Fifteen-Year Cumulative Incidence of Age-Related Macular Degeneration

The Beaver Dam Eye Study

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Purpose: To describe the 15-year cumulative incidence of signs of early and late age-related macular degeneration (AMD).

Design: Population-based cohort study.

Participants: We included 3917 persons, 43 to 86 years of age at the time of a baseline examination in 1988 through 1990 and with information collected in follow-up in 1993 through 1995, and/or 1998 through 2000, and/or 2003 through 2005.

Methods: Grading of stereoscopic fundus photographs using the Wisconsin Age-Related Maculopathy Grading System.

Main Outcome Measures: Cumulative incidence of drusen type and size, pigmentary abnormalities, geographic atrophy, and exudative AMD accounting for competing risk of death.

Results: The 15-year cumulative incidence was 14.3% for early AMD (the presence of either soft indistinct drusen or the presence of pigmentary abnormalities together with any type of drusen) and 3.1% for late AMD (presence of exudative AMD or geographic atrophy). There was an increased incidence of AMD lesions with age ($P<0.05$). Individuals ≥ 75 years of age at baseline had significantly ($P<0.01$) higher 15-year incidences of the following characteristics than people 43 to 54 years of age: larger drusen (125 μm in diameter, 24.1% vs 10.6%), soft indistinct drusen (18.7% vs 6.5%), retinal pigmentary abnormalities (20.2% vs 3.7%), exudative macular degeneration (4.4% vs 0.4%), and pure geographic atrophy (3.2% vs 0%). Controlling for age, compared with those with small numbers of only small hard drusen (1–2), those with large numbers of only hard drusen (≥8) had an increased 15-year age-adjusted incidence of both soft indistinct drusen (16.3% vs 4.7%) and pigmentary abnormalities (10.6% vs 2.7%). Eyes with soft indistinct drusen or pigmentary abnormalities at baseline were more likely to develop late AMD at follow-up than eyes without these lesions (17.8% vs 1.2% and 12.9% vs 1.7%, respectively).

Conclusions: We document the long-term incidence of signs of AMD and a continuum from small hard drusen to late AMD in older persons in the population. The 15-year cumulative incidence of late AMD in people ≥ 75 years of age (8%) indicates a public health problem of significant proportions because the United States population this age is expected to increase by 54% between 2005 and 2025. *Ophthalmology 2007;114:253–262*

Despite new medical and surgical interventions, age-related macular degeneration (AMD) remains a leading cause of vision loss in people ≥ 65 years of age in the United States.[1,2] A growing body of information regarding its natural history has come from case series, clinical trials, and epidemiologic studies.[3–23] This has been supplemented by observations made in clinicopathologic studies.[24–29] There are few epidemiologic data from long-term studies and fewer yet that have examined the relationship of small hard drusen to the incidence of large soft drusen, pigmentary abnormalities, and other more severe lesions of AMD.[15,18,19,22,23] The purpose of this report is to describe the 15-year cumulative incidence and interrelationships of lesions associated with early and late AMD

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in a large population-based cohort. It builds on earlier observations made at the 5- and 10-year follow-up examinations of the Beaver Dam Eye Study cohort allowing unique long-term observation of the natural history of AMD from early to late stages.[16,18]

Materials and Methods

Population

Methods used to identify the population and descriptions of the population have appeared in previous reports.[2,30–33] A private census of the population of Beaver Dam, Wisconsin (99% white) was performed from fall 1987 to spring 1988.[30] Of the 5924 enumerated persons 43 to 84 years of age, 4926 participated in the baseline examination in 1988 to 1990.[31] Of these, 3684 (81.1%) participated in the 5-year follow-up examination in 1993 to 1995.[32] Comparisons between participants and nonparticipants at baseline and the 5-year follow-up examination have appeared elsewhere.[31,32] Of the 3334 surviving participants in the baseline and second examination, 2764 (82.9%) participated in the 10-year follow-up examination between March 1, 1998 and June 9, 2000.[33] Comparisons between participants and nonparticipants at baseline and the 10-year examination have appeared elsewhere.[33] Of the 2480 surviving participants who were examined at the baseline and 5- and 10-year follow-up examinations, 2119 (85.4%) participated in the 15-year follow-up examination between March 31, 2003 and April 30, 2005.[2] Comparisons between participants and nonparticipants at the 15-year follow-up have been presented elsewhere.[2] In general, persons who did not participate in the 15-year follow-up were older at baseline than those who did. After adjusting for age, persons who did not participate were more likely to have fewer years of education completed and higher systolic blood pressure than persons who participated. After adjusting for age and gender, participants with early and late AMD at baseline were as likely to participate as those in whom AMD was absent (data not shown). The mean and median times between the baseline and 15-year follow-up examination were 14.9 years (standard deviation, 0.5 years) and 14.8 years, respectively.

Procedures

Similar procedures were used at baseline and follow-up examinations.[16,18,34–38] Informed signed consent was obtained at the beginning of each examination as well as Institutional Review Board approval. Pertinent parts of the examination at both baseline and follow-up examinations 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 2119 people who were examined at all 4 examinations, 2078 (98.1%) had gradable fundus photographs in at least 1 eye at the baseline and at the 5- and 10-year follow-up examinations. Of these 2078 people, 2042 (98.3%) had gradable photographs (1989 in both eyes, 26 in the right eye only, and 27 in the left eye only) at the 15-year follow-up examination. Of the 2042 people with gradable photographs in at least 1 eye at all examinations, 25 (1.2%) were excluded from the analyses because of the presence of confounding lesions at follow-up unrelated to AMD in both eyes. An additional 61 (3.0%) people had 1 eye excluded from these analyses (because of the presence of confounding lesions unrelated to AMD), and 52 others had 1 eye excluded because it was ungradable.

Details of the grading procedure have been described previously.[36–38] In brief, a circular grid was placed on 1 photographic slide of the stereoscopic pair, which divided the macular area into 9 subfields, consisting of a central circle (a single subfield), inner ring (comprised of the 4 inner subfields), and outer ring (comprised of 4 outer subfields). 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 9 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 acetate were used to estimate size of drusen and areas involved by drusen, increased retinal pigment, and retinal pigment epithelial (RPE) depigmentation.

Two gradings were performed for each eye at each examination.[16,18,34–38] First, a preliminary masked grading was done by 1 of 2 senior graders. Next, detailed gradings were performed by 1 of 3 other experienced graders. 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.[36,37] Next, a series of edits and reviews was performed. The presence and severity of specific lesions at the fourth examination (e.g., maximum drusen size, type, area, and pigmentary abnormalities) as determined by detailed grading were compared to that of the preliminary grading. Standardized edit rules were used to adjudicate disagreements.[16,18,38] Finally, the detailed graders were asked to make side-by-side comparisons between 10- and 15-year follow-up photographs for eyes that showed change for AMD lesions between these 2 examinations. These edits were masked as to whether the photographs were taken at 10- or 15-year follow-up examination. After the masked longitudinal review of 10- and 15-year visits was done, the senior grader (SMM) and principal investigator (RK) performed a final unmasked review of all 4 visits for progression and regression. All eyes newly classified with late and early AMD were also confirmed at this time. Additional information on gradability at previous examinations can be found in the prevalence and 5- and 10-year incidence papers.[16,18,38]

Definitions

Definitions of the incidence, progression, regression, and disappearance of early and late AMD and their component lesions have been presented elsewhere.[16,18] To evaluate change in lesions between visits, it was necessary to have data from corresponding gradable subfields at the visits. Corresponding subfields were not used in defining early and late AMD summary measures.

Incidence was determined for maximum drusen size ($<$63 μm, $\geq$63 μm to $<$125 μm, $\geq$125 μm to $<$250 μm, and $\geq$250 μm in diameter), drusen type (hard distinct, soft distinct, or soft indistinct/reticular), 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.

The incidence of early AMD was defined by the presence of either soft indistinct drusen or RPE depigmentation, or increased retinal pigment together with any type of drusen at follow-up when none of these lesions was present at baseline. The incidence of late AMD 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 of AMD in either eye was examined using the 6-step Beaver Dam Eye Study AMD severity scale (as a $\geq$2-step increase in severity from level 1 [no AMD] or levels 2 or 3 [minimal to moderate early AMD] and a $\geq$1-step increase in

Table 1. Fifteen-Year Cumulative Incidence* of Age-Related Macular Degeneration (AMD) by Age at Baseline, Beaver Dam Eye Study (BDES), 1988–2005

Characteristic	All Ages		43–54 Years		55–64 Years		65–74 Years		75–86 Years		OR (95% CI)†
	No. at Risk	%	*No. at Risk*	%	*No. at Risk*	%	*No. at Risk*	%	*No. at Risk*	%	
Early AMD	3084	14.3	1158	6.9	906	12.7	753	25.3	267	24.4	2.3 (2.1–2.6)
Drusen size (diameter)											
<63 μm	142	60.3	40	83.2	28	69.7	46	50.0	28	27.1	1.0 (0.7–1.3)
≥63 μm, <125 μm	2395	23.9	1010	20.3	707	26.6	513	26.6	165	26.1	1.5 (1.4–1.7)
≥125 μm, <250 μm	3226	15.8	1202	10.0	949	17.4	783	22.3	292	20.1	1.8 (1.6–2.0)
≥250 μm	3671	7.4	1254	2.0	1056	7.6	951	13.0	410	13.1	2.5 (2.2–2.9)
Drusen type											
Soft distinct	2890	13.4	1133	10.2	853	15.5	668	16.2	236	15.8	1.6 (1.4–1.8)
Soft indistinct	3298	13.4	1216	6.5	981	13.3	802	23.4	299	18.7	2.2 (1.9–2.4)
Increased drusen area	3755	32.0	1256	22.7	1073	32.7	985	41.5	441	37.9	1.9 (1.8–2.1)
Any pigment abnormality	3391	9.8	1193	3.7	969	9.0	875	15.8	354	20.2	2.6 (2.2–2.9)
Increased retinal pigment	3409	9.8	1193	3.5	974	9.0	879	16.1	363	20.3	2.6 (2.3–3.0)
RPE depigmentation	3595	7.5	1229	1.8	1038	7.9	940	12.6	388	14.6	2.6 (2.3–3.0)
Late AMD	3830	3.1	1266	0.4	1088	2.6	1014	5.8	462	7.6	3.5 (2.8–4.4)
Exudative AMD	3850	2.0	1266	0.4	1090	2.1	1018	2.9	476	4.4	2.9 (2.2–3.8)
Pure geographic atrophy	3832	1.3	1271	0.0	1087	0.8	1014	3.0	460	3.2	4.2 (2.9–6.1)
Progression of AMD											
BDES severity scale	3855	12.2	1266	4.0	1093	11.2	1021	21.5	475	19.7	2.6 (2.3–2.9)
AREDS severity scale	3828	25.0	1265	13.5	1082	25.4	1015	36.7	466	33.4	2.1 (1.9–2.3)

AREDS = Age-Related Eye Disease Study; CI = confidence interval; OR = odds ratio; RPE = retinal pigment epithelial.
*Cumulative incidence calculated using competing risks; number at risk varies by difference in prevalence of lesion at baseline.
†Odds ratio and 95% CI per increasing category of age.

severity from level 4 [severe early AMD] or level 5 [geographic atrophy] to level 6 [exudative AMD]). Progression was also assessed using the newly developed 11-step Age-Related Eye Disease Study (AREDS) AMD severity scales (as a ≥2-step increase in severity). Both scales are described in detail elsewhere.[39,40]

Disappearance of soft indistinct drusen was defined as its presence in at least 1 subfield at any visit and its absence in all subfields at a later follow-up examination. Eyes with disappearance of soft indistinct drusen due to appearance of RPE depigmentation or late AMD were excluded (n = 82 eyes) in this analysis. The categories of incidence and disappearance of drusen were not mutually exclusive.

Change in drusen area for an eye was assessed for each of the 3 separate concentric areas defined by the grading grid: within the central circle (a single subfield), the inner ring (composed of the 4 inner subfields), and the outer ring (composed of 4 outer subfields). Change was defined as an increase or decrease of ≥2 steps on the 9-step scale (<63 μm, 63–124 μm, 125 μm to 1.5% of the subfield, 1.6%–3.0% of the subfield, 3.1%–6.2% of the subfield, 6.3%–12.4% of the subfield, 12.5%–24.9% of the subfield, 25%–49.9% of the subfield, and ≥50% of the subfield). There was 1 exception. If no drusen were present in the central circle, a ≥3-step increase in area in that subfield had to be achieved for it to be defined as "change" (because there is no difference between the second and third step of the coding scale for the central circle). An "overall" change in drusen area was determined by summing the scores of the 3 areas (overall scores could range from −3 to +3). If the sum of the scores for the central subfield and the inner and outer rings was ≥1, the eye was considered to have an increase in drusen area; if it was 0, the eye was considered to have no net change; and if the value was ≤−1, the eye was considered to have a decrease in drusen area.

Statistical Methods

SAS version 9 was used for analyzing the data (SAS Institute Inc., Cary, NC). Age (defined at the time of the baseline examination) was treated categorically in the following groups: 43 to 54, 55 to 64, 65 to 74, and 75 to 86 years of age. The calculations of cumulative incidence and disappearance and interrelationships of lesions associated with early and late AMD allow persons who were right censored (not seen after the baseline and 5- or 10-year examination owing to death or nonparticipation) to contribute information to the estimates. These estimates also account for the competing risk of death.[41] A person only needed to have gradable photographs at the baseline and 5-year follow-up examination or die between baseline and the 5-year follow-up to contribute to the estimates. Included in the analyses were 3917 persons: 2042 people examined with gradable photographs at all 4 visits, 629 examined with gradable photographs at baseline and at the 5- and 10-year follow-up only; 893 people examined with gradable photographs at baseline and at the 5-year follow-up only; and 353

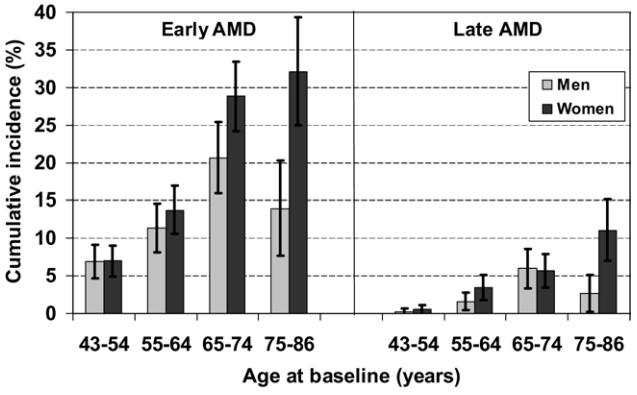

Figure 1. Fifteen-year cumulative incidence and 95% confidence intervals of early and late age-related macular degeneration (AMD) by age and gender in the Beaver Dam Eye Study. The overall age-adjusted differences between men and women and the incidence of early ($P = 0.16$) and late ($P = 0.16$) AMD were not statistically significantly different.

Table 2. Fifteen-Year Age-Adjusted Incidence of Age-Related Macular Degeneration (AMD)

Baseline Lesion	Incident				
	SD Drusen, OR (95% CI)*	*SI Drusen, OR* (95% CI)*	*Increased Drusen Area, OR* (95% CI)*	*Increased Retinal Pigment OR* (95% CI)*	*RPE Depigmentation OR* (95% CI)*
Drusen > 125 μm vs. < 63 μm in diameter		6.2 (4.0, 9.4)	3.9 (3.1, 5.0)	7.2 (5.0, 10.3)	9.5 (6.4, 14.1)
SD vs. HD drusen		3.6 (2.7–4.8)	2.8 (2.2–3.6)	2.6 (1.7–3.9)	2.9 (1.8–4.7)
SI vs. SD or HD drusen			3.0 (2.4–3.9)	5.6 (3.9–7.9)	7.3 (5.1–10.4)
Drusen area > 16877 μm^2 vs. ≤ 2596 μm^2	3.1 (2.1–4.5)	7.6 (5.2–11.2)	2.6 (2.1–3.3)	5.5 (3.7–8.3)	9.3 (5.3–16.4)
Pigmentary abnormalities present vs. absent	1.8 (1.1–3.1)	8.5 (6.1–11.8)	3.8 (3.0–4.9)		
Increased pigment present vs. absent	1.9 (1.1–3.2)	8.4 (6.0–11.8)	3.8 (2.9–4.8)		
RPE depigmentation present vs. absent	1.5 (0.7–3.3)	8.1 (5.1–12.7)	3.6 (2.6–4.9)		

CI = confidence interval; GA = geographic atrophy; HD = hard distinct drusen; OR = odds ratio; RPE = retinal pigment epithelial; SD = soft distinct drusen; SI = soft indistinct
*Odds ratios adjusted for age in groups (43–54, 55–64, 65–74, 75–86 years).

people who died before the 5-year follow-up. The latter group contributes only mortality information for cumulative incidence estimates. The numbers at risk for each AMD outcome (Table 1) vary due to prevalent disease at baseline.

In some analyses, we included persons who were not examined at the 5- and/or 10-year follow-up examination but participated in the 15-year follow-up examination to contribute to the analyses (n = 222 additional). For these persons, we used an imputation that assumes the event had not occurred during the missing examination phase(s).

To investigate the relationship between age and AMD, we present results in the worse eye but note the relationships were similar in right and left eyes. Progression using the 6-step Beaver Dam Eye Study AMD severity scale and the AREDS AMD severity scale includes progression in either eye. Interrelationships between AMD lesions are presented in right eyes, but we note that the relationships were similar for left eyes (data not shown).

Age-adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated from discrete logistic hazard regression models.[42] The test of trend between age and incidence rates were tested by treating age, categorized as previously described, as a continuous variable in the Cox proportional hazards model and computing the chi-square statistic for the parameter estimate. The same method was used to examine trend in other risk factors. Where appropriate, cumulative incidence estimates were adjusted for age in 3 categories using the direct method.[43] The baseline Beaver Dam population was used as the referent population with the distribution of age as follows: 58% were age 43 to 64 years, 26% were age 65 to 74 years, and 16% were 75 to 86 years of age.

Results

The 15-year cumulative incidences of early and late AMD and characterizing lesions by age are presented in Table 1. For most lesions, the cumulative incidences rose with age from 43 to 54 to 65 to 74 years at baseline and remained largely unchanged or slightly decreased in those ≥75 years of age (Table 1). While controlling for age, there were no statistically significant ($P<0.05$) differences between the 15-year cumulative incidence of early or late AMD in men and women in those ≤75 years of age at baseline (Fig 1). Although there was no statistically significant interaction for age and gender (for early AMD, P of interaction = 0.37 and for late AMD P of interaction = 0.16), women in the oldest group had a higher cumulative incidence of early and late AMD than men ($P<0.05$). There were no differences in incidence between right and left eyes (data not shown).

The 15-year cumulative rate of progression in either eye was 12.2% using the Beaver Dam Eye Study AMD severity scale (Table 1). Progression was associated with both age at baseline (OR per age group, 2.5; 95% CI, 2.2–2.9) and baseline level of severity (OR per increasing level, 1.5; 95% CI, 1.3–1.8). The 15-year cumulative rate of progression of ≥2 steps in either eye was 25.0% using the AREDS AMD severity scale (Table 1). Progression was associated with both age at baseline (OR per increasing age group, 2.1; 95% CI, 1.9–2.3) and baseline level of severity (OR per level, 1.3; 95% CI, 1.2–1.3). There was an interaction found between age and severity level at baseline and AMD progression using both severity scales. Older persons (≥75 years of age at baseline) were at lower risk of progression compared with younger persons (65–74 years of age at baseline) with more severe AMD levels (data not shown).

Large drusen size and area, more severe drusen type (soft indistinct more severe than soft distinct), and the presence of pigmentary abnormalities were associated with an increased age-adjusted cumulative incidence of more severe AMD lesions in both eyes (Table 2 [right eye]; data not shown for left eye). While controlling for age, right eyes with large drusen (125 μm in diameter) present at baseline were more likely to develop soft indistinct drusen, an increase in drusen area, increased retinal pigment, RPE depigmentation, pure geographic atrophy, or exudative macular degeneration than right eyes with only small drusen (<63 μm in diameter). Similarly, soft drusen and larger drusen area at baseline were associated with increased odds of incident pigmentary abnormalities, and pigmentary abnormalities at baseline were associated with increased odds of incident large drusen, soft drusen, and larger drusen area. After controlling for age, eyes with soft drusen or pigmentary abnormalities at baseline were more likely to develop late AMD at follow-up than eyes without these lesions (17.8% vs. 1.2% and 12.9% vs. 1.7%, respectively).

When only small (<63 μm in diameter) hard drusen were present at baseline, larger drusen area (9087–186 526 μm^2, equivalent to approximately 8–144 small drusen approximately 40 μm in diameter) was associated with increased age-adjusted cumulative incidence of soft indistinct drusen (16.3% vs. 4.7%) and pigmentary abnormalities (10.6% vs. 2.7%) compared with right eyes with smaller drusen area (1298–2596 μm^2, equivalent to approximately 1–2 small hard drusen). The relation of drusen type

Lesions in Right Eyes by AMD Lesions at Baseline in the Beaver Dam Eye Study, 1988–2005

Outcome				
Pigmentary Abnormalities OR* (95% CI)	*Early AMD* OR* (95% CI)	*Pure GA* OR* (95% CI)	*Exudative AMD* OR* (95% CI)	*Late AMD* OR* (95% CI)
7.3 (5.1, 10.6)	5.5 (3.5, 8.7)	14.5 (5.9, 35.7)	60.4 (17.7, 206)	29.6 (14.4, 60.7)
2.4 (1.5–3.6)	3.0 (2.2–4.1)	1.2 (0.3–5.7)	7.4 (2.4–22.6)	3.6 (1.5–8.6)
5.7 (4.0–8.1)		14.6 (6.8–31.1)	18.3 (8.9–37.4)	17.5 (10.3–29.8)
5.5 (3.6–8.3)	5.2 (3.7–7.5)	24.0 (3.2–179)	40.4 (5.5–297)	32.3 (7.8–133)
		15.2 (7.3–31.6)	7.2 (3.6–14.1)	10.8 (6.5–18.0)
		15.8 (7.6–32.8)	5.8 (2.9–11.7)	9.8 (5.9–16.3)
		11.1 (5.0–24.4)	7.8 (3.6–16.6)	10.5 (5.9–18.5)

or reticular drusen.

or size and area to the age-adjusted cumulative incidence of increased retinal pigment, RPE depigmentation, geographic atrophy, exudative macular degeneration, and early and late AMD is presented in Table 3. Larger area of soft distinct drusen was not statistically significantly related to the incidence of pigmentary abnormalities. Right eyes with soft indistinct drusen or drusen ≥125 μm in diameter and larger areas of drusen were at higher risk of developing pigmentary abnormalities and late AMD ($P<0.001$ for all associations). When soft indistinct drusen were present, eyes with pigmentary abnormalities and greater drusen

Table 3. Relationship of Type and Size of Drusen and Drusen Area at Baseline to the Age-Adjusted* 15-Year Cumulative Incidence of Pigment Abnormalities, Early and Late Age-Related Macular Degeneration (AMD) in Right Eyes in the Beaver Dam Eye Study, 1988–2005

Drusen Type and Size by Drusen Area (μm²)	Inc Pig		RPE Depig		Any PA		Early AMD		Pure GA		Exud AMD		Late AMD	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Drusen type														
Hard distinct														
1298–2596	783	2.7	782	1.9	783	2.7	771	5.2	803	0.1	796	0.2	795	0.4
2597–5192	512	5.8	519	4.3	511	5.7	507	11.3	527	1.6	524	0.2	524	1.8
5193–9086	530	5.4	537	4.3	529	5.6	523	14.5	559	1.7	551	0.0	550	1.8
9087–186 526	760	10.4	788	6.3	757	10.6	750	17.7	816	0.4	813	1.1	810	1.5
Soft distinct														
5193–28 008	64	16.5	68	11.4	63	15.0	62	22.3	77	0.0	75	1.6	75	1.6
28 009–45 559	52	7.8	55	3.7	50	5.3	49	20.4	61	0.0	56	0.0	56	0.0
45 560–80 935	56	14.9	63	10.1	56	14.9	55	29.0	72	1.3	71	0.0	71	1.3
80 936–2 427 827	48	24.5	59	22.8	48	24.5	48	53.3	64	1.3	61	11.8	61	13.1
Soft indistinct														
5193–69 803	59	21.7	60	21.0	58	21.8			77	3.0	77	2.8	76	5.6
69 804–157 685	45	14.6	56	14.7	45	14.6			77	0.9	77	2.3	76	3.1
157 686–393 743	50	42.3	64	37.4	50	42.3			70	8.2	76	19.0	73	26.9
393 744–8 330 254	46	32.5	57	41.2	42	35.8			72	25.3	82	21.3	76	41.0
Drusen size														
<63 μm in diameter														
1298–2596	783	2.7	782	1.9	783	2.7	771	5.2	803	0.1	796	0.2	795	0.4
2597–5192	512	5.8	519	4.3	511	5.7	507	11.3	527	1.6	524	0.2	524	1.8
5193–9086	459	5.8	465	4.9	458	6.1	454	14.5	481	1.4	475	0.0	475	1.5
9087–186 526	505	9.5	516	5.8	503	9.5	498	14.7	529	0.4	527	0.2	524	0.6
63–124 μm in diameter														
5193–28 008	290	11.4	305	8.1	288	11.8	280	21.4	333	1.3	329	1.5	328	2.8
28 009–45 559	59	12.1	62	6.8	58	9.8	50	19.4	70	0.0	69	0.0	69	0.0
45 560–80 935	87	15.7	95	13.3	87	15.9	68	28.8	108	2.7	106	0.0	106	2.7
80 936–2427 827	63	16.9	68	10.5	63	16.9	48	31.1	76	0.0	75	8.4	75	8.4
≥125 μm in diameter														
5193–69 803	89	13.5	94	11.5	87	13.7	58	23.1	107	0.0	103	1.9	102	1.9
69 804–157 685	53	22.8	68	12.9	53	22.8	19	56.7	89	0.8	86	5.1	85	5.8
157 686–393 743	55	47.3	72	41.1	55	47.3	8	73.9	76	7.6	83	20.0	80	26.8
393 744–8330 254	50	31.8	62	40.5	46	34.8	4	34.2	76	24.0	86	20.1	80	39.3

Exud AMD = exudative age-related macular degeneration; GA = geographic atrophy; inc pig = increased retinal pigment; PA = pigmentary abnormalities; RPE depig = retinal pigment epithelial depigmentation.
*Age-adjusted cumulative incidence calculated with the direct method: 43–64 years, 58%; 65–74 years, 26%; ≥75 years, 16%.

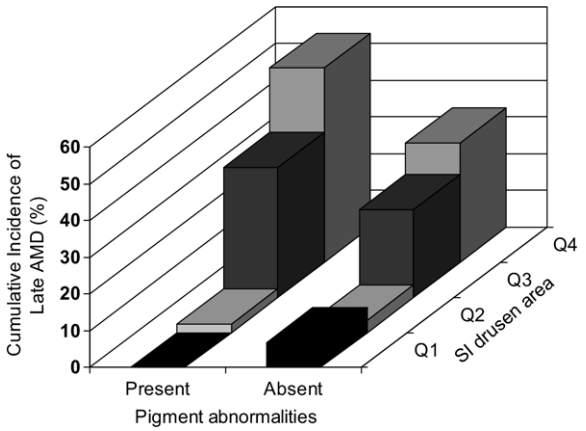

Figure 2. Relation of the presence of pigmentary abnormalities and increased drusen area in right eyes with soft indistinct (SI) drusen present at baseline (n = 300) to the 15-year age-adjusted cumulative incidence of late age-related macular degeneration (AMD) in the right eye in the Beaver Dam Eye Study. Area cut points are listed in Table 3. The first quartile (Q) of drusen area is the equivalent of about one to two 200-μm diameter drusen, the second is the equivalent of about 3 to 5 drusen of this size, the third is the equivalent of about 6 to 12 drusen of this size, and the fourth quartile is the equivalent of about 13 to 265 drusen of this size.

area were more likely to develop signs of late AMD than eyes with smaller drusen area and no pigmentary abnormalities present at baseline (Fig 2). These relations were similar in left eyes (data not shown).

There were 825 eyes with soft indistinct drusen in persons that participated at a later follow-up examination. To examine disappearance of soft indistinct drusen without evidence of progression of AMD, we excluded eyes where soft indistinct drusen disappeared in association with incident RPE depigmentation or late AMD (n = 82). The overall cumulative disappearance of soft indistinct drusen was 18% (n = 141 eyes). Seventy-nine of these 141 eyes were followed 5 or 10 years after disappearance of soft indistinct drusen. Four (5%) of these developed RPE depigmentation and/or late AMD. In contrast, 164 of the 514 (32%) eyes in which the soft indistinct drusen had not disappeared between baseline and the 5-year follow-up developed signs of RPE depigmentation and/or late AMD over the next 10-year period. After controlling for age, there was a statistically significant decreased risk of developing RPE depigmentation or late AMD in eyes in which soft indistinct drusen had disappeared compared to eyes in which they had not disappeared (OR, 0.2; 95% CI, 0.08–0.6).

Figure 3 shows the relationship of AMD severity at baseline in right eyes and the 15-year cumulative incidence of late AMD. For each step increase along either the Beaver Dam Eye Study or AREDS severity scales, there was an increased odds of developing late AMD (for the Beaver Dam Eye Study severity scale [OR per step increase, 6.0; 95% CI, 4.5–7.8] and for the AREDS severity scale [OR per step increase, 2.7; 95% CI, 2.3–3.1]). Risk of progression to late endpoints was low for eyes with AREDS severity levels 1 through 3, then rose thereafter. Risk of progression to late endpoints in the Beaver Dam severity scale was low for level 1 and rose thereafter. Findings were similar in left eyes (data not shown).

There were 193 persons with early AMD in both eyes at baseline who were examined at a follow-up examination. Of these, 46 developed late AMD (15-year cumulative incidence, 25.9%), 26 developed exudative AMD (15-year cumulative incidence, 14.8%), and 21 developed pure geographic atrophy (15-year cumulative incidence, 13.5%).

There were 27 persons who had uniocular late AMD at baseline (16 with exudative AMD and 11 with pure geographic atrophy) who were examined at follow-up. Of these, 12 developed late AMD in the other eye over the 15-year period (38.7% cumulative incidence), 7 developed exudative AMD (34.4% cumulative incidence), and 8 developed pure geographic atrophy (32.0% cumulative incidence). The latter 2 were not mutually exclusive. Of these, 4 developed pure geographic atrophy by the 5- or 10-year follow-up examinations and 3 went on to develop exudative AMD by the 15-year examination. Five of 8 persons who developed pure geographic atrophy and 2 of 7 persons who developed exudative AMD had pure geographic atrophy in the fellow eye at baseline. Those persons with uniocular geographic atrophy at baseline were 4.1 times (95% CI, 1.4–12.4; $P = 0.01$) as likely to develop late AMD in the uninvolved eye as those persons who had early AMD in both eyes at baseline (after age adjustment). The odds of developing late AMD in the uninvolved eye among those with uniocular exudative AMD at baseline compared with either eye of those who had early AMD in both eyes at baseline (OR, 1.9; 95% CI, 0.7–5.0 after adjustment) were not statistically significant ($P = 0.22$).

To provide estimates of burden of incident early and late AMD in survivors, we reran the models, as described in "Materials and Methods," so that only those surviving 15 years contribute information (Fig 4). Incident early AMD occurred in 15.0% of survivors and varied from 7.3% in those 43 to 54 years of age at baseline to 53.2% in those ≥75 at baseline; for late AMD, it was 3.6% and varied from 0.4% in those 43 to 54 at baseline to 23.0% in those ≥75 at baseline; for neovascular AMD, it was 2.1% and varied from 0.4% in those 43 to 54 to 12.0% in those ≥75 at baseline; and for pure geographic atrophy, it was 1.6% and varied from 0% in those 43 to 54 to 10.5% in those ≥75 at baseline.

When persons who had missed either the 5- and/or the 10-year examinations were included in the analyses, there was little difference from estimates in overall 15-year cumulative incidence of early AMD (14.3% vs. 14.3% imputed) and late AMD in the worse eye (3.1% vs. 3.3% imputed); however, slightly higher estimates of incident late AMD in the worse eye resulted in those who were ≥75 years of age (7.6% vs. 8.5% imputed).

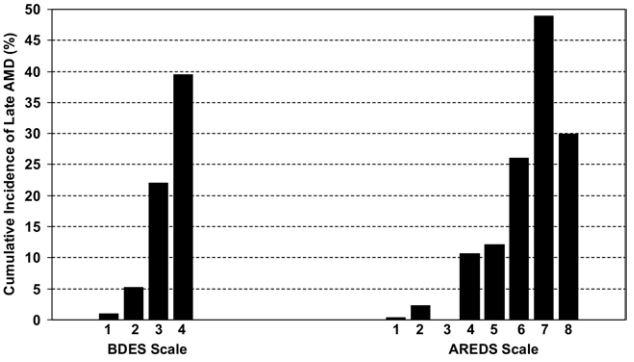

Figure 3. Age-adjusted 15-year cumulative incidence in right eyes of late age-related macular degeneration (AMD) by baseline 6-step Beaver Dam Eye Study (BDES) and 11-step Age-Related Eye Disease Study (AREDS) AMD severity scales. Because levels 5 and 6 of the Beaver Dam Eye Study scale and levels 9 to 11 of the AREDS scale are late AMD, eyes at these levels are not at risk of progression to late AMD. Incidence rates for late AMD were adjusted for age with the direct method: 43 to 64 years, 58%; 65 to 74, 26%; and ≥75, 16%.

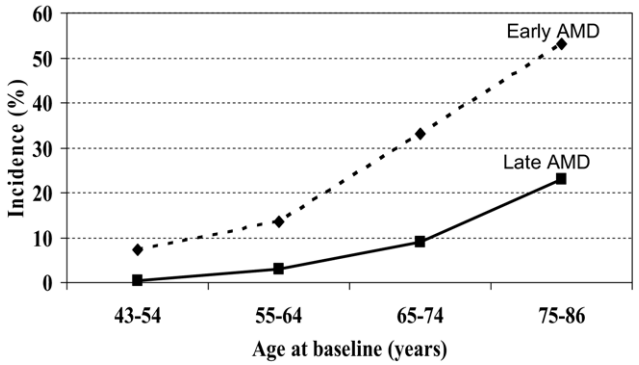

Figure 4. Proportion of survivors to the 15-year follow-up who had an incident early and late age-related macular degeneration (AMD) outcome by age in the Beaver Dam Eye Study.

There were only 13 persons 85 years of age at baseline who were seen at the 5-year follow-up, limiting our ability to examine incidence in this age group. There were 67 persons at risk of incident AMD who were ≥85 at the 10-year follow-up examination who returned for the 15-year follow-up examination. Their 5-year incidence of early AMD in the worse eye was 24%, and of late AMD, 10%. The 5-year incidence of exudative AMD in the worse eye was higher than that of pure geographic atrophy in persons 53 to 74 (0.8% vs. 0.2%), and was similar in those who were 75 to 84 (2.1% vs. 2.5%), and was lower in those ≥85 (1.9 vs. 8.2%). In persons who were ≥90 (n = 69) at the 15-year follow-up, the prevalence of early AMD in the worse eye was 61.5%, for late AMD it was 23.2%, for exudative AMD it was 13.2%, and for pure geographic atrophy it was 11.7%.

Discussion

Using standardized detailed procedures for obtaining stereoscopic color fundus photographs of the macula and an objective system for grading those photographs for AMD, we found a 15-year cumulative incidence accounting for the competing risk of death of 14% for early AMD and 3% for late AMD in the Beaver Dam population 43 to 86 years of age at baseline. In addition, we report a high 15-year cumulative incidence of early (24%) and late AMD (8%) in those who were ≥75 at baseline. We also provide further evidence that the natural history of AMD follows a continuum from large numbers of small hard drusen to early stages of AMD, showing that increased area of these lesions predicts 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 AMD.

The 15-year cumulative incidence of exudative AMD in the worse eye in the Beaver Dam population was 2.0%, and for pure geographic atrophy, it was 1.3%. There is only 1 other population-based estimate of similar long-term incidence of AMD.[23] In a 14-year follow-up of 359 Danish persons 60 to 80 years of age at baseline that used a similar grading system to detect AMD from fundus photographs, the 14-year (noncumulative) incidence of early and late AMD in either eye reported was 38 % and 17%, respectively.[23] Such comparisons with this and other population-based studies with shorter follow-up that have used similar methodologies to detect and define AMD are limited by differences in distributions of exposures (e.g., smoking and other unmeasured confounders).[19–22]

The estimated 15-year cumulative incidence of 8% of late AMD in people ≥75 years of age in the Beaver Dam Eye Study is consistent with its relatively higher prevalence in people this age.[38,44–54] In Beaver Dam, 23% of those ≥90 at the 15-year follow-up had signs of late AMD. Whereas the incidence of exudative AMD was higher than that of pure geographic atrophy in younger persons, the incidence of pure geographic atrophy was 4 times as high as that of exudative AMD in persons ≥ 85. This may be due to different pathogenetic factors (e.g., smoking, hypertension) for both conditions that differ by age.

Our findings may underestimate the actual incidence of late AMD in Caucasians of North European ancestry because of higher rates of nonparticipation or ungradable fundus photographs in older people (≥75 years) in our study. However, inclusion of data from those in this age group who missed an examination led to an approximate 10% increase in estimates of incident late AMD in the cohort. The incidence derived from Beaver Dam data when applied to the U.S. population may be an overestimate if lower rates of late AMD in blacks and Hispanics are truly lower than those for non-Hispanic whites.[46,52,54–59] In addition, based on the AREDS findings of a 28% reduction in progression to late AMD by use of antioxidant and zinc supplements in persons with moderately severe early AMD (AREDS groups 3 and 4 at baseline), the Beaver Dam data may overestimate future incidence due to more widespread use of the supplements.[2] Regardless, as the American population ages, our findings of an 8% incidence of late AMD in people ≥ 75 indicates a public health problem of significant proportions.

We have previously reported incidence rates of AMD using the Kaplan–Meier (product limit) method.[16,18,60] In this report, we use a competing risk approach to account for death in this aging population.[41] The Kaplan–Meier method produces higher estimates of cumulative incidence, especially in the oldest age group (e.g., 20.1% vs. 7.6% for incidence of late AMD in persons ≥ 75 years). The Kaplan–Meier method produces higher incidence rates because the method assumes persons who die would have gotten AMD at the same rate as those that did not die. Therefore, the Kaplan–Meier method is a hypothetical estimate of the probability of disease development assuming that those who did not come in for further examinations develop AMD at the same rates as those who did, ignoring that death might have intervened before AMD developed. We were interested in estimating the probability of getting the disease before death. Thus, we now estimate this cumulative incidence by the competing risk model.

We have previously used a 6-step severity scale in examining associations of risk factors with progression of AMD.[39] The findings from the 15-year follow-up showed a strong relation between increasing severity on that scale with increased risk of progression to late AMD. The AREDS AMD severity scale was recently developed using

data collected on 3000 persons followed over 5 years participating in the AREDS clinical trial.[40] It had not been previously validated using long-term population-based incidence data. Our data suggest that progression along either severity scale may also be a useful surrogate for progression to late AMD.

An important objective of the Beaver Dam Eye Study has been to provide information on the long-term evolution and natural history of the lesions of AMD and their relation to late stages of AMD. Data from our study show a strong relation of the larger area of large soft indistinct drusen increasing the risk of development of pigmentary abnormalities and the presence of both being strongly predictive of late AMD. For example, the presence of drusen $\geq$ 125 μm in diameter involving an area in the macula of 157 683 to 393 743 μm^2 (equivalent to 13–32 drusen of this size) was associated with a 15-year age-adjusted cumulative incidence of 47% for pigmentary abnormalities and 27% for late AMD; for a similar area of soft indistinct drusen, the 15-year cumulative incidence of pigmentary abnormalities was 42%; for late AMD, it was 27%. This is consistent with previous observations that these lesions increase the risk of end-stage AMD and provide further evidence that their presence defines an early stage of AMD.[3–10,15,17,19,25–30]

Although the more severe stages of early AMD are becoming better defined, the earliest lesions defining the presence of the disease remain to be determined. Because 1 or 2 small hard drusen are found in 94% of the population and eyes with 1 or 2 of these drusen have almost no risk of progression to late AMD over 15 years of follow-up, eyes with these lesions are not considered to have the disease nor to be at high risk of developing the disease.[15,16,18,19,21,38] However, the 15-year results from the Beaver Dam Eye Study show that when compared to eyes with small numbers of only hard drusen (1–2), eyes with large areas of only small hard drusen ($\geq$9087 μm^2, estimated as $\geq$8) have an increased 15-year incidence of soft indistinct drusen (16.3% vs. 4.7%), pigmentary abnormalities (10.6% vs. 2.7%), and late AMD (1.5% vs. 0.4%). This is consistent with the findings in the Chesapeake Bay Waterman Study, in which eyes with $\geq$5 small drusen at baseline were 11 times as likely to develop larger drusen at follow-up than eyes with fewer drusen.[15] A follow-up even longer than 15 years is necessary to quantitate the risk of late AMD associated with larger areas of small hard retinal drusen in younger individuals.

Soft drusen and pigmentary abnormalities may regress and disappear.[15,16,18,22] 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. There was a cumulative disappearance of soft indistinct drusen of 18% in the absence of the appearance of more severe lesions such as RPE depigmentation, geographic atrophy, or exudative macular degeneration. These eyes were at an approximate 80% lower risk of progression to more severe AMD in the 5- to 10-year period that followed. In the Chesapeake Bay Waterman Study, large drusen (defined as $>$63 μm in diameter) disappeared in 34% of participants,[15] and in the Melton Mowbray study, 20% of soft drusen regressed over a 7-year period.[22] Factors leading to disappearance or regression of these lesions remain to be studied.

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 15-year period. The severity of AMD increases consistently with age such that, in people $\geq$75 years of age, 8% developed signs of late AMD.[31] Because AMD is a slowly progressive disease, long-term study of the natural history of this disease is important in developing risk estimates in middle-aged persons with early stages of it.

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