Lung Cancer 127 (2019) 90–95

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Association of oral health with lung cancer risk in a low-income population of African Americans and European Americans in the Southeastern United States

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ARTICLE INFO

Keywords:
Lung cancer
Oral health
Tooth loss
Tooth decay
Periodontal disease
Health disparities

ABSTRACT

Objectives: Previous studies have suggested that poor oral health might increase the risk of lung cancer among European- and Asian- descendants. The association has not been investigated among African Americans or socially disadvantaged populations. In this nested case-control study, we investigated whether oral health was associated with lung cancer risk among a low-income population of African Americans and European Americans in the Southeastern United States.

Materials and methods: A total of 403 incident lung cancer cases and 1612 matched controls from the Southern Community Cohort Study were included. Multivariate conditional logistic regression models were fitted to evaluate the risk of lung cancer linked to tooth loss, tooth decay, and history of periodontal disease.

Results: Tooth loss was significantly associated with an increased risk of lung cancer: the odds ratio (OR) of more than 10 teeth lost was 1.64 (95% CI: 1.00, 2.69). Tooth decay was also significantly associated with increased lung cancer risk; those with ≥ 6 decaying teeth had an OR of 1.65 (1.18, 2.31). An increased lung cancer risk was significantly associated with a history of periodontal disease among African Americans (OR = 1.56, 95% CI: 1.05, 2.31) and heavy smokers (OR = 2.05, 95% CI: 1.38, 3.05).

Conclusion: Poor oral health is associated with increased lung cancer risk, and this association appears to vary by race and smoking behavior among a low-income population of African Americans and European Americans in the Southeastern United States.

1. Introduction

Lung cancer accounts for approximately 13% of all cancer diagnoses in the United States [1]. The vast majority of lung cancer is attributed to cigarette smoking, but other factors, including radon exposure, air pollution, and dietary habits, are also involved in lung cancer etiology [2,3]. Recently, oral health has been hypothesized as a putative risk indicator in lung cancer. Several studies have suggested that poor oral health is associated with increased risk of lung cancer in European- and Asian- descendants [4–8]. Oral bacterial infections, which induce inflammation of the gums and tooth loss [9], can progress to systemic inflammation [10] and the generation of nitrosamines [11], an aggravation that may be linked to an incremental increased risk of developing various chronic diseases [12], as well as cancers [13]. Furthermore, poor oral health is often the result of smoking [14] and/or limited access to regular dental care [15], suggesting that poor oral health, especially among socioeconomically disadvantaged populations [16], may predispose them to a greater likelihood of developing lung cancer.

The association of poor oral health with lung cancer risk has not been investigated among African Americans or among socially disadvantaged populations. African Americans experience a higher incidence of lung cancer than other racial groups [17]. In addition, African Americans are at higher risk for poor oral health. Thus, in the present study, we focused on racial disparities in poor oral health and lung cancer risk. We conducted a nested case-control study within the Southern Community Cohort Study (SCCS), which includes a low-income population (half of the SCCS participants have annual household incomes of less than the US $15,000) and a large population of African Americans (two-thirds of the SCCS participants) living in the southeastern United States. Our objective was to evaluate whether oral health status is associated with lung cancer risk, and whether race and

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https://doi.org/10.1016/j.lungcan.2018.11.028
Received 7 May 2018; Received in revised form 29 October 2018; Accepted 23 November 2018

smoking status can modify this potential association.

2. Materials and methods

2.1. Study population

The present population-based nested case-control study was drawn from the SCCS, a prospective cohort designed to explore the underlying causes of racial disparities in health outcomes. The detailed information regarding the SCCS has been reported elsewhere [18,19]. Briefly, between March 2002 and September 2009, 84,797 adults (40–79 years old) were recruited from 12 southeastern American states (Alabama, Arkansas, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, Virginia, and West Virginia). Approximately 86% of the participants were recruited from 71 Community Health Centers (CHCs) where healthcare services are provided that are mainly focused on low-income and uninsured people, and 14% of the participants were recruited through written materials by mailings in these geographic areas. Computer-assisted personal interviews were performed by trained interviewers to collect baseline data regarding the participants' demographic characteristics, medical history, and potential health risk factors, including dietary habits, physical activity, smoking, alcohol consumption, and anthropometric characteristics. All participants were regularly followed-up, and data linkages to the states' cancer registries and/or the National Death Index mortality records were used to ascertain incident cancers.

2.2. Ascertainment of lung cancer

By the end of 2015, a total of 403 incident lung cancer cases with oral health data available were ascertained. Lung cancer cases were identified by using the tenth revision of the International Statistical Classification of Diseases (ICD-10: C340–C349). All cases were individually matched with four controls on age at enrollment (± 2 years), sex, race (African American, European American, or others), the recruitment source (CHC or general population), and recruitment site (for CHC) of study enrollment. Ultimately, a total of 2015 individuals, including 403 incident lung cancer cases and 1612 matched-controls, were selected for the present study.

2.3. Assessment of oral health

At the first follow-up survey for the SCCS (2008–2011), self-reported data on tooth loss, tooth decay, and history of periodontal disease were collected by the following questions and response categories: "About how many adult teeth have you lost in your lifetime due to tooth decay or gum disease?" (none, 1–4, 5–10, > 10 but not all of them, and all of them); "How many decayed teeth or cavities do you currently have that have not been treated?" (none, 1–2, 3–5, > 5, and no teeth); "Has a dentist or doctor ever told you that you have gum disease (gingivitis or periodontitis)?" (no or yes); and "At what age were you diagnosed with gum disease (gingivitis or periodontitis)?" (a continuous variable, reported in years).

2.4. Statistical analysis

The baseline characteristics of lung cancer risk factors (i.e., age, sex, body mass index [BMI], race, education, household income, marital status, history of chronic obstructive pulmonary disease [COPD], alcohol drinking, smoking status, and pack-years) were compared between the lung cancer cases and controls using Student's *t*-test for continuous variables or chi-square test for categorical variables. Multiple imputation methods were used to impute missing data for tooth loss (n = 18; 0.9% missing), tooth decay (n = 5; 0.3% missing), periodontal disease (n = 35; 1.7% missing), age of periodontal disease (n = 46; 2.3% missing) and other covariates (less than 0.1% missing) by SAS PROC MI. Based on oral health information, tooth loss was grouped into four categories: none, 1–4, 5–10, and more than 10, and tooth decay categorized as none, 1–5, and 6 or more. Age of periodontal disease was divided into two groups as ≥ 40, and < 40 (early onset of periodontal disease). The results, based on the original data and the imputed data, were first compared in crude models. Multivariate logistic regression models were fitted with adjustment for BMI (continuous), education (years of schooling: less than 12 years, 12 years, above 12 years), household income (< $15,000, $15,000-$25,000, > $25,000), history of COPD (yes, no), alcohol drinking (never, ever), smoking status (never, former, current), and race-specific median pack-years (African Americans: ≥ 17.5 pack-years; European Americans: ≥ 33.0 pack-years; other races: ≥ 31.0 pack-years). Linear trend tests for tooth loss and tooth decay were conducted by using the Wald test. All associations were further evaluated in the stratified analyses by race, smoking status, and pack-years; likelihood ratio test tested interactions between oral health status and those factors. All analyses were performed using the SAS software (version 9.4; SAS Institute, Cary, NC, USA).

3. Results

The baseline characteristics of lung cancer cases and controls are presented in Table 1. The proportion of current smoking was much higher in cases than in controls (71.5% vs. 32.1%, respectively, $P < 0.001$). Among smokers, lung cancer cases also showed a much higher number of pack-years than controls (38.2 vs. 26.0 pack-years, respectively, $P < 0.001$). Lung cancer cases were more likely to be less educated, earn less income, have a history of COPD, be alcohol drinkers, and have a lower BMI, compared with controls (all $P < 0.05$).

Tooth loss was significantly associated with an increased risk of lung cancer (Table 2). Results were similar whether we used original data only or included imputed missing data; thus, we show only the results including imputed missing data in further analyses. Using no tooth loss as the reference, the OR (95% CI) for developing lung cancer gradually increased by greater numbers of tooth loss (P for trend < 0.001): 1.37 (0.85, 2.21) for 1–4 lost, 1.54 (0.95, 2.50) for 5–10 lost, and 3.33 (2.14,

Table 1
Baseline characteristics of study population, the Southern Community Cohort Study.

	Case (N = 403)	Control (N = 1612)	*P*
Age at enrollment, mean (SD)	57.1 (8.6)	56.9 (8.7)	0.72
Age at first interview, mean (SD)	61.8 (8.4)	61.6 (8.4)	0.67
BMI, mean (SD)	27.5 (6.5)	30.2 (7.1)	< 0.001
Sex, N (%)			
Men	185 (45.9)	740 (45.9)	–
Women	218 (54.1)	872 (54.1)	
Race, N (%)			
African Americans	230 (57.1)	920 (57.1)	–
European Americans	159 (39.5)	636 (39.5)	
Other	14 (3.5)	56 (3.5)	
Years of schooling, N (%)			
Less than 12 years	153 (38.0)	426 (26.4)	< 0.001
12 years	140 (34.8)	516 (32.0)	
Above 12 years	110 (27.2)	671 (41.6)	
Household income, N (%)			
< $15,000	243 (60.2)	798 (49.5)	< 0.001
$15,000-$25,000	84 (20.9)	335 (20.8)	
> $25,000	76 (18.9)	479 (29.7)	
Smoking status, N (%)			
Never	25 (6.2)	624 (38.7)	< 0.001
Former	90 (22.3)	469 (29.1)	
Current	288 (71.5)	519 (32.1)	
Pack-years, mean (SD)*	38.2 (27.0)	26.0 (26.4)	< 0.001
Ever drinker, N (%)	221 (54.8)	782 (48.5)	0.02
History of COPD, N (%)	77 (19.1)	131 (8.1)	< 0.001

*Among smokers

Table 2
Association of oral health with lung cancer risk, the Southern Community Cohort Study.

	Case (%) (N = 403)	Control (%) (N = 1612)	Original data[†]		Missing data were imputed			
			Crude		Crude		Adjusted[‡]	
			OR	95% CI	OR	95% CI	OR	95% CI
Tooth loss								
None	27 (7.0)	217 (13.5)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
1 to 4	67 (17.4)	413 (25.6)	1.40	(0.87, 2.25)	1.37	(0.85, 2.21)	1.20	(0.70, 2.03)
5 to 10	61 (15.8)	343 (21.3)	1.53	(0.94, 2.49)	1.54	(0.95, 2.50)	1.22	(0.71, 2.09)
More than 10	230 (59.7)	639 (39.6)	3.32	(2.13, 5.18)	3.33	(2.14, 5.20)	1.64	(1.00, 2.69)
P for trend				< 0.001		< 0.001		0.02
Tooth decay								
None	104 (26.1)	673 (41.8)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
1 to 5	114 (28.6)	522 (32.4)	1.47	(1.09, 1.99)	1.49	(1.10, 2.01)	1.12	(0.79, 1.58)
6 or more	180 (45.2)	417 (25.9)	2.98	(2.24, 3.96)	2.99	(2.25, 3.97)	1.65	(1.18, 2.31)
P for trend				< 0.001		< 0.001		< 0.01
Periodontal disease[a]								
No	267 (67.8)	1209 (76.2)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Yes	127 (32.2)	377 (23.8)	1.52	(1.19, 1.93)	1.53	(1.20, 1.94)	1.44	(1.09, 1.91)

[†] Due to missing information on tooth loss, tooth decay, and periodontal disease, a total of 18 (tooth loss), 5 (tooth decay), and 35 (periodontal disease) were not included in the analyses.
[‡] Adjusted for BMI, education, household income, COPD, alcohol drinking, smoking status, and pack-years; and missing data on oral health were imputed.
[a] Ever diagnosed with periodontal diseases (gingivitis or periodontitis).

Table 3
Association of oral health with lung cancer risk by race, the Southern Community Cohort Study.

	African American				European American				*P* interaction
	Case (N = 230)	Control (N = 920)	OR[†]	95% CI	Case (N = 159)	Control (N = 636)	OR[†]	95% CI	
Tooth loss									
None	12 (5.6)	108 (11.7)	1.00	(Reference)	15 (9.6)	95 (14.9)	1.00	(Reference)	0.34
1 to 4	41 (19.0)	239 (26.0)	1.68	(0.78, 3.58)	25 (16.0)	159 (25.0)	0.75	(0.34, 1.67)	
5 to 10	39 (18.1)	211 (22.9)	1.67	(0.77, 3.62)	18 (11.5)	122 (19.2)	0.65	(0.28, 1.53)	
More than 10	124 (57.4)	362 (39.4)	2.11	(1.03, 4.32)	98 (62.8)	260 (40.9)	1.04	(0.49, 2.19)	
P for trend				0.05				0.51	
Tooth decay									
None	53 (23.5)	331 (36.0)	1.00	(Reference)	45 (28.5)	312 (49.1)	1.00	(Reference)	0.72
1 to 5	78 (34.5)	362 (39.3)	1.06	(0.68, 1.66)	34 (21.5)	142 (22.3)	1.48	(0.81, 2.70)	
6 or more	95 (42.0)	227 (24.7)	1.67	(1.06, 2.63)	79 (50.0)	182 (28.6)	1.61	(0.95, 2.74)	
P for trend				0.02				0.08	
Periodontal disease[a]									
No	159 (71.0)	711 (78.7)	1.00	(Reference)	96 (61.5)	454 (71.9)	1.00	(Reference)	0.62
Yes	65 (29.0)	192 (21.3)	1.56	(1.05, 2.31)	60 (38.5)	177 (28.1)	1.31	(0.86, 2.01)	

[†] Adjusted for BMI, education, household income, COPD, alcohol drinking, smoking status, pack-years; and missing data on oral health were imputed.
[a] Ever diagnosed with periodontal diseases (gingivitis or periodontitis).

5.20) for more than 10 in a crude model. After adjusting for BMI, education, household income, COPD, alcohol drinking, smoking status, and pack-years, the associations were attenuated (OR = 1.20, 95% CI: 0.70, 2.03 for 1–4 teeth lost; OR = 1.22, 95% CI: 0.71, 2.09 for 5–10 lost; and OR = 1.64, 95% CI: 1.00, 2.69 for more than 10, *P* for trend = 0.02; Table 2). When stratified by race, the positive association between tooth loss and lung cancer risk was only observed in African Americans (after adjusting for all covariates: OR = 2.11, 95% CI 1.03, 4.32 for more than 10 tooth loss, *P* for trend = 0.05). No significant interaction was found by race (*P* interaction = 0.34; Table 3).

Tooth decay was also associated with an increased risk of lung cancer (Table 2). When compared to no tooth decay, an increasing number of decayed teeth showed a higher risk for developing lung cancer in the multivariate model (OR = 1.12, 95% CI: 0.79, 1.58 for 1–5 decayed teeth; and OR = 1.65, 95% CI: 1.18, 2.31 for 6 or more decayed teeth; *P* for trend < 0.01). The significant positive association of tooth decay with lung cancer risk was observed in African Americans (OR = 1.67, 95% CI 1.06, 2.63 for 6 or more decayed teeth, *P* for trend = 0.02), but there was no evidence of interaction by race (*P* interaction = 0.72; Table 3).

History of periodontal disease (gingivitis or periodontitis) was also associated with an increased risk of lung cancer after adjusting for potential confounding factors (OR = 1.44, 95% CI: 1.09, 1.91, Table 2). The positive association was more evident among African Americans (OR = 1.56, 95% CI: 1.05, 2.31) than European Americans (OR = 1.31, 95% CI: 0.86, 2.01). However, earlier age (< 40 years) at diagnosis of the periodontal disease did not show a significant association with lung cancer risk overall (OR = 0.80, 95% CI: 0.34, 1.88).

As shown in Table 1, 93.8% of cases included in the study are current or former smokers. To evaluate whether the association between oral health and lung cancer risk differed by smoking intensity, we performed analyses stratified by smoking pack-years. The association of oral health with lung cancer was more evident among those with a higher (≥ race-specific median) cumulative smoking exposure than those with a lower (< race-specific median) cumulative smoking (*P* for interaction < 0.001, < 0.001, and 0.03 for tooth loss, tooth decay and

Table 4
Association of oral health with lung cancer risk by pack-years, the Southern Community Cohort Study.

	≥ Median*				< Median*			
	Case (N = 245)	Control (N = 406)	OR†	95% CI	Case (N = 134)	Control (N = 596)	OR†	95% CI
Tooth loss								
None	9 (3.8)	41 (10.1)	1.00	(Reference)	13 (10.3)	76 (12.7)	1.00	(Reference)
1 to 4	41 (17.4)	78 (19.2)	1.80	(0.65, 4.97)	21 (16.7)	150 (25.2)	1.22	(0.60, 2.48)
5 to 10	39 (16.5)	72 (17.7)	2.73	(0.96, 7.77)	18 (14.3)	139 (23.3)	0.93	(0.45, 1.93)
More than 10	147 (62.3)	215 (53.0)	2.88	(1.12, 7.45)	74 (58.7)	231 (38.8)	1.56	(0.81, 3.00)
P for trend				< 0.001				0.20
						P interaction: < 0.001		
Tooth decay								
None	54 (22.4)	139 (34.2)	1.00	(Reference)	47 (35.3)	234 (39.3)	1.00	(Reference)
1 to 5	67 (27.8)	128 (31.5)	1.26	(0.73, 2.19)	35 (26.3)	207 (34.7)	0.73	(0.45, 1.17)
6 or more	120 (49.8)	139 (34.2)	1.64	(0.99, 2.70)	51 (38.4)	155 (26.0)	1.30	(0.81, 2.07)
P for trend				< 0.001				0.62
						P interaction: < 0.001		
Periodontal disease[a]								
No	160 (66.9)	293 (74.0)	1.00	(Reference)	91 (69.5)	442 (74.9)	1.00	(Reference)
Yes	79 (33.1)	103 (26.0)	2.05	(1.38, 3.05)	40 (30.5)	148 (25.1)	1.97	(1.18, 3.32)
						P interaction: 0.03		

Note: Median value of pack-years was divided race-specific; African Americans ≥ 17.5, European Americans ≥ 33.0, Other races ≥ 31.0.
† Adjusted for age at baseline, race, smoking status, alcohol drinking, education, household income, COPD, and BMI; and missing data on oral health were imputed.
[a] Ever diagnosed with periodontal disease (gingivitis or periodontitis).

periodontal disease, respectively) (Table 4). Among heavy smokers, the ORs for developing lung cancer were 2.88 (95% CI: 1.12, 7.45) for those with more than 10 teeth lost compared to no tooth loss, 1.64 (95% CI: 0.99, 2.70) for those with 6 or more decayed teeth compared to no tooth decay, and 2.05 (95% CI: 1.38, 3.05) for those with a history of periodontal disease compared to those without a history of periodontal disease (Table 4). In addition, the risk increase associated with tooth loss or tooth decay was significant only among smokers who had more than the race-specific median pack-years.

We also evaluated the association between oral health and lung cancer risk by lung cancer subtypes. The associations did not differ between adenocarcinoma and squamous cell carcinoma (data not shown). However, the sample size is not large in the subgroup analyses.

4. Discussion

In this population-based nested case-control study, we found that poor oral health, including tooth loss, tooth decay, and a history of periodontal disease, was associated with an increased risk of lung cancer among the SCCS population. These positive associations were more evident among African Americans and heavy smokers.

Results from our study support previous reports that tooth loss was significantly associated with increased lung cancer risk. In the Health Professionals Follow-Up Study, among European American male populations with high educational attainment, having fewer teeth was associated with an increased risk of lung cancer [6]. A Japanese hospital-based case-control study also reported a 1.5-fold increased lung cancer risk for those who had lost all teeth compared to those with at least 21 teeth remaining [4]. Hujoel et al.'s study, based on the NHANES I Epidemiologic Follow-up Study, found that individuals who had lost all teeth had a ~2-fold increased risk for lung cancer in an age- and gender-adjusted model, but the association became non-significant after adjusting for confounding factors such as race, socioeconomic status, smoking duration, and pack-years [5]. A very recent study from the Atherosclerosis Risk in Communities study (ARIC) reported that having lost all teeth was significantly associated with increased lung and bronchus cancer risk among the European American population, but not among the African American population [20].

In the present study, periodontal disease was positively associated with lung cancer risk. Results from previous studies are inconsistent. Results from the Health Professionals Follow-Up Study (5) and Women's Health Initiative Observational Study [7] reported a positive association bwtween periodontal disease and lung cancer with an HR of 1.36 and 1.25, respectively. However, results from the Swedish Twin Registry found that periodontal disease did not significantly increase the risk of lung cancer [8]. The results of a Taiwanese study using National Health Insurance data revealed that patients with periodontitis did not have a significantly higher risk of lung cancer [21]. The NHANES I Epidemiologic Follow-up Study reported that lung cancer risk was associated with periodontitis (HR = 1.73, 95% CI: 1.01, 2.97) only, not gingivitis (HR = 1.31, 95% CI: 0.68, 2.53) [5]. We did not collect information for periodontitis and gingivitis separately, and thus, are not able to evaluate the specific effects of periodontitis and gingivitis separately. In a very recent study conducted within ARIC [20], severe periodontitis was significantly associated with increased lung cancer risk among the European American population. The association among African Americans was not significant, perhaps due to the small sample size [20].

We found evidence that the associations between oral health and lung cancer risk may differ by smoking intensity. When stratified by intensity of cumulative smoking exposure, the association of poor oral health with lung cancer risk was more evident among smokers who have higher pack-year histories than smokers who have lower pack-year histories, and the interaction was significant. Previous studies have proven the harmful effects of smoking on oral health [14,22]. Rad and colleagues demonstrated that long-term smoking significantly reduces the whole-mouth salivary flow rate that helps maintain healthy oral conditions, thus aggravating oral health resulting from dry mouth [23]. In addition, results from The Veterans Administration Dental Longitudinal Study suggested that smoking cessation could help prevent tooth loss, and suggested that long-term smoking cessation could reduce the risk to the level of never smokers [24].

Although the underlying mechanisms of oral health and lung cancer risk are not clear, several biologically plausible hypotheses support our findings. First, recent research has suggested that periodontal pathogens induce an inflammatory response that is characterized by increased levels of C-reactive protein, IL-1β, IL-6, TNF-α, and matrix metalloproteinases [25–28]. Also, patients with periodontitis have

higher levels of C-reactive protein compared to patients without periodontitis [29]. Thus, exposure to the chronic inflammation that is caused by poor oral health may initiate and promote lung cancer development, and smoking can aggravate inflammation and carcinogenesis. Second, poor oral health could generate a potent carcinogen, nitrosamine [30]. It has been reported that people with poor oral health have higher nitrosamine levels, which are driven by nitrate-reducing bacteria, in their oral cavities [11,31]. Third, oral bacteria could themselves produce adverse effects on human health, e.g., toxin-producing bacteria could disturb the normal cell cycle and growth [32]. The oral microbiome is the primary source of lung bacteria, and our ongoing study has found that several oral bacteria are associated with lung cancer risk [33]. Interestingly, Yan et al. have reported that patients with lung cancer have high levels of salivary microbiota, such as *Capnocytophaga* and *Veillonella* [34]. Also, Meyer et al. have speculated that bacteria may play a more direct carcinogenic role in lung or oral cancer, rather than an inflammatory role [13].

The present study has several strengths. First, we performed a population-based nested case-control study that included a relatively large number of African Americans and a low-income population, while most previous studies have been conducted among European- and Asian-descendants from populations with relatively higher socioeconomic statuses. As such, our results provide unique and important insights regarding features of oral health and lung cancer risk among the low-income population and among African Americans, who are at greater risk for both poor oral health and lung cancer. Second, the prospective design allows us to evaluate the potential causal associations between oral health and lung cancer. Third, comprehensive exposure data were collected from the SCCS participants that allowed us to adjust for potential confounders in the data analyses. The present study also has several limitations that warrant consideration. First, the information on oral health was self-reported. Because oral health information was collected before lung cancer diagnosis, however, the misclassification is likely to be small. Recent research has demonstrated that the accuracy of self-reported periodontal disease is moderate among postmenopausal women with the severe disease and who regularly visit a dentist [35]. Second, sample sizes are relatively small for European Americans and for some of the strata, such as for never smokers, and the point estimates may not be stable. Further studies are needed to confirm our findings.

5. Conclusions

Our findings indicate that poor oral health, as measured by tooth loss, tooth decay, and periodontal disease, is associated with an increased risk of lung cancer, and that this association is more evident among African Americans and heavy smokers. Based on our results, an increase in promoting oral health and tobacco cessation programs among African Americans and low-income populations in the United States could help reduce the incidence of lung cancer.

Ethical approval

All participants provided informed written consent before entering the study. The SCCS protocol was reviewed and approved by institutional review boards at Vanderbilt University and Meharry Medical College.

Conflict of interest

The authors declare no potential conflicts of interest.

Acknowledgments

This work was supported by the National Institutes of Health (R01CA207466, R01CA092447, U01CA202979, and U54CA163072). Data collection was performed by the Survey and Biospecimen Shared Resource which is supported in part by the Vanderbilt-Ingram Cancer Center (P30CA68485). The authors thank the study participants and research staff of the Southern Community Cohort Study for their contribution to this study. We thank Ms. Nan Kennedy and Dr. Mary Shannon Byers for assistance with editing and manuscript preparation.

Data on SCCS cancer cases used in this publication were provided by the Alabama Statewide Cancer Registry; Kentucky Cancer Registry, Lexington, KY; Tennessee Department of Health, Office of Cancer Surveillance; Florida Cancer Data System; North Carolina Central Cancer Registry, North Carolina Division of Public Health; Georgia Comprehensive Cancer Registry; Louisiana Tumor Registry; Mississippi Cancer Registry; South Carolina Central Cancer Registry; Virginia Department of Health, Virginia Cancer Registry; Arkansas Department of Health, Cancer Registry, 4815 W. Markham, Little Rock, AR 72,205. The Arkansas Central Cancer Registry is fully funded by a grant from National Program of Cancer Registries, Centers for Disease Control and Prevention (CDC). Data on SCCS cancer cases from Mississippi were collected by the Mississippi Cancer Registry which participates in the National Program of Cancer Registries (NPCR) of the Centers for Disease Control and Prevention (CDC). The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the CDC or the Mississippi Cancer Registry.

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