RESEARCH ARTICLE

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Genetic Polymorphism of *MDM2* Gene Associates with Breast Cancer Incidence in the Lower Northern Thailand

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Abstract

Objective: Breast cancer remains the most prevalence among women worldwide, including those in lower northern Thailand. This study aimed to investigate the association between selected genetic polymorphisms and breast cancer incidence in this regional population. **Methods:** DNA samples were obtained from 184 breast cancer patients and 176 healthy controls. Twelve biallelic genetic markers across nine genes were genotyped using PCR-RFLP, TaqMan probe, and KASP-PCR genotyping assays. Allelic frequencies were calculated for each marker, and odds ratios (OR) was used to assess the association between genetic polymorphism and breast cancer risk. **Result:** Among the loci studied, only the deletion allele of *MDM2* rs150550023 showed a significant association with breast cancer risk in the lower northern Thai population (OR = 1.44; 95 % CI = 1.033 - 2.008, p = 0.016). This allele was found at a high frequency (23.3%). **Conclusion:** These findings suggest that the deletion allele of *MDM2* rs150550023 may serve as a potential genetic marker for breast cancer susceptibility in the lower norther Thai population.

Keywords: Genetic polymorphism- Breast cancer- *MDM2* gene- lower norther Thailand

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Introduction

Breast cancer is a significant global public health problem as it is the most common cancer diagnosed among women and causes of death in women in every region of the world. According to the American Cancer Society data, the breast cancer incidence in the united state continued an upward trend annually during 2012-2021 [1]. In Thailand, breast cancer is also the most prevalent cancer among women and is associated with a high mortality rate [2]. The global and national incidence rates are 46.32 and 35.7 cases per 100,000 people per year, respectively with corresponding mortality rates of 13 and 14 per 100,000 person-years [2]. Based on Thai cancer registry, breast cancer ranked first among all cancers in Thai women, with a mean annual age-standardized incidence rate (ASR) of 34.0 between 2019 and 2021) [3].

Evidence indicates that age, sex, hormonal exposure, family history, genetic mutation and lifestyles are risk factors of breast cancer [4, 5]. Early detection poses a significant procedure to improve breast cancer prevention, screening and treatment. However, challenges still remain in combating breast cancer in many countries including Thailand due to the limit of resources, socioeconomic disparities and policy [2]. Due to different genetic backgrounds among populations, there is a need for research and data collection to gain more understanding of the specific risk factors of breast cancer in different populations. In recent years, the role of genetic polymorphism – particularly single nucleotide polymorphisms (SNP) – has gained increasing attention in breast cancer research. These polymorphisms may influence cancer susceptibility through gene-gene and gene-environment interactions.

The mechanism of breast tumorigenesis is highly complex. Polygenic play important roles in multistep progression of the cancer. Numerous genes involved in this process have been extensively studied and reported [6, 7]. Among them, the murine double minute 2 (*MDM2*) gene have been identified as a key regulator through its interaction with TP53 gene, significantly contributing to control of cell proliferation and apoptosis during tumor development. The human *MDM2* is located on chromosome 12q14.3-15, comprises 11 exons and encodes a protein consisting of 491 amino acids. The p53-MDM2 interaction pathway is well documented and frequently highlighted in cancer research. While the p53 protein functions in preserving genomic integrity, *MDM2* serves as a key negative regulator by functioning as an E3 ubiquitin ligase that promotes p53 degradation [8, 9].

Genetic polymorphisms, particularly the SNPs, of the *MDM2* gene have been shown correlated with cancer risk in various organs such as lungs [10], gastric [11], bladder [12], colorectal [13], and including breast [14]. Based on

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meta-analysis findings, the rs2279744 variant (SNP309) in the *MDM2* gene has been proposed as an informative genetic marker associated with increased breast cancer risk, particularly in Asian population [14]. Moreover, rs150550023 indel polymorphism in the *MDM2* promoter region was observed in relation to potential shifts in gene expression within the p53-MDM2 regulatory pathway. A potential synergistic effect with rs2279744 (SNP309) variant of the MDM2 gene was observed, with mRNA levels of MDM2, p53, p21, and BAX showing and increase of approximately 1.5 to 3 times in tumors with homozygous deletion genotype tissues [15]. This suggests that the polymorphism in the *MDM2* gene could be used as a biologically plausible candidate for genetic risk.

As mentioned earlier, tumorigenesis is multifactorial, with genetic background of the population plays a crucial role alongside external factors. Various genetic polymorphism loci have been studied in different populations, including in northern Thailand. Despite limited reports on the genetic variations in Thais, here, this study reports the genetic variation of twelve biallelic loci across nine genes relating to breast cancer development process in the lower norther Thailand. We found that only the deletion allele of *MDM2* rs150550023 showed a significant association with breast cancer risk in the lower northern Thai population, with a high allele frequency of 0.233. By incorporating newly selected loci into previously reported samples [16], we expanded our genetic dataset and gained additional genetic insights into the lower northern Thai people. Our findings could identify potential biomarkers for early breast cancer prediction, as well as for cancer prevention strategies.

Materials and Methods

Samples

The samples use in this study consisted of whole blood collected from 184 female breast cancer patients and 176 healthy female volunteers. All samples were obtained by oncologists at Buddhachinaraj Hospital, Phitsanulok, Thailand, and were originally collected as part of a previous study [16]. Genomics DNA was newly extracted from these blood samples using the GF-1 blood DNA Extraction Kit (Vivantis, Malaysia) and stored at -20 degree Celsius until further use.

Genotyping

To genotype up to 12 the polymorphic selected loci associated with breast cancer development process, four different polymerase chain reaction (PCR)-based genotyping methods, each employing distinct detection assays, were used, as summarized in Table 1. Briefly, for *XRCC1* rs1799782 and rs25487, PCR-restriction fragment length polymorphism (PCR-RFLP) we performed using 2X HS Taq Master Mix (Bioline, Canada) with specific forward and reverse primers [17, 18]. The PCR products were then digested with restriction enzyme *Mspl* according to the manufacturer's instructions, and the resulting fragments were visualized by 1.5% agarose gel electrophoresis. For *MDM2* rs150550023, PCR was conducted using specific primers labeled with 6-FAM fluorescent dye, and genotyping was performed via fragment analysis using an ABI3130 Genetic analyzer, (Thermo Scientific, USA). The TaqMan probe assays (Thermo Scientific, USA) were applied to genotype *MTHFR* rs1801131 and rs1801133, following the manufacturer's protocol. We also included the KASP™ genotyping assay (LGC, United Kingdom) for DNA genotyping of the *APE1* rs1130409, *CDH1* rs16260, *ERCC1* rs3212964, *HER2* rs1058808 and rs1136201, *HIF-1alpha* rs11549467 and *HMGB1* rs1045411 loci, in accordance with the manufacturer guidelines.

Statistical analysis

Allele and genotype frequencies in both cases and controls were calculated based on genotype distributions for each SNP. The odds ratio (OR) for each genotype and each allele associated with breast cancer incidence, along with 95% confidence intervals (95% CI), and significance level ($p< 0.05$), was calculated using the GIGA calculator online software via odd ratio calculator option (https://www.gigacalculator.com/calculators/odds-ratio-calculator.php). Hardy-Weinberg equilibrium analysis for each locus was assessed using the simple calculator of Hardy-Weinberg equilibrium software (http://www.dr-petrek.eu/documents/HWE.xls).

Results

In this study, 12 polymorphic loci located within 9 genes were genotyped in 184 breast cancer patients and 176 healthy controls. The genes included *MDM2*, *XRCC1, MTHFR, APE1, CDH1, ERCC1, HER2, HIF-1alpha*, and *HMGB1*. The specific loci analyzed were *MDM2* rs150550023, *XRCC1* rs1799782 and rs25487, *MTHFR* rs1801131 and rs1801133, *APE1* rs1130409, *CDH1* rs16260, *ERCC1* rs3212964, *HER2* rs1058808 and rs1136201, *HIF-1alpha* rs11549467 and *HMGB1* rs1045411. Among these, *XRCC1* rs1799782 showed no variation in the study population, while all other loci exhibited polymorphism. As shown in Supplementary Table 1, both allele and genotype frequencies are reported for each locus in both cases and controls. Additionally, Hardy-Weinberg equilibrium analysis (also presented in Supplementary Table 1) revealed that several loci had genetic distributions consistent with equilibrium ($p> 0.05$), suggesting that the sample population is sufficiently large and not significantly affected by evolutionary pressures.

Based on genotype and allele frequencies of all 12 polymorphic loci, as shown in Supplementary Table 1, *MDM2* rs150550023 a 40-base pair deletion polymorphism was the only variant that showed a statistically significant association with breast cancer risk. The deletion allele was more frequent in breast cancer patients (30.43%) than in healthy controls (23.3%), yielding an odds ratio of 1.44 (95% CI = 1.033 – 2.008, p = 0.016). Significant associations were also observed in the dominant model (OR = 1.47, 95% CI = 0.972 – 2.235, p = 0,034) and homozygous deletion model (OR = 2.29, 95% CI = 0.980 – 5.348, p = 0.029). All other loci showed no significant differences between cases and control groups.

Table 1. Genotyping Methods, Primer Sequences and Product Size of the Genes

Genes / locus	Genotyping methods	Primer sequence (5' > 3')	PCR product (Bp)	References
XRCC1 rs1799782; G>A; Arg194Trp	PCR-RFLP (Mspl*)	F: 5' GCCCCGTCCCAGGTA 3' R: 5' TCACTTTCCCAGAACCCCGA 3,	HWT: 292, 179, 20 HVA: 491 HET: 491, 292, 179, 20	[17]
XRCC1 rs25487; C>T; Arg399Gln	PCR-RFLP (Mspl*)	F: 5' TTGTCGTTTCTCTGTGTCCA 3' R: 5' ATACTCTTTTCCGACCTCCT 3'	HWT: 341, 274 HVA: 615 HET: 615, 341, 274	[17]
MDM2 rs150550023; (40 base pairs deletion in promoter region)	Fragment analysis	F: 5' 6 FAM-TTTCCTTTCTGGTAG-GCTGG 3' R: 5' CACCTACTTTCCCACAGAGA 3'	HIS: 262 HDL: 222 HET: 262, 222	[18]
MTHFR rs1801131; T>G; Glu429Ala	TaqMan probe	Commercial Kit	-	Thermo scientific, USA
MTHFR rs1801133; G>A; Ala222Val	TaqMan probe	Commercial Kit	-	Thermo scientific, USA
APE1 rs1130409; T>G; Asp148Glu	KASP-PCR	Commercial Kit	-	LGC Genomics, UK
CDH1 rs16260; C>A; -160C>A in promoter region	KASP-PCR	Commercial Kit	-	LGC Genomics, UK
ERCC1 rs3212964; T>C; (intron)	KASP-PCR	Commercial Kit	-	LGC Genomics, UK
HER2 rs1058808; C>G; Pro1170Ala	KASP-PCR	Commercial Kit	-	LGC Genomics, UK
HER2 rs1136201; A>G; Ile655Val	KASP-PCR	Commercial Kit	-	LGC Genomics, UK
HIF-1α rs11549467; G>A; Ala588Thr	KASP-PCR	Commercial Kit	-	LGC Genomics, UK
HMGB1 rs1045411; C>T; (in 3' UTR)	KASP-PCR	Commercial Kit	-	LGC Genomics, UK

Note: *, restriction enzyme; HWT, homozygous wide type; HVA, homozygous variant; HET, heterozygous; HIS, homozygous insertion; HDL, homozygous deletion

Discussion

This study examined 12 polymorphic loci located within nine genes—*MDM2*, *XRCC1, MTHFR, APE1, CDH1, ERCC1, HER2, HIF-1alpha,* and *HMGB1* to identify potential biomarkers for breast cancer risk in the lower northern Thai population. These loci were functionally grouped based on their roles in tumorigenesis: cell growth and proliferation (*HER2, MTHFR, MDM2*) [15, 19-23], inflammation (*HIF-1alpha, HMGB1*) [24-26], DNA repair (*APE1, ERCC1, XRCC1*) [27-29], and cell-cell adhesion and tissue integrity (*CDH1*) [30], all of which represent critical pathways in the hallmarks of cancer [31, 32].

The selected polymorphic loci in this study were chosen based on prior evidence of association with breast cancer, including non-synonymous variants, single-nucleotide substitutions, and deletion polymorphism (summarized in Table 1). Based on the allelic frequency analysis, all selected loci were found to be polymorphic, except for rs1799782 of *XRCC1*, which was fixed in this study population. Interestingly, this locus has previously been reported as polymorphic and significantly associated with the breast cancer risk in Chinese [33], Saudi populations [34], emphasizing the importance of genetic background in disease susceptibility.

Among the 12 loci examined, only *MDM2* rs150550023, a 40 base pair deletion polymorphism in promoter region of the gene, showed a statistically significant association with breast cancer risk in lower northern Thai population (OR = 1.44, 95% CI = 1.033 – 2.008, p = 0.016). This variant, previously known as rs3730486 or del1518 and now officially designated rs150550023 according to NCBI reference SNP database build 154 [15], had a deletion allele frequency of 30.4% in patients compared to 23.3% in controls. Our finding consistent with studies conducted in Southeast Iran [9], Mexico [35], which also reported increased breast cancer risk associated with the deletion allele. However, other studies have yielded inconsistent results [36], possibly due to population-specific genetic backgrounds, environmental exposures, or gene-environment interactions. These findings support the need

for population-based studies and careful consideration when applying genetic markers to precision medicine strategies.

In the previous report, our team identified four informative loci – out of fifteen examined – that were significantly associated with breast cancer risk in the lower northern Thai population [16]. Building on those findings, the present study incorporated the homozygous deletion genotype of *MDM2* rs150550023 into the previously reported genotype combinations. However, only one individual matched the complete five-locus genotype pattern, preventing the calculation of odds ratio for that specific combination. This rare occurrence underscores the need for larger sample sizes or multi-center studies to validate the potential cumulative effects of rare genotypes combinations.

In conclusion, our study highlights that *MDM2* rs150550023 polymorphism is significantly associated with breast cancer risk in the lower northern Thai population and may serve as a candidate genetic biomarker for identifying risk prediction. This is particularly relevant in public health contexts, where early identification of high-risk individuals can inform prevention strategies, targeted screening programs, and personalized care. These findings support the growing recognition that cancer susceptibility may be influenced by population-specific genetic backgrounds, and they emphasize the importance of conducting genomic studies in diverse populations. Although access to detailed demographic and clinical data was limited due to constraints in medical record retrieval, the sample size was sufficient to support the meaningfulness of the observed associations. Future multi-center studies involving larger and more diverse populations within Thailand and globally will contribute to a broader understanding of cancer susceptibility and advance global precision oncology efforts.

Author Contribution Statement

MS participated in construction of hypothesis, study design, laboratory works, data analysis, writing manuscript and supervision of this work. MN performed molecular techniques and data analysis. SD performed laboratory works and data analysis.

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Approval

Authors have approved the final version of the article.

Ethical Declaration

This study was approved by Naresuan University Institution Review board of Naresuan University, Thailand (COE no. 006/2024).

Data Availability

All data generated or analyzed during this study are included in this published article.

Conflict of Interest

All authors declare no conflict of interest.

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