RESEARCH ARTICLE

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Genetic Polymorphism of the *Glutathione S-transferase Pi 1 (GSTP1)* and Susceptibility to Cervical Cancer in Human Papilloma Virus Infected Northeastern Thai Women

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Abstract

Objective: We aimed to investigate any association between a genetic polymorphism of the detoxification *GSTP1* gene and risk of cervical cancer in northeastern Thailand. **Materials and Methods:** Genotyping of *GSTP1* was performed for 198 squamous cell cervical cancer (SCCA) patients and 198 age-matched healthy controls with the PCR-RFLP method. **Results:** The respective frequencies of the *G* allele were 0.33 and 0.26 in the controls and cases, the difference being significant (OR = 0.69 [95% CI: 0.50-0.95, p=0.0192]). Among women infected with high-risk types of HPV, being a heterozygous carrier was associated with a reduced risk of cervical cancer (adjusted OR = 0.32 [95% CI: 0.12-0.91, p=0.031]). Similarly, a decreased risk was observed in heterozygous women with a non-smoking partner (adjusted OR = 0.27 [95% CI: 0.09-0.83, p=0.023]). **Conclusions:** *GSTP1* polymorphism could influence susceptibility to cervical cancer among northeast Thai women; either as a independent factor or in combination with high-risk HPV infection. Dual-testing of HPV and the *GSTP1* might prove an effective screening tool for cervical cancer.

Keywords: *Glutathione S-transferase pi 1*- susceptibility- cervical cancer- human papilloma virus

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Introduction

Cervical cancer remains one of the most common cancers afflicting women worldwide (Ferlay et al., 2015) including Thailand (National Cancer Institute, 2012). Infection with a high-risk type of human papilloma viruses (HPV) is recognized as a main causal factor for development of cervical cancer (zur Hausen, 1991; Moscicki et al., 2001; Settheetham-Ishida, et al., 2005; Carter et al., 2011). Since not all HPV-exposed individuals develop cervical cancer (Settheetham-Ishida, et al., 2004), several studies have investigated other exogenous risk factors such as exposure to sexual experience with several partners, and/or sex at an early age, and smoking. It is assumed that susceptibility to cervical cancer might be because of one's genetic makeup with the polymorphic state causing differences in the metabolism of carcinogens (Ying et al., 2012).

Glutathione S-transferases (GSTs) form a super family of phase II metabolic enzymes involved in the conjugation reaction of xenobiotics; catalyzing reactions between glutathione and a variety of potentially toxic and carcinogenic electrophilic compounds (Ali-Osman et al., 1997). There are at least eight subclasses of GSTs codified as cytosolic or microsomal enzymes (Strange et al., 2001). Several types of allelic variations have been found among the polymorphic states including *GSTM1*, *GSTT1*, and *GSTP1* (Canbay et al., 2003; Csejtei et al., 2008; Ghatak et al., 2016; Mittal et al., 2006; Srivastava et al., 2005; Tiwawech et al., 2005).

GSTP1, located on chromosome 11q13, participates in detoxification of various potential carcinogens produced by the metabolism of polycyclic aromatic hydrocarbons (e.g., benzo[a] pyrene: BaP—a common constituent of tobacco smoke) (Ritchie et al., 2007). The *GSTP1* harbors a A>G transition in codon 105, resulting in amino acid Ile>Val substitutions (I105V) (Ali-Osman et al., 1997; Mo et al., 2009). This polymorphism has been reported to modify the active electrophile-binding site of GSTP1 (Mo et al., 2009), and might be involved in cancer development in several organs, e.g., gall bladder (Pandey et al., 2006), prostate gland (Mittal et al., 2006; Qadri et al., 2011; Srivastava et al., 2005), stomach (Ghatak et al., 2016), and thyroid gland (Granja et al., 2004). The association of the *GSTP1* polymorphism and the risk of cervical cancer across geographic areas and ethnic groups is, however, inconclusive (García-González et al, 2012). In the current study, we investigated whether the polymorphism in codon

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105 of the *GSTP1* could be a biomarker for susceptibility to cervical cancer. We also examined the synergistic effect of the *GSTP1* polymorphism and environmental carcinogens as well as high-risk HPV infection on cervical cancer development.

Materials and Methods

Study subjects

Subjects of this case-control study were recruited at Khon Kaen General Hospital and Srinagarind (university) Hospital, Khon Kaen Province, Northeast Thailand, between February 2009 and August 2011. The participants were 198 cases with pathologically-defined squamous cell carcinoma of the cervix (SCCA) and 198 age-matched healthy controls with normal cytology (i.e., as determined by Pap smear test) and histology. The controls were age-matched within five years with cases. Data on the passive exposure to tobacco smoke and high-risk HPV infection were shared from previous studies (Natphopsuk et al., 2012; 2013).

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).

Genotyping of the GSTP1

Blood samples were taken in EDTA tubes from both the patient and the control groups. Genomic DNA extraction was performed using the GF-1 Blood DNA Extraction Kit (Vivantis, USA). The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was used to determine *GSTP1* gene polymorphism. The sequences for the primer pairs were: 5'-ACC CCA GGG CTC TAT GGG AA-3' and 5'- TGA GGG CAC AAG AAG CCC CT 3' (Kiran et al., 2010). The PCR product of 176-bp in length was digested by BsmAI (New England, USA) and electrophoresed on 4% agarose gel (Vivantis, USA), visualized using ethidium bromide staining. BsmAI recognizes only the GTCTC sequence in the *G* allele so as to generate a 91 bp and an 85 bp fragment, while the *A* allele remains uncut.

Statistical analysis

The genotype and allele frequencies between the case and control were compared using the χ^2 test. The associations between selected variables and risks for SCCA were applied using StataSE for the uni- and multi-variate logistic regression analyses with the odds ratio (OR) 95%CI. The genotype distribution was tested using the Hardy-Weinberg equilibrium. Differences were considered statistically significant when the p-value was < 0.05.

Results

The respective prevalence of the *GSTP1* genotype *AA*, *AG*, and *GG* in the controls vs. cases was 45.45%, 42.93% and 11.62% vs. 56.57%, 35.86%, and 7.58%. No significant deviation from the Hardy-Weinberg equilibrium in the genotype distribution was observed in either the cases or controls ($p > 0.5$ by χ^2 test). The respective frequency of the *G* allele in the controls and cases was 0.33 and 0.26. The *G* allele was associated with a lower risk for cervical cancer (OR = 0.69 [95% CI: 0.50- 0.95, p = 0.0192]) Table 1.

Interaction between the polymorphism of *GSTP1* and the risk for cervical cancer among high-risk HPV

Table 1. Association of *GSTP1* Polymorphism and Risk for Cervical Cancer

GSTP1 genotype	Cases n (%)	Controls n (%)	OR [95% CI, p-value]	Adjusted OR[a] [95% CI, p-value]
AA	112 (56.57)	90 (45.45)	1	1
AG	71 (35.86)	85 (42.93)	0.67 [0.43-1.04, 0.062]	0.55 [0.29-1.04, 0.068]
GG	15 (7.58)	23 (11.62)	0.52 [0.24-1.12, 0.070]	0.53 [0.19-1.46, 0.218]
GG+AG	86 (43.43)	108 (54.55)	0.64 [0.42-0.97, 0.027*]	0.55[0.30-0.99, 0.048*]
Allele distribution[b]				
A	0.74	0.67	1	NA
G	0.26	0.33	0.69 [0.50- 0.95, 0.0192*]	NA

OR, odds ratio; CI, confidence interval; * $p < 0.05$; [a], adjusted for multiple logistic regression for partners' smoking, oral contraceptive use and HPV infection; [b], frequency; NA, not applicable

Table 2. GSTP1 Polymorphism and Risk for Cervical Cancer in High-risk HPV Infection

GSTP1 genotype	Case n (%)	Control n (%)	OR [95% CI, p-value]	Adjusted OR[a] [95% CI, p-value]
AA	90 (45.45)	7 (3.54)	1	1
AG	54 (27.27)	12 (6.06)	0.35 [0.13-0.94, 0.038*]	0.32 [0.12-0.91, 0.031*]
GG	11 (5.56)	3 (1.52)	0.29 [0.06-1.27, 0.099]	0.29 [0.06-1.33, 0.111]
GG+AG	65 (32.83)	15 (7.58)	0.34 [0.13-0.87, 0.025*]	0.32 [0.12-0.85, 0.022*]

OR, odds ratio; CI, confidence interval; * $p < 0.05$; [a], adjusted for multiple logistic regression for partners' smoking and oral contraceptive use

Table 3. *GSTP* Genotype and Risk for Cervical Cancer Among Smoking Status of Partners

Smoking status of partner	*GSTP* genotype	Case n (%)	Control n (%)	OR [95% CI, p-value]	Adjusted OR[a] [95% CI, p-value]
Non-smoker	*AA*	35 (17.68)	41 (20.71)	1	1
	AG	16 (8.08)	42 (21.21)	0.45 [0.21-0.93, 0.031*]	0.27 [0.09-0.83, 0.023*]
	GG	4 (2.02)	8 (4.04)	0.59 [0.16-2.11, 0.414]	0.33 [0.06-1.87 0.209]
	GG+AG	20 (10.10)	50 (25.25)	0.47[0.24-0.93, 0.031*]	0.28[0.10-0.81, 0.018*]
Smoker	*AA*	77 (38.89)	49 (24.75)	1	1
	AG	55 (27.78)	43 (21.72)	0.81 [0.48-1.39, 0.452]	0.79 [0.35-1.79, 0.577]
	GG	11 (5.56)	15 (7.58)	0.47 [0.20-1.10, 0.081]	0.75 [0.21-2.71, 0.663]
	GG+AG	66 (33.33)	58 (29.29)	0.72 [0.44-1.20, 0.208]	0.78 [0.36-1.68, 0.532]
Current smoker	*AA*	42 (21.21)	21 (10.61)	1	1
	AG	34 (17.17)	18 (9.09)	0.94 [0.44-2.05, 0.885]	0.70 [0.24-2.10, 0.529]
	GG	9 (4.55)	10 (5.05)	0.45 [0.16-1.28, 0.133]	0.80 [0.19-3.43, 0.762]
	GG+AG	43 (21.72)	28 (14.14)	0.77 [0.38-1.56, 0.464]	0.73 [0.27-1.97, 0.536]
Former smoker	*AA*	35 (17.68)	28 (14.14)	1	1
	AG	21 (10.61)	25 (12.63)	0.67 [0.31-1.44, 0.308]	0.97 [0.27-3.47, 0.969]
	GG	2 (1.01)	5 (2.53)	0.32 [0.06-1.78, 0.192]	0.37 [0.02-6.66, 0.498]
	GG+AG	23 (11.62)	30 (15.15)	0.61 [0.29-1.28, 0.193]	0.87 [0.25-2.97, 0.823]

OR, odds ratio; CI, confidence interval; * $p < 0.05$;[a], adjusted for multiple logistic regression for oral contraceptive use and HPV infection

carriers is presented in Table 2. Among women with the high-risk type of HPV infection, a lower risk for cervical cancer was observed among heterozygous carriers (adjusted OR = 0.32 [95% CI: 0.12-0.91, p = 0.031]). The combination of *GG* and *AG* genotypes, having the *G* allele, had a reduced risk for developing cervical cancer (adjusted OR = 0.32 [95% CI: 0.12-0.85, p = 0.022]).

For individuals with a smoking partner, the association between smoking and risk of cervical cancer was not found for any *GSTP1* genotype ($p > 0.05$); notwithstanding, a decreased risk for developing cervical cancer was observed in heterozygous women with a non-smoking partner (OR = 0.45 [95% CI: 0.21-0.93, p = 0.031]) and adjusted OR = 0.27 [95% CI: 0.09-0.83, p = 0.023] (Table 3).

Discussion

We investigated the genetic polymorphisms of *GSTP1* in 198 SCCA patients with 198 age-matched, normal controls. A protective effect against cervical cancer was associated with the presence of the *G* allele; this finding agrees with reports from Korea (Jee et al., 2002), India (Sobti et al., 2006), where *GSTP1* (*AG+GG*) was found to have a survival advantage and a reduced risk of death (Abbas et al., 2015). This result, however contrasts with Italian (Palma et al., 2010) and Turkish (Kiran et al., 2010) studies, where no relationship between *GSTP1* polymorphism and cervical cancer was observed.

GSTP1 is the dominant GST isoenzyme involved in the detoxification of electrophilic compounds by glutathione conjugation (Elsaid et al., 2015). The GST enzyme contains two binding sites: a G-site for binding reduced glutathione (GSH) and an H-site for binding electrophilic substrates (Willmore et al., 2005). The results of conjugation between GSH and the electrophile will be converted to mercapturic acid and excreted in the urine (Johansson et al., 1998). The polymorphic amino acid residue 105 of *GSTP1* was positioned close to the substrate binding H-site for electrophilic substrates, which is expected to affect substrate affinity (Johansson et al., 1998; Qadri et al., 2011). The protein encoded by the *G* allele has been reported and that this valine (Val) residue has a higher catalytic efficiency than the isoleucine (lle) residue with carcinogenic aromatic epoxides (Hu et al., 1997; Sundberg et al., 1998). The structure of GSTP1 Val has more surrounding water molecules (5 vs. 4 in Ile) that are linked to a channel of 3 additional water molecules, largely conserved among class Pi GSTs and proposed to influence the catalytic process (Johansson et al., 1998). While the Ile variant is reported to be ~2-3 times more stable than the Val variant (i.e., under increasing thermo-stability) (Johansson et al., 1998), the heterozygous state (Ile/Val) gets advantages from both Ile and Val, which might be the reason for the decreased risk of cervical cancer.

The interactions between *GSTP1* polymorphism and HPV infection and smoking were also investigated in the current study. It is well-accepted that infection with HPV is a crucial risk factor for cervical cancer. In the present study, the heterozygous state (Ile/Val) had a significantly lower risk for cervical cancer among women with a high-risk HPV infection. Besides enzymatic detoxification, GSTP1 has other non-enzymatic functions that can influence apoptosis; by inhibiting the c-Jun-NH_2 kinase (JNK) and the TNF receptor associated factor 2 (TRAF2) pathways (Adler et al., 1999). The E7 protein of HPV-16 was reported to occupy the space between Cys47 and Cys101 of GSTP1, preventing the formation of intra- and inter-molecular disulfide, when GSTP1 is in its free form (Tew et al., 2011; Adler et al., 1999). As a consequence, HPV-16 E7 binding might protect GSTP1

from forming dimers and larger aggregates which cannot accommodate Jun–JNK (Tew et al., 2011; Adler et al., 1999). The E7 protein has, moreover, been associated with a decrease in oxidized GSTP1; by interfering with JNK signaling, which in turn results in increased levels of reduced GSTP1 (Tew et al., 2011). Thus, an increased level of reduced GSTP1 will accommodate Jun–JNK; thereby inhibiting JNK phosphorylation of c-Jun, which is an inactive transcription (Adler et al., 1999). The polymorphism in the amino acid residue 105 of GSTP1 from Ile to Val might be linked to a change in the enzymatic activity of GSTP1 (Mo et al., 2009). Thus, women with a high-risk, Val variant HPV would be more able to resist HPV E7 and thereby have a lower risk for cervical cancer over against those with only the Ile variant. Women with only one Val variant (i.e., the heterozygous state) would still have a function from the Ile variant in terms of thermos-stability.

Since smoking among women in northeastern Thailand is rare, smoking habit was evaluated as passive smoking (i.e., the subject's partner smoked). Cigarette smoke comprises several thousand compounds; some of which are carcinogens (Lodovici and Bigagli, 2009). Our previous study confirmed that passive smoking was associated with a significantly increased risk of cervical cancer among northeastern Thai women (Natphopsuk et al., 2012). The protective effect against cervical cancer of the Ile/Val genotype among women with a non-smoking partner was found in the current study, which may confirm that with respect to carcinogenic aromatic epoxides, the Val residue has a higher catalytic efficiency than the Ile residue (Hu et al., 1997; Sundberg et al., 1998), resulting in more effective detoxification of the carcinogens generated by smoking. A study of Korean smokers revealed that the Ile/Ile variant increased the risk for cervical cancer 3.9 times compared to the *GSTP1 Ile/Val + Val/Val* variant (Jee et al., 2002). Studies demonstrating controversial results also exist; however, the risk for cervical cancer increased among (passive) smokers with the *Ile/Val* state (OR 6.4, 95%CI =2.25-18.38, p = 0.0005) (Sobti et al., 2006). Palma et al. did not, moreover, find any association between *GSTP1* polymorphism and the risk of cervical cancer; notwithstanding the presence or absence of a smoking habit (Palma et al., 2010).

Taken together, we conclude that *GSTP1* polymorphism could influence susceptibility to cervical cancer both as a single factor and in combination with high-risk HPV infection and non-smoking partner among Northeast Thai women.

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