Association between daily cigarette consumption and hypertension moderated by *CYP2A6* genotypes in Chinese male current smokers

T Liu[1], **RF Tyndale**[2], **SP David**[3,4,5], **H Wang**[1], **X-Q Yu**[6], **W Chen**[6], **X-Z Wen**[7], and **W-Q Chen**[1]

[1]Department of Biostatistics and Epidemiology, Guangdong Provincial Key Laboratory of Food, Nutrition and Health, School of Public Health, Sun Yat-Sen University, Guangzhou, China

[2]The Center for Addiction and Mental Health and the Departments of Psychiatry, Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada

[3]Center for Education in Family & Community Medicine and the Division of Family & Community Medicine, Stanford University, Stanford, CA, USA

[4]SRI International, Menlo Park, CA, USA

[5]Center for Primary Care & Prevention and the Department of Family Medicine, Brown Alpert Medical School, Pawtucket, RI, USA

[6]Department of Nephrology, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

[7]Department of Community Health, Brown Alpert Medical School, Providence, RI, USA

Abstract

The purpose of this study was to assess whether cytochrome P450 enzyme 2A6 (*CYP2A6*) genotypes moderate the association between smoking and hypertension. In this study, 954 Chinese male current smokers from a community-based chronic disease screening project in Guangzhou were interviewed with a structured questionnaire about socio-demographic status, smoking and other health-related behaviors. Blood was collected for DNA extraction and *CYP2A6* genotyping. Hypertension was defined according to 2007 ESH-ESC Practice Guidelines. A multivariate logistic regression was performed to examine the interaction between smoking quantity and *CYP2A6* genotypes on hypertension after adjusting for age, education level and other potential confounders. Multivariate analyses indicated that smoking more than 15 cigarettes per day significantly increased the risk of hypertension (odds ratio (OR)=1.59, 95% confidence interval (CI)=1.21-2.10) compared with smoking 1-15 cigarettes per day, and further suggested that smoking interacted with normal *CYP2A6* metabolizer genotype to increase the risk of

Correspondence: Professor W-Q Chen, Department of Biostatistics and Epidemiology, Guangdong Provincial Key Laboratory of Food, Nutrition and Health, School of Public Health, Sun Yat-Sen University, 74, Zhongshan Road 2, Guangzhou 510080, China, chenwq@mail.sysu.edu.cn.

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hypertension. Smokers consuming more than 15 cigarettes per day with normal *CYP2A6* metabolizer genotypes had the highest risk of hypertension (OR=2.04, 95% CI=1.11-3.75) compared with those consuming 1-15 cigarettes per day with slower *CYP2A6* metabolizer genotypes. These findings demonstrated that smoking quantity was positively associated with hypertension and that *CYP2A6* genotypes may moderate this relationship.

Keywords

cigarette smoking; CYP2A6; genetic polymorphisms; interaction

Introduction

Cigarette smoking is a well-documented risk factor for cardiovascular diseases, including atherosclerosis, coronary artery disease, acute myocardial infarction, hypertension and sudden cardiac death.[1 - 3] Multiple prospective studies have consistently shown that cigarette smoking is associated with increased risk of hypertension.[4 - 8] Cigarette smoking can stimulate sympathetic nervous activation,[9] oxidative stress,[10] vasopressor effects,[11] cause endothelial dysfunction,[12] vascular inflammation[13] and injury,[14] and increase arterial stiffness;[15] factors that might contribute to the development of hypertension.[16,17] However, the precise mechanisms underlying the etiological contribution of cigarette smoking to hypertension is still not well understood.

It has been well proved that nicotine is the main reason of smoking dependence, and approximately 80% of the inhaled nicotine from smoking is metabolized to cotinine by C-oxidation in liver, then the cotinine is further metabolized into trans-3-hydroxycotinine that is finally excreted in urine as the major nicotine metabolite.[18] Almost all the process of nicotine metabolization is mediated by cytochrome P450 2A6 (CYP2A6) enzyme, which is mainly expressed in liver.[18] The enzymatic activity of the CYP2A6 enzyme is moderated by variation in the *CYP2A6* gene, which has in turn been associated with variation in smoking behaviors.[19] To date, over 30 variants in the *CYP2A6* gene have been identified (http://www.cypalleles.ki.se/cyp2a6.htm). Numerous studies have found an association of genetic variation in *CYP2A6* with a number of aspects of smoking, including age of smoking onset, smoking duration,[20,21] likelihood of smoking cessation,[22] depth and amount of smoke inhalation,[23] and the number of cigarettes smoked per day.[24 - 26] Moreover, *CYP2A6* genotype appears to moderate the relationship between cigarette smoking and smoking-related cancers, such as lung cancer,[26 - 28] nasopharyngeal carcinoma,[29] pancreatic cancer,[30] bladder cancer,[31] and head and neck cancer.[32] However, little is known about the interactive effect between cigarette smoking and *CYP2A6* genotype on the development of hypertension.

The present study aimed to assess the interaction between smoking quantity and *CYP2A6* genotype on hypertension in Chinese male current smokers.

Methods

Subjects

Subjects were from a community-based chronic disease-screening project conducted in Guangzhou and Zhuhai of China from July 2006 to June 2007.[32] In that project, a total of 7293 residents (2465 males and 4828 females) aged 20 years or above were randomly selected using a stratified multistage sampling method. In this population, 1440 participants were smokers (1059 current smokers and 381 former smokers, or 1327 male smokers and 113 female smokers). To minimize the confounding effect of smoking status and gender only, male current smokers were included in the analysis of interaction between amounts of daily cigarette consumption and *CYP2A6* genotype on hypertension. Of the 1025 current male smokers, 71 refused to have blood samples drawn and were therefore excluded for a total of 954 male current smokers in these analyses (Figure 1). This study was approved by the Ethics Committees of Sun Yat-sen University in Guangzhou of China and a written informed consent was obtained from all study participants.

Data collection

A face to face interview was conducted by well-trained medical students or clinical doctors using a structured questionnaire inquiring about socio-demographic characteristics (for example, age, gender, income, education level, marital status, occupation) and smoking behaviors. The survey was completed at local health care centers, and a blood specimen was obtained from each subject for *CYP2A6* genotyping.

Measurement of smoking behaviors

In the present study, smoking included current smoking and former smoking. A current smoker was defined by having smoked more than 100 cigarettes in one's lifetime and having smoked at least one cigarette daily at the time of the interview.[33] A 'former smoker' was someone who had smoked more than 100 cigarettes in their lifetime, but reported that they had quit smoking. Former smokers included ex-daily smokers and ex-non-daily smokers.[33] Current smokers reported their most recent average number of cigarettes consumed per day, and they were categorized into two groups according to the median of daily cigarette consumption: smokers who consumed 1 - 15 cigarettes per day and smokers who consumed more than 15 cigarettes per day.[34]

Definition of alcohol consumption and exercise

Alcohol consumption was divided into two categories (ever or never) based on whether a subject had at any time consumed alcohol at least three times a week for more than 6 months.[35] Physical activity was also classified into two categories: regular physical activity, defined as leisure time physical activity engaged in any intensity for 30min at least three times a week, or no regular physical activity.[36]

Measurement and definition of obesity and abdominal obesity

Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). Participants with a BMI $23 \, \text{kg m}^{-2}$ and $<30 \, \text{kg m}^{-2}$ were classified as overweight, and

those with a BMI 30 kg m^{-2} were classified as obese.[37] Waist-to-hip ratio (WHR) was calculated by dividing the waist circumference by the hip circumference. Abdominal obesity was defined by WHR 0.90.[38]

CYP2A6 genotyping

Blood was collected from 954 male current smokers. The selection of *CYP2A6* alleles assayed in the present study was based on two factors: (a) the impact of the variant on CYP2A6 enzyme function, and (b) the frequency of the variant in Chinese populations. The genotyping of *CYP2A6*4, *5, *7, *9* and *10* were performed using the methods previously published by our group.[38] Normal, intermediate, slow and poor *CYP2A6* metabolizer genotypes are defined here on the basis of the predicted pharmacokinetic impact of genotypes resulting from the different variant alleles studied. The *CYP2A6*9* allele was considered a 'decrease of function' allele (D), and *4, *5, *7* and *10* were considered 'loss of function' (L) alleles. 'Normal metabolizers' were defined as having neither a D nor an L allele (that is, *1/*1*). 'Intermediate metabolizers' had only one D allele (for example, *1/ *9*), which was associated with approximately 75% of the activity of normal metabolizers. 'Slow metabolizers' had either one L allele or two D alleles (for example, *1/*4* or *9/*9*), which were associated with 50% of the activity of normal metabolizers. 'Poor metabolizers' had either one L and one D allele or two L alleles (for example, *9/*4* or *4/*4*), which were associated with <25% of the activity of normal metabolizers.[25,39] In this study, the frequencies of normal, intermediate, slow and poor metabolizers in current smokers were 441 (46.2%), 137 (14.4%), 254 (26.6%) and 122 (12.8%), respectively.[39] Considering the number of subjects with both heavy smoking and hypertension was few (11/122) in the current smokers with poor *CYP2A6* metabolizer genotype, we combined poor *CYP2A6* metabolizer genotype with slow *CYP2A6* metabolizer genotype and named them the 'slower *CYP2A6* metabolizer genotype', which may increase the statistical power.

Diagnostic criteria for hypertension

Systolic blood pressure and diastolic blood pressure were measured three times in each subject in the morning using a mercury sphygmomanometer in the sitting position after a 15-min rest, and the values were then averaged. Every smoker was asked not to smoke after getting up until finishing the blood pressure measurement. Hypertension was defined as systolic blood pressure 140 mm Hg and/or diastolic blood pressure 90 mm Hg according to the 2007 ESH-ESC Practice Guidelines,[40] or as self-reported diagnosed hypertension requiring antihypertensive drugs.Family history of hypertension was defined as self-reported of one or more hypertensive parents or grandparents.

Statistical analysis

For continuous variables, mean ± s.d. was calculated. Categorical variables were given as percentage of subjects with the respective attribute. χ^2 tests were performed to test the differences of these attributes between male current smokers with and without blood samples.

A binary logistic regression was performed to assess the interaction between smoking quantity (1 = smoking 1-15 cigarettes per day, 2 = smoking more than 15 cigarettes per day)

and *CYP2A6* genotypes (1 = slower, 2 = intermediate, 3 = normal metabolizers) on hypertension. In this binary logistic regression, age, education level, alcohol consumption, physical exercise, family history of hypertension, BMI and WHR were first entered into the model for adjusting for their potential confounding effect; smoking quantity and *CYP2A6* genotypes were then entered into the model to test for their main effects, and an interaction term between smoking quantity and *CYP2A6* genotypes was then added into the model to test their interaction effect. In addition, according to smoking quantity and *CYP2A6* genotypes, the subjects were divided into six groups taking smokers who consumed 1-15 cigarettes per day with slower *CYP2A6* metabolizer genotype as the reference group; the effect sizes on hypertension of the other five groups were assessed by a binary logistic regression with adjusting for age, education level, alcohol consumption, physical exercise, family history of hypertension, and BMI and WHR. The six odds ratios (ORs) are presented graphically.

The frequencies of *CYP2A6 *4, *5, *7, *9* and *10* alleles were in Hardy-Weinberg equilibrium (*P*>0.05). All *P* values were two-sided and statistical significance was *P* = 0.05. All the analyses were conducted with SPSS 13.0 (SPSS, Inc., Chicago, IL, USA).

Results

A comparison of the characteristics of male current smokers with different smoking quantities

There were significant differences of education level, alcohol consumption, exercise, abdominal obesity, hypertension and *CYP2A6* genotypes between the two groups (details are presented in Table 1).

The interaction between smoking quantity and *CYP2A6* genotypes on hypertension

Table 2 and Figure 1 present the interaction of smoking quantity with *CYP2A6* genotypes on hypertension. After adjusting for age, education, alcohol consumption, physical exercise, family history of hypertension, BMI and WHR, the smokers who consumed more than 15 cigarettes per day had a significantly higher risk of hypertension than the smokers who consumed 1-15 cigarettes per day (OR=1.59, 95% confidence interval (CI) = 1.21-2.10). In addition, normal *CYP2A6* metabolizers had a significantly higher risk of hypertension than slower metabolizers (OR=1.75, 95% CI=1.30-2.36). The interaction analysis showed a significant interaction effect between smoking more than 15 cigarettes per day and normal *CYP2A6* metabolizer genotype on hypertension
(OR $_{\text{Normal metabolizers} \times \text{smoking} > 15 \text{ cigarettes per day}}$ = 2.04, 95% CI = 1.11 - 3.75) (Table 2). In the six groups of current smokers stratified by smoking quantity and *CYP2A6* genotypes, adjusted ORs for hypertension increased from those with slower *CYP2A6* metabolizer genotype, intermediate metabolizer genotype and normal metabolizer in both smoker groups, while the smokers who consumed more than 15 cigarettes per day with normal *CYP2A6* metabolizer genotype had the highest risk of hypertension (OR = 2.74, 95% CI=1.82-4.12) compared with the smokers who consumed 1-15 cigarettes per day with slower *CYP2A6* metabolizer genotype (Figure 2).

Discussion

In the present cross-sectional study in a community-based sample of Guangzhou and Zhuhai in Southern China, we found among current Chinese smokers that there was a significantly higher prevalence of hypertension in the smokers who consumed more than 15 cigarettes per day than the smokers who consumed 1-15 cigarettes per day. Interestingly, we further observed that smoking quantity and *CYP2A6* genotypes might interact on risk for hypertension, such that the smokers who consumed more than 15 cigarettes per day with a normal *CYP2A6* metabolizer genotype had significantly increased risk for hypertension compared with the smokers who consumed 1-15 cigarettes per day with a slower *CYP2A6* metabolizer genotype.

Association between cigarette smoking and hypertension

The effect of cigarette smoking on hypertension remained consistent in recently published studies. Four prospective studies 3 in men consistently showed that heavy smoking (consuming more than 20 cigarettes per day) significantly increased the risk of incident hypertension with adjustment for age, BMI, physical exercise, alcohol intake and other confounders,[5,6,8,41] and a prospective study in women found that smoking more than or equal to 15 cigarettes per day had a similar effect on increasing the risk for hypertension.[7] Moreover, a population-based cross-sectional study in 12417 men indicated that current smoking was positively and significantly associated with systolic hypertension after adjusting for age, alcohol intake and BMI,[42] and another cross-sectional study in a population-based sample of Vietnamese men found that men with smoking durations of over 30 years, or with lifetime smoking of over 20 pack-years, had a significantly higher rate of hypertension than those who had never smoked after controlling for age and BMI.[43] Similar results were also obtained in the present study where we found that current smokers who consumed more than 15 cigarettes per day had a significantly higher risk for hypertension than the smokers who consumed 1-15 cigarettes per day after adjusting for age, education level, alcohol consumption, physical exercise, family history of hypertension, BMI and WHR. Together these studies confirm that cigarette smoking is an important risk factor for hypertension.

The interaction between smoking quantity and *CYP2A6* genotypes on hypertension

The CYP2A6 enzyme not only activates some tobacco-specific nitrosamines into ultimate carcinogens but also alters smoking behaviors because of its participation in nicotine metabolic inactivation.[44]. Previous studies have reported that *CYP2A6* genetic variation is related to smoking behaviors[45,46] and the relationship between smoking quantity and risk of multiple cancers.[44,47] Here, an interaction between smoking more than 15 cigarettes per day and *CYP2A6* genotype on hypertension was observed, after adjustment for confounding factors. Compared with the smokers who consumed 1-15 cigarettes per day with slower *CYP2A6* metabolizer genotypes, the smokers who consumed more than 15 cigarettes per day with normal *CYP2A6* metabolizer genotypes had the highest risk of hypertension.

A potential explanation for the observed relationship between *CYP2A6* genotypes, smoking and hypertension is as follows. Compared with light smokers, heavy smokers may be

exposed to more harmful substances from cigarettes than light smokers. Moreover, smokers with normal *CYP2A6* metabolism may smoke with increased mean puff volume and total puff volume compared with reduced *CYP2A6* metabolizers, which could increase their overall exposure to harmful cigarette smoke constituents.[23] As noted above, some harmful substances from cigarette smoke may cause oxidative stress,[10] vasopressor effects,[11] endothelial dys-function,[12] vascular injury,[14] increased arterial stiffness[15] and markers of inflammation,[13] all of which may be linked with the development of hypertension in smokers.[16,17] Therefore, the combined effect of heavy smoking and normal *CYP2A6* genotypes on smoking topography may increase inhaled cigarette toxicant exposure, thereby contributing to the risk of developing hypertension. In addition, we also analyzed the actual systole and diastolic blood pressure (mm Hg) in individuals with different *CYP2A6* genotypes, and found higher systolic and diastolic blood pressure in normal *CYP2A6* metabolizers than that in other *CYP2A6* genotype metabolizers, although without statistical significance (see Appendix Table).

Limitations

Several limitations may influence the interpretation of results. First, this was a cross-sectional study design. Therefore, the data do not permit making conclusions about a causal relationship. Second, the data was retrospectively collected with a self-administrated questionnaire that may lead to recall bias. Third, antihypertensive medication was not assessed, which might impact the measurement of blood pressure and the relationship between smoking, genotype and hypertension. Fourth, sample selection bias might result in less healthy individuals being over-represented among those who did not take part in the study. Moreover, females were not included in the final analyses because of very few female smokers, limiting generalizability. However, we do not expect that such selection biases substantially affected our findings. Another potential limitation is that although higher frequency variants with functional impact were assessed, not all *CYP2A6* genetic variants were assayed in this study, which might lead to misclassification of *CYP2A6* genotypes. Furthermore, because of the relative size of the final study sample, statistical power was insufficient to analyze the effect of smoking quantity (continuous measure, or more detail categories, such as 1 - 5, 5-10 cigarettes per day) on hypertension. Finally, participants' dietary and drug histories were not investigated that might affect the activity of CYP2A6[(ref. 18)] and further distort the relationship of *CYP2A6* genotypes with hypertension. For instance, grapefruit juice can inhibit CYP2A6-mediated coumarin metabolism,[48] but phenobarbital and rifampin can induce CYP2A6 activity.[49]

In summary, this study revealed that smoking quantity was positively associated with hypertension and *CYP2A6* genotypes might moderate this relationship in Chinese male current smokers. These findings expand on our understanding of the effect, and possible mechanisms involved, in the relationship between cigarettes smoking and hypertension.

Acknowledgments

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What was known about this topic

- Smoking is a risk factor of hypertension.

- Smoking and *CYP2A6* genotype interacts to affect the risk for smoking-related cancers.

- Whether *CYP2A6* genotypes moderate the association between smoking and hypertension is unknown.

What this study adds

- Smoking more than 15 cigarettes per day significantly increased the risk of hypertension compared with smoking 1-15 cigarettes per day.

- Smoking more than 15 cigarettes per day interacted with normal *CYP2A6* metabolizer genotype to increase the risk of hypertension compared with the smokers who consumed 1-15 cigarettes per day also with slower CYP2A6 metabolizer genotype.
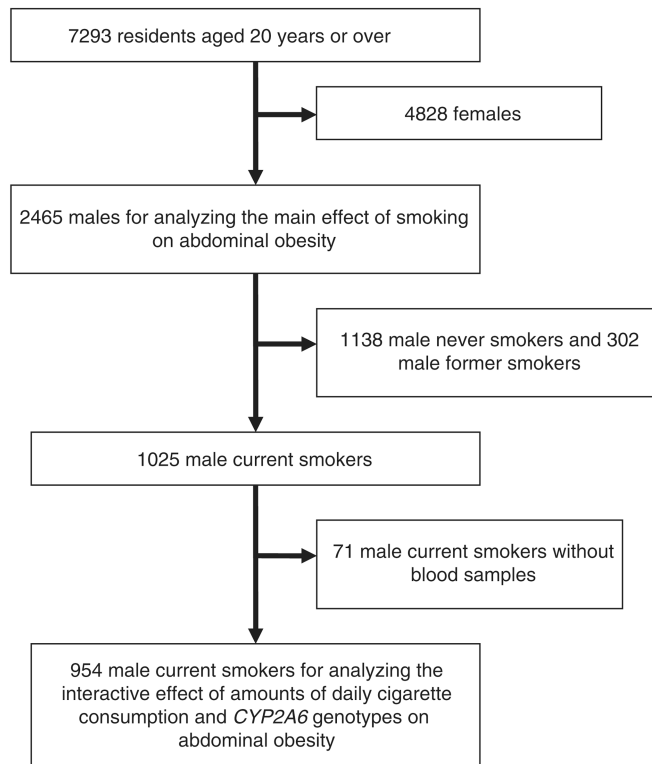
Figure 1.
Study subjects selection diagram.
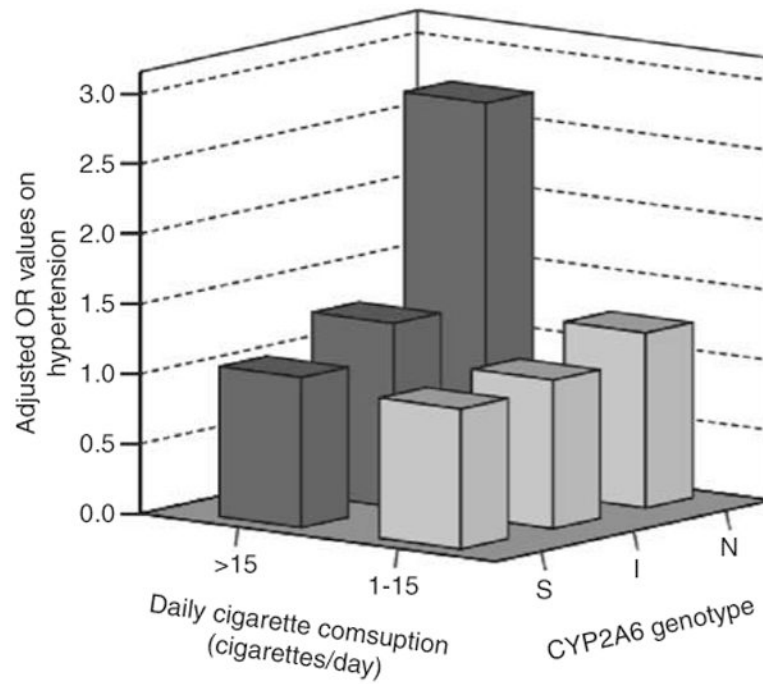
Figure 2.
Effect size (adjusted ORs) of smoking quality and *CYP2A6* genotypes on hypertension stratified by both levels of daily cigarette consumption and *CYP2A6* genotypes in 954 Chinese male current smokers. The group with smokers who consumed 1 - 15 cigarettes per day and *CYP2A6* slow metabolizer genotype was the reference group (OR=1). The adjusted variables were age, education level, physical exercise, alcohol consumption, family history of hypertension, BMI and WHR. N, *CYP2A6* normal metabolizer genotype; I, *CYP2A6* intermediate metabolizer genotype; S, *CYP2A6* slower metabolizer genotype.

Table 1

Comparisons of study subject characteristics with different smoking quantity

Variables	Current smokers with 1-15 cigarettes per day (n = 545)		Current smokers with more than 15 cigarettes per day (n = 409)		χ^2	P value
	No	%	No	%		
Age (years)					7.17	0.208
20 - 29	43	7.9	18	4.4		
30-39	65	11.9	49	12.0		
40-49	85	15.6	80	19.6		
50-59	181	33.2	140	34.2		
60-69	131	24.0	97	23.7		
70-86	40	7.4	25	6.1		
Occupation					7.56	0.373
Worker	131	24.0	104	25.4		
Farmer	69	12.7	46	11.2		
Person in charge	32	5.9	20	4.9		
Technician	31	5.7	12	2.9		
Service personnel	73	13.4	47	11.5		
Retired personnel	121	22.2	101	24.7		
Jobless	64	11.7	57	13.9		
Others	24	4.4	22	5.4		
Education					11.04	0.026
Illiteracy	12	2.2	9	2.2		
Elementary school	83	15.2	66	16.1		
Junior middle school	185	33.9	153	37.4		
Senior middle school or vocational secondary school	174	31.9	143	35.0		
College or above	91	16.7	38	9.3		
Family monthly income (yuan)					2.83	0.586
<1000	75	13.8	53	13.0		
1000-2999	172	31.6	145	35.5		
3000-4999	148	27.2	114	27.9		

Variables	Current smokers with 1-15 cigarettes per day (n = 545)		Current smokers with more than 15 cigarettes per day (n = 409)		χ^2	P value
	No	%	No	%		
5000	95	17.4	59	14.2		
Do not know or refuse to answer	55	10.1	39	9.5		
Family history of hypertension					0.17	0.680
No	377	69.2	288	70.4		
Yes	168	30.8	121	29.6		
Alcohol consumption					7.02	0.030
No	364	66.8	239	58.4		
Yes	154	28.3	145	35.5		
Former drinker	27	5.0	25	6.1		
Exercise					6.60	0.010
No	190	34.9	176	43.0		
Yes	355	65.1	233	57.0		
BMI					3.87	0.145
Normal	256	47.0	166	40.6		
Overweight	275	50.5	231	56.5		
Obesity	14	2.6	12	2.9		
Abdominal obesity					12.23	<0.001
No	358	65.7	223	54.5		
Yes	187	34.3	186	45.5		
Hypertension					14.30	<0.001
No	379	69.5	236	57.7		
Yes	166	30.5	173	42.3		
CYP2A6 genotype					3.76	0.153
Slower metabolizers	229	42.0	147	35.9		
Intermediate metabolizers	73	13.4	64	15.6		
Normal metabolizers	243	44.6	198	48.74		

Abbreviation: BMI, body mass index.

Table 2

Interaction between smoking quantity and *CYP2A6* genotypes on hypertension in 954 Chinese male current smokers

	Hypertension		Model 1	Model 2	Model 3
	Controls N (%)	Cases N (%)	Adjusted OR (95% CI)[b]	Adjusted OR (95% CI)[b]	Adjusted OR (95% CI)[b]
Hypertension[a]					
Daily cigarettes consumption					
1-15 cigarettes per day	381 (62.0)	164 (48.4)	1		
>15 cigarettes per day	234 (38.0)	175 (51.6)	1.59* (1.21-2.10)		1.07 (0.68-1.71)
CYP2A6 genotype					
Slower metabolizers	264 (42.9)	112 (33.0)		1	1
Intermediate metabolizers	93 (15.1)	44 (13.0)		1.10 (0.71-1.70)	1.06 (0.59-1.90)
Normal metabolizers	258 (42.0)	183 (54.0)		1.75* (1.30-2.36)	1.25 (0.84-1.88)
Interaction effect					
Intermediate metabolizers × (> 15 cigarettes per day)					1.16 (0.49-2.75)
Normal metabolizers × (> 15 cigarettes per day)					2.04* (1.11-3.75)

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Dependent variable: hypertension (0 = no, 1 = yes).

[b] Binary logistic regression model adjusted for age, education level, physical exercise, alcohol consumption, family history of hypertension, BMI and WHR.

*P<0.05

Appendix

The associations of CYP2A6 genotypes with systolic and diastolic blood pressure in 954 Chinese male current smokers

CYP2A6 genotypes	n (%)	Systolic blood pressure (mm Hg)						Diastolic blood pressure (mm Hg)					
		Mean±s.d.	F	P	Mean±s.e.[a]	F	P	Mean±s.d.	F	P	Mean±s.e.[a]	F	P
Slower metabolizers	376 (39.4%)	124.0 ± 18.6	1.81	0.165	124.0 ± 0.9	2.47	0.085	80.8 ± 11.0	0.47	0.623	80.7 ± 0.5	0.86	0.422
Intermediate metabolizers	137 (14.4%)	125.5 ± 20.5			125.2 ± 1.6			80.7 ± 10.3			80.8 ± 0.9		
Normal metabolizers	441 (46.2%)	126.6 ± 18.3			126.8 ± 0.9			81.5 ± 10.9			81.6 ± 0.5		

[a] General linear model adjusted for age, education level, physical exercise, alcohol consumption, family history of hypertension, BMI and WHR.