Incidence of nonmelanoma skin cancer in a cohort of patients with vitiligo

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Background: Nonmelanoma skin cancer (NMSC) incidence in patients with vitiligo has not been studied.

Objective: We sought to quantify the incidence of NMSC in patients with vitiligo.

Methods: A cohort of 477 patients with vitiligo and no history of NMSC seen in an outpatient academic center between January 2001 and December 2006 was established. All charts for patients with vitiligo were reviewed for incident NMSC, and histopathology verified. Age-adjusted (2000 US Standard Million) incidence rates were calculated and compared to US rates.

Results: Six patients with NMSC were identified; all were Caucasian (>61 years). Age-adjusted incidence rates were: basal cell carcinoma, male 1382/100,000; basal cell carcinoma, female 0; squamous cell carcinoma, male 465/100,000; squamous cell carcinoma, female 156/100,000. Except for basal cell carcinoma in females, all rates were higher than US rates but not statistically significant.

Limitations: Comparison incidence rates from the general patient population during the same time period were unavailable.

Conclusion: Health care providers should be aware of the possible risk of NMSC in Caucasian patients with vitiligo. (J Am Acad Dermatol 2008;60:929-33.)

Vitiligo affects approximately 1% of the US population and is characterized by idiopathic destruction of melanocytes, possibly immune mediated, resulting in depigmented or hypopigmented macules and patches.[1] Melanin is thought to be protective against the harmful effects of ultraviolet (UV) radiation,[2] such as skin cancer. Fitzpatrick skin phototypes I and II are more susceptible to skin cancer, and skin phototypes V and VI, with high levels of constitutive pigmentation, have the lowest incidence of skin cancer.[3-5] Hence, it is counterintuitive that, despite the loss of photoprotective melanin and considering that UV radiation is used therapeutically for vitiligo, only anecdotal reports of nonmelanoma skin cancer (NMSC) in patients with vitiligo have been published.[6-11]

Psoralen plus UVA (PUVA) photochemotherapy was reported for the treatment of psoriasis in 1974.[12]

Abbreviations used:

BCC:	basal cell carcinoma
HFHS:	Henry Ford Health System
KPNW:	Kaiser Permanente Northwest
NH:	New Hampshire
NMSC:	nonmelanoma skin cancer
PUVA:	psoralen plus ultraviolet A
SCC:	squamous cell carcinoma
UV:	ultraviolet

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In 1976, a follow-up study of the long-term impact of PUVA in psoriasis was initiated in 16 US centers. In the first year after PUVA therapy, 18 skin cancers (13 basal cell carcinoma [BCC] and 5 squamous cell carcinoma [SCC]) were detected; by 2.1 years of follow-up, 48 NMSCs (19 BCC and 29 SCC) were reported.[13] Conversely, PUVA was reported for the treatment of vitiligo in 1976,[14] and two subsequent studies, involving 326 and 59 patients, failed to show an association of skin cancer in patients with vitiligo treated with PUVA.[15,16] An initial case report of SCC in vitiligo after prolonged PUVA therapy was not reported until 2 decades later.[17] It is commonly believed that patients with vitiligo do not have an increased risk, and perhaps have even a lower incidence of skin cancer than the general population.[8]

Because skin cancer has been rarely reported in patients with vitiligo and its incidence among these individuals is currently unknown, we designed a study with the purpose of determining the incidence of NMSC in a cohort of patients with vitiligo seen in a large group practice health care system in the Detroit, MI, metropolitan area (academic department of dermatology), and to compare these data with available incidence rates in the United States.[18]

METHODS

Data sources

This study was approved by the Henry Ford Hospital Institutional Review Board. Our design was a cohort study with a population derived from the comprehensive electronic medical record database of the Henry Ford Health System (HFHS), Detroit, MI. The HFHS is comprised of a large multispecialty and primary care group practice and a health maintenance organization. Payor distribution, as of 2006, was composed of health maintenance organization 32%, Medicare 34%, Medicaid 11%, commercial insurance 14%, and other insurers/self-pay 9%, which demonstrates that the HFHS patient population encompasses all age groups, races, and social settings. Approximately 3.1 million outpatient visits per year occur at HFHS with patients from both urban and suburban areas.

Design and patients

As designed a priori, patients had to have the *International Classification of Diseases, Ninth Revision* diagnostic code for vitiligo (709.01) recorded from January 1, 2001, to December 31, 2006, in the HFHS medical record database to be included in the cohort. To ascertain that the patients were being followed up in HFHS, it was required that the *International Classification of Diseases, Ninth Revision* code be recorded in at least two separate encounters by a dermatologist during this time range. A total of 518 patients were identified, and all patients had been examined in the department of dermatology. To validate the diagnosis, all 518 medical records (100%) were individually reviewed to ascertain the confirmed diagnosis of vitiligo given by a dermatologist, which was verified in 479 patients. Two additional patients with vitiligo had NMSC before the study's start date (January 1, 2001) and, hence, were also excluded (477 patients; 92%). The medical records of these 477 patients were further reviewed to identify any incident biopsy-confirmed NMSC during the study period. All histopathology slides of patients who developed skin cancer during the study inclusion period were obtained, and Melan-A and Fontana-Masson stains were performed on the original tissue blocks to determine whether the skin cancers were located on vitiliginous or normal-appearing skin. These slides were re-reviewed for confirmation of skin cancer and the presence of pigmentation by a board-certified dermatopathologist (Marsha Chaffins, MD). Skin type, history of phototherapy, and sun-exposure history were also documented during chart review of the encounter notes of the patients who developed skin cancer.

Data analysis

The records of all 518 cohort members (100%) that fit inclusion criteria were individually reviewed. Our final sample is comprised of only those patients who had confirmed diagnosis of vitiligo given by a dermatologist and no history of NMSC (n = 477). Age was calculated as of January 1, 2001. Entry into the study was defined using date of enrollment in the health system, which was set as either January 1, 2001, for established patients, or for those who were new to the health system (enrolled after January 1, 2001), as the date on which they were first seen in the system. To determine censorship or end of follow-up, the study end date (December 31, 2006), date of last office visit to the HFHS (if left health system during study period), or date of histopathologic diagnosis or skin cancer was used. Total person-years of observation were calculated. Crude annual incidence rates per 100,000 population were calculated and age-adjusted rates, using the 2000 US Standard Million (2000 US Census Bureau population estimates), the most recent age distribution of the US population available.

The annual incidence rates reported in this study refer to persons with NMSC, not the number of tumors, so a person with more than one skin cancer was counted once. Incidence is a key measure for

epidemiologic risk factor studies. However, incidence rates of NMSC in the United States and other countries are not routinely calculated because vital statistics typically focus on malignancies that are commonly fatal or challenging to treat, such as melanoma.[18] NMSCs are not captured in the US Surveillance Epidemiology and End Results nor in statewide cancer registries and, hence, comparison populations are limited. A report by Miller and Weinstock[18] of projected 1994 incidence rates of NMSC (age adjusted; 1970 US Standard Million) using the Kaiser-Permanente Northwest (KPNW) health maintenance organization from Portland, OR, provides a comparable population with our cohort in terms of latitude, age, and health care access. Karagas et al[19] also reported the 1993 to 1994 age-adjusted incidence rate of BCC and SCC in Caucasian New Hampshire (NH) residents (1970 US Standard Million). Using these reports as estimates of general population rates, we age adjusted the incidence rates in our vitiligo cohort to the 1970 US Standard Million to allow comparison. The 95% confidence intervals were calculated for our incidence rates.

RESULTS

Demographic characteristics of the cohort of HFHS patients with vitiligo are presented in Table I. The average patient age was 34 years (median 36 years). The average Caucasian patient age was 38 years (median 39 years). Ages ranged from 2 to 86 years.

The Caucasian patients from this cohort had 861 total person-years of observation and the full sample had 1939 total person-years of observation. The average observation time was 4.3 years and 4.1 years, respectively. Six patients developed NMSC: 4 BCCs and two SCCs, all on sun-exposed body sites. Medical record review showed that none of the patients with vitiligo were reportedly treated with UV radiation in the department of dermatology of the HFHS or other institutions. On histopathology review, skin cancer was present on vitiliginous skin in two individuals. All cohort patients developing skin cancer were Caucasian (5 male and 1 female). Fitzpatrick skin phototype and history of sun exposure was not available for these 6 Caucasian patients. The age at diagnosis of NMSC ranged from 61 to 89 years (mean age of 78.2 years). The results and the characteristics of those with vitiligo who developed skin cancers are described in Table II.

Annual incidence rates in the Caucasian patients with vitiligo, age adjusted to the 2000 US Standard Million, were: BCC, male 1382/100,000; SCC, male 465/100,000; SCC, female 156/100,000. The annual incidence rates per 100,000 population, age adjusted to the 2000 and 1970 US Standard Million population with 95% confidence intervals are displayed in Table III, for BCC and SCC, men and women. Calculated incidence rates (1970 US Standard Million) were then compared with previously reported incidence rates of NMSC (KPNW cohort [1994], Oregon and NH cohort [1993-1994]) (Fig 1).[18] With the exception of BCCs in female patients, which were not observed in the HFHS cohort, the annual incidence rates of NMSC in Caucasian patients with vitiligo from the HFHS cohort were higher than the incidence rates in both cohorts. However, the confidence intervals around the HFHS estimates encompass the estimates, so those differences cannot be considered statistically significant.

Table I. Demographic characteristics of cohort of patients with vitiligo from the Henry Ford Health System (n = 477)

Characteristic	n (%)
Race	
Caucasian	200 (42)
African American	141 (29)
Asian/Pacific Islander	27 (6)
Hispanic	10 (2)
Middle Eastern	10 (2)
Native American	9 (2)
Unavailable	80 (17)
Age at baseline, y	
<18	156 (33)
18-49	189 (39)
>50	132 (28)
Gender	
Male	228 (48)
Female	249 (52)

DISCUSSION

We report the incidence of NMSC in a cohort of 477 patients with vitiligo. Compared with estimates of NMSC rates in two general US Caucasian populations, incidence rates of skin cancer are higher but not statistically significantly different in this vitiligo cohort for Caucasian patients.

NMSC was found on sun-exposed sites of Caucasian patients with vitiligo (age ≥ 61 years) in both vitiligo-affected and unaffected skin. None of them were reportedly treated with UV radiation in the department of dermatology of the HFHS or other institutions.

The BCC:SCC ratio encountered in the HFHS cohort is 2:1. In previous epidemiologic studies, the BCC:SCC ratio varied depending on the population studied, ranging from 2.8:1 in Tasmania[20]; 6:1 to 9:1 in northern Europe[21]; 2.8:1 for male patients and

Table II. Characteristics of the cases of nonmelanoma skin cancer identified in patients with vitiligo

Type of skin cancer	Site of skin cancer*	Vitiliginous skin†	History of UV phototherapy treatment	Race	Gender	Age at diagnosis, y
BCC	Right pre-auricular	-	-	Caucasian	Male	89
BCC	Bilateral temples	-	-	Caucasian	Male	83
BCC	Right nasolabial fold	+	-	Caucasian	Male	75
BCC	Left neck	-	-	Caucasian	Male	61
SCC	Right forearm	+	-	Caucasian	Male	84
SCC	Left upper back	-	-	Caucasian	Female	77

BCC, Basal cell carcinoma; *SCC*, squamous cell carcinoma; *UV*, ultraviolet.
*As indicated by pathology report.
†As confirmed by histopathology and Melan-A and Fontana-Masson stains.

Table III. Estimates of nonmelanoma skin cancer incidence in Caucasian patients with vitiligo from the Henry Ford Health System, per 100,000 population, age adjusted to the 2000 and 1970 US Standard Million

	Incidence rate/100,000 age-adjusted 2000 US S (95% CI)	Incidence rate/100,000 age-adjusted 1970 US S (95% CI)
BCC male	1382 (0,2846)	1080 (0,2197)
BCC female	0	0
SCC male	465 (0,1377)	338 (0,1001)
SCC female	156 (0,461)	112 (0,332)

BCC, Basal cell carcinoma; *CI*, confidence interval; *S*, Standard Million; *SCC*, squamous cell carcinoma.

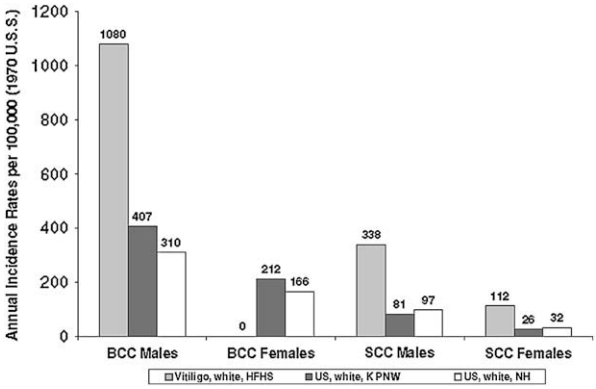

Fig 1. Comparison of age-adjusted incidence rates of skin cancer/100,000 population in Henry Ford Health System (*HFHS*) cohort with those found in Kaiser-Permanente health plan (*KPNW*) and state of New Hampshire (*NH*), adjusted to 1970 US Standard Million. *BCC*, Basal cell carcinoma; *SCC*, squamous cell carcinoma.

4.5:1 for female patients in Manitoba, Canada[22]; and up to 11:1 in the United States.[19] Interestingly, the study by Demers et al[22] demonstrated that in Manitoba, Canada, the BCC:SCC ratio was age dependent, ranging from 8.8:1 in men and 21.8:1 in women in the age group younger than 40 years, to 1.6:1 in men and 1.5:1 in women in the age group older than 89 years. Hence, the BCC:SCC ratio identified in this study is specific to the studied population, and perhaps the higher proportion of SCC in relation to BCC observed may be explained by the fact that all skin cancers identified in our cohort were diagnosed in patients 61 years of age and older.

Advanced age, Caucasian race, and male gender are known risk factors for NMSC,[23] and the development of skin cancer in 6 elderly Caucasian patients may reflect a high level of cumulative sun exposure.

There are limitations to our analysis. The overall number of patients with vitiligo identified for the cohort, although large, is still not large enough to yield precise rates, as reflected by the wide confidence intervals presented in Table III. Incidence rates of NMSC in the United States are not routinely calculated. Current incidence rates and the incidence for the overall HFHS population were both unavailable. Hence, our comparison is limited to incidence rates of NMSC from the 1994 KPNW Oregon and 1993 to 1994 NH cohorts. Therefore, our HFHS vitiligo cohort may appear to have higher rates in part because of secular changes. We are limited in that this study examined only a 5-year time period, with an average patient observation period of slightly more than 4 years. Regardless, these analyses do not support the notion that people with vitiligo have lower rates of NMSC.

Our rates may not be representative of the rates experienced by the overall vitiligo US population. Although diverse, our sample was not large enough to detect skin cancer in nonCaucasian races in which skin malignancy is rare; the number of non-Caucasians with NMSC in the United States is estimated to be less than 1% the number of Caucasians.[18] The case identification was based on retrospective review; on the other hand, it was validated by medical record abstraction of all cases. Although histologic

confirmation of skin cancer is considered a standard practice in the United States, cases of BCC and SCC that were diagnosed clinically without biopsy or cases diagnosed in other health care systems may have been missed. We did not have the ability to consider other potentially important NMSC risk factors, such as sun exposure and skin type of Caucasian patients.

To our knowledge, this is the first time that incidence rates of NMSC have been reported for patients with vitiligo. Although 3 previous studies, published in 1992,[16] 1995,[15] and 1997,[24] failed to show the development of skin cancer in patients with vitiligo, there have been more recent case reports of SCCs and keratoacanthomas in such patients.[6-11] Our findings suggest that there may be an increased or equal risk of NMSC in patients with vitiligo.

Conclusion

We report the incidence of NMSC among Caucasian patients in a cohort of 477 patients with vitiligo, compared with two general US populations. This study suggests that there may be an increased or equal risk of NMSC in patients with vitiligo. We believe that our findings may contradict the long-standing belief of decreased skin cancer risk in Caucasian patients with vitiligo, and that health care providers should not underestimate the risk of this most common cancer in their patients with this disorder. Incidence in non-Caucasians could not be assessed.

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