

**Title Page****Title:**

Clinical whole-body skin examination reduces the incidence of thick melanomas.

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## **Clinical whole-body skin examination reduces the incidence of thick melanomas.**

### **ABSTRACT**

Survival from melanoma is strongly related to tumour thickness, thus earlier diagnosis has the potential to reduce mortality from this disease. However, in the absence of conclusive evidence that clinical skin examination reduces mortality, evidence-based assessments do not recommend population screening. We aimed to assess whether clinical whole-body skin examination is associated with a reduced incidence of thick melanoma and also whether screening is associated with an increased incidence of thin lesions (possible overdiagnosis).

A population-based case-control study of all Queensland residents aged 20-75 years with a histologically confirmed first primary invasive cutaneous melanoma diagnosed between January 2000 and December 2003. Telephone interviews were completed by 3,762 eligible cases (78.0%) and 3,824 eligible controls (50.4%)

Whole-body clinical skin examination in the three years before diagnosis was associated with a 14% lower risk of being diagnosed with a thick melanoma (>0.75mm) (OR= 0.86, 95% CI=0.75, 0.98). Risk decreased for melanomas of increasing thickness: the risk of being diagnosed with a melanoma 0.76-1.49mm was reduced by 7% (OR=0.93, 95% CI 0.79, 1.10), by 17% for melanomas 1.50-2.99mm (OR=0.83, 95% CI=0.65, 1.05) and by 40% for melanomas  $\geq$ 3mm (OR=0.60, 95% CI=0.43, 0.83). Screening was associated with a 38% higher risk of being diagnosed with a thin invasive melanoma ( $\leq$ 0.75mm) (OR=1.38, 95% CI=1.22, 1.56).

This is the strongest evidence to date that whole-body clinical skin examination reduces the incidence of thick melanoma. Because survival from melanoma is

strongly related to tumour thickness, these results suggest that screening would reduce melanoma mortality.

## INTRODUCTION

While the incidence of melanoma has increased dramatically in white-skinned populations throughout the world over past decades,<sup>1-3</sup> this has not been matched by a corresponding increase in mortality.<sup>1,2</sup> Most of the increase in incidence has been in thin lesions<sup>1,2</sup> due at least in part to increased awareness and improved diagnosis. Survival following treatment is related strongly to the thickness, or depth of invasion, of the tumour at diagnosis,<sup>4,5</sup> with five-year survival following tumour excision ranging from 95% for lesions  $\leq 1.00\text{mm}$  to as low as 45% for lesions  $>4.00\text{mm}$ .<sup>4</sup> Thus, overall case fatality rates have improved<sup>2,6</sup> as the proportion of thin lesions has increased.<sup>1,7</sup> As most melanoma mortality occurs in patients diagnosed with lesions thicker than 1mm (unpublished data, Queensland Cancer Registry), improvements in earlier diagnosis, if accompanied by a corresponding reduction in the incidence of thick lesions, have the potential to reduce deaths from this disease.

One method that may improve earlier diagnosis is skin screening, either by skin self-examination or clinical skin examination by a doctor. For self-examination, a case-control study from the United States showed a significantly reduced mortality associated with ever having conducted skin self-examination, but also an unexpected reduction in melanoma incidence.<sup>8</sup> No studies have examined the question of whether screening by a doctor would reduce mortality from melanoma. We found that melanomas detected by doctors were more likely to be thin ( $<0.75\text{mm}$ ) than those detected by the patient themselves or by their partner or

friends,<sup>9</sup> suggesting that screening by a doctor may be of benefit. However, there is no conclusive evidence that self-screening or screening by a doctor will reduce melanoma mortality and evidence-based assessments have concluded that there is insufficient evidence to recommend either for or against routine screening for melanoma.<sup>10, 11</sup> Nevertheless, recent population surveys in Queensland have shown that approximately 40% of adults aged 20-75 have had at least one whole-body skin screening examination by a doctor in their lifetime and 20% have had one in the past 12 months,<sup>12</sup> 26% have practiced whole-body skin self-examination in the past 12 months,<sup>13</sup> and that the overall prevalence of skin screening is increasing (Youl, unpublished data<sup>14</sup>), at substantial cost to the health system. The rapid increase in the diagnosis of thin melanomas also raises the question of whether increased surveillance, including screening, leads to the diagnosis of thin melanoma which would not progress (overdiagnosis).<sup>15-17</sup> The most conclusive evaluative study of screening is a randomised trial with mortality as the endpoint. However, while such a trial has been planned and piloted,<sup>18</sup> the cost of the whole trial has proved to be prohibitive .

We conducted a population-based case-control study to examine the association between whole-body skin screening by a doctor and thickness of melanoma at diagnosis. The objectives were to assess if such screening is associated with a reduced incidence of thick melanoma, which would be consistent with an ultimate mortality benefit, and also to assess if screening is associated with an increased incidence of thin lesions.

## METHODS

### *Case ascertainment*

Queensland residents aged between 20 and 75 years diagnosed with histologically confirmed first primary invasive cutaneous melanoma (not including acral lentiginous melanoma) between 1 January 2000 and 31 December 2003 were eligible as cases. During this period, 94.1% of all melanomas diagnosed in Queensland were within this age group. All patients with melanoma of 0.75mm or greater thickness were selected. For convenience, these are referred to throughout this manuscript as “thick melanomas”. To improve sampling efficiency and reduce cost, a random sample of 60% of patients with thinner invasive melanoma (<0.75mm) were selected. Patients with non-cutaneous melanoma, metastatic disease with unknown primary, a confirmed previous melanoma or a melanoma with unknown thickness were excluded from the sampling frame. In situ melanomas were not included. For the small number of patients simultaneously diagnosed with more than one melanoma, the thickest melanoma was taken as the relevant lesion for the purpose of this study. Eligible patients were identified from the population-based Queensland Cancer Registry, to which cancer notifications have been a legal requirement since 1982. Letters explaining the study and seeking permission to contact the patient were sent to all treating doctors. Non-responding doctors were telephoned after one week. After permission was obtained, patients were invited by letter to participate.

### *Control ascertainment*

Potential controls were selected from the Queensland Electoral Roll using stratified random sampling, based on 5-year age groups and sex distribution of the melanoma cases as determined from the Queensland Cancer Registry. Letters explaining the

study and consent forms were sent by mail, with follow-up consisting of two further mail outs and two reminder telephone calls as necessary. Persons with a confirmed diagnosis of melanoma were replaced.

#### *Data collection*

Information on screening history, melanoma risk factors and demographics was collected from cases and controls using computer assisted telephone interviews. This structured interview was preceded by sending the respondent pictorial and other material to assist with the assessment of freckling, naevi and other items. The core interview had been developed and extensively piloted in a previous study in Queensland.<sup>18</sup>

Screening history: Information was collected from both cases and controls on self-screening, screening by partners and other lay people, and screening by a doctor, referred to here as clinical skin examination. Screening history was collected only up to the point of first awareness of the presenting sign or symptom of melanoma in cases, and an equivalent “reference date” in controls. Reference dates for controls were based on the distribution of time between the date of first awareness of the presenting sign or symptom of melanoma and the date of interview of the cases. Within this distribution, controls were allocated reference dates randomly, such that the distribution of time between reference date and interview was the same as for cases.

Clinical skin examination (CSE) was determined by asking: “During the last 3 years before [you first believed something was wrong (cases) / reference date (controls)],

had a doctor deliberately checked all or nearly all of your whole body for the early signs of skin cancer?" For cases, this clinical skin examination did not include the initial examination by a doctor as part of the diagnostic process, unless this was a whole-body clinical skin examination of an asymptomatic patient, i.e., a skin screening examination. The validity of self-reports of clinical skin examination was quantified in a separate study.<sup>19</sup>

Melanoma risk factors: Many factors have been related to melanoma risk, but multivariate models based on the analyses of case-control studies in several countries show a reasonably small number of critical variables.<sup>20, 21</sup> Risk factors assessed in this study as potential confounders were: ethnicity (recoded to UK, European and Other); natural hair colour at age 21 (blonde/red, black/brown); eye colour (blue/grey/green/hazel, black/brown); colour of skin before tanning (very fair/fair, olive/brown/asian); tendency to burn when exposed to sun for an hour without protection (sunburn, no sunburn); degree of freckling, based on previously sent pictorial prompts (none/few, many); number of moles on the back (none, 1-10, 11-30, 31-50, 50 or more); childhood sunburn experience (never, up to 10 times, more than 10 times) and age first arrived in Australia (born in Australia, 1-19 years, 20-39 years, 40-75 years). Average sun exposure during the respondent's lifetime was calculated and categorized based on the respondent's recollection of the amount of time generally spent outside during specific periods in their life (light <400 hrs/yr, moderate 400-599 hrs/yr, heavy 600-799 hrs/yr, very heavy 800 hrs/yr and more). Respondents were also asked whether they have blood relatives with a history of melanoma (yes/no) or blood relatives with a history of non-melanoma skin cancers (yes/no). Respondents were also asked whether they had ever been

diagnosed with other sorts of skin cancer (yes/no), and if they had ever had a mole removed from their skin (yes/no).

Remoteness of residence, based on geographical area of residence, was assessed using the Accessibility/Remoteness Index of Australia (ARIA) classification,<sup>22</sup> with the categories collapsed to “Highly accessible” (Capital City), Moderately Accessible/Accessible” (Other urban/rural) and “Remote/Very Remote” (Remote).

Demographics: Basic demographic data included sex, age (ten year age groups from 20-29 to 70 years and over), education (Primary, Junior, Senior and above), current employment status (full-time, part-time, not working, retired) and current marital status (married/partner, separated/divorced/widowed/never married).

#### *Response rates for controls*

The total number of potential controls selected for this study was 7,787. Of these, 193 were found to be ineligible (166 had a melanoma diagnosis and 27 were deceased). Of the 7,594 eligible participants, consent was obtained from 3,972 (52.3%). Of the remainder, 2,053 (27.0%) refused, 1,203 (15.8%) were unable to be contacted and 366 (4.8%) were contacted but did not reply. Interviews were completed by 3,824 (50.4%) control participants.

Among the eligible potential controls, females were more likely to participate than males (54.1% of females and 51.1% of males,  $p=0.0087$ ) and the average age of respondents was higher than non-respondents (53.7 years and 50.5 years respectively,  $p<0.0001$ ). There was little difference in the rate of participation for

controls who lived in and around the state capital versus those in more regional and rural parts of the state (53.1% and 51.4%,  $p=0.17$ ).

#### *Response rates for cases*

We identified 4,839 potentially eligible cases, of whom 15 were deceased. Of the 4,824 eligible cases, consent was obtained for 3,877 (80.4%). Among the remainder, doctor's consent was not obtained for 325 (6.7%), 369 (7.6%) refused, 200 (4.1%) were contacted but did not reply and 53 (1.1%) were unable to be contacted (no current address or telephone number). Interviews were completed by 3,762 (78.0%) eligible cases.

Among the eligible cases, females were significantly more likely to participate than males (82.7% compared with 78.7%,  $p<0.01$ ) and participation was lower among patients with thicker tumours (81.8% participation for those with tumours  $\leq 0.75$ mm; 82.7% for tumours 0.76-1.49mm; 76.0% for tumours 1.5-2.99mm; 74.2% for tumours  $\geq 3.00$ mm;  $p<0.001$ ). There was little difference in participation according to mean age at diagnosis (52.9 years for participants and 52.7 years for non-participants ( $p=0.69$ )).

#### *Test-retest reliability*

The test-retest reliability of the questionnaire was assessed by re-interviewing 164 cases and 104 controls one to three months after their first interview. We used Cohen's Kappa statistic<sup>23</sup> to assess the agreement between the two interviews. There was good agreement for the question on clinical skin examination for both

cases and controls (K (cases)=0.714, 95%CI=0.60, 0.83; K (controls)=0.785, 95%CI=0.66, 0.91), with concordance values of 87% and 90% respectively.

#### *Additional data from the Queensland Cancer Registry*

Interview data for melanoma cases were combined with pathology data held by the Queensland Cancer Registry including tumour thickness, histology and level of invasion. Although the current recommended cut points within the T classification for melanoma thickness are 1mm, 2mm and 4mm,<sup>4</sup> this was only officially implemented in 2003. This study, which commenced data collection in January 2000, was designed prior to the revised classification being released. Therefore the selection and stratification of cases in this study, and subsequent analyses, were based on the previous thickness classification<sup>24, 25</sup> which uses cut points of 0.75mm, 1.5mm and 3mm. The presentation of our results by thickness in this paper reflects this.

#### *Statistical analysis*

In this analysis, self-reported screening histories for patients with thick (>0.75mm) and thin ( $\leq$ 0.75) melanoma were each compared separately to population controls to calculate the associations between screening by a doctor and the risk of thick melanoma, and between screening by a doctor and the risk of thin melanoma. If clinical skin examination does reduce the incidence of thick melanoma by allowing it to be diagnosed while it is more superficial, the odds ratio for thick melanomas would be less than one. If clinical skin examination increases the frequency of thin melanomas, then the odds ratio for thin melanomas would be greater than one.

Potential confounders included those factors listed above related to melanoma risk, and demographic factors potentially related to the experience of screening. As a previous diagnosis of skin cancer or having had a mole removed may have been the reason for clinical skin examination, even if not in the causal pathway, we left these variables out of the list of potential confounders.<sup>26</sup> Initially a polytomous model containing all the potential confounders was fitted, using the case (4 levels of thickness) / control (1 level) status as the outcome variable. This model was then refined by stepwise removal of variables with no statistically significant association with the outcome measure (in this instance taken to be when  $p > 0.20$ , based on the likelihood ratio test) after adjusting for the other variables in the model.

Adjusted odds ratios and 95% confidence intervals were calculated from the parameter estimates of the final polytomous regression model.

The total number of subjects deleted from the final regression model due to missing values was 259 (3.4% of all subjects). This proportion of excluded subjects was slightly higher for cases (4.0%) than for controls (2.8%).

To assess whether there was evidence of a linear association between tumour thickness and clinical skin examination, we used a linear regression model for cases only with the log-transformed thickness as the outcome variable, adjusting for the same potential confounders as for the main analysis.

We repeated the main analysis, restricting it to only those respondents who had reported no previous history of skin cancer, and having had no moles previously removed.

Since the original study design and sampling methodology were based on the Breslow staging system, we used those categories for the primary analysis. However we repeated the analysis using thickness categories based on the current AJCC staging system<sup>27</sup>, introduced after the current study was designed and sampling was underway. Because relatively few melanomas were greater than 4.0mm thickness, all melanomas greater than 2.0mm thickness were grouped together in this analysis.

To estimate the number of deaths that might be prevented by clinical screening in our sample, we estimated the average 5- and 10-year survival for screened and unscreened cases. We calculated thickness-specific 5- and 10-year cause-specific survival for all melanoma patients diagnosed between 1990 and 2003 [source: Queensland Cancer Registry] and applied these estimates to the number of screened and unscreened cases in each thickness category in our sample. We then compared the expected mortality within 5 and 10 years between the two groups.

All analysis was conducted using SAS 9.1.<sup>28</sup>

Ethical approval for the study was granted by the Behavioral and Social Sciences Ethical Review Committee of the University of Queensland. Informed consent was obtained from each study participant.

## RESULTS

The final sample for analysis was 3,762 cases and 3,824 controls. The proportion of cases who reported having had a clinical skin examination within the 3 years before the melanoma was first noticed (35.3%) was higher than that for controls (28.3%; based on the reference date). For the cases, the percentage who had a clinical skin examination within 3 years of diagnosis was inversely associated with thickness ( $\chi^2$  test for trend=44.37, df=1,  $p<0.001$ ): 38.7% among those with melanomas  $\leq 0.75$ mm thick, 30.3% among those with melanomas between 0.76 and 1.49mm, 28.2% for those with melanomas between 1.50 and 2.99mm, and 22.5% for people with melanomas  $\geq 3$ mm thick (Table 1).

Among the controls, we found that older respondents, those with higher education, those who were married, had olive or brown skin colour, had an increased number of moles on the back, increased number of childhood sunburn experiences, lived in the south east corner of Queensland (capital city), had a family history of melanoma, a family history of nonmelanoma skin cancer, a previous diagnosis of skin cancer or had a mole removed were all independently more likely to report having had a clinical skin examination in the three years prior to the reference date (Table 2).

The final list of potential confounders resulting from the model building process comprised sex, age, education, employment status, marital status, eye colour, hair colour, skin colour, degree of freckling, number of moles on back, age at first arrival in Australia, average lifetime sun exposure, family history of melanoma (blood relatives), family history of non-melanoma skin cancer (blood relatives), and ethnic status.

After adjustment for these variables, whole-body clinical skin examination in the three years before melanoma diagnosis was associated with a 14% lower risk of being diagnosed with thick melanoma ( $>0.75\text{mm}$ ) (OR= 0.86, 95% CI=0.75, 0.98), with the risk decreasing with increasing thickness (Table 1). The risk of being diagnosed with a melanoma 0.76-1.49mm was reduced by 7%, (OR=0.93, 95% CI 0.79, 1.10), by 17% for melanomas 1.50-2.99mm (OR=0.83, 95% CI=0.66, 1.05) and by 40% for melanomas  $\geq 3\text{mm}$  in diameter (OR=0.60, 95% CI=0.43, 0.83) (Table 1). Screening was associated with a 38% higher risk of being diagnosed with a thin melanoma ( $\leq 0.75\text{mm}$ ) (OR=1.38, 95% CI=1.22, 1.56). There was a significant inverse linear association between melanoma thickness and having had a clinical skin examination – the average thickness was 18% less (95% CI =13%, 22%) for those who had had a clinical skin examination ( $\beta=-0.196$ ,  $df=1$ ,  $p<0.001$ )

Results were similar and in the same direction within strata defined by sex and separately by age (20-49 years, 50-74 years (Table 3). Consistent with this, an additional model (full results not shown) including the interaction terms of clinical skin examination and sex and clinical skin examination and age found no statistically significant interaction ( $\chi^2=4.83$ ,  $df=4$ ,  $p=0.31$  and  $\chi^2=20.11$ ,  $df=20$ ,  $p=0.45$  respectively).

Similar results were observed when we limited the analysis to those people who reported no previous history of skin cancer, and reported they had not had a mole removed (Table 1). The main difference between the full analysis and this reduced analysis was that in the reduced analysis, the association was slightly stronger for melanomas 1.50-2.99mm and  $\geq 3.00\text{mm}$  (Table 1).

We repeated the analysis using a modified definition of exposure. Specifically, we did not include in our definition of “whole-body clinical skin examination in the past three years” those examinations at which the melanoma was first detected (Table 4). After adjustment for potential confounders in this analysis, there was no longer any association with clinical skin examination and thin melanomas. For melanomas thicker than 0.75 mm, the trend of decreasing odds ratios with increasing thickness remained. In this analysis, the risk of melanoma greater than 3.00mm was reduced by 45% (OR=0.55, 95% CI=0.39, 0.77).

Results were similar and in the same direction when the analysis was repeated using categories based on the current AJCC staging system. After adjustment, whole-body clinical skin examination in the three years before melanoma diagnosis was associated with an 18% lower risk of being diagnosed with thick melanoma (>1.00mm) (OR= 0.82, 95% CI=0.69, 0.99), with the risk decreasing with increasing thickness. The risk of being diagnosed with a melanoma 1.01-2.00mm was reduced by 13%, (OR=0.87, 95% CI 0.70, 1.09) and by 27% for melanomas >2.00mm (OR=0.73, 95% CI=0.55, 0.98). Screening was associated with a 32% higher risk of being diagnosed with a thin invasive melanoma ( $\leq$ 1.00mm) (OR=1.32, 95% CI=1.18, 1.47).

After applying the thickness-specific Queensland cause-specific survival estimates to the thickness distribution of the screened and unscreened cases in our sample, we estimated that the average 5- and 10-year survival for unscreened cases would be 93.8% and 90.4%, and for screened cases it would be 95.5% and 92.6%

respectively. Adjusting for the differences in numbers of screened and unscreened cases, we estimated that compared to unscreened cases, the screened cases would have 26% fewer melanoma deaths within 5 years and 23% fewer deaths within 10 years of diagnosis.

## **DISCUSSION**

Our results indicate that whole-body clinical skin examination in the three years prior to melanoma diagnosis is associated with a 14% reduction in the incidence of all thick melanoma (>0.75mm), including a 7% reduction in the incidence of melanoma 0.76-1.49mm thick, a 16% reduction in the incidence of melanoma 1.5-2.99mm thick, and a 40% reduction in the incidence of melanoma  $\geq 3.00$ mm thick. Overall, there was a regular and significant trend towards lower incidence of melanomas of increasing thickness.

Could this association be due to bias? The comparison of screening histories between melanoma patients and population controls is open to the problem of recall bias, common to all similar retrospective study designs. We asked about screening histories using a standard, well-tested and reliable question, which we have found previously to have high validity when compared against medical records,<sup>19</sup> with no detectable difference in accuracy of recall between melanoma patients and others. Even if it were the case that recently diagnosed melanoma patients have different recall abilities than healthy controls, there is no reason to suggest that patients with different thicknesses of melanoma would show differential recall, therefore it is unlikely that recall bias would have produced the trend of reducing odds ratios with increasing melanoma thickness that was observed.

It is also possible that if screening does result in earlier diagnosis, cases who die or are seriously ill relatively soon after diagnosis are those least likely to have been screened.<sup>29</sup> These are also likely to have been the thicker cases and failure to interview these cases may bias the association between screening and thick melanoma towards the null. To minimise the potential for this selection bias, we interviewed cases as soon as possible after diagnosis, with a median time between diagnosis and interview for cases of 5 months, and 8 months (between reference date and interview) for controls. Nevertheless, there was a significant inverse association between participation rates and thickness which may have resulted in our underestimating the association with screening. There is also the possibility of selection bias for the controls; if there were a higher prevalence of screening in the 51% of responding eligible controls than in non-respondents, the results would tend to underestimate the odds ratio for the association between screening and diagnosis of melanoma. While this is possible, it is difficult to see how this potential source of bias would have resulted in the opposite associations with screening that we observed for thin and thick melanomas and the inverse trend observed within thick melanomas.

Confounding, by factors which are associated with both the experience of screening and also with the diagnosis of melanoma of a particular depth, is another possible explanation for these results. We controlled for known melanoma risk factors demonstrated to be associated with screening participation. We avoided including in the model those factors which may be intermediate in the causal pathway between screening and melanoma diagnosis by depth, such as previous removal of lesions.

These results are consistent with the hypothesis that clinical skin examination results in earlier detection and treatment of tumours which would otherwise have been diagnosed later, leading to a reduction in the incidence of thick melanoma. Would such a reduction in the incidence of thick melanoma associated with screening mean that screening would result in a reduction in melanoma mortality? Advancing the diagnosis is a necessary condition for a reduction in mortality but it is not sufficient. Screening is more likely to detect slowly growing lesions than fast growing lesions (length bias) and as a consequence is more likely to detect lesions that would not kill the person in their lifetime. Additionally, if lesions that would have been diagnosed as thick lesions in the normal course of events are detected by screening chronologically earlier but after they had metastasised, there would be little impact on eventual mortality. When we applied the expected five- and ten-year survival estimates for Queensland by thickness to the thickness distribution of the screened and unscreened cases, we estimated that, in the absence of these biases, screening may reduce fatality by at least 20%. However, a randomised trial with mortality as the outcome is the only means of actually determining the extent to which screening might reduce mortality.

There are two possible explanations for the observed 38% increase in thin ( $\leq 0.75\text{mm}$ ) melanoma associated with whole-body clinical skin examination. It cannot be assumed that all thin melanomas removed would have progressed to invasive disease if left alone. Some of the increase in the incidence of thin lesions may be due to the diagnosis of non-progressive lesions, i.e. lesions that have no potential for metastasis.<sup>15-17</sup> This potential over-diagnosis would have no impact on

the future incidence of thick lesions. However, given the observed reduction in the incidence of thick lesions, some of the increase in thin lesions is likely to be due to a shift from thick to thin melanoma as a result of screening. It is not possible to estimate the relative size of these two effects from cross-sectional data.

Population-based surveys indicate that whole-body clinical skin screening has increased in Queensland in recent years and with increasing awareness and the rapid increase in skin cancer screening clinics in Queensland,<sup>30</sup> this is likely to continue. It is likely that this population has not reached a steady state in regard to the prevalence of skin screening. Therefore, one would expect that the immediate increase in incidence of thin lesions that would be seen at the start of a screening program would not yet have become apparent in a matching reduction in thick lesions. The data presented here are consistent with there having already been some shift from thick to thin lesions in our sample due to earlier diagnosis as the result of whole-body skin examination.

These results provide the strongest evidence to date that whole-body clinical skin examination reduces the incidence of thick melanoma. Because survival from melanoma is strongly related to melanoma thickness and most melanoma mortality occurs in patients diagnosed with lesions thicker than 1mm, these results suggest that screening would reduce melanoma mortality.

Finally, it is important to consider whether the evidence presented here is sufficient to recommend population-based skin screening. The decision to introduce a population-based screening program is one that is based both on scientific evidence

of benefit and also a careful examination of costs and hazards. The current study provides the best evidence to date and, in the absence of a randomised trial, the best evidence we are likely to achieve for some time that skin screening by a doctor will reduce mortality from melanoma. It does not provide information on costs either to the patient or to the health system. Therefore, the decision whether or not to undergo skin screening is one that should remain an individual one to be discussed between the patient and his or her doctor in the light of this new evidence that skin screening is likely to improve earlier diagnosis and reduce the incidence of thick melanoma.

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Table 1: Odds ratios for (self-reported) clinical skin examination in 3 years prior to first noticing something wrong: Results of polytomous regression model

| Control / Thickness  | Had a doctor skin screen in last 3 years? | Unadjusted <sup>1</sup> |         | Adjusted <sup>2</sup>   |         | "De novo screening" (adjusted) <sup>3</sup> |         |
|----------------------|---|-------------------------|---------|-------------------------|---------|---|---------|
|                      |   | Odds Ratio <sup>4</sup> | p-value | Odds Ratio <sup>4</sup> | p-value | Odds Ratio <sup>4</sup>                     | p-value |
| 0.01-0.75mm [n=2049] | 792 (38.7%)                               | 1.61 [1.44-1.81]        | <0.001  | 1.38 [1.22 , 1.56]      | <0.001  | 1.35 [1.12 , 1.63]                          | 0.002   |
| 0.76-1.49mm [n=1017] | 308 (30.3%)                               | 1.10 [0.94-1.28]        | 0.221   | 0.93 [0.79 , 1.10]      | 0.393   | 0.93 [0.73 , 1.19]                          | 0.572   |
| 1.50-2.99mm [n=443]  | 124 (28.0%)                               | 0.98 [0.78-1.22]        | 0.829   | 0.83 [0.66 , 1.05]      | 0.128   | 0.67 [0.45 , 1.00]                          | 0.047   |
| 3.00mm + [n=253]     | 57 (22.5%)                                | 0.73 [0.54-0.99]        | 0.041   | 0.60 [0.43 , 0.83]      | 0.002   | 0.56 [0.32 , 0.97]                          | 0.037   |
| Controls [n=3824]    | 1083 (28.3%)                              | 1.00                    |         | 1.00                    |         | 1.00  |         |

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1. Results of polytomous regression model with melanoma thickness as the outcome variable (4 thickness levels, and the control group) and reported CSE as the independent variable, and including age group and sex to account for the frequency matching of cases with controls.
  2. Same as (1), except also adjusted for education, employment status, marital status, eye colour, hair colour, skin colour, degree of freckling, number of moles on back, age first arrival in Australia, average lifetime sun exposure, family history of melanoma (blood relatives), family history of non-melanoma skin cancer (blood relatives) and ethnic status.
  3. Same as (2), except only includes respondents who have not had a mole previously removed nor a previous diagnosis of skin cancer (n=4135)
  4. Controls are the reference category

Table 2: Factors associated with having had a clinical skin examination (CSE) within the three years prior to the reference date among the 3,824 control participants only

|                                   | % CSE | Adjusted odds ratio <sup>†</sup><br>(95% CI) | P-value |
|-----------------------------------|-------|--|---------|
| <b>Sex</b>                        |       |  |         |
| Male (n = 2,203)                  | 29.1  | 1.05 [0.9-1.3]                               | 0.584   |
| Female (n = 1,621)                | 27.3  | 1.00   |         |
| <b>Age</b>                        |       |  |         |
| 20 – 29 (n=184)                   | 20.1  | 1.10 [0.7-1.8]                               | 0.023   |
| 30 – 39 (n=445)                   | 26.7  | 1.22 [0.8-1.8]                               |         |
| 40 – 49 (n=780)                   | 28.2  | 1.35 [0.9-2.0]                               |         |
| 50 – 59 (n=1002)                  | 32.0  | 1.61 [1.2-2.3]                               |         |
| 60 – 69 (n=878)                   | 30.0  | 1.41 [1.1-1.9]                               |         |
| 70 – 75 (n=535)                   | 23.0  | 1.00   |         |
| <b>Education</b>                  |       |  |         |
| Years 11-12 & upwards (n = 2,405) | 31.4  | 1.00   | <0.001  |
| Years 7 to 10 (n = 1,129)         | 24.2  | 0.71 [0.6-0.9]                               |         |
| Primary (n = 285)                 | 19.0  | 0.56 [0.4-0.8]                               |         |
| <b>Employment status</b>          |       |  |         |
| Full-time (n=1630)                | 28.9  | 1.00   | 0.069   |
| Part-time (n=559)                 | 28.6  | 1.03 [0.8-1.3]                               |         |
| Not working (n=473)               | 23.7  | 0.91 [0.7-1.2]                               |         |
| Retired (n=1162)                  | 29.3  | 1.36 [1.0-1.8]                               |         |
| <b>Marital Status</b>             |       |  |         |

|   |      |                |       |
|---|------|----------------|-------|
| Married/partner (n=3032)                            | 30.0 | 1.00           | 0.001 |
| Separated/divorced/widowed/never married<br>(n=790) | 21.8 | 0.72 [0.6-0.9] |       |
| Eye Colour  |      |                |       |
| Blue/Grey/Green/Hazel (n=2918)                      | 29.4 | 1.09 [0.9-1.3] | 0.380 |
| Brown/Black (n=906)                                 | 24.7 | 1.00           |       |
| Hair colour   |      |                |       |
| Brown/black (n = 3,023)                             | 27.2 | 1.00           | 0.055 |
| Blonde/Red (n = 801)                                | 32.7 | 1.21 [1.0-1.5] |       |
| Skin colour   |      |                |       |
| Olive/brown (n = 774)                               | 26.1 | 1.00           | 0.041 |
| Very Fair/Fair (n=3,050)                            | 28.9 | 0.79 [0.6-1.0] |       |
| Tendency to burn after sun exposure                 |      |                |       |
| No sunburn (n = 265)                                | 18.9 | 0.76 [0.5-1.1] | 0.125 |
| Sunburn (n = 3,558)                                 | 29.0 | 1.00           |       |
| Degree of freckling                                 |      |                |       |
| None/Few (n = 3295)                                 | 27.6 | 1.00           | 0.453 |
| Many-Heaps (n = 486)                                | 32.7 | 1.09 [0.9-1.4] |       |
| Number of moles on back                             |      |                |       |
| None (n=1038)                                       | 22.7 | 1.00           | 0.001 |
| 1-10 (n=1955)                                       | 27.9 | 1.22 [1.0-1.5] |       |
| 11-30 (n=590)                                       | 35.4 | 1.54 [1.2-2.0] |       |
| 31-50 (n=116)                                       | 40.5 | 2.03 [1.3-3.1] |       |
| 50 or more (n=71)                                   | 36.6 | 1.69 [1.0-2.9] |       |
| Childhood sunburn experience                        |      |                |       |

|  |      |                |       |
|--|------|----------------|-------|
| Never (n=545)  | 18.9 | 1.00           | 0.013 |
| Up to 10 times (n=2459)                                      | 28.3 | 1.33 [1.0-1.7] |       |
| More than 10 times (n=771)                                   | 34.9 | 1.57 [1.2-2.1] |       |
| Age first arrived in Australia                               |      |                |       |
| Born in Australia (n=3258)                                   | 29.4 | 1.00           | 0.071 |
| 1-19 years (n=221)   | 23.5 | 0.76 [0.5-1.1] |       |
| 20-39 years (n=273)  | 21.6 | 0.76 [0.3-1.1] |       |
| 40-75 years (n=72)   | 18.1 | 0.58 [0.3-1.1] |       |
| Average lifetime sun exposure                                |      |                |       |
| Light (n = 403)  | 30.8 | 1.17 [0.9-1.6] | 0.624 |
| Moderate (n=1123)  | 29.8 | 1.04 [0.8-1.3] |       |
| Heavy (n=1222)   | 27.8 | 0.98 [0.8-1.2] |       |
| Very heavy (n=1076)  | 26.4 | 1.00           |       |
| Remoteness of residence                                      |      |                |       |
| Capital city (n=2706)  | 29.9 | 1.00           | 0.005 |
| Other urban/rural (n=1003)                                   | 23.5 | 0.76 [0.6-0.9] |       |
| Remote (n=115)   | 32.2 | 1.30 [0.8-2.0] |       |
| Family history of melanoma (blood relatives)                 |      |                |       |
| Yes (n=553)  | 36.2 | 1.25 [1.0-1.5] | 0.039 |
| No (n=3271)  | 27.0 | 1.00           |       |
| Family history of non-melanoma skin cancer (blood relatives) |      |                |       |
| Yes (n=826)  | 39.6 | 1.34 [1.1-1.6] | 0.003 |
| No (n=2998)  | 25.2 | 1.00           |       |
| Ethnic status  |      |                |       |

|                                   |      |                  |        |
|-----------------------------------|------|------------------|--------|
| UK (n=2540)                       | 29.5 | 1.00             | 0.284  |
| European (n=361)                  | 26.0 | 1.08 [0.8-1.4]   |        |
| Other (n=876)                     | 26.3 | 0.88 [0.7-1.1]   |        |
| Previous diagnosis of skin cancer |      |                  |        |
| Yes (n=734)                       | 48.0 | 2.52 [2.1-3.1]   | <0.001 |
| No (n=3090)                       | 23.7 | 1.00             |        |
| Ever had a mole removed           |      |                  |        |
| Yes (n=982)                       | 38.2 | 1.62 [1.36-1.92] | <0.001 |
| No (n=2806)                       | 25.0 | 1.00             |        |

† Adjusted odds ratios calculated from the parameter estimates of a logistic regression model with the p values from the likelihood ratio chi-squared test.

Table 3: Odds ratios for clinical skin examination (within 3 years) showing adjusted odds ratios from the main model stratified by sex and age group.

|                          | 0.01-0.75mm           | 0.76-1.49mm        | 1.50-2.99mm        | 3.00mm +             |
|--------------------------|-----------------------|--------------------|--------------------|----------------------|
| Males                    | 1.54 [1.31 , 1.82] ** | 0.96 [0.78 , 1.19] | 0.85 [0.63 , 1.15] | 0.62 [0.42 , 0.91] * |
| Females                  | 1.20 [0.99 , 1.45]    | 0.90 [0.70 , 1.16] | 0.79 [0.54 , 1.16] | 0.55 [0.29 , 1.03]   |
| 20-49 years <sup>1</sup> | 1.32 [1.08 , 1.62] *  | 0.98 [0.76 , 1.27] | 0.67 [0.41 , 1.07] | 0.48 [0.22 , 1.06]   |
| 50-74 years              | 1.43 [1.22 , 1.67] ** | 0.91 [0.74 , 1.12] | 0.90 [0.68 , 1.18] | 0.62 [0.43 , 0.89] * |

Note: \*: p<0.05; \*\*: p<0.01

1: Model for 20-49 years included modified categories of age since arrival (born in Australia versus rest) due to zero response categories.

Table 4: Odds ratios for (self-reported) clinical skin examination in 3 years prior to first noticing something wrong: Results of polytomous regression model (excluding asymptomatic clinical skin examinations carried out at the time of first detection).

| Control / Thickness  | Had a doctor skin screen in last 3 years? | Unadjusted <sup>1</sup> |         | Adjusted <sup>2</sup>   |         | "De novo screening" (adjusted) <sup>3</sup> |         |
|----------------------|---|-------------------------|---------|-------------------------|---------|---|---------|
|                      |   | Odds Ratio <sup>4</sup> | p-value | Odds Ratio <sup>4</sup> | p-value | Odds Ratio <sup>4</sup>                     | p-value |
| 0.01-0.75mm [n=2049] | 634 (30.9%)                               | 1.14 [1.01-1.28]        | 0.032   | 0.95 [0.84 , 1.08]      | 0.436   | 0.75 [0.61 , 0.92]                          | 0.007   |
| 0.76-1.49mm [n=1017] | 269 (26.5%)                               | 0.91 [0.78-1.06]        | 0.219   | 0.76 [0.65 , 0.90]      | 0.002   | 0.71 [0.54 , 0.92]                          | 0.011   |
| 1.50-2.99mm [n=443]  | 114 (25.7%)                               | 0.88 [0.70-1.10]        | 0.255   | 0.74 [0.58 , 0.94]      | 0.013   | 0.60 [0.40 , 0.90]                          | 0.013   |
| 3.00mm + [n=253]     | 52 (20.6%)                                | 0.66 [0.48-0.90]        | 0.009   | 0.55 [0.39 , 0.77]      | <0.001  | 0.52 [0.30 , 0.91]                          | 0.023   |
| Controls [n=3824]    | 1083 (28.3%)                              | 1.00                    |         | 1.00                    |         | 1.00  |         |

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1. Results of polytomous regression model with melanoma thickness as the outcome variable (4 thickness levels, and the control group) and reported CSE as the independent variable , and including age group and sex to account for the frequency matching of cases with controls.
  2. Same as (1), except also adjusted for sex, age, education, employment status, marital status, eye colour, hair colour, skin colour, degree of freckling, number of moles on back, age at first arrival in Australia, average lifetime sun exposure, family history of melanoma (blood relatives), family history of non-melanoma skin cancer (blood relatives), and ethnic status.
  3. Same as (2), except includes only respondents who have not had a mole removed previously nor a previous diagnosis of skin cancer (n=4135)
  4. Controls are the reference category