

ARIC Manuscript Proposal # 1143

PC Reviewed: 03/21/06
SC Reviewed: _____

Status: _____
Status: _____

Priority: _____
Priority: _____

1.a. **Full Title:** Age-Related Maculopathy and Incident Cancer

b. **Abbreviated Title (Length 26 characters):** Age-Related Maculopathy and Incident Cancer

2. **Writing Group (list individual with lead responsibility first):**

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3. **Timeline:**

4.

The intent of this analysis is to investigate the prospective association of the age-related maculopathy (ARM) at Visit 3 to incident cancer risk. Initial analyses and writing will take place between March and April 2006, and final writing and manuscript submission between September and November 2006.

4. **Rationale:**

ARM is a leading cause of blindness in elderly people in the United States. The presence of ARM has been hypothesized to be associated with decreased survival¹⁻⁷, though the underlying cause of the association is unclear. Cancer is a major cause of deaths. Its potential association with ARM, nonetheless, has not been investigated.

There are several possibilities to suggest that ARM may be related to cancer. First, ARM and cancer may share several common risk factors. For example, smoking is an established risk factor for both ARM and various types of cancers, in particular, lung cancer. Moreover, there is also serologic evidence to suggest that *Chlamydia pneumoniae* infection, a common cause of acute respiratory tract infection that has been linked with lung cancer, is associated with the development and progression of ARM⁸⁻¹¹. Second, recent studies have identified a common polymorphism of the complement factor H (CFH) gene as a likely candidate involved in the development of ARM¹²⁻¹⁵. Investigators have further suggested that inflammation might play an important role in the etiology of ARM.¹⁶⁻²⁰ This is supported by histological appearance of choroidal neovascularization secondary to ARM, which demonstrates tissue invasion of a multitude of inflammatory cells.²¹ Cancer has also been closely related to inflammation. Inflammatory processes are believed to contribute to tumor growth, progression and invasion.²¹. In addition, the CFH gene was also found to be associated with a number of cancers, including

lung^{22,23}, bladder²⁴ and ovarian cancer²⁵, further reinforcing the potential pathogenic role of inflammation in linking ARM and cancer risk. Third, oxidative stress may be another potential mechanism. The role of oxidative stress in the pathogenesis of ARM has been highlighted in recent studies²⁶. There is evidence that oxidative damage to lipids in Bruch membrane is important in the etiology of ARM.²⁷⁻³⁰ Similarly, there is also evidence directly supporting the notion that inactivation of antioxidant enzymes and its attendant oxidative stress are causal events in carcinogenesis^{29,31-33}. Finally, angiogenesis, a complex multi-stage process requiring orchestrated interactions among various pro- and anti-angiogenic stimuli, is known to have a central role in the development of both cancer³⁴ and neovascular ARM^{35,36}. While tumor growth and subsequent metastasis rely on the inappropriate growth of blood vessels, ARM-related choroidal neovascularization occurs as result of vascular recruitment induced by angiogenesis^{37,38}. The collective data from these studies provide evidence for the possible biological links between ARM and cancer.

Cancer mortality and ARM has been evaluated in a very limited number of epidemiological studies¹. In a population-based cohort study of persons with type 2 diabetes, moderate visual impairment (visual acuity of 20/80 to 20/160) was shown to be independently associated with an increased risk of cancer mortality (RR 1.61; 95% CI, 0.63-4.08), although the specific association of early ARM with cancer mortality was not reported^{1,39}. In a study of 13,569 persons aged 75 years or older in the United Kingdom, no association between ARM and cancer mortality was seen³⁹. This study, however, was limited by the definition of ARM, which was determined from self reported data.

Since ARIC study defines ARM based on fundal photography, we propose to examine these data to further clarify the potential association between ARM and cancer.

5. Main Hypothesis/Study Questions:

Is early ARM associated with incident cancer?

- (1) If so, is association related to lung cancer or non-lung cancer?
- (2) If so, is this related to a particular ARM lesion (drusen, pigmentary change etc)?
- (3) If so, is the association explained by age, gender, race, cigarette smoking status, hypertension and cardiovascular risk factors?

6. Data (variables, time window, source, inclusions/exclusions):

- (1) ARM variables. Any ARM, early ARM, late ARM and specific ARM lesions (drusen, pigmentary changes)
- (2) All-cancer incidence, lung cancer incidence, non-lung cancer incidence
- (3) Covariates: age, sex, race, center, prevalent CHD and MI, diabetes and hypertension status, blood pressure, hemostatic and inflammatory markers (von Willebrand factor, factor VIIIc, fibrinogen, WBC), cigarette smoking, alcohol consumption, body mass index (variables from ARIC visit 1-3, except for von Willebrand factor, factor VIIIc, WBC, fibrinogen available ARIC visit 1 only)
- (4) Exclusion criteria: From participants at ARIC visit 3 (n=12,887), exclude persons who whose race is not black/white, with ungradeable retinal photographs or missing retinal variables for ARM at visit 3.

Power estimates: Based on approximately **500** ARM cases at visit 3 and **947** incident cancers from visit 3 to 2000 in the ARIC cohort, a sample size of 10,000 will have adequate power (power 80%, alpha 5%) to detect a RR of 1.40 or higher

7.a. Will the data be used for non-CVD analysis in this manuscript? Yes No

b. If Yes, is the author aware that the file ICTDER01 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? Yes No
(This file ICTDER01 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? Yes No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER01 must be used to exclude those with value RES_DNA = "No use/storage DNA"? Yes No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: <http://bios.unc.edu/units/csc/ARIC/stdy/studymem.html>
 Yes No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

- Klein R, Clegg L, Cooper LS, et al. Prevalence of age-related maculopathy in the Atherosclerosis Risk in Communities Study. *Arch Ophthalmol* 1999;117:1203-10.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes No

11.b. If yes, is the proposal

- A. primarily the result of an ancillary study (list number* _____)
- B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____)

*ancillary studies are listed by number at <http://www.csc.unc.edu/aric/forms/>

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

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