The Association of CYP1A1 Gene With Cervical Cancer and Additional SNP–SNP Interaction in Chinese Women

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Aims: The aim of this study was to investigate the association between CYP1A1 gene polymorphism and cervical cancer risk, and the impact of SNP–SNP interaction on cervical cancer risk in Chinese women. **Methods:** A total of 728 females with a mean age of 60.1 ± 14.5 years old were selected, including 360 cervical cancer patients and 368 normal controls. Logistic regression was performed to investigate association between single-nucleotide polymorphisms (SNP) and cervical cancer risk. Generalized multifactor dimensionality reduction (GMDR) was used to analyze the SNP–SNP interaction. **Results:** Logistic analysis showed a significant association between rs4646903 and increased cervical cancer risk. The carriers of homozygous mutant of rs4646903 polymorphism revealed increased cervical

cancer risk than those with wild-type homozygotes, OR (95%CI) were 1.45 (1.20–1.95). There was a significant two-locus model ($P = 0.0107$) involving rs4646903 and rs1048943, indicating a potential SNP–SNP interaction between rs4646903 and rs1048943. Overall, the two-locus models had a cross-validation consistency of 10 of 10, and had the testing accuracy of 60.72%. Subjects with TC or CC of rs4646903 and AG or GG of rs1048943 genotype have the highest cervical cancer risk, compared to subjects with TT of rs4646903 and AA of rs1048943 genotype, OR (95%CI) was 2.03 (1.42–2.89). **Conclusions:** rs4646903 minor alleles and interaction between rs4646903 and rs1048943 were associated with increased cervical cancer risk. J. Clin. Lab. Anal. 30:1220–1225, 2016. © 2016 Wiley Periodicals, Inc.

Key words: cancer risk; CYP1A1; interaction; polymorphism

INTRODUCTION

Cervical cancer is the second most common cancer in women worldwide (1, 2), and is a serious health problem and a leading cause of cancer death in Chinese women. Each year, nearly 500,000 women develop this disease worldwide and approximately 80% cases are in developing countries (3). The human papilloma virus (HPV) appears to be a necessary factor in the development of almost all cases (>90%) of cervical cancer (4). The HPV E6 and E7 proteins are viral genes expressed in virtually all HPV-positive cervical carcinomas, and many experiments have shown that these are cooperative viral oncoproteins that inactivate p53 and retinoblastoma (pRb) tumor suppressors, promoting carcinogenesis (5, 6).

Cytochrome P450 (CYP) enzymes are pivotal to the metabolic activation of PAHs to epoxide intermediates. These intermediates are converted into the ultimate carcinogens, diol-epoxides, via epoxide hydrolase. CYP1A1 was believed to be the most important enzyme catalyzing activation of these pro-carcinogenic PAHs (7). CYP enzyme catalyze phase I metabolism reaction. CYP1A1 is a member of the CYP family that

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Received 5 April 2016; Accepted 2 May 2016

DOI 10.1002/jcla.22006

Published online in Wiley Online Library (wileyonlinelibrary.com).

participates in the metabolism of xenobiotics and endogenous compounds, particularly polycyclic aromatic hydrocarbons such as benzo[a]pyrene (8). A commonly studied single-nucleotide polymorphism (SNP) in the CYP1A1 gene has been indicated to associate with cancer risk, which was localized on chromosome 15q22 (9). The commonly studied is the 3801TNC polymorphism (also referred to as 2A, m1, or rs4646903), which is characterized by the T to C mutation at nucleotide 3801 in the 30 flanking region of the CYP1A1 gene. In the past decades, a number of molecular epidemiological studies have been done to evaluate the association between CYP1A1 T3801C polymorphism and different types of cancer risk in different populations. However, the results were inconsistent or even contradictory. The multiple genotypes were result of many SNP and multiple SNP-SNP interactions. Till now, however, no study focused on the impact of CYP1A1 SNP-SNP interactions on cervical cancer risk were conducted in Chinese population. So the aim of this study was to investigate the association between CYP1A1 gene polymorphism and cervical cancer risk, and the impact of SNP-SNP interaction on cervical cancer risk in Chinese women.

MATERIALS AND METHODS

Subjects

This was a case-control study. Participants were consecutively recruited between July 2010 and March 2014 from Affiliated Hospital of Medical College, Qingdao University. Cervical cancer patients were selected from our hospital and the inclusion criteria for patients were as follows: 1) Age was from 30 to 70 years old and with Chinese Han ethnicity; 2) de

novo histopathologically proven carcinoma cervix; 3) All stages (I-IV) as per the guidelines of International Federation of Gynecology and Obstetrics (FIGO). Subjects with age more than 70 years old, history of other cancers, prior chemotherapy, radiotherapy or chemoradiotherapy and any co-morbid conditions such as allergy, cardiovascular disease, diabetes, infection and inflammatory response, were excluded. Healthy controls were randomly selected from a population screening program for risk factors of tumor for women in the same regions and 1:1 matched to cases on the basis of age (± 3 years) and sex, and subjects with history of any kinds of tumor were also excluded. The selection criteria for the controls included no individual history of cancer, no history of cervical intraepithelial neoplasia, normal cervical cytology and HPV examination, or normal pathological examination of the cervix within the past 2 years. At last, a total of 728 females with a mean age of 60.1 ± 14.5 years old were selected, including 360 cervical cancer patients and 368 normal controls (Fig. 1). Blood samples were collected from each participant. Informed consent was obtained from all participants. The protocol of this study was approved by Qingdao University.

Body Measurements

Data on demographic information, diet, smoking, and drinking information for all participants were obtained using a standard questionnaire administered by trained staffs. Current smokers were defined as those who have smoked for at least 100 cigarettes and still smoked at the time of the interview, individuals with no history of cigarette smoking were considered as never smokers (10, 11). Currently, alcohol consumption was defined as more than one drink of any type

Fig. 1. A flowchart on cervical cancer cases and controls population selection.

per month or not currently drinking as less than one drink of any type per month (12); Body weight, height, and waist circumference (WC) were also measured according to standardized procedures (13). Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Blood samples were collected in the morning after at least 8 hr of fasting. All plasma and serum samples were frozen at -80°C until laboratory testing.

Genomic DNA Extraction and Genotyping

Some SNPs of the CYP1A1 gene were selected according the following standards, including: 1) which have been reported associations with cervical cancer; 2) the minor allele frequency (MAF) of which was greater than 2%; 3) which were not well studied in the previous studies. Four SNPs of CYP1A1 were selected for genotyping in the study: rs4646903, rs1048943, rs4646422, and rs2606345. All SNPs were detected by Taqman fluorescence probe. ABI Prism7000 software and allelic discrimination procedure was used for genotyping. Genomic DNA from participants was extracted from EDTA-treated whole blood, using the DNA Blood Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. A 25 μl reaction mixture including 1.25 μl SNP Genotyping Assays (20 $\times$), 12.5 μl Genotyping Master Mix (2 $\times$), 20 ng DNA, and the conditions were as follows: initial denaturation for 10 min and 95°C , denaturation for 15 s and 92°C , annealing and extension for 90 s and 60°C , 50 cycles. Probe sequences of all SNPs were shown in Table 1.

Statistical Analysis

The mean and standard deviation (SD) for normally distributed continuous variables, and percentages for categorical variable, were calculated and compared. The categorical data were analyzed using χ^2 test. Further, continuous variables were analyzed using Student's *t*-test. Hardy–Weinberg equilibrium (HWE) was performed using SNPstats (available online at <http://bioinfo>.

iconcologia.net/SNPstats). Logistic regression was performed to investigate association between SNP and cervical cancer by additive and recessive model and using gender, age, high-fat diet, low-fiber diet, smoking, and alcohol status, BMI and WC as covariates in the analysis. Generalized multifactor dimensionality reduction (GMDR) (14) was used to analyze the SNP–SNP interaction, cross-validation consistency, the testing balanced accuracy, and the sign test, to assess each selected interaction were calculated. Permutation testing was also conducted to gain empirical *P* values of prediction accuracy as a benchmark based on 10,000 shuffles.

RESULTS

A total of 728 females with a mean age of 60.1 ± 14.5 years old were selected, including 360 cervical cancer patients and 368 normal controls. Participants characteristics stratified by cases and controls are shown in Table 2. The mean of TC, HDL, BMI, and WC were significantly different between cases and controls.

TABLE 2. General characteristics of study participants in case and control group

Variables	Cases group (<i>n</i> = 360)	Control group (<i>n</i> = 368)	<i>P</i> values
Age (years)	60.7 $\pm$ 16.8	59.4 $\pm$ 16.2	0.288
Smoke <i>N</i> (%)	12 (3.3)	18 (4.9)	0.290
Alcohol consumption <i>N</i> (%)	10 (2.8)	13 (3.5)	0.260
High fat diet <i>N</i> (%)	96 (26.7)	104 (28.3)	0.630
Low fiber diet <i>N</i> (%)	108 (30.0)	93 (25.3)	0.154
WC (cm)	88.1 $\pm$ 10.8	85.8 $\pm$ 10.5	0.004
BMI (kg/m ²)	26.8 $\pm$ 6.7	24.3 $\pm$ 6.2	<0.001
FPG (mmol/l)	6.4 $\pm$ 2.6	6.2 $\pm$ 2.3	0.272
TG (mmol/l)	2.0 $\pm$ 0.8	1.9 $\pm$ 0.9	0.114
TC (mmol/l)	5.2 $\pm$ 1.3	5.0 $\pm$ 1.1	0.025
HDL (mmol/l)	1.24 $\pm$ 0.33	1.31 $\pm$ 0.27	0.002

Note: Means $\pm$ standard deviation for age, FPG, WC, BMI, duration of diabetes; FPG, fast plasma glucose; TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; WC, waist circumference; BMI, body mass index.

TABLE 1. Description and Probe sequence used for Taqman fluorescence probe analysis for 4 SNPs

SNP ID	Chromosome	Functional Consequence	Major/minor alleles	Probe sequence
rs4646903	15:74719300	Downstream variant 500B	T/C	5'- TTGTTTCACTGTAACCTCCACCTCC[A/C/T] GGGCTCACACGATTCTCCACCTCA-3'
rs1048943	15:74720644	Missense	A/G	5'-CAAGCGGAAGTGTATCGGTGAGACC[A/C/G/T] TTGCCCGCTGGGAGGTCTTTCTCTT-3'
rs2606345	15:74724835	Intron variant	A/C	5'- GCTCCCTGCAGTTGGCAATCTGTCA[A/C] CCTGATTGTCTCCAGCAAAGGACA-3'
rs4646422	15:74722964	Missense	A/G	5'- CTGAAGAATCCACCAGGGCCATGGG[A/G] CTGGCCTCTGATTGGGCACATGCTG-3'

The frequency for rs4646903 minor alleles was higher in cases than that in normal controls, C allele of rs4646903 was 27.6% in cervical cancer cases and 20.9% in normal controls subjects ($P = 0.003$) (Table 3). Logistic analysis showed a significant association between genotypes of variants in rs4646903 and increased cervical cancer risk, after adjustment for gender, age, high-fat diet, low-fiber diet, smoking, and alcohol status, BMI and WC. The carriers of homozygous mutant of rs4646903 polymorphism revealed increased cervical cancer risk than those with wild-type homozygotes, OR (95%CI) was 1.45 (1.20–1.95).

We employed the GMDR analysis to assess the impact of the SNP–SNP interaction among 4 SNPs on cervical cancer risk, after adjustment for covariates including gender, age, high-fat diet, low-fiber diet,

alcohol status, BMI, and WC. Table 4 summarizes the results obtained from GMDR analysis for two- to four-locus models. There was a significant two-locus model ($P = 0.0107$) involving rs4646903 and rs1048943, indicating a potential SNP–SNP interaction between rs4646903 and rs1048943. Overall, the two-locus models had a cross-validation consistency of 10 of 10, and had the testing accuracy of 60.72%.

In order to obtain the odds ratios and 95%CI for the joint effects of rs4646903 and rs1048943 on cervical cancer risk, we conducted interaction analysis between the two SNPs using logistic regression. We found that subjects with TC or CC of rs4646903 and AG or GG of rs1048943 genotype have the highest cervical cancer risk, compared to subjects with TT of rs4646903 and AA of rs1048943 genotype, OR

TABLE 3. Genotype and allele frequencies of four SNPs between cervical cancer case and control group

SNPs	Genotypes and Alleles	Frequencies <i>N</i> (%)		OR (95%CI) ^a	<i>P</i> -values	H-W test for controls
		Cases (<i>n</i> = 360)	Controls (<i>n</i> = 368)			
rs1048943	AA	199 (55.3)	217 (59.0)	1.00	0.531	0.381
	AG	141 (39.2)	135 (36.7)	1.10 (0.91–1.39)	0.314	
	GG	20 (5.6)	16 (4.3)	1.14 (0.86–1.58)		
	GG+AG	161 (44.8)	151 (41.0)	1.11 (0.90–1.40)		
	A	539 (74.9)	569 (77.3)			
G	181 (25.1)	167 (22.7)				
rs4646903	TT	188 (52.2)	227 (61.7)	1.00	0.008	0.327
	TC	145 (40.3)	128 (34.8)	1.42 (1.18–1.83)	0.010	
	CC	27 (7.5)	13 (3.5)	1.87 (1.24–2.36)		
	TC+CC	172 (47.8)	141 (38.3)	1.45 (1.20–1.95)		
	T	521 (72.4)	582 (79.1)			
C	199 (27.6)	154 (20.9)				
rs4646422	AA	191 (53.0)	210 (57.1)	1.00	0.461	0.383
	AG	146 (40.6)	140 (38.0)	1.06 (0.93–1.21)	0.277	
	GG	23 (6.4)	18 (4.9)	1.23 (0.86–1.32)		
	GG+AG	169 (47.0)	158 (42.9)	1.10 (0.91–1.25)		
	A	528 (73.3)	560 (76.1)			
G	192 (26.7)	176 (23.9)				
rs2606345	AA	198 (55.0)	216 (58.7)	1.00	0.315	0.348
	AC	138 (38.3)	136 (37.0)	1.04 (0.82–1.30)	0.314	
	CC	24 (6.7)	16 (4.3)	1.21 (0.88–1.45)		
	AC+CC	162 (45.0)	152 (41.3)	1.06 (0.84–1.32)		
	A	534 (74.2)	568 (77.2)			
C	186 (25.8)	168 (22.8)				

^aAdjusted for gender, age, smoking, alcohol consumption, high-fat diet, low-fiber diet, BMI, and WC.

TABLE 4. Best SNP–SNP interaction models, as identified by GMDR

Locus no.	Best combination	Cross-validation consistency	Testing accuracy	<i>P</i> -values ^a
2	rs4646903 rs1048943	10/10	0.6072	0.0107
3	rs4646903 rs1048943 rs4646422	9/10	0.5399	0.1719
4	rs4646903 rs1048943 rs4646422 rs2606345	8/10	0.5590	0.0547

^aAdjusted for gender, age, alcohol consumption, high-fat diet, low-fiber diet, BMI, and WC.

TABLE 5. Interaction between rs4646903 and rs1048943 on cervical cancer risk

rs4646903	rs1048943	OR (95% CI) ^a	P values
TT	AA	1.00	—
TT	AG or GG	1.06 (0.88–1.27)	0.132
TC or CC	AA	1.21 (1.08–1.49)	0.021
TC or CC	AG or GG	2.03 (1.42–2.89)	<0.001

^aAdjusted for gender, age, alcohol consumption, high-fat diet, low-fiber diet, BMI, and WC.

(95%CI) was 2.03 (1.42–2.89), after adjustment for gender, age, alcohol status, high-fat diet, low-fiber diet, BMI, and WC. (Table 5)

DISCUSSION

This is the first study to report an association between cervical cancer risk and the CYP1A1 gene polymorphism in Chinese Han population. In this study, we found a significant association between genotypes of variants in rs4646903 with increased cervical cancer risk, after covariates adjustment. The carriers of homozygous mutant of rs4646903 polymorphisms revealed increased cervical cancer risk than those with wild-type homozygotes. CYP1A1 is an important member of the CYP family present mainly in extrahepatic tissues and is responsible for the metabolism of a large number of xenobiotics as well as a small number of endogenous substrates (15). Studies on this gene have involved in several diseases, including cancer (16), coronary artery disease (CAD) (17) and so on. The association of gene polymorphisms of CYP1A1 with susceptibility to several types of cancer, such as cancer in lung, bladder, pancreatic, breast, ovarian, prostate and gynecological malignancies including cervical cancer, has been evaluated in different populations (18–20). However, few studies focused on the association between cervical cancer risk and the CYP1A1 gene polymorphism were conducted in Chinese Han population. Abbas et al. (21) conducted a study in Indian population and indicated that presence of the C allele of rs4646903 and G of rs1048943 may be the risk alleles for cervical cancer susceptibility. Moreover, CYP1A1 rs4646903 and rs1048943 polymorphisms show considerable association with tobacco smoking in their study population. The CYPs belong to the phase I family of metabolizing enzymes participating in detoxification of many carcinogens by formation of reactive intermediates that can damage DNA, lipids and proteins (22, 23). CYP1A1 metabolically converts environmental procarcinogens into reactive intermediate metabolites that have carcinogenic effects

(24). Polymorphic variants influencing the enzyme activity of CYP1A1 along with environmental factors such as tobacco smoking also play important roles in different interindividual susceptibilities to gynecological cancers in women as well as other cancers (25).

Cervical cancer was result of impact of many gene polymorphisms and SNP–SNP interactions. The study by Ivansson et al. (26) is the first to show an interaction between the genes on chromosome 2q33 and IFNG polymorphisms in susceptibility to cervical cancer in Swedish women, they have shown by analysis of specific genotype combinations that genetic variation at 2q33 in combination with variation in, or in the vicinity of IFNG is associated with susceptibility to cervical cancer. However, it was from then that no study focused on the impact of interaction among several SNPs of CYP1A1 on cervical cancer was conducted, particularly in Chinese population. To our knowledge, this is the first study on impact of interaction among several SNPs in CYP1A1 gene on cervical cancer in Chinese women. We found that subjects with TC or CC of rs4646903 and AG or GG of rs1048943 genotype have the highest cervical cancer risk, compared to subjects with TT of rs4646903 and AA of rs1048943 genotype. The current knowledge of carcinogenesis indicates a multi-factorial and multistep process that involves various genetic alterations and several biological pathways. Thus, it is unlikely that risk factors of cancer work in isolation from each other. And the same polymorphisms may play different roles in cancer susceptibility, because cancer is a complicated multi-genetic disease, and different genetic backgrounds may contribute to the discrepancy. And more importantly, the low penetrance genetic effects of single polymorphism may largely depend on interaction with other polymorphisms and/or a particular environmental exposure. So studies on impact of interaction between CYP1A1 gene and environmental factors on cervical cancer risk should be conducted in the future.

The limitations of this study should be considered. First, more SNPs in CYP1A1 gene should be included in the study; in addition, interaction analysis should be conducted for gene–environmental factors.

In conclusion, we found a significant association between genotypes of variants in rs4646903 with increased cervical cancer risk, after covariates adjustment. The carriers of homozygous mutant of rs4646903 polymorphisms revealed increased cervical cancer risk than those with wild-type homozygotes. We also found a potential SNP–SNP interaction between rs4646903 and rs1048943 using GMDR model, subjects with TC or CC of rs4646903 and AG or GG of rs1048943 genotype have the highest cervical

cancer risk, compared to subjects with TT of rs4646903 and AA of rs1048943 genotype.

ACKNOWLEDGMENTS

This study was funded by Shandong Provincial Natural Science Foundation, China (ZR2015HQ031). The writing of this article was supported by the Affiliated Hospital of Medical College, Qingdao University and Yantai Yuhuangding Hospital. We thank all the partners and staffs who helped us in the process of this work. Shuhong Li and Guiqin Li contributed equally to this work.

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