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A Community-Based Study of Cigarette Smoking Behavior in Relation to Variation in Three Genes Involved in Dopamine Metabolism: Catechol-O-methyltransferase (*COMT*), Dopamine Beta-Hydroxylase (*DBH*) and Monoamine Oxidase-A (*MAO-A*)

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Abstract

Objective—Cigarette smoking behavior may be influenced by *catechol-O-methyltransferase* (*COMT*), *dopamine beta-hydroxylase* (*DBH*), and *monamine oxidase-A* (*MAO-A*), genes that play roles in dopamine metabolism. The association between common polymorphisms of these genes and smoking behavior was assessed among 10,059 Caucasian volunteers in Washington County, MD in 1989.

Methods—Age-adjusted logistic regression was used to measure the association between variants of these single nucleotide polymorphisms and smoking initiation and persistent smoking.

Results—Overall, no association was seen between each genotype and smoking behavior. However, among younger (<54 years) women, the *COMT* GG genotype was positively associated with smoking initiation (OR=1.3; 95% CI: 1.1, 1.5), and the *MAO-A* TT genotype was inversely associated with persistent smoking (OR=0.5; 95% CI: 0.3, 0.9). Men who smoked fewer than 10 cigarettes per day were more likely to be persistent smokers if they had the *COMT* GG (OR=1.7; 95% CI: 1.0, 2.9) or the *DBH* GG (OR=1.6; 95% CI: 1.0, 2.6) genotypes.

Conclusion—Overall the results of this large community-based study do not provide evidence to support the presence of important associations between variants of *COMT*, *DBH*, or *MAO-A* and smoking initiation or persistent smoking.

Keywords

tobacco; cigarette smoking; *COMT*; *DBH*; *MAO-A*

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INTRODUCTION

In the United States, smoking is the major preventable cause of premature mortality (Centers for Disease Control 2004). The addictive nature of nicotine influences the intensity and duration of exposure to tobacco toxins that lead to smoking-caused diseases.

A complex interplay of social influences contributes to the initiation and maintenance of cigarette smoking. For example, among youths, exposure to parents, siblings, and peers who smoke cigarettes, as well as exposure to pro-smoking media messages are strong risk factors for smoking initiation (US Department of Health and Human Services 1994). Given exposure to the social influences to smoke, individual characteristics such as poor school performance can be conceptualized as social susceptibility factors that affect the likelihood of progressing on the pathway to smoking. Once an individual tries smoking cigarettes, variants in genes related to the metabolism of cigarette smoke constituents, such as nicotine, may also affect the likelihood of progressing to regular smoking (smoking initiation) and remaining a smoker (smoking persistence).

In fact, estimates indicate genetic variation may account for 44–56% (Li et al. 2003, Sullivan, Kendler 1999, Vink, Willemsen & Boomsma 2005) of smoking initiation, 46–59% of persistent smoking (Li et al. 2003) and 67–75% of nicotine addiction (Sullivan, Kendler 1999, Vink, Willemsen & Boomsma 2005). Genotypic variation may influence specific stages of smoking behavior. Studies have identified polymorphisms of genes responsible for the production of acetylcholine (Greenbaum et al. 2006), serotonin (Lerer et al. 2006), tryptophan (Sullivan et al. 2001) and dopamine (Sullivan et al. 2001) that may differentially influence smoking initiation and nicotine dependence.

In this study, we investigated two specific aspects of cigarette smoking behavior, smoking initiation and smoking persistence, in relation to single nucleotide polymorphisms (SNPs) in three genes that encode enzymes involved in different aspects of dopamine metabolism: *catechol-O-methyltransferase (COMT)*, *dopamine beta-hydroxylase (DBH)*, and *monamine oxidase-A (MAO-A)*. The MAO-A and COMT enzymes contribute to dopamine metabolism in the brain, whereas DBH plays a role in converting dopamine to norepinephrine. The drive to continue to smoke is partially due to behavioral reinforcement from the stimulant effects and antidepressant nature of cigarette smoking. These effects occur when nicotinic cholinergic receptors in the central nervous system are stimulated by nicotine, leading to the release of the neurotransmitters serotonin and dopamine (Julien 1998). Variation in dopamine metabolism may influence inter-individual susceptibility to the smoking-induced nicotine response and therefore affect the likelihood that one becomes a smoker and, once a smoker, the likelihood of quitting smoking.

We studied specific SNPs in these genes for several reasons. The *COMT* 1947 A>G polymorphism is a functional SNP associated with a 2–3 fold variation in enzyme activity (Syvanen et al. 1997), which may result in variation in dopamine activity. *COMT* has been linked with alcohol and substance abuse (Tiihonen et al. 1999, Kauhanen et al. 2000, Vandenberg et al. 1997). Cigarette smoke (Rose et al. 2001) decreases MAO activity, thus increasing brain dopamine concentrations, which in turn could contribute to the addictiveness of smoking and enhance the likelihood of smoking initiation and smoking persistence (McKinney et al. 2000). Furthermore, in the *MAO-A* 1460 C>T SNP, the T allele reduces MAO-A enzyme activity (Hotamisligil, Breakefield 1991). Higher DBH plasma concentrations may influence drug dependence (Cubells et al. 2000, Gabel et al. 1995). However, so far the evidence concerning variants in the *COMT*, *DBH* and *MAO-A* genes in relation to smoking behaviors has been inconsistent (Beuten et al. 2006, Colilla et al. 2005, David et al. 2002, Enoch et al. 2006, Guo et al. 2007, Han et al. 2008, Jin et al. 2005, Johnstone et al. 2002,

Johnstone et al. 2004, McKinney et al. 2000, Munafo et al. 2008, Tochigi et al. 2007, Ton et al. 2007).

Currently, the social and cultural contributions to smoking initiation and smoking persistence are better understood than the role of inter-individual genetic susceptibility. The need to enrich the body of evidence concerning the potential genetic role in the etiology of cigarette smoking behavior with a large-scale, community-based study motivated the present investigation. We tested the hypothesis that variants in the *COMT*, *DBH* and *MAO-A* genes are associated with smoking initiation and persistent smoking.

METHODS

Population

This cross-sectional study was embedded in a prospective community-based cohort study established in Washington County, Maryland. In 1989, the CLUE II cohort study was conducted as a follow-up study to the CLUE Cohort (CLUE I) conducted in 1974. The name CLUE refers to the recruiting campaign slogan “Give us a clue to cancer and heart disease.” Blood specimens and baseline data were collected from 25,802 participants in CLUE I and 32,898 participants in CLUE II. About one third of CLUE I participants (N=8,394) also participated in CLUE II and formed the “Odyssey Cohort”. For this study, Caucasian adults in either the Odyssey Cohort or in a sub-cohort comprised of an age-stratified 10% random sample of CLUE II participants (N=3,076) were included, for a total of 10,278 participants (Figure 1). Of these, only those with complete data on smoking status at baseline and complete genotype data on at least one of the SNPs were included (n=10,059). Twenty-four men who were heterozygous at *MAO-A* 1460 C>T were excluded, because *MAO-A* is sex-linked

This study was approved by the Institutional Review Board at the Johns Hopkins University Bloomberg School of Public Health.

Genotype Assessment

The alkaline lysis method (Klitsch, Neuhuber 2000) was utilized to extract DNA from the buffy coat of the blood specimens collected in 1989 and stored at -70°C . Taqman assays were used to genotype *COMT* (rs4680), *DBH* (rs77905) (analyzed by Celera Genomics; Rockville, MD in 2002), and *MAO-A* (rs1801291) (analyzed by Applied Biosystems; Foster City, CA in 2003–4). The percent concordance for *COMT* was 91.7% among samples that overlapped with a previous study (n=252).

Outcome Assessment

Age, race, sex, education, and smoking history were collected in the 1989 questionnaire. The two outcomes in the present study were smoking initiation (ever smokers compared to never smokers) and persistent smoking (current smokers compared to former smokers).

Among those who were current smokers in 1989 and who provided smoking status in at least one follow-up survey in 1998, 2000 and 2003 (n=949), we also carried out a longitudinal sub-study. Participants were categorized as successful quitters if they self-reported their smoking status as “former smoker” in 1998, 2000 or 2003, and did not self-report their smoking status as “current smoker” on any of the subsequent surveys; otherwise they were considered to be persistent smokers. The association between the gene variants and persistent smoking was assessed by comparing persistent smokers to successful quitters.

Statistical Analysis

COMT, *DBH* and *MAO-A* were tested for Hardy-Weinberg equilibrium (HWE) among never smokers with the chi-squared test.

All analyses were stratified by gender. The associations between genotypes and smoking behavior were measured using odds ratios (OR) and 95% confidence intervals (CI). Logistic regression, adjusted for age, was carried out for each gene assuming a recessive model: GG vs. AG/AA for *COMT*, GG vs. AG/AA for *DBH* and TT/TO vs. CT/CC/CO for *MAO-A*. Dominant and additive models were also considered, but were not found to improve the fit of the data over the recessive model so we only report results of the recessive model. To assess the independent effects of each polymorphism, a third model was adjusted for potential confounders and the other two polymorphisms. Gene-by-gene interactions were assessed using the likelihood ratio test from the base model without the interaction term to the model extended to include the cross-product term. To evaluate the presence of effect modification, stratified analyses were carried out by age (median age 54 years) and by smoking intensity (≤ 10 , 11–29, and 30+ cigarettes per day) among persistent smokers. P-values for interactions were estimated with the likelihood ratio test by comparing models with and without a cross-product term between genotype and age category or category of cigarette consumption. All analyses were two-sided with $\alpha=0.05$, and were performed by Intercooled STATA 8.2 (StataCorp 2001).

RESULTS

Only the *MAO-A* polymorphism (women only, because the gene is on the X-chromosome) was found to be in HWE among never-smokers. The *COMT* and *DBH* polymorphisms deviated significantly from HWE (chi-squared=5.2; $p=0.02$ and chi-squared=9.9; $p=0.001$, respectively).

The final study population included 10,059 people, 38.5% male and 61.5% female. Men were significantly more likely than women to have a positive smoking history (61% versus 38%), but the likelihood of current smoking was similar in men and women (18% versus 16%). On average, current smokers were significantly younger than former or never smokers (Table 1).

Overall, no significant associations were observed between polymorphisms of *COMT*, *DBH* or *MAO-A* and smoking initiation (Table 2) or persistent smoking (Table 3).

A statistically significant age-by-genotype interaction (p -interaction 0.03) was observed among women for the *COMT* GG genotype, which was positively and statistically significantly associated with smoking initiation among younger (OR=1.25; 95% CI: 1.04, 1.50) but not among older (OR=0.91; 95% CI 0.76–1.10) women. Among men, a statistically significant interaction (p -interaction 0.04) was observed between the *COMT* AG/AA genotype and smoking intensity in persistent smokers, with a statistically significant association among those who smoked ≤ 10 cigarettes per day (OR=1.73; 95% CI: 1.04, 2.87) but not among those who smoked 11–29 (OR=0.88; 95% CI: 0.61, 1.26) or ≥ 30 (OR=1.30; 95% CI 0.86, 1.96) cigarettes per day, respectively) (Table 4). Among men the association between the *COMT* AG/AA genotype and persistent smoking differed between younger (OR=1.29; 95% CI: 0.93, 1.78), and older (OR=1.02; 95% CI 0.72, 1.44) men, but neither the age-specific odds ratios nor the test for interaction (p -interaction 0.63) was statistically significant.

Among men only, the association between *DBH* and persistent smoking was stronger among light smokers than heavier smokers (p -interaction 0.01). Men with the *DBH* GG genotype were more likely to be persistent smokers if they smoked ≤ 10 cigarettes per day (OR=1.59; 95%

CI: 1.00, 2.54), but not if they smoked 11–29 (OR=0.72; 95% CI 0.52–1.00) or ≥ 30 (OR=1.22; 95% CI 0.84, 1.76) cigarettes per day (Table 4).

Among women, the age-stratified analyses revealed the *MAO-A* TT genotype was inversely associated with persistent smoking in younger (OR=0.65; 95% CI: 0.42, 1.01) but not among older (OR=1.02; 95% CI 0.66, 1.58) women, though this was not a statistically significant interaction (p -interaction=0.3). For each gene, allelic frequencies did not vary across ten-year age categories, suggesting that the observed age-by-genotype differences do not appear to be due to survival biases by genotype.

The results of the longitudinal sub-study of smoking persistence were consistent with the cross-sectional analyses (Table 5). Specifically, no overall associations were seen between *DBH* or *MAO-A* and persistent smoking in the longitudinal analyses. The only potentially notable difference was that the *COMT* GG genotype (vs. AG/AA) was slightly inversely associated with persistent smoking among women (OR=0.71; 95% CI: 0.47, 1.08), but this association was not statistically significant and was not seen among men (OR=0.97; 95% CI 0.55, 1.71).

Analyses that included all three genotypes did not yield associations that differed from the analyses of each SNP individually, suggesting the associations between each gene and smoking outcome was not confounded by the other genes studied. No significant gene-gene interactions in relation to smoking initiation or persistent smoking were observed (all p -interaction>0.3).

DISCUSSION

We carried out a community-based study to determine if common variants in genes related to dopamine metabolism were associated with cigarette smoking initiation and persistence. This investigation was hypothesis-driven, using a candidate gene approach with genes selected based on the fact that they encode for enzymes involved in dopamine metabolism and on prior research that indicated potential linkages between these genes and addictive behaviors.

In the total study population, there were no notable associations between *COMT*, *DBH* or *MAO-A* and smoking initiation and persistent smoking. Our results are consistent with previous reports of no association between *COMT* and smoking initiation (David et al. 2002, Guo et al. 2007) and persistent smoking (David et al. 2002, Guo et al. 2007). However, one study found the G allele to be associated with persistent smoking among women (Colilla et al. 2005), and another found it to be associated with current smoking status (Enoch et al. 2006). The associations between *COMT* and other smoking outcomes have been examined with mixed results. One study found no association between *COMT* genotype and smoking intensity (David et al. 2002, McKinney et al. 2000), whereas another found the GG genotype to be associated with smoking at least one pack per day (Tochigi et al. 2007). In studies that examined *COMT* in relation to smoking abstinence in randomized treatment trials of smoking cessation, observations have varied from no association (Ton et al. 2007), to the AG/GG genotypes being associated with quicker relapse (Munafo et al. 2008), to the GG genotype being associated with smoking abstinence (Han et al. 2008). In another study, the G allele was observed to be protective against nicotine dependence (Beuten et al. 2006).

DBH and *MAO-A* have previously been investigated in relation to cigarette smoking behavior in only a few studies. *DBH* has not been previously studied in relation to our study outcomes of smoking initiation or smoking persistence, though in one study no association was observed between variants of the *DBH* 1368 A>G and cigarette smoking intensity (Johnstone et al. 2002).

The null association we observed between *MAO-A* 1460 SNPs and smoking initiation and persistent smoking conflicts with a previous observation of a positive association between the

T allele of *MAO-A 1460* and current smoking status among Chinese men (Jin et al. 2005). With respect to smoking intensity, two studies of *MAO-A 1460* variants reported no association (Johnstone et al. 2002, Tochigi et al. 2007).

In the present study, the overall results were null. However, associations were observed among population subgroups, specifically, those who smoked fewer cigarettes per day (*COMT*, *DBH*) or who were younger (*COMT*, *MAO-A*). Even in these subgroups, the statistically significant associations were not strong and were not consistently present in both men and women. Weighed against the overall null results in the total study population and the inconsistencies in the subgroup analyses, the results of the subgroup analyses should only be viewed as hypothesis generating.

The associations with persistent smoking among light smokers, but not among heavier smokers, may be due to a differential effect according to nicotine dose, i.e., the large amounts of nicotine consumed by heavy smokers may overshadow the relatively minor influence that a single SNP may exert on dependence. If so, an association may only become apparent in the setting of lower nicotine doses consumed by lighter smokers.

Associations may be observed among younger—but not older—smokers due to variation of the effect of specific alleles during different development stages. In our study, among those <54 years old, positive associations were observed between the GG genotype of *COMT 1947 A>G* and persistent smoking in men and smoking initiation in women. Perhaps the association seen solely among younger participants could be influenced by the doubling of *COMT* activity in the prefrontal cortex from birth to late adulthood (Tunbridge et al. 2006). We also observed an association among women <54 years old with the TT genotype of *MAO-A 1460 C>T* being less likely to be persistent smokers. Among women, age may be acting as a surrogate for menopausal status if the hormonal milieu influences enzyme production. In animal studies (Gundlah, Lu & Bethea 2002, Holschneider et al. 1998), ovarian steroids decreased brain levels of *MAO-A*. Conversely, skepticism is warranted because the observed pattern of associations between *COMT* and *MAO-A* with smoking behavior among younger participants and between *COMT* and *DBH* and persistent smoking among light smoking men may simply be due to chance.

Study Limitations and Strengths

Certain features of the present study warrant caution in drawing inferences, including the cross-sectional study design and deviations from HWE. The *COMT* and *DBH* allelic frequencies deviated significantly from HWE among never smokers. The departures from HWE may indicate genotyping error (Hosking et al. 2004), or may result from violations in the Hardy-Weinberg assumptions such as random mating or selection. Of note, *DBH* also deviated from HWE among Caucasians in the SNP500 database (National Cancer Institute 2006). Additionally, the percent concordance for *COMT* was 91.7% among samples that overlapped with a previous study. Therefore, it is less likely that deviations from HWE for *DBH* and *COMT* indicate that genotyping quality was poor in our study. Another potential limitation is population stratification. We reduced the potential for population stratification to have a major impact on our results by restricting the analysis to Caucasians, though allelic variation may remain across the population substructure of those included in the study.

Multiple testing may also be raised as an issue, due to the large number of analyses and sub-analyses carried out. However, we focused on the patterns of associations rather than concentrating on p-values to draw inferences. Replication of our findings by others will help to sort out the true associations from the potential false-positive findings.

The main strengths of our study are the large sample size and community-based study design. The present study is the largest study to date to investigate the relationships between cigarette smoking and *COMT*, *DBH* and *MAO-A*. The sample size provided enough statistical precision to detect meaningful gender-specific differences between genotypes and cigarette smoking, as well as analyses stratified by median age and smoking intensity.

The community-based design enhanced the generalizability of our results. For example, the allelic frequencies observed among Caucasians in our study did not vary significantly from those reported in the SNP500 database. However, by limiting our study to Caucasians, our findings may not be generalizable to other racial/ethnic groups.

By using information from follow-up surveys, the longitudinal sub-study better captured changes in smoking. However, the much smaller sample size of the longitudinal study precluded further in-depth analyses. Nevertheless, the inferences were strengthened by the corroboration of the overall null results observed in the main cross-sectional study by the generally null results of the longitudinal sub-study.

Conclusions

The overall results of our study do not support the presence of any association between the *COMT*, *DBH* and *MAO-A* SNPs we studied and smoking initiation or persistence.

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Figure 1.

Description of study populations in the cross-sectional study and sub-study with participants from the CLUE I and CLUE II studies in Washington County, Maryland.

Table 1

Distribution of descriptive characteristics and genotypes of participants by smoking status in Washington County, Maryland, 1989.

	Never Smokers		Former Smokers		Current Smokers	
MEN (n=3,871)						
Participants [*]	1,507	38.9	1,681	43.4	683	17.6
Age in 1989 ^{†‡}		51.4 (50.7, 52.2)		57.8 (57.2, 58.5)		47.5 (46.5, 48.5)
Education [§]	264	17.5	450	26.8	168	24.6
	1,243	82.5	1,231	73.2	515	75.4
Number of Cigarettes per day [†]	---			25.6 (24.8, 26.4)		24.5 (23.5, 25.5)
<i>COMT</i> [*]						
	371	26.2	394	25.6	173	27.4
	734	50.3	804	52.2	317	50.2
	310	21.9	341	22.2	142	22.5
	352	21.7	413	25.4	154	23.2
<i>DBH</i> [*]						
	696	42.9	770	47.4	331	49.9
	412	28.2	441	27.2	178	26.8
<i>MAO-A</i> [*]						
	1,067	73.0	1,181	72.7	490	73.1
	395	27.0	443	27.3	180	26.9
WOMEN (n=6,188)						
Participants [*]	3,829	61.9	1,342	21.7	1,017	16.4
Age in 1989 ^{†‡}		54.4 (53.9, 54.9)		55.1 (54.4, 55.9)		48.7 (47.9, 49.6)
Education [§]	858	22.4	301	22.4	276	27.1
	2,971	77.6	1,041	77.6	741	72.9
Number of Cigarettes per day ^{†‡}	---			17.3 (16.5, 18.1)		19.3 (18.6, 19.9)
<i>COMT</i> [*]						
	948	26.9	365	29.7	248	26.6
	1,817	51.6	593	48.2	468	50.2
	757	21.5	272	22.1	216	23.2
	973	26.2	341	26.2	235	23.8
<i>DBH</i> [*]						
	1,812	48.8	616	47.3	493	50.0
	928	25.0	345	26.5	258	26.2
<i>MAO-A</i> [*]						
	1,954	52.4	669	51.5	527	53.2
	1,475	39.6	515	39.7	390	39.4
	298	8.0	114	8.8	73	7.4

* Number, percentage

[†] Mean (95% CI)[‡] Indicates statistically significant ($p \leq 0.05$) heterogeneity.

Table 2

The association between genotypes of the *COMT*, *DBH* and *MAO-A* genes and smoking initiation, stratified by sex and median age in Washington County, Maryland, 1989.

			MEN		WOMEN	
			Ever Smokers	Never Smokers	Odds Ratio*	95% Confidence Interval
<i>COMT</i>	Total	AA/AG	1,688	1,105	1.0	
		GG	483	310	1.00	
	<54 years old	AA/AG	798	616	1.0	0.85, 1.17
<i>DBH</i>		GG	186	163	0.88	0.69, 1.11
	54≤ years old	AA/AG	890	489	1.0	0.88, 1.39
		GG	297	147	1.11	0.81, 1.09
<i>MAO-A</i>	Total	AA/AG	1,668	1,048	1.0	
		GG	619	412	0.94	0.71, 1.08
	<54 years old	AA/AG	752	561	1.0	0.81, 1.24
		GG	275	230	0.88	0.88, 1.18
	54≤ years old	AA/AG	916	487	1.0	0.79, 1.20
		GG	344	182	1.07	0.86, 1.32
	Total	CO/CC/CT	1,671	1,067	1.0	
		TO/TT	623	395	1.02	
	<54 years old	CO/CC/CT	746	574	1.0	
		TO/TT	282	225	0.97	
	54≤ years old	CO/CC/CT	925	493	1.0	
		TO/TT	341	170	1.11	

* Analysis adjusted for age

† Indicates $p \leq 0.05$.

Table 3

The association between genotypes of the *COMT*, *DBH* and *MAO-A* genes and persistent smoking, stratified by sex and median age in Washington County, Maryland, 1989.

		Number Current	Number Former	MEN Odds Ratio *	95% Confidence Interval	Number Current	Number Former	WOMEN Odds Ratio *	95% Confidence Interval
<i>COMT</i>	Total	490	1,198	1.0		716	958	1.0	
		142	341	1.15		216	272	1.01	
	<54 years old	336	462	1.0	0.91, 1.46	440	401	1.0	0.82, 1.25
	54≤ years old	89	97	1.29	0.93, 1.78	139	131	0.95	0.72, 1.25
<i>DBH</i>	Total	53	244	1.0		276	557	1.0	
		485	1,183	1.02	0.72, 1.44	77	141	1.13	0.82, 1.55
	<54 years old	178	441	1.0	0.82, 1.26	728	957	1.0	0.82, 1.20
	54≤ years old	323	429	1.01	0.82, 1.45	258	345	0.99	0.82, 1.23
<i>MAO-A</i>	Total	121	154	1.0		166	409	1.06	
		162	754	1.0	0.66, 1.29	284	548	1.0	0.82, 1.38
	<54 years old	57	287	0.92	0.77, 1.19	92	200	0.92	0.69, 1.23
	54≤ years old	490	1,181	1.0	0.69, 1.22	917	1,184	1.0	0.60, 1.12
Analysis adjusted for age									
Indicates $p \leq 0.05$.									

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Table 4

The association between genotypes of the *COMT*, *DBH* and *MAO*, *A* genes and persistent smoking, stratified by sex and smoking intensity in Washington County, Maryland, 1989.

Smoking intensity	Number Current	Number Former	MEN Odds Ratio [*]	95% Confidence Interval	Number Current	Number Former	WOMEN Odds Ratio [*]	95% Confidence Interval
≤10 per day	80	257	1.0		191	421	1.0	
	31	63	1.73 [†]	1.04, 2.87	62	127	1.08	0.76, 1.53
11–29 per day	229	509	1.0		371	336	1.0	
	57	156	0.88	0.61, 1.26	118	83	1.15	0.82, 1.60
30≤ per day	181	432	1.0		154	201	1.0	
	54	122	1.30	0.86, 1.96	36	62	0.68	0.42, 1.12
≤10 per day	78	258	1.0		199	436	1.0	
	39	82	1.59	1.00, 2.54	66	149	0.98	0.70, 1.38
11–29 per day	230	492	1.0		382	319	1.0	
	68	206	0.72	0.52, 1.00	139	124	0.92	0.69, 1.24
30≤ per day	177	433	1.0		147	202	1.0	
	71	153	1.22	0.84, 1.76	53	72	1.01	0.65, 1.57
≤10 per day	87	245	1.0		252	530	1.0	
	34	93	1.00	0.63, 1.60	18	49	0.78	0.44, 1.36
11–29 per day	215	507	1.0		482	399	1.0	
	79	191	0.95	0.68, 1.31	42	42	0.70	0.44, 1.13
30≤ per day	188	429	1.0		183	255	1.0	
	67	159	1.00	0.68, 1.45	17	23	1.12	0.56, 2.21

Analysis adjusted for age

states $p \leq 0.05$.

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Table 5
The association between genotypes of the *COMT*, *DBH* and *MAO*, *A* genes and persistent smoking, among those followed longitudinally from 1989 to 2003 in Washington County, Maryland.

		Number Quit	Number Persisted	MEN Odds Ratio [*]	95% Confidence Interval	Number Quit	Number Persisted	WOMEN Odds Ratio [*]	95% Confidence Interval
<i>COMT</i>	AA/AG	126	109	1.0		202	209	1.0	
	GG	37	29	0.97		69	51	0.71	0.47, 1.08
<i>DBH</i>	AA/AG	127	112	1.0	0.55, 1.71	217	206	1.0	
	GG	43	36	0.90	0.53, 1.53	69	72	1.10	0.74, 1.62
<i>MAO-A</i>	CO/CC/CT	127	111	1.0		274	255	1.0	
	TO/TT	49	40	1.14	0.68, 1.91	21	22	1.15	0.61, 2.17

^{*} Analysis adjusted for age
[†] Indicates $p \leq 0.05$.