8-22-2024

Epidemiologic Trends in Cutaneous Squamous Cell Carcinoma from 2011 to 2021 at All Africa Leprosy, Tuberculosis, and Rehabilitation Training Center (ALERT) in Addis Ababa, Ethiopia

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Epidemiologic trends in cutaneous squamous cell carcinoma from 2011 to 2021 at All Africa Leprosy, Tuberculosis, and Rehabilitation Training Center (ALERT) in Addis Ababa, Ethiopia

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Background: Cutaneous squamous cell carcinoma (cSCC) is the most common keratinocyte carcinoma in dark-skinned ethnic groups. Available studies are primarily focused on white populations, with fewer data available for black Africans, including Ethiopians. Therefore, less priority may be given to treatment and prevention in this population.

Objective: To determine the prevalence and risk factors of cSCC among patients presenting to All Africa Leprosy, Tuberculosis, and Rehabilitation Training Center , Addis Ababa, Ethiopia.

Methods: A literature review was performed to determine existing knowledge. A retrospective descriptive cross-sectional study was then conducted based on stored data of confirmed cases of cSCC from 2011 to 2021 at ALERT. Demographics, other parameters related to cSCC (size, anatomic location, degree of differentiation, metastasis, and recurrence), and potential risk factors including scars, burns, HIV status, xeroderma pigmentosum, and leprosy were collected and entered on a prepared data extraction sheet and analyzed using SPSS version 25 manufactured by IBM.

Results: Among 15,075 total pathologic samples reviewed, 3.8% (n = 570) were reported histopathologically as invasive cSCC (n = 437), keratoacanthoma, or (squamous cell carcinoma in-situ (Bowen disease). 50.3% (n = 287) occurred in female, and the mean age of affected patients was 50.1 years (SD 17.2). Nearly 70% were reported after >1 year of symptoms, including morphologic change, ulceration, and nonhealing wound. HIV status was not universally screened but was positive in 9.8% (46/437). Cases were commonly found to occur on the lower extremities (X^2 = 2.7196, Pr = 0.099) and >4 cm in size (46.3%). Among 274 cases with adequate histologic description, 82.5% (n = 226) were well-differentiated. Loco-regional metastases comprised 6.0% (n = 34) and 46.7% (n = 266) had ulceration.

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Funding sources: The COALESCE Program at Emory University.

Patient consent: The authors obtained written consent from patients for their photographs and medical information to be published in print and online and with the understanding that this information may be publicly available. Patient consent forms were not provided to the journal but are retained by the authors.

IRB approval status: The study was reviewed and approved by the AHRI/ALERT Ethical Review Committee (AAERC) with the protocol number: PO/27/21.

Accepted for publication July 22, 2024.

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2666-3287

https://doi.org/10.1016/j.jdin.2024.07.014

Conclusion: The biologic significance of ulceration in this population is unclear. Ulceration may indicate chronic wounds or Marjolin's ulcers. High rates of metastasis call for a better understanding of risk factors, preventive measures, and early diagnosis. This model of research may serve as a foundation for future nationwide investigations through the Federal Ministry of Health of Ethiopia's Disease Prevention and Control Directorate. (JAAD Int 2024;17:99-103.)

Key words: African dermatology; dermato-oncology; epidemiology; global health; international dermatology; prevention; resource-limited healthcare; skin of color.

INTRODUCTION

Skin cancer is one of the most common cancers worldwide, with an increasing incidence and healthcare burden over the last few decades.[1-3] Skin cancer in dark-skinned Africans remains relatively less common than in Caucasians but is associated with increased morbidity and mortality. Limited existing literature shows that the epidemiology, risk factors and clinical features of cutaneous squamous cell carcinoma (cSCC) may be different from those in the lighter-skinned patients.[4,5] Furthermore, there is a lack of literature to confirm the incidence of these tumors in African populations, including Ethiopians. This paucity of data may partly stem from poor medical record keeping in African countries, including Ethiopia.[4] According to the latest WHO data published in 2018, skin cancer-related mortality in Ethiopia comprised 0.04% of total mortality. The age-adjusted death rate is 0.50 per 100,000, which ranks Ethiopia 170th globally.[6] Unlike in Caucasians for whom basal cell carcinoma predominates, cSCC is the most common keratinocyte carcinoma in blacks, representing 30% of skin cancers, with an incidence of 3 per 100,000.[5] cSCC is the most common skin cancer in Ethiopia; however, the incidence is not well documented.[7,8]

Most available studies on cSCC focus on White populations. There are very few studies examining the prevalence, risk factors, and clinical and histologic patterns of cSCC in skin of color, all of which may directly contribute to early diagnosis, appropriate treatment, and prevention.[5,9] As a result, there is a significant knowledge gap pertaining to the clinical and biological behavior of cSCC in skin of color. To date, there is no widely accepted prevention strategy in this population.[10] Despite advances in treatment, early diagnosis and prevention of cSCC is still an important measure to ensure good outcomes.[11] As a result, standard of practice in Ethiopia includes treatment of lesions like keratoacanthoma and squamous cell carcinoma in-situ Bowen Disease (BD) as presumed cSCC due to the perceived high rates of conversion of these lesions to invasive cSCC.[5,12] Multiple studies have demonstrated the prognostic significance of histologic features such as tumor thickness, differentiation, and perineural invasion.[4,5,7,13] However, these findings are not routinely reported by dermatopathologists and pathologists in many parts of the world.

CAPSULE SUMMARY

- Less priority may be given to treatment and prevention of cutaneous squamous cell carcinoma in black African populations due to the scarcity of data available regarding prevalence and risk factors.
- High rates of ulceration and metastasis reveal the need for a better understanding of cutaneous squamous cell carcinoma risk factors, preventive measures, and early diagnosis.

cSCC in Ethiopia presents a number of challenges including late presentation due to lack of awareness. While a handful of small and older studies report on the pattern of skin cancer only, no studies that discuss epidemiologic trends of cSCC in Ethiopian population exist to date in the literature. We conducted this study to address these knowledge gaps in the literature by examining cSCC among Ethiopian patients reporting to a tertiary referral centre.

MATERIALS AND METHODS

A retrospective study was conducted using histopathology reports stored for the last 10 years at the Armauer Hansen Hospital Research Institute pathology unit. Ethical clearance was obtained from ethical review committee of the Armauer Hansen Hospital Research Institute/ALERT Ethics Review Committee unit. Data were collected June − August 2021. All cases of biopsy proven cSCC, keratoacanthoma, and BD were considered for inclusion. Incomplete medical records were excluded. Once cases were included, the data extraction format included age, sex, tumor characteristics (anatomical location, size,

Abbreviations used:

ALERT:	All Africa Leprosy, Tuberculosis, and Rehabilitation Training Center
BCC:	basal cell carcinoma
BD:	Bowen disease
cSCC:	cutaneous squamous cell carcinoma
EDV:	epidermodysplasia verruciformis
HIV:	human immunodeficiency virus
SD:	standard deviation
UV:	ultraviolet
WHO:	World Health Organization
XP:	xeroderma pigmentosum

degree of differentiation, metastasis, and recurrence), and potential risk factors including scars, burns, HIV status, XP, and leprosy (Table I and Results). Data were deidentified, entered, and stored securely in REDcap. The data were later analyzed with SPSS version 25 software program.

RESULTS

Sociodemographic and clinical characteristics

Among 15,075 cases examined at the Armauer Hansen Hospital Research Institute histopathology laboratory over these last 10 years, a total of 570 cases were reported histopathologically as invasive cSCC (n = 437) or keratoacanthoma (n = 12) and BD (n = 121). The sex distribution was nearly even (49.7% male and 50.3% female). The age distribution of the patients in this study ranges from 5 to 95 with mean age of 50.1 years (SD: 17.2). Among 559 reports with clearly reported age values, there was a relatively higher proportion (24.3%) of patients in the age group greater than 65 years and a lower number of cases (3.2%) in the age group less than 19 years old (Table I).

Duration of symptoms, HIV status, and other risk factors

Data pertaining to duration of symptoms was available for 352 patients and were categorized into 4 groups: less than 1, 1-4, 5-10, or greater than 10 years. For each of the categories, respectively, the analysis revealed a distribution of 32.4% (114/352), 50.0% (176/352), 12.8% (45/352), and 4.8% (17/352). HIV status was screened for in 437 patients, with a positivity rate of 9.8% (46/437), although bearing no association with cSCC (X^2 = 16.78, Pr = 0.000). Among various other risk factors screened for, burn, osteomyelitis, trauma, and scarring individually occurred in 5.3% (30/570) in aggregate. Other potentially predisposing skin disorders were also screened for, with a combined prevalence of 6.0% (34/570). XP, leprosy, EDV, and BCC were among the predisposing skin disorders with a relative proportion of 41.2% (14/34), 47.1% (16/34), 8.8% (3/34), and 2.9% (1/34), respectively. Notably, among the 14 cases of XP, 13 occurred in patients age <19 (n = 18).

Anatomic location of the lesions

A total of 556 reports described the anatomic location of the lesions, which were further categorized and analyzed as head and neck, trunk, upper limb, and lower limb. The distribution of the lesions was 25.0% (139/556), 2.9% (16/556), 9.0% (50/556), and 63.1% (351/556) for each of the categories, respectively. A chi-square test of independence was performed to examine the association among the 4 anatomic locations and the 437 reported cSCC. The result showed that the lower limbs (X^2 = 2.7196, Pr = 0.099) had a mild association, and the rest showed no significant association.

Type of cancer diagnosed, metastasis, recurrence, and risk factors

Along with 76.7% (n = 437) of histopathologically confirmed invasive cSCC cases, the predominantly reported in-situ or cSCC subtype lesions were BD and keratoacanthoma comprising 21.2% (n = 121) and 2.1% (n = 12), respectively. While metastasis was reported in 6.0% (n = 34) of cSCC cases, recurrence also prevailed in 3.7% (n = 16) cases.

Gross description of the lesions

There was no consistent reporting of gross tumor size in the gross morphology reporting system of analyzed data in this study; however, among 162 reported cases with measured gross tumor size, the size was grouped into 3 categories; less than 2, between 2 and 4, and greater than 4 cm. The proportion of the 3 groups of gross tumor size in cSCC was 23.5% (n = 38), 30.3% (n = 49), and 46.3% (n = 75), respectively. Moreover, among the 437 invasive cSCC cases, 55.4% (n = 242) had ulceration and 1.4% (n = 6) presented with pigmentation.

Histopathology features

The degree of differentiation retrieved from each histopathology report form was further classified into 3 groups: well, moderately, and poorly differentiated. Among 274 total reports with adequate descriptions of differentiation, 82.5% (n = 226) revealed well-differentiated patterns, and the remaining 4.4% (n = 12) and 13.1% (n = 36) showed moderate and poor differentiation, respectively. The infiltrative growth pattern (with stromal desmoplasia) was also analyzed across all cSCC reports and appeared in 72.1% (n = 315) of cases. Although considered important to be reported along with

Table I. Characteristics of cSCC at ALERT

Age cat/y	Frequency (%)	Metastasis (%)	Degree of differentiation		
			WD (%)	MD (%)	PD (%)
<19	18 (3.2)	0 (0)	7 (3.1)	0 (0)	2 (5.6)
19-34	84 (15.0)	4 (11.8)	31 (13.7)	0 (0)	5 (13.9)
35-44	102 (18.3)	7 (20.6	40 (17.6)	2 (16.7)	1 (2.8)
45-54	120 (21.5)	10 (29.4)	44 (19.4)	6 (50)	12 (55.6)
55-64	99 (17.7)	8 (23.5)	43 (18.9)	3 (25)	6 (16.7)
> 65	136 (24.3)	5 (16.1)	62 (27.3)	1 (8.3)	9 (25)
Total	570 (100)	34 (100)	227 (100)	12 (100)	36 (100)

cSCC, Cutaneous squamous cell carcinoma; *MD*, moderately differentiated; *PD*, poorly differentiated; *WD*, well differentiated.

other features, tumor thickness was reported in only 8 cases with an average thickness of 3.9 mm.

DISCUSSION

There is a significant knowledge gap in our understanding of the clinical presentation and biological behavior of cSCC in skin of color. Although cSCC is the most common skin cancer in blacks, little is known regarding the disease burden, risk factors, predominant histologic pattern, and clinical and biologic behavior of cSCC in this population, all of which would provide prognostically relevant information. While cSCC is the most common skin cancer in Ethiopia,[4,8] cSCC reporting in Ethiopia remains substandard due to lack of awareness, infrastructure, standardization, and access to appropriate healthcare providers. This study highlights the potential area that need further understanding to better understand the clinicopathologic patterns of cSCC in Black patients, which may differ from those in White patients.

While cSCC is most commonly associated with chronic UV exposure, especially in Caucasian patients, different risk factors have been identified for black Africans. These include immunosuppression, inadequately treated traumatic chronic leg ulcers, burn scars (Marjolin's ulcer), areas of past physical or thermal trauma, prior sites of radiation therapy, albinism, and areas of chronic inflammation[14-16] This disparity may reflect the tendency for blacks to present with more advanced disease, potentially as a result of delays in diagnosis or the presence of inherently more aggressive tumors.[15,16] As a result, cSCC in blacks is associated with mortality rates ranging from 17% to 30%.[13,16-20]

A previous, retrospective analysis of cSCC in black Africans showed that women were affected more than men. The majority of cSCC were found on the lower extremities and ulcerated at the time of diagnosis.[5] Another retrospective study on the pattern of skin cancer in Tikur Anbessa Teaching Hospital indicated that cSCC was most common among all skin cancers encountered (126/228, 55.2%). Most cases (67/126, 53.2%) were seen on the lower extremities, followed by the face (19/126, 15.1%). Age distribution for cSCC favored individuals older than 40 (68.2%) and males (1.6:1).[7]

According to a study at ALERT Hospital, Ethiopia, from 2007 to 2010, cSCC was the most diagnosed malignancy, accounting for 8% of total cases and 38% of malignant neoplasms. cSCC seen in this study occurred in non-sun exposed areas, particularly the lower extremity, and were associated with chronic ulceration, such as with leprosy ulcer, chronic osteomyelitis sinus, and previous burns.[8] Our study supports these risk factors as highlighted by the prevalence of lower extremity skin cancers (63.1%), chronicity of symptoms, and rate of ulceration (46.7%).

cSCC that develops within a chronic scarring process, the most common scenario in blacks, tends to be more aggressive and is associated with a 20% to 40% risk of metastasis, compared with 1% to 4% in Whites.[5,19,20] Our study highlighted a metastasis rate of 6%, consistent with this belief.

Our study highlights previously reported trends in Black and African populations, including that the lower extremities tend to be the most common location for cSCC. Given the consistently reported high rates, a low threshold for biopsy may be warranted in patients with >1 year of nonhealing lower extremity wounds to rule out CSCC. In terms of tumor morphology, most cSCCs reported were well-differentiated and characterized by an infiltrative growth pattern. The need for better preventative measures and earlier diagnosis is underscored by numerous findings: >75% of patients reported symptoms for > 1 year. More than 40% of lesions measured >4 cm at the time of presentation, with a majority of diagnosed cSCCs presenting with ulceration. Six percent of cases were furthermore found to be metastatic. Furthermore, HIV status was found to be positive in at least 1 in 10 patients; however, the absence of systematic screening for HIV in all cSCC patients limits our ability to deduce the prevalence of

HIV in this sample. This data underscore the need for more rigorous screening and better reporting of HIV status in all patients diagnosed with cSCC. All but one case of concomitant XP were reported in patients' age <19, where the prevalence of XP was 72%. While the propensity to develop skin cancer with XP is well known, the overall prevalence of this condition and other potential genetic risk factors in this setting is not well understood.

Limitations to this retrospective cross-sectional analysis include collection of data from a single center. Specifically, the morphologic variety of cases in our study may not be representative of the overall range of cSCC in Ethiopia. Thus, we believe that there is need to conduct larger, multicentric prospective studies to corroborate these findings.

The findings from this study may help healthcare providers increase their knowledge about cSCC in an African urban hospital setting. This supports the need for the development of programs that increase awareness of cSCC in the community, especially in patients with chronic lower extremity wounds, which in turn may be crucial to earlier diagnosis and more successful treatment of cSCC. The findings of this study will be an input for "The Noncommunicable Case Team within the Disease Prevention and Control Directorate of the Federal Ministry of Health of Ethiopia" and will serve as a basis for future nationwide longitudinal studies.

Conflicts of interest

None disclosed.

REFERENCES

1. Gloster HM Jr, Neal K. Skin cancer in skin of color. *J Am Acad Dermatol*. 2006;55(5):741-760. quiz 761-744.
2. Bradford PT. Skin cancer in skin of color. *Dermatol Nurs*. 2009; 21(4):170-178.
3. Gohara M. Skin cancer: an African perspective. *Br J Dermatol*. 2015;173:17-21.
4. Fania L, Didona D, Di Pietro FR, et al. Cutaneous squamous cell carcinoma: from pathophysiology to novel therapeutic approaches. *Biomedicines*. 2021;9(2):171.
5. Sober AJ. Diagnosis and management of skin cancer. *Cancer*. 1983;51(12 Suppl):2448-2452.
6. Bezabih M. Patterns in skin cancers in Tikur Anbessa hospital. *Ethiop J Health Sci*. 2001;11(1):313-322.
7. Cassarino DS, DeRienzo DP, Barr RJ. Cutaneous squamous cell carcinoma: a comprehensive clinicopathologic classification: part two. *J Cutan Pathol*. 2006;33(4):261-279.
8. Khazaei Z, Ghorat F, Jarrahi A, Adineh H, Sohrabivafa M, Goodarzi E. Global incidence and mortality of skin cancer by histological subtype and its relationship with the human development index (HDI); an ecology study in 2018. *World Cancer Res J*. 2019;6(2):e13.
9. Linares MA, Zakaria A, Nizran P. Skin cancer. *Prim Care*. 2015; 42(4):645-659.
10. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. *Br J Dermatol*. 2012;166(5):1069-1080.
11. WHO. Cancer in Sub-Saharan Africa. *International Agency for Research on Cancer*. 2024;49(4):3366887749. Rishab.
12. Gimbel DC, Legesse TB. Dermatopathology practice in Ethiopia. *Arch Pathol Lab Med*. 2013;137(6):798-804.
13. Cives M, Mannavola F, Lospalluti L, et al. Non-melanoma skin cancers: biological and clinical features. *Int J Mol Sci*. 2020; 21(15):5394.
14. Halder RM, Bang KM. Skin cancer in blacks in the United States. *Dermatol Clin*. 1988;6(3):397-405.
15. Halder RM, Bridgeman-Shah S. Skin cancer in African Americans. *Cancer*. 1995;75(S2):667-673.
16. Rowe DE, Carroll RJ, Day CL Jr. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. *J Am Acad Dermatol*. 1992;26(6):976-990.
17. Mora RG. Surgical and aesthetic considerations of cancer of the skin in the black American. *J Dermatol Surg Oncol*. 1986; 12(1):24-31.
18. Mora RG, Perniciaro C. Cancer of the skin in blacks. I. A review of 163 black patients with cutaneous squamous cell carcinoma. *J Am Acad Dermatol*. 1981;5(5):535-543.
19. Sabin SR, Goldstein G, Rosenthal HG, Haynes KK. Aggressive squamous cell carcinoma originating as a Marjolin's ulcer. *Dermatol Surg*. 2004;30(2):229-230.
20. Kallini JR, Hamed N, Khachemoune A. Squamous cell carcinoma of the skin: epidemiology, classification, management, and novel trends. *Int J Dermatol*. 2015;54(2):130-140.