1. Title: Intake of Antioxidant Vitamins and Zinc in Diet and Supplements and the Prevalence of Age-Related Maculopathy

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3. Timeline:

March 1996: Send to ARIC Coordinating Center (1) the Brand-Name Based Supplement Database used in the Beaver Dam Eye Study Cohort for use in developing a similar database for ARIC and (2) List of recommended supplement variables to derive.

September 1996: Receive dietary and supplement datasets in SAS format from the ARIC Coordinating Center. Receive retinal data from the Retinal Reading Center.

February 1997: Complete analyses and first draft of manuscript.

4. Rationale:

Age-related macular degeneration is the leading cause of blindness in older adults. Current treatment options are of limited effectiveness for most forms of the condition. Means to prevent the development of this condition are being sought to limit the impact of this condition on health care costs and the quality of life of Older Americans. Dietary factors are among the modifiable factors which are being considered for their potential to prevent or slow the development of age-related maculopathy (ARM).

Two pathogenic mechanisms which might contribute to the development of ARM include oxidant damage to the area of the retina which involves central vision (the macula) and arteriosclerosis of retinal blood vessels which nourish this area. Studies in experimental animals indicate that the retina is susceptible to oxidative damage due to its high concentration of polyunsaturated fatty acids and exposure to light as a source of damaging oxidants. Moreover, deficiencies of nutrients which function as antioxidants cause retinal damage in experimental animals.

The observation of lipid deposits in fellow eyes of people with macular degeneration in one eye suggests that arteriosclerotic processes may accompany this condition, as well. Such deposits may interfere with the flow of metabolites in and out of the cells which conduct the metabolic work for the photoreceptors in the retina (the retinal pigment epithelium). Arteriosclerosis which occurs systemically might also contribute to the degenerative process by limiting blood flow to this region of the retina. In the Rotterdam Aging Study, the presence of carotid artery plaques and peripheral arterial disease was associated with higher rates of ARM.

One set of dietary factors which may influence the development of ARM are those which have the potential to reduce the extent of oxidant damage in the macula or in lipoproteins (Oxidation may in turn increase their atherogenicity). They include nutrients which can function as direct antioxidants (vitamins C and E and carotenoids) or which function as cofactors in systems which protect against oxidant damage (riboflavin, zinc, selenium). There is support for the notion that the intake of antioxidant nutrients may be related to the onset of ARM in humans. Low levels of carotenoids in the serum or intake of fruits and vegetables containing carotenoids were related to higher odds for ARM in two (NHANESI and the Eye Disease
Case-Control Study), but not all (Baltimore Longitudinal Study of Aging, Beaver Dam Eye Study, study of general practitioner patients in North London) previous studies. Associations with other antioxidant nutrients are inconsistent between studies (vitamin C and E) or not well studied. One reason for inconsistency in past studies may be the use of smaller samples and/or cross-sectional study designs in which dietary changes subsequent to the onset of ARM may confound results. There is a need for additional epidemiologic data on these relationships in larger samples. The sample of people in the ARIC study is both large and racially and geographically diverse.

Studies of people with earlier forms of the condition may provide insights about factors related to early stages in the pathogenesis of ARM and are less likely than studies of the advanced condition to be influenced by changes in diet or supplements which occur as a result of having ARM. The prevalence of early ARM in the ARIC population (5%) permits a study of dietary factors related to early stages of this condition. The fact that few people with early stages are aware of the presence of ARM and the collection of dietary data six years before ARM data were obtained, lessens the opportunity for associations to be influenced by recent diet change related to ARM.

Low zinc intakes have been hypothesized to be related to the development of ARM, based on the high concentration of zinc in the retina and the degenerative changes which occur in the retina of animal and human deprived of zinc. In one small, double-blind, placebo controlled, clinical trial, the use of zinc supplements was related to less worsening of advanced ARM. Only one previous study (in the Beaver Dam Cohort) has examined relationships between early ARM and levels of zinc in the diet. In this study, higher intake of zinc from food and supplements was associated with lower rates of age-related maculopathy. These relationships will be investigated prospectively in the same Beaver Dam, WI population. Investigation of these relationships in the ARIC population will provide needed confirmation of this relationship in a separate population. Furthermore, the ARIC investigation may contribute new information regarding the strength of the relationship in a population of people with lower levels of zinc in the diet. The ARIC population includes African American persons who, on average, were found to have lower intake of zinc than white persons in the Second National Health and Nutrition Examination survey, independent of income and socioeconomic status. If zinc is causally related to the onset of early ARM, this relationship may be stronger among participants in the ARIC study.

Thus, investigation of relationships between dietary factors and ARM in the ARIC population will provide needed confirmatory evidence for associations found in prospective studies in other populations. The large sample size and racial diversity in the ARIC population will permit investigation of consistency of these associations among people with different racial backgrounds. For some dietary factors, the intake of nutrients among ARIC participants may be lower, enhancing the opportunity to detect inverse associations with level of nutrient in the diet if they exist. The large sample size will also permit exploration of interactions among different dietary factors which may be related to ARM.

5. Main Hypothesis:

(1) ARIC participants with intakes of antioxidant nutrients and zinc from diet and supplements in the highest quintiles in 1987-89 will have lower rates of early and late ARM in 1993-95 than those in the lowest quintiles.

This relationship will persist regardless of:

- history of cigarette smoking
- history of beer drinking
- race
- use of supplements subsequent to 1989

This relationship will be stronger in:
participants taking supplements containing antioxidant nutrients for at least ten years

(2) The intake of fruits and vegetables, which contain many unmeasured antioxidant chemicals, in the highest vs. lowest quintiles will be related to lower rates of ARM, as well. This relationship will persist in people who did not take supplements at baseline.

6. Data:

(A) Retinal data required from 1993-5 Visits:
- soft drusen
- increased retinal pigment
- retinal pigment degeneration
- geographic atrophy
- neovascular/exudative macular degeneration
- retinal arteriolar narrowing

(B) Dietary data:
(1) Estimates of intake at baseline (1987-89) from foods using updated Willett databases:
- energy
- macronutrients:
  - animal fat
  - vegetable fat
  - saturated fat
  - monounsaturated fat
  - oleic
  - polyunsaturated fat
  - linoleic
  - cholesterol
  - Keys score
  - omega 3 fatty acids
  - protein
  - carbohydrate
  - crude fiber
  - alcohol

(2) Estimates of intake at baseline from foods and supplements (estimate 1987-89 intake using supplement type and duration of variables gathered at Visit 3):
- minerals:
  - zinc
  - calcium
  - iron
  - magnesium
  - selenium
  - copper
- vitamins:
  - vitamin C
  - thiamine
  - riboflavin
  - niacin
  - B6
  - folate
  - retinol
carotene
vitamin D
vitamin E
individual carotenoids available:
  alpha-carotene
  beta-carotene
  lutein+zeaxanthin
  cryptoxanthin
  lycopene
servings of:
fruits and vegetables
carrots
spinach, collards and other greens
dark yellow squash and sweet potatoes
tomatoes
broccoli
peaches, apricots or plums
oranges or citrus juice
milk
yogurt
ice cream
cottage cheese or other cheese
margarine
butter
dark meat fish
other fish
canned tuna fish
shellfish
total servings of beef, pork, or lamb
eggs

Estimates (above) of food and nutrient intake at Visit 3

Years of supplement use:
multivitamins
any supplement providing:
  vitamin C
  vitamin E
  zinc
  beta-carotene
  vitamin A
  riboflavin
  selenium

(C) Blood lipids at baseline:
total cholesterol
total tryglycerides
HDL cholesterol
LDL cholesterol
LDL subfractions
Apoprotein fractions
(D) Measures of Arteriosclerosis at 6 year visits and year 1 to year 6 change; Ultrasonigraphically determined carotid wall thickness

(E) Other risk factors at baseline and 6-year follow-up:
  - history of cigarette smoking (never, past, current)
  - numbers of cigarettes/day
  - average weekly intake of the following alcoholic beverages:
    - beer
    - wine
    - hard liquor
  - history of past heavy drinking
  - education
  - income
  - race
  - gender
  - height
  - weight
  - body mass index
  - systolic and diastolic blood pressure measurements
  - history of:
    - diabetes with insulin use
    - diabetes without insulin use
    - cancer
    - MI
    - stroke
    - peripheral vascular disease
    - death since baseline

7. Analyses and Statistical Power:

Logistic regression analyses will be used to quantitate the magnitude of associations between ARM at the third visit and nutrient levels in baseline diets. Associations will be tested using both crude and energy-adjusted nutrient values. The choice of energy adjustment method will depend on whether relationships between energy and ARM are observed. If there are no associations, a nutrient density approach will be used. If, on the other hand, energy intake is related to ARM, then the residual approach will be used and energy will be added as a covariate in analyses.

Associations between ARM and nutrient intake will be evaluated for confounding influences and for effect modification by stratification and evaluation of the impact of suspected confounders on risk estimates. Final logistic regression models will be adjusted for identified potential confounders or interaction terms which influence the odds ratios.

The magnitude of associations that can be detected with certainty in this sample was estimated for representative nutrients, using recent estimates of the prevalence of ARM in the ARIC sample (6.5%). An odds ratio, for a linear trend across quintiles of intake, corresponding to the association between the first and fifth quintiles of 1.4, can be detected with 81% power in the entire sample.

When there is no evidence of threshold effects, the continuous range of nutrient intake values will be utilized in regression models resulting in even greater statistical power. Estimates of differences in mean levels of zinc and vitamin E intake in people with and without ARM that could be detected at varying levels of power were calculated using dietary intake data collected in the Beaver Dam, WI population (using similar food frequency questionnaire methods to those used in ARIC). These estimates consider variability in intake of
these nutrients from foods and supplements. Because of skewness in the data, the estimates consider variability in intake of these nutrients from foods and supplements. Because of skewness in the data, the estimates are based on log-transformed values and geometric mean values are given. For zinc, a main nutrient of interest, a difference between mean values in people with and without ARM of 0.83 mg (8% of mean value) can be detected with greater than 90% power in the entire sample. For vitamin E, a difference between mean values of 2.0 alpha-tocopherol equivalents (15% of mean values) can be detected at this level of power. Larger differences for both nutrients can be detected with certainty in smaller subgroups. For example, in subgroups as small as 1000 people, a difference between mean zinc intake of 1.3 mg (10% of mean values) can be detected and a difference between mean vitamin E intake of 2.9 alpha-tocopherol equivalents (22% of mean values) can be detected with a power of greater than 90%. Therefore, we estimate that there is adequate statistical power available to test the primary hypotheses in the entire sample and in smaller subgroups.