ARIC Manuscript Proposal #3115

PC Reviewed: 2/13/18	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Oral pathogens causally linked with periodontal disease and cancer incidence and mortality in ARIC

b. Abbreviated Title (Length 26 characters): Oral pathogens and cancer risk

2. Writing Group: Michaud, Moss, Offenbacher, Beck, Platz, along with ARIC cancer investigators Joshu and Prizment, biostatisticians Lu and Barber, and other interested ARIC investigators

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. EAP (ARIC author on behalf of the team) **[please confirm with your initials electronically or in writing]**

First author: **Dominique S. Michaud, ScD**
Address: Department of Public Health & Community Medicine
Tufts University Medical School
136 Harrison Avenue
Boston, MA 02111
Phone 617-636-0482
E-mail: Dominique.Michaud@tufts.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 A. Platz, ScD, MPH**
Address: Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe St., Room E6132
Baltimore, MD 21205
Phone: 410-614-9674
Fax: 410-614-2632
E-mail: eplatz1@jhu.edu

3. Timeline: Expect to complete this work by December 2019

4. Rationale: The proposed work, in which we will investigate the association between oral pathogens causally linked with periodontal disease in relation to cancer risk, follows from our prior ARIC study on clinically assessed periodontal disease and cancer risk (1). Here we describe the evidence for associations between periodontal disease and cancer, what is known about bacterial infections and cancer risk, and gaps in knowledge about oral pathogens and cancer risk

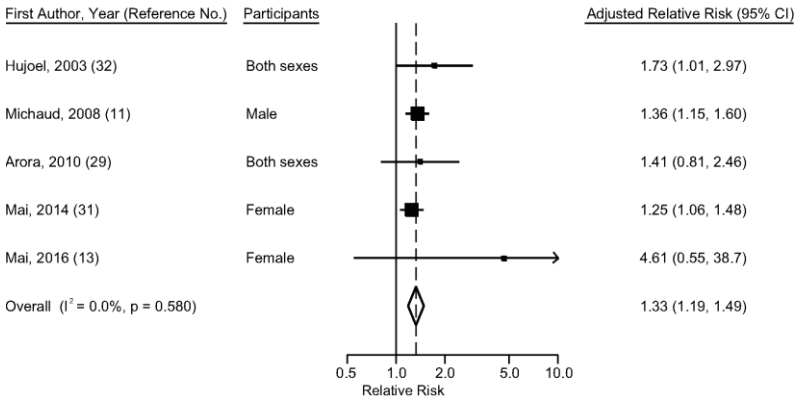
that ARIC may be able to fill given the dental examination and the prior measurement of antibodies against oral pathogens, detection of oral pathogen nucleic acids, and cytokine responses.

In a recent review (2017), a member of our team (Dr. Michaud) performed a meta-analysis of observational studies that had reported associations for periodontal disease and cancer risk (2). In that review, she concluded that the data published to date support positive associations between periodontal disease and total cancer risk, with the most consistent evidence for lung, colorectal, head and neck, and pancreatic cancers (2). Our team's findings in ARIC (1) are very consistent with that meta-analyses of previous studies. For total cancer incidence, we observed a significant increased risk of total cancer (Hazard ratio [HR]=1.24; 95% confidence interval [CI] 1.07-1.44) and cancer mortality (HR=1.52, 95% CI 1.17-1.97) for those with severe periodontitis (compared to mild/no periodontitis). Previous studies had reported associations ranging between 1.14 and 1.20 for periodontal disease versus no periodontal disease (2). In ARIC, associations were the most notable for lung and colorectal cancers, and possibly for pancreatic cancer. Summaries of these findings and consistency with the literature are described next two sections.

Lung cancer

The findings for periodontal disease and lung cancer from the meta-analysis summarized in Figure 1 (2) suggest that periodontal disease is associated with lung cancer. The associations for periodontal disease and lung cancer risk in ARIC are even stronger; we reported an HR of 2.60 (95% CI 1.65-4.08) between severe periodontal disease and lung cancer risk. The positive associations for lung cancer were observed even among never smokers in ARIC. Associations between lung bacterial infections and lung cancer have been observed in several studies (3). There is fairly strong evidence that pulmonary *Mycobacterium tuberculosis* (TB) infection is associated with lung cancer, even among never smokers. In a meta-analysis of 30 studies, the pooled RR for the association between TB and lung cancer was 1.76 (95% CI 1.49-2.08) (4). Similarly, pneumonia that is often caused by various non-TB bacterial and other pathogens is associated with increased risk of lung cancer. In a meta-analysis of 22 studies, the pooled RR for pneumonia and lung cancer was 1.43 (95% CI 1.22-1.68) (4). To date, no prospective study has examined the association between oral bacteria and risk of lung cancer, including no studies on antibodies to oral bacteria and lung cancer.

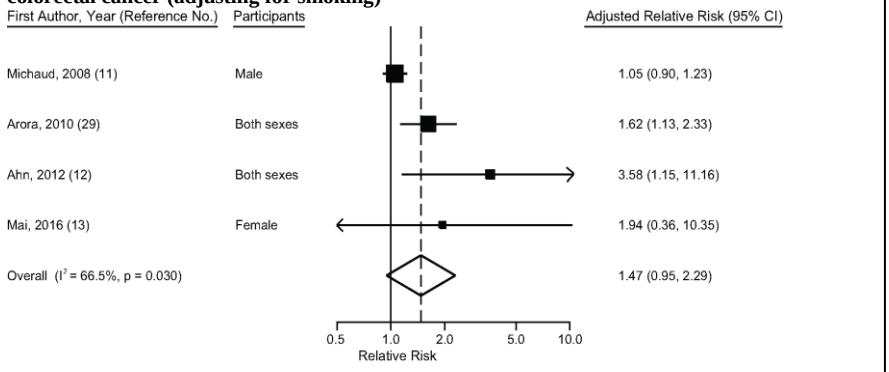
Figure 1. Random-effects meta-analysis of 5 cohort studies on periodontal disease and lung cancer (adjusting for smoking)



Colorectal cancer

The strongest evidence for a role of oral bacteria in cancer has arisen from studies on colorectal cancer. Although the association between periodontal disease and colorectal cancer risk was borderline statistically significant in the meta-analysis (Figure 2), it was based on only four cohort studies (2). The findings from ARIC were consistent with about a ~50% increase in risk of colorectal cancer (HR = 1.51, 95% 0.95-2.42), and the association was stronger among never smokers (HR = 2.12, 95% CI 1.00-4.47). These borderline positive associations are consistent with the growing number of studies, both human and animal, providing strong support for the role of oral bacteria in colorectal carcinogenesis (5-9). A number of studies conducted in humans have isolated *Fusobacterium* (an oral pathogen) in colon tumors (5-9) and a recent study published in *Science* demonstrated that the same bacterial species (e.g. *Fusobacterium, Selenomas, Prevotella* – all oral bacteria) are present in the primary and distant metastatic lesions (9). Experimental mouse models have provided a causal framework demonstrating that *Fusobacterium* can promote colorectal tumor growth through known cancer pathways and that antibodies targeted to *Fusobacterium* can reduce tumor growth (6,9). In addition, new studies indicate that metabolites produced by gut bacteria directly influence the colonic immune response that may play a key functional role in carcinogenesis through mechanisms including Treg homeostasis regulation (10-12).

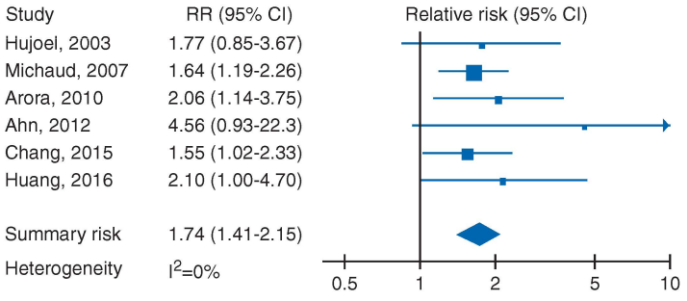
Figure 2. Random-effects meta-analysis of 4 cohort studies on periodontal disease and colorectal cancer (adjusting for smoking)



Pancreatic cancer

A number of studies have reported positive associations between periodontal disease and pancreatic cancer (Figure 3) and none, to date, have reported relative risks below 1.5 (13). The findings in ARIC are consistent with these prior studies, albeit based on 48 cases and not statistically significant (HR=1.65, 95% CI 0.72-3.77). Recently, two large cohort studies observed positive associations between pre-diagnostic positivity for *Porphyromonas gingivalis* and subsequent pancreatic cancer risk; one of the studies, which was conducted by Dr. Michaud, measured antibodies to bacteria in blood and observed a 2-fold increased risk (14), and the second study measured bacteria directly in saliva and observed a 1.6-fold increased risk (15). *Aggregatibacter actinomycetemcomitans*, another periodontal pathogen, was also associated with 2-fold increase in pancreatic cancer risk in one of these studies (15). The finding from the study measuring

Figure 3. Meta-analysis of studies on periodontal disease and pancreatic cancer



antibodies in pre-diagnostic blood confirms that antibodies to oral pathogens can be measured in human blood samples that have been frozen for numerous years prior to analysis.

5. Main Hypothesis/Study Questions:

Question 1. Are circulating antibodies against certain oral bacteria associated with subsequent cancer incidence and mortality?

We hypothesize that seropositivity for keystone pathogens (i.e., less abundant bacteria that disproportionately affect the microbial environment) or pathobionts (i.e., bacteria that are normally symbionts but can be disease promoting) associated with periodontal disease is associated with an increased cancer risk, in particular with cancers for which we previously observed associations for periodontal disease:

- Seropositivity for *Fusobacterium, Selenomas,* and *Prevotella* species (i.e., pathobionts – see ref 8 above) is associated with increased risk of colorectal cancer,
- Seropositivity for *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* (i.e., keystone pathogens – see refs 14 and 15 above) is associated with increased risk of pancreatic cancer.

As indicated in Rationale above, we expect these associations to be complex. Antibodies against keystone pathogens or inflammophilic pathobionts may reflect a history of high bacteria load in the gums due to dysbiosis (i.e., an imbalance among microbes or the body's inability to adapt to this imbalance) and development of periodontitis, and thus, we would expect a positive association between seropositivity and cancer risk, with a strengthening association with increasing antibody concentration (reflecting more robust response or repeated/chronic exposure to these bacteria over time). However, overall antibody levels (total IgG, non-specific) may also reflect a stronger immune response that prevents dysbiosis from developing by holding in check or helping to clear keystone pathogens, and thus, we might expect an inverse association with total IgG, as previously observed for pancreatic cancer risk (14).

To clarify what we may observe for the main research question, we will also address joint categories of clinically-assessed periodontal disease AND antibodies against oral pathogens of interest.

- Participants who have both periodontal disease and antibodies against keystone pathogens (i.e., *P. gingivalis* and *A. actinomycetemcomitans*) may have the highest risk of colorectal cancer because the onset of the gum disease was earlier, or more aggressive (elevated antibodies indicating onset of dysbiosis in the oral cavity) and by visit 4 had developed periodontitis.
- Participants who do not have periodontal disease but who are seropositive for keystone pathogens are either more likely to have cleared these agents (thus not developing signs of periodontitis) or in the early phases of dysbiosis, and may have not yet developed sufficient inflammation of the gums for an increase risk in cancer to be noticeable. Alternatively, if these individuals have a higher risk of cancer, this might suggest the risk is independent of periodontal disease (but dependent on infection). Participants who have periodontal disease but who are seronegative to keystone pathogens are those who either have another cause of their periodontal disease (e.g., other agents or non-bacterial causes) or are unable to mount a sufficient antibody response. Among these individuals, elevated levels of pathobionts may be identified, which would suggest that other pathways resulted

in dysbiosis of commensal bacteria. The risk of colorectal cancer may still be high in those individuals, if for example, antibodies to *Fusobacterium* are elevated (these antibodies are not as strongly linked to periodontitis as *P. gingivalis*). We hypothesize that participants with low antibody levels to all key pathogens and pathobionts have the lowest risk of colorectal cancer.

Question 2. Does the detectability of oral pathogen DNA in dental plaque differ between those with and without a subsequent cancer diagnosis?

We hypothesize that oral pathogen DNA is more likely to be detected in dental plaque of participants who are subsequently diagnosed with cancer than those who are not in the same direction as proposed in Question 1.

Question 3. Are levels of interleukin-1 beta (IL-1beta) and prostaglandin E2 (PGE2) measured in gingival crevicular fluid (GCF) as an indicator of the immune response to periodontitis and thus active periodontal disease associated with subsequent cancer incidence and mortality?

We hypothesize that detectable IL1beta and PGE2 levels in GCF are associated with an increased risk of cancer incidence and mortality.

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

Analytic population: Men and women who attended the clinical dental examination at Visit 4 and have data available on levels of circulating antibodies against oral pathogens and/or immune markers in gingival crevicular fluid and/or oral pathogen DNA in dental plaque, who did not have a history of cancer by Visit 4, and who consented to studies on chronic diseases including cancer. Participants not eligible for the dental examination will be excluded (i.e., edentulous, contraindications for dental probing, declined examination).

Cancer cases and non-cases diagnosed after ARIC Visit 4/dental examination

	Number of eligible participants			
	Had the dental exam and is otherwise eligible	Gingival crevicular fluid measurements	Antibodies against oral pathogens	Oral pathogen DNA in dental plaque
Total Cancer Incidence				
Non-cases	4755	4349	3613	1011
Cases	1301	1182	936	267
Total Cancer Death				
Non-cases	5658	5172	4268	1202
Cases	398	359	281	76
Lung Cancer Incidence				
Non-cases	5904	5395	4440	1245
Cases	152	136	109	33
Lung Cancer Death				
Non-cases	5962	5447	4481	1256

Cases	94	84	68	22
Colorectal Cancer Incidence				
Non-cases	5940	5425	4463	1252
Cases	116	106	86	26
Colorectal Cancer Death				
Non-cases	6025	5503	4526	1270
Cases	31	28	23	8
Pancreatic Cancer Incidence				
Non-cases	6014	5496	4527	1267
Cases	42	35	22	11
Pancreatic Cancer Death				
Non-cases	6012	5494	4522	1264
Cases	44	37	27	14
Total participants	6056	5531	4549	1278

Exposures: All exposures were measured using biospecimens collected at visit 4.

Antibodies against oral pathogens measured in blood: Antibodies against - ***Porphyromonas gingivalis****; **Prevotella intermedia**; **Prevotella nigrescens**; Tannerella forsythensis; Treponema denticola**; Fusobacterium nucleatum**; **Aggregatibacter actinomycetemcomitans**; Campylobacter rectus; Eikenella corrodens; Parvimonas micra; Veillonella parvula; Capnocytophaga ochracea; **Seleomonas noxia**; Actinomyces viscosus; Streptococcus intermedius; Streptococcus sanguis; and Streptococcus oralis* – were measured previously by team members Drs. Beck and Offenbacher et al. (16) in serum using the checkerboard immunoblotting technique. The method provides quantification of serum IgG concentrations with a limit of detection (LOD) of 20 ng/mL. These bacteria were targeted because of their causal links with periodontal disease and because persons with periodontal disease have higher serum concentrations of IgG against these bacteria than those who do not. The agents shown in bold font are of particular interest to cancer as indicated in the Rationale.

Oral pathogens measured in dental plaque: ***Prevotella intermedia***, *Campylobacter rectus*, ***Fusobacterium nucleatum***, and ***Prevotella nigrescens***; ***Porphyromonas gingivalis***, *Tannerella forsythia*, and *Treponema denticola*; and ***Aggregatibacter actinomycetemcomitans*** DNA was measured by Drs. Beck and Offenbacher et al. (17) in subgingival microbial plaque samples collected during the dental examination using the checkerboard DNA-DNA hybridization method. The checkboard method is semi-quantitative and has an LOD of a count of about 104. The agents shown in bold font are of particular interest to cancer as indicated in the Rationale.

Inflammatory mediators of the causal link between oral pathogens and periodontal disease: Concentrations of interleukin 1 beta (IL-1beta) and prostaglandin E2 (PGE2) were measured previously by Drs. Beck and Offenbacher et al. (18) in gingival crevicular fluid by ELISA. For the analysis, the mean across all collection sites will be averaged as done previous (18).

Periodontal disease and severity: With respect to cancer risk, we previously classified these same participants with respect to periodontal disease and severity at Visit 4 (MS #2762; (1)) and will be classifying them with respect to periodontal profiles developed in ARIC (19) (MS #3048).

Outcome: We will include first primary cancer cases and cancer deaths occurring after Visit 4 through 2012 among participants eligible for this analysis. In particular, we will focus on lung, colorectal, and pancreatic cancers for incidence. We will use the ARIC cancer case files, which were developed using data from the MN, NC, MD, and MS state cancer registries, medical records, and hospital discharge codes (20). Counts for each exposure by outcome are shown in the Table above.

Other variables: Age, race, BMI, current smoking status and packyears smoked at Visits 1 to 4; alcohol drinking at Visit 4 (never, former, or current drinker), diabetes status at Visit 4 (diagnosed: MD diagnosis, medications; undiagnosed: fasting glucose ≥126 mg/dL at any visit and/or glycated hemoglobin ≥6.5% at Visit 2; at risk for diabetes: fasting glucose of 100 to <126 mg/dL at visit 4; if not fasting, prior visit concentration will carried forward); ever use of hormone replacement therapy (women only; Visits 1, 3, and 4).

Data analysis: All analyses will be performed using SAS. Tests will be 2-sided and $p<0.05$ will be considered to be statistically significant. As this is not an agnostic search for bacteria that may be associated with cancer, we will not perform corrections for multiple testing.

Q1. To determine whether antibodies against periodontal disease bacteria (especially the ones in bold under Exposures) are associated with total, lung, colorectal, and pancreatic cancer incidence and total cancer mortality, we will use Cox proportional hazards regression to estimate hazard ratios (HR) and 95% confidence intervals (CI) for bacteria-specific IgG concentration (above the median vs at or below; or quantiles) adjusting for age (continuous), education (<high school, high school, >high school), and field center*race (black from suburban Minneapolis, Forsyth County or Washington County; white from Forsyth County or Washington County; black from Jackson; with white from Minneapolis as the reference group). We will repeat these analyses adjusting for risk factors for periodontal disease/antibodies against oral pathogens and/or cancer – smoking (current, former, never; packyears smoked [continuous]), BMI (continuous), diabetes status (diagnosed, undiagnosed, at risk for diabetes, none), alcohol drinking (never, former, or current drinker), and SES/access to and uptake of care (from the work to be done in MS #3048). If the HR of cancer appears to increase (IgG for keystone bacteria or pathobionts) or decrease (total IgG) with IgG concentration, we will test for trend by entering antibody concentration as a continuous variable and testing its coefficient using the Wald test. We will confirm the proportional hazards assumption by entering a term for the cross product of concentration and time, which we will test using the likelihood ratio test. Given our prior findings of possible differences in association between periodontal disease and cancer risk, for total cancer, we will stratify these analyses by sex and by race, and will test for statistical interaction by including a cross-product term between antibody (binary, or continuous) and sex or race and testing using the likelihood ratio test.

Next, we will cross classify participants with respect to both IgG concentration and clinically-assessed periodontal disease as follows: IgG at or below the median AND no periodontal disease (reference group); IgG above the median AND no periodontal disease; IgG at or below the median and periodontal disease; and IgG above the median AND periodontal disease. In addition, we will use other cutpoints for IgG concentration (e.g., above the 25th percentile, above

the 80th percentile) and periodontal disease (e.g., moderate or worse, severe). We will enter these joint categories into the Cox models as described above.

Q2. To address whether the detectability of oral pathogen DNA in dental plaque (especially the ones in bold under Exposures) differs between those with and without a subsequent cancer diagnosis, we will calculate the prevalence of seropositivity for each bacterium, the median count for each bacteria, and the median number of bacteria for which seropositive in participants who did and did not go on to have a diagnosis of total, lung, colorectal, and pancreatic cancer or who did and did not die of cancer. We will use the chi-square test (prevalences) or the Wilcoxon rank sum test (medians) to determine whether the prevalences or medians differ between cases and non-cases. Given the sample size, we may also be able to use the statistical analysis strategy describe under Q1 for antibodies to estimate the association between the detectability of oral pathogen DNA and cancer risk; for other outcomes, the sample size with measured oral pathogen DNA is likely too small.

Q3. To evaluate whether IL-1 beta and PGE2 concentrations measured in gingival crevicular fluid (GCF) are associated with total, lung, colorectal, and pancreatic cancer incidence and total cancer mortality we will use the same statistical analysis strategy as for Q1. We will model IL-1beta or PGE2 concentration in categories (e.g., above the median [versus at or below the median]; or quantiles). If the HR of cancer appears to increase (or decrease) with concentration, we will test for trend by entering concentration as a continuous variable and testing its coefficient using the Wald test. As in Q1, we will confirm the proportional hazards assumption and also will stratify by sex and by race.

Methodologic challenges:

Q1 and 3. Power

With respect to Q1, we have sufficient power to detect moderate and larger associations between IgG and total cancer incidence (936 cancer cases in 4549 participants): for a 2-sided test with alpha=0.05 and a power of 80%, the minimum detectable HR is 1.25 when the prevalence of high IgG level is 0.5 (median) in the analytic cohort. The minimum detectable HRs for lung and colorectal cancer incidence and total cancer mortality are 1.85, 2.01, and 1.47, respectively. We may have sufficient power for lung cancer mortality (minimum detectable HR=2.20). For colorectal cancer mortality and pancreatic cancer incidence and mortality we have the power to detect large associations (e.g., CRC mortality: HR=4.59). Associations of 1.2 to 2.2 are in the ranges we observed previously for periodontal disease and these outcomes (see Rationale). In Dr. Michaud's prior work on antibodies against *P. gingivalis*, she observed OR=2.14 (95% CI 1.05 to 4.36) (14). If the IgG associations are similar to what we observed for periodontal disease cancer and for antibodies against one oral pathogen and pancreatic cancer, then we expect that this analysis is sufficiently powered to address this research question. If these associations are more complex than anticipated (as described under Q1), we expect that by modeling joint IgG and periodontal disease categories, we will better classify the participants by exposure and non-exposure, and possibly enhance power to detect associations.

With respect to Q3, the sample size is larger than for Q1, thus the minimum detectable associations for IL-1beta and PGE2 are smaller (e.g., for total cancer incidence 1.23 and

mortality 1.40) given the same assumptions including the cutpoint at the median for concentration.

With respect to Q2, the sample size is smaller than for Q1 and Q2. We may have sufficient power to evaluate oral pathogen DNA in plaque with total cancer incidence (minimum detectable HR=1.53) and mortality (HR=2.13). We have the power to detect on large associations for the other outcomes.

Q1. Limits of detection

In prior work conducted by Drs. Beck, Offenbacher et al., the prevalence of detectable IgG concentration ranged from 68.0% (*Veillonella parvula*) to 97.5% (*Actinobacillus actinomycetemcomitans*) in ARIC (21). In their prior studies using these data for other outcomes they divided these continuous distributions into above the median (vs at or below) and into quartiles. We propose to do the same, but we will also explore the use of a reference group at or below the LOD when the sample size allows (combination of number of cancer events and the prevalence of at or below the LOD); we expect this group to be the least likely to have had exposure to these pathogens.

Q1 and 3. Multiple agents

Given priors, we will not perform corrections for multiple testing. However, we are mindful of the number of tests we will be performing (antibodies and DNA for multiple bacteria). Thus, for Q1, we will also perform analyses considering clusters of bacterial species often found together in gingival biofilm as was done previously by some of the coauthors [Group 1 - *P. gingivalis, T. denticola, and T. forsythensis*, Group 2 - *P. intermedia, P. nigrescens, C. rectus, F. nucleatum, and P. micra*]; and separately *A. actinomycetemcomitans* (16). We will sum IgG concentrations across the agents in each and then enter terms for quantiles (or continuous for testing for trend) into the Cox model.

Q1, 2 and 3. Generalizability

The total number of participants in the dental examination was 6,793. Of these, 6,056 were possibly eligible for the proposed analysis because they did not have a cancer diagnosis prior to visit 4/dental examination and consented to non-CVD research. We will assess whether those with and without these measurements differ on their characteristics in such a way that missingness influences the findings with cancer.

This study does not include participants who were edentulous because edentulism was an exclusion criterion for the dental examination. Edentulism can be caused by severe periodontal disease, but also for reasons such as poor dental care. Thus, we will not able to comment on associations to be studied in this proposal in those who are edentulous.

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 ICTDER04 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

EAP did this task
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)?

The team includes the ARIC dental exam and ARIC cancer investigators.

This manuscript proposal is directly related to MS #2762 and MS #3048 from the same investigators.

Many manuscript proposals include periodontal disease and/or other dental-related measures, including MS1892, MS2191, MS2449, MS2453, MS942, MS1079, MS658, MS566, MS995, MS858, MS913, MS1593, MS852, and MS1937.

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
___ A. primarily the result of an ancillary study (list number* 1996.0 (Dental Exam), 2011.07 (ARIC cancer), 1995.04 (cancer)**)**
___ 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.

OK - EAP

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.

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13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes X No.

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