Is screening for melanoma in average risk subjects beneficial?

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Abstract

Routine skin examination, either conducted by a doctor or by self-screening, is widely practised in Australia, although authoritative groups and clinical guidelines do not recommend screening. This inconsistency is due to the very limited information from studies with the ability to assess the value of screening. There are no randomised trials of the effects of screening for melanoma on end points like mortality. As a consequence, we have no rigorous evidence to show or disprove the value of routine skin cancer screening. Partial body self-screening is particularly prevalent, and whole-body screening and screening by a doctor are also commonly done. This high level of screening activity results in greater intervention. This may be beneficial; but there are also concerns that substantial numbers of non-progressive lesions are being detected and removed. These and other issues are explored.

One of the most contentious issues in regard to skin cancer is whether we should be encouraging or discouraging routine screening of average risk people for early melanoma, in addition to surveillance or case-finding in high risk individuals. This is perhaps the most difficult issue in the prevention and early diagnosis of melanoma. Bill McCarthy has given a valuable summary of Australian experience in these areas.[1]

It seems obvious that regular skin examination should lead to earlier diagnosis of melanoma, thinner tumours at diagnosis and therefore fewer deaths. However, in public health and policy terms, cancer screening requires evidence of overall benefit. The often stated requirement is to have evidence of a reduction in mortality, or at least in morbidity, produced by offering screening to a general population and supported by the results of one or more randomised trials. Thus, randomised trials showing benefits have been the rationale for the publicly funded programs of population screening for breast cancer by mammography and the current pilot programs of colorectal cancer screening. The other established cancer screening program, Pap smears for cervical cancer, was introduced before large scale clinical trials became established as an evaluation method, so the justification of that screening program is based on the results of cohort and case control studies. However, there is no evidence from randomised trials that skin screening can reduce deaths or morbidity from melanoma.

Recommendations on screening policy

Australian practice on melanoma screening is very mixed. There is no organised screening program. On the other hand, screening is widely practised and much of the screening is paid for through the Medicare system. Screening in the private sector is a considerable growth industry. Many expert groups who base their findings on 'evidence-based' reviews of scientific literature do not recommend screening. The NHMRC-approved clinical guidelines developed by the Australian Cancer Network in 1997 (a revision is in progress) do not recommend screening on a population basis:[2] "There is no evidence that population screening for melanoma is a cost effective way of controlling melanoma mortality". The US Preventive Services Task Force[3], The Cancer Council Australia,[4] and the Royal Australian College of General Practitioners do not recommend screening of average-risk subjects. These groups do recommend surveillance of high-risk subjects and advocate awareness and good clinical management of skin lesions, but even for high-risk subjects there is no level one or two (randomised trial) evidence. The RACGP (the 'red book') recommends screening for skin cancer in high-risk individuals, giving it grade III – C evidence ('poor evidence').[5] In contrast, the American Cancer Society,[6] the American Academy of Dermatology[7] and a National Institutes of Health Consensus Conference[8] support regular screening, on its own or linked to a general health check.

Skin screening in Australia

Despite this lack of consensus, screening for melanoma is widely practised in Australia. A telephone survey of a random sample of 3100 adults aged 30 or more in Queensland, conducted in 1998 with a response rate of 67%, showed that 79% of subjects said that they or another non-medical person had deliberately checked the skin on all or parts of their body for early signs of skin cancer in the past year, not including checks of particular moles or spots. This is the highest prevalence of self-screening yet reported.[9] Using the stricter criterion of 'whole-body' checks, 26% reported practising whole body self-examination at least once in the last 12 months and 34% in the last three years. Whole-body self-examination was increased in those under age 50, those with more education and those with more concern about skin cancer. Self-examination in the last three years was increased to over 60% if their doctor had suggested it, had instructed them in how to do it or if the doctor has done a skin examination. Men and women showed similar rates of skin self-examination.

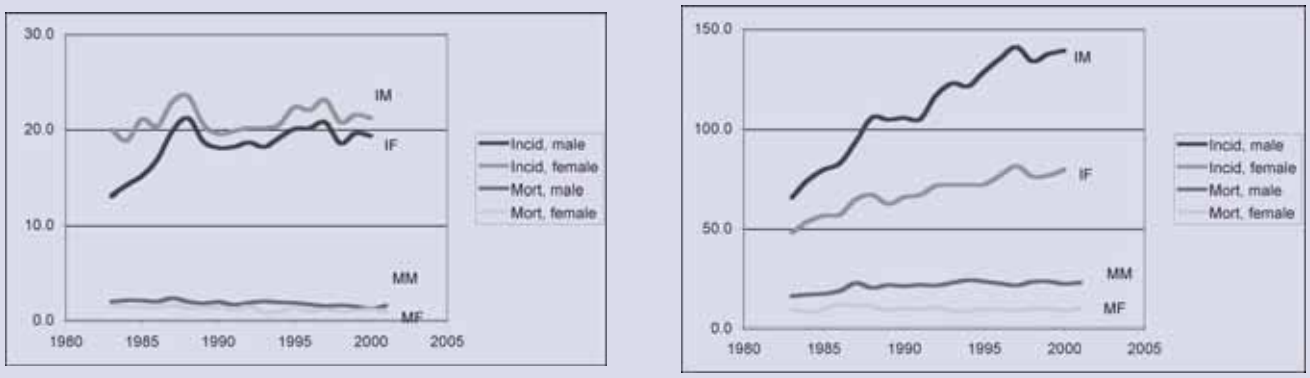
Of the same group, 11% had had a whole body skin cancer check by a doctor within the last year and 31% reported a partial body check.[10] The frequency was only slightly higher in women and in younger adults. Those who had had skin examinations were at higher risk of melanoma as judged by skin type, numbers of moles and history of non-melanoma skin cancer (NMSC).

Screening for skin cancer is a substantial business in Australia. As well as general practitioners and dermatologists offering screening to higher risk patients or more generally, there is a growing number of walk-in skin clinics in which screening examinations are carried out either using clinical examination alone, or using dermoscopy or computerised imaging systems. Skin screening is also offered to employee groups using various methods. None of these services has provided any valid information on their clinical results.

Evidence about screening: survival and trends in melanoma

What then is the evidence for, or against, the benefits of screening? In Australia survival rates for melanoma are 90% in

Figure 1:



Incidence and mortality rates, per 100,000 population, by year, 1983 to 2000, Australia, for ages up to 49 years (left graph), and for ages over 50 (right graph); age-standardised within each age range. The two graphs have different vertical scales. Data from Australian Institute of Health and Welfare.

men and 95% in women (five-year relative survival, patients diagnosed 1992-97).[11] This shows effective early diagnosis as well as good treatment. This has been used as an argument for screening; in that, if this good situation is due to high awareness and early clinical diagnosis, doing more screening should improve it further; but it also means that any further benefits from the introduction of a systematic screening program would be limited by the already excellent survival of patients under current care. The overall mortality rates, all ages, for melanoma have been stable in men since about 1987-88. In women there has been a modest decrease since about the same time. The trends vary by age. At ages under age 50, there has been a small but clear decrease in mortality in both men and women. At these ages, after rises in the late 1980s, the incidence rates have shown variations, but around a stable long term trend (see Figure 1: data from Australian Institute of Health and Welfare).

Above age 50, the mortality rate for women has been stable since the 1980s and the men's rate has been stable since about 1995 (see Figure 1). But the incidence of melanoma is still rising sharply in the over 50 age group. Over the last 20 years the incidence in women over 50 has increased by more than 50% and the incidence is men has more than doubled. In Queensland from 1979-80 to 1999, age-adjusted incidence rates increased in all depth categories, with the greatest proportional increase for lesions less than 1.5mm thick.[12] In 1979-80, 64% of incident invasive melanomas in men and 79% in women were less than 1.5mm thick. By 1997, this had increased to 79% in men and 83% in women. However, this change in the proportional distribution was due to an increase in the incidence of thin lesions rather than a decrease in the incidence of thicker lesions. The population-based incidence rate of melanomas more than 3mm deep increased from 2.5 to 4.7 per 100,000 population per year in men over the 20 years and from 1.6 to 1.9 per 100,000 in women. So while the proportion of thick melanomas has decreased, the population incidence of deeply invasive melanoma, which will be the main driver of melanoma mortality, has been increasing over time.

The incidence trends by thickness also vary by age. In NSW from 1989 to 1996, at ages 15-34 the incidence rates of all melanoma, thin (<1mm) and thick (>1mm), decreased, while at ages over 65 the incidence of all types increased. In the intermediate age group of 50-64, the incidence of thin melanoma increased while that of thick melanoma decreased.[13] These trends suggest a real reduction in incidence in adults under age 50.

The short-term objective of screening and early diagnosis programs, which are designed to ultimately reduce deaths from melanoma, should be the reduction on a population basis of the incidence rate of deeply invasive melanoma. It would be helpful to study trends and clinical and epidemiological characteristics of deeply invasive melanoma as a specific target.

Some 20% of incident melanomas in Queensland in 1997 were thicker than 1.5mm. Deeply invasive melanomas are over-represented in men over the age of 50.[14] The presenting features of thin and thick melanoma differ, with the classical textbook definition of ABCD (asymmetry, border, colour, diameter) characteristics applying mainly to the diagnosis of thin melanomas. Thick melanomas present differently, with more red or uncoloured lesions, more frequent itch and bleeding, and other atypical presentations. Nodular melanoma, which forms a high proportion of thick melanoma, often has atypical characteristics and the diagnosis may be delayed.[15,16] So although most doctors and the general public have been made aware of the classical ABCD features of melanoma, these apply best to thin, probably slow growing and radial growth phase melanoma, rather than to the deeply invasive, nodular or vertical growth phase melanomas which result in a sizable proportion of deaths.

The question of non-progressive lesions

Early intervention for a lesion which is not progressive will not be beneficial. There is substantial evidence that a proportion of thin melanomas may not progress or progress only very slowly.[17-20] There was a very rapid rise in the incidence of melanomas in Australia in the 1980s, due mainly to a great increase in thin (less than 0.75mm depth) lesions. In-situ lesions also increased. At this time the total number of people having skin lesions removed was increasing by 14% per year and a careful analysis of this situation suggested that increased diagnosis of a non-metastasising form of melanoma could be a major part of the explanation.[17]

The issue is whether we are detecting and removing substantial numbers of lesions which are classified pathologically as early invasive or in-situ melanoma, but are not progressive, and therefore represent unnecessary intervention. This concept is not unexpected or unusual in cancer screening situations. Indeed, any cancer screening test, whether it be a high technology method such as mammography or spiral CT, or a low technology method such as clinical examination of the skin, is by definition a method designed to identify for intervention lesions which have previously been ignored. The

natural history of these lesions is unknown when the screening method is introduced. In a population group, each 'early' lesion detected is a progressive lesion (which if left alone would progress to an 'advanced' lesion); the number of early lesions removed will be matched by an equal reduction in the number of advanced lesions which are diagnosed. At the other extreme, if none is progressive, the increase in the number of early lesions removed will have no effect on the incidence rate of advanced lesions subsequently detected. The reality is likely to be that some but not all of the early lesions are progressive, so that the increase in early lesions detected is linked to a smaller reduction in the frequency of advanced lesions. Whether the proportion of all lesions which are non-progressive is very large or very small is at the root of the controversy over prostate cancer screening by PSA testing and similar issues in the management of various types of lesions detected by mammography or Pap smears. It should not surprise us that some early melanomas which we are detecting and removing may not be progressive. On a population basis, a randomised trial could establish what proportion of lesions detected and removed would be progressive. For the individual, we need a biological marker to distinguish potentially fatal melanomas from those that will not progress.

Evaluation of melanoma screening

There are no randomised trials of the effects of screening for melanoma on end points like mortality. Indeed, there are no non-randomised trials and no controlled cohort studies as there are for cervical cancer screening. The lack of good scientific evidence about screening for melanoma is a serious deficiency. The only controlled study which addresses this is a case-control study carried out nearly 10 years ago in the US[21] which showed that subjects who practised skin self-examination (defined as 'a careful, deliberate and purposeful examination of the skin') and were diagnosed with melanoma had a reduced risk of progression to advanced disease (risk ratio 0.58, 95% limits 0.31 to 1.11). This result has been confirmed recently in a survival analysis of the same group of melanoma patients, with 5.4 years' median follow-up; the mortality hazard ratio associated with 'skin awareness' was 0.5 (limits 0.3 to 0.9).[22] This is consistent with screening leading to earlier diagnosis of melanoma and producing an advantage in terms of survival, but is open to lead-time and other biases. However, the other results of the case-control study are more difficult to explain.23 There was a reduced risk of melanoma incidence in those doing self-screening (risk ratio 0.66, 95% limits 0.44 to 0.99), which is unexpected. The main mechanism by which incidence could be reduced is by self-screening leading to the recognition and removal of precursor lesions, but there is no direct evidence of this from the study.[23] By combining both effects, the authors estimated that self-examination may reduce mortality from melanoma by 63% (risk ratio 0.37, 95% limits 0.16 to 0.84). However the reduction in incidence could also indicate observation bias or uncontrolled confounding within the study, raising questions about the validity of the other results. There was also the opposite of the expected dose-response effect; those who practised self-screening most carefully had less benefit than those who used it only casually. Assessing screening by case-control methods is inherently difficult and while this is a well-performed study, alternative explanations of the results cannot be easily ruled out.

There have been economic assessments, but these are totally dependent on the assumption that mortality will be reduced by a reasonable amount, for example 20%, which is made by analogy to other cancer screening programs. These show that if such a mortality reduction was produced by screening, it would be cost-effective.

A randomised trial of screening for melanoma

A randomised controlled trial, with melanoma mortality as the endpoint, would be the definitive means of determining whether screening is effective. The pilot work for a randomised controlled trial of a community-based screening program for melanoma has been done in Queensland. The full trial design was based on 44 Queensland communities with an aggregate population of 560,000 persons aged 30 years or over. Communities were paired according to their size, broad geographic location and socio-economic status based on standard indicators and randomised within pairs into intervention or control groups. This design provides 85% power to detect a 20% reduction in mortality in the 15 years from the beginning of the intervention period.[12,24]

The pilot phase involved randomisation to select nine intervention and nine control communities, running the screening program in the intervention communities and the evaluation of its short term effects. In the intervention communities, the community-based melanoma screening program was delivered over three years, comprising a community education program to promote self-screening, encouragement of prompt medical attention for suspicious lesions, promotion of whole-body clinical skin examination by GPs and an education and support program for general practitioners. No program activities were conducted in control communities. The first hurdle was to see if the program would be acceptable to the communities and particularly to the general practitioners. The answer was a definitive yes, with almost all the 100 or so general practitioners in the intervention communities agreeing to be involved in the program, attending briefing and educational sessions and accepting the materials prepared for distribution by them. In each community, a lay coordinator was appointed. The program was based on established theories of behavioural change and designed to facilitate the uptake of skin self-screening and doctor screening and its diffusion through the community. General practitioner workload was an issue; in several communities the GPs requested that additional services be provided through other general practitioners who were contracted to organise supplementary skin cancer sessions, usually at the practice facilities of the regular GPs in the area. This showed that it would be unrealistic to introduce population screening for melanoma based on general practice without supplementation of GP resources, at least in smaller communities.

The primary goal of the pilot program was to ensure that during the three-year intervention period, the proportion of the adult population who have had at least one whole-body skin examination by a general practitioner was increased to at least 60%. The sample size calculations for the full trial were based on the assumption that 60% screening participation could be achieved and that in the control communities the amount of screening would remain at around 20%. In the full trial, deaths from melanoma, deaths from all causes, incident cases of melanoma and the thickness of melanoma at diagnosis would be monitored amongst all adults aged 30 years who were resident in the intervention or control communities from the start of the intervention period, during the three year intervention period and for another 10 years after. This could be done with routine mortality collections and state cancer registry notifications. Short-term outcomes were measured through pre and post-intervention surveys by telephone and postal methods in the intervention and control communities.

A trial like this is a complex endeavour. Planning began in 1991 and funding for the pilot program was given by the Queensland Cancer Fund in 1997. Despite much effort, it has been impossible to fully fund the trial. The original plan was for the intervention to be mounted and completed in all intervention communities by the end of 2005, with mortality and other clinical outcomes monitored through to the end of 2015. So even if the Queensland trial had gone ahead, we would still be many years away from having a definitive answer to the question of mortality benefit. It could well be argued that such a result would not be helpful as by the time it came, attitudes towards skin cancer screening would be even more entrenched than at present. For example, in Germany a publicly-funded program of screening for skin cancer is being developed in which all adults over age 30 can have a full body examination by a specially trained general practitioner. Those who have an abnormality detected are referred to a dermatologist for further assessment and follow-up. This program is justified on the current burden of skin cancer morbidity and mortality and on the argument that early diagnosis will be cost effective in reducing extensive disease. The lack of randomised trial evidence has not prevented this policy being instituted. Nor has it prevented the substantial uptake of screening and the growth of various screening facilities in Australia. This example raises the general question of whether large scale long-term prospective trials are essential to assess cancer screening. The same question is debated in regard to prostate screening, helical CT screening for lung cancer and other developments. We have in progress a case control study in Queensland that can certainly assess the relationship between screening and depth of invasion at diagnosis. It may be able to estimate the proportion of lesions detected by screening which are non-progressive. With follow-up, it could relate screening to recurrence of melanoma and death from melanoma in the same way as the previous case control study. However, a key issue is whether the results of a case-control study will be acceptable to policy makers and to clinicians, particularly if the results conflict with current perceptions?

Conclusions

Screening for cancer on a population basis should be based on good evidence. There is no rigorous evidence to show or disprove the value of routine skin cancer screening. There are no available results from randomised trials or cohort studies, the only analytical study result being a single case-control study. Despite this, screening is widely practised. The main argument for the effectiveness of screening is based on the assumption that earlier diagnosis will produce mortality benefits, which in turn is based on the large differences in post-diagnosis survival by depth of invasion, for patients diagnosed in normal clinical practice. The great increase in the excision of thin melanomas has not been matched by a similar decrease in the diagnosis of thick melanomas. However, overall mortality trends are encouraging and a beneficial effect of early clinical diagnosis is likely. It is the particular contribution of screening which is difficult to assess.

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