Medical Hypotheses 81 (2013) 846–850

Contents lists available at SciVerse ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Melanoma. Shall we move away from the sun and focus more on embryogenesis, body weight and longevity? ☆

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ARTICLE INFO

Article history:
Available online xxxx

ABSTRACT

There are many observations regarding the behaviour of melanoma which points away from sunshine as the main cause of this tumour. Incidence data shows that the increase is mostly seen for thin melanomas which cannot be attributed to sun exposure but increasing screening over the last 20 years. Melanoma behaves in a similar fashion all over the world regarding age of onset, gender differences and histological subtypes. An excess of naevi is the strongest risk factor for melanoma and their appearance and involution throughout life, and the differences in naevus distribution according to gender is giving us a lot of clues about melanoma biology. Melanoma like all cancers is a complex disease with the involvement of many common and low penetrance genes many of them involved in pigmentation and naevogenesis but these only explain a very small portion of melanoma susceptibility. Genes involved in melanocyte differentiation early on in embryogenesis are also becoming relevant for melanoma initiation and progression. Reduced senescence and longevity as well as body weight and energy expenditure are also relevant for melanoma susceptibility. These observations with links between melanoma and non-sun related phenotypes as well as gene discoveries should help to assess the relative contribution of genetic and environmental factors in its causation.

This review, whilst not wishing to dismiss sunshine altogether is attempting to redress the balance especially as the primary prevention of melanoma with avoidance of sun exposure has not been proven to reduce melanoma incidence and mortality and may be harmful.

Melanoma incidence and mortality

The main argument for implicating sunshine as the cause of melanoma is the difference in melanoma incidence between Australia and Europe. The other argument is the rapid rise in melanoma incidence over the last 30 years which has been attributed to changes in sun seeking behaviour over the same period. [1,2]. However, there are some clues in the epidemiological data which, when looked at carefully, do not point to sunshine as being the main cause for these observations. When examining the incidence of melanoma in Australia, for example, the rapid rise in incidence has mainly been for very thin melanomas which have hardly had any impact on mortality which has remained fairly flat over the same period [2,3]. The delivery of dermatology services in Australia is very different from many European countries and especially the UK. Dermatologists and general practitioners in Australia offer rapid access melanoma screening following frequent public health campaigns and many naevi are excised during the screening process. These screening campaigns have led to a rapid rise in the number of very thin and borderline melanomas which in turn inflates overall incidence [4].

Comparing mortality and incidence data in melanoma is also important as it gives further clues to the types of melanomas removed following screening campaigns. The incidence of melanoma has risen dramatically in all countries where access to dermatologists is relatively easy and public health campaigns have been quite active. However, mortality has remained relatively stable and in some countries is even dropping with a widening between the mortality and incidence curves over the last 20 years [1].

This also supports the fact that most melanomas removed from screening campaigns are very thin and are likely to be biologically different. Data from Eastern European countries also supports this. A rise in incidence of melanoma in Eastern European countries has only occurred in countries where access to dermatologists has become easier with public health campaigns over that least 15 years. In other Eastern European countries, where this was not in place over the same period, the lower incidence and greater thickness

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http://dx.doi.org/10.1016/j.mehy.2013.05.031

of melanomas is comparable to figures seen in the UK 30 years ago [5]. Whilst there is no suggestion that we should not be detecting melanoma early, the impact of active screening and public health campaigns on melanoma incidence needs to be recognised and changes in sun exposure should not be blamed as the cause for this rapid rise in incidence without supporting evidence. The impact of screening on breast and prostate cancer incidence with the detection of many early lesions has been well documented and this is no different for melanoma [4].

Melanoma behaviour: site, histological subtypes and gender

Another argument to downplay the role of sunshine in melanoma is the fact that melanoma is a tumour which behaves in a very similar fashion within similar ethnic groups all over the world despite very different levels of UV exposure. Population based melanomas outside the familial setting have a mean age of onset in the mid-fifties and this is constant in the UK or Australia [6]. If sunshine was such a driver for melanoma in Australia, this should, in theory, lower the age of onset. The relative proportions of different histological subtypes of melanoma such as superficial spreading, nodular melanoma and lentigo maligna (with invasion) are also very similar across all countries. The distribution of melanomas on the body is also telling. Melanomas in males tend to occur more commonly on the trunk whilst melanomas in females are mostly seen on the legs [7]. This observation is again somehow attributed to differences in sun exposure habits between males and females but the data does not support this as the difference in body sites according to gender is constant across all Caucasian populations irrespective of sun exposure. This difference is most likely to be explained by differences in melanocyte differentiation between males and females. Indeed when counting naevi in small children and following them up with age, boys and girls already differ in their naevus distribution with more naevi on the limbs especially arms and legs in girls and more naevi on the trunk in boys which reflects the distribution of melanomas in adults [8,9]. It is possible that intense and repeated sunlight exposure in childhood may increase the number of small naevi as total naevus counts are higher in Australia compared to the UK but it is likely that small lentigines are also miscounted as naevi on sun exposed sites [6]. Males also show consistently higher number of naevi than females and this is also seen in different parts of the world irrespective of sun exposure [8,9]. The types of naevi also vary greatly according to body sites as intradermal naevi which are mature lesions with a low risk of transformation into melanoma are common on the face for example but are more rarely seen on the limbs for examples. On the other hand, junctional and atypical naevi which are more unstable lesions in terms of melanoma risk are very rare on the face and are most common on the trunk and proximal limbs. Sun exposure again cannot explain these observations as the face is a chronically sun exposed site yet does not tend to have unstable melanocytic lesions such as junctional and atypical naevi. Specific gene expression in melanocytes from various body sites is likely to explain these observations and the mouse model provides clues about differences in behaviour of melanocytes on the cephalic region compared to limbs and dorsal areas and this has also been observed for fibroblasts [10].

There is also a significant increase in survival from melanoma in all populations in females so gender specific factors are crucial in the field of melanoma [1]. Brain tumours also show a significant increased survival in females and as melanocyte and neurones both come from the neural crest, it is likely that gender differences in neural crest cells differentiation explain these findings [11]. With the advances in genetics, these differences in naevi and melanoma behaviour according to histological subtypes and gender can hopefully be investigated in more detail but will need large and well phenotyped datasets to achieve this.

Biology of naevi as strongest risk factor for melanoma

The number and types of naevi (such as atypical naevi) is the strongest risk factor for melanoma in all Caucasian populations and the magnitude of the odds ratios (5–20) is much greater than any odds ratios ever reported for sun exposure and skin colour (1.5–2) (Fig. 1) [12,13]. Naevi confer the same magnitude of risk for melanoma at all latitudes showing again that sunlight is not that important for this association [14]. Looking into the biology of naevi is likely to lead to very interesting clues regarding the pathogenesis of melanoma. Melanocytes derive from the neural crest cells and their differentiation and migration to the skin occur during embryogenesis. This involves many genes such as MITF, WNT signalling, SOX10 and SOX 9 to mention only a few [15]. Interestingly, one of these genes, MITF has recently been reported to be involved later on in adulthood in melanoma susceptibility and invasion [16,17]. BRAF somatic mutations are also very common in naevi and melanoma and this led recently to the first therapy ever conferring an increased survival in melanoma [18,19]. Bastian and colleagues have looked at genetic signatures in melanoma tumours according to histological subtypes and body sites [20]. BRAF mutated melanomas are more common on the trunk and limbs compared to head and neck tumours and this again was thought to be due to differences in sun exposure but this

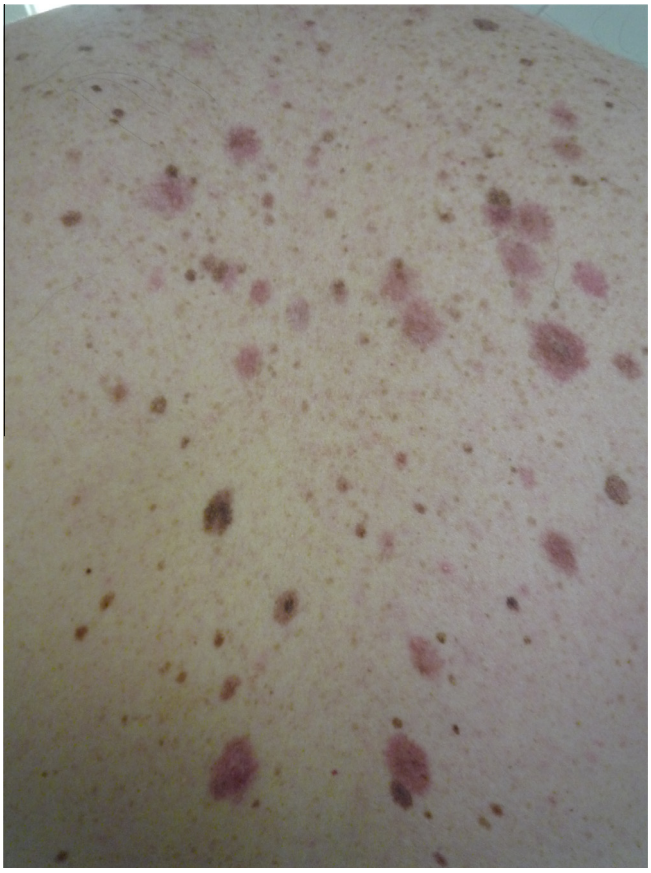

Fig. 1. The atypical mole syndrome (AMS). Naevi genetics has helped in discovering new melanoma genes but this phenotype is also helpful as it does unravel some associations between melanoma risk factors and other phenotypes such as reduced ageing and longer telomeres.