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Cigarette Smoking, Androgen Levels, and Hot Flushes in Midlife Women

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Abstract

Précis—Cigarette smoking is associated with hot flushes through a mechanism that may not involve alterations in hormone levels or their ratios.

Objective—To test the hypothesis that cigarette smoking is associated with hot flushes through a mechanism involving androgen levels, progesterone levels, sex hormone binding globulin levels, or the ratio of androgens to estrogens.

Methods—Women with and without hot flushes were recruited from Baltimore, Maryland and the surrounding counties. Women were between 45 and 54 years of age, with at least three menstrual periods in the previous 12 months, and were not postmenopausal. Study participants completed a questionnaire and gave a blood sample for hormone measurements.

Results—Current smokers had significantly higher androstenedione levels and a higher androgen to estrogen ratio than never smokers. Current smokers had significantly lower progesterone levels compared to never smokers. Former and current cigarette smokers had increased odds of experiencing hot flushes compared to never smokers (former: OR 1.41, 95% CI 0.99, 2.01; current: OR 2.43, 95% CI 1.28, 4.62). This association, however, was not attenuated by the addition of hormones to the smoking and hot flush model.

Conclusion—Cigarette smoking is associated with hot flushes through a mechanism that may not involve alterations in hormone levels or their ratios.

Introduction

Hot flashes are the most common complaint of women during the menopausal transition (1). Despite the decades of research that have been performed, few risk factors for hot flashes have been identified. One of the most common risk factors studied in association with hot flashes is cigarette smoking. Our previous work showed that women who had ever smoked cigarettes had a 1.6 fold increased odds of experiencing hot flashes compared to women who had never smoked cigarettes (2). In addition, women who were heavy smokers had a 4 fold increased odds of experiencing hot flashes compared to women who were never smokers (2). We

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hypothesized that the reason cigarette smoking is associated with hot flashes is because the chemicals in cigarette smoke lower estrogen levels in women (3-5), and low estrogen levels have been associated with hot flashes (1,6-9). This hypothesis, however, was not supported because estrogen levels did not mediate the association between cigarette smoking and hot flashes (2).

It may be that cigarette smoke is modulating other hormone levels, therefore altering the odds of experiencing hot flashes. For example, higher androgen levels have been observed in smokers compared to non-smokers (10-17). Though estrogen levels are similar in smokers and non-smokers, higher androgen levels raise the androgen to estrogen ratio, which has been shown to be associated with hot flashes (18). Further, progesterone levels have been reported to be associated with smoking status (13) and low progesterone levels have been associated with hot flashes (18).

Little is known about the association between androgen levels, progesterone levels, and smoking status, or whether androgen and progesterone levels associated with smoking status mediate the association between cigarette smoking and hot flashes. Thus, a cross-sectional study was employed to study the associations between cigarette smoking, and androgen levels, the androgen to estrogen ratio, and progesterone levels. In addition, we also examined whether the hormones associated with cigarette smoking mediated the association between cigarette smoking and hot flashes.

Materials and Methods

Study population and design

Sample methods have been previously described in detail elsewhere (2,19). Briefly, this study was conducted among residents of Baltimore, Maryland and the surrounding counties during 2000-2004. The names and addresses of women residing in the selected area who were 45 to 54 years of age were obtained from AccuData America (Fort Meyers, Florida). All women on the list were mailed an invitation to participate in a cross-sectional study of midlife health. Interested participants contacted the clinic, and if the staff determined they were eligible to participate, a visit was scheduled. All clinic visits were scheduled in the morning (8:30-10:00 AM) and the women were instructed to fast overnight prior to the visit. At the clinic visit, participants were weighed, measured, and had their blood drawn for hormone assays. Each woman was eligible for study participation if she was between 45 and 54 years of age and had intact ovaries and a uterus. To ensure that women enrolled in the study were not post-menopausal, women were eligible only if they reported having at least 3 menstrual periods in the last 12 months. Women were excluded if they were pregnant, were taking hormone replacement therapy or hormonal contraception, or had a history of cancer. All participants in this study gave written informed consent according to procedures approved by the University of Illinois, University of Maryland School of Medicine, and Johns Hopkins University Institutional Review Boards.

The participants also completed the study specific questionnaire, which included questions regarding demographic information, reproductive history, menstrual cycle characteristics, hormonal contraceptive use, menopausal symptoms, hormone replacement therapy use, medical and family history, smoking history, and alcohol consumption. A woman was considered to be an 'ever smoker' if she answered 'yes' to the question "Have you ever smoked cigarettes?" A woman was considered to be a 'current smoker' if she answered 'yes' to the question "Do you still smoke cigarettes?" Women were also asked to estimate how many cigarettes they smoke(d) per day and how many years they have (had) been smoking cigarettes. Current alcohol users were defined as those women who had consumed at least 12 alcoholic beverages in the previous 12 months. Body mass index (BMI) was calculated using the National

Institutes of Health on-line BMI calculator. Participants were characterized as normal weight (BMI ≤ 24.9 kg/m²), overweight (BMI 25.0-29.9 kg/m²), or obese (BMI ≥ 30.0 kg/m²).

Information was also collected via the study questionnaire about hot flashes. Specifically, information was collected on whether the woman had ever experienced hot flashes, whether the woman had a hot flash in the last 30 days, the number of hot flashes experienced within the past 30 days, the severity and frequency of hot flashes, and the length of time each woman had experienced hot flashes. In terms of severity, each woman was asked to describe her hot flashes as mild (sensation of heat without sweating), moderate (sensation of heat with sweating), or severe (sensation of heat with sweating that disrupts usual activity). In terms of frequency of hot flashes, each woman was asked to describe her hot flashes as occurring every hour, every 2-5 hours, every 6-11 hours, every 12-23 hours, 1-2 days per week, 3-4 days per week, 5-6 days per week, 2-3 days per month, 1 day per month, less than 1 day per month, or never. Each woman was also asked to describe the duration of her hot flashes as occurring for less than 1 month, 1-5 months, 6-11 months, 1-2 years, 3-4 years, or 5 years or longer.

Hormone assays

Serum concentrations of sex hormone binding globulin (SHBG), estradiol, estrone, testosterone, androstenedione, progesterone, and dehydroepiandrosterone sulfate (DHEA-S) were measured using enzyme-linked immunosorbent assays (ELISA). ELISA kits for estradiol, testosterone, androstenedione, and DHEA-S were obtained from Diagnostic Systems Laboratories, Inc. (Webster, TX). ELISA kits for estrone, progesterone, and SHBG were obtained from American Laboratory Products Company (Windham, NH). The assays were run using the manufacturers' instructions. All assays were conducted in the same laboratory by a single investigator. All samples were run in duplicate and mean values for each participant were used in the analysis. The laboratory personnel were masked with respect to any information concerning study subjects. For quality control purposes, samples from both women with hot flashes and women without hot flashes were run within the same laboratory batches. In addition, positive controls containing known amounts of estradiol, estrone, testosterone, androstenedione, progesterone, DHEA-S, or SHBG were included in each batch. Further, some samples were run in multiple assays to ensure that the assay values did not dramatically shift over time.

The minimum detection limits and intra-assay coefficients of variation were as follows: estradiol 7pg/ml, $3.3 \pm 0.17\%$; estrone 10pg/ml, $4.8 \pm 0.25\%$; testosterone 0.04ng/ml, $2.2 \pm 0.56\%$; androstenedione 0.03ng/ml, $2.5 \pm 0.60\%$; DHEA-S 15ng/ml, $1.9 \pm 0.63\%$; progesterone 0.1ng/ml, $2.1 \pm 0.65\%$; and SHBG 0.1nmol/L, $2.4 \pm 0.67\%$. No estradiol, estrone, testosterone, androstenedione, DHEA-S, or SHBG samples were below the limit of detection. For progesterone samples that were below the limit of detection (n=66), the value was set at the limit of detection (0.1ng/ml). The average inter-assay coefficient of variation for all assays was less than 5%.

The free estradiol index (FEI) was estimated using a conversion factor to change pg/ml of estradiol to nmol/L: $100 \times (\text{total estradiol} \times 0.003671) / \text{SHBG}$. The free testosterone index (FTI) was also estimated using a conversion factor to change ng/ml of testosterone to nmol/L: $100 \times (\text{total testosterone} \times 3.467) / \text{SHBG}$. The other hormones measured in this study do not bind appreciably to SHBG; therefore free index calculations for these hormones were not performed.

Statistical analyses

Sample size calculations were performed prior to starting the main study on hot flashes. Based on our preliminary data, we estimated that smokers would have a 2 fold increase in the odds

of experiencing hot flashes compared to nonsmokers ((95% CI = 1.2-3.5). We also assumed that about 20% of the women in the target population would be current smokers or have a lifetime history of smoking. Under these assumptions, we calculated that 165 women who reported experiencing hot flashes and 165 who reported never experiencing hot flashes would be necessary to detect a statistically significant 2 fold difference with a power of 80% and a 2-sided alpha of 0.05. Sample size calculations based on detecting significant differences in mean estradiol levels between those women with and without hot flashes were also calculated based on data from published literature (8); these calculations showed that, for the estradiol analyses, 50 women with hot flashes and 50 women without hot flashes would be needed for the study .

Women were excluded from this analysis if they were missing data on smoking status (1 woman with hot flashes). In all analyses, hormone levels and body mass index were log transformed, as none of these variables were normally distributed when graphed. Characteristics of women with and without hot flashes and of smokers and non-smokers were compared using Chi-square analyses. Associations between hormone levels and smoking status were examined using general linear models. To examine whether cigarette smoking was associated with the experiencing of hot flashes, the odds ratio (OR) of experiencing hot flashes was calculated using a logistic regression model. To examine whether any association between cigarette smoking and hot flashes was due in part to hormone levels, each hormone that was found to be associated with smoking status was added to the confounder-adjusted cigarette smoking and hot flash model. Factors were considered confounders if they were associated ($p < 0.1$) with cigarette smoking and hot flash status. Variables remaining in the final analyses were age, race, body mass index, alcohol use, and number of days since last menstrual period. The number of pack-years smoked was calculated as: (the number of cigarettes smoked per day * the number of years smoked) / 20. All analyses were performed using SPSS Version 11.0 (Chicago, IL). A p-value of less than 0.05 was considered to be statistically significant.

Results

Characteristics of the study sample are shown in Table 1. Women with hot flashes were more likely to be older, of black race, obese ($\text{BMI} \geq 30.0 \text{ kg/m}^2$), and not current alcohol users compared to women without hot flashes. Of the women who reported ever experiencing hot flashes, approximately two-thirds reported having hot flashes in the last 30 days, roughly two-thirds reported experiencing moderate or severe hot flashes, and about half reported having hot flashes on a daily or weekly basis.

Women who currently smoke cigarettes were more likely to be younger than women who formerly smoked or never smoked cigarettes (Table 2). In addition, women who currently smoke were more likely to be of black race and obese compared to women who formerly smoked or never smoked. Former smokers were more likely to consume alcohol than never smokers. In regards to hot flashes, current and former smokers were more likely to have experienced recent (in the last 30 days), moderate, or severe hot flashes compared to never smokers. There was no difference reported, however, in the frequency of hot flashes between the smoking groups.

Mean levels of androstenedione, progesterone, and the ratio of total androgens to total estrogens differed significantly by smoking status (Table 3). Specifically, former and current smokers had higher androstenedione levels than women who had never smoked cigarettes. Conversely, progesterone levels were lower in current smokers compared to former and never smokers. Further, there was a tendency for a higher ratio of total androgens to total estrogens among women who reported being smokers at the time of enrollment into the study ($p = 0.04$). Levels of SHBG and the free estrogen index (FEI) and the free testosterone index (FTI) were similar between all categories of smokers (data not shown).

Table 4 shows the relation between cigarette smoking and hot flashes. In agreement with our previously published data (2), the confounder-adjusted (age, race, BMI, alcohol use, and days since last menstrual period) odds of experiencing any hot flashes was significantly increased in women who had ever smoked (odds ratio (OR): 1.55, 95% confidence interval (95% CI): 1.11, 2.17) compared to women who had never smoked cigarettes. When ever smokers were separated into former and current smokers, the former smokers were 1.4 times and the current smokers 2.4 times more likely to report experiencing any hot flashes compared to never smokers. For women who ever smoked cigarettes, the greater number of pack-years smoked was associated with a greater odds of reporting hot flashes (1-25 pack-years OR: 1.36, 95% CI: 0.96, 1.95; >25 pack-years OR: 2.59, 95% CI: 1.32, 5.07) compared to women who never smoked cigarettes. In addition, although the numbers were small, current smokers who had smoked 1-25 pack-years were 6.2 times more likely to experience any hot flashes compared to never smokers. There were no women without hot flashes in the >25 pack-years category. In addition, current smokers who smoked up to a pack a day of cigarettes were twice as likely to experience hot flashes compared to never smokers.

The odds of experiencing any hot flashes remained significantly elevated, and relatively unchanged, for women who were ever smokers compared to never smokers after additional adjustment for those hormones shown to be associated with smoking: androstenedione (OR: 1.57, 95% CI: 1.12, 2.19), progesterone (OR: 1.52, 95% CI: 1.08, 2.13), and T+ASD/E2+E1 (OR: 1.49, 95% CI: 1.06, 2.09). The odds of experiencing hot flashes were also relatively unchanged for the other categories of cigarette smoking examined when the hormone variables were added to the model.

In addition to examining the association between cigarette smoking and any hot flashes, the odds of experiencing hot flashes within the last 30 days, moderate or severe hot flashes, and hot flashes that last for a period of a year or more were examined. Results similar to those seen for cigarette smoking and any hot flashes were observed (data not shown).

Discussion

In this study, we observed that current cigarette smoking is associated with higher androstenedione levels, a higher total androgen to total estrogen ratio, and lower progesterone levels. In addition, we observed that hormone levels did not mediate the association between current cigarette smoking and the experiencing of hot flashes.

Our data indicating androstenedione levels are higher in current smokers are consistent with several previous studies (10,12-17,20). Androstenedione is predominately derived from the adrenal gland, therefore these data are also consistent with the observation that one mode of action of nicotine in cigarette smoke is to stimulate the adrenal gland (21). Our data suggest that smoking may permanently alter the amount of androstenedione produced by the adrenal because the level of androstenedione was similar among current and former smokers, but significantly lower in never smokers. In addition, androstenedione levels in former smokers were not significantly different by time since smoking cessation (data not shown). In addition, nicotine may stimulate the pituitary to produce adrenocorticotrophic hormone (ACTH), which also stimulates the adrenal to produce more androstenedione (15). Longcope and Johnston (12) also have suggested that there is a decrease in the clearance of androstenedione in smokers compared to non-smokers leading to increased androstenedione levels. Luteinizing hormone (LH) levels have been shown to also be increased in smokers (12), suggesting along with increased ACTH levels that nicotine is stimulating the pituitary and hypothalamus. The hypothalamus contains nicotinic cholinergic receptors. When nicotine binds to these receptors increases in heart rate, blood pressure and respiration become apparent (22). These are some of the same "symptoms" of hot flashes. Because higher androstenedione levels are noted in

smokers, but do not mediate the association between smoking and hot flashes, androstenedione is not likely part of the causal pathway of hot flashes and is therefore an additional effect of cigarette smoking. Even though testosterone, estradiol, and estrone levels were not affected by cigarette smoking, it then makes sense to find a higher total androgen to total estrogen ratio in current smokers compared to non-smokers because androstenedione levels are elevated.

Our results do not concur with previous studies that measured progesterone levels in smokers. We report significantly lower progesterone levels in smokers compared to non-smokers. In previous studies of pre-menopausal women, there was no difference detected in progesterone levels between smokers and non-smokers (11,23). In a study of post-menopausal women, however, progesterone levels were noted to be higher in smokers compared to non-smokers (13). There may be several reasons for these differences. All of the previous studies had small sample sizes and the ages of the women were different than in our study. Pre-menopausal smokers also appear to have a more robust hypothalamus-pituitary-ovarian axis that allows them to maintain hormone levels at levels similar to non-smokers. This is shown in numerous studies of pre-menopausal smokers and non-smokers who have similar levels of all hormones studied (11-12,23-25).

We previously showed that low progesterone levels are associated with experiencing hot flashes (18). Therefore, we were surprised to find that although progesterone levels were significantly lower in smokers compared to non-smokers, progesterone did not mediate the association between smoking and hot flashes. This finding indicates that progesterone is not within the causal pathway of cigarette smoking and its relation to hot flashes.

Hot flashes have been studied for many years and a good, simple, reliable method of determining hot flashes (other than by interview or questionnaire) has not been developed for wide use in large studies. Freedman (26) has performed studies measuring various physiological (core body temperature, respiratory exchange ratio, skin temperature, skin conductance, sweat rate), as well as biological (MHPG: 3-methoxy-4-hydroxyphenylglycol) parameters in association with hot flashes. Unfortunately, none of these measurements correlates with a woman's perception of a hot flash 100% of the time. The work to develop more sensitive approaches to collecting hot flash data may allow the association between androgen levels, hot flashes and cigarette smoking to be explored more fully in the future.

There are several limitations of this study that may affect the interpretation of results. First, smoking history was obtained by self-report; therefore there may be some misclassification of exposure in this study. There is no reason to suspect, however, that this misclassification would differ based on hot flash status, and hence, the estimates reported would be biased towards the null and may actually be larger than those observed. In addition, because this study was of a cross-sectional design, we were unable to determine the temporality of the association between smoking and hot flashes. Based on questionnaire data, it appeared that age of smoking preceded age of hot flashes among those who were both smokers and reported experiencing hot flashes. Finally, we only collected one blood sample per subject in the study. Variability was limited by collecting all samples during the same two hour window in the morning after an overnight fast and adjusting analyses involving hormone levels for number of days since last menstrual period.

From the data presented here and in previous studies, it appears that cigarette smoking stimulates the production of androstenedione from the adrenal. Although androstenedione levels are increased and progesterone levels are decreased in smokers compared to non-smokers, hormone levels may not be involved in the association between cigarette smoking and hot flashes. Rather the effect is probably a more direct stimulatory action of nicotine on the nicotinic receptors in the hypothalamus.

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Table 1

Characteristics of women with and without hot flashes

Variable	Women with hot flashes*	Women without hot flashes*	p-value
Sample size (n)	362	266	
<i>Participant characteristics</i>			
Age (years) (n,%)			
45-49	213 (58.8)	193 (72.6)	<0.001
50-54	149 (41.2)	73 (27.4)	
Race (n,%)			
White	292 (80.7)	229 (86.1)	0.005
Black	66 (18.2)	28 (10.5)	
Other	3 (0.8)	8 (3.0)	
Body Mass Index (kg/m ²) (n,%)			
<=24.9	141 (39.0)	127 (47.7)	0.001
25.0-29.9	91 (25.1)	81 (30.5)	
>=30.0	129 (35.6)	58(21.8)	
Current alcohol use (n,%)			
No	139 (38.4)	76 (28.6)	0.01
Yes	223 (61.6)	190 (71.4)	
<i>Hot Flash characteristics</i>			
Hot flashes in the last 30 days (n,%)			
No	115 (31.8)	Not applicable	
Yes	244 (67.4)		
Severity of hot flashes (n,%)			
Mild	133 (36.7)	Not applicable	
Moderate	197 (54.4)		
Severe	31 (8.6)		
Frequency of hot flashes (n,%)			
Daily	81 (22.4)	Not applicable	
Weekly	99 (27.3)		
Monthly	158 (43.6)		

* Some columns may not add up to 100% due to missing values.

Table 2

Characteristics of smokers and non-smokers

Variable	Current smokers [*]	Former smokers [*]	Never smokers [*]	p-value
Sample size (n)	58	242	328	
<i>Participant characteristics</i>				
Age (years) (n,%)				
45-49	46 (79.3)	143 (59.1)	217 (66.2)	0.01
50-54	12 (20.7)	99 (40.9)	111 (33.8)	
Race (n,%)				
White	40 (69.0)	207 (85.5)	274 (83.5)	0.04
Black	16 (27.6)	31 (12.8)	47 (14.3)	
Other	1 (1.7)	3 (1.2)	7 (2.1)	
Body Mass Index (kg/m ²) (n,%)				
<=24.9	19 (32.8)	98 (40.5)	151 (46.0)	0.02
25.0-29.9	13 (22.4)	67 (27.7)	92 (28.0)	
>=30.0	26 (44.8)	76(31.4)	85 (25.9)	
Current alcohol use (n,%)				
No	19 (32.8)	66 (27.3)	130 (39.6)	0.008
Yes	39 (67.2)	176 (72.7)	198 (60.4)	
<i>Hot Flash characteristics</i>				
Hot flashes in the last 30 days (n,%)				
No	27 (46.6)	139 (57.4)	215 (65.5)	0.007
Yes	31 (53.4)	103 (42.6)	110 (33.5)	
Severity of hot flashes (n,%)				
Mild	9 (15.5)	49 (20.2)	75 (22.9)	0.006
Moderate	28 (48.3)	81 (33.5)	88 (26.8)	
Severe	5 (8.6)	17 (7.0)	9 (2.7)	
Frequency of hot flashes (n,%)				
Daily	8 (13.8)	34 (14.0)	39 (11.9)	0.71
Weekly	13 (22.4)	36 (14.9)	50 (15.2)	
Monthly	18 (31.0)	68 (28.1)	72 (22.0)	

^{*} Some columns may not add up to 100% due to missing values.

Table 3

Associations between hormone levels and smoking status

Hormone	Never Smoker	Former Smoker	Current Smoker	<i>p</i> for difference in means
	Geometric mean (95% CI)*	Geometric mean (95% CI)*	Geometric mean (95% CI)*	
Testosterone (ng/ml)	0.47 (0.44, 0.50)	0.47 (0.44, 0.51)	0.47 (0.40, 0.55)	0.8
Androstenedione (ng/ml)	1.93 (1.83, 2.03)	2.11 (1.98, 2.25)	2.20 (1.94, 2.51)	0.01
DHEA-S (ng/ml)	372.04 (349.67, 396.23)	385.29 (358.17, 414.47)	366.13 (315.13, 425.39)	0.8
Progesterone (pg/ml)	0.87 (0.74, 1.01)	0.79 (0.66, 0.95)	0.55 (0.38, 0.79)	0.04
Estradiol (pg/ml)	96.26 (88.24, 104.90)	101.09 (91.38, 111.83)	94.26 (76.63, 116.05)	0.8
Estrone (pg/ml)	134.56 (124.84, 145.04)	132.16 (103.65, 144.32)	124.09 (103.65, 148.71)	0.5
T+ASD/E2+E1	9.88 (9.19, 10.61)	10.76 (9.89, 11.72)	11.68 (9.82, 13.90)	0.04

* Adjusted for age, race, body mass index, and current alcohol use.

Table 4

Association between smoking status and any hot flashes

Smoking status	Women with hot flashes (n=362)	Women without hot flashes (n=266)	Confounder adjusted model OR (95% CI)	Confounder plus androstenedione adjusted model OR (95% CI)	Confounder plus progesterone adjusted model OR (95% CI)	Confounder plus T +ASD/E2+E1 adjusted model OR (95% CI)
<i>Ever smoked</i>						
No	47.5	58.6	1.00	1.00	1.00	1.00
Yes	52.5	41.4	1.55 (1.11, 2.17)	1.57 (1.12, 2.19)	1.52 (1.08, 2.13)	1.49 (1.06, 2.09)
<i>Current smoking status</i>						
Never	47.5	58.6	1.00	1.00	1.00	
Former	40.9	35.3	1.41 (0.99, 2.01)	1.42 (1.00, 2.03)	1.40 (0.98, 2.00)	1.36 (0.95, 1.95)
Current	11.6	6.0	2.43 (1.28, 4.62)	2.45 (1.29, 4.67)	2.24 (1.17, 4.28)	2.29 (1.19, 4.39)
<i>Ever smoked: number of pack-years</i>						
Never smoker	47.5	58.6	1.00	1.00	1.00	1.00
1-25 pack-years	38.4	35.3	1.36 (0.96, 1.95)	1.38 (0.96, 1.97)	1.33 (0.93, 1.91)	1.34 (0.93, 1.92)
>25 pack-years	11.9	4.9	2.59 (1.32, 5.07)	2.68 (1.36, 5.31)	2.55 (1.30, 5.01)	2.32 (1.18, 4.59)
Missing	2.2	1.1				
<i>Currently smoke: number of pack-years</i>						
Never smokers	47.5	58.6	1.00	1.00	1.00	1.00
Former smokers	40.9	39.8	1.26 (0.89, 1.78)	1.27 (0.90, 1.80)	1.24 (0.88, 1.76)	1.23 (0.86, 1.74)
1-25 pack-years	7.7	1.5	6.23 (2.09, 18.54)	6.35 (2.13, 18.96)	5.65 (1.89, 16.93)	5.49 (1.83, 16.49)
<i>Currently smoke: packs per day</i>						
Never smoker	47.5	58.6	1.00	1.00	1.00	1.00
Former smoker	40.9	35.3	1.41 (0.99, 2.01)	1.42 (1.00, 2.03)	1.40 (0.98, 2.00)	1.36 (0.95, 1.95)
<=1 pack/day	10.2	6.0	2.11 (1.10, 4.07)	2.14 (1.11, 4.12)	1.91 (0.98, 3.70)	1.97 (1.01, 3.85)