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SHORT COMMUNICATION

Prediction of the Occurrence of Melanoma and Non-melanoma Skin Cancer in Patients with Vitiligo

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Vitiligo is the most common depigmentary disorder, with a prevalence of approximately 0.5% worldwide (1). Vitiligo is a progressive disease characterized by the destruction of melanocytes in the epidermis, in which auto-immune processes are possibly involved, resulting in depigmented macular skin lesions (2). These melanocytes protect the skin cells against the carcinogenic effects of sunlight and chemicals (3).

A genome-wide association study of individuals with vitiligo found significant associations between vitiligo and several genes that regulate immunity (4, 5). Vitiligo has also been associated with a polymorphism in the *TYR* gene, which encodes tyrosinase, the main enzyme involved in melanin synthesis. Discrete allelic linkages seem to correlate with different immune recognition of tyrosinase in vitiligo and melanoma, suggesting that strong anti-tyrosinase expression protects patients with vitiligo against melanoma (4–6).

On the other hand, due to the loss of melanocytes and, therefore, of melanin (7), it can be reasoned that patients with vitiligo have an increased risk of developing melanoma.

The development of non-melanoma skin cancer (NMSC) in patients with vitiligo is still debated (8). A literature search was performed to obtain all the available evidence regarding the occurrence of melanoma and NMSC in patients with vitiligo.

METHODS

Search strategy and selection

A search was conducted in PubMed, Embase and the Cochrane library databases. Synonyms for domain, determinant and outcome were combined (Table SI[1]). Found articles were independently screened on title and abstract by 2 authors (SMH and RWJK) based on the inclusion and exclusion criteria shown in Fig. 1. The remaining articles were screened on full text by the same independent authors. References of the selected articles were hand searched for possible missed articles; no relevant articles were found.

RESULTS

On 29 November 2014, 1,024 articles were retrieved. After screening on relevance, using inclusion and exclusion criteria, 5 articles were selected for further assessment

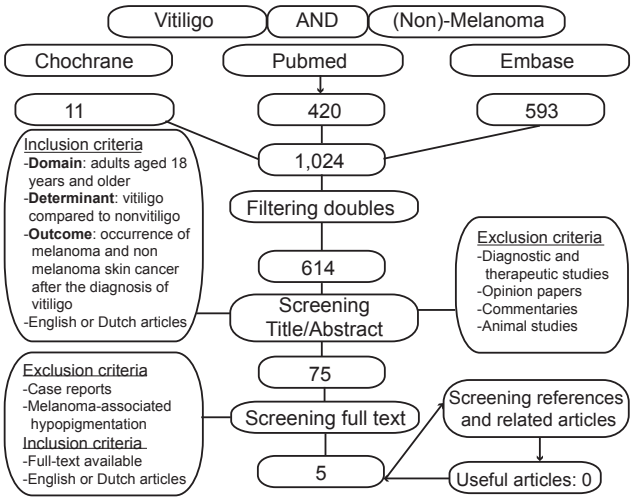

Fig. 1. Search strategy and outcome regarding screening of databases for articles about the risk of skin cancer in patients with vitiligo.

(Fig. 1). Paradisi et al. (4) studied the relative risk (RR) of melanoma and NMSC in a cohort of 10,040 patients with vitiligo compared with 25,956 patients seen for vascular surgery. Overall, the crude RR for melanoma was 0.24 (95% confidence interval (95% CI) 0.13–0.45) in patients with vitiligo compared with those with a non-dermatological condition. The crude RR for NMSC was 0.19 (95% CI 0.14–0.17). Teulings et al. (8) published a case-control study among 1,307 patients with vitiligo and their partners without vitiligo. After adjusting for risk factors (>100 naevi and child sunburn), vitiligo was associated with a 3-fold decreased probability of melanoma (odds ratio (OR) 0.32, 95% CI 0.12–0.88) and NMSC (OR 0.28, 95% CI 0.16–0.50). It is notable that all melanomas in patients with vitiligo ($n = 7$) occurred in normal pigmented skin. Two patients reported the occurrence of a basal cell carcinoma (BCC) in a vitiliginous lesion. Lindelöf et al. (9) included 1,052 patients with vitiligo in a retrospective cohort study to determine the prevalence of melanoma and squamous cell carcinoma (SCC). Only one patient developed melanoma. We calculated an absolute risk of developing melanoma of 0.001 (95% CI 0.0002–0.0054) for patients with vitiligo. There were no cases of SCC in this study population. Hexsel et al. (10) retrospectively screened 477 Caucasian patients with vitiligo. For this study, we calculated an absolute risk of 0.013 (95% CI 0.0058–0.0272) with a BCC:SCC ratio of 2:1. In 2 patients cancer developed in vitiliginous skin. In another

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study, by Schallreuter et al. (11), 136 patients with vitiligo were assessed retrospectively, and no patients were found to have either BCC or SCC.

DISCUSSION

The best-available evidence obtained from our literature search consisted of retrospective cohort and case-control studies. We excluded a study by Schallreuter et al. (12) and a study by Nordlund et al. (13) because both aimed to determine the prevalence of vitiligo in a population of patients with melanoma, whereas we were interested in the prevalence of melanoma in patients with vitiligo. We also found case reports regarding this subject, but we excluded them from our critical appraisal because of the low level of evidence. Ideally, we would have preferred to discuss follow-up studies. Paradisi et al. (4) presented the largest study examining the risk of patients with vitiligo developing both melanoma and NMSC. Although this study also had good internal validity, there was a difference in age distribution in the 2 study groups. In the study by Teulings et al. (8) participants completed a questionnaire at home. Patients may lack knowledge regarding, for example, the type of skin cancer they have had during their lifetime. As an alternative, patients should be asked to complete the questionnaire with the assistance of a physician. Lindelöf et al. (9) showed that patients with vitiligo have a decreased risk of developing melanoma. This study did not describe factors that could have influenced the outcome. Both Teulings et al. (8) and Lindelöf et al. (9) also had a relatively large study group, to supporting our outcome. In studies by Hexsel et al. (10) and Schallreuter et al. (11) patients were accurately screened on the occurrence of NMSC; however, in Schallreuter et al.'s study (11) there was selection bias present as only Caucasians were included.

When studying the occurrence of skin cancer in patients with vitiligo, it is important to pay attention to age, skin type and sun exposition as risk factors (14). Three studies (8, 10, 11) clearly described that their study population included both Caucasian and non-Caucasian participants or only Caucasian participants. None of the studies described the extent of vitiligo in relation to cancer risk. There may have been an underestimation of the risk of developing skin cancer in both patients with vitiligo and patients without vitiligo in the appraised studies, because patients who died from melanoma or NMSC were not included.

There are probably several mechanisms to explain the negative association between vitiligo and skin cancer: (*i*) Patients with vitiligo will probably have been told to protect their skin against the sun (4, 8, 9); (*ii*) the role of the anti-melanocyte immune response in vitiligo (2); (*iii*) it is theoretically unlikely that melanoma would form in vitiligo lesions because melanocytes are absent from these lesions (3); (*iv*) in patients with vitiligo there seems to be an overexpression of the p53 tumour suppressor gene, which might explain the low risk of BCC and SCC (4, 8, 11); and (*v*) in patients with vitiligo there is overproduction of proinflammatory cytokines, such as interleukin-1 and tumour necrosis factor alpha (TNF-α), which stimulate the production of superoxide dismutase and glutathione peroxidase, thus reducing the risk of skin cancer (15).

The authors declare no conflicts of interest.

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