ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #373

1. Title:
Relation of Dietary Lipids to Age-Related Maculopathy

2. Writing Group:
(lead) Mares-Perlman, JA; Klein, R; Hubbard, L; Cooper, LS; Sorlie, P; Stevens, J; Folsom, A

3. Timeline:
Analyses will begin when the first dietary and supplement databases are received from the ARIC Coordinating center (suggested target: September, 1996). Analyses will be completed in April, 1997.

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 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 extremity arterial disease were 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 influence the extent of oxidant damage in the macula or to lipoproteins (which 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). These factors will be considered in a separate manuscript.

A second set of dietary factors which may alter the development of ARM are those which alter the levels and types of lipids in the blood. In this proposed manuscript, we will investigate associations between the intake of lipids in the diet and the occurrence of ARM. There is a large body of evidence that high levels of dietary fat, particularly saturated fat, increase blood cholesterol levels and lead to an increased risk for atherosclerosis. One recent study (The Eye-Disease Case Control Study), reported higher levels of serum cholesterol in people with incident advanced exudative macular degeneration. However, cross-sectional studies have indicated either no relationship or an inverse relationship between levels of cholesterol in the serum and ARM. In one previous retrospective cohort study (in the Beaver Dam cohort), intakes of saturated fat and cholesterol in the highest vs lowest quintiles were associated with 80% and 60% increased
odds for early ARM. Investigation of relations between levels of lipids in the diet and ARM in the ARIC population permit us to evaluate whether this finding can be confirmed in a separate population. The consistency of such relationships across races and geographical regions in the United States can also be evaluated. Moreover, the availability of extensive data on blood lipids and the extent of arteriosclerotic changes also permit an thorough evaluation of the likelihood that dietary lipids are linked to ARM because of their influence on serum lipids and the extent of arteriosclerosis.

5. Main Hypotheses:
1. ARIC participants with intakes of animal fat and cholesterol in the highest versus lowest quintiles in 1987-89 will have:
   A. higher rates of ARM
2. These relationships will be stronger in people with low intake of antioxidants from diet and supplements.
3. These relationships will persist regardless of:
   -race
   -history of cigarette smoking
   -history of beer drinking
4. These relationships will be explained by higher levels of LDL cholesterol and lower levels of HDL cholesterol at baseline and higher rates of six year arteriosclerotic changes in people with higher intakes of saturated fat and cholesterol.

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 variables gathered at Visit 3):
         - minerals:
            - zinc
            - calcium
            - iron
magnesium
selenium
copper

vitamins:
  vitamin C
  thiamin
  riboflavin
  niacin
  B6
  folate
  retinol
carotene
vitamin D
vitamin E
individual carotenoids if 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 triglycerides
- HDL cholesterol
- LDL cholesterol
- LDL subfractions
- Apoprotein fractions

Estimates of plasma levels of individual fatty acids in participants at the Minnesota site (n=4,009)

E. Measures of Arteriosclerosis at 6 year visits and year 1 to year 6 change:
- Ultrasonographically determined carotid wall thickness

F. 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 employed to evaluate relationships between the energy-adjusted levels of lipids in the diet at baseline and the prevalence of specific lesions of early and late ARM at the third visit. Systematic evaluations of confounders and effect modifiers will be undertaken.

Sample Size Calculations:
The magnitude of associations that can be detected with certainty in this sample was estimated, 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 of saturated fat, corresponding to the association between the first and fifth quintiles of 1.4, can be detected with 81% power in the entire sample.
In no thresholds appear to exist, we will use the continuous range of nutrient intake values which will be even more statistically powerful. Estimates of differences in mean levels of nutrient 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). For saturated fat, a main nutrient of interest, a difference between mean values in people with and without ARM of 0.5% saturated fat (as% energy) can be detected with 97% power in the entire sample. Larger differences can be detected with certainty in subgroups. For example, in subgroups as small as 1000 people, a difference between mean saturated fat intake of 1.2% (an 8% increase in mean levels in Beaver Dam) can be detected with a power of 85%. Therefore, there is adequate statistical power available to test the hypothesized associations.