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Article type : Research Letter

Clinicopathological characteristics and prognosis of patients with multiple primary melanomas

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Word count: 1,079

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/bjd.15855](https://doi.org/10.1111/bjd.15855)

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Figures: 0

Tables: 0

Funding sources: NRA is supported by the Australian Postgraduate Award

Conflicts of interest: none declared

This narrative review provides an evidence-based overview of existing literature on the epidemiology, clinicopathological characteristics and prognostic outcomes of tumours arising in patients with multiple primary melanomas (MPM). PubMed and MEDLINE were searched for original research papers and review articles from 2000 to 2016 using the term ‘multiple primary melanoma.’ Population-wide increases in life expectancy, advances in early detection and increasing incidence of melanoma give rise to an expanding group of patients that are at an increased risk of developing subsequent primary tumours.^{1,2}

A personal history of melanoma is a potent risk factor for the development of a subsequent primary melanoma.³ Between 1.2% and 8.2% of melanoma patients develop MPM.^{4,7} Registry data from Victoria, Australia indicates that the mean annual rates of subsequent melanomas are approximately 0.4%.⁸ The above reported rates may underestimate the lifetime rates due to limited data capture and follow up periods.^{2,7} Variability may also arise due to differences in ambient ultraviolet radiation across geographic regions.

Among patients with MPM, 26-40% of melanomas develop as synchronous lesions (*i.e.* subsequent primary melanoma diagnosed within three-months of incident primary melanoma), while the remainder develop as asynchronous lesions.^{4,7} The risk of a subsequent primary melanoma is highest in the first year following diagnosis of the incident primary melanoma; however, this risk remains increased for at least 20 years.^{2,4,6,7,9}

Several studies have demonstrated that males are at higher risk of multiple primary melanomas.^{2,4,10,11} The presence of dysplastic naevi is also a well-recognised risk factor for the development of MPM.^{5,12,13} The incidence of MPM has been reported to be significantly increased in patients with dysplastic naevi, with rates at 1-year and 5-years of 11.1% and 23.6%, respectively, compared to 4.8% and 9.7% in patients without dysplastic naevi.⁵ A high naevus count and a positive family history of melanoma have also been reported as risk factors for MPM.^{5,12,13} Germline mutations of *CDKN2A* and *CDK4* genes are associated with both a family history of melanoma and development of MPM.^{5,14} In patients with MPM, the frequency of *CDKN2A* mutation is higher in those with a family history of melanoma compared to those without (47% vs. 8-12%, respectively).^{5,14} The presence of multiple *MC1R* variants has been shown to be associated with MPM in patients with *CDKN2A* mutations.¹⁵ Another study has demonstrated that MPM patients have an increased probability of

being *MC1R* variant carriers and have a higher probability of carrying two or more variants.¹⁶ Helsing *et al.* similarly demonstrated allele dose-dependent increase in MPM risk for carriers of red hair colour *MC1R* variants.¹⁷

In a recent genome-wide association study in an Australian cohort, the microphthalmia-associated transcription factor (*MITF*) E318K variant was enriched in patients with multiple primary melanomas (OR 4.22, 95%CI 1.52-10.91) and in patients with both a family history of melanoma and multiple primary melanomas (OR 8.37, 95%CI 2.58-23.90).¹⁸ In the international population-based Genes, Environment and Melanoma (GEM) case-control study, single nucleotide polymorphisms in *TERT/CLPTM1L*, *TYRP1*, *MTAP*, *TYR* and *MX2* were significantly associated with the occurrence of multiple primary melanomas.¹⁹ This provides evidence that several putative low-penetrance susceptibility loci for melanoma are related to the risk of subsequent melanoma development.¹⁹

Furthermore, some studies have found that the body site of the first primary invasive melanoma has no effect on the risk of developing a subsequent invasive melanoma.^{5,20} However, other studies have determined that head and neck melanomas are over-represented in MPM patients, suggesting a possible role for chronic sun exposure.² A few studies suggest that subsequent melanomas are more likely to occur at the same body site as the initial melanoma.²⁰ Anatomical site concordance of incident and subsequent primary melanomas is reported to range between 49% and 56%.^{5,7,9,21} This highlights the importance of close surveillance of the same body region as the initial primary melanoma in the follow up of melanoma patients.²⁰

Subsequent primary melanomas are thinner and more likely to be in situ than incident primary melanomas.^{2,5-7,12} This may be explained by early detection due to enhanced clinical surveillance.^{6,12} In support of the early detection hypothesis, a retrospective study demonstrated that patients with MPM who adhered to regular follow-up had significantly thinner subsequent primary melanomas compared to those who did not (0.36 vs. 1.22 mm, $p=0.02$).¹²

Available research on the prognosis of patients with MPM is limited as most large prognostic studies have excluded patients with MPM as there is some ambiguity surrounding which primary melanoma was responsible for the metastatic disease. Nonetheless, most of the existing literature suggests that patients with MPM have enhanced survival compared to patients with single primary melanomas.^{7,10,22} In contrast, a Queensland population-based study determined that patients with MPM have an increased melanoma-specific mortality.²³ These authors reported that their results markedly differ from the existing literature due to possible survival bias in other studies (*i.e.* survival after multiple primary melanomas is often measured from the time of first melanoma diagnosis). To overcome this, their study used a delayed entry analysis.²³

The reported enhanced survival of patients with MPM in the vast majority of studies may be due to an “immunisation effect” to common melanoma tumour antigens, whereby there is an immune response

to each subsequent melanoma.²² Thus, the broad host immune response to the greater antigenic diversity results in slower tumour progression.^{22,24} It is conceivable that this immunological surveillance is weaker in Queensland due to ultraviolet-induced immune suppression from chronic exposure at latitudes closer to the equator, which may, in part, explain the Queensland investigators' discrepant findings.

Murali and colleagues' cohort study demonstrated that patients with MPM, compared to patients with a single primary melanoma, had a significantly improved median survival from the time of diagnosis of first distant metastasis (11.2 vs. 7.7 months, $p < 0.001$).²⁴ After controlling for known confounders, the number of primary melanomas was an independent prognostic marker in patients with distant metastatic disease.²⁴ While there was a difference in the rate of progression to death following a diagnosis of distant metastasis, there was no significant difference in the distant disease-free interval.²⁴ Therefore, host factors, including the immune response, may differ in patients with MPM, which may be related to the priming of the immune system to multiple clones of tumour cells.²⁴ Moreover, more indolent tumour behaviour may be an alternate, but not mutually exclusive, possibility to account for the reported survival benefit.

Understanding disease biology in patients with MPM is important for predicting prognosis. Further research should be targeted at exploring the intrinsic tumour factors, biologic mechanisms, host factors and the role of immunological surveillance that may underpin the reported improved survival in these patients.

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Title:

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Date:

2018-01-01

Citation:

Adler, N. R., Kelly, J. W., Haydon, A., McLean, C. A. & Mar, V. J. (2018). Clinicopathological characteristics and prognosis of patients with multiple primary melanomas. BRITISH JOURNAL OF DERMATOLOGY, 178 (1), pp.E44-E45. <https://doi.org/10.1111/bjd.15855>.

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