Cutaneous squamous cell carcinomas of the lower extremity: A distinct subset of squamous cell carcinomas

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Background: Some patients develop a disproportionate number of cutaneous squamous cell carcinomas (SCCs) on their lower extremity (LE).

Objective: We sought to characterize the clinical features, treatment, and outcome in patients who develop multiple LE SCCs.

Methods: We identified 22 patients with 4 or more biopsy-diagnosed LE SCCs during a 4.5-year study period. The location, size, treatment, and clinical outcome of each LE SCC were recorded.

Results: Of the 22 patients studied, 18 were female. Of the 360 SCCs our patients developed, 260 (72.2%) were on the LE. The incidence of SCCs in these patients was nearly 7 times greater than the incidence of basal cell carcinoma in the same patients.

Limitations: The number of patients is small and limits definitive conclusions about prevalence of SCCs on the LE in the general population.

Conclusions: LE SCCs are a distinct subset of cutaneous SCCs and may have distinctive clinical features and biologic behavior requiring additional study. (J Am Acad Dermatol 2014;70:70-4.)

Key words: basal cell carcinoma; carcinogen; epidemiology; female; immunosuppression; leg; lower extremity; squamous cell carcinoma; ultraviolet radiation.

Environmental ultraviolet (UV) radiation has been widely acknowledged as the single most important carcinogen in cutaneous squamous cell carcinoma (SCC).1 Lower extremity (LE) SCCs, like SCCs in general, appear to be sunlight related, but SCC occurs more frequently on the head and neck and upper extremities.2-4 One striking feature of LE SCCs is that they occur more commonly in women.2-5

In clinical practice, we observe patients who have an unexpectedly high number of SCCs on their LE, who may present with significantly more SCCs on their LE compared with other sun-exposed sites. This pattern of tumor occurrence may suggest that SCCs of the LE could represent a distinct subset of SCCs. We sought to evaluate these clinical observations by characterizing a patient population with increased SCCs of the LE.
METHODS
The medical records of all patients seen in the Section of Dermatologic Surgery and Cutaneous Oncology at Yale School of Medicine who were given a diagnosis of SCC on their LE (thigh, shin, calf, knee, ankle, foot, leg) during the 4.5-year period from January 1, 2008, to June 30, 2012, were reviewed. The study was approved by the Institutional Review Board of the Yale School of Medicine. We included those patients who had at least 4 biopsy-proven diagnoses of SCCs (including SCC of the keratoacanthoma subtype but excluding SCC in situ) on their LE. We excluded patients who were immunocompromised (organ transplant recipient, HIV positive) or were undergoing UV radiation therapy for psoriasis. In all, 22 patients met our inclusion criteria. The following data were extracted and maintained in a standard database software application (Excel, Microsoft, Redmond, WA): patient age, gender, family history of skin cancer, medical history of skin cancer, and smoking history. The body site, biopsy date, treatment method, treatment date, size, and histopathologic characteristics including presence of perineural and/or intravascular invasion were also recorded. Physician notes, pathology reports, and photographs where necessary were used to determine the specific anatomic locations of the diagnosed skin cancers.

For statistical analysis, 1-sample Student t test was used to compare the mean proportion of all SCCs occurring on the LE with other anatomic sites and with basal cell carcinoma (BCC). Two-sample t test was used to compare the mean diameters of lesions that were treated with different treatment modalities.

RESULTS
Patient demographics and history
Of the 22 patients (all Caucasian), 18 (82%) were female and 4 (18%) were male with an average age of 80.5 years (SD 7.9 years, range 62-92 years). Four patients (18%) had a history of cancer other than nonmelanoma and melanoma skin cancer. Six patients (27%) stated that they had an immediate family member (parent, sibling, or child) with a history of skin cancer.

Clinical features and treatment
In all, 22 patients accounted for 360 SCCs (not including SCCs in situ), of which 260 (72.2%) were on the LEs; 74 SCCs in situ, of which 33 (44.6%) were on the LEs; 54 BCCs, of which 11 (20.4%) were on the LE. During the study period, the patient with the greatest number of SCCs had a total of 55 of which 33 were on the LE. The median number of SCCs on a patient during the study period was 11.5. The subjects in our study developed between 34.8% to 100% of their SCCs on their LE. Figs 1 to 3 summarize in detail the anatomic distribution of biopsy-diagnosed SCCs, SCCs in situ, and BCCs. The anterior aspect of the LE had 1.51 times more SCCs compared with the posterior aspect of the LE, as judged by biopsy location descriptions in dermatopathology reports. Lesions that were on the foot, or documented as neither front or back were not included in this analysis.

Of the 275 LE SCCs where the treatment could be confirmed, 112 were not treated beyond the original biopsy. In 105 of these cases, the tangential biopsy at the clinical base of the lesion served as excision of the lesion and was usually combined with electrodessication with the intention of completely treating the lesion. In 4 cases, Mohs microscopically controlled surgery (MCS) was performed on a clinically diagnosed SCC for which initial biopsy had not been performed. In 3 lesions, MCS was scheduled but not performed after the biopsy as there was no residual lesion on the surgery day.

Of the 163 lesions that were treated again after the initial biopsy date, 130 received MCS, 1 received photodynamic therapy with topical 20% δ-aminolevulinic acid, and 32 received re-excision with electrodessication. The difference between the average diameter of the LE SCCs that were treated completely at the time of initial biopsy (11.1 mm) and those that received MCS (12.4 mm) was not significant \( (P = .078) \). MCS was curative in all cases despite the variability in the time interval between the initial biopsy and surgery (average: 39.9 days, SD: 20.7 days, range: 7-118 days). One LE SCC (0.38%) demonstrated evidence of perineural invasion, and no lesion had evidence of intravascular invasion.

DISCUSSION
This study confirms and elaborates on a clinical subset of SCCs and establishes that our patient population developed SCCs of the LE disproportionate to the development of UV-induced skin.
cancers of the head and neck or upper extremities. Epidemiologic studies consistently find that fewer than 10% of BCCs and SCCs occur on the LE in both men and women, whereas over 60% of BCCs and SCCs are on the head and neck region. In contrast, our patients as a whole had 72.2% of SCCs on their LE, 10 times more than the proportion they developed on the head and neck. The 18 women in our study had between 36.4% and 100% of all SCCs on the LE, and the average was statistically significantly different ($P < .001$) from other published data of 7.5%. The 4 men in our study had between 34.8% and 100% of all SCCs on the LE, much elevated from the epidemiological data of 3.8%. Not all of our findings can be adequately explained by UV exposure alone. Although the high incidence of SCCs on the LE in women may be explained by clothing and lifestyle, another consideration is the impact of the use of moisturizers and cosmetics, which may increase the skin’s sensitivity to UV radiation.

The higher incidence of SCCs on the LE documented in this study strongly suggests regional anatomic variation in cutaneous susceptibility to SCCs. In our patients, SCCs occurred more frequently on the LE than BCCs: overall, 72.2% (260 of 360) of SCCs and 20.4% (11 of 54) of BCCs were on the LE. Furthermore, our patients have 6.67 times higher overall incidence of SCCs compared with BCCs, whereas BCCs are much more common than SCCs epidemiologically. This ratio is similar to that seen in immune-suppressed organ transplant recipients. Systemic immunosuppression has also been associated with SCCs. We hypothesize that local immunosuppression in the LE may be a factor in the relatively increased incidence of SCCs in this anatomic region. In support of this, BCCs and Kaposi sarcoma in a locally immunocompromised LE have been reported in the literature.

In addition to local immunosuppression, other factors that may be involved include trauma or carcinogens. The lower leg, particularly the anterior surface, is prone to trauma, and SCCs have been

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**Fig 1.** Anatomic distribution of squamous cell carcinoma in the study subjects.
associated with sites of injury. Trauma could explain the predominance of SCCs on the front of the leg versus the back of the leg. In addition, the anterior surface of the leg may receive more sun exposure in patients who lie supine to tan frequently thus increasing both local UVB-induced immune suppression and UV-induced genetic changes disposing to the development of SCCs in excess of BCCs.

SCCs of the LE in our study are not particularly aggressive. The time gap between the initial biopsy and MCS varied from 7 to 118 days but that did not affect prognosis. There was no statistically significant size difference between the LE SCCs that were treated at the time of initial biopsy (removal by excision at base of lesion with electrodesiccation) alone and those that received additional treatment after the biopsy date.

We believe that SCCs of the LE represent a specific clinical subset of SCCs. Our patients have patterns of skin cancer presentation that deviate in some important ways from data already published: SCCs are more than 6 times more common than BCCs in our patients, a complete reversal of the pattern in the population at large; SCCs in the current study show much greater tendency to occur on the LE than BCCs. Further study is underway to determine the genotypic characteristics of the LE SCCs both within the particular patient and across the patient population. Analysis of the biology of local immune function may also help explain the cause and behavior of LE SCCs.

**REFERENCES**