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Article:

Development and validation of a melanoma risk score based on pooled data from 16 case-control studies

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Running title: Development and validation of a melanoma risk score

Keywords: Melanoma, risk, imputation, pooled analysis

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Requests for reprint should be directed to the corresponding author.

Conflicts of interest: none

Word count: 3984

Total number of figures and tables: 5

Abstract

Background

We report the development of a cutaneous melanoma risk algorithm based upon 7

factors; hair colour, skin type, family history, freckling, nevus count, number of large

nevi and history of sunburn, intended to form the basis of a self-assessment webtool

for the general public.

Methods

Predicted odds of melanoma were estimated by analysing a pooled dataset from 16

case-control studies using logistic random coefficients models. Risk categories were

defined based on the distribution of the predicted odds in the controls from these

studies. Imputation was used to estimate missing data in the pooled datasets. The

30th, 60th and 90th centiles were used to distribute individuals into four risk groups

for their age, sex and geographic location. Cross-validation was used to test the

robustness of the thresholds for each group by leaving out each study one by one.

Performance of the model was assessed in an independent UK case-control study

dataset.

Results

Cross-validation confirmed the robustness of the threshold estimates. Cases and

controls were well discriminated in the independent dataset (area under the curve

0.75, 95% CI 0.73-0.78). 29% of cases were in the highest risk group compared with

7% of controls, and 43% of controls were in the lowest risk group compared with 13% of cases.

Conclusion

We have identified a composite score representing an estimate of relative risk and successfully validated this score in an independent dataset.

Impact

This score may be a useful tool to inform members of the public about their melanoma risk.

Introduction

Cutaneous melanoma continues to increase in incidence in white populations, especially in Europe (1) . There is evidence of stabilization in incidence rates in some countries within Europe (in Lithuania, Estonia, Slovakia, Ireland and Scotland) and notably outside Europe, in Israel, Australia, New Zealand, the USA and Canada, showing a marked cohort effect (1). The large increase in incidence over the past 50 years and more recent stabilization of rates in several countries suggest that behavioural factors, probably related to sun exposure, underlie the cohort-based trends. These observations reinforce the view that change in sun-related behaviour remains a desirable aim for melanoma prevention(2).

Red hair, freckling and skin reported to burn rather than tan are unequivocally associated with increased risk for melanoma in meta-analyses and pooled data analyses (3, 4). A more potent phenotypic risk factor is the presence of many melanocytic nevi and large (or clinically atypical) nevi, as confirmed by meta-analyses (5) and pooled-data analyses (6). These phenotypes are strongly genetically determined, and genes associated both with nevus phenotype and pigmentation have been shown to be associated with melanoma risk in genome-wide association studies (7). It is therefore not surprising that family history of melanoma, defined as melanoma in a first degree relative, also has been consistently identified as a risk factor (3).

Although these phenotypic risk factors are well described in the medical literature, it is important that the general public is able to extrapolate an understanding of their own risk from the existing published evidence. We constructed a risk tool to allow individuals to assess their lifetime risk of melanoma that will benefit both those at average as well as at increased risk relative to the underlying risk in their population, using variables that can be reliably self reported by members of the general public. The aim of this analysis was to construct this risk algorithm based on our previous pooled data analyses of melanoma case-control studies performed at different latitudes (4, 6) and then to test the algorithm in an independent UK melanoma case-control study (8, 9).

Materials and Methods

We carried out a pooled data analysis of melanoma case-control data sets from studies conducted in Europe (temperate climate), North America (temperate and warmer climate), Australia and Hawaii (hotter climate) in the period 1979 to 1999. Previous analyses of these data are presented in two papers on sun-exposure patterns (4) and the nevus phenotype (6) associated with risk. These two papers comprehensively described the approaches taken to pooled data analysis. Since our model is designed to underpin a risk tool for public usage, we considered only variables that were deemed self-reportable by members of the public, even though other variables had been shown to be significantly associated with risk of melanoma (e.g. solar keratoses) and our model may have had better predictive value with their inclusion. Genetic data were excluded for the same reason. A summary is provided here.

Data Collection

Eligible studies were identified first as those reported in a systematic meta-analysis conducted by Gandini et al. containing analyses conducted prior to 2002 (3, 5, 10). Second, studies conducted between 2002 and 2007 were identified using a MEDLINE search. Twenty-six studies met the inclusion criteria, and all authors who could be traced were invited to participate. The authors of sixteen studies participated. The pooled dataset consisted of eight studies from Europe, five from North America, one from Hawaii and two from Australia. In each of these studies,

data had been collected on some or all of the following variables: nevus phenotype, hair color, sunburn history, Fitzpatrick skin type, freckling, family history of melanoma and age. Data on eye colour were also collected but this variable was found to be highly correlated with hair colour and was dropped from the final model. The variables were grouped into categories where it was clear that this was appropriate (table 1). These variables were established risk factors for melanoma as described above (3, 5, 10), further details can be found in the supplementary information.

Generating estimates for the effect of covariates used in the risk algorithm

The pooled data were analysed using a logistic random coefficients model to account for heterogeneity between studies. Pooled odds ratios (OR) were estimated for the effect of each categorical variable on melanoma risk adjusted for the other six variables (table 1), age and sex using winBUGS (a more detailed explanation can be found in (6)). The Western Canada study (Elwood et al. 1985) (11) was omitted from the final model as there were no nevus count data available.

Creating the risk score

The estimated odds of disease from the above model were used to define a "risk score", formed by multiplicatively combining the estimates in table 1. This

composite estimated odds ratio (OR) was considered the estimated relative risk of an individual developing melanoma compared with an individual from the same population who had the lowest possible risk (black hair, fewer nevi than half the population, had not been sunburnt, had no freckles, no large nevi, had a Fitzpatrick skin type of III or IV and had no family history of melanoma).

Categorisation of risk and calculation of thresholds

To provide more stable and interpretable risk estimates, we used controls from the pooled analysis as a sample of the combined population and generated an estimate of the background population distribution of the risk score. Table 2 lists each of the included studies. Some variables were not recorded in all of the studies. In addition 1.5% of all data were missing at the individual level for recorded variables. Missing data rates are described in supplementary table 1. To calculate a risk score for individuals within these studies, we used imputation as described below to fill in the missing values.

Imputation of missing data using Multiple Imputation by Chained Equations (MICE)

We assumed that the data could be treated as missing at random (MAR) and implemented MICE to impute missing values using the "mice" library in R 3.0.2(12). We ran the imputation analysis in 30 chains over 15 iterations. Each 'chain' is a separate run of the analysis, with different random assignments of the missing data

points, upon which the imputation is performed independently of the chains.

Further details of the imputation process can be found in the supplementary

methods. The composite melanoma risk score was computed for each individual in

each chain and the results from each of the 30 chains were merged together into one

composite dataset. We used the 30th, 60th and 90th centiles to distribute individuals

into four risk groups; Low, relative to peers, Medium-Low, relative to peers,

Medium-High, relative to peers and High, relative to peers. Peers are defined as

individuals of the same age and sex drawn from the same population.

Attributable risk

We calculated attributable risk using the cases in the Leeds case-control data set by

imputed missing values as described above, calculating risk scores for each

individual and applying the method of Bruzzi et al. (13).

Robustness of thresholds

We investigated the robustness of the threshold estimates by dropping each study in

turn and recalculating the 20th, 30th, 40th, 50th, 60th, 80th and 90th centiles, using

MICE to impute missing values as above. Large deviation from the threshold values

computed using all data with data from a particular study omitted shows that the

individual study has a large influence on the algorithm.

Validation in independent data taken from the Leeds case-control study

To test the efficacy of the risk algorithm, we investigated its performance in data collected from 960 population-ascertained incident melanoma cases and 513 controls recruited to a case-control study performed in Leeds, UK (8, 9). Further details can be found in the supplementary information. Data on the variables used to build the risk tool were extracted from questionnaires and classified in the same manner as for the pooled data described above.

Composite melanoma risk scores were calculated based on the phenotypic and environmental data recorded for these cases and controls. A receiver operator curve (ROC) was constructed and the area under the curve (AUC) was estimated using the 'pROC' library in R (14). 95% confidence intervals were computed for the ROC curves using DeLong's method (15). Cases and controls were also grouped into risk categories using the threshold estimates calculated from the pooled data, and a difference between the risk classification of cases and controls was tested using a chi-square test.

Most users of a risk tool aimed at the public will not have access to professional assessment of mole counts and freckling. We therefore assessed how using self-reported mole counts and freckling scores affected the classification of cases in the Leeds controls. Further details of the methods used to do this can be found in the supplementary material.

Results

Calculating the risk score

The composite risk score based on the seven variables has a theoretical
approximate range of 1 to 233 (table 1). This score is the combined odds of
developing melanoma compared to the combined odds for a person in the lowest
theoretical category of risk for someone of the same sex and age. In the pooled data
we observed the full range of theoretical risk score (1-233, supplementary figure 1).
In the Leeds melanoma data we saw a reduced range of scores (1-188,
supplementary figure 2).

Risk categories

Thresholds for the pre-defined risk categories derived from controls in the pooled
data are shown in table 3. Individuals are classified as being low risk (< 3.32),
medium-low risk (3.32-8.46), medium-high risk (8.46-32.80) or high risk (≥32.80)
relative to the background risk in the population. For example, a person with red
hair, Fitzpatrick skin type I, freckling, but has no large nevi, a low nevus count, who
has not been severely sunburnt and has no family history of melanoma in a first-
degree relative would have a risk score of 4.62 (1.76x1.66x1.58 from estimates in
table 1) and would be categorized as "medium-low risk, relative to peers" (using the
thresholds in table 3).

<u>Testing the robustness of threshold estimates using 'leave-one-study-out' cross-</u>
<u>validation</u>

To test the robustness of the thresholds we removed each study in turn, performed MICE using the same settings on the remaining data, and then recalculated threshold values. Table 3 shows the results of omitting each study on the threshold values at 7 different points in the distribution. There was no evidence that omitting any of the studies caused gross distortion of the threshold values.

<u>Validation using the Leeds case-control data</u>

The risk score was computed for each individual in the Leeds case-control study as above. Initially we used only complete cases to reduce the number of assumptions made about the data. ROC curve analysis showed that the raw composite score was capable of distinguishing cases from controls reasonably well (AUC=0.75, 95% CI 0.73-0.78 , figure 1). Cases and controls were also classified into four risk groups using the threshold values generated using the 30th, 60th and 90th centile values of the controls from the pooled data analysis. The proportion of cases and controls that fall into each of the four risk groups is shown in table 4. Cases and controls were well separated (chi-squared test: $p<2.2 \times 10^{-16}$); 29% of cases are in the highest risk group compared with 7% of controls, and 43% of controls are in the lowest risk group compared with 13% of cases. However, the Leeds population had a greater

proportion of controls at "low risk, relative to peers" compared to pooled controls, as in the latter the controls were by definition approximately distributed in the risk groups as 30%, 30%, 30% and 10%.

Finally, we imputed missing data in the Leeds cohort using MICE and repeated the above analyses. There was a small improvement in the model (AUC=0.77) but no difference in the distribution of controls (supplementary table 2).

We estimated overall attributable risk from the Leeds dataset to be 87.8%.

Agreement between self-reported and nurses' counts of moles

We assessed the reliability of self-reported versus nurse-assessed mole counts and freckling in the Leeds control group. Supplementary figure 3 shows a Bland-Altman plot comparing self-reported counts of moles on the back with nurse counts of the back in the Leeds controls. The mean difference between the two counts is 3 moles, and the 95% limits of agreement are wide (-23.5, 29.4). Larger discrepancies are seen for individuals as the average mole count increases; in the majority of these instances the patient has overestimated the number of moles on their back (difference > 0).

Reasoning that laypersons might identify patterns of moles more accurately than individual moles, Leeds cohort participants were also asked which of four diagrams

best represented their mole count (supplementary figure 4). Their responses were compared to the nurse-assessed mole counts grouped using the centile thresholds implemented in the risk model (0-50%, 51-75%, 75-90%, >90%). 37% of individuals classified themselves in the same nevus score rank as the nurses (supplementary table 3) even though the measures are not equivalent. Finally, there was agreement about the presence of any freckling in 63% of controls although the two variables are still highly significantly associated (supplementary table 4, chi-squared test 3×10^{-5}).

With respect to risk classification in the pooled data, we compared how well individuals are classified when the self-reported counts or nurse counts are used (supplementary table 5) in both cases and controls. A good correlation between the two sets of measurements is seen using the self-reported counts; 97% of individuals are classified within one rank of the nurse counts, and 57% are classified in exactly the same group. However, there is a net improvement in the classification of cases into higher risk groups and controls into lower risk groups when the nurse counts are used (NRI=0.29); the majority of the improvement is due to increased classification of cases into higher risk groups (p(ranked higher | case) = 0.35). We also compared the performance of the model using self-reported measures to the nurse reported measures using ROC curve analysis. The discriminatory ability of the model is lower when self-reported mole counts are used (AUC=0.70, 95% CI 0.66-0.73), which is similar to an alternative model where mole count and freckling were omitted (AUC=0.69, 95% CI 0.66-0.73).

Absolute risk

While we have presented our model to produce categories of risk relative to the underlying population risk for someone of a similar age and sex, with some small modifications it is possible to produce absolute risk estimates as well. Using data taken from the Cancer Research UK and UK Office for National Statistics websites (16-18), it is possible to estimate that the absolute risk for a 30-year old woman from the UK with the risk factors discussed earlier would be approximately 0.04% over the next 5 years. Further details can be found in the supplementary data.

Discussion

The leveling off of melanoma incidence rates in some countries, continued rise in others, and the effects of birth cohort on incidence (1) all suggest modifiable environmental exposures may affect incidence. There is strong evidence of effects of intermittent high exposure to the sun on melanoma risk (10). Therefore the need for melanoma prevention advice directed at sun protection is clear. Our study was designed to construct a risk algorithm based upon large melanoma case-control data sets to enable members of the public to estimate their own risk relative to that of others in their population. Use of this algorithm to motivate change in sun-related behavior is based on the theory that primary prevention advice is more effective when the targeted persons believe themselves to be at relatively high risk; a study of modification of the behavior of adolescents in the sun has provided empirical support for this theory(19). On the other hand, individuals who are told that they have relatively low risk may well decide that they can ignore sensible sun protection measures in the sun. Any tailored risk measurements must avoid underplaying the dangers of risky behavior in the sun for all individuals.

Other melanoma risk tools have been implemented previously for public use. The tool provided by the NCI (20, 21) gives an estimate of absolute risk and focuses exclusively on one population (the United States). A recent study has similarly produced a model that predicts the absolute 5-year risk of melanoma for individuals in New Zealand but the authors recommend that external validation is performed before it is used for clinical practice(22). The online risk tool produced by the New

South Wales Government(23) produces no final estimate of risk but instead provides short explanations for why each question was asked to inform users of the risk factors. The Harvard School of Public Health web-tool produces an estimate of risk that is relative to peers of the same age and sex for individuals over 40 (24).

Eiser et al have previously suggested that numerical information may be interpreted as more exact than it is (25, 26). The primary approach we have taken is to provide a classification of risk into categories relative to population risk, but we have also shown that our estimates can easily be used to produce an estimate of 10- or 5-year absolute risk by combining with local data. Similar classification systems to ours have been suggested in the past (27, 28). In one instance categorical groupings were used to assign rough estimates of 10-year risk(29). We propose that our algorithm, which is based on data taken from multiple case-control studies worldwide, may be applicable to more than just one population, although as yet we have only tested it on one (Leeds, UK). The distribution of controls in the Leeds study differs from that in the pooled case-control studies, and is weighted towards more controls being classified in lower risk groups.

Conveying risk effectively is a difficult and complex issue (30) and beyond the scope of this paper to explore fully. In practical applications of our risk tool, ideally both risk relative to the baseline population and estimates of absolute risks would be provided. We have demonstrated that it is easy to adapt our model to output absolute risks, given appropriate local data on melanoma incidence and overall

mortality rates, although more sophisticated methods may be required to account for geographical variation in incidence rates in larger countries such as the USA(21).

The beneficial effects of sun exposure include higher vitamin D levels, which are essential for bone health and might be important for many other aspects of health, such as prevention of cancer (31) and diseases associated with the metabolic syndrome (32) although this has not been proven. It may therefore be sub-optimal to recommend very high levels of sun protection for individuals at lower risk of melanoma, especially in temperate climates, where there is less sunshine. This project had the second aim of assisting members of the public to identify themselves as at lower risk than their peers, so that advice on sun avoidance could be better tailored to the individual. The data sets were built almost entirely from data from white-skinned individuals as they are the population most affected by melanoma. The incidence of melanoma in black and Asian populations is much lower, and likely our algorithm would not be applicable to these populations.

A weakness of the study is that the risk algorithm was built and tested using case-control data. Consequently, the odds ratios that the risk score is built upon are potentially subject to the biases inherent to case-control designs, such as recall bias, selection bias, participation bias, and/or confounding. We have also made an assumption that since the odds ratio estimates for each factor used to build the risk score were derived from a multivariable joint analysis, they can be treated as independent and therefore can be combined multiplicatively. We have not

accounted for potential interactions between factors in this model. Interactions are notoriously difficult to show, and a model that included all potential interactions between the factors would contain too many variables to be practical. A strength of the study is that the data sets used were very large and detailed. As with all pooled data sets, the data are from disparate studies. Reassuringly, however, in the previously reported analyses the estimates of relative risk of melanoma in relation to sunburn (4) and nevus phenotype were remarkably consistent across all the studies (6). The point estimates of the odds of melanoma for an individual are highly imprecise, particularly at the extremes of the distribution. Therefore we have taken the approach of categorizing risk into broad groups.

A challenging aspect of this analysis was that several variables were not recorded in all studies; this was addressed by imputation using MICE. Of particular concern is the large mole variable, which is only available for 7 of the 16 studies and is defined differently in different studies (e.g. large moles were defined by a research nurse as >8mm in Kanetsky 2001 but self-reported ≥ 5mm in LeMarchand 2006). However we did not see much perturbation in the threshold scores when each study was dropped in turn.

The analyses carried out resulted in a composite score representing an estimate of relative risk for individuals compared with those with the lowest level of risk factors. The AUC in the ROC analysis was 0.75, suggesting that the measure explained a substantial proportion of the risk. Recently Vuong et al. identified 28 melanoma

prediction models generated from 19 studies published before April 2013, in which

discrimination ranged from an AUC of 0.62 to 0.86(33) so our model is competitive

in this regard. It is likely that we could have increased the AUC if we had used

additional variables such as genetic factors. However, we hope ultimately to

provide a tool that will be used by individuals reporting their own risk factors.

Therefore, it was practical to use simple measures that can be self-reported.

We generated 4 different risk groups based upon a distribution of risk estimates in

the controls using the 30th, 60th and 90th centiles as cut-points. Cases and controls

were well differentiated. Approximately 7% of controls in the Leeds data were

found in the highest risk group compared with 29% of cases.

We have shown evidence that risk prediction is more accurate when professionally

measured freckling and mole count variables are used. This may be a potential

weakness for developing a risk tool using this algorithm, as the results may be

misleading in the presence of misclassification. Nonetheless the majority of

individuals were classified in the same group irrespective of whether self-reported

or professionally derived variables were used. For a risk tool aimed at the public it

may be best to leave out these variables as there was evidence that models that

omitted the self-reported variables lost no discriminatory power. However there

was a substantial improvement in classification when professionally derived

variables were used, particularly for ranking cases in higher risk groups, so ideally

these variables should be incorporated in some form. We made a strong assumption

that the qualitative groups in the diagrams match well to the equivalent centile groups in the risk tool. However there is substantial variation in mole count distributions between populations so this assumption may well be violated. Diagrams which better matched users to the four quantile groups would presumably perform better; this argues for the need to tailor self-estimation of nevi to each individual population if diagrams are to be used.

In summary we have generated an algorithm for use in white populations to predict risk of melanoma. Practical application of this algorithm to general use in the future will require several more steps including validation in other cohorts from other regions to test its generalisability. We hope to continue to refine the algorithm as additional data sets become available in low latitude and high latitude regions. Using simple measures, the algorithm can be used to help identify higher and lower risk individuals, relative to others of the same age and sex within a population, for whom the hazards of sun exposure would be different, and to produce estimates of absolute risk when combined with population-specific data.

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Table 1: Odds ratios for melanoma from a multivariable logistic random coefficients model including these factors, adjusted for age, sex, effect of study assessed in a pooled analysis of 15 case-control studies.

Risk factor	OR (95% CI)**	
	n= 12387	n
Hair color		
Brown/Black	1	7704
Red	1.76 (1.41, 2.16)	3608
Blond	1.41 (1.19, 1.67)	942
Skin type		
III+IV	1	7508
I+II	1.66 (1.36, 2.01)	3666
Freckling		
No	1	5129
Yes	1.58 (1.25, 2.01)	5050
Family history of melanoma		
No	1	9054
Yes	1.74 (1.21, 2.46)	614
Total body nevus count distribution*		
0-50%	1	1354

50-75%	1.64 (1.12, 2.30)	638
75-90%	2.72 (1.89, 3.81)	794
>90%	5.50 (3.73, 7.89)	701
Large nevi on body (≥5mm)		
None	1	1851
1-2	2.26 (1.29, 3.68)	1041
≥ 3	4.10 (2.19, 7.08)	712
Sunburn†		
No	1	3080
Yes	1.28 (1.05, 1.27)	6070

* Nevus count was ranked within each study and classified into four centile groups (0-50%, 50-75%, 75-90%, >90%). Nevus count is an age-dependent variable, so centile groups were generated separately for the under 50 and 50 and over age groups in each study and then combined as one variable

 ** Risk score odds ratios are combined multiplicatively. For example, an individual with black hair, skin type III, no freckling or family history of melanoma, but with a high nevus count including at least 3 large nevi and previous history of a serious sunburn would have a score of 28.9 (5.50x4.10x1.28)

† Classified as one or more instances of sunburn thoughout subject's lifetime

Table 2. Variables present in each study used in the Multiple Imputation by Chained Equations (MICE) imputation.

Study	Hair colour	Skin type	Freckling	Family history	Total nevus count	Large nevi	Sunburn	Others
Bataille 1996(34)	Yes	Yes	Yes	Yes	Body+Arms	Arms	Yes	Atypical nevi
Berwick 1996(35)	Yes	Yes	Yes	Yes	Arms	No	Yes	Raised nevi
Elwood 1985(11)	Yes	Yes	No*	Yes	No	No	Yes at 15	None
Elwood 1990(36)	Yes	Yes	Yes	No	Arms	Arms	Yes	None
Green 1985(37)	Yes	Yes	Yes	Yes	Arms	No	Yes	None
Holly 1995(38)	Yes	Yes	Yes	Yes	No	Body	Yes	None
Holman 1984(39)	Yes	Yes	No	Yes	Arms	No	Yes	Raised nevi
Kanetsky 2001(40)	Yes	Yes	Yes	Yes	Body	Body	Yes	Atypical nevi
Kennedy 2003(41)	Yes	Yes	Yes	No	Body	No	Yes	Atypical nevi
LeMarchand 2006 (42)	Yes	Yes	Yes	Yes	Body+Arms†	Body+Arms	Yes at 15	Raised nevi

Mössner 2007(43)	**Yes**	**Yes**	**No**	**No**	**Arms**	**No**	**No**	**None**
Osterlind 1988(44)	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**Arms**	**Yes at 15**	**Raised nevi**
Swerdlow 1986(45)	**Yes**	**Yes**	**No**	**Yes**	**Body+Arms**	**Body**	**Yes at 20**	**None**
Titus-Ernstoff 2005(46)	**Yes**	**Yes**	**Yes**	**Yes**	**Body+Arms**	**No**	**Yes**	**Atypical nevi**
Westerdahl 1994(47)	**Yes**	**No**	**Yes**	**No**	**Arms**	**No**	**Yes**	**Raised nevi**
Westerdahl 2000(48)	**Yes**	**Yes**	**Yes**	**Yes**	**Arms**	**No**	**Yes**	**Raised nevi**

† Trained interviewers counted moles on the arms, moles on the body were self-counted.

* Freckling data was collected but not used due to freckling being assessed retrospectively to adolescence in this study.

Table 3: Sensitivity analysis. Estimates of threshold values omitting each study in turn. For each row the data from the indicated study is omitted and the risk score thresholds are calculated based on the data in the other 15 studies.

Study Omitted	Centile						
	20%	30%	40%	50%	60%	80%	90%
Bataille 1996(34)	2.25	3.38	4.74	6.15	8.60	20.41	34.15
Berwick 1996(35)	2.02	2.87	3.65	5.25	7.04	15.84	28.00
Elwood 1985(11)	2.13	3.04	4.30	5.81	7.87	18.86	32.03
Elwood 1990(36)	2.02	2.89	3.72	5.50	7.50	17.65	29.48
Green 1985(37)	2.14	2.94	4.10	5.54	8.25	20.27	34.21
Holly 1995(38)	2.14	2.91	3.77	5.50	7.63	17.65	29.48
Holman 1984(39)	2.26	3.38	4.83	6.86	9.71	22.55	35.70
Kanetsky 2001(40)	2.24	3.04	4.56	5.88	8.29	19.44	32.25
Kennedy 2003(41)	2.10	2.89	3.75	5.50	7.81	18.58	32.47
LeMarchand 2006 (42)	2.26	3.38	4.80	6.49	9.13	22.03	35.63
Mössner 2007(43)	2.10	2.91	3.90	5.50	7.87	17.78	32.02
Osterlind 1988(44)	2.24	3.32	4.57	5.94	8.34	19.31	32.02
Swerdlow 1986(45)	2.14	3.04	4.57	5.94	8.61	20.69	35.63
Titus-Ernstoff 2005(46)	2.14	2.89	3.77	5.50	7.81	18.66	32.03
Westerdahl 1994(47)	2.14	3.32	4.57	6.15	8.69	21.88	35.63
Westerdahl 2000(48)	2.24	3.32	4.74	6.45	8.76	22.55	35.63
NONE†	**2.24**	**3.32**	**4.57**	**5.94**	**8.46**	**19.66**	**32.80**

† Individuals are classified into the Low, Medium-Low, Medium-High and High

groups based on the 30th, 60th and 90th percentiles.

Table 4: Number and percentage of cases and controls in each risk band for the

Leeds dataset†.

	Case (%)	Control (%)	Pooled controls* (%)
Low, relative to peers**	93 (13)	181 (43)	128 (30)
Medium-Low, relative to peers	160 (22)	137 (32)	128 (30)
Medium-High, relative to peers	265 (36)	77 (18)	128 (30)
High, Relative to peers	213 (29)	30 (7)	43 (10)

*Expectation of how controls in the Leeds case-control data would be distributed if they followed the distribution pattern of the controls in the pooled analyses.

** Peers are defined as individuals of the same age and sex drawn from the same population.

† Chi squared test $p < 2.2 \times 10^{-16}$

Figure legend

Figure 1 ROC curve showing discrimination between cases and controls in the

Leeds melanoma case-control study using the risk algorithm: (AUC=0.75, 95% CI

0.73-0.78)**.**