ORIGINAL ARTICLE

Association of Genetic Variants in hOGG1 and APE1 Genes with Breast Cancer Risk in a Rural Population: A Hospital Based Case-Control Study

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Abstract:

Background: Breast Cancer (BC) is a major concern of health risk in urban and rural areas of India. *Aim and Objectives:* This study was aimed to find out the frequency of polymorphisms in DNA repair genes, human 8-oxoguanine DNA glycosylase 1 (hOGG1) at codon (cd) 326 and Apurinic/apyrimidinic endonuclease 1 (APE1) at cd 148 in patients of BC from Maharashtra and to evaluate their association with BC development. *Material and Methods:* We used Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) to examine gene polymorphisms in 170 patients with BC and 200 in age and sex matched disease-free controls. *Results:* The results indicated that there was no significant difference in the genotype distribution between BC patients and controls for hOGG1 ($p>0.05$). The result showed that allele frequencies of APE1 Glu148 (OR=4.78; 95% CI= (2.55-8.95); $p= <0.0001$) genotype significantly increased the risk of BC. *Conclusion:* This study indicates that polymorphisms in cd148 of APE1 gene could play a role in modifying genetic susceptibility of individual to breast cancer in Maharashtrian patients.

Keywords: Breast Cancer**,** Genetic Polymorphism, human 8-oxoguanine DNA glycosylase 1, Apurinic/apyrimidinic endonuclease 1, Polymerase Chain Reaction-Restriction Fragment Length Polymorphism

Introduction:

Breast Cancer (BC) is the second most common cancer worldwide and one of the most common causes of death among women [1]. The etiologic factors for breast cancer involve the reproductive events that manipulate the levels of hormones, early age of menarche, delayed menopause, use of contraceptives, exposure to heterocyclic aromatic compounds and environmental pollutants [2-3]. For a country like India with huge population, varied culture, geographical variations, risk factors are likely to be literacy, diet, age at menarche and menopause, age at first delivery, family history of BC [4]. It is understood that along with the environmental factors, a combination of individual lifestyle habits and genetic factors may contribute to breast carcinogenesis. Although, the genetic factors are considered of great importance to cancer risk through the modulation of DNA repair, the etiology of BC is complex and remains unknown. Several DNA repair mechanisms play a crucial role in maintenance of genomic integrity by means of various repair pathways. But, it is not yet clear which DNA repair pathways are most important for protection against BC in case of DNA injury.

There is a significant evidence that inadequate repair of DNA damage plays a major role in the progression of cancer [5]. Base Excision Repair (BER) pathway is suggested to be a major determinant of cancer risk [6]. It is a key repair pathway that is accountable for conserving

genome stability and consequently protecting from cancer by repairing numerous lesions and strand breaks of DNA which is uninterruptedly caused by endogenous and exogenous mutagens [7]. Also, when a single base is damaged, the BER pathway enzymes are responsible for recognizing and repairing the damaged base [8]. The first step in BER pathway uses DNA glycosylases, to remove the damaged base to form an abasic or AP site by cleaving the N-glycosyl bond between the sugar and the base. The formation of 8-hydroxy-2-deoxyguanine (8-OHdG) is one of the most abundant oxidative products of cellular DNA, belived to play an important role in carcinogenesis [9], because it is highly mutagenic agent causing GC to TA transversions during DNA replication. The human 8-oxoguanine DNA glycosylase 1 (hOGG1) and Apurinic/apyrimidinic endo-nuclease 1 (APE1) genes play an important role in the BER pathway [10-11] where, hOGG1 has primary activity to remove the 8-OHdG from DNA whereas APE1 repairs basic AP sites in DNA.

Genetic susceptibility is related to polymorphisms in DNA repair genes which are likely to play a role in the development of cancer. Few molecular epidemiologic studies have evaluated the association of functional genetic variants in the BER genes including hOGG1 and APE1 with various cancer risk [11-12]. However, previous reports on the association between polymorphisms and cancer risk have provided contradictory results rather than convincing [13-16]. Also, the earlier data pertaining the association of the hOGG1 and APE1 polymorphisms with BC susceptibility are not consistent and therefore the influence of polymorphism of those genes is still unclear [17-18]. However, to the best of our knowledge, there are no published report on the association between hOGG1 Ser326Cys of exon 7 and APE1 variant Asp148Glu and BC in Indian population. In earlier studies we have shown that the polymorphisms in BER pathway genes especially XRCC1 cd 280, XRCC4, XRCC7 and NER pathway gene, XPD codon 199 plays an important role in susceptibility of BC in rural population of Maharashtra [19-21]. In continuation with this, we also hypothesized that the inherited polymorphisms in hOGG1 and APE1 may contribute to genetic susceptibility to BC. To test this hypothesis the present study proposed to investigate the associations of polymorphisms in those two genes with the development of BC in Maharashtrian population. We determined the genotypic frequency of polymorphisms of the (A) hOGG1 Ser326Cys codon326 in the exon-7 and (B) APE1 Asp 148Gln codon 148 in the exon-5 using the restriction enzymes MboII, BfaI respectively.

Material and Methods:

Study subjects:

This study was a hospital based case-control study. Study participants included 170 patients, who were newly diagnosed with BC and 200 healthy, cancer free, age matched females as controls. All cases ranged in age from 24-75 years (Mean±SD) 50.04±12.06, were recruited immediately after being diagnosed during the year July 2013-August 2016. Trained interviewers used a structured questionnaire to collect personal interview data from the participants regarding demographic factors and known risk factors.

Place of Study:

This study was conducted in Krishna Institute of Medical Sciences University from rural areas of South-Western Maharashtra of India.

Ethics and Biosafety:

The study protocol was approved by the Institutional Ethics and Biosafety Committee of

Krishna Institute of Medical Sciences. Informed consent was obtained before collecting the blood samples and confidentiality of results was maintained.

Selection of Cases and Controls:

Incident cases of breast cancer were identified using Mammography, tissue biopsy and Fine Needle Aspiration Cytology (FNAC) at the Department of Surgery, Department of Oncology at the Krishna Hospital & Medical Research Centre (KH&MRC) and the Department of Pathology of Krishna Institute of Medical Sciences. Controls were randomly selected from a group of population visiting to KH&MRC for blood donation and other purposes.

Inclusion and Exclusion Criteria:

Then patients confirmed to have high grade lesions based on their biopsy were included in this study. Age matched controls willing to participate in the study were included in this study with the informed consent. Control subjects who were relatives of cases or had a prior history of cancer were excluded from the study.

Genomic DNA isolation from Whole Blood Samples:

Genomic DNA was extracted from five milliliter of peripheral blood using Purelink genomic DNA extraction and purification Kit (Invitrogen, Life technologies) following the manufacturer's instructions.

Genotyping Assays:

Genotyping of hOGG1 and APE1 genes were performed by PCR-RFLP methods. The primers were designed to amplify the regions of DNA that contain polymorphic sites of interest: (A) hOGG1 Ser326Cys codon326 in the exon-7 and (B) APE1 Asp 148Gln codon 148 in the exon-5. The primers selected to amplify the exons of hOGG1 and APE1 containing the polymorphisms of interest were (Forward 5′-CTGTTCAGTGCCGACCTGCGC CGA-3′ and Reverse 5′-ATCTTGTTGTGCAAA CTGAC-3′ for hOGG1 codon 326, exon7, and (Forward5′-CTGTTTCATTTCTATAGGCTA-3′ Reverse 5′AGGAACTTGCGAAAGGCTTC-3′) for APE1 codon 148 exon 5. The PCR amplification were carried out separately under different conditions in 20 micro liter (µL) reaction mixtures containing 1X PCR buffer (10 mili molar (mM) Tris-HCl (pH 9.0), 50 mM KCl 1.5 mM MgCl2), 0.2 mM each dNTP, 10 picomole (pmol) of each primer, 1U *Taq DNA* polymerase (GeNei, Merck Bioscience) and 100 nanogram (ng) of purified genomic DNA template. The reaction mixtures were subjected to PCR amplification with a Master Cycler Gradient PCR (Eppendorf). The PCR conditions for amplification of hOGG1 codon 326 of 247 bp (denaturation at 95^0C- 5 min, 35 cycles of 95^0C- 30 sec, 64^0C- 30 sec, 72^0C- 30 sec and final extension at 72^0C- 5 min), APE1 codon 148 of 164 bp, (95^0C- 5 min, 35 cycles of 95^0C- 20 sec, 55^0C- 20 sec, 72^0C- 20 sec, 72^0C- 5 min). After performing PCR programme for each of the reactions, the PCR products were analyzed by agarose gel electrophoresis. After confirmation of DNA amplification, each PCR product of hOGG1 exon 7 and APE1 exon 5 were digested at 37°C with 2 unit of MboII and BfaI respectively. After the overnight incubation, digestion products were separated on a 3% agarose (GeNei, Merck Biosciences) gel at 100 V for 30 min, stained with ethidium bromide and photographed with gel documentation system.

Statistical Analysis:

The association of *hOGG1 and APE1* genotypes with risk of BC were determined using odds ratio (OR). ORs and 95% confidence intervals (CIs) were calculated by the univariate and multivariate

logistic regression analyses with adjustment of risk factors.

Results:

Characteristics of the Study Subjects:

During the study period 170 women with BC met the eligibility criteria for this study and 200 controls were selected to match these cases. The characteristics of age and sex matched cases and controls are presented in table 1. The mean age in years was 50.04 (median: 50, range 25-75) for the cases and 40.60 (median: 37.5 range 24-75) for the controls. There were no significant differences between the cases and controls with respect to ethnicity.

Table 1: Demographic Characteristics of Breast Cancer Cases and Healthy Controls from Rural Areas of Maharashtra.

Variable	Cases N=170		Controls N=200		*P*-Value based on $\chi 2$
Age (Mean ± SD) years	50.04 ±12.06		40.60 ± 13.73		
	No.	(%)	No.	(%)	
⩽ 50	95	55.88	149	74.50	<0.05
51-60	38	22.35	32	16.00	
61-70	28	16.47	15	7.50	
>70	9	5.30	4	2.00	
Diet					
Vegetarian	40	23.53	64	32.00	0.01
Mixed	130	76.47	136	68.00	
Education					
High School	71	41.76	75	37.50	
High School Graduate (12 y)	8	4.71	26	13.00	<0.001
College /Graduate	12	7.06	25	12.50	
No School	79	46.47	74	37.00	
Economic Status					
Middle	42	24.71	52	26.00	<0.05
Poor	104	61.18	103	51.50	
Rich	24	14.11	45	22.50	
Family History of Cancer					
Yes	42	24.71	0	0.00	0.1
No	128	75.29	0	0.00	

Table 2: The Genotype Frequencies of hOGG1 and APE1 Gene Variants in Untreated Breast Cancer Patients and Controls

Gene	Genotype	Cases (N= 170) N (%)	Control (N = 200) N (%)	Odds' Ratio (95% CI)	*P* value	Adjusted Odds Ratio (95% CI)	*P* value
hOGG1 (C1245G) Ser326Cys cd326 Exon7	Ser/Ser	85 (50.00)	125 (62.50)	1		1	
	Ser/Cys	56 (32.95)	50 (25.00)	1.64 (1.02-2.63)	0.03	0.54 (0.31-0.95)	0.035
	Cys/Cys	29 (17.05)	25 (12.50)	1.70 (0.93-3.11)	0.08	0.45 (0.22-0.91)	0.027
	Ser/Cys+Cys/Cys	85 (50.00)	75 (37.50)	1.66 (1.10-2.52)	0.01	0.55 (0.34-0.88)	0.013
APE1 (T2197G) Asp148Glu cd 148 Exon5	Asp/Asp	73 (42.95)	132 (66.00)	1		1	
	Asp/Glu	52 (30.58)	51 (25.50)	1.84 (1.14-2.98)	0.01	0.53 (0.30-0.92)	0.024
	Glu/Glu	45 (26.47)	17(08.50)	**4.78 (2.55-8.95)**	**<0.0001**	**0.15 (0.07-0.31)**	**<0.001**
	Asp/Glu+ Glu/Glu	97 (57.05)	68 (34.00)	2.57 (1.69-3.93)	<0.0001	0.36 (0.22-0.58)	<0.001

p value determined based on χ2

Association hOGG1 and APE1 genotype variants with breast cancer risk.

The distribution of the polymorphism Ser326Cys of hOGG1 and Asp148Gln of APE1 genes and concordance of the polymorphisms are presented in table 2.

(A) hOGG1 (Ser326Cys) codon326 in exon-7.

Table-2 displays the distribution of genotypes and frequency of alleles of the C1245G polymorphisms in patients with BC and controls. The frequency of hOGG1Ser/Ser wild type homozygotes was 50.00 % in cases and 62.50 % in controls whereas hOGG1Cys/Cys variant homozygotes was 17.05 % in cases and 12.50 % in controls. The frequency of hOGG1Ser/Cys heterozygotes was 32.95% in cases and 25.00% in controls (Table 2). Though BER pathway genes are known to be associated with BC development but, when we compared to hOGG1Ser/Cys genotype we did not find significant association with BC risk.

(B) APE1 (Asp148 Glu) Codon 148 in exon-5

The amplification of APE1 codon 148 resulted in 147 bp. The PCR amplified products upon treatment with BfaI yielded wild-type (2197T) alleles of 144 and 20bp fragments, and the polymorphic (G) allele produces 164 bp. The frequency of *APE1TT* homozygotes was 42.95% in cases and 66.00% in controls whereas the frequency of *APE1GG* allele was significantly lower in the controls (08.50%) than in the cases (26.47%). The frequency of *APE1T/G* heterozygotes was 30.58% in cases and 25.50% in controls (Table 2). The Glu allelic frequency of 2197 was higher in the breast cancer patients than that in the control group (OR=4.78; 95% CI= (2.55-8.95); *p*= <0.0001) (Table 2) which indicate strong association of variant allele of APE1 with BC development.

Table 3: Genotype Frequencies of hOGG1 and APE1 gene Polymorphism in Breast Cancer Cases with ER/PR status

Gene	Genotype	ER/PR +ve N=102	ER/PR-ve N=68	Odds' Ratio	95% CI	χ^2	P-value
hOGG1 (C1245G) Ser326Cys cd326 Exon7	Ser/Ser	53 (0.52)	32 (0.47)	1			
	Ser/Cys	36 (0.35)	23 (0.34)	0.94	0.44-1.87	0.16	0.87
	Cys/Cys	13 (0.13)	13 (0.19)	0.60	0.24-1.46	1.11	0.26
	Ser/Cys+Cys/Cys	49 (0.48)	36 (0.53)	0.82	0.44-1.57	0.62	0.53
APE1 (T2197G) Asp148Glu cd 148 Exon5	Asp/Asp	45 (0.44)	30 (0.44)	1			
	Asp/Glu	34 (0.33)	20 (0.29)	1.13	0.55-2.32	0.34	0.73
	Glu/Glu	23 (0.23)	18 (0.27)	0.85	0.39-1.84	0.40	0.68
	Asp/Glu+ lu/Glu	57 (0.56)	38 (0.56)	1.00	0.53-1.85	0.00	1.00

(C) Effect of ER/PR Status on the Association of hOGG1 Ser326Cys & APE1 Asp148Glu with Breast Cancer.

The association of breast cancer risk with the hOGG1 Ser326Cys and APE1 Asp148Glu variants based on the Estrogen Receptor (ER) status of the cancer patients was also investigated. The genotype distribution in the ER/PR+ve (n=102) and ER/PR-ve (n=68) was independently compared (Table 3). Neither hOGG1 nor *APE1* variants showed risk in ER/PR+ve and ER/PR-ve breast cancer patients.

(D) Effect of Age at 1st delivery on the Association of hOGG1 Ser326Cys & APE1 Asp148Glu with Breast Cancer.

To examine the association of the polymorphisms with the median age at the time of breast cancer diagnosis, we stratified the patients according to the age (Table 1) as ⩽ 50 (n=95) or >50 (n=75) years and compared them with age-matched controls. The analyses showed association of GG allele of hOGG1 at codon 326 of exon7 (OR= 2.08; 95% CI= (1.24-3.54, p=<0.005) and GG allele of APE1 at codon 148 of exon 5 (OR= 2.04; 95% CI= (1.20-3.46), p=<0.05) with breast cancer risk in women at or below 50 years of age (Table 4). It was earlier reported that hOGG1 and APE1 were associated with breast cancer development in relation to early age of delivery however, when we compared hOGG1 codon 326 and *APE1* codon 148 in this concern, only APE1 variant (OR=2.0; 95% CI= (1.11-3.59), p= <0.01) showed increased risk of breast cancer in patients with delivery age group below 15-20 years higher risk (Table 4).

Table 4: Stratification Analysis of the Demographic Factors including Age, Tobacco Smoking, Age at First Delivery and Distribution of Genotypes of the hOGG1 and APE1 Genes in the Patients with Breast Cancer and the Control Group from Population of Maharashtra

		Demographic Factors							
Gene	**Genotype**	**Age (Cases/Control)**		**Tobacco status (Cases/Control)**		**Age @ 1st Delivery (Cases/Control)**			
		⩽ 50 N=95/149	**> 50 N=75/51**	**Tobacco Users N=94/74**	**Tobacco nonusers N=76/126**	**15-20 N= 126/74**	**21-25 N= 37/114**	**26-30 N= 6/9**	**31-35 N= 1/3**
hOGG1 (C1245G) Ser326Cys cd326 Exon7	Ser/Ser	44/96	40/29	49/49	35/78	62/40	19/73	3/7	1/1
	Ser/Cys+ Cys/Cys	51/53	35/22	45/25	41/48	64/34	18/41	3/2	0/2
	OR (95% CI)	2.08 (1.24-3.54)	1.15 (0.56-2.36)	1.80 (0.95-3.37)	1.90 (1.06-3.38)	1.21 (0.68-2.15)	1.68 (0.79-3.56)	3.50 (0.37-32.97)	0.20 (0.004-8.82)
	P value	0.005	0.69	0.06	0.02	0.50	0.17	0.27	0.40
APE1 (T2197G) Asp148Glu cd 148 Exon5	Asp/Asp	46/98	29/33	36/51	41/81	55/45	16/75	1/7	1/1
	Asp/Glu+ Glu/Glu	49/51	46/18	58/23	35/45	71/29	21/39	5/2	0/2
	OR (95% CI)	2.04 (1.20-3.46)	2.90 (1.38-6.08)	3.57 (1.87-6.80)	1.53 (0.86-2.74)	2.00 (1.11-3.59)	2.52 (1.18-5.37)	17.50 (1.22-250.3)	0.20 (0.004-8.82)
	P value	**0.007**	0.004	**0.0001**	0.14	**0.01**	0.01	0.03	0.40

Discussion:

In this case-control study we investigated the relationship between newly reported genotype polymorphisms of DNA repair genes especially involved in BER pathway and the elevated risk for BC mainly from the rural areas of Maharashtra. To evaluate the association of hOGG1, APE1 variants and risk of BC, crude and adjusted ORs and their 95% CIs were calculated using both homozygous genotypes or combined with their respective heterozygous genotypes. Comparable wild type genotype frequencies of hOGG1 codon 326 showed wide distribution in the Maharashtrian population in controls as well as BC cases. Also, when we investigated the relationship between the polymorphisms of APE1 and the risk of breast cancer in a Maharashtrian population, we found association between the APE1 codon 148 at Asp148Glu polymorphism and breast cancer. The results showed that Asp148Glu variation may increase the risk of breast cancer by approximately 3.5-fold in Maharashtrian patients (OR=4.78; 95% CI= (2.55-8.95); p= <0.0001). Furthermore,

the results also indicate that the Asp148Glu polymorphism was associated with increased risk of breast cancer among subgroups of older subjects (>50 years), in ER positive group as well as ER negative group. It is possible that the older individuals who showed higher risk with breast cancer were more likely due to aging rather than direct genetic effects. It is more plausible that alteration in the *APE1* gene may be more influential in early onset of breast cancer however, such an association was not observed in our younger group of patients (age ⩽ 50 years) probably due to small sample size. This is the first report that deals with the APE1 variation Asp148Glu which significantly contributes to breast cancer susceptibility in females and suggests the importance of APE1 in breast carcinogenesis.

The polymorphism in DNA repair genes has been extensively investigated for its associations with cancer risk and the results were conflicting in different types of cancer or different populations. Several epidemiological studies have investigated the association between genetic polymorphisms in hOGG1, APE1 and susceptibility to several kinds of cancers including lung [22], esophageal [23] stomach [24] prostate [25], breast cancers [18] among different ethnic groups including Brazilians, Japanese and Chinese populations. Very recently a meta-analysis study showed association of an important risk factor, hOGG1 Ser326Cys polymorphism and breast cancer in Asian women [26]. We have also reported earlier that hOGG1 polymorphisms could be associated to head and neck cancer development in the south-western Maharashtra [27]. Some recent meta-analysis studies [28] suggest that Asian populations are at higher risk of developing cancer than the non-Asian populations with APE1 Asp148Glu variant. In relation to this observation our results also confirmed that the Glu residue at position 148 of the APE1 confers significant risk of breast cancer in Maharashtrian females. Very few studies from India have reported the genetic polymorphisms in the DNA repair genes, hOGG1 and APE1 with respect to a variety of cancer risks including gastric [29], gallbladder [30] prostate cancers [12]. These previous observations suggest that hOGG1Ser326Cys, APE1Asp148Gln polymorphisms may or may not influence different cancer susceptibility in different populations with varied incidence of cancer, whereas, few other studies failed to find positive evidence for hOGG1 polymorphisms in breast carcinoma risk. On the other hand, inadequate information is available on the association of polymorphisms of DNA repair genes including hOGG1, APE1 genes and their susceptibility to breast cancer from rural population of Maharashtra where the rate of BC is high. Therefore in this study, we investigated the relationship between the development of breast cancer and genetic polymorphisms in hOGG1 and APE1 genes with from a pool of unexplored Maharashtrian population.

Conclusion:

In conclusion, to our knowledge this study is the first one to show that APE1 *T2197G* at codon 148 polymorphism could be associated with susceptibility to breast cancer in Western Maharashtrian women.

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