ความสัมพันธ์ระหว่างความหลากหลายทางพันธุกรรมของยีน *XPD* ที่ตำแหน่ง 312 (*XPD* 312 gene) กับความเสี่ยงต่อการเกิดโรคมะเร็งเต้านมในหญิงไทย

วิชุดา ไตรรัตน์อภิชาต[1] ดนัย ทิวาเวช[2, 3] และ ธีรกุล อาภรณ์สุวรรณ[4*]

[1]บัณฑิตศึกษาสาขาเทคนิคการแพทย์ ภาควิชาเทคนิคการแพทย์ คณะสหเวชศาสตร์ มหาวิทยาลัยธรรมศาสตร์ จังหวัดปทุมธานี
[2]ภาควิชากายวิภาคศาสตร์ คณะวิทยาศาสตร์การแพทย์ มหาวิทยาลัยนเรศวร จังหวัดพิษณุโลก
[3]กลุ่มงานวิจัย สถาบันมะเร็งแห่งชาติ กรุงเทพมหานคร
[4]ภาควิชาเทคนิคการแพทย์ คณะสหเวชศาสตร์ มหาวิทยาลัยธรรมศาสตร์ จังหวัดปทุมธานี

บทคัดย่อ

มะเร็งเต้านมเป็นโรคมะเร็งชนิดที่พบมากที่สุดในสตรีไทย ความหลากหลายทางพันธุกรรมของยีน *XPD* ซึ่งเกี่ยวข้องกับกระบวนการซ่อมแซมดีเอ็นเอ (DNA repair) เป็นปัจจัยเสี่ยงอย่างหนึ่งต่อการเกิดโรคมะเร็ง งานวิจัยนี้จึงมีวัตถุประสงค์เพื่อศึกษาความสัมพันธ์ระหว่างความหลากหลายของยีน *XPD* ที่ตำแหน่งกรดอะมิโน 312 กับความเสี่ยงต่อการเกิดโรคมะเร็งเต้านมในสตรีไทย โดยสกัดดีเอ็นเอจากตัวอย่างเลือดของกลุ่มผู้ป่วยมะเร็งเต้านม 100 ราย และกลุ่มคนปกติ 100 ราย แล้วนำมาวิเคราะห์หาความหลากหลายของยีน *XPD* ที่ตำแหน่งกรดอะมิโน 312 โดย วิธี real-time polymerase chain reaction (RT-PCR) ซึ่งผลการศึกษาไม่พบความสัมพันธ์ระหว่างการเกิดความหลากหลายของยีน *XPD* ที่ตำแหน่งกรดอะมิโน 312 กับความเสี่ยงต่อการเกิดโรคมะเร็งเต้านมอย่างมีนัยสำคัญ (crude OR:1.31, 95% CI: 0.64-2.71; $p = 0.462$) และเมื่อปรับตัวแปรที่อาจมีผลเกี่ยวข้องกับการเกิดมะเร็งเต้านม ได้แก่ อายุ ภาวะหมดประจำเดือน และประวัติครอบครัวเป็นมะเร็งเต้านม ก็ยังไม่พบความสัมพันธ์ดังกล่าว (adjusted OR: 1.14, 95% CI: 0.75-1.73; $p = 0.621$) จึงสรุปได้ว่า การเกิดความหลากหลายของยีน *XPD* ที่ตำแหน่งกรดอะมิโน 312 ไม่มีความสัมพันธ์กับความเสี่ยงต่อการเกิดโรคมะเร็งเต้านม

คำสำคัญ: มะเร็งเต้านม การซ่อมแซมด้วยการตัดออกของนิวคลีโอไทด์ ยีน *XPD* ซิงเกิลนิวคลีโอไทด์-โพลีมอร์ฟิซึม เทคนิค real-time PCR

***ผู้รับผิดชอบบทความ E-mail address:** teerakul_suwan@hotmail.com
รับบทความ: 9 ธันวาคม 2560 แก้ไขบทความ: 17 กรกฎาคม 2561 รับตีพิมพ์บทความ: 24 กรกฎาคม 2561

Association between *XPD* Codon 312 Polymorphisms and Breast Cancer Risk in Thai Women

Vichuda Triratapichat[1], Danai Tiwawech [2,3] and Teerakul Arpornsuwan[4*]

[1]*Graduate Program in Medical Technology, Department of Medical Technology, Faculty of Allied Health Sciences, Thammasat University, Pathum thani Province, Thailand*
[2]*Department of Anatomy, Faculty of Medical Science, Naresuan University, Pisanulok Province, Thailand*
[3]*Research and Technology Assessment Division, National Cancer Institute, Bangkok, Thailand*
[4]*Department of Medical Technology, Faculty of Allied Health Sciences, Thammasat University, Pathum thani Province, Thailand*

Abstract

Breast cancer is the most common cancer in Thai women. Polymorphic variants of *XPD* gene, which involve DNA repair systems, were found to be associated with several cancers. The aim of this study was to investigate the association between *XPD* codon 312 polymorphisms and breast cancer susceptibility in Thai women. In this study, DNA was isolated from the peripheral blood sample of 100 patients with breast cancer and 100 healthy controls for determinination of *XPD* codon 312 polymorphisms by real-time polymerase chain reaction (RT-PCR). The results show that no significant associations were found between breast cancer risk and *XPD* codon 312 polymorphisms (crude OR: 1.31, 95% CI: 0.64-2.71; $p = 0.462$). Variable parameters comprising age and menopause status did not alter the findings (adjusted OR: 1.14, 95% CI: 0.66-1.98; $p = 0.635$) suggesting that *XPD* codon 312 polymorphisms is not associated with breast cancer risk.

Keywords: Breast cancer, Nucleotide excision repair, *XPD* gene, Single nucleotide polymorphisms, Real-time polymerase chain reaction

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***Corresponding author E-mail address:** teerakul_suwan@hotmail.com

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Introduction

Breast cancer (BC) is a major public health problem in many countries and remains the most frequently diagnosed cancer in women worldwide. In Thailand, the incidence rate for BC is 28.6/100,000 and the rate is steadily increasing[1].The exact cause of BC is unknown but the risk factors for developing BC may include older age, having a family history of BC, not having children or pregnant over age 30, using hormone therapy for a long time and obesity. Furthermore, obtaining environmental factors such as ionizing radiation and chemical carcinogens may be an important factor that increases the risk of BC. According to a recent study, exposure of these factors may contribute to DNA damage such as oxidized bases, bulky DNA adducts, and DNA strand breaks. The gene mutations and gene malfunctions that contribute to BC pathogenesis are more likely to achieve suboptimal DNA repair[2].

There are several pathways to repair the DNA damages. Among these is the nucleotide excision repair (NER) pathway that removes DNA damage including cross-links, oxidative damage and bulky adducts[3]. The xeroderma pigmentosum group D *(XPD)* gene or excision repair cross-complementing rodent repair deficiency group 2 *(ERCC2)* is located on chromosome 19q 13.3 encoding a helicase. The XPD is a protein in the transcription and NER pathway removing DNA cross-links, UV-induced DNA damage, and bulky chemical adducts[4, 5]. Mutations of the *XPD* gene were associated with defective NER, transcription defects and abnormal response to apoptosis[6].

Single-nucleotide polymorphism (SNP) is a variation in a single nucleotide that occurs at a specific position in the genome. Many SNPs of *XPD* gene have been reported but the codon 312 and codon 751 polymorphisms which result in amino acid changes from aspartic acid to asparagine and lysine to glutamine, respectively, are commonly studied[7]. These polymorphisms have been associated with increased levels of DNA adduct and lower DNA repair capacity[7, 8]. Many studies have reported an association between *XPD* codon 312 polymorphism and risk of various cancers including lung cancer[9], prostate cancer[10], and upper aero-digestive tract[11]. The A allele of Asp312Asn was significantly associated with BC risk[12]. It was consistent with the report of AA genotype of *XPD* Asp312Asn polymorphism that had a 3.5-fold increase risk of BC[13]. In contrast, Kuschel *et al.* and Lee *et al.* found no association[14, 15]. However, there are no reports of an association between *XPD* codon 312 polymorphisms and risk of BC in Thailand. The aim of the present study was to determine the allelic frequencies of the *XPD* codon 312 polymorphisms using RT-PCR. The association of genetic polymorphisms in *XPD* codon 312 with BC susceptibility was also investigated.

Materials and Methods

Subjects

A total of 200 subjects were recruited from National Cancer Institute, Ministry of Public Health at Bangkok, Thailand. They were divided into 2 groups: a breast cancer group and a control group. The breast cancer group was 100 Thai women (mean age=53.1 ± 9.4) with histo-pathologically proven diagnosis of breast cancer between May 2014 and November 2014 from National Cancer Institute at Bangkok, Thailand. The control group was 100 healthy Thai women (mean age = 43.5 ± 8.4) with no sign or symptoms of malignancy, autoimmune, chronic liver and chronic inflammation disease. All of the 100 cases were pretreatment BC patients with no history of pathologic secondary amenorrhea, hysterectomy or oophorectomy. The clinico-pathological features of BC patients were summarized in Table 1. These patients were graded according to the modified criteria as described by the American Joint Committee on Cancer TNM staging system. The protocol of the present study was approved by the ethics committee of National Cancer Institute and Thammasat University, Thailand.

Blood sample collection

Three milliliters of venous blood were collected in EDTA test tubes. All blood samples from a total of 200 cases were centrifuged at 2,500 rpm for 20 min, then the buffy coat containing white blood cells were transferred into 1.5 mL Eppendorf tubes and kept at -20°C for DNA extraction.

DNA extraction

Genomic DNA (gDNA) was extracted from white blood cells using a innuPREP Blood DNA Mini Kit (Analytik Jena, Germany) as described by the instruction manual. The quality of the gDNA was analyzed by spectro-photometer and preserved at -20 °C until use.

XPD codon 312 polymorphisms detection

Genotyping of *XPD* codon 312 was analyzed by RT-PCR with TaqMan probes (Applied Biosystems, USA). The real-time PCR was performed in a final volume of 20 µL, containing 2 µL of gDNA (30-35 ng/mL), 10 µL of TaqMan Genotyping Master Mix, 0.5 µlL of TaqMan probe with specific primers (5'-TGGCCCCTGTCTGACTT-GTCCC-3' and 5'-GACGGGGAGGC-GGGAAAGGGACT-3') (RefSeqGene (LRG_461) on chromosome 19Sequence ID: NG_007067.2) (Wang *et al*., 2010) and 7.5 µL of double distilled water. The PCR mixture was incubated at 60°C for 30 sec followed by AmpliTaq Gold Enzyme activation at 95°C for 10 min. Then, gDNA was amplified by RT-PCR program comprising 40 cycles of denaturation at 95°C for 15 sec and annealing at 60°C for 1 min followed by holding at 60°C for 30 sec. The amplified target sequences were analyzed in the end-point mode using the Allelic Discrimination Sequence Detector

Table 1 Clinicopathological characteristics of the cases and controls

Characteristics	Breast cancer group (%)	Control group (%)	*p*
Age (year)			
<40	7 (7)	38 (38)	< 0.05
40-60	70 (70)	60 (60)	
>60	23 (23)	2 (2)	
Mean ± SD	53.1±9.4	43.5±8.4	
Menopause			<0.05
Pre	35 (35)	73 (73)	
Post	65 (65)	27 (27)	
Tobacco smoking			
Yes	0 (0)	0 (0)	
No	100 (100)	100 (100)	
Alcohol consumption			0.651
Yes	2 (2)	3 (3)	
No	98 (98)	97 (97)	

Patient characteristics	number
Tumor size	
< 2 cm	31
2-5 cm	63
> 5 cm	6
Lymph node metastasis	
Negative	48
Positive	52
AJCC pathological stage	
I-II	63
III-IV	37

Software (Applied Biosystems). The genotyping of *XPD* codon 312 were GG genotype (homozygous wild type), AA genotype (homozygous mutant type) and GA genotype (heterozygous type) that perfect match to TaqMan probes with VIC® dye, FAM™ dye and both VIC® and FAM™ dyes, respectively.

Statistical Analysis

Chi-Square test (X^2) was used to compare the differences of genotype and allele frequencies between cases and controls. Odd ratios (OR) and 95% confidence interval (CI) calculated by logistic regression method were used to examine the association between the *XPD* codon 312 polymorphisms and risk of BC. Data were considered significantly different when p -values were less than 0.05. All data were calculated with SPSS version 16.0.

Results

The characteristics of the case and control cohorts are shown in Table 1. Drinking alcohol and tobacco smoking produced no significant differences between cases and controls. However, age and menopause status of BC caused/gave significant differences between cases and controls. The clinicopathological parameters are shown in Table 1. Among all patients, 63 patients (63%) had the tumor size of 2-5 cm. About 63% and 37% of BC patients had pathological staging for stage I-II and III-IV, respectively.

The frequency of G allele (wild type) was 90% in BC group and 92% in controls. In addition, the frequency of A allele (mutant type) was 10% in BC group and 8% in controls. These data showed that the frequency of allele A were not significantly different between control and BC groups (adjusted OR: 1.10, 95% CI: 0.65-1.84) (p = 0.721) (Table 2).

The genotypic distributions of *XPD* codon 312 polymorphisms are shown in Table 2. The genotype frequencies of GG and AG were 80% and 20% in BC group and 84% and 16% in control group, respectively. However, the genotype frequency of AA for both BC and control group was not detectable in this study.

The data show that genotype frequencies of *XPD* codon 312 polymorphisms were not significantly different between control and BC groups. When using the GG genotype as a reference group there was no significant association between *XPD* codon 312 polymorphisms and risk of BC (crude OR: 1.31, 95% CI: 0.64-2.71) (p=0.462). When adjusted with variables that might influence BC, ie. age and menopause status, we found that these variables did not alter the findings. (adjusted OR: 1.14, 95% CI: 0.66-1.98) (p=0.635) (Table 2)

Discussion

Nucleotide excision repair (NER) pathway is an important system to repair DNA damage. Defects in this pathway may lead to defect or lower repair capacity of DNA that

Table 2 Correlation between *XPD* codon 312 polymorphisms and the risk of breast cancer

Genotype	Control group N (%)	Breast cancer group N (%)	Crude OR (95 % CI)	*p*	Adjusted OR[a] (95% CI)	*p*
Genotype						
GG (ref.)	84 (84)	80 (80)	1		1	
AG	16 (16)	20 (20)	1.31 (0.64-2.71)	0.462	1.14 (0.66-1.98)	0.635
AA	0 (0)	0 (0)	-		-	
AA+AG	16 (16)	20 (20)	1.31 (0.64-2.71)	0.462	1.14 (0.66-1.98)	0.635
Allele						
G allele (ref.)	184 (92)	180 (90)	1		1	
A allele	16 (8)	20 (10)	1.28 (0.64-2.54)	0.485	1.10 (0.65-1.84)	0.721

OR, odd ratio; CI, confidence interval, [a]adjusted for age and menopause status.

increases risk of genetic mutations and carcinogenesis. *XPD* is a DNA dependent ATPase/helicase, which is a part of the transcription factor TFIIH, plays an important role in opening the DNA helix during the process of NER[16]. Mutation of the *XPD* gene may decrease helicase activity, resulting in reducing DNA repair and transcription capacity and abnormal responses to apoptosis[17]. Several studies have examined the functional significance of the *XPD* codon 312 polymorphisms. The studies reported that the variant alleles of *XPD* codon 312 have been shown to result in significantly lower DNA repair capacity[18]. There are many epidemiological studies that show the association between *XPD* codon 312 polymorphisms and the risk of several cancers including lung cancer[9], upper aerodigestive tract cancer[11] and prostate cancer[10]. However, other studies did not show the association between *XPD* codon 312 polymorphisms and the risk of lung cancer[19], skin cancer[20] and esophageal cancer[21]. In this study, we investigated the polymorphisms distribution of the *XPD* codon 312 and analyzed the relationship between *XPD* codon 312 polymorphisms and susceptibility to BC.

As regard *XPD* codon 312 polymorphisms in the present study, the frequency of A (mutant) allele was 10 % in BC patients and 8% in controls. The results show that the frequencies of *XPD* 312 variant alleles were

not significantly different between patients and the control group ($p = 0.621$). This study demonstrated that the allelic frequencies of the A allele at *XPD* codon 312 in healthy controls were 0.080, which were similar to several reports for example, in Thai population by Pakakasama *et al.* (0.074)[22] and Chinese population reported by Liang *et al.* (0.065)[23], Yuan *et al.* (0.088)[24], Yu *et al.*(0.053)[25], but were lower than in Taiwanese (0.245)[12], Americans (0.341)[26], European (0.401)[27] and Egyptian (0.50)[13] (Table 3). These data revealed that the frequencies of *XPD* 312 variant alleles have ethnic and geographical differences.

Several epidemiologic studies have examined an association between *XPD* codon 312 polymorphisms and BC risk. Wang *et al.*, who studied in Taiwanese patients, reported that the heterozygotes and homozygotes of the A allele of *XPD* codon 312 was associated with a higher risk of BC[12]. Another study in Egypt, demonstrated that AA genotype of *XPD* codon 312 polymorphisms increased the risk of BC[13]. Also in France by Bernard-Gallon *et al.*, who found the heterozygous type for *XPD* codon 312 polymorphisms was associated with breast cancer development in women receiving menopause substitution treatment[28]. However, in this study, the association between *XPD* codon 312 polymorphisms and risk of BC was investigated. The results did not demonstrate the difference in the genotypes of *XPD* codon 312 between patients and control groups. It was also found that *XPD* codon 312 polymorphisms were not associated with BC risk. The findings are consistent with the results of Kuschel *et al.*, Jorgensen *et al.* and Lee *et al.*, that found no evidence of association of *XPD* codon 312 polymorphisms and BC risk[14, 15, 29]. The discrepancies in the findings concerning the role of *XPD* polymorphisms in BC may be explained by genetic factors and environmental factors, which differ among

Table 3 Allele frequencies of *XPD* codon 312 in other ethnic population

First author	Year	Country	Ethnicity	Allele frequency
Hussien	2012	Egypt	African	0.500
Yuan	2012	China	Asian	0.088
Wang	2010	Taiwan	Asian	0.245
Pakakasama	2007	Thailand	Asian	0.074
Debniak	2006	Poland	European	0.401
Mechanic	2006	USA	American	0.341
Mechanic	2006	USA	African-American	0.127

the population. By reviewing the previous studies, Tang *et al.* reported that *XPD* codon 312 polymorphisms were not associated with breast cancer, although they were associated with increased levels of PAH—DNA adduct in tumor tissue, which may contribute to tumor development[30]. Nevertheless, Lunn *et al.* found that *XPD* codon 312 polymorphisms did not appear to affect DNA repair capacity[8]. In addition, *XPD* plays a role in apoptosis. Rzeszowska-Wolny *et al.* reported that the frequency of apoptotic cells was significantly higher in individuals with alleles coding for Asn at *XPD* 312[31]. Seker *et al.* also found that homozygous for the variant A allele had a higher apoptotic response than heterozygous or homozygous for the G allele[32]. The limitation of this study is small sample size, which makes it difficult to find significant relationships from the data, as statistical tests normally require a larger sample size to ensure a representative distribution of the population.

In conclusion, the findings suggest that *XPD* codon 312 polymorphisms are not associated with BC risk in Thai population.

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