Cigarette Smoking and the Risk of Dying from Tobacco-related Malignancies by Race

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Abstract. *Background: The aim was to investigate whether differential risks from cigarette smoking contribute to the disproportionate burden of tobacco-related malignancies other than lung cancer (TRM-nonLC) suffered by African Americans (AAs) compared to Caucasians. Materials and Methods: Data from two prospective cohort studies (39% AAs) established in 1960 and followed through 1990 and 2000 in the southeastern U.S. were pooled (N=5,363). Each cohort had 30 years minimum follow-up. Results: Compared to Caucasians, the association between cigarette smoking and TRM-nonLC was significantly weaker in the AA men (hazards ratio (HR) 1.0 in AA men versus 3.6 in Caucasian men) and non-significantly weaker in the AA women (HR 1.1 in AA women versus 2.7 in Caucasian women). Conclusion: In these study cohorts, differential susceptibility to tobacco-caused carcinogenesis was, by itself, an unlikely contributing factor to the racial disparity in tobacco-related malignancies.*

Cigarette smoking is a major contributor to the overall cancer burden, causing approximately 30% of all cancer deaths in the United States (1). This is because cigarette smoking is causally linked with malignancies of the lung, esophagus, pancreas, oral cavity, bladder, larynx, kidney, stomach, and uterine cervix and acute myeloid leukemia (2). In the United States, African Americans (AAs) suffer disproportionately higher tobacco-related cancer incidence and mortality rates than Caucasians (3). This racial disparity is not fully explained by differences in historical smoking patterns (4), raising the possibility that it may be due to differential susceptibility to smoking-caused cancer. We previously examined this hypothesis specifically for lung cancer in a biracial cohort established in Charleston, South Carolina in 1960 (5). Our findings did not support the hypothesis that differential susceptibility to cigarette smoking is a major contributor to the racial disparity in lung cancer. In this report, these earlier findings for lung cancer were followed-up to primarily investigate tobacco-related malignancies other than lung cancer (TRM-nonLC). Henceforth, the term TRM-nonLC refers to the following nine tobacco-caused malignancies other than lung cancer: esophageal, pancreatic, oral, bladder, laryngeal, kidney, stomach, acute myeloid leukemia and cervical.

AAs have mortality rates from TRM-nonLC that are 13% higher than Caucasians (3). More evidence is needed to understand why this racial disparity exists, as racial differences in the association between smoking and cancer risk have been studied for only six of the nine TRM (6-21), often with inconsistent findings, but with hints that the association between smoking and cancer may be stronger among AAs, particularly AA men. The current study was carried out to further investigate whether there is a racial difference in susceptibility to smoking-caused malignancies, using data from two prospective cohort studies that were racially heterogeneous from the Southeastern U.S. in areas of high cancer rates with high racial disparities in these cancer rates (22), that were followed for 30 years or more.

Materials and Methods

This study was approved by the Institutional Review Board of the Medical University of South Carolina. Data from two population-based prospective cohort studies, the Evans County Heart Study (ECHS) and the Charleston Heart Study (CHS), were pooled. Key characteristics of these two cohorts are summarized in Table I. The ECHS had 3,102 participants at baseline in 1960, with mortality follow-up through 1990 (23, 24). In the CHS, there were 2,283 baseline participants in 1960 with mortality follow-up through 2000 (25,26). Out of these, 22 individuals were excluded due to missing

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Key Words: Cigarette smoking, tobacco-caused cancer, race.

Table I. *Key features of the Evans County Heart Study (ECHS) and the Charleston Heart Study (CHS).*

Study	Location	Year of baseline data collection	Baseline sample size	Last follow-up	Duration of follow-up (years)	Race %AA	Baseline measurement of cigarette smoking	Relevant covariates
ECHS	Evans County, GA, USA	1960	3102	1990	30	38	Non-current, Current	Age, gender, education, BMI, SBP, DBP
CHS	Charleston, SC, USA	1960	2283*	2000	40	39	Never, Former (cpd), Current (cpd)	Age, gender, education, BMI, SBP, DBP

*This includes n=102 African American (AA) men recruited in 1963. BMI: Body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; cpd: cigarettes per day.

years of education, leaving 5,363 participants for the pooled analyses. Both the ECHS and CHS were population-based cohorts originating in the southeastern region of the United States in 1960 consisting of substantial proportions of AAs with a high smoking prevalence. These similarities provide justification for a pooled analysis. The pooled analysis included a variable indicating cohort to adjust for potential cohort effects; this variable was not a statistically significantly predictor in the analyses.

The CHS categorized smoking status as never, former, or current. However, the ECHS recorded only a dichotomy of current smoking (yes/no) at baseline and thus, this measure served as the primary variable to denote smoking status in the pooled analyses. In addition the CHS recorded the number of cigarettes smoked per day among the ever smokers and follow-up smoking status on a portion of the cohort between 1984 and 1990. Covariates considered in the analyses included gender, years of education (≤4, 5-8, 9-12, >12 years), body mass index (BMI; <25, 25-29, or >29 kg/cm^2) and blood pressure, classified as hypertensive or not hypertensive, with a systolic blood pressure ≥ 140 mm Hg or a diastolic blood pressure ≥90 mm Hg considered to be hypertensive.

Mortality data were obtained through linkage to the National Center for Health Statistics National Death Index and the Social Security Death index. International Classification of Diseases (ICD)-9 and ICD-10 codes were used to categorize the cause of death. A total of 3,530 (66%) deaths occurred by the end of follow-up.

All the analyses were stratified by gender because of differences in historical smoking patterns and tobacco-related cancer rates between men and women. Competing risks Cox proportional hazards models with age at death as the outcome were used to estimate hazards ratios (HR) and corresponding 95% confidence intervals (CI). The competing risks approach was chosen to account for deaths due to other causes which cannot be assumed to occur independently of deaths to smoking-caused malignancies (*i.e.*, patients at higher risk for smoking-caused malignancies are also at higher risks for other causes of death compared to non-smokers). The proportional hazards assumption was tested using log-log plots. The parallel log-log plots for AAs and Caucasians indicated the assumption held true. Lung cancer is the leading cause of cancer death and is most strongly associated with cigarette smoking, and we have previously published results from one of these cohorts (CHS) for lung cancer (5). Thus analyses were performed for all the TRM-nonLC, and then separate ancillary analyses for all the smoking-caused malignancies combined, including lung cancer. For the analyses focusing on all the TRM-nonLC, the event of interest was death from smoking-caused cancer except lung cancer, competing events were all other deaths including those from lung cancer, and individuals who were still alive at the last follow-up were censored at their last known age. A similar approach was used for defining the event categories for all the smoking-caused malignancies (*i.e.*, events were death due to smoking-caused cancer and deaths due to all other causes). For each race-gender category the age-adjusted relative risk of death from TRM-nonLC for cigarette smoking was first estimated. A fully-adjusted multiple regression model was then fitted that further adjusted for gender, years of education, BMI, and hypertension. The racial difference in the association between smoking and cancer was formally tested with the *p*-value for the race-by-smoking interaction term from gender-specific analyses.

Results

The pooled study population included 127,749 person-years of follow-up, with 126 deaths from TRM-nonLC (Table II). Compared to the Caucasians, the AAs had significantly fewer years of education and a significantly higher prevalence of hypertension. The AA women had significantly higher BMI than the Caucasians. Current cigarette smoking rates were higher in the Caucasian than AA women (24.5% *versus* 15.0%, *p*-value <0.01), but did not differ by race among the men (55.5% *versus* 57.1%, *p*-value=0.27).

Multivariable analyses showed that the risk of dying from TRM-nonLC was significantly greater among the men compared to the women in both the blacks (HR=1.8; 95% CI: 1.0, 3.1) and the whites (HR=2.2; 95% CI: 1.3, 3.6), and was significantly positively associated with higher education (>=12 *vs*. 1-4 years) among the Caucasians (HR=6.2; 95% CI: 1.4, 27.3) but not the AAs (HR=1.5; 95% CI: 0.6, 3.9).

In the fully adjusted model, there was no association between cigarette smoking and death from TRM-nonLC among the AA men (HR=1.0; 95% CI: 0.5, 2.0) in comparison to an increased risk associated with smoking among the Caucasian men (HR=3.6; 95% CI: 1.7, 7.6) (Table III). The difference in risk by race for men was statistically significant (*p* for race-by-smoking interaction=0.02). A similar pattern was observed among the women, with a hazard ratio of 1.1 (95% CI: 0.4, 3.0) in the AAs and 2.7 (95% CI: 1.2, 6.2) in the Caucasians, but the racial difference in the magnitude of these

Table II. *Descriptive characteristics of the pooled Evans County Heart Study and Charleston Heart Study cohorts.*

	Males			Females		
	African American (n=971) (PY*=21,974) %	European American (n=1593) (PY=35,666) %	*p*-value	African American (n=1096) (PY=25,982) %	European American (n=1703) (PY=44,127) %	*p*-value
Age (Years)						
15-24	8.4	7.4		8.3	6.3	
25-34	7.6	6.8		4.9	6.5	
35-44	26.0	25.6		27.9	27.3	
45-54	28.7	29.3		24.9	28.4	
55-64	16.9	19.1		18.8	17.7	
65-79	12.4	11.7		15.2	13.9	
Mean(SD)	47.1 (14.2)	47.5 (13.9)	0.24	48.2 (14.5)	48.2 (13.9)	0.96
Education (Years)						
≤4	52.1	12.4		50.7	10.2	
5-8	29.1	35.6		35.6	32.5	
9-12	8.7	36.4		10.2	43.4	
>12	10.1	15.6	<0.01	3.5	13.9	<0.01
Mean (SD)	5.5 (4.5)	9.0 (3.7)		5.0 (3.5)	9.2 (3.5)	
Body Mass Index (kg/cm^2)						
<25	54.6	52.7		38.9	58.2	
25-29	32.1	36.5		27.7	25.1	
>29	11.0	9.9	0.01	31.7	15.9	<0.01
Missing	22 (2.3%)	15 (0.9%)		19 (1.7%)	13 (0.8%)	
Mean(SD)	25.0 (4.2)	25.0 (3.9)		27.6 (6.6)	25.1 (5.2)	
Hypertension						
No	30.8	47.5		26.3	49.6	
Yes	68.9	52.0	< 0.01	73.7	50.4	<0.01
Missing	3 (0.3%)	8 (0.5%)		1 (0.1%)	2 (0.1%)	
Smoking Status						
Non-current	42.9	44.5		85.0	75.5	
Current	57.1	55.5	0.27	15.0	24.5	<0.01
Total deaths (n), TRM**						
Lung	34	91	0.01	5	40	<0.01
Esophagus	12	5	0.01	3	2	0.38
Pancreas	5	7	0.80	6	8	0.87
Oral	0	6	0.05	1	0	0.23
Bladder	2	8	0.24	1	0	0.23
Larynx	1	1	0.73	0	0	N/A
Kidney	2	7	0.33	0	6	0.04
Stomach	12	2	<0.01	7	6	0.33
Acute Myeloid Leukemia	1	2	0.87	1	2	0.80
Cervix	N/A	N/A	N/A	5	5	0.55

*PY: Person-years; **TRM: tobacco-related malignancies.

associations was not statistically significant (*p* for race-by-smoking interaction=0.29). In ancillary analyses, cigarette smoking was positively associated with the risk of death from all TRM (including lung cancer) in all the race-gender categories; the associations were statistically significant for all the categories except the AA women (Table III). In both sexes, the association between smoking and death from all TRM was statistically significantly weaker in the blacks than whites.

Ancillary analyses of the CHS data indicated that on average the whites smoked more cigarettes per day than the blacks. When stratified by the number of cigarettes smoked per day, the association between smoking and death from TRM-nonLC was stronger in the whites than the blacks regardless of the numbers of cigarettes smoked per day (HR in AAs *versus* Caucasians for 1-10, 11-20, and >20 cigarettes per day: 1.1 *versus* 2.3; 1.5 *versus* 3.2 and 1.0 *versus* 5.4,

Table III. *Hazards ratios (and 95% confidence limits) for the associations between current-versus-non-current cigarette smoking and tobacco-related malignancies (A. excluding lung cancer, and B. including lung cancer) according to race and gender, pooled Evans County Heart Study and Charleston Heart Study cohorts.*

A. All tobacco-related malignancies other than lung cancer (TRM-nonLC)

	Males		Females	
	African Americans	European Americans	African Americans	European Americans
Age-adjusted	1.1 (0.6, 2.1)	3.4 (1.6, 7.3)	1.1 (0.4, 3.0)	2.3 (1.0, 5.1)
Fully-adjusted*	1.0 (0.5, 2.0)	3.6 (1.7, 7.6)	1.1 (0.4, 3.0)	2.7 (1.2, 6.2)

B. All tobacco-related malignancies (including lung cancer)

	Males		Females	
	African Americans	European Americans	African Americans	European Americans
Age-adjusted	2.3 (1.4, 4.0)	5.2 (3.3, 8.4)	1.5 (0.6, 3.5)	6.3 (3.7, 10.7)
Fully-adjusted*	2.2 (1.2, 3.8)	5.4 (3.4, 8.6)	1.4 (0.6, 3.4)	6.6 (3.8, 11.4)

*Fully-adjusted: age plus years of education, body mass index, and hypertension.

respectively). Among the CHS baseline current smokers, a larger proportion of the Caucasian males compared to the AA males (71% *versus* 56%) had quit smoking by follow-up between 1984 and 1990. The opposite trend was observed in the females with a smaller proportion of the Caucasians quitting smoking than the AAs (56% *versus* 70%).

Discussion

In a pooled study of two prospective cohort studies with more than 127,000 years of follow-up, we investigated the hypothesis that the association between cigarette smoking and risk of death from TRM-nonLC is greater in AAs than Caucasians. Contrary to our expectation, but in agreement with our previous lung cancer study (5), the results indicated that smoking was a strong risk factor for dying from TRM-nonLC in Caucasians but not among AAs.

We believe this is the first study to investigate the racial differences in the association between cigarette smoking and an index of combined TRM. The results from previous studies suggested a stronger association between smoking and risk of esophageal and oral pharyngeal cancer (6, 7, 10) in whites than blacks, which is consistent with the findings here. In contrast, prior studies of the other TRM (pancreatic, bladder, stomach, and cervical) tended to suggest that the association between smoking and risk of cancer may be stronger among AAs, particularly among AA men (8, 9, 11-16).

The present study had several limitations. The pooled analyses were limited to a comparison of current-*versus*-non-current smokers, leaving former smokers within the non-current smoker category along with never smokers. Smoking status also did not account for smoking duration or quantity (*e.g.*, pack years). The stronger association between cigarette smoking and risk of smoking-caused cancer death among the Caucasians in the present study may have at least partially been driven by greater smoking frequency, but when the CHS data was stratified by the number of cigarettes smoked per day, the risk of death from TRM-nonLC was still higher in the whites than the blacks.

The one-time baseline measurement of cigarette smoking could be problematic, particularly if the likelihood of quitting during follow-up differed by race. Whereas in 1965 the smoking prevalence was 3% higher in AAs than Caucasians, by 1993 smoking prevalence was 6% greater in AAs (27). Thus, rates of quitting were slightly higher among Caucasians during this time-period. The historical patterns and the data from the CHS among males suggested that any bias toward the null would likely be small and would be stronger for Caucasians than AAs. Additional limitations included using cancer mortality rather than incidence as the outcome, combining all nine TRM, a heterogeneous group of malignancies, into a single outcome, and even so having a limited number (n=126) of cancer deaths. Also various risk factors for TRM were not included in the analyses and these risk factors vary considerably across the cancer types. Thus, the study provided a novel, but relatively crude, examination of an important question, with inferences limited by a number of important considerations.

This investigation involved cohorts established in 1960 and from the southeastern United States and the observed associations may or may not pertain to other time-periods and/or places. Since the 1960s, the prevalence and patterns of cigarette smoking have changed substantially. For example, between 1965 and 1993, smoking prevalence decreased from 50% to 32% in men and 32% to 27% in women (27). The percentage of cigarettes smoked that yielded <15 mg of tar increased from 2% in 1967 to 87% in 1999 (28). Menthol cigarettes increased from 16% of the market in 1963 to 26% in 1999 (28). However, for example, no substantial evidence has documented whether or not menthol cigarettes change a smoker's risk of TRM as a whole, but the evidence clearly indicates that menthol cigarettes are not associated with greater risk of lung cancer than non-menthol cigarettes (29-32).

The present study is strengthened by the fact that it included two mature cohorts with a large proportion of AAs (39%), a high prevalence of current cigarette smoking (38%), and up to 40 years of follow-up. In these unique cohorts, cigarette smoking did not account for the racial disparity in mortality from TRM-nonLC. Further studies that include other known risk factors, a larger sample size, and more

detailed cigarette smoking data should be carried out to better understand the contribution of cigarette smoking to racial disparities in tobacco-related malignancies.

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Received July 26, 2011
Revised September 13, 2011
Accepted September 14, 2011