Markedly reduced incidence of melanoma and nonmelanoma skin cancer in a nonconcurrent cohort of 10,040 patients with vitiligo

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Background: Genetic findings suggesting a lower susceptibility to melanoma in patients with vitiligo are supported by recent clinical studies. Nonmelanoma skin cancer (NMSC) has also been studied, but mainly in small samples, and with conflicting results.

Objective: We sought to study the relative risk (RR) of melanoma and NMSC in patients with vitiligo compared with that in patients seen for vascular surgery.

Methods: The frequency of melanoma and NMSC was compared between patients with vitiligo and patients seen for vascular surgery. Occurrence of skin cancer was compared by computing RR and modeled using multiple logistic regression.

Results: Overall, the crude RR for melanoma was 0.24 (95% confidence interval [CI] 0.13-0.45) in patients with vitiligo compared with those with a nondermatologic condition (occurrence 1.1‰, 95% CI 0.5‰-2.0‰ in patients with vitiligo and occurrence 4.5‰, 95% CI 3.8‰-5.4‰ in the control cohort). The crude RR for NMSC was 0.19 (95% CI 0.14-0.17) and the occurrence was 3.8‰ (95% CI 2.7‰-5.2‰) among patients with vitiligo and 19.6‰ (95% CI 18.0‰-21.4‰) in control subjects. Patients with vitiligo who underwent phototherapy had a markedly higher risk of both cancers.

Conclusions: In our large study, patients with vitiligo have a decreased risk of developing skin neoplasms, even considering that a larger proportion in this patient group is exposed to higher levels of ultraviolet radiation. (J Am Acad Dermatol 2014;71:1110-6.)

Key words: cutaneous melanoma; nonmelanoma skin cancer; vitiligo.

Vitiligo is a common acquired skin disease affecting approximately 0.5% of the general population.[1] It is characterized by idiopathic destruction of melanocytes, possibly immune-mediated, resulting in depigmented macules and patches. $CD8^+$ cells may destroy melanocytes through recognition of melanocyte differentiation antigens.[2-5] A genome-wide association study of individuals with vitiligo found significant associations between vitiligo and several genes that regulate immunity.[6] 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

Abbreviations used:

CI:	confidence interval
NMSC:	nonmelanoma skin cancer
PUVA:	psoralen plus ultraviolet A
RR:	relative risk
UV:	ultraviolet

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with different immune recognition of tyrosinase in vitiligo and melanoma, suggesting that strong antityrosinase expression protects patients with vitiligo against melanoma.[6,7] Whereas the autoimmunity of patients with vitiligo may protect them against melanoma, lack of melanin may involve greater photodamage and thus an increased risk of melanoma and nonmelanoma skin cancer (NMSC). Little is known about the lifetime risk of melanoma in patients with vitiligo, whereas 2 studies of NMSC incidence in patients with the disease have provided contradictory findings.[8,9] A recent survey[10] on the risk of melanoma and NMSC in patients with vitiligo found a decreased risk of both neoplasms.

This study was performed to estimate the relative risk (RR) of melanoma and NMSC in a cohort of patients with vitiligo compared with patients seen for vascular surgery.

CAPSULE SUMMARY

- The risk of skin neoplasms (melanoma and nonmelanoma skin cancer) in patients with vitiligo is still debated.
- This study showed that patients with vitiligo had a decreased risk of melanoma and nonmelanoma skin cancer versus those with a nondermatologic condition.
- Further studies, preferably adopting a prospective concurrent design, are needed to corroborate this finding.

METHODS

This single-center study was performed at Istituto Dermopatico dell'Immacolata, Istituto di Ricovero e Cura a Carattere Scientifico, a research hospital in Rome acting as an Italian reference center for skin diseases. Patients referring to the vascular surgery units of our institution were chosen as control subjects based on the fact that they had come to our institution for a nondermatologic problem, the underlying assumption being that they presumably originate from the same reference population as the patients with vitiligo.[11] This choice, though less than ideal, mainly because of the difference in age distribution in the 2 study populations, allows us to have a direct comparison of the risk. This shortcoming is addressed in the analysis through stratification (Table I) and through multiple adjustment (Table II).

However, this population would still be preferable as a control group, rather than one composed of common dermatologic diseases, such as psoriasis or atopic dermatitis, that would allow to obtain a large enough sample with a more similar age distribution. In fact, by definition, dermatologic conditions derive from skin alterations that in many cases involve local and systemic alterations of the immune system. Such alterations are likely to influence the risk of skin tumors. For instance, in psoriasis[12] and atopic dermatitis[13] it has been shown that subjects affected by these diseases have a reduced number of melanocytic nevi, suggesting that cytokine networks involved in such conditions might inhibit melanogenesis, melanocyte growth, and/or progression to nevi.

The information about the conditions of interest was retrieved from several databases, using the *International Classification of Diseases, Ninth Revision, Clinical Modification* codes for vitiligo (ie, 709.01), melanoma (ie, 172.*), and NMSC (ie, 173.*), and the hospitalization unit for the patients seen for vascular surgery. Unfortunately, the *International Classification of Diseases, Ninth Revision, Clinical Modification* codes from 172.0 to 172.9 do not differentiate squamous cell carcinoma from basal cell carcinoma.

All diagnoses of skin cancer are carried out clinically and dermoscopically by dermatologists, and they are all independently confirmed by experienced pathologists. All coding at our institute is carried out in a centralized office by specialized staff.

Information was retrieved from several databases—diagnoses at discharge from hospitalization, day hospital, or day surgery, and clinical diagnoses from the outpatient records—for the period 1997 through April 2013. Data about phototherapy treatments were retrieved from the administrative database where all procedures and payments are recorded. For the purposes of this study, the databases were searched and linked as of April 13, 2013.

All records including a diagnosis of vitiligo were selected, as were all records documenting at least 1 access to the vascular surgery clinics. Using as a search key the fiscal code, a unique personal code that is used to access the Italian National Health System, an internal linkage procedure was carried out to exclude repeated observations on the same patient. Once the study population was thus established, the 2 groups were linked to the above-mentioned databases specifically for the *International Classification of Diseases, Ninth Revision, Clinical Modification* codes of melanoma and NMSC. Finally, a linkage was performed to see whether the study patients had undergone phototherapy. In our institute, since the year 2001, all patients with vitiligo prescribed phototherapy undergo narrowband ultraviolet (UV)B, whereas