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Melanoma: What Are the Gaps in Our Knowledge?

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Cutaneous malignant melanoma (MM) falls into two main groups, based on aetiology [1–3]. First, a small minority of patients have acral MM, in which the disease occurs on the palms and soles. The incidence of acral MM is similar in people with widely different skin colours (and hence with different amounts of skin melanin), and at different latitudes. The palms and soles have a thick epidermis, and so few harmful photons of ultraviolet radiation (UVR) will penetrate to the germinative layers. Acral melanomas are therefore not believed to be causally related to UVR, and their aetiology remains a mystery. They will not be discussed further in this article.

By contrast, more than 90% of MM occurs on non-acral sites and is thought to be caused by UVR [2,4]. The evidence for such causality comes from a variety of fields. MM is most common in those with pale skin, which has a relative lack of melanin, a substance that blocks photons from penetrating deeply into skin [2]. African people with very dark skin are hundreds of times less sensitive to the harmful effects of UVR than white Northern Europeans. Even within white Northern European populations, MM rates vary in relation to more subtle degrees of difference in sun sensitivity. Those with red hair, pale skin, and a tendency to freckle are about three times more likely to develop MM than those without these three features [2,5]. The dramatically elevated rate of MM in those with European ancestry in Australia is therefore what we would expect: susceptibility of the host coupled with enhanced environmental exposure leads to a high disease risk [4].

However, it is not just epidemiology that implicates a key role for UVR. Patients with the rare Mendelian

Research in Translation discusses health interventions in the context of translation from basic to clinical research, or from clinical evidence to practice.

Linked Research Article

This Research in Translation discusses the following new study published in *PLoS Medicine*:

Viros A, Fridlyand J, Bauer J, Lasithiotakis K, Garbe C, et al. (2008) Improving melanoma classification by integrating genetic and morphologic features. PLoS Med 5(6): e120. doi:10.1371/journal.pmed.0050120

Boris Bastian and colleagues present a refined morphological classification of primary melanomas that can be used to improve existing melanoma classifications by defining genetically homogeneous subgroups.

disorder xeroderma pigmentosa (see http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=278700) have a dramatically increased risk of most types of skin cancer, including MM. This disorder is characterised acutely by sun-burn in response to tiny amounts of UVR, and both this sun-burn and the elevated cancer rates are a result of an inability to repair the DNA damage induced by UVR. The lesson is quite clear: it is not sunlight per se, but the highly mutagenic UVR part of the electromagnetic spectrum that is important for skin carcinogenesis.

Given that we know the major host and environmental factors that lead to non-acral melanomas, one might think that we know enough to reduce the incidence of MM. But our ability to change people's behaviour so that they reduce their exposure to UVR remains limited. In addition, as our knowledge of MM has increased, so has the incidence of disease. Puzzling gaps therefore remain in our knowledge of the aetiology of non-acral melanomas. So what important things do we not know?

Gaps in Our Knowledge of the Aetiology

First, although MM is related to UVR exposure, the body site distribution of MM does not match the distribution of

some other sun-related cancers, such as squamous cell carcinoma (SCC) of the skin [6,7]. SCC is most common on the backs of the hands, the face, and the scalps of bald men: these are the sites that receive the highest cumulative dose of UVR. By contrast, when the body site distribution of MM is mapped out, we see that sites such as the shoulders and back in men, and lower legs in women, show relatively higher rates of MM. I say relatively because obviously the different body sites differ in surface area, but the point is that we see a difference between SCC and melanoma on the basis of the same human anatomy. If the amount of UVR received is to explain MM aetiology, then we need to factor in some other modifying hypothesis. Perhaps the pattern of exposure is important, with sites that are intermittently exposed behaving differently from those that are continually exposed. It is this line of argument that contributed to the hypothesis that acute episodes of "sun-burning" (rather than cumulative dose of UVR) may be important [3,6,8].

Second, SCC rates increase exponentially with age, as do most human cancers. Melanoma is again different, with a curious interaction between age and site [7]. MM on sun-

Abbreviations: MM, malignant melanoma; SCC, squamous cell carcinoma; UVR, ultraviolet radiation

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exposed sites such as the face increases with age, as does SCC, but on other body sites the incidence peaks far earlier in adult life [2]. Perhaps there are different mechanisms operating at different sites? What we do know is that whatever aetiological differences there are, the prognosis of the resulting tumours (using standard indicators) is similar at the different sites.

Third, the incidence of melanoma has increased steadily in most European-derived populations over the last 40 years or more. Rates vary by country, but annual increases of 3%–7% are the norm [2]. Conventional wisdom is that increased exposure to the sun in the form of changes in behaviour (essentially increases in, and changed patterns of, leisure) underpin these rates [9]. The case is persuasive, but we still lack objective measures of personal sun exposure over the lifetime of individuals. Studies using UVR-sensitive badge monitoring of individuals do show that whatever the ambient UVR, personal behaviour is a key factor in determining sun exposure: many children in Northern England will receive more UVR than children in Queensland, Australia [10].

But there is another aspect of the increase in diagnosed cases that is perhaps more critical still, a phenomenon that is seen in many other tumour types that receive more medical attention: we may be picking up "earlier" lesions, but at the cost of not knowing the biological behaviour of the lesions we detect. The question can be usefully framed as follows: to what extent does melanoma histopathology reflect biological behaviour? To understand this issue, we need to look more closely at what happens in the clinic rather than just in the research laboratory.

The Clinical Picture

In the early part of the 20th century, the clinical picture of melanoma was of a highly malignant tumour that presented late and carried a high mortality at five years of about 80% [1]. Then, as is still largely the case today, there was no curative treatment for metastatic disease. Judged in terms of absolute tumour mass MM appears to metastasise early and, in the absence of insights into how to treat metastatic disease, the mantra has been to detect melanoma early before it has

Five Key Papers in the Field

Yee EFT, Hoffman RM, Berwick M (2007) Early diagnosis of melanoma: What do we know? Gital Dermatol Venereol 142: 55-70 [3].
An authoritative and lucid review that critically examines most aspects of melanoma epidemiology, with an emphasis on the diagnosis of early lesions.

Landi MT, Bauer J, Pfeiffer RM, Elder DE, Hulley B, et al. (2006) MC1R germline variants confer risk for BRAF-mutant melanoma. Science 313: 521-522.
An intriguing paper, building on previous work by others suggesting that the aetiological pathways for melanomas at different body sites may be different, which proposes links between two hitherto unrelated molecular pathways.

Welch HG, Woloshin S, Schwartz LM (2005) Skin biopsy rates and incidence of melanoma: Population based ecological study. BMJ 331: 481.
A provocative paper that suggests that over-diagnosis based on increasing biopsy rates may account for some of the putative increases in reported melanoma rates

Edman RL, Klaus SN (2000) Is routine screening for melanoma a benign practice? JAMA 284: 883-886.
A welcome attempt to counter the widespread assumption that population screening for melanoma has no down-sides.

Burton RC, Coates MS, Hersey P, Roberts G, Chetty MP, et al. (1993) An analysis of a melanoma epidemic. Int.J Cancer 55: 765.
Based on analysis of epidemiological trends in Australia, this was the first paper to argue that there may exist a subset of melanomas that do not metastasise.

metastasised. Although we have no evidence for the value of population screening for MM, over the last century greater access to health care and increasing knowledge and concern about MM led to patients presenting earlier with lesions that might be MM [3]. Rather than a five-year death rate of 80% or greater, we now see a survival rate at five years of 80% or more [2]. It would seem natural to attribute the increased survival of patients with MM to the increased detection of early disease.

The most useful prognostic predictor for MM is the Breslow thickness [11], essentially a measure in millimetres of the vertical depth of the lesion measured on a routine histopathology slide. A number of different morphological terms (e.g., nodular melanoma, superficial spreading melanoma) have been used to classify melanoma, but they add little if anything to the information provided by the Breslow thickness (although they my reflect aetiological differences). Over time, the mean Breslow thickness has declined in many populations, a testament to earlier and earlier detection of MM.

The "Non-Metastasising Hypothesis"

The combination of increasing incidence of a disease with a reduction in case fatality has led to other hypotheses [9]. In the 1990s, based on examination of epidemiological trends in Australia, Burton and Armstrong [12] argued that dramatic increases in thin melanomas (in terms of Breslow thickness) and no reduction in the number of thick MMs suggested that many lesions being detected were (in their words) "non-metastasising MM". The argument was that on top of the real increases in MM capable of metastases, increased sampling led to lesions that were biologically more benign being histopathologically classed as MM—a scenario familiar to students of other human cancers such as breast and prostate. This scenario is also seen in the skin with non-melanoma cancers: actinic keratoses, lesions with multiple genetic changes that were once thought to be the hallmark of cancer, regress without any treatment in most cases [13]. The more you look for squamous cell carcinomas, the more actinic keratoses you biopsy.

However, the "non-metastasising MM" hypothesis [12] is frustratingly difficult to prove in the real world where we study patients rather than laboratory mice. If a clinician finds a skin lesion that looks remotely suspicious of a melanoma, it must be excised—usually a simple, almost trivial procedure. But once the lesion is fixed in formalin, all we have as our guide is the pathologist's interpretation of morphology—not the natural history of the lesion, the standard test of biological behaviour. How can we infer

natural history when the sample has been removed?

There would seem to be two possible solutions to this conundrum, one old and one new. First, if some histopathological changes that are considered typical of MM are found more widely, say in patients who die for other reasons, then it may be possible to estimate their prevalence and use these base rates to inform the significance of such changes in a clinical context of a suspicious lesion. We already know that the histopathological interpretation of melanocytic lesions is difficult, and that there is significant variation in reporting between even specialist melanoma pathologists [3,14], so any design must allow for such factors. Today it might be far harder to gain regulatory approval for such a study than it would have been a generation ago.

The second approach is to hope that technology and the vogue for large patient cohorts (as part of large collaborative studies) may help us. A study in this issue of *PLoS Medicine*, of a cohort of 302 archival tissues of primary cutaneous melanomas, provides such an example [15]. Boris Bastian and colleagues examined a range of (histopathological) morphological criteria and related these changes to mutations in *BRAF* and *NRAS*, two genes previously known to be important in melanoma pathogenesis. The authors then showed, in an independent cohort, that

these morphological changes could be used as a proxy for genetic analyses and clinical outcome predictions. The emphasis on morphology gleaned from routine histopathological samples is important: it remains salutary that examination of melanocytic lesions using microscopic morphology remains more informative than any products of the genomics revolution—or any other "-omics" for that matter.

The ability to mine data from retrospective collections, where long-term survival information is available, is therefore very important. But the potential utility of such collections may also change. Just as the Breslow thickness [11] allows us to distinguish groups of patients with very thin lesions who have an uncertain prognosis from patients without melanoma [2], new technologies—if they can be applied to the small fixed biopsy samples of melanoma—might allow us to gradually detect more and more markers that predict outcome. Gradually, if one is an optimist at least, we may bootstrap our knowledge of those lesions that "look like MM" but show clinical outcomes that are indistinguishable from those of age-matched controls. There may be no Eureka moment, rather just a gradual tightening of confidence limits on what we may say. ■

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