ARIC Manuscript Proposal # 1075r

PC Reviewed: _05/13//05	**Status: _A___**	**Priority: _2__**
SC Reviewed: __05/13/05	**Status: __A__**	**Priority: _2__**

1.a. Full Title: Metabolic syndrome and Incidence of Lung Cancer in the ARIC Cohort

b. Abbreviated Title (Length 26 characters): Met. Syndrome and Lung cancer

2. Writing Group:

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3. Timeline: Analysis to start immediately, first draft by September 2005.

4. Rationale:

Metabolic syndrome is characterized as a clustering of metabolic conditions: central obesity, insulin resistance, dyslipidaemia, and hypertension which, when present together in an individual, are associated with risk of cardiovascular disease and type 2 diabetes (1). Prevalence of metabolic syndrome is high among US adults and analyses of trends indicate a significant increase in incidence in recent years (2). This increasing prevalence has important implications with respect to the health of the population. The association between metabolic syndrome and risk of coronary heart disease and stroke has been established in many studies (1).

Current definitions of the metabolic syndrome do not include indicators of inflammation although association of metabolic syndrome with inflammation has been established (3,7). Inflammatory markers, such as CRP, are elevated in persons with metabolic syndrome as are levels of proinflammatory cytokines.

Chronic inflammation, which results in continuous production of growth stimuli, activation of reactive oxygen species, increased expression of chemokines, cytokines and cell adhesion molecules, and inhibition of apoptosis, plays an important role in the development of both atherosclerosis and cancer (6). A question arises then: is metabolic syndrome, with the underlying inflammatory changes, a risk factor for cancer? Recent data suggest that metabolic syndrome may indeed contribute significantly to the development of cancer. Laukkanen et al have shown an association between metabolic syndrome and risk of prostate cancer in men (4). Furberg et al. have shown that low levels of HDL-C, combined with obesity, both elements of the metabolic syndrome, are positively associated with the risk of breast cancer (5). A number of epidemiological studies have found a positive association between components of the metabolic syndrome, specifically insulin resistance and hip waist ratio, and the risk of colon cancer (8). In a confirmatory factor analysis study of the factor structure of the metabolic syndrome, insulin resistance and obesity were shown to be the most important elements of the metabolic syndrome (9). Insulin resistance leads to increase in the levels of the insulin-like growth factor-1 (IGF-1). Blood levels of this growth peptide have been shown to be elevated in prostate, breast, colorectal, and lung cancer (10). There is therefore an increasing body of evidence that components of the metabolic syndrome may be important risk factors in cancer development.

The subject of this proposal is lung cancer and its association with the metabolic syndrome. Lung cancer is the second most frequent form of cancer and one resulting in greatest mortality. The five year survival rate for this cancer is approximately 10% and it has not changed appreciably within the last 25 years; therefore identification of new risk factors associated with this cancer, which may aid in its therapeutic management, is greatly needed.

Evidence pointing in the direction of inflammatory changes in lung cancer includes elevated COX-2 levels, especially in non-small cell carcinoma, increased levels of cytokines (TNF-α, Il-1) and the positive therapeutic effect of Aspirin and NSAIDs on risk of lung cancer (11). As mentioned before, levels of IGF-1 are increased in lung cancer indicating increased insulin resistance. However, despite the evidence that insulin resistance and inflammation may play an important role in the development of lung

cancer, there are no prospective studies of the association of those components of the metabolic syndrome and the risk of lung cancer.

In this current study therefore, we would like to use the ARIC cohort data to investigate the effect of metabolic syndrome and its individual components, diagnosed at baseline (Visit 1), on the development of incident lung cancer.

5. Main Hypothesis/Study Questions:

1. What is the risk of developing lung cancer in persons meeting criteria for metabolic syndrome?
2. How does that risk depend on the individual components of the metabolic syndrome as defined according to the NCEP ATPIII guidelines?
3. How does that risk depend on the presence of coronary heart disease?
4. How does that risk depend on baseline levels of serum albumin?

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

This project will utilize the ARIC cohort study data as well as ARIC ancillary data obtained from the ARIC cancer study.

Exclusions: missing triglyceride, HDL cholesterol, and fasting glucose data

Variables:

Outcome: incident lung cancer (1987-2000)

Independent variables: HDL cholesterol, waist circumference, fasting glucose, triglycerides, hypertension, prevalent baseline CHD, follow-up time for incident CHD, lung cancer diagnosis date, visit 1 date, albumin, fibrinogen.

Confounding variables: gender, age, race, smoking (status, pack-years).

Analysis:

Metabolic syndrome will be determined according to the NCEP ATP III guidelines as present if at least three of the component variables (HDL, waist circumference, fasting glucose, triglycerides, and hypertension) are outside of the predetermined range.
Cox proportional hazard ratios (adjusted for age, race, gender, and smoking) will be determined to analyze the association of lung cancer and metabolic syndrome.

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

b. If Yes, is the author aware that the file ICTDER02 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? __X__ Yes ____ No
(This file ICTDER02 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 __X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 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://www.cscc.unc.edu/ARIC/search.php

___X___ 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)?

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

11.b. If yes, is the proposal
__X_ A. primarily the result of an ancillary study (list number* _1995.04**_)**
___ 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.cscc.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.

References:

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6. Balkwill F., Montovani A. “Inflammation and Cancer: Back to Virchow?” The Lancet 2001;357:539-545
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8. Komninou D, Ayonote A, Richie JP, Rigas B “Insulin Resistance and Colon Cancer” Exp. Biol. Med. 2003;228:396-405
9. Shen B-J, Todaro JF, Niaura R et al., “Are Metabolic Risk Factors One Unified Syndrome? Modeling the Structure of the Metabolic Syndrome X” Am. J. Epidemiol. 2003;157:701-711
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11. Brown JR and DuBois RN “Cyclooxygenase as a target in lung cancer” Clin. Cancer Res. 2004;10:4266s-4269s