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Obesity in relation to lung cancer incidence in African American women

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Abstract

Purpose—Although a number of studies have found an inverse association between body mass index (BMI) and risk of lung cancer, there is little information on this relation in African Americans, who experience a higher incidence of lung cancer.

Methods—We assessed the relation of BMI to incidence of lung cancer in the Black Women's Health Study, an ongoing prospective follow-up of 59,000 women in the United States. Cox proportional hazard models were used to estimate hazard ratios for various levels of BMI relative to BMI 18.5–24.9 kg/m^2 ("normal weight") with adjustment for age, education, pack-years of smoking, and other covariates. Two other anthropometric measures, waist circumference (WC) and waist/hip ratio (WHR) were also assessed. A total of 323 primary lung cancer cases were identified from 1995 to 2011.

Results—The hazard ratio (HR) for BMI ≥30 relative to BMI 18.5–24.9 was 0.69 (95% confidence interval 0.51–0.92). As expected, cigarette smoking was strongly associated with increased risk of lung cancer. In analyses stratified by smoking status, the HR for BMI ≥30 relative to BMI 18.5–24.9 was 0.62 (0.38–1.00) among current smokers, 0.90 (0.56–1.42) among former smokers, and 0.83 (0.41–1.70) among never smokers (p for interaction= 0.28). Control for pack-years of smoking or age started smoking had little effect on the hazard ratios. WC and WHR were not materially associated with lung cancer risk.

Conclusion—Our results indicate that high BMI is associated with a lower risk of lung cancer in African American women, particularly among current smokers.

Introduction

Cigarette smoking is the primary risk factor for lung cancer.[1,2] Long-term smokers experience a 10- to 20-fold risk of developing lung cancer compared to never smokers.[3,4] Although African Americans tend to smoke fewer cigarettes per day than white men and women in the United States (U.S.), they have a higher incidence of lung cancer.[5–7] This disparity is hypothesized to be due to racial differences in metabolism of tobacco carcinogens.[8,9]

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Conflict of interest
The authors declare that they have no conflict of interest.

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Overall obesity, as measured by body mass index (weight in kilograms/height in square meters ≥30), is associated with increased risk of several cancers,[10,11] but has been associated with a reduced risk of lung cancer in several epidemiologic studies.[12–14] The findings may be due to confounding by cigarette smoking, as smokers tend to be thinner on average than non-smokers.[15,16] A recent report from the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study, a cohort study of 617,119 adults, suggest that the observed association may be independent of smoking effects.[14] The study also found the association to be stronger among women than men. Some studies have also assessed waist circumference (WC) and waist-hip ratio (WHR), which are measures of central obesity, with inconsistent results.[15,17–19]

There is little information on the relation of obesity to lung cancer among African Americans specifically.[20] Using data from the Black Women's Health Study, a large ongoing prospective cohort study, we evaluated the relation of obesity to lung cancer incidence among African American women, overall and separately among smokers and nonsmokers.

Methods

In 1995, 59,000 African American women from across the U.S. enrolled in the Black Women's Health Study (BWHS) by completing mailed health questionnaires. The women are followed through biennial health questionnaires, with 80% follow-up of the original cohort through the most recent completed questionnaire cycle. The study protocol was approved by the Boston University Medical Center Institutional Review Board and is reviewed annually.

The baseline questionnaire collected data on age, height, weight, waist circumference, hip circumference, cigarette smoking, and many other factors, including place of residence, years of education, alcohol consumption, number of births, age at first birth, physical activity, and family history of cancer. Biennial follow-up questionnaires provided data on new cancer diagnoses and updated information on weight, cigarette smoking, and other factors.

Data on cigarette smoking at baseline included age started smoking, number of cigarettes smoked per day, duration of smoking, and interval since last smoked for ex-smokers. Follow-up questionnaires asked about current smoking status and number of cigarettes smoked per day. Based on data from 1,172 women who returned duplicate questionnaires in 1997, the weighted kappa for category of number of cigarettes smoked per day reported in the two questionnaires was 0.83. Pack-years of smoking were calculated by multiplying the number of cigarettes per day by the number of years smoked and dividing the product by 20.

Self-reported weight and height at baseline were used to calculate BMI (weight in kilograms divided by squared height in meters). BMI was categorized as <18.5 kg/m^2 (underweight), 18.5–24.9 kg/m^2 (normal weight), 25.0–29.9 kg/m^2 (overweight) and 30.0+ kg/m^2 (obese). Self-reported waist circumference (WC), measured in inches, was categorized into quintiles: <28, 28–29, 30–32, 33–36, 37+. Waist and hip circumference at baseline were used to calculate waist-hip ratio (WHR; waist circumference in inches divided by hip circumference in inches). WHR was categorized into quintiles: <0.71, 0.71–0.75, 0.76–0.80, 0.81–0.86, 0.87+. In a validation study of 115 BWHS participants conducted in 2001–2002, the Spearman correlation was 0.93 for technician-measured height with self-reported height from the 2001 questionnaire; 0.97 for measured weight with self-reported weight from the 2001 questionnaire; 0.75 for measured waist circumference with self-reported waist circumference from the 1995 questionnaire; and 0.74 for measured hip circumference with self-reported hip circumference from the 1995 questionnaire.[21,22]

The present analyses included follow-up through 2011. Participants were excluded from analysis if they reported lung cancer at baseline (N=72), were pregnant at baseline (N=1,024), had missing data on smoking status (N=108) or height or weight at baseline (N=768), or had a BMI of less than 15 or more than 60 (N=85), leaving 56,944 women for the present analyses.

Medical records and/or cancer registry data were obtained for women who reported lung cancer during follow-up and were reviewed by the study oncologist (M.C.). After exclusion of lung cancer cases that were metastases from other sites (N=49), disconfirmed (N=7), or that could not be confirmed as a primary cancer (N=53), 323 incident cases of primary lung cancer were available for analysis, of which 103 were identified through death certificate data on date of diagnosis and underlying cause of death. Histology data were available for 222 cases, of which 47% were adenocarcinoma, 15% were squamous cell, 9% were small cell, 4% were large cell, and 25% were other or unspecified type.

Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of cigarette smoking and body size with lung cancer incidence. Women contributed person-time to the analyses from 1995 until a diagnosis of lung cancer, death, loss to follow-up, or 2011, whichever came first. Age-adjusted HRs were estimated from models with stratification by age in one-year intervals. Multivariable HRs further adjusted for years of education (≤12, 13–15, 16+), vigorous physical activity (none, <5, ≥5 hours/week), current alcohol consumption (<1, 1–6, ≥7 drinks/week), parity (0, 1, 2, 3+ births), age at first birth (<20, 20–24, 25+ years old), family history of lung cancer, and region (Northeast, South, Midwest, West). Analyses of body size also controlled for smoking (never smoker, <10, 10–19, 20–29, 30–39, 40+ pack-years). Cigarette smoking and all covariates that changed over time were treated as time-dependent variables and were updated during follow-up with use of the Andersen-Gill data structure.[23] To test for trend across categories of exposure, we included an ordinal term in the regression. Interactions of smoking with body mass index were tested by the likelihood ratio test, comparing models with and without interaction terms. SAS version 9.2 (SAS Institute Inc., Cary, NC) was used for the analyses.

Results

As shown in Table 1, women who had a BMI of 30 or greater at baseline in 1995 were older, had fewer years of education, were less likely to exercise, were less likely to live in the West, and were more likely to smoke 15 or more cigarettes a day and to have started smoking before age 18 as compared with women with BMI 18.5–24.9. Relative to women who were never smokers at baseline in 1995 (Table 1), women who had smoked for 20 or more pack-years had completed fewer years of education, consumed more alcoholic drinks per week, were more likely to have a family member with lung cancer, and were less likely to live in the South.

As expected, cigarette smoking was associated with an increased incidence of lung cancer (Table 2). Incidence increased with increasing number of pack-years of smoking to a HR of 16.9 (95% CI 11.1–25.7) for ≥40 pack-years relative to never smoking.

As shown in Table 3, high body mass index was associated with a reduced incidence of lung cancer: the multivariable HR for BMI ≥30 relative to BMI 18.5–24.9 was 0.69 (95% CI 0.51–0.92). A similar association with BMI was observed for the most common histologic subtype, adenocarcinoma, with a multivariable HR of 0.56 (95% CI 0.33–0.97). Based on 9 exposed cases, the HR for very low BMI (<18.5 kg/m^2) was 2.70 (95% CI 1.36–5.42). Associations were essentially unchanged with further adjustment for WC or WHR (data not shown).

Table 4 presents analyses of BMI in relation to lung cancer stratified by smoking status. The HR for BMI ≥30 relative to BMI 18.5–24.9 was 0.62 (95% CI 0.38–1.00; p trend<0.01) among current smokers; 0.90 (95% CI 0.56–1.42; p trend=0.06) among past smokers; and 0.83 (95% CI 0.41–1.70; p trend=0.23) among never smokers. The interaction of smoking with BMI was not statistically significant (p=0.28).

The HR for the highest quintile of WC (37+ inches) compared to the lowest quintile of WC (<28 inches) was 0.64 (95% CI 0.44–0.94, p trend =0.01, after control for confounding variables other than BMI (Table 5). After control for BMI, the estimate was 0.85 (95% CI 0.54–2.35) and p trend was 0.23. In age-adjusted analyses, the HR for the highest quintile of WHR (0.87+) versus the lowest (<0.71) was 1.51 (95% CI 1.03–2.21) and the p-value for trend across quintiles was 0.07 (Table 5). In multivariable models, the HR for highest versus lowest quintile of WHR was reduced to 1.27 (95% CI 0.86–1.87), with p trend = 0.39. Most of the change was due to control for cigarette smoking, as smokers tend to have a higher WHR: 26.1% of current smokers, 20.5% of former smokers, and 18.4% of never smokers were in the highest WHR quintile. In analyses of WC and WHR within strata of cigarette smoking, there were no significant trends for risk of lung cancer to decrease or increase with increasing WC or WHR (data not shown).

In a sensitivity analysis that excluded the 1,482 participants with a prevalent cancer at baseline, results were closely similar to those already presented. In another analysis that excluded 103 lung cases with missing histologic data, the results were also unchanged.

Discussion

The present results indicate that obesity is associated with a reduced incidence of primary lung cancer, at least among current smokers and possibly among past smokers and never smokers as well. Although we cannot rule out an effect of uncontrolled confounding by cigarette smoking on the association of BMI with lung cancer risk, control for duration and intensity of smoking resulted in little change in the HRs.

Since the 1950s, an overwhelming body of evidence has established a causal link between cigarette smoking and lung cancer risk.[24] Cigarette smoking has been shown to be an independent risk factor for lung cancer in all populations studied, including African Americans.[1,3,5,25–33] The present findings of a greatly increased risk of lung cancer in African American women who smoke are in agreement with previous findings.[34]

Our finding of an inverse association between BMI and risk of incident lung cancer in women is similar to results from several other studies.[17,35] A meta-analysis of the subject, which included 6 studies in women and 11 in men, estimated that each 5 kg/m^2 increase in BMI led to a 20% decreased risk of lung cancer in women and a 24% decreased risk in men.[10] Subsequent to the meta-analysis, an Austrian cohort of 145,931 adults reported a decrease in risk of lung cancer with increasing BMI, with similar HRs for men and women.[36] In a Japanese cohort of 27,539 adults, there was a decrease in lung cancer risk for obese men compared to normal weight men and an increase in risk for obese women compared to normal weight women.[37]

A number of studies have assessed the relation of BMI to lung cancer risk within categories of smoking status, with several finding an inverse association among current smokers and a weaker association among past or never smokers.[10,12,14,38,39,18,20] In the BWHS, the

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association of BMI with risk was strongest among current smokers. The meta-analysis, with 5 studies that had results stratified by smoking, estimated a 24% decreased risk of lung cancer in association with a 5 kg/m^2 increase in BMI among smokers and no association among non-smokers.[10] The NIH-AARP Diet and Health Study observed a decreased risk for men and women per unit increase in BMI among current smokers and a weaker inverse association among former and never smokers.[14] In the Women's Health Initiative, a cohort of 161,809 women, an inverse association was observed among current smokers and a weaker trend was observed in former smokers.[18] In the Canadian National Breast Screening Study, a cohort of 89,835 women, there was evidence for inverse associations between BMI and lung cancer in current smokers and in former smokers, but not in never-smokers.[12] In the Singapore Chinese Health Study, a cohort of 63,257 participants, an inverse trend for BMI was observed among current smokers.[38] In a U.S. case-control study, an inverse association of BMI with lung cancer risk in men was observed among current and former smokers, but not among never smokers.[20] Among women, the inverse association was observed across all categories of smoking status. Other studies have not observed inverse associations. A matched case-control study in New York state found a significant positive relation of high BMI to risk of lung cancer overall and in former smokers.[39] The association was similar for men and women. In a cohort of 1,213,829 Korean men and women, there was a lower risk of lung cancer among non-smoking obese men compared to non-smoking normal weight men and an increased risk of lung cancer among smoking obese men compared to smoking normal weight men; there were too few female smokers to assess the corresponding associations among women.[40]

With regard to WC, there was no evidence in the present study of an association with lung cancer risk. Previous findings are mixed. In the Women's Health Initiative, there was a non-significant inverse association between WC and lung cancer in the multivariable model; however, this association became positive, while remaining non-significant, with further control for BMI.[18] Among former smokers, WC was significantly associated with lung cancer risk.[18] In the Iowa Women's Health Study, high WC had a non-significant inverse association in the multivariable model in an early follow-up of the cohort, while a longer follow-up found a significant positive relation with lung cancer.[17,19] When stratified by smoking status, the positive association was significant among current smokers. A non-significant inverse association with WC was observed for adenocarcinoma, while a positive association with WC was observed for squamous cell lung cancer.[19] Due to sample size, we were unable to undertake a stratified analysis by histologic subtype. Previous studies suggest that WHR may not act as an independent risk factor for lung cancer.[15,17–19] Two of these studies observed a positive association in age-adjusted models that was not significant after adjustment for covariates.[18,19] Our results are compatible with these findings. We and others found that current smokers were more likely to have a higher WHR.[41] This finding would explain why controlling for smoking reduced the HRs for the association of higher WHR with risk of lung cancer.

There may be a biological basis for an inverse association of obesity with lung cancer risk. A potential mechanism for our observed association is through the relationship between obesity and endogenous estrogens. In postmenopausal women, adipose tissue is the primary site for estrogen synthesis and the formation of estrogen is not regulated by hormonal feedback mechanisms.[42–44] Indeed, several studies have found a positive association between BMI and serum estrogen levels in postmenopausal women.[43–45] Estrogen receptors have been found in both normal and tumorous lung tissue.[46,47] Smith et al hypothesized that estrogen compounds may out-compete carcinogenic aromatic hydrocarbons from cigarette smoke for estrogen receptors in lung tissue, thereby reducing exposure at the target tissues.[14] Another possible explanation is that obesity, by altering the distribution of ventilation within the lungs,[48] may alter the exposure of different lung regions to tobacco smoke in a manner that influences cancer risk.

Our analysis was limited by the sample size of cases, which prevented assessment of obesity in relation to histologic subtypes of lung cancer other than adenocarcinoma. Height, weight, waist circumference, and hip circumference were self-reported. A validation study conducted in 2001–2002 on a sample of BWHS participants showed a high degree of accuracy in self-reported weight and height, and less accurate but still good reporting of waist and hip circumference.[21,22] Errors in reporting weight, height, and waist and hip circumferences, and the tendency of heavier women to underreport their body size would have tended to bias the estimates towards the null.[49] Nevertheless, we observed the expected association of risk of type 2 diabetes with obesity in these data.[50] Residual confounding from smoking and other risk factors could have contributed to the observed inverse association of BMI with lung cancer incidence.[51]

Our study also has a number of strengths. The prospective nature of data collection in the Black Women's Health Study, a longitudinal cohort study, obviates reporting bias. Retention of the cohort was high, limiting potential bias due to selective losses. We were able to assess and control for pack-years of smoking with updated data throughout follow-up, whereas some other studies had to rely on baseline data on this important covariate. We did not include underweight women in the reference category for the BMI analyses, because their weight may have reflected illness. Lastly, other studies of BMI and lung cancer did not present data for African American women. Our study focuses on these women, who have a high prevalence of obesity compared to U.S. white women.

In conclusion, our findings suggest that obesity is associated with a decreased risk of incident lung cancer in African American women, particularly among current smokers. Further research should be aimed at elucidating the mechanisms by which obesity may reduce risk and understanding why the effect is most notable in smokers.

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Table 1

Body mass index and pack-years of smoking according to baseline characteristics (age-standardized[a]) among 56,835 women in the Black Women's Health Study, 1995–2011

	Body mass index			Pack-years of smoking		
	18.5–24.9 (N=20,843)	25–29 (N=17,953)	≥30 (N=17,162)	Never smoker (N=36,621)	<20 (N=15,186)	≥20 (N=4,024)
Age in 1995, mean	36.5	40.8	40.9	37.0	41.4	48.5
Education, 16+ yrs, %	51	43	38	49	36	33
Vigorous exercise, 5+ hr/wk, %	17	14	8	13	13	13
Alcoholic drinks, 7+/wk, %	6	6	6	3	11	11
Family history of lung cancer, %	7	8	8	7	8	11
Geographic region						
Northeast, %	27	27	27	25	32	36
South, %	30	31	31	33	26	26
Midwest, %	22	24	25	23	24	22
West, %	21	18	17	19	18	16
Body mass index, 30+, %				28	30	30
Pack-years of smoking, 20+, %	7	7	7			
Smoked 15+ cigarettes/day, %	11	12	13	0	18	99
Started smoking at age <18, %	13	15	15	0	39	63
Current smokers, %	17	18	16	0	47	65
Former smokers, %	17	20	22	0	53	35

[a] Values are standardized to the age distribution of the study population

Table 2

Cigarette smoking in relation to incidence of lung cancer among 56,835 women in the Black Women's Health Study, 1995–2011[a]

			Age-adjusted		Multivariable[b]	
	No. of Cases	Person-years	HR	(95% CI)	HR	(95% CI)
Never smoker	46	504,685	1.00		1.00	
Smoking status						
Former smoker	140	175,421	4.68	(3.34–6.56)	2.40	(1.57–3.68)
Current smoker	137	109,004	11.94	(8.53–16.71)	4.42	(2.79–6.99)
Pack-years						
<10	43	138,675	2.91	(1.92–4.42)	2.77	(1.82–4.22)
10–19	70	69,595	7.01	(4.79–10.25)	6.35	(4.32–9.35)
20–29	34	28,928	8.24	(5.24–12.95)	7.50	(4.76–11.84)
30–39	62	19,346	14.86	(9.99–22.11)	13.19	(8.81–19.74)
40+	52	12,586	18.95	(12.54–28.62)	16.92	(11.13–25.71)
p for trend				<0.01		<0.01
Cigarettes per day						
<5	36	83,408	3.48	(2.24–5.40)	3.27	(2.10–5.09)
5–14	108	115,373	7.02	(4.95–9.96)	6.30	(4.42–8.99)
15–24	86	58,373	9.21	(6.40–13.26)	8.29	(5.73–11.99)
25+	44	21,927	11.22	(7.36–17.08)	10.14	(6.63–15.51)
p for trend				<0.01		<0.01
Age started smoking						
<16	79	51,889	14.20	(9.85–20.47)	5.09	(3.15–8.25)
16–17	65	56,260	8.95	(6.12–13.09)	3.66	(2.26–5.92)
18–19	65	73,491	5.80	(3.96–8.49)	2.78	(1.74–4.45)
20+	62	90,301	3.92	(2.66–5.76)	2.06	(1.30–3.28)
p for trend				<0.01		0.10

[a]Abbreviations: HR=Hazard Ratio, CI=Confidence Interval

[b]Adjusted for age, education, physical activity, alcohol consumption, parity, age at first birth, family history of lung cancer, and geographic region. Models for smoking status and age started smoking were additionally adjusted for pack-years of smoking.

Table 3

Body mass index in relation to incidence of lung cancer among 56,835 women in the Black Women's Health Study, 1995–2011

			Age-adjusted		Multivariable[a]	
	No. of Cases	**Person-years**	**HR**	**(95% CI)**	**HR**	**(95% CI)**
All primary lung cancer						
Body mass index (kg/m^2)						
<18.5	9	12,744	3.83	(1.93–7.62)	2.70	(1.36–5.42)
18.5–24.9	101	290,699	1.00		1.00	
25.0–29.9	122	249,935	0.88	(0.67–1.14)	0.85	(0.65–1.11)
30+	91	235,733	0.70	(0.53–0.94)	0.69	(0.52–0.93)
p for trend				<0.01		<0.01
Adenocarcinoma only						
Body mass index (kg/m^2)						
<18.5	2	12,734	2.69	(0.64–11.26)	2.14	(0.51–9.08)
18.5–24.9	33	290,617	1.00		1.00	
25.0–29.9	46	249,846	1.01	(0.65–1.59)	1.00	(0.63–1.57)
30+	23	235,654	0.54	(0.32–0.93)	0.56	(0.33–0.97)
p for trend				<0.01		<0.01

[a]Adjusted for age, education, physical activity, alcohol consumption, parity, age at first birth, family history of lung cancer, geographic region, and pack-years of smoking.

Table 4

Body mass index in relation to incidence of lung cancer, stratified by smoking status

			Multivariable[a]	
	No. of Cases	**Person-years**	**HR**	**(95% CI)**
Never smokers				
Body mass index				
<18.5	1	9,168	1.73	(0.23–13.19)
18.5–24.9	17	201,281	1.00	
25.0–29.9	12	151,545	0.64	(0.30–1.36)
30+	16	142,693	0.83	(0.41–1.70)
p for trend				0.23
Former smokers				
Body mass index				
<18.5	4	1,479	8.70	(2.87–26.40)
18.5–24.9	32	51,442	1.00	
25.0–29.9	56	61,107	0.98	(0.63–1.52)
30+	48	61,390	0.90	(0.56–1.42)
p for trend				0.06
Current smokers				
Body mass index				
<18.5	4	2,095	1.56	(0.55–4.42)
18.5–24.9	52	37,976	1.00	
25.0–29.9	54	37,283	0.93	(0.63–1.37)
30+	27	31,651	0.62	(0.38–1.00)
p for trend				<0.01

[a]Adjusted for age, education, physical activity, alcohol consumption, parity, age at first birth, family history of lung cancer, and geographic region. Models for former smokers and current smokers were additionally adjusted for pack-years of smoking.

Table 5

Waist circumference and waist-hip ratio in relation to incidence of lung cancer

			Age-adjusted		Multivariable[a]		Multivariable[b]	
	No. of Cases	Person-years	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Waist circumference (inches)								
<28	50	137,612	1.00		1.00		1.00	
28–29	62	167,228	0.76	(0.52–1.10)	0.74	(0.51–1.08)	0.81	(0.55–1.19)
30–32	50	98,356	0.80	(0.54–1.19)	0.72	(0.49–1.08)	0.83	(0.54–1.28)
33–36	60	158,076	0.57	(0.39–0.84)	0.52	(0.36–0.76)	0.63	(0.41–0.97)
37+	63	124,960	0.77	(0.53–1.12)	0.64	(0.44–0.94)	0.85	(0.54–1.35)
p for trend				0.08		0.01		0.23
Waist-hip ratio								
<0.71	46	139,769	1.00		1.00		1.00	
0.71–0.75	52	129,728	1.17	(0.79–1.74)	1.18	(0.79–1.76)	1.20	(0.80–1.78)
0.76–0.80	64	132,773	1.29	(0.88–1.88)	1.19	(0.81–1.74)	1.25	(0.85–1.84)
0.81–0.86	56	134,731	1.12	(0.76–1.65)	0.96	(0.65–1.42)	1.02	(0.69–1.51)
0.87+	63	130,396	1.51	(1.03–2.21)	1.16	(0.79–1.70)	1.27	(0.86–1.87)
p for trend				0.07		0.71		0.39

[a]Adjusted for age, education, physical activity, alcohol consumption, parity, age at first birth, family history of lung cancer, geographic region, and pack-years of smoking.

[b]Adjusted for covariates listed above and body mass index.