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Epidemiology of age-related macular degeneration

Barbara S. Hawkins,[1] Alan Bird,[2] Ronald Klein,[3] Sheila K. West[1]

[1]The Wilmer Ophthalmological Institute, Baltimore, MD; [2]Moorfields Eye Hospital, London, United Kingdom; [3]University of Wisconsin, Madison, WI

For more than two decades, researchers have sought to identify "risk factors" for age-related macular degeneration (AMD), a major cause of irreversible vision loss in the Western world, particularly in the elderly. Two issues have complicated this search: failure to differentiate between different stages of AMD and misinterpretation of measures of association (odds ratios) and risk (risk ratios) derivable from different research designs. Fortunately, in more recent epidemiologic studies, more attention has been given to these issues. Three groups of potential "risk factors" that have been studied were reviewed: those known to be risk factors for car diovascular disease, environmental factors, and racial and ethnic factors. Of these, only tobacco smoking, a known risk factor for cardiovascular disease, has been demonstrated to be associated with AMD consistently across many studies of different design, carried out within different populations. The available evidence supports at least a doubling of risk of late AMD associated with long-term smoking, a factor that is under the control of the individual. The preponderance of evidence has not supported other factors to the same degree. Presently, racial and ethnic factors are high priorities for further research.

Magnitude of the Public Health Problem

Prevalence and incidence data from community- and clinic-based studies [1-20] (Table 1) have been used to estimate the one-year incidence of vision-limiting or vision-threatening choroidal neovascularization (CNV) secondary to AMD, the "wet" form of AMD. Of the 30 million people in the United States who were 65 years of age or older in 1990, CNV developed in one or both eyes of 150,000 to 200,000 of them during the next year. In addition, a somewhat smaller number lost vision due to geographic atrophy, the "dry" form of AMD. In others, soft drusen and retinal pigment abnormalities developed in their eyes; these lesions signal increased risk of vision loss in the future [16-18].

In a 1995 review of the epidemiology of AMD, Vingerling and colleagues [21] reported a consistent finding across multiple population-based studies of an increase in prevalence of the late lesions of AMD with age, from near absence at age 50 to about 2% prevalence at age 70 and about 6% at age 80. The portion of the United States population over the age of 64 is projected to double in the next 25 years. Thus, it is important to identify factors, particularly factors that can be modified by either personal or medical interventions, that alter the risk of AMD and progression from early lesions without vision loss to late stages and consequent vision loss. It should be noted that the factors associated with early AMD may be different from those associated with progression to neovascular AMD or geographic atrophy. More recent epidemiologic studies have paid particular attention to the different stages and forms of AMD.

Correspondence to: Barbara S. Hawkins, PhD, 550 North Broadway, 9th Floor, Baltimore, MD, 21205-2010; Phone: (410) 955-8318; FAX: (410) 955-0569; email: bhawkins@jhmi.edu

Factors Associated with or Predictive of Increased Risk of AMD

The speakers focused on three groups of personal, environmental, and systemic factors that may modify the risk or visual impact of AMD: factors already proven to be associated with cardiovascular (macrovascular) disease, environmental exposures, and genetic predisposition due to race or ethnicity. Although a small increase in the risk of AMD associated with a highly prevalent factor may translate to a large number of individuals affected with AMD or at risk of vision loss in the future, typically factors that at least double the risk are of most interest. Because of the strong relation of AMD to age, only factors that suggest at least a doubling of risk or association may be reliable.

The epidemiologic literature uses the term "risk factor" to represent several different concepts. Attributes or exposures may be risk markers, determinants of disease susceptibility or outcome, or modifiable risk factors [22]. Although risk and prognosis for an individual may depend upon all of these factors, those that are potentially modifiable hold out the greatest hope for decreasing the incidence of AMD and the visual impairment associated with it. The statistic used to quantify association is the odds ratio. This statistic is appropriate when evaluating attributes or exposures using data from a case-control or cross-sectional study [23]. It is defined as the ratio of the odds of the attribute being present (versus absent) in individuals with the condition, such as AMD, to the odds of the attribute being present in individuals without the condition (Figure 1). The statistic used to quantify risk is the risk ratio, sometimes termed the relative risk. It is appropriate when evaluating factors using data from a prospective study, such as a cohort study, follow-up study, or controlled trial. The risk ratio is defined as the ratio of the risk of disease or outcome among those with the attribute or exposure of inter-

est to the risk in those without the attribute or exposure (Figure 2). Although odds ratios often are calculated from prospective study data, in general, they should not be considered to provide estimates of risk.

Regardless of whether the odds ratio or risk ratio has been estimated, it is important to examine the confidence interval (typically, a 95% confidence interval) around the estimate. Estimates of odds ratios or risk ratios that have confidence intervals that include only values greater than 1.0 are considered to be statistically significant and to support a positive association or increased risk, respectively. Studies that include larger numbers of cases have narrower confidence intervals, that is, provide a more precise estimate of association or risk. Another issue to consider when interpreting findings from epidemiologic studies is the choice of the reference (control or "low risk" group). If the estimated prevalence or incidence rate in the reference group is much lower than for the general population, odds ratios or risk ratios may be inflated and should be interpreted cautiously. It is possible that in a single investigation, no matter how large and well-designed, an estimate may be exceptionally low (or high) due to chance. A third consideration is whether odds ratios (or risk ratios) have been adjusted for known risk factors, particularly age in studies of AMD. Because many of the proposed risk factors for AMD are themselves age-related, for example, hypertension, lifetime sunlight exposure, and total pack-years of cigarette smoking, the statistical model used for adjusting crude estimates of association or risk must be specified carefully. Finally, it is important to consider the findings from a single study in the context of the totality of evidence, either qualitatively or quantitatively in a formal meta-analysis. A study that produces findings that are quite different from those of others warrants careful scrutiny of the design, conduct, and analysis for possible explanations of discrepant findings.

Figure 1. Calculation of Odds Ratio. Illustration of method of calculating a crude odds ratios from cross-sectional or case-control studies. Although odds ratios often are calculated from prospective study data, in general they should not be considered to provide estimates of risk.

	Disease	
Attribute or Exposure	Yes (Cases)	No (Controls)
Present (Exposed)	a	b
Absent (Unexposed)	c	d

Odds of attribute or exposure in cases:

$$\frac{a}{c}$$

Odds of attribute or exposure in controls:

$$\frac{b}{d}$$

Odds ratio:

$$\frac{\frac{a}{c}}{\frac{b}{d}} = \frac{a \times d}{b \times c}$$

Figure 2. Calculation of Risk Ratio. Illustration of method of calculating crude risk ratios from cohort, follow-up, and other prospective studies.

	Attribute or Exposure at Inception	
Outcome	Present (Exposed)	Absent (Unexposed)
Disease (Case)	a	b
No disease (Control)	c	d

Risk of disease when attribute present:

$$\frac{a}{a+b}$$

Risk of disease when attribute absent:

$$\frac{c}{c+d}$$

Risk Ratio:

$$\frac{\frac{a}{a+b}}{\frac{c}{c+d}}$$

Potential Cardiovascular Risk Factors for AMD

Data from three population-based studies, the Beaver Dam Eye Study [8], the Blue Mountains Eye Study [10], and the Rotterdam Study [9], were summarized quantitatively to examine the association between AMD and four risk factors known to be associated with macrovascular disease: smoking history, hypertension, lipid profile, and atherosclerotic vascular disease.

Smoking is known to depress antioxidants and to alter choroidal blood flow. Thus, it has been hypothesized that smoking may alter the metabolism of the retinal pigment epithelium (RPE). Evidence from two case-control studies [24,25] suggest that both current smoking and a history of smoking are associated with a higher risk of AMD. Three population-based studies support association of neovascular AMD with current smoking; estimated odds ratios range from 2.5 to 5.6. Weaker associations (estimated odds ratios greater than 1.0 but less than 2.0) of current or past smoking with early AMD and a history of smoking with neovascular AMD were found. These associations have been supported by follow-up studies [19,20] in which the incidence of AMD was found to increase with either the number of years of smoking or the number of pack-years smoked. Risk ratios of 2.0 or greater were found for 40 to 45 pack-years or more.

Hypertension is believed to damage the choroidal vasculature. Individual investigations have suggested that hypertension, defined in various ways, is associated with somewhat increased odds [8] and increased risk [14,18] of AMD. None of the three population-based studies found an association between hypertension and AMD. Fewer data are available for evaluating possible associations of AMD with serum lipid levels and with atherosclerotic carotid artery disease. Findings to date are inconsistent.

Thus, among cardiovascular risk factors, smoking is most strongly and consistently associated with AMD. Odds ratios and risk ratios estimated in most studies have been 2.0 or greater. More importantly, smoking is a factor that is a modifiable risk factor, that is, under the control of the patient.

Potential Environmental Risk Factors for AMD

The data linking AMD with exposure to ultraviolet (UV) radiation, antioxidant status, and antioxidant intake are more problematic. Biologically plausible hypotheses have been advanced for these associations but the mechanisms, particularly for UV radiation, may be complex. Furthermore, the amount of exposure to UV radiation is difficult to ascertain reliably. The epidemiologic evidence is mixed. Even in those studies that have provided data to support an association of UV exposure with AMD, the estimates of association or risk were relatively modest, that is, less than 1.4.

Findings regarding antioxidant status and intake with AMD have been inconclusive. The ongoing Age-Related Eye Disease Study, sponsored by the National Institutes of Health, should provide the strongest evidence to support or to refute an association of antioxidant intake with late AMD.

Potential Racial and Ethnic Determinants of AMD

The lower prevalence of AMD in some non-caucasian racial groups has been well documented. In particular, neovascular AMD in Barbadians of African descent [11] and as a cause of visual impairment among African-Americans [26] is uncommon. Recently, anecdotal cases and more formal investigations in Japanese and other Asian populations have [27,28] suggest increasing prevalence of AMD in these populations. There is evidence that the distribution of macular lesions that characterize AMD is different in Asian populations from caucasian populations [29,30], suggesting different phenotypical expression. The Inuit in Greenland have been reported to have a strikingly high prevalence of AMD with a distinctive phenotype [31,32]. There is a consensus that more epidemiologic data are needed before conclusions can be drawn regarding the magnitude of associations with race or ethnicity.

SUMMARY

Besides older age, the best established risk factor for AMD is a history of smoking tobacco. Other factors have been insufficiently investigated or else the evidence of an association is inconclusive or supports less than a doubling of risk. As suggested in this brief review, future research is needed into the reasons for differences in prevalence or phenotypic expression of AMD in different racial and ethnic groups. Even in the U.S., the prevalence of AMD in Hispanic and Asian subpopulations has not been documented. Careful synthesis of data from completed studies is necessary to evaluate the weight of evidence for and against potential risk factors. In addition, synthesis of available data is necessary to establish whether the most influential factors are genetic, environmental, or personal and under the control of the individual.

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