Epidemiology

Age-Related Macular Degeneration and Cancer Mortality in the Atherosclerosis Risk in Communities Study

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Objective: To examine the prospective association of early age-related macular degeneration (AMD) with cancer mortality.

Methods: A population-based cohort study of 10,029 persons aged 49 to 73 years free of cancer. The AMD signs were evaluated from retinal photographs taken in 1993 through 1995. Cancer mortality was determined from death records.

Results: There were 464 cases of early AMD. Over 10 years, there were 234 cancer deaths (71 lung cancer deaths). After controlling for age, sex, race, field center, education, smoking status, pack-years of smoking, body mass index (calculated as weight in kilograms divided by height in meters squared), and diabetes mellitus, early AMD was associated with cancer mortality (rate ratio [RR], 1.68; 95% confidence interval [CI], 1.03-2.73). This association was overall stronger in African American individuals (RR, 3.93; 95% CI, 1.67-9.22) than white individuals (RR, 1.28; 95% CI, 0.71-2.32) and for lung cancer deaths (RR, 2.14; 95% CI, 0.97-4.72) than non-lung cancer deaths (RR, 1.50; 95% CI, 0.81-2.78). In African American individuals, early AMD was associated with a 5-fold higher risk of lung cancer deaths (RR, 5.28; 95% CI, 1.52-18.40).

Conclusions: Middle-aged African American individuals with early AMD may be at increased risk of dying of cancer, particularly lung cancer. This association was not present in white individuals and needs confirmation in other studies.

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sampling from 4 US communities: Forsyth County, North Carolina; Jackson, Mississippi (African American individuals only); suburbs of Minneapolis, Minnesota; and Washington County, Maryland.

Of the 15792 participants at baseline, 12,887 (86% of the survivors) returned for the third examination in 1993 through 1995, when retinal photography was first performed. Of the 12,887 who returned for this examination, we excluded 38 participants whose race was neither African American nor white (because of small numbers in other racial groups) and 42 African American residents in Minneapolis and Maryland (so that race and center could be adjusted in 5 categories: Minnesota, Maryland, Mississippi, North Carolina white individuals, and North Carolina African American individuals), 271 participants with no retinal photographs, 1311 participants who reported having cancer at any of the first 3 examinations, and 989 with prevalent coronary heart disease and 207 with prevalent stroke at the third examination (2 major competing causes of death), leaving 10,029 participants for this analysis.

Institutional review boards at study sites approved the study. Informed consent was obtained from all participants and the study was conducted in accordance with the Declaration of Helsinki.

RETNAL PHOTOGRAPHY AND AMD GRADING

The assessment of AMD has been previously reported. In brief, a 45° nonmydriatic retinal photograph centered on the region of the optic disc and the macula of 1 randomly selected eye was taken after 5 minutes of dark adaptation. Graders, masked to the subject’s identity, evaluated the photographs for AMD based on a simplified version of the Wisconsin AMD grading system. The presence of soft drusen, retinal pigment epithelial (RPE) depigmentation, increased retinal pigment, pure geographic atrophy, and signs of exudative macular degeneration were determined. Soft drusen was defined as those having a diameter larger than 63 µm. Early AMD was defined as the presence of either soft drusen alone, RPE depigmentation alone, or a combination of soft drusen with increased retinal pigment and/or RPE depigmentation in the absence of late AMD. Late AMD was defined as the presence of exudative AMD or pure geographic atrophy. Quality control procedures, based on repeated assessment of 520 photographs, showed weighted $k$ values of 0.67 to 0.81 for intrgrader and 0.55 to 0.92 for intergrader comparisons.

CANCER MORTALITY

ARIC participants were contacted annually to ascertain vital status. If a participant was reported as deceased by next of kin or another designated contact person, the date and location of death, as well as any hospitalizations prior to death, were ascertained. When a participant was not located during annual follow-up, an attempt was made to determine vital status via search of hospital records and the National Death Index. Death certificates were obtained for virtually all deaths. For this study, we included all deaths occurring through December 2002. International Classification of Diseases, Ninth (ICD-9) and Tenth (ICD-10) Revision codes were used to classify the underlying cause of death assigned by state health departments into 3 broad categories and the following cause-specific mortality definitions were used: all cancer (140-208), lung cancer (162-162.9), and nonlung cancer (140-208 excluding 162-162.9) using ICD-9 codes and all cancer (00-97), lung cancer (33-34), and nonlung cancer (00-97 excluding 33-34) using ICD-10 codes.

DEFINITION OF OTHER VARIABLES

Participants had standardized questionnaires and evaluation of vascular risk factors at each examination, including blood pressure, height, and weight. Diabetes mellitus was defined as a fasting glucose level of 126 mg/dL or higher (to calculate glucose in millimoles per liter, multiply by 0.0555), a nonfasting glucose level of 200 mg/dL or higher, or a self-reported history of physician-diagnosed diabetes or treatment for diabetes. Fasting blood samples were obtained for levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, glucose, and plasma fibrinogen and white blood cell (WBC) counts. All variables were based on the third examination, except for WBC counts and plasma fibrinogen levels (samples from baseline).

STATISTICAL ANALYSIS

Death certificates were obtained for virtually all suspected deaths; study participants without death certificate data were considered alive and censored at December 31, 2002. Person-years of follow-up were defined as date of retinal photography to date of death or December 31, 2002. We calculated Kaplan-Meier cumulative cancer survival and used Cox models to estimate the hazard rate ratio (RR) of cancer deaths by AMD status. We initially adjusted for age (years), sex, race, and field center and further for education status (< high school, high school, or greater), cigarette smoking (current, former, or never), pack-years of smoking (continuous), body mass index (calculated as weight in kilograms divided by height in meters squared), and diabetes (absent or present). We included a second multivariable model further adjusting for HDL cholesterol and plasma fibrinogen levels and WBC count. We repeated analyses separately for lung cancer deaths and nonlung cancer deaths. In supplementary analyses, we used flexible nonparametric logistic regression with the generalized additive modeling approach (PROC GAM in SAS version 9.2; SAS Institute Inc, Cary, North Carolina) to calculate the odds ratios (ORs) of early AMD and cancer mortality, adjusting for all covariates in the multivariable model. These models examine the effect of confounding by age and other factors without linearity assumptions. We also repeated the analysis excluding the first 4 years of follow-up because early cancer deaths may be more likely to be biased by noncausal associations. Finally, we tested for consistency in associations by subgroup analyses by categories of race, sex, and cigarette smoking. Potential interaction with race, sex, cigarette smoking status, and cancer type (lung vs nonlung cancer) was examined by including appropriate cross-product terms in the Cox models; none of the interaction terms were statistically significant ($\alpha=.10$). Analyses were carried out using SAS version 9.1 (SAS Institute Inc).

RESULTS

There were 478 individuals (4.8%) with AMD in the population. Of these, 464 had early AMD and 14 had late AMD. Over a 10-year period (average, 8 years), 234 persons died of cancer, including 71 lung cancer and 163 nonlung cancer deaths. There were insufficient cases of late AMD for meaningful analysis, so all subsequent analyses were confined to early AMD.

Table 1 shows the baseline characteristics of participants according to early AMD status and cancer mortality. In general, compared with persons without AMD, participants with early AMD were significantly older and less

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likely to be African American and had fewer pack-years of smoking but were similar in most other characteristics. Compared with participants who did not die of cancer, participants who died of cancer were significantly older, more likely to be male, less likely to be high school graduates, and more likely to smoke with more pack-years of smoking, and to have diabetes, higher fasting glucose levels, lower HDL cholesterol levels, and higher WBC count and fibrinogen levels.

The Figure shows that individuals with early AMD were more likely to die of cancer than those without early AMD. Table 2 shows associations of early AMD and specific AMD signs with cancer mortality. After controlling for age, sex, and race/center, the presence of early AMD was associated with higher risk of cancer death (RR, 1.70). Further adjustment for education, smoking status, pack-years of smoking, body mass index, and diabetes (RR, 1.68) and for HDL cholesterol level, WBC count, and fibrinogen level (RR, 1.71) did not substantially change the association. The associations for specific AMD signs were largely similar. When we repeated the multivariable analyses in Table 2 using flexible generalized additive models, the results were essentially similar. For example, the OR (95% confidence interval [CI]) of all cancer deaths associated with early AMD in the multivariable model 2 was 1.64 (1.03–2.61). In analyses that excluded the first 4 years of follow-up, associations of early AMD and cancer mortality remained statistically significant (multivariable RR, 1.68; 95% CI, 1.01–2.79).

Table 3 shows that in supplementary analyses, the association of early AMD and all cancer deaths was stronger in African American individuals (RR, 3.93) than white individuals (RR, 1.28) but largely similar in men (RR, 1.78) and women (RR, 1.48) and in current (RR, 1.64) and past/never (RR, 1.71) cigarette smokers. Overall, associations were stronger for lung cancer mortality (RR, 2.14 vs 1.50 for nonlung cancer mortality in the total cohort), particularly among African American individuals (RR, 5.28). Additionally, current smokers had higher risk of lung cancer death associated with early AMD (RR, 2.62 vs 1.55 in never or ex-smokers), whereas never or ex-smokers had a higher risk of nonlung cancer death associated with early AMD (RR, 1.73 vs 0.66 for current smokers). However, none of the interactions shown in Table 3 were statistically significant ($P > .10$), with the possible exception of race for all cancer mortality ($P = .06$). In addition, there was also no significant interaction between type of cancer and early AMD in the model with all cancer deaths as the outcome ($P = .21$).
Approximately 7 million Americans have early AMD signs and are at risk of visual loss. Our study demonstrates that persons with early AMD have a higher risk of cancer mortality, independent of cigarette smoking and other risk factors. In subgroup analyses, the associations were stronger for lung cancer deaths than nonlung cancer deaths and in African American individuals. We showed that African American individuals with early AMD signs...
had a 5-fold higher risk of lung cancer mortality than those without early AMD.

There are few studies for direct comparison. Previous studies have focused largely on the relationship between AMD and all-cause or cardiovascular mortality.2-7 In the ARIC cohort, early AMD was not associated with either all-cause mortality (multivariable RR, 1.01; 95% CI, 0.78-1.31)8 or cardiovascular mortality specifically (multivariable RR, 1.00; 95% CI, 0.51-1.96).34 The relationships of AMD, visual impairment, and other ocular diseases with cancer-specific mortality have been evaluated in only a limited number of studies.7,10,35 In a cohort study of type 2 diabetes, moderate visual impairment (visual acuity of 20/80 to 20/160) was associated with a higher risk of cancer mortality, although the specific association of AMD and cancer mortality was not reported.33 In another cohort study of 13,509 persons 75 years or older in the United Kingdom, no association between self-reported AMD and cancer mortality was seen.7 More recent data from the Beaver Dam Eye Study found no association between early AMD, as determined from retinal photographs, and cancer mortality in white persons.10 Our study now demonstrates an association of early AMD and cancer mortality that was stronger and statistically significant only in African American individuals. The reason for this is unclear, but the lack of a significant association in our white participants is consistent with the Beaver Dam Eye Study findings.

We propose several plausible pathophysiological mechanisms linking AMD to cancer. First, AMD and cancer may share similar risk factors, in particular, cigarette smoking. In our models, the associations were independent of both cigarette smoking status and pack-years of smoking, although we cannot be certain we have totally excluded residual confounding from the effects of chronic smoking. Second, there is some evidence that C. pneumoniae infection, a common cause of acute respiratory tract infection linked with lung cancer,26 may also be associated with the development and progression of AMD,19,20 offering another potential explanation for our findings. Third, recent studies have identified systemic inflammation and the genes coding these inflammatory pathways as an important pathogenic factor in the development of both early AMD signs, including drusen, and late stages of AMD.11-17 Studies indicate that the complement factor H (CFH) gene is involved in a large proportion of AMD cases.11-13 Inflammation has long been known to influence cancer growth, progression, and invasion.30,37 and the CFH gene has also been specifically associated with different types of cancers, including lung,21 bladder,38 and ovarian22 cancer. These observations suggest that inflammation may be a key pathophysiological process for both AMD and cancer. In our study, however, controlling for non-specific inflammatory markers (WBC count and fibrinogen levels) had minimal impact on the association between AMD and cancer mortality. Finally, oxidative stress is another possible shared mechanism. There is experimental evidence of oxidative damage to the lipids in the Bruch membrane in eyes with AMD.14,15 Concomitantly, inactivation of antioxidant enzymes and attendant oxidative stress are believed to be causal processes in carcinogenesis.24,25 In summary, these data provide possible biological links underlying our study findings. However, these hypotheses would require further validation from future studies.

Our finding that the association of early AMD and cancer mortality was stronger in African American individuals must be interpreted cautiously. Although there are known differences in the epidemiology of AMD between white and African American individuals, we did not hypothesize this a priori. In addition, this finding was based on subgroup data with small numbers of cancer deaths in African American individuals with early AMD. The stronger association in African American individuals might also be due to inadequate adjustments for potential confounders (eg, cigarette smoking status and socioeconomic factors). Nonetheless, an earlier ARIC study found that there has been no consistent pattern to suggest that cancer mortality is associated with socioeconomic status or personal income.39 There is evidence, for example, that even when census tract poverty rate is accounted for, African American individuals still have higher cancer mortality than non-Hispanic white individuals.40 Thus, our finding of a higher risk of cancer death in African American individuals with early AMD may reflect the existence of unknown biological, genetic, or socioeconomic factors.41

Strengths of our study include a prospective design, a community-based study population, standardized AMD evaluation from photographs, and validated ascertainment of deaths. There are several limitations. First, whether AMD is related to cancer cannot be directly inferred because our outcome was cancer mortality and not incident cancer. Thus, early AMD may not be related to cancer development per se but to cancer survival. Second, we used a single 45° nonstereoscopic fundus photograph taken through nonpharmacologically dilated pupils to determine the presence of AMD. Age-related macular degeneration is less likely to be detected and the grading more variable with this approach.42 Additionally, although AMD is often symmetrical between eyes, some people with AMD would be missed because of the possibility of the involved eye not being photographed. However, if AMD indeed is casually associated with cancer mortality, misclassification of these persons (AMD cases misclassified as controls) would indicate that the true association between AMD and cancer mortality is in fact stronger than the data presented herein. Third, because of the insufficient number of late AMD cases in our study population, whether more advanced AMD signs are also associated with cancer mortality is uncertain. Further, AMD signs were graded using a simplified version of the Wisconsin system in the ARIC study. This approach did not allow us to examine the different types of drusen (eg, intermediate vs large) and their relationship with cancer mortality and might have also led to additional misclassification. However, such misclassification would likely be nondifferential in nature and would have biased the results toward the null. Fourth, our current study was not powered to detect interaction, nor did we have an a priori hypothesis of potential interaction. Thus, the results of stratified analyses shown in Table 3 should be
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REFERENCES


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**Archives Web Quiz Winner**

Congratulations to the winner of our April quiz, Michael Ober, MD, Director of Retinal Research, Department of Ophthalmology, Henry Ford Health Systems, West Bloomfield, Michigan. The correct answer to our April challenge was familial fleck retina. For a complete discussion of this case, see the Photo Essays section in the May *Archives* (Audo I, Tsang SH, Fu AD, Barnes JA, Holder GE, Moore AT. Autofluorescence imaging in a case of benign familial fleck retina. *Arch Ophthalmol.* 2006;125[5]:714-715).

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