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Identification and management of high-risk individuals

About 3.3% of Australian women and 4.0% of men will develop melanoma at some time in their life, but individual risk varies widely about these averages. The aetiology of melanoma is now understood to involve both environmental and genetic factors and individual risk represents the sum of both types of influences.

It is reasonable to posit that successful and timely diagnosis of melanoma will be enhanced if clinicians are aware of high-risk groups in the population, and that people in these groups are aware of their status.

3.1 Strongest predictors of future cutaneous melanoma

The systematic meta-analyses of studies of melanoma risk factors between 1966 and 2002 by Gandini et al¹⁻³ provide the highest-level evidence available on risk associated with common and atypical melanocytic naevi, skin phototype and pigmentation, indices of sun exposure and family history of melanoma. Further systematic searches of the literature were undertaken for this review, but no studies identified since then warrant modification of their conclusions, which are summarised below and provide a basis for comprehensive clinical risk assessment.

3.2 Baseline risks due to age and sex

Clinical assessment of the probability that a patient is presenting with, or may develop, melanoma must start with their baseline risk due to the patient's age, sex and ethnicity.⁴⁻⁶ Age is one of the strongest risk factors for melanoma, as with all cancer. For example, a 70-year-old Australian man is eight times more likely to develop melanoma in the next ten years (2.5% risk), and a 70-year-old woman three times more likely (1.0%) than is a 30-year-old man or woman (0.3%). In New Zealand a 70 year old man or woman is, respectively, more than ten times (2.2% risk) or four times (1.4%) more likely to develop melanoma in the next ten years than is a 30 year old man or woman (0.2% and 0.3% respectively). Ethnic origin is also a strong risk factor. For example, in Los Angeles County, USA, in 1993–1997, non-Hispanic whites were, on average, six times more likely to develop melanoma in a year than Hispanic whites, 19 times more likely than blacks, and 24 times more likely than people of East Asian origin living in the County.⁷

The potential to focus detection and prevention efforts where they will be most efficient is greatest where absolute risks are highest, namely in the elderly and in high-risk (relative risk at least five- to ten-fold) younger and middle-aged adults. While there are no widely accepted algorithms for clinical estimation of melanoma risk, many of the risk factors below can be considered as contributing independently in a global risk assessment. It is important to recognise which factors are capable of conferring high risk in their own right, as opposed to many of the best-known risk factors, which are relatively weak (two-fold relative risk).

3.3 Previous melanoma or other skin cancer

Retrospective large-scale studies in several cancer registries have shown that a history of previous melanoma is a powerful predictor of future melanoma, with estimated relative risks ranging above ten. The risk is highest in the first one to two years after diagnosis and may be partly accounted for by increased surveillance. A history of non-melanoma skin cancer or premalignant lesions such as actinic keratoses confers relative risks of around four-fold in meta-analysis.³

3.4 Melanocytic naevi

Melanoma risk increases with naevus count, whether counted over the whole body or restricted to one body site, such as the arms. Those with the highest counts (> 100 naevi, whole body) had seven times (6.89; 95% CI 4.63–10.3) the risk of people with the lowest counts (< 15 naevi) in meta-analysis.¹

Total body counts of clinically atypical (dysplastic) naevi are strongly associated with melanoma risk, independent of the count of common melanocytic naevi. Those with the highest counts (> 5 atypical naevi) had six times (6.4; 95% CI 3.8–10.3) the risk of those with no atypical naevi in meta-analysis.¹

The thresholds that define high- and low-risk groups by naevus count in different population are not yet well defined.

3.5 Skin and hair colour, skin phototype and freckling

Meta-analyses of studies done mainly in populations of European origin show that light versus medium/dark skin colour, red-blond versus black hair, and blue versus dark brown eyes, confer risk increases of about two-fold. Similarly, a person with a Fitzpatrick phototype I (burn easily, never tan) is about twice as susceptible to melanoma as one with phototype IV (always tan, never burn), as are the most heavily freckled versus those without freckles.³ These phenotypes are not independent of one another and while combinations may further increase risk, they do not multiply it.

The dramatic variation of melanoma incidence across ethnic groups is partly accounted for by these variations in skin type, though there are additional genetic (e.g. MC1R variation, see 3.9 *Genetic risk factors and testing*) and cultural/behavioural determinants (e.g. clothing and sun-seeking practices).

3.6 Sun exposure and its surrogates

Sun exposure is the main driver of melanoma incidence at the population level, with significant contributions made by total lifetime exposure, an intermittent pattern of exposure and exposure in childhood and adolescence (as indicated by the ambient solar UV irradiance at the place of residence). However, none of these exposures can be measured readily or retrospectively outside research settings and in any case, the relative risks for the highest categories of exposure, compared with the lowest, are rarely > 1.5. These low relative risks, however, may be due, at least in part, to inaccuracy in the

measures of exposure. Prior sunburns confer relative risks of up to 2.0 in meta-analyses.² However, such a history has limited clinical predictive value in regions such as Australia and New Zealand where the prevalence of sunburn is so high.

There are no reliable clinical surrogates for prior amount or pattern of sun exposure since they are all confounded by the effect of individual susceptibility to those endpoints. However, the presence of actinic damage is detectable clinically and confers a relative risk of 2.0 (95% CI 1.2–3.3).³

3.7 Family history of melanoma

One first-degree relative with melanoma approximately doubles melanoma risk in international meta-analyses (1.7; 95% CI 1.4–2.1).³ Robust population-based estimates are not yet available in Australia and New Zealand on the risk conferred by additional affected relatives of different degrees of relationship, but data from other common cancers suggest that each close affected relative doubles the risk of that cancer. Relatives affected at an earlier age than average, or who have experienced more than one melanoma, further raise the likelihood that strong familial and genetic risk factors are present (see 3.9 *Genetic risk factors and testing*).

Evidence summary	Level	Reference
Major risk factors for melanoma are, for the most part, well characterised in population-based studies. They include patient age and sex; history of previous melanoma or non-melanoma skin cancer; family history of melanoma, including age of onset and multiplicity of any melanoma cases; the number of common melanocytic naevi; number of clinically atypical naevi; skin and hair pigmentation type and response to sun exposure; and evidence of actinic skin damage. Present alone or in combination, they can substantially increase risk	I	1–6

Recommendation	Grade
1. Clinical assessment of future risk of melanoma take into account: <ul style="list-style-type: none"> • person's age and sex • history of previous melanoma or non-melanoma skin cancer • number of naevi (common and atypical) • family history of melanoma • skin and hair pigmentation • response to sun exposure • evidence of actinic skin damage 	B

3.8 Management of high-risk individuals

See Chapter 5.7 for detailed evidence and recommendations on early melanoma diagnosis.

The direct relationship between survival of patients with melanoma and lesion thickness (thicker lesions having a poorer prognosis) suggests that early detection of primary melanoma by regular review may decrease mortality from the disease. Regular skin examination can be done by the person himself or herself, perhaps aided by a partner or carer, or by a clinician. Both of these can be aided by total body photography, which provides a baseline that may aid recognition of new and changing lesions. The clinician examination can be aided by dermoscopy and short-term digital monitoring, in which suspicious lesions are photographed and reviewed at three months.⁸ In individuals with multiple naevi there is no evidence that prophylactic removal of lesions that are not clinically suspicious reduces prospective risk of melanoma.

Prospective studies of high-risk groups have repeatedly demonstrated that the average thickness of melanomas detected is reduced under regular surveillance. Therefore, to the extent that the prognosis of primary melanoma is related to its thickness, surveillance may be inferred to benefit such patients. However, to date none of these studies have involved systematic comparisons of alternative methods or protocols of surveillance, and such studies are unlikely to be done. Recommendations can therefore only be based on expert opinion and comparisons with historical experience. A screening interval of six months is regarded as sound practice, provided that patients also self-screen in the interim.

Evidence summary	Level	Reference
High-risk individuals may benefit from regular clinical surveillance for new melanomas and education to self-screen, based on expert opinion. There is no evidence to compare the relative effectiveness of specific surveillance techniques in high-risk patients, as opposed to those at average risk	III-2	8

Recommendation	Grade
2. Individuals at high risk of melanoma and their partner or carer be educated to recognise and document lesions suspicious of melanoma, and to be regularly checked by a clinician with six-monthly full body examination supported by total body photography and dermoscopy as required	C

3.9 Good practice point

- Prophylactic removal of nonsuspicious lesions is not recommended since it is unlikely to increase survival and therefore may incur unnecessary procedures and give false reassurance as many new melanomas in high-risk individuals will occur outside pre-existing naevi

3.10 Genetic risk factors and testing

Inherited mutations in the genes encoded by the CDKN2A locus, p16INK4A and p14ARF are strongly associated with melanoma risk, especially in the context of a family history of melanoma. The international GenoMEL consortium has systematically collated and synthesised evidence on the prevalence of these mutations in familial melanoma.^{9–11} These studies have incorporated and superseded the data presented since 1993 by individual member groups and represent the highest level of evidence available about the prevalence of these mutations and the risk of melanoma associated with them.

There are important differences between countries in the contribution of CDKN2A mutations to familial risk of melanoma, and the international literature previously suggesting that 20–40% of familial melanoma kindreds carry CDKN2A mutations is now known to be an overestimate in the Australian context. Only 10% of clusters of three to four cases carry such mutations, but 25% of five-case clusters, for example. However, the number of relatives in the cluster who have had multiple primary melanoma, or early median age of onset among the relatives (e.g. < 40 years) strongly influences the chance of a mutation in a high susceptibility melanoma gene being present.¹⁰

Limited data exist on the prevalence of these mutations outside the context of familial melanoma in Australia. However rates of < 0.5% in melanoma cases, and 2% in large series of cases with a second primary, not selected for family history, have been reported.^{12,13}

CDKN2A mutations do not confer a clinically recognisable phenotype on carriers. In particular, they do not directly cause atypical naevus syndrome, which appears to have complex genetic origins.

There is wide variation in estimates of risk conferred by carrying a CDKN2A mutation (penetrance) and strong evidence exists that it varies across different populations and is influenced by other independent risk factors for melanoma.⁹ However, in the context of familial melanoma in Australia, estimates of risk conferred are in the range ten- to twenty-fold. In contrast, mutations detected in the absence of familial melanoma, for example in cases of multiple primary melanoma unselected for family history, appear to confer much lower risks: four- to five-fold.¹²

Because of these uncertainties about risk conferred, and the lack of evidence that individuals at high familial risk should be managed differently according to their mutation test results, current consensus recommendations from GenoMEL emphasise that clinical testing for CDKN2A mutations has a very limited role at present which is confined to highly selected, well-characterised melanoma families.¹⁴

Variation in the melanocortin-1 receptor (MC1R) gene is strongly associated with skin and hair pigmentation and also contributes to melanoma risk independent of these clinical features. Large studies in populations, as well as in the context of familial melanoma have given reliable estimates of the degree of melanoma risk conferred by the red-hair associated (RHC) subset of MC1R variants. Risks vary from around 2.0 per RHC allele in the population, to 3.0 in the context of familial melanoma. These risks are at least additive: carriers of two RHC alleles have risks four- to six-fold higher than those with no RHC alleles. These alleles also amplify the risk to carriers of CDKN2A mutations.¹⁵ However, MC1R variants contribute to skin pigmentation, phototype and freckling and it is not yet clear how genetic testing of MC1R variants might be incorporated into clinical risk assessment independent of these other risk factors.

Evidence summary	Level	Reference
CDKN2A mutations cause high melanoma risk in the context of familial melanoma, though their prevalence is low, even in that setting	I	9–13
It is unclear at present whether individual risk management should be influenced by the results of genetic testing for CDKN2A mutations	IV	14

Recommendation

	Grade
3. Screening for a mutation such as the CDKN2A gene be contemplated only after a thorough clinical risk assessment (the patient is at personal high risk of melanoma), confirmation of a strong family history of melanoma (there is a significant probability of a family mutation), and appropriate genetic counselling	C

References

- Gandini S, Sera F, Cattaruzza MS, Pasquini P, Abeni D, Boyle P et al. Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. *Eur J Cancer* 2005; 41(1):28–44.
- Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *Eur J Cancer* 2005; 41(1):45–60.
- Gandini S, Sera F, Cattaruzza MS, Pasquini P, Zanetti R, Masini C et al. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. *Eur J Cancer* 2005; 41(14):2040–2059.
- AIHW (Australian Institute of Health and Welfare), AACR (Australasian Association of Cancer Registries). *Cancer in Australia: an overview, 2006*. Cancer series no. 37, Cat no. CAN 32. Canberra, AIHW. 2007.
- Australian Institute of Health and Welfare (AIHW). *Australian Cancer Incidence and Mortality*. Canberra: AIHW, 2007.
- New Zealand Health Information Service. *Cancer: New registrations and deaths 2003*. See also accompanying tables at <http://www.nzhis.govt.nz/publications/cancer.htm>. 2007. Wellington, New Zealand Ministry of Health.
- Parkin DM, Whelan SL, Ferlay J, Storm H. *Cancer Incidence in Five Continents, Vol I to VIII*. IARC CancerBase No. 7 <<http://www-dep.iarc.fr/>> accessed 17th November 2007. 2005. Lyon, IARC Press.
- Thompson JF, Scolyer RA, Kefford RF. Cutaneous melanoma. *Lancet* 2005; 365(9460):687–701.
- Bishop DT, Demenais F, Goldstein AM, Bergman W, Bishop JN, Bressac-de Paillerets B et al. Geographical variation in the penetrance of CDKN2A mutations for melanoma. *J Natl Cancer Inst* 2002; 94(12):894–903.
- Goldstein AM, Chan M, Harland M, Hayward NK, Demenais F, Bishop DT et al. Features associated with germline CDKN2A mutations: a GenoMEL study of melanoma-prone families from three continents. *J Med Genet* 2007; 44(2):99–106.

11. Goldstein AM, Chan M, Harland M, Gillanders EM, Hayward NK, Avril MF et al. High-risk melanoma susceptibility genes and pancreatic cancer, neural system tumors, and uveal melanoma across GenoMEL. *Cancer Res* 2006; 66(20):9818–9828.
12. Berwick M, Orlow I, Hummer AJ, Armstrong BK, Krickler A, Marrett LD et al. The prevalence of CDKN2A germ-line mutations and relative risk for cutaneous malignant melanoma: an international population-based study. *Cancer Epidemiol Biomarkers Prev* 2006; 15(8):1520–1525.
13. Aitken J, Welch J, Duffy D, Milligan A, Green A, Martin N et al. CDKN2A variants in a population-based sample of Queensland families with melanoma. *J Natl Cancer Inst* 1999; 91(5):446–452.
14. Kefford R, Bishop JN, Tucker M, Bressac-de Paillerets B, Bianchi-Scarra G, Bergman W et al. Genetic testing for melanoma. *Lancet Oncol* 2002; 3(11):653–654.
15. Palmer JS, Duffy DL, Box NF, Aitken JF, O’Gorman LE, Green AC et al. Melanocortin-1 receptor polymorphisms and risk of melanoma: is the association explained solely by pigmentation phenotype? *Am J Hum Genet* 2000; 66(1):176–186.

