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Melanoma: is hair the root of the problem?

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Why are children more vulnerable to sun exposure?

Epidemiological studies indicate that sunburns in prepubertal children are associated with an increased risk of melanoma later in life (Autier and Dore, 1998; Oliveria et al., 2006; Williams and Pennella, 1994; Zanetti et al., 1992). Migrant studies to Australia have shown that individuals arriving before age 10 have a similar melanoma risk to those born in Australia, while individuals arriving after age 15 exhibit about a quarter of the melanoma incidence (Oliveria et al., 2006). Likewise, studies have shown that in individuals who migrate to an area near the equator, the risk of melanoma decreases if the individual is older at the age of migration (Oliveria et al., 2006). These studies suggest that children are more vulnerable to sun exposure, vis-a-vis the risk for the development of cutaneous melanoma, which raises the question, *'What are the factors that may explain an increased vulnerability of children to sun exposure?'*

Epidemiology of melanoma and its relationship to vellus hair

Prepubertal children have a much higher proportion of vellus hair compared to adults, which led us to investigate whether there may be a relationship between vellus hair and melanoma incidence that may explain an increased vulnerability of children to sun exposure. Methods and supplementary information are provided in Appendix 1.

Mean melanoma incidence (±standard deviation) was $0.11 \pm 0.101\%$ in men and $0.12 \pm 0.062\%$ in women. This difference was not statistically significant ($t = 0.24$, $P = 0.81$). The relationship between the number of vellus hair follicles and body surface area and melanoma incidence for both genders is plotted in Figure 1A,B (sun exposure level 2) and Figure 2A,B (sun exposure level 3). In the comparison of body sites subject to level 2 sun exposure on men (back, upper arm, chest, and leg) and women (back and thigh), there is no correlation between body surface area (BSA) and melanoma incidence, (Figure 1A, $R^2 = 0.0237$), while a positive correlation exists between number of vellus hair follicles and melanoma incidence, (Figure 1B, $R^2 = 0.2644$). However, in the comparison of body sites subject to level 3 sun exposure on men (forearm), and women (forearm, upper arm, and leg), a strong positive correlation is seen in terms of both BSA and melanoma incidence (Figure 2A, $R^2 = 0.8721$), and also in terms of number of vellus hair follicles and melanoma incidence (Figure 2B, $R^2 = 0.652$). (Our postulation for the strong positive correlation seen in Figure 2A in terms of BSA and melanoma incidence *is further discussed in the latter part of this manuscript.*)

Multiple linear regression analyses indicated that the most parsimonious model for prediction of melanoma incidence considered the total number of vellus hair follicles per body site and exposure level ($F = 0.01$, $R^2 = 0.42$). Thus, these two predictors explained 42% of the variation in melanoma incidence. Inclusion of a variable representing gender did not add information to the model ($t = 0.19$, $P = 0.85$). For the model, there was a positive relationship between the total number of vellus hair follicles per body site and melanoma incidence ($t = 3.03$, $P = 0.007$), adjusted for exposure level (Figure 3). The mean melanoma incidence was 14% higher with high lifetime, but mainly intermittent sun exposure, when compared to low lifetime exposure.

The results from the these analyses confirm that not only is sun exposure level an important predictor of melanoma, but, in addition, areas on the body with higher numbers of vellus hair follicles have an increased vulnerability to developing melanoma. The models also suggest that anatomical areas of the body with higher numbers of vellus hair follicles are a far more important predictor of melanoma than anatomical areas with larger surface areas; therefore, indicating that hair follicles are potential culprits in melanomagenesis.
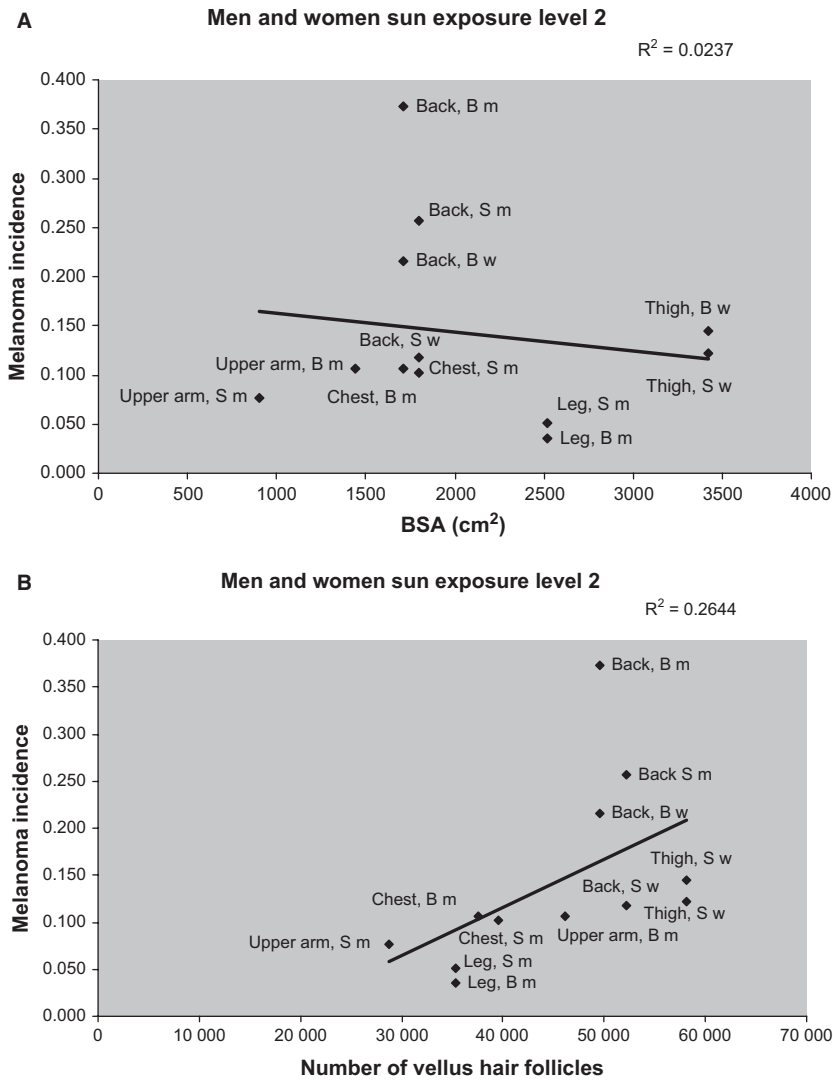
A

Men and women sun exposure level 2

$R^2 = 0.0237$

[Figure A: scatter plot with Melanoma incidence (y-axis, 0.000–0.400) vs BSA (cm^2) (x-axis, 0–4000). Data points labeled: Back, B m; Back, S m; Back, B w; Thigh, B w; Back, S w; Upper arm, B m; Chest, S m; Upper arm, S m; Chest, B m; Thigh, S w; Leg, S m; Leg, B m]

B

Men and women sun exposure level 2

$R^2 = 0.2644$

[Figure B: scatter plot with Melanoma incidence (y-axis, 0.000–0.400) vs Number of vellus hair follicles (x-axis, 0–70 000). Data points labeled: Back, B m; Back S m; Back, B w; Thigh, S w; Chest, B m; Back, S w; Thigh, S w; Upper arm, B m; Upper arm, S m; Chest, S m; Leg, S m; Leg, B m]

Figure 1. Relationship between the incidence of cutaneous melanoma and body surface area (BSA) (A) or number of vellus hair follicles (B), for sun exposure level 2 (low lifetime, mainly intermittent). Legend data points represent Body site, Country, and Gender. Body site is listed and followed by abbreviations S m, S w, B m, and B w, which represent Switzerland men, Switzerland women, British Columbia men, and British Columbia women, respectively.

As hair-type variations exist between children and adults, with children having a much higher proportion of vellus hair, these epidemiological observations suggest that sun exposure and subsequent development of melanoma in children are related to hair variations. In this commentary, we discuss a dual vulnerability of the vellus hair follicle to ultraviolet radiation (UVR) resulting from increased transmission of the photons in sunlight in vellus compared to terminal hair and from the relatively superficial location of its stem cell niche. In addition, we discuss ideas regarding skin evolution and a possible co-evolution of hair, as well as hair depilation and how its increase may relate to the increase in melanoma incidence observed over the past few decades. Finally, we conclude that vellus hair follicles likely play a substantial role in the early events of melanomagenesis.

Hair-type variations between children and adults

At birth, all hair follicles are present, and no further follicles will develop throughout life. However, from birth until adulthood, follicle properties change as does the type of hair produced because of hormonal changes associated with puberty (Blume-Peytavi, 2008; Randall, 2008). Based on properties such as the depth of the follicle, the length of the hair cycle, the amount of pigment, the relative diameter and the presence or absence of the medulla in the shaft, hair is categorized into three main groups: vellus, intermediate, and terminal hair. The major differences among these three groups are summarized in Table 1 and discussed in detail.
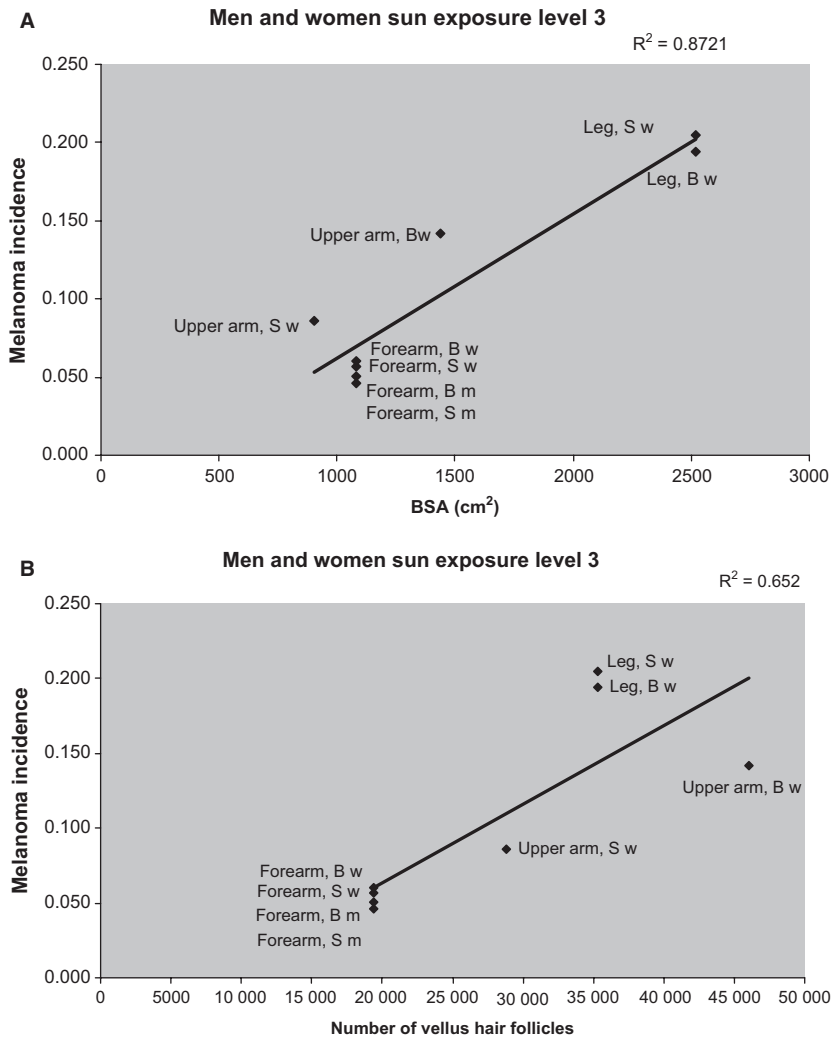
A

Men and women sun exposure level 3

B

Men and women sun exposure level 3

Figure 2. Relationship between the incidence of cutaneous melanoma and body surface area (BSA) (A) or number of vellus hair follicles (B), for sun exposure level 3 (high lifetime, mainly intermittent). Legend data points represent Body site, Country, and Gender. Body site is listed and followed by abbreviations S m, S w, B m, and B w, which represent Switzerland men, Switzerland women, British Columbia men, and British Columbia women, respectively.

In children, vellus hair is the primary hair type. From birth until puberty, vellus hair is present on all skin surfaces of the body, excluding the palms, soles, and lips (Blume-Peytavi, 2008; Randall, 2008; Schneider et al., 2009). Vellus hair follicles are small and produce fine hair with little pigment and grow no longer than 2 mm and no thicker than 30 μm (Blume-Peytavi, 2008; Blume et al., 1991; Randall, 2008). Vellus follicles extend into the dermis, but not into the subcutaneous fat layer. The hair shaft of vellus hair is comprised of two layers: the cuticle and the cortex. The outermost layer, the cuticle, is composed of corneocytes. This layer is very thin and enables light to transmit into the inner layer, the cortex, that contains vertically oriented cornified fibrous cells, which are dense with keratin (Blume-Peytavi, 2008; Blume et al., 1991).

During puberty, vellus hair follicles in some areas of the body, in response to androgen stimulation, relocate deeper within the skin and evolve into larger terminal hair follicles. This process occurs in the pubic and axillary regions in men as well as women and on the face, chest, limbs, upper pubic diamond, and oftentimes the back in men (Blume-Peytavi, 2008; Randall, 2008). Terminal hair follicles produce coarse, pigmented hair and are large, growing longer than 2 mm in length and thicker than 60 μm in diameter. They also extend through the dermis and into the subcutaneous fat layer. Like vellus hair, terminal hair contains cortex and cuticle layers; however, also present in terminal hair is a third layer known as the medulla, the innermost layer consisting of a horizontal arrangement of irregular-shaped vacuolated cells. In the terminal hair of children, the medulla
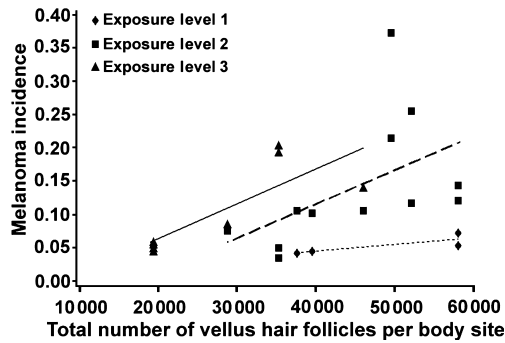
Figure 3. Scatter plot of melanoma incidence versus total number of vellus hair follicles per body site. Linear regression lines are superimposed on the scatter plot and correspond to regression results for sun exposure level 1 (minimum lifetime), level 2 (low lifetime, mainly intermittent), and level 3 (high lifetime, mainly intermittent).

Table 1. Major properties of different hair types

Hair type	Pigment	Diameter	Length	Medulla
Vellus	Little pigment	$<30\ \mu m$	<2 mm	Absent
Intermediate	Little pigment	$>30\ \mu m$; $<60\ \mu m$	>2 mm	Fragmented/ absent
Terminal	Pigmented	$>60\ \mu m$	>2 mm	Present; extent varies according to terminal hair type

is incomplete or absent (Blume-Peytavi, 2008). A recent study has found expression of 24 keratins in the medulla, which include several additional keratins that are not found in the cortex and cuticle (Langbein et al., 2010). The significance of the additional keratins found in the medulla is currently unknown.

Post-puberty, hair follicles on the body that do not become terminal hair as a result of hormonal influence will remain primarily as vellus hair, while in some areas, an intermediate hair type may develop (Blume-Peytavi, 2008) and intermediate hair is often times seen on areas such as the limbs of women. Intermediate hair follicles are slightly larger than vellus hair follicles and also have little pigment. They produce hair that is greater than 2 mm in length and thicker than 30 μm but less than 60 μm in diameter. Like vellus hair, intermediate hair has two layers, the cuticle and the cortex, and may or may not have a medulla (Blume-Peytavi, 2008).

Vellus hair vulnerability

Taking into consideration the different characteristics of vellus and terminal hair (a pictorial representation of these relevant features is shown in Figure 4), we

addressed the question, '*Why might hair be significant in the pathogenesis of melanoma?*' We postulate that it is because hair follicles contain stem cell niches. In the outer root sheath of the lower permanent portion of the hair follicle below the sebaceous gland is a very key part of the hair follicle called the bulge region (Randall, 2008; Schneider et al., 2009; Slominski et al., 2005). The bulge region houses multipotential stem cells that have the ability to differentiate into keratinocytes, neurons, glia, smooth muscle cells, and melanocytes (Yu et al., 2006). The bulge region stem cells have the ability to migrate within the hair follicle to populate areas such as the hair bulb, or they can even leave the bulge region to populate the epidermis (Kwon et al., 2008; Nishimura et al., 2002; Slominski et al., 2005). Physical or chemical injury is a major factor that provokes the stem cells to migrate from the bulge region into the epidermis (Randall, 2008; Yu et al., 2006).

In vellus hair follicles, the bulge region is located approximately 362 μm from the surface of the skin
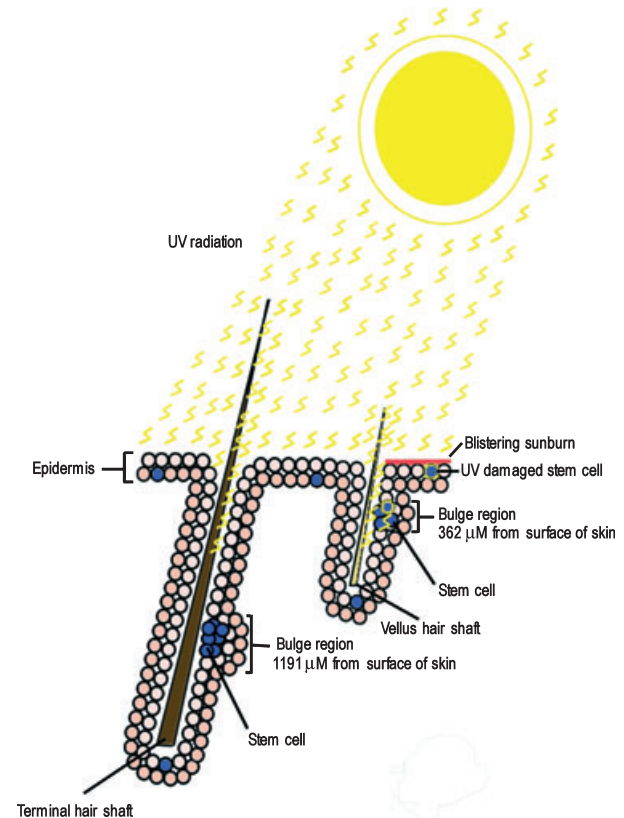

Figure 4. Transmission of electrons to the bulge area. UVR is absorbed and transmitted along the hair shaft. Small amounts scatter into the bulge region causing oxidative damage in stem cells. As a result, adaptive changes and repair occur in stem cells. Over time, continued UVR exposure causes further changes in stem cells. When epidermal injury occurs, stem cells from the bulge region migrate to the epidermis to initiate cutaneous repair but the damaged melanocyte now has the potential to become a melanoma.

while the bulge region of terminal hair follicles is located much deeper, approximately 1191 μm from the skin surface (Vogt et al., 2007).

Of additional interest, the bulge region of terminal hair follicles has recently been shown to fit the classical criteria of an area of immune privilege (IP) (Meyer et al., 2008), meaning that stem cells of the bulge region are more resistant to immune attack. While it does not appear that there have yet been studies on bulge region IP in vellus hair, there may be similarities regarding IP in the hair follicle types as they ultimately arose from the same follicle.

Cells in IP regions mirror some escape mechanisms observed in melanoma such as the downregulation of MHC molecules on cell surfaces that protect tumorigenic cells from cytokine CD8 + T. While we are unable to find evidence supporting or refuting that cells migrating from the bulge region into the epidermis retain some degree of IP, it would be remarkable if melanoma's notorious ability to escape from immunosurveillance reflected its origin in an IP protected area, such as the hair follicle bulge region.

Regarding the pathogenesis of melanoma, we hypothesize that hair follicles and their respective stem cell rich bulge regions may be involved. More precisely, because vellus hair is finer, lighter in pigment, shorter in length and with only two layers, and located four times closer to the surface of the skin compared to terminal hair, we hypothesize that the stem cell compartment of vellus hair follicles is exposed to higher doses of UVR from the sun than terminal hair. Longer, thicker, more pigmented terminal scalp hair may additionally serve as protection from UVR, through its ability to effectively cover skin surfaces (Green et al., 2006). Therefore, although terminal hair may not be completely innocent in the pathogenesis of melanoma, we believe that vellus hair plays a far more critical role.

'Critical Period' of exposure coincides with vellus hair evolution

As previously discussed, epidemiological data supports an increased risk of melanoma resulting from sun exposure under the age of 15 (Oliveria et al., 2006). This critical period appears to coincide with the ages prior to the onset of puberty in which children would have almost exclusively vellus hair follicles. Furthermore, because all hair follicles are present at birth and because children have a smaller BSA compared to adults, this suggests that the vellus hair follicles on children are at a much higher density on their skin (Blume-Peytavi, 2008), possibly resulting in a more focused exposure of the bulge region of the vellus hair to UVR. This increased exposure may partially explain why children under the age of 15 are more susceptible to developing melanoma than if exposure occurs later in life. As children reach the age of puberty, occurring at approximately 11–14 yr in girls

and 13–16 yr in boys (Siervogel et al., 1982), androgens activate the switch from vellus to terminal or intermediate hair follicles, reducing the proportion of vellus hair. Also, after the growth spurt, BSA is more similar to the BSA of an adult, and therefore, hair follicles are at a lower density. Thus, these structural, biological, and epidemiological considerations have prompted us to try to identify a quantitative link between hair follicles and the incidence of melanoma.

Has hair evolved with skin?

With several million hair follicles from head to toe, it is reasonable to consider that hair has evolved much like skin, with the ability to either limit or enhance UVR absorption. Over hundreds of thousands of years, natural selection has caused a notable variation of skin pigmentation among humans, which has a strong correlation with the UVR intensity to geographical locations of human populations (Parra, 2007). Darker skin pigmentation is observed in areas near the equator with higher UVR intensities, while lighter skin pigmentation is observed in latitudes farther from the equator with diminished UVR intensities. It is believed that dark skin was advantageous in areas of high UVR intensity because of its ability to protect from sunburn (and resulting secondary infections), sweat gland damage, and folate photolysis with adverse reproductive consequences. Likewise, it is believed that light skin was necessary in areas with low UVR intensities to efficiently absorb ultraviolet B radiation, which is essential for the synthesis and production of the active form of vitamin D within the skin (Parra, 2007). Considering that skin pigmentation evolved to either limit or enhance UVR absorption, it is plausible that hair has also evolved in a similar manner.

Hair as a fiber-optic cable

What could be the evolutionary or physiological advantage for allowing light to pass through hair? Hair may be an example of natural fiber optics, allowing UVR to be transmitted along the hair shaft and deep into the skin. A previous study has found strong similarities between human hair and fiber optics, noting that the keratinocytes of the hair shaft are organized in compressed linear columns, which are of similar arrangement to strands of commercial fiber optics (Iyengar, 1998). Furthermore, it has been shown that the melanocytes of the bulb of the hair follicle become excited upon skin exposure to UVR, and re-orient their dendrites toward the hair shaft. This excitation occurs with no chance of direct UVR exposure, which suggests that, like a fiber-optic cable, the light is absorbed from the superficial exposed hair shaft and transmitted down the shaft to the base of the hair bulb deep within the dermis (Iyengar, 1998). How this occurs, however, is not clearly understood although extensive modeling has been explored (Sun et al., 2009).

We, therefore, suggest that, because of its physical properties, vellus hair may function more efficiently as a

fiber-optic cable compared to intermediate and terminal hair as vellus hair is short, fine, lightly pigmented, and only has two layers. The outermost layer of vellus hair, the cuticle, in fact, allows light to pass into the innermost layer, the cortex. Furthermore, the cortex of vellus hair consists of vertically oriented cells, which, as Iyengar (1998) noted, are of similar arrangement to strands of commercial fiber optics. It appears that vellus hair possesses properties that enhance light absorption and transmission. In contrast, terminal hair, which is longer, thicker, and more heavily pigmented, also has a third layer, the medulla, which may play a role in its protective properties. The medulla contains additional keratins not found in vellus hair, which are arranged in a horizontal rather than vertical fashion for which the purpose is currently unknown (Langbein et al., 2010). But, in contrast to the fiber-optic-like vertical arrangement of cells that Iyengar (1998) observed in vellus hair, perhaps, the horizontally arranged keratins found in the medulla of terminal hair may play a role in inhibiting light transmission.

It is important to note that previous speculation that polar bear hair functions as fiber optics has been controversial with more recent research refuting the possibility (Koon, 1998). Koon showed that in polar bear hair, light transmission was quickly lost as it traveled down the length of the hair shaft; he argued against the possibility of polar bear hair acting as a fiber optic. Based on Koon's argument, it might be inferred that human hair also lacks the ability to transmit light. However, comparing polar bear to human hair is like comparing apples to oranges as fundamental structural differences exist within the hair types. First, human vellus hair is 2 mm or less in length, while the lengths of polar bear hairs used in the experiments (Koon, 1998) were 15, 10, and 7 mm. In addition, the diameter of human vellus hair is less than 30 μm, while the diameter of polar bear hair is 100–150 μm (Grojean et al., 1980). Furthermore, the core of polar bear hair is hollow, while the core of human terminal hair is medullated with horizontally arranged cells, and the core of vellus hair, lacking a medulla, has a cortex with vertically arranged cells, which we believe may facilitate photon transmission. Polar bear and human hair are sufficiently different that even evidence questioning light transmission in polar bear hair does not negate the possibility of light transmission in human hair. However, there is a definite need for further research to explore the possibility of photon transmission within human hair, especially taking into consideration our observations of a correlation between melanoma and human vellus hair.

In elaboration of our results reported in the results section, we observed that on body sites subject to sun exposure level 2, there was no correlation between BSA and melanoma incidence among men and women (Figure 1A), while there was a positive correlation between number of vellus hair follicles and melanoma incidence, thus supporting our hypothesis that vellus hair may play an important role in the development of melanoma. However, in body sites subject to sun exposure level 3, we observed strong positive correlations for both BSA (Figure 2A) and melanoma incidence, as well as in number of vellus hair follicles and melanoma incidence (Figure 2B). Upon careful observation of the body sites plotted in Figure 2A,B for men (forearm), and women (forearm, upper arm, and leg), we note that a remarkably high melanoma incidence is seen on the legs of women. The high incidence of melanoma observed on the legs of women in sun exposure level 3 may explain the strong positive correlations seen in BSA and melanoma incidence in Figure 2A. Women are considered to receive sun exposure level 3 on their legs, while men are considered only to receive sun exposure level 2 on their legs; However, even despite sun exposure level, there still remains a great difference in the melanoma incidence observed on the legs of women (.194, and .205 in British Columbia and Switzerland, respectively) in comparison with the legs of men (.036, and .051 in British Columbia and Switzerland, respectively).

This discordance may be explained by the differing proportions of hair types on the legs of women and men, as well as the tendency for women to shave their legs. The legs of women are mainly comprised of vellus and intermediate hair types, while in men, terminal hair is primarily present. We speculate that in addition to having a vulnerability to UVR as a result of hair type, an explanation for the elevated incidence of melanoma observed in the legs of women may be behavioral. A common ritual among women is to shave their legs, which causes alteration of the hair shaft. As a result of shaving, the hair shaft becomes shorter and straight cut, which may enhance fiber-optical properties, transmitting energy more efficiently compared to longer, blunt-tipped unaltered hair.

Is there a correlation between increased hair removal and increased melanoma incidence?

Is it possible that the increase in melanoma incidence may be reflective of societal increases in hair removal practices? Over the past century, hair removal rituals have greatly increased, not only among women but among men as well. Beginning in the 1920s, women began removing underarm hair by shaving and decades later they began removing leg hair. Today, it is not uncommon for women to also remove hair from their arms, and hair removal practices are not restricted to women. A recent study has shown that there is a body depilation (shaving or trimming of body hair) trend among men that is not strictly limited to men participating in athletics such as bodybuilders, swimmers, and cyclists. According to a US study of college-aged men, 63.6% depilate body hair below the neck. (McCreary

et al., 2007) The men surveyed either depilate completely with the use of a razor (71%) or trim their hair with scissors (27%) in areas such as the chest (56%), abdomen (47%), back of neck (37%), upper legs (27%), groin (74%), and arm pits (33%). Hair removal is occurring via many forms including shaving, waxing, the use of nair, and laser hair removal. Because hair removal is not permanent, the hair shaft will eventually regenerate and emerge from the skin as a shorter hair shaft during its initial re-growth phases at which point it may have an increased vulnerability to UVR. Therefore, we propose that hair alterations as a result of their removal may contribute to the continuing increase in overall melanoma incidence.

Hair shaft variations among populations

Similar to skin variations, notable hair variations can be seen among Asian, European, and African populations in terms of shape of cross section and fiber, diameter, moisture, and mechanical properties (Franbourg et al., 2003; Fujimoto et al., 2008). In a study comparing vellus hair follicle density among Caucasians, Asians, and African Americans, the only significant difference was observed on the forehead, while a slightly greater hair follicle density was also observed on the upper arm of individuals of African descent (Mangelsdorf et al., 2006). A majority of the human population has dark hair, while blond and red hair are mainly observed among European populations (Parra, 2007). Perhaps hair variations exist because of hair's fiber-optical properties. For example, populations, such as Africans, who are exposed to intense UVR may have developed dark, course, kinky hair to decrease the ability to transduce energy to protect from high UVR exposure. On the other hand, populations, such as northern Europeans, in areas of low UVR evolved light, fine, straight hair, which efficiently functions as fiber optics to maximize UVR absorption to allow sufficient vitamin D production within the skin.

Our hypothesis

We propose that vellus hair, functioning similarly to a fiber-optic cable may provide an explanation for the increased vulnerability of children to UVR and subsequent melanomagenesis and for the disproportionately higher incidence of melanoma seen in the legs of women. Hair may be an accomplice in the development of melanoma by sanctioning the passage of UVR deep into the skin and to the specialized multipotential stem cell niche in the bulge region of the hair follicle.

A pathway to melanoma may begin with sun exposure in the following manner (Figure 4): UVR is transmitted along the hair shaft, with just enough UVR scattering from the hair shaft to the bulge region to cause oxidative and denaturing damage leading to repair and adaptive changes within the stem cells. Over time,

possibly many years, and with intense intermittent UVR exposure, some of the stem cells become further compromised through additional oxidative genotoxic stress. Finally, after the occurrence of epidermal injury, (perhaps a blistering sunburn in adult life), damaged stem cells from the bulge region migrate to the epidermis to aid in tissue repair and reconstruction where they subsequently undergo a further damaging event, causing them to transform into melanoma. It only takes one stem cell destined to become a melanocyte that has developed superior survival qualities owing to UVR exposure and other stressors to become transformed and result in a melanoma.

It is important to note that relatively few melanomas arise directly from the hair follicle. However, this observation does not affect our two-hit hypothesis: the initial insult occurring to the melanocyte stem cell in the bulge region of the hair follicle and the second occurring after the damaged stem cell has migrated away from the hair follicle and into the epidermis.

Furthermore, while our hypothesis supports the idea that UVR is a contributing factor in melanomagenesis, it is important to mention that there has been controversy over the involvement of UVR in melanomagenesis (Meyskens et al., 2006). While the involvement of UVR in melanomagenesis continues to be debated, a recent extensive review of recent evidence supports the contention that UVR plays a role in melanomagenesis (von Thaler et al., 2010).

Therefore, the possible role of the bulge region of the hair follicle in melanomagenesis remains to be directly explored. Perhaps if we continue to dig deeper within the hair follicle, we might uncover the 'root' that underlies melanomagenesis.

Acknowledgements

References

Autier, P., and Dore, J.F. (1998). Influence of sun exposures during childhood and during adulthood on melanoma risk. EPIMEL and EORTC Melanoma Cooperative Group. European Organisation for Research and Treatment of Cancer. Int. J. Cancer 77, 533–537.

Blume, U., Ferracin, J., Verschoore, M., Czernielewski, J.M., and Schaefer, H. (1991). Physiology of the vellus hair follicle: hair growth and sebum excretion. Br. J. Dermatol. 124, 21–28.

Blume-Peytavi, U. (2008). Hair Growth and Disorders. (Berlin: Springer).

Bulliard, J.L., De Weck, D., Fisch, T., Bordoni, A., and Levi, F. (2007). Detailed site distribution of melanoma and sunlight exposure: aetiological patterns from a Swiss series. Ann. Oncol. 18, 789–794.

Elwood, J.M., and Gallagher, R.P. (1998). Body site distribution of cutaneous malignant melanoma in relationship to patterns of sun exposure. Int. J. Cancer *78*, 276–280.

Franbourg, A., Hallegot, P., Baltenneck, F., Toutain, C., and Leroy, F. (2003). Current research on ethnic hair. J. Am. Acad. Dermatol. *48*, S115–119.

Fujimoto, A., Kimura, R., Ohashi, J. et al. (2008). A scan for genetic determinants of human hair morphology: EDAR is associated with Asian hair thickness. Hum. Mol. Genet. *17*, 835–843.

Green, A.C., Kimlin, M., Siskind, V., and Whiteman, D.C. (2006). Hypothesis: hair cover can protect against invasive melanoma on the head and neck (Australia). Cancer Causes Control *17*, 1263–1266.

Grojean, R.E., Sousa, J.A., and Henry, M.C. (1980). Utilization of solar radiation by polar animals: an optical model for pelts. Appl. Opt. *19*, 339–346.

Iyengar, B. (1998). The hair follicle: a specialised UV receptor in the human skin? Biol. Signals Recept. *7*, 188–194.

Koon, D. (1998). Is Polar Bear Hair Fiber Optic? Appl. Opt. *37*, 3198–3200.

Kwon, H., Liu, P.H., Lew, D.-H., Nishimura, E.K., and Orgill, D.P. (2008). Hair Follicle Melanocyte Cells as a Renewable Source of Melanocytes for Culture and Transplantation. In EPlasty, Open Science Co LLC, Springfield.

Langbein, L., Yoshida, H., Praetzel-Wunder, S., Parry, D.A., and Schweizer, J. (2010). The Keratins of the Human Beard Hair Medulla: The Riddle in the Middle. J. Invest. Dermatol. *130*, 55–73.

Mangelsdorf, S., Otberg, N., Maibach, H.I., Sinkgraven, R., Sterry, W., and Lademann, J. (2006). Ethnic variation in vellus hair follicle size and distribution. Skin Pharmacol. Physiol. *19*, 159–167.

McCreary, D.R., Hildebrandt, T.B., Heinberg, L.J., Boroughs, M., and Thompson, J.K. (2007). A Review of Body Image Influences on Men's Fitness Goals and Supplement Use. Am. J. Mens Health *1*, 307–316.

Meyer, K.C., Klatte, J.E., Dinh, H.V., Harries, M.J., Reithmayer, K., Meyer, W., Sinclair, R., and Paus, R. (2008). Evidence that the bulge region is a site of relative immune privilege in human hair follicles. Br. J. Dermatol. *159*, 1077–1085.

Meyskens, F.L., Young, A.R., and Berwick, M.. (2006). Cutaneous Malignant Melanoma: What is the Role of Ultraviolet Radiation. In American Society of Clinical Oncology: Educational Track 2006. American Society of Clinical Oncology, Alexandria.

Nishimura, E.K., Jordan, S.A., Oshima, H., Yoshida, H., Osawa, M., Moriyama, M., Jackson, I.J., Barrandon, Y., Miyachi, Y., and Nishikawa, S. (2002). Dominant role of the niche in melanocyte stem-cell fate determination. Nature *416*, 854–860.

Oliveria, S.A., Saraiya, M., Geller, A.C., Heneghan, M.K., and Jorgensen, C. (2006). Sun exposure and risk of melanoma. Arch. Dis. Child. *91*, 131–138.

Otberg, N., Richter, H., Schaefer, H., Blume-Peytavi, U., Sterry, W., and Lademann, J. (2004). Variations of hair follicle size and distribution in different body sites. J. Invest. Dermatol. *122*, 14–19.

Parra, E.J. (2007). Human pigmentation variation: evolution, genetic basis, and implications for public health. Am. J. Phys. Anthropol. Suppl. *45*, 85–105.

Randall, V.A. (2008). Androgens and hair growth. Dermatol. Ther. *21*, 314–328.

Sacco, J.J., Botten, J., Macbeth, F., Bagust, A., and Clark, P. (2010). The average body surface area of adult cancer patients in the UK: a multicentre retrospective study. PLoS ONE *5*, e8933.

Schneider, M.R., Schmidt-Ullrich, R., and Paus, R. (2009). The hair follicle as a dynamic miniorgan. Curr. Biol. *19*, R132–142.

Siervogel, R.M., Roche, A.F., Himes, J.H., Chumlea, W.C., and McCammon, R. (1982). Subcutaneous fat distribution in males

and females from 1 to 39 years of age. Am. J. Clin. Nutr. *36*, 162–171.

Slominski, A., Wortsman, J., Plonka, P.M., Schallreuter, K.U., Paus, R., and Tobin, D.J. (2005). Hair follicle pigmentation. J. Invest. Dermatol. *124*, 13–21.

Sun, F., Chaney, A., Anderson, R., and Aguilar, G. (2009). Thermal modeling and experimental validation of human hair and skin heated by broadband light. Lasers Surg. Med. *41*, 161–169.

von Thaler, A.K., Kamenisch, Y., and Berneburg, M. (2010). The role of ultraviolet radiation in melanomagenesis. Exp. Dermatol. *19*, 81–88.

Vogt, A., Hadam, S., Heiderhoff, M., Audring, H., Lademann, J., Sterry, W., and Blume-Peytavi, U. (2007). Morphometry of human terminal and vellus hair follicles. Exp. Dermatol. *16*, 946–950.

Williams, M.L., and Pennella, R. (1994). Melanoma, melanocytic nevi, and other melanoma risk factors in children. J. Pediatr. *124*, 833–845.

Yu, H., Fang, D., Kumar, S.M., Li, L., Nguyen, T.K., Acs, G., Herlyn, M., and Xu, X. (2006). Isolation of a novel population of multipotent adult stem cells from human hair follicles. Am. J. Pathol. *168*, 1879–1888.

Zanetti, R., Franceschi, S., Rosso, S., Colonna, S., and Bidoli, E. (1992). Cutaneous melanoma and sunburns in childhood in a southern European population. Eur. J. Cancer *28A*, 1172–1176.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Vellus hair follicles and melanoma incidence.

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Appendix 1

Methods

Epidemiological data

A literature review of epidemiological studies regarding malignant melanoma was conducted. The purpose was to obtain comprehensive data on vellus hair follicle density at different body sites. For men and women, studies from Switzerland and British Columbia gave detailed information on the number of cases of cutaneous malignant melanoma as well as body sites, percent of body surface area, and sun exposure levels of body sites (Bulliard et al., 2007; Elwood and Gallagher, 1998; Otberg et al., 2004). Vellus hair follicle information was obtained from Otberg et al. (Bulliard et al., 2007; Elwood and Gallagher, 1998; Otberg et al., 2004). Data were available for six body sites: back, chest, upper arm, forearm, thigh, and leg. There were four sun exposure levels: level 1 (minimum lifetime), level 2 (low lifetime, mainly intermittent), level 3 (high lifetime, mainly intermittent), and level 4 (high lifetime, constant). Based on available data, we were able to examine body sites with sun exposures levels 1–3, but no body site data was available for pairing with vellus hair follicle data for body sites with sun exposure level 4. The analysis cohort had 24 units in which the unit of analysis was composed of a combination of country (n = 2), gender (n = 2), and site (n = 6) (see Supplementary Table S1). For each country of origin and gender, the total number of vellus hair follicles

per body site was calculated for each of the 24 specific combinations of sun exposure level and corresponding body site(s) as the product of BSA (cm^2) and number of vellus hair follicles per cm^2. BSA (%) was calculated as $BSA/18\,000 \times 100\%$ The constant, 18 000, represents the average value for human body surface area in cm^2 (Sacco et al., 2010). Similarly, for each country of origin and gender, the melanoma incidence was calculated separately for the 24 specific combinations of sun exposure level and corresponding body site(s). For example, there were 57 melanoma cases detected in 788 Swiss men at sun exposure level 1 (hip, thigh, knee, and popiteal space), corresponding to a melanoma incidence of 0.072.

Statistical evaluation and modeling approach
Intuitively, anatomical body regions with equal sun exposure levels would be expected to exhibit a positive relationship, indicating higher melanoma incidence in anatomical regions with larger BSAs. With this in mind, scatter plots were drawn to illustrate the relationship between the incidence of cutaneous melanoma and BSA for anatomical regions among men and women. Similar plots were drawn to illustrate the relationship between the incidence of cutaneous melanoma and vellus hair follicles. Multiple linear regression analysis was applied to examine the relationship between the primary outcome, melanoma incidence, and predictors including gender, country, BSA, total number of vellus hair follicles per body site, and exposure level. Models including main effects and interactions between total number of vellus hair follicles per body site and exposure level and between gender and exposure level also were examined. Exposure level was modeled as a three-level categorical variable. The modeling strategy was to identify the most parsimonious set of predictors that were statistically significantly related to melanoma incidence. The multiple coefficient of determination, R^2, and residual plots were examined to assess the ability of the fitted equation to explain variation in the data and goodness-of-fit to the model.