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Relationship Between Amounts of Daily Cigarette Consumption and Abdominal Obesity Moderated by *CYP2A6* Genotypes in Chinese Male Current Smokers

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Abstract

Background—Cigarette smoking is an important risk factor for abdominal obesity. However, the degree to which the *CYP2A6* genotype moderates the relationship between smoking and abdominal obesity has not been established.

Purpose—This study aims to investigate whether or not the relationship between smoking quantity and abdominal obesity is influenced by *CYP2A6* genotypes.

Methods—Nine hundred fifty-four male current smokers were selected. A venous specimen was collected to test serum cotinine and *CYP2A6* genotype, and all smokers were divided into heavy (>15 cigarettes/day) and light smokers (≤15 cigarettes/day).

Results—Heavy smoking increased the risk of abdominal obesity (odds ratio (OR)=1.57; 95% CI, 1.13–2.19) compared with light smoking. Furthermore, heavy smoking had a positive interactive effect with *CYP2A6* poor metabolizer genotype on abdominal obesity (OR=3.90; 95% CI, 1.25–12.18). Moreover, *CYP2A6* poor metabolizer genotypes were associated with slower nicotine metabolism.

Conclusions—Heavy smoking may increase the risk of abdominal obesity—particularly in smokers with *CYP2A6* poor metabolizer genotypes.

Keywords

Cigarette smoking; *CYP2A6* genotypes; Abdominal obesity; Interaction

Introduction

Obesity, generally defined as an excess accumulation of body fat [1], is regarded as one of the most important and common public health problems worldwide posing increased risks for type 2 diabetes, many cancers, and heart disease and its risk factors [2, 3]. Cigarette smoking has been associated with body weight and body shape in previous studies. Current smokers tend to have lower body mass index (BMI) but larger waist circumference and waist-to-hip ratios than non-smokers [4–6]. Given that abdominal obesity is a major risk factor for the development of many chronic illnesses and overall mortality [3, 7–9], research exploring the association between abdominal obesity and smoking has major public health implications. Previous studies indicated that waist circumference was more precise than waist-to-hip ratios to assess abdominal obesity [10]. Therefore, in the present study, we chose waist circumference to assess abdominal obesity and further investigated the effect of smoking on waist circumference.

Previous studies suggest that the relationship between smoking and abdominal obesity may be explained by increased plasma levels of nicotine, rather than other constituents of cigarette smoke [6, 11, 12]. Nicotine may increase plasma cortisol levels [13], which in turn could contribute to increased accumulation of abdominal fat [12]. Moreover, it is well

established that approximately 70% to 80% of inhaled nicotine is metabolized to cotinine (an inactive metabolite) mainly by *CYP2A6* enzyme [14] and that the activity of *CYP2A6* enzyme is moderated by variation in the *CYP2A6* gene [15, 16]. However, it is unclear whether cigarette smoking and *CYP2A6* genotypes have an interactive effect on abdominal obesity.

Therefore, the present study aimed to assess whether or not *CYP2A6* genotypes interact with amount of daily cigarette consumption to affect abdominal obesity in Chinese male current smokers.

Methods

Study Subjects

Subjects were from a community-based chronic disease screening project conducted in Guangzhou and Zhuhai of China from July 2006 to June 2007 [17]. In that project, a total of 7,293 residents (2,465 males and 4,828 females) aged 20 years or over were randomly selected using a stratified multistage sampling method. In this population, 1,440 participants were smokers (1,059 current smokers and 381 former smokers or 1,327 male smokers and 113 female smokers). The present study focused on interactions between smoking and *CYP2A6* metabolizer status on abdominal obesity. Therefore, given that there were so few female smokers in the group, thereby limiting statistical power, the genotyped study population was limited to the 1,025 male current smokers in the cohort. Of the 1,025 current male smokers, however, 71 refused to provide blood samples resulting in a final study sample of 954 male current smokers. Figure 1 provides additional details on the selection of the study sample. This study was approved by the Ethics Committees of Sun Yat-sen University in Guangzhou, China, and written informed consent was obtained from all participants.

Data Collection

All the sampled subjects were interviewed with a structured questionnaire by trained medical students or clinical doctors inquiring about their socio-demographic characteristics, smoking behaviors, consumption of alcohol, caffeine, diet, and physical activity [17]. Anthropometric indices including height, weight, and waist circumference were also measured and blood samples were collected via venipuncture. All clinical evaluations and data collection were conducted at local health care centers, and methods for data collection are described in detail elsewhere [17].

Measurement and Definition of Cigarette Smoking and Other Lifestyle Factors

A “current smoker” was defined by having smoked greater than 100 cigarettes in one’s lifetime and having smoked at least one cigarette daily at the time of the interview [18]. Daily average cigarette consumption was reported for current smokers. Alcohol, tea and coffee consumption were divided into two categories (ever or never) based on whether a subject had at any time consumed alcohol, tea or coffee at least 3 times a week for more than 6 months [19]. Physical activity was also classified into two categories: regular physical

activity defined as leisure time physical activity engaged in any intensity for 30 min at least three times a week, otherwise defined as no regular physical activity group [20].

Measurement of Obesity and Abdominal Obesity

Body height was measured to the nearest centimeter. Body weight was measured to the nearest 0.1 kg using a digital bathroom scale while the subjects were barefoot and wearing light clothing. BMI was calculated as weight (in kg) divided by the square of height (in m). Participants with a BMI of ≥ 23 and <30 kg/m² were classified as overweight, and those with a BMI of ≥ 30 kg/m² were classified as obese [21]. Waist circumference at the navel level and hip circumference were measured in duplicate with the subjects standing and at the end of expiration under normal breathing, and the average value was used in the present study. Abdominal obesity was defined by waist circumference of ≥ 85 cm [22].

CYP2A6 Genotyping

The selection of *CYP2A6* alleles assayed in the present study was based on two factors: (a) the impact of the genetic variant on *CYP2A6* enzyme function and (b) the frequency of the variant in Chinese populations. The genotyping of *CYP2A6**4 [23], *CYP2A6**9 [24], *CYP2A6**5 [25], *CYP2A6**7, and *CYP2A6**10 [26] was performed, with minor modifications to the *CYP2A6**5 assay and with the first and second amplification primers changed to the R6 [27] and R0 [28] as we have previously described [29]. The 954 current male smokers were divided into four groups (normal, intermediate, slow, and poor *CYP2A6* metabolizer genotypes) based on the predicted pharmacokinetic impact of genotypes resulting from the different variant alleles studied [29].

Measurement of Serum Cotinine Concentration

Serum cotinine (the main metabolite of nicotine with a half-life of 16 h) concentrations were measured in the 954 current male smokers rather than nicotine directly because of the relatively shorter half-life of nicotine (1–2 h) compared to cotinine (13–18 h) [14], which makes accurate assessment of individual nicotine levels directly not possible. Given that approximately 70% to 80% of inhaled nicotine is metabolized to cotinine [14], we posited that for a given number of cigarettes smoked, the higher level of serum cotinine concentrations observed, the lower bioavailability of nicotine. Therefore, it was further assumed that smokers with higher levels of serum cotinine would have a higher BMI and/or lower waist circumference when their daily cigarettes consumption was controlled. The serum cotinine was tested by enzyme-linked immunosorbent assay kit, provided by Immulysis Corporation, Pomona, CA, USA. The technique is sensitive to within ± 1 ng/ml.

Statistical Analysis

For continuous variables, means \pm standard deviation were calculated. Categorical variables were given as percentage of subjects with the respective attribute. Several Chi-square tests were performed to test the differences between the baseline characteristics of male current smokers with and without blood samples.

A series of binary logistic regression models was used to analyze the binary relationships between amounts of daily cigarette consumption (0 = 1–15 (light smokers) cigarettes/day, 1 = larger than 15 cigarettes/day (heavy smokers)) defined by the median of cigarettes per day (i.e., 15), serum cotinine (0 < 225.31 and 1 ≥ 225.31 ng/ml) defined by the median of cotinine level (i.e., 225.31 ng/ml), *CYP2A6* genotypes (0 = normal metabolizers, 1 = intermediate metabolizers, 2 = slow metabolizers, and 3 = poor metabolizers) and abdominal obesity in 954 current male smokers with blood samples.

Daily cigarette consumption and *CYP2A6* genotypes measures were first entered into a binary logistic regression model of abdominal obesity defined by waist circumference, then an interaction term between amounts of daily cigarette consumption and *CYP2A6* genotypes was further added into the model. Current smokers were divided into eight groups, stratified by heavy/light smoking and *CYP2A6* genotype with light smokers possessing normal metabolizer genotypes as the reference group. The effect sizes for the comparisons of risk for abdominal obesity between these groups were assessed by a binary logistic regression. A three-dimensional bar graph of the eight corresponding odds ratios (OR) illustrate these comparisons (Fig. 2). In these logistic regression models, all independent variables were introduced using the “enter method.”

Potential confounding factors were adjusted for in the analysis, including age, occupation, family monthly income, alcohol consumption, exercise, coffee consumption, tea consumption, and BMI. Confounding factors were defined as the factors that explain or produce all or part of the difference between the measure of association and the measure of effect that would be obtained with a counterfactual ideal [30].

The frequencies of *CYP2A6**4, *CYP2A6**5, *CYP2A6**7, *CYP2A6**9, and *CYP2A6**10 alleles were in Hardy–Weinberg distribution ($p > 0.05$) and were of similar frequency to those previously observed in Chinese samples [29]. All p values were two-sided ($\alpha = 0.05$). All analyses were conducted with SPSS 13.0 software (SPSS, Inc., Chicago, IL USA).

Results

Comparison of Characteristics Between Male Current Smokers with and Without Blood Samples

There were significant differences of age, occupation, family history of hypertension, exercise, BMI, and abdominal obesity distribution between the two groups of subjects. More details are presented in Table 1.

Association among Smoking Quantity, Serum Cotinine, *CYP2A6* Genotypes, and Abdominal Obesity in Current Smokers

Table 2 presents the results of associations among smoking quantity, serum cotinine, *CYP2A6* genotypes, and abdominal obesity in male current smokers ($n = 954$) after adjusting for potential confounders. Heavy smokers had a higher risk of abdominal obesity than light smokers (OR = 1.57; 95% CI, 1.13–2.19). Smokers with higher levels of serum cotinine had a significant lower waist circumference (OR = 0.61; 95% CI, 0.41–0.90) and smoked significantly more cigarettes than smokers with lower serum cotinine. Smokers with

CYP2A6 poor metabolizer genotype smoked fewer cigarettes per day (OR=0.59; 95% CI, 0.38–0.90) and had lower levels of serum cotinine (OR=0.52; 95% CI, 0.34–0.79) than smokers with *CYP2A6* normal metabolizer genotype.

Interaction Between Cigarette Smoking and *CYP2A6* Genotypes on Abdominal Obesity

After adjustment for potential confounding factors, there was an interaction between heavy smoking and *CYP2A6* genotype on abdominal obesity such that individuals with *CYP2A6* poor metabolizer genotypes were more likely to have abdominal obesity if they were heavy smokers compared with light smokers (OR_{*CYP2A6* poor metabolizer genotype × heavy smoking}=3.90; 95% CI, 1.25–12.18) (Table 3). Moreover, although not statistically significant, compared with the light smokers with normal *CYP2A6* metabolizer genotypes, heavy smokers with poor *CYP2A6* metabolizer genotype trended towards a higher risk of abdominal obesity (OR=2.07; 95% CI, 0.85–5.01) (Fig. 2).

Discussion

To our knowledge, this is the first study to report analyses of joint associations between daily cigarette consumption and *CYP2A6* genotypes with abdominal obesity. In this cross-sectional study, it was found that heavy smokers, as indicated by consuming >15 cigarettes/day, had a larger waist circumference compared with light smokers. After adjustment for amount of daily cigarette consumption and other potential confounding factors, serum cotinine was negatively correlated to waist circumference. More importantly, heavy cigarette smoking interacted with *CYP2A6* genotypes on abdominal obesity as defined by waist circumference, suggesting that subjects with poor metabolizer *CYP2A6* genotypes who are heavy smokers are a high risk group for abdominal obesity when compared with light smokers with normal metabolizer *CYP2A6* genotypes.

The Effect of Cigarette Smoking on Abdominal Obesity

It is well documented that smoking may increase the risk of abdominal obesity. For example, Rose and colleagues observed that current cigarette smoking was associated with greater central adiposity [31]. Moreover, several studies have reported that current smokers tend to have larger waist circumference or waist-to-hip ratios than never smokers [5, 6, 32–35], and a study by Mizuno and colleagues found that obese smokers had a larger waist circumference than obese non-smokers and that there was no difference in waist circumference between smokers and non-smoker in non-obese subjects [36]. Similarly, the present study observed that heavy smokers had a larger waist circumference compared with light smokers. Furthermore, the Framingham Heart Study and a study in Japan respectively found that cigarette smoking was associated with higher accumulation of visceral adipose tissue compared to never smokers [37, 38].

The mechanism by which cigarette smoking increases the accumulation of visceral adipose tissue is unclear, but three hypotheses have been proposed. The first proposed mechanism is that smoking's anti-estrogenic effect [11], which is related to a hormonal imbalance, can lead to abdominal obesity [39]. The second hypothesis is that higher levels of nicotine intake may increase plasma cortisol levels [13], and that this elevation of plasma cortisol is associated

with abdominal adiposity [12]. The third theory posits that cigarette smoking may also induce a heightened activity of gluteal adipose tissue lipoprotein lipase, resulting in up-regulation of the uptake and storage of triglyceride fatty acids by the abdominal adipocytes and consequent increases in abdominal fat mass [6]. In addition, a higher prevalence of other unhealthy habits (e.g., less physical exercise, higher alcohol consumption, and less consumption of fresh vegetables and fruits) among heavy smokers may also influence the abdominal obesity [12, 40].

Interaction between Cigarette Smoking and *CYP2A6* Genotypes on Abdominal Obesity

CYP2A6 is the major enzyme mediating nicotine metabolism which can alter smoking behaviors due to differential nicotine clearance, in addition to its role in activating a number of tobacco-specific nitrosamines including 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), N-nitrosornicotine, N-nitrosodiethylamine, and polycyclic aromatic hydrocarbons into potentially carcinogenic forms [41]. Most of the functionally important polymorphic alleles of *CYP2A6* either result in abolished activity (*2, *4, *5, and *20) or reduced activity (*6, *7, *10, *11, *12, *17, *18, and *19), and *CYP2A6* genetic variation is related to smoking behavior [42, 43] and tobacco-related cancer risk [41, 44]. Smokers with more rapid nicotine metabolism are at higher increased risk of lung cancer [45, 46], nasopharyngeal carcinoma [47], pancreatic cancer [48], bladder cancer [49], and head and neck cancer [50] compared with smokers with low rates of nicotine metabolism. A possible mechanistic explanation for these apparent *CYP2A6* by smoking interactions on risk of cancer may be that compared to smokers with slower nicotine metabolism, smokers with faster nicotine metabolism smoke more cigarettes and have increased rates of bioactivation of many carcinogens, such as bioactivated NNK, that may contribute to the increased risk of tobacco-related cancers [46].

An interaction between amount of daily cigarette consumption and *CYP2A6* genotypes on abdominal obesity was observed in the present study. When controlling for age, occupation, education, family income, exercise, caffeine intake and BMI, heavy smokers with poor metabolizer genotypes were at significantly increased risk of abdominal obesity compared with light smokers with the normal metabolizer genotype. As mentioned above, approximately 80% of nicotine is metabolized by *CYP2A6* into cotinine via C-oxidation, and cotinine is further metabolized into trans-3hydroxycotinine by the same enzyme, which is subsequently excreted in the urine [41]. Differences in the rate of nicotine metabolism are associated with *CYP2A6* enzymatic activity, which is moderated by *CYP2A6* genetic polymorphisms [41, 46, 51]. We would therefore expect that when individuals with *CYP2A6* poor metabolizer genotypes, relative to those with normal metabolizer genotypes, smoke more than 15 cigarettes per day, they metabolize nicotine into cotinine more slowly, leading to the accumulation of higher levels of nicotine in the body. The relatively higher levels of plasma nicotine in heavy smoking poor metabolizers compared with those who metabolize more quickly could contribute to increased risk for abdominal obesity as described above [12, 13].

Limitations

Some limitations need to be mentioned in the present study. A cross-sectional study design was used in the present study, which limited our ability to infer a causal relationship. Second, 71 male smokers without blood samples were excluded from the present study (they differed on some demographic characteristics from the smokers with blood samples, such as age, occupation, and family history of hypertension), which could alter generalizability. In addition, fat mass and lean mass (such as gluteal muscle mass) were not measured preventing us from assessing the effect of smoking on body composition in smokers. Not all *CYP2A6* genetic variants were assayed, which might result in individuals being grouped in faster metabolic groups than they should have (e.g., some in the normal group likely have untested variants); this would tend to reduce statistical power. Cotinine was measured, instead of the more pharmacologically relevant nicotine, due to the fast and variable rates of nicotine metabolism. Thus, it was not possible to (a) examine nicotine levels directly and (b) to test whether there was an inverse relationship between cotinine and nicotine, for any given level of smoking, and whether this relationship was altered by genotype. The statistical power was insufficient (67.4%) to analyze the effect of smoking quantity (continuous measure) on abdominal obesity. Finally, participants' dietary and drug histories were not investigated either, both of which might affect the activity of *CYP2A6* [14] and could distort the relationship of *CYP2A6* genotypes, amounts of daily cigarette consumption and abdominal obesity.

Conclusions

In summary, heavy smoking was significantly positively associated with abdominal obesity, and the association between amounts of daily cigarette consumption and abdominal obesity may be moderated by *CYP2A6* genotypes in Chinese male current smokers. These findings extend our understanding of the effect of cigarettes smoking on abdominal obesity.

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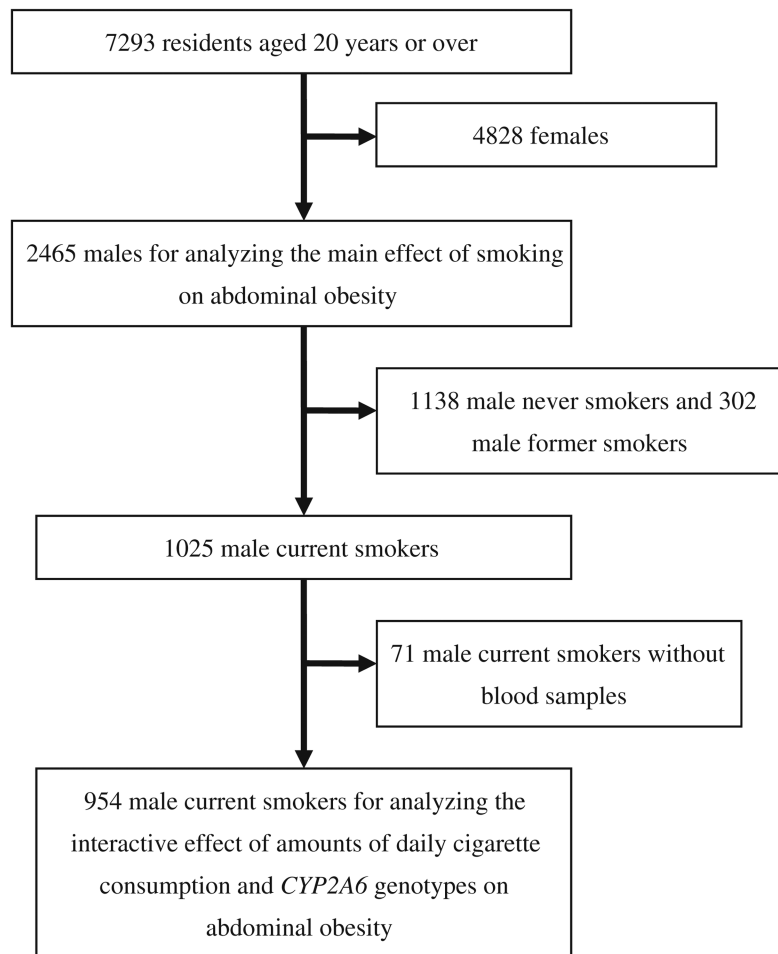


Fig. 1. Study participants selection diagram

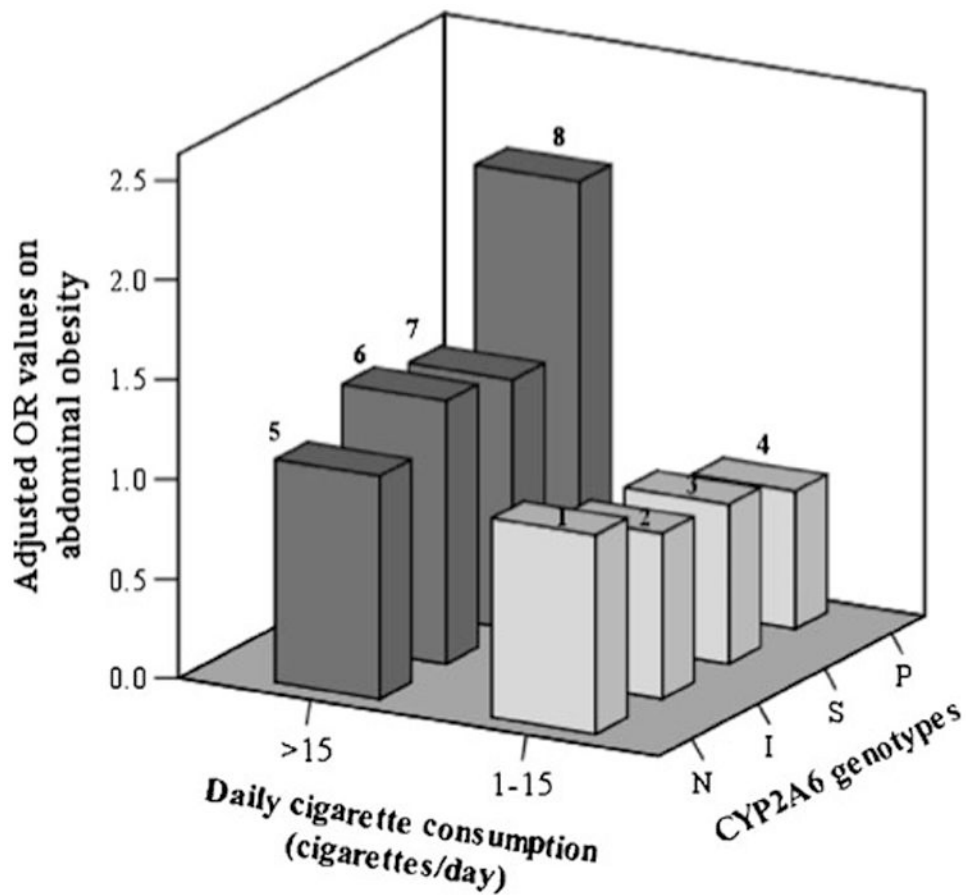


Fig. 2. Effect sizes (adjusted ORs) of amounts of daily cigarette consumption and *CYP2A6* genotypes on abdominal obesity in eight groups stratified by both daily cigarette consumption and *CYP2A6* genotypes in 954 current male smokers with blood samples. The group that consumed 1–15 cigarettes/day and *CYP2A6* normal metabolizer genotype was the reference group (OR=1). The adjusted variables were age, occupation, education, family income, alcohol consumption, exercise, coffee consumption, tea consumption, and BMI. The number of smokers in the eight groups were 243 (group 1), 73 (group 2), 146 (group 3), 83 (group 4), 198 (group 5), 64 (group 6), 108 (group 7), and 39 (group 8), respectively. N normal *CYP2A6* metabolizer genotype, I intermediate *CYP2A6* metabolizer genotype, S slow *CYP2A6* metabolizer genotype, P poor *CYP2A6* metabolizer genotype

Table 1
Comparisons of characteristics of 1,025 male current smokers with and without blood samples

Variables	Current smokers without blood samples (n=71)		Current smokers with blood samples (n=954)		χ^2	p value
	N	%	N	%		
20~29	9	12.7	38	4.0	52.10	<0.001
30~39	25	35.2	108	11.3		
40~49	9	12.7	203	21.3		
50~59	17	23.9	325	34.1		
60~69	5	7.0	216	22.6		
70~86	6	8.5	64	6.7		
Occupation						
Worker	18	25.4	235	24.6	16.31	0.022
Farmer	13	18.3	115	12.0		
Person in charge	1	1.4	52	5.5		
Technician	6	8.5	43	4.5		
Service personnel	16	22.5	120	12.6		
Retired personnel	9	12.7	222	23.3		
Jobless	5	7.0	121	12.7		
Others	3	4.2	46	4.8		
Education						
Illiteracy	2	2.8	21	2.2	5.52	0.238
Elementary school	17	23.9	149	15.6		
Junior middle school	18	25.4	338	35.4		
Senior middle school or vocational secondary school	22	31.0	317	33.3		
College or above	12	16.9	129	13.5		
Family monthly income (yuan)						
<1,000	13	18.3	128	13.4	1.98	0.739
1,000~2,999	20	28.2	317	33.2		
3,000~4,999	18	25.4	262	27.5		
5,000	13	18.3	153	16.0		
Don't know or refuse to answer	7	9.8	94	9.9		

Variables	Current smokers without blood samples (n=71)		Current smokers with blood samples (n=954)		χ^2	p value
	N	%	N	%		
Family history of hypertension						
No	58	81.7	665	69.7	4.57	0.033
Yes	13	18.3	289	30.3		
Alcohol consumption						
No	51	71.8	603	63.2	2.41	0.300
Yes	18	25.4	299	31.3		
Former drinker	2	2.8	52	5.5		
Exercise						
No	38	53.5	366	38.4	6.36	0.012
Yes	33	46.5	588	61.6		
Obesity						
Normal	43	60.6	422	44.2	8.17	0.017
Overweight	28	39.4	506	53.0		
Obese	0	0.0	26	2.8		
Abdominal obesity						
No	54	76.1	581	60.9	6.44	0.011
Yes	17	23.9	373	39.1		

Table 2
The associations between amounts of daily cigarette consumption, serum cotinine, CYP2A6 genotypes, and abdominal obesity in 954 current male smokers with blood samples

	Number (%)	Abdominal obesity	Amounts of daily cigarette consumption (>15 cigarettes/day)	Serum cotinine (>225.31 ng/ml)
		Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Amounts of daily cigarette consumption				
1–15 cigarettes/day	545 (57.1)	1		
>15 cigarettes/day	409 (42.9)	1.57* (1.13–2.19) ^a		
Serum cotinine				
<225.31 ng/ml	477 (50.0)	1	1	
≥225.31 ng/ml	477 (50.0)	0.61* (0.41–0.90) ^b	2.53* (1.92–3.32) ^c	
CYP2A6 genotypes				
CYP2A6 normal metabolizer genotype	441 (46.2)	1	1	1
CYP2A6 intermediate metabolizer genotype	137 (14.4)	0.72 (0.41–1.26) ^a	1.03 (0.70–1.53) ^c	1.08 (0.73–1.60) ^c
CYP2A6 slow metabolizer genotype	254 (26.6)	0.90 (0.57–1.41) ^a	0.89 (0.65–1.22) ^c	0.89 (0.65–1.22) ^c
CYP2A6 poor metabolizer genotype	122 (12.8)	0.94 (0.53–1.66) ^a	0.59* (0.38–0.90) ^c	0.52* (0.34–0.79) ^c

* $p < 0.05$

^a Binary logistic regression adjusted for age, occupation, education, family income, alcohol consumption, exercise, coffee consumption, tea consumption, and BMI

^b Binary logistic regression adjusted for age, occupation, education, family income, alcohol consumption, exercise, coffee consumption, tea consumption, daily cigarettes consumption, and BMI

^c Binary logistic regression adjusted for age, occupation, education, family income, alcohol consumption, exercise, coffee consumption, and tea consumption

Table 3
The interaction effect between amounts of daily cigarette consumption and CYP2A6 genotypes on abdominal obesity in 954 current male smokers

	Abdominal obeseit		Main effect of amounts of daily cigarette consumption		Main effect of CYP2A6 genotypes		Interaction effect	
	Controls (N (%))	Cases (N (%))	Model 1 Adjusted OR (95% CI)	Model 2 Adjusted OR (95% CI)	Model 3 Adjusted OR (95% CI)	Model 3 Adjusted OR (95% CI)	Model 3 Adjusted OR (95% CI)	
Waist circumference (abdominal obesity) ^a								
Daily cigarettes consumption								
1–15 cigarettes/day	358 (61.6)	187 (50.1)	1			1		
>15 cigarettes/day	223 (38.4)	186 (49.9)	1.57* (1.13–2.19) ^b			1.21 (0.69–2.10) ^b		
CYP2A6 genotype								
NM	270 (46.5)	171 (45.8)		1				
IM	91 (15.7)	46 (12.3)		0.72 (0.41–1.26) ^b		0.36* (0.16–0.81) ^b		
SM	147 (25.3)	107 (28.7)		0.90 (0.57–1.41) ^b		0.74 (0.41–1.37) ^b		
PM	73 (12.5)	49 (13.2)		0.94 (0.53–1.66) ^b		1.21 (0.69–2.10) ^b		
Interaction effect								
IM×(>15 cigarettes/day)						1.50 (0.60–3.74) ^b		
SM×(>15 cigarettes/day)						2.36 (0.67–8.31) ^b		
PM×(>15 cigarettes/day)						3.90* (1.25–12.18) ^b		

NM CYP2A6 normal metabolizer genotype, IM CYP2A6 intermediate metabolizer genotype, SM CYP2A6 slow metabolizer genotype, PM CYP2A6 poor metabolizer genotype

* $p < 0.05$

^a Dependent variable in the binary logistic regression model (0=normal and 1=abdominal obesity)

^b OR value adjustment for age, occupation, education, family income, alcohol consumption, exercise, coffee consumption, tea consumption, and BMI