DOI:10.31557/APJCB.2020.5.2.35

RESEARCH ARTICLE

Genetic Polymorphism of Glutathione S-transferase and Cervical Cancer Susceptibility in Northeastern Thailand

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Abstract

Background: Exposure to certain carcinogens together with host genetic predisposition likely has an influence on cervical carcinogenesis. **Objective:** Our aim was to evaluate synergistic effects of glutathione S-transferase (*GST*) polymorphisms and risk behaviors (i.e., smoking and contraceptive use) on squamous cell cervical cancer (SCCA) development in northeastern Thailand. **Methods:** Subjects were 198 (SCCA) patients and 198 age-matched healthy controls. Multiplex PCR and PCR-RFLP were used to determine *GSTT1* and *GSTA1* gene polymorphism, respectively. **Results:** Interaction between the four polymorphic loci of *GSTs* (*GSTM1*, *GSTT1*, *GSTP1* and *GSTA1*) and increased risk for cervical cancer was not observed. The three genotypes of *GSTM1* consistently showed significant risks of smoking with a lower OR for the Null individuals (1.741) at around one -fourth of wild type homozygous individuals (8.000). The effects of *GST* polymorphisms on cervical cancer risk under the use of hormonal contraceptives apparently did not occur. **Conclusions:** The predisposition of smoking risk is related to the *GST* genotype. It is suggested that knowing one's own genotype data will contribute to the prevention of SCCA by controlling risk habits.

Keywords: Polymorphism- genetic- glutathione S-transferase- cervical cancer- Northeastern Thailand

Asian Pac J Cancer Biol, **5 (2)**, 35-41

Submission Date: 02/12/2020 Acceptance Date: 05/02/2020

Introduction

Cervical cancer remains the most common cancer and the leading cause of cancer-related deaths among women worldwide [1], including in Thailand [2]. Cervical cancer is usually considered to be caused by human papillomavirus (HPV) infection [3]. Nowadays, preventive HPV vaccines are available but these vaccines are effective in clearing only certain types of HPV infection. Other risk factors such as chemical substances and genetic backgrounds might be associated with risk of cervical cancer development. Tobacco smoke contains numerous carcinogens [4]; polycyclic aromatic hydrocarbons (PAHs), and volatile N-nitrosamines; all of which are considered to be primary carcinogens [5].

Smoking exposure is a leading cause of many types of cancer such as of lung and cervix [6-7]. Estrogen-containing oral contraceptives might affect carcinogenesis by controlling cell proliferation and survival [8] and prolonged use of oral contraceptives results in an increased risk of cervical cancer [6]. Moreover, involvement of many genetic polymorphisms in the risk of cervical cancer has been supported by epidemiological studies [9]. Certain alleles of the genes involved in detoxification process could elevate susceptibility to cancer through a mal-detoxification of potential carcinogens [10-11]. Exposure to certain carcinogens together with host genetic predisposition likely has an influence on cervical carcinogenesis; thus, investigations into the genetic aspects of the risk for cervical cancer development are needed.

Glutathione-S-transferases (GSTs) are involved in phase II detoxification of both exogenous and endogenous substrates, which GSTs do by catalyzing the conjugation

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between reduced glutathione (GSH) and substances (including environmental xenobiotics, carcinogens, chemotherapeutic agents or products of oxidative stress) [10]. These metabolizing enzymes are encoded by the glutathione-S-transferase genes (*GSTs*). Eight classes of cytosolic *GST* (corresponding gene) are recognized in mammalian species (viz., alpha (*GSTA*), mu (*GSTM*), theta (*GSTT*), pi (*GSTP*), sigma (*GSTS*), kappa (*GSTK*), omega (*GSTO*), and zeta (*GSTZ*) [12]. Allelic variants of the *GSTs* result in altered detoxification efficiency and are found to be polymorphic in many human populations [13]. It is thus agreeable to assume allelic variants of *GSTs* affect respective carrier susceptibility to various diseases including cancers [14].

Polymorphism of these genes results in alteration of enzymatic activity. For example, the *TT* genotype of the *GSTA1* single nucleotide polymorphism (SNP) T69C had a lower enzymatic activity compared to the *CC* genotype [15]. A functional polymorphism of the *GSTP1* at codon 105 contributes to the change of enzymatic stability and activity of the hydrophobic substrate binding site or electrophile-binding active site of the GST Pi peptide [16]. It has been reported that product of the *Val* allele has less conjugation capacity than that of the *Ile* allele [17]. GSTM1 and GSTT1 have a common and broad range of substrate specificities and as such they detoxify the reactive metabolites of benzo-a-pyrene and other polycyclic aromatic hydrocarbons [18]. A complete deletion of the *GSTM1*—which is frequently found in several populations—results in a null (homozygous) or partial loss (heterozygous) of enzymatic activity [19]. Several studies have reported that the homozygous deletion type of the *GSTM1* is correlated with several types of cancer (i.e., colorectal, head and neck, lung, breast and prostate) [20]. A number of investigations have not, however, found any association between *GSTM1* polymorphism and cancers [10-11]. The complete absence of enzymatic activity caused by a homozygous status (null genotype) of the *GSTT1* deleted allele has been reported to increase the risk of prostate and colorectal cancers [21-22]. To contrast, the null genotype of the *GSTT1* was not significantly associated with an elevated risk of gastric and colorectal cancer in the Korean population nor any cervical abnormality in a multi-ethnic population [23-24].

With the aim of preventing or reducing the incidence of squamous cell carcinomas of the cervix (SCCA) among Northeastern Thai women, we conducted several epidemiological studies and found that HPV infection, smoking habit, and sexual behavior were the major risks for the development of SCCA [25]. As for the potential co-risk factors, we focused on genetic predispositions related to the *GSTs* and performed genotyping of the *GSTM1* and *GSTP1* [26-27]. In the current study, we added the *GSTT1* and *GSTA1* genotype data and re-evaluated for any synergistic effects of the four *GST* polymorphisms and the risk behaviors (i.e., smoking and contraceptive use on the SCCA development).

Materials and Methods

Study subjects

This case-control study comprised 198 cases of pathologically-confirmed SCCA and 198 age-matched healthy volunteers (within 5 years) with normal cytology and histology. The participants were recruited from Khon Kaen General Hospital and Srinagarind Hospital, Khon Kaen Province, Northeast Thailand, between February 2009 and August 2011. Data on the passive exposure to tobacco smoke and high-risk HPV infection were shared in previous studies [6-25]. All of the participants were informed about the purpose and methodology of the research and each signed informed consent prior to enrollment. The study was reviewed and approved by the Ethics Committee of Khon Kaen University (HE 450333) and Khon Kaen Hospital (No.03/02/2554). Data on the passive exposure to tobacco smoke and oral contraceptive use were documented in two previous studies [6-25].

DNA extraction and genotyping

The peripheral blood samples were taken and kept in EDTA tubes from both the patient and control groups. Genomic DNA extraction was performed using the GF-1 Blood DNA Extraction Kit (Vivantis, USA).

GSTT1 polymorphism was detected using the multiplex PCR method with the following two primer pairs: 5'-CAGTTGTGAGCCACCGTACCC-3', and 5'-CGATAGTTGCTGGCCCCCTC-3', 5'-CCAGCTCACCGGATCATGGCCAG-3' and 5'-CCTTCCTTACTGGTCCTCACATCTC-3'. The PCR mixture was performed using a total volume of 25 µl, containing 1 µl of DNA template, 12.5µl of KOD buffer, 5 µl of dNTP, 0.2 mM of each primer, and 0.5 unit of KOD FX (Toyobo, Japan). The cycle condition follows: an initial denaturation at 94°C for 2 min, followed by 30 cycles of denaturation at 98°C for 10 sec, and annealing and extension at 68°C for 90 sec. The PCR product (1460 bp and/or 466 bp) was analyzed by electrophoresis on 1.5% agarose gels.

The *GSTA1* C69T polymorphism was determined using the PCR-RFLP method. The sequences for the primer pair were: 5'-GCA TCA GCT TGC CCT TCA-3' and 5'-AAA CGC TGT CAC CGT CCT G 3'. The PCR product of the 400-bp long was digested by EarI (New England, USA) and electrophoresed on 2.5 % agarose gel (Vivantis, USA), then visualized using ethidium bromide staining. The *T* allele generates a 308 bp and 92 bp fragment, while the *C* allele remains uncut.

The genotyping data for *GSTM1* and *GSTP1* were adapted from Natphopsuk et al. [26] and Phuthong et al. [27], respectively.

Statistical analysis

The genotype distribution was tested using the Hardy-Weinberg equilibrium. The genotype and allele frequencies between the cases and controls were compared using the $\chi 2$ test with Yates' correction when required. The associations between selected variables and risks for SCCA were represented using the odds ratio (OR) with

a 95% CI by using StataSE for the uni- and multi-variate logistic regression analyses. Differences were considered statistically significant when the P-value was < 0.05.

Results

Genotype distribution and allele frequency of each *GST* polymorphism (*GSTT1*, *GSTA1*, *GSTM1*, and *GSTP1*) are presented in Table 1. No significant deviation from the Hardy-Weinberg equilibrium in the genotype distribution among the controls was observed (P > 0.05 by $\chi 2$ test). There was no sign of altered risks for the development of cervical cancer except for the *GSTP1 G* allele; for which the presence resulted in a reduction of risk [33]. Interaction between the four polymorphic loci of *GSTs* (*GSTT1*, *GSAT1*, *GSTM1*, and *GSTP1*) and an increased risk for cervical cancer was not observed (data not shown).

Polymorphisms of *GST*, moreover, are associated with a higher risk of developing cervical cancer among smoking women [28]. In the present study, the effects of *GST* polymorphisms on cervical cancer risk vis-à-vis the sexual partner's tobacco smoking were inconclusive in a standard case-control comparison, P>0.05 (Table 2). Our previous study confirmed that passive smoking was itself associated with a significantly increased risk of cervical cancer among northeastern Thai women [6]. Accordingly, we evaluated the degree of risk of smoking (passive) vis-à-vis each genotype-based subpopulation to determine whether or not any genetic predisposition existed (Table 3). The effects of *GST* polymorphisms on cervical cancer risk under the use of hormonal contraceptives apparently did not occur (Table 4); however, it should be noted that the individuals with the *GSTT1* null genotype were found to show a trend of increase in cervical cancer risk among women taking oral contraceptives (adjusted OR: 4.25 (95%CI=1.00-18.01, P=0.050). We could not find any altered risk by the use of oral contraceptives in each genotype-based sub population (data not shown).

Discussion

The frequency of the *GSTT1* null genotype (35.86%) was similar to previous reports among Asian population (30.0-41.4%) [29-31]. The finding in the current study of no relationship between the *GSTT1* deletion type and risk of cervical cancer agreed with other reports among various Asian and European populations [28-32]. Few studies have reported a significant correlation between the *GSTT1* null genotype and cervical cancer [33]; however,

Table 1. Each *GST* Polymorphism and Risk for Cervical Cancer

GST Genotypes	Controls n (%)	Cases n (%)	Crude OR [95%CI, *P*]	Adjusted OR[a] [95%CI, *P*]
GSTT1				
+/+	34 (17.17)	34 (17.17)	1	1
+/-	93 (46.97)	100 (50.51)	1.08 [0.60-1.94, 0.7970]	1.43 [0.62-3.29, 0.401]
-/-	71 (35.86)	64 (32.32)	0.90 [0.48-1.68, 0.7272]	1.26 [0.52-3.04, 0.603]
Present allele	0.41	0.42	1	NA
Null allele	0.59	0.58	1.08 [0.81-1.43, 0.6653]	NA
GSTA1				
CC	141 (71.21)	147 (74.24)	1	1
CT	53 (26.77)	43 (21.72)	0.78 [0.48-1.27, 0.2888]	0.78 [0.39-1.54, 0.468]
TT	4 (2.02)	8 (4.04)	1.92 [0.50-8.88, 0.2886]	1.15 [0.21-6.25, 0.868]
C allele	0.85	0.85	1	NA
T allele	0.15	0.15	0.96 [0.65-1.42, 0.8429]	NA
GSTM1 (Natphopsuk et al., 2015)				
+/+	15 (7.58)	15 (7.58)	1	1
+/-	58 (29.29)	53 (26.77)	0.91 [0.38-2.22, 0.8266]	1.48 [0.41-5.31, 0.549]
-/-	125 (63.13)	130 (65.66)	1.04 [0.45-2.39, 0.9191]	1.16 [0.35-3.86, 0.801]
Present allele	0.22	0.21	1	NA
Null allele	0.78	0.79	0.93 [0.66-1.30, 0.7298]	NA
GSTP1 (Phuthong et al., 2018)				
AA	90 (45.45)	112 (56.57)	1	1
AG	85 (42.93)	71 (35.86)	0.67 [0.43-1.04, 0.0623]	0.55 [0.29-1.04, 0.068]
GG	23 (11.62)	15 (7.58)	0.52 [0.24-1.12, 0.0704]	0.53 [0.19-1.46, 0.218]
AG and GG	108 (54.55)	86 (43.43)	0.64 [0.42-0.97, 0.027*]	0.55 [0.30-0.99, 0.048*]
A allele	0.67	0.74	1	NA
G allele	0.33	0.26	0.69 [0.50-0.95, 0.019*]	NA

[a]adjusted multiple logistic regression for partner's smoking, oral contraceptive use and HPV infection NA, not applicable; *P value<0.05

Table 2. *GST* Polymorphisms and Risk for Cervical Cancer among Passive Smokers

GST Genotypes	Controls n (%)	Cases n (%)	Crude OR [95%CI, *P*]	Adjusted OR[a] [95%CI, *P*]
GSTT1				
+/+	19 (18.73)	28 (19.58)	1	1
+/-	55 (57.14)	67 (46.85)	0.83 [0.42-1.64, 0.585]	1.07 [0.37-3.13, 0.904]
-/-	33 (24.49)	48 (33.57)	0.99 [0.47-2.05, 0.972]	1.95 [0.61-6.20, 0.257]
GSTA1				
CC	76 (38.38)	109 (55.05)	1	1
CT	29 (14.65)	29 (14.65)	0.70 [0.39-1.26, 0.233]	0.83 [0.34-2.05, 0.689]
TT	2 (1.01)	5 (2.53)	1.74 [0.33-9.22, 0.513]	0.71 [0.08-6.02, 0.753]
GSTM1				
+/+	5 (4.67)	12 (8.39)	1	1
+/-	27 (25.23)	37 (25.87)	0.57 [0.18-1.81, 0.342]	1.13 [0.20-6.45, 0.890]
-/-	75 (70.09)	94 (65.73)	0.52 [0.18-1.55, 0.241]	0.67 [0.13-3.40, 0.630]
GSTP1 (Phuthong et al., 2018)				
AA	49 (45.79)	77 (53.85)	1	1
AG	43 (40.19)	55 (38.46)	0.81 [0.48-1.39, 0.452]	0.79 [0.35-1.79, 0.577]
GG	15 (14.02)	11 (7.69)	0.47 [0.20-1.10, 0.081]	0.75 [0.21-2.71, 0.663]

[a]adjusted multiple logistic regression for partner's smoking, oral contraceptive use and HPV infection

Table 3. Risk Evaluation of Smoking by *GSTs* Genotype

GST Genotypes	Smoking status	Controls	Cases	Crude OR [95%CI, *P*]
GSTT1				
+/+	Non-smoking	15	6	1
	Smoking	19	28	3.684 [1.21-11.20, 0.0182*]
+/-	Non-smoking	38	33	1
	Smoking	55	67	1.403 [0.78-2.52, 0.2579]
-/-	Non-smoking	38	16	1
	Smoking	33	48	3.455 [1.66-7.19, 0.0007**]
GSTA1				
CC	Non-smoking	65	38	1
	Smoking	76	109	2.453 [1.49-4.03, 0.0003**]
TC	Non-smoking	24	14	1
	Smoking	29	29	1.714 [0.74-3.96, 0.2049]
TT	Non-smoking	2	3	1
	Smoking	2	5	1.667 [0.15-18.87, 0.6788]#
GSTM1				
+/+	Non-smoking	10	3	1
	Smoking	5	12	8.000 [1.52-42.04, 0.0099*]
+/-	Non-smoking	31	16	1
	Smoking	27	37	2.655 [1.22-5.80, 0.0132*]
-/-	Non-smoking	50	36	1
	Smoking	75	94	1.741 [1.03-2.94, 0.0377*]
GSTP1				
AA	Non-smoking	41	35	1
	Smoking	49	77	1.841 [1.04-3.28, 0.0307*]
AG	Non-smoking	42	16	1
	Smoking	43	55	3.358 [1.67-6.77, 0.0005**]
GG	Non-smoking	8	4	1
	Smoking	15	11	1.467 [0.35-6.13, 0.8657]#

#Yates' correction; *P value<0.05; **P value<0.01

Table 4. *GST* Polymorphisms and Oral Contraceptive Use

GST Genotypes	Controls n (%)	Cases n (%)	Crude OR [95%CI, *P*]	Adjusted ORa [95%CI, *P*]
GSTT1				
+/+	14 (17.50)	14 (14.89)	1	1
+/-	40 (50.00)	48 (51.06)	1.20 [0.51-2.81, 0.675]	2.97 [0.78-11.32, 0.110]
-/-	26 (32.50)	32 (34.04)	1.23 [0.50-3.04, 0.652]	4.25 [1.00-18.01, 0.050]
GSTA1				
CC	58 (29.29)	70 (35.35)	1	1
CT	22 (11.11)	21 (10.61)	0.79 [0.40-1.58, 0.506]	0.65 [0.23-1.79, 0.400]
TT	0 (0.00)	3 (1.52)	-b	-b
GSTM1				
+/+	5 (6.25)	8 (8.51)	1	1
+/-	17 (21.25)	24 (25.53)	0.88 [0.25-3.17, 0.848]	1.46 [0.23-9.50, 0.689]
-/-	58 (72.50)	62 (65.96)	0.67 [0.21-2.16, 0.500]	0.93 [0.17-5.03, 0.935]
GSTP1				
AA	35 (43.75)	48 (51.06)	1	1
AG	36 (45.00)	39 (41.49)	0.79 [0.42-1.48, 0.462]	0.83 [0.32-2.15, 0.697]
GG	9 (11.25)	7 (7.45)	0.57 [0.19-1.67, 0.303]	0.62 [0.14-2.76, 0.526]

[a]adjusted multiple logistic regression for partner's smoking, oral contraceptive use and HPV infection, b drop because of a zero count cell

inter-ethnic differences including behavioral risk factors might account for this discrepancy.

Decreased expression of *GSTA1* in individuals with the TT genotype results in the accumulation of oxidative DNA damage, suggesting an altered potential for carcinogenesis of the *GSTA1* polymorphism [34]; this explanation is quite reasonable. However, many conflicting results have been reported even for the same types of cancer; significant and not significant associations for bladder cancer [35-36] and colorectal cancer [37]. We failed to show an association between *GSTA1* polymorphism and SCCA; the low T allele frequency requires a larger sample size to draw a conclusion. Since cancer types and ethnic backgrounds might underlie genetic predispositions, there remains room for the contribution of *GSTA1* polymorphism to SCCA development.

The three genotypes of *GSTM1* consistently showed significant risks of smoking with a lower OR for the Null individuals at around one -fourth of wild type homozygous individuals. Conflicting results of *GSTM1* polymorphism and SCCA development [28] may be attributed to this fact. We simply expect that the lower enzyme activity results in the higher OR; however, in another deletion type polymorphism, *GSTT1*, OR for the individuals with Null genotype and with the wild type homozygous were similar to each other. This indicates the presence of possible intervention of compensatory effects by other GSTs. As for the *GSTA1*, the low T allele frequency may limit us to draw the conclusion with the present small sample size. In a study analyzing the same set of *GST* polymorphisms and colorectal cancer, the presence of *GSTP1 Ile/Val* (A/G) significantly decreased the risk of colorectal cancer [38], whereas the smoking risk was higher among heterozygous individuals than the *Ile* (A) homozygous individuals. It would be premature to conclude the presence or absence of genetic predisposition of *GST* polymorphisms in SCCA development.

A modified influence of the *GSTT1* deletion on the association between combined (estrogen plus progestin) oral contraceptive use and sex hormone metabolism was demonstrated [39]. The use was also involved in cervical cell proliferation resulting in increased risks of cervical cancer [6]. The use of oral contraceptives possibly enhances HPV E6/E7 expression and thus results in HPV-related cervical cancer development [40].

In the current study, we investigated the possible role of the common *GST* polymorphisms in the development of cervical cancer in northeastern Thailand. The results showed that the genotypes *GSTM1*, *GSTT1*, *GSTP1*, and *GSTA1* did not contribute independently towards cervical carcinogenesis; however, in the genotype-based sub population, the predisposition of smoking risk is related to the *GST* genotype. It is therefore suggested that knowing one's own genotype data will contribute to the prevention of cervical carcinoma by controlling risk habits.

Acknowledgements

This study was partly supported by (a) an Invitation Research Grant from Faculty of Medicine, Khon Kaen University, (b) a Research Fund from Khon Kaen University, and (c) JSPS Core University Program. The authors thank the staff and patients who took part in this study and Mr. Bryan Roderick Hamman for assistance with the English-language presentation of the manuscript under the aegis of the Publication Clinic, Research Affairs, Faculty of Medicine, Khon Kaen University.

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