Smoking, Fibrinogen and Cancer Mortality

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Associations of race, smoking history and fibrinogen levels with cancer mortality were investigated prospectively using the ARIC study. Our cohort consisted of 14,320 participants aged 45–64 at baseline. In an adjusted Cox regression, black current heavy smokers (≥15 cigarettes per day) demonstrated higher risk of respiratory/intrathoracic organ cancer mortality than nonblack current heavy smokers. Black former heavy smokers were also found to be at an increased risk of respiratory/intrathoracic organ cancer mortality when compared to nonblack former heavy smokers. Elevated fibrinogen levels were associated with an increased risk of respiratory/intrathoracic organ cancer mortality. Compared to fibrinogen <259 mg/dl, fibrinogen 294–335 mg/dl had an adjusted hazard ratio of 3.68 (95% CI: 1.80–7.55), and fibrinogen ≥336 mg/dl had an adjusted hazard ratio of 3.78 (95% CI: 1.84–7.75). Fibrinogen was also a predictor of other types of cancer mortality among black participants, but not among nonblack participants. For 10 race/smoking history categories, fibrinogen levels ranged from a mean of 287 mg/dl for nonblack former light smokers to a mean of 338 mg/dl for black current heavy smokers. Smokers had higher fibrinogen levels than nonsmokers, and black smokers had higher fibrinogen levels than nonblack smokers. Smoking carries high risks of cancer mortality for African Americans. A factor that needs to be considered in the overall assessment of risk is fibrinogen level, which has been linked to angiogenesis and metastases of tumors.

Key words: smoking ■ fibrinogen ■ neoplasm

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INTRODUCTION

African Americans who smoke <30 cigarettes per day have been shown in one cohort study to have a higher risk of lung cancer than Caucasians who smoke a comparable number of cigarettes.[1] The results of a case-control study were different in that African Americans who smoked <21 cigarettes per day had no greater risk of lung cancer than Caucasians.[2] However, African-American males who smoked ≥21 cigarettes per day had more risk than Caucasian males who smoked the same number of cigarettes. The reasons for racial differences may be related to smoking behavior or physiology. The degree of inhalation influences the uptake of carcinogens, and African Americans have higher cotinine levels, a metabolite of nicotine measurable in the blood, than Caucasians who smoke the same number of cigarettes.[3] African Americans tend to prefer menthol brands, but most studies do not indicate that preference is related to lung cancer.[4] In this study, we evaluate the degree to which a physiological reason—that is, fibrinogen level—is responsible for racial differences in risk of cancer mortality attributed to smoking history.

Fibrinogen is a hemostatic factor that is important for tumor promotion of new blood vessel formation, a process known as angiogenesis.[5] In addition, fibrinogen is thought to influence metastatic potential.[6] Comparison of control and fibrinogen-deficient mice showed fibrinogen has an important role in sustained adhesion and survival of tumor cells within the lung.[7] Fibrinogen deficiency reduced the incidence of spontaneous macroscopic metastases in the lung and regional lymph nodes, and reduced pulmonary micrometastases.[8] Further study suggested that fibrinogen impedes natural killer cell elimination of tumor cells.[9]

Fibrinogen is known to be elevated in current smok-

ers compared to nonsmokers. In men, fibrinogen remained higher in former smokers than life-long nonsmokers for 15 years after they quit. In women, there was no relationship between fibrinogen and length of time of abstention.[10] African Americans are also known to have higher fibrinogen levels than Caucasians.[11] Therefore, the purpose of this study was to explore the relationship between fibrinogen levels, degree of smoking and cancer mortality risk among different races in a prospective cohort study.

METHODS

The Atherosclerosis Risk in Communities (ARIC) Study is a cohort of 15,792 participants aged 45–64, from four U.S. communities. The locations included were Forsyth County, NC; Jackson, MS (African Americans only), the suburbs of Minneapolis, MN; and Washington County, MD. In the public use data set, participants were classified as either nonblack or black. The nonblack participants were mostly Caucasians but included 14 American Indians and 34 Asian participants. The baseline examination (visit 1) was in 1986–1989, and follow-up examinations were in 1990–1992 (visit 2), 1993–1995 (visit 3) and 1996–1998 (visit 4). We conducted a longitudinal analysis using information from visit 1 to classify participants and then followed them to December 31, 1998.

We defined five smoking history categories using interview information from visit 1. Participants were first classified as never, former or current smokers. Former and current smokers were then further classified by response to the question: "On the average of the entire time you smoked, how many cigarettes did you usually smoke per day?" Heavy smokers were defined as those who had smoked ≥15 cigarettes per day, and light smokers as those who had smoked <15 cigarettes per day. We used a cut-off of 15 cigarettes per day to make our results comparable to Godtfredsen et al.[12] and because 15 cigarettes per day is close to the mean for former and current African-American smokers in the ARIC study.

Fibrinogen was measured in fasting (eight-hour) blood samples (obtained at visit 1) by the thrombin-time titration method, with reagents and reference materials (Fibriquick) obtained from General Diagnostics (Organon-Technika Co.).[13-15] Fibrinogen was analyzed both as a continuous variable and as quartiles of the cohort.

We used gender, age, body mass index (BMI), exercise and education as control variables. BMI was calculated from weight and height measurements as kg/m^2.

Table 1. Characteristics of participants by race/smoking category

				Current Smokers (%) / Number of Participants			
	Age First Smoked (Years)	Age Quit[1] (Years)	Fibrinogen (mg/dl)	Visit 1	Visit 2	Visit 3	Visit 4
Nonblack							
Never smokers	–	–	289[f2]	0% (4,242)[3]	0.2% (4,077)	0.1% (3,859)	0.1% (3,591)
Former light smokers	19.4[c]	36.1[a]	287[f]	0% (1,083)	5.3% (1,037)	3.2% (973)	2.7% (895)
Former heavy smokers	17.7[e]	41.4[a]	291[f]	0% (2,647)	4.9% (2,507)	4.2% (2,331)	3.9% (2115)
Current light smokers	21.9[a]	–	300[e]	100% (487)	78.8% (449)	58.8% (393)	47.6% (355)
Current heavy smokers	18.2[de]	–	322[c]	100% (2,045)	84.0% (1,825)	71.7% (1,555)	62.9% (1,346)
Black							
Never smokers	–	–	313[d]	0% (1,784)	1.1% (1,543)	1.4% (1,320)	1.1% (1,171)
Former light smokers	19.9[c]	40.4[a]	311[d]	0% (468)	5.2% (404)	3.1% (350)	2.0% (307)
Former heavy smokers	17.8[e]	42.9[a]	319[c]	0% (430)	7.5% (361)	6.0% (298)	4.1% (269)
Current light smokers	21.3[b]	–	328[b]	100% (541)	81.3% (439)	66.8% (367)	58.4% (303)
Current heavy smokers	18.6[d]	–	338[a]	100% (593)	85.6% (464)	75.8% (368)	68.2% (289)

1: Age that former smokers quit smoking; 2: Means within a column followed by the same letter are not significantly different (α=0.05). For example, black never smokers have significantly higher mean fibrinogen levels than nonblack never smokers; 3: Total number of participants, at each visit, in parentheses.

BMI was used as a control variable because women in the upper BMI quintile of the Iowa Women's Health Study have been shown to be at decreased risk of lung cancer.[16]

Exercise was characterized using a sports index derived from answers to a modified version of a questionnaire developed by Baecke et al.[17] The index was semicontinuous and ranged from 1 (low) to 5 (high). The sports index was a sum of the yearly frequency, weekly duration, and intensity (low, medium or high) of up to four self-reported sport activities plus answers to three additional questions about self-rated amount of leisure time activity compared with others of the same age, frequency of sweating and general frequency of sport play.[18] Exercise physiology research assistants used standard references to assign intensity codes to the types of sports or exercises.[19] Exercise was used as a control variable because leisure-time physical activity has been shown in a meta-analysis to decrease the risk of lung cancer.[20]

Education was classified as three categories: 1) ≤11 years of schooling, 2) high-school graduate or vocational school, and 3) college, graduate school or professional school. Education was used as a covariate because socioeconomic characteristics have been shown to be related to lung cancer, colorectal cancer and all-cancer mortality.[21,22]

To account for current smokers quitting at a later date, and former smokers who resumed smoking at a later date, we included the current number of cigarettes that a participant smoked per day as a time-dependent control variable. The current number of cigarettes smoked per day at visits 1–4 was used to create this variable. If a participant was not smoking at a particular visit, the value of this variable was 0 for that time interval.

Participants who died of cancer during the first three years following baseline were excluded from our analyses. These persons probably had undiagnosed cancer at visit 1. It is possible that fibrinogen levels at baseline were high in these participants due to their having undiagnosed cancer.

Our cohort consisted of 14,320 participants aged 45–64 at baseline. Events were classified as either mortality due to malignant neoplasm of respiratory and intrathoracic organs (International Classification of Diseases, 9th Revision codes 160–165) or other types of cancer mortality. We excluded from our cohort 873 participants who reported a previous diagnosis of cancer; 90 persons who died of cancer during the first three years following baseline; 300 participants missing fibrinogen tests; and 209 persons missing smoking, BMI, exercise or education variables. In addition to undergoing clinical examinations, participants were contacted annually to determine their follow-up status. Of the 14,320 persons in our cohort, 1,196 died before December 31, 1998. The remainder had a mean follow-up time of 10.4 years, with the minimum follow-up being six years.

We used the statistical package SAS® (Statistical Analysis System, Research Triangle Park, NC) for all analyses. Analysis of Variance (ANOVA) and Student-Newman-Keuls multiple-range test were used to test for differences in mean age first smoked, age stopped smoking and fibrinogen levels between race/smoking categories. Two types of adjusted Cox's regressions were performed. The first type included race, smoking categories, fibrinogen (per one standard deviation) and interactions of the three variables. In the case of respiratory/intrathoracic organ cancer mortality, there were no interactions, and we performed an additional adjusted Cox's regression with race/smoking categories and fibrinogen quartiles.

RESULTS

Characteristics of participants by race/smoking category are presented in Table 1. Mean age that participants first smoked ranged from 17.7–21.9, with heavy smokers having begun smoking at a younger age than light smokers. There were no significant differences in the mean age that former smokers quit smoking. Former smokers who did not smoke at visit 1 were unlikely to resume smoking at later examinations, but 7.5% of black former heavy smokers did resume smoking by visit 2.

Table 2. Adjusted Cox's regression using race, smoking history, fibrinogen and interactions to predict mortality due to malignant neoplasm of respiratory and intrathoracic organs[1]

	Hazard Ratio	95% CI	P
Race	1.53	0.04–58.08	0.82
Smoking[2]	2.12	1.16–3.84	0.01
Fibrinogen[3]	1.67	1.19–2.35	<0.01
Race X smoking	1.53	0.49–4.74	0.46
Fibrinogen X smoking	0.96	0.86–1.06	0.41
Race X fibrinogen	1.02	0.52–2.00	0.96
Race X fibrinogen X smoking	0.92	0.75–1.14	0.47

1: Adjusted for number of cigarettes smoked per day at most recent visit, gender, age, body mass index, exercise and education; 2: Smoking history in 5 categories; 3: Fibrinogen per 65 mg/dl (one standard deviation).

Fibrinogen levels varied by race and smoking status. Mean fibrinogen levels ranged from 287 mg/dl for nonblack former light smokers to 338 mg/dl for black current heavy smokers. Nonblack current smokers had significantly higher fibrinogen levels than nonblack nonsmokers, and black current smokers had higher fibrinogen levels than black nonsmokers. Black never smokers had significantly higher fibrinogen levels than nonblack never smokers. Differences due to race were also found for former light smokers, former heavy smokers, current light smokers and current heavy smokers, with blacks having higher fibrinogen levels than nonblacks in each comparison.

The results of the first adjusted Cox's regression for respiratory/intrathoracic organ cancer mortality are shown in Table 2. Fibrinogen was significant (HR 1.67, 95% CI: 1.19–2.35 per 65 mg/dl), and there were no interactions of fibrinogen with race or smoking (p>0.10). A similar analysis of all other types of cancer mortality showed a race x smoking interaction (p=0.06); therefore, we analyzed the races separately (Table 3). For nonblack participants, fibrinogen was not a significant predictor of cancer mortality other than respiratory/intrathoracic organ cancer mortality. For black participants, fibrinogen was a significant predictor of other types of cancer mortality (HR 1.43, 95% CI: 1.02–1.99 per 65 mg/dl). For both nonblack and black participants there was no fibrinogen x smoking interaction (p>0.10).

The results of the second adjusted Cox's regression for respiratory/intrathoracic organ cancer mortality are shown in Tables 4 and 5. Black current heavy smokers had the highest respiratory/intrathoracic organ cancer mortality rate (6.7 cases per 1,000 person-years) of any of the race/smoking categories evaluated. Nonblack current heavy smokers had significantly lower risk of respiratory/intrathoracic organ cancer mortality (HR 0.52, 95% CI: 0.32–0.87) than black current heavy smokers (Table 4). Nonblack former heavy smokers had significantly lower risk of respiratory/intrathoracic organ cancer mortality (HR 0.40, 95% CI: 0.20–0.82) than black former heavy smokers. For current light smokers, former light smoker and never smokers, there were no dif-

Table 3. Adjusted Cox's regressions using smoking history, fibrinogen and the interaction of the two to predict cancer mortality other than respiratory/intrathoracic organ cancer mortality, by race[1]

	Hazard Ratio	95% CI	P
Nonblack			
Smoking[2]	0.88	0.55–1.41	0.60
Fibrinogen[3]	1.08	0.85–1.37	0.55
Fibrinogen X smoking	1.05	0.95–1.15	0.34
Black			
Smoking[2]	1.90	0.97–3.74	0.06
Fibrinogen[3]	1.43	1.02–1.99	0.04
Fibrinogen X smoking	0.91	0.80–1.04	0.15

1: Adjusted for number of cigarettes smoked per day at most recent visit, gender, age, body mass index, exercise and education; 2: Smoking history in five categories; 3: Fibrinogen per 65 mg/dl (one standard deviation).

Table 4. Adjusted Cox's regression using race and smoking history to predict mortality due to malignant neoplasm of respiratory and intrathoracic organs[1]

	Hazard Ratio	95% CI	Cases per 1,000 Person-Years[2]
Nonblack			
Never smokers	0.05	0.02–0.14	0.1
Former light smokers	0.09	0.02–0.38	0.2
Former heavy smokers	0.38	0.20–0.72	1.3
Current light smokers	0.39	0.16–0.97	1.7
Current heavy smokers	0.52	0.32–0.87	3.5
Black			
Never smokers	0.09	0.02–0.30	0.2
Former light smokers	0.15	0.04–0.66	0.6
Former heavy smokers	0.93	0.44–1.96	4.1
Current light smokers	0.55	0.25–1.20	2.5
Current heavy smokers	1.00	–	6.7

1: Adjusted for number of cigarettes smoked per day at most recent visit, gender, age, body mass index, exercise, education and fibrinogen; 2: Calculated excluding the first three years of follow-up.

Table 5. Adjusted Cox's regression using fibrinogen to predict mortality due to malignant neoplasm of respiratory and intrathoracic organs[1]

	Hazard Ratio	95% CI	Cases per 1,000 Person-Years[2]
Fibrinogen (mg/dl)			
<259	1.00	–	0.4
259–293	1.59	0.71–3.55	0.7
294–335	3.68	1.80–7.55	2.0
≥336	3.78	1.84–7.75	2.4

1: Adjusted for number of cigarettes smoked per day at most recent visit, gender, age, body mass index, exercise, education and race/smoking history; 2: Calculated excluding the first three years of follow-up.

ferences due to race between comparable smoking categories. Black never smokers and black former light smokers had significantly less risk of respiratory/intrathoracic organ cancer mortality than black current heavy smokers.

Fibrinogen levels ≥294 mg/dl were significantly related to respiratory/intrathoracic organ cancer mortality, with fibrinogen 294–335 mg/dl having a hazard ratio of 3.68 (95% CI: 1.80–7.55) and fibrinogen ≥336 mg/dl having a hazard ratio of 3.78 (95% CI: 1.84–7.75) compared to fibrinogen <259 mg/dl (Table 5). While black participants have higher fibrinogen levels than nonblack participants, the proportion with fibrinogen <294 mg/dl ranged from 29.2–44.9%, indicating substantial variation in risk due to fibrinogen levels among black participants.

DISCUSSION

Our results were similar to Haiman et al.[1] and Stellman et al.[2] in that differences between black and nonblack participants were found; however, it should be noted that Haiman et al. and Stellman et al. looked specifically at lung cancer, and that our results apply to broader classes of cancer and to mortality and not morbidity. The fact that black former heavy smokers have higher risk of respiratory/intrathoracic organ cancer mortality than nonblack former heavy smokers is disturbing and leaves open the question of whether differences in past smoking behavior, susceptibility to carcinogens or treatment for cancer is responsible.[23]

Substantial risk of cancer mortality can be attributed to fibrinogen levels. The difference in mean fibrinogen values between nonblack never smokers and black never smokers is 24 mg/dl, or 8%. This racial difference in fibrinogen combined with the inherent risk of smoking raises the total cancer risk of many African-American smokers and former smokers to levels above that of Caucasian smokers and former smokers. Participants in this study who had ceased smoking for a mean of 11–18 years had 4–10% lower fibrinogen levels than their current smoking counterparts. For example, black former heavy smokers had mean fibrinogen levels 19 mg/dl lower than black current heavy smokers. A reduction in fibrinogen levels may be one mechanism by which smoking cessation reduces lung cancer risk. Fibrinogen may also present a potential target for chemotherapeutic and chemopreventive drugs, especially in African Americans.

CONCLUSIONS

Smoking carries high risks of cancer mortality for African Americans. A factor that needs to be considered in the overall assessment of risk is fibrinogen level, which has been linked to angiogenesis and metastases of tumors. Smokers have higher fibrinogen levels than nonsmokers, and black smokers have higher fibrinogen levels than nonblack smokers. High fibrinogen levels are an additional reason why African Americans should not smoke.

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