Risk factors and timing of subsequent cutaneous squamous cell carcinoma in patients with cutaneous squamous cell carcinoma: A retrospective cohort study

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Background: Information about the frequency and timing of subsequent cutaneous squamous cell carcinoma (cSCC), along with associated risk factors, is limited. However, this information is crucial to guide follow-up care for these patients.

Objective: To evaluate the risk and timing of subsequent cSCC in patients who presented with an initial diagnosis of cSCC.

Methods: Retrospective review of an institutional review board–approved, single-institution registry of invasive cSCC. All patients had at least 2 primary cSCCs diagnosed on 2 separate dates 2 months apart.

Results: A total of 299 primary cSCCs were included. At 6 months from initial cSCC diagnosis, 18.06% (n = 54) of patients developed subsequent cSCC; at 1 year, 31.77% (n = 94); at 3 years, 67.56% (n = 202); and at 5 years, 87.96% (n = 263) developed subsequent cSCC. Risk factors associated with subsequent cSCC include age at initial diagnosis (hazard ratio [HR], 1.02; 95% confidence interval, 1.004-1.027; $P = .008$), T2 stage (HR, 1.66; 95% CI, 1.07-2.57; $P = .025$), and poor tumor grade. Tumor grades well, moderate, and unknown have HRs of 0.21 ($P < .001$), 0.16 (P .001), and 0.25 ($P = .001$), respectively.

Conclusions: Of patients who develop subsequent cSCC, 18.06% do so within 6 months, and 31.77% do so within 1 year of initial cSCC diagnosis. Patients with advanced age, poor histologic differentiation, and American Joint Committee on Cancer T2 stage are at highest risk. Close clinical follow-up after the initial diagnosis is recommended. (J Am Acad Dermatol 2021;84:719-24.)

Key words: clinical research; cutaneous oncology; dermatologic surgery; full-body skin examination; general dermatology; medical dermatology; MMS; Mohs surgery; oncology; squamous cell carcinoma; total body skin examination.

Cutaneous squamous cell carcinoma (cSCC) is the second most common form of skin cancer, with more than 900,000 cases diagnosed annually.[1] cSCC usually carries an excellent prognosis with surgical treatment. Rates of distant metastasis are reported between 2% and 3%.[2] However, certain clinical and histologic risk factors are associated with an increased risk of local recurrence, metastasis, and disease-specific death. These risk factors include clinical tumor diameter greater than 2 cm, tumor thickness greater than 6 mm, level of invasion into the fat, perineural invasion, poor

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differentiation, lymphovascular invasion, anatomic location on hair-bearing lip and ear, and immunosuppression.[3]

Patients diagnosed with cSCC are at an increased risk for developing subsequent skin cancers.[4] Although regular outpatient dermatologic follow-up of patients with an initial diagnosis of primary cSCC is routine, there are limited data to determine the frequency of follow-up required for these patients. Dermatologists and primary care providers are regularly confronted with having to decide when to recommend follow-up and at what time interval.

The American Academy of Dermatology recommends in-office screenings for new primary skin cancers at least annually with adjustment of the frequency of follow-up depending on individual patient risk factors.[5] Early detection and treatment could reduce morbidity and mortality from these cancers. Indeed, screening has been shown to significantly decrease mortality in melanoma in a population-based screening project.[6] Our study aimed to determine: (1) the risk of developing a subsequent cSCC after initial cSCC diagnosis, (2) the time interval, and (3) the risk factors associated with subsequent cSCC. These data will help better inform recommendations for the frequency of dermatologic follow-up.

CAPSULE SUMMARY

- Patients with squamous cell carcinoma are at increased risk for subsequent skin cancers.
- Of patients who develop subsequent squamous cell carcinomas, about 19% do so within 6 months. Patients with advanced age, poor histologic differentiation, and American Joint Committee on Cancer T2 stage are at highest risk. Close clinical follow-up after the initial diagnosis is recommended.

METHODS

Study design

An institutional review board–approved, single-institution registry of patients diagnosed with invasive cSCC between January 1, 2010, and December 31, 2012 was used for this retrospective cohort study. For each patient diagnosed with a cSCC in this 2-year time period, all preceding (earliest, January 1997) and subsequent cSCCs were recorded (latest, November 2018). Data were collected from the electronic health record and stored in REDCap, an electronic data capture tool. Patients with a diagnosis of cSCC in situ, unknown primary tumor location, and incomplete medical records detailing diagnosis or treatment were excluded. The data set unitized for final analysis consists of patients who had at least 2 primary cSCCs diagnosed on 2 separate dates, at least 2 months apart. If a patient had multiple cSCCs diagnosed on either the first or the second diagnosis date, the largest-diameter cSCC was chosen for the analysis; if the cSCCs were the same size, 1 was randomly chosen. The cSCC diagnosed on the first date was defined as the index cSCC, and the cSCC diagnosed on the second date was defined as the subsequent cSCC. Recurrent cSCCs were not counted as development of subsequent cSCC. American Joint Committee on Cancer (AJCC) Staging Manual, 8th edition was used for staging.[7]

Statistical analysis

Quantitative variables are summarized with median (interquartile range [IQR]), and categorical variables are summarized with frequency of occurrence. Time-to-event analysis (survival analysis) was used to determine time to subsequent cSCC. A Cox proportional hazard model was used determine the risk factors associated with the development of subsequent cSCC; for this model, there were no censored patients because the event was diagnosis of a subsequent cSCC. The results of these models were used to plot Kaplan-Meier curves, where survival was stratified for each significant categorical variable, with all other variables held constant. The analysis was done in R, version 3.5 (RStudio Inc, Boston MA). *P* values less than .05 were considered significant.

RESULTS

There were 1248 patients in the original data set, and after exclusion criteria, there were 299 patients with known smoking status, tumor data (ie, anatomic location and tumor size data), and 2 or more cSCCs that were diagnosed at least 2 months apart. Without these exclusions, there were 399 patients who developed subsequent cSCC (399/1248 = 31.97%). The median age at initial diagnosis was 70.8 years (IQR, 62.9-80.4). Most of the patients were male (62.9%, n = 188), 26.4% (n = 79) were immunosuppressed, and 61.5% (n = 184) had a positive tobacco smoking history. The median time between index and subsequent cSCC diagnosis was 2.00 years (IQR, 0.74-3.55). The median cSCC size was 1.20 cm (IQR, 0.90-1.60). The majority of the cSCCs were well differentiated (71.2%, n = 213) and at the T1 stage (81.9%, n = 245), and almost half (46.8%, n = 140) were localized to the head and neck. Demographics and visit characteristics of the study population as

Abbreviations used:

AJCC:	American Joint Committee on Cancer
CI:	confidence interval
cSCC:	cutaneous squamous cell carcinoma
HR:	hazard ratio
IQR:	interquartile range
NMSC:	nonmelanoma skin cancer

well as characteristics of the 299 index cSCCs are summarized in Table I.

With respect to anatomic location, 46.8% (n = 140) of index cSCCs and 43.8% (n = 131) of subsequent cSCCs were localized to the head and neck. There were 93 (31.1%) patients whose index and subsequent cSCCs were on both the head and neck and 121 patients (40.5%) whose index and subsequent cSCCs were on both the trunk and extremities. There were 38 patients (12.7%) whose index cSCC was on the trunk and extremities and subsequent cSCC was on the head and neck. There were 47 patients (15.7%) whose index cSCC was on the head and neck and subsequent cSCC was on the trunk and extremities.

Age at initial diagnosis (hazard ratio [HR], 1.02; 95% confidence interval [CI], 1.004-1.027; $P = .008$), AJCC T2 stage (HR, 1.66; 95% CI, 1.07-2.57; $P = .025$), and poor tumor grade were significant risk factors for the development of subsequent cSCC in Cox proportional hazards modeling. For age at initial diagnosis, there is a 2% increase in hazard for every additional year older a patient is at the index diagnosis. For tumor grade, the reference level is *poor*; thus, all other tumor grades were compared to it. The tumor grades of well, moderate, and unknown have HRs of 0.21 ($P < .001$), 0.16 ($P < .001$), and 0.25 ($P = .001$), respectively (Table II). Within 6 months of the initial diagnosis, 18.06% of patients had a subsequent diagnosis of cSCC; at 1 year, 31.77%; at 3 years, 67.56%; and at 5 years, 87.96% of subsequent cSCCs had occurred (Fig 1). Figs 2 and 3 present disease-free survival stratified according to tumor grade and T stage, respectively, while the other variables in the model are held constant. Distant metastasis (HR, 2.59; 95% CI, 1.13-5.95; $P = .024$) and treatment type (Mohs micrographic surgery: HR, 2.35; 95% CI, 1.31-4.23; $P = .004$; wide local excision: HR, 2.40; 95% CI, 1.33-4.33; $P = .004$; and local destruction: HR, 1.89; 95% CI, 0.99-3.59; $P = .054$) were included in the Cox proportional hazards model; however, they are deemed clinically irrelevant because they were not present at the time of initial diagnosis.

DISCUSSION

There were 1248 patients in our original data set. After exclusion criteria, there were 299 patients with known smoking status, tumor data (ie, anatomic location and tumor size data), and 2 or more cSCCs that were diagnosed at least 2 months apart. Without these exclusions, there were 399 patients in our study who developed subsequent cSCC (399/1248 = 31.97%). About 19% of patients developed a subsequent cSCC within 6 months of the initial cSCC diagnosis; 32% of patients were diagnosed with a second primary cSCC within 1 year, 68% within 3 years, and by 5 years 88% of subsequent cSCCs had occurred. The median time between the index and subsequent cSCC was 2 years. The risk factors associated with development of subsequent cSCC were increased age at index diagnosis, poor histologic differentiation of index cSCC, and AJCC T2 stage of index cSCC. Figs 2 and 3 show a decrease in disease-free survival for patients with poor tumor grade and AJCC T2 stage, respectively. These data strongly support routine oncologic follow-up for patients diagnosed with cSCC for at least 5 years after the initial diagnosis of cSCC. The data also support increasing the frequency of oncologic follow-up for older patients and those presenting with more advanced or aggressive cSCC.

Patients who develop cSCC are known to be at increased risk for developing subsequent skin cancers[4]; however, the literature characterizing follow-up recommendations is limited. The American Academy of Dermatology released new guidelines of care for the management of basal cell carcinoma and cSCC in 2018. According to these guidelines, patients who have been diagnosed with basal cell carcinoma or SCC should receive a total body skin examination at least annually.[5] The authors of the guidelines believe that preventative and routine follow-up skin examinations for patients with a history of cSCC are important to ensure that cSCCs are diagnosed at an early stage to reduce morbidity and mortality. A delay in routine follow-up can delay diagnosis, which can increase the risk of poor outcomes, including larger surgical defects, increased need for costly reconstructions, nodal staging, metastasis, and death. We sought to determine the risk and timing of developing a subsequent cSCC after initial cSCC diagnosis and the risk factors associated with subsequent cSCC to help inform recommendations for the frequency of dermatologic follow-up.

Twenty-six percent of the patients in our study were immunosuppressed, and the incidence of cSCC in immunosuppressed individuals has been

Table I. General characteristics of the study population and characteristics of the initial cSCC

Variable	Value	n
Age at initial diagnosis, y, median (IQR)	70.8 (62.9-80.4)	299
Sex, n (%)		299
Female	111 (37.1)	
Male	188 (62.9)	
Race, n (%)		299
White	297 (99.3)	
Nonwhite	2 (0.67)	
Smoker, n (%)		299
Yes	184 (61.5)	
No	115 (38.5)	
Years between first and second tumor, median (IQR)	2.00 (0.74-3.55)	299
Immunosuppressed, n (%)		299
Yes	79 (26.4)	
No	220 (73.6)	
Alive, n (%)		299
Yes	222 (74.2)	
No	77 (25.8)	
Cause of death, n (%)		77
Unrelated to skin cancer	67 (87.0)	
Skin cancer	6 (7.79)	
Tumor grade, n (%)		299
Unknown	4 (5.19)	
Well	213 (71.2)	
Moderate	43 (14.4)	
Poor	10 (3.34)	
Unknown	33 (11.0)	
Depth of invasion, n (%)		299
Skin	290 (97.0)	
Fat	4 (1.34)	
Muscle	2 (0.67)	
Bone	1 (0.33)	
Deep invasion beyond fat	2 (0.66)	
Primary cSCC anatomic location, n (%)		299
Head and neck	140 (46.8)	
Trunk and extremities	159 (53.2)	
Perineural involvement, n (%)		299
Yes	5 (1.67)	
No	294 (98.3)	
Dermatologic follow-up before lesion diagnosis, n (%)		299
<3 months	30 (10.0)	
3-6 months	32 (10.7)	
6-12 months	55 (18.4)	
No appointments within 1 year	182 (60.9)	
Tumor size, cm, median (IQR)	1.20 (0.90-1.60)	299
Tumor stage, n (%)*		299
T1	245 (81.9)	
T2	40 (13.4)	
T3	14 (4.68)	

cSCC, Cutaneous squamous cell carcinoma; *IQR*, interquartile range.
*The American Joint Committee on Cancer Staging Manual 8th edition was used for staging.

Table II. Cox proportional hazards model results for time to subsequent cSCC

Variable	Hazard ratio (95% CI)	*P* value
Age at first diagnosis	1.02 (1.004-.027)	**.008**
Sex: male (vs female)	1.01 (0.78-1.31)	.963
Smoker: yes (vs no)	1.21 (0.93-1.56)	.149
Immunosuppressed: yes (vs no)	1.3 (0.98-1.72)	.067
Tumor grade*		
Moderate (vs poor)	0.16 (0.07-0.35)	**<.001**
Unknown (vs poor)	0.25 (0.11-0.56)	**.001**
Well (vs poor)	0.21 (0.1-0.46)	**<.001**
Primary tumor location: trunk and extremities (vs head and neck)	1.03 (0.77-1.36)	.86
Perineural involvement: yes (vs no)	0.39 (0.13-1.14)	.084
Frequency of dermatologic follow-up before lesion diagnosis, months		
3-6 (vs <3)	1.25 (0.73-2.13)	.41
6-12 (vs <3)	1.1 (0.68-1.76)	.699
>12 (vs <3)	0.83 (0.55-1.26)	.373
Tumor size, cm	1.04 (0.88-1.23)	.628
Tumor stage†		
T2 (vs T1)	1.66 (1.07-2.57)	**.025**
T3 (vs T1)	0.91 (0.32-2.6)	.86

Boldface indicates statistical significance.
cSCC, Cutaneous squamous cell carcinoma.
*For tumor grade, the reference level is *poor*, meaning that each other histologic tumor grade is compared to it.
†The American Joint Committee on Cancer Staging Manual, 8th edition was used for staging.

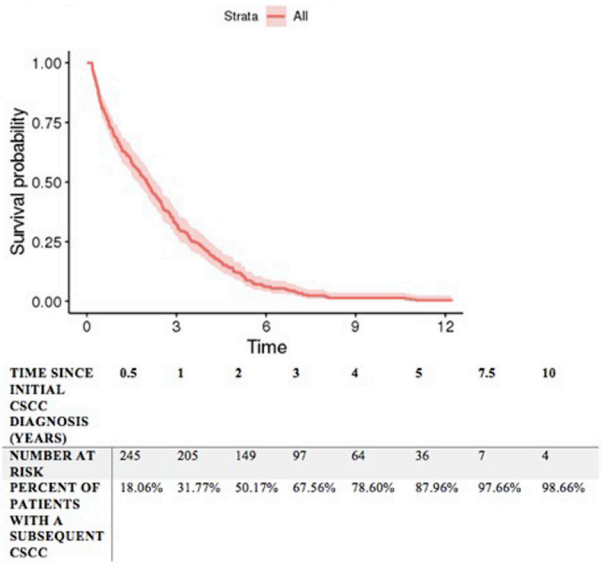
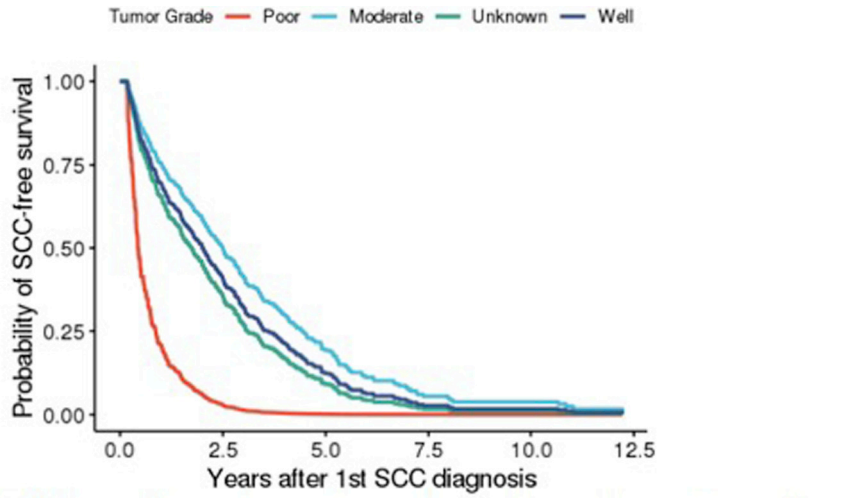


Fig 1. Kaplan-Meier curve: disease-free survival by year. *SCC*, Squamous cell carcinoma.

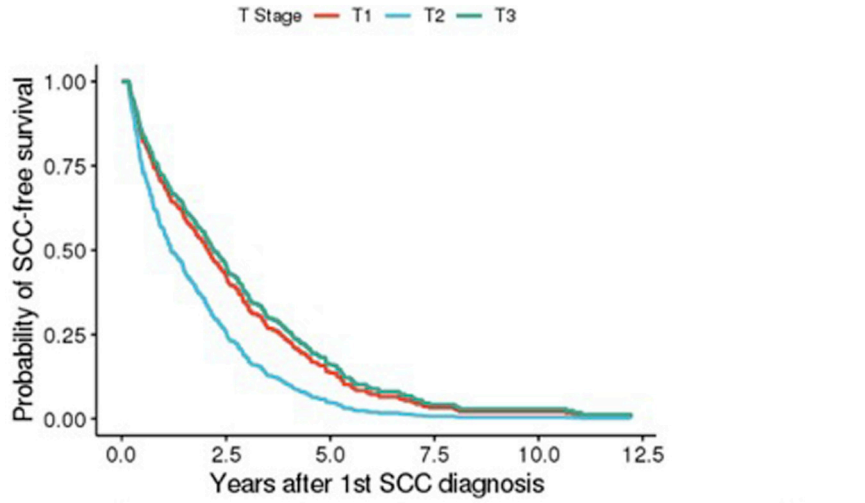
estimated to be 65 to 250 times greater than that in the general population.[8,9] These individuals tend to have more histologically aggressive cSCCs and



TIME (YEARS)	0.5	1	2	3	4	5	7.5	10
WELL	178	152	108	66	42	26	5	3
MODERATE	37	30	24	18	15	7	2	1
POOR	3	1	1	1	0	0	0	0
UNKNOWN	27	22	16	12	7	3	0	0

Number at Risk

Fig 2. Kaplan-Meier curve by tumor grade: disease-free survival. *CSCC*, Cutaneous squamous cell carcinoma.



TIME (YEARS)	0.5	1	2	3	4	5	7.5	10
T1	206	176	127	82	53	34	7	4
T2	29	22	16	11	8	2	0	0
T3	10	7	6	4	3	0	0	0

Number at Risk

Fig 3. Kaplan-Meier curve by T stage: disease-free survival. *SCC*, Squamous cell carcinoma.

worse outcomes. A study on solid organ transplant recipients in South Australia by Maiolo et al[10] found that nearly two thirds of the patients who develop 1 skin cancer will develop at least a second. In their study, a second skin cancer was identified in 75% of their patients within 5 years, with a median time of 2 years. In our study, the median time between the initial and subsequent diagnosis of cSCC was also 2 years, and by 5 years, 88% of patients were diagnosed with a second primary cSCC. Their results suggested that increasing age, increased time elapsed since transplant, and male sex are risk factors for the development of skin cancer after solid organ transplant. We did not find male sex to be associated with an increased risk for subsequent cSCC. Like multiple other studies, we did find that increasing

age was associated with an increased risk of subsequent cSCC.[8,10,11] Maiolo et al recommended that patients with an initial diagnosis of cSCC should receive follow-up every 6 to 12 months initially, increasing to every 3 to 6 months after a second skin cancer diagnosis.[10] Given our findings, we too recommend close oncologic follow-up after the initial diagnosis of cSCC.

Although all patients with cSCC are assumed to be at a higher risk for subsequent cSCCs, the risks for a second cSCC after a first diagnosis are significantly lower over time than the risks for a third cSCC after a second, a fourth after a third, a fifth after a fourth, and so on.[4] A prospective observational cohort study of 1284 patients with newly diagnosed nonmelanoma skin cancer (NMSC) in 2015 reported the risk for a subsequent NMSC after the first lifetime NMSC to be 14.5% at 1 year, 31.1% at 3 years, and 40.7% at 5 years, whereas the risk after a nonfirst NMSC was reported as 43.9% at 1 year, 71.1% at 3 years, and 82.0% at 5 years.[4] The secondary analyses of the risks for a subsequent SCC after a prior SCC diagnosis generated results consistent with the analyses for the pooled NMSC sample. In addition, the analysis showed that at 10 years, approximately 40% of patients diagnosed as having a first lifetime NMSC did not develop another tumor. In other words, patients diagnosed with a single lifetime NMSC have a good chance of remaining free of subsequent NMSCs. The researchers suggested that patients presenting with their first lifetime NMSC may benefit from preventive counseling, whereas patients presenting with a history of NMSC may benefit from more aggressive or more frequent screening for subsequent tumors. Although in our study only 1.34% of patients had not been diagnosed with a second cSCC by 10 years (Fig 1), we included only patients with at least 2 lifetime diagnoses of cSCC. If we had included patients with only 1 lifetime diagnosis of cSCC, this number most likely would have been higher. Out of 1248 patients in our original data set, only 31.9% (n = 399) developed subsequent cSCC. Thus, more studies looking at disease-free survival after first lifetime cSCC and at risk for subsequent cSCC stratified by number of instances are needed to validate their results. However, it is difficult to predict if any given patient with an initial diagnosis of cSCC will be among those who never develop a subsequent cSCC, and thus, a more conservative approach to recommending follow-up, especially to those with high-risk factors, is advisable.

Our study had several limitations. First, it is limited by its retrospective, single-institution design. Second, several risk factors could not be included in the analysis, including Fitzpatrick skin type, history of actinic keratosis, family history of skin cancer, and history of sun exposure, because of lack of consistent data capture in the electronic medical record.

CONCLUSION

This study is unique in that it elaborates on the timing of subsequent cSCCs after index cSCC diagnosis and determines which risk factors are associated with increased risk of subsequent cSCC. We provide evidence to support the need for close clinical follow-up of patients with an initial diagnosis of cSCC. Patients with advanced age, poor differentiation on histology, and AJCC T2 stage can benefit from even closer monitoring. Skin cancer screening and follow-up recommendations can be improved with a better understanding of the risk factors and frequency of subsequent cSCC. As such, further investigation with larger prospective cohort studies is necessary to validate our results.

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