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Association of cardiovascular risk factors with disease severity in cerebral cavernous malformation type 1 subjects with the common Hispanic mutation

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Abstract

Background—Cerebral Cavernous Malformations (CCM) are enlarged vascular lesions affecting 0.1 to 0.5% of the population worldwide and causing hemorrhagic strokes, seizures, and neurological deficits. Familial CCM type 1 (CCM1) is an autosomal dominant disease caused by mutations in the Krev Interaction Trapped 1 (*KRIT1/CCM1*) gene, and is characterized by multiple brain lesions whose number and size increase with age. The number of lesions varies widely for unknown reasons, even among carriers of similar ages with the same mutation. The purpose of this study was to investigate whether cardiovascular (CV) risk factors influence potential markers of familial CCM1 disease severity, such as lesion count and history of intracerebral hemorrhage.

Methods—We analyzed baseline data from 185 Hispanic subjects, enrolled in the Brain Vascular Malformation Consortium (BVMC) study between June 2010 and March 2013. All subjects were carriers of the founder Q455X “Common Hispanic Mutation” (CHM) in the *KRIT1* gene, and had a clinical diagnosis of CCM or had an affected first or second degree relative with CCM. We performed a cross-sectional study, collecting detailed clinical information of CCM1-CHM subjects and cerebral susceptibility-weighted magnetic resonance imaging to assess lesion count. Linear or logistic regression analysis of log-lesion count or history of intracerebral hemorrhage and CV risk factors (age, gender, obesity, diabetes, hypertension, hyperlipidemia and smoking status) and related quantitative traits (body mass index, glycosylated hemoglobin levels, blood

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pressure, lipid levels and pack-years of cigarette smoking) was performed accommodating familial clustering.

Results—CCM1-CHM subjects were mainly female (63.8%) and symptomatic at presentation (63.2%). Lesion count was highly variable (mean ± SD: 57.7 ± 110.6; range: 0–713); 90% of CCM1-CHM subjects had multiple lesions at enrollment. Age ($p < 0.001$) was positively correlated with lesion count and male gender (P=0.035) was associated with a greater number of lesions. Obesity (P=0.001) and higher body mass index (P=0.002) were associated with fewer lesions. No association with hypertension was detected, however, systolic blood pressure (P=0.002) was associated with fewer lesions. No significant association with lesion count was observed for diabetes, hyperlipidemia, smoking status or for related quantitative traits. History of intracerebral hemorrhage was not significantly associated with any CV risk factors; however, we found borderline associations of hemorrhage with obesity (P=0.062), systolic blood pressure (P=0.083) and pack-years of cigarette smoking (P=0.055). After correction for multiple testing, age and obesity remained significantly associated with lesion count in CCM1-CHM subjects.

Conclusions—These results suggest that several CV risk factors explain some of the variability in lesion count in Hispanic CCM1-CHM subjects. Although age, gender, obesity, body mass index and systolic blood pressure may influence familial CCM1 disease severity, further longitudinal studies in larger sample sizes are essential to confirm these findings.

Keywords

cerebrovascular disease; familial cerebral cavernous malformations type 1 (CCM1); common Hispanic mutation; disease severity; brain lesion count; intracerebral hemorrhage; cardiovascular risk factors

Introduction

Cerebral Cavernous Malformations (CCM) are enlarged vascular lesions without intervening brain parenchyma, affecting 0.1 to 0.5% of the population worldwide. The lesions consist of a cluster of abnormal, dilated capillaries containing extravasated blood products of various ages [1]. Lesions are low-flow without shunting of blood, primarily detected by brain or spinal cord magnetic resonance imaging (MRI) evidenced by the typical pattern of blood breakdown products [2]. CCM can manifest as an acute cerebral hemorrhage resulting in permanent neurologic deficits or even death [3]. Both sporadic and familial forms of CCM exist, with familial cases often having multiple lesions.

Familial CCM is an autosomal dominant disease, caused by heterozygous mutations in three genes (*CCM1*, *CCM2* and *CCM3*), and displays variable expressivity [4, 5]. To date, studies of the *CCM1/KRIT1* (Krev Interaction Trapped 1) gene in CCM patients have identified more than 90 mutations, all leading to a premature termination codon and explaining 53% of familial CCM [4]. Interestingly, a founder mutation (Q455X, rs267607203) in the *KRIT1* gene has been identified in Hispanic families of Spanish and Mexican descent that settled in the southwest United States and termed the “Common Hispanic Mutation” (CHM) [6, 7]. Due to this founder mutation and its transmission through multiple generations of large

families, CCM disproportionately affects Hispanics and is a major health burden in the state of New Mexico.

Familial CCM1 patients present with a wide range of symptoms, lesions, and disease severity even among carriers of the same gene mutation [3, 8]. The causes of this variability are unknown, with the exception of age [3, 8, 9], but are likely due to other genetic factors, environment or lifestyle. As U.S. Hispanics have a high prevalence of CV risk factors [10], we hypothesized that these risk factors may influence the severity of CCM disease. This is particularly important as CV diseases are major causes of death for U.S. Hispanics [10]. However, the extent to which CV disease and CV risk factors overlap with CCM is not known nor has the relationship been investigated in prior studies. Thus, the purpose of this study was to investigate whether CV risk factors influence potential markers of familial CCM1 disease severity, such as lesion count and history of intracerebral hemorrhage [11], in Hispanic CCM1-CHM subjects.

Methods

Study Population

We used data collected from CCM1-CHM subjects enrolled in the Brain Vascular Malformation Consortium (BVMC) study (Project 1) between June 2010 and March 2013. The BVMC is a prospective cohort study designed to better understand the natural history and to identify modifiers of disease severity in individuals affected with CCM1-CHM. Subjects were eligible for the study if they: 1) were of Hispanic descent; 2) had a clinical diagnosis of CCM or had an affected first or second degree relative with CCM; 3) carried the specific CHM in the *KRIT1* gene (Q455X, rs267607203); and 4) were older than 6 years of age. To date, 229 of 347 subjects screened were eligible and enrolled, and 201 had completed all baseline study visits. After excluding subjects who had missing data for CV risk factors or lesion count, the final sample size included 185 Hispanic CCM1-CHM subjects from 43 families with at least two members and 31 singletons. The study was approved by the local ethics committee, and written informed consent was obtained from all study participants.

Molecular Screening

Some participants (21.6%) had genetic testing results confirming CHM by a clinical laboratory; all other suspected cases were confirmed by PCR amplification followed by standard sequencing of the CHM in *KRIT1* (Q455X, rs267607203) at the UCSF Genomics Core Facility on an Applied Biosystems 3730×l capillary sequencer (forward primer: GCCCGGCCAGTAAAATGT, reverse primer: GGGCAGGGACTTACCTGTTT, sequencing direction: forward). Genomic DNA for screening was extracted from saliva specimens using Oragene (DNA Genotek) kits and manufacturer's standard protocols. Sequences were double-scored by two investigators blinded to clinical status using Sequencher software (Gene Codes). Sequencing was performed in one direction and 25% of samples were repeated for quality control with 100% concordance observed.

Clinical Characteristics

Detailed clinical information was collected for all patients through in-person interviews and medical examinations. Weight and height were measured for all participants by trained personnel. Body mass index (BMI) was calculated as the weight in kilograms (kg) divided by the square of height in meters (m). *Z*-score BMI was calculated as the number of standard deviations away from the mean based on the distribution of the reference population [12]. Obesity was defined as having a BMI ≥ 30 kg/m^2 for adults (≥18 years of age) and a *Z*-score BMI ≥ 1.64 for children (<18 years) according to standard clinical definitions [10]. Diabetes was defined as having a clinical diagnosis of type 1 or type 2 diabetes or currently taking antihyperglycemic medications. Hypertension was defined as having a clinical diagnosis, or currently taking antihypertensive medications. Hyperlipidemia was defined as having a clinical diagnosis, or currently taking antihyperlipidemic medications. Smoking status was assessed via questionnaires and defined as current or former cigarette smokers. The number of pack-years was calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked.

Fasting blood samples were taken after an overnight fast and sent to a clinical diagnostic laboratory for biochemical analysis. Fasting plasma glucose was measured to assess the level of glycosylated hemoglobin (HbA1c). Standardized enzymatic methods were used to determine total cholesterol (mg/dl), high-density lipoprotein (HDL, mg/dl), low-density lipoprotein (LDL, mg/dl) and triglyceride (mg/dl) levels. Both systolic and diastolic blood pressures (SBP and DBP) were measured in mmHg according to standard protocols at the baseline visit.

Clinical assessment also included information on characteristics of presenting symptoms leading to CCM diagnosis and classified as acute cerebral hemorrhages, seizures, focal neurological symptoms, and headaches using standardized guidelines [13]. MRI was performed for all patients at study enrollment using a volume T1 acquisition (MPRAGE, 1mm slice reconstruction). Lesion counting was based on concurrent evaluation of axial susceptibility-weighted imaging (SWI), which is a volume acquisition, with 1.5 mm reconstructed images and axial T2 gradient echo, 3 mm images. Lesions were counted by the study neuroradiologist (B.H.) who was blinded to clinical and family data.

Statistical Analysis

Continuous data are reported as means ± standard deviation. Lesion count was log-transformed to reduce skewness before linear regression analysis. Because of the known positive correlation of log-lesion count with age in CCM1-CHM subjects [9], analyses on this marker were adjusted for age at enrollment. After screening each possible predictor one at a time, a multivariable model included all predictors that were significantly associated with lesion count. Logistic regression analysis was also performed to assess association between history of intracerebral hemorrhage and CV risk factors. Quantitative trait analysis of CV risk factors was restricted to adults (≥18 years of age) because guidelines differ for children and the number of children in the cohort was small (N=42). Finally, we performed sensitivity analysis further adjusting models for medication use for hyperglycemia, hypertension or hyperlipidemia, respectively. All analyses accounted for clustering within

families by using robust standard errors. CV risk factors with nominal *P*-values ≤ 0.05 are reported. Correction for multiple testing was applied for two markers of disease severity (lesion count and history of intracerebral hemorrhage) and sixteen measures of CV risk (age, gender, obesity, diabetes, hypertension, hyperlipidemia, smoking status, BMI, HbA1C, SBP, DBP, total cholesterol, HDL, LDL, triglycerides and pack-years of cigarette smoking) simultaneously (number of tests: 2 × 16). All analyses were performed using STATA 12.1 statistical software (StataCorp; College Station, TX).

Results

Participant Characteristics

Table 1 shows the descriptive statistics of CCM1-CHM subjects included in this study. The majority of subjects were female (63.8%) and symptomatic at presentation (63.2%) with intracerebral hemorrhage as the main clinical symptom leading to CCM diagnosis followed by seizure, headache, and non-hemorrhagic focal neurologic deficit (NH-FND). In our study, the number of affected members per family enrolled varied between one (41.9%) and nine (1.3%). Hispanic CCM1-CHM subjects presented with a wide range in lesion count and 89.7% of subjects had more than 2 lesions on MRI at enrollment (Table 1). Three subjects (1.6%) had no lesions, five subjects (2.7%) harbored only one and 16 subjects (8.6%) harbored more than 200 lesions.

The prevalence of CV risk factors in Hispanic CCM1-CHM subjects are summarized in Table 2 and was relatively close to those reported for the U.S. population or U.S. Hispanics [10, 14]. Details regarding related CV quantitative traits such as blood pressure measurements and lipids levels are also presented in Table 2.

CV Risk Factors and Potential Markers of Disease Severity

We first assessed whether CV risk factors (age, gender, obesity, diabetes, hypertension, hyperlipidemia, and smoking status) were association with log-lesion count. As with previous studies [3, 8, 9], we found a positive linear correlation between increasing age and log-lesion count (R^2 = 0.45) among CCM1-CHM carriers. On average, lesion count increased by 5% for every one-year increase in age (95% CI: 4%–6%, P<0.001). Male CCM1-CHM subjects had, on average, 42% more lesions (95% CI: 2%–98%, P=0.035) in comparison to females (Table 3). Further, obesity was inversely associated with lesion count independent of age, with 43% fewer lesions at baseline for obese subjects compared to non-obese subjects (P=0.001). No significant association with lesion count was observed for diabetes, hypertension, hyperlipidemia and smoking status (Table 3). In multivariable analysis, age (P<0.001) and male gender (P=0.042) remained significantly associated with more lesions, whereas obesity (P=0.001) remained associated with fewer lesions at baseline (Table 3). Second, we assessed whether CV risk factors were associated with a history of intracerebral hemorrhage and no significant association was detected. However, we found a borderline association with obesity (P=0.062) and a lack of intracerebral hemorrhage history (Supplementary Table 1).

Quantitative Traits Related to CV Risk Factors

Similarly, we evaluated whether quantitative traits related to CV risk factors were associated with markers of disease severity in adults. First, we assessed the effect of each quantitative trait (BMI, HbA1C, SBP, DBP, total cholesterol, HDL, LDL, triglycerides and pack-years of cigarette smoking) with dog-lesion count separately in a model adjusting for age and gender. BMI and SBP were significantly inversely associated with lesion count (Table 4). For every 5 units increase in BMI, lesion count decreased by 17% (P=0.002). For every 10 units increase in SBP, lesion count decreased by 16% (P=0.002). No significant association with lesion count was observed for HbA1c, DBP, lipid levels, or pack-years of cigarette smoking (Table 4). Interestingly, BMI (P=0.035) and SBP (P=0.011) both remained significant independent predictors of lesion count in multivariable analysis (Table 4). However, after correction for multiple testing, age ($P_{corrected}$<0.001) and obesity ($P_{corrected}$=0.032) remained significantly associated with log-lesion count in CCM1-CHM subjects.

Second, we assessed the association of each quantitative trait with a history of intracerebral hemorrhage separately in a univariate model. No significant association was detected, however we found borderline associations for systolic blood pressure (P = 0.083) and pack-years of cigarette smoking (P = 0.055) with a lack of intracerebral hemorrhage history (Supplementary Table 1).

As a sensitivity analysis, we further adjusted HbA1C, blood pressure, and lipid level analyses for whether subjects were taking antihyperglycemic, antihypertensive or antihyperlipidemic medications, respectively. Medication use was associated with neither lesion count nor history of intracerebral hemorrhage in any of the analyses and results did not change whether we included this covariate in the model or not (data not shown).

Discussion

In this study, we identified novel CV risk factors associated with variability in lesion count independent of age in Hispanic CCM1-CHM subjects. Specifically, we found that increasing age and male gender were associated with greater number of lesions. Further, we found that obesity and its related quantitative trait, BMI, were associated with fewer lesions at baseline. Finally, higher SBP was also associated with fewer lesions, despite a lack of association with hypertension. After correction for multiple testing across two markers of disease severity and sixteen measures of CV risk, age and obesity retained their statistically significant association. No association with lesion count was observed for diabetes, hyperlipidemia, smoking status or for their related quantitative traits. Further, no statistically significant association with history of intracerebral hemorrhage was detected.

The clinical features of patients and wide range in lesion count are consistent with previous studies in CCM1 families. Indeed, we found a similar percentage of symptomatic patients (63.2 *vs.* 62.4% in our study and previously reported for 202 *CCM1/KRIT1* mutation carriers [8], respectively), with seizure as one of the main initial clinical symptom (34.0 *vs.* 55.0%). In addition, the majority of *CCM1* mutation carriers had multiple lesions (89.7 *vs.* 90.0%). However, in our study only 2.7% of CCM1-CHM subjects harbored one CCM lesion in comparison to 13% of all *CCM1* mutation carriers [8] and the mean CCM lesion count was

considerably higher (57.7 *vs.* 4.9 on T2-weighted MRI and 19.8 on gradient-echo sequences). This may in part be explained by the fact that the MRI techniques used in 2004 [8] were probably less sensitive to those used in the current study. Our findings also extend previous findings showing that demographic factors influence lesion count. We confirmed the positive correlation between age and lesion previously reported in Caucasian CCM1 families by Denier and colleagues [3, 8]. In addition, we found that male Hispanic CCM1-CHM subjects had approximately 42% more lesions in comparison to females at baseline after accounting for age; this has not been reported in other CCM cohorts. Thus, it seems that Hispanic CCM1-CHM carriers share similarities with previously described *CCM1* mutation carriers but they also might have specific characteristics.

The main novel finding from our study is that obesity followed an inverse pattern of association with CCM1 disease severity with obese subjects having fewer rather than greater number of lesions at baseline. Further, obesity was borderline associated with a lack of intracerebral hemorrhage history in Hispanic CCM1-CHM subjects. In our sample, the prevalence of obesity was high in adults (40.6%) as well as in children (21.4%), but comparable to the U.S. Hispanic population (35% for adults and 18% for children) [10, 14]. The inverse associations of obesity and markers of CCM1 disease severity were initially surprising to us, but others have reported a phenomenon named the “obesity-survival paradox” which appears in a wide range of illnesses such as end-stage renal disease, heart failure, coronary artery disease and stroke [15, 16], among others. For instance, obese and overweight patients are at increased risk for an initial stroke event, but at decreased risk for recurrent events and had improved survival and functional outcomes in comparison to lean patients [17]. Further, the occurrence of a major vascular event after an ischemic stroke has been shown to be lower in overweight and obese subjects in comparison to lean subjects [18]. The reason for the paradox has yet to be defined but in our study, a possible reason of the relationship between obesity and CCM1 disease severity may be reverse causation due to neurologic impairment. Indeed, subjects with severe CCM may have neurologic impairment possibly resulting in swallowing problems which could lead to weight loss and consequently to decreased BMI. Another reason that the association might not be causal is there could be unmeasured confounding factors for which we have not been able to adjust. And, of course, chance could be at work, although our results remained statistically significant even after Bonferroni correction. Importantly, these results are from baseline data and are cross-sectional in nature. However, the BVMC study enrolled eligible subjects based on CHM-positive status and not on phenotype, thus ensuring a broad spectrum of disease severity. As an association finding in an epidemiologic study does not prove causation, longitudinal data would be helpful to better elucidate causal relationships between these CV risk factors and CCM1 disease severity.

Our study had several limitations. First, diabetes, hypertension and hyperlipidemia risk factors were based on self-reported data of a diagnosis for the condition or currently taking medications for the condition, which may result in misclassification and may explain the lack of association for these CV risk factors with markers of CCM1 disease severity. However, in our sample, the frequency of CV risk factors was relatively close to that reported for the U.S. population or Hispanic Americans. For example, we found no diabetics

in our Hispanic CCM1-CHM children, which is consistent with a prevalence of 0.18% in U.S. youths and 0.22% in Hispanic American youths [19]. Similarly, in our study 13.3% of Hispanic CCM1-CHM adults had diabetes, which is close to 11.8% of Hispanic American adults who had diagnosed diabetes mellitus [10]. Second, bias due to measurement error could have arisen as blood pressure was measured only one time, instead of three times as recommended [20] and laboratory measures (HbA1c and lipid levels) were assessed on only one blood sample. For this reason, the degree of association between SBP and lesion count in Hispanic CCM1-CHM adults, and lack of association with HbA1c, DBP or lipid levels, should be considered with caution. Finally, in this study, we did not examine the influence of other important CV risk factors such as genetic and lifestyle factors (physical inactivityand nutrition) on CCM1 disease severity. Nevertheless, our study is based on a unique cohort of genetically homogeneous familial CCM1 subjects relatively well informed for CV risk factors. Indeed, participants were all of Hispanic descent, harboring the same founder mutation and recruited at a single center.

In conclusion, we have identified several novel CV risk factors associated with lesion count in Hispanic CCM1-CHM subjects. Although age, gender, obesity, BMI and SBP may influence familial CCM1 disease severity, further longitudinal studies in larger sample sizes are essential to better understand the role of CV risk factors in CCM1 disease severity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Clinical Characteristics of the 185 Hispanic CCM1-CHM Subjects

Characteristics	N	Prevalence (%)
Gender (Female)	118	63.8
Family size (N Affected Members)		
1	31	41.9
2	15	20.3
3 – 9	28	37.8
Symptoms at Enrollment		
Asymptomatic	39	21.1
Headache	105	56.8
Seizure	63	34.0
Hemorrhage	59	31.9
NH-FND	11	5.9

Characteristics	Mean ± SD	Range
Age at Diagnosis (years)	31.3 ± 19.5	0.3–83.8
Age at Enrollment (years)	38.2 ± 19.7	6.6–84.9
Lesion Count	57.7 ± 110.6	0 – 713

NH-FND: non-hemorrhagic focal neurologic deficit

Table 2

Prevalence of CV Risk Factors in CCM1-CHM Subjects

	Children < 18 y of Age		Adults ≥ 18 y of Age	
CV Risk Factors	**N**	**Prevalence (%)**	**N**	**Prevalence (%)**
Gender (female)	23	54.8	95	66.4
Obesity	9	21.4	58	40.6
Diabetes	0	0.0	19	13.3
Hypertension	0	0.0	35	24.5
Hyperlipidemia	0	0.0	39	27.3
Smoking status	2	4.8	57	39.9
Related Quantitative Traits	**Mean ± SD**	**Range**	**Mean ± SD**	**Range**
Age at enrollment (years)	11.4 ± 3.3	6.6 – 17.5	46.1 ± 15.1	18.0 – 84.9
Z-score BMI or BMI (kg/m^2)	0.4 ± 1.4	−2.7 – 2.8	29.1 ± 6.8	17.0 – 50.9
HbA1C (%)	5.5 ± 0.3	5.0 – 6.0	5.9 ± 1.0	4.8 – 14.3
SBP (mmHg)	108.3 ± 11.4	74 – 128	126.2 ± 16.8	86.0 – 168.0
DBP (mmHg)	64.2 ± 9.2	43.0 – 83.0	77.9 ± 12.0	50.0 – 110.0
Total Chol (mg/dL)	157.2 ± 30.8	106.0 – 236.0	187.4 ± 40.0	113.0 – 296.0
HDL (mg/dL)	52.7 ± 13.5	22.0 – 80.0	52.4 ± 18.4	22.0 – 130.0
LDL (mg/dL)	85.9 ± 27.9	31.0 – 155.0	105.0 ± 32.3	37.0 – 215.0
Triglycerides (mg/dL)	92.6 ± 46.4	43.0 – 269.0	150.0 ± 87.9	42.0 – 543.0
Pack-years of cigarette smoking	1.0 ± 0.0	-	9.7 ± 14.2	1.0 – 74.0

Table 3

CV Risk Factors Associated with Lesion Count in CCM1-CHM Subjects at Study Enrollment. Table gives proportional increase (PI) (or decrease if less than 1) in lesion count associated with each risk factor, along with 95% confidence intervals and *P*-values.

	* Model 1		** Multivariable Model	
CV Risk Factors	**PI (95%CI)**	***P*-value**	**PI (95%CI)**	***P*-value**
Age at enrollment	-	-	1.05 (1.04–1.06)	< **0.001**
Male Gender	1.42 (1.02–1.98)	**0.035**	1.41 (1.01–1.96)	**0.042**
Obesity	0.57 (0.41–0.78)	**0.001**	0.57 (0.42–0.78)	**0.001**
Diabetes	0.91 (0.47–1.79)	0.794	-	-
Hypertension	0.72 (0.47–1.11)	0.137	-	-
Hyperlipidemia	0.99 (0.70–1.43)	0.992	-	-
Smoking status	0.93 (0.64–1.34)	0.696	-	-

* Each risk factor was adjusted for age at enrollment

** Included all risk factors significantly associated with lesion count in **Model 1**

Table 4

CV Quantitative Traits Associated with Lesion Count in CCM1-CHM Adults (≥18 years of age) at Study Enrollment. Table gives proportional increase (PI) (or decrease if less than 1) in lesion count associated with each quantitative trait, along with 95% confidence intervals and *P*-values.

	* Model 1		** Multivariable Model	
Quantitative Traits	**PI (95%CI)**	***P*-value**	**PI (95%CI)**	***P*-value**
Age (5 units - years)	-	-	1.38 (1.32 – 1.46)	**<0.001**
BMI (5 units - kg/m^2)	0.83 (0.74 – 0.93)	**0.002**	0.87 (0.76 – 0.99)	**0.035**
HbA1C (10 units - %)	0.96 (0.17 – 5.22)	0.960	-	-
SBP (10 units - mmHg)	0.84 (0.76 – 0.93)	**0.002**	0.87 (0.79 – 0.97)	**0.011**
DBP (10 units - mmHg)	0.88 (0.75 – 1.02)	0.098	-	-
Total Chol (10 units - mg/dL)	1.01 (0.97 – 1.06)	0.559	-	-
HDL (10 units - mg/dL)	1.06 (0.93 – 1.21)	0.387	-	-
LDL (10 units - mg/dL)	1.03 (0.97 – 1.09)	0.355	-	-
Triglycerides (10 units - mg/dL)	0.98 (0.96 – 1.01)	0.167	-	-
Pack-years of cigarette smoking (10 units)	1.07 (0.94 – 1.21)	0.311	-	-

* Each quantitative trait was adjusted for age at enrollment and gender

** Included all quantitative traits significantly associated with lesion count in **Model 1**