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CYP1A1 gene polymorphisms in modifying association between Passive smoking and primary dysmenorrhea

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Abstract

Purpose—This study is to investigate whether the association between passive smoking exposure and primary dysmenorrhea is modified by two susceptibility genes, *CYP1A1*MspI and *CYP1A1*HincII.

Methods—We recruited 1645 women textile workers from 1997 to 2000 in Anqing, China, collecting the information about passive smoking, status of primary dysmenorrhea, and blood samples. We analyzed the association of CYP1A1 gene polymorphisms and passive smoking exposure with primary dysmenorrhea using multiple logistic regression.

Results—In the passive smoking group, women who have C/C6235 genotype (OR = 1.8, 95%CI = 1.0–3.3) in *CYP1A1*MspI and Ile/Ile462 genotype (OR = 2.9, 95%CI = 1.1–7.7) in *CYP1A1*HincII was associated with an increased risk of dysmenorrhea. When stratified by women genotype, the adjusted OR of dysmenorrhea was 1.6 (95%CI = 1.2–2.1) for passive smoking group with Ile/Ile462 genotype, and 1.5 (95%CI = 1.0–2.1) with C/C6235 genotype, compared to non passive smoking group, respectively. The data further showed that there was a significant combined effect between passive smoking and the *CYP1A1* MspI C/C6235 and *HincII* Ile/Ile462 genotype (OR=2.4, 95%CI =1.2–4.9).

Conclusions—*CYP1A1* MspI and *HincII* genotypes modified the association between passive smoking and primary dysmenorrhea.

Keywords

tobacco smoke pollution; primary dysmenorrhea; polymorphism; genetic; Cytochrome P-450 CYP1A1

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INTRODUCTION

Dysmenorrhea is a common gynecologic disorder in women of reproductive age, and categorized as primary (in the absence of organic pelvic lesions) and as secondary (in the presence of organic diseases such as endometriosis, adhesive disease, and uterine pathology) (1,2). Primary dysmenorrhea can be defined as painful menstruation without pelvic abnormalities, and may be accompanied by vomiting, fatigue, back pain, headaches, dizziness, and diarrhea. It is experienced by as many as half of all young women from the beginning and usually lifelong, and requires little diagnostic information other than careful history taking (3). The prevalence of primary dysmenorrhea is estimated to be from 45% to 95% among reproductive-aged women (4). This condition accounts for significant school absenteeism, lost working time, and reduced quality of life (5,6,7). In the United States it is estimated that about 600 million working hours are lost annually as a result of primary dysmenorrhea (5), and it is now recognized as an important women's health issue (8).

A growing body of evidence demonstrates an association between environmental and occupational exposures and adverse reproductive outcomes. Although limited data are available for primary dysmenorrhea, epidemiological studies have shown a link between primary dysmenorrhea and several environmental risk factors, including current cigarette smoking (9–12), body mass index (13), and contraceptive use (14). Especially, passive smoking is presently widespread in the population, and one of important risk factors to some adverse reproductive outcomes in women (15,16). According to the study of Hornsby et al (9), women exposed to environmental tobacco smoke reported more days with dysmenorrhea on average (2.6 days) compared to unexposed women (2.0 days). Our previous study also showed a significant dose–response relationship between exposure to environmental tobacco smoke and an increased incidence of primary dysmenorrhea in this cohort of young women (17). However, not all individuals who are exposed to these environmental/occupational chemicals have adverse reproductive outcomes, the reason for this variability was largely unknown, but may be related to genetic susceptibility. Tobacco smoke contains approximately 4000 compounds (18). The most important carcinogens in tobacco smoke are polycyclic aromatic hydrocarbons (PAHs), arylamines, and N-nitrosamines (19).

The ability of an individual to convert toxic metabolites of cigarette smoke to less harmful moieties is critical for minimizing the adverse health effects of these compounds. For example, the detoxification of PAHs in humans involves two parts: phase I, in which the inhaled hydrophobic PAHs are converted mainly through aryl hydrocarbon hydroxylase activity into hydrophilic, and phase II, in which reactive hydrophilic intermediates such as epoxides bind covalently to macromolecules, especially DNA. These intermediates may be more toxic than the original form (20,21). Aryl hydrocarbon hydroxylase, encoded by cytochrome P450 1A1 (*CYP1A1*) gene, is a well studied phase I enzyme and is particularly relevant to the metabolism of chemicals in cigarette smoke; *CYP1A1* gene is highly polymorphic in the population (22) and their polymorphisms have been associated with their encoded enzyme activities (23). Moreover, variants of *CYP1A1* also play an important role in the estrogen metabolism, and have been implicated in women's health conditions, including breast cancer, onset of menarche (24,25). Our previous data reported that *CYP1A1*-HincII variant had the trend of decreasing the risk of dysmenorrhea (26). Therefore, interindividual differences in susceptibility to the adverse health effects of cigarette smoke are in part attributable to different maternal genotypes associated with these enzymes. Failure to account for such genetic factors may limit our ability to investigate the role of exposure to environmental tobacco smoke in primary dysmenorrhea. Although it is biologically plausible, literature on genetic susceptibility to primary dysmenorrhea is scant.

In china, the prevalence of tobacco use is much higher among men than women, for example, a 1996 national study of smoking prevalence found that 70 percent of men but only 4 percent of women currently smoked. However, 70 percent of nonsmoking Chinese women between the ages of 20 and 50 years reported exposure to passive smoke. Among exposed women, 72 percent reported that their passive smoke exposure occurred daily. Among women reporting passive smoke exposure in the national Chinese survey, 82 percent reported exposure at home compared with 28 percent in public places and 19 percent at work (27). This setting provides a good opportunity to study the effect of passive smoking exposure on dysmenorrhea. Thus, we hypothesized that among women who were passively exposed to tobacco smoke, a panel of genetic susceptibility factors including metabolic enzyme activities would influence the level of toxic substrates reaching the endometrial blood flow and further affect the dysmenorrhea. In this report, *CYP1A1* MspI and HincII gene polymorphisms are used to characterize genetic susceptibility and to assess the interaction between metabolic gene and passive cigarette smoking. All the data were from a large prospective cohort study in Anqing, China.

METHODS

Study sites and population

The current study is part of a prospective reproductive health study among women textile workers from 1997 to 2000 in Anqing, China, which is an urban area located ~200 km west of Shanghai. The study protocols were approved by the human subject committee of the Chinese institutions involved in the study and by the institutional review board of the Harvard School of Public Health. All employees of the textile mills received health care, including prenatal, delivery and postnatal care, in the affiliated hospital. The eligibility criteria for women in the field enrollment were as follows: full-time employed women workers; newly married; aged 20 to 34 years; and no active-smoking. All the women were nulliparous. Women were excluded if they were already pregnant before enrollment.

Procedures

We used the Chinese marriage registration system to identify newly wed couples and those planning a first pregnancy. Upon enrollment, physical examination was performed, and height and weight were measured according to a standard protocol. A structured baseline questionnaire was administered by a trained interviewer to all the women and their husbands at enrollment to collect information concerning occupational exposures, personal habits such as cigarette smoking and alcohol consumption, living environment, exposure to passive smoking, dietary intake, menstrual and reproductive history, and contraceptive use. Blood samples were obtained from women via venipuncture by a skilled phlebotomist. The study protocols were approved by the Human Subject Committee of Beijing Medical University. We obtained written informed consent from each woman. The genomic DNA was extracted according to standard protocol (28).

Assessment of dysmenorrhea

The current analysis is a part of longitudinal study to examine reproductive outcomes including fecundity. All participants were questioned about the information on menstrual state during the previous recent 3 months. From the baseline questionnaire, was defined using the OLDCART mnemonic as abdominal pain or low back pain during menstrual bleeding, 2 or more days of primary dysmenorrhea during menstrual bleeding, moderate to severe pain intensity, varying from 5.0 to 10.0 on the visual analogue scale (VAS). All the participants should have no medical history of other gynecological diseases, hormonal treatment, oral contraceptives or intrauterine devices.

Assessment of passive smoking

There is evidence showing that cotinine level is quite positively related to self-report of passive smoke exposure (39, 30). So, the information on passive smoking was based on women self-reporting and was obtained from baseline questionnaire in this study. Passive smoking was assessed by use of different items from the questionnaire. Each woman recorded the mean number of cigarettes smoked per day at home by the regular household members. In our study, the specific question in the questionnaire was, "On average, what is the number of cigarettes someone smoked indoors at home while you were exposed in last month?" Exposure to tobacco smoke at workplace was not considered because any employee of the textile mills was not allowed to smoke. Therefore, we defined "non-passive smoking" as none of regular household members smoked at home and "passive smoking" as regular household members smoked at home.

Genotyping

Detection of the cytochrome P450 1A1 (CYP1A1) HincII polymorphism—

CYP1A1 HincII polymorphism was analysed according to Katoh et al (31). Primers used for the amplification were 5-GTCTCCCTCTGGTTACAGGA-3 and 5-GAA AGACCT CCCAGC -GGTCA-3. Digestion with the HincII for 3–4 h at 37° resulted in diagnostic fragments visualized by ethidium bromide staining and ultraviolet transillumination after electrophoresis on a 5% polyacrylamide gel. This process resulted in 139-, 120-, 32-, and 19-bp PCR products and was able to detect all 3 possible genotypes for the polymorphism: Ile/Ile462 (homozygous wild type), Ile/Val462 (heterozygous variant type), and Val/Val 462 (homozygous variant type).

Detection of the Cytochrome P450 1A1 (CYP1A1) MspI Polymorphism—

The detailed method for detection of *CYP1A1* MspI polymorphism can be found elsewhere (23). Briefly, primers used for initial PCR amplification were 5-TCACTCGTCTAAATAC-TCAACCCTG-3, and 5-AGGAGTCTTGTCTCATGCCT-3. After initial PCR amplification of this product, additional primers "nested" within the first product were used for reamplification. The two primers used the second set were 5-CAGTGAAGAGGTGTAGCCGCT-3 and 5-GAGGCA GGTG GATCACTTGAGCTC-3, respectively. Digestion with the *MspI* for 3–4 hours at 37° resulted diagnostic fragments visualized by ethidium bromide staining and ultraviolet transillumination after electrophoresis on a 2% agarose gel. This process resulted in 295-, 160-, and 135-bp PCR products and was able to detect all 3 possible genotypes for the polymorphism: T/T6235 (homozygous wild type), T/C6235 (heterozygous variant type), and C/C6235 (homozygous variant type).

Statistical methods

We use multiple logistic regression models to estimate the separate and combined associations of passive cigarette smoking and *CYP1A1* HincII and MspI genotypes in relation to primary dysmenorrhea with adjustment of major covariates. We first examined the association between *CYP1A1* genotypes and primary dysmenorrhea without consideration of passive cigarette smoking. We then investigated whether the association between passive smoking and primary dysmenorrhea is modified by *CYP1A1* genotypes by estimating the association between passive smoking and primary dysmenorrhea in total samples as well as in stratified subgroups by the specific *CYP1A1* genotypes. To further assess gene-environment interaction, we examined the combined association of passive smoking and *CYP1A1* genotypes with primary dysmenorrhea in twelve subgroups defined by passive smoking status (no, yes) and *CYP1A1* genotypes for MspI (T/T6235, T/C6235, C/C6235) and HincII (Ile/Ile462, Ile/Val462/Val/Val462).

All the analysis were adjusted for the following important potential confounders: maternal ages (<24, 24–28, and ≥28 years), education (elementary, middle, and high or above), shift work

(no, yes), noise exposure (no, yes), vibration (no, yes), physical labor stress (light, moderate, heavy), perceived stress (no, yes), age of menarche, and BMI. All p values were 2-sided and defined as $P = 0.05$ for the statistical significance. We use statistical software SAS (SAS Institute Inc, Cary, NC) for all analysis.

RESULTS

The data for analysis included 1645 subjects (521 with primary dysmenorrhea and 1124 without such a status). Table 1 (see additional file 1) shows the characteristics for women with primary dysmenorrhea and women without, and also provided inferential statistics (odds ratios and 95 percent confidence intervals) for the discrete variables. The two groups were similar in terms of age, BMI, age of menarche, education, vibration exposure, shift work, noise exposure, pregnancy history, and physical labor stress. Women with primary dysmenorrhea tended to have more perceived stress ($P = 0.033$) and more likely to be passive smokers ($P = 0.002$) than their counterparts.

Table 2 (see additional file 2) represents the effect of *CYP1A1* gene polymorphisms on primary dysmenorrhea in total samples and different passive smoking exposure groups. In total samples, C/C6235 genotype in *CYP1A1*MspI was associated with a slightly increased risk of primary dysmenorrhea (OR = 1.5, 95% CI = 1.0–2.3). After being stratified by passive smoking, women carrying Ile/Ile462 genotype in *CYP1A1*HincII (OR = 2.9, 95% CI = 1.1–7.7) and C/C6235 genotype in *CYP1A1*MspI (OR = 1.8, 95% CI = 1.0–3.3) are more likely to have primary dysmenorrhea than other genotype groups.

Table 3 (see additional file 3) presents adjusted ORs of dysmenorrhea in relation to passive smoking exposure for subgroups defined by *CYP1A1*HincII genotypes and *CYP1A1*MspI genotypes. The adjusted OR of primary dysmenorrhea was 1.6 (95% CI = 1.2–2.1) for passive smoking group with HincII Ile/Ile462 genotype compared to non passive smoking group. The adjusted OR of dysmenorrhea was 1.5 (95% CI = 1.0–2.1) for passive smoking group with MspI C/C6235 genotype compared to non passive smoking group.

We further assessed the combined association between passive smoking exposure and dysmenorrhea for subgroups defined by both *CYP1A1*MspI and *CYP1A1*HincII genotypes. Women with C/C6235 in MspI and Ile/Ile462 in HincII had the highest risk of primary dysmenorrhea (OR=1.7, 95% CI=1.2–2.4).

DISCUSSION

This study has showed several interesting findings. Passive smoking was significantly associated with dysmenorrhea. In addition, stratified by genotypes of HincIIa or MspI, there were significantly association between primary dysmenorrheal and passive smoking. When passive smoking and *CYP1A1* genotypes were considered together, the largest association was found on passive smoking women with Ile/Ile462 in *CYP1A1*HincII and C/C6235 in *CYP1A1*MspI, among the nonexposed group, *CYP1A1* genetic susceptibility alone did not contribute to a significant adverse effect, suggesting that *CYP1A1* genotypes would modify the effect of passive smoking on primary dysmenorrhea.

This study has several unique features. It is one of the few studies to examine passive smoking in relation to primary dysmenorrhea, with regard to the role of genetic susceptibility in evaluating adverse effects of passive smoking on primary dysmenorrhea. It is based on a great number of female workers from Anqing, China where epidemiologic and clinical data were collected with a validated questionnaire and consistent methods by trained research workers which offers an opportunity to test the gene-passive smoke interaction without substantial sociodemographic and environmental confounders.

Several previous reports have examined genetic polymorphisms and the risk of dysmenorrhea. An Australian twin study suggested that Genetic factors accounted for 39% of the longitudinally stable variation in menstrual flow, for 55% of pain, and for 77% of limitation by the menstrual pain (32). Wu D et al found that both variant *CYP2D6* and *GSTM1* genotypes were associated with increased risk of recurrent dysmenorrhea (33). When both the *CYP2D6* and *GSTM1* genotypes were considered together, the highest risk of recurrent dysmenorrhea was found among women with variant genotypes in both *CYP2D6* and *GSTM1*. Another study showed that after potential confounders were adjusted, *CYP1A1/HincII* variant had the trend of decreasing the risk of dysmenorrhea and the *GSTT1* variant genotypes showed a significantly increased risk of dysmenorrhea (26).

Although there are few published data on genetic susceptibility to passive cigarette smoking in relation to primary dysmenorrhea, this susceptibility is biologically plausible. Persons exposed to environmental tobacco smoke are subjected to most of the same constituents as those contained in mainstream smoke, but the pattern and amounts of exposure differ (34). The potential passive smoke mechanisms are essentially the same as those for active smoking (11,35), including vasoconstriction and reduced endometrial blood flow due to nicotine, which is common in women with painful menses (10). Crofts et al. found that variant genotypes at the HincII site were significantly associated with increased *CYP1A1* gene inducibility (36). They also observed a significant interaction between the HincII polymorphism and smoking at the mRNA level. Consistently, our study found that women carrying *CYP1A1* MspI variant genotype C/C6235 or *CYP1A1* HincII wild genotype Ile/Ile462 had significantly the higher risk of primary dysmenorrhea compared with the reference groups in presence of passive smoking, which may be results of reduced ability to convert toxic metabolites of cigarette smoke to less harmful hydrophilic compound. Overall, our findings showed the evidence that the interindividual differences in susceptibility to the adverse health effects of passive cigarette smoking are in part attributable to different women's genotypes of *CYP1A1*, and indicated that the women with C/C6235 genotype in *CYP1A1* MspI and Ile/Ile462 genotype in *CYP1A1* HincII are more susceptible to passive cigarette smoking and consequently tend to have the higher risk of primary dysmenorrhea.

Our study had several methodological limitations. First, we did not have biochemical measurements of passive smoking exposure. Second, primary dysmenorrhea was measured by self-report. We did not further analyze subgroups of recurrent/severe primary dysmenorrhea or the timing of passive smoking exposure within a specific menstrual cycle in relation to the risk of primary dysmenorrhea. Third, our measurement of potential confounders was based on self-report rather than objective measurements, which may have limited our ability to control some confounders. Finally, the association between genetic susceptibility to passive smoking and primary dysmenorrhea in this study may be causal, or a marker for other unknown genes or biologic pathways, or due to confounding by other unmeasured toxins or risk factors. Although our findings from observational study are biologically plausible and highly consistent, they are only suggestive, not conclusive. Further studies are needed to validate our findings.

CONCLUSION

In summary, we have demonstrated that passive smoking is associated with primary dysmenorrhea under the modification of *CYP1A1* gene polymorphisms. This study provides evidence of combined effects of gene-environment and supports the importance of assessing the role of genetic susceptibility in the evaluation of reproductive toxins. It has important implications for women's reproductive health.

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Table 1
Characteristics of the study population by dysmenorrhea status

Characteristics	Primary Dysmenorrhea N (%)		OR(95%CI)	p
	No (N=1124)	Yes (N=521)		
Age (years)				
<24 [†]	166 (72.17)	64 (27.83)	1	---
24~28	763 (67.28)	371 (32.72)	1.3(0.9~1.7)	0.147
>28	195 (69.4)	86 (30.6)	1.1(0.8~1.7)	0.493
BMI (Kg/m ²)				
<20 [†]	391 (69.8)	175 (30.92)	1	---
20~25	585 (68.74)	266 (31.26)	1.0(0.8~1.3)	0.893
>25	148 (64.91)	80 (35.09)	1.2(0.9~1.7)	0.255
Age of menarche (years)				
<13 [†]	331 (66.7)	170 (33.93)	1	---
13~15	564 (69.37)	249 (30.63)	0.9(0.7~1.1)	0.212
>15	229 (69.18)	102 (30.82)	0.9(0.6~1.2)	0.348
Educational level				
<Middle school [†]	465 (69.2)	207 (30.80)	1	---
High school	462 (67.84)	219 (32.16)	1.1(0.8~1.3)	0.592
>High school	197 (67.47)	95 (32.53)	1.1(0.8~1.5)	0.595
Exposure to vibration				
No [†]	1007 (68.46)	464 (31.54)	1	---
Yes	117 (67.24)	57 (32.76)	1.1(0.8~1.5)	0.745
Shift work				
No [†]	468 (68.52)	215 (31.48)	1	---
Yes	656 (68.19)	306 (31.81)	1.0(0.8~1.3)	0.887
Exposure to noise				
No [†]	754 (69.43)	332 (30.57)	1	---
Yes	370 (66.19)	189 (33.81)	1.2(0.9~1.4)	0.181
Perceived Stress				
No [†]	880 (69.68)	383 (30.32)	1	---
Yes	244 (63.87)	138 (36.13)	1.3(1.0~1.7)	0.033
History of pregnancy				
no [†]	741 (68.17)	346 (31.83)	1	---
yes	383 (68.64)	175 (31.36)	1.0(0.8~1.2)	0.847
Physical labor stress				
light [†]	534 (69.62)	233 (30.38)	1	---
moderate	471 (67.48)	227 (32.52)	1.1(0.9~1.4)	0.377
heavy	119 (66.11)	61 (33.89)	1.2(0.8~1.7)	0.36
Passive smoking				
No [†]	611 (71.71)	241 (28.29)	1	---
Yes	513 (64.69)	280 (35.31)	1.4(1.1~1.7)	0.002

Characteristics	Primary Dysmenorrhea N (%)		OR(95%CI)	p
	No (N=1124)	Yes (N=521)		

[†]Reference category.

Table 2
Adjusted Odds Ratios and 95% Confidence Intervals of Dysmenorrhea with genetic polymorphisms of CYP1A1HincII and CYP1A1MspI by passive smoking status^a

Polymorphisms	Primary Dysmenorrhea											
	Total						Passive Smoking status					
	No						Yes					
	N(%)	OR [*]	95%CI	P	N(%)	OR [*]	95%CI	P	N(%)	OR [*]	95%CI	p
HincII												
Val/Val462 [†]	14(20.3)	1	---	---	9(22.5)	1	---	---	5(17.2)	1	---	---
Ile/Val462	184(32.4)	1.8	1.0~3.3	0.063	91(31.7)	1.6	0.7~3.5	0.257	93(33.1)	2.4	0.9~6.6	0.086
Ile/Ile462	323(32.0)	1.8	1.0~3.2	0.068	141(26.9)	1.3	0.6~2.7	0.568	182(37.7)	2.9	1.1~7.7	0.037
MspI												
T/T6235 [†]	41(25.2)	1	---	---	22(24.7)	1	---	---	19(25.7)	1	---	---
T/C6235	257(30.7)	1.3	0.9~1.9	0.203	120(27.8)	1.2	0.7~2.0	0.575	137(33.7)	1.5	0.8~2.6	0.182
C/C6235	223(34.6)	1.5	1.0~2.3	0.035	99(29.8)	1.3	0.8~2.3	0.324	124(39.6)	1.8	1.0~3.3	0.038

* Estimates were derived from logistic regression models with adjustment for age, BMI, age of menarche, education, vibration exposure, shift work, noise exposure, pregnancy history, perceived stress and physical laboring stress.

[†] Reference category.

^a T/T6235 indicates homozygous wild type; Ile/Ile462 indicates homozygous wild type, Ile/Val462 indicates heterozygous variant type, and Val/Val 462 indicates homozygous variant type; T/C6235 indicates heterozygous variant type; C/C6235 indicates homozygous variant type.

Table 3
Association of passive smoking with primary dysmenorrhea stratified by genotypes of CYP1A1HincII^a and CYP1A1MspI^b

Polymorphisms	Passive Smoking	dysmenorrhea	OR*	95%CI	P
<i>CYP1A1/HincII</i>					
Val/Val462 [†]	No	9(22.5)	1	referent	---
	Yes	5(17.2)	1	0.3~4.1	0.985
Ile/Val462 [†]	No	91(31.7)	1	---	---
	Yes	93(33.1)	1.1	0.7~1.5	0.735
Ile/Ile462 [†]	No	141(26.9)	1	---	---
	Yes	182(37.7)	1.6	1.2~2.1	<0.001
<i>CYP1A1/MspI</i>					
T/T6235 [†]	No	22(24.7)		referent	
	Yes	19(25.7)	0.9	0.4~2.0	0.862
T/C6235 [†]	No	120(27.8)	1	---	---
	Yes	137(33.7)	1.3	1.0~1.8	0.055
C/C6235 [†]	No	99(29.8)	1	---	---
	Yes	124(39.6)	1.5	1.0~2.1	0.026