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Single Nucleotide Polymorphisms (SNPs) of *OGG1* (Ser326Cys) and *APE1* (Asp148Glu; –141T/G) Genes and Breast Cancer Risk in Filipino Women

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Base excision repair (BER) pathway involves repair of damaged DNA caused by spontaneous decay of DNA, reactive oxygen species, and ionizing radiation. Polymorphisms of genes involved in the pathway have been reported to be associated with cancer risk. In this study, the association of BER gene polymorphisms with breast cancer risk in Filipino women was assessed. The polymorphisms studied included X-ray repair cross-complementing group 1 (*XRCC1*, Arg399Gln), 8-oxoguanine DNA glycosylase (*OGG1*, Ser326Cys), and apurinic/apyrimidinic endonuclease 1 (*APE1*, Asp148Glu; –141T/G). A total of 186 participants (93 breast cancer cases and 93 breast cancer-free control) were recruited for the study. The genotyping of samples was performed using polymerase chain reaction with confronting two-pair primers (PCR-CTPP). The association of polymorphisms of BER genes with breast cancer risk and gene-environment interaction was determined using the unconditional logistic regression model. Distributions of *OGG1* and *APE1* genotypes were in Hardy-Weinberg equilibrium (HWE); however, *XRCC1* genotype distribution deviated from HWE and was not further analyzed. The analysis showed that *OGG1* Ser326Cys, *APE1* Asp148Glu, and *APE1* –141T/G had no significant association with breast cancer risk. Also, there is no significant interaction between the three BER gene variants and family history of cancer. Lastly, no significant increased risk was observed when the combined effects of risk alleles of the three BER gene variants were determined. In conclusion, the study suggests that *OGG1* Ser326Cys, *APE1* Asp148Glu, and *APE1* –141T/G are not good indicators of breast cancer risk in Filipino women.

Keywords: *APE1*, base excision repair, breast cancer, *OGG1*, single nucleotide polymorphism

INTRODUCTION

Breast cancer is the most common type of cancer among Asian women with an incidence rate of 22.3% (911,014 cases) of all female cancers in 2018 (Bray *et al*. 2018). In the Philippines, it accounts for 31.4% (24,798 cases) of all new cancer cases among women in the same year. This polygenic disease is present in the mammary glands and is affected by factors such as age, family history of cancer, lifestyle, race and ethnicity, and exposure to radiation and carcinogens (Feng *et al*. 2018). The development of breast

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cancer is closely related to DNA damage repair systems in breast cells. These repair systems are very important in maintaining genome integrity; hence, problematic repair systems have been associated with abnormal cell growth and cancer (Wallace *et al*. 2012).

The BER pathway is one of the repair systems of cells to counteract endogenous DNA damage (Krokan and Bjørås 2013). It removes damaged DNA bases caused by alkylating agents, ionizing radiation, and reactive oxygen species (Wallace *et al.* 2012). BER has two sub-pathways – the short-patch BER and long-patch BER. Both sub-pathways start with the DNA glycosylase removing the damaged base and leaving an abasic (AP) site. Monofunctional DNA glycosylases do this by N-glycosidic bond hydrolysis while bifunctional glycosylases like 8-oxoguanine DNA glycosylase (OGG1) have additional AP-lyase activity that removes the damaged base and introduce nicks *via* β-elimination (Hegde *et al*. 2008). Both glycosylases generate products that act as substrates of apurinic/apyrimidinic endonuclease 1 (APE1) producing a gap in the polynucleotide chain. In the short-patch BER, DNA polymerase β (pol β) fills this gap with a single nucleotide and the nicks are sealed by DNA ligase III complexed with a scaffolding protein, X-ray repair cross-complementing group 1 protein (XRCC1) (Wallace *et al*. 2012). In the long-patch BER, the DNA polymerase (pol δ, ε) introduces 2–15 nucleotides, thus creating a flap in the DNA. The flap is removed by flap-structure endonuclease 1 and the nicks are sealed by DNA Ligase I in complexed with proliferating cell nuclear antigen (Krokan and Bjørås 2013).

Single nucleotide polymorphisms (SNPs) of BER genes can potentially affect the functions of proteins they encode, thus also affecting the capacity of BER to correct DNA damage. Common polymorphic variants of genes like *OGG1* Ser326Cys, *APE1* Asp148Glu, and *XRCC1* Arg399Gln have been studied to determine their association with breast cancer. In postmenopausal women, the *OGG1* Ser326Cys Cys/Cys allele was found to increase risk in Thai women by two-fold (Sangrajrang *et al*. 2008) but not in Han Chinese (Luo *et al*. 2014). In contrast, the *APE1* Asp148Glu Glu/Glu allele was shown to be protective in Thais (Sangrajrang *et al*. 2008), while the Asp/Glu allele was associated with breast cancer risk in Koreans (Kim *et al.* 2013) and Indians (Mitra *et al*. 2008). Among Caucasians, *OGG1* Ser326Cys, *APE1* Asp148Glu, and *XRCC1* Arg194Trp were found to have no significant association with breast cancer (Zhang *et al*. 2006). Lastly, the absence of associations of *XRCC1* Arg399Gln was found among Thais (Sangrajrang *et al*. 2008) but not in Han Chinese (Luo *et al*. 2014) and Indian women (Mitra *et al*. 2008).

Several studies have examined the association of polymorphisms of BER genes and breast cancer risk in various populations but with different results. To date, the association of BER genes and breast cancer risk among Filipino women has not been assessed. This study aims to contribute to the global data on the association of BER genes and breast cancer risk by race. Moreover, the role of BER polymorphisms in Filipino women might help potentiate these genes as biological markers for early cancer detection. To our knowledge, this is the first report to investigate the association of BER genes with breast cancer risk in Filipino subjects.

MATERIALS AND METHODS

Ethical Clearance

Ethical clearance (IRB-2016-12-201-IS) was obtained from the University of Santo Tomas Hospital (USTH) Institutional Review Board. All study participants gave their written informed consent. Clinical data of cases like age of cancer diagnosis, tumor site, tumor grade, tumor-node-metastasis stage, and treatment received were retrieved from clinical and histopathological records. Other pertinent information like age, alcohol and tobacco use, family history of cancer, reproductive health, environmental and psychological factors, and sedentary behavior was obtained through personal interviews.

Study Population

Filipino female patients with histologically confirmed breast cancer, aged 18 yr and above, seen between January 2016 and March 2018 at the USTH, Manila, Philippines were recruited for the study. Histological confirmation of breast cancer was performed by microscopic examination of hematoxylin and eosin-stained tissues by a pathologist.

The cases were either newly diagnosed, receiving treatment, or in remission. They were age-matched (± 2 yr) with clinically healthy controls who were not suspected of any malignancy and were all living in Metro Manila, Philippines. All recruited participants were of Filipino descent and not descendants of interracial marriages of parents and grandparents. Approximately 5 mL of peripheral blood was collected in ethylenediaminetetraacetic acid tubes from both cases and controls. The cellular elements were immediately separated from the plasma and stored at –20 °C until molecular analysis.

DNA Extraction and Genotyping

Genomic DNA was performed using ReliaPrep™ Blood gDNA Miniprep System (Promega, USA) following the manufacturer's protocol. The analysis was performed on the four common nonsynonymous BER SNPs: *OGG1* Ser326Cys (C/G; in exon 7), *XRCC1* Arg399Gln (G/A;

in exon 10), *APE1* Asp148Glu (T/G; in exon 5), and *APE1* –141T/G (in promoter region). PCR-CTPP was used to amplify the target genes. Table 1 shows the set of primers used for the amplification of BER genes based on the study of Luo and colleagues (2014). PCR-CTPP was performed in a 20-µL reaction volume containing 2 µL of genomic DNA, 10.0 µL of Go Taq® Colorless Master Mix (2x) (Promega), 0.20 µM of each primer, and 6.4 µL of ultra-pure water. Amplification was performed using the following thermocycler settings: 95 °C for 10 min, then 30 cycles of 95 °C for 1 min, 64 °C (*OGG1* Ser326Cys) or 66 °C (*XRCC1* Arg399Gln) or 58 °C (*APE1* –141T/G) or 60 °C (*APE1* Asp148Glu) for 1 min, and 72 °C for 1 min. PCR products were analyzed using agarose gel electrophoresis. Ten percent (10%) of the case and control samples were randomly chosen, and PCR products were sent to Macrogen, South Korea for sequencing to validate the genotyping results. Reference sequences of the BER genes were retrieved from GenBank, National Center for Biotechnology Information. Sequence alignment was performed on all sequences using the reference BER gene sequences and the SnapGene® software (from GSL Biotech; available at snapgene.com).

Statistical Analysis

Categorical (pregnancy, smoking status, drinking status, and family history of cancer) and continuous (patient age at menarche and at menopause) variables were compared between breast cancer patients and control using Fisher's exact test and Mann-Whitney U test, respectively. In the smoking and drinking status of subjects, numbers of former and current smokers and drinkers were combined because of low counts. The HWE was determined using the χ^2 test. Unconditional logistic regression was used to estimate the odds ratio (OR) and 95% confidence interval (CI) for the association between genetic variants of *OGG1*, *XRCC1*, and *APE1* and breast cancer risk. Interactions between genotypes and risk factors were assessed using the likelihood ratio tests. Reported OR was adjusted for age, age of menarche, menopausal status, pregnancy, smoking status, alcohol use, and family history of cancer. Bonferroni correction was done to minimize false positives. The combined effect of gene variants was determined based on the homozygous risk alleles present in an individual. A $p < 0.05$ was considered as statistically significant. Statistical analyses were performed using STATA Release 14 (StataCorp LP, College Station, Texas, USA).

RESULTS

There were 186 participants (93 breast cancer cases and 93 clinically healthy controls) recruited for the study. Table 2 shows the clinical characteristics of the case and control participants. Age, age at menarche, age at menopause, pregnancy, smoking status, and family history of cancer are comparable between case and control subjects. For drinking status, the control group has a higher prevalence of alcohol drinkers compared to the case group ($p = 0.036$).

Table 1. List of PCR-CTPP primer sequences for the amplification of *OGG1*, *XRCC1*, and *APE1* variants.

Gene	SNP ID	Primer name	Sequence (5'–3')	Annealing temperature	Allele amplicon size	
OGG1 Ser326Cys[a]	rs1052133	OGG1_F1		64 °C	Ser (C)	252 bp[d]
		OGG1_R1	TGGCTCCTGAGCATGGCGGG		Cys (G)	194 bp
		OGG1_F2	CAGTGCCGACCTGCGCCAATG			
		OGG1_R2	GGTAGTCACAGGGAGGCCCC			
XRCC1 Arg399Gln[b]	rs25487	XRCC1_F1		66 °C	Arg (G)	447 bp
		XRCC1_R1	TGGCGTGTGAGGCCTTACCTCC		Gln (A)	222 bp
		XRCC1_F2	TCGGCGGCTGCCCTCCCA			
		XRCC1_R2	AGCCCTCTGTGACCTCCCAGGC			
APE1 Asp148Glu[c]	rs1130409	APE1_F1		60 °C	Asp (T)	136 bp
		APE1_R1	TCCTGATCATGCTCCTCC		Glu (G)	335 bp
		APE1_F2	TCTGTTTCATTTCTATAGGCGAT			
		APE1_R2	GTCAATTTCTTCATGTGCCA			
APE1 –141T/G	rs1760944	APE1-P_F1		58 °C	T	167 bp
		APE1-P_R1	ACACTGACTTAAGATTCTAACTA		G	236 bp
		APE1-P_F2	ACTGTTTTTTTCCCTCTTGCACAG			
		APE1-P_R2	TGAGCAAAAGAGCAACCCCG			

Polymorphic bases are underlined. All primer sets were based on the study of Luo and colleagues (2014). [a]*OGG1* – 8-oxoguanine DNA glycosylase gene; Ser – serine; Cys – cysteine. [b]*XRCC1*: X-ray repair cross-complementing group 1 gene; Arg – arginine; Gln – glutamine. [c]*APE1* – apurinic/apyrimidinic endonuclease 1 gene; Asp – aspartic acid; Glu – glutamic acid. [d]bp – base pair.

Table 2. Selected characteristics of breast cancer cases and control participants.

Characteristics	Cases (n = 93) mean ± standard deviation or n (%)	Controls (n = 93) mean ± standard deviation or n (%)	*p*-value
Mean age (yr)	53.6 ± 11.4	54.3 ± 11.7	0.706
< 50	35 (37.6)	35 (37.6)	
≥ 50	58 (62.4)	58 (62.4)	
Age at initial diagnosis (yr)	51.3 ± 10.9		
< 50	43 (46.2)		
≥ 50	50 (53.8)		
Age at menarche (yr)	93 (13.1 ± 1.88)	93 (13.3 ± 1.72)	0.408
Age at menopause (yr)	61 (48.5 ± 4.61)	56 (48.3 ± 5.20)	0.915
Pregnancy			0.115
No	20 (21.5)	11 (11.8)	
Yes	73 (78.5)	82 (88.2)	
Smoking			1.00
Never	83 (89.2)	84 (90.3)	
Former/current	10 (10.8)	9 (9.7)	
Drinking			0.0361
Never	78 (83.9)	65 (69.9)	
Former/current	15 (16.1)	28 (30.1)	
Immediate family history of cancer			1.00
No	71 (76.3)	70 (75.3)	
Yes	22 (23.7)	23 (24.7)	
Extended family history of cancer			0.396
No	67 (72.0)	73 (78.5)	
Yes	26 (28.0)	20 (21.5)	

SNPs of *OGG1* Ser326Cys, *XRCC1* Arg399Gln, *APE1* Asp148Glu, *and APE1* –141T/G were determined using PCR-CTPP. PCR-CTPP is a genotyping technique that uses two sets of primers that amplify specific alleles within the target DNA sequence (Hamajima 2001). It generates two PCR bands for homozygous alleles and three bands for heterozygous alleles. Figure 1 shows PCR-CTPP products in an agarose gel and DNA sequence chromatograms of representative genotyping data using *OGG1* Ser326Cys primer sets. The majority of the randomly sequenced PCR products have good quality DNA sequence chromatograms, but some chromatograms had poor quality. Sequences with good quality chromatograms have 100% concordance with PCR-CTPP results.

Table 3 shows the genotype frequencies of *OGG1* Ser326Cys, *XRCC1* Arg399Gln, *APE1* Asp148Glu, and *APE1* –141T/G in the control group. SNPs of *OGG1* and *APE1* were in HWE but not *XRCC1* ($p < 0.05$), thus excluded from further analysis. The deviation of *XRCC1* from HWE may be due to the non-specificity of the primer sets used, which led to genotyping error. Table 4 shows the genotype and allelic frequencies of *OGG1* and *APE1* SNPs in the case and control groups. There was no significant association observed between genetic variants of *OGG1* Ser326Cys, *APE1* Asp148Glu, or *APE1* –141T/G and breast cancer risk.

A subgroup analysis stratified by a family history of cancer showed no significant interaction between family history of cancer and polymorphisms of *OGG1* and *APE1* (Table 5). There were no significant differences between cases and control groups with *OGG1* genotypes. The *APE1* Asp148Glu Asp/Glu genotype showed significant (p = 0.011) increased risk of breast cancer in subjects with history of cancer in extended family (OR = 21.11, 95% CI = 1.99–223.70) but did not survive Bonferroni correction (p=0.05/7; p = 0.007). The *APE1* Asp148Glu Glu/Glu genotype showed a protective effect for subjects with family history of cancer (immediate family: OR = 0.57; extended family: OR = 0.53) but the effect was not statistically significant (p = 0.59 and p = 0.53, respectively). The *APE1* –141T/G TG genotype showed significant (p = 0.031)

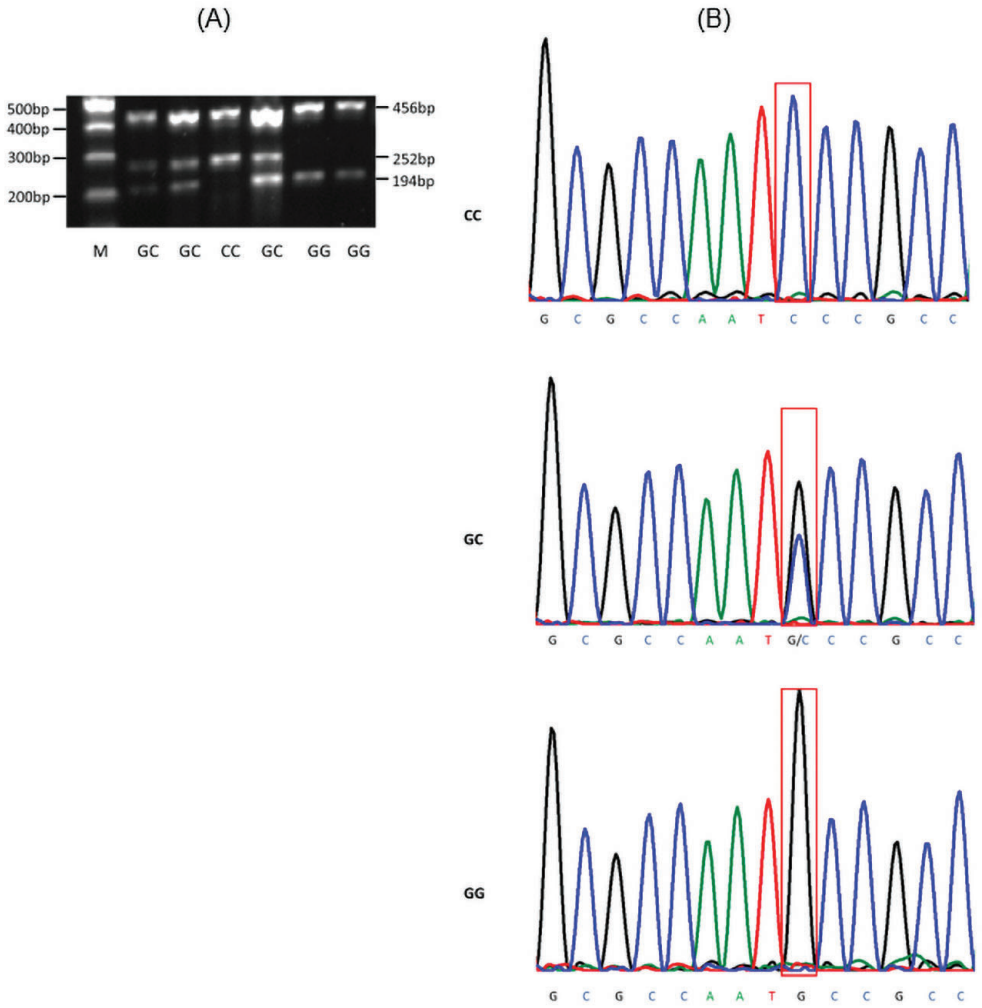

Figure 1. PCR-CTPP products of *OGG1* Ser326Cys. A) Agarose gel electrophoresis of *OGG1* Ser326Cys PCR-CTPP products. Homozygous CC (Ser/Ser) amplicon sizes were 496 base pairs (bp) and 252 bp; heterozygous GC (Ser/Cys) amplicon sizes were 496 bp, 252 bp, and 194 bp; and homozygous GG (Cys/Cys) amplicon sizes were 496 bp and 194 bp. B) Representative sequence chromatograms showing the allele positions (red box). Heterozygous allele is seen as double peaks in the chromatogram.

increased risk of breast cancer in subjects with history of cancer in immediate (OR = 6.23, 95% CI = 1.18–32.81) and extended family (OR = 6.28, 95% CI = 1.11–35.73; p = 0.039); these outcomes lost significance after Bonferroni correction. The GG genotype also showed an increased risk of breast cancer in subjects with a history of cancer in immediate (OR = 16.37) and extended family (OR = 5.28), but it was not statistically significant (p = 0.054 and p = 0.22, respectively). Possible interactions of the three gene loci with smoking and drinking status were also determined; however, the frequency of subjects with a minor allele was very low. Subjects with minor homozygous genotype and heterozygous genotype were combined but the analysis also showed no significant interactions of the three gene loci with smoking and drinking status (data not shown).

The association of gene-gene interactions of the three SNPs and breast cancer risk was also determined (Table 6). Individuals with two or three risk genotypes were combined in the analysis because of the very low frequency of subjects with three risk genotypes. The analysis showed no significant association of SNP-SNP interactions and breast cancer risk (p = 0.71–0.96).

DISCUSSION

Our study examined associations of BER genes *OGG1* Ser326Cys, *APE1* Asp148Glu, and *APE1* –141T/G with breast cancer risk in Filipino women. Comparing the minor allele frequencies of these genes in the control

Table 3. Observed and expected genotypic frequencies of *OGG1, XRCC1*, and *APE1* in the control participants.

Gene	Genotype	Observed	Expected	*p* (HWE)[d]
OGG1	CC	22 (23.4%)	22.26 (23.9%)	0.914
Ser326Cys[a]	CG	47 (50.5%)	46.48 (50.0%)	
	GG	24 (25.8%)	24.26 (26.1%)	
XRCC1	GG	21 (22.6%)	33.72 (36.3%)	< 0.001
Arg399Gln[b]	GA	70 (75.3%)	44.56 (47.9%)	
	AA	2 (2.2%)	14.72 (15.8%)	
APE1	TT	33 (35.5%)	36.80 (39.6%)	0.0914
Asp148Glu[c]	TG	51 (54.8%)	43.40 (46.7%)	
	GG	9 (9.7%)	12.80 (13.8%)	
APE1	GG	31 (33.3%)	34.33 (36.9%)	0.148
–141T/G	GT	51 (54.8%)	44.35 (47.7%)	
	TT	11 (11.8%)	14.32 (15.4%)	

[a]*OGG1* – 8-oxoguanine DNA glycosylase gene; Ser – serine; Cys – cysteine. [b]*XRCC1* – X-ray repair cross-complementing group 1 gene; Arg – arginine; Gln – glutamine. [c]*APE1* – apurinic/apyrimidinic endonuclease 1 gene; Asp – aspartic acid; Glu – glutamic acid. [d]HWE – Hardy-Weinberg equilibrium

Table 4. Genotypes and allele frequencies in the breast cancer case and control participants.

Gene polymorphism			Cases, n (%)	Controls, n (%)	OR[a] (95% CI)	*p*-value
OGG1 Ser326Cys[b]	Genotype	Ser/Ser (CC)	19 (20.4%)	22 (23.7%)	1.00 (reference)	
		Ser/Cys (CG)	48 (51.6%)	47 (50.5%)	1.11 (0.49–2.50)	0.804
		Cys/Cys (GG)	26 (28.0%)	24 (25.8%)	1.07 (0.42–2.68)	0.893
	Allele	Ser (C)	87 (46.3%)	92 (48.9%)	1.00 (reference)	
		Cys (G)	101 (53.7%)	96 (51.1%)	1.11 (0.74–1.67)	0.606
APE1 Asp148Glu[c]	Genotype	Asp/Asp (TT)	43 (46.2%)	33 (35.5%)	1.00 (reference)	
		Asp/Glu (TG)	38 (40.9%)	51 (54.8%)	1.64 (0.83–3.24)	0.151
		Glu/Glu (GG)	12 (12.9%)	9 (9.7%)	1.34 (0.48–3.79)	0.578
	Allele	Asp (T)	126 (67.0%)	117 (62.2%)	1.00 (reference)	
		Glu (G)	62 (33.0%)	71 (37.8%)	0.81 (0.53–1.24)	0.332
APE1 –141T/G	Genotype	TT	42 (45.2%)	31 (33.3%)	1.00 (reference)	
		TG	41 (44.1%)	51 (54.8%)	1.67 (0.86–3.23)	0.132
		GG	10 (10.8%)	11 (11.8%)	1.53 (0.55–4.29)	0.416
	Allele	T	127 (67.6%)	115 (61.2%)	1.00 (reference)	
		G	61 (32.4%)	73 (38.8%)	0.76 (0.50–1.16)	0.197

[a]OR – odds ratio. The OR was adjusted for age, age of menarche, menopausal status, pregnancy, smoking status, alcohol use, and family history of cancer using unconditional logistic regression. [b]*OGG1* – 8-oxoguanine DNA glycosylase gene; Ser – serine; Cys – cysteine. [c]*APE1* – apurinic/apyrimidinic endonuclease 1 gene; Asp – aspartic acid; Glu – glutamic acid

Table 5. Gene-environment interaction for breast cancer between genotypes and family history of cancer.

Genotype	History of cancer in immediate family						History of cancer in extended family					
	No			Yes			No			Yes		
	No. of cases / controls	OR[a] (95% CI)	*p*-value	No. of cases / controls	OR[a] (95% CI)	*p*-value	No. of cases / controls	OR[a] (95% CI)	*p*-value	No. of cases / controls	OR[a] (95% CI)	*p*-value
***OGG1* Ser326Cys[b]**												
Ser/Ser (CC)	14/15	1.00 (reference)		5/7	1.00 (reference)		11/20	1.00 (reference)		8/2	1.00 (reference)	
Ser/Cys (CG)	35/36	1.08 (0.41–2.82)	0.87	13/11	1.28 (0.24–6.73)	0.77	34/34	0.75 (0.29–1.95)	0.55	14/13	4.06 (0.46–35.74)	0.21
Cys/Cys (GG)	22/29	0.89 (0.31–2.57)	0.82	4/5	2.42 (0.27–21.43)	0.43	22/19	0.64 (0.22–1.86)	0.42	4/5	12.78 (0.78–210.01)	0.07
P-interaction			0.7186						0.0741			
***APE1* Asp148Glu[c]**												
Asp/Asp (TT)	32/25	1.00 (reference)		11/8	1.00 (reference)		33/28	1.00 (reference)		10/5	1.00 (reference)	
Asp/Glu (TG)	32/38	1.39 (0.64–3.01)	0.40	6/13	3.19 (0.58–17.48)	0.181	27/38	1.40 (0.65–3.01)	0.386	11/13	21.11 (1.99–223.70)	0.011
Glu/Glu (GG)	7/7	1.80 (0.51–6.34)	0.36	5/2	0.57 (0.73–4.40)	0.590	7/7	1.52 (0.4–0.21)	0.503	5/2	0.53 (0.04–7.16)	0.630
P-interaction			0.3132						0.6771			
APE1 –141T/G												
TT	28/26	1.00 (reference)		14/5	1.00 (reference)		30/27	1.00 (reference)		12/4	1.00 (reference)	
TG	34/37	1.12 (0.52–2.41)	0.776	7/14	6.23 (1.18–32.81)	0.031	29/37	1.37 (0.64–2.94)	0.422	12/14	6.28 (1.11–35.73)	0.039
GG	9/7	0.86 (0.25–2.90)	0.807	1/4	16.37 (0.95–281.81)	0.054	8/9	1.56 (0.78–5.07)	0.464	2/2	5.28 (0.37–76.33)	0.222
P-interaction			0.0965						0.4958			

[a]The OR was adjusted for age, age of menarche, menopausal status, pregnancy, smoking status, alcohol use, in a subgroup stratified by family history of cancer using unconditional logistic regression. [b]*OGG1* – 8-oxoguanine DNA glycosylase gene; Ser – serine; Cys – cysteine. [c]*APE1* – apurinic/apyrimidinic endonuclease 1 gene; Asp – aspartic acid; Glu – glutamic acid.

Table 6. Combined effects of risk alleles of *OGG1* and *APE1* to breast cancer risk.

No. of risk alleles	Cases, n (%)	Controls, n (%)	OR[a] (95% CI)	*p*-value
0	53 (57.0%)	55 (59.1%)	1.00 (reference)	
1	32 (34.4%)	32 (34.4%)	1.13 (0.58–2.19)	0.713
2-3	8 (8.6*)	6 (6.5%)	0.97 (0.29–3.22)	0.962

[a]The OR was adjusted for age, age of menarche, menopausal status, pregnancy, smoking status, alcohol use, and family history of cancer using unconditional logistic regression.

group with other Asian populations showed that the *OGG1* Ser326Cys minor allele frequency is similar to the Thai population (Sangrajrang *et al*. 2008) and slightly lower than the Chinese Han (Luo *et al*. 2014) and Korean (Kim *et al.* 2013) populations. The minor allele frequency of *APE1* Asp148Glu is comparable to the North Indian (Mitra *et al*. 2008) and Thai population (Sangrajrang *et al*. 2008), and slightly lower than the Chinese Han (Luo *et al*. 2014) and Korean (Kim *et al.* 2013) populations. Lastly, the minor allele frequency of *APE1* –141T/G is lower than the Chinese population (Ding *et al*. 2014; Luo *et al*. 2014).

The human OGG1 is a BER enzyme encoded by *OGG1* on chromosome 3p26 (Wallace *et al.* 2012). It is a bifunctional protein having a DNA glycosylase and an AP lyase activity (Hegde *et al*. 2008). It repairs oxidized DNA bases like 7, 8-dihydro-8-oxo-2′-deoxyguanosine produced by reactive oxygen species. It has also been proposed to be a transcriptional modulator of genes involved in inflammation (Wang *et al.* 2018). Because of these important functions, many studies have investigated the possible associations of *OGG1* with cancer risk. Our findings conform to the results from three meta-analyses

(Wei *et al.* 2011; Peng *et al.* 2014; Zou *et al.* 2016) that found no associations (p = 0.074–0.971) for all genetic models between *OGG1* Ser326Cys and breast cancer (ORs 1.00–1.08). However, the meta-analysis of Qiao and colleagues (2018) showed significant (p = 0.021) lower risk (OR = 0.77, 95% CI 0.61–0.96) of breast cancer for *OGG1* Ser326Cys using the dominant model. A study on Thai women showed a two-fold increased risk (OR = 2.05, 95% CI = 1.14–3.69, p = 0.016) of breast cancer in postmenopausal women with the *OGG1* Cys allele (Sangrajrang *et al*. 2008). On the other hand, the Cys allele was reported to have a significant (p = 0.005) protective effect (OR = 0.32, 95% CI 0.15–0.71) against breast cancer in Han Chinese women with low BMI (< 24 kg/m^2) (Luo *et al.* 2014). This implies that non-overweight Han Chinese women who carry the Cys allele have a 67.7% lower risk of developing breast cancer. The non-association of *OGG1* Ser326Cys variant with breast cancer risk in some studies may be explained by the reduced but similar enzymatic activity of Ser326Cys variant to the wild type enzymatic activity (Wallace *et al.* 2012). Also, inconsistencies of results may be due to inadequate data on gene-gene and gene-environment interactions, and different sample sizes and sources of controls (Zou *et al.* 2016).

Apurinic/apyrimidinic endonuclease 1 (APE1/APEX1) is a multifunctional BER enzyme encoded by the *APEX1* gene mapped at chromosome 14q11.2-12 (Wallace *et al.* 2012). It has AP endonuclease activity, 3' phosphodiesterase activity, and 3'–5' exonuclease activity. It also acts as an oxidation-reduction (redox) factor important in the activation of several transcription factors involved in inflammation, apoptosis, angiogenesis, and survival pathways, which are important to cancer development (Thakur *et al*. 2014). In this study, Asp148Glu – the most common polymorphic variant of *APEX1* – has no significant association with breast cancer risk. This agrees with the meta-analysis studies that have shown no association of *APE1* Asp148Glu variant with breast cancer risk (Wu *et al.* 2012; Qiao *et al.* 2018). On the other hand, a significant (p = 0.026) protective effect (OR 0.60, 95% CI 0.38–0.94) was observed in Thai women with the Glu allele (Sangrajrang *et al*. 2008) while this same allele has shown a three-fold increased risk (OR 3.35, 95% CI 1.36–8.26, p = 0.0085) of breast cancer in North Indian women (Mitra *et al.* 2008). While there are inconsistencies in results, the observed lack of association of *APE1* Asp148Glu variant with breast cancer risk is supported by *in vitro* analysis of its effect on HeLa cells, which showed that although the variant exhibited reduced interaction with other BER protein complexes like XRCC1 and pol β, the effect was benign because its AP endonuclease activity and redox regulatory function were maintained (Lirussi *et al.* 2016).

The APE1 –141T/G variant showed no significant association with breast cancer risk in Filipino subjects (OR 0.76, p = 0.197), an outcome concordant (OR 0.98, p = 0.892) with the study of Han Chinese women (Luo *et al.* 2014). Similarly, no association was observed in North Chinese women using the additive, dominant, and recessive models (ORs 0.94–1.12, p = 0.414–0.869) (Ding *et al*. 2014). The –141T/G allele lies in the promoter region of APE1, which affects the binding affinity of the octamer-binding transcription factor Oct-1 to the promoter region, thus affecting the mRNA expression level of *APE1* (Lu *et. al* 2009). When the DNA damage is extensive, a lower expression level of *APE1* favors apoptosis as an alternative to DNA repair.

An individual has a unique set of gene variants that may contribute to the person's susceptibility to cancer. Low penetrance genes like the BER genes may have a cumulative effect on DNA repair activity and on the individual's cancer risk. However, our study showed that the combined effects of risk alleles of *OGG1* Ser326Cys, *APE1* Asp148Glu, and *APE1* –141T/G were not associated with breast cancer risk among Filipino subjects. Our findings contrasted with outcomes in Thai (Sangrajrang *et al*. 2008), Korean (Kim *et al.* 2013), and Han Chinese populations (Luo *et al.* 2014), which increased risks of breast cancer when two or more homozygous risk alleles of *XRCC1*, *OGG1*, and *APE1* were present. The fact that the significant findings we generated did not survive Bonferroni correction indicates larger populations of subjects are needed to establish the association of the BER genes and breast cancer risk in the Filipino population.

There are several strengths of the study. To our knowledge, this study is the first to report associations of BER genes *OGG1* and *APE1* with breast cancer risk in Filipino women. Significant associations were checked for false positives using the Bonferroni test to correctly report associations. Also, the errors in genotyping were minimized by randomly validating the results using a different method. Limitations of our study include the following. First, the study was conducted with small sample sizes, which resulted in limited statistical power to establish the associations. This may account for the low frequencies and inflated ORs observed when subgroup analysis based on family history was performed. Second, the lack of detailed information on the daily amount of alcohol consumed and the number of smoked cigarettes. Lastly, the data on the specific type and subtypes of breast cancer present in the case group was lacking.

CONCLUSION

The case-control study showed no significant association between *OGG1* and *APE1* polymorphisms and breast cancer risk in the selected Filipino women population. Larger populations may be needed to validate this result and establish the interaction of the BER gene polymorphisms with different breast cancer risk factors.

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STATEMENT ON CONFLICT OF INTEREST

The authors declare no conflict of interest.

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