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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).

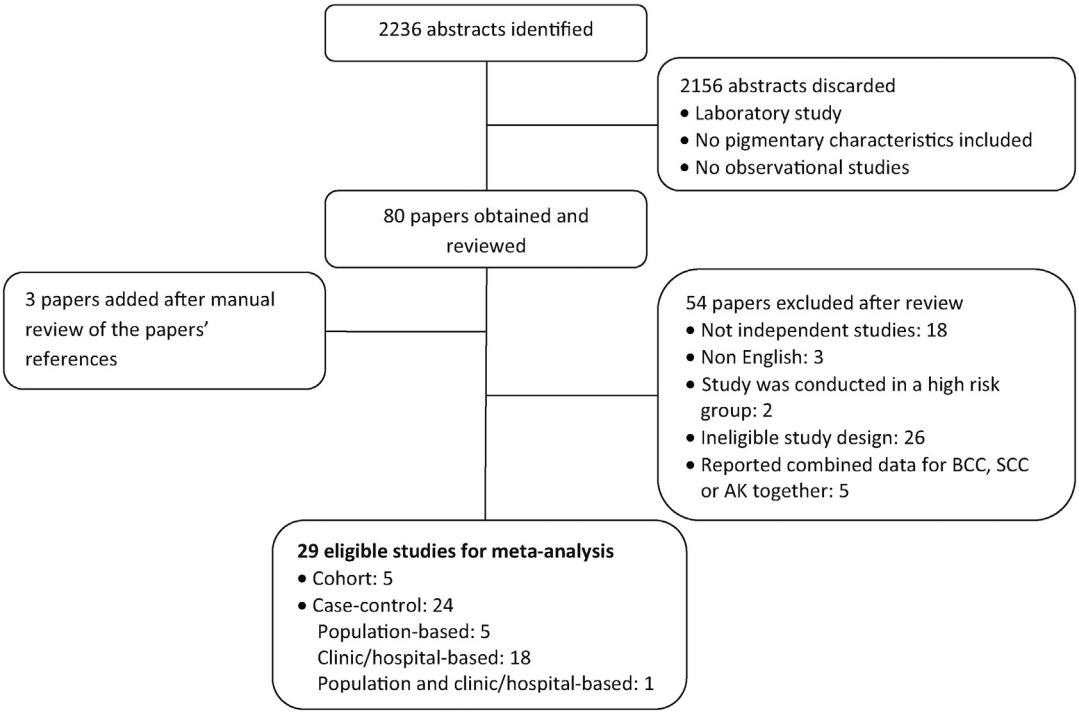

Fig. 1. Flow chart of literature search for studies on the association between pigmentary traits, sun sensitivity, freckling and melanocytic nevi and risk of basal cell carcinoma of the skin.