ARIC Manuscript Proposal # 3134

PC Reviewed: 3/20/18   **Status:** _____   **Priority: 2**
SC Reviewed: _____   **Status:** _____   **Priority:** ____

1.a. Full Title: Lipid-lowering drug use and total and site-specific cancer incidence and mortality in the Atherosclerosis Risk in Communities (ARIC) Study

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

2. Writing Group:

    Writing group members: Michael Marrone, Elizabeth Platz, Corinne Joshu, Alison Mondul, John Barber, Meera Chappidi, Anna Prizment, David Couper, other ARIC investigators are welcome.

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

    First author: **Michael Marrone**
    Address: 615 N. Wolfe St. Rm E6132

         E-mail: mmarron6@jhu.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 Platz**
    Address: 615 N. Wolfe St. Rm E6132

         Phone: 410 614 9674   Fax: 410 614 2632
         E-mail: eplatz1@jhu.edu

3. Timeline: The proposed project is an analysis of existing data. We anticipate the analysis of the existing data will take 12 months from the time of manuscript approval.

4. Rationale:

    Since coming to market in 1987, statin drugs have become one of the most commonly prescribed medications with potent cholesterol-lowering properties and attractive safety profile.[1] It is estimated that 28% of adults 40 years and older were taking statin drugs in the US in 2013.[2] The overall benefit from taking statins is not limited to those with hyperlipidemia with improved cardiovascular disease outcomes in individuals with

normal total and low-density lipoprotein (LDL) cholesterol levels; indicative of additional pharmacologic properties of statins independent of lowering cholesterol.[3] Such pleiotropic effects of statins, which include anti-inflammatory, anti-proliferative, and pro-apoptotic effects, have led investigators to investigate the association between statins and cancer outcomes.[3,4]

The cholesterol-lowering effects of statins are achieved through inhibiting the HMG-CoA reductase enzyme in the mevalonate pathway, crucial to cholesterol synthesis. Recent attention to cancer energetics and metabolism has implicated the mevalonate pathway in tumorigenesis.[4] Intermediate and downstream products in this pathway are necessary for essential cellular functions including membrane integrity, cell signaling, protein synthesis, and cell cycle progression. Although, the exact mechanism through which statins may reduce cancer risk, whether directly related to lower serum cholesterol or through the pleiotropic actions described above, is uncertain.[4,5]

Several observational epidemiologic investigations as well as ancillary analysis of randomized controlled trials have investigated the relationship between statin drug use and total and site-specific cancer incidence.[6] Of the site-specific cancers, the epidemiologic evidence base supports a reduced risk of advanced prostate cancer incidence.[7] Indeed, recent analyses in ARIC have revealed an inverse association for prostate cancer mortality with stronger associations with longer duration of use overall in both white and black men.[8]

The inverse association between statins and lethal and fatal prostate cancer might suggest a similar inverse association between statins and other cancer types through common biologic mechanisms. In fact, statins appear to be associated with a reduced risk of some other site-specific cancers including colorectal, gastric, esophageal, and hepatocellular cancer.[6] Although the relationship between statin use and total and site-specific cancer has been previously studied, the current evidence base has focused mainly on cancer incidence and is limited in the ability to account for change in lipid profiles over time as well as other metabolic perturbations associated with total and site-specific cancer (e.g., diabetes), and to examine associations in important subgroups (e.g., African Americans).

However, some studies also points to harmful effects of statin drugs with an increased risk of any incident cancer in older individuals.[6] Given the heterogeneity in the association between statins and total and site-specific cancer incidence, the timing at which statin therapy is initiated and maintained may have a differential effect on cancer outcomes; due to the timing of first use in relation to the natural history of cancer development, or secular trends in the type of statin drugs prescribed overtime. In fact, the increased risk of cancer among older adults is consistent with the use of pravastatin, a type of hydrophilic statin that first came on the market in the US in 2006.

The goal of the current analysis is to leverage the rich longitudinal collection of lipid profiles and anthropometric measures collected across ARIC study visits to determine the independent association between lipid-lowering drug use and total and site-specific cancer outcomes. ARIC is ideal for examining the association between lipid-lowering

drug use and total and site-specific cancer incidence and mortality given the large diverse population with multiple cancer endpoints. Finally, additional evidence on the role of statins in specific subgroups of the population including men and women separately as well as in white and African American participants will provide a valuable contribution to understanding which groups may benefit the most from statin chemoprevention. This proposal compliments two previously approved proposals focused on prostate cancer (manuscript submitted for publication) and bladder cancer (analysis is ongoing and results will be incorporated into the manuscript that is produced from this manuscript proposal).

5.   Main Hypothesis/Study Questions:

Hypothesis: Pre-diagnostic use of lipid-lowering drugs is associated with a reduced risk of total and site-specific cancer incidence and mortality in men and women, consistent with prior findings in ARIC of an inverse association between lipid-lowering medication use and prostate cancer mortality.[8]

Question 1: what is the association between *current use of lipid-lowering drugs* and subsequent total and site-specific cancer incidence and mortality in men and women (excluding prostate cancer)?

Question 2: what is the association between *duration of lipid-lowering drug use* and total and site-specific cancer incidence and mortality (excluding prostate cancer) in men and women?

Question 3: what is the association between the *timing of first use of lipid-lowering drugs* and total and site-specific cancer incidence and mortality in men and women (excluding 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 analysis of lipid-lowering drug use in ARIC participants without a cancer diagnosis at baseline. Baseline for analysis will be ARIC study visit 2 (1990-1992) when lipid-lowering drugs began to be used routinely in clinical practice.

Analysis: We will use cause-specific hazard ratios to estimate the association between time-updated lipid-lowering drug use (Y/N) reported at ARIC study visits 2-4 and annual follow-up calls and total and site-specific cancer incidence and mortality through December 2012. We will also investigate the association with duration of use (<15 yrs/>= 15yrs) based on the time of first use through time of censoring.

To investigate the association of timing of first use, compared to never users, we will use two different strategies in separate analyses to classify participants: 1) the study visit in which participants first reported lipid-lowering drug use (v2: 1990-92; v3: 1993-95; v4: 1996-98; >1998); and 2) the decade of life in which participants first reported lipid-lowering drug use (<50; 50-59; 60-69; >=70). In both cases, the reference group will be participants reporting never using lipid-lowering drugs while each category of first use of lipid-lowering drugs will be considered as late entries. This approach allows us to assess changing patterns in the association between lipid-lowering drug use and total and site-specific cancer across different therapeutic eras of lipid-lowering medication use. We recognize the secular trends in patterns of lipid-lowering drug use may not coincide with ARIC study visits, and we will explore alternative patterns of use accordingly. The second approach classifying first use by decade of life will allow us to investigate changing patterns in the associations according to the timing of first use in relationship to unobserved natural history of cancer development. For these analyses, we will explore parametric models to account for the time-varying effects of lipid-lowering drug use implicit in the question of interest and will consider using age as the time scale in both analyses. If parametric models are deemed more appropriate for these analyses, relative hazards may not be estimated given non-proportionality. In such cases we will graph the cumulative hazards for each category including never users to illustrate changing patterns in survival according to timing of first use.

Exclusions: Participants with prevalent cancer at baseline (visit 2) and those who did not consent to non-CVD research.

Exposure: Lipid-lowering drug use including statins, fibrates, bile acid sequestrants, and niacin, ascertained from information collected during in-person ARIC study visits 2-4 and annual follow-up calls from 2006 to 2012. We will also consider the use of statins separately from other lipid-lowering drugs. If sufficient data is available, we will explore differences in the associations by individual statin and type of statin (hydrophilic vs. lipophilic).

Outcomes: Total cancer incidence defined as the first primary cancer diagnosis (excluding prostate cancer) in men and women free of any cancer diagnosis at baseline. Total cancer mortality will be defined as the death from any cancer, excluding prostate, listed as the underlying cause of death on death certificates. Site-specific cancer incidence and mortality will be evaluated for individual cancers that have sufficient number of events. We will investigate incidence and mortality of pre-specified clustering of cancer types – obesity-associated cancers, hormone-associated cancers, smoking-associated cancers, GI cancers, and vitamin-D associated cancers.

Covariates: For total cancer, we will adjust for covariates common across cancer types including age, sex, race*ARIC field center (list the combinations as in your glycemia manuscript), smoking status (updated), education status, BMI (updated), alcohol consumption, family history of cancer, aspirin and NSAID use (updated), and undiagnosed, at-risk for diabetes, and diagnosed diabetes. We will optimize adjusted models for site-specific cancer with site-specific covariates accordingly: breast cancer

(HRT use, age at menarche, parity, age of first birth, total number of months breast feeding); colon cancer (red meat consumption); and liver cancer (cirrhosis). We will use time-updated values for time-varying covariates including smoking status, BMI, and undiagnosed, at-risk, and diagnosed diabetes as per ARIC Cancer Analysis Guidelines:

ARIC Cancer analysis guidance: diabetes

First consider how you wish to define diabetes. Is the natural history of the disease of importance and do you wish to classify individuals as non-diabetic, at-risk, undiagnosed diabetic, and diagnosed diabetic? Or does a binary indicator of presence/absence suffice?

If the later: ARIC has 2 derived variables (one with 126 mg/dL cutpoint [current ADA cutpoint, more sensitive] and the other with a more stringent cut-point of 140 mg/dL [prior ADA cutpoint, more specific])

If you are interested in the natural history of diabetes, then we recommend that you derive a series of variables using information on medications to treat diabetes, self-report of a physician diagnosis of diabetes, fasting status, and serum glucose levels.

ARIC Cancer recommendation: Use the following classification scheme, which is hierarchical

1) Diagnosed diabetes:
   a. Use of a medication to treat diabetes, or
   b. Doctor told them that they have diabetes

   Once classified as diagnosed diabetes, retain that status for all subsequent visits.

2) Undiagnosed diabetes
   a. If fasting, serum glucose ≥126 mg/dL
   b. If non-fasting, serum glucose ≥200 mg/dL

   Subsequently, a participant with undiagnosed diabetes can be reclassified based on changes in medications use, diagnoses, and serum glucose levels.

3) At risk for diabetes (pre-diabetes)
   a. If fasting, 100 mg/dL ≤ serum glucose < 126 mg/dL
   b. If not fasting, 140 mg/dL ≤ serum glucose < 200 mg/dL

Subsequently, a participant at risk for diabetes (pre-diabetes) can be reclassified based on changes in medications use, diagnoses, and serum glucose levels.

4) "Normal" (non-diabetic/not at risk for diabetes)
   a. If fasting, <100 mg/dL
   b. If not fasting, < 140 mg/dL

Subsequently, a participant who is "normal" (non-diabetic/not at risk for diabetes) can be reclassified based on changes in medications use, diagnoses, and serum glucose levels.

Stratification variables: We will stratify total cancer and site-specific cancer analyses by gender and race. Stratification for site-specific cancer will be dependent and number of events. The table below provides the number of events necessary to achieve 80% power to detect as statistically significant associations (hazard ratios) or larger across exposure prevalence. In prior analyses of statin use and prostate cancer, the HRs ranged from 0.24 to 0.79 with 19.5% of men in the analysis reporting statin use at visit 4.[8] Based on 20% of the population exposed, we would need as many as 593 events for an HR of 0.75 and only 137 events for an HR of 0.55. With increasing prevalence of statin use the number of events declines across all HRs. To investigate if the hypothesized inverse association of lipid-lowering drug use is due to reduced serum cholesterol, we will stratify by total cholesterol prior to the initiation of lipid-lowering drug use ($<$ vs. $>=$ 5.2 nmol/L). We will also evaluate the associations for statin drug use separately from all other lipid-lowering drugs.

Limitations: We do not have medication dose and will not be able identify if the hypothesize association varies by dosage. Another limitation is the small number of incident cases and death for site-specific cancers limiting our ability to evaluate all pre-specified subgroup analyses in site-specific cancers with too few events.

Table. Number of events required to achieve 80% power for varying hazard ratios and exposure prevalence.

	Proportion exposed			
Hazard Ratio	**0.20**	**0.30**	**0.40**	**0.50**
0.85	1857	1415	1238	1189
0.75	593*	452	395	379
0.65	264*	201	176	169
0.55	137*	105	92	88

* number of events based on the exposure prevalence and hazard ratios reported in prior analysis of statin use and prostate cancer in ARIC[8]

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 ICTDER 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

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 # 2812: Chappidi M, Joshu C, Platz E, Mondul A.
- ARIC manuscript # 1520: Mondul A, Platz E, Selvin E, Coresh, J, Folsom A. Statins, cholesterol, and prostate cancer in the Atherosclerosis Risk in Communities (ARIC) Study. Analysis ongoing.

- 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. HDLcholesterol 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.

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; 2011.07)
___   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/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

References

1.   Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in Prescription Drug Use Among Adults in the United States From 1999-2012. *Jama.* 2015;314(17):1818-1831.
2.   Salami JA, Warraich H, Valero-Elizondo J, et al. National Trends in Statin Use and Expenditures in the US Adult Population From 2002 to 2013: Insights From the Medical Expenditure Panel Survey. *JAMA cardiology.* 2017;2(1):56-65.
3.   Hindler K, Cleeland CS, Rivera E, Collard CD. The role of statins in cancer therapy. *The oncologist.* 2006;11(3):306-315.
4.   Pisanti S, Picardi P, Ciaglia E, D'Alessandro A, Bifulco M. Novel prospects of statins as therapeutic agents in cancer. *Pharmacological research.* 2014;88:84-98.
5.   Solomon KR, Freeman MR. Do the cholesterol-lowering properties of statins affect cancer risk? *Trends in endocrinology and metabolism: TEM.* 2008;19(4):113-121.
6.   Bonovas S. Statins: do they have a potential role in cancer prevention and modifying cancer-related outcomes? *Drugs.* 2014;74(16):1841-1848.
7.   Bansal D, Undela K, D'Cruz S, Schifano F. Statin use and risk of prostate cancer: a meta-analysis of observational studies. *PloS one.* 2012;7(10):e46691.
8.   Mondul AM, Joshu CE, Barber JR, et al. Lipid-lowering drug use and risk of fatal prostate cancer in black and white men in the Atherosclerosis Risk in Communities (ARIC) Study. *In process.* 2018.