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Review

A meta-analysis of pigmentary characteristics, sun sensitivity, freckling and melanocytic nevi and risk of basal cell carcinoma of the skin

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ABSTRACT

Objective: To calculate pooled risk estimates of the association between pigmentary characteristics and basal cell carcinoma (BCC) of the skin.
Methods: We searched three electronic databases and reviewed the reference lists of the retrieved articles until July 2012 to identify eligible epidemiologic studies. Eligible studies were those published in between 1965 and July 2012 that permitted quantitative assessment of the association between histologically-confirmed BCC and any of the following characteristics: hair colour, eye colour, skin colour, skin phototype, tanning and burning ability, and presence of freckling or melanocytic nevi. We included 29 studies from 2236 initially identified. We calculated summary odds ratios (ORs) using weighted averages of the log OR, using random effects models.
Results: We found strongest associations with red hair (OR 2.02; 95% CI: 1.68, 2.44), fair skin colour (OR 2.11; 95% CI: 1.56, 2.86), and having skin that burns and never tans (OR 2.03; 95% CI: 1.73, 2.38). All other factors had weaker but positive associations with BCC, with the exception of freckling of the face in adulthood which showed no association.
Conclusions: Although most studies report risk estimates that are in the same direction, there is significant heterogeneity in the size of the estimates. The associations were quite modest and remarkably similar, with ORs between about 1.5 and 2.5 for the highest risk level for each factor. Given the public health impact of BCC, this meta-analysis will make a valuable contribution to our understanding of BCC.

1. Introduction

Basal cell carcinoma (BCC), the most commonly diagnosed type of cancer [1], is an important public health problem in most Caucasian populations. Incidence rates of BCC vary significantly around the world, and even within countries. The incidence is substantially higher in Australia (884/100,000/year in 2002) [2], than in populations from Europe, the United Kingdom and North America where it ranges from 70 to 500/100,000/year depending on the population studied [3–14]. There is some evidence that incidence rates are continuing to rise in several populations [15–18]. While BCC, particularly on the face, can cause substantial individual morbidity, the burden of this disease is mostly related to the costs associated with treatment. In Australia the annual cost has been estimated to be in the order of 200 million dollars [19].

The primary cause of BCC is exposure to solar ultraviolet radiation (UVR), and phenotypic characteristics that increase sensitivity to UVR are known to increase risk of BCC. However to date there has been no comprehensive review to assess whether risk estimates vary across studies and to calculate summary estimates of risk. The relative importance of different phenotypic characteristics has not been previously addressed. Capturing accurate estimates of odds ratio (OR) may enable better targeted prevention and screening efforts. Thus the aim of this work was to evaluate systematically the epidemiological evidence describing the relationship between BCC and pigmentary characteristics.

Abbreviations: BCC, basal cell carcinoma; UVR, ultraviolet radiation; CI, confidence interval; OR, odds ratio; RR, relative risk; AK, actinic keratoses; SCC, squamous cell carcinoma.

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2. Methods

This meta-analysis was conducted according to MOOSE guidelines for reviews of observational studies [20].

2.1. Data sources

Eligible studies since 1965 up to July 2012 were identified by searching the following databases and by hand-searching the reference lists of the retrieved articles.

- Medline 1950 (U.S. National Library of Medicine, Bethesda, MD), using PubMed software as the search interface
- Conference Papers Index 1982 (CSA, Bethesda, MD), using the CSA Illumina search interface
- ISI Science Citation Index, using the ISI Web of Science VR search interface

For computer searches, we used the following MeSH terms or text words (using both the UK and the US spellings): "Carcinoma, Basal Cell"[Mesh] OR "Basal Cell Carcinomas" OR "Basal Cell Epithelioma" OR "Basal Cell Epitheliomas" OR "Nonmelanoma skin cancer" OR "Non-melanoma skin cancer" OR "Non melanoma skin cancer" OR "NMSC" OR "BCC", "Eye Colour", "Hair Colour", "Skin Colour", "Skin Phototype", Freckle, Freckling, "Melanocytic nevi", nevi, "Melanocytic naevi", naevi, Mole', Pigmentation, Pigmentary. Studies that had been commonly cited in the literature were also included as citation search terms in the ISI Science Citation Index to identify subsequent studies that had referenced them.

2.2. Study selection

We included observational studies of case–control and cohort designs in the meta-analysis provided that they permitted quantitative assessment of the association between histologically confirmed BCC and eye colour, hair colour, tanning and burning ability, skin phototype, skin colour, melanocytic nevi and freckling.

We only included studies reporting the associations in adult populations (>18 years old) and published in English. We read the abstracts of all identified studies to exclude those that were clearly not relevant. The full texts of the remaining articles were read to determine if they met the study inclusion criteria. Where multiple reports from one study were found, the most recent or most complete publication was used. Studies in which all cases were selected from considerably high risk populations (pre-cancerous skin lesions, familial BCCs) were also excluded. We did not exclude any studies from the analysis because of the study quality; however we performed sensitivity analyses, omitting each study, to determine whether the results could have been influenced significantly by one or more than one studies.

2.3. Data extraction

The primary computerised literature search and hand-searching the reference lists of the retrieved articles identified 83 potentially eligible studies. After initial review we excluded 54 studies because they were not independent of other included studies ($n = 18$), were not in English ($n = 3$) [21–23], they reported data from an ineligible study design (*e.g.* case-series, trials) ($n = 26$), they reported combined data for BCC, squamous cell carcinoma (SCC) or actinic keratoses (AK) together ($n = 5$) [24–28]. Studies in which all cases were selected from high risk populations (pre-cancerous skin lesions, familial BCCs) ($n = 2$) [29,30] were also excluded. We retrieved 29 articles for further assessment, all of which met the eligibility criteria: 5 cohort studies and 24 case–control studies (Fig. 1). Of the eligible case–control studies, 5 were population-based, 18 were clinic/hospital-based and one was both population and clinic/hospital-based (Table 1).

A single reviewer (MK) extracted the following information for each study: country, year of publication, study design, sample size, variables for which analysis was done, whether information was self-reported or recorded by an observer, whether the variable was adjusted for time spent outdoors, skin colour/type or not, and results (RR, OR and 95% CIs).

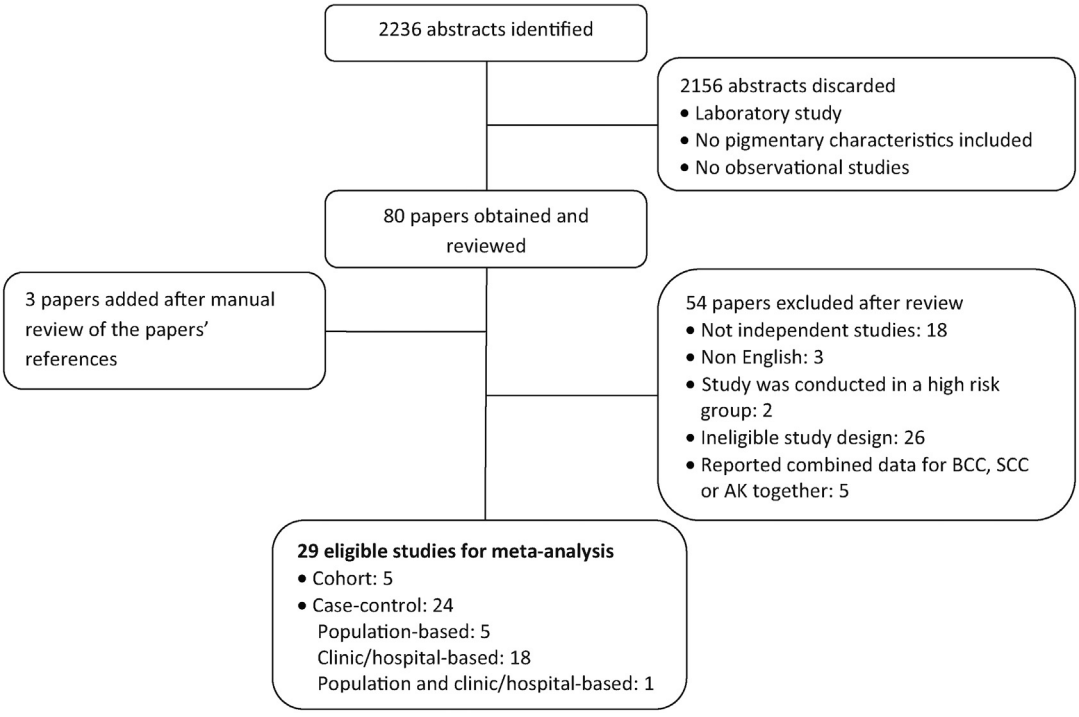


Fig. 1. Flow chart of literature search for studies on the association between pigmentary traits, sun sensitivity, freckling and melanocytic nevi and risk of basal cell carcinoma of the skin.

Table 1
Characteristics of the 29 studies included in the meta-analysis of pigmentary traits, sun sensitivity, freckling and melanocytic nevi and risk of basal cell carcinoma of the skin.

First Author	Year	Study Location	Sample size	Hair colour	Eye colour	Skin colour	Skin phototype	Tanning/ burning	Childhood freckling	Adulthood freckling	Arm nevi	Whole body nevi
Cohort			*Cases/Cohort*									
Qureshi A [50]	2011	USA	9423/113139	✓							✓	
Kiiski V [71]	2010	The Netherlands	524/10820	✓	✓							
Van Dam R [47]	1999	USA	3273/317672	✓	✓			✓			✓	
Green A [72]	1996	Australia	250/2095	✓		✓					✓	
Vitasa BC [73]	1990	USA	40/808		✓			✓	✓			
Population-based case–control			*Cases/Controls*									
Dwyer T [74]	2002	Australia	220/483	✓	✓			✓				
Rosso S [75]	1999	Switzerland	146/144	✓	✓			✓				
Gallagher R [39]	1995	Canada	226/406	✓	✓	✓		✓	✓			
Kricker A [46]	1991	Australia	226/1021	✓	✓			✓	✓			
Hogan DJ [76]	1989	Canada	538/738	✓	✓	✓	✓		✓			
Clinic/Hospital-based case–control			*Cases/Controls*									
Ferrucci LM [41]	2011	USA	377/390	✓	✓	✓		✓		✓		
Dessinioti C [45]	2011	Greece	199/200	✓	✓	✓	✓	✓				✓
Gon A [77]	2011	Brazil	127/280	✓	✓		✓		✓			
Jankovic S [36]	2010	Montenegro	100/100	✓	✓	✓		✓				✓
Walther U [78]	2004	Germany	213/411	✓	✓		✓			✓		
Corona R [79]	2001	Italy	166/158				✓			✓		
Naldi L [48]	2000	Italy	528/512	✓	✓	✓		✓		✓	✓	
Vlajinac HD [40]	2000	Yugoslavia	200/399	✓	✓	✓			✓			✓
Lock-Andersen J [44]	1999	Denmark	145/174	✓	✓		✓					
Lock-Andersen J [49]	1999	Denmark	145/119								✓	✓
Lear JT [43]	1997	England	403/503	✓	✓		✓					
Gamble JF [38]	1996	USA	174/239	✓	✓	✓			✓			
Maia M [42]	1995	Brazil	259/518	✓	✓		✓		✓			
Wei Q [80]	1993	USA	88/135				✓					
Gafa L [81]	1991	Italy	108/266			✓		✓				
Friedman–Birnbaum R [82]	1991	Israel	77/93	✓	✓							
Vitaliano PP [83]	1980	USA	366/294			✓		✓				
Gellin GA [37]	1965	USA	861/1938	✓	✓	✓		✓				
Both Population-based & Clinic/Hospital case–control			*Cases/Controls*									
Zanetti R [84]	1996	Italy, Spain, France	1549/1795	✓	✓			✓				

2.4. Statistical analysis

We used the method of DerSimonian and Laird [31] to pool OR estimates, using weighted averages of the log OR, considering random effects. We assessed the heterogeneity among studies using Cochrane Q test and I^2 statistics. The Cochrane Q test is calculated as the weighted sum of squared differences between individual study effects and the pooled effect between studies [32]. The I^2 statistic describes the percentage of variation across studies ($I^2 = 100\% \times (Q-\mathrm{df})/Q$) [33]. We also conducted separate analyses by study design, geographic location, year of publication (before and after 2000), method of assessment (observed or self-reported) and whether the variable was adjusted for time spent outdoors, and skin colour/type or not. We assessed publication bias using the Begg rank correlation method and the Egger method [34,35], and performed the meta-analyses using Stata statistical software (StataCorp. 2009: Release 11. College Station, TX, USA).

3. Results

3.1. Hair colour

A total of 23 studies presented data on the association between hair colour and BCC (Table 1). Thirteen studies presented effect estimates for risk of BCC associated with red hair, 12 with blond, 10 with red/blond and 11 with light brown hair colour. In all studies, the reference group was dark hair (Table 2).

There was a clear gradient in BCC risk according to hair colour. Compared to those classified as having dark hair, red hair conferred the highest risk (OR 2.02; 95% CI: 1.68, 2.44) (Fig. 2a) followed by red/blond hair (OR 1.69; 95% CI: 1.24, 2.29), blond (OR 1.38; 95% CI: 1.12, 1.71) and light brown hair (OR 1.27; 95% CI: 1.06, 1.53) (Table 2).

With the exception of red hair, there was significant heterogeneity in risk estimates across studies, but little difference in the estimates from population-based compared with clinic/hospital-based studies. No particular study explained the significant heterogeneity in these estimates. However, stratifying by various characteristics such as year of publication, method of assessment (observed or self-reported), covariate control (adjusted for skin colour/type or not), study design and source of information removed the heterogeneity for blond hair colour. Stratifying by year of publication, method of assessment and covariate control removed the heterogeneity for light brown hair colour (Table 2 & Table S1 (a) and (b)).

For all hair colours, the pooled OR was attenuated when restricted to studies that had adjusted for skin colour/type except red/blond where there was only one paper that had adjusted for skin colour. The pooled OR was slightly higher when hair colour was self-reported rather than observer-recorded except for red hair in which the OR was slightly lower (Table S1 (a) and (b)).

3.2. Eye colour

Twenty-two studies presented data on the association between eye colour and BCC (Table 1). Eighteen studies presented the associations between blue/blue-grey eye colour, 15 with green/green-grey-hazel, and 4 with blue-grey/green-hazel eye colour and

Table 2
Meta-analysis results using a random effects model: Risk of basal cell carcinoma associated with pigmentary traits, sun sensitivity, freckling and melanocytic nevi.

	All studies				Case–control studies				Cohort studies			
	Studies	OR (95% CI)	I^2 (%)	*P* het	Studies	OR (95% CI)	I^2 (%)	*P* het	Studies	OR (95% CI)	I^2 (%)	*P* het
Hair colour												
Red *vs.* Dark	13	2.02 (1.68, 2.44)	32.2	0.125	9	2.63 (1.94, 3.57)	2.1	0.417	4	1.79 (1.50, 2.13)	33.6	0.211
Blond *vs.* Dark	12	1.38 (1.12, 1.71)	71.6	0.000	9	1.38 (1.07, 1.78)	39.8	0.102	3	1.38 (0.94, 2.03)	92.0	0.000
Red/Blond *vs.* Dark	10	1.69 (1.24, 2.29)	84.5	0.000	10	1.69 (1.24, 2.29)	84.5	0.000	–	–	–	–
Light brown *vs.* Dark	11	1.27 (1.06, 1.53)	67.6	0.001	9	1.22 (0.97, 1.54)	50.8	0.039	2	1.39 (0.96, 2.02)	91.9	0.000
Eye colour												
Blue/blue-grey *vs.* Dark	18	1.68 (1.37, 2.07)	84.2	0.000	15	1.78 (1.42, 2.25)	79.4	0.000	3	1.16 (0.91, 1.47)	56.1	0.127
Green/green-grey-hazel *vs.* Dark	15	1.61 (1.35, 1.92)	66.9	0.000	14	1.68 (1.39, 2.03)	55.4	0.006	1	1.19 (1.07, 1.32)	–	–
Blue-grey/green-hazel *vs.* Dark	4	1.58 (1.16, 2.13)	35.4	0.200	4	1.58 (1.16, 2.13)	35.4	0.200	–	–	–	–
Skin colour												
Fair/Light *vs.* Dark/Olive	12	2.11 (1.56, 2.86)	83.0	0.000	11	2.14 (1.54, 2.95)	84.1	0.000	1	2.0 (1.18, 3.39)	–	–
Medium *vs.* Dark/Olive	6	1.37 (0.90, 2.09)	59.5	0.030	5	1.51 (0.90, 2.54)	65.7	0.020	1	0.98 (0.54, 1.76)	–	–
Skin phototype												
I/II *vs.* III/IV	9	1.70 (1.17, 2.47)	83.3	0.000	9	1.70 (1.17, 2.47)	83.7	0.000	–	–	–	–
Tanning/burning												
'Burn never tan' *vs.* 'tan never burn'	11	2.03 (1.73, 2.38)	94.4	0.000	10	2.01 (1.71, 2.37)	95.0	0.000	1	2.72 (1.13, 6.55)	–	–
'Often burn then tan' *vs.* 'tan never burn'	8	1.55 (1.12, 2.14)	98.1	0.000	7	1.54 (1.01, 2.35)	98.3	0.000	1	1.51 (1.37, 1.67)	–	–
'Tan/rarely burn' *vs.* 'tan never burn'	5	1.69 (1.27, 2.25)	69.7	0.010	5	1.69 (1.27, 2.25)	69.7	0.010	–	–	–	–
Freckling in childhood												
Present *vs.* Absent	8	1.57 (1.29, 1.92)	49.5	0.054	7	1.47 (1.24, 1.74)	33.8	0.170	1	3.66 (1.51, 8.86)	–	–
Freckling in adulthood												
Present *vs.* Absent	4	0.94 (0.63, 1.38)	76.1	0.006	4	0.94 (0.63, 1.38)	76.1	0.006	–	–	–	–
Melanocytic nevi on the arm												
Present *vs.* Absent	5	1.43 (1.16, 1.77)	77.4	0.001	2	2.58 (0.97, 6.85)	84.5	0.011	3	1.27 (1.12, 1.44)	43.1	0.172
Melanocytic nevi on whole body												
Present *vs.* Absent	4	1.77 (1.68, 1.86)	0.0	0.426	4	1.77 (1.68, 1.86)	0.0	0.426	–	–	–	–

risk of BCC (Table 2). For 3 studies [36–38] we combined the categories 'blue' and 'grey'. For 2 studies we combined categories 'green/grey' and 'hazel' [39,40], and for 2 studies categories 'green' and 'hazel' [38,41]. In all cases the reference group was dark eye colour.

Having eyes of any colour other than dark was associated with an increased risk of BCC. Blue/blue-grey eye colour conferred the highest risk (OR 1.68; 95% CI: 1.37, 2.07) (Fig. 2b), and blue-grey/green-hazel (OR 1.58; 95% CI: 1.16, 2.13) and green/green-grey-hazel (OR 1.61; 95%CI: 1.35, 1.92) marginally lower risk.

There was significant heterogeneity across studies. The estimates from population-based studies and from cohort studies were lower than those from clinic/hospital-based studies and there was considerable variability according to study location (Table 2 & Table S2). However even within many of these strata the heterogeneity remained and no one study was responsible for this. For all eye colour categories the pooled OR was slightly attenuated when restricted to studies that had adjusted for skin colour/type. In general the pooled ORs were slightly lower when eye colour was self-reported rather than observer-recorded (Table S2).

3.3. Skin colour

Twelve studies presented data on skin colour and BCC risk (Table 1). Twelve studies presented effect estimates for risk of BCC associated with fair skin and 6 with medium skin colour (Table 2). For one study we combined the categories 'fair' and 'very fair' [41]. The reference colour was dark/olive (dark, olive or dark/olive).

We conducted a meta-analysis of the association between skin colour and risk of BCC using 'fair' *vs.* 'dark/olive' and 'medium' *vs.* 'dark/olive' comparisons as the data were presented in this way for the majority of studies. Fair skin colour was associated with a more than 2-fold increased risk of BCC (OR 2.11; 95% CI: 1.56, 2.86) (Fig. 2c) compared to dark/olive skin colour, whereas the effect size of medium skin colour was smaller and non-significant. There was evidence of significant heterogeneity in risk estimates between studies (Table 2).

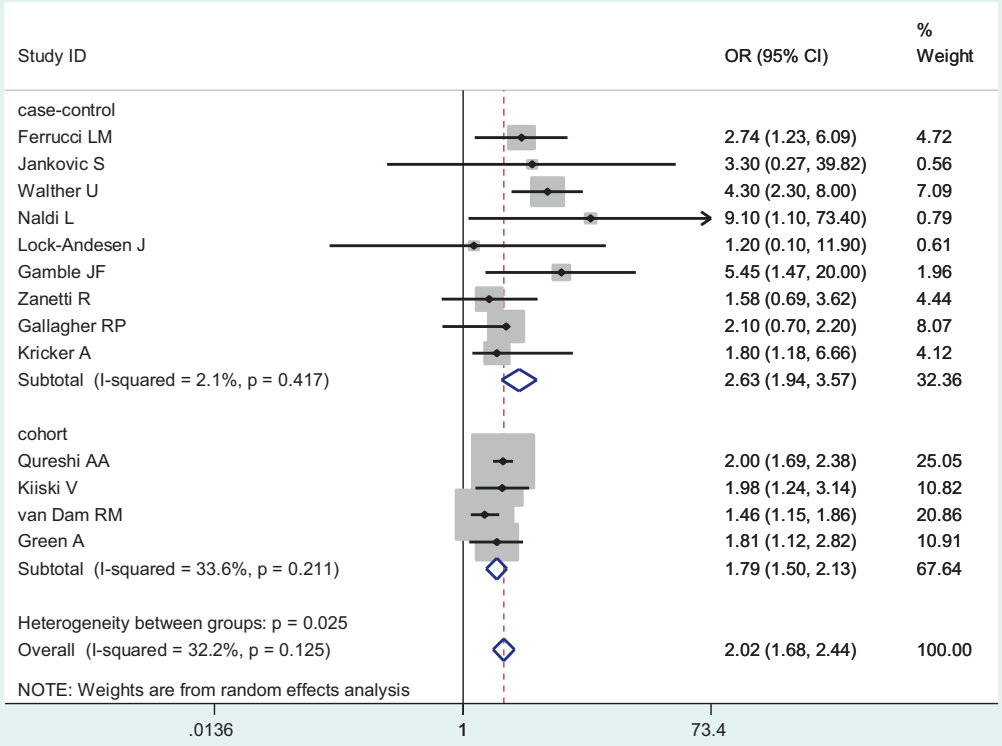
When we omitted the one study [38] that used 'medium/dark' rather than 'dark/olive' as the reference category, the pooled OR for fair skin was increased (OR 2.31; 95% CI: 1.64, 3.28).

For fair skin colour, the pooled OR was higher for clinic/hospital-based studies than for population-based studies, but the reverse was true for medium skin colour. The pooled OR was slightly higher when fair skin colour was recorded by an observer rather than self-reported (Table 2 & Table S3).

3.4. Skin reaction to sun exposure

Most studies analysed skin reaction to sun exposure and risk of BCC. However some used skin phototype as the exposure variable and others used tanning/burning ability with no classification into phototype. We were unable to combine these exposure variables due to differences in the categorisation and reference categories used and have therefore presented these separately below.

a



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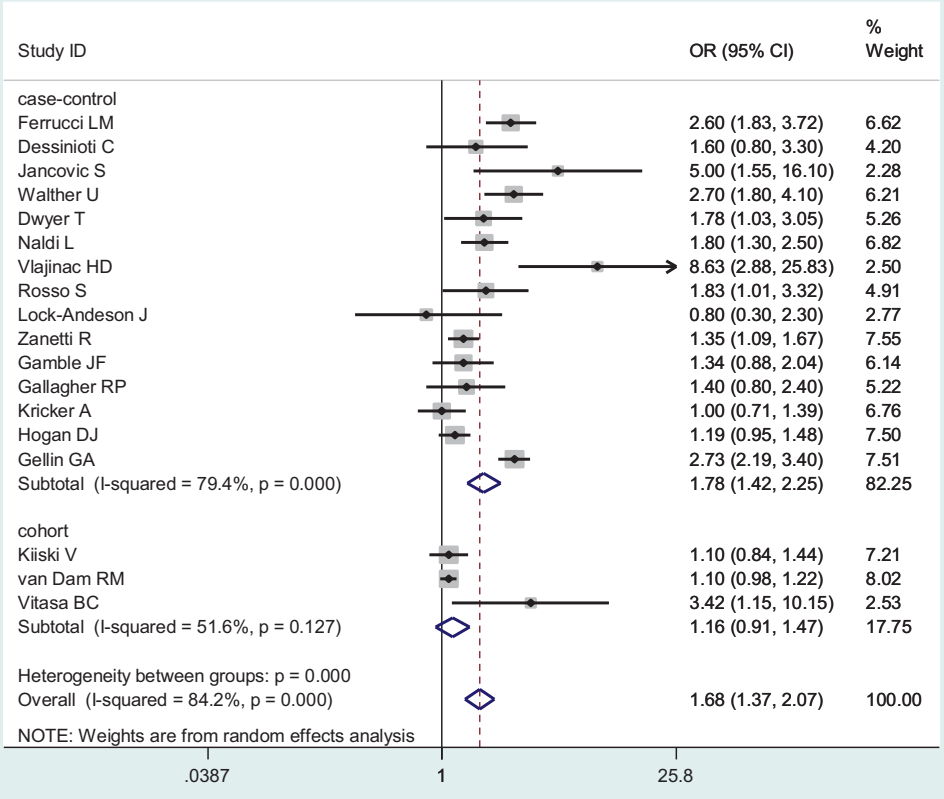
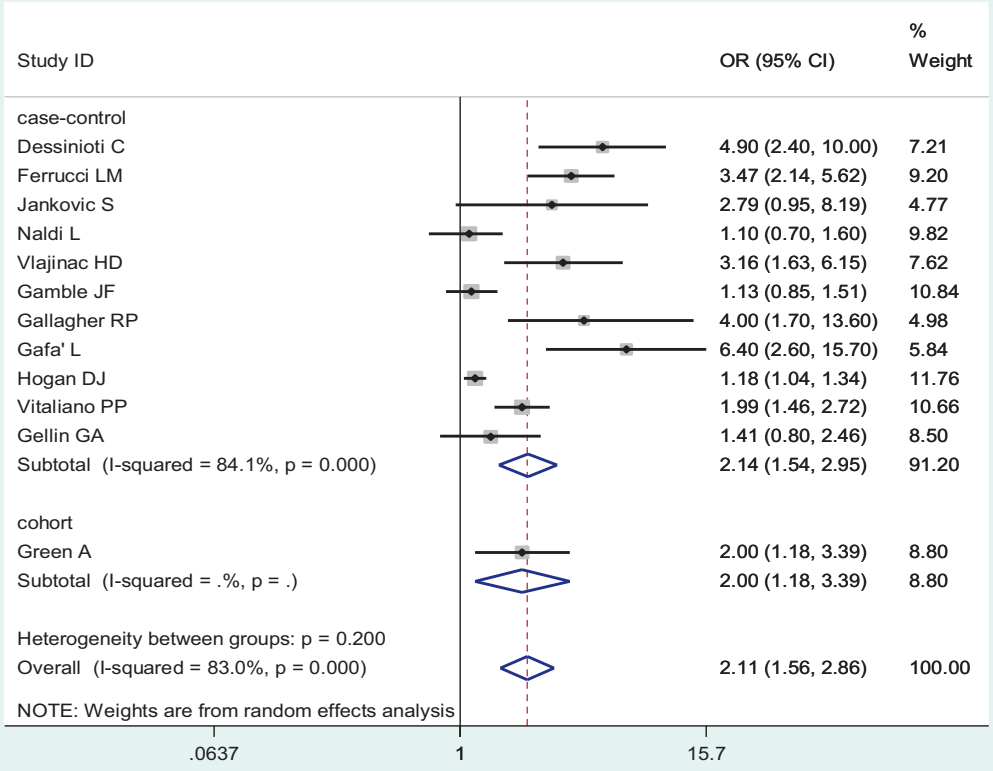


Fig. 2. (a–e): Forest plots of the association between red *versus* dark hair colour (a), blue/blue-grey *versus* dark eye colour (b), fair *versus* dark/olive skin colour (c), 'burn never tan' *versus* 'tan never burn' (d), presence *versus* absence of freckling in childhood (e) and BCC using a random effects model. Each line represents an individual study result with the width of the horizontal line indicating 95% CI, the position of the box representing the odds ratio, and the size of the box being proportional to the weight of the study.

c



d

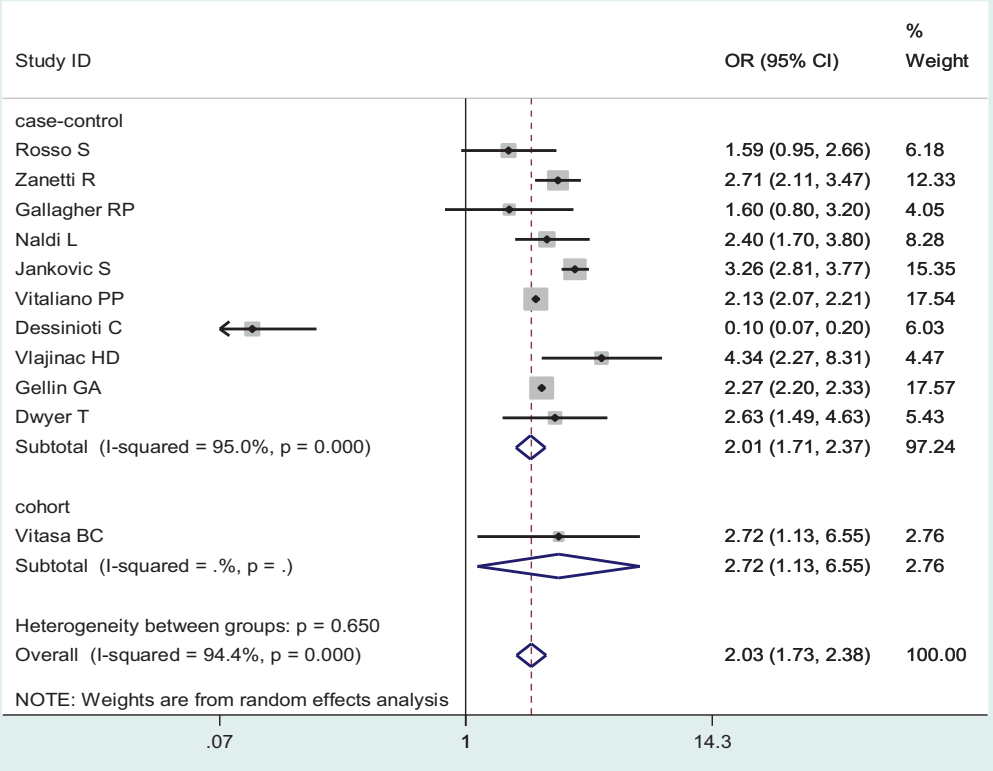


Fig. 2. (*Continued*).

e

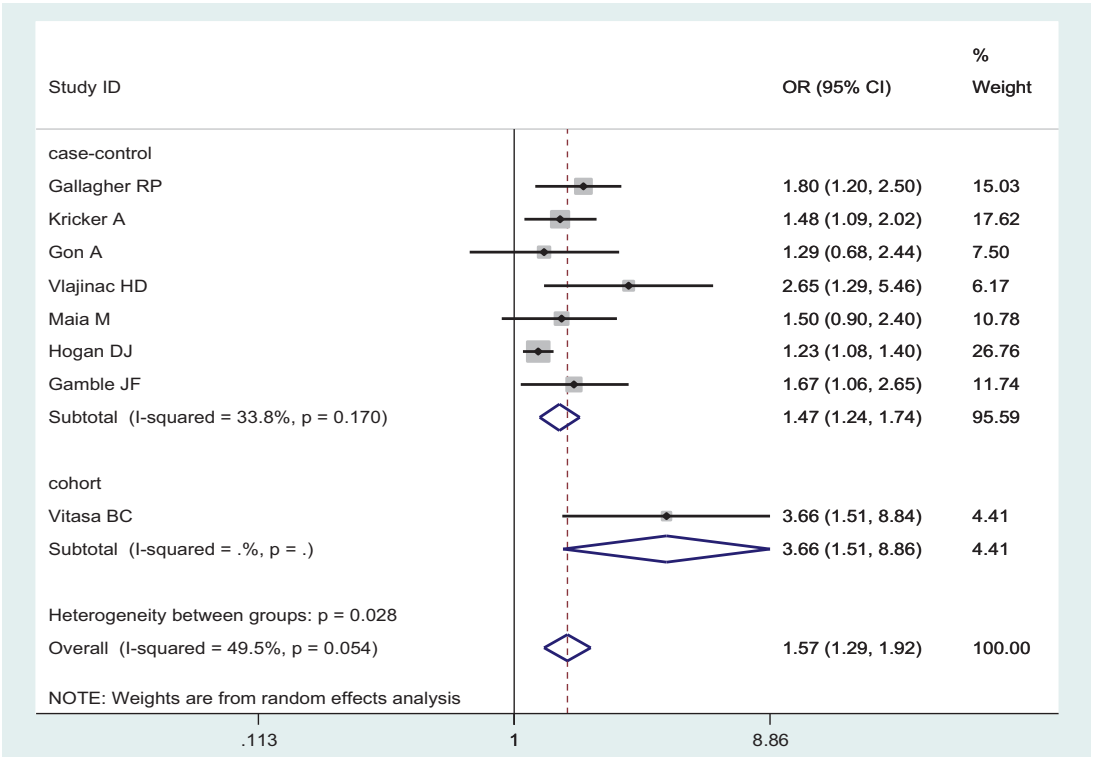


Fig. 2. (*Continued*).

3.5. Skin phototype

Nine studies presented data on skin phototype and BCC risk (Table 1). Six studies presented data on phototype I/II *vs.* III/IV; one study on I/II/III *vs.* IV/V/VI [42], one on I *vs.* IV [43], and another on 4 levels of skin phototype (I, II, III, IV) [44]. For the latter study there was no linear trend in skin phototype; patients with skin phototype I had a lower risk of BCC than patients with skin phototypes II and III. For this study we used the OR for category 'II'.

We conducted a meta-analysis comparing risk in people with skin type I/II with that in those with skin type III/IV. The pooled OR was 1.70 (95% CI: 1.17, 2.47) with evidence of significant heterogeneity ($p < 0.001$) (Table 2 & Table S4). In a sensitivity analysis excluding one study [42] which presented data in different format (I/II/III *vs.* IV/V/VI) there was a small reduction in the overall estimate (OR 1.58; 95% CI: 1.04, 2.40).

In one study phototype III/IV was paradoxically associated with increased BCC risk compared with phototype I/II (OR 3.9; 95% CI: 1.8, 8.5) [45]. Omitting this study resulted in a higher pooled OR (2.05; 95% CI: 1.56, 2.69).

3.6. Tanning/burning

Fourteen studies presented data on skin reaction to sun exposure and BCC risk (Table 1). The definition of skin reaction to sun exposure varied, as did the number of categories. We analysed the data in the following categories: 'burn never tan', 'often burn then tan', 'tan/rarely burn', 'tan never burn', with the latter as the reference category (Table 2).

Compared to people who tanned and never burned, those who burned and never tanned were at the highest risk of BCC (OR 2.03; 95% CI: 1.73, 2.38) (Fig 2d), with somewhat lower risks for those in the 'often burn then tan' (OR 1.55; 95% CI: 1.12, 2.14) and 'tan/rarely burn' categories (OR 1.69; 95%CI: 1.27, 2.25). There was evidence of significant heterogeneity in the risk estimates and the estimates from population-based studies were mostly lower than for clinic-based studies (Table 2 & Table S5).

In one study phototype category 'burn never tan' was paradoxically associated with decreased BCC risk compared with 'tan never burn' (OR 0.1; 95% CI: 0.07, 0.2) [45]. Omitting this study resulted in a higher pooled OR (2.42; 95% CI: 2.21, 2.67).

3.7. Freckling

3.7.1. Childhood

Eight studies presented data on the presence of freckling in childhood and risk of BCC (Table I). All studies presented data on 'yes *vs.* no' or 'present *vs.* absent' except one study which presented data for 3 categories of freckle count [46]. For this study we combined the categories 'scattered' and 'moderate/heavy' (weighted for category size). The pooled OR was 1.57 (95% CI: 1.29, 1.92) (Fig. 2e). There was no marked difference in the pooled estimates between clinic/hospital-based and population-based studies (1.65 *vs.* 1.57) (Table 2 & Table S6).

3.7.2. Adulthood

Four studies presented data on presence of freckling on the adult face and risk of BCC (Table 1). The pooled OR for freckling present *vs* absent was 0.94 (95% CI: 0.63, 1.38) with significant heterogeneity ($p = 0.006$) (Table 2 & Table S6).

3.8. Melanocytic nevi

3.8.1. On the arms

A total of 5 studies presented data on the relationship between melanocytic nevi equal to or greater than 2–3 millimetres on the arms or forearms and risk of BCC (Table 1). Three studies reported nevus counts from the arms, one study from the forearms [47] and one from the upper arms [48]. The reference category was 'none' in all studies except one, in which '0–15' was the reference

category [49]. This was also the only study which presented the results as crude ORs stratified by sex. All studies presented data for 3 or 4 categories of nevi count. As the categories of naevus count were not the same across all studies, it was not possible to meta-analyse for a cut-off point, therefore we dichotomised exposure to compare 'presence' *vs.* 'absence' of nevi. The pooled OR of BCC risk for people with one or more melanocytic nevi compared with those without any nevi was 1.43 (95% CI: 1.16, 1.77) with evidence of significant heterogeneity ($p = 0.001$) (Table II & Table S7). The pooled OR from the cohort studies was lower than that from case–control studies (Table S7). Excluding the study that used 0–15 nevi as the reference category [49] did not alter the pooled OR.

Since it is relatively rare to have no nevi, we also calculated the risk of having more than five compared with having fewer than five nevi on the arm for three studies that used the same category cut-off points [47,48,50]. The OR was 1.35 (95% CI: 1.18, 155), and there was no evidence of heterogeneity.

3.8.2. On the whole body

Four studies presented data on the relationship between melanocytic nevi on the whole body, equal to or greater than 2 mm in diameter, and BCC risk (Table 1). We compared 'presence' *vs.* 'absence' of nevi. The pooled OR of BCC for people with one or more melanocytic nevi compared with those with none was 1.77 (95% CI: 1.68, 1.86) and there was no evidence of heterogeneity ($p = 0.426$) (Table 2). Stratified analyses are shown in supplementary Table 7, but the number of studies was too small to compare the factors robustly.

There is evidence that counting nevi on the arms provides a satisfactory method to predict distribution of nevi on the whole body [51,52]. Hence, we combined the studies that reported nevi on the arms and those that reported nevi on the whole body. The pooled OR for all 9 studies showed that the presence of nevi was associated with significantly increased risk of BCC (OR 1.60; 95% CI: 1.33, 1.93) (Table S7).

We were unable to calculate the pooled OR for a cut-off point for whole body nevi due to marked difference in the categories of nevi count.

Table 3
Results of publication bias tests using the Egger weighted regression method and the Begg rank correlation method for the analyses of pigmentary traits and risk of BCC.

	P for bias	
	Begg method	Egger method
Hair colour		
Red *vs.* Dark	0.502	0.137
Blond *vs.* Dark	0.837	0.631
Red/Blond *vs.* Dark	1.000	0.043
Light brown *vs.* Dark	1.000	0.537
Eye colour		
Blue/Blue-grey *vs.* Dark	0.130	0.034
Green/Green-grey-hazel *vs.* Dark	0.373	0.011
Blue-grey/green-hazel *vs.* Dark	0.734	0.899
Skin colour		
Fair/Light *vs.* Dark/Olive	0.150	0.002
Medium *vs.* Dark/Olive	0.260	0.136
Skin phototype		
I/II *vs.* III/IV	0.175	0.333
Tanning/burning		
'Tan/rarely burn' *vs.* 'tan never burn'	0.806	0.128
'Often burn then tan' *vs.* 'tan never burn'	0.386	0.972
'Burn never tan' *vs.* 'tan never burn'	0.533	0.717
Freckling in childhood		
Present *vs.* Absent	0.174	0.007
Freckling in adulthood		
Present *vs.* Absent	0.734	0.815
Melanocytic nevi on the arm		
Present *vs.* Absent	0.462	0.269
Melanocytic nevi on whole body		
Present *vs.* Absent	0.089	0.217

3.9. Publication bias

There was no evidence of publication bias using the Begg rank correlation method for the analyses of all variables. There was evidence of significant publication bias using the Egger method for the analyses of blue/blue-grey eye, green/green-grey-hazel eye, fair/light skin and presence of freckling in childhood (Table 3).

4. Disscusion

To our knowledge this is the first study to systematically evaluate available epidemiologic evidence about the magnitude of the relationship between pigmentary characteristics and risk of BCC using estimates of OR derived through meta-analysis. We found strongest associations with red hair, fair skin colour, and having skin that burns and never tans. All other factors had weaker but positive associations with BCC, with the exception of freckling of the face in adulthood. However, the associations were quite modest and remarkably similar, with ORs between about 1.5 and 2.5 for the highest risk level for each factor.

One of the most notable observations of this review and meta-analysis was the significant heterogeneity for almost all exposures analysed. While we did not specifically adjust for study quality or exclude any studies on the basis of quality, we examined potential sources of heterogeneity including study design, sources of cases and controls, study location, whether the phenotypic characteristic was self-reported or recorded by an observer, and adjustment for potential confounders, but no single factor consistently accounted for all of the heterogeneity. Similarly, for most analyses, no single study was responsible for the significant heterogeneity we observed. The differences in risk estimates across studies were significantly greater than expected by chance alone, and were most likely due to differences in phenotypes among the study populations, as well as to cultural influences on the way that risk factors such as skin colour were reported.

The studies contributing to the pooled OR estimates were prone to the usual biases associated with observational studies, including selection bias, recall bias, and measurement error. The pooled OR estimates of nevi, skin colour, eye colour, and freckling in adulthood were arguably less likely to have been influenced by recall bias, as in most studies these were observed by independent personnel rather than by the participants themselves. However there are no published standards for measurement of these variables and in most studies it was unclear if observers were blinded to skin cancer status prior to examination. Approximately half of the studies used self-reported hair colour, but for red hair in particular this is likely to be relatively accurate. Self-reported skin sensitivity is an unreliable means of assessing skin type [53–55], and definitions of tanning and burning are likely to vary according to sunburn experience. This may explain the lack of consistent trend in our skin sensitivity analyses.

We contend that the best way to reduce the economic burden of BCC will be through prevention rather than screening, particularly as screening is likely to uncover a reservoir of lesions that would not otherwise cause problems or come to the attention of the health system [56]. The association between sun exposure and BCC is complex, and it appears that sun exposure in childhood might be more important than that in adulthood [39]. There is little evidence

that reducing cutaneous UVR through the use of sunscreen in adulthood alters the subsequent risk of BCC [57]. Thus implementing effective sun protection practices in childhood and adolescence may offer the best means of BCC prevention.

There is evidence that clinicians giving specific advice leads to greater and more sustained behaviour change than broad public health messages [58–60]. Communicating individual risk directly to patients may be one tool that clinicians could use. There have been a number of models developed for predicting long-term risk of melanoma [61], other cancers [62–66] and coronary artery disease [67,68]. There is currently limited information about whether communicating personal risk leads to long-term change of lifestyle behaviours, but the evidence suggests that it improves screening uptake and compliance with medication [69,70]. Therefore the use of individualised risk prediction for future BCC in a clinical setting, for example at the time of childhood immunisations, is a strategy that could be tested. However, to predict risk more accurately, we need to consider the effects of combinations and interactions of all these factors, which is not possible using currently published data. Large-scale cohort studies are required to enable the development of robust models that can be trialled for prevention of BCC.

This study has some strengths and weaknesses. We carefully searched several databases and hand searched the reference lists of all retrieved articles. However we did not attempt to find unpublished studies and did not include any studies that were not written in English. While we did not exclude studies on the basis of any quality parameters, we conducted a very comprehensive set of stratified analyses to assess the effects of factors such as study design, source of information and control of confounding.

BCC continues to be a considerable burden to individuals and health systems in many populations throughout the world. This comprehensive review has highlighted the relatively modest and heterogeneous associations with individual pigmentary characteristics. Finding ways to reduce the incidence of BCC will require large-scale studies which enable comprehensive population-specific assessment of interactions, ideally accounting for histological subtype and possibly incorporating genotype. This will enable the development of more targeted and effective preventive strategies.

Author contributions

Dr(s) Khalesi, and Neale had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design*: Khalesi, Neale. *Acquisition of data*: Khalesi. *Analysis and interpretation of data*: Khalesi, Whiteman, Tran, Olsen, Neale. *Drafting of the manuscript*: Khalesi, Whiteman, Tran, Kimlin, Olsen, Neale. *Statistical analysis*: Khalesi, Tran. *Study supervision*: Neale.

Conflict of interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.canep.2013.05.008.

References

[1] AIHW. Cancer in Australia: an Overview 2012. Cancer series no. 74. Cat. no. CAN 70. Canberra: AIHW, 2012.
[2] Staples MP, Elwood M, Burton RC, Williams JL, Marks R, Giles GG. Non-melanoma skin cancer in Australia: the 2002 national survey and trends since 1985. Med J Aust 2006;184(1):6–10.
[3] Brewster DH, Bhatti LA, Inglis JH, Nairn ER, Doherty VR. Recent trends in incidence of nonmelanoma skin cancers in the East of Scotland: 1992-2003. Br J Dermatol 2007;156(6):1295–300.
[4] Stang A, Ziegler S, Buchner U, Ziegler B, Jockel KH, Ziegler V. Malignant melanoma and nonmelanoma skin cancers in Northrhine-Westphalia, Germany: a patient- vs. diagnosis-based incidence approach. Int J Dermatol 2007;46(6):564–70.
[5] Birch-Johansen F, Jensen A, Mortensen L, Olesen AB, Kjaer SK. Trends in the incidence of nonmelanoma skin cancer in Denmark 1978-2007: rapid incidence increase among young Danish women. Int J Cancer 2010;127(9):2190–8.
[6] Lipozencic J, Celic D, Strnad M, Toncic RJ, Pasic A, Rados J, et al. Skin cancers in Croatia, 2003–2005: epidemiological study. Coll Antropol 2010;34(3):865–9.
[7] Flohil SC, de Vries E, Neumann HA, Coebergh JW, Nijsten T. Incidence: prevalence and future trends of primary basal cell carcinoma in the Netherlands. Acta Derm Venereol 2011;91(1):24–30.
[8] Bath-Hextall F, Leonardi-Bee J, Smith C, Meal A, Hubbard R. Trends in incidence of skin basal cell carcinoma. Additional evidence from a UK primary care database study. Int J Cancer 2007;121(9):2105–8.
[9] Demers AA, Nugent Z, Mihalcioiu C, Wiseman MC, Kliewer EV. Trends of nonmelanoma skin cancer from 1960 through 2000 in a Canadian population. J Am Acad Dermatol 2005;53(2):320–8.
[10] Jung GW, Metelitsa AI, Dover DC, Salopek TG. Trends in incidence of non-melanoma skin cancers in Alberta: Canada, 1988–2007. Br J Dermatol 2010;163(1):146–54.
[11] Chuang TY, Popescu A, Su WP, Chute CG. Basal cell carcinoma. A population-based incidence study in Rochester: Minnesota. J Am Acad Dermatol 1990;22(3):413–7.
[12] Scotto J, Fears TR, Fraumeni JF. Incidence of nonmelanoma skin cancer in the United States. Bethesda, MD: US Dept. of Health and Human Services, National Institutes of Health, 1983.
[13] Reizner GT, Chuang TY, Elpern DJ, Stone JL, Farmer ER. Basal cell carcinoma in Kauai, Hawaii: the highest documented incidence in the United States. J Am Acad Dermatol 1993;29(2 Pt 1):184–9.
[14] Harris RB, Griffith K, Moon TE. Trends in the incidence of nonmelanoma skin cancers in southeastern Arizona: 1985–1996. J Am Acad Dermatol 2001;45(4):528–36.
[15] Ko CB, Walton S, Keczkes K, Bury HP, Nicholson C. The emerging epidemic of skin cancer. Br J Dermatol 1994;130(3):269–72.
[16] Holme SA, Malinovszky K, Roberts DL. Changing trends in non-melanoma skin cancer in South Wales: 1988–98. Br J Dermatol 2000;143(6):1224–9.
[17] Skellett AM, Hafiji J, Greenberg DC, Wright KA, Levell NJ. The incidence of basal cell carcinoma in the under-30s in the UK. Clin Exp Dermatol 2012.
[18] Doherty VR, Brewster DH, Jensen S, Gorman D. Trends in skin cancer incidence by socioeconomic position in Scotland: 1978–2004. Br J Cancer 2010;102(11):1661–4.
[19] AIHW. Health System Expenditures on Cancer and Other Neoplasms in Australia, 2000-01. Australian Institute of Health and Welfare; 2005 , cat. no. HWE 29.
[20] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of observational studies in epidemiology (MOOSE) group. JAMA 2000;283(15):2008–12.
[21] Ruiz Lascano A, Kuznitzky R, Garay I, Ducasse C, Albertini R. Risk factors for basal cell carcinoma. Case–control study in Cordoba. Medicina (B Aires) 2005;65(6):495–500.
[22] Sanchez G, Nova J, de la Hoz F. Risk factors for basal cell carcinoma: a study from the National dermatology center of Colombia. Actas Dermosifiliogr 2012;103(4):294–300.
[23] Raznatovic M, Maksimovic N, Jankovic J, Music D. [Impact of some constitutional characteristics on the development of basal cell carcinoma]. Vojnosanit Pregl 2007;64(6):375–9.
[24] Rocha FP, Menezes A, Almeida Junior HL, Tomasi E. Risk markers and risk factors for actinic keratosis and basal cell carcinoma: a case–control study. An Bras Dermatol 2004;79(4):441–54.
[25] Healy E, Collins P, Barnes L. Nonmelanoma skin cancer in an Irish population: an appraisal of risk factors. Ir Med J 1995;88(2):58–9.
[26] Ferreira FR, Nascimento LFC, Rotta O. Fatores de risco para câncer da pele não melanoma em Taubaté, SP: um estudo caso-controle. Rev Assoc Med Bras 2011;57:431–7.

[27] Lichte V, Dennenmoser B, Dietz K, Häfner HM, Schlagenhauff B, Garbe C, et al. Professional risk for skin cancer development in male mountain guides–a cross-sectional study. J Eur Acad Dermatol Venereol 2010;24(7):797–804.
[28] Herity B, O'Loughlin G, Moriarty MJ, Conroy R. Risk factors for non-melanoma skin cancer. Ir Med J 1989;82(4):151–2.
[29] Liboutet M, Portela M, Delestaing G, Vilmer C, Dupin N, Gorin I, et al. MC1R and PTCH gene polymorphism in French patients with basal cell carcinomas. J Invest Dermatol 2006;126(7):1510–7.
[30] Foote JA, Harris RB, Giuliano AR, Roe DJ, Moon TE, Cartmel B, et al. Predictors for cutaneous basal- and squamous-cell carcinoma among actinically damaged adults. Int J Cancer 2001;95(1):7–11.
[31] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7(3):177–88.
[32] Hardy RJ, Thompson SG. Detecting and describing heterogeneity in meta-analysis. Stat Med 1998;17(8):841–56.
[33] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21(11):1539–58.
[34] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50(4):1088–101.
[35] Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple: graphical test. BMJ 1997;315(7109):629–34.
[36] Janković S, Maksimović N, Janković J, Ražnatović M, Marinković J, Tomić-Spirić V. Risk factors for basal cell carcinoma: results from the case–control study. Cent Eur J Med 2010;5(6):666–73.
[37] Gellin GA, Kopf AW, Garfinkel L. Basal cell epithelioma. A controlled study of associated factors. Arch Dermatol 1965;91:38–45.
[38] Gamble JF, Lerman SE, Holder WR, Nicolich MJ, Yarborough CM. Physician-based case–control study of non-melanoma skin cancer in Baytown: Texas. Occup Med (Lond) 1996;46(3):186–96.
[39] Gallagher RP, Hill GB, Bajdik CD, Fincham S, Coldman AJ, McLean DI, et al. Sunlight exposure: pigmentary factors, and risk of nonmelanocytic skin cancer. I. Basal cell carcinoma. Arch Dermatol 1995;131(2):157–63.
[40] Vlajinac HD, Adanja BJ, Lazar ZF, Bogavac AN, Bjekic MD, Marinkovic JM, et al. Risk factors for basal cell carcinoma. Acta Oncol 2000;39(5):611–6.
[41] Ferrucci LM, Cartmel B, Molinaro AM, Gordon PB, Leffell DJ, Bale AE, et al. Host phenotype characteristics and MC1R in relation to early-onset basal cell carcinoma. J Invest Dermatol 2011.
[42] Maia M, Proenca NG, de Moraes JC. Risk factors for basal cell carcinoma: a case–control study. Rev Saude Publica 1995;29(1):27–37.
[43] Lear JT, Tan BB, Smith AG, Bowers W, Jones PW, Heagerty AH, et al. Risk factors for basal cell carcinoma in the UK: case–control study in 806 patients. J R Soc Med 1997;90(7):371–4.
[44] Lock-Andersen J, Drzewiecki KT, Wulf HC. Eye and hair colour: skin type and constitutive skin pigmentation as risk factors for basal cell carcinoma and cutaneous malignant melanoma. A Danish case–control study. Acta Derm Venereol 1999;79(1):74–80.
[45] Dessinioti C, Tzannis K, Sypsa V, Nikolaou V, Kypreou K, Antoniou C, et al. Epidemiologic risk factors of basal cell carcinoma development and age at onset in a Southern European population from Greece. Exp Dermatol 2011;20(8):622–6.
[46] Kricker A, Armstrong BK, English DR, Heenan PJ. Pigmentary and cutaneous risk factors for non-melanocytic skin cancer–a case–control study. Int J Cancer 1991;48(5):650–62.
[47] Van Dam RM, Huang Z, Rimm EB, Weinstock MA, Spiegelman D, Colditz GA, et al. Risk factors for basal cell carcinoma of the skin in men: results from the health professionals follow-up study. Am J Epidemiol 1999;150(5):459–68.
[48] Naldi L, DiLandro A, D'Avanzo B, Parazzini F. Host-related and environmental risk factors for cutaneous basal cell carcinoma: evidence from an Italian case–control study. J Am Acad Dermatol 2000;42(3):446–52.
[49] Lock-Andersen J, Drzewiecki KT, Wulf HC. Naevi as a risk factor for basal cell carcinoma in Caucasians: a Danish case–control study. Acta Derm Venereol 1999;79(4):314–9.
[50] Qureshi AA, Zhang M, Han J. Heterogeneity in host risk factors for incident melanoma and non-melanoma skin cancer in a cohort of US women. J Epidemiol 2011;21(3):197–203.
[51] Fariñas-Alvarez C, Ródenas JM, Herranz MTMD-R. The naevus count on the arms as a predictor of the number of melanocytic naevi on the whole body. Br J Dermatol 1999;140(3):457–62.
[52] English JSC, Swerdlow AJ, Mackie RM, O'Doherty CJ, Hunter JAA, Clark J, et al. Site-specific melanocytic naevus counts as predictors of whole body naevi. Br J Dermatol 1988;118(5):641–4.
[53] Rampen FH, Fleuren BA, de Boo TM, Lemmens WA. Unreliability of self-reported burning tendency and tanning ability. Arch dermatol 1988;124(6):885–8.
[54] Youn JI, Oh JK, Kim BK, Suh DH, Chung JH, Oh SJ, et al. Relationship between skin phototype and MED in Korean, brown skin. Photodermatol Photoimmunol Photomed 1997;13(5-6):208–11.
[55] Sanclemente G, Zapata J-F, García J-J, Gaviria Á, Gómez L-F, Barrera M. Lack of correlation between minimal erythema dose and skin phototype in a colombian scholar population. Skin Res Technol 2008;14(4):403–9.
[56] Valery PC, Neale R, Williams G, Pandeya N, Siller G, Green A. The effect of skin examination surveys on the incidence of basal cell carcinoma in a Queensland community sample: a 10-year longitudinal study. J Investig Dermatol Symp Proc 2004;9(2):148–51.
[57] Green A, Williams G, Neale R, Hart V, Leslie D, Parsons P, et al. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. Lancet 1999;354(9180):723–9.
[58] Heitmann C, Greiser E, Dören M. The impact of the Women's health initiative randomized controlled trial 2002 on perceived risk communication and use of postmenopausal hormone therapy in Germany. Menopause 2005;12(4):405–11.
[59] Falk M, Magnusson H. Sun protection advice mediated by the general practitioner: an effective way to achieve long-term change of behaviour and attitudes related to sun exposure? Scand J Prim Health Care 2011;29(3):135–43.
[60] Smith BJ, Ferguson C, McKenzie J, Bauman A, Vita P. Impacts from repeated mass media campaigns to promote sun protection in Australia. Health Promot Int 2002;17(1):51–60.
[61] Quéreux G, JNgC M, Jumbou O, Lequeux Y, Dréno B. Validation of the self-assessment of melanoma risk score for a melanoma-targeted screening. Eur J Cancer Prev 2012. Epub ahead of print.
[62] Gail MH, Costantino JP. Validating and improving models for projecting the absolute risk of breast cancer. J Natl Cancer Inst 2001;93(5):334–5.
[63] Freedman AN, Slattery ML, Ballard-Barbash R, Willis G, Cann BJ, Pee D, et al. Colorectal cancer risk prediction tool for white men and women without known susceptibility. J Clin Oncol 2009;27(5):686–93.
[64] Freedman AN, Seminara D, Gail MH, Hartge P, Colditz GA, Ballard-Barbash R, et al. Cancer risk prediction models: a workshop on development, evaluation, and application. J Clin Oncol 2005;97(10):715–23.
[65] Patil V, Wahab S, Zodpey S, Vasudeo N. Development and validation of risk scoring system for prediction of cancer cervix. Indian J Public Health 2006;50(1):38–42.
[66] Wang W, Chen S, Brune KA, Hruban RH, Parmigiani G, Klein AP. PancPRO. Risk assessment for individuals with a family history of pancreatic cancer. J Clin Oncol 2007;25(11):1417–22.
[67] Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97(18):1837–47.
[68] Stephens JW, Ambler G, Vallance P, Betteridge DJ, Humphries SE, Hurel SJ. Cardiovascular risk and diabetes. Are the methods of risk prediction satisfactory? Eur J Cardiovasc Prev Rehabil 2004;11(6):521–8.
[69] Edwards A, Unigwe S, Elwyn G, Hood K. Effects of communicating individual risks in screening programmes: cochrane systematic review. BMJ 2003;327(7417):703–9.
[70] Burke LE, Dunbar-jacob JM, Hill MN. Compliance with cardiovascular disease prevention strategies: a review of the research. Ann Behav Med 1997;19(3):239–63.
[71] Kiiski V, de Vries E, Flohil SC, Bijl MJ, Hofman A, Stricker BH, et al. Risk factors for single and multiple basal cell carcinomas. Arch Dermatol 2010;146(8):848–55.
[72] Green A, Battistutta D, Hart V, Leslie D, Weedon D. Skin cancer in a subtropical Australian population: incidence and lack of association with occupation. The Nambour Study Group. Am J Epidemiol 1996;144(11):1034–40.
[73] Vitasa BC, Taylor HR, Strickland PT, Rosenthal FS, West S, Abbey H, et al. Association of nonmelanoma skin cancer and actinic keratosis with cumulative solar ultraviolet exposure in Maryland watermen. Cancer 1990;65(12):2811–7.
[74] Dwyer T, Blizzard L, Ashbolt R, Plumb J, Berwick M, Stankovich JM. Cutaneous melanin density of Caucasians measured by spectrophotometry and risk of malignant melanoma: basal cell carcinoma, and squamous cell carcinoma of the skin. Am J Epidemiol 2002;155(7):614–21.
[75] Rosso S, Joris F, Zanetti R. Risk of basal and squamous cell carcinomas of the skin in Sion, Switzerland: a case–control study. Tumori 1999;85(6):435–42.
[76] Hogan DJ, To T, Gran L, Wong D, Lane PR. Risk factors for basal cell carcinoma. Int J Dermatol 1989;28(9):591–4.
[77] Gon A, Minelli L. Risk factors for basal cell carcinoma in a southern Brazilian population: a case–control study. Int J Dermatol 2011;50(10):1286–90.
[78] Walther U, Kron M, Sander S, Sebastian G, Sander R, Peter RU, et al. Risk and protective factors for sporadic basal cell carcinoma: results of a two-centre case–control study in southern Germany. Clinical actinic elastosis may be a protective factor. Br J Dermatol 2004;151(1):170–8.
[79] Corona R, Dogliotti E, D'Errico M, Sera F, Iavarone I, Baliva G, et al. Risk factors for basal cell carcinoma in a Mediterranean population: role of recreational sun exposure early in life. Arch Dermatol 2001;137(9):1162–8.
[80] Wei Q, Matanoski GM, Farmer ER, Hedayati MA, Grossman L. DNA repair and aging in basal cell carcinoma: a molecular epidemiology study. Proc Natl Acad Sci U S A 1993;90(4):1614–8.
[81] Gafa L, Filippazzo MG, Tumino R, Dardanoni G, Lanzarone F, Dardanoni L. Risk factors of nonmelanoma skin cancer in Ragusa, Sicily: a case–control study. Cancer Causes Control 1991;2(6):395–9.
[82] Friedman-Birnbaum R, Linn S, Eidlitz-Markus T, Harth Y, Cohen E. Seborrheic skin and acne vulgaris as protective factors against the development of basal cell epithelioma. Dermatologica 1991;183(3):160–3.
[83] Vitaliano PP, Urbach F. The relative importance of risk factors in nonmelanoma carcinoma. Arch Dermatol 1980;116(4):454–6.
[84] Zanetti R, Rosso S, Martinez C, Navarro C, Schraub S, Sancho-Garnier H, et al. The multicentre south European study 'Helios'. I: Skin characteristics and sunburns in basal cell and squamous cell carcinomas of the skin. Br J Cancer 1996;73(11):1440–6.