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EPIDEMIOLOGY

Interaction of genetic polymorphisms in cytochrome P450 2E1 and glutathione S-transferase M1 to breast cancer in Taiwanese woman without smoking and drinking habits

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Abstract P450 (CYP) and glutathione S-transferase (GST) are involved in the activation and detoxification of many potential carcinogens. Although, the interaction between environmental exposure and genetic polymorphisms of cytochrome P450 2E1 (CYP2E1) and glutathione S-transferase M1 (GSTM1) in breast cancer has been assessed, the gene–gene interactions between CYP2E1 and GSTM1 related to breast cancer have not been focused on and reported. We conducted a hospital-based case-control study to investigate whether the genetic interaction effects of CYP2E1 and GSTM1 modify the risk of developing breast cancer independent of the effect of cigarette smoking and alcohol consumption. Individuals with the C2/C2 genotype of CYP2E1 had a lower risk (OR = 0.24, 95% CI = 0.08–0.74) when compared with those with the C1/C1 genotype. However, there was no significant difference (OR = 1.05, 95% CI = 0.73–1.50) in the GSTM1 genotype frequency between the cases with breast cancer and that of the controls. When individuals with the genotype of C1/C1 or C1/C2 of CYP2E1 and the wild-type of GSTM1 were compared with those of C2/C2 of CYP2E1 and the null-type of GSTM1 however, we found a significantly increased risk (OR = 3.50, 95% CI = 1.01–16.55) in the breast cancer patients. Our findings indicated a gene–gene interaction between CYP2E1 and GSTM1 was accessible to developing breast cancer in Taiwanese women without the habits of cigarette smoking and alcohol consumption even though independent effects of CYP2E1 and GSTM1 were weak or non-significant and suggest that environmental carcinogen besides cigarette and alcohol consumption could induce breast cancer.

Keywords CYP2E1 · GSTM1 · Polymorphism · Breast Cancer · PCR · RFLP

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Introduction

Breast cancer has become one of the main cancers for women in Taiwan as well as in the Western nations. Risk factors for breast cancer include both those that cannot be changed such as genetics and age, and those that can be changed such as lifestyles or the environments [1, 2]. The changes, or mutations, of certain genes such as BRCA1 or BRCA2 are responsible for the occurrence of breast cancer in some people according to ethnology. Nevertheless, the influence of heredity in breast cancer cases is only 5–10% according to the reports of the International Agency for Research on Cancer [3]. The lifestyle risk factors including smoking, alcohol consumption, diet, and physical activity which can change the risk of developing breast cancer have been supported and more emphasized by recent studies [4–6].

Cytochrome P450 (CYP) and glutathione S-transferase (GST) enzymes are involved in the activation and detoxification of potential carcinogens through diet, smoking, and alcohol consumption, etc. The genetically determined differences in the metabolism related to the CYP and GST have been reported to be associated with host susceptibility in various cancers [7]. Among the various CYP, P450 2E1 (CYP2E1) plays an important role in the metabolism of alcohol, and tobacco-derived N-nitrosamines as the Phase I enzymes. It has been reported that the polymorphism or the expression of CYP2E1 could relate to the development of human breast cancer [8, 9]. However, Glutathione S-transferases (GSTs) are a family of important Phase II enzymes involved in the detoxification of potential carcinogens such as tobacco smoke. Recent studies also reveal that the polymorphisms of GSTs are related to breast cancer alone, or when they are accompanied with cigarette smoking or alcohol consumption [10–13]. Phase I and Phase II enzymes, usually, translated from different chromosomes, act sequentially and independently in the detoxification of potential carcinogens. The CYP2E1 could be induced by ethanol and be involved in the activation of N-nitrosamines. However, the different types of polymorphism of CYP2E1 have different activities. These harmful intermediaries could play an important role in breast carcinogenicity and could soon be metabolized by GSTs, but the activities were also influential according to the polymorphism of GSTs. It still remains uncertain if there is any gene–gene interaction between these two enzymes in the development of breast cancer since there is no solid evidence yet. Besides, most of the breast cancer patients in Taiwan are non-smokers and non-drinkers, and it is impossible to identify the environmental and genetic interaction. Therefore, the purpose of this study is to not only investigate the independent effect of the different genotypes of CYP2E1 and GSTM1 to breast cancer without the habits of cigarette smoking and alcohol consumption, but to also emphasize the gene–gene interaction or the joint effect between the polymorphism of CYP2E1 and GSTM1, which could be related to breast cancer.

Materials and methods

Study subjects

The study population consisted of a consecutive series of breast cancer patients and non-cancer control subjects admitted to Kaohsiung Medical University Hospital, Kaohsiung, Taiwan between March 1999 and September 2001. Non-smoking and non-drinking women with a first diagnosis of the histopathologically confirmed incidence of breast cancer and from whom a blood sample was available, were selected as cases (n = 265). Non-smoking and non-drinking female control subjects (n = 237) who were individuals without a present or previous history of breast cancer, were simultaneously recruited in the same hospital for their annual general health check-ups. In addition, women with benign breast tumors, mastitis, benign calcification, etc. or cancer such as lung cancer, liver cancer, etc. (which could relate to polymorphisms of metabolic enzyme) were excluded from both groups. Approximately 1% of the cases and 5% of the approached control subjects were excluded from the final study groups because of refusal to participate, lack of blood collection, or failure to isolate DNA from the blood samples. According to the above criteria, 262 cases and 225 control subjects were eligible for the study. Informed consent and simple demographic characteristic information including age and menopause were obtained from all participants by questionnaires at the time of blood withdrawals. The study was approved by the Ethics Committee of Kaohsiung Medical University Hospital.

Laboratory analysis

DNA was purified from peripheral blood lymphocytes by sodium dodecyl sulfate/proteinase K treatment and phenol/chloroform extraction. Polymerase chain reaction (PCR) restriction fragment length polymorphism analysis of CYP2E1, which had been originally described by other studies, was modified to identify its genotype [14, 15]. The primer sequences which were used in the PCR reactions were 5′-CCAGTCGAGTCTACATTGCA-3′/5′-TTCATTCTGTCTTCTAACTGG-3′ for *Rsa*I sites. Samples of DNA (500–1000 ng) were added to the PCR mixture containing 61.5 μl water, 10 μl 10× PCR buffer, 2 μl deoxyribonucleoside triphosphate, 5 μl of each primer and 0.5 μl of Taq polymerase (Boehringer-Mannheim). The PCR con-

dition was 35 cycles of 1 min at 94°C for denaturation, 1 min at 55°C for annealing, and 1 min 72°C for primer extension. The PCR product (20 μl) was digested with 10 U *Rsa*I (410-bp product).

In order to detect the deletion of the GSTM1, a modified multiplex PCR method was performed by using CYP2E1 gene as an internal control, as described originally by other studies [16, 17]. The primer sequences were 5′-GAACTCCCTGAAAAGCTAAAGC-3′/5′-GTTGGGCTCAAATATACGGTGG-3′ to amplify a 215-bp fragment for GSTM1. Samples of DNA (500 ng) were added to the PCR mixture containing 25.5 μl water, 5 μl 10× PCR buffer, 1 μl of each deoxyribonucleoside triphosphate, 1.5 μl of GST primer, 1 μl CYP2E1 primer, and 0.5 μl (5 U/μl) of Taq polymerase. The PCR condition was 5 min at 95°C, followed by 35 circles of 1 min at 95°C for denaturation, 1 min at 60°C for annealing, and 1 min 30 s at 72°C for primer extension, and a final extension at 72°C for 5 min. The products of PCR were confirmed by the DNA sequence analysis.

Statistical analysis

Data were analyzed by SAS for window (Ver. 8.02). Two-tailed P-value <0.05 was considered as a significantly statistic difference. Student t test was performed to assess continuous variables such as age, nevertheless, chi-square tests for contingency tables were used to assess differences in binominal variable such as menopausal status across case and control group of women. The unconditional logistic regression model was performed to estimate the odds ratio (OR) and their 95% confidence intervals (95% CI) and to adjust the confound effect of covariate between genotypes with and without breast cancer. Gene–gene interaction was assessed in logistic regression model by including dummy variables for each category defined by the cross-classification of the interacting variables, except for the reference category. The concept and analysis methods of interaction between different variables have been described in detail by Greenland et al. [18].

Results

The present study was based on 262 women with newly diagnosed breast cancer, ranging in age from 27 to 83 years with the mean age of 49.11 years, whereas, the mean age of the control group was 49.73. The frequencies of post-menopausal status in case and control were 35% and 39%, respectively. There was no statistical significance between cases and controls in distribution of age and frequency of menopausal status. The frequencies of other clinical manifestations in breast cancer patients including clinical stages according to the TNM system, cancer site, and pathological diagnosis are shown in Table 1.

In Table 2, the frequencies in different genotype of CYP2E1 for the breast cancer patients and the controls were 61.83% (C1/C1), 35.88% (C1/C2), 2.29% (C2/C2), and 52.56% (C1/C1), 34.22% (C1/C2), 6.22% (C2/C2), respectively. In the genotype of GSTM1, the frequencies were 46.95% (null-type) and 53.05% (wild-type) in the cases, and 45.78% (null-type) and 54.22% (wild-type) in the controls. The genotypes of CYP2E1 and GSTM1 were in Hardy–Weinberg equilibrium as shown in Table 2. Even though, there was no statistical significance between case and control group in age and menopausal status, we still performed multiple unconditional logistic regression models to estimate odds ratios of genotypes of CYP2E1 and GSTM1 and control the age and menopausal status. Table 2 shows the adjusted odds ratios (aOR) of polymorphisms of CYP2E1 and GSTM1 with 95% CI adjusted by age, menopausal status. The aORs for C1/C2 and C2/C2 genotypes, with the reference of the C1/C1 genotype, were 1.0 (95% CI = 0.69–1.49) and 0.39 (95% CI = 0.08–0.76) in CYP2E1 correspondingly. The risk of the C2/C2 genotype was statistically significantly decreased ($P<0.05$) in the development of breast cancer compared to those with the C1/C1 genotype. In GSTM1, the aOR for the null-type compared to the null-type was 1.09 (95% CI = 0.81–1.55). The risk was slightly increased but non-significant ($P>0.05$).

From the results mentioned above, we combined the C1/C1 and C1/C2 of CYP2E1 as the risk group since there is no significant difference between these two genotypes. Then, we grouped all the study subjects into 4 groups according to different genotypes of CYP2E1 and GSTM1. Meanwhile, we set the reference group to be C2/C2 of CYP2E1 and the wild-type of GSTM1 because of the lower risk from the above-mentioned results. The other groups included C2/C2 of CYP2E1 and the null-type of GSTM1, C1/C1 or C1/C2 of CYP2E1 and the wild-type of GSTM1, and C1/C1 or C1/C2 of CYP2E1 and the null-type of GSTM1. All the aORs of the combined genotypes of CYP2E1 and GSTM1 are shown in Table 3. The aOR for C1/C1 or C1/C2 of CYP2E1 and the null-type of GSTM1 is 3.94 (95% CI = 1.03–17.55) compared to the genotype of the reference. The risk is significantly increased. Nevertheless, the aOR of a person with genotypes of C1/C1 or C1/C2 of CYP2E1 and the wild-type of GSTM1 compared to the reference group is increased but non-significantly. The frequencies of C2/C2 genotype of CYP2E1 were low in our data collection, so we combine the first two groups (C2/C2 of CYP2E1 and both types of GSTM1) as one group and compare it with the reference, the estimated risks were almost the same as the uncombined analyses as shown in Table 3.

Table 1 General characteristics of the breast cancer patients

Characteristics	Breast cancer patients	Controls	*P*-value
Total number of subjects	262	225	
Age (yr, mean±SD)	49.11±11.0	49.05±16.7	>0.05
Menopausal status			
Premenopausal	171 (65%)	137 (61%)	>0.05
Postmenopausal	91 (35%)	88 (39%)	
Clinical stage			
Stage I	47 (17.9%)	–	
Stage II	198 (75.6%)	–	
Stage III	17 (6.5%)	–	
Cancer site			
Left breast	131 (50.0%)	–	
Right breast	126 (48.0%)	–	
Bi-site	5 (2.0%)	–	
Pathological diagnosis			
Ductal carcinoma	237 (90.5%)	–	
Lobular carcinoma	23 (4.9%)	–	
Other neoplasms	12 (4.6%)	–	

Discussion

Cytochrome P450 (CYP) enzymes are the major Phase I xenobiotics metabolizing enzymes expressed predominantly in the liver [19]. The gene expression is under the control of liver-enriched transcription factors interacting with the *cis*-acting regulatory sequences which are mainly present in the 5′-flanking region of the genes. CYP2E1 is known to be of great importance for the metabolism of ethanol, and small molecular weight precarcinogens including nitrosamines in cigarettes. This enzyme is easily reduced to cause the production of reactive oxy radicals which are able to induce lipid peroxidation and other signs of oxidative stress in the cells [20].

Table 2 Estimated aORs and 95% CI of polymorphism of CYP2E1 and GSTM1 in breast cancer and controls by multiple logistic regression

Genotype	Cases (*N*=262) No. (%)	Control (*N*=225) No. (%)	aOR[a]	95% CI
CYP2E1				
C1/C1	162 (61.83)	134 (52.56)	1	
C1/C2	94 (35.88)	77 (34.22)	1.00	0.69–1.49
C2/C2	6 (2.29)	14 (6.22)	0.39	0.08–0.76*
P-value[b]	0.20	0.81		
GSTM1				
Wild-type	139 (53.05)	122 (54.22)	1	
Null-type	123 (46.95)	103 (45.78)	1.09	0.81–1.55
P-value[b]	0.42	0.37		

Aberration: aOR = Adjusted Odds Ratio, CI = confidence interval

[a]Independent variables including age, menopause, and each covariate

[b]*P*-value for Hardy–Weinberg equilibrium

*P-value < 0.05

Choi et al. have reported the CYP2E1 allele may influence individual susceptibility to breast cancer [8] although the mechanism is still unclear. Our study also suggested the same results. Some interesting research has been published recently regarding the CYP2E1 expression in normal or tumor breast tissue [9, 21, 22] which was intended to reveal the role of the CYP2E1 enzyme in the carcinogenic process of breast cancer. However, unfortunately, the evidence revealed by the above-mentioned research is conflicting and controversial, which makes if even more confusing in regard to the understanding of the mechanism of the CYP2E1 enzyme in carcinogenicity of breast cancer. As Kapucuoglu et al. [9] have noted that different methods of assay techniques could be responsible for the disagreements in the CYP2E1 expression. Since few papers have been published regarding the CYP2E1 expression in mRNA and protein level, the evidence is still limited. Therefore, before any concrete conclusion is drawn about the role of CYP2E1 in carcinogenicity, more evidence is required. In spite of the uncertainty of the carcinogenic role about CYP2E1, we suspect local activation of environmental factors such as alcohol, or other pre-carcinogen to potentially reactive metabolites by the CYP2E1 enzyme in breast tissue may play a role in initiating the carcinogenic process after we carefully examined the evidence of Choi et al. [8], Kapucuoglu et al. [9], and this present study.

On the other hand, GSTs belonging to Phase II xenobiotic metabolizing enzymes are a family of important enzymes which are involved in the detoxification of a wide variety of known and suspected carcinogens found in cigarettes. An individual with homozygous deletion (null) of the GSTM1 gene results in lack of the production of these iso-enzymes. The null GSTM1 genotypes have been reported to be associated with an elevated risk of breast cancer and this association may be modified by cigarette smoking or alcohol consumption [11, 12]. Nevertheless, the main effect of the polymorphisms of GST without environmental factors did not confer a substantial risk of the breast cancer to carriers in recent pooled analysis [13]. In brief, these previous studies revealed the different types of the polymorphism of CYP2E1 and GSTM1 which should interact with environmental factors, and subsequently increase the risks of breast cancer [8–14].

The prevalence of drinking and smoking is very low for breast cancer cases in Taiwan [23]. For this reason, we confined the study population in non-smokers and non-drinkers and attempted to determine the relationship between metabolic enzyme and breast cancer. As mention above, gene-environment interaction, not genetic factors alone, play an important role in development of breast can-

Table 3 Estimated aORs of interaction of polymorphism of CYP2E1 and GSTM1 by case-controls study design

Genotype					
CYP2E1	GSTM1	Case No.	Controls No.	aOR[a] (95%CI)	aOR[a, b] (95% CI)
C2/C2	Wild-type	3	9	1	1
C2/C2	Null-type	1	5	0.67 (0.03–9.18)	
C1/C1, C1/C2	Wild-type	121	108	3.00 (0.76–13.25)	3.50 (0.97–11.20)
C1/C1, C1/C2	Null-type	135	103	3.94 (1.03–17.55)*	4.18 (1.21–15.00)*

Aberration: OR = odds ratio, CI = confidence interval

[a]Adjusted by age and menopause

[b]The first two classifications were merged as the reference group

*P-value < 0.05

cer. This might be the reason why we did not find very a significant effect of the polymorphisms of CYP2E1 or GSTM1 in breast cancer patients who were free of smoking and drinking in our study. However, the gene–gene interaction can be found in this study. The combination of different polymorphisms of CYP2E1 and GSTM1 did modify the risk of breast cancer. An association between the polymorphism of CYP2E1 (Phase I) with GSTM1 (Phase II) genotype and the risk of breast cancer is biologically plausible. Even though, the independent relationships between breast cancer and the polymorphisms of Phase I and Phase II enzyme were weak or not conclusive [13], nevertheless, the polymorphisms of gene–gene interaction could provide some useful clues to identify the risk of polymorphisms of metabolic enzymes in the carcinogenicity of breast cancer. As far as we know, this is the first report to assess the gene–gene interaction of Phase I and Phase II enzymes related to the development of breast cancer in Taiwan.

Despite the unique findings mentioned above, this study had several limitations. First of all, we did not evaluate the interaction of genotypes and the environmental factors such as diet, passive smoking, and other possible life-style risk factors. In Taiwan, few breast cancer patients have the habit of smoking and alcohol consumption, which differs from those in the Western nations [23]. The potential interaction between these genes and the environmental factors could be enormous and would require more cases and controls for analysis, which could not be carried out technically. Secondly, besides age and menopause, other personal factors such as being overweight or suffering from obesity, physical activities, and hormone replacement therapy, were not adjusted for either. We assumed personal risk factors were not related to the polymorphisms of metabolic enzymes, because they were equally distributed in both the cases and the controls. In fact, there is no report which reveals the relationship between such factors and metabolic enzymes. Thirdly, since we chose the controls from the same hospital as the cases, selection bias might exist in a hospital-based design even though there were no differences in the distributions of age between the cases and controls in this study. Nevertheless, we could not evaluate selection bias because no similar study about the gene–gene interaction has been reported. The OR, polymorphisms of GSTM1 and breast cancer estimated by us is within the 95% CI of a pool-analysis of the polymorphisms of GSTM1 and breast cancer relationships. Those findings will enhance the accuracy in the estimating OR of the gene–gene interaction. Lastly, the issue of precision regarding the size of samples should be considered in this study. The sample size of this present study, which included 262 cases and 225 controls is not small. Owing to the rare allele frequency of C2 of CYP2E1, the numbers of both the cases and the controls with the C2/C2 genotype are extremely small. Consequently, a wider range 95% confidence interval resulted in Table 3. We decided to merge the fist two groups as the reference group shown in Table 3 to increase the sample size and obtain a more precise estimation. There is a little difference between the two estimations shown in Table 3, but it does not affect the significant risk effects of individuals with the combination of C1 allele of CYP2E1 and the null genotype of GSTM1 compared with those in the reference groups, respectively. Besides, the protective effect of the C2/C2 genotype has been addressed by various studies in development of breast cancer, gastric cancer, or even, nasopharyngeal cancer in Taiwan [23–25]. The accuracy of the results in this present study could be not a questionable issue despite the small size of samples.

In conclusion, our results indicate that CYP2E1 and GSTM1 could represent a weak association for the development of breast cancer in Taiwan. The gene–gene interaction of metabolic enzymes will modify or increase the risk of carcinogenicity and suggest that environmental risk factors besides cigarette smoking and alcohol consumption would be involved in the carcinogenicity of breast cancer. Additional research is needed to confirm these findings, preferably with more cases to identify the association between the environmental exposure such as passive smoking of non-smokers with the polymorphisms of metabolic enzymes and breast cancer.

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