Choroidal Nevi in a White Population

The Blue Mountains Eye Study

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Objective: To determine the prevalence, morphologic characteristics, associations, and frequency of features reported to predict growth of choroidal nevi in a large population-based sample.

Methods: A total of 3654 subjects aged 49 to 97 years participating in the Blue Mountains Eye Study had a detailed eye examination, including photography of 6 standard retinal fields. Nevi were graded from photographs.

Results: Nevi were present in 6.5% of the population (n = 232), and were distributed equally between eyes. There was a slight decrease in nevus prevalence with increasing age. Nevus prevalence was higher in women than men, but this difference was not statistically significant. The mean nevus diameter was 1.25 mm (SD, 0.72 mm; range, 0.5 to >4.5 mm). Eighty-seven percent of nevi were blue gray and 6% had a hypomelanotic or amelanotic appearance. There were no significant associations between nevi and iris or skin color or sun-induced skin damage, but nevi were significantly less frequent in persons with blond hair. No nevus associations were found with visual impairment, cataract, or glaucoma. Clearly visible drusen were seen on 42% of nevi and were larger and more centrally distributed as nevus size increased. Features previously identified as predicting nevus growth, such as serous elevation and orange or other pigment, were seen rarely.

Conclusion: Choroidal nevi in the general population are frequent, small, have few features that are commonly reported to indicate potential for growth, and rarely affect visual acuity.


CHOROIDAL NEVI are a common incidental finding in many fundus examinations. They are seen on ophthalmoscopy as round or oval areas of discrete increased choroidal pigment with detectable but not sharp borders. Nevi are usually described as having a slate-blue or green-gray color and may be slightly raised by 1 to 2 mm. The clinical significance of choroidal nevi relates to their rare potential for malignant transformation, and reported association with visual impairment and differential diagnoses, which include choroidal melanoma, choroidal hemangioma, neovascular age-related macular degeneration, and other conditions. Reported nevus prevalence rates vary widely: from 0.2% to 30% (Table 1). This wide variation is likely due to different examination methods and inclusion criteria for nevi, as well as differences in study populations, some of which could be susceptible to selection bias. Most studies have been of clinic groups from autopsy series. Few population-based studies to date have examined the prevalence of choroidal nevi. Because of the paucity of population-based data, we aimed to describe the prevalence, morphologic characteristics, frequency of features reported to predict growth, and associations with choroidal nevi and overlying drusen in a defined largely white population.

RESULTS

No participants reported a history of diagnosis or treatment for ocular melanoma. None of the larger nevi found had features present at the clinical examination, including elevation, to suggest that they were choroidal melanomas.

PREVALENCE OF CHOROIDAL NEVI AND OCULAR DISTRIBUTION

Seventy-one participants without gradeable photographs of both eyes were excluded. Of 3583 participants with photographs, 232 (6.5%) had 1 or more choroidal nevi. There was a borderline significant trend for nevi to be slightly more prevalent in younger age groups (Table 2). Nevus...
SUBJECTS AND METHODS

Subjects were participants in the Blue Mountains Eye Study, which involves residents aged 49 years or older living in 2 adjacent postcodes in the Blue Mountains area west of Sydney, Australia. Details of the population and study methods have been previously reported.\textsuperscript{18-20} The population is stable and representative of Australia for socioeconomic status. Of 4433 eligible residents, 3654 (82.4%) participated in the study during 1992 to 1994. White subjects represented 3626 (99%) of the study population.

Subjects had retinal and optic disc photographs taken after full-pupil dilatation, using a fundus camera (Zeiss FF3, Carl Zeiss, Oberkochen, Germany) and Kodachrome 25 film (Eastman Kodak, Rochester, NY). Stereo photographs centered on the macula and disc, and nonstereo photographs of lateral macular, upper and lower temporal arcade, and nasal retinal zones were taken, to include a total field of greater than 70°. During photographic grading, 35-mm slide transparencies were viewed against a fluorescent viewing box rated at 6200° K using a Donaldson stereoviewer. The overall magnification was 15 times.

Subjects were administered a detailed questionnaire covering medical and eye health history by trained interviewers and were given a detailed eye examination. This included an external eye and slitlamp examination, visual acuity assessment with an Early Treatment Diabetic Retinopathy Study chart before and after subjective refraction,\textsuperscript{19} screening visual field test,\textsuperscript{2} and applanation tonometry. Iris color was assessed as blue, hazel green, tan brown, or dark brown by comparing the undilated appearance of each eye with 3 standard photographs used in the Beaver Dam Eye Study.\textsuperscript{22} Nonexposed skin color was assessed by a single examiner as very fair, fair, light olive, dark olive, or brown black. The questionnaire asked about natural hair color as a young adult and was classified as blond, red, brown, or black. Sun-induced skin damage to the face and arms was assessed by the same examiner as absent, mild, moderate, or severe.

GRADING AND DEFINITIONS

We defined a nevus as an unequivocal pigmented choroidal lesion at least 500 µm in diameter and slate blue or green gray. Choroidal lesions resembling nevi that were partly or largely depigmented were graded as patchy hypomelanic or amelanotic nevi. Care was taken to differentiate ti-groid fundi from nevi. The following pigmented lesions were excluded: optic disc nevi (melanocytomas), pigment clumps, and pigmented scars. An ophthalmologist (P.M.) examined clinically all participants and excluded the presence of melanoma on the basis of size and elevation.

Measurements of nevus diameter were obtained using the calibrated macular grid developed for the Wisconsin Age-Related Maculopathy Grading System (WARMGS).\textsuperscript{23} These grids have 3 concentric circles, centered on the fovea, with diameters of 1000, 3000, and 6000 µm. The grid was used to estimate nevus position relative to the fovea. Nevi were assessed as falling within the circle containing the largest proportion of the lesion. Nevus characteristics were recorded, including number, shape (round, oval, or irregular), color, edge characteristics (straight, serrated, or fluffy, presence of satellite lesions), posterior margin position, and quadrantal distribution relative to the optic disc. Overlying retina was examined for presence of orange pigment, subretinal fluid, pigment clumping, and drusen.

Maximum size of drusen overlying nevi was assessed using a set of 3 measuring circles (63 µm, C<sub>0</sub>; 125 µm, C<sub>1</sub>; and 250 µm, C<sub>2</sub>) also developed for the WARMGS.\textsuperscript{23} The predominant drusen type (distinct or indistinct), area involved by drusen, and the distribution of drusen overlying nevi (central, peripheral, or both) were assessed. Grading was performed in a manner similar to that used in grading the signs of age-related maculopathy.\textsuperscript{18} Distinct C<sub>0</sub> drusen were small, unequivocal lesions able to be seen with the direct ophthalmoscope. Indistinct C<sub>0</sub> drusen were not included in the assessment of drusen area. Drusen characteristics were considered ungradeable if focus was poor. Intrgrader reliability of features graded was assessed for 21% of nevi. Presence and severity of nuclear, cortical, and posterior subcapsular cataract was assessed using masked grading of slitlamp and retroillumination lens photographs.\textsuperscript{22} Open-angle glaucoma was diagnosed from typical glaucomatous field loss combined with matching optic disc rim thinning and enlarged cup/disc ratio.\textsuperscript{21}

ANALYSIS

The Statistical Analysis System (SAS Institute Inc, Cary, NC) was used. Nevus associations with age, sex, and other variables were assessed using logistic regression. Trends were tested using the Mantel-Haenszel test. Odd ratios and 95% confidence intervals are presented.
(1.9%) lay within the central grading circle (diameter, 1000 µm), and 38 nevi (14.4%) involved the inner circle (diameter, 3000 µm). Thus, about half of all nevi lay wholly within the posterior pole of the eye. The posterior margin of 6.1% of nevi involved the edge of the optic disc, 42.0% of nevi were within 2 disc diameters of the disc, and 57.6% were beyond 2 disc diameters. Forty percent of all nevi were upper temporal to the disc and 45.1% were lower temporal. Only 6.4% and 7.2% were upper or lower nasal to the disc, respectively. This difference is probably because of the much larger area of temporal field photographed.

**DRUSEN AND OTHER FEATURES**

Accurate grading of the characteristics of drusen overlying nevi was possible for 210 nevi (79.5%). Drusen were seen overlying 98% of nevi, with the majority graded as

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### Table 1. Prevalence Studies of Choroidal Nevi by Sample Type and Study Size

<table>
<thead>
<tr>
<th>Source, y</th>
<th>No. of Subjects</th>
<th>Prevalence, %</th>
<th>Age, y</th>
<th>Comments, Examination Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autopsy Eyes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naumann,9 1970</td>
<td>200</td>
<td>11</td>
<td>All ages</td>
<td>Grading of fundus photographs</td>
</tr>
<tr>
<td>Hale et al,10 1965</td>
<td>3119</td>
<td>4.2</td>
<td>18-41</td>
<td>Transillumination and light microscopy</td>
</tr>
<tr>
<td><strong>Clinic Based</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilder,11 1946</td>
<td>3882</td>
<td>0.2</td>
<td>18-38</td>
<td>Surgical trauma cases</td>
</tr>
<tr>
<td>Lang and Daumann,12 1982</td>
<td>2300</td>
<td>1.1</td>
<td>18-41</td>
<td>Pilots and recruits*</td>
</tr>
<tr>
<td>Albers,13 1940</td>
<td>847</td>
<td>6.9</td>
<td>&gt;30</td>
<td>White chemical workers*</td>
</tr>
<tr>
<td>Albert et al,14 1980</td>
<td>302</td>
<td>10.9</td>
<td>&gt;30</td>
<td>White control group*</td>
</tr>
<tr>
<td>Ganley and Comstock,15 1973</td>
<td>250</td>
<td>30.0</td>
<td>&lt;90</td>
<td>Three groups of subjects (office sample, census sample, and subjects with fundus scars)*</td>
</tr>
<tr>
<td><strong>Population Based</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gass,16 1977</td>
<td>197</td>
<td>4.0</td>
<td>49 (mean)</td>
<td>White patients with cutaneous melanoma*</td>
</tr>
<tr>
<td>Rodriguez-Sains,17 1986</td>
<td>147</td>
<td>1.3</td>
<td>47 (mean)</td>
<td>White control patients*</td>
</tr>
<tr>
<td>Present study</td>
<td>3583</td>
<td>6.5 (8.6)‡</td>
<td>&gt;49</td>
<td>White subjects, grading of fundus photographs covering posterior 70°</td>
</tr>
<tr>
<td>Smith and Ganley,18 1972</td>
<td>842</td>
<td>1.9</td>
<td>&gt;13</td>
<td>White subjects,* posterior to equator</td>
</tr>
</tbody>
</table>

* Use of indirect ophthalmoscopy stated.  † Information not given.  ‡ Corrected to represent entire fundus.

### Table 2. Age and Sex Distribution of Choroidal Nevi in the Blue Mountain Eye Study Population

<table>
<thead>
<tr>
<th>No. (%) of Participants With Choroidal Nevus by Age</th>
<th>&lt;60 y</th>
<th>60-69 y</th>
<th>70-79 y</th>
<th>≥80 y</th>
<th>Total</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>42/569 (7.4)</td>
<td>52/707 (7.4)</td>
<td>35/545 (6.4)</td>
<td>7/203 (3.5)</td>
<td>136/2024 (6.7)</td>
<td>.08</td>
</tr>
<tr>
<td>Men</td>
<td>31/438 (7.1)</td>
<td>38/587 (6.5)</td>
<td>17/396 (4.3)</td>
<td>10/138 (7.3)</td>
<td>96/1559 (6.2)</td>
<td>.34</td>
</tr>
<tr>
<td>Both</td>
<td>73/1007 (7.3)</td>
<td>90/1294 (7.0)</td>
<td>52/941 (5.5)</td>
<td>17/341 (5.0)</td>
<td>232/3583 (6.5)</td>
<td>.05</td>
</tr>
</tbody>
</table>

* Mantel-Haenszel $\chi^2$ test for trend.

### Table 3. Drusen Characteristics as a Function of Nevus Size

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>&lt;1.0</th>
<th>1.0-1.9</th>
<th>2.0-2.9</th>
<th>3.0-3.9</th>
<th>≥4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%)</td>
<td>97 (36.7)</td>
<td>131 (48.9)</td>
<td>29 (11.0)</td>
<td>5 (1.9)</td>
<td>4 (1.5)</td>
</tr>
<tr>
<td>Nevus with centrally placed drusen, %</td>
<td>7.7</td>
<td>13.7</td>
<td>37.5</td>
<td>66.7</td>
<td>50.0</td>
</tr>
<tr>
<td>Mean area of nevus involved by drusen, %</td>
<td>6.4</td>
<td>1.9</td>
<td>2.9</td>
<td>1.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Category of largest drusen, No. (%) of cases*</td>
<td>C0 indistinct 59 (78.7)</td>
<td>58 (52.7)</td>
<td>6 (27.2)</td>
<td>1 (25.0)</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>C1 distinct</td>
<td>10 (13.3)</td>
<td>35 (31.8)</td>
<td>6 (27.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;C1</td>
<td>3 (4.0)</td>
<td>17 (15.5)</td>
<td>10 (45.5)</td>
<td>3 (75.0)</td>
<td>2 (66.7)</td>
</tr>
</tbody>
</table>

* Includes only nevi able to be graded for drusen size. See “Grading and Definitions” subsection of “Subjects and Methods” section for description of categories.
small indistinct C₀ lesions. However, only 40.5% of nevi had overlying drusen that could be readily seen during ophthalmoscopy (distinct C₀ lesions or drusen measuring C₁ or C₂ in size). The distribution of drusen overlying nevi was graded as central on 20.0% of nevi, peripheral on 41.2%, or distributed both centrally and peripherally on 38.8%. Drusen tended to be larger (P < .001) and more centrally distributed (P = .01) with increasing nevus size (Table 3). There was only 1 nevus (diameter, 2.4 mm) with overlying orange pigment. Two nevi (diameters, 1.9 and 0.6 mm) had pigment clumping unrelated to other abnormality and 2 nevi (diameters, 1.9 and 3.5 mm, respectively) had minor retinal edema overlying the nevus.

ASSOCIATIONS INVESTIGATED

No statistically significant associations were found between choroidal nevi and iris color, skin color, or examiner-assessed sun-related skin damage. However, nevi were significantly less frequent in people with blond hair (36/763; 4.7%) compared with other hair colors (196/2791; 7.0%) (odds ratio, 0.66; 95% confidence interval, 0.46-0.95). No associations were found between
nevi and presence of other eye diseases (glaucoma or crotal, nuclear, or posterior subcapsular cataract) or diabetes.25 Although 51 nevi (19.3%) lay within 1500 µm of the foveal center, there were no cases of nevi in which visual acuity reduction could be attributed to the nevus. In 36 of this group, the median refracted visual acuity was 20/20. In 15 cases, visual acuity was reduced but the visual impairment was attributed to cataract and other age-related disease.

REPRODUCIBILITY OF GRADING

After completion of grading, 21% of the nevi were regraded. Reproducibility of the grading was high for nevus diameter (κ = 0.93) and site (κ = 0.94). Grading for nevus edge (κ = 0.49) and shape (κ = 0.61) was less reliable, and grading for the characteristics of drusen overlying nevi (size, distribution, predominant type) was moderately reliable (κ statistics, 0.84, 0.77, and 0.64, respectively).

COMMENT

Choroidal nevi were first described by Fuchs in 1882.2 In 1905, de Schweinitz and Shumway26 proposed that these lesions could give rise to malignant melanomas. It is now accepted that malignant melanomas of the choroid may rarely develop from choroidal nevi.1,3,4,27 However, it remains controversial whether the malignant cells arise from neoplastic transformation of preexisting nevus cells or whether melanomas arise de novo and induce a nevuslike structure within the malignant lesion because of some shared oncogenic stimulus to both nevus cells and melanoma.28,29

Despite the histogenesis controversy, it seems likely that at some stage in its development, a choroidal melanoma will potentially resemble a choroidal nevus and be harbored within the “nevus” population until its ophthalmoscopic features give warning of its malignant portent and it ceases to be classed as a nevus. There is, therefore, great clinical interest in the follow-up of patients with choroidal nevi, and efforts continue to assess reliable indicators of likely growth and malignant potential.1,30 The present population-based survey of nevi provides useful baseline information to interpret follow-up studies of choroidal nevi.

To highlight the low probability of melanomas developing from existing choroidal nevi, Ganley and Comstock8 used a mixed clinical and population sample. They estimated that 1 choroidal melanoma would result from 4800 nevi per year, assuming all melanomas developed from lesions diagnosed initially as choroidal nevi. Using comparable data from our study, an incidence of 1 melanoma per 4300 nevi per year for both women and men could be estimated. In calculating this, we used recent data from the New South Wales Cancer Registry for choroidal melanoma incidence in the state of New South Wales for persons 50 years or older. The annual melanoma incidence rate for persons 50 years or older was 2.07 per 100 000 for women and 1.93 per 100 000 for men (oral and written communication, M. Coates, Bsc, MS; and C. Fleming, BOptom; New South Wales Cancer Council, New South Wales Cancer Council, 1997). It is possible that these rates may be higher than published annual incidence rates from the United States and Europe of 0.6 per 100 000, for all ages combined.27 There were no melanomas found in our small population. We used a nevus prevalence found of 9.8% in women and 8.3% for men, after correcting for the 25% of nevi likely to be missed by the photographs. The correction was derived from Naumann et al,31 who suggested from combined clinical and histopathologic findings, that three quarters of choroidal nevi are located at the posterior pole and immediate surrounds, a similar retinal area to that documented in our subjects.

Prevalence rates from past studies of choroidal nevi have varied widely, probably because of different examination methods and samples (Table 1). In a histopathologic examination of 100 eyes, 102 nevi were found, of which only 10 had been diagnosed clinically.3 The causes of clinical oversight were considered to be small nevi, opaque media, and lack of dense pigment that reduced contrast. Few data are available on the prevalence of choroidal nevi in persons of noncaucasian race, although they have been considered to be rare.33 In a nevus prevalence study of 250 office-based patients, Gass found a high prevalence rate (30%), with an increase in prevalence in older age groups.1 However, we found a slight decrease in prevalence with increasing age. We are not able to explain this decrease, although it could have resulted from the smaller sample of people in the older age groups or the effects of media opacity on diagnosis of subtle nevi. When comparing nevus prevalence rates using photographic grading with those of past studies that used indirect ophthalmoscopy, one must recognize that about 25% of nevi will be missed by the limitation of the photographic field, as outlined above.

Many studies have been undertaken to elucidate features of nevi that might best predict growth and malignant potential.30-34 Orange pigment (lipofuscin), subretinal fluid, and pigment clumps, all presumably caused by retinal epithelial damage as an underlying nevus enlarges, have been associated with lesion growth.1,30,33,35 As it is widely accepted that the likelihood of significant growth and malignant change in a population-based sample of nevi is small, then it seemed likely that indicators of growth and malignancy would be correspondingly scarce in our study sample. This proved to be the case after comparing these morphologic predictors with the data obtained from our population. Only 1 participant in our series had signs of minimal orange pigment. Two subjects had signs of subretinal fluid and pigment clumping and in both these cases the nevi looked otherwise small and benign.

Most clinical series investigating factors predictive of nevus growth have found that larger, elevated lesions are more likely to grow and become malignant than are smaller, flatter lesions.1,30-34 Gass suggested that nevi with diameters greater than 6 mm and thickness greater than 2 mm were more likely to grow but that this did not necessarily imply malignant growth.1 Tamlar and Maumenee7 observed nevi of less than 2 disc diameter (3 mm) and noted no growth after 9 years. Our average lesion measured only 1.25 mm in diameter (SD, 0.72 mm), which suggests a low likelihood of significant growth for most lesions, as might be expected in a population sample. Unfortunately, we do not have data on nevus height, although we can anecdotal report that the lesions we studied gave an impression of being quite flat in almost all cases.
The significance of drusen overlying nevi is equivocal, but the sign is thought to indicate low growth potential.1,25,30,33 One difficulty when interpreting drusen data between studies is that drusen descriptions have not been standardized and drusen detection methods have varied. Although Naumann et al25 found that 26% of nevi had overlying drusen histologically, they conceded that ophthalmoscopy was more reliable for drusen detection and later reported drusen in 51% of cases using ophthalmoscopy.33 Hale et al33 found drusen over 80% of nevi using transillumination on postmortem eyes. To standardize the grading of overlying drusen, we used the WARMGS29,31 and our grading identified different prevalence rates for drusen differing in size and type. Indistinct C0 drusen were seen overlying 98% of nevi, yet ophthalmoscopically visible distinct C6 or larger drusen were found on only 42% of nevi. Our finding of larger drusen overlying larger nevi supports the concept that this sign reflects chronicity of the nevus.

Several series29,30,34 have suggested an association between nevus growth and proximity of its posterior edge to the optic disc. However, of 264 nevi in our study, 42% of nevi were within 2 disc diameter of the disc, suggesting that this is a relatively common feature. Although several articles have reported a relatively common reduction in visual acuity from choroidal nevi,27,31 we found no cases with nevi involving the macular area in which reduced vision could be attributed to the nevus. After excluding subjects with a demonstrable cause of reduced vision, the remainder had a median refracted visual acuity of 20/20. Gonder et al27 noted reduced acuity in 11% of 206 patients referred to an oncology clinic for assessment of pigmented choroidal tumors. These posterior lesions averaged 4.3 mm in basal diameter and 0.7 mm in thickness, which was much larger than those in our study. The authors attributed the visual impairment to serous foveal detachment (50%), photoreceptor degeneration (42%), and subretinal choroidal neovascularization (8%).

In conclusion, our study has documented prevalence and characteristics of choroidal nevi in a large, representative, older population. Most nevi found were relatively small, without features predictive of growth or malignant transformation. Visual acuity was not affected by these small nevi. Characteristics of drusen overlying choroidal nevi were also documented.

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REFERENCES


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