Risk of subsequent cutaneous squamous cell carcinoma in patients with melanoma

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Background: Patients with melanoma are at increased risk for cutaneous squamous cell carcinomas (SCCs).

Objective: We sought to examine the incidence of subsequent SCC among melanoma survivors and the impact of patient and melanoma characteristics on SCC risk.

Methods: Kaiser Permanente Northern California members given the diagnosis of melanoma from 2000 to 2005 (n = 6378) were followed up through 2009 for a pathology-confirmed SCC. Cox models were used to estimate SCC risk.

Results: The crude SCC incidence rate was 2.41 per 100 person-years, and was higher among males and older subjects. In adjusted models stratified by age, SCC risk was higher among males (hazard ratio [HR] 1.43, 95% confidence interval [CI] 1.22-1.67), those with history of nonmelanoma skin cancer (HR 2.56, 95% CI 2.19-2.98), and those with higher tumor sequence numbers (HR 1.35, 95% CI 1.01-1.80). SCC risk was lower among non-Hispanic whites (HR 0.39, 95% CI 0.17-0.86).

Limitations: SCC risk was not examined among members without melanoma.

Conclusions: SCCs arise in approximately 12% of patients with melanoma over a 5-year period and are more common among males, whites, patients older than 60 years, those with prior reportable cancers, and those with history of nonmelanoma skin cancer. Clinicians should be vigilant for SCCs among these individuals at high risk, and counsel melanoma survivors about their increased risk for SCCs. (J Am Acad Dermatol 2014;71:521-8.)

Key words: epidemiology; incidence; melanoma; risk factors; skin cancer; squamous cell carcinoma.

Previous studies have shown that cutaneous melanoma and cutaneous squamous cell carcinoma (SCC) coaggregate in families[1] and that the incidence of SCC is increased among patients with melanoma.[2-7] This increase may be a result of shared genetic susceptibility, such as innate pigmentation, environmental exposures, and increased skin cancer surveillance in individuals given the diagnosis of melanoma. More recently, reports have shown markedly increased incidence of SCCs in patients with melanoma treated with BRAF

Abbreviations used:

CI:	confidence interval
HR:	hazard ratio
KPNC:	Kaiser Permanente Northern California
NCCR:	Northern California Cancer Registry
NMSC:	nonmelanoma skin cancer
SCC:	squamous cell carcinoma
SEER:	Surveillance, Epidemiology, and End Results
SIR:	standardized incidence rates
SNOMED:	Systematized Nomenclature of Medicine

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inhibitors,[8,9] possibly because of the paradoxical activation of mitogen-activated protein kinase signaling.[10,11] However, data on the incidence rates of SCCs among melanoma survivors not exposed to BRAF treatment and variables that predict subsequent SCC risk among melanoma survivors are lacking.

The objective of this study was to estimate crude and standardized incidence rates (SIR) of SCC among a cohort of Kaiser Permanente of Northern California (KPNC) members given the diagnosis of melanoma between 2000 to 2005 followed up through 2009 (before therapeutic use of BRAF inhibitors). A secondary aim was to examine whether patient characteristics such as age, gender, and race/ethnicity and melanoma tumor characteristics such sequence number, anatomic site, size, stage, and histologic subtype were associated with SCC risk.

CAPSULE SUMMARY

- Squamous cell carcinomas arise in approximately 12% of patients with melanoma over a 5-year period and are more common among the elderly, males, whites, those with prior cancers, and those with history of nonmelanoma skin cancer.
- Clinicians should be vigilant for squamous cell carcinomas among these individuals at high risk, and counsel melanoma survivors about their increased risk for squamous cell carcinomas.

METHODS

Study population

The cohort consisted of all KPNC members given the diagnosis of cutaneous melanoma between January 1, 2000, and December 31, 2005, as identified through the KPNC Northern California Cancer Registry (NCCR). The KPNC NCCR reports information on all cancers (except nonmelanoma skin cancer [NMSC]) collected on a population of approximately 3.3 million KPNC members to the State of California and the Surveillance, Epidemiology, and End Results (SEER) program. All NCCR cancers are coded using the *International Classification of Diseases for Oncology, Third Edition*. We restricted our cohort to any *International Classification of Diseases for Oncology, Third Edition* code in the 8700 series and topography codes C44.0 to C44.9. Subjects with noncutaneous primary tumors (ocular, mucosal) and health plan members whose melanomas were diagnosed outside KPNC (NCCR nonanalytic cases) or who had no membership after diagnosis were excluded (n = 37). The KPNC institutional review board approved this study.

Outcome

Subjects were followed up from the date of their melanoma diagnosis until their censoring date, defined as the earliest of: (1) subsequent SCC, (2) disenrollment from the health plan defined as a gap of more than 90 days, (3) death, or (4) the end of the study period on December 31, 2009. The primary outcome was SCC after the diagnosis of melanoma as identified from health plan pathology records screened up to each subject's censoring date.

Subjects with potential SCCs were identified from electronic pathology records on all pathology specimens received for examination from KPNC medical facilities. Each pathology specimen at KPNC is automatically assigned Systematized Nomenclature of Medicine (SNOMED) codes using a standardized approach to categorize diagnoses by organ (topography code) and by morphologic alterations (morphology code). The pathology records of all study members were queried for any report with a skin SNOMED topology code and cutaneous SCC morphology code, along with any skin specimen with the text strings "squam," "Bowen," "SCC," or "keratoacanthoma" in the diagnosis text. All pathology reports for potential SCC cases were reviewed and assigned case status (definite SCC, possible SCC, no SCC) by the study dermatologist (M. M. A.). Tumors assigned to the "possible SCC" category included entities such as "atypical squamoproliferative lesion" or vague diagnoses such as "probable SCC" that were rendered when the lesion was transected and then not able to be fully visualized by the pathologist.

Covariates

Data elements obtained from the KPNC electronic administrative databases included gender, age, race/ethnicity, and history of NMSC as identified by SNOMED codes. Melanoma variables included the sequence number (which indicates the tumor's chronological position, relative to the individual's other SEER-reportable cancers), anatomic site, histologic subtype, Breslow depth, and extent of disease (in situ, localized, regional, distant). We divided anatomic site into head and neck, trunk, upper limbs, lower limbs, overlapping, and not-otherwise-specified categories and categorized it as sun-exposed (head and neck and upper limbs) versus sun-protected (trunk and lower extremities) areas.