A Prospective Study of Plasma Selenoprotein P and Lung Cancer Risk Among Low-Income Adults

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Abstract

Background—Epidemiologic studies have shown increased risks of lung cancer among adults with low blood levels of selenium, although evidence is inconsistent. In the United States the incidence of lung cancer is higher and mean serum selenium levels lower among blacks than whites, but prior studies have not assessed the selenium-lung cancer association among blacks.

Methods—From the prospective Southern Community Cohort Study we identified 372 participants who provided blood samples and subsequently developed lung cancer. Selenoprotein P (SEPP1), the most abundant selenoprotein in plasma and a biomarker of selenium nutriture, was measured in the plasma from these individuals and from 716 matched controls.

Results—Mean SEPP1 levels were significantly ($P <0.0001$) lower among blacks than whites. Conditional logistic regression models accounting for smoking revealed a significant trend of increasing odds ratios (OR) of lung cancer with decreasing SEPP1 tertiles among blacks ($P =.0006$) but not whites ($P =.69$) (P for interaction $=.10$). The ORs and corresponding 95% confidence intervals (CI) of lung cancer risk among those with lowest vs highest tertile levels of SEPP1 were 2.4 (1.5–3.0) among blacks and 1.1 (0.6–2.1) among whites.

Conclusions—Among a mostly low-income population in the southeastern US, lower levels of SEPP1 were associated with an increasing risk of lung cancer among blacks but not whites.

Impact—The combined findings of higher prevalence of low selenium status and higher lung cancer risk associated with low status raise the possibility that selenium deficiency may contribute to observed racial disparities in lung cancer incidence.

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INTRODUCTION

A potential benefit of higher selenium status on the risk of lung cancer has been reported, although the evidence is mixed and the benefit appears to be primarily limited to populations in which selenium status is low (1-3). Within the United States, plasma selenium levels tend to be lower among residents of the southeast and among blacks than whites (4), but prior studies of lung cancer and selenium have not included sizeable numbers of southerners or blacks. Herein we assess whether lung cancer risk might be related to selenium status within the Southern Community Cohort Study (SCCS), a prospective cohort of low-income black and white adults in the southeastern United States.

MATERIALS AND METHODS

Study population

The SCCS is a prospective cohort study being conducted to evaluate factors in the onset, outcome and disparities in cancer and other chronic diseases. Details of the methods have been described elsewhere (5). In brief, during 2002-2009 adults were recruited from community health centers (CHCs) across a 12-state region (AL, AR, FL, GA, KY, LA, MS, NC, SC, TN, VA, WV). Since CHCs provide basic and preventative health care in underserved areas, most of the enrollees, two-thirds of whom reported themselves as black, were of low income (6). Eligible participants were 40 to 79 years of age, had not been under treatment for cancer for at least the past year, and were English speaking. Participants signed a consent form approved by the Institutional Review Boards of Meharry Medical College and Vanderbilt University before submitting to a comprehensive computer-assisted interview by a trained interviewer on demographics, anthropometry, medical history, diet, physical activity, use of tobacco, alcohol, medications, and other characteristics. Biologic specimens (blood, saliva, and/or urine samples) were provided by approximately 90% of the cohort participants recruited from the CHCs, with 54% providing a blood sample. The blood samples were collected in two 10-ml tubes, one with EDTA preservative, from non-fasting study subjects upon their entry into the cohort at the CHCs. The vast majority (>95%) of blood samples were processed at Vanderbilt within 24 hours of collection and all samples have been kept in frozen storage at −80°C. The blood components were separated into aliquots of serum, plasma, red blood cells, buffy coat, and clot. One plasma aliquot was retrieved for the selenium assay described below.

Lung cancer case identification

Cases for the present study include all individuals diagnosed with lung cancer (International Classification of Diseases-Oncology [ICD-O-3] codes C340-C349) after entry into the SCCS, who also donated a blood specimen at baseline. Incident cancers were identified through linkage with the state cancer registries in the study area and from National Death Index (NDI) mortality records, with approximately 13% identified only from NDI (ICD10

codes C33-C34). Utilizing these methods, we identified 396 cases for the current analyses. We then excluded those individuals who identified as neither black nor white (n=3) or were missing smoking data (n=9), reducing our case count to 384.

Control selection

Two controls for each case were selected from SCCS participants who donated blood at baseline and had not been diagnosed with lung cancer at the time of the index case's diagnosis. Controls were individually matched on race, sex, age at enrolment (+/− 2 years), date and place (CHC) of sample collection (+/− 6 months), and menopausal status for women. Controls were also excluded if race was reported as neither black nor white (n=6) or if missing smoking data (n=15). After removing the remaining individuals who were now in a matched set without one case and at least one control, the final study population for the present study consisted of 372 cases and 716 matched controls.

Selenoprotein P (SEPP1) assay

SEPP1 is an extracellular protein produced in many tissues but primarily by the liver. SEPP1 transports selenium from the liver to extrahepatic tissues and protects against oxidative injury. It has been suggested to be the most appropriate measure of selenium nutritional status in healthy persons (7-9). From stored plasma samples donated by the lung cancer cases and controls at entry into the SCCS, we measured SEPP1 by ELISA, with daily calibration through a standard curve using purified human SEPP1 at the Burk Vanderbilt laboratory (10). The matching of cases and controls was maintained in the assays, with individual cases and their matched controls being assayed simultaneously within batches.

Statistical analysis

Plasma levels of SEPP1 were categorized into tertiles based on the distribution in the cases and controls combined. The Mantel-Haenszel chi-square test was used to assess differences in baseline characteristics of study participants by tertile of SEPP1 level.

To compute odds ratios (ORs) and 95% confidence intervals (CIs) of the association of SEPP1 levels and lung cancer risk we used conditional logistic regression with matched case-control sets as the strata. To test for a linear trend across antibody tertile of SEPP1 levels, a continuous variable was created with the values of 0, 1, and 2 for the three tertiles. The potential confounders of cigarette smoking status, income, education, family history of lung cancer, and body mass index (BMI in units of kg/m^2) were considered. Only those associated with both the exposure and outcome in the data, and that affected the main association by 10% or more, were included in the adjusted models. This led to the inclusion of smoking status, represented in dummy variables comparing never smokers and former smokers to current smokers, and also the inclusion of the continuous variable of pack-years. Additional analyses dividing the population into five alternative smoking categories (never, former, current <10 cigarettes per day [cpd], current 10-19 cpd, and current 20 cpd) resulted in little difference in results and are not presented.

Effect modification by race and sex was evaluated by creating separate conditional logistic regression models for each category (black and white, and male and female, respectively),

and by evaluating the interaction term using the likelihood ratio test. Effect modification by smoking status was evaluated through separate models for current smokers versus non-current smokers, using unconditional logistic regression, as we did not have the power to examine this association among the minority of matched sets that were concordant for smoking status. The unconditional logistic regression analyses were then adjusted for the previous matching variables of age, race, and sex, in addition to pack-years of smoking. To test for effect modification by smoking, we performed multivariable-adjusted conditional logistic regression in the entire population, with the inclusion of an interaction variable representing current smoking and median SEPP1 trend variable, and assessed the strength of this interaction by the likelihood ratio test.

To minimize the potential of reverse causality – whereby illness itself decreases, or leads to lower, SEPP1 levels – we performed two additional sets of analyses. First, we compared differences in mean SEPP1 levels among the cases by stage at diagnosis (localized, regional, or distant cancer), and then re-performed the same conditional logistic regression as described above, excluding the 51% of cases (and their matched controls) with more severe (i.e., distant) disease. Secondly, we performed the same analyses in two sub-sets of the study population, the first excluding those cases and their matched controls diagnosed within one year of blood draw, and the second excluding those cases and their matched controls diagnosed within two years of blood draw, to see if the associations between SEPP1 and lung cancer risk changed with lengthening the average time interval between blood sampling and cancer diagnosis.

All statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

Comparing study participants by level of plasma SEPP1 in tertiles, blacks, women, younger individuals (40–49 years old), and individuals of normal weight (BMI of 18.3–24.9) were significantly more likely to be categorized in the lower third than whites, men, individuals over 50, and overweight and obese individuals respectively (Table 1). Mean SEPP1 levels were significantly lower among blacks than whites (5.02 vs. 5.45, $P<0.0001$). When the association between race and SEPP1 tertile was assessed via odds ratios, the crude ORs, relative to tertile 3 (T3), for decreasing SEPP1 tertiles 2 and 1 among blacks vs whites were 1.7 and 2.5, respectively, so that the blacks had two and one-half the odds of having SEPP1 levels in the lowest tertile (T1) than whites (data not shown).

Overall, decreasing levels of plasma SEPP1 were associated with an increasing risk of lung cancer among blacks (P for trend = 0.0006); the smoking-adjusted OR comparing those in the low vs. high tertiles (T1 vs. T3) of SEPP1 was 2.4 (95% CI = 1.5 to 3.0) (Table 2). This pattern was not seen among whites (P for trend = 0.69; OR comparing T1 vs T3 of 1.1 [95% CI = 0.6 to 2.1]), although the interaction terms of SEPP1 level and race did not quite reach significance (P for interaction = 0.10).

When examining the association of SEPP1 level and lung cancer risk by smoking status, the association appeared slightly stronger among non-current smokers (P for trend = 0.004; OR

comparing T1 vs. T3 of 2.6 [95% CI = 1.3 to 5.0]) than among current smokers (*P* for trend = 0.02; OR comparing T1 vs. T3 of 1.6 [95% CI = 1.0 to 2.3]) (Table 3).

To examine the possibility that the associations observed were due to reverse causality, as might happen if the development of lung cancer may decrease SEPP1 levels, we performed sensitivity analyses, comparing the entire population to the sub-group of cases (and their matched controls) whose diagnoses came at least one year or two years after blood draw (Supplementary Table 1). The trend of increasing risk of lung cancer with decreasing SEPP1 tertile persisted among blacks (*P* for trend = 0.01; OR comparing T1 vs. T3 of 2.1 [95% CI = 1.2 to 3.7]) after excluding cases and their matched controls diagnosed within two years of SCCS entry. However, the exclusions among whites resulted in a more similar pattern between blacks and whites (for whites, excluding cases and their matched controls diagnosed within two years of SCCS entry, OR comparing T1 vs. T3, 1.5 [95% CI = 0.7 to 3.4]). Additionally, we examined the association of SEPP1 levels and lung cancer risk excluding the 51% of cases and their matched controls with distally metastasized cancer (Supplementary Table 2). The associations remained essentially unchanged for blacks, but the black-white difference was again diminished.

DISCUSSION

In this population of primarily low-income blacks and whites in the southeast United States, low SEPP1 levels were associated with increased risk of lung cancer, with the effect seen primarily among blacks, whose odds of having low SEPP1 tertile levels were more than twice as high than for whites. As SEPP1 has been suggested to be the most sensitive predictor of selenium nutritional status (9), the present study supports and is consistent with the previous literature on selenium and lung cancer, for which the majority of studies find elevated risks among those with low selenium blood levels, particularly for populations where overall selenium nutriture is low (1,2). This is the first investigation, however, to include substantial numbers of blacks, the first conducted across a broad area of the southeast where soil selenium availability tends to be lower than in other regions of the United States, as well as the first to assess SEPP1 as the selenium biomarker, in lung cancer risk. The findings of lower selenium status among blacks than whites, combined with an apparently stronger link to lung cancer risk among blacks than whites, raise the possibility that low selenium status may contribute to the higher incidence and mortality among black than white American men even though total tobacco consumption is lower among blacks (11-13). This hypothesis is particularly supported in our population, where black lung cancer cases had accumulated on average one-third lower the amount of pack years than white lung cancer cases at baseline (means of 30.2 and 51.7, respectively).

The association between risk of lung cancer and selenium intake and/or status appears to be complex, with our and other data pointing towards an elevated risk among those of low selenium nutriture. The dose-response relation appears to be nonlinear, however, possibly best described by a U-shaped curve with declining lung cancer risk as selenium deficiencies are corrected but flattening and then rising lung cancer incidence at the highest selenium levels (1-3). The study subjects in the SCCS, particularly blacks, tend to be in the low to middle portions of such a curve, likely enhancing our ability to show a significant

association with higher lung cancer risk among those with the lowest selenium status. Ours is the first study to suggest a potentially greater impact of low selenium status on blacks than whites, thus caution is required in interpretation of the racial differential, especially since there was some diminution of the black-white difference when cases diagnosed within two years of cohort entry were excluded from the analysis. Nevertheless, the difference between SEPP1 levels in blacks and whites was striking, with low levels considerably more prevalent among blacks than whites. Prior research using NHANES assays of serum selenium (not SEPP1) have revealed lower mean levels among blacks than whites nationally (4). Within an independent sample of over 380 SCCS study subjects, we also have found mean plasma selenium levels to be lower among blacks than whites, but the differential for elemental selenium was not as great as the differential for SEPP1, suggesting that the selenoprotein may be a stronger distinguisher of racial differences in selenium status (14).

Findings from observational studies such as ours are subject to the potential influences of bias, confounding and chance, although confounding by socioeconomic and health care status that has afflicted many black-white comparisons is minimized by the design of the SCCS, where both blacks and whites are of very similar, mostly low, education and income and where all study subjects were recruited across similar health care settings at community health centers. Randomized trials tend to avoid such shortcomings. Three intervention trials have investigated the potential protective effect of selenium supplementation on the primary prevention of lung cancer. In the Nutritional Prevention of Cancer trial, conducted in a population of approximately 1,300 adults selected because of residence in areas of the eastern United States with low-selenium levels, initial findings after an average of 4.5 years of follow-up found that individuals receiving the selenium supplement (200 μg/d Se as selenized yeast) had a 44% reduction in risk of lung cancer (HR = 0.56; 95% CI = 0.31 to 1.01) (15). In an update of the findings, after an average of 7.9 years of follow-up, the lower risk for the intervention group was attenuated and became not significant (HR = 0.74; 95% CI = 0.44 to 1.24), but a sub-group analysis found that selenium supplementation was associated with decreased risk of lung cancer among individuals in the lowest tertile of baseline plasma selenium (HR = 0.42; 95% CI = 0.18 to 0.96) (16). Similarly, in a trial of nearly 30,000 adults in Linxian China, an area endemic for esophageal cancer where selenium status is low, supplementation with a combination of selenium (50 μg/d Se as selenized yeast), beta carotene and alpha tocopherol was associated with a lower risk of incident lung cancer during the 5 years of supplementation (HR = 0.55 [95% CI = 0.26 to 1.14]) that was not observed in a post-trial 10-year follow up (overall 15-year HR = 0.98 [95% CI = 0.71 to 1.35]) (17-20). Finally, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) trial of over 35,000 American men with relatively high baseline serum selenium status showed no lung cancer benefit from selenium supplementation (200 μg/d as L-selenomethionine) alone or in combination with vitamin E (HR = 1.12 [95% CI = 0.73 to 1.72] for selenium alone and HR = 1.16 [95% CI= 0.76 to 1.78] for selenium plus vitamin E) (21). Hence the randomized trial data cannot rule in or out a modest impact of selenium supplementation on lung cancer risk, but tend to be consistent with a potential near-term benefit when the supplements correct mild selenium deficiencies and no benefit (or a slight increase) in lung cancer risk when the supplements are provided to fully selenium nourished

groups. None of the trials enabled adequate assessment of selenium supplementation among blacks.

This cohort study of lung cancer in relation to SEPP1 has a number of strengths and weaknesses which temper interpretation of the findings. Limitations include the modest total number of 372 lung cancer cases, with only one third among whites, limiting subgroup analyses, the relatively short follow up (maximum 9 years) of the cohort precluding precise evaluation of ORs across groups defined by time since blood draw, the one-time collection of blood specimens at cohort entry, population coverage primarily limited to low-income adults, and the lack of data on this population on genetic variants associated with selenium of SEPP1 metabolism. While only 50% of our cases were known adenocarcinomas or squamous cell cancers, when examining the race-specific SEPP1 association with lung cancer separately for these two histologies, we found no appreciable differences from the main findings (data not shown). Additionally, lung cancer cases in the current study are a sub-set of all lung cancer cases in the SCCS, as we could only include those individuals who donated a blood specimen at baseline. However, the demographic and socio-economic characteristics of cases in the current study are generally representative of the cases in the SCCS overall, although the cases in the present study were more likely to be white (35% vs. 30%) but less likely to both have a family income of $15,000 or more (28% vs. 34%) or to have achieved a high school education or more (50% vs. 58%) than the average SCCS lung cancer case. Strengths are more numerous and include the well-characterized underlying SCCS population with large numbers of blacks and whites with very similar backgrounds enhancing the internal validity of black-white comparisons, the prospective follow up and systematic ascertainment of lung cancer cases avoiding problems inherent in case-control studies, the selection of SCCS participants closely matched on demographic as well as blood collection factors as controls, and the novel measurement of SEPP1, the major selenium protein and a potentially promising biomarker. While the limitations of observational studies such as ours preclude making etiologic inferences, the findings are suggestive of a potentially greater impact upon lung cancer risk of low selenium status among blacks than whites and warrant additional investigation to confirm whether the patterns seen in this southeastern underserved population may exist more broadly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Characteristics of study subjects by selenoprotein-P (SEPP1) level

	Tertile 1		Tertile 2		Tertile 3	
	N	%	N	%	N	%
SEPP1 level, mean (range), mg/L	4.11 (1.5-4.7)		5.13 (4.8-5.5)		6.32 (5.6-10.1)	
Race*						
Black	282	39.8	232	32.8	194	27.4
White	97	25.5	116	30.5	167	44.0
Sex**						
Male	194	31.6	192	31.3	228	37.1
Female	185	39.0	153	32.9	133	28.1
Age**						
40 – 49	108	40.0	91	33.7	71	26.3
50 – 59	154	33.6	157	34.3	147	32.1
60 – 79	117	32.5	100	27.8	143	39.7
Education						
<High school	167	34.0	141	28.7	183	37.3
High school	136	35.1	143	36.9	109	28.1
>High school	76	36.4	64	30.6	69	33.0
Household income						
<$15,000	239	33.2	246	34.1	236	32.7
$15,000 – <$25,000	100	42.4	64	27.1	72	30.5
$25,000 – <$50,000	32	33.3	26	27.1	38	39.6
$50,000	5	21.7	9	39.1	9	39.1
Cigarette smoking status						
Never smoker	83	36.9	80	35.6	62	27.6
Former smoker	79	30.3	72	27.6	110	42.2
Current smoker	217	36.1	196	32.6	189	31.4
Body mass index**						
24.9	147	39.1	138	36.7	91	24.2
25.0 – 29.9	101	31.1	95	29.2	129	39.7
30.0	129	34.0	110	29.0	140	36.9

*
P<0.0001 comparing individuals by SEPP1 level in tertiles

**
P<0.05 comparing individuals by SEPP1 level in tertiles

Table 2

Association of selenoprotein-P (SEPP1) tertiles with lung cancer risk

	Cases (n)	Controls (n)	OR1	95% CI	OR2	95% CI
Blacks						
Tertile 1	112	170	**2.20**	**1.42, 3.40**	**2.42**	**1.48, 2.95**
Tertile 2	80	149	**1.78**	**1.15, 2.74**	**1.91**	**1.17, 3.12**
Tertile 3	48	146	1.00	ref	1.00	ref
P for trend				**0.0005**		**0.0006**
Whites						
Tertile 1	36	61	1.21	0.70, 2.10	1.13	0.60, 2.12
Tertile 2	39	77	1.04	0.62, 1.74	1.16	0.65, 2.08
Tertile 3	54	113	1.00	ref	1.00	ref
P for trend				0.50		0.69

NOTE: bold indicates statistically significant at $P < 0.05$.

Abbreviations: OR1, odds ratio from a conditional logistic regression model with no additional adjustment; OR2, odds ratio from a conditional logistic regression model additionally adjusted for smoking in dummy variables (comparing never smokers and former smokers to current smokers) and the continuous variable of pack-years ; CI, confidence interval

Table 3

Association of selenoprotein-P (SEPP1) tertiles with risk of lung cancer, stratified by smoking status

	Cases (n)	Controls (n)	OR[a]	95% CI
Current smokers				
Tertile 1	106	111	**1.56**	**1.03, 2.34**
Tertile 2	97	99	**1.71**	**1.13, 2.59**
Tertile 3	72	117	1.00	ref
P for trend				**0.02**
Not current smokers				
Tertile 1	42	120	**2.58**	**1.34, 4.98**
Tertile 2	25	127	1.49	0.75, 2.97
Tertile 3	30	142	1.00	ref
P for trend				**0.004**

NOTE: bold indicates statistically significant at *P* < 0.05.

Abbreviations: OR, odds ratio; CI, confidence interval

[a] unconditional logistic regression, adjusting for age, race, sex, and pack-years of smoking (for current and former smokers only