Original Article

Malignant transformation of choroidal nevus according to race in 3334 consecutive patients

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Purpose: To evaluate choroidal nevus demographics, clinical features, imaging features, and the rate of transformation into melanoma by race. **Methods:** In this observational case series, There were 3334 participants (3806 choroidal nevi) at a single tertiary-referral center evaluated between January 2, 2007, and August 7, 2017. Retrospective chart and multimodal imaging review was performed. Patient demographics, tumor features, and outcomes were compared between different races using Chi-squared test, Fisher's exact test, *t*-test, and analysis of variance. The main outcome measure was clinical features of choroidal nevus and the rate of transformation into melanoma by race. **Results:** Of the 3334 patients, there were Caucasian (n = 3167, 95%) and non-Caucasian (n = 167, 5%). The non-Caucasian races included African-American (n = 27, <1%), Hispanic (n = 38, <1%), Asian (n = 15, <1%), Asian Indian (n = 2, <1%), Middle Eastern (n = 4, <1%), and unknown (n = 83, 3%). By comparison (Caucasian versus vs. non-Caucasian), there were differences in the mean age at presentation (61 vs. 56 years, $P < 0.0001$), female sex (63% vs. 52%, $P < 0.01$), dysplastic nevus syndrome (<1% vs. 1%, $P < 0.01$), and previous cutaneous melanoma (5% vs. 1%, $P = 0.03$). A comparison of tumor features revealed differences in presence of symptoms (12% vs. 20%, $P < 0.01$) and ≥3 nevi per eye (3% vs. <1%, $P = 0.04$). A comparison of imaging features showed no differences. A comparison of outcome of nevus transformation into melanoma revealed no difference (2% vs. 3%, $P = 0.29$). However, of those nevi exhibiting growth to melanoma, ultrasonographic hollowness was less frequent in Caucasians (29% vs. 67%, $P = 0.04$). **Conclusion:** In this analysis of 3334 patients with choroidal nevus, we found differences in the mean age of presentation, sex, dysplastic nevus syndrome, previous cutaneous melanoma, presence of symptoms, and multiplicity of nevus per eye by race. However, there was no difference in the rate of transformation into melanoma by race.

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_1217_19

Quick Response Code:

Key words: Choroid, eye, melanoma, nevus, race, transformation

Choroidal nevus is a common intraocular tumor with estimated prevalence of 0.2%–30%.[1-5] Choroidal nevus is usually found incidentally on ophthalmoscopy and generally remains stable over time.[2,6-8] However, there is a risk for vision loss if the nevus is located under the foveola, and, more importantly, there is a risk for malignant transformation.[4,6,9] Clinical and imaging features that predict risk for nevus transformation to melanoma can be remembered by the mnemonic "To Find Small Ocular Melanoma Doing IMaging" (TFSOM-DIM), representing Thickness >2 mm (by ultrasonography), Fluid subretinal (by optical coherence tomography (OCT), Symptoms vision loss, Orange pigment (by autofluoresence), Melanoma hollow (by ultrasonography), and DIaMeter >5 mm.[10] The 5-year estimates for the nevus growth into melanoma have been found at 1% with zero risk factors, 11% with one factor, 22% with two factors, and 34% or greater with three or more factors.[10,11]

Epidemiological studies have previously examined the prevalence of choroidal nevus by race. In the United States, the National Health and Nutrition Examination Survey (NHANES) reported highest prevalence of choroidal nevus in Whites (5.6%), compared with Blacks (0.6%), Hispanics (2.7%), and others (2.1%).[1] This racial predilection has been confirmed by other studies, which additionally found no difference in nevus size, shape, color, location, or presence of drusen by race.[3,5] However, these studies were based on the analysis of fundus photographs, which can underrepresent the entire fundus (only providing 45° view, often centered in the fovea or optic disc, missing the ocular equatorial region and periphery) and can misrepresent the nevus features [camera over- or underexposure can alter nevus appearance (size, color, shape), and hide drusen]. Therefore, to best assess for race-based differences in the aforementioned qualities, a large-scale, well-documented cohort would be ideal. Herein, we evaluate a large cohort of 3334 patients with choroidal nevus from a single center and comparatively study the presenting features and outcomes by race, including the rate of malignant transformation.

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Received: 28-Jun-2019 Revision: 13-Aug-2019
Accepted: 12-Sep-2019 Published: 22-Nov-2019

Cite this article as: Marous CL, Shields CL, Yu MD, Dalvin LA, Ancona-Lezama D, Shields JA. Malignant transformation of choroidal nevus according to race in 3334 consecutive patients. Indian J Ophthalmol 2019;67:2035-42.

Methods

Study population

A retrospective medical record review was performed on all patients with the clinical diagnosis of choroidal nevus managed at the study site between January 2, 2007, and August 7, 2017. Institutional review board approval was obtained for this retrospective study. All patients were examined by one of the senior authors.

Primary variable: Race

The patients were classified into Caucasian or non-Caucasian based on their personal identification. The latter was further subdivided into African-American, Hispanic, Asian, Asian Indian, or Middle Eastern. A classification of unknown/other was used if race was not recorded or did not belong to the aforementioned categories.

Secondary variables: Ophthalmic

All participants were examined using modern techniques of indirect ophthalmoscopy of the entire fundus and high-resolution magnification ophthalmoscopy (Goldman or 60-diopter lens with slit-lamp biomicroscopy) to clinically evaluate the nevus and associated tumor features. Details of each choroidal nevus were recorded on large fundus drawings in all patients.

The following clinical data were collected at initial presentation including age at diagnosis, sex, extraocular disease (dysplastic nevus syndrome, skin melanoma, neurofibromatosis), ocular history (ocular melanocytosis, uveal melanoma), and best-corrected visual acuity using Snellen charts. The best-corrected visual acuity was divided into three categories, including 20/20–20/40 (considered functionally good vision), 20/50–20/100 (considered functionally intermediate vision), and 20/200 or worse (considered legally blind). The clinical features included involved eye, symptoms (decreased visual acuity, flashes or floaters, visual field defect, lack of symptoms), the number of nevi per patient and per eye, nevus location by epicenter quadrant (macula, superior, temporal, inferior, nasal), epicenter anteroposterior location (macula, macula to equator, or equator to ora serrata), the distance of tumor margin to the optic disc (in mm) and foveola (mm), tumor largest basal diameter (mm), and thickness (mm) by ultrasonography, the degree of pigmentation (pigmented, nonpigmented, or mixed), and presence of a halo. If an eye had more than one nevus, all nevi were included in the growth analysis but demographics were reported per unique patient, and ocular history and visual acuity analysis were reported per unique eye. The imaging features were gathered on OCT, fundus autofluorescence (FAF), and ultrasonography. Using OCT, the features included subretinal fluid (SRF) (overlying the nevus, <3 mm from nevus, 3–6 mm from nevus, or >6 mm from nevus), drusen, retinal edema, retinal pigment epithelial (RPE) alterations (atrophy, hyperplasia, fibrous metaplasia, detachment), retinal invasion, choroidal neovascular membrane (CNV), surface configuration (dome, lumpy bumpy, excavated, flat), and location in the choroid (inner, outer, full thickness). Using FAF, the features included presence of orange pigment and RPE trough. Using ultrasonography, the features included nevus configuration (flat or dome) and echogenicity (hollow or solid).

The outcomes included growth with or without transformation to melanoma, overall growth (mm) (basal diameter and thickness), growth rate (mm/year) (basal diameter and thickness), OCT showing an increase in SRF or increase in drusen, FAF showing an increase in orange pigment, and ultrasonography showing an increase in acoustic hollowness.

Data analysis

A series of analyses were performed for comparison of demographic, clinical, and imaging features per race. The Caucasian group was compared with the non-Caucasian racial groups (African-American, Hispanic, Asian, Asian Indian, Middle Eastern, and unknown) using Chi-squared test, Fisher's exact test, *t*-test, and analysis of variance, as appropriate. A *P* value <0.05 was considered statistically significant.

Results

Of the 3334 patients, the race included Caucasian ($n = 3167$, 95%) and non-Caucasian ($n = 167$, 5%). The non-Caucasian races included African-American ($n = 27$, <1%), Hispanic ($n = 38$, <1%), Asian ($n = 15$, <1%), Asian Indian ($n = 2$, <1%), Middle Eastern ($n = 4$, <1%), and unknown ($n = 83$, 3%).

A comparative analysis (Caucasian vs. non-Caucasian) of the demographics is listed in Table 1. The Caucasian patients had older mean age at presentation (61 vs. 56 years, $P < 0.001$), greater frequency of female sex (62% vs. 52%, $P < 0.01$), lower frequency of dysplastic nevus syndrome (<1% vs. 1%, $P < 0.01$), and greater frequency of prior skin melanoma (5% vs. 1%, $P = 0.03$). Specific racial subset analysis (Caucasian vs. specific race) revealed younger mean age at presentation for African-American (61 years vs. 52 years, $P = 0.003$), Hispanic (61 years vs. 56 years, $P = 0.04$), and Asian (61 years vs. 45 years, $P = 0.003$) race; greater frequency of dysplastic nevus syndrome in Hispanic (<1% vs. 3%, $P < 0.01$); greater frequency of ocular melanocytosis in Hispanic (1% vs. 5%, $P = 0.02$) and Asian Indian (<1% vs. 50%, $P < 0.01$); and better visual acuity in Asian Indian (≤20/200 2% vs. 0%, $P = 0.03$) race.

A comparative analysis (Caucasian vs. non-Caucasian) of the clinical features is listed in Table 2. The Caucasians had more frequent bilateral eye involvement (8% vs. 4%, $P = 0.04$), lower frequency of symptoms (12% vs. 19%, $P < 0.01$), greater number of nevi per patient (1.2 vs. 1.1, $P < 0.01$), greater number of nevi per eye (1.1 vs. 1.1, $P < 0.01$), greater frequency of ≥3 nevi per eye (3% vs. <1%, $P = 0.04$), and smaller nevus thickness (1.5 vs. 1.6, $P = 0.03$). Specific racial subset analysis (Caucasian vs. specific race) revealed greater frequency of symptoms in Hispanic (12% vs. 24%, $P < 0.01$) and Asian Indian (12% vs. 100%, $P < 0.01$) race; greater mean number of nevi per patient in Middle Eastern (1 vs. 2, $P = 0.02$); greater frequency of quadrantic location of macula in Hispanic (27% vs. 37%, $P = 0.01$) and superior in Asian Indian (21% vs. 100%, $P < 0.01$); and greater frequency of anteroposterior location of macula in Hispanic (27% vs. 42%, $P = 0.04$) and macula to equator in Asian (61% vs. 46%, $P < 0.01$) race.

A comparative analysis of nevus imaging features is listed in Table 3. There were no significant differences in comparison of Caucasian versus non-Caucasian. Specific racial subset analysis (Caucasian vs. specific race) revealed greater frequency of nevus location in the inner choroid in Hispanic (23% vs. 39%, $P < 0.01$) and full-thickness choroid in Middle Eastern

Table 1: Choroidal nevus transformation into melanoma in 3806 cases using multimodal imaging (demographics per race)

Demographics	Caucasian *n*=3167 (%)	African-American *n*=27 (%)	Caucasian vs. African-American *P*	Hispanic *n*=38 (%)	Caucasian vs. Hispanic *P*	Asian *n*=13 (%)	Caucasian vs. Asian *P*	Asian Indian *n*=2 (%)	Caucasian vs. Asian Indian *P*	Middle Eastern *n*=4 (%)	Caucasian vs. Middle Eastern *P*	Unknown/ Others *n*=83 (%)	Non-Caucasian *n*=167 (%)	Caucasian vs. non-Caucasian *P*	Total *n*=3334 (%)
Age, mean [median, (range) years]	61 [63, (0-102)]	52 [54 (2-73)]	**0.003**	56 [59 (10-94)]	**0.04**	45 [42 (14-74)]	**0.003**	52 [52 (33-71)]	0.44	63 [61 (49-82)]	0.81	57 [58 (18-93)]	56 [57 (2-94]	**<0.001**	61 [63 (0-102]
Sex															
Male	1185 (37)	9 (33)	0.66	20 (53)	0.05	7 (54)	0.22	2 (100)	0.07	3 (75)	0.12	37 (45)	78 (48)	**<0.01**	1263 (38)
Female	1982 (63)	18 (67)		18 (47)		6 (46)		0 (0)		1 (25)		43 (52)	86 (52)		2068 (62)
Extraocular disease															
Dysplastic nevus syndrome	3 (<1)	0 (0)	0.86	1 (3)	**<0.01**	0 (0)	0.92	0 (0)	1	0 (0)	1	1 (2)	2 (1)	**<0.01**	5 (<1)
Skin melanoma	154 (5)	0 (0)	0.24	0 (0)	0.16	0 (0)	0.42	0 (0)	0.75	0 (0)	0.65	0 (0)	2 (1)	**0.03**	156 (5)
Neurofibromatosis	4 (<1)	0 (0)	0.86	0 (0)	0.82	0 (0)	0.89	0 (0)	1	0 (0)	0.92	0 (0)	0 (0)	0.65	4 (<1)
Ocular history															
Ocular melanocytosis	38 (1)	0 (0)	0.57	2 (5)	**0.02**	0 (0)	0.69	1 (50)	**<0.01**	0 (0)	0.82	0 (0)	3 (2)	0.50	41 (1)
Uveal melanoma	93 (3)	1 (4)	0.47	1 (3)	0.56	1 (8)	0.16	0 (0)	0.81	0 (0)	0.73	5 (8)	7 (4)	0.21	100 (3)
Fellow eye	68 (2)	1 (4)		1 (3)		1 (8)		0 (0)		0 (0)		4 (5)	6 (4)		74 (2)
Same eye	25 (<1)	0 (0)		0 (0)		0 (0)		0 (0)		0 (0)		1 (2)	1 (1)		26 (<1)
Visual acuity*	*n*=3399	*n*=28		*n*=39		*n*=13		*n*=2		*n*=5		*n*=86	*n*=173		*n*=3572
20/20-20/40	3064 (90)	26 (92)	0.32	32 (82)	0.07	13 (100)	0.23	1 (50)	**0.03**	4 (80)	0.29	75 (82)	151 (87)	0.21	3215 (90)
20/50-20/100	266 (8)	1 (4)		6 (15)		0 (0)		1 (50)		1 (20)		8 (12)	17 (10)		283 (8)
20/200 or worse	69 (2)	1 (4)		1 (3)		0 (0)		0 (0)		0 (0)		3 (6)	5 (3)		74 (2)

*Data are collected per unique patient except visual acuity, which is collected per unique eye, Bolded values are statistically significant

Table 2: Choroidal nevus transformation into melanoma in 3806 cases using multimodal imaging (tumor features per race)

Clinical features	Caucasian *n*=3622 (%)	African-American *n*=29 (%)	Caucasian vs. African-American *P*	Hispanic *n*=41 (%)	Caucasian vs. Hispanic *P*	Asian *n*=13 (%)	Caucasian vs. Asian *P*	Asian Indian *n*=2 (%)	Caucasian vs. Asian Indian *P*	Middle Eastern *n*=7 (%)	Caucasian vs. Middle Eastern *P*	Unknown/ Others *n*=92 (%)	Non-Caucasian *n*=184 (%)	Caucasian vs. non-Caucasian *P*	Total *n*=3806 (%)
Involved eye*	3167	27		38		13		2		4		83	167		3334
Right	1531 (48)	13 (48)	0.41	18 (47)	0.21	9 (69)	0.10	2 (100)	0.14	1 (25)	**<0.01**	44 (53)	87 (52)	**0.04**	1618 (49)
Left	1392 (44)	13 (48)		19 (50)		4 (31)		0 (0)		1 (25)		37 (42)	74 (44)		1466 (44)
Both	244 (8)	1 (4)		1 (3)		0 (0)		0 (0)		2 (50)		2 (5)	6 (4)		250 (7)
Symptoms															
Decreased visual acuity	208 (6)	3 (10)	0.23	5 (12)	**<0.01**	0 (0)	0.29	1 (50)	**<0.01**	1 (14)	0.25	7 (10)	18 (10)	**<0.01**	226 (6)
Flashes, floaters	184 (5)	1 (3)		5 (12)		1 (8)		1 (50)		0 (0)		6 (8)	15 (8)		199 (5)
Visual field defect	43 (1)	0 (0)		0 (0)		0 (0)		0 (0)		0 (0)		1 (1)	1 (0.5)		44 (1)
No symptoms	3179 (88)	26 (87)		29 (71)		12 (92)		0 (0)		6 (86)		57 (80)	148 (80)		3327 (87)
Number of nevi															
Per patient: mean [median (range)]	1 [1 (1-10)]	1 [1 (1-3)]	0.30	1 [1 (1-2)]	0.18	1 [1 (1-2)]	0.30	2 [2 (1-2)]	0.66	2 [2 (1-3)]	0.02	1 [1 (1-4)]	1 [1 (1-4)]	<0.01	1 [1 (1-10)]
Per eye: mean [median (range)]	1 [1 (0-6)]	1 [1 (1-2)]	0.54	1 [1 (1-2)]	0.47	1 [1 (1-2)]	0.61	2 [2 (1-2)]	0.73	1 [1 (1-2)]	0.60	1 [1 (1-2)]	1 [1 (1-3)]	<0.01	1 [1 (0-6)]
1	3114 (86)	28 (93)	0.21	36 (88)	0.25	12 (92)	0.45	1 (50)	0.08	5 (71)	0.12	63 (89)	160 (87)	0.04	3274 (86)
2	394 (11)	2 (7)		5 (12)		1 (8)		1 (50)		2 (29)		8 (11)	23 (13)		417 (11)
3	78 (2)	0 (0)		0 (0)		0 (0)		0 (0)		0 (0)		0 (0)	1 (<1)		79 (2)
>3	33 (1)	0 (0)		0 (0)		0 (0)		0 (0)		0 (0)		0 (0)	0 (0)		33 (1)
Quadrantic location															
Macula	986 (27)	7 (23)	0.22	15 (37)	**0.01**	2 (15)	0.32	0 (0)	**<0.01**	3 (43)	0.08	31 (34)	58 (32)	0.16	1044 (27)
Superior	755 (21)	7 (23)		11 (27)		3 (23)		2 (100)		1 (14)		15 (18)	39 (21)		794 (21)
Temporal	634 (17)	3 (13)		7 (17)		3 (23)		0 (0)		1 (14)		14 (15)	28 (15)		662 (17)
Inferior	718 (20)	7 (23)		7 (17)		3 (23)		0 (0)		0 (0)		17 (16)	34 (18)		752 (20)
Nasal	529 (15)	5 (17)		1 (2)		2 (15)		0 (0)		2 (29)		15 (16)	25 (14)		554 (15)
Anteroposterior location															
Macula	1001 (27)	7 (23)	0.36	17 (42)	0.04	2 (15)	<0.01	0 (0)	0.25	2 (29)	0.33	24 (34)	60 (33)	0.14	1061 (28)
Macula-equator	2196 (61)	18 (60)		19 (46)		6 (46)		2 (100)		5 (71)		41 (58)	103 (56)		2299 (60)
Equator-ora serrata	423 (12)	5 (17)		5 (12)		5 (39)		0 (0)		0 (0)		6 (8)	21 (11)		444 (12)
Proximity to optic disc (mm)	5.2 (5.0, 0.0-23.0)	5.7 (4.8, 0.0-15.0)	0.52	5.4 (5.0, 0.0-16.0)	0.71	6.3 (7.0, 0.0-12.0)	0.28	7.0 (7.0, 6.0-8.0)	0.49	3.8 (3.0, 2.0-7.0)	0.33	4.9 (5.0, 0.0-15.0)	5.2 (5.0, 0.0-16.0)	0.92	5.2 (5.0, 0.0-23.0)
Proximity to foveolar (mm)	5.0 (4.0, 0.0-20.0)	5.7 (5.0, 0.0-12.0)	0.31	4.6 (3.0, 0.0-19.0)	0.55	6.2 (6.0, 0.0-12.0)	0.25	9.0 (9.0, 8.0-10.0)	0.14	3.4 (2.5, 1.0-6.5)	0.29	4.6 (4.0, 0.0-15.0)	4.9 (4.0, 0.0-19.0)	0.66	5.0 (4.0, 0.0-20.0)
Largest basal diameter (mm)	4.6 (4.0, 0.1-20.0)	4.5 (3.5, 1.0-16.0)	0.88	4.2 (3.5, 0.5-9.0)	0.41	5.5 (3.0, 1.0-20.0)	0.31	5.5 (5.5, 5.0-6.0)	0.68	4.4 (4.0, 1.5-8.0)	0.84	4.5 (3.5, 0.3, 18.0)	4.5 (3.5, 0.3-20.0)	0.70	4.6 (4.0, 0.1-20.0)
Thickness (mm)	1.5 (1.4, 0.1-6.5)	1.6 (1.4, 0.1-3.7)	0.10	1.5 (1.4, 0.1-3.3)	0.76	1.8 (1.5, 0.1-6.7)	0.08	1.7 (1.7, 1.5-1.8)	0.67	1.8 (1.5, 1.0-3.3)	0.23	1.6 (1.5, 0.1-3.2)	1.6 (1.5, 0.1-6.7)	**0.03**	1.5 (1.4, 0.1-6.7)
Color															
Pigmented	3040 (84)	26 (90)	0.28	38 (93)	0.10	12 (92)	0.25	2 (100)	0.54	5 (71)	0.07	59 (83)	160 (87)	0.13	3200 (84)
Nonpigmented	244 (7)	2 (7)		2 (5)		1 (8)		0 (0)		0 (0)		6 (9)	13 (7)		257 (9)
Mixed	336 (9)	1 (3)		1 (2)		0 (0)		0 (0)		2 (29)		6 (9)	11 (6)		347 (7)
Halo present	206 (6)	2 (7)	0.78	0 (0)	0.13	0 (0)	0.38	0 (0)	0.73	0 (0)	0.52	7 (8)	10 (5)	0.52	216 (6)

*Data are collected per unique eye except involved eye, which is collected per unique patient

Table 3: Choroidal nevus transformation into melanoma in 3806 cases using multimodal imaging (imaging features per race)

Imaging features	Caucasian *n*=3622 (%)	African-American *n*=30 (%)	Caucasian vs. African-American *P*	Hispanic *n*=41 (%)	Caucasian vs. Hispanic *P*	Asian *n*=13 (%)	Caucasian vs. Asian *P*	Asian Indian *n*=2 (%)	Caucasian vs. Asian Indian *P*	Middle Eastern *n*=7 (%)	Caucasian vs. Middle Eastern *P*	Unknown/ Others *n*=71 (%)	Non-Caucasian *n*=184 (%)	Caucasian vs. non-Caucasian *P*	Total *n*=3806 (%)
OCT	3262 (90)	28 (93)		38 (93)		12 (92)		2 (100)		6 (86)		64 (90)	169 (92)		3431 (90)
SRF															
Overlying nevus	163 (5)	0 (0)	0.08	2 (5)	0.41	1 (8)	0.40	0 (0)	0.60	1 (17)	0.28	4 (6)	9 (5)	0.30	172 (5)
<3 mm from nevus	103 (3)	0 (0)		2 (5)		0 (0)		0 (0)		0 (0)		4 (6)	7 (4)		110 (3)
3-6 mm from nevus	23 (1)	1 (4)		0 (0)		0 (0)		0 (0)		0 (0)		1 (2)	2 (1)		25 (1)
>6 mm from nevus	5 (<1)	0 (0)		0 (0)		0 (0)		0 (0)		0 (0)		0 (0)	0 (0)		5 (0)
Drusen	1454 (45)	10 (36)	0.35	19 (51)	0.50	3 (25)	0.18	1 (50)	0.89	2 (33)	0.58	25 (39)	70	0.42	1524 (45)
Retinal edema	133 (4)	0 (0)	0.20	1 (3)	0.42	0 (0)	0.40	0 (0)	0.73	1 (17)	0.24	4 (6)	6 (4)	0.25	139 (4)
RPE atrophy	396 (12)	5 18)	0.36	2 (5)	0.20	0 (0)	0.60	0 (0)	0.60	0 (0)	0.36	5 (8)	13 (8)	0.08	409 (12)
RPE hyperplasia	139 (4)	0 (0)	0.19	2 (5)	0.86	1 (8)	0.72	0 (0)	0.72	0 (0)	0.54	1 (2)	4 (2)	0.06	143 (4)
Fibrous metaplasia	177 (5)	3 (11)	0.22	2 (5)	0.99	0 (0)	0.41	0 (0)	0.74	0 (0)	0.56	6 (9)	12 (7)	0.35	189 (6)
PED over nevus	108 (3)	2 (7)	0.26	1 (3)	0.82	0 (0)	0.52	0 (0)	0.79	1 (17)	0.07	1 (2)	5 (3)	0.81	113 (3)
Retinal invasion	5 (<1)	0 (0)	0.84	0 (0)	0.81	0 (0)	0.89	0 (0)	0.99	0 (0)	0.92	0 (0)	0 (0)	0.61	5 (<1)
CNV over nevus	30 (1)	0 (0)	0.61	0 (0)	0.55	0 (0)	0.74	0 (0)	0.89	0 (0)	0.81	0 (0)	0 (0)	0.82	30 (<1)
Surface configuration of nevus															
Dome	1797 (55)	17 (63)	0.32	20 (54)	0.37	7 (58)	0.62	2 (100)	0.20	3 (50)	0.64	39 (61)	99 (59)	0.25	1896 (56)
Lumpy bumpy	37 (1)	0 (0)		0 (0)		0 (0)		0 (0)		0 (0)		1 (2)	1 (<1)		38 (1)
Excavated	25 (1)	0 (0)		0 (0)		0 (0)		0 (0)		0 (0)		1 (2)	1 (<1)		26 (1)
Flat	1386 (43)	10 (37)		17 (46)		5 (42)		0 (0)		3 (50)		23 (36)	66 (40)		1452 (43)
Location in choroid															
Inner	706 (23)	8 (30)	0.21	13 (39)	**<0.01**	2 (17)	0.51	0 (0)	0.22	2 (33)	**0.03**	17 (27)	48 (30)	0.05	754 (23)
Outer	1774 (57)	16 (59)		12 (36)		8 (67)		2 (100)		1 (17)		38 (60)	85 (52)		1859 (57)
Full thickness	607 (20)	3 (11)		8 (24)		2 (17)		0 (0)		3 (50)		8 (13)	29 (18)		636 (20)
FAF	3462 (96)	28 (68)		41 (100)		12 (92)		2 (100)		6 (86)		70 (99)	178 (97)		
Orange pigment	95 (3)	0 (0)	0.37	1 (2)	0.92	1 (8)	0.24	0 (0)	0.81	0 (0)	0.68	3 (4)	5 (3)	0.99	100 (3)
RPE trough	96 (3)	0 (0)	0.37	4 (10)	**<0.01**	0 (0)	0.56	0 (0)	0.81	1 (17)	**0.04**	1 (1)	7 (4)	0.36	103 (3)
Ultrasonography	3275 (90)	27 (90)		38 (93)		12 (92)		2 (100)		6 (86)					
Configuration															
Flat	2183 (67)	15 (56)	0.22	25 (66)	0.92	8 (67)	1	1 (50)	0.62	3 (50)	0.39	43 (61)	107 (63)	0.37	2290 (66)
Dome	1092 (33)	12 (44)		13 (34)		4 (33)		1 (50)		3 (50)		24 (36)	62 (37)		1154 (34)
Echogenicity															
Hollow	298 (9)	2 (7)	0.75	2 (5)	0.41	1 (8)	0.92	0 (0)	0.65	0 (0)	0.44	4 (6)	11 (7)	0.25	309 (9)
Solid	2968 (91)	25 (93)		36 (95)		11 (92)		2 (100)		6 (100)		62 (94)	157 (93)		3125 (91)

OCT=Optical coherence tomography; SRF=Subretinal fluid; RPE=Retinal pigment epithelium; CNV=Choroidal neovascular membrane; FAF=Fundus autofluorescence

(20% vs. 50%, $P = 0.03$) and greater frequency of RPE trough on autofluorescence in Hispanic (3% vs. 10%, $P < 0.01$) and Middle Eastern (3% vs. 17%, $P = 0.04$) race.

Of the 3334 patients, follow-up was established in 2075 patients, with a mean follow-up duration of 3 years (median 3, range <1–11 years). Comparison by race (Caucasian vs. African-American vs. Hispanic vs. Asian vs. Asian Indian vs. Middle Eastern vs. other) revealed no difference in the mean follow-up duration (3 vs. 3 vs. 3 vs. 4 vs. n/a vs. 1 vs. 2 years, $P = 0.27$).

A comparative analysis of benign nevus enlargement is listed in Supplemental Table 1. There were no differences in the characteristics of benign growth in generalized comparison (Caucasian vs. non-Caucasian) or by specific racial subset analysis (Caucasian vs. specific race).

A comparative analysis of nevus growth into melanoma is listed in Table 4. There were no significant differences in overall risk for transformation to melanoma in Caucasian versus non-Caucasian, or by specific racial subset analysis (Caucasian vs. specific race). The only difference detected in those with transformation into melanoma was ultrasonographic tumor hollowness, which was less common in the Caucasian compared with the non-Caucasian race (29% vs. 67%, $P = 0.04$).

Discussion

Previous studies have documented a higher prevalence of choroidal melanoma in Caucasians compared with non-Caucasians.[6,12-15] One of the earlier studies, by Phillpotts *et al.* in 1995, examined records of 2586 patients with posterior uveal melanoma diagnosed at the Wills Eye Hospital Ocular Oncology Service between 1974 and 1987.[16] Of these, only 0.4% ($n = 10$ patients) were Black. Comparatively, the 1990 US Census data estimated African-Americans to be the largest minority race at 12.1% of the total population.[16,17] A similar but more comprehensive review by Shields *et al.* in 2009 examined 8033 eyes with uveal melanoma.[12] Of these, 98% were found in Caucasians, which comprised 75.1% of the US population in 2000. Less than 2% of the study patients with melanoma were non-Caucasians, which comprised 24.9% of the US population in 2000.[12] These findings reflect an established propensity of uveal melanoma in Caucasians at a rate far higher than population figures would suggest and those of non-Caucasians race at a rate far lower than anticipated.[12,18]

Similar differences by race have been noted with regard to the prevalence of cutaneous melanoma.[19,20] Wang *et al.* observed the highest age-adjusted incidence of cutaneous malignant melanoma in non-Hispanic Whites, followed by Hispanic Whites, and then Blacks with the lowest incidence.[19] More specifically, the incidence per 100,000 person-years of cutaneous malignant melanoma was 11.73 in non-Hispanic Whites, 2.25 in Hispanic Whites, 0.66 in Asian/Pacific Islanders, and 0.51 in Blacks.[19] These racial differences were attributed to cutaneous protective factors including the degree of skin pigmentation and exposure to ultraviolet light.[19]

The difference in choroidal melanoma prevalence by race could arise in one or a combination of several theories. One possibility is that fair-skinned, blue-eyed Caucasian individuals typically demonstrate less pigmentation in the choroid with a lack of the protective effect from pigment-laden melanocytes from environmental toxins or solar irradiation. Another theory relates to the higher prevalence of choroidal nevi in Caucasian patients, known to carry a risk, and possibly a greater probability, for malignant transformation. Other possibilities might relate to a difference in genetic mutation susceptibility or exposures in different races.

Similar to choroidal melanoma prevalence patterns, the prevalence of choroidal nevus by race in the United States is unequivocally higher in Whites as evident in the NHANES, which found choroidal nevus prevalence in Whites (5.6%), Blacks (0.6%), Hispanics (2.7%), and others (2.1%).[1] Greenstein *et al.*, in a 2011 study of 6176 subjects in a healthy cohort of patients, also found choroidal nevus prevalence higher in Whites (4.1%) compared with Blacks (0.7%), Hispanics (1.2%), and Chinese (0.4%).[3] Future studies could delineate the underlying host or environmental features that represent these differences.

In this analysis, we focused on choroidal nevus features and outcomes based on patient race. We found a lower prevalence of non-Caucasians (5.0%) with choroidal nevus, but we did not find differences in the risk of growth by race. However, we did observe differences in presenting and imaging features comparing Caucasians to non-Caucasians, as Caucasians demonstrated older age of presentation, fewer symptoms, female sex predilection, less frequent history of dysplastic nevus syndrome, more frequent history of previous cutaneous melanoma, less frequent ocular melanocytosis, greater mean number of nevi per eye, and less frequent retinal pigment epithelium trough on FAF. Of those with documented growth into melanoma, the Caucasians showed less frequent ultrasonographic tumor hollowness compared with the non-Caucasians. The relative increased prevalence of dysplastic nevus syndrome in Hispanic patients was not anticipated. The relative increased prevalence of ocular melanocytosis in Asian Indians with choroidal nevus was not surprising and might reflect the fact that this condition could be more common in pigmented races.[21]

Regarding differences in clinical features such as age at presentation, sex, involved eye, symptoms, the mean number of nevi per eye, and nevus location, they should be interpreted with caution given the low number of subjects in many of the non-Caucasian racial subgroups. One important finding in this analysis was that for patients with nevus transformation into melanoma, ultrasonographic tumor hollowness was less common in Caucasians compared with non-Caucasians (29% vs. 67%, $P = 0.04$). This difference could be due to the intrinsic factors in the nevus or melanoma itself on a cellular level that differ by race. Yiu *et al.* found that distribution and pigmentation of uveal melanocytes are the major determinants of choroidal morphology; species with larger, more darkly pigmented, and more densely dispersed melanocytes across the choroidal stroma had more hyporeflective choriocapillaris on EDI(enhanced depth imaging)-OCT compared with those with smaller, less pigmented, more loosely distributed melanocytes.[22] These factors could potentially influence acoustic hollowness of choroid nevus on ultrasonography.

There are limitations that should be realized in this analysis. The retrospective nature of our study along with some incomplete patient follow-up and smaller cohort size in non-Caucasian groups, likely due to the inherently low

Table 4: Choroidal nevus transformation into melanoma in 3806 cases using multimodal imaging (growth with transformation to melanoma in 91 of 3806 cases per race)

Growth features	Caucasian *n*=85 (%)	African-American *n*=1 (%)	Caucasian vs. African-American *P*	Hispanic *n*=0 (%)	Caucasian vs. Hispanic *P*	Asian *n*=0 (%)	Caucasian vs. Asian *P*	Asian Indian *n*=0 (%)	Caucasian vs. Asian Indian *P*	Middle Eastern *n*=0 (%)	Caucasian vs. Middle Eastern *P*	Unknown/ Others *n*=5 (%)	Non-Caucasian *n*=6 (%)	Caucasian vs. non-Caucasian *P*	Total *n*=91 (%)
Growth with transformation to melanoma	85 (4)	1 (6)	n/a	0 (0)	n/a	0 (0)	n/a	0 (0)	n/a	0 (0)	n/a	5 (5)	6 (6)	0.29	91 (4)
Overall growth (mm)															
Basal diameter	2.54 (2.00, 0.00-8.00)	2.00 (2.00, 2.00-2.00)	n/a	-	n/a	-	n/a	-	n/a	-	n/a	2.33 (2.00, 1.00-4.00)	2.25 (2.00, 1.00-4.00)	0.76	2.51 (2.00, 0.00-8.00)
Thickness	1.25 (0.80, 0.20-12.00)	1.30 (1.30, 1.30-1.30)	n/a	-	n/a	-	n/a	-	n/a	-	n/a	1.35 (1.15, 0.70-2.40)	1.34 (1.20, 0.70-2.40)	0.47	1.11 (0.80, 0.20-5.70)
Growth rate (mm/year)															
Basal diameter	1.5 (0.8, 0.0-8.0)	4.4 (4.4, 4.4-4.4)	n/a	-	n/a	-	n/a	-	n/a	-	n/a	1.4 (0.7, 0.6-2.7)	2.1 (1.7, 0.6-4.4)	0.64	1.5 (0.7, 0.0-8.0)
Thickness	0.7 (0.4, <0.1-3.8)	2.9 (2.9, 2.9-2.9)	n/a	-	n/a	-	n/a	-	n/a	-	n/a	0.9 (0.8, 0.4-1.6)	1.3 (1.2, 0.4-2.9)	0.35	0.7 (0.4, <0.1-3.8)
OCT															
Increase in SRF	51 (62)	0 (0)	n/a	-	n/a	-	n/a	-	n/a	-	n/a	5 (100)	5 (83)	0.36	56 (64)
Increase in drusen	3 (4)	0 (0)	n/a	-	n/a	-	n/a	-	n/a	-	n/a	0 (0)	0 (0)	n/a	3 (3)
FAF															
Increase in orange pigment	33 (44)	0 (0)	n/a	-	n/a	-	n/a	-	n/a	-	n/a	3 (60)	3 (50)	0.59	36 (44)
Ultrasonography															
Increase in acoustic hollowness	23 (29)	1 (100)	0.11	-	n/a	-	n/a	-	n/a	-	n/a	3 (60)	4 (67)	0.04	27 (31)

OCT=Optical coherence tomography; SRF=Subretinal fluid; FAF=Fundus autofluorescence

frequency of this tumor in those races, limited statistical comparison and validity. Understanding that choroidal nevus transformation into melanoma is a rare event, small patient numbers could mean that the study was underpowered to detect a difference in malignant transformation by race even if one does exist. In addition, even though we made an effort to perform standard protocol imaging in all patients, not all patients received every imaging technique as listed in Table 3, which limited comprehensive comparison between groups. Despite these limitations, useful observations to guide management can be concluded from this analysis.

Conclusion

In conclusion, based on patient race, we found that the risk of choroidal nevus transformation into melanoma did not differ per race. However, of those with choroidal nevus growth into melanoma, Caucasians were less likely to display ultrasonographic tumor hollowness. Future studies with larger numbers of non-Caucasian patients are required to confirm these findings. Patients of any race with choroidal nevus are at risk for malignant transformation and should have annual eye examinations to monitor for tumor growth.

Financial support and sponsorship

Support was provided, in part, by the Eye Tumor Research Foundation, Philadelphia, PA (CLS), an unrestricted grant from Research to Prevent Blindness, Inc., New York, NY (LAD), the Heed Ophthalmic Foundation, San Francisco, CA (LAD), and a grant from the VitreoRetinal Surgery Foundation Minneapolis, MN (LAD). The funders had no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, and in the preparation, review, or approval of the article.

Conflicts of interest

There are no conflicts of interest.

References

1. Qiu M, Shields CL. Choroidal nevus in the United States adult population: Racial disparities and associated factors in the National Health and Nutrition Examination Survey. Ophthalmology 2015;122:2071-83.
2. Nangia V, Jonas JB, Agarwal S, Khare A, Lambat S, Panda-Jonas S. Choroidal nevi in adult Indians: The Central India Eye and Medical Study. Br J Ophthalmol 2012;96:1443-4.
3. Greenstein MB, Myers CE, Meuer SM, Klein BE, Cotch MF, Wong TY, *et al.* Prevalence and characteristics of choroidal nevi: The multi-ethnic study of atherosclerosis. Ophthalmology 2011;118:2468-73.
4. Shields CL, Furuta M, Mashayekhi A, Berman EL, Zahler JD, Hoberman DM, *et al.* Visual acuity in 3422 consecutive eyes with choroidal nevus. Arch Ophthalmol 2007;125:1501-7.
5. Ng CH, Wang JJ, Mitchell P, Amirul Islam FM, Wong TY. Prevalence and characteristics of choroidal nevi in an Asian vs white population. Arch Ophthalmol 2009;127:314-9.
6. Singh AD, Kalyani P, Topham A. Estimating the risk of malignant transformation of a choroidal nevus. Ophthalmology 2005;112:1784-9.
7. Jonas JB, You QS, Xu L, Wang YX. Choroidal nevi in adult Chinese. Ophthalmology 2008;115:1102-1102.e1.
8. Factors predictive of growth and treatment of small choroidal melanoma: COMS Report No. 5. The Collaborative Ocular Melanoma Study Group. Arch Ophthalmol 1997;115:1537-44.
9. Shields CL, Furuta M, Berman EL, Zahler JD, Hoberman DM, Dinh DH, *et al.* Choroidal nevus transformation into melanoma: Analysis of 2514 consecutive cases. Arch Ophthalmol 2009;127:981-7.
10. Shields CL, Dalvin LA, Ancona-Lezama D, Yu MD, Di Nicola M, Williams BK Jr, *et al.* Choroidal nevus imaging features in 3806 cases and risk factors for transformation into melanoma in 2355 cases. The 2020 Taylor R. Smith and Victor T. Curtin Lecture. Retina 2018; doi: 10.1097/IAE.0000000000002440. [Epub ahead of print] PMID: 30608349.
11. Shields CL, Cater J, Shields JA, Singh AD, Santos MC, Carvalho C. Combination of clinical factors predictive of growth of small choroidal melanocytic tumors. Arch Ophthalmol 2000;118:360-4.
12. Shields CL, Furuta M, Thangappan A, Nagori S, Mashayekhi A, Lally DR, *et al.* Metastasis of uveal melanoma millimeter-by-millimeter in 8033 consecutive eyes. Arch Ophthalmol 2009;127:989-98.
13. Shields CL, Shields JA, Kiratli H, Nagori S, Mashayekhi A, Lally DR, *et al.* Risk factors for growth and metastasis of small choroidal melanocytic lesions. Trans Am Ophthalmol Soc 1995;93:259-79.
14. Shields CL, Kaliki S, Furuta M, Mashayekhi A, Shields JA. Clinical spectrum and prognosis of uveal melanoma based on age at presentation in 8033 cases. Retina 2012;32:1363-72.
15. Shields CL, Kaliki S, Cohen MN, Shields PW, Furuta M1, Shields JA. Prognosis of uveal melanoma based on race in 8100 patients: The 2015 Doyne Lecture. Eye 2015;29:1027-35.
16. Phillpotts B, Sanders RJ, Shields JA, Griffiths JD, Augsburger JA, Shields C L. Uveal melanomas in black patients: A case series and comparative review. J Natl Med Assoc 1995;87:709-14.
17. US Department of Commerce. Population profile of the United States 1995. Current Population Reports, Special Studies Series 1995. p. 23-189. Available from: https://www.census.gov/prod/1/pop/profile/95/p23-189.pdf.
18. Humes KR, Jones NA, Ramirez RR. Overview of race and Hispanic origin: 2010 census briefs. U.S. Department of Commerce March 2011. Available from: https://www.census.gov/prod/cen2010/briefs/c2010br-02.pdf.
19. Wang Y, Zhao Y, Ma S. Racial differences in six major subtypes of melanoma: Descriptive epidemiology. BMC Cancer 2016;16:691.
20. Hu S, Parmet Y, Allen G, Parker DF, Ma F, Rouhani P, *et al.* Disparity in melanoma: A trend analysis of melanoma incidence and stage at diagnosis among whites, Hispanics, and blacks in Florida. Arch Dermatol 2009;145:1369-74.
21. Gonder JR, Ezell PC, Shields JA, Augsburger JJ. Ocular melanocytosis. A study to determine the prevalence rate of ocular melanocytosis. Ophthalmology 1982;89:950-2.
22. Yiu G, Vuong VS, Oltjen S, Cunefare D, Farsiu S, Garzel L, *et al*. Effect of uveal melanocytes on choroidal morphology in rhesus macaques and humans on enhanced-depth imaging optical coherence tomography. Invest Ophthalmol Vis Sci 2016;57:5764-71.

Supplemental Table 1: Choroidal nevus transformation into melanoma in 3806 cases using multimodal imaging (growth without transformation to melanoma in 146 of 3806 cases per race)

Growth features	Caucasian *n*=141 (%)	African-American *n*=1 (%)	Caucasian vs. African-American *P*	Hispanic *n*=3 (%)	Caucasian vs. Hispanic *P*	Asian *n*=0 (%)	Caucasian vs. Asian *n*	Asian Indian *n*=0 (%)	Caucasian vs. Asian Indian *n*	Middle Eastern *n*=0 (%)	Caucasian vs. Middle Eastern *n*	Unknown/ Others *n*=1 (%)	Non-Caucasian *n*=5 (%)	Caucasian vs. non-Caucasian *P*	Total *n*=146 (%)
Growth without transformation to melanoma	141 (6)	1 (6)	0.92	3 (14)	0.13	0 (0)	n/a	0 (0)	n/a	0 (0)	n/a	1 (2)	5 (3)	0.57	146 (6)
Overall growth (mm)															
Basal diameter	0.9 (1.0, −1.2-4.0)	1.0 (1.0, 1.0-1.0)	n/a	2.0 (2.0, 2.0-2.0)	n/a	-	n/a	-	n/a	-	n/a	n/a	1.5 (1.5, 1.0-2.0)	0.45	0.9 (1.0, −1.2-4.0)
Thickness	0.3 (0.3, −1.8-1.1)	0.2 (0.2, 0.2-0.2)	n/a	0.2 (0.4, −0.5-0.6)	0.23	-	n/a	-	n/a	-	n/a	n/a	0.2 (0.3, −0.5-0.6)	0.96	0.3 (0.3, −1.8-1.1)
Growth rate (mm/year)															
Basal diameter	0.5 (0.4, −4.0-4.1)	0.8 (0.8, 0.8-0.8)	n/a	0.7 (0.7, 0.7-0.7)	n/a	-	n/a	-	n/a	-	n/a	0 (0)	0.8 (0.8, 0.7-0.8)	0.57	0.5 (0.4, −4.0-4.1)
Thickness	0.2 (0.1, −6.1-1.41)	0.2 (0.2, 0.2−0.2)	n/a	0.1 (0.2, −0.3-0.4)	0.99	-	n/a	-	n/a	-	n/a	0 (0)	0.1 (0.2, −0.3-0.4)	0.92	0.2 (0.1, −6.1-1.4)
OCT															
Increase in SRF	4 (3)	0 (0)	n/a	0 (0)	n/a	-	n/a	-	n/a	-	n/a	0 (0)	0 (0)	n/a	4 (4)
Increase in drusen	5 (3)	0 (0)	n/a	0 (0)	n/a	-	n/a	-	n/a	-	n/a	0 (0)	0 (0)	n/a	5 (4)
FAF															
Increase in orange pigment	1 (1)	0 (0)	n/a	0 (0)	n/a	-	n/a	-	n/a	-	n/a	0 (0)	0 (0)	n/a	1 (1)
Ultrasonography															
Increase in acoustic hollowness	3 (2)	0 (0)	n/a	0 (0)	n/a	-	n/a	-	n/a	-	n/a	0 (0)	0 (0)	n/a	3 (2)

OCT=Optical coherence tomography; SRF=Subretinal fluid; FAF=Fundus autofluorescence