行政院國家科學委員會專題研究計畫 成果報告

環境危險因子、代謝基因之多型性與子宮頸前癌和子宮頸癌之相關性探討

研究成果報告(精簡版)

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中　華　民　國　97 年 10 月 30 日

國科會研究計畫期末報告

計畫題目:

中文: 環境危險因子、代謝基因之多型性與子宮頸前癌和子宮頸癌之相關性探討

英文: Environmental hazards, polymorphisms of metabolizing genes, and cervical intraepithelial neoplasm risk

計畫編號: NSC 96-2314-B-040-002

執行期限: 96/02/01-97/07/31

目　　錄

（一） 計畫中文摘要

研究背景: 衛生署資料顯示，子宮頸癌為臺灣婦女癌症發生率的第一位，約每十萬位婦女，就有 49.8 位罹患子宮頸癌。許多流行病學研究發現，高危險性人類乳突狀病毒感染、抽煙、暴露二手煙等，是導致婦女罹患子宮頸癌的重要因素。但是，有些個體雖暴露於以上的危險因素之中，但並未罹患子宮頸癌。因此，個人的基因型態在決定其是否罹患子宮頸癌上扮演重要角色。有研究指出 phase II 酵素，例如 *GSTM1*、 *GSTT1*、 *GSTA1* 及 *GSTP1* 可將致癌物質轉換為親水性代謝物以排出體外。因此個體代謝致癌物質及去毒化的能力，可能會影響其是否會罹患癌症。本研究探討 phase II 酵素，例如 *GSTM1*、 *GSTT1*、 *GSTA1* 及 *GSTP1* 基因多型性與子宮頸癌的相關性。**研究方法:** 本研究至目前為止共收集 127 位罹患子宮頸上皮內細胞瘤(cervical intraepithelium neoplasm，簡稱:CIN)以上的個案及 340 位健康對照者，研究中以 PCR-RFLP 探討基因與子宮頸上皮內細胞瘤的相關性，並以問卷調查方式收集社會人口學及環境危險因子等相關資料，以探討基因與基因，及基因與環境中危險因子與子宮頸癌的相關性。**初步結果:** 本研究初步結果發現，個體具 I/V 或 V/V 型的 GSTP1 基因多型性相較於 I/I 型基因多型性者有 3.37 倍(95% CI: 1.30-8.72)的危險性會罹患子宮頸上皮內細胞瘤。而其他基因的基因多型性，例如 *GSTM1*、 *GSTT1* 及 *GSTA1* 則與罹患子宮頸上皮內細胞瘤無顯著相關性。**結論:** 個體具 I/V 或 V/V 型的 GSTP1 基因多型性可能與婦女罹患子宮頸上皮內細胞瘤有關。

（二） 計畫英文摘要

Background: According to the report from Department of Health, cervical cancer (49.8 per 100,000 females) was the most prevalent malignancy in Taiwanese women. It was also the fifth leading cause of cancer deaths among women (8.3 per 100,000 females). Many epidemiologic researchers have found that high-risk HPV (human papillomavirus) infection, active cigarette smoking, passive smoking, reproductive condition, and sexual behavior were the major risk factors of cervical cancer. However, those factors can't fully explain the entire pathogenesis of cervical cancer. Some individuals under the exposure to those risk factors didn't develop cervical intraepithelial neoplasm (CIN), suggesting genetic components may play another pivotal role in cervical carcinogenesis. Phase II enzymes, such as *GSTM1* (μ), *GSTA1* (α), *GSTT1* (θ), and *GSTP1* (π) have been suggested as detoxifying genes because of their ability to regulate the conjugation of a wide range of xenobiotics, including environmental carcinogens, in order to excrete as hydrophilic metabolites. Individuals with different abilities to metabolize and detoxify carcinogens show different risks to develop cancer. Although a few studies investigated the association between metabolize enzyme gene polymorphism phase II GST, and the progression of cervical neoplasm, the results are still controversial. In this study, we conduct a case–control study to investigate the role of genetic susceptibility in the development of cervical neoplasm. **Methods:** Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) was used to measure gene polymorphisms in both healthy controls and CIN patients. **Results:** A significant different frequencies of GSTP1 genotypes was found between healthy controls and CIN patients. The adjusted odds ratios (AORs) with their 95% confidence intervals (CIs) for individuals with I/V or V/V of GSTP1 compared to individuals with I/I of GSTP1 was 3.37 fold risk (95%CI: 1.30-8.72) to induce CIN1, however, there was not a significant different frequency between healthy controls and individuals with ≥ CIN2. As well, no significant difference was found between healthy controls and cervical intraepithelial neoplasm patients among GSTM1, GSTT1, and GSTA1 gene polymorphism. **Conclusions:** Individuals with I/V or V/V of GSTP1 gene polymorphism is considered as a factor increasing the susceptibility of cervical intraepithelial neoplasm.

研究背景及目的

Introduction

According to the Department of Health, cervical cancer (49.8 per 100,000 females) was the most prevalent malignancy in Taiwanese women [1]. It was also the fifth leading cause of cancer deaths among women (8.3 per 100,000 females) [2]. High-grade squamous intraepithelium neoplasms, which are often found by exfoliated cytology screening (pap smear), include moderate dysplasia (cervical intraepithelium neoplasm II: CIN2) and severe dysplasia (CIN3) are known to be precancerous cervical lesions. If not treated, at least 25% will progress to carcinoma in situ or invasive cancer [3]. Although many epidemiologic researchers have found that high-risk HPV (human papillomavirus) infection (Types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 59, and 68) [4, 5], active cigarette smoking [6-8], passive smoking, reproductive condition [9-11], and sexual behavior (probably related with human papillomavirus, HPV, or herpes simplex infection) were the major risk factors of cervical cancer, these factors do not fully explain the entire pathogenesis of cervical cancer [12, 13]. Some of the individuals, exposure to major risk factors, didn't progress to have CIN. Thus, genetic components may play other critical roles in cervical carcinogenesis. Individuals with modified abilities to metabolize and detoxify carcinogens show an increased or decreased risk of cancer [14]. The most recognized groups of susceptibility factor are phase II GST genotypes, such as GSTM1, GSTT1, GSTA1, and GSTP1, the members of which are involved in the activation-inactivation of carcinogens [15]. *GSTM1* (μ), *GSTT1* (θ),GSTA1, and *GSTP1* (π) have been suggested as candidate cancer susceptibility genes because of their ability to regulate the conjugation of a wide range of xenobiotics, including environmental carcinogens, in order to excrete hydrophilic metabolites [16]. Null variants of *GSTM1* or *GSTT1* that are associated with a lack of enzyme function exist at both of these loci. Individuals who are carriers of homozygous null in the *GSTM1* or *GSTT1* genes might be at a particularly high risk for chemical–induced DNA damage and may therefore be at increased cancer risk [16, 17]. In addition, a single nucleotide substitution (A→G) at position 313 of the *GSTP1* gene, resulting in replacing isoleucine with valine, substantially reduces GSTP1 enzyme activity [18]. As well, the SNP at C-69T result in decreased GST expression [19]. A numerous epidemiologic studies have suggested that deficiency of GSTM1, GSTT1, GSTA1, or GSTP1 activity may increase cancer risk at many sites [16, 20-40]. Throughout the search of Medline, there are a few research groups to investigate the association between genetic polymorphisms of *GSTM1*, *GSTT1*, *GSTA*1, or *GSTP1* and cervical neoplasm risk [21-30]. However, the risk of null in the *GSTM1* or

GSTT1 genes on cervical neoplasm still in a controversy. Korea [28] has reported the significant association between *GSTT1*, but not *GSTM1*, and cervical carcinoma risk. Patients with *GSTT1* null genotypes have a 1.9-fold risk (95% CI = 1.2-2.9) to develop cervical carcinoma than those with *GSTT1* positive genotypes. Contrary, Sharma [24] collected 142 cervical cancer cases and 96 healthy controls in India. They found homozygous GSTM1 null genotype individuals have 2.5 fold risk (95%CI=1.4-4.5) to develop cervical cancer, but not homozygous GSTT1 null genotype (OR=1.7, 95%CI=0.8-3.8). Joseph[22] have a similar results with the finding of Sharma, Joseph found deleted GSTM1 genotype individuals have 2.4 fold risk (95%CI=1.53-3.78) to induce cervical cancer, but not deleted GSTT1 genotype (OR=1.84, 95%CI=0.95-3.57). Au [25] analysed genotype from US population, they found the GSTM1 null genotype was associated with a significant 3.4 fold risk (95%CI=1.0-11.8) to develop cervical cancer compared with those who were GSTM1 positive. Sierra-Torres [23] had a consist results with Au. Sierra-Torres and his colleague conducted a clinical case-control study and found GSTM1 null genotype was associated with a 3.3 fold risk (95%CI=1.0-11.8) to have neoplasia in Texas. Rebbeck[16] had suggested that the risk conferred to individuals who carry homozygous deletions in *GSTM1* or *GSTT1* appears to be small in magnitude (e.g., OR < 2.0). Other studies[21, 29, 30] found both GSTM1 null genotype and GSTT1 null genotype were not associated with cervical neoplasm development. Different ethnic population or small sample sizes in previous studies (< 200 cases and 200 controls) may result in those inconsistent findings. Although a few studies investigated the association between metabolize enzyme gene polymorphism phase II GST [21-30] and the progression of cervical neoplasm, the results still controversial, additionally, none of the study has been investigated the association between GSTA1 gene polymorphism and cervical intraepithelial neoplasm. In this present research project, we will investigate the relationship between phase II GST gene polymorphism and cervical intraepithelial neoplasm.

Materials and methods

I. Study Population

The Chung Shan Hospital, Taichung, Taiwan, is implementing one policy to screen Pap smears for the women who are more than 20 years old (≥20 yrs) or who have intercourse experience. Therefore, integrated with this health-promotion policy, a hospital-based case-control study was conducted in this study. Our study population were women over twenty years old (≥20 yrs) who had not positive Pap smear results before. After their Pap smears' statuses were reported to the Chung Shan Hospital, these women were contacted as early as possible by our trained public health nurses and explain the study protocol. After their agreement, the public health nurses interviewed them using a structured questionnaire and also asked them to provide exfoliated cervical epithelial cell for detection high-risk HPV infection. Our potential study cases were the women with lesions CIN1 and greater than CIN1 (≥CIN1) confirmed by biopsies. The potential controls, served as the first control group, were randomly selected from women who participate the Pap smear program of Chung Shan Hospital and whose Pap smear results were negative during the study period. The case-control ratio was 1:1 - 1:4 with matching on age at the same year, residency at the same administrative district, and time that the Pap smear was performed (within 6 months with cases)

II. Questionnaire

a. Conduction of questionnaire

Trained public health nurses conducted personal interviews to collect epidemiologic data using a standardized questionnaire. Informed consent was obtained from all subjects. The information collected including demographic characteristics, educational levels, parents' ethnicity, family history of cancer, tea consumption, use of substances (cigarette tobacco, areca, and alcohol), ETS exposure, exposure to special X-ray examinations or hair dye, occupation (especially whether they were professional chefs or not), sexual and reproductive history, and times of prior cervical smears as well as cooking and kitchen ventilation status.

b. Information about substance uses

Information on habitual substance use including whether the subject had been a habitual areca chewer, cigarette smoker, or alcoholic beverage drinker in her lifetime, what year the subject started and quit, the duration of consumption and the daily

amount consumed, and type of alcoholic beverage consumed. Subjects who report smoking more than 7 cigarettes per week for at least 1 year will be defined as cigarette smokers, those who report regularly chewing betel quid for at least 6 months will be defined as betel chewers, and those who report drinking beer, wine, or distilled spirits more than one time per week for at least 6 months will be defined as alcoholic beverage drinkers. Subjects who exposure to second hand smoking during their childhood and adulthood, such as a parent, husband, or cohabitant, per week for at least 1 year will be considered second hand smoking. Women who had cooked in restaurant kitchens at least one year will be considered professional chefs.

III. Detection high-risk HPV infection

a. collection of cervical specimens

Specimens were taken from each study participant's cervix by a trained public health nurse using a Cytobrush (DIGENE, Gaithersburg, MD, USA). The Cytobrush was immersed in 1 ml specimen transport medium (STM). Those were swirled to release the cells. The technicians examining the specimens for high-risk HPV infection in this study were blinded to the findings of Pap smears and cervical biopsies.

b.High-risk HPV DNA detected using Hybrid Capture II assay

The Cytobrush specimens in the STM solution were initially stored at 4^{o}C until the HPV analysis and then analyze using a commercial kit for performing Hybrid Capture II method (DIGENE, Gaithersburg, MD, USA) according to manufacturer's instructions. This enzyme-linked immunosorbent assay was based on a sandwich hybridization followed by a nonradioactive alkaline phosphatase reaction with chemoluminescence in micro-plates. The hybrid complex of high-risk HPV, including subtype 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68, can be detected by the DIGENE DML 2000 Luminometer. The results were analyzed by DIGENE DML2000 Software and the Penticum II PC System. Light measurements were expressed as relative light units (RLU). A solution with 10 pg/ml of high-risk HPV served as positive control. The ratio of a specimen's RLU to the corresponding positive control's RLU was considered a measurement of viral load. In addition, according to manufacturer's instructions, a RLU ratio ≥ 1.0 in a specimen was positive indication of the presence of HPV DNA, whereas a ratio < 1.0 is a negative [41]

VI. Genotyping Polymorphysims

Purgene DNA isolation kit (Gentra systems, Inc., MN) was used to extract high molecular weight DNA from blood specimens. According to the manufacturer, this kit extracts 50-250 μg DNA from 3 ml stored whole blood. This genomic DNA was served as a template for PCR amplification of each polymorphic gene. Additional DNA was stored at –20^{o}C for future analysis of relevant candidate polymorphisms. One technician performing genotyping was blinded to the study subjects' condition.

a. Genotyping of GSTM, GSTP1, and GSTT1

The gene variations test and the primers were modified [42]. The gene detections were amplified by the polymerase chain reaction (PCR). Briefly, each PCR mix contained 100 ng of genomic DNA with 25 mM N-【Tris (hydroxymethyl) methyl】-3-aminopropanesulfonic acid (TAPS, pH 9.3), 50b mM KCL, 2 mM $MgCl_2$, 1 mM β-mercaptoethanol, 200 uM of each dNTP, 0.25 ug/ul of activated calf thymus DNA, and two units of SuperThem fold DNA polymerase (JMR Holdings, Kent, UK). The PCR reaction used the following sequence: 94^{O}C for 10 min, then 35 cycles with each cycle consisting of 94 ^{O}C for 60s, 54 ^{O}C for 45s, and 72 ^{O}C for 120s. Finally, the PCR tubes were incubated at 72 ^{O}C for 10 min.

b. Genotyping of *GSTA*

The GSTA1*A and GSTA1*B, C-69T variation on the promoter region of GSTA1 gene was amplified with a forward primer 5'-CCCTACA TGGTATAGGTGAAAT-3' AND A REVERSE PRIMER 5'-GTGCTAAGGACACATATTAGC A-3' under the 55^{o}C annealing temperature for 30 PCR cycles. Then, the PCR product is digested with HinfI.

VIII. Statistical Analysis

Analysis of categorical variables (e.g., gender, age, HPV infection, and **genotypes**) were done using chi-squared tests [43]. Logistic regression was used to assess the univariate significance of the association between case/control status with predictors measured of interest.

Results

Three hundred and forty healthy controls as well as one hundred and twenty-seven patients with ≥ CIN1 were recruited in our study. The demographical characteristics are shown in table 1. Except for number of lifetime sexual partners and HPV infection status, there was not a significant difference between healthy controls and cervical intraepithelial neoplasm patients.

The frequencies of phase II GST genotypes, such as GSTM1, GSTT1, GSTA1, and GSTP1, were studied in 127 individuals with ≥ CIN1 and compared to 334 healthy controls. A significant different frequencies of GSTP1 genotypes was found between healthy controls and CIN patients (Table 2). The adjusted odds ratios (AORs) with their 95% confidence intervals (CIs) for individuals with I/V or V/V of GSTP1 compared to individuals with I/I of GSTP1 was 3.37 (95%CI: 1.30-8.72) between 334 healthy controls and 19 individuals with ≥ CIN1, however, there was not a significant different frequency between healthy controls and individuals with ≥ CIN2 (Table 3). As well, no significant difference was found between healthy controls and cervical intraepithelial neoplasm patients among GSTM1, GSTT1, and GSTA1 gene polymorphism (Table 2 & 3).

Conclusions:

Individuals with I/V or V/V of GSTP1 gene polymorphism is considered as a factor increasing the susceptibility of cervical intraepithelial neoplasm.

Table 1. Distributions of demographic characteristics and other potential confounders were examined by Fisher's exact test.

Variable	Controls (n=340)	CIN1 (n=19)	≥ CIN2 (n=108)	p value
	n (%)	n (%)	n (%)	
Age (yrs)				
< 46	163 (47.9)	11 (57.8)	71 (65.7)	
≥ 46	177 (52.1)	8 (42.2)	37(34.3)	p=0.38
Smoking status				
No Smoker	290 (85.4)	13 (68.0)	78 (72.3)	
Smoker	50 (14.5)	6 (32.0)	30 (27.7)	p=0.38
Second hand smoker				
No	176 (52.0)	10 (52.6)	57(52.7)	
Yes	164 (48.0)	9 (47.4)	51 (47.3)	p=0.31
Number of lifetime sexual partners				
≤ 1	312 (91.8)	14 (73.6)	72 (66.6)	
> 1	28 (8.9)	5 (26.3)	36 (33.7)	p=0.007
HPV infection				
No	283 (83.1)	15 (78.9)	18 (16.7)	p=0.002
Yes	57 (16.9)	4 (21.1)	90 (83.3)	

Table 2. The association between gene types and cervical intraepithelial neoplasm were examined by Fisher's exact test.

Variable	Controls (n=334)	CIN1 (n=19)	≥ CIN2 (n=54)	SCC (n=54)	p value
	n (%)	**n (%)**	**n (%)**	**n (%)**	
GSTP1					
II	235 (70.4)	8 (42.1)	37 (68.5)	34 (62.9)	
IV	93 (27.8)	11 (57.9)	15 (27.8)	16 (29.7)	
VV	6 (1.8)	0 (0)	2 (3.7)	4 (7.4)	p=0.03

GSTA					
AA	273 (81.7)	13 (68.4)	39 (72.2)	46 (85.2)	
AB	59 (17.7)	6 (31.6)	13 (24.1)	7 (12.9)	
BB	2 (0.6)	0 (0)	2 (3.7)	1 (1.9)	p=0.1
GSTT1					
Null	165 (49.4)	6 (31.6)	28 (51.8)	27 (50.0)	
Present	169 (50.6)	13 (68.4)	26 (48.2)	27 (50.0)	p=0.48
GSTM	.				
Null	189 (56.6)	12 (63.2)	27 (50.0)	28 (51.8)	
Present	145 (43.4)	7 (36.8)	27 (50.0)	26 (48.2)	p=0.67

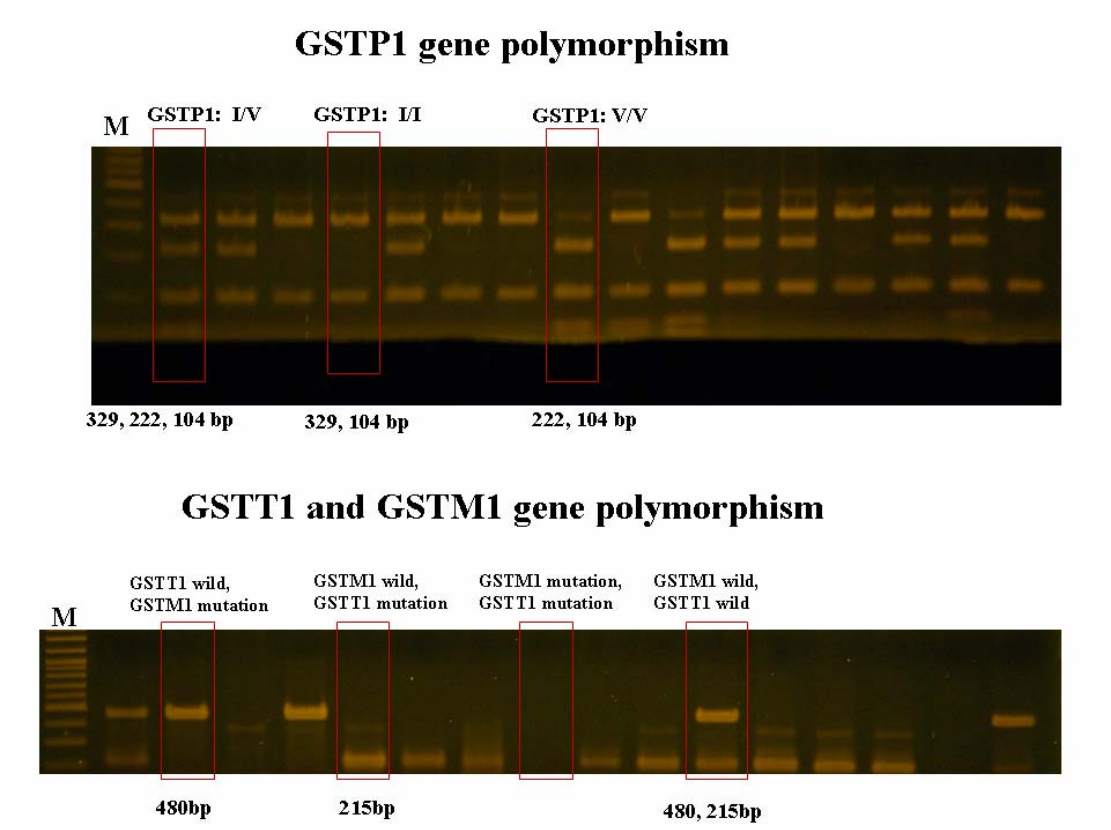
Table 3. Adjusted odds ratio (AOR) and 95% confidence intervals (CI) of gene polymorphism and cervical intraepithelial neoplasm.

Variable	Controls (n=334)	CIN1 (n=19)	OR (95% CI)	AOR (95% CI)	≥ CIN2 (n=108)	OR (95% CI)	AOR (95% CI)
	n (%)	n (%)			n (%)		
GSTP1							
II	235 (70.4)	8 (42.1)	1.00	1.00	71 (65.7)	1.00	1.00
IV or VV	99 (29.6)	11 (57.9)	3.26(1.27-8.36)	3.37 (1.30-8.72)	37 (34.3)	1.23 (0.78-1.96)	1.22 (0.76-1.93)
GSTA							
AA	273 (81.7)	13 (68.4)	1.00	1.00	85 (78.7)	1.00	1.00
AB or BB	61 (18.3)	6 (31.6)	2.06 (0.75-5.65)	2.19 (0.78-6.13)	23 (21.3)	1.21 (0.70-2.07)	1.20 (0.70-2.06)
GSTT1							
Null	165 (49.4)	6 (31.6)	1.00	1.00	55 (50.9)	1.00	1.00
Present	169 (50.6)	13 (68.4)	2.11 (0.78-5.69)	2.26 (0.82-6.18)	53 (49.1)	0.94 (0.61-1.45)	0.94 (0.68-1.45)
GSTM							
Null	189 (56.6)	12 (63.2)	1.00	1.00	55 (50.9)	1.00	1.00
Present	145 (43.4)	7 (36.8)	0.76 (0.29-1.98)	0.75 (0.28-2.00)	53 (49.1)	1.25 (0.81-1.94)	1.24 (0.80-1.92)

The odds ratios (ORs) with analyzed by their 95% CI were estimated by logistic regression models.

The adjusted odds ratios (AORs) with their 95% CI were estimated by multiple logistic regression models, after controlling for age, smoking status, second hand smoker, number of lifetime sexual partners, and HPV infection.

Fig 1


GSTP1 gene polymorphism
M
GSTP1: I/V
GSTP1: I/I
GSTP1: V/V
329, 222, 104 bp
329, 104 bp
222, 104 bp
GSTT1 and GSTM1 gene polymorphism
M
GSTT1 wild, GSTM1 mutation
GSTM1 wild, GSTT1 mutation
GSTM1 mutation, GSTT1 mutation
GSTM1 wild, GSTT1 wild
480bp
215bp
480, 215bp

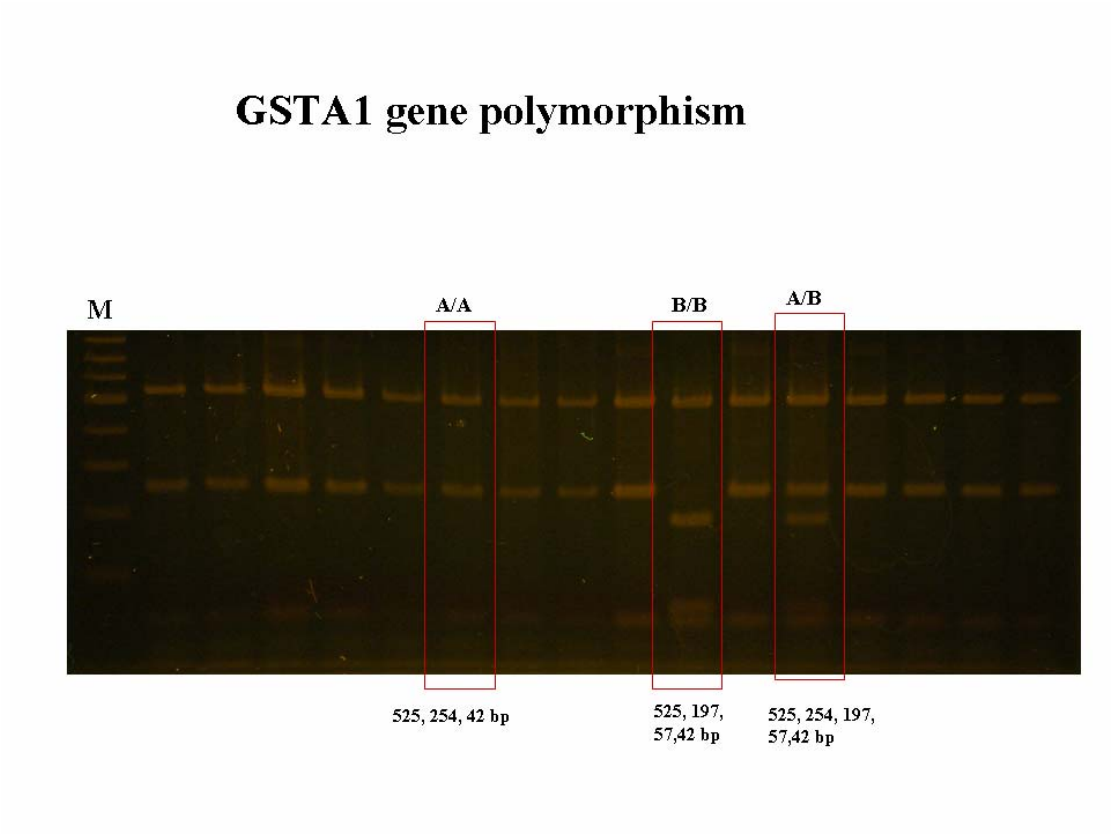


Figure Legends

Figure 1. Polymerase chain reaction-restriction fragment length polymorphism of gene types.

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計畫成果

(1) **Hsiu-Ting Tsai,** Po-Hui Wang, Yi-Torng Tee, Long-Yau Lin, Yih-Shou Hsieh*, Shun-Fa Yang*: Imbalanced serum concentration between cathepsin B and cystatin C in patients with pelvic inflammatory disease. **Fertility and Sterility** (Impact Factor: 3.168, Rank: 6/60); in press (SCI 期)

(2) Kuo-Shuen Chen, Po-Hui Wang, Shun-Fa Yang, Ding-Bang Lin, Dong-Yih Kuo, Long-Yau Lin, Ming-Tsang Wu, Chiao-Wen Lin, Sheuan Lee, Ming-Chih Chou, Yi-Jiun Lin; **Hsiu-Ting Tsai***, Yih-Shou Hsieh*: Significant elevation of a Th2 cytokine, interleukin-10, in pelvic inflammatory disease. **Clin Chem Lab Med** (Impact Factor: 1.741 , Rank: 12/26); in press (SCI 期刊)

(3) Shun-An Lee, **Hsiu-Ting Tsai,** Hsiu-Chung Ou, Chin-Ping Han, Yi-Torng, Tee, Yi-Chen Chen, Ming-Tsang Wu, Ming-Chin Chou. Po-Hui Wang*, Shun-Fa Yang*: Plasma interleukin-1β, -6, -8 and tumor necrosis factor-α as highly informative markers of pelvic inflammatory disease. **Clin Chem Lab Med** (Impact Factor: 1.741 , Rank: 12/26); 2008; 46 (7): 997-1003. (SCI 期刊)

(4) Po-Hui Wang, Jiunn-Liang Ko, **Hsiu-Ting Tsai**, Shun-Fa Yang, Chih-Ping Han, Long-Yau Lin*, Gin-Den Chen*: Clinical Significance of Matrix Metalloproteinase-2 in Cancer of Uterine Cervix: A Semiquantitative Study of Immunoreactivities Using Tissue Array. **Gynecologic Oncology** (Impact Factor: 2.614, Rank: 12/60); 2008; 108: 533-542 (SCI 期刊)

(5) Chien-Gang Hsu, Long-Yau Lin*, Jiunn-Liang Ko, Shun-Fa Yang, Han Chang, Ching-Yi Lin, **Hsiu-Ting Tsai**, Shiuan-Chih Chen, Shu-Chen Chen, Po-Hui Wang*: High expression of human nonmetastatic clone 23 type 1 in cancer of uterine cervix and its association with poor cell differentiation and worse overall survival. **JOURNAL OF SURGICAL ONCOLOGY** (Impact Factor: 2.384 , Rank: 26/139), in press (SCI 期刊)

(6) Po-Hui Wang, **Hsiu-Ting Tsai,** Yi-Torng Tee, Long-Yau Lin, Shun-Fa Yang, and Yih-Shou Hsieh: Significant Elevation of Plasma Matrix Metalloproteinase-9 Level and Its Ratio to Matrix Metalloproteinase-2 in Patients with Pelvic Inflammatory Disease. **Fertility and Sterility** (Impact Factor: 3.168, Rank: 6/60); in press (SCI 期刊)

評值

本研究內容與原計畫相符成度約達 80%。

本研究對婦科醫學而言具有顯著的貢獻，此研究結果可得知與子宮頸癌有關的基因型，及基因與基因或基因與環境中危險因子的相互作用下，是否會增加或減少婦女罹患子宮頸癌的危險性。