit relative to that of CMMs, the uveal area of both eyes and in both genders was first estimated along with the average body surface and the total number of CMMs during specified time periods, as detailed earlier [4]. Briefly, the mean uveal area was estimated to be 34 cm^2 for males and 33 cm^2 for females. Given the average numbers for body surfaces of Swedish males and females [17] and 1542 uveal melanomas reported in men and 1455 in women along with 17 090 male and 18 334 female CMMs during the collection period, the uveal melanoma density was estimated as 41–50 times higher than the average density of CMMs (Table II).

Some biological implications

The observed densities of melanomas in the mucous membranes of the vulva and anal canal cited here as well as in subungual (acral) and uveal sites were significantly higher than expected and similar to or even higher than the well-established peak density of melanomas on the face. Moreover, the large differences in observed vs. expected densities (based on all reported CMMs) indicate that CMMs, on average, are usually less dense than the melanomas documented here.

Similarly, related biological differences have been reported; Review of these reports is beyond the scope of this brief communication. Suffice it to say that mutations in the genes BRAF, NRAS and KIT involved in the mitogen-activated protein kinase (MAPK) pathway differ; BRAF-, and NRAS gene mutations are very rare [24,25] or absent [26] in mucosal or uveal melanomas but present in CMMs [27]. The KIT gene mutations which have recently attracted great interest as the target for therapeutic trials, are most common in acral and mucosal melanomas but rare in CMMs and absent in uveal melanomas [28].

However, malignant tumours are the products of more sources than accumulated genetic mutations. They are also dependent on the impact of the surrounding tissue microenvironment. For example, the microenvironment of uveal melanocytes which differs from that of cutaneous melanocytes, is a highly vascularised locale where melanocytes are exposed to blood-borne factors, and repose in direct contact with vascular endothelial cells and fibroblasts. In contrast, cutaneous melanocytes are in a close contact with epithelial cells, and are less available to blood-borne factors from vessels in the dermis. Uveal melanocytes are attached to each other unlike cutaneous epidermal melanocytes which appear to be surrounded individually by clusters of keratinocytes forming the "epidermal melanin unit". The melanosomes are transferred from the cutaneous melanocytes to the adjacent keratinocytes, whereas the uveal melanocytes retain their melanosomes. Several reports have recently extensively described how complicated changes in the microenvironment of melanocytes may lead to the disruption of the normal melanocyte homeostasis and pave the way for cutaneous melanoma genesis [29,30]. However, the microenvironment of melanocytes in various mucosal membranes has, to my knowledge, not been studied.

One factor associated with the density of melanomas could be the spatial density of melanocytes. Their density in the skin varies both among individuals and between various anatomical sites within the same individual [31] but, to my knowledge no similar report of the spatial melanocyte density, or melanosome maturation, of normal mucosal membranes has been published.

A distinct difference is apparent in the greater density of melanomas of the uvea, and of mucosa and glabrous skin as compared to CMMs. This phenomenon is clear-cut at the border zone between the hairy skin and glabrous skin of the vulva's lateral and the medial sides of labium majus, respectively [16]. One may speculate that the difference is somehow related to the hair follicles. These follicles are reservoirs for stem cells of several kinds including the melanocyte lineage [32,33]. The role of the follicular melanocytic cells in the melanoma genesis is still uncertain. However, the observation of a higher density of melanomas in areas without hair follicles as compared to hairy skin speaks against an important role of follicular melanocytic cells.

One should keep in mind that melanocytes, at least in the skin, are multipotent cells; Except for producing melanin they are, for example, potential accessory immuno-competent and secretory cells, i.e. part of inflammatory/-immune responses, able to phagocytise microorganisms, and possibly to serve as antigen-presenting cells and they can also produce several cytokines [30].

A large number of reports suggesting possible non-UV related causes of melanoma have been published, far too many to review in this paper. Just to mention, that experimental evidence indicates that numerous xenobiotics such as carcinogenic environmental toxins, transition metals, and drugs are filtered by and bound to the melanins, sometimes over long periods of time by means of different kinds of chemical binding (reviewed in [34]). However, proof of the importance of environmental carcinogens as risk factors in causing non-UV related melanomas is still pending.

Viruses involved in the genesis of non-UV related melanoma have also been discussed. In fact melanoma-associated endogenous retrovirus-like particles were found in human melanoma cells along with sequences in the genome homologous to human endogenous retrovirus K (HERV-K) [35,36]. However, the infectivity and the pathogenic role of these viruses are at present unclear. Other viruses like human papilloma viruses (HPV) [37,38], herpes viruses (HHV) [39] or polyoma viruses [40] have been sought in mucosal melanomas but rarely identified, if at all.

Conclusions

Despite sound evidence that non-UV associated melanomas occupy a marked spatial density, as this review cites, these observations should be interpreted with caution. They are based on approximate figures, and the densities of CMMs are average values. However, the results clearly indicate that the density of primary melanomas at some sun-shielded sites is significantly higher than the average density of CMMs and similar to or even greater than the density of melanomas in chronically sun-exposed facial skin. The discrepancy between the density of volar/plantar and subungual melanomas as well as between vulvar and vaginal melanomas suggests that acral and mucosal melanomas at different anatomical sites should be analysed separately and not jointly as homogenous groups of "acral" or "mucosal" melanomas. The high spatial density of some mucosal melanomas, along with subungual and uveal melanomas, as described here, adds to a growing list of recently discovered biological differences between CMMs and melanomas at sun-shielded sites. Moreover, this high density indicates that novel factors underlie the origins of some melanomas and that some of these factors may be equivalent in strength to UV radiation. The results also suggest specific anatomical sites that favour the emergence and proliferation of melanomas, independent of UV radiation. This information about spatially dense melanomas in sun-shielded body sites is important as a guide, first, to our search for etiologic and pathogenic factors in the genesis of all melanomas and, second, for identifying possible co-factors in UV light-driven melanomas. The related discoveries should disclose new targets for the prevention and treatment of these fatal melanomas.

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