ARIC Manuscript Proposal # 1520

PC Reviewed: 6/9/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Statins, cholesterol, and prostate cancer in the Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): Statins and prostate cancer

2. Writing Group:

Writing group members: Alison Mondul, Elizabeth Platz, Elizabeth Selvin, Josef Coresh, Aaron Folsom, others ARIC investigators are welcome

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

First author: Alison Mondul / cc: Elizabeth Platz
Address: 615 N. Wolfe St. Rm E6132

Phone: 410 614 9674 (Platz) Fax: 410 614 2632
E-mail: amondul@jhsph.edu / cc: eplatz@jhsph.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: Elizabeth Selvin, PhD, MPH
Assistant Professor of Epidemiology and Medicine
Welch Center for Prevention, Epidemiology, and Clinical Research and the Johns Hopkins Bloomberg School of Public Health
Address: 2024 E. Monument St., Suite 2-600
Baltimore, MD 21287

Phone: 410-614-3752 Fax: 410-955-0476
E-mail: lselvin@jhsph.edu

3. Timeline: The proposed project is an analysis of existing data. We anticipate the analysis of the existing data will take 6-12 months from the time of manuscript approval. We are discussing with Drs. Folsom and Selvin the possibility of collecting more detailed information on the diagnosis of cancers, including prostate cancer, in ARIC. Analysis of

the additional information on prostate cancer, specifically stage and grade at diagnosis, will take 3-6 months from the time of availability of that data.

4. Rationale:

Statin drugs (HMG Co-A Reductase Inhibitors) have been associated with a decreased risk of prostate cancer with a poorer prognosis in epidemiologic studies (1-6). One proposed mechanism by which statin drugs may influence risk of prostate cancer is through cholesterol-lowering (7). Given that prostate cancer cells exhibit cholesterol dysregulation and recent studies show that Akt cell survival signaling is cholesterol-sensitive, it is plausible that cholesterol-lowering could influence prostate carcinogenesis. Results from older observational studies have been mixed (8-20), but three recent studies of total cholesterol and prostate cancer by Platz et al. (21,22) and Mondul et al. (23)have observed that men with lower cholesterol are less likely to develop prostate cancer with a poorer prognosis.

Although these results are intriguing, several questions about the association between cholesterol and prostate cancer remain. The previous studies on cholesterol and prostate cancer were unable to examine the association between lipoprotein subfractions, such as high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides, and Apolipoproteins AI and B, and prostate cancer. Further, these previous studies were only able to examine the association between cholesterol measured at one time point and subsequent risk of prostate cancer. Because ARIC has detailed data on lipoprotein subfractions and has collected these data at multiple time points, it is a rich resource for studying the influence of lipoprotein subfractions on prostate cancer risk as well as whether cholesterol-lowering or maintaining low cholesterol over time have different associations with prostate cancer risk.

A previous study in ARIC examined the association between metabolic syndrome and prostate cancer, including each of the components of metabolic syndrome separately. Thus, the associations between quartiles of triglycerides and HDL cholesterol and prostate cancer in ARIC have been published. However, the exposure of interest of this previous study was the metabolic syndrome, not cholesterol and its various components, including cholesterol-lowering medication use. Thus, our study would examine the cholesterol and lipoprotein subfractions in more detail than in the metabolic syndrome paper. We will incorporate time-dependent modeling strategies and examine change in cholesterol over time. We also hope that additional follow-up and, thus, more cases will be available for our analysis than were available at the time the metabolic syndrome paper was published.

5. **Main Hypothesis/Study Questions**:

Our overall hypothesis is that low cholesterol, whether through the use of cholesterol lowering drugs or other means, reduces the risk of prostate cancer overall, and especially prostate cancer with a worse prognosis.

Question 1: Is lower total cholesterol associated with a lower risk of prostate cancer?

Question 2: What are the associations of HDL, LDL, apolipoproteins AI and B, and triglycerides with prostate cancer? We hypothesize that HDL and apolipoprotein AI may be inversely associated with risk of prostate cancer, whereas LDL, apolipoprotein B, and triglycerides may be positively associated with risk of prostate cancer.

Question 3: What are the associations of consistently low cholesterol, decreasing cholesterol, increasing cholesterol, and consistently high cholesterol, with prostate cancer? We hypothesize that cholesterol-lowering may provide more benefit than maintaining either low or high cholesterol.

Question 4: Is statin drug use associated with a lower risk of prostate cancer?

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).

Study Design: Prospective cohort

Analysis: Cox proportional hazards models

Exclusions: Women, men who had cancer at baseline, men who were missing cancer information at baseline, men who did not fast at least 8 hours. These exclusions are the same as those used in previous prostate cancer analyses in ARIC (24).

Exposures: Total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, apolipoprotein AI and apolipoprotein B. We will examine baseline values, time-dependent updated values (e.g., simple and cumulative updated), and categories of change in these values over time. We will likely categorize these variables using quartiles as well as clinical cut-points. HDL cholesterol and triglycerides have been examined in relation to colon cancer and lung cancer previously in this cohort (25,26). In those studies, HDL cholesterol was categorized into quartiles as well as "high" and "low" based on the cardiovascular disease risk cutpoint of 50 mg/dL. Triglycerides were also categorized as "high" and "low" based on the cutpoint of 150 mg/dL. We will use these same cutpoints in our analyses. We may also examine the associations between very high or very low (i.e. top and bottom 10% or 5%, depending upon numbers of cases in those categories) values of the exposures. Statin use will be examined as an exposure variable, as well, and will be modeled as baseline use as well as time-dependent updated use.

Outcome: Incident prostate cancer. As mentioned above, we are discussing with Drs. Folsom and Selvin the possibility of collecting information on stage and grade of the prostate cancer at diagnosis.

Covariates: Age, race, waist-hip ratio, body mass index, diabetes (self-reported and/or based on glucose measurements, possibly incorporating timing of diagnosis – there may be a different relationship between recently diagnosed diabetes and prostate cancer than between longer-term diabetes and prostate cancer), cardiovascular disease co-morbidities, smoking, alcohol consumption, physical activity, education level, dietary factors (particularly calcium intake), aspirin and other NSAIDS, medications to treat diabetes (particularly metformin), family history of prostate cancer, other health screenings including an annual physical examination (as a surrogate for PSA screening, which is not available).

Stratification Variables: We will stratify by race (depending on number of cases), cholesterol-lowering medication use (for the cholesterol analyses), cholesterol level (for the cholesterol-lowering medication use analyses), and BMI. We may restrict to non-diabetics and/or men without major cardiovascular co-morbidities. In order to limit the possibility of detection bias, we would ideally like to stratify by PSA screening status, but that information is not available in ARIC. We could restrict to men who had other health screenings such as routine physical examinations because PSA screening for prostate cancer is generally conducted as part of such exams.

Limitations: ARIC has very detailed information on cholesterol exposures, but there is limited information on statin use as well as prostate cancer outcomes, and no information on prostate cancer screening. We will likely be limited in our ability to examine baseline statin use because in 1987-1989, when the baseline questionnaire was administered, statin drugs were still infrequently prescribed compared to other cholesterol-lowering medications. Further, no information is available on dose of statin used. Stage and grade information is not currently available in ARIC, although we are exploring avenues for collecting these data. Although the most consistent associations between statins or cholesterol and prostate cancer have been with prostate cancer that has a poorer prognosis (i.e. higher stage or grade prostate cancer), several studies have observed inverse associations with total prostate cancer, as well (1,3,27-29). Thus, we believe that, given the richness of the ARIC data on cholesterol, examining the associations with total prostate cancer is warranted.

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 ICTDER03 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 ICTDER03 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 ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
____ Yes ____ No

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
____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)?

- ARIC manuscript # 568: Kucharska-Newton AM, Rosamond WD, Mink PJ, Alberg AJ, Shahar E, Folsom AR.HDL-cholesterol and incidence of breast cancer in the ARIC cohort study. Ann Epidemiol. 2008 Sep;18(9):671-7. PubMed PMID: 18794007; PubMed Central PMCID:PMC2566531.

- ARIC manuscript #1075: Kucharska-Newton AM, Rosamond WD, Schroeder JC, McNeill AM, Coresh J, Folsom AR; Members of the Atherosclerosis Risk in Communities Study. HDL-cholesterol and the incidence of lung cancer in the Atherosclerosis Risk in Communities (ARIC) study. Lung Cancer. 2008 Sep;61(3):292-300. Epub 2008 Mar 14. PubMed PMID:18342390; PubMed Central PMCID: PMC2580072.

- ARIC manuscript #957: Ahmed RL, Schmitz KH, Anderson KE, Rosamond WD, Folsom AR. The metabolic syndrome and risk of incident colorectal cancer. Cancer. 2006 Jul 1;107(1):28-36. PubMed PMID: 16721800.

- ARIC manuscript #1078: Tande AJ, Platz EA, Folsom AR. The metabolic syndrome is associated with reduced risk of prostate cancer. Am J Epidemiol. 2006 Dec 1;164(11):1094-102. Epub 2006 Sep 12. PubMed PMID: 16968859.

- ARIC manuscript # 1210: Folsom AR, Peacock JM, Boerwinkle E. Sequence variation in proprotein convertase subtilisin/kexin type 9 serine protease gene, low LDL cholesterol, and cancer incidence. Cancer Epidemiol Biomarkers Prev. 2007 Nov;16(11):2455-8. PubMed PMID: 18006936.

- ARIC manuscript #1153: Circulating caveolin-1 levels and prostate cancer

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

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ 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.

AM

References:

(1) Shannon J, Tewoderos S, Garzotto M, Beer TM, Derenick R, Palma A, et al. Statins and prostate cancer risk: a case-control study. Am.J.Epidemiol. 2005 Aug 15;162(4):318-325.
(2) Platz EA, Clinton SK, Giovannucci E. Association between plasma cholesterol and prostate cancer. AACR Meeting Abstracts 2006 November 1;2006(3):A179.
(3) Flick ED, Habel LA, Chan KA, Van Den Eeden SK, Quinn VP, Haque R, et al. Statin use and risk of prostate cancer in the California Men's Health Study cohort. Cancer Epidemiol.Biomarkers Prev. 2007 Nov;16(11):2218-2225.
(4) Jacobs EJ, Rodriguez C, Bain EB, Wang Y, Thun MJ, Calle EE. Cholesterol-lowering drugs and advanced prostate cancer incidence in a large U.S. cohort. Cancer Epidemiol.Biomarkers Prev. 2007 Nov;16(11):2213-2217.
(5) Murtola TJ, Tammela TL, Lahtela J, Auvinen A. Cholesterol-lowering drugs and prostate cancer risk: a population-based case-control study. Cancer Epidemiol.Biomarkers Prev. 2007 Nov;16(11):2226-2232.
(6) Friedman GD, Flick ED, Udaltsova N, Chan Pharm DJ, Quesenberry CP,Jr, Habel LA. Screening statins for possible carcinogenic risk: up to 9 years of follow-up of 361 859 recipients. Pharmacoepidemiol.Drug Saf. 2008 Jan;17(1):27-36.
(7) Solomon KR, Freeman MR. Do the cholesterol-lowering properties of statins affect cancer risk? Trends Endocrinol.Metab. 2008 May-Jun;19(4):113-121.
(8) Kark JD, Smith AH, Hames CG. Serum retinol and the inverse relationship between serum cholesterol and cancer. Br.Med.J.(Clin.Res.Ed) 1982 Jan 16;284(6310):152-154.
(9) Wallace RB, Rost C, Burmeister LF, Pomrehn PR. Cancer incidence in humans: relationship to plasma lipids and relative weight. J.Natl.Cancer Inst. 1982 Jun;68(6):915-918.
(10) Hiatt RA, Fireman BH. Serum cholesterol and the incidence of cancer in a large cohort. J.Chronic Dis. 1986;39(11):861-870.
(11) Knekt P, Reunanen A, Aromaa A, Heliovaara M, Hakulinen T, Hakama M. Serum cholesterol and risk of cancer in a cohort of 39,000 men and women. J.Clin.Epidemiol. 1988;41(6):519-530.
(12) Thompson MM, Garland C, Barrett-Connor E, Khaw KT, Friedlander NJ, Wingard DL. Heart disease risk factors, diabetes, and prostatic cancer in an adult community. Am.J.Epidemiol. 1989 Mar;129(3):511-517.
(13) Chyou PH, Nomura AM, Stemmermann GN, Kato I. Prospective study of serum cholesterol and site-specific cancers. J.Clin.Epidemiol. 1992 Mar;45(3):287-292.
(14) Smith GD, Shipley MJ, Marmot MG, Rose G. Plasma cholesterol concentration and mortality. The Whitehall Study. JAMA 1992 Jan 1;267(1):70-76.
(15) Schuit AJ, Van Dijk CE, Dekker JM, Schouten EG, Kok FJ. Inverse association between serum total cholesterol and cancer mortality in Dutch civil servants. Am.J.Epidemiol. 1993 May 1;137(9):966-976.
(16) Steenland K, Nowlin S, Palu S. Cancer incidence in the National Health and Nutrition Survey I. Follow-up data: diabetes, cholesterol, pulse and physical activity. Cancer Epidemiol.Biomarkers Prev. 1995 Dec;4(8):807-811.

(17) Eichholzer M, Stahelin HB, Gutzwiller F, Ludin E, Bernasconi F. Association of low plasma cholesterol with mortality for cancer at various sites in men: 17-y follow-up of the prospective Basel study. Am.J.Clin.Nutr. 2000 Feb;71(2):569-574.
(18) Mydlo JH, Tieng NL, Volpe MA, Chaiken R, Kral JG. A pilot study analyzing PSA, serum testosterone, lipid profile, body mass index and race in a small sample of patients with and without carcinoma of the prostate. Prostate Cancer.Prostatic Dis. 2001;4(2):101-105.
(19) Wuermli L, Joerger M, Henz S, Schmid HP, Riesen WF, Thomas G, et al. Hypertriglyceridemia as a possible risk factor for prostate cancer. Prostate Cancer.Prostatic Dis. 2005;8(4):316-320.
(20) Bravi F, Scotti L, Bosetti C, Talamini R, Negri E, Montella M, et al. Self-reported history of hypercholesterolaemia and gallstones and the risk of prostate cancer. Ann.Oncol. 2006 Jun;17(6):1014-1017.
(21) Platz EA, Clinton SK, Giovannucci E. Association between plasma cholesterol and prostate cancer in the PSA era. Int.J.Cancer 2008 Jul 21;123(7):1693-1698.
(22) Platz EA, Till C, Goodman PJ, Parnes HL, Figgs WD, Albanes D, et al. Men with low serum cholesterol have a lower risk of high grade prostate cancer in the Prostate Cancer Prevention Trial. American Association for Cancer Research Frontiers in Cancer Prevention Meeting 2008 Nov. 2008.
(23) Mondul AM, Clipp SL, Helzlsouer KJ, Platz EA. Association of Plasma Total Cholesterol Concentration with Incident Prostate Cancer in the CLUE II Cohort. 2008.
(24) Tande AJ, Platz EA, Folsom AR. The metabolic syndrome is associated with reduced risk of prostate cancer. Am.J.Epidemiol. 2006 Dec 1;164(11):1094-1102.
(25) Kucharska-Newton AM, Rosamond WD, Mink PJ, Alberg AJ, Shahar E, Folsom AR. HDL-cholesterol and incidence of breast cancer in the ARIC cohort study. Ann.Epidemiol. 2008 Sep;18(9):671-677.
(26) Kucharska-Newton AM, Rosamond WD, Schroeder JC, McNeill AM, Coresh J, Folsom AR, et al. HDL-cholesterol and the incidence of lung cancer in the Atherosclerosis Risk in Communities (ARIC) study. Lung Cancer 2008 Sep;61(3):292-300.
(27) Singal R, Khurana V, Caldito G, Fort C. Statins and Prostate Cancer Risk: A Large Case Control Study in Veterans. Journal of Clinical Oncology, 2005 ASCO Annual Meeting Proceedings 2005;23(16S):1004.
(28) Farwell WR, Scranton RE, Lawler EV, Lew RA, Brophy MT, Fiore LD, et al. The association between statins and cancer incidence in a veterans population. J.Natl.Cancer Inst. 2008 Jan 16;100(2):134-139.
(29) Boudreau DM, Yu O, Buist DS, Miglioretti DL. Statin use and prostate cancer risk in a large population-based setting. Cancer Causes Control 2008 Mar 6.