Early detection of melanoma: a consensus report from the Australian Skin and Skin Cancer Research Centre Melanoma Screening Summit

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More than 15,000 new cases of invasive (stage 1–4) melanomas are diagnosed in Australia each year, the majority at early stages (1–2).[1] Melanoma is Australia's fourth most commonly diagnosed invasive cancer overall (excluding keratinocyte cancers) and is the most common cancer diagnosed in adolescents and young Australians (707 cases among those aged 15 to 24 diagnosed between 2010–14). However, it is still rare in this young population, with an age standardised rate of 44.1/1Mill).[1,2] More than 55,000 Australians have had a diagnosis of invasive melanoma in the past five years.[1] In addition to invasive melanoma, it is estimated that over 23,700 new cases of *in situ* melanoma will be diagnosed in 2019.[1] More than 1,700 Australians die from melanoma each year, with mortality rates continuing to rise, increasing from 4.7/100,000 in 2004 to 5.6/100,000 in 2019.[1]

For the large majority of invasive melanoma that are localised at diagnosis, survival is strongly related to tumour thickness (5-year survival 98% for tumours <0.8 millimetre [mm] thickness, compared to 54% for tumours greater than 4 mm).[3] Despite this, more deaths are attributable to thin melanomas (<1 mm) than very thick melanomas (≥4 mm) because of the much larger proportion of cases diagnosed as thin.[4]

Abstract

Introduction: A Melanoma Screening Summit was held in Brisbane, Australia, to review evidence regarding current approaches for early detection of melanomas and explore new opportunities.

Results: Formal population-based melanoma screening is not carried out in Australia, but there is evidence of considerable opportunistic screening as well as early detection. Biopsy rates are rising and most melanomas are now diagnosed when in situ. Based on evidence review and expert opinion, the Summit attendees concluded that there is currently insufficient information in terms of comparative benefits, harms and costs to support change from opportunistic to systematic screening. Assessment of gains in precision and cost-effectiveness of integrating total body imaging, artificial intelligence algorithms and genetic risk information is required, as well as better understanding of clinical and molecular features of thin fatal melanomas.

Conclusions: Research is needed to understand how to further optimise early detection of melanoma in Australia. Integrating risk-based population stratification and more precise diagnostic tests is likely to improve the balance of benefits and harms of opportunistic screening, pending assessment of cost-effectiveness.

Implications for public health: The Summit Group identified that the personal and financial costs to the community of detecting and treating melanoma are rising, and this may be mitigated by developing and implementing a more systematic process for diagnosing melanoma.

Key words: melanoma, screening, prevention, early detection, skin cancer

In addition to the risk of death, receiving a melanoma diagnosis carries psychological burden. Fear of recurrence or of developing a subsequent primary melanoma is seen among a proportion of people diagnosed with either *in situ* or invasive melanomas.[5]

The incidence of invasive melanoma in Australia continues to rise in older age groups, but it has plateaued and decreased in younger age groups over recent years.[6,7] In contrast, over a 20-year period, incidence of *in situ* melanoma has increased in all age groups.[3] Based on Medicare data, skin biopsy rates have also increased by 66% over the past decade[8] and the economic burden is increasing steadily.

Given this overall burden, a Melanoma Screening Summit was held in Brisbane, Australia, to review the evidence of the benefits, harms, costs and opportunities for melanoma screening programs and their effectiveness, and to explore possible gains in Australia of the generation and evaluation of new research evidence.

The Melanoma Screening Summit was convened by the Australian Skin and Skin Cancer Research Centre (www.assc.org.au) over two days at the Translational Research Institute in Brisbane (25–26 March 2019). The Summit brought together representatives from research institutions, government departments, cancer control agencies, specialist medical colleges and consumers (Box 1).

The summit comprised a series of invited talks from experts to provide the most up-to-date evidence on approaches to melanoma detection in Australia, followed by a closed workshop attended by international and national leaders in melanoma control from multiple disciplines, including clinicians, researchers, consumers and policy experts (hereafter referred to as the Summit Group). The proceedings were summarised to help inform the roadmap to further optimise the early detection of melanoma in Australia, including research priorities.

Current Australian screening policy and practice

For cancers amenable to screening, the aim of screening programs is to detect disease at the pre-invasive or early invasive stage, before symptoms develop, in order to prevent cancer deaths and maintain quality of life. Some common terms are highlighted in Box 2.

Formal population-based screening is currently carried out in Australia for breast, cervical and colorectal cancers, but not for melanoma, due to insufficient evidence that screening would reduce melanoma mortality, including absence of randomised controlled trial evidence.[9]

The introduction of organised melanoma screening would require strong evidence of benefits outweighing harms at a population level, and evidence for cost-effectiveness.

Evidence base for melanoma screening

The natural history of melanoma development involves progression from normal melanocytes to pre-invasive cancer, invasive cancer, metastasis and death. Screening aims to detect primary melanoma before it has spread; that is, at the pre-invasive or localised invasive stage, while it is still confined within the skin and is curable by excision. As summarised by the United States Preventive Services Task Force[9] and the Australian Clinical Practice Guidelines for the Diagnosis and Management of Melanoma,[14] there is insufficient evidence that population screening reduces melanoma mortality.[9] A pilot study of population-based melanoma screening conducted in 2003/2004 in Schleswig-Holstein, Germany, showed a strong reduction in melanoma mortality, but a subsequent nationwide skin cancer screening program did not reduce mortality. A number of possible explanations for this have been posited including the lower penetrance of the nationwide program.[15] In Australia, the pilot of a randomised controlled trial of melanoma screening and a case-control study both suggested that screening using a whole-body visual inspection of the skin by a doctor (clinical skin examination) reduces the incidence of thick melanomas and increases the incidence of thin melanomas. In the pilot trial, 18 towns

were randomised to receive either free melanoma screening (among those aged 30 years or older) or no formal screening. Melanoma incidence increased in towns with screening over the three-year trial period, with most of the increase in thin (≤0.75 mm) and in situ melanomas, while in the control towns melanoma incidence decreased slightly.[16] In the case-control study, people who had received a clinical skin examination within three years prior to their diagnosis were 38% more likely to have a thin (≤0.75 mm) melanoma and 40% less likely to have a thick (≥3 mm) melanoma.[17] However, data for mortality and cost-effectiveness were not available. One reason why it may be difficult to reduce mortality by screening is the difficulty of detecting fast-growing and often fatal melanomas such as those of nodular or amelanotic subtypes. About 15% of all incident melanomas belong to these uncommon subtypes[18] but they are responsible for up to 30% of all deaths.[19] The nodular melanoma subtype has been reported to be associated with a 54% increased risk of melanoma death compared to superficial spreading melanoma, even when controlling for thickness, ulceration, stage and other prognostic variables.[19]

Overdiagnosis

Currently, there is insufficient data on the contribution of opportunistic screening to overdiagnosis. The harms of overdiagnosis include psychological stress and the risks and costs of tests, treatment and ongoing surveillance, both individually and to the health system. Overdiagnosis is unavoidable in cancer screening, but some have proposed that this can be reduced by targeted screening, which focuses on those with high risk who are more likely to have a relevant event.[20]

Overdiagnosis can be suspected when cancer incidence rises with little to no corresponding

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Box 1: Organisations represented at the Melanoma Screening Summit.

Australia and New Zealand Melanoma Trials Group, Australian Skin and Skin Cancer Centre, Cancer Council Australia, Cancer Council New South Wales, Cancer Council Queensland, Cancer Council Victoria, Cancer Institute NSW, Centenary Institute, Central Brisbane Dermatology, Danger Sun Overhead, Department of Health, Dermatology Research Centre, James Cook University, Mater Research Group, Melanoma Institute Australia, Melanoma Patients Australia, Melanoma Tasmania, Oregon Health & Science University, Princess Alexandra Hospital, QIMR Berghofer Medical Research Institute, Queensland University of Technology, Skin Cancer College Australasia, Stanford University Medical Centre and Cancer Institute, The Australasian College of Dermatology, The Skin Hospital, The University of Luebeck, The University of Melbourne, The University of Queensland (UQ), UQ Diamantina Institute, The University of Sydney, University of Southern Queensland, University of the Sunshine Coast, Workplace Health and Safety Queensland.

Box 2: Definition of key terms.

Principles of screening: The World Health Organization has formulated principles of screening, including having a screening test with high sensitivity and specificity, a clear referral system for management and follow-up, evidence of cost-effectiveness, and benefits that outweigh potential harms overall.[10]

Population-based screening is defined as an organised program in which a screening test is offered to all people in an eligible group, usually defined by sex and/or age.

Targeted screening is an organised program, as above, but starts with stratification of the eligible population according to risk, followed by the offer of a screening test to people in the high risk stratum.[11]

Opportunistic screening is the ad hoc application of a screening test, initiated either by a patient or their doctor, often as part of a routine medical visit. Opportunistic screening is not systematic, usually has lower rates of participation, higher disparities in screening uptake, and no quality assurance program.[12,13]

Overdiagnosis is defined as detecting cancers that, in the absence of screening, would not present symptomatically or cause harm during the patient's lifetime.[11]

rise in mortality, and Australian melanoma data appears to fit this pattern.[21] Concerns about possible overdiagnosis of melanoma in Australia were first raised 15 years ago.[22] From 1982 to 2015, age-standardised melanoma incidence rose from 27 to 52 cases per 100,000 persons, and over a similar period melanoma mortality rose much more slowly from 4.7 to 5.6 deaths per 100,000.[1] In 2019, the Australian Institute for Health and Welfare reported that the incidence of *in situ* melanoma rose by 115% between 2004 and 2015. Overdiagnosis would ideally be quantified using data from long-term randomised controlled trials.[8] Alternatives using non-trial data sources include ecological and cohort studies, modelling studies, histopathology and imaging studies. A new 'lifetime risk' method for estimating overdiagnosis was recently published that compares current (2012) and past (1982) lifetime risks for melanoma (adjusted for the competing risk of death and changes in risk factors), to estimate excess lifetime probability of a cancer diagnosis that may be attributed to overdiagnosis.[23] Applying this method to routinely collected Australia-wide melanoma and *in situ* melanoma data, it has been estimated that in 2012, 54% of melanomas diagnosed in women (15% of invasive), and 58% of melanomas diagnosed in men (22% of invasive) may have been overdiagnosed.[24] These data suggest that overdiagnosis of melanoma in Australia appears to be primarily (but not solely) driven by an excess of *in situ* melanoma diagnoses.[25]

Costs of treatment and screening

The fiscal burden of skin cancer in Australia is high, estimated to be about $1 billion each year, to which treatment for advanced melanoma was estimated to contribute $355.2 million and treating keratinocyte cancers was estimated to be $703.0 million (95% CI, $674.6–$731.4 million).[26,27] Targeted or immunological therapies for advanced melanoma improve disease-free survival but are very costly.[8] These costs are expected to rise steeply as more therapies and combinations become available and as they are increasingly used in neo-adjuvant and adjuvant settings. The productivity cost to Australian society of each premature death from melanoma averages approximately $288,000.[28] These costs could potentially rise or be brought forward if previously unidentified keratinocyte cancers are detected during a melanoma screening program.

The cost of screening must be weighed against the cost and morbidity of treating late-stage disease and the lost productivity resulting from premature death.[29] Earlier studies estimated that the number needed to screen and the cost to detect one melanoma are comparable to those observed for mammography breast cancer detection.[30] Recent studies of the cost-effectiveness of screening or surveillance have had variable results; however, targeting high-risk groups for screening and surveillance appears more cost-effective than an untargeted approach.[30] Despite causing more than 560 deaths each year, in the absence of good evidence for their quality-of-life impact, the diagnosis of keratinocyte cancers (especially basal cell carcinomas) has largely been seen as a cost rather than a benefit of screening for melanoma. However, the early detection of keratinocyte cancers may lessen the need for or the extent of surgery and prolonged treatment, and these potential benefits need further study.

Technology advances to target screening towards those at highest risk

In the absence of a population-based unified approach to melanoma screening, the Royal Australian College of General Practitioners recommends that Australians at increased risk of skin cancer, including melanoma, have opportunistic clinical skin examinations.[31] The Australian Clinical Practice Guidelines for Management of Cutaneous Melanoma recommend that people at very high risk of melanoma should have regular surveillance and be educated about skin self-examination and sun protection.[32] Risk assessment tools are available, but few have been validated or prospectively assessed[33-35] and they are rarely used in clinical practice to target melanoma. New and emerging risk assessment tools that integrate germline genetic information could increase the precision with which risk is assigned.[36,37]

Targeting people at high risk is important because as the incidence of melanoma in the screened group rises, the number needed to screen to prevent one melanoma death reduces. Using an example based on age and sex alone, the number needed to screen to prevent one melanoma death is 26,000 when screening women 18 years or older, but only 3,500 when screening men 50 years or older. The efficacy of screening could be further improved by increasing the accuracy of the screening test.

Regarding diagnostic accuracy, conventional dermoscopy is well known to improve the sensitivity of melanoma detection in the hands of specialists and primary care clinicians.[38-40] Technologies such as two-dimensional total body imaging or sequential digital dermoscopy highlight concerning lesions and allow change over time to be monitored.[40] Advanced imaging technologies such as three-dimensional total body photography supported by artificial intelligence, and liquid biomarkers, have the potential to further improve the accuracy of melanoma diagnosis and minimise excision of benign lesions.[41-43] These technology advances could inform a more systematic approach to melanoma screening in the future, but their utility in practice needs, including ensuring equitable access and training of the primary care workforce, requires further evaluation.[44-47] Prospective studies are needed to assess how to optimally integrate these advanced imaging systems with more complex diagnostic categories, on various skin types, and also to determine how best to use artificial intelligence algorithms to enhance clinical decision making without introducing bias.[42,48]

Novel randomised trial designs

Randomised controlled trials are the gold standard for establishing definitive answers about whether or not screening is beneficial. In the early 2000s, the Queensland Melanoma Screening trial was designed as a community-based trial that could have answered the questions about benefits and harms of population-based screening, including mortality, but due to funding limitations, it did not progress beyond its pilot phase. In the pilot, the trial showed that people will attend if screening is offered and that a large number of melanomas – but also keratinocyte cancers and benign lesions – will be diagnosed. To attempt such a trial now would require a much larger sample, as more background opportunistic screening is occurring now compared to 20 years ago; new targeted and immunotherapies have also led to increases in survival for advanced melanoma making a mortality endpoint more elusive. Unless the trial was restricted to people at higher risk of disease, the sample size required to detect a clinically significant difference in mortality may now be too large to be feasible (estimated to range between 82,000 per group if men 50 years or older were targeted to 320,000 if the general population 18 years or older was targeted).

Using an adaptive enrichment trial design may be useful for minimising the sample size required.[49] Key issues to clarify are the optimal outcome measure (e.g. thickness, metastasis, or mortality [noting that the latter is now strongly influenced by new systemic treatments]), the definition of high-risk groups that would benefit, and the optimal trade-off between the benefits, harms and cost-effectiveness of screening.

In summary, recent technology advances may influence clinical efficacy and effectiveness, as well as cost-effectiveness of melanoma screening, by detecting melanomas early while reducing the number of unnecessary excisions. Research will address how potential harms of screening, including false positive rates, overdiagnosis, overtreatment and fear of recurrence can be lessened. The Summit Group discussed key gaps in current melanoma screening knowledge and from this identified research priorities and long-term opportunities as detailed in Table 1. A full summary is available on the ASSC website.[50]

Discussion and recommendations

Unlike breast, cervical and colorectal cancer, there is no organised screening program for melanoma in Australia. However, there is evidence that opportunistic screening is widespread and there has been an increase in dedicated primary care skin cancer clinics offering this service over the past 20 years. Whilst there was consensus by the Summit

that there is a need to improve the current model of opportunistic screening, attendees concluded there is insufficient information on the best path forward at this time. The key gaps are lack of knowledge about the additional benefits, harms and costs of introducing a formal targeted screening program.

Currently, the case for melanoma population-based screening meets many, but not all, of the principles of screening as specified by the World Health Organization, including a screening test with high sensitivity and specificity, a clear referral system for management and follow-up, data on clinical effectiveness and cost-effectiveness, and benefits that outweigh potential harms.[10] Previous assessments of the viability of melanoma screening, for example by the United States Preventive Services Task Force, were based on general population screening in asymptomatic adults using a visual inspection of the skin. However, as the Summit report highlights, the development of new and emerging risk stratification tools, imaging technology advances and imminent integration of AI algorithms could have a major impact on the key evaluation parameters to consider. For example, the use of total body imaging and sequential dermoscopy has been reported to improve the sensitivity and specificity of the screening test, thus leading to better efficacy and cost parameters in high-risk populations.[51]

There is a lack of knowledge about the penetration, benefits, harms and costs of opportunistic screening for melanoma.

It is critical to address this gap, in order to assess the value of moving to a more systematic approach. The Summit participants also agreed that more data are required to provide definitive evidence for the clinical effectiveness as well as cost-effectiveness of advanced risk stratification and imaging technologies, given that only a small proportion of melanomas lead to death.[52] Further work includes determining whether a targeted risk-based screening approach would be feasible and, if so, how risk criteria could be used to tailor aspects of the screening program, such as starting age, screening intervals and stopping age. Other issues to be addressed include the management of equivocal or precancerous lesions to minimise the number of unnecessary excisions while also being cognisant of the potentially severe consequences related to underdiagnosis.

In summary, the Summit Group concluded further research is needed to understand how to best optimise melanoma early detection in Australia, particularly in light of emerging technologies and treatments for advanced melanomas that may change the balance of benefits and harms of different screening strategies.

Acknowledgements

Table 1: Short and long-term research priorities for optimising early detection of melanoma.		
Gaps in knowledge	**Short-term research priorities**	**Long-term research priorities/potential outcomes**
Who is accessing opportunistic screening, how frequently, and what are the outcomes and costs.	Investigate current clinical pathways to melanoma diagnosis and treatment. Analyse variation in clinical outcomes.	Systematically evaluate and analyse the potential benefits and harms of organised approaches to the early detection of melanoma, compared with the current clinical pathways.
		Comprehensive clinical outcomes register for melanoma allowing analysis of benefits, harms, costs to the economy and the patient, highlighting variations in clinical care across Australia.
Would population-based screening or targeted screening save more lives or be cost effective, over and above what is already happening opportunistically?	Prospective assessment and validation of risk assessment tools, imaging technologies and approaches for risk-based, targeted screening and surveillance.	Systematically evaluate and analyse the potential benefits and harms of population-based screening vs targeted screening.
What is the best approach to risk stratification? What is the role of new and emerging tools and technologies such as 3D total body imaging, biomarkers, or polygenic risk score stratification tools in risk-stratification?	Investigate accuracy of risk prediction tools and the advantages of incorporating imaging, biomarker and/or genetic information.	Evaluation of the implementation of risk-based, targeted screening and surveillance strategies.
How can those melanomas with very poor prognosis be detected earlier?	Work towards non-invasive, cost-effective technologies that reliably detect potentially fatal melanoma and clearly differentiate them from indolent lesions.	Comprehensive assessment of risk factors and detection approaches for high-risk melanoma subtypes especially early forms of nodular, acral and/or amelanotic melanoma.
How can the cost benefit ratio from melanoma early detection and treatment be optimised?	Modelling studies of cost-effectiveness. Model the future economic burden of melanoma to the Australian healthcare system, based on current and predicted trends, under different screening scenarios.	Cost-effectiveness analysis of prospective studies of melanoma screening strategies.
What is the quality of life impact of different melanoma early detection pathways?	Develop a better understanding of quality of life, psycho-social, and behavioural impacts of the detection of melanoma and keratinocyte cancers.	Prospective evaluation of quality of life, behavioural and psychosocial outcomes from screening studies.

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