ARIC MANUSCRIPT PROPOSAL #706

PC Reviewed: 01/06/00	Status: Approved	Priority: 2
SC Reviewed:	Status: Approved	Priority: 2

1.a. Full Title: Glutathione S-transferase polymorphisms, cigarette smoking, and markers of inflammation, endothelial function, and the immune response

b. Abbreviated Title (Length 26): GST-smoking mediators

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

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3. Timeline: Begin analyses 1/2000 First draft 7/2000

4. Rationale:

Metabolic polymorphisms of glutathione S-transferases have been associated with risk of lung, bladder, and colon cancer, especially among smokers. Recent case-cohort analyses in ARIC have suggested an interaction between glutathione S-transferase M1 (GSTM1) or T1 (GSTT1) genotypes, smoking, and risk of CVD outcomes, including incident CHD (Li et al., submitted), peripheral arterial disease (Li et al., manuscript in preparation), and increased carotid intimal-medial thickness (Olshan et al., manuscript in preparation).

Several intermediate mechanisms have been proposed to explain these apparent gene-smoking interactions. One possible mechanism is that individuals with functional alleles of the GSTM1 or GSTT1 genes have a greater capacity to detoxify or activate <u>specific</u> carcinogens or mutagens found in cigarette smoke. Alternatively, individuals with functional alleles of these genes may have increased capacity to detoxify reactive oxygen intermediates or oxidized lipids formed in response to cigarette smoke and other sources of oxidative stress. Once oxidized lipids are formed and deposited in the arterial wall, they are thought to invoke a number of local and systemic responses, including activation of endothelial cells, increased production of chemokines and cellular adhesion molecules to recruit leukocytes, and increased production of pro-inflammatory cytokines leading to a low-grade acute phase response.

5. Main Hypotheses:

The following hypotheses will be tested separately for GSTM1 and GSTT1 genotypes:

- a) Independent effect of smoking: Among participants with functional GST alleles, current smokers will have significantly different circulating concentrations of <u>acute phase proteins and other markers of inflammation</u> (higher CRP, fibrinogen, and white cell count, lower albumin), <u>soluble cellular adhesion molecules</u> (higher E-selectin, L-selectin, P-selectin, ICAM-1, and VCAM-1), <u>chemotactic cytokines</u> (higher MCP-1), and markers of <u>endothelial function</u> (higher factor VIIIc and vWF) compared to non-smokers.
- b) Independent effect of genotype: Among non-smokers, individuals with a GST null genotype will have significantly different circulating concentrations acute phase proteins and other markers of inflammation, soluble cellular adhesion molecules, chemotactic cytokines, and markers of endothelial function compared to individuals with functional GST alleles.
- c) *Interdependent effects of smoking and genotype:* The combined effect of *current smoking* and a *GST null genotype* will be greater than additive for levels of the molecular markers listed above.

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

The hypotheses will be tested in a cross-sectional analysis using data from the Visit 1 cohort random sample (n=989). The proposed molecular markers and GSTM1 and GSTT1 genotypes have already been measured in this subset of participants. Analysis will be conducted using linear regression, with circulating levels of the each analyte as the dependent variable and combinations of smoking and GST genotypes as the primary independent variables. SUDAAN or another comparable program will be used to conduct weighted analysis to account for the stratified random sampling of the CRS. All analyses will initially include a minimal set of covariates (age, gender, and ethnicity/center). Later analyses will adjust for other major CVD risk factors (diabetes, hypertension, LDL and HDL cholesterol, BMI). To reduce the probability of type I error with multiple dependent variables, we will consider either adjusting the nominal level of significance for multiple comparisons or conducting multivariate analysis using SUDAAN. The latter approach may be more appropriate if the proposed variables are markers of the same pathophysiologic process.

References:

- Li R, Boerwinkle E, Olshan AF, Chambless LE, Pankow JS, Tyroler HA, Bell DA, Heiss G. Glutathione S-transferase genotype as a susceptibility factor in smoking-related coronary heart disease. (submitted to *Atherosclerosis*)
- Olshan AF, Li R, Pankow JS, Bray M, Tyroler HA, Chambless LE, Boerwinkle LE, Pittman GS. Glutathione S-transferase polymorphisms and the risk of preclinical atherosclerosis. (manuscript in preparation)
- Li R, Folsom AR, Sharrett AR, Couper D, Bray M, Tyroler HA. Interaction of the glutathione Stransferase genes and cigarette smoking on risk of lower extremity arterial disease. (manuscript in preparation)