Biomedical
Research & Therapy

ISSN: 2198-4093
www.bmrat.org

Original Research

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Association between SNP rs9485372 in TAB2 gene and breast cancer risk in Vietnamese women

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Abstract

Background: Breast cancer is a complex and common cancer in women. In the purpose of prevention and treatment of the disease, many studies have been conducted recently all over the world. The genetic factor is known as an important factor has been studied to provide information for early diagnosis. Within several genetic factors involved in the development of breast cancer, *TAB2* gene in 6q25.1 is a breast cancer susceptibility locus. The SNP r9485372 in *TAB2* gene is associated with breast cancer in East Asian population including Chinese and Korean but not in Indian and Japanese. In this study, we conducted a case-control study to evaluate the association of this SNP with breast cancer risk in the Vietnamese population. **Methods**: 109 controls and 111 cases were genotyped by HRM method and logistic regression analysed. **Results**: We found that the frequency of SNP alleles is roughly similar to East Asian population: the major allele is G occupied 59.63%, the minor allele is A with 40.37% in the Vietnamese population. The allelic distribution of SNP rs9485372 was not significantly different between case and control group ($OR_{A\ vs.\ G}$ (95% CI) = 0.93 (0.64 - 1.37), P-value = 0.73). **Conclusion**: Our finding thus suggested that this SNP is not significantly associated with breast cancer in Vietnamese women. However, the power of this study is quite low at only 4.46% that was partly caused by a small sample size. Hence, a further study needs to be conducted with a larger sample size in the future to confirm the association of this SNP with breast cancer in Vietnamese women.

Keywords

Breast cancer, rs9485372, Vietnamese population

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Competing interests: The authors declare that no competing interests exist.

Received: 22 May 2017
Accepted: 09 Jul 2017
Published: 28 Jul 2017

Biomedical
Research & Therapy

ISSN: 2198-4093
www.bmrat.org

Introduction

Breast cancer (BC), one of the most common cancers in women, is the leading cause of cancer death of women in the world. There were 1,383,500 new cases of BC and these caused approximately 458,400 deaths worldwide in 2002 (Levin, 2008). Till 2012, incidence and mortality of BC have increased up to 1671,000 new cases and 522,000 deaths, respectively (Ferlay et al., 2015). In Vietnam, breast cancer incidence has risen steadily, with an estimated 11,067 new cases in the country (GLOBOCAN, 2012). Breast cancer was ranked first mortality of common cancer in Vietnamese women (with 4600 deaths in 2012) (GLOBOCAN, 2012). However, the mortality to incidence ratio of breast cancer in Vietnam is much higher than the world (0.42 and 0.32, respectively). One of the reasons for this difference is the late diagnosis. In Vietnam, almost patients were detected breast cancer in the late stages that decreases the efficiency of treatment and increases mortality (DucNB, 2010). A statistics analysis revealed that five-year relative survival rate decreased when the breast cancer was diagnosed in advanced stages (DeSantis, Siegel, & Jemal, 2013). According to DeSantis et al., five-year relative survival rate decreases sharply from 99% for localized stage to 24% for distant-stage. Early cancer detection plays an important role in extending survival time of patients. Early detection can greatly increase the chances for successful treatment (WHO, 2016). Breast cancer can be considered a sporadic disease because it is mainly caused by interplaying between the genetic factor and environmental factors such as alcohol consumption, smoking, and diet (Martin & Weber, 2000). The majority of breast cancer is sporadic, only 5%-10% of breast cancer cases are hereditary (Balmain, Gray, & Ponder, 2003; Rizzolo, Silvestri, Falchetti, & Ottini, 2011). Known genes (BRCA1 and BRCA2) which play roles in the the development of breast cancer count for approximately 20% of the familial risk, and less than 5% of total breast cancer (Balmain et al., 2003). Most of the genetic variants related to tumorigenesis of sporadic breast cancer are unknown (Balmain et al., 2003). It is suggested that remaining risk of breast cancer may result from the contribution of multiple common variants in the genome, namely polygenic model (Pharoah et al., 2002). Although a common variant has only a modest effect on tumorigenesis of disease, a combination of these variants can have a greater effect on the disease (Onay et al., 2006; Pharoah et al., 2002). Therefore, the discovery of common variants relating to breast cancer is important to fully understand the mechanism of this disease and predict the risk of breast cancer development.

Nowadays, there are many Single Nucleotide Polymorphisms (SNPs), common variants, have been identified to associate with cancers including breast cancer by GWAS studies (Cai et al., 2014; Easton et al., 2007; Long et al., 2010; Long et al., 2012; Shu et al., 2012; Zheng et al., 2009). In recent GWAS studies, scientists have identified approximately 100 genetic loci associated with breast cancer (Wen et al., 2016). The 6q25.1 chromosomal region was considered a breast cancer susceptibility locus. There are many GWAS studies suggested that

ISSN: 2198-4093
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various SNPs located on this region have significantly associated with breast cancer risk, such as rs2253407 (Gaudet et al., 2013), rs9383935, rs2228480, rs3798758 (Wang et al., 2014), rs2046210 (Zheng et al., 2009), rs3757318 (Turnbull et al., 2010). SNP rs9485372 (G>A) is also located on 6q25.1 region and has been proven to strongly associated with breast cancer in East Asian women by many studies (Long et al., 2012; Wen et al., 2016; Zheng et al., 2013). Rs9485372 is an intronic SNP and located on the TGF-beta activated kinase 1/ MAP3K7 binding protein 2 (TAB2) gene, which belongs to the 6q25.1 chromosomal region. TAB2 protein is encoded by *TAB2* gene and take part in TGF-beta pathway, which is critical in the development of breast cancer (Benson, 2004). TAB2 links signal from the transforming growth factor-β (TGF-β) receptor and TRAF proteins to the TGF-β-activated kinase 1 (TAK1) and activates TAK1 (Takaesu et al.). Activated TAK1 indirectly activates NF-κB.by phosphorylation inhibition kappa B kinase complex (IKK) (Takaesu et al.). Once activated, NF-κB will target genes promoting tumor cell proliferation, survival, migration (Van Waes, 2007). Although the biological mechanism of the association between SNP rs9485372 and breast cancer remains to be determined, it is possible that this association may be mediated through *TAB2* gene (Long et al., 2012). A 4-stage study conducted in East Asian women has showed that the $OR_{A\ vs.\ G}$ (95% CI) was 0.88 (0.81–0.95), 0.86 (0.81–0.92), 0.94 (0.88–1.00) and 0.90 (0.85–0.94) with p-value was 1.4x10-3, 6.3x10-6, 0.05, 4.2x10-5, respectively, for stage I to IV (Long et al., 2012). The pooled analysis which was then performed with all samples from 4 stages produced $OR_{A\ vs.\ G}$ (95% CI) of 0.90 (0.87– 0.92) and P-value of 3.8x10-12 (Long et al., 2012). These results have revealed a strong association of SNP rs9485372 with breast cancer risk. The positive association of this SNP was confirmed by studies of Zheng et al. and Wen et al. (Wen et al., 2016; Zheng et al., 2013). The results of these studies revealed that G allele of this SNP increased the risk of BC while A allele had an ability to reduce BC risk in East Asian women. Nevertheless, the association between this SNP and breast cancer was not significant in Indian population and African-American population (Long et al., 2013; Nagrani et al., 2017). Although many studies have demonstrated the association of SNP rs9485372 with breast cancer in Asian women, there was no study investigating this association in the Vietnamese population. Hence, the aim of our study is to estimate the association of SNP rs9485372 with breast cancer risk in Vietnamese women.

Materials-Methods

Study population

111 breast cancer women and 109 healthy women without breast cancer were recruited from Oncology Hospital, Ho Chi Minh city, Vietnam. Breast cancer was diagnosed by clinical and radiological examinations (mammography and/or ultrasonography), and was then confirmed by the histopathological assessment of biopsies. The participants had received and signed the consent form which

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was approved by the Ethical Committee of Oncology Hospital – HCMC Vietnam under the decision number 177/HĐĐĐ-CĐT, 18th November 2014. The collected whole blood samples were stored in EDTA containing tubes at -20°C till DNA extraction.

DNA extraction

Genomic DNA was extracted by salting-out method following protocol of Hue et al (Hue, Chan, Phong, Linh, & Giang, 2012) with some adjustments for whole blood samples, then stored at -20°C until performing PCR reaction.

Genotyping methods

HRM (high resolution melting) method was used to identify the genotypes of DNA samples in this study. The DNA sequence around the SNP rs9485372 was first obtained from NCBI SNP database and used as input data to design PCR primers which amplify a fragment including interested SNP by Primer3Plus (http://primer3plus.com/cgi-bin/dev/primer3plus.cgi). Next, designed primers were checked specificity at NCBI Primer-BLAST tool (https://www.ncbi.nlm.nih.gov/tools/primer-blast/). The PCR product was then predicted by using UCSC In-silico PCR tool (https://genome.ucsc.edu/cgi-bin/hgPcr). The melting curves of the product were predicted by uMelt HETS (https://www.dna.utah.edu/hets/). The best primer pair (rs9485372-F-5'-TCAATGTGGTACTGTGCCTAGTTTT-3' and rs9485372-R-5'-TCTCTCCACAGGGAATAGTGATATGT-3'), which amplified a 100bp-fragment including interested SNP and have 3 different curves corresponding to 3 genotypes (GG, GA, AA) were accepted for HRM analysis.

The PCR reaction was performed in LighCycler 96 System (Roche Diagnostics Penzberg Germany) and used Roche HRM master mix (Roche Diagnostics, Germany). Thermal cycle of PCR in HRM analysis consisted of an initial pre-incubation at 95°C for 5 minutes, followed by 40 cycles of denaturation at 95°C for 30 s, annealing for 30s at 58°C (Ta) and elongation at 72°C for 30 s. Heteroduplexes were then generated by heating the reaction to 95°C for 1.5 minutes and cooling to 40°C (Ramp rate of 2.2°C/s) for 60s. Finally, the heteroduplexes was heat to 65°C for 30s (ramp rate of 1.5°C/s) and to 95°C for 1s in order to record the fluorescent signal. The best conditions for HRM analysis was optimized with the controls and used for genotyping samples. HRM components for a 10µL reaction consisted of: 1X PCR buffer, 200µM each dNTP, 2.0mM $MgCl_2$, 0.3µM forward primer, 0.3µM reverse primer, 15ng DNA and molecular water.

Association analysis

Association analysis was conducted by R version 3.3.2. Firstly, Hardy–Weinberg equilibrium (HWE) had been analyzed. HWE P-value > 0.05 was considered the HWE in sample sets. The logistic regression analysis was then performed to

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estimate the association between SNP rs9485372 and breast cancer risk. All statistical tests which had a P-value < 0.05 were considered statistically significant. Finally, the statistical power of the case-control study was analyzed.

Results

Genotyping

To determine the genotype of samples, three controls corresponding three genotypes (GG, GA, AA) were first identified by the initial genotyping reaction of some random samples. **Figure 1A, B, C** show 3 HRM curves of 3 controls that were analyzed through 3 channels: melting peak, melting curve, and different plot. These controls were also confirmed by sequencing **(Fig. 1D,E,F)**. After identifying controls, these controls were used for genotyping optimization to get 3 best discriminate HRM curves. The optimal condition for genotyping reaction which was mentioned in the method was applied to identify the genotype of samples. Total 220 samples including 111 of case set and 109 of control set were successfully genotyped (**Fig. 2**).

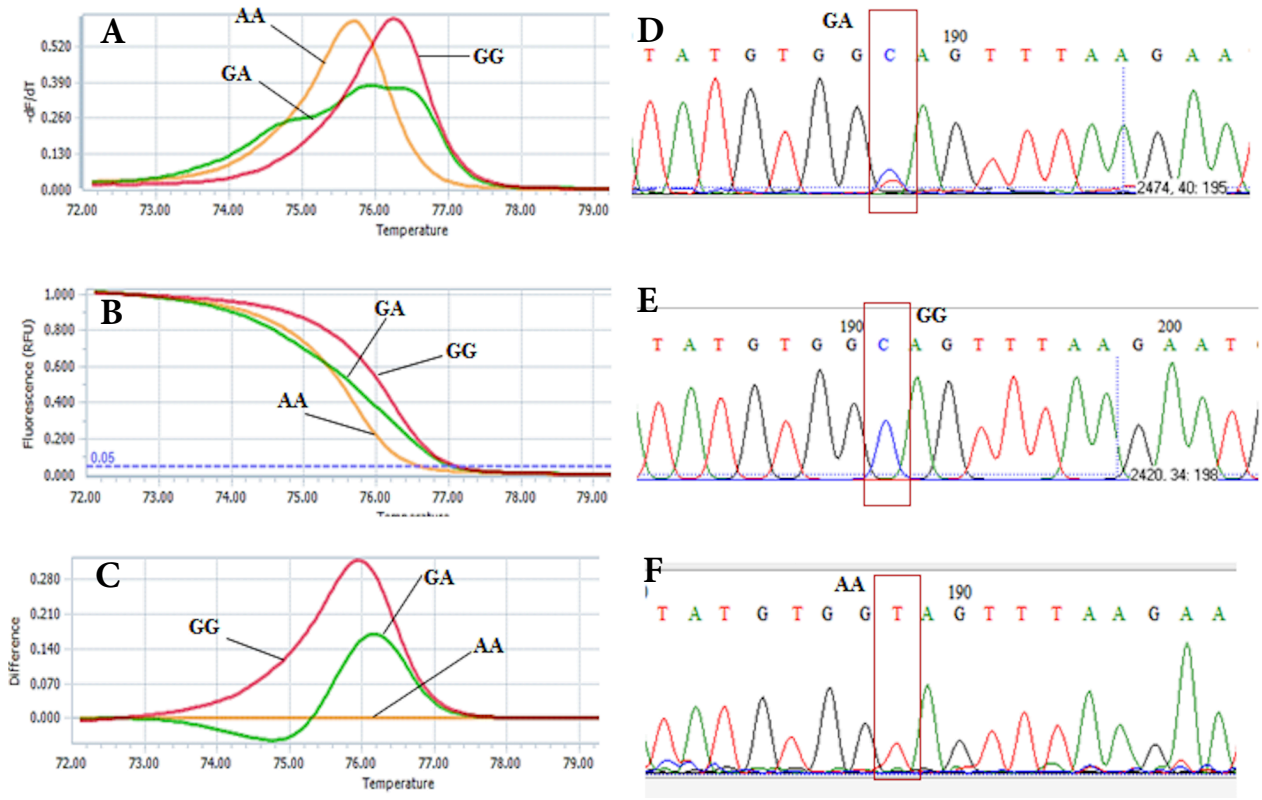

Figure 1. Identify 3 controls by HRM analysis and sequencing. GA, GG, AA genotype controls were identified by 3 analysis channels, melting peak (**A**), melting curve (**B**), different plot (**C**) and confirmed by sequencing (**D, E, F**).

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Alleles' frequency and Hardy-Weinberg equilibrium (HWE)

Allele and genotype frequencies were calculated based on the number of each allele and genotype that were identified by HRM analysis (Table 1). The frequency of minor allele (A allele) counted for 38.84% in case set and 40.37% in control set. It is likely that the A allele in control set appears more frequently than in case set.

HWE p-value was 1 in each group, indicating that both control and case groups were in Hardy Weinberg equilibrium (Table 1). Thus, the selected sample sets can represent the population. The association analysis of this SNP can be a reliable reflection of the relationship of this SNP and breast cancer in Vietnamese.

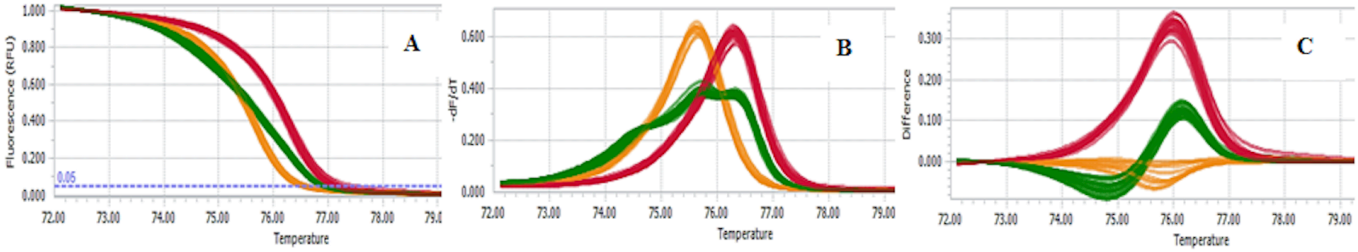

Figure 2. Three genotype groups of rs9485372 in melting curve (A), melting peak (B), different plot (C) analysis. The red, green and orange curve represented GG, GA and AA genotype, respectively.

Table 1. Allele and genotype frequency of SNP rs9485372 and HWE of sample sets

	Genotype (%)			Allele (%)		HWE P-value
	AA	GA	GG	A	G	
Case (111)	17 (15.32)	52 (46.85)	42 (37.84)	90 (38.74)	136 (61.26)	1
Control (109)	18 (16.51)	52 (47.71)	39 (35.78)	88 (40.37)	130 (59.63)	1
Total (220)						0.89

Association analysis

Based on allele and genotype frequency of the interested SNP, association analysis was then conducted by R version 3.3.2. Table 2 shows an association of SNP rs9485372 with breast cancer. OR per A allele was 0.93, revealing that the A

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allele may have a protective effect on risk of breast cancer. However, the Chi-squared test showed 0.73 of p-value for allele difference between case population and control population (P-value > 0.05) (Table 2). It suggested that SNP rs9485372 was not significantly associated with breast cancer risk in the Vietnamese population. In addition, genotypic association analysis revealed that the number of the minor allele in genotype also have an effect on reducing breast cancer risk. AA genotype with two A alleles is more protective ($OR_{AA\ vs.\ GG}$ = 0.88) than GA genotype which has only one A allele ($OR_{AG\ vs.\ GG)}$ = 0.93). It seems that A allele has a recessive effect on the disease. Nevertheless, the p-value for additive model, recessive model, and the dominant model was 0.94, 0.81 and 0.75, respectively, which is much higher than the threshold (P-value = 0.05) (Table 2). Therefore, there was a non-significant association between this SNP and breast cancer in the Vietnamese population.

Table 2. Association analysis of SNP rs9485372

Association analysis	Analysis model		OR	95% CI	P-value
Allelic analysis	**A vs G**		0.93	0.64 - 1.37	0.73
Genotypic analysis	**Additive**	AA vs GG	0.88	0.40 - 1.94	0.94
	Additive	GA vs GG	0.93	0.52 - 1.66	0.94
	Recessive	AA vs (GA+GG)	0.91	0.44 – 1.88	0.81
	Dominant	(AA+GA) vs GG	0.92	0.53 – 1.58	0.75

The power analysis

After identifying the association of SNP rs9485372 with breast cancer, the statistical power of our study was also computed to confirm the estimated association. With 220 samples including 109 controls and 111 cases, the power of this study was just 4.46%, which much lower than expectation (80%). The result revealed that non-significant association was not reliable. One reason for the low power of the study is small sample size. To raise the power up to 50% or more and have enough confidence to conclude the association between SNP rs9485372 with breast cancer in Vietnamese, a larger sample size needs to be investigated. Table 3 shows some predicted sample sizes that could be investigated to increase the power of the study. An estimated sample size of 12500 case/control will be investigated to reach 80% of power for this study (Table 3).

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Table 3. Predicting power, sample size for this study

Power (%)	4.46	50	60	70	80
Case/ Control	111/ 109	6105/ 6105	7785/ 7785	9808/ 9808	12472/ 12472

Discussion

Our study is the first study that investigated the association of SNP rs9485372 and breast cancer in Vietnamese population. In this case-control study, the frequency of a minor allele (A allele) was 40.37% in control and slightly decrease to 38.74% in case. In previous studies, the frequency of A allele in control in East Asian population ranged from 42% to 45.4%. Distribution of this allele in Vietnamese is roughly similar to its distribution in East Asian. It is possible that Vietnamese population and East Asian are in the same geographical distribution and may share the genetic variants through evolution. When the frequency of alleles similar with other populations in East Asia, the association between this SNP in Vietnamese is expected as seen in other studies (Long et al., 2012; Wen et al., 2016; Zheng et al., 2013). However, our study found that the $OR_{A\ vs.\ G}$ (95% CI) of this SNP was 0.93 (0.64-1.37) with an estimated 0.73 of P-value. It suggested that SNP rs9485372 might not be associated with breast cancer risk and the A allele does not affect the risk of breast cancer in Vietnamese.

A number of previous studies have shown a significant association of this SNP with breast cancer in East Asian population (Long et al., 2012; Wen et al., 2016; Zheng et al., 2013). In 2012, with approximately 40,000 cases and controls from Chinese, Korean, and Japanese population, Long et al. indicated SNP rs9485372 was strongly associated with breast cancer risk ($OR_{A\ vs.\ G}$ (95% CI) = 0.90 (0.87–0.92), P-value = $3.8x10^{-12}$) (Long et al., 2012). After that a replicated study of Zeng et al. (samples include 23 637 cases and 25 579 controls) suggested the same result ($OR_{A\ vs.\ G}$ (95% CI) = 0.90 (0.87–0.92), P-meta = 2.27×10^{-13}) (Zheng et al., 2013). Another study conducted in 2016 also suggested the association of this SNP with breast cancer in both ER negative and positive status ($OR_{G\ vs.\ A}$=1.15, one-side p=3.93x10-5 in ER-negative; $OR_{G\ vs.\ A}$=1.11 one-side p=2.72x10-5 in ER-positive population (Wen et al., 2016). With a large number of samples, these studies have shown a high power and the result is trustable. The positive association of SNP rs9485372 with breast cancer may be mediated through *TAB2* gene. SNP rs9485372 is located on intron region of *TAB2* gene and may have an effect on splicing of TAB2 mRNA. Hence, this SNP may affect expression and function of TAB2 and associate with breast cancer.

The non-significant association between the SNP rs9485372 with breast cancer in Vietnamese women (OR (95% CI) = 0.93 (0.64-1.37), P-value = 0.73) in our study is different from previous studies may due to a small sample size (109

ISSN: 2198-4093
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controls and 111 cases). However, our finding is consistent with some other studies. As seen in the study conducted in East Asian, Long et al. revealed that though this SNP was significantly associated with breast cancer in East Asian ($OR_{A\ vs.\ G}$ (95% CI) = 0.90 (0.87–0.92), P-value = 3.8x10-12, approximately 40,000 samples), but non-significant association was observed in Japanese population with roundly 2,000 samples ($OR_{GA\ vs.\ GG}$ (95% CI) and $OR_{AA\ vs.\ GG}$ were 0.93(0.76–1.13) and 0.84(0.66–1.07), respectively, P-value = 0.15) (Long et al., 2012). Another study in Indian population showed that this SNP was not significantly associated with breast cancer ($OR_{G\ vs.\ A}$ (95% CI) = 1.09 (0.94–1.25), P-value = 0.228, approximately 2,400 samples) (Nagrani et al., 2017). SNP rs9485372 was also indirectly evaluated association with breast cancer in African-American women by association of SNP rs9485370 which is in strong LD with rs9485372. With roundly 2,000 samples, this study showed that SNP rs9485372 had a non-significant association with breast cancer in African-American women (OR (95% CI) for heterozygote and homozygote were 1.13 (0.74-1.74) and 1.16 (0.77-1.76), respectively, P-value = 0.533) (Long et al., 2013).

According to previous studies, there are different conclusions about the association between SNP rs9485372 and breast cancer in different populations. It suggests that association of SNP rs9485372 with breast cancer depends on the ethnic group. Although this SNP is located on *TAB2* gene related to the development of breast cancer, the association of this SNP with breast cancer was not observed in Vietnamese women and other populations. The reason for this non-significant association is unclear but it may be due to epigenetic regulation that may play important role in expression and function of *TAB2* gene. Various environmental factors such as nutrition, behavior which occur during development of an individual can produce long-lasting epigenetic changes in the gene. It may regulate and affect the expression of *TAB2* gene (Faulk & Dolinoy, 2011). Therefore, the association of SNP rs9485372 with breast cancer was not consistent between populations.

With 109 controls and 111 cases, our study revealed that SNP rs9485372 is not significantly associated with breast cancer in Vietnamese ($OR_{A\ vs.\ G}$ (95% CI) = 0.93 (0.64-1.37), P-value = 0.73). Nevertheless, the power of this study is very low, roundly 4.46%. It may be due to a small sample size. Thus, a future study needs to be conducted with a larger sample size to confirm this finding.

Conclusion

In conclusion, our study is the primary research screening the association of SNP rs9485372 with breast cancer in Vietnamese women. With a quite small sample size including 109 controls and 111 cases, our study suggested that SNP rs9485372 was not significantly associated with breast cancer in Vietnamese women ($OR_{A\ vs.\ G}$ (95% CI) = 0.93 (0.64 - 1.37), P-value = 0.73), but the power of

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this study is very low, roundly 4.46%. Hence, the future study needs to be investigated with a larger sample size in order to confirm the result of our study.

Abbreviations

95% CI: 95% confidence interval
BC: breast cancer
GWAS: Genome Wide Association Study
HRM: High Resolution Melting
HWE: Hardy-Weinberg equilibrium
IKK: Inhibition Kappa B Kinase complex
NCBI: National Center for Biotechnology Information
NF-κB: Nuclear Factor- Kappa B
OR: Odd ratio
PCR: Polymerase Chain Reaction
SNP: Single nucleotide polymorphism
TAB2: TGF-beta activated kinase 1/MAP3K7 binding protein 2
TAK1: TGF-β-activated kinase 1
TGF: Transforming Growth Factor
TRAF: TNF receptor–associated factor 6
WHO: World Health Organization

Acknowledgements

We thank all physicians and staff of Oncology Hospital of Ho Chi Minh City, Vietnam for collecting blood samples for this study. This research is funded by Vietnam National Foundation for Science and Technology Development (NAFOSTED) under grant number 106-YS.01-2013.09

Author Contribution

Nguyen Thi Lan Huong contributed to acquisition, analysis, interpretation of data, drafting of manuscript. Nguyen Thi Ngoc Thanh reviewed and edited the manuscript for intellectual content. Nguyen Thi Hue oriented, gave important idea and revised the manuscript of this review. All authors gave final approval of the version to be published.

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