ARIC Manuscript Proposal #2762

PC Reviewed: 6/7/16   **Status: <u>A</u>**   **Priority: <u>2</u>**
SC Reviewed: _____   **Status: _____**   **Priority: ____**

1.a. Full Title: Periodontal disease and cancer risk in the Atherosclerosis Risk in Communities (ARIC) Study

  b. Abbreviated Title (Length 26 characters): Periodontal disease and cancer

2.   Writing Group:
    Writing group members: Dominique Michaud, Alexandra Peacock-Villada, Corinne Joshu, Steve Offenbacher, James Beck (invited), Anna Prizment, Elizabeth Platz; other ARIC investigators are welcome

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

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3.   Timeline: The proposed manuscript is an analysis of existing data. We anticipate it will take 6-12 months from receipt of the data (analysis will be done at Johns Hopkins) to submission of a manuscript to the ARIC Publications Committee.

4. Rationale:

Many of the established risk factors for cancer, including smoking, obesity, diabetes and physical inactivity, share some commonality in that they are all associated with systemic inflammation and immune perturbations, and likely share common pathways to cancer development. Advanced periodontal disease, through local inflammation, bone destruction and tooth loss, can have a major systemic impact on the body, which extends beyond the oral cavity [1]. Poor oral health and development of periodontitis are associated with changes in bacterial communities in the mouth, and changes in the immune status [2], which may also be involved in the carcinogenesis.

We reported positive associations between periodontal disease and cancer risk in the Health Professionals Follow-up Study (HPFS) among all participants [3], which was stronger for smoking-related cancers (including lung, kidney, bladder, head and neck, pancreatic cancers) and remained elevated among *never* smokers and was stronger among those with severe periodontitis (HR = 2.57, 95% CI = 1.56-4.21) [4]. Three other prospective cohort studies with data on periodontal disease, the NHANES I study [5], the NHANES III study [6] and the Women's Health Initiative (WHI)[7], have reported positive associations for periodontitis and cancers, including pancreatic, lung, and orodigestive cancers. In addition, antibodies to a periodontal pathogen (*P. gingivalis*) have been associated with elevated risk of pancreatic and orodigestive cancers in two different prospective studies [6, 8]; to date, there are no null studies on this topic. Retrospective studies have examined these associations, especially for head and neck cancers [9, 10], but as these are prone to bias, and reverse causation, they cannot provide strong support for causality.

Most of the large cohort studies on cancer have no data on periodontal disease status, number of teeth lost and reasons for the lost teeth, and those studies with measurements on these factors often rely on self-report of periodontal disease status, which are prone to substantial measurement error. Consequently, it is quite amazing that we find such consistent and strong associations for periodontal disease and cancer risk.

5. Main Hypothesis/Study Questions:
The overall objective of this proposal is to examine the association between periodontal disease and cancer risk in the ARIC cohort.

Hypothesis 1: Periodontal disease will be associated with increased risk of cancer independent of known and suspected cancer risk factors. Associations are expected to be similar in blacks and whites.

Hypothesis 2: More advanced periodontal disease (moderate and severe) will be more strongly associated with risk of cancer than mild/no periodontal disease (using Visit 4 measurements), and associations will be strongest for smoking-related cancers, independent of known and suspected cancer risk factors.

Hypothesis 3: Periodontal disease will be associated with all cancer and smoking-related cancers among never smokers. Associations are expected to be similar in blacks and whites.

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 study with Visit 4 as baseline for the analysis.

Inclusion/Exclusion: Participants with a cancer diagnosis at baseline (Visit 4), and those with missing data on periodontal disease covariates will be excluded from the analysis.

Exposures:
    (1) Periodontal disease status based on self-reported data at Visit 4. Periodontal measures will be based on self-report of periodontal disease and severity will be determined by self-report of periodontal/gum surgery (or periodontal disease plus 20 or fewer teeth remaining).

    (2) Periodontal disease status based on dental measurements from Visit 4. Periodontitis will be categorized as no/mild or moderate/severe based on extent of attachment level (AL), as previously described in this cohort [11].

Outcome: All incident cancers and smoking-related cancers. For question (1): 1,769 incident cancers are available in 8,889 participants who completed the dental questionnaire at Visit 4 (baseline for this analysis). For question (2): 1,099 incident cases, of which 327 are smoking associated cancers, are available in 5,650 participants who had the dental examination at Visit 4 (baseline for this analysis).

Other variables of interest: Age, race*field center, sex, family history of cancer, education, height, smoking status, smoking pack-years, body mass index, waist-to-hip ratio, physical activity, vitamin supplement use, statin and aspirin use, diabetes and hypertension status, energy intake, alcohol consumption, exogenous hormone use, menopausal status, age at menopause.

Analysis:
  (1) Cox proportional hazard regression will be used to calculate the multivariable-adjusted relative risk of incident cancer in relation to self-reported periodontal disease status and gum/periodontal disease surgery based on Visit 4. All cancer and smoking-related cancers will be examined separately by race and smoking status.

(2) Cox proportional hazard regression will be used to calculate the multivariable-adjusted relative risk of incident cancer in relation to periodontal disease measurements obtained on Visit 4. All cancer and smoking-related cancers will be examined separately by race and smoking status.

Power: For question 2 (which has the smaller sample size) we performed power calculations. We will have 80% power to detect a RR of 1.17 in the population with dental exams for all cancers (first diagnosis of any first primary cancer) when comparing mod/severe periodontal disease with those with none/mild periodontal disease (alpha=0.05, 2 sided test) and 80% power to detect a RR of 1.37 for smoking-associated cancers. Given that previously reported associations in those with periodontitis have been larger (RR of 1.45 and 2.57, respectively for total cancer and smoking-related cancers [4]), we will have sufficient power to examine these associations in the ARIC study.

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)?

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* 2011.07; 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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2.   Hajishengallis G, Sahingur SE. Novel inflammatory pathways in periodontitis. Adv Dent Res 2014; 26: 23-29.
3.   Michaud DS, Liu Y, Meyer M et al. Periodontal disease, tooth loss, and cancer risk in male health professionals: a prospective cohort study. Lancet Oncol 2008; 9: 550-558.
4.   Michaud DS, Kelsey KT, Papathanasiou E et al. Periodontal disease and risk of all cancers among male never smokers: an updated analysis of the Health Professionals Follow-up Study. Ann Oncol 2016.
5.   Hujoel PP, Drangsholt M, Spiekerman C, Weiss NS. An exploration of the periodontitis-cancer association. Ann Epidemiol 2003; 13: 312-316.
6.   Ahn J, Segers S, Hayes RB. Periodontal disease, Porphyromonas gingivalis serum antibody levels and orodigestive cancer mortality. Carcinogenesis 2012; 33: 1055-1058.
7.   Mai X, LaMonte MJ, Hovey KM et al. History of periodontal disease diagnosis and lung cancer incidence in the Women's Health Initiative Observational Study. Cancer Causes Control 2014; 25: 1045-1053.
8.   Michaud DS, Izard J, Wilhelm-Benartzi CS et al. Plasma antibodies to oral bacteria and risk of pancreatic cancer in a large European prospective cohort study. Gut 2013; 62: 1764-1770.
9.   Eliot MN, Michaud DS, Langevin SM et al. Periodontal disease and mouthwash use are risk factors for head and neck squamous cell carcinoma. Cancer Causes Control 2013.
10.   Meyer MS, Joshipura K, Giovannucci E, Michaud DS. A review of the relationship between tooth loss, periodontal disease, and cancer. Cancer Causes Control 2008.
11.   Nakib SA, Pankow JS, Beck JD et al. Periodontitis and coronary artery calcification: the Atherosclerosis Risk in Communities (ARIC) study. J Periodontol 2004; 75: 505-510.