

Malignant Skin Tumors in Patients with Oculocutaneous Albinism

Makiko Yasumizu¹, Chikako Nishigori², Masakazu Kawaguchi³, Tomoya Takata⁴, Naoki Oiso⁵, Tamio Suzuki³, Ayano Umekoji¹, Daisuke Tsuruta¹ and Kazuyoshi Fukai*¹

¹Department of Dermatology, Graduate School of Medicine, Osaka City University, Osaka, Japan

²Division of Dermatology, Department of Internal Related, Kobe University Graduate School of Medicine, Kobe, Japan

³Department of Dermatology, Faculty of Medicine, Yamagata University, Yamagata, Osaka-Sayama, Japan

⁴Department of Dermatology, Kochi University, Kochi, Japan

⁵Department of Dermatology, Faculty of Medicine, Kinki University, Osaka-Sayama, Japan

*Corresponding author: Kazuyoshi Fukai, Department of Dermatology, Graduate School of Medicine, Osaka City University, Osaka, Japan, Tel: +81-6-6645-3826; Fax: +81-6-6645-3828; E-mail: fukai@msic.med.osaka-cu.ac.jp

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Abstract

Background: Patients with oculocutaneous albinism (OCA) are prone to develop skin cancers.

Aim and Objectives: To analyze reports of skin cancers in albinos published in the English and the Japanese literature in order to prepare guidelines for the successful management of skin cancer in albinos.

Methods and Materials: We searched on PubMed, Web of Knowledge for English literature, and Ichushi-Web for the Japanese literature.

Results: Between 1978 and 2013, 11 malignant melanoma, 4 basal cell carcinoma, and 6 squamous cell carcinoma cases were reported in Japan. The subtypes of the 11 malignant melanomas were nodular in 7 cases, superficial spreading in 3 cases, and metastatic lesions in 1 case. Amelanotic melanomas comprised 7 of the 11 malignant melanoma cases in Japanese patients with OCA. Twenty-five malignant melanoma, 50 basal cell carcinoma, and 151 squamous cell carcinoma cases were reported worldwide in the English literature during the period between 1952 and 2013.

Conclusion: Regular skin monitoring by board-certified dermatologists is required for adult OCA patients.

Keywords: Oculocutaneous albinism; Skin cancer; Melanoma; Basal cell carcinoma; Squamous cell carcinoma

5) database for Japanese language reports; all publications were available at the end of May 2014.

Introduction

Oculocutaneous albinism (OCA) patients are well known to be susceptible to skin cancer. Among 164 northern Tanzanians with OCA, 127 and 69 exhibited actinic cheilitis and actinic keratosis, respectively, and 14 developed squamous cell carcinoma (SCC) [1]. Malignant melanoma (MM) development has been shown to be strongly associated with sun exposure [2]. Recent sequencing analyses revealed that ultraviolet light induces somatic genome alterations that might lead to MM development [3,4].

A guideline for the management of Japanese albinos is now being prepared, in which, the significance of sunscreens will be stressed. However, data about the development of skin cancers in Japanese albinos is insufficient. Therefore, we conducted a survey on the occurrence of skin cancers in OCA patients in both the Japanese and English literatures.

Materials and Methods

We searched the PubMed and Web of Knowledge (version 5.10) databases for English language reports and the Ichushi-Web (version

Results

In the English literature, 25 MM [5-12] (Table 1), 50 BCC [13-17] (Table 2), and 151 SCC [1,12-14] (Table 3) cases were reported between 1952 and 2013. Most of the reported cases were in African subjects, but Caucasians were included and comprised 6 MM cases and 1 BCC case. We found no reported cases of SCC in Caucasian albinos.

In Japan, 11 MM, 4 BCC, and 6 SCC cases were reported (Tables 4, 5) between 1984 and 2013. The 11 reported MM cases included 7 cases of nodular melanoma, 3 cases of superficial spreading melanoma, and 1 case of metastatic lesions. Amelanotic melanomas occurred in 7 cases. No cases of acral lentiginous melanoma were reported, despite this being the most prevalent MM type in Japan. These numbers are depicted in Figure 1; the occurrence of MM in Japanese OCA patients appears to be substantial.

We summarized a case series of malignant skin tumors in non-Asian individuals and in Japanese persons with OCA. In the Japanese OCA patients, BCCs and SCCs were not common, whereas the incidence of MM was substantial.

Author(s)	Year	No. of Cases	Ethnicity	Ref. No.
Bhende	1952	1	Indian	47
Young	1957	1	NR	48
Leonardi	1958	1	NR	49
Higginson	1960	1	African	41
Kennedy	1963	1	NR	5
Oettle	1963	1	African	50
Duron	1965	1	NR	59
Garrington	1967	1	Caucasian	51
Oluwasanmi	1969	1	NR	53
Halama	1974	1	NR	6
Alpert	1978	1	Caucasian	7
Stoll	1981	1	African	54
Scott	1982	1	NR	8
Wood	1982	1	NR	52
Pehamberger	1984	1	Caucasian	55
Luande	1985	1	NR	9
Kinnear	1985	1	NR	56
Levine	1992	1	Caucasian	10
Ihn	1993	1	Asian	11
Casswell	1989	1	Caucasian	57
Schulze	1989	1	Caucasian	58
		1	Hispanic	
Perry	2001	1	NR	12
Asuquo	2009	1	African	44
Mabula	2012	1	African	46

Note: The report by Ihn H et al. [11] describes a Japanese patient who is likely the same patient in the other report by Ihn H et al. [21].

Table 1: Twenty-five cases of malignant melanoma with oculocutaneous albinism in the English literature.

Among OCA patients, BCC and/or SCC cases were generally reported in Africans, likely due to intense exposure to ultraviolet light, insufficient medical access, and the non-prevalence of sunscreen application. We initially imagined that the numbers of BCC and/or SCC cases would be much higher among Japanese OCA patients because the incidence rates of BCC, SCC, and MM among skin cancer cases in the general Japanese population are 44%, 28%, and 20%, respectively [18-34]. However, we only identified 4 reported BCC cases and 6 reported SCC cases over a period of approximately 3 decades. This might be caused by 3 factors: first, the existence of unreported BCC and SCC cases in OCA patients; second, the under diagnosis of OCA because of skin and hair color compensation during adulthood; and third, the relative rarity of such cancer cases.

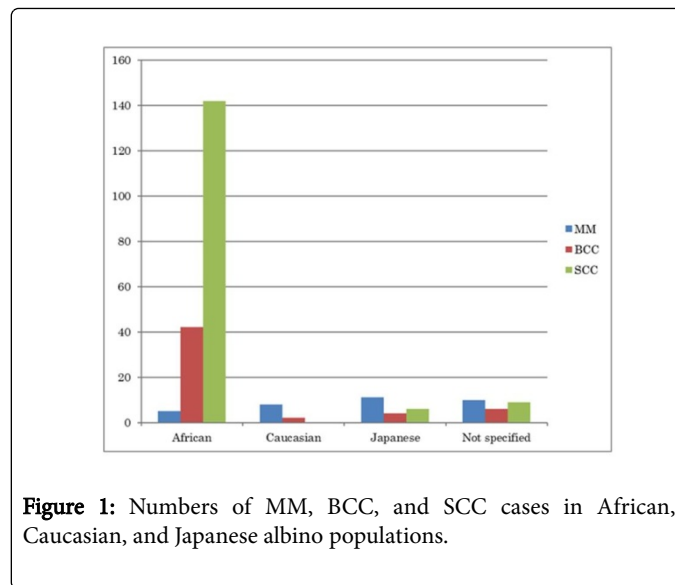


Figure 1: Numbers of MM, BCC, and SCC cases in African, Caucasian, and Japanese albino populations.

Discussion

In western Africa, most OCA patients are classified as having OCA type 2 (OCA2), which is caused by the same intragenic P gene deletion mutation as the founder effect [35,36]. Japanese patients with mild OCA2 are frequently undiagnosed and are recognized as having noticeably pale skin and brown hair during infancy and normal pale skin and dark brown hair as adults [37]. We recently identified a polymorphism in the P gene, A481T, that is associated with skin color in the Japanese population.

Author(s)	Year	No. of cases	Ethnicity	Ref. No.
Cohen et al.	1952	1	African	40
Higginson et al.	1960	2	African	41
Oluwasanmi et al.	1969	6	NR	53
Itayemi et al.	1979	3	African	42
Kromberg et al.	1989	2	African	39
Yakubu et al.	1993	3	African	14
Colebunders et al.	2004	1	African	15
Asuquo et al.	2007	5	African	16
Adegbidi et al.	2007	4	African	43
Asuquo et al.	2009	1	African	44
Opara et al.	2010	5	African	45
Baskurt et al.	2011	2	Caucasian	17
Mabula et al.	2012	15	African	46

Table 2: Fifty cases of basal cell carcinoma with oculocutaneous albinism in the English literature.

Furthermore, we recently determined a relationship between a decrease-of-function polymorphism in the P gene and the occurrence of SCC, including actinic keratosis. Therefore, it is quite conceivable

that many cases of SCC and BCC among Japanese albinos are unreported.

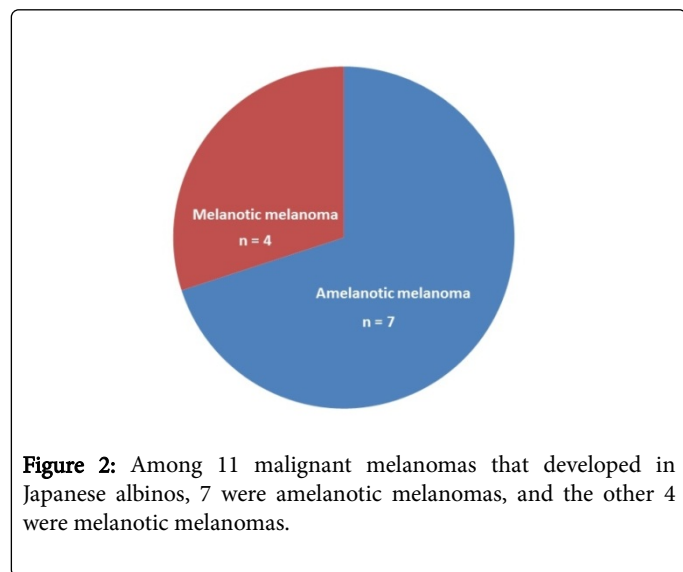


Figure 2: Among 11 malignant melanomas that developed in Japanese albinos, 7 were amelanotic melanomas, and the other 4 were melanotic melanomas.

In this study, we identified a trend in which the incidence of MM was higher in Japanese OCA patients than in African or Caucasian patients. The number of diagnosed Japanese OCA patients is approximately 5000, and MM occurred in 11 of these patients during a 35-year period. Therefore, the annual ratio of MM development in OCA patients is estimated to be approximately 1/16,000, whereas that in the general population is estimated to be 1/100,000 [38]. In fact, we recently identified an association between another decrease-of-function polymorphism in the P gene and the occurrence of MM [39-60].

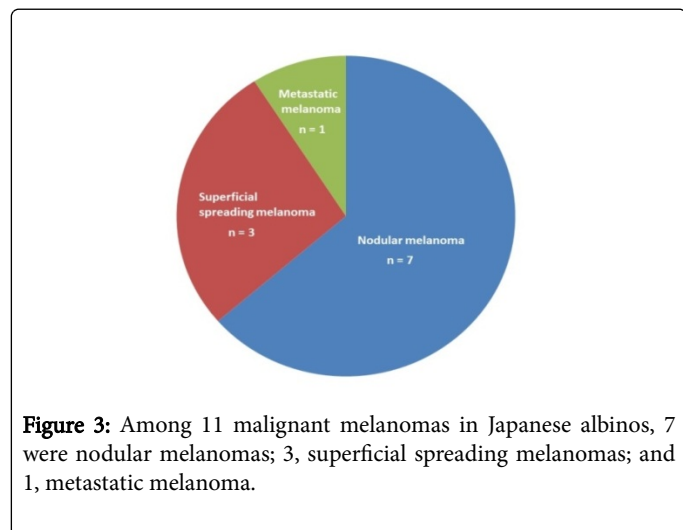


Figure 3: Among 11 malignant melanomas in Japanese albinos, 7 were nodular melanomas; 3, superficial spreading melanomas; and 1, metastatic melanoma.

In this report, it was first suggested that the incidence of amelanotic melanomas in Japanese albinos was 64% (7 out of 11; Figure 2). It is conceivable that amelanotic melanomas develop in patients with severe forms of albinism, for example, those with OCA type 1A. However, reports about the development of skin cancers in albinos usually do not have information about genetic analysis. The diagnosis of amelanotic melanoma is generally difficult via macroscopic examination. Therefore, any small skin tumor occurring in albinos should be carefully examined by board-certified dermatologists.

Author(s)	Year	No. of cases	Ethnicity	Ref. No.
Cohen et al.	1952	1	African	40
Higginson et al.	1960	2	African	41
Oluwasanmi et al.	1969	6	NR	53
Itayemi et al.	1979	3	African	42
Kromberg et al.	1989	2	African	39
Yakubu et al.	1993	3	African	14
Colebunders et al.	2004	1	African	15
Asuquo et al.	2007	5	African	16
Adegbidi et al.	2007	4	African	43
Asuquo et al.	2009	1	African	44
Opara et al.	2010	5	African	45
Baskurt et al.	2011	2	Caucasian	17
Mabula et al.	2012	15	African	46

Table 3: One-hundred fifty-one cases of squamous cell carcinoma with oculocutaneous albinism in the English literature.

Author	Year	MM	BCC	SCC	No. of Cases	Ref. No.
Yoshioka J	1978	+	-	-	1	18
Ikeda S	1981	+	-	-	1	19
Nagao H	1991	-	+	+	2	20
Ihn H	1992	+	-	-	1	21
Inaba Y	1992	+	-	-	1	22
Yuasa T	1996	+	-	-	1	23
Hirose I	1999	-	+	+	1	24
Hozumi H	2002	-	+	+	1	25
Sakurane J	2003	+	-	-	1	26
Sakai H	2005	+	-	-	1	27
Obata M	2005	-	-	+	1	28
Tsuji T	2011	+	+	Bowen	1	29
Inazuka Y	2012	+	-	-	1	30
Minagawa T	2012	-	-	+	1	31
Fukai T	2013	+	-	-	1	32
Aizawa A	2013	+	-	-	1	33

Table 4: Malignant skin tumors in patients with oculocutaneous albinism in the Japanese literature.

According to statistical reports of MM in Japan, the frequencies of acral lentiginous melanoma (ALM), superficial spreading melanoma (SSM), nodular melanoma (NM), and lentigo maligna melanoma

(LMM) are 44%, 19%, 14%, and 8%, respectively.³⁸ However, the frequencies of the above MM types among Japanese albinos were 0%, 30%, 70%, and 0%, respectively.

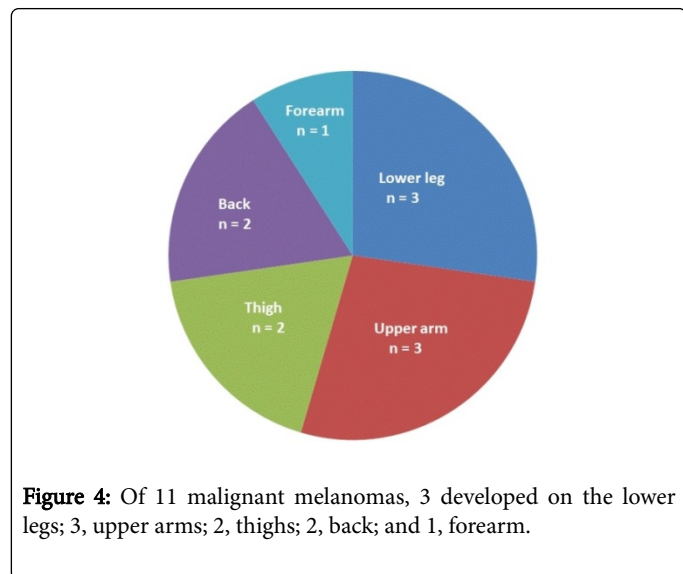


Figure 4: Of 11 malignant melanomas, 3 developed on the lower legs; 3, upper arms; 2, thighs; 2, back; and 1, forearm.

It is noteworthy that ALM, the most common MM type in the general Japanese population, has not been reported. The frequency of SSM, which is thought to be associated with intermittent severe sun-damage, was higher among albino MMs, whereas the frequency of LMM, which is associated with chronic sun-exposure, was not observed. The most striking finding was that as many as 70% of albino MM cases were classified as NMs (Figure3). The cause of the high prevalence of NM among Japanese albinos might also be related to intermittent severe sun-damage and the consequent oxidative stress; however, this remains to be examined in the future.

Author	Year	Amelanotic	Location	Type	Sex	Age	Ref. No.
Yoshioka	1978	No	Lower leg	NM	F	32	18
Ikeda	1981	No	Lower leg	NM	F	30	19
Ihn	1992	No	Forearm	SSM	M	58	21
Inaba	1992	Yes	Back	NM	F	45	22
Yuasa	1996	Yes	Upper arm	NM	M	64	23
Sakurane	2003	Yes	Upper arm	NM	F	68	26
Sakai	2005	Yes	Lower leg	SSM	F	70	27
Tsuji	2011	No	Back	SSM	F	71	29
Inatsuka	2012	Yes	Upper arm	Meta	F	66	30
Fukai	2013	Yes	Thigh	NM	M	44	32
Aizawa	203	Yes	Thigh	NM	F	56	33

Table 5: Malignant melanoma in Japanese patients with oculocutaneous albinism.

It is important to note that MM occurred on the upper arms in 3 Japanese OCA patients and on the thighs in 2 patients because these regions are considered somewhat “blind” areas when applying

sunscreen agents (Figure 4). Patients with OCA are advised to apply sunscreen agents to all sun-exposed areas, including the upper arms and thighs. Gene mutation analyses were not performed in any of the reports of albino MMs. The accumulation of such data is certain to be useful with respect to sun-protection protocols for albinos.

References

- Lookingbill DP, Lookingbill GL, Leppard B (1995) Actinic damage and skin cancer in albinos in northern Tanzania: findings in 164 patients enrolled in an outreach skin care program. *J Am Acad Dermatol* 32: 653-658.
- Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, et al. (2005) Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *Eur J Cancer* 41: 45-60.
- Curtin JA, Fridlyand J, Kageshita T, Patel HN, Busam KJ, et al. (2005) Distinct sets of genetic alterations in melanoma. *N Engl J Med* 353: 2135-2147.
- Pleasant ED, Cheetham RK, Stephens PJ, McBride DJ, Humphray SJ, et al. (2010) A comprehensive catalogue of somatic mutations from a human cancer genome. *Nature* 463: 191-196.
- Kennedy BJ, Zelickson AS (1963) Melanoma in an Albino. *JAMA* 186: 839-841.
- Halama J, Szeigole M (1974) Casuistics of malignant melanoma in albinos. *Strahlenther Onkol* 147: 136-138.
- Alpert LI, Damjanov I (1978) Malignant melanoma in an albino: diagnosis supported by ultrastructure. *Mt Sinai J Med* 45: 447-450.
- Scott MJ Jr, Giacobetti R, Zuger C (1982) Malignant melanoma with oculocutaneous albinism. *J Am Acad Dermatol* 7: 684-685.
- Luande J, Henschke CI, Mohammed N (1985) The Tanzanian human albino skin. *Natural history. Cancer* 55: 1823-1828.
- Levine EA, Ronan SG, Shirali SS, Das Gupta TK (1992) Malignant melanoma in a child with oculocutaneous albinism. *J Surg Oncol* 51: 138-142.
- Ihn H, Nakamura K, Abe M, Furue M, Takehara K, et al. (1993) Amelanotic metastatic melanoma in a patient with oculocutaneous albinism. *J Am Acad Dermatol* 28: 895-900.
- Perry PK, Silverberg NB (2001) Cutaneous malignancy in albinism. *Cutis* 67: 427-430.
- Datubo-Brown DD1 (1991) Primary malignant skin tumors in Nigerians. *J Natl Med Assoc* 83: 345-348.
- Yakubu A, Mabogunje OA (1993) Skin cancer in African albinos. *Acta Oncol* 32: 621-622.
- Colebunders R1, Bottieau E, Van den Brande J, Colpaert C, Van Marck E (2004) Merkel cell carcinoma and multiple basal cell carcinoma in an African albino woman with HIV infection. *HIV Med* 5: 452-454.
- Asuquo ME, Agweye P, Ugare G, Ebughe G (2007) Basal cell carcinoma in five albino Africans from the south-eastern equatorial rain forest of Nigeria. *Int J Dermatol* 46: 754-756.
- BaÅYkurt H, Celik E, YeÅYiladali G, Tercan M (2011) Importance of hereditary factors in synchronous development of Basal cell carcinoma in two albino brothers: case report. *Ann Plast Surg* 66: 640-642.
- Yoshioka J, Kitamura W (1978) Akuseishuyou wo gappeisita oculocutaneous albinism no 1 rei. *Rinshohifuka* 32: 355-364.
- Ikeda S, Makita A, Tajima K (1981) Zenshinsei hakuhiou (Shirako) ni mirareta kokusi oyobi akusei kokushokushu. *Iyakunomon* 21: 81-85
- Nagao H, Arakawa K, Arata J (1991) Hifu-akuseishuyo wo shoujita zenshinsei-hakuhiou no 2 rei. *Skin cancer* 6: 90-94.
- Ihn H, Nakamura K, Abe M, et al (1992) Tasai-na gappeishou wo tomonatta gan-hifu-hakuhiou-kanja ni mirareta akusei-kokushokushu no 1 rei. *Skin cancer* 7: 158-162.
- Inaba Y, Mihara I (1992) Gan-hifuhakuhiou ni hasseisita akusei-kokushokushu. *Rinshohifuka* 46: 129-135.

23. Yuasa T, et al. (1996) Hakushihou ni gappeisita akusei-kokushokushu. *Rinshouhifuka* 50: 926-929.
24. Hirose I, Akaba N, Shinokawa Y, Kaji T (1999) Zenshinsei-hakuhishou ni shoujita tahatsusei-hifu-akuseishuyu-rei. *Nihon-keiseigeka-gakkai-zasshi* 19: 711-712.
25. Hozumi H, et al. (2002) Chirosinaze-insekata-hakuhishoukanja no migikasi ni shoujita henpeijouhi-gan to kiteisaibou-gan. *Nishinihonhifuka* 64: 443-436.
26. Sakurane J, et al. (2003) Albinism ni tomonatta amelanotic melanoma no 1 rei. *Nihon-hifukagakkai-zasshi* 113: 197-198.
27. Sakai H, Shirai Y, Terao M, Shrabe H (2005) Tahatsusei-nikkoukakukashou wo yusuru hakuhishoukanja ni shoujita akuseikokushokushu. *Hifunokagaku* 4: 325-326.
28. Obata M (2005) Kourei-hakushishou kannja ni okeru sigaisen hatsugan no 1 rei. *Nihonhifukagakkai-zasshi* 115: 907-909.
29. Tsuji T, et al. (2011) Hifu-akuseishuyou wo tahatsu-shita gan-hifu-hakuhishou no 1 rei. *Nishinihonhifuka* 73: 319-320.
30. Inatsuka Y, Nagata K, Hatano Y, Okayama N (2012) Hakuhishou ni shoujita akuseikokushokushu no 1 rei. *Nishinihonhifuka* 74: 100-102.
31. Minagawa T, Kaneko T, Matsuzaki Y, Nakano H, Sawamura D, et al. (2012) Yukyokusaibougan to Bowen-byou wo tomonatta gan-hifu-hakuhishou no 1 rei. *Nihonhifukagakkai-zasshi* 122: 637-638.
32. Fukai T, Hirasawa Y, Hasegawa T, Ikeda S (2013) Gan-hifu-hakuhishoukanja ni hasshou sita akuseikokushokushu no 1 rei. *Nihonrinshouhifukaikaizasshi* 30: 238-239.
33. Aizawa A, Asano Y, Matsuyama A, et al (2013) Gan-hifu-hakuhishoukanja ni hasseisita akuseikokushokushu no 1 rei. *Nihonhifukagakkai-zasshi* 123: 163-164.
34. Ishihara K (2007) Akusei shuyou no toukei kako. *Skin Cancer* 22: 209-216.
35. Durham-Pierre D, Gardner JM, Nakatsu Y, King RA, Francke U, et al. (1994) African origin of an intragenic deletion of the human P gene in tyrosinase positive oculocutaneous albinism. *Nat Genet* 7: 176-179.
36. Spritz RA, Fukai K, Holmes SA, Luande J (1995) Frequent intragenic deletion of the P gene in Tanzanian patients with type II oculocutaneous albinism (OCA2). *Am J Hum Genet* 56: 1320-1323.
37. Abe Y, Tamiya G, Nakamura T, Hozumi Y, Suzuki T (2013) Association of melanogenesis genes with skin color variation among Japanese females. *J Dermatol Sci* 69: 167-172.
38. Fujisawa Y, Otsuka E, Yamamoto A, Yamazaki N, Saida T, et al. (2012) Statistics of melanoma in Japan: Analysis of a 2006-2007 nation-wide survey and a 2005-2010 follow-up survey. *Skin Cancer* 27: 195-204.
39. Kromberg JG, Castle D, Zwane EM, Jenkins T (1989) Albinism and skin cancer in Southern Africa. *Clin Genet* 36: 43-52.
40. Cohen L, Shapiro MP, Keen P, Henning AJ (1952) Malignant disease in the Transvaal. I. Cancer of the skin; first statistical report from the Radiation Therapy Department of the Johannesburg group of hospitals. *S Afr Med J* 26: 932-939.
41. Higginson J, Oettle AG (1960) Cancer incidence in the Bantu and "Cape Colored" races of South Africa: report of a cancer survey in the Transvaal (1953-55). *J Natl Cancer Inst* 24: 589-671.
42. Itayemi SO, Abioye AA, Ogan O, Daramola JO, Oluwasanmi JO (1979) Aggressive basal cell carcinoma in Nigerians. *Br J Dermatol* 101: 465-468.
43. Adegbi H, Yedomon H, Atadokpede F, Bailey-Pognon MC, do Ango-Padonou F (2007) Skin cancers at the National University Hospital of Cotonou from 1985 to 2004. *Int J Dermatol* 46 Suppl 1: 26-29.
44. Asuquo ME, Ngim O, Ebughe G, Bassey EE (2009) Skin cancers amongst four Nigerian albinos. *Int J Dermatol* 48: 636-638.
45. Opara KO, Jiburum BC (2010) Skin cancers in albinos in a teaching Hospital in eastern Nigeria - presentation and challenges of care. *World J Surg Oncol* 8: 73.
46. Mabula JB, Chalya PL, Mchembe MD, Jaka H, Giiti G, et al. (2012) Skin cancers among Albinos at a University teaching hospital in Northwestern Tanzania: a retrospective review of 64 cases. *BMC Dermatol* 12: 5.
47. Bhende YM (1952) Malignant amelanotic melanoma of skin in albino. *Indian J Med Sci* 6: 755-759.
48. Young TE (1957) Malignant melanoma in an albino; report of a case. *AMA Arch Pathol* 64: 186-191.
49. Leonardi R, Grasso S (1958) [Melanoblastoma in albino; histological findings]. *Minerva Dermatol* 33: 24-26.
50. Oettle AG (1963) "Skin cancer in Africa". Conference on Biology of Cutaneous Cancer.
51. Garrington GE, Scofield HH, Cornyn J, Lacy GR Jr (1967) Intraoral malignant melanoma in a human albino. *Oral Surg Oral Med Oral Pathol* 24: 224-230.
52. Wood C, Graham D, Willsen J, Strefling A (1982) Albinism and amelanotic melanoma: occurrence in a child with positive test results for tyrosinase. *Arch Dermatol* 118: 283-284.
53. Oluwasanmi JO, Williams AO, Alli AF (1969) Superficial cancer in Nigeria. *Br J Cancer* 23: 714-728.
54. Stoll DB, Ruschak P, Kauh Y, Martin J, Luscombe H (1981) Lentigo maligna in a woman with oculocutaneous albinism. *Arch Dermatol* 117: 360-361.
55. Pehamberger H, Hönigsmann H, Wolff K (1984) Dysplastic nevus syndrome with multiple primary amelanotic melanomas in oculocutaneous albinism. *J Am Acad Dermatol* 11: 731-735.
56. Kinnear PE, Tuddenham EG (1985) Albinism with haemorrhagic diathesis: Hermansky-Pudlak syndrome. *Br J Ophthalmol* 69: 904-908.
57. Casswell AG, McCartney AC, Hungerford JL (1989) Choroidal malignant melanoma in an albino. *Br J Ophthalmol* 73: 840-845.
58. Schulze KE, Rapini RP, Duvic M (1989) Malignant melanoma in oculocutaneous albinism. *Arch Dermatol* 125: 1583-1586.
59. Durón RA (1965) [Malignant melanoma in albinos]. *Rev Med Hondur* 33: 149-156.
60. Yoshizawa J, Abe Y, Oiso N, Fukai K, Hozumi Y, et al. (2014) Variants in melanogenesis-related genes associate with skin cancer risk among Japanese populations. *J Dermatol* 41: 296-302.