

Ten-Year Incidence and Progression of Age-related Maculopathy

The Beaver Dam Eye Study

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Purpose: The aim of the study was to describe the 10-year incidence and progression of retinal drusen, retinal pigmentary abnormalities, and signs of late age-related maculopathy.

Design: Population-based cohort study.

Participants: The study included 4926 persons, 43 to 86 years of age at the time of a baseline examination from 1988 through 1990, living in Beaver Dam, Wisconsin, of whom 3684 participated in a 5-year follow-up examination and 2764 participated in a 10-year follow-up.

Methods: Characteristics of drusen and other lesions typical of age-related maculopathy were determined by grading stereoscopic color fundus photographs using the Wisconsin Age-Related Maculopathy Grading System.

Main Outcomes Measures: Incidence of drusen type and size, pigmentary abnormalities, geographic atrophy, and exudative degeneration.

Results: The 10-year incidence of early age-related maculopathy was 12.1% and of late age-related maculopathy it was 2.1%. There was a statistically significant increased incidence of age-related maculopathy lesions with age ($P < 0.05$). Individuals 75 years of age or older at baseline had significantly ($P < 0.01$) higher 10-year incidences of the following characteristics than people 43 to 54 years of age: larger sized drusen (125 μm –249 μm , 26.3% vs. 3.3%; $\geq 250 \mu\text{m}$, 16.2% vs. 1.0%), soft indistinct drusen (22.2% vs. 2.2%), retinal pigment abnormalities (19.5% vs. 0.8%), exudative macular degeneration (4.1% vs. 0%), and pure geographic atrophy (3.1% vs. 0%). Compared with those with small numbers of only small, hard drusen (1–2), those with large numbers of only hard drusen (8 or more) had an increased 10-year incidence of both soft drusen (12.3% vs. 6.7%) and pigmentary abnormalities (4.9% vs. 1.7%). Eyes with soft indistinct drusen or retinal pigmentary abnormalities at baseline, were more likely to develop late age-related macular degeneration at follow-up than eyes without these lesions (15.1% vs. 0.4% and 20.0% vs. 0.8%, respectively).

Conclusions: These population-based estimates document the high incidence of signs of age-related maculopathy in people 75 years of age or older. Our findings demonstrate that large numbers of hard drusen predict the incidence of soft drusen and pigmentary abnormalities and that the presence of the latter lesions significantly increases the risk for the development of geographic atrophy and exudative macular degeneration. *Ophthalmology* 2002;109:1767–1779 © 2002 by the American Academy of Ophthalmology.

Age-related macular degeneration is a leading cause of loss of vision in persons 65 years of age or older in the United

States.^{1–4} Most information regarding its natural history has come from case series of patients attending ophthalmology clinics,^{5–13} clinical trials of the late stages of the disease,^{14–16} or clinicopathologic studies.^{17–22} Estimates of progression to late stages of age-related maculopathy (ARM) have usually been based on the study of the uninjured fellow eye of people with unocular late age-related macular degeneration.^{5–7,10–12,15,16} Only a few studies have examined the incidence of late age-related macular degeneration in people free of this condition in both eyes.^{6,9,10,23–26} In addition, there are few population-based data regarding the association of small hard drusen to the incidence of large soft drusen, pigmentary abnormalities, and other more severe lesions of ARM.^{23,24} The purpose of this report was to describe the 10-year incidence, progression, regression, and interrelationships of lesions associated with early and late ARM in a large population-based cohort.

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Table 1. Definitions of Changes in Lesions Associated with Age-related Maculopathy

| | Incidence | | Progression | Disappearance | | Regression |
|--|--|---|---|---|---|---|
| | Maximum at Baseline* | Maximum at Follow-up* | | Maximum at Baseline* | Maximum at Follow-up* | |
| Drusen size | 0 [†] 0 to <63 μm 0 to <125 μm 0 to <250 μm ≥250 μm | <63 μm 63 to <125 μm 125 μm to <250 μm ≥250 μm | Same maximum size as baseline but ≥2 additional involved subfields | 0 <63 μm 63 to <125 μm 125 to <250 μm ≥ 250 μm | — 0 0 to <63 μm 0 to <125 μm 0 to >250 μm | Same maximum size as baseline but ≥2 fewer involved subfields |
| Drusen type | None, HI None, HI, HD None, HI, HD, SD SI | HD SD SI — | Same maximum type as baseline but ≥2 additional involved subfields | None, HI HD SD SI | — None, HI None, HI, HD None, HI, HD, SD | Same maximum as baseline but ≥2 fewer involved subfields |
| Retinal pigment epithelial depigmentation (RPE depigmentation) | The advent of definite RPE depigmentation in any subfield when none was present in any subfield at baseline | | Same maximum score as baseline but ≥2 additional involved subfields OR An increase in the maximum score from baseline | The absence of RPE depigmentation in all subfields when RPE depigmentation was definitely present in at least one subfield at baseline | | Same maximum score as baseline but ≥2 fewer involved subfields OR A decrease in the maximum score from baseline |
| Increased retinal pigment | (same as RPE depigmentation) | | (same as RPE depigmentation) | (same as RPE depigmentation) | | (same as RPE depigmentation) |
| Pure geographic atrophy | The advent of definite geographic atrophy in any subfield when no geographic atrophy was present in any subfield at baseline | | An increase of ≥2 additional involved subfields from baseline OR The extension from the outer/inner subfields into the central circle when the central circle was not involved at baseline | The absence of geographic atrophy in all subfields when geographic atrophy was definitely present in at least one subfield at baseline | | A decrease of ≥2 involved subfields from baseline OR The center circle becoming uninvolved |
| Exudative ARM Retinal pigment epithelial detachment and/or Subretinal hemorrhage and/or Subretinal fibrous scar | The advent of any exudative ARM in any subfield when no exudative ARM was present in any subfield at baseline | | An increase of ≥2 additional involved subfields from baseline OR The extension from the outer/inner subfields into the central circle when the central circle was not involved at baseline OR The appearance of more severe exudative ARM lesions | The absence of any exudative lesion in all subfields when an exudative lesion was definitely present in at least one subfield at baseline | | A decrease of ≥2 involved subfields from baseline OR The center circle becoming uninvolved |

ARM = age-related maculopathy; HD = hard distinct; HI = hard indistinct; SD = soft distinct; SI = soft indistinct.

* Baseline and follow-up conditions must be true.

† Whenever 0, none, or absent appear in the table, questionable is included.

Materials and Methods

Population

Methods used to identify the population and descriptions of the population have appeared in previous reports.^{27,28} A private census of the population of Beaver Dam, Wisconsin (99% white) was

performed from fall 1987 to spring 1988 in people 43 to 84 years of age. Of the 5924 eligible individuals, 4926 participated in the baseline examination from 1988 through 1990.²⁸ Of these, 3684 (81.1%) participated in the 5-year follow-up examination from 1993 through 1995. Comparisons between participants and non-participants at baseline and the 5-year follow-up examinations have appeared elsewhere.^{28,29}

Table 2. Ten-year Incidence of Drusen by Size and Type, Increased Retinal Pigment, Retinal Pigment Epithelial Depigmentation, Geographic Atrophy, and Exudative Macular Degeneration in the Right Eye

| Lesion | No. Missing* | No. with Lesion Present at Baseline | No. at Risk | Incidence (%) |
|--|--------------|-------------------------------------|-------------|---------------|
| Drusen size | | | | |
| <63 μm | 107 | 3006 | 362 | 65.4 |
| $\geq 63 \mu\text{m}$ to <125 μm in diameter | 93 | 847 | 2535 | 14.0 |
| $\geq 125 \mu\text{m}$ to <250 μm in diameter | 91 | 327 | 3057 | 8.8 |
| $\geq 250 \mu\text{m}$ in diameter | 90 | 87 | 3298 | 4.0 |
| Drusen type | | | | |
| Soft distinct | 90 | 535 | 2850 | 7.5 |
| Soft indistinct | 91 | 282 | 3102 | 8.0 |
| Pigmentary abnormalities | | | | |
| Increased retinal pigment | 58 | 245 | 3172 | 6.0 |
| RPE depigmentation | 80 | 125 | 3270 | 4.5 |
| Geographic atrophy | 39 | 14 | 3422 | 0.6 |
| Exudative macular degeneration | 115 | 13 | 3347 | 0.9 |

RPE = retinal pigment epithelium.

* Number missing because lesion was ungradable at baseline or follow-up.

Of those surviving, 3684 (81%) took part in the baseline and second examinations, 2764 (82.9%) participated in the 10-year follow-up examination between March 1, 1998 and June 9, 2000. The mean and median times between the baseline and 10-year follow-up examinations were 10.1 years and 10 years, respectively.

Comparisons between participants and nonparticipants at the 10-year follow-up have been presented elsewhere.³⁰ In general, persons who did not participate in the 10-year follow-up were older at baseline than those who did. After adjusting for age, persons who did not participate were more likely to be retired, to have completed fewer years of education, and to have lower income, poorer visual acuity, a history of never drinking alcohol, a higher number of packs-years smoked, and a poorer cardiovascular risk profile than persons who participated. After adjusting for age and gender, participants with early ARM at baseline were as likely to participate as those in whom ARM was absent (data not shown).

Procedures

Similar procedures were used at baseline and follow-up examinations.²⁷⁻³⁵ Informed consent was obtained at the beginning of each examination. Pertinent parts of the examination at both baseline and follow-up consisted of taking stereoscopic 30° color fundus photographs centered on the disc (Diabetic Retinopathy Study standard field 1) and macula (Diabetic Retinopathy Study standard field 2) and a nonstereoscopic color fundus photograph temporal to but including the fovea of each eye.

Of the 2698 people with gradable fundus photographs at the baseline and 5-year follow-up examinations, 2685 (99.5%) had gradable photographs at the 10-year visit (2617 in both eyes, 31 in the right eye only, and 37 in the left eye only). Of the 2685 people with gradable photographs in at least 1 eye at all examinations, 22 (0.8%) were excluded from the analyses because of the presence of confounding lesions unrelated to ARM. For this reason, an additional 67 persons (2.5%) had 1 eye excluded from these analyses

Table 3. Ten-Year Progression, Regression, and Disappearance of Drusen by Size and Type, Increased Retinal Pigment, Retinal Pigment Epithelial Depigmentation, Geographic Atrophy, and Exudative Macular Degeneration in the Right Eye

| Lesion | No. at Risk | Progression* (%) | No. at Risk | Regression† (%) | No. at Risk | Disappearance‡ (%) |
|--|-------------|------------------|-------------|-----------------|-------------|--------------------|
| Drusen size | | | | | | |
| <63 μm | 1951 | 28.6 | 1344 | 48.9 | 2159 | 14.8 |
| $\geq 63 \mu\text{m}$ to <125 μm in diameter | 519 | 15.0 | 65 | 17.8 | 520 | 16.6 |
| $\geq 125 \mu\text{m}$ to <250 μm in diameter | 239 | 18.4 | 35 | 30.4 | 246 | 32.1 |
| $\geq 250 \mu\text{m}$ in diameter | 86 | 12.8 | 24 | 30.8 | 87 | 58.2 |
| Drusen type | | | | | | |
| Soft distinct | 252 | 11.3 | 26 | 7.1 | 253 | 12.5 |
| Soft indistinct | 272 | 42.0 | 91 | 32.2 | 282 | 34.5 |
| Pigmentary abnormalities | | | | | | |
| Increased retinal pigment | 245 | 53.8 | 121 | 34.6 | 245 | 12.0 |
| RPE depigmentation | 125 | 45.1 | 56 | 50.1 | 125 | 8.1 |
| Geographic atrophy | 9 | 55.6 | 9 | 0 | 12 | 0 |
| Exudative macular degeneration | 12 | 33.3 | 12 | 16.7 | 13 | 23.1 |

RPE = retinal pigment epithelium.

* Progression is described here as including only those with condition at baseline and excludes eyes in which eight or nine subfields have lesions.

† Regression is described here as including only those with condition in three or more subfields at baseline.

‡ Disappearance is described here as including only those with condition at baseline in the absence of a larger lesion.

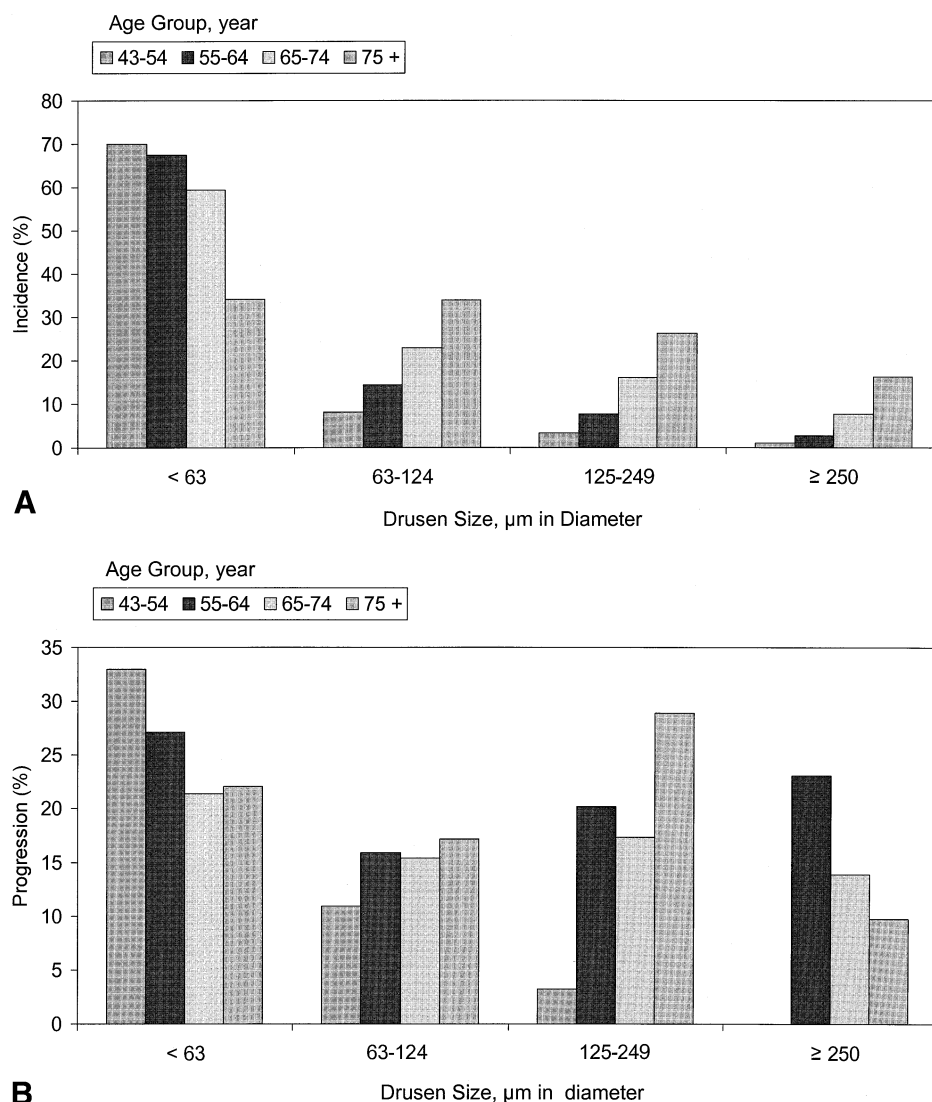


Figure 1. Relation of age to 10-year (A) incidence and (B) progression rates of various sized drusen in the right eye in the Beaver Dam Eye Study.

and 67 others had 1 eye excluded because it was ungradable at one or more examination. For purposes of this report, the 2663 people with at least 1 eye evaluable at all 3 examinations (right eye, $n = 2592$; left eye, $n = 2600$; both eyes, $n = 2529$) are included in the analyses. Additional data from 945 people seen only at the baseline and 5-year follow-up examinations also contributes to the analysis.

Details of the grading procedure have been described previously.³¹⁻³⁵ In brief, a circular grid was placed on the photographic slide, which divided the macular area into nine subfields, consisting of a central (a single subfield), inner (comprising the four inner subfields), and outer (comprising the four outer subfields) circle. Some lesions were graded in each subfield, other lesions only in Diabetic Retinopathy Study field 2 as a whole, and still others in additional fields. For the purpose of this report, measurements made only within the nine subfields defined by the grid are presented. Circles of defined size (63 μm , 125 μm , 175 μm , 250 μm , 322 μm , 350 μm , and 644 μm in diameter) printed on clear plastic were used to estimate size of drusen and areas involved by drusen, increased retinal pigment, and retinal pigment epithelial depigmentation.

Two gradings were performed for each eye.^{24,30-35} First, a

preliminary masked grading was carried out by one of two senior graders (SMM). Next, detailed gradings were performed by one of three other experienced graders. For detailed grading, each eye was graded independently of the fellow eye. The assessment consisted of a subfield-by-subfield, lesion-by-lesion evaluation of each photograph set using the Wisconsin Age-Related Maculopathy Grading System.^{33,34} Next, a series of edits and reviews was performed. The presence and severity of specific lesions at the third examination (e.g., maximum drusen size, type, area, and pigmentary abnormalities, as determined by detailed grading) were compared with that of the preliminary grading. Standardized edit rules were used to adjudicate disagreements.^{24,34} As a result of this edit, changes were made for at least 1 lesion in 1456 of the 5874 eyes (24.8%) graded at the 10-year follow-up.

Finally, the detailed graders were asked to make side-by-side comparisons between baseline, 5-year, and 10-year follow-up photographs for eyes that showed change for ARM lesions between baseline and follow-up. These edits were masked as to whether the photographs were taken at baseline or follow-up. As a result of this edit, changes were made for at least 1 ARM-related lesion in 2255 of the 11,748 eyes (19.2%) graded at baseline and follow-up.

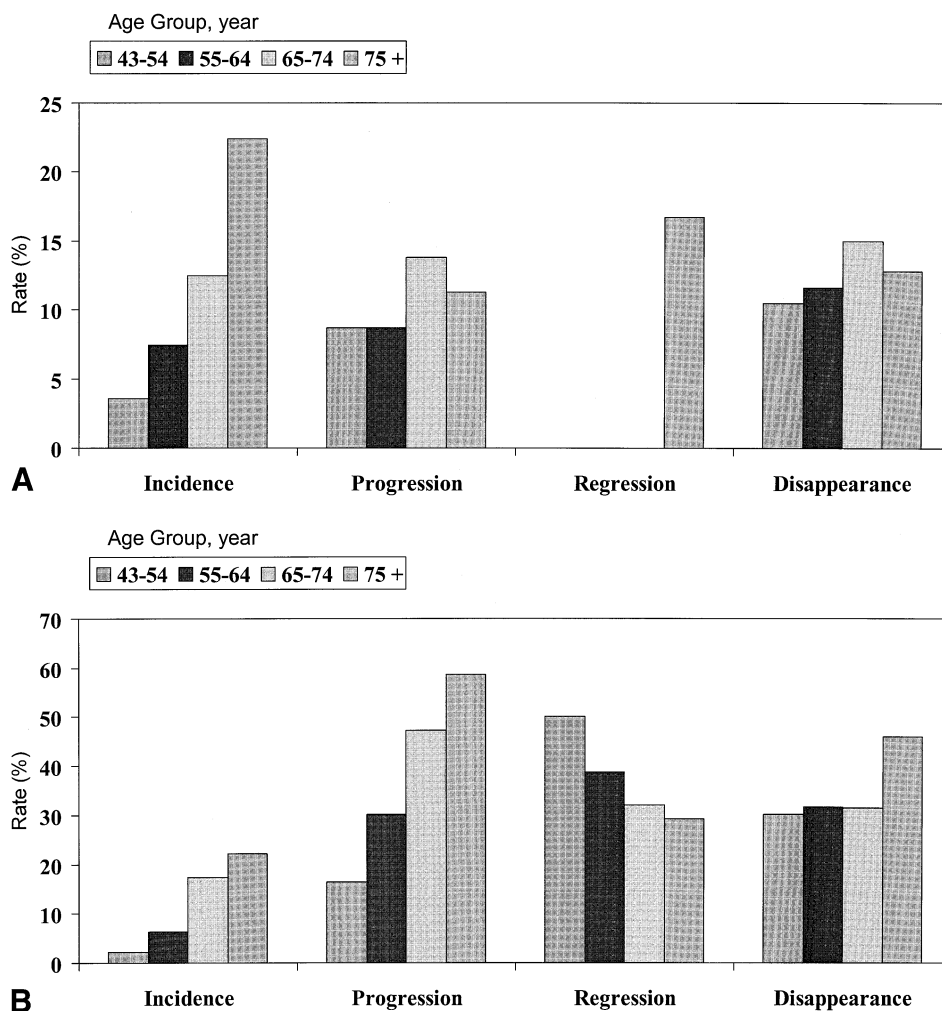


Figure 2. Relation of age to 10-year incidence, progression, regression, and disappearance rates of (A) soft distinct drusen and (B) soft indistinct drusen in the right eye in the Beaver Dam Eye Study.

Definitions

Definitions of the incidence and progression of early and late ARM and their component lesions are summarized in Table 1.^{24,33-35}

To evaluate change in lesions between visits, it was necessary to have data from corresponding gradable subfields at both visits. For example, the inner superior subfields for the specific eye would have to be gradable for a specific lesion at the first and second, the first and third, or all visits to contribute to estimates of incidence or progression of that lesion.

Incidence was determined for each maximum drusen size, each drusen type, increased retinal pigment, RPE depigmentation, signs of exudative macular degeneration, and pure geographic atrophy. The incidence of a specific lesion was defined by its presence at follow-up when it was not present at baseline in any of the subfields that could be graded at both examinations. For example, an eye was considered to have incident soft, indistinct drusen if none of the subfields had this lesion at baseline and this lesion was present in one or more subfields at follow-up.

The incidence of early ARM was defined by the presence of either soft indistinct drusen or the presence of any type of drusen associated with RPE depigmentation or increased retinal pigment at follow-up when none of these lesions was present at baseline. The incidence of late ARM was defined by the appearance of

either exudative macular degeneration or pure geographic atrophy at follow-up when neither lesion was present at baseline.

Progression was also defined specifically for each lesion (Table 1). For example, progression of a specific size or type of drusen was defined by the presence of that lesion in at least one subfield at baseline and its appearance in two or more additional corresponding gradable subfields at either the 5- or 10-year follow-up,

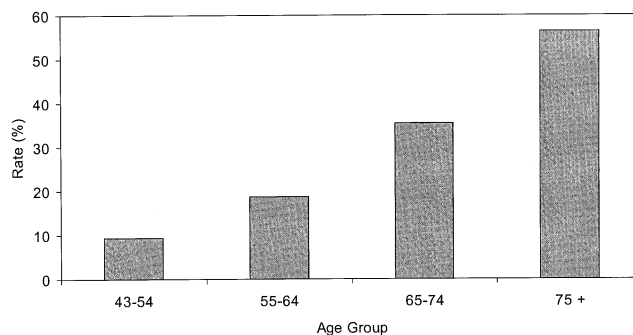


Figure 3. Relation of age to the 10-year development of increased drusen area in the right eye in the Beaver Dam Eye Study.

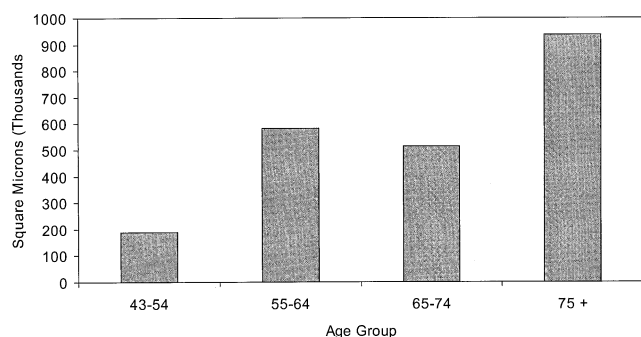


Figure 4. Relation of age to the average change in overall drusen area from baseline to the 10-year follow-up in the right eye in the Beaver Dam Eye Study.

in the absence of developing a larger drusen or more severe type of drusen. Regression of a specific size (or type) of drusen in an eye was defined by a decrease in its size (or severity) in two or more corresponding gradable subfields from baseline to either the 5- or 10-year follow-up, with a similar size (or type) drusen remaining in at least one of these subfields at follow-up (Table 1). Disappearance of a lesion was defined as its presence in at least one subfield at baseline and its absence in all subfields at either the 5- or 10-year follow-up. The categories of incidence, progression, regression, and disappearance were not mutually exclusive. Changes in drusen area have been defined elsewhere.²⁴

Statistical Methods

The SAS statistical software was used for analyzing the data.³⁶ In all analyses, age (defined at the time of the baseline examination) was treated categorically in the following groups: 43 to 54 years, 55 to 64 years, 65 to 74 years, and 75 years of age or older. Approaches used in the analyses allowed those who were right censored (not seen after the 5-year examination because of death or dropout) to contribute information to the estimates. Cumulative events were estimated using the Kaplan-Meier (product limit) survival approach.³⁷ Multivariate risk ratios and 95% confidence intervals (CIs) were calculated from the Cox proportional hazard model.³⁸ The relationships between age and rate estimates were tested by treating age, categorized as previously described, as a continuous variable in the Cox proportional hazards model and computing the chi-square test statistic for the parameter estimate. The same method was used to examine trends in other risk factors.

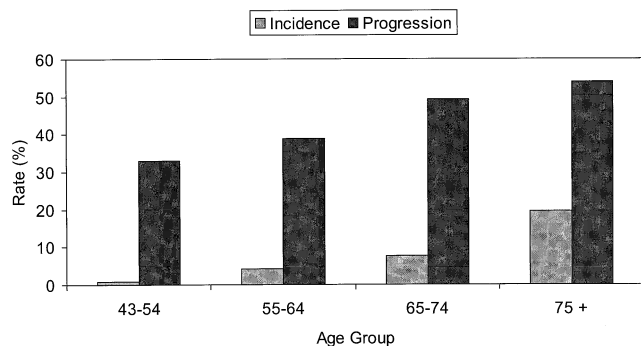


Figure 5. Relation of age to the 10-year incidence and progression rates of retinal pigment epithelium depigmentation in the right eye in the Beaver Dam Eye Study.

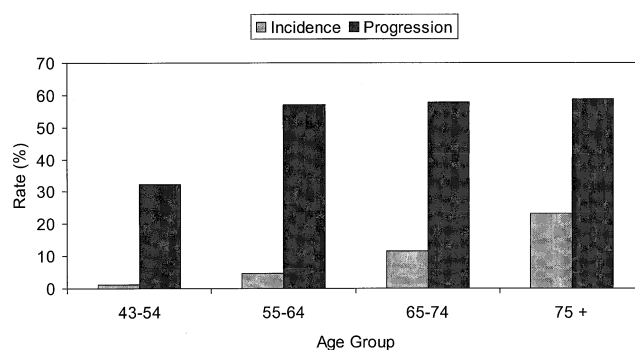


Figure 6. Relation of age to the 10-year incidence and progression rates of increased retinal pigment in the right eye in the Beaver Dam Eye Study.

Results

Because the 10-year change of different lesions in the right and left eyes are similar, analyses for lesions associated with ARM will be presented for the right eye only. The 10-year change of maximum size drusen in right eyes is given in Tables 2 and 3. The numbers at risk for incidence, progression, regression, and disappearance of maximum size drusen vary because of differences in definitions. Some photographs were not gradable for a given lesion at all visits. For example, those at risk for development of a specific drusen size may have drusen smaller than the minimum for each group at baseline. Incidence is more likely and disappearance less likely for smaller than for larger drusen. The incidence of small drusen (<63 μm in diameter) decreased with age (test of trend, $P = 0.04$), whereas the incidence of larger drusen increased with age (test of trend, $P < 0.01$ for larger drusen; Fig 1A). Over the 10-year period of the study, persons 75 years of age or older at baseline were 5.2 times (95% CI, 3.3,8.1) as likely to develop drusen 63 μm or larger to less than 125 μm in diameter, 10.0 times (95% CI, 6.6,17.0) as likely to develop drusen 125 μm or larger to less than 250 μm in diameter, and 17.0 times (95% CI, 8.5,35.0) as likely to develop drusen 250 μm or larger in diameter as persons 43 to 54 years of age. The relation of progression of drusen to age was not consistent among drusen of different sizes (Fig 1B). There was no relationship of regression or disappearance of large drusen with age (data not shown). There were no statistically significant ($P < 0.10$) differences between the 10-year change of various size drusen in men and women or between right and left eyes (data not shown). Incidence of drusen 63 μm or larger to less than 125 μm in diameter in the worse eye was 19.9% (95% CI, 19.0,20.8); for drusen 125 μm or larger to less than 250 μm in diameter, it was

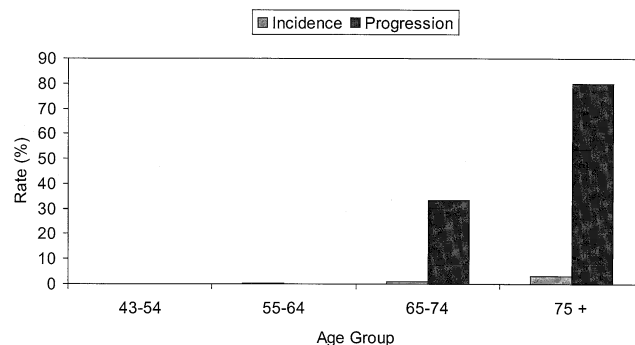


Figure 7. Relation of age to the 10-year incidence and progression rates of geographic atrophy in the right eye in the Beaver Dam Eye Study.

Table 4. Relation of Age and Gender to the 10-year Incidence of Early Age-related Maculopathy in the Beaver Dam Eye Study

| Age (yrs) | By Right Eye | | | | By Participant | | | |
|---------------|--------------------------|--|--------------------------|---|--------------------------|--|--------------------------|---|
| | No. at Risk at Baseline* | Incidence of Early Age-related Maculopathy (%) | No. at Risk at Baseline* | Incidence of Late Age-related Maculopathy (%) | No. at Risk at Baseline* | Incidence of Early Age-related Maculopathy (%) | No. at Risk at Baseline* | Incidence of Late Age-related Maculopathy (%) |
| Men | | | | | | | | |
| 43-54 | 533 | 3.0 | 567 | 0.0 | 513 | 4.7 | 576 | 0.0 |
| 55-64 | 412 | 6.7 | 465 | 1.1 | 384 | 10.6 | 482 | 1.5 |
| 65-74 | 282 | 17.6 | 349 | 4.2 | 265 | 21.7 | 368 | 4.6 |
| 75+ | 67 | 17.0 | 96 | 1.0 | 66 | 28.7 | 103 | 5.8 |
| Total | 1294 | 7.8 | 1477 | 1.3 | 1228 | 10.9 | 1529 | 1.7 |
| Women | | | | | | | | |
| 43-54 | 632 | 2.5 | 658 | 0.0 | 623 | 3.7 | 674 | 0.1 |
| 55-64 | 485 | 6.6 | 534 | 0.6 | 472 | 10.7 | 550 | 0.6 |
| 65-74 | 413 | 19.7 | 503 | 2.5 | 389 | 24.8 | 531 | 4.3 |
| 75+ | 122 | 34.5 | 185 | 9.1 | 119 | 40.8 | 212 | 11.3 |
| Total | 1652 | 9.8 | 1880 | 1.6 | 1603 | 13.0 | 1967 | 2.4 |
| Men and women | | | | | | | | |
| 43-54 | 1165 | 2.7 | 1225 | 0.0 | 1136 | 4.1 | 1250 | 0.1 |
| 55-64 | 897 | 6.7 | 999 | 0.8 | 856 | 10.7 | 1032 | 1.0 |
| 65-74 | 695 | 18.9 | 852 | 3.2 | 654 | 23.6 | 899 | 4.4 |
| 75+ | 189 | 28.9 | 281 | 6.6 | 185 | 36.7 | 315 | 9.5 |
| Total | 2946 | 8.9 | 3357 | 1.4 | 2831 | 12.1 | 3496 | 2.1 |

* The number at risk at baseline were those seen at follow-up.

12.4% (95% CI, 11.8,13.0); and for drusen 250 μm or larger in diameter it was 6.4% (95% CI, 5.9,6.9).

Over the 10-year period, soft indistinct drusen were more likely to change than soft distinct drusen (Tables 2 and 3). The incidence of soft distinct drusen (test of trend, $P < 0.01$) and incidence and progression of soft indistinct drusen (test of trend, $P < 0.01$) increased with age (Fig 2A,B). Persons 75 years of age or older at baseline were 7.0 times (95% CI, 4.2,12.0) as likely to develop soft distinct drusen, and were 12.0 times (95% CI, 7.1,20.0) as likely to develop soft indistinct drusen as persons 43 to 54 years of age. Of the 25 right eyes in which soft distinct drusen disappeared, 2 developed RPE depigmentation and 1 developed exudative macular degeneration. Retinal pigment epithelium depigmentation developed or progressed in 16, and geographic atrophy or exudative macular degeneration developed in 6 of the 70 right eyes with disappearance of soft indistinct drusen. After adjusting for age, there were no statistically significant differences in the 10-year change of different types of drusen between men and women or between right and left eyes (data not shown). Incidence of soft

distinct drusen in the worse eye was 10.3% (95% CI, 9.7,10.9) and soft indistinct drusen was 10.2% (95% CI, 9.6,10.8).

Of the right eyes, 16.9% had an increase in drusen area, 3.3% had a decrease, and 79.8% had no net change between the first and third examination. The average increase in drusen area among the 16.9% of right eyes in which drusen area increased was 0.521 mm² (approximately 0.3 disc areas). The incidence of increased drusen area varied with age from 9.4% in right eyes of persons 43 to 54 years of age to 56.4% in those 75 years of age or older (test of trend, $P < 0.01$; Fig 3). Persons 75 years of age or older at baseline were 11.8 times (95% CI, 8.6,16.2) as likely to have an increase in drusen area as persons 43 to 54 years of age. The average change in drusen area in these eyes increased with age (Fig 4). After adjusting for age, there were no differences in the incidence of increased drusen area between men and women or between right or left eyes (data not shown).

The incidence, progression, and disappearance of increased retinal pigment were higher than for RPE depigmentation (Tables 2 and 3). Geographic atrophy or exudative macular degeneration

Table 5. Relation of Drusen Size at Baseline to the 10-year Incidence of Drusen Type, Increase in Area of Drusen, Retinal Pigment Epithelium Depigmentation, Increased Retinal Pigment, Pure Geographic Atrophy, and Exudative Macular Degeneration in the Right Eye

| Maximum Drusen Diameter | Drusen Type | | | | | | Increased Drusen Area | Retinal Pigment Epithelium Depigmentation | | Increased Retinal Pigment | | Any Pigmentary Abnormalities | | Pure Geographic Atrophy | | Exudative Macular Degeneration | | |
|-------------------------|---------------|------|---------------|------|-----------------|------|-----------------------|---|------|---------------------------|------|------------------------------|------|-------------------------|------|--------------------------------|------|------|
| | Hard Distinct | | Soft Distinct | | Soft Indistinct | | | n | % | n | % | n | % | n | % | n | % | |
| | n | % | n | % | n | % | | | | | | | | | | | | |
| None | 362 | 68.6 | 380 | 3.9 | 362 | 1.7 | 316 | 9.9 | 364 | 1.2 | 366 | 2.7 | 368 | 2.7 | 381 | 0.0 | 355 | 0.0 |
| <63 μm | — | — | 2173 | 5.8 | 2173 | 4.7 | 2073 | 14.2 | 2144 | 1.9 | 2118 | 3.1 | 2115 | 3.1 | 2191 | 0.0 | 2158 | 0.0 |
| ≥63 μm to <125 μm | — | — | 315 | 24.4 | 464 | 23.0 | 486 | 40.7 | 483 | 7.1 | 452 | 11.3 | 450 | 11.7 | 527 | 0.3 | 517 | 1.0 |
| ≥125 μm to <250 μm | — | — | — | — | 90 | 31.9 | 216 | 55.2 | 202 | 21.3 | 168 | 25.8 | 167 | 25.8 | 229 | 4.4 | 229 | 4.5 |
| ≥250 μm | — | — | — | — | 13 | 50.8 | 63 | 42.6 | 54 | 54.3 | 39 | 44.4 | 37 | 43.8 | 59 | 11.7 | 64 | 24.4 |

n = number at risk at baseline.

Table 6. Relation of Drusen Type at Baseline to the 10-year Incidence of Increase in Drusen Area, Retinal Pigment Epithelium Depigmentation, Increased Retinal Pigment, Pure Geographic Atrophy, and Exudative Macular Degeneration in the Right Eye

| Drusen Type | Increased Drusen Area | | Retinal Pigment Epithelium Depigmentation | | Increased Retinal Pigment | | Any Pigmentary Abnormalities | | Pure Geographic Atrophy | | Exudative Macular Degeneration | |
|-------------------------|-----------------------|------|---|------|---------------------------|------|------------------------------|------|-------------------------|-----|--------------------------------|-----|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| None or hard indistinct | 316 | 9.9 | 374 | 1.2 | 375 | 2.7 | 375 | 2.7 | 378 | 0 | 362 | 0 |
| Hard distinct | 2368 | 16.7 | 2420 | 2.6 | 2375 | 3.9 | 2372 | 4.0 | 2465 | 0 | 2447 | 0 |
| Soft distinct | 228 | 47.5 | 223 | 10.8 | 200 | 15.6 | 198 | 14.5 | 246 | 1.2 | 239 | 2.0 |
| Soft indistinct | 242 | 55.3 | 206 | 29.6 | 169 | 31.3 | 166 | 31.1 | 241 | 6.5 | 248 | 9.7 |

n = number at risk at baseline.

developed in four of the eight right eyes in which RPE depigmentation disappeared. The incidence and progression of pigmentary abnormalities increased with age ($P < 0.01$; Figs 5 and 6). There were no differences in the 10-year change of pigmentary abnormalities between men and women. Incidence of increased retinal pigment in the worse eye was 8.5%, and for RPE depigmentation it was 6.3%. Incidence of both increased with increasing age (data not shown).

The overall incidence of early ARM in right eyes was 8.9% (95% CI, 8.3,9.5), and it increased with age (test of trend, $P < 0.01$; Table 4). Over the 10-year period, persons 75 years of age or older at baseline were 14.0 times (95% CI, 8.3,22.0) as likely to develop early ARM as persons 43 to 54 years of age. There was no difference in the age-adjusted incidence of early ARM between eyes. The incidence of early ARM was 2.0 times (95% CI, 0.9,5.0) as likely in women at least 75 years of age or older compared with men in this age group. This relation was of borderline statistical significance ($P = 0.07$). Overall, incidence of early ARM in either eye was 12.1% (95% CI, 11.4,12.8) and increased with age.

The 10-year incidence of pure geographic atrophy in right eyes was 0.6% (95% CI, 0.5,0.7). Progression occurred in 55.6% of right eyes (Table 3). Incidence increased with age (test of trend, $P < 0.01$; Fig 7). Geographic atrophy did not occur before 55 years of age. Persons 75 years of age or older were 9.8 times (95% CI, 3.7,26.1) as likely to develop pure geographic atrophy as persons who were younger at baseline. The incidence in the worse eye was 0.8% (95% CI, 0.6,1.0).

The 10-year incidence of exudative macular degeneration in right eyes was 0.9% (95% CI, 0.7,1.1; Table 2). Disappearance of exudative macular degeneration occurred in one right eye in which a detachment of the RPE was present at baseline. Incidence in-

creased with age from 0% in those younger than 55 years of age to 4.1% in those 75 years or older at baseline (test of trend, $P < 0.01$; Fig 8). The incidence of exudative macular degeneration in the worse eye was 1.4% (95% CI, 1.2,1.6), rising from 0.1% in those younger than 55 years of age to 6.8% in those 75 years of age or older.

Right eyes with drusen 125 μm or larger and less than 250 μm in diameter at baseline were more likely to develop soft indistinct drusen (risk ratio [RR], 3.9; 95% CI, 2.4, 6.3), an increase in drusen area (RR, 3.6; 95% CI, 2.7, 4.7), increased retinal pigment (RR, 4.3; 95% CI, 2.9, 6.6), RPE depigmentation (RR, 5.4; 95% CI, 3.4, 8.5), pure geographic atrophy (4.4% vs. 0.1%), or exudative macular degeneration (4.5% vs. 0.2%) than right eyes, with only smaller drusen present at baseline (Table 5). Right eyes with soft distinct drusen were more likely to develop an increase in drusen area; soft, indistinct drusen (data not presented); pigmentary abnormalities; or signs of late ARM than eyes with only hard drusen present at baseline (Table 6). Similarly, right eyes with soft, indistinct drusen were more likely to develop an increase in drusen area (RR, 3.3; 95% CI, 2.5, 4.3), pigmentary abnormalities (RR, 5.3; 95% CI, 3.6, 7.9), geographic atrophy (6.5% vs. 0.1%), or exudative macular degeneration (9.7% vs. 0.2%) than right eyes that had only soft distinct or hard distinct drusen present at base-

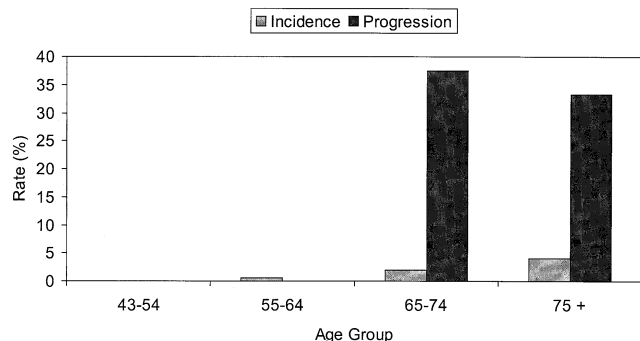


Figure 8. Relation of age to the 10-year incidence and progression rates of exudative macular degeneration in the right eye in the Beaver Dam Eye Study.

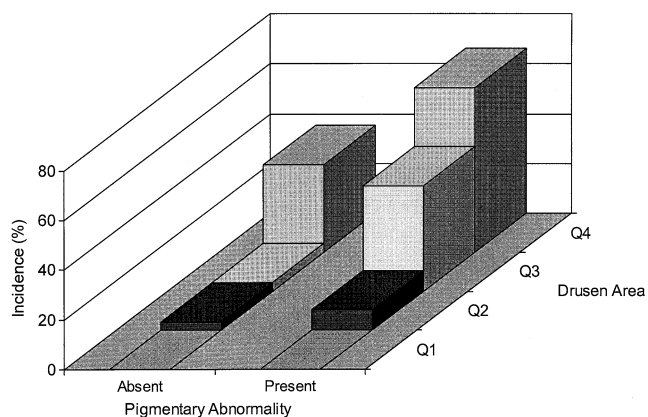


Figure 9. Relation of the presence of pigmentary abnormalities and increased drusen area in eyes with soft indistinct drusen present at baseline ($n = 263$) to the 10-year incidence of late age-related maculopathy in the right eye. The first quartile of drusen area is the equivalent of about 1 to 2 drusen, 200 μm in diameter, the second is the equivalent of approximately 3 to 5 drusen of this size, the third is the equivalent of approximately 6 to 12 drusen of this size, and the fourth quartile is the equivalent of approximately 13 to 265 drusen of this size.

Table 7. Relation of Type and Size of Drusen and Drusen Area at Baseline to the 10-year Incidence of Pigmentary Abnormalities, Geographic Atrophy, and Exudative Macular Degeneration in the Right Eye at Follow-up

| Drusen Area (μm^2) | Retinal Pigment Epithelium Depigmentation | | Increased Retinal Pigmentation | | Any Pigmentary Abnormalities | | Pure Geographic Atrophy | | Exudative Macular Degeneration | |
|------------------------------------|---|------|--------------------------------|------|------------------------------|------|-------------------------|------|--------------------------------|------|
| | No. at Risk* | % | No. at Risk* | % | No. at Risk* | % | No. at Risk* | % | No. at Risk* | % |
| Drusen type | | | | | | | | | | |
| Hard distinct | | | | | | | | | | |
| 1298–2596 | 730 | 1.1 | 728 | 1.7 | 728 | 1.7 | 736 | 0.2 | 728 | 0.2 |
| 2597–5192 | 483 | 1.7 | 473 | 3.3 | 471 | 3.4 | 487 | 0.0 | 485 | 0.0 |
| 5193–9086 | 339 | 3.4 | 432 | 3.0 | 432 | 3.2 | 449 | 0.0 | 445 | 0.0 |
| 9087–186,526 | 473 | 2.2 | 461 | 4.1 | 460 | 4.9 | 483 | 0.0 | 481 | 0.0 |
| Soft distinct | | | | | | | | | | |
| 5193–28,008 | 59 | 8.8 | 56 | 13.5 | 55 | 11.9 | 67 | 0.0 | 65 | 0.0 |
| 28,009–45,559 | 54 | 9.9 | 52 | 13.9 | 51 | 11.0 | 60 | 0.0 | 56 | 1.8 |
| 45,560–80,935 | 57 | 5.9 | 49 | 11.8 | 49 | 11.8 | 62 | 2.3 | 62 | 0.0 |
| 80,936–2,427,827 | 53 | 21.2 | 43 | 25.7 | 43 | 25.7 | 57 | 2.9 | 56 | 7.6 |
| Soft indistinct | | | | | | | | | | |
| 5193–69,803 | 56 | 14.6 | 55 | 20.2 | 54 | 20.5 | 68 | 0.0 | 65 | 0.0 |
| 69,804–157,685 | 57 | 8.2 | 45 | 18.0 | 45 | 18.0 | 72 | 2.1 | 73 | 3.4 |
| 157,686–393,743 | 56 | 41.3 | 45 | 45.5 | 45 | 45.5 | 59 | 8.3 | 62 | 7.4 |
| 393,744–8,330,254 [†] | 49 | 63.3 | 35 | 58.4 | 33 | 60.3 | 57 | 24.8 | 63 | 32.7 |
| Drusen size | | | | | | | | | | |
| <63 μm in diameter | | | | | | | | | | |
| 1298–2596 | 730 | 1.1 | 728 | 1.7 | 728 | 1.7 | 736 | 0.2 | 728 | 0.2 |
| 2397–5192 | 483 | 1.7 | 473 | 3.3 | 471 | 3.4 | 487 | 0.0 | 485 | 0.0 |
| 5193–9086 | 439 | 3.4 | 432 | 3.0 | 432 | 3.2 | 449 | 0.0 | 445 | 0.0 |
| 9087–186,526 | 473 | 2.2 | 461 | 5.1 | 460 | 4.9 | 483 | 0.0 | 481 | 0.0 |
| 63–124 μm in diameter | | | | | | | | | | |
| 5193–28,008 | 272 | 6.8 | 259 | 10.0 | 257 | 11.0 | 290 | 0.0 | 286 | 0.0 |
| 28,009–45,559 | 61 | 8.0 | 59 | 14.8 | 58 | 12.7 | 69 | 0.0 | 66 | 1.5 |
| 45,560–80,935 | 83 | 6.0 | 72 | 13.3 | 73 | 13.2 | 89 | 1.7 | 88 | 0.0 |
| 80,936–2,427,827 | 61 | 11.6 | 56 | 14.5 | 56 | 14.5 | 64 | 0.0 | 66 | 7.8 |
| $\geq 125 \mu\text{m}$ in diameter | | | | | | | | | | |
| 12,266–69,803 | 84 | 13.1 | 79 | 15.9 | 78 | 16.0 | 95 | 0.0 | 91 | 0.0 |
| 69,804–157,685 | 65 | 11.1 | 50 | 17.9 | 50 | 17.9 | 80 | 1.9 | 79 | 3.2 |
| 157,686–393,743 | 61 | 41.8 | 47 | 50.1 | 47 | 50.1 | 64 | 7.7 | 67 | 6.9 |
| 393,744–8,330,254 [†] | 54 | 63.0 | 39 | 55.8 | 37 | 57.4 | 61 | 26.2 | 67 | 29.1 |

* Varies because of missing data.

[†] Equivalent of 0.2 to 4.7 disc areas, assuming 1 disc area is 1,767,146 μm^2 .

line (Table 6). When only small, hard drusen (<63 μm in diameter) were present at baseline, larger drusen area (9087–186,526 μm^2 , equivalent to approximately 8–144 small drusen) was associated with increased incidence of soft distinct (7.5% vs. 4.3%) and indistinct (6.7% vs. 2.8%) drusen compared with right eyes with smaller drusen area (1298–2596 μm^2 , equivalent to approximately 1–2 small drusen). The relation of drusen type or size and area to the incidence of increased retinal pigment, RPE depigmentation, geographic atrophy, and exudative macular degeneration are presented in Table 7. A larger area of soft distinct drusen was not statistically significantly related to incidence of pigmentary abnormalities. Right eyes with soft indistinct drusen or drusen larger than 125 μm in diameter and larger areas of involvement by drusen were at higher risk of developing pigmentary abnormalities and late ARM. When soft indistinct drusen were present, right eyes with pigmentary abnormalities and greater drusen area were more likely to have signs of late ARM than eyes with less drusen area and no pigmentary abnormalities present at baseline (Fig 9). These relations were similar in left eyes (data not shown).

In right eyes with increased retinal pigment or RPE depigmentation present at baseline, soft distinct (RR, 2.0; 95% CI, 1.1, 3.6)

or soft indistinct (RR, 6.5; 95% CI, 4.5, 9.3) drusen, an increase in drusen area (RR, 3.5; 95% CI, 2.7, 4.5), geographic atrophy (8.2% vs. 0.1%), or exudative macular degeneration (RR, 11.0; 95% CI, 4.7, 24.0) was more likely to develop at follow-up compared with eyes without pigmentary abnormalities at baseline (Table 8). Similar relationships were found in left eyes (data not shown).

There were 190 persons with early ARM in both eyes at baseline who were examined at a follow-up examination. Of these, late ARM developed in 24 (12.6%), exudative macular degeneration developed in 16 (8.4%), and pure geographic atrophy developed in 8 (4.2%).

There were 26 persons who had unioocular, late ARM at baseline (15 with exudative macular degeneration and 11 with pure geographic atrophy) who were examined at follow-up. Of these, late ARM developed in 10 (38.5%) in the other eye over the 10-year period, exudative macular degeneration developed in 4 (15.4%), and pure geographic atrophy developed in 8 (30.8%); of which, pure geographic atrophy developed in 2 [7.7%] by the 5-year examination and then went on to exudative macular degeneration developed between the 5- and 10-year examinations. Five of eight persons in whom pure geographic atrophy and one of the

Table 8. Relation of Pigmentary Abnormalities at Baseline to the 10-year Incidence of Drusen Type, Increase in Drusen Area, Pure Geographic Atrophy, and Exudative Macular Degeneration in the Right Eye

| | Drusen Type | | | | Increased Drusen Area | | Pure Geographic Atrophy | | Exudative Macular Degeneration | |
|--------------------------------|---------------|------|-----------------|------|-----------------------|------|-------------------------|-----|--------------------------------|-----|
| | Soft Distinct | | Soft Indistinct | | No. at Risk | % | No. at Risk | % | No. at Risk | % |
| | No. at Risk | % | No. at Risk | % | | | | | | |
| Increased retinal pigmentation | | | | | | | | | | |
| Absent | 2749 | 7.2 | 2949 | 6.7 | 2838 | 18.7 | 3161 | 0.1 | 3106 | 0.5 |
| Present | 96 | 15.8 | 144 | 35.3 | 227 | 53.1 | 215 | 8.4 | 227 | 6.1 |
| RPE depigmentation | | | | | | | | | | |
| Absent | 2798 | 7.4 | 3022 | 7.4 | 3050 | 19.8 | 3252 | 0.3 | 3215 | 0.5 |
| Present | 45 | 15.2 | 67 | 38.9 | 114 | 55.4 | 107 | 8.9 | 116 | 9.4 |
| Any pigmentary abnormalities | | | | | | | | | | |
| Absent | 2746 | 7.2 | 2944 | 6.6 | 2931 | 18.6 | 3155 | 0.1 | 3099 | 0.4 |
| Present | 99 | 15.4 | 150 | 36.0 | 235 | 53.7 | 224 | 8.2 | 236 | 6.5 |

RPE = retinal pigment epithelium.

four persons in whom exudative macular degeneration developed had pure geographic atrophy in the fellow eye at baseline. Those persons with unocular geographic atrophy at baseline were 6.3 times (95% CI, 0.9,42.1) as likely to develop late ARM in the uninvolved eye as those persons who had early ARM in both eyes at baseline (after age adjustment). There was a higher risk of developing late ARM in the uninvolved eye among those with unocular exudative macular degeneration at baseline compared with those who had early ARM in both eyes at baseline (RR, 3.7; 95% CI, 0.9,15.3; after age adjustment), however, this association was not statistically significant.

Discussion

Using standardized detailed procedures for obtaining stereoscopic color fundus photographs of the macula and an objective system for grading those photographs for maculopathy, we found a 10-year cumulative incidence of 12.1% for early ARM and 2.1% for late ARM in the Beaver Dam population aged 43 to 86 years at baseline. In addition, we have reported that large numbers of small hard drusen predict the incidence of soft drusen and pigmentary abnormalities and that the presence of the latter lesions significantly increases the risk for the development of geographic atrophy and exudative macular degeneration.

The 10-year cumulative incidence of exudative macular degeneration in at least one eye in the Beaver Dam population was 1.4%, and of pure geographic atrophy was 0.8%. Our data are comparable with those previously reported in the 7-year follow-up of an older English cohort in Melton Mowbray, Leicestershire,²⁵ and with the 5-year incidence in the Blue Mountains, Australia.²⁶ To our knowledge, there are no other long-term population-based reports of incidence of late age-related macular degeneration. The 3-year cumulative incidence of late ARM in 86 patients with bilateral drusen attending an ophthalmology clinic in England was 23.5%, 18% of whom developed exudative macular degeneration.⁹ This is higher than the 16.4% of persons in Beaver Dam with signs of early ARM in both eyes in whom late ARM developed and the 10.7% in whom exu-

datave macular degeneration developed over 10 years. The difference may reflect the bias incurred when observing patients attending specialty clinics. Most of the other estimates of annual incidence of late ARM have been based on persons attending ophthalmologic or specialty clinics and have ranged from 4% to 12% in those with one eye with late ARM.³⁹

The 10-year incidence of 9.5% of late macular degeneration (both geographic atrophy and exudative macular degeneration) in people 75 years of age or older in Beaver Dam is consistent with the relatively higher prevalence of this condition in people this age group.^{2,35,40-49} Extrapolating rates from communities with different racial compositions may lead to different estimates, because lower prevalences of late macular degeneration have been reported in blacks and Hispanics compared with non-Hispanic whites.⁴⁸ The incidence derived from Beaver Dam data may even underestimate the actual incidence of late macular degeneration in whites of North European ancestry because of higher rates of nonparticipation or ungradable fundus photographs in older people in the study. Nevertheless, as the American population ages, our findings of a 5.5% incidence of late ARM in people 65 years of age or older indicates a public health problem of significant proportions, because it is expected that those in the United States population of this age will increase by 63% from 16.6 million in 2000 to 27 million people by 2025, and there are few successful medical interventions to date for the prevention of late ARM.^{50,51}

Women 75 years of age or older had approximately twice the incidence of early ARM as men 75 years of age or older. The reason for this finding is not known. It is consistent with the higher prevalence of exudative macular degeneration in women compared with men this age,³⁵ and it is not explained by selective mortality (R. Klein, unpublished data, 2001).

An important objective of the study was to describe the interrelation of lesions defining ARM. We found that large drusen, soft indistinct drusen, a large area of drusen, and pigmentary abnormalities are strongly predictive of late

age-related macular degeneration. For example, the presence of large drusen ($\geq 125 \mu\text{m}$ in diameter) involving an area of 157,683 to 393,743 μm^2 (equivalent to 13–32 drusen of this size) was associated with a 10-year cumulative incidence of 14.0% for late ARM. This is consistent with previous observations that these lesions increase the risk of end-stage disease.^{5–12,15,16,23–26} Because of these observations, as well as results of clinicopathologic studies, we believe that these lesions indicate the presence of ARM. These data suggest that the presence of large drusen involving a large area of the retina, with or without the presence of pigmentary abnormalities and, in the absence of pure geographic atrophy or exudative macular degeneration, may more appropriately be called age-related macular degeneration than early ARM. These data, along with those from other population-based studies^{40,41,49} and the Age-Related Eye Disease Study,⁵¹ will facilitate the development of a detailed classification system of age-related macular degeneration severity similar to the Early Treatment Diabetic Retinopathy Study severity scale for diabetic retinopathy.⁵²

Although the late stages of age-related macular degeneration are well-defined, the earliest stages defining the presence of the disease remain to be determined. Because one or two small, hard drusen are found in 94% of the population and eyes with one or two of these drusen have almost no risk of progression to late age-related macular degeneration over 10 years of follow-up, eyes with these lesions are not considered to have the disease or to be at high risk of developing the disease.^{34,35} However, the 10-year results from the Beaver Dam Eye Study show that when present at baseline, large areas of small, hard drusen ($\geq 157,686 \mu\text{m}^2$) were associated with an approximate 2.5 times increased risk of developing soft indistinct drusen, a 3.3-times increased risk of developing pigmentary abnormalities, and a 2.7 times increased risk of developing large drusen ($\geq 125 \mu\text{m}$ in diameter). This is consistent with the findings in the Chesapeake Bay Waterman Study, in which eyes with five or more small drusen at baseline were 11 times as likely to have larger drusen at follow-up than eyes with fewer drusen.²³ Further follow-up is necessary to quantify the long-term risk of late ARM associated with larger areas of small, hard retinal drusen in younger individuals.

As has been previously reported by others, soft drusen and pigmentary abnormalities may regress and disappear.^{23,25,53} Masked side-by-side comparisons of the photographs from the Beaver Dam Eye Study examinations minimized the effect of media opacity, photographic artifacts, and grader error as a cause of disappearance of these lesions in our study. Approximately 27.5% of the disappearance of soft indistinct drusen was accompanied by the appearance of more severe lesions such as RPE depigmentation, geographic atrophy, or exudative macular degeneration. In the Chesapeake Bay Waterman Study, large drusen (defined as $>63 \mu\text{m}$ in diameter) disappeared in 34% of participants,²³ and in the Melton Mowbray study, 20% of soft drusen regressed over a 7-year period.²⁵ The prognostic implications of true disappearance or regression of these lesions is unknown and remains to be studied by long-term follow-up of the cohort.

In summary, the Beaver Dam Eye Study data provide

evidence of the progressive nature of maculopathy (soft drusen, pigmentary abnormalities, exudative macular degeneration, and pure geographic atrophy) over a 10-year period. The severity of ARM increases consistently with age such that, in people 75 years of age or older, 9.5% developed signs of late ARM.³¹ Further understanding of the long-term natural history of this disease is important in developing risk estimates and a severity scale to be used for further study of this disease.

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OPHTHALMIC PATHOLOGY FELLOWSHIP

Research to Prevent Blindness and the American Ophthalmological Society–Knapp Fund is offering a two-year postgraduate fellowship for training in ophthalmic pathology with an annual stipend of \$52,500. Applicants must be graduates of a medical school accredited by the American Medical Association, citizens of the United States, and have plans for an academic career. Deadline for submission of applications: January 15, 2003 for fellowship starting in July 2003. Please direct all inquiries and requests for applications materials to:

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