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Meta-analysis

Prevalence of Squamous and Basal Cell Carcinomas in African Albino Skin Cancers: A Systematic Review and Meta-analysis of Proportion

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Abstract

Introduction: Keratinocyte carcinomas are the most common malignant conditions in Caucasian populations. African albinos have hypomelanized sensitive skin that is quite susceptible to photo carcinogenesis. Of the keratinocyte carcinomas, Squamous Cell Carcinoma (SCC) has been found more frequent in pigmented Africans, while Basal Cell Carcinoma (BCC) predominates in Caucasians. The aim of the present study was to estimate the prevalence of cutaneous SCC and BCC in all histologically confirmed skin cancer lesions in African albinos.

Data Source: Five databases: African journals on line (AJOL), PUBMED, Europe PMC, Google scholar, and Cochrane library were searched for relevant articles.

Study Selection: Included studies were case series and cross sectional studies of histologically confirmed skin cancers in African albinos. Data extraction and synthesis was informed by Meta-analysis of Observational Studies in Epidemiology Guideline. By random effect meta-analysis, we calculated the pooled prevalence of SCC and BCC in skin cancer lesions of the African albino.

Results: We abstracted 695 skin cancer lesions from 540 African albinos (275 male and 241 female albinos with sex not stated in 24 subjects). There were 419 SCCs and 249 BCCs. By meta-analysis, the pooled prevalence of SCC was 64% (95% CI: 50-77%). In addition, the prevalence for BCC was 31% (95% CI: 19-45%).

Conclusion: Squamous cell carcinoma is the predominant type of keratinocyte carcinoma reported in African albinos.

Keywords: Keratinocyte Carcinoma, African Albino, Squamous Cell Carcinoma, Basal Cell Carcinoma, Skin Cancer

Introduction

Keratinocyte carcinomas (SCC and BCC) are the most common malignant neoplasm in fair skinned populations.[1] It was estimated that over five million non-melanoma skin cancers existed in the United States and that over three million people had been treated for non-melanoma skin cancers in 2012.[2] Also incidence rates for SCC and BCC has been found to be very high in parts of Australia and England.[1,3,4]

In contrast, pigmented Africans have low risk for cutaneous malignancies. A comprehensive review estimates that skin cancer accounts for 20% to 30% of all neoplasms in Caucasians but only 1% to 2% in black people.[5] While the keratinocyte carcinomas and cutaneous melanomas seemingly account for about 40% of all malignant neoplasms in the US whites[6], a number of hospital studies in Africa discloses that skin cancers constitute only 5.5 to 13% of all diagnosed malignancies.[7-9]

However, a subpopulation of Africans, the African albinos, have elevated risks for skin cancer. Albinos tend to develop multiple cutaneous malignancies at younger ages and, at sun exposed body sites. This increased propensity for cutaneous malignancies derives from a genetically inherited disorder in skin melanization, which bequeaths the albino with hypomelanized, sun-sensitive skin susceptible to cutaneous carcinogenesis.[10]

Studies show that epidemiology and the incidence proportion of the keratinocytes carcinomas (SCC and BCC) differ in Caucasians and pigmented Africans. Caucasians have propensity for multiple keratinocyte carcinomas which feature more at sun-exposed body sites, and with respect to incidence proportion there is a preponderance of BCC over SCC in Caucasians.[11] BCC to SCC incidence ratio of about 4:1 has been

previously reported but recent studies suggest that this ratio narrows significantly with increasing age.[2,11,12] In contrast, pigmented Africans rarely develop BCC. In a recent analysis of 450 African patients with primary cutaneous malignancy in a Nigerian hospital, 39 had BCC and 74% (29/39) of these occurred in African albinos.[13] Most keratinocyte carcinomas in pigmented Africans are SCC carcinomas, often occurring in non-sun exposed sites and arising from or commonly associated with chronic inflammatory conditions and scars.[14]

The epidemiology of keratinocyte carcinomas in African albinos mirrors that of the Caucasians in some respect. Like the Caucasian, keratinocyte carcinomas in African albino tend to be multifocal and more at sun exposed body sites.[13] However, there have been variations in the incidence proportion of keratinocyte carcinomas reported in African albinos. While some studies[15] report a preponderance of SCC over BCC, similar to pigmented Africans, some other studies[16,17] have found BCC to be more frequent than SCC in African albinos consistent with the situation in Caucasians. With these reported discrepancies in view, we undertook a systematic review and meta-analysis of all existing studies reporting on skin cancers in African albinos aiming to establish the prevalence of the various types of keratinocyte carcinomas (SCC and BCC) among African albinos with skin cancer.

Materials and Methods

Methods adapted for this review had been previously described in our first manuscript which focused on cutaneous melanoma and which is currently under review.

Four indexing sites and databases were thoroughly searched for eligible publications: African journals on line (AJOL), PUBMED, Europe PMC, Google Scholar, and Google browser. Search terms included skin cancer, cutaneous malignancy, melanoma, squamous cell carcinoma, basal cell carcinoma, African albinos. The indexing sites were searched iteratively, first, with the key terms stringed together as complete sentences and then, with the key words combined in various fashion using Boolean operators. The search was not restricted by language or year of publication. Articles for further consideration were uploaded to Rayyan QCRI, a web app for exploring and filtering searches for eligible studies in systematic reviews. Finally, 46 full text articles were assessed for eligibility.

A study was considered eligible if it was a case series or cross sectional study reporting skin cancer in African albino with histological classification. In the included studies, African albino were the overall subject of the study or were identified as a sub group in larger samples of Africans. Excluded studies were those in which the malignant diagnosis was not histologically confirmed and all skin cancer cases in albino individuals not of African descent or of African descent but not reported from sub-Saharan Africa.

Data extracted from the articles included author, year of study, country of study, type of study, brief description of study, total number of subjects, number of albinos with skin cancer, sex distribution of albinos with skin cancer, mean and median age of albinos with skin cancer, and histologic types of albino skin cancer. The process of data extraction was independently undertaken by the authors and disagreements were resolved by discussion and consensus among the authors.

The methodological quality of the included study was assessed using a modification of Newcastle Ottawa scale adapted for case series[18]. This tool consists of eight items under four domains. Some of the items are related to reports of adverse drug event and thus not relevant to determining the validity of studies included in our review. Our quality assessment was based on scores in the domain of selection, ascertainment and reporting (Table 1).

Table 1. Risk of Bias Assessment Tool[18]

A.	**Selection**(Does the patient(s) represent(s) the whole experience of the investigator (center) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported)
i.	Cases were selected over a specified range of period?
ii.	Selection approach unclear?
B.	**Ascertainment of outcome:** (How were the cases ascertained?)
i.	Clinical records?
ii.	Self-report or other methods?
C.	**Reporting:**
i.	Cases described in sufficient details?
ii.	Cases scanty with some missing information?

The Metafor package of R statistical software was used in order to calculate the prevalence proportions of SCC and BCC in the aggregate skin cancer burden of the African albino. African albinos often presented multiple or multifocal skin tumors thus, the proportion of SCC and BCC for each of the included studies were calculated using the total number of cancer lesions reported in that study as the denominator. Then, using the restricted maximum-likelihood estimator of random effect model, we calculated the weighted average proportions for the two keratinocyte carcinomas after transformation of the raw proportions by Freeman-Turkey double arcsine method in order to achieve normality and variance stability[19]. Heterogeneity across the included studies were assessed using I^2, τ^2 and, Cochrane Q test. I^2 values below 25% were considered low heterogeneity; 25-75% moderate heterogeneity and above 75% high heterogeneity. Cochran *p*-values below 0.1 were considered significant. Publication bias was assessed by Funnel plot and Egger's unweighted regression test.

Results

Data base search yielded 575 potentially relevant records most of which were irrelevant articles that were excluded following title and abstract screening. Forty-six full text articles were acquired and assessed for eligibility of which 23 fulfilled the inclusion criteria (Figure1).

The characteristics of the 23 included studies are shown in Table 2. The studies were 23 case series and cross sectional studies with publication year ranging from 1953 to 2020. Most of the studies were carried out in Nigeria followed by Tanzania. Specifically, 10 of the studies[20–29] had only albino skin cancer subjects; four studies[16,30–32] equally had only albino subjects but reported on skin cancers and other skin diseases and nine studies[13,33–40] had mixed samples of albinos and non-albinos.

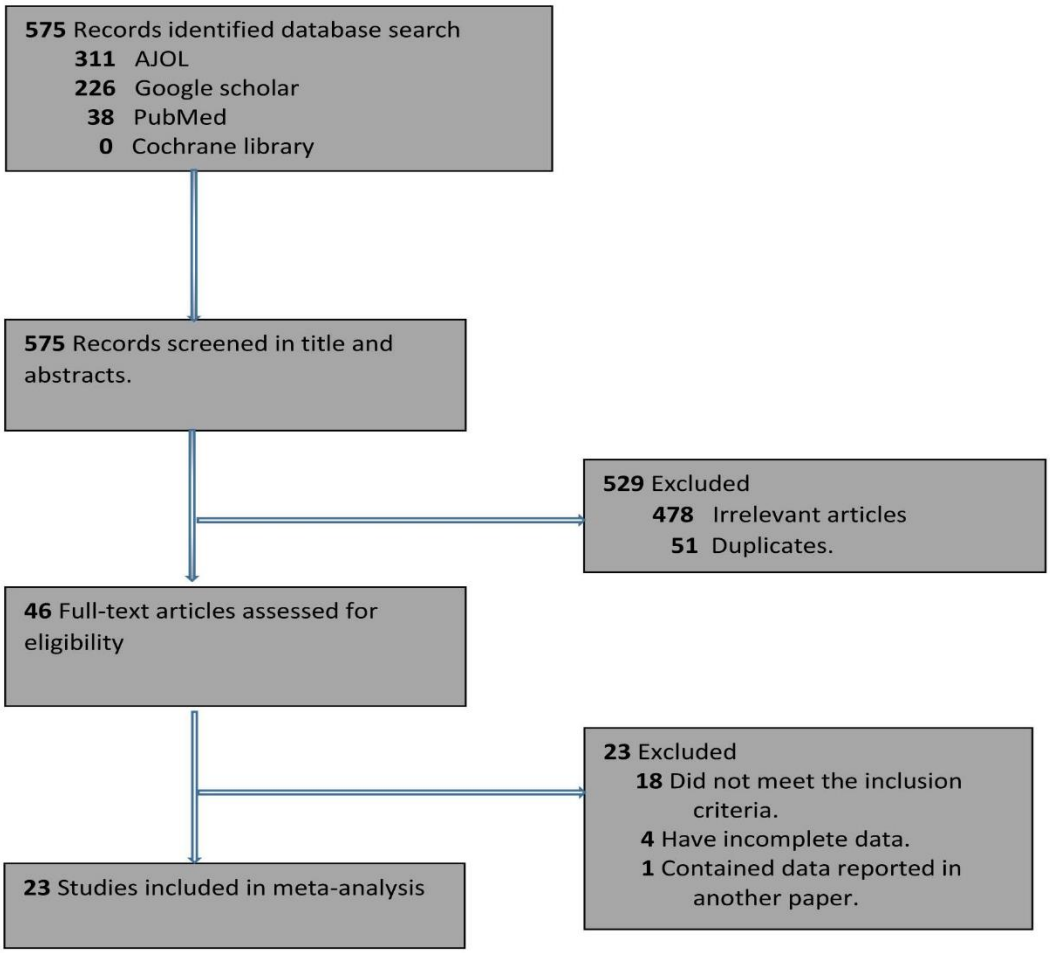

Figure 1. PRISMA Flow Chart of Article Selection Process.

Table 2. Included Studies, Country of Study, Number of Albinos and Skin Cancer Type

Author; Year	Country	NO of albinos with skin cancer	Skin cancer type*					Males	Females
			SCC	BCC	CM	Others	Total		
ShapiroMP; 1953	South Africa	12	9	3	0	0	12	8	4
Datubo-BrownDD; 1991	Nigeria	3	3	0	0	0	3	0	0
YakubuA; 1993	Nigeria	18	15	3	0	0	18	12	6
OluwasanmiJ; 1969	Nigeria	15	8	6	0	1	15	12	3
AlexanderG; 1981	Tanzania	10	21	0	0	0	21	9	1
LookingbillDP; 1995	Tanzania	10	7	3	0	1	11	5	5
AsuquoME; 2010	Nigeria	9	5	5	1	0	11	5	4
OparaKO; 2010	Nigeria	20	32	5	0	1	38	10	10
BangalyT; 2019	Guinea	30	40	0	0	1	41	12	18
KipronoAS; 2014	Tanzania	86	72	61	1	0	134	41	45
MabulaJB; 2012	Tanzania	64	48	15	1	0	64	38	26
EmadiSE; 2017	Kenya	20	8	15	0	0	23	13	7
NthumbaPM; 2011	Kenya	8	0	8	0	0	8	5	3
EnechukwuAN; 2020	Nigeria	18	9	22	0	9	40	9	9
Awe OO; 2018	Nigeria	22	15	5	2	0	22	11	11
AlukoOlokun; 2015	Nigeria	35	12	16	0	7	35	17	18
OripelayeMM; 2018	Nigeria	12	8	4	0	0	12	0	0
AsuquoME; 2013	Nigeria	4	7	0	0	0	7	2	2
MadubukoR; 2018	Nigeria	9	8	1	0	0	9	0	0
AdegbidiH; 2007	Benin Republic	5	1	12	0	0	13	3	2
SakaB; 2020	Togo	33	21	31	0	2	54	17	16
OkaforCO; 2020	Nigeria	86	64	33	0	0	97	38	48
ChidothelA; 2014	Malawi	7	6	1	0	0	7	6	1

*SCC-squamous cell carcinoma; BCC-basal cell carcinoma; CM-cutaneous melanoma.

Score for methodological quality of the studies ranged from 3 to 6 by the assessment tool we used. Twenty-one of studies were assessed to be of high quality and two were deemed low quality.

From the 23 studies, we identified 540 African albinos presenting 695 histologically confirmed skin cancers. These were composed of 274 males and 241 females with sex missing in 24 cases. There were 419 SCC and 249 BCC among the 695 cancer lesions (Table 3).

Table 3. Skin Cancer Type and Sex of 540 African Albinos with Cutaneous Malignancy

Variable	Frequency
Sex	
Male	275
Female	241
Missing	24
Total	540
Skin cancer type	
Squamous cell carcinoma	419
Basal cell carcinoma	249
Cutaneous melanoma	5
Others**	22
Total	695

*some patients presented multifocal cancers; ** 9 basosquamous carcinoma, 10 adenoid cystic carcinoma, 1 malignant adnexal tumour, 1 sarcoma and 1 unspecified histology.

By random effect meta-analysis, the pooled prevalence of SCC for the 23 studies was 64% (95CI; 50-77%). For BCC, the pooled prevalence was 31% (95CI; 19-41%). Figure 2 is a forest plot showing the individual study prevalence of SCC, the pooled prevalence and the heterogeneity statistics.

Individual study prevalence and pooled prevalence of BCC are similarly displayed in Figure 3. There was high heterogeneity in the prevalence estimations across all the included studies (Cochrane Q (df $_{22}$) = 195, p = <0.01). Also, I^2 the ratio of between study variance to total variance was 89% (95% CI: 85-96) just as τ^2, another measure of variance between studies, was 0.1 (95% CI: 0.05-0.2) further highlighting the heterogeneity of the prevalence estimations across studies.

Sensitivity analysis did not significantly alter the pooled estimation or the heterogeneity statistics. Also, the moderator analyses was done using sample size greater than 20, country of study (Nigeria vs others) and study specifying multifocal tumour as moderating variables. Observed heterogeneity was not explained by any of the moderating variables as R^2, the amount of heterogeneity accounted by the moderators was 0%.

Eggers test of funnel plot asymmetry was not significant (z = 0.60, p = 0.55), suggesting lack of publication bias in the present review (Figure 4).

Discussion

African albinos have creamy white skin, sandy yellow hair and brown hazel eyes, which are the phenotypic consequence of inherited genetic defects in melanin synthesis and pigmentation of their skin, hair and ocular tissues.[41] This adverse genetic inheritance and distinctive

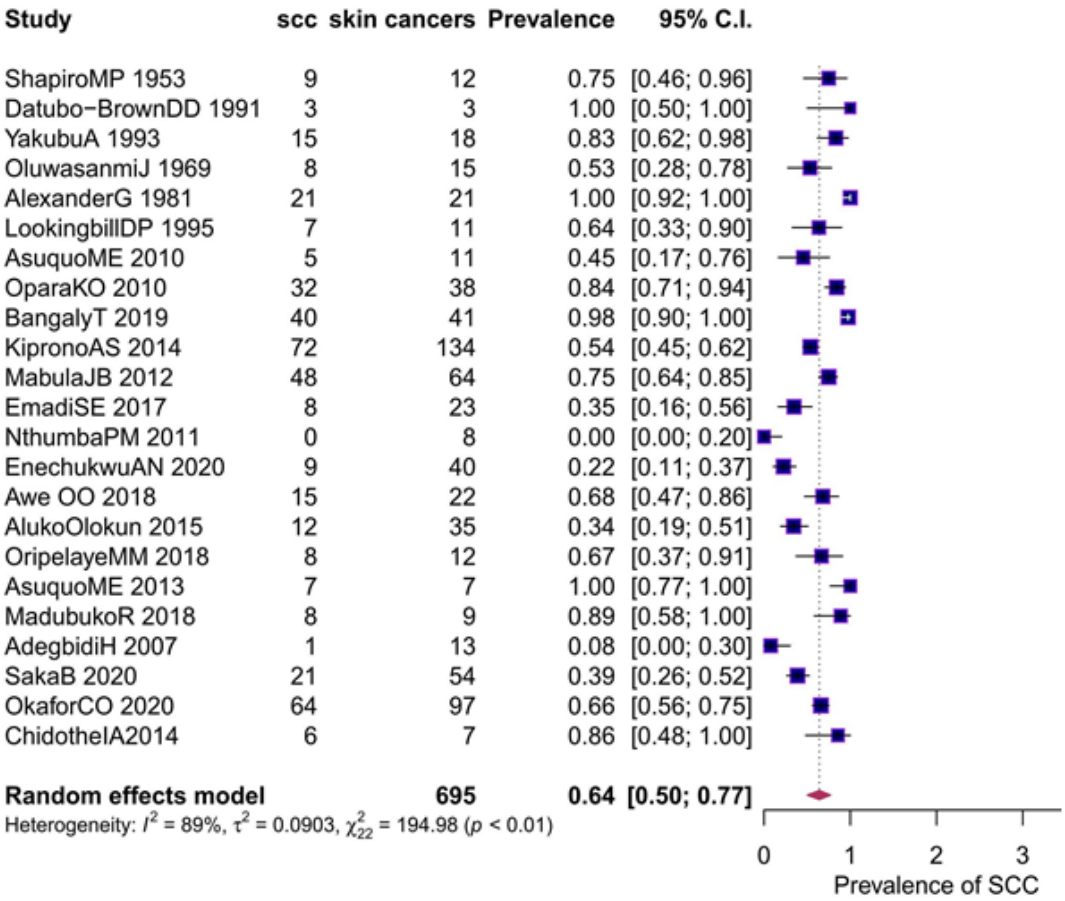

Figure 2. Forest Plot Showing the Pooled Prevalence of Squamous Cell Carcinoma in 23 Included Studies.

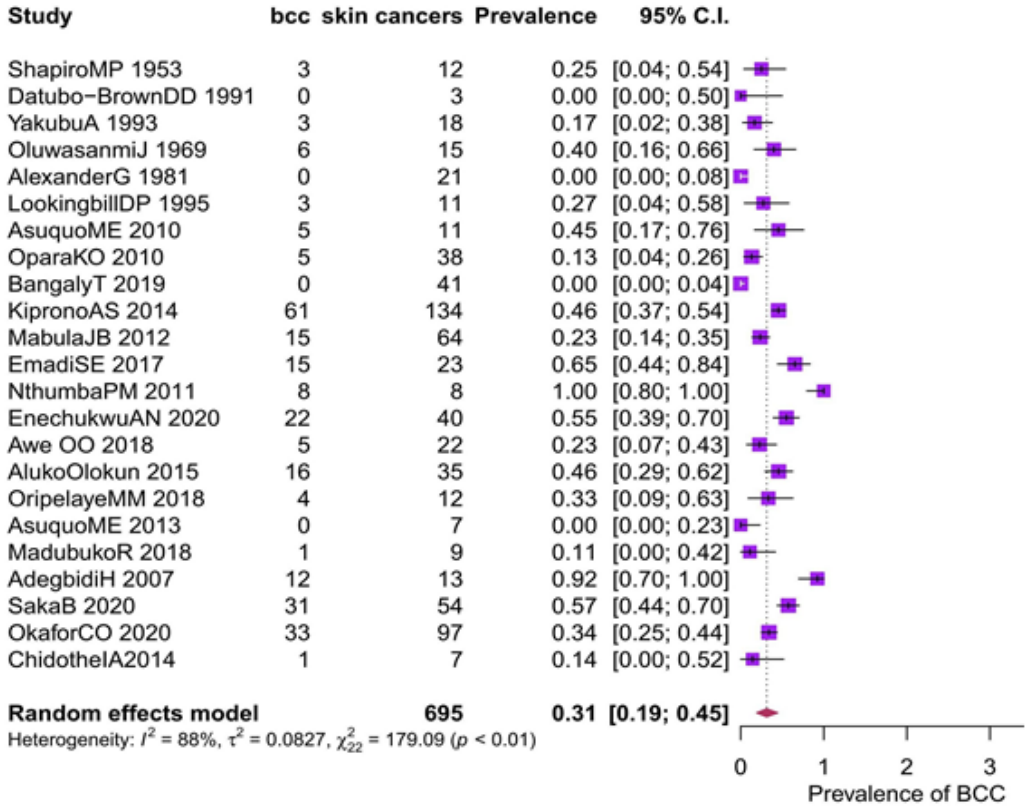

Figure 3. Forest Plot Showing the Pooled Prevalence of Basal Cell Carcinoma.

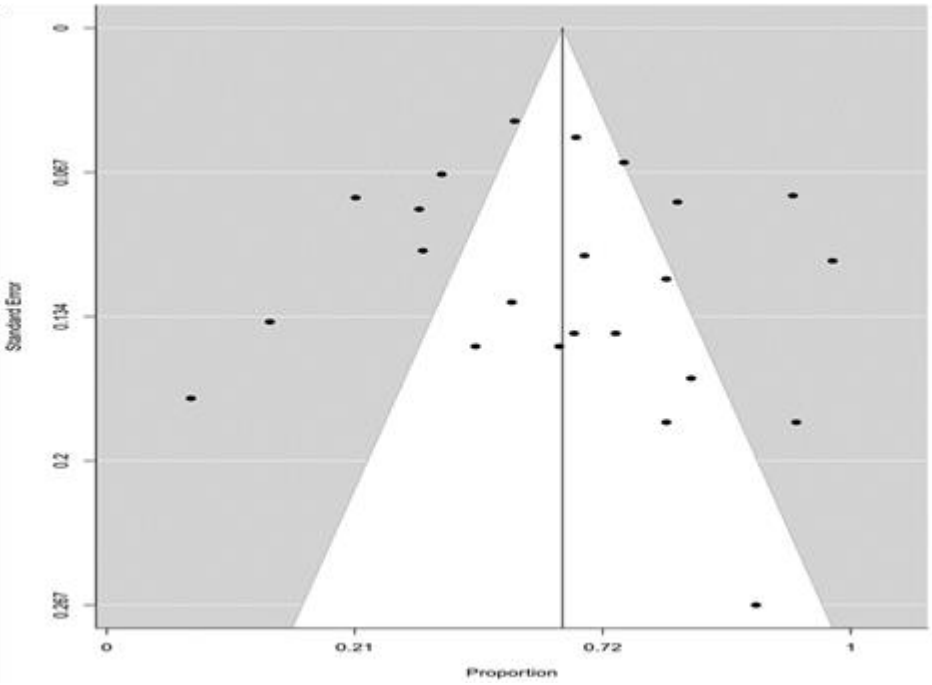

Figure 4. Funnel Plot of Included Studies.

physical appearance in a population of black, pigmented people, predisposes the African albino to some existential challenges such as social discrimination and, in some places, physical assault with body dismemberment.[42,43] Health wise, they uniformly develop visual abnormalities and have an elevated risk for photodermatosis and skin cancer.[10,30]

For the African albino, however, skin cancer is a very important health problem. Being deficient in protective melanin pigment and inhabiting a climate of high ambient sunshine predisposes the African albino to the photo carcinogenic effect of high UV radiation. Epidemiologic studies of skin cancer in Africans report that, compared with normally pigmented Africans, African albinos have higher frequency of keratinocyte cancers which occur at significantly younger ages and develop multiple and or recurrent lesions which feature more at sun exposed body sites.[24]

Meta-analysis, originally applied in synthesizing results of clinical trials and determining the effects of treatment interventions has found escalating use in deriving precise estimates of disease frequency such as incidence rate and prevalence proportions.[44]

The present systematic review synthesized data from eligible case series and cross sectional studies of skin cancers in African albinos and attempted to establish the prevalence proportion of SCC and BCC using the methods of meta-analysis.

Elaborating prevalence as a variable, Barendregt et al.,[44] have stated that disease prevalence is a proportion which is derived by dividing the number of cases of the disease in a population by the population number. Its value always lies between 0 and 1, and sum over multi-categories amounts to 1.[44] A very notable feature of skin cancer in African albinos is the propensity for multifocal or multiple tumours with an individual patient sometimes presenting histologically different cancer types. Thus, the number of skin cancer lesions we abstracted (695) was more than the number of albinos with skin cancer (540). The prevalence or proportion of SCC and BCC was determined in all the histologically confirmed skin cancer lesions of the African albino.

The pooled prevalence of SCC was 64% while that of BCC was 31% and these represents average proportion of SCC and BCC in all the studies weighted by the inverse of their sampling variances. Heterogeneity statistics indicate a lack of homogeneity in reported proportions across all the included studies. This was not explainable by sensitivity or moderator analysis. Small sample sizes and variations in study settings could be responsible. In spite of the observed hetero-geneity, the estimated prevalence figures appear valid. This is because, by crude unweighted pooling of the

individual study proportions (analogous to the ditched 'vote counting' method previously used in meta-analysis of clinical trials and interventions), the proportion of SCC among all histologically confirmed skin cancer lesions in African albino would be 60.2% (419/695) and that of BCC, 35.8% (249/695). These figures are quite comparable to pooled prevalence established by meta-analyses.

Marçon et al., in Brazil suggest that the frequency of BCC might be equal to SCC in albinos and that studies reporting more SCC are hospital excision biopsies of advanced tumours in which SCC are more likely to predominate, being the more aggressive of the two tumours and often require surgical attention. This view seems to be supported by the fact that two studies that reported more BCC than SCC in African albinos feature biopsies taken at routine dermatological examination and surveillance programme.[16,17]

Publication bias has been explained, chiefly, in terms of preferential publication of manuscripts with statistically significant results to the exclusion of those with non-significant results. But some other study characteristics such as funding source, research setting, and prevailing theories at the time of publication have been found to equally influence publication.[45] Though publication bias could confound systematic reviews, it has been questioned if the traditional methods employed in the assessment of publication bias for comparative studies are appropriate for observational studies of the type used in meta-analysis of proportions. The studies examined in meta-analysis of proportion, being non-comparative, are not subject to considerations of statistical significance and direction of result, which are known to preferentially influence publication of clinical trials.[19,45,46] Nevertheless, we assessed for publication bias using funnel plot. Eggers test of funnel plot asymmetry was non-significant, suggesting lack of publication bias in the published studies.

The present study faced some strengths and limitations. First, it is, to the best of our knowledge, the first meta-analysis on skin cancer in African albinos and thus represents the largest study of albinos with skin cancer to date. The study was able to yield data, which bolstered the previously reported epidemiologic trends of skin cancer and statistically established that the prevalence for SCC and BCC in skin cancer lesions. The study is limited by the small sample sizes of the available studies and dearth of publications devoted exclusively to the subject of albino skin cancer. In addition, as this study was a review, we could not validate the histological types of the skin cancers reported by the included studies.

Conclusion

In conclusion, we estimated the prevalence proportion of SCC and BCC in histologically confirmed skin cancer lesions in African albinos. The pooled average prevalence proportion of SCC amongst all histologically confirmed skin cancer lesions in African albinos was 64% (95% CI: 50-77%) and prevalence of BCC was 31% (95% CI: 19-45%). Squamous cell carcinoma is the predominant type of keratinocyte carcinoma reported in African albinos. This predominance of keratinocyte carcinomas in African albinos relates more with the pattern of occurrence in pigmented Africans rather than Caucasians.

Conflict of Interest

The authors declare no conflicts of interest.

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