Research letter

Risk of skin cancer in people with vitiligo: a systematic review and meta-analysis

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Dear Editor, Vitiligo is a chronic disorder causing skin depigmentation, with around 1% global prevalence. It affects people of all ages, skin types and sexes. Due to the absence of melanin in lesional skin there is a theoretical concern that there might be a higher risk of skin cancer in people with vitiligo. However, some studies have shown that the genetic and autoimmune profiles of patients with vitiligo may confer a degree of protection against the development of melanoma and nonmelanoma skin cancer (NMSC). Therefore, the aim of this systematic review was to quantify the risk of skin cancer (melanoma and NMSC) in people with vitiligo compared with those without vitiligo.

We registered the review protocol with PROSPERO on 19 July 2017 (CRD42017072493) and reported our study following the MOOSE guidelines. We searched three databases (PubMed, Embase and Web of Science), from inception to 12 July 2017, for observational studies meeting the inclusion criteria (see the protocol for further details). We also searched the British Association of Dermatologists clinical guideline for vitiligo and the U.K. E-Theses depository for any relevant studies. Two authors (L.B. and S.L.) independently performed title/abstract and full-text screening, quality assessment [using the Joanna Briggs Institute (JBI) critical appraisal tool] and data extraction. Disagreements were resolved by discussion with another author (S.R.). Random effects meta-analysis was used to combine the results.

In total 2177 studies were identified, of which 12 full-text articles were assessed for eligibility. Of these, five studies were eligible to be included in the review. We searched the

| Study          | Type of study | Country | Setting         | Number of people included in the study | Patient characteristics | Skin cancer studied | Comparison group | Quality assessment |
|----------------|---------------|---------|-----------------|----------------------------------------|-------------------------|---------------------|------------------|-------------------|
| Sharquie 2016 | Cross-sectional | Iraq     | Hospital        | 100 with vitiligo and 500 controls | Age 9–71 years, 59 male and 41 female | BCC, SCC            | Healthy controls | Low               |
| Paradisi 2014 | Cross-sectional | Italy    | Hospital        | 10 040 with vitiligo and 25 956 controls | 6418 (63.9%) age <40 years, 5457 (54.4%) female | Melanoma, NMSC | Patients admitted to the same hospital for vascular surgery | Low               |
| Teulings 2013  | Cross-sectional | Netherlands | Hospital      | 1307 with vitiligo and 788 controls | Median age 61 years (IQR 55–66), 1311 (62.6%) female | Melanoma, NMSC | Family members or friends of patients with vitiligo | Low               |
| Schallreuter 2002 | Cross-sectional | Germany   | Hospital        | 136                                     | 93 (68.4%) female, all white and age 14–70 years (mean 42.4) | BCC, SCC            | Self-comparison | Low               |
| Harrist 1984  | Cohort        | India     | Not clear       | 230                                     | East Indians, no information on age or sex | Melanoma, BCC, SCC | Self-comparison | Low               |
| Beral 1983    | Case–control  | Australia | Hospital        | 287 with skin cancer and 574 controls | Female, white, age 18–54 years | Melanoma | 1 : 2 age-matched controls without melanoma | High              |

BCC, basal cell carcinoma; SCC, squamous cell carcinoma; NMSC, nonmelanoma skin cancer; IQR, interquartile range. *Patients with vitiligo for cross-sectional and cohort studies and patients with cancer for case–control studies. **Includes BCC and SCC. *Excludes BCC and SCC.
references of the five studies and also their Google Scholar citations, and identified one extra study. Of the six studies included in the review, four were included in the meta-analysis. Details of the search strategy and the PRISMA flow diagram are available on request to the corresponding author.

All studies but one were hospital based.\textsuperscript{1-8} Four studies were cross-sectional,\textsuperscript{1-4} of which three compared people with vitiligo vs. people without vitiligo, and one compared vitiliginous skin vs. nonvitiliginous skin on the same group of patients (Table 1).\textsuperscript{6} The remaining two studies were cohort\textsuperscript{7} and case–control\textsuperscript{8} studies. The number of people with vitiligo in the included studies ranged from 19 to 10,040. Only one study was deemed to be of high quality,\textsuperscript{8} scoring 7 out of 10 using the JBI tool. The main reason for poor quality was lack of comparability between people with and without vitiligo. One study adjusted for phototherapy.\textsuperscript{4}

The meta-analyses for NMSC and melanoma used the combined results from three studies each\textsuperscript{1-5,8} which included a total of 11,447 and 11,366 people with vitiligo, respectively. The two studies excluded from the meta-analysis found no events of skin cancer in either the vitiligo or nonvitiligo groups (366 patients excluded).\textsuperscript{6,7} Compared with people without vitiligo, people with vitiligo had a significantly lower risk of NMSC; the crude odds ratio (OR) was 0.29 [95% confidence interval (CI) 0.14–0.58, $I^2 = 75.9\%$]. The same pattern occurred for melanoma, but the crude OR was not statistically significant (OR 0.52, 95% CI 0.15–1.78, $I^2 = 85.3\%$). Forest plots are available on request to the corresponding author.

This review supports the current view that vitiligo may be protective of skin cancer. This could be due to the genetic and autoimmune profile of vitiligo, or the fact that patients with vitiligo are more careful regarding sun protection than those without vitiligo. This is the first review in this clinical area that has searched the literature comprehensively and synthesized data in a systematic way. However, our review is limited by the small number of included studies and high heterogeneity due to methodological and clinical differences between the included studies. Furthermore, the lack of studies has prohibited subgroup analysis and assessment of publication bias.

The main methodological limitation of the included studies was lack of adequate comparison with the controls. Furthermore, most of the studies either had an inappropriate study design or were hospital based, limiting the internal and external validity of the results. Finally, it is important to acknowledge that studies assessing the association between melanoma and vitiligo may have biased results because vitiligo occurring during melanoma or treatment of melanoma is very difficult to differentiate from vitiligo itself. Future research implications include the need for a population-based longitudinal study with appropriate comparisons. Once more appropriate research has been conducted in this field, clinicians may be able to reassure people with vitiligo that they are not at increased risk of skin cancer.

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