ORIGINAL RESEARCH

Patient Demographics and Prognostic Factors of Skin Appendage Carcinoma: An Analysis of the NCDB

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ABSTRACT

Background: Skin appendage carcinoma (SAC) is a rare malignancy with limited literature due to its low prevalence. This study explores demographic and prognostic factors for SAC in the United States.
Methods: Data from the National Cancer Database (NCDB) were analyzed to identify factors affecting SAC mortality. Descriptive statistics and Cox regression analysis were employed.
Results: SAC is slightly more common in males and frequently occurs in the face, scalp, and neck regions. Age and Charlson-Deyo comorbidity scores were significant prognostic factors, with older age and higher scores linked to decreased survival. Private insurance predicted better survival compared to Medicaid, Medicare, or no insurance.
Conclusion: Individualized clinical interventions considering patient age, insurance status, and comorbidities are crucial. SAC does not exhibit disparities in survival based solely on race or socioeconomic status, but equitable access to care is essential for improving outcomes.

INTRODUCTION

Skin appendage carcinoma (SAC), or adnexal carcinoma, is a rare malignancy arising from either hair follicles, sebaceous glands, or sweat glands.[1] SAC is characterized as a histological subtype of malignant adnexal tumors of the skin.[2] These skin appendage tumors (SAT) can arise from various primary sites, leading to their classification based on the level of appendageal differentiation: hair follicles, sebaceous glands, eccrine sweat glands, or apocrine sweat glands.[3] It has been previously reported that most are of apocrine and eccrine differentiation, followed by sebaceous tumors.

While SAC is a rarely occurring cancer, incidence rates (IR) of these cutaneous-type appendageal carcinomas have been increasing around the world, partially in association with the aging population.[5,6,7] The SAC incidence rate has risen from 2.0 per 1 million person-year in 1978-1982 to 5.1 per 1 million person-year as of 2002-2005.4 Due to the predominance of SAC in the head and neck, it is postulated that UV radiation may be a contributing factor. However, the exact reasoning for the rise in IR is not well understood.

The incidence of SAC has been shown to be higher in females, with a male-to-female IR of 1:51 in the United States, whereas these tumors favor a slightly higher male predominance in Europe.[4,5] In addition, previous studies have demonstrated racial disparities, with non-Hispanic White individuals having the highest incidence rate, while Hispanic White, Black, and Asian/Pacific Islander individuals have significantly lower rates.[5]

SAC can behave aggressively locally but also has the potential for regional and distant metastasis. Thus, early recognition and subsequent wide excision of SAC in its early stages can serve as an important prognostic factor to control the disease and improve survival.[5] The survival rate for skin appendage carcinoma varies greatly by the disease stage at diagnosis. A population-based study of 1,801 patients using the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute data from 1978 through 2005 reports that the five-year relative survival rates for cutaneous appendageal carcinomas are 99% for localized disease and 43% for distant disease.[5] A smaller study of 23 patients reported a five-year overall survival (OS) rate of 78%.[8]

Due to the rarity of this cancer, limited studies have studied the tumor characteristics, including the demographic profiles of affected patients and its effect on mortality. By analyzing the National Cancer Database (NCDB), we describe the demographic and social factors influencing the risk of SAC and the primary sites commonly presented, including which factors affect mortality risk.

METHODS

This retrospective cohort study analyzed patients diagnosed with histologically confirmed SAC between 2004 and 2019. Patient data was sourced from the National Cancer Database (NCDB), jointly sponsored by the American College of Surgeons and the American Cancer Society. The NCDB compiles information from over 1,500 Commission on Cancer-accredited facilities and covers more than 70% of new cancer diagnoses in the United States and Puerto Rico. De-identified patient data from the NCDB was accessed and granted through the Participant User Data Files program.

Patients with skin appendage carcinoma were identified using ICD-O-3 code 8390-3. Exclusion criteria included missing data, and data with less than ten cells were not reported per Cancer Quality Improvement Program (CQIP) guidelines.

Patients were analyzed based on various factors, including age, sex, race, ethnicity, income, education, insurance status, primary anatomic site, region, and Charlson-Deyo comorbidity score. A total of 1,115 patients with SAC were initially identified. Cases with missing data were excluded for a final cohort of 815 patients. Age was split into two categories: those younger than the age of 65 years and those 65 years and older. Race was categorized into three groups: White, African-American, and Other. The "Other" category included subgroups such as American Indian, Aleutian or Eskimo, Chinese, Japanese, Filipino, Hawaiian, Korean, Vietnamese, Kampuchean, Asian Indian or Pakistani NOS, Asian Indian, Micronesian NOS, Other Asian, Asian NOS, Oriental NOS, and Pacific Islander NOS. Ethnicity was categorized by Hispanic status. The income quartile was determined by median household income determined by the 2016 to 2020 census in the patient's zip code of residence at the time of diagnosis.

Education was measured into quartiles by the percentage of residents in the patient's zip code who had a high school degree based on the 2016 to 2020 census. Insurance status was determined by the primary payor at diagnosis and categorized into five groups: uninsured, private, Medicare, Medicaid, and other insurance. The primary anatomical site was classified into seven groups using ICD-O-3 topography codes: head or face or neck, lower limb or hip, thorax, abdomen, pelvis, trunk, and other soft tissues. Comorbidities were assessed using the Charlson-Deyo score which assigns weighted points to 17 comorbid conditions based on their severity and association with mortality risk. Higher scores indicate a greater burden of comorbid disease and patients were divided into groups with scores of 0, 1, 2, and ≥3.

Survival analysis involved creating Kaplan-Meier tables to calculate the cohort's median overall survival after diagnosis. A multivariable Cox hazard regression model was employed to identify independent prognostic factors. The variables included in the multivariable Cox model were age, sex, race, ethnicity, income, education, insurance status, facility type, facility region, and Charleson-Deyo score.

Descriptive statistics and unadjusted survival analysis were conducted using IBM Statistical Package for the Social Sciences (SPSS) version 29 (IBM Corp., Armonk, NY). $P < 0.05$ indicated statistical significance. It has been determined by the Creighton University Institutional Review Board (IRB) that this project is exempt from the IRB review board as this project does not involve human subjects under 45 CFR 46.102(e).

RESULTS

A total of 815 cases of SAC were found within the NCDB. Although the number of cases diagnosed with SAC has fluctuated from year to year, with some years showing fewer cases than the previous year, the overall trend from 2004 to 2019 has been increasing. This is reflected in the diagnosis per year trendline, which has an R-squared value of 0.36, indicating a moderate correlation (**Figure 1**). Demographic and socioeconomic characteristics of patients, including age, race, and other factors, are summarized (**Table 1)**. Most patients are over 65 years of age (63.8%), with the mean age at diagnosis at 69.1 years (SD=13.1). The majority of the cases analyzed were White (89.8%), male (57.6%), non-Hispanic (91%), located in the Atlantic regions (39.9%), insured by Medicare (55.1%), and had a median household income in the top quartile ($74,063 or more, 44.9%). Patients had relatively good health with an average Charlson-Deyo Score of 0.3 (SD=0.7).

The distribution of tumors based on the primary site showed that the most common location for SAC was the skin of the face. (23.9%), followed by the skin of the scalp and neck (22.2%), the skin of the trunk (18.7%), and the skin of the upper limb and shoulder (14.2%) (**Table 2**).

Kaplan-Meier analysis revealed that 318 patients out of 815 experienced a mortality event, resulting in an overall survival rate of approximately 61% and a mortality rate of approximately 39% over the study period. The mean survival time after diagnosis was 120.8 months (SE 3.6, 95% CI 113.8-127.7), and the median survival time after diagnosis was 126.9 months (SE 8.2, 95% CI 110.8-143.0).

When accounting for other variables, some demographic variables contributed to an increased risk of mortality (**Table 3**). Age

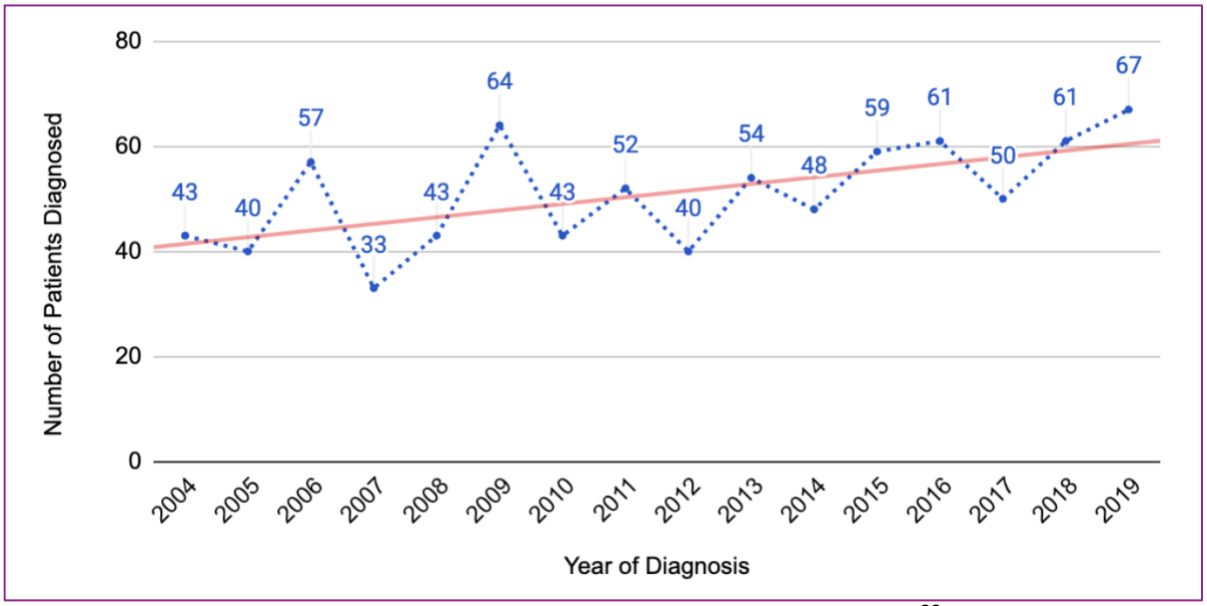

Figure 1. Diagnostic trend of SAC from 2004 to 2019. R^{22}=0.36

Table 1. Demographic and Socioeconomic Characteristics of Patients with Skin Appendage Carcinoma

Demographic/Socioeconomic Factor	Variable	Number of Patients
Sample size (N)	n/a	482,448 (42%)
Age	Mean Age	69.1 years (SD=13.1)
	<65 Years	295 (36.2%)
	65 Years or Older	520 (63.8%)
Sex	Male	469 (57.6%)
	Female	346 (42.4%)
Race	White	732 (89.8%)
	Black	66 (8.1%)
	Other	13 (2.1%)
Ethnicity	Non-Hispanic	742 (91%)
	Hispanic	34 (4.2)
	Unknown	39 (4.8%)

Insurance status	Not Insured	22 (2.7%)
	Private insurance/managed care	288 (35.3%)
	Medicaid	27 (3.3%)
	Medicare	449 (55.1%)
	Other	29 (3.6%)
Median annual income	1=Less than $46,277	115 (14.1%)
	$46,227 - $57,856	163 (20.0%)
	$57,857 - $74,062	171 (21.0%)
	$74,063 or more	366 (44.9%)
Education (percent in zip code without high-school diploma)	15.3% or more	151 (18.5%)
	9.1% - 15.2%	204 (25.0%)
	5.0% - 9.0%	257 (31.5%)
	Less than 5.0%	203 (24.9%)
Facility type	Community Cancer Program	66 (8.1%)
	Comprehensive Community Cancer Program	269 (33.0%)
	Academic/Research Program	349 (42.8%)
	Integrated Network Cancer Program	131 (16.1%)
Geographic location	New England	60 (7.4%)
	Middle Atlantic:	164 (20.1%)
	South Atlantic:	161 (19.8%)
	East North Central:	125 (15.3%)
	East South Central	39 (4.8%)
	West North Central	75 (9.2%)
	West South Central:	67 (8.2%)
	Mountain:	21 (2.6%)
	Pacific:	103 (12.6%)
	0	656 (80.5)

Charlson-Deyo comorbidity index	1	109 (13.4%)
	2	29 (3.6%)
	>3	21 (2.6%)

Table 2. Primary Site Location Distribution of Skin Appendage Carcinoma

Primary Site	Variable	Number of Patients
Location of Primary Site	n/a	815
	Skin of lip, NOS	16 (2.0%)
	Eyelid	35 (4.3%)
	External ear	32 (3.9%)
	Skin of other and unspecified parts of face	181 (22.2%)
	Skin of trunk:	195 (23.9%)
	Skin of scalp and neck:	152 (18.7%)
	Skin of upper limb and shoulder:	116 (14.2%)
	Skin of lower limb and hip:	74 (9.1%)
	Skin, NOS, or other:	14 (1.7%)

Table 3. Cox Regression Analysis of Demographic and Socioeconomic Factors for Skin Appendage Carcinoma

Factor	Variable	Hazard Ratio	Confidence Interval: Lower Bound	Confidence Interval: Upper Bound	P-Value
Age, years	18-64				<.001
	65+	2.230	1.537	3.235	<.001
Sex	Male				.387
	Female	.976	.770	1.236	.387
Race	White				.339
	Black	.837	.525	1.335	.455
	Other	.275	.038	1.984	.200

Ethnicity	Non-Hispanic				
	Hispanic	.939	.495	1.781	.848
Insurance status	Not Insured				<.001
	Private insurance/managed care	.342	.179	.654	.001
	Medicaid	.920	.397	2.133	.845
	Medicare	.599	.315	1.138	.117
	Other	.679	.284	1.624	.384
Median annual income	1=Less than $46,277				.904
	$46,227 - $57,856	1.136	.748	1.726	.548
	$57,857 - $74,062	1.042	.660	1.645	.859
	$74,063 or more	1.005	.628	1.610	.983
Education (percent in zip code without high-school diploma)	15.3% or more				.126
	9.1% - 15.2%	.963	.663	1.397	.842
	5.0% - 9.0%	.683	.446	1.046	.079
	Less than 5.0%	.931	.575	1.505	.769
Facility type	Community Cancer Program				.748
	Comprehensive Community Cancer Program	.960	.624	1.475	.851
	Academic/Research Program	.933	.607	1.432	.750
	Integrated Network Cancer Program	1.121	.699	1.797	.635
Geographic location	New England				.886
	Middle Atlantic:				.793
	South Atlantic:				.970
	East North Central:				.919
	East South Central				.575
	West North Central				.472

	West South Central:				.615
	Mountain:				.183
	Pacific:				.979
Charlson-Deyo comorbidity index	0				.013
	1	1.106	.796	1.538	.548
	2	1.632	.942	2.830	.081
	>3	2.494	1.344	4.627	.004

older than 65 years had over twice the increase in mortality compared to those younger than 65 years (HR 2.397, p<0.001). Patients with a Charlson-Deyo score of 3 or more were 2.5 times more likely to experience a risk of mortality compared to those with a Charlson-Deyo score of zero (HR 2.49, p=0.04). Those with private insurance were less likely to experience hazards compared to those without insurance (HR 0.34, p=0.001). Sex, race, ethnicity, income, education, facility type, and facility location did not significantly differ in hazard.

DISCUSSION

Previous research on skin appendage carcinoma is limited due to its low prevalence. This study is one of the largest studies exploring the presenting characteristics of SAC in the U.S. Demographic prognostic factors on SAC mortality rates have not yet been studied to this extent.

Many of the descriptive statistics for our patient cohort support the previously reported characteristics of patients diagnosed with SAC, including race predilection and age.[2,5,6,7] We discovered that SAC is slightly more common in males than females, inconsistent with another large study reporting a female predominance in the United States.[5] Thus, our study has not been able to support a true difference in sex preference.

Our study supports the understanding that the most common primary anatomical site for skin appendage tumors is the face, scalp, and neck regions.[9,10] Our study also supports that SAC correlates with age. However, tumors, compared to carcinomas, arising from skin appendages typically appear in younger patients. Benign tumors are not well recorded in the NCDB as the focus on malignant neoplasms takes precedence in NCDB's mission.[11,12,13]

Similar to other skin cancers, many of our cases were localized to the southern region of the United States, indicating a possible UV correlation.[14] However, over 20% of the cases were found in the Middle Atlantic, and over 12% in the Pacific regions. Since the NCDB facility locations is not based on equal geographic surface area, population density could also factor in regional distribution.

Age is a significant prognostic factor in SAC, similar to other types of skin cancers and previous institutional reports.[2] While this finding may seem intuitive, it underscores the importance of ensuring that older patients

receive prompt care and timely referrals. Early intervention is essential to improving outcomes in this population, as delays in treatment can lead to worse prognoses. Therefore, heightened awareness and proactive management of SAC in older patients are crucial for optimizing survival rates and overall health outcomes. Currently, surgical resection is the standard treatment for skin appendage carcinoma. Older patients may be less likely to undergo surgical resection due to surgical risks, leading to poorer outcomes.

Similarly, a Charlson-Deyo comorbidity score of 3 or higher is a significant prognostic factor. Patients with a Charlson-Deyo score of 3 or higher faced decreased survival rates compared to those with a score of zero, highlighting the importance of managing patients with multiple comorbidities. Early intervention and coordinated care for patients with high Charlson-Deyo scores could enhance overall health outcomes. However, since the NCDB reports mortality due to all-cause rather than cancer-specific mortality, patients with a higher comorbidity index could face increased mortality due to other causes.

Our analysis indicates that private insurance is a better predictor of survival for patients with SAC than those with no insurance, Medicaid, Medicare, or other types of insurance. Patients with private insurance may have better access to healthcare resources, including early diagnostic services and unrestricted specialist consultations, that might otherwise delay necessary medical interventions. Receiving timely and comprehensive care could be critical for managing SAC effectively. In contrast, patients with Medicaid, Medicare, or no insurance may face longer wait times for appointments, limited access to specialists, and restrictions on certain treatments, especially in dermatology.[14] These limitations can lead to delayed diagnoses and suboptimal management of the disease, ultimately affecting survival outcomes. New therapies, such as surgery with adjuvant radiation for high-risk skin adnexal carcinoma of the head and neck, have also been shown to provide promising cancer control in the localized area.[15] Given these findings, improving access to comprehensive care and reducing treatment delays for patients without private insurance should be a priority. Ensuring that all patients receive timely and appropriate care regardless of their insurance status could help mitigate these disparities and improve survival rates for SAC.

Facility type did not affect the hazard ratio in SAC. Since facility volume is closely related to the Commission on Cancer facility category assignments, with community cancer programs treating between 100 and 500 newly diagnosed cases per year and comprehensive community cancer programs and academic programs treating more than 500 cases per year, it follows that facility volume by proxy also does not impact the hazard ratio.

While other skin cancers face survival disparities in race, ethnicity, education, or facility type or location where treatment was received, SAC does not face these barriers. Therefore, clinical interventions should be tailored to the individual, considering the patient's age, insurance-related accessibility, and any existing comorbidities.

Study limitations:

A significant strength of our study lies in the relatively large sample size, considering the rarity of SAC. The limitations of this study include the use of retrospective data obtained from the NCDB. Although the NCDB covers approximately 70% of new cancer diagnoses in the United States, it may not fully represent

the entire population with SAC and does not capture population-level data, preventing calculation of true incidence rates.. Since SAC is recognized by its ICD or histology code, cases not biopsied could have been missed. Additionally, data from cancer facilities not participating in the NCDB registry is not included. Lastly, the NCDB only records overall survival and does not differentiate between SAC-specific mortality and all-cause mortality.

CONCLUSION

Given the rarity of the disease, this study provides significant insights into the demographic and prognostic factors affecting SAC in the United States. There has been an upward trend in the diagnosis of SAC since 2004, with a predilection for White, non-Hispanic, older men in the South regions aligning with previously-known skin cancer rates. Age, Charlson-Deyo comorbidity scores, and insurance status are critical predictors of survival, emphasizing the need for prompt and comprehensive care for older patients and those with higher comorbidities. Contrary to other skin cancers, SAC does not exhibit disparities in survival based on race, ethnicity, education, or facility type. These findings underscore the importance of individualized clinical interventions, considering patients' specific health profiles and ensuring equitable access to healthcare resources for the individual.

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References:

1. Fulton EH, Kaley JR, Gardner JM. Skin adnexal tumors in plain language: A practical approach for the general surgical pathologist. *Archives of Pathology & Laboratory Medicine*. 2019;143(7):832-851. doi:10.5858/arpa.2018-0189-ra.
2. Oyasiji T, Tan W, Kane J, et al. Malignant adnexal tumors of the skin: A single institution experience. *World Journal of Surgical Oncology*. 2018;16(1). doi:10.1186/s12957-018-1401-y.
3. Lee DA, Grossman ME, Schneiderman P, Celebi JT. Genetics of skin appendage neoplasms and related syndromes. *J Med Genet*. 2005;42(11):811-819. doi:10.1136/jmg.2004.025577
4. AIRTUM Working Group, Busco S, Buzzoni C, et al. Italian cancer figures--Report 2015: The burden of rare cancers in Italy. *Epidemiol Prev*. 2016;40(1 Suppl 2):1-120.
5. Blake PW, Bradford PT, Devesa SS, Toro JR. Cutaneous appendageal carcinoma incidence and survival patterns in the United States: a population-based study. *Arch Dermatol*. 2010;146(6):625-632. doi:10.1001/archdermatol.2010.105
6. Stam H, Lohuis PJFM, Zupan-Kajcovski B, Wouters MWJM, van der Hage JA, Visser O. Increasing incidence and survival of a rare skin cancer in the Netherlands. A population-based study of 2,220 cases of skin adnexal carcinoma. *J Surg Oncol*. 2013;107(8):822-827.
7. Mallone S, De Vries E, Guzzo M, et al. Descriptive epidemiology of malignant mucosal and uveal melanomas and adnexal skin carcinomas in Europe. *Eur J Cancer*. 2012;48(8):1167-1175.
8. Stam H, van de Wiel BA, Klop WMC, et al. Skin adnexal carcinoma of the head and neck: a retrospective study in a tertiary referral center. *Eur Arch Otorhinolaryngol*. 2015;272(4):1001-1010.
9. Ireland AM, Harvey NT, Berry BD, Wood BA. Pediatric cutaneous adnexal tumours: a study of 559 cases. *Pathology*. 2017;49(1):50-54.
10. Jayalakshmi P, Looi LM. Cutaneous adnexal neoplasms in biopsy specimens processed in the Department of Pathology, University of Malaya. *Ann Acad Med Singapore*. 1996;25(4):522-525.

11. Stewart AK, Bland KI, McGinnis LS Jr, Morrow M, Eyre HJ. Clinical highlights from the National Cancer Data Base, 2000. *CA Cancer J Clin*. 2000;50(3):171-183.
12. Menck HR, Cunningham MP, Jessup JM, et al. The growth and maturation of the National Cancer Data Base. *Cancer*. 1997;80(12):2296-2304.
13. McCabe RM. National Cancer Database: The Past, Present, and Future of the Cancer Registry and Its Efforts to Improve the Quality of Cancer Care. *Semin Radiat Oncol*. 2019;29(4):323-325.
14. Resneck J Jr, Pletcher MJ, Lozano N. Medicare, Medicaid, and access to dermatologists: the effect of patient insurance on appointment access and wait times. *J Am Acad Dermatol*. 2004;50(1):85-92.
15. Kaundinya T, Kundu RV, Feinglass J. The epidemiology of skin cancer by UV index: cross-sectional analysis from the 2019 behavioral risk factor surveillance survey. *Arch Dermatol Res*. 2023;315(3):613-615.
16. Wang LS, Handorf EA, Wu H, Liu JC, Perlis CS, Galloway TJ. Surgery and Adjuvant Radiation for High-risk Skin Adnexal Carcinoma of the Head and Neck. *Am J Clin Oncol*. 2017;40(4):429-432.