ARIC Manuscript Proposal # 1210

PC Reviewed: _12/19_/06	**Status: __A__**	**Priority: _2__**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: PCSK9 variants and cancer

b. Abbreviated Title (Length 26 characters): PCSK9 variants and cancer

2. Writing Group:

Writing group members: Aaron Folsom, Jonathan Cohen, Eric Boerwinkle, Jim Peacock, Helen Hobbs

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __af___ **[please confirm with your initials electronically or in writing]**

F**irst author**:

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3. Timeline: paper by March 07

4. Rationale: Low cholesterol has been associated with increased risk of cancer, particularly colon cancer, in prospective studies. Pre-statin clinical trials also suggested cholesterol lowering may be associated with increased cancer risk. This has been observed less frequently in statin trials. Most investigators believe this association is not causal, but instead due to subclinical cancer lowering cholesterol levels.

ARIC and the Dallas Heart Study recently showed mutations in PCSK9 were associated with substantially reduced LDL cholesterol and CHD incidence (1). This suggested that moderate lifelong reduction in LDL kept CHD risk low. Whether PCSK9 variants are associated with cancer risk is unknown.

Two mutations contributed to low LDL-C in blacks (142X and 679X) and these were compared with neither mutation. In whites, a single SNP (42L) was examined.

As part of an ancillary study, ARIC cohort members' cancers through 2000 were identified. Numbers of first primaries were: Forsyth (n=500), Mpls (n=502), Wash Co (n=468), and Jackson (n=425). There were roughly equal numbers of breast, prostate, colon, and lung cancer. We did not see an association between baseline LDL-C and breast, prostate, lung, or colon cancer in this cohort previously.

5. Main Hypothesis/Study Questions:
PCSK9 variants associated with lower LDL-C levels are associated with reduced cancer incidence in ARIC

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Dependent variable: race-specific total cancer incidence; look at subtypes in whites but may not have power for blacks

Independent variable: PCSK9 mutations, as defined previously (1)

Covariates: should be little confounding by other factors, but will consider main risk factors: age, sex, smoking, BMI, HRT, drinking status, diabetes, etc. Because of the rarity of the variants, we may need to look at covariates one at a time. Lipids are intervening variables (not confounders).

Analysis: Will verify no association between cancer risk factors and PCSK9 variants, in which case, we mainly will do race-specific simple proportional hazards models with PCSK9 as the predictor of incident cancer. If any association is observed, we will model LDL-C to see if it may contribute to the association as an intervening variable.

Refs
1. Cohen JC et al. NEJM 2006;354:1264-72.
2. Ahmed RL et al. Cancer 2006;107:28-36.
3. Tande AJ et al. Am J Epidemiol. 2006;164:1094-1102.
4. Newton A, et al. ARIC ms on lung cancer in preparation.
5. Mink PJ. Dissertation on breast cancer.

7.a. Will the data be used for non-CVD analysis in this manuscript? _xx___ 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? __xx__ 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? __xx__ 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 ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
__xx__ 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

__xx____ 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)?

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

11.b. If yes, is the proposal
_xx__ A. primarily the result of an ancillary study (list number* _____)
___ B. primiarly 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.