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Prevalence and Characteristics of Choroidal Nevi: the Multi-Ethnic Study of Atherosclerosis

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Abstract

Objective—To describe the prevalence of choroidal nevi in four racial/ethnic groups (white, black, Hispanic, and Chinese) in the United States (US).

Design—Cross-sectional study.

Participants—Participants of the second examination of the Multi-Ethnic Study of Atherosclerosis (MESA), involving 6176 persons aged 45–85 years without clinical cardiovascular disease at baseline selected from 6 US communities.

Methods—Fundus images were taken using a 45° digital camera through dark-adapted pupils and were graded for choroidal nevi using the modified Wisconsin Age-Related Maculopathy Grading System and the Blue Mountains Eye Study protocol.

Main Outcome Measure—Choroidal nevi.

Results—The overall prevalence of choroidal nevi in the whole cohort was 2.1%, with prevalences higher in whites (4.1%) than blacks (0.7%), Hispanics (1.2%) and Chinese (0.4%, $P < 0.001$ for any differences among groups). The lowest prevalence of choroidal nevi occurred in those 75–84 years old. The nevi were subfoveal in 4% of eyes with nevi and were not associated with a decrease in visual acuity. Characteristics of the nevi (size, shape, location, color, drusen on surface) did not differ among racial/ethnic groups. With the exception of associations with higher C-reactive protein levels (odds ratio [OR] per mg/dL on the logarithmic scale 1.23; 95% confidence interval [CI] 1.06–1.43; $P = 0.01$) and lower systolic blood pressure (OR per 10 mmHg 0.90; 95% CI 0.82–0.99; $P = 0.04$), choroidal nevi were not associated with other potential risk

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factors (e.g., sex, smoking status, alcohol consumption, lipid levels, coagulation factors or kidney disease).

Conclusions—Low prevalences of choroidal nevi were found in the four groups participating in MESA cohort, with whites having higher prevalence than the other racial/ethnic groups. The higher prevalence in whites than in other groups was not explained by any of the factors studied. When choroidal nevi were present, their characteristics did not differ among racial/ethnic groups.

Choroidal nevi are common incidental findings upon ophthalmogic examination and are usually benign.[1,2] However, they have been associated with increased risk of developing uveal melanoma and, when subfoveal, may affect vision.[1–15] They may also cause anatomic changes in the overlying retina.[2] Most of the information regarding the prevalence and characteristics of choroidal nevi has come from case series and clinico-pathologic correlations.[1,16,17] Based on these observations, varying prevalence of choroidal nevi (ranging from 0.2 to 30%) have been reported.[1,8,16,18–25] The large variation in estimated prevalence reflects differences in populations studied as well as methods used to detect and define their presence. For example, higher frequencies of choroidal nevi have been found in histopathological studies and clinical case series where indirect ophthalmoscopy has been used to detect their presence than in population-based studies where gradings of fundus photographs of the posterior pole have been used.[1,8,16,18–25]

To our knowledge, there have been only three population-based studies, one in whites and two in Asian cohorts, in which the prevalence of choroidal nevi has been estimated.[18,19,25] The two Asian cohorts had lower estimates of prevalence (1.4% in Malaysians and 2.9% in Chinese) as compared to a white cohort (6.5%). Despite observations of the lower prevalence of choroidal nevi in blacks and Hispanics compared to whites, there is no study directly comparing the frequencies of these lesions in different racial/ethnic groups using the same method of ascertainment in the same study. The purpose of this paper is to report the prevalence and characteristics of choroidal nevi and associations with characteristics of the cohort in four racial/ethnic groups: whites, blacks, Hispanics, and Chinese in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort.

Methods

Study population

The MESA is an ongoing 10-year longitudinal study supported by the National Heart, Lung, and Blood Institute with the goals of identifying risk factors for subclinical atherosclerosis and its quantitative progression and for transition from subclinical disease to clinically apparent events. The cohort has been described in detail elsewhere.[26] In brief, the MESA cohort included 6814 men and women aged 45 to 84 years at baseline (July 2000 to July 2002) without clinical cardiovascular disease at baseline who were recruited from six field centers in the United States: Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St. Paul, Minnesota. It excluded those individuals with malignancies that would affect participation at follow-up. Participation rates among those screened were approximately 70% for whites, 61% for blacks, 59% for Hispanics, and 48% for Chinese. Fundus photography was part of the second examination in September 2002 to February 2004, immediately following the baseline examination.

Tenets of the Declaration of Helsinki were followed, institutional review board approval was granted at each study site, and the work is HIPAA compliant. Written informed consent was obtained from each participant.

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Retinal photography and nevus grading

Both eyes of each participant were photographed in a similar fashion using a 45° 6.3-megapixel digital nonmydriatic camera (Canon, Lake Success, NY). Two photographic fields were taken of each eye, the first centered on the optic disc and the second centered on the fovea. Participants' images were graded masked to participant characteristics for the presence of nevi using the Wisconsin Age Related Maculopathy Grading System and Blue Mountains Eye Study (BMES) protocols.[18,27–29] An analysis was then conducted on all eyes identified as having a choroidal nevus present. The number of nevi, their shape (oval, round, or irregular), color (slate blue, green-gray, hypomelanotic, amelanotic, or brown), position relative to the fovea (subfoveolar, subfoveal, macula or extramacular), proximity of posterior margin to the optic disc, quadrant distribution relative to the optic disc, presence of orange pigment, pigment clumping, subretinal fluid, and overlying drusen were recorded.[18,19] OcuLab (Digital Healthcare, Cambridge, UK) was used to measure maximum diameter, surface area, and distance from fovea to the proximal edge of each nevus. These values were measured in micrometers per pixel, converted using 4500 μm as the standard distance from the center of the optic disc to the center of the fovea.

Assessment and Definitions of Cardiovascular and other Characteristics

A choroidal nevus was defined as an unequivocal pigmented slate blue or green-gray choroidal lesion measuring at least 350 μm in diameter. Choroidal lesions resembling nevi that were partially depigmented were graded as patchy hypomelanotic nevi. This was the same definition as used in other population-based studies except the criteria for the largest diameter in the MESA was 350 μm, which was smaller than the 500 μm criteria used in the other studies.[18,19,25] Congenital hypertrophy of the retinal pigment epithelium, pigment clumps, and pigmented scars were excluded. There were no choroidal melanomas detected in this cohort.

Participants underwent a comprehensive interview, clinical examination, and laboratory investigation for the assessment of cardiovascular risk factors, which has been described in detail in previous publications.[26,30] Variables for this analysis were based on data collected at the second examination unless not available, in which case data from the baseline examination were used. Resting blood pressure was measured using a standardized protocol.[27] Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or current use of antihypertensive medications. Diabetes mellitus was defined as fasting glucose ≥ 7.0 mmol/L (126 mg/dL) or use of insulin or oral hypoglycemic medication. Body mass index was defined as weight in kg divided by the square of height in meters. A detailed questionnaire was used to obtain information about education levels, medical history (e.g., hypertension, diabetes), cigarette smoking, and alcohol consumption. Fasting (≥ 8 hours) blood samples were drawn from participants and analyzed for all the blood factors examined in this study by use of standardized protocols.[30,31] Biomarkers of inflammation (e.g., serum high sensitivity C-reactive protein, interleukin-6) and endothelial dysfunction (e.g., serum soluble intercellular adhesion molecule-1) were also measured as described elsewhere.[30]

Statistical analysis

Choroidal nevi were analyzed as a binary outcome variable. Associations with age and sex were analysed using χ^2 tests and reported as numbers and proportions. Prevalence of nevi by age was evaluated by categorizing the population into four age groups (45–54, 55–64, 65–74, and 75–85 years). Race/ethnicity was also analyzed using the χ^2 test. Nevus characteristics such as size, shape, color, and location were compared among racial/ethnic groups. Nevus associations with other variables (e.g., diabetes, smoking) were assessed

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using logistic regression controlling for age and race/ethnicity. $P < 0.05$ was regarded as statistically significant.

Results

The crude prevalence of choroidal nevi in individuals in the whole cohort was 2.1% (95% confidence interval [CI] 1.8–2.5%) and was higher in whites (4.1%) than in Hispanics (1.2%), blacks (0.7%), and Chinese (0.4%, Table 1). There was no significant difference in the prevalence of choroidal nevi among Hispanics, blacks, and Chinese Americans ($P = 0.13$). Within the cohort, the prevalence of choroidal nevi did not vary by sex, and was highest in persons 55–74 years of age and lowest in persons 75–84 years of age.

Of the 141 nevi found in 132 persons, 89% were described as gray-green, 79% as oval or irregular, 64% as outside the macula, 4% as subfoveal, and 4% as touching the disc. All but one nevus were > 500 μm in their largest diameter. The average surface area of the nevi was 2,770,588 μm^2 or about 1 ½ disc areas (standard deviation [SD] 4,609,188 μm^2; range 68,716–43,445,290 μm^2), the average maximum diameter was 2043 μm (SD 1250 μm; range 350–9,861 μm) and the average distance from the disc was 3762 μm (SD 2149 μm; range 0–8706 μm). Drusen were found on the surface of 25% of nevi, and one nevus had orange pigment, but none had subretinal fluid present. Nevus characteristics (e.g., for maximum diameter, shape, color, surface area, and distance to fovea) were similar among the four racial/ethnic groups (Table 2).

Of the 132 eyes with a choroidal nevus, four had visual impairment (best corrected visual acuity of 20/40 or worse), 127 had normal vision, and one was missing visual acuity data. Of the four eyes with impaired vision, none had severe visual impairment (best corrected visual acuity of 20/200 or worse). Eight eyes had nevi in the foveal region, but none of them had impaired vision.

While controlling for age and race/ethnicity, higher serum C-reactive protein (odds ratio [OR] per mg/dL C-reactive protein on the log scale 1.23; 95% CI 1.06–1.43; $P = 0.01$) was directly associated and systolic blood pressure (OR per 10 mmHg 0.90; 95% CI 0.82–0.99; $P = 0.04$) was inversely associated with the presence of nevi (Table 3, available at http://aaojournal.org). There was no relation of smoking status, alcohol consumption, diabetes duration, blood glucose levels, lipid levels, coagulation factors or microalbuminuria with the presence of nevi. When analyses were restricted to only whites, only C-reactive protein was associated with choroidal nevi (data not shown). Neither C-reactive protein nor systolic blood pressure was related to choroidal nevi in nonwhites (data not shown).

We examined the relationships of risk factors for specific drusen characteristics. While controlling for race/ethnicity, there were borderline relationships between older age (OR per year 1.04; 95% CI 1.00–1.09; $P = 0.08$) and between higher serum HDL cholesterol (OR per 10 mg/dL 1.26; 95% CI 0.93–1.64; $P = 0.08$) and the odds of having a nevus with overlying drusen compared to those without. There were no other associations between risk factors and the odds of having a nevus with or without drusen or other nevus characteristics (data not shown).

Controlling for age, gender, systolic blood pressure, and serum C-reactive protein, the odds of having a nevus was 4.89 (95% CI 3.27–7.34) times greater for whites compared to the three other racial/ethnic groups. Controlling for age, gender, systolic blood pressure, and serum C-reactive protein, the odds of having a nevus were 3.53 (95% CI 2.06–6.03) times greater for whites compared to Hispanics, 5.83 (95% CI 3.16–10.73) for whites compared to blacks, and 8.82 (95% CI 2.77–28.08) for whites compared to Chinese.

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Discussion

The MESA provided a unique opportunity to examine the prevalence and characteristics of choroidal nevi in digital images of the posterior pole of the retina using standardized protocols in four racial/ethnic groups. We report a low prevalence of 2.1% of participants in the entire cohort, with the prevalence in whites approximately 3 ½, 6, and 10 times as frequent as in Hispanics, blacks, and Chinese Americans, respectively. The nevi were subfoveal in 4% of eyes and were not associated with visual impairment in any of these eyes. The presence of nevi did not differ between men and women, and except for associations with serum C-reactive protein and systolic blood pressure, nevi were not associated with any other systemic factors studied.

The 4.1% prevalence of nevi in whites in the MESA is lower than the 6.5% reported in whites in the BMES.[18] This is not explained by the definition of choroidal nevus used in the studies. It may be explained by fewer and non-stereoscopic fields used in the MESA (two non-stereoscopic 45° digital photographic fields of the disc and macula) than in the BMES (six stereoscopic 30° film photographic fields of the disc, macula, lateral macula, upper and lower temporal arcade, and nasal retina). Not including large areas of the mid- and far peripheral retina in the MESA and BMES likely explains the lower estimates reported in whites in these studies than in some other studies using indirect ophthalmoscopy.[1,8]

In the MESA, there was a higher prevalence of choroidal nevi in whites compared to other racial/ethnic groups. This is similar to higher prevalence of skin and iris nevi and conjunctival and choroidal melanoma in whites compared to other racial/ethnic groups.[1,32–46] The reasons for a higher prevalence of choroidal nevi and melanoma in whites are not known. It may be due in part to easier detection of nevi in more pale fundi, or it could be due to differences in genetic and environmental factors among the different racial/ethnic groups that affect growth and pigmentation of small cell rests deposited in the neural crest that ultimately become choroidal nevi. The prevalence of nevi in the Chinese Americans participating in the MESA (0.4%) is lower than the 2.9% reported in the Beijing Eye Study cohort, which used the same definition and area of the retina captured in the photographs.[25] The reason for this difference between Chinese living in the United States and those living in China is not known, but again may reflect differences in defining and detecting these lesions among studies. When present, anatomic characteristics of choroidal nevi such as size, color, and location were similar among different racial/ethnic groups in the MESA, confirming earlier observations.[19,25,47]

There are few descriptions of associations of choroidal nevi with risk factors beyond age, sex, and race/ethnicity. In a clinic-based case series, Gass et al. reported that choroidal nevi were rare in infants and increased in prevalence until the fifth decade of life, and that there was no difference in prevalence between the sexes.[1] The lowest prevalence of choroidal nevi in the MESA, in the oldest group 75–84 years of age, may reflect a detection bias, due in part to decreasing media clarity or selective mortality. In the Beijing Eye Study, no associations were found between a history of alcohol consumption, smoking, and living in a rural versus an urban environment and the presence of choroidal nevi in Chinese.[25] Similarly, we did not find associations with smoking and alcohol consumption and choroidal nevi in the MESA cohort. While controlling for age, race/ethnicity, and gender, C-reactive protein was positively associated and systolic blood pressure was inversely associated with the presence of choroidal nevi in the MESA. While C-reactive protein has been used for staging malignant melanoma of the skin, we could find no previous reports of an association of it or of other markers of chronic inflammation with choroidal or skin nevi.[48,49] We also could not find any previous reports of an association of choroidal nevi with blood pressure.

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These findings may be a result of chance given the large number of characteristics examined, and need to be further evaluated in other studies.

Nevi of the skin are common, with an average number of 30 for each individual, and tend to increase in number until about 40 years of age. They are more common in persons with lighter skin color. Monozygotic twins have significantly higher correlations of nevi counts than dizygotic twins,[50,51] suggesting important genetic determinants of nevi of the skin. Additionally, giant congenital melanocytic nevi have been reported to cluster in families.[52] It has been hypothesized that candidate genes for these include those for neural development and melanocyte proliferation. Malignant melanomas of the skin are thought to arise from nevi, usually from dysplastic nevi. While there are no studies describing the familial aggregation of benign choroidal nevi, there is evidence to suggest familial aggregation of uveal melanoma[53–55] and an association between that condition and atypical nevi of the skin and cutaneous melanoma.[56] Thus, it seems likely that genetic determinants of choroidal nevi may exist, and as with skin nevi, the effects of genes are likely to be modified by environmental and other personal and ethnic characteristics. We cannot evaluate potential genetic correlates but we may be detecting the effect of some of the modifiers of genetic predisposition to choroidal nevi.

While there are many strengths to our study, including the grading of digital images for detection of choroidal nevi using standardized protocols in four racial/ethnic groups, there are a number of limitations. First, limited area graded using fundus photography of the posterior pole is likely to underestimate the prevalence of choroidal nevi that occur in the periphery. It is assumed but not known that the distribution of nevi outside of the area of retina graded is similar among the racial/ethnic groups and is not likely to affect the comparisons of prevalence among the racial/ethnic groups in our study. Second, the low prevalence of nevi found limits the power of this study to detect associations with risk factors. Third, possible misclassification of nevi may affect the prevalence and associations reported. Fourth, the cross-sectional nature of the study limits our ability to examine antecedent-consequent relationships and to examine changes in nevus characteristics over time.

In summary, choroidal nevi were infrequent in this multi-ethnic cohort of adults aged 45–85 years, and when present, were found predominantly in whites, who were nearly 10 times more likely to have nevi than Chinese-Americans. However, the characteristics of the choroidal nevi, when present, were similar among the different racial/ethnic groups. Few characteristics beyond race/ethnicity and age were associated with their presence or explained differences in prevalence of this lesion among different racial/ethnic groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Age, Sex, and Race/Ethnicity Distribution of Participants with Choroidal Nevi in the Multi-Ethnic Study of Atherosclerosis.

	No./Total (%)				No./Total (%)				
	All	**Men**	**Women**	**P-value for sex**	**White**	**Chinese**	**Black**	**Hispanic**	**P-value for race/ethnic group**
Age, years									
45–54	30/1805 (1.7)	19/842 (2.3)	11/963 (1.1)	0.06	21/684 (3.1)	2/213 (0.9)	1/485 (0.2)	6/422 (1.4)	0.002
55–64	46/1728 (2.7)	17/816 (2.1)	29/912 (3.2)	0.20	37/667 (5.5)	0/209 (0.0)	6/471 (1.3)	3/381 (0.8)	<0.001
65–74	45/1816 (2.5)	22/883 (2.5)	23/933 (2.5)	0.97	35/739 (4.7)	1/205 (0.5)	3/511 (0.6)	6/361 (1.7)	<0.001
75–84	11/827 (1.3)	6/405 (1.5)	5/422 (1.2)	0.71	8/352 (2.3)	0/100 (0.0)	2/207 (1.0)	1/168 (0.6)	0.20
P-value for age	0.05	0.71	0.01		0.03	0.43	0.25	0.60	
Crude rate	132/6176 (2.1)	64/2946 (2.2)	68/3230 (2.1)		101/2442 (4.1)	3/727 (0.4)	12/1675 (0.7)	16/1332 (1.2)	
Age-Standardized prevalence*	2.0								

*Based on age distribution of the United States 2000 standard population

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Ophthalmology. Author manuscript; available in PMC 2012 December 1.

Table 2

Features of Choroidal Nevi in Four Racial/Ethnic Groups in the Multi-Ethnic Study of Atherosclerosis.

	Choroidal Nevi, No. (%)					
Characteristic	**Overall (N=141)**	**White (N=110)**	**Chinese (N=3)**	**Black (N=12)**	**Hispanic (N=16)**	**P-value**
Diameter, mm						
0–1	19 (13.5)	16 (14.5)	0 (0.0)	2 (16.7)	1 (6.3)	0.44
1–2	68 (48.2)	53 (48.2)	3 (100.0)	6 (50.0)	6 (37.5)	
>2	54 (38.3)	41 (37.3)	0 (0.0)	4 (33.3)	9 (56.2)	
Shape						
Round	30 (21.3)	21 (19.1)	0 (0.0)	5 (41.7)	4 (25.0)	0.14
Oval	55 (39.0)	42 (38.2)	3 (100.0)	5 (41.7)	5 (31.3)	
Irregular	56 (39.7)	47 (42.7)	0 (0.0)	2 (16.6)	7 (43.7)	
Color						
Blue-gray or green-gray	126 (89.4)	98 (89.1)	3 (100.0)	11 (91.7)	14 (87.4)	0.93
Hypomelanotic	2 (1.4)	1 (0.9)	0 (0.0)	0 (0)	1 (6.3)	
Amelanotic	1 (0.7)	1 (0.9)	0 (0.0)	0 (0)	0 (0)	
Brown	12 (8.5)	10 (9.1)	0 (0.0)	1(8.3)	1 (6.3)	
Position						
Subfoveolar	3 (2.1)	1 (0.9)	0 (0.0)	0 (0.0)	2 (12.5)	0.27
Subfoveal	5 (3.6)	5 (4.6)	0 (0.0)	0 (0.0)	0 (0.0)	
Macular	43 (30.5)	34 (30.9)	1 (33.3)	3 (25.0)	5 (31.3)	
Extramacular	90 (63.8)	70 (63.6)	2 (66.7)	9 (75.0)	9 (56.2)	
Posterior margin touching disc	6 (4.3)	5 (4.5)	0 (0.0)	1 (8.3)	0 (0.0)	0.66
Relative to optic disc						
<2 disc diameters	69 (48.9)	51 (46.4)	2 (66.7)	5 (41.7)	11 (68.7)	
>2 disc diameters	66 (46.8)	54 (49.1)	1 (33.3)	6 (50.0)	5 (31.3)	
Quadrant relative to optic disc						
Upper temporal	51 (36.1)	41 (37.3)	2 (66.7)	5 (41.6)	3 (18.8)	0.62
Upper nasal	20 (14.2)	16 (14.5)	0 (0.0)	2 (16.7)	2 (12.5)	
Lower temporal	50 (35.5)	40 (36.4)	0 (0.0)	3 (25.0)	7 (43.7)	

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Choroidal Nevi, No. (%)						
Characteristic	Overall (N=141)	White (N=110)	Chinese (N=3)	Black (N=12)	Hispanic (N=16)	P-value
Lower nasal	20 (14.2)	13 (11.8)	1 (33.3)	2 (16.7)	4 (25.0)	
Drusen present	35 (24.8)	23 (20.9)	0 (0.0)	4 (33.3)	8 (50.0)	0.05
Orange pigment present	1 (0.7)			1 (8.3)		
Other pigment present	0 (0.0)			0 (0.0)		
Subretinal fluid present	0 (0.0)			0 (0.0)		
Pigment clumping present	2 (1.4)			2 (16.7)		