ARIC Manuscript Proposal #2851

1.a. Full Title: The impact of neighborhood racial residential segregation on risk for smoking-associated cancers in the Atherosclerosis Risk in Communities (ARIC) Study

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

2. Writing Group:
   Writing group members: Miranda R. Jones, Elizabeth A. Platz, Corinne E. Joshu, Other interested ARIC investigators

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

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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).
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3. Timeline:
   Data analysis – 6 months
   First draft of manuscript – 6 months

4. Rationale:
   In the US, race/ethnicity is highly correlated with residential location, with whites and minorities often living segregated from one another.1,2 This differential residential location (i.e., racial residential segregation) may produce important differences in disease risk.1 Racial residential segregation can result in lower risk for health outcomes by fostering social networks3,4.
reinforcing positive health behaviors, and limiting the exposure of minority populations to discrimination. Racial residential segregation could also potentially increase risk for adverse health outcomes by limiting access to economic and health resources, limiting access to quality health care and increasing psychosocial stress, racism and exposure to health hazards including environmental toxicants and negative health behaviors. One such negative health behavior is smoking, which is the leading cause of preventable mortality in the US. Indeed, racial residential segregation has been associated with smoking among pregnant black women. Individuals may adopt negative behaviors such as smoking to buffer or reduce the chronic stress of discrimination. Higher segregation may also reflect structural attributes associated with smoking such as less stringent tobacco control policies, targeted marketing of tobacco products or limited access to smoking cessation treatment.

Studies have investigated racial residential segregation with health outcomes, including self-rated health, all-cause mortality, cardiovascular disease, and cancer. Studies of racial residential segregation with cancer prognostic characteristics and outcomes, have included tumor size, cancer stage, cancer mortality and cancer case-fatality among those diagnosed with cancer. However findings of these cancer studies, have been mixed; some found positive associations between residential segregation and cancer outcomes (higher segregation, higher risk of poorer outcomes), some finding inverse associations and one finding no association.

Racial residential segregation is multidimensional. In particular, 5 dimensions have been proposed: concentration, evenness, exposure, clustering and centralization. Previous studies, however have mostly examined a single measure of racial residential segregation or only a single dimension. Examining multiple measures and dimensions of racial residential segregation can give insight into potential mechanisms underlying the association between residential segregation and cancer and other health outcomes.

Between 1987-1989, ARIC recruited 15,792 adults aged 45-64 years from 4 US communities: Forsyth Co., NC; Jackson, MS; Minneapolis, MN; and Washington Co., MD. Two communities (Washington Co., MD and Minneapolis, MN) recruited mostly white participants and all participants recruited from Jackson, MS were black. Forsyth Co., NC recruited both black and white participants. Home addresses for ARIC study participants have been geocoded with high accuracy and previously linked to census tract and census block group data from the years 1990 and 2000 US Censuses to examine associations with neighborhood socioeconomic status and local food environments. Using the same methods, we will link home address for ARIC participants to data from the 2010 US Census.

Despite declines in rates in past decades, African-Americans continue to be disproportionately burdened by cancer incidence and mortality. Racial residential segregation may help to explain these disparities. ARIC can make important contributions to the literature on this topic. Understanding the role of racial residential segregation to cancer outcomes can facilitate the identification of policies or neighborhood-level interventions to address the characteristics of segregated neighborhoods that lead to adverse health outcomes. These findings can inform additional strategies for preventing and reducing cancer disparities in the US by identifying
potential points of intervention at the neighborhood level. In particular, this project can directly inform opportunities for intervention in ARIC communities.

Given the potential for differential effects of racial residential segregation on cancer risk by race, the ARIC study will allow us to explore disparities in cancer due to racial residential segregation separately for whites and blacks. The availability of individual-level data on cancer risk factors will improve our ability to investigate associations of neighborhood residential segregation on cancer risk beyond previous studies that were not able to account for cancer prognostic characteristics, treatment or major individual- and neighborhood-level risk factors (e.g., smoking status, alcohol, body mass index, physical activity and individual and neighborhood socioeconomic status).

5. Main Hypothesis/Study Questions:
   1. Neighborhood racial residential segregation will be associated with incidence and mortality for smoking-associated cancers among ARIC participants without prevalent cancer at baseline.
   2. Neighborhood racial residential segregation will be associated with cancer prognostic characteristics and case-fatality among ARIC participants who develop a smoking-associated cancer during follow-up.

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
Longitudinal study.

Inclusion/exclusion
All ARIC participants with geocoded home address data and data on cancer outcomes will be included.

Exposure: Racial residential segregation
We will use geocoded baseline home address data and census-tract data from the 1990, 2000 and 2010 US Census to implement measures of neighborhood racial residential segregation (Table 1). Non-Hispanic whites will be the majority (reference) population and non-Hispanic blacks will be the minority population (these are the two racial groups recruited into ARIC). For each measure of racial residential segregation, levels will be categorized as low, moderate or high using established cutpoints or tertiles for measures for which no established cutpoints exists.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Dimension</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>Racial composition</td>
<td>Concentration</td>
<td>Percentage of a group’s population in a census tract</td>
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<tr>
<td>Dissimilarity index</td>
<td>Evenness</td>
<td>Percentage of a group’s population that would have to move for each census tract to have the same percentage of that group as the metropolitan area overall</td>
</tr>
<tr>
<td>Gini coefficient</td>
<td>Evenness</td>
<td>Mean absolute difference between minority populations weighted across all pairs of census tracts</td>
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<tr>
<td>Interaction index</td>
<td>Exposure</td>
<td>Exposure of minority group members to members of the majority group</td>
</tr>
<tr>
<td>Isolation index</td>
<td>Exposure</td>
<td>Extent to which minority members are exposed only to one another</td>
</tr>
<tr>
<td>Spatial proximity</td>
<td>Clustering</td>
<td>Extent to which census tracts inhabited by minority members adjoin one another</td>
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</table>
Outcome: Smoking-associated cancers
Smoking-associated cancers will be defined as cancers of the lung, esophagus, larynx, oropharynx, stomach, liver, kidney, bladder, pancreas, stomach, cervix, colorectum and acute myeloid leukemia. For cancer mortality, we will additionally include prostate cancer. Among ARIC participants without prevalent cancer at baseline outcomes we will examine incidence and mortality for smoking-associated cancers. Among ARIC participants who develop a smoking-associated cancer during follow-up outcomes we will examine cancer prognostic characteristics (tumor stage, grade) and case-fatality.

Statistical analysis
To examine associations of neighborhood racial residential segregation with risk for smoking-associated cancers we will examine 1) incidence and mortality for smoking-associated cancers among ARIC participants without prevalent cancer at baseline; and 2) cancer prognostic characteristics and case-fatality among ARIC participants who develop a smoking-associated cancer during follow-up.

1. Incidence and mortality for smoking-associated cancers among ARIC participants without prevalent cancer at baseline. For participants without prevalent cancer at baseline (N=14,741), we will use mixed-effects Cox proportional hazards models to compute hazard ratios for incidence and mortality for smoking-associated cancers combined by comparing levels (low/moderate/high) of neighborhood racial residential segregation as assessed using each measure. We will repeat these analyses for the most common smoking-associated cancers: lung (incidence, mortality), colorectal (incidence), and prostate (men, mortality).

2. Cancer prognostic characteristics and case-fatality among ARIC participants who develop a smoking-associated cancer during follow-up. For participants who are diagnosed with a first primary smoking-associated cancer including prostate cancer during follow-up (N=2,459), we will compare cancer prognostic characteristics (tumor stage, grade) and case-fatality comparing levels (low/moderate/high) of neighborhood racial residential segregation assessed at the US Census year (1990, 2000 or 2010) closest to the time of diagnosis for each measure. We will use mixed-effects multinomial logistic regression for tumor stage and grade and mixed-effects Cox proportional hazards models for case-fatality. For analyses of prognostic characteristics, we will compare odds of diagnosis with local vs. regional/advanced cancer and odds of diagnosis with well-differentiated vs. moderately/ poorly/ undifferentiated cancer for any smoking-associated cancer. We will repeat the case-fatality analyses for the most common causes of cancer death: lung, colorectal, and prostate (men) cancers.

Models will include a census-tract specific random intercept to account for the clustering of individuals and will be adjusted for demographics (age, sex, race, and individual and neighborhood-level socioeconomic status). Models for case-fatality will additionally adjust for cancer prognostic characteristics and first course of treatment. In subanalyses, we will adjust for individual-level smoking and other major modifiable cancer risk factors (alcohol use, BMI,
physical activity); these models will be thoughtfully interpreted to address the possible influence of neighborhood context beyond individual-level risk factors.

Analyses will be presented overall (combined smoking-associated cancers that both men and women are at risk for) and separately for men and women (before and after including sex-specific smoking-associated cancers).

All statistical analyses and graphical displays will be performed using R statistical software.

**Challenges**

Three of the ARIC communities were homogenous by race when they were recruited in the late 1980s. Based on Census data, these cities/counties have undergone demographic shifts from 1990 to 2010; they are no longer primarily white or black communities and we do not anticipate insufficient variation in racial residential segregation in these ARIC sites. According to the 2000 U.S. Census, the percentage of white residents was 89.7% in Washington Co., MD, 65.1% in Minneapolis, MN, 27.8% in Jackson, MS and 68.5% in Forsyth Co., NC; the percentage of black residents was 7.8% in Washington Co., MD, 18.0% in Minneapolis, MN, 70.6% in Jackson, MS and 25.6% in Forsyth Co., NC.46 Nevertheless, if the variation proves insufficient when using data for all census years proposed (i.e., US Census 1990, 2000 and 2010), then we will restrict our primary analyses of associations of racial residential segregation with smoking and cancer outcomes to racial residential segregation measures estimated using data from census year(s) for which there variation.

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)?

- Proposal# 2838 (first author: Maya McDoom-Echebiri): Neighborhood socioeconomic characteristics and progression to hypertension at older age in the Atherosclerosis Risk in Communities Study
- Proposal# 454 (first author: Ana V. Diez-Rouz): The relationship of neighborhood characteristics to incidence of cardiovascular disease in the ARIC cohort
- Proposal# 1638 (first author: Rachel Huxley): Burden of smoking-related morbidity and mortality and benefits associated with smoking cessation in a middle-aged US population: The Atherosclerosis Risk in Communities Study

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 and 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.csc.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.csc.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.

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.
REFERENCES


