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Review Article

Dermatology Section

Cutaneous Melanoma in African Albinos: A Systematic Review

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ABSTRACT

Introduction: Cutaneous melanoma (CM) is reported rare in African albinos inspite of their non or hypomelanised sun-sensitive skin and inhabitance of high ultravoilet index environment. The precise prevalence of CM has not been established in African albinos.

Aim: To highlight the frequency of CM in all histologically confirmed skin cancer lesions in African albinos.

Materials and Methods: The search was conducted on 28th May 2020 and updated on 8th September 2020 for systematic review. Five databases- African Journals On Line (AJOL), PubMed, Europe PubMed Central, Google scholar and Cochrane library were systematically searched for relevant articles. Included studies were case reports and cross-sectional studies of histologically confirmed skin cancers in which African albinos were the overall subject of the study or were identified as a sub group in mixed sample with normally pigmented Africans.

Results: There were 715 skin cancer lesions presenting in 556 African albino skin cancer patients. Only six CM were identified. Over 80% (22/27) of the reviewed studies reported no case of CM. Out of the six melanomas two were acral lentiginous, two nodular, while the histologic subtype was unspecified in two cases.

Conclusion: The frequency of CM amongst histologically confirmed skin cancer lesions in African albinos is extremely low. Given that only a fraction of albinos develops skin cancer, authors extrapolate that prevalence of CM in the general population of African albinos is infinitesimal. Elucidating the processes inhibiting melanomagenesis in African albino could provide targets for melanoma therapy in the wider population.

Keywords: Basal Cell Carcinoma, Hypomelanised skin, Squamous cell carcinoma, Skin cancer

INTRODUCTION

African albinos have inherited deficiency in melanisation of skin and ocular tissues and their fair coloured, Fitzpatrick type I or II skin phenotype shares some features of the Caucasian skin. For instance, they have higher frequency of keratinocyte cancers compared with normally pigmented Africans, younger mean age of onset and multiple or recurrent lesions featuring more at sun exposed body sites [1]. Also, Basal Cell Carcinoma (BCC) which is the most common cutaneous malignancy in Caucasians, is rare in Africans generally and over 70% of BCC diagnosed in Africans occur exclusively in albinos [2-7].

Some identified constitutional and environmental risk factors for melanoma in white populations have, in addition to family history, included fair skin, presence of moles, freckling and sun burns [8-10]. In fact, attempt at explanation of the 26- fold higher incidence of Cutaneous Melanoma (CM) in United States non Hispanic whites compared with African Americans and the predominant acral location of CM in Africans has considered pigmentation status as a possible factor [8,11].

However, there is a paucity of CM reported in African albinos inspite of their non or hypomelanised skin and habitation in a high to extreme Ultravoilet (UV) index environment. This unique situation of the African albino with respect to melanoma complicates the concept of skin pigmentation (or lack of it), and photocarcinogenesis as factors for melanomagenesis, or raises the possibility of the albino phenotype exerting some stabilising effect on melanocyte genome or protective influence against melanomagenesis.

While a number of case series reports have pointed to its rarity, no study, to the best of our knowledge has provided any estimate of prevalence for CM in a large population of African albinos, the largest number of African albino skin cancer patients in published works being 86 [1,7]. Hence, authors undertook a systematic review of studies reporting on skin cancers in African albinos aiming to synthesise data on the occurrence of CM in all histologically confirmed skin cancer lesions of the African albino reported in medical literature.

MATERIALS AND METHODS

Literature Search and Study Selection

A thorough search for relevant articles was undertaken in five indexing sites and databases: AJOL, PubMed (including Europe PMC), Google scholar and Cochrane library. The search was conducted on 28th May 2020 and updated on 8th September 2020 for the present systematic review. In first round of search, the databases were searched iteratively with the following string of key terms, "skin cancer in African Albinos", "cutaneous malignancy in African albinos", "Skin cancer in Africans". In a second round of PubMed search, the key words were combined using Boolean operators: "Skin cancer" OR "Cutaneous malignancy" OR "Melanoma" OR "Squamous cell carcinoma" OR "BCC" AND "Albino Africa*". Second round of Google scholar query was done using the following: skin cancer "African albinos" and "cutaneous malignancy African albinos". The 'cited by' and 'related article' features of Google scholar were used to search for other relevant articles. Authors equally browsed the reference lists of retrieved studies for additional relevant article. Literature search was not limited by language or year of publication. Titles acquired from the searches were screened for eligibility by the authors using Rayyan QCRI, a web app for exploring and filtering searches for eligible studies in systematic review [12]. The study was guided by an apriori protocol though not registered.

Inclusion and Exclusion criteria: The review aimed to ascertain from the literature, the number of African albinos who had been diagnosed of skin cancer and the histological cancer type. To this end, a study was considered eligible if it was a cross sectional study, a case series or case report of skin cancer in African albinos, reported with histological classification. In an included study, African albino was the overall subject

of the study or was identified as a sub group in larger mixed sample of Africans. Also, included were case series of cutaneous diseases in African albinos in which there was a distinct category of histologically confirmed cutaneous malignancies. Excluded were all studies in which the malignant diagnosis was not histologically confirmed and all cases not originating from sub-Saharan Africa.

Data Extraction

Data extracted from the articles had been predetermined at the protocol stage of the study. It 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 of albinos with skin cancer, histologic types of skin cancer. These variables were extracted into an Microsoft Excel spreadsheet. The process of data extraction was independently undertaken by the two authors and disagreements were resolved by discussion and consensus.

Risk of Bias Assessment of Individual Studies

Quality of included study was assessed using a modification of Newcastle Ottawa scale adapted for case series [13]. This tool consists of eight items under four domains. Some of the original items (Two items) are related to reports of adverse drug event and thus not relevant to determining the validity of studies included in our review. Thus, quality assessment was done by the two authors using six-item framework grouped under three domains namely case selection, ascertainment of outcome and reporting. Each of the included study scored one or two points in each of these three domains [Table/Fig-1]. Disagreements were resolved by discussions and consensus among the authors. An aggregate score of 3 or 4 was considered low quality while score of 5 or 6 was appraised high quality.

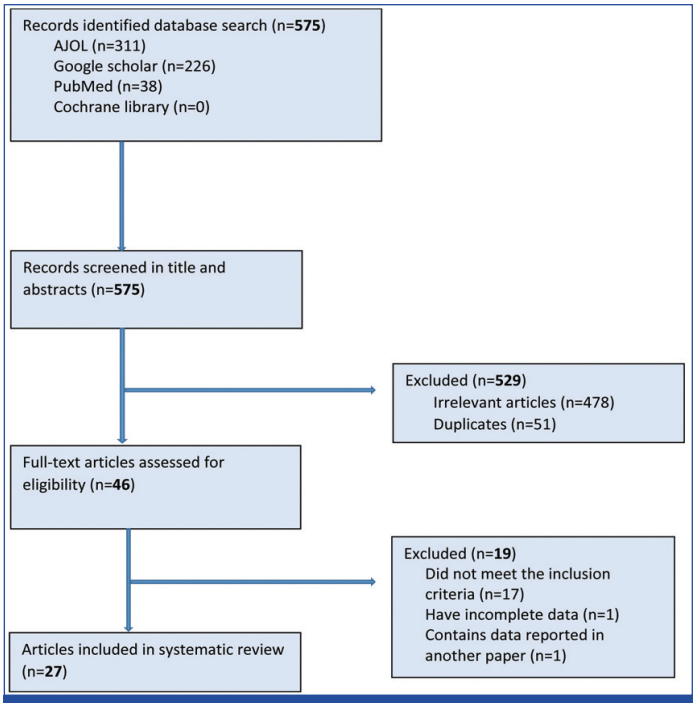
Domain	Six-items frame
A. Selection : Does the patient(s) represent(s) the whole experience of the investigator (center) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?	i. Cases were selected over a specified range of period?-2
	ii. Selection approach unclear ?-1
B. Ascertainment of outcome: How were the cases ascertained?	i. Clinical records?-2
	ii. Self-report or other methods?-1
C. Reporting	i. Cases described in sufficient details?-2
	ii. Cases scanty with some missing information?-1

[Table/Fig-1]: Risk of bias assessment tool [13].

RESULTS

[Table/Fig-2] shows the flowchart for screening and study selection. Systematic database search yielded 575 potentially useful publications. Most of these (529) were irrelevant articles or redundant duplications and were thus excluded following title and abstract screening. Forty-six full text articles were acquired and assessed for eligibility of which 27 fulfilled the inclusion criteria for systematic review. Number of studies by country and number of albino skin cancer subjects together with number of CM reported for each country is shown in [Table/Fig-3]. Nigeria had most number of studies and albino skin cancer subjects followed by Tanzania.

Characteristics of the 27 included studies are shown in [Table/Fig-4]. There are no definite trends in pattern of publication by year but four years (2010, 2015, 2018 and 2020) had peak number of three publications each. Given that our major aim was to ascertain the frequency of CM in histologically confirmed cases of skin cancers in African albinos, authors included studies that featured mixed samples of normally pigmented Africans and albinos, provided the histological types of cancer were clearly specified in the albino group. Specifically, ten of the studies [1,14-22] had only albino skin cancer subjects; four studies [23-26] had only albino subjects but reported on skin cancers and other skin diseases while nine



[Table/Fig-2]: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram of article selection process.

Country	Number of studies	Total number of Albino cancer patients	No. of Cutaneous Melanomas
Nigeria	13	268	3
Tanzania	4	170	2
Kenya	2	28	0
Malawi	2	8	0
Congo	2	2	1
South Africa	1	12	0
Togo	1	33	0
Guinea	1	30	0
Benin Republic	1	5	0
Total	27	556	6

[Table/Fig-3]: Number of studies, total number of albino cancer patients and number of Cutaneous Melanomas (CM) for each country of study.

studies [4,7,27-33] had mixed sample of albinos and non albinos. Three of the reviewed articles [34-36] were case reports, one of which documents a case of Acral Lentiginous Melanoma (ALM) in a pregnant albino woman [35]. Another case report [37] of CM in an albino was found to be duplicated in a later case series by the same authors and was reviewed together with the case series [19]. One article [38] that reported 59 skin cancer lesions in 19 african albinos was excluded because it was vague on the histopathological typing of the lesion. Another report [39] was also excuded because it was a duplication of data reported in a different publication [15].

[Table/Fig-5] presents the risk of bias or study quality score for the included studies. Total 22 of the studies were adjudged high quality while five studies were considered low quality as per the assessment criteria.

From the 27 studies, authors identified 556 African albinos presenting 715 histologically confirmed skin cancers. They include 285 males and 247 females with sex not stated in 24 subjects. Of the 715 cancer lesions, only six were CM [Table/Fig-3]. Total 22 studies comprising 374 albino skin cancer subjects reported no case of CM and thus, had individual study prevalence of CM of 0%. Reporting one case each of CM are three studies [1,15,18] comprising 159 albino skin cancer subjects and one case report [35]. One study involving 22 albinos reported 2 CM [19].

Of the six cases of CM, histological subtype was given as ALM in two studies [1,35]. One of the ALM [35] was present on the left

Author and year of study	Country	Brief description of study	No. of albinos with skin cancer	No. of skin cancer lesions in albinos	No. of cutaneous melanoma
Shapiro MP et al., 1953 [27]	South Africa	Case series of 50 cases of skin cancer referred for radiotherapy	12	12	0
Datubo-Brown DD, 1991 [28]	Nigeria	Case series of 18 skin cancer cases seen at a university teaching hospital over 3 years	3	3	0
Yakubu A and Mabogunje OA, 1993 [29]	Nigeria	Case series of 775 black African and 18 albino skin cancer patients seen at a teaching hospital	18	18	0
Oluwasanmi J et al., 1969 [30]	Nigeria	Case series of 435 skin cancers registered at a cancer registry	15	15	0
Alexander G and Henschke UK, 1981 [14]	Tanzania	Case series of 10 Albino skin cancer patients treated with radiotherapy	10	21	0
Lookingbill DP et al., 1995 [23]	Tanzania	Case series of 164 albino patients examined for actinic skin damage	10	11	0
Asuquo ME et al., 2010 [15]	Nigeria	Case series of albinos with a histologic diagnosis of skin cancer seen at a University Teaching Hospital over a seven year period	9	11	1
Opara KO and Jiburum BC, 2010 [16]	Nigeria	Case series of 20 albinos managed at a plastic surgery unit of a teaching hospital	20	38	0
Bangaly T et al., 2019 [17]	Guinea	Case series of 30 albino skin cancer patients attending a surgical oncology clinic in Conakry	30	41	0
Kiprono SK et al., 2014 [1]	Tanzania	Case series of 86 Albino skin cancer patients	86	134	1
Mabula JB et al., 2012 [18]	Tanzania	Case series 64 albino skin cancers seen at medical center from 2001 to 2010	64	64	1
Emadi SE et al., 2017 [24]	Kenya	A study of skin lesions in 151 albinos at a District Hospital in Nairobi, Kenya	20	23	0
Nthumba PM et al., 2011 [4]	Kenya	Review of cutaneous malignancies in a teaching hospital	8	8	0
Enechukwu AN et al., 2020 [25]	Nigeria	A study of skin lesions in 90 albinos	18	40	0
Awe OO and Azeke TA, 2018 [19] and Awe OO et al., 2015 [37]	Nigeria	2015-Case report of cutaneous melanoma 2018-22 albinos with histopathologic diagnosis of skin cancer	22	22	2
Aluko-Olokun B and Olaitan AA, 2015 [31]	Nigeria	37 Human Immunodeficiency Virus (HIV) positive patients with skin cancers	35	35	0
Oripelaye MM et al., 2018 [32]	Nigeria	72 primary skin cancer diagnosed in a teaching hospital	12	12	0
Asuquo ME et al., 2013 [20]	Nigeria	Case series of 4 albino skin cancers patients	4	7	0
Roli MC and Abel O, 2018 [26]	Nigeria	Study of photodermatosis in 73 albinos	9	9	0
Adegbidi H et al., 2007 [33]	Benin	Case series of 16 Skin cancer patients in Cotonou	5	13	0
Saka B et al., 2020 [21]	Togo	Report of 33 albinos with skin cancer, out of 280 examined for skin lesions	33	54	0
Okafor OC and Onyishi NT, 2020 [7]	Nigeria	Case series of 450 Africans with skin cancer in a Nigerian teaching hospital	86	97	0
Chidothe IA and Masamba L, 2014 [22]	Malawi	7 albinos receiving chemotherapy for skin cancer	7	7	0
Mapurisa G and Masamba L, 2010 [36]	Malawi	Case report of a skin cancer in an albino	1	1	0
Nday DK et al., 2015 [34]	Congo	Case report of basal cell carcinoma in an albino	1	1	0
Atipo-Tsiba PW et al., 2015 [35]	Congo	Case report of skin cancer in an albino	1	1	1

[Table/Fig-4]: Characteristics of included studies.

S. no.	Author and year of study	A Selection	B Ascertainment of outcome	C Reporting	Aggregate score*
1	Shapiro MP et al., 1953 [27]	2	2	2	6
2	Datubo-Brown DD, 1991 [28]	1	2	1	4
3	Yakubu A and Mabogunje OA, 1993 [29]	2	2	2	6
4	Oluwasanmi J et al., 1969 [30]	2	2	2	6
5	Alexander GA and Henschke UK, 1981 [14]	1	2	2	5
6	Lookingbill DP et al., 1995 [23]	2	2	1	5
7	Asuquo ME et al., 2010 [15]	2	2	2	6
8	Mapurisa G and Masamba L, 2010 [36]	1	2	1	4
9	Opara KO and Jiburum BC, 2010 [16]	2	2	2	6
10	Nday DK et al., 2015 [34]	1	2	1	4
11	Bangaly T et al., 2019 [17]	2	2	2	6
12	Kiprono SK et al., 2014 [1]	2	2	2	6
13	Awe OO et al., 2015 [37]	1	2	1	4
14	Mabula JB et al., 2012 [18]	2	2	2	6
15	Emadi SE et al., 2017 [24]	2	2	2	6

16	Nthumba PM et al., 2011 [4]	1	2	2	5
17	Enechukwu AN et al., 2020 [25]	2	2	1	5
18	Awe OO and Azeke TA, 2018 [19]	2	2	1	5
19	Atipo-Tsiba PW et al., 2015 [35]	1	2	2	5
20	Aluko-Olokun B and Olaitan AA., 2015 [31]	1	1	2	4
21	Oripelaye MM et al., 2018 [32]	1	2	2	5
22	Asuquo ME et al., 2013 [20]	1	2	2	5
23	Roli MC and Abel O, 2018 [26]	2	2	2	6
24	Adegbidi H et al., 2007 [33]	2	2	2	6
25	Saka B et al., 2020 [21]	2	2	2	6
26	Okafor OC and Onyishi NT, 2020 [7]	2	2	2	6
27	Chidothe IA and Masamba L, 2014 [22]	1	2	2	5

[Table/Fig-5]: Risk of bias assessment score for each of the included study.
*Aggregate score: 3, 4 (low quality); 5, 6 (high quality)

periorbital region of a 25-year-old pregnant woman while the sex and site of occurrence was not given in the second case of ALM. No histological subtype or sex of patient was specified for two studies [18,19]. Asuquo ME et al., reports a single case of nodular melanoma in the right forearm of a 41-year-old male albino patient with associated regional lymphadenopathy [Table/Fig-6] [15].

Study	No. of CM	Sex/Age of albino	Body site	Histological subtype
Kiprono SK et al., 2014 [1]	1	NA	NA	Acral lentiginous
Mabula JB et al., 2012 [18]	1	NA	Limb	NA
Atipo-Tsiba PW et al., 2015 [35]	1	F/25 years	Periorbital	Acral lentiginous
Asuquo ME et al., 2010 [15]	1	M/41 years	Forearm	Nodular
Awe OO and Azeke TA, 2018 [19] and Awe OO et al., 2015 [37]	2	M/26 years	Neck	Nodular

[Table/Fig-6]: Clinico-pathological features of Cutaneous Melanoma (CM) in African albinos
*CM: Cutaneous melanoma; †NA: Not available

DISCUSSION

Cutaneous Melanoma (CM) is ranked the 5th most common malignancy in annual incidence of cancers in the United states with more than 100,000 cases projected to be diagnosed in 2020 [11,40,41]. Though less prevalent than keratinocyte carcinomas, it nevertheless, is responsible for the vast majority of overall skin cancer mortality [8,42]. In general, Africans have lower risk for cutaneous melanocytic and keratinocyte malignancies. While keratinocyte carcinomas and CM account for about 40% of all malignancies in the US whites [43], skin cancers of all types constitute only about 5.5 to 13% of all diagnosed malignancies in African hospitals with CM reported to be the most prevalent or second most prevalent type of skin cancer in the general population of black Africans [2-6,44].

The inherited genetic condition of albinism and its phenotypic manifestation of hypomelanised sun sensitive skin causes a range of actinic skin damage in affected Individuals of which skin cancers are the most hazardous. Various reports [24,25,45] estimate that prevalence of skin cancers in general population of African albinos ranges from 13-23% and that 100% of albinos over 30 years have premalignant lesions [23]. In fact, some historical studies credit skin cancer with decreased life-expectancy of African albinos [46]. But one puzzling epidemiologic feature of skin cancer in African albinos has been the paucity of CM in most reports. While the fact of low incidence of CM in African albinos has been corroborated by many workers over the years, no study, to the best of our knowledge has attempted to establish a prevalence of CM in a substantial sample of African albinos, the largest study sample of albino skin cancer patients in published works being 86 [1,7].

The present systematic review synthesised data from eligible case series of skin cancers in African albinos and attempted to highlight the frequency of CM in all published cases of skin cancer in African albinos. Authors anticipated that aggregating all published cases of skin cancer in African albinos would give a better indication of prevalence of CM in people with this rare genetic inheritance. A very notable feature of skin cancer in African albinos is the propensity for multifocal or multiple primary tumours with an individual patients sometimes presenting histologically different cancer types. This explains why the number of skin cancer lesions authors abstracted (715) which was more than the number of albinos with skin cancer (556). Some studies do not distinguish between multifocal and solitary tumours of similar histology in statistical counts and so the absolute number of skin cancer lesions might have been underreported.

Authors found only six CMs among 715 histologically confirmed skin cancer lesions diagnosed in 556 African albinos even when our review was not limited in time. These cases represent what has been reported for all periods. Eighty-one percent (81%) of the studies in our review recorded no case of CM. Two studies in which pigmented Africans and African albinos were compared pari-passu reported CM in 18% and 19% of the pigmented group and no case of CM in the albinos [7,29]. Thus, the scarce extraction from the literature, in our view is a true reflection and a confirmation of rare incidence rather than under reporting.

Albinism and African albinos present a unique natural model for investigation of UV rays induced cutaneous carcinogenesis. African albinos though progenies of Black Africans, could be considered natural knockouts for melanisation and pertaining to keratinocyte carcinomas, their hypomelanised sun sensitive skin shares epidemiologic similarity with Caucasian skin. Thus, the paucity of CM in African albinos compared with pigmented Africans and Caucasians is a paradox yet to be explained. Caucasians have more than 20 times higher incidence of CM compared with Blacks [47,48] and this greater susceptibility of Caucasians to melanoma has been attributed, in part, to fair skin and ultravoilet radiation [10]. However, the fair skin of albinism seems not to impose any risk of CM on the African albinos who suffer far fewer CM than Caucasians and pigmented Africans. Basic research is needed to unravel the biological underpinning of this epidemiological feature. We speculate that the albino phenotype has some stabilising effect on the melanocyte genome and that the African albino has, in addition to the baseline protection of the African ancestry, some additional shield against CM conferred by his inherited genetic disorder.

There was a prolonged debate about the role of solar UVR in melanomagenesis [49,50]. While solar UVR has been accepted as a critical risk factor for CM in fair-skinned individuals [10], its role

in dark skinned people is not recognised. Melanomas in Blacks commonly occur in the lower limb, a non sun exposed body site and are most commonly of the acral lentiginous subtype [7,42,51]. Of the six CM authors abstracted, two were acral lentiginous, two nodular, while the histologic subtype was unspecified in the rest. The melanomas occurred in sites other than the lower limb and at much younger age.

To the best of our knowledge, this is the first systematic review 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 highlighted the frequency of CM in African albinos. It underscores a consistent paucity of CM in the fair-skinned, hypomelanised African albinos who, otherwise, have propensity for debilitating and multifocal keratinocyte carcinomas. The molecular underpinnings of this epidemiological feature need to be elucidated as it suggests a non contributory role for UV radiation or some inhibitory influence by albino phenotype on melanomagenesis in African albinos.

Limitation(s)

The study does not synthesise a single prevalence figure for CM in the general population of African albinos due to the nature and design of the available individual studies. There is dearth of publications focusing on the subject of skin cancer in African albinos and much of the available studies are generally of weak design: hospital based case series and case reports. These types of studies offer lower level of evidence and carries higher risk of bias than comparative studies. The protocol for the study was not preregistered and this might be considered a limitation also.

CONCLUSION(S)

In conclusion, authors tried to determine the frequency of CM in histologically confirmed skin cancer lesions in African albinos. Only six CM were present in 715 skin cancer lesions. Because of this very low frequency and considering that only a fraction of albinos develop skin cancer, authors extrapolate that the prevalence of CM in the general population of African albinos is infinitesimal. Elucidating the processes inhibiting melanomagenesis in African albino may provide targets for melanoma therapy in the wider population.

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