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# POLYMORPHISMS IN APE1 AND HOGG1 DNA REPAIR GENES AND RISK OF CERVICAL CANCER IN MAHARASHTRIAN WOMEN: A HOSPITAL BASED CASE-CONTROL STUDY

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## ABSTRACT

**Background:** Cervical cancer is a major concern of health risk in urban and rural parts of India. Maharashtrian population is not subjected to investigate cervical cancer susceptibility in association with genetic determinants as risk factor to cause cervical cancer. This study was aimed to find out frequency of polymorphisms in DNA repair genes including Apurinic/apyrimidinic endonuclease 1 (APE1) and 8-oxoguanine DNA glycosylase 1 (OGG1) gene in patients of cervical cancer from Maharashtra, and to evaluate their association with risk of cervical cancer. **Methods:** We used polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) to examine gene polymorphisms in 350 patients with cancer of cervix and 400 age and sex matched normal controls. **Results:** The results obtained indicated that there was no significant difference in the genotype distribution between cervical cancer patients and controls for APE1 Asp148Glu allele of codon 148 in exon 5. The result showed that genotype frequencies of hOGG1 Ser326Cys of codon 326 in exon 7 (OR=5.40; 95% CI= (3.78-7.73); *p*= <0.0001) were increased significantly. **Conclusion:** This study indicates that polymorphisms and haplotypes in hOGG1 gene appear to influence genetic susceptibility of individual to cervical cancer in Maharashtrian patients.

**KEYWORDS:** Cervical cancer**,** Genetic polymorphism, APE1, hOGG1, PCR-RFLP.

## INTRODUCTION

Cervical cancer (CC) is one of the most common and well known reasons for cancer causing death in women worldwide. In developing countries, the highest incidence rates of CC are observed in Africa, South, Central and Southeast Asia (Jemal et al., 2011). India has highest burden of CC where approximately 1, 34,420 women are diagnosed with the disease every year, and of them 72,825 deaths accounting for nearly one-fifth of the global CC burden alone (Shreedevi et al., 2015). Over the last few years, it is universally accepted that along with the tobacco and alcohol habits, the etiological factors involved in cervical carcinogenesis are either reproductive factors, sexual habits, early age of intercourse, multiple sex partners, infection with high risk Human Papilomavirus (HPV), other sexually transmitted diseases, co-infection with Human Immunodeficiency Virus (HIV) or nutritional diet, use of oral contraceptives and low socioeconomic status (HPV-ICMR 2012). Maharashtra is known for development of cervical cancer with association of increasing age, low education level, early age of first sexual intercourse (Sauvaget et al., 2011). Sometimes apart from those mentioned etiologic factors, development of CC is associated with individual's genetic framework. Identification of such genetic determinants associated with CC may help to identify mechanisms underlying behind carcinogenesis.

DNA repair genes are the major components in DNA repair system which help in restoration altered DNA structure by means of different mechanisms. Sometimes, genetic alterations in DNA repair genes can modulate DNA repair capacity which may be lead to cancer risk. Among DNA repair genes, base excision repair (BER) mechanism is suggested to be a key repair pathway in maintaining genome stability and integrity. Therefore, it is also suggested to be a major determinant of cancer risk, as it is involved in repair of numerous lesions and strand breaks of DNA caused by endogenous and exogenous mutagens. Apurinic/apyrimidinic endonuclease 1 (APE1) is an essential enzyme in the BER pathway, which plays an important role in repairing DNA damage caused by oxidation and alkylation. The 8-

oxoguanine DNA glycosylase 1 (hOGG1) gene also plays a critical role in the BER pathway. The genetic polymorphisms in APE1 and hOGG1 plays crucial role in carcinogenesis have been identified in several studies (Canbay et al., 2010, Canbay et al., 2011, Xue et al., 2013). The most frequently studied polymorphism in hOGG1 gene is in exon 7, where amino acid substitution, from serine to cysteine at codon 326 ($Ser^{326}Cys$, rs1052133) has been proposed to alter hOGG1 function and increase cancer susceptibility in breast, colon and gastric cancers (Romanowicz-Makowska et al., 2008 Arizono et al., 2008, Sun et al., 2010). Similarly, DNA repair gene APE1 Asp148Glu (rs1130409) variants in codon 148 of exon 5 are the most common and extensively studied polymorphisms associated with risk of breast cancer (Luo et al., 2014, AlMutairi et al., 2015). Few studies from India also showed the positive correlation of genetic variations in APE1 and hOGG1 genes with development of variety of cancers (Srivastava et al., 2009, Gangwar et al., 2009, Srivastava et al., 2010).

To the best of our knowledge, though many studies have assessed the association between APE1 Asp148Glu and hOGG1 Ser326Cys polymorphism, the interpretations of numerous studies on the association of APE1 and hOGG1 polymorphisms to the cancer risk remain conflicting and contradictory (Malik et al., 2010, Upadhyay et al., 2010, Li et al., 2011, Mittal et al., 2012). Based on literature, when we considered cervical carcinogenesis, hardly any of the studies reported positive association of polymorphisms in those reported BER genes with cervical carcinogenesis all around the world (Shekari et al., 2008, Wang et al., 2013) while other remain inconclusive (Niwa et al., 2005). Also there are no published evidences on the association between those DNA repair genes and cancer of cervix in Maharashtrian population. Therefore, we hypothesized that the polymorphic alleles APE1 148Glu and hOGG1 326Cys may be associated with the risk of CC, and so we performed a case-control study to investigate the combined effect of genetic polymorphisms of each of these genes on the risk of CC in Maharashtrian women subjects. Thus, this is the first study that investigates polymorphism in APE1 Asp148Glu and hOGG1 Ser326Cys and their association with cervical cancer risk in rural population of south-western Maharashtra.

## MATERIALS AND METHODS

### Study subjects

This study was a hospital based case-control study. In this study, study subjects included 350 newly diagnosed CC patients and 400 healthy, cancer free, age matched females as controls. All cases ranged in age from 20-80 years (Mean ± SD) (48.67 ±13.78) were recruited immediately after being diagnosed during the year 2014-2017. 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 "Deemed to be University" from South-Western Maharashtra of India.

### Selection of cases and controls

Incidence cases of CC were identified using colposcopy at Department of Obstetrics and Gynecology of the Krishna Hospital & Medical Research Centre (KH&MRC) and cell cytology at Department of Pathology of Krishna Institute of Medical Sciences. Controls were randomly selected from a group of women visiting to KH&MRC for blood donation and other purposes.

### Inclusion & Exclusion criteria

Relatives of cases or had a prior history of cancer were excluded from the study. All 100 percent cases and controls agreed to provide a blood sample included in this study.

### Genomic DNA isolation from whole blood

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

### Genotyping assays

Genotyping of APE1 and hOGG1 genes were performed by PCR-RFLP methods with appropriate primer sets. The primers were designed to amplify the regions of DNA that contain polymorphic sites of interest: (A)APE1 Asp148Glu of codon 148 in the exon-5 (SNP rs1130409) and (B) hOGG1 Ser326Cys of codon 326 in the exon 7 (SNP rs1052133). The primers selected to amplify the specific SNPs of interest were; Sense primer 5´-CTG TTT CAT TTC TAT AGG CTA-3´; Antisense primer 5´-AGG AAC TTG CGA AAG GCT TC-3´ for APE1 and Sense primer 5′-CTG TTC AGT GCC GAC CTG CGC CGA-3′; Antisense primer 5′-ATC TTG TTG TGC AAA CTG AC-3′ for hOGG1 gene. The PCR amplifications were performed in separate reactions of 20 micro liter (µL) reaction volumes containing 200 nanogram of genomic DNA, 10 picomoles of each above mentioned primers, 200 micro molar each dNTPs, 10 mili molar (mM) Tris-HCl (pH 9.0), 50 mM KCl 1.5 mM MgCl2 and 1 unit of Taq DNA polymerase (GeNei, Merck Biosciences). The reaction mixtures were subjected to PCR amplification with different PCR conditios in a Master Cycler Gradient PCR. The PCR cycle conditions for amplification of APE1 codon 148 of 164 bp (Initial denaturation at $95^0$C- 5 minutes, 35 cycles of $95^0$C- 20 sec, $55^0$C- 20 sec, $72^0$C- 20 sec and final extension at $72^0$C- 10 min) and hOGG1 codon 326 of 247 bp, (Initial denaturation at $95^0$C- 5 min, 35 cycles of $95^0$C- 30 sec, $64^0$C- 30 sec, $72^0$C- 30 sec and final extension at $72^0$C- 10 min). After PCR amplification, the PCR products were confirmed by agarose gel electrophoresis followed by restriction digestion of each PCR products with appropriate restriction enzymes with

specific conditions. 1 unit of BfaI and MboII were used for digestion of PCR products of APE1 and hOGG1 codons 148 and 326 respectively. The results of restriction digestion were analyzed by 2.0% agarose gel electrophoresis at 100 V for 30 min, stained with ethidium bromide and photographed with gel documentation system (BioRad Laboratories).

**Statistical analysis**

The association between the APE1, hOGG1 genotypes and risk of CC development were studied using odds ratio (OR). Both univariate and multivariate logistic regression analyses were employed to calculate the adjusted ORs and 95% confidence intervals (CIs) with adjustment of variables to determine the CC risk associated with genotypes. For each polymorphism the $\chi 2$ test was used to evaluate differences in the frequency distribution of selected demographic variables and the frequencies of allele and genotype of the polymorphisms between CC cases and the controls.

**Ethics and Biosafety**

The study protocol was approved by Institutional Ethics and Biosafety Committee of Krishna Institute of Medical Sciences "Deemed to be University" for the use of human subjects in research.

## RESULTS

**Characteristics of the subjects**

Total of 350 women cases with CC and 400 controls were selected to match these cases were assessed during this study. The mean ± SD age of cases and controls was 48.67 ± 13.78 (median: 50, range 25-75) and controls 46.37 ± 13.90 (median: 33.5 range 24-75) years respectively. The overall demographical details with characteristics of the study population including both CC cases and healthy controls were summarized in Table-I.

**Table I: Distribution comparisons of selected demographic characteristics of cervical cancer cases and healthy controls from rural areas of Maharashtra in India.**

| Variable | Cases N=350 | | Controls N=400 | | *P*-Value based on $\chi 2$ |
|---|---|---|---|---|---|
| **Age** (Mean ± SD) years | 48.67 ±13.78 | | 46.37 ± 13.90 | | <0.03 |
| | No. | (%) | No. | (%) | |
| ≤ 50 | 215 | 61.40 | 284 | 71.00 | |
| 51-60 | 59 | 16.90 | 69 | 17.20 | |
| 61-70 | 57 | 16.30 | 34 | 08.50 | |
| >70 | 19 | 05.40 | 13 | 03.20 | |
| **Tobacco smoking Status** | | | | | **<0.001** |
| Tobacco users | 189 | 54.00 | 113 | 28.20 | |
| Tobacco no users | 161 | 46.00 | 287 | 71.80 | |
| **Age @ Ist Pregnancy(Yrs)** | | | | | **<0.001** |
| 15-20 | 276 | 78.90 | 181 | 45.25 | |
| 21-25 | 73 | 20.90 | 178 | 44.50 | |
| 26-30 | 00 | 0.00 | 36 | 09.00 | |
| 31-35 | 01 | 0.20 | 05 | 01.25 | |
| **Diet** | | | | | 0.59 |
| Vegetarian | 97 | 27.70 | 118 | 29.50 | |
| Mixed | 253 | 72.30 | 282 | 70.50 | |
| **Education** | | | | | 0.001 |
| High School | 139 | 39.71 | 108 | 27.00 | |
| High School graduate (12 y) | 24 | 06.86 | 49 | 12.25 | |
| College /Graduate | 43 | 12.29 | 129 | 32.25 | |
| No School | 144 | 41.14 | 114 | 28.50 | |
| **Economic status** | | | | | 0.001 |
| Rich | 55 | 15.71 | 107 | 26.75 | |
| Middle | 97 | 27.71 | 161 | 40.25 | |
| Poor | 198 | 56.58 | 132 | 33.00 | |
| **Family history of Cancer** | | | | | |
| Yes | 62 | 17.71 | 10 | 02.50 | 0.001 |
| No | 288 | 82.29 | 390 | 97.50 | |

**Analysis of association of Asp148Glu in APE1 and Ser326Cysin hOGG1 genotype polymorphism with cervical cancer risk**

We determined the frequency of polymorphisms in APE1 and hOGG1 genes implicated in DNA repair in CC patients and matched controls in order to evaluate their association with the risk of CC. The distribution of the polymorphism Asp148Glu of codon 148 in APE1 and Ser326Cys of codon 326 in exon 7 of hOGG1 genes and concordance of the cases and controls are presented

in table-II. We carried out an allelic association analysis for *rs1130409* SNP of APE1 and *rs1052133* SNP *of hOGG1* where we found that hOGG1 Ser326Cys was significantly associated with risk of CC. When we studied substitution polymorphism, we found the frequency of APE1 2197TT wild type alleles at codon 148 of exon 5 was 80.86%, 2197TG heterozygote alleles was 13.14 whereas 22197GG homozygous variant allele was 6.00 in the studied cases where as that of the frequencies for the controls were 68.25, 21.25 and 10.50 for wild, heterozygous and homozygous variant type alleles. The logistic regression analysis revealed that GG homozygous allele (OR: 0.48, 95% CI: 0.27-0.83 $p$<0.009) and heterozygote TG allele (OR: 0.52, 95% CI: 0.35-0.77 $p$<0.001) of Asp148Glu at exon 5 of APE1 had negative association with CC risk. In contrast when we studied hOGG1 polymorphism in *rs1052133* SNP, we found strong association of variant allele 1245GG with cervical cancer development (OR: 5.40 95% CI: (3.78-7.73; $p$<0.0001). The frequency of hOGG1 1245CC wild type alleles at codon 326 of exon 7 was 19.71%, 1245CG heterozygote alleles was 21.71% and for 1245GG homozygous variant alleles was 58.58% in the cases where that of the frequencies for the controls were 50.50, 21.75 and 27.75% respectively. Women carrying the hOGG1 Ser326Cys variant (GG) genotype showed strong association with risk for cervical cancer (OR = 5.40, 95% CI = 3.78–7.73 $p$<0.0001 for GG allele and (OR = 2.55, 95% CI = 1.69–3.85 $p$<0.0001 for CG allele.

**Table II: The genotype frequencies of *APE1 & hOGG1* gene variants in untreated CC patients and controls.**

| GENE | Genotype | CASES (n= 350) (%) | CONTROL (n = 400) (%) | Odds' Ratio (OR) (95% CI) | *P* value | Adjusted Odds Ratio (95% CI) | *P* value |
|---|---|---|---|---|---|---|---|
| ***APE1 T2197G Asp148Glu codon 148 Exon 5 rs1130409*** | Asp/Asp | 283 (80.86) | 273 (68.25) | 1 | | 1 | |
| | Asp/Glu | 46 (13.14) | 85 (21.25) | 0.52 (0.35-0.77) | 0.001 | 0.56 (0.36-0.85) | 0.007 |
| | Glu/Glu | 21 (06.00) | 42(10.50) | 0.48 (0.27-0.83) | 0.009 | 0.59 (0.33-1.06) | 0.08 |
| | Asp/Glu+ Glu/Glu | 67 (19.14) | 127 (31.75) | 0.50 (0.36-0.71) | 0.0001 | 0.54 (0.38-0.77) | 0.001 |
| ***hOGG1 C1245G Ser326Cys Codon 326 Exon 7 rs1052133*** | Ser/Ser | 69 (19.71) | 202 (50.50) | 1 | | 1 | |
| | Ser/Cys | 76 (21.71) | 87 (21.75) | 2.55 (1.69-3.85) | **0. 0001*** | 2.57 (1.7-3.90) | 0.0001 |
| | Cys/Cys | 205 (58.58) | 111 (27.75) | **5.40 (3.78-7.73)** | **<0.0001*** | 5.19 (3.62-7.45) | **<0.0001*** |
| | Ser/Cys+ Cys/Cys | 281 (80.29) | 198 (49.50) | 4.15 (2.99-5.77) | **<0.0001*** | 4.05 (2.91-5.77) | **<0.0001*** |

*: Indicates significant Odds Ratio (p<0.05)
$p$ value determined based on $\chi 2$

**Effect of age of cancer occurrence, tobacco status and age at I$^{st}$ pregnancy on the association of APE1 and hOGG1 with cervical cancer risk**

The genotype distributions of the selected APE1 and hOGG1 gene polymorphisms in cases and controls and their associations with CC risk are summarized in Table III. Variables including age, nutrition, tobacco chewing and smoking and age at first pregnancy were adjusted for in the subsequent multivariate logistic regression analyses. The logistic regression analysis showed that none of the SNPs other than *rs1052133* was associated with CC risk in homozygotes or heterozygotes after being adjusted for age, tobacco smoking status and the earlier age at first pregnancy. When we compared CC genotype of *rs1052133* with CG/GG genotypes showed increased association with CC risk after adjustment with age (OR =4.82, 95% CI =2.70–8.81, $P$<0.0001), tobacco status (OR =3.61, 95% CI =3.21–7.17, $P$<0.0001) and early age at first pregnancy (OR =5.12, 95% CI =3.35–7.97, $P$<0.0001). To examine the association of the polymorphisms with the median age at the time of CC diagnosis, we stratified the patients according to the age (Table 1) as ≤ 50 (n= 215) or >50 (n = 135) years and compared them with age-matched controls. However, when we compared APE1 codon 148 in relation with age below 50 years we found negative association with CC development (OR =0.57, 95% CI = 0.37-0.87, $P$<0.009 ). When we compared age for the first pregnancy, only APE1 148 variant (OR=0.47; 95% CI= (0.30-0.74), $p$ <0.001) showed negative risk of CC in patients with pregnancy age group below 15-20 years higher risk (Table-3).

**Table III: Stratification analysis of the demographic factors including age of cancer occurence, tobacco chewing status, age at first pregnancy and distribution of genotypes of the APE1 and hOGG1 genes in the patients with CC and the control group from population of Maharashtra.**

| Gene | Genotype | Demographic Factors | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Age (Cases/Control) | | Tobacco status (Cases/Control) | | Age @ 1st pregnancy Cases/Control | | | |
| | | ≤ 50 N=216/286 | > 50 N=134/114 | Users N=189/113 | Non-Users N=161/287 | 15-20 N=277/183 | 21-25 N=72/178 | 26-30 N=0/34 | 31-35 N=1/5 |
| ***APE1 T2197G Asp148Glu codon 148 Exon-5 rs1130409*** | Asp/Asp | 174/201 | 109/72 | 152/69 | 131/204 | 232/130 | 50/117 | 0/23 | 1/3 |
| | Asp/Glu+ Glu/Glu | 42/85 | 25/42 | 37/44 | 30/83 | 45/53 | 22/61 | 0/11 | 0/2 |
| | OR (95% CI) | 0.57 (0.37-0.87) | 0.39 (0.22-0.70) | 0.38 (0.22-0.64) | 0.56 (0.93-2.50) | 0.47 (0.30-0.74) | 0.84 (0.46-1.52) | 2.04 (0.03-109.5) | 0.46 (0.01-16.88) |
| | P value | 0.009 | 0.001 | 0.003 | 0.0.09 | 0.001 | 0.58 | 0.72 | 0.67 |
| ***hOGG1 C1245G Ser326Cys Codon326 Exon-7 Rs1052133*** | Ser/Ser | 46/145 | 23/57 | 34/50 | 35/152 | 50/97 | 19/78 | 0/25 | 0/2 |
| | Ser/Cys+ Cys/Cys | 170/141 | 111/57 | 155/63 | 126/135 | 227/86 | 53/100 | 0/9 | 1/3 |
| | OR (95% CI) | 3.80 (2.54-5.66) | 4.82 (2.70-8.61) | 3.61 (3.21-7.17) | 4.05 (2.60-6.29) | 5.12 (3.35-7.97) | 2.17 (1.19-8.18) | 2.68 (0.04-145.1) | 2.14 (0.05-77.54) |
| | P value | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.01 | 0.62 | 0.67 |

## DISCUSSION

In this hospital based case-control study, to evaluate the association of polymorphisms in BER pathway genes especially APE1 and hOGG1 with cervical cancer risk, crude and adjusted odds ratio and their 95% confidential intervals were calculated using both homozygous genotypes or combined with their respective heterozygous genotypes. When we investigated and compared the polymorphisms of APE1 and hOGG1 and their association with development of CC in Maharashtrian women, we found hOGG1 Cystine variant allele associated with risk of CC. Also, when we investigated the relationship between the polymorphisms of APE1 and the risk of CC in a Maharashtrian population, we found negative association between the APE1 codon 148 at Asp148Glu polymorphism and CC. Furthermore, the results also indicate that the Ser326Cys polymorphism was associated with increased risk of cervical cancer among subgroups of older subjects (>50 years). It is possible that the older individuals who showed higher risk association with cervical cancer were more likely due to aging rather than direct genetic effects. It is more plausible that alteration in the hOGG1 gene may be more influential in early onset of cervical 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 hOGG1 variation Ser326Cys which significantly contributes to cervical cancer susceptibility in females and suggests the importance of hOGG1 in cervical 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 APE1, hOGG1 and susceptibility to several kinds of cancers including prostate (Zang et al., 2010), bladder (Gangwar et al., 2008), gall bladder, (Shrivastava 2009) gastric, (Canbey et al., 2010) and breast cancers **[**Romanowicz-Makowska et al 2008**]** among different populations. Very few studies from India have reported the genetic polymorphisms in hOGG1 and APE1 genes with respect to a variety of cancer risks including gastric (Malik et al., 2010), gallbladder (Shrivastava et al., 2010) prostate cancer (Mandal et al., 2012). These previous observations suggest that hOGG1 Ser326Cys, APE1 Asp148Gln polymorphisms may or may not influence different cancer susceptibility in different populations with varied incidence of cancer, but our earlier studies showed positive evidence for hOGG1 polymorphisms in oral cancer risk (Datkhile et al., 2016) and susceptibility women with breast cancer to polymorphism in APE1 Asp148Gln at codon 148 (Datkhile et al., 2017). However, there were no reports available on association of genetic polymorphisms of APE1 and hOGG1, genes and their susceptibility to cervical cancer from rural population of Maharashtra. Therefore in this study, we investigated the relationship between the development of CC and genetic polymorphisms in APE1 and hOGG1genes from a pool of unexplored Maharashtrian population and showed that hOGG1 gene may play a role in cervical carcinogenesis in Maharashtrian women.

## CONCLUSION

In conclusion, this study suggests that functional hOGG1 Ser 326 Cys polymorphism at codon 326 of exon 7 could play an important role in the development of CC in a western Maharashtrian women which may provide a deeper insight into the genetic determinants in cervical cancer risk in the rural unexplored population.

**Conflict of Interest**: None declared.

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**REFERENCES**


1. Jemal A, Bray F, Center MM, Ferlay F, Ward E, Forman D. Global cancer statistics. Ca Cancer J Clin, 2011; 61: 69-90.
2. Shreedevi A, et al. Epidemiology of cervical cancer with special focus on India. Int. J. Womens Health, 2015; 7: 405-414.
3. Human Papilloma Virus ICMR: High power Committee to Evaluate Performance of ICMR, 2012–2013. New Delhi, India: ICMR; 2014. Disease Specific Documents for XII plan.
4. Sauvaget C, Nene BM, Jayant K, Kelkar R, Malvi SG, Shastri SS, Sankaranarayanan R. Prevalence and determinants of high-risk human papillomavirus infection in middle-aged Indian women. Sex Transm Dis, 2011; 38(10): 902-906.
5. Canbay E, Agachan B, Gulluoglu M, Isbir T, Balik E, et al. Possible associations of APE1 polymorphism with susceptibility and HOGG1 polymorphism with prognosis in gastric cancer. Anticancer Res, 2010; 30: 1359–1364.
6. Canbay E, Cakmakoglu B, Zeybek U, Sozen S, Cacina C, et al. Association of APE1 and hOGG1 polymorphisms with colorectal cancer risk in a Turkish population. Curr Med Res Opin, 2011; 27: 1295–1302.
7. Xue X, Yin Z, Lu Y, Zhang H, Yan Y, et al. The Joint Effect of hOGG1, APE1, and ADPRT Polymorphisms and Cooking Oil Fumes on the Risk of Lung Adenocarcinoma in Chinese Non-Smoking Females. PLoS ONE, 2013; 8(8): e71157. doi:10.1371/journal.pone.0071157.
8. Romanowicz-Makowska H, Smolarz B, Makowski M, Polac I, Pertynski T Ser326Cys polymorphism in DNA repair genes hOGG1 in breast cancer women. Pol J Pathol, 2008; 59: 201–204.
9. Arizono K, Osada Y, Kuroda Y. DNA repair gene hOGG1 codon 326 and XRCC1 codon 399 polymorphisms and bladder cancer risk in a Japanese population. Japan J Clin Oncol, 2008; 38: 186–91.
10. Sun LM, Shang Y, Zeng YM, Deng YY, Cheng JF. HOGG1 polymorphism in atrophic gastritis and gastric cancer after Helicobacter pylori eradication. World J Gastroenterol, 2010; 16: 4476–4482.
11. Luo H, Li Z, Qing Y, Zhang SH, Peng Y, Li Q, Wang D. Single Nucleotide Polymorphisms of DNA Base-excision Repair Genes (APE1, OGG1 and XRCC1) Associated with Breast Cancer Risk in a Chinese Population. Asian Pac J Cancer Prev, 2014; 15(3): 1133-1140.
12. AlMutairi F, Pathan AAK, Alanazi M, Sahalby M, Alabdlkarim HA, Alamri A et al., "Association of DNA Repair Gene APE1 Asp148Glu Polymorphism with Breast Cancer Risk," Disease Markers, vol. 2015, Article ID 869512, 10 pages, 2015. https://doi.org/10.1155/2015/869512.
13. Srivastava A, Srivastava K, Pandey SN, Choudhuri G, Mittal B. Single nucleotide polymorphisms of DNA repair genes OGG1 and XRCC1: association with gallbladder cancer in North Indian population. Ann Surg Oncol, 2009; 16: 1695–703.
14. Srivastava K, Srivastava A, Mittal B. Polymorphisms in ERCC2, MSH2, and OGG1 DNA repair genes and gallbladder cancer risk in a population of Northern India. Cancer, 2010; 116: 3160–3169.
15. Gangwar R, Ahirwar DK, Mandhani A, Mittal RD. Influence of *XPD* and *APE1* DNA Repair Gene Polymorphism on Bladder Cancer Susceptibility in North India. Urology, 2009; 73(3): 675-680.
16. Malik MA, Zargar SA, Mittal B. Lack of influence of DNA repair gene hOGG1 codon 326 polymorphisms of gastric cancer risk in the Kashmir valley. Asian Paccificb Journal of Cencer prevention, 2010; 11: 165-168.
17. Upadhyay R, Malik MA, Zargar SA, Mittal B. OGG1 Ser326Cys polymorphism and susceptibility to esophageal cancer in low and high at-risk populations of northern India. J Gastrointest Cancer, 2012; 41: 110–115.
18. Li Z, Guan W, Li MX et al. Genetic polymorphism of DNA base-excision repair genes (APE1, OGG1 and XRCC1) and their correlation with risk of lung cancer in a Chinese population," Archives of Medical Research, 2011; 42(3): 226–234.
19. Mittal RD, Mandal RK, and Gangwar R. Base excision repair pathway genes polymorphism in prostate and bladder cancer risk inNorth Indian population," Mechanisms of Ageing and Development, 2012; 133(4): 127–132.
20. Shekari M. Sobti RC, Tamandani DM, MalekZadeh K, Kaur P, Suri V. Association of genetic polymorphism of the DNA base excision repair gene (*APE-1 Asp/148 Glu*) and HPV type (16/18) with the risk of cervix cancer in north Indian population. Cancer Biomarker, 2008; 4: 63-71.
21. Wang M, Chu H, Wang S, Wang M, Wang W, Han S, et al. Genetic variant in APE1 gene promoter contributes to cervical cancer risk. Am J Obstet Gynecol, 2013; 209(4): 360.e1-7.
22. Niwa Y, Matsuo K, Ito H, Hirose K, Tajima K, Nakanishi T, Nawa A, Kuzuya K, Tamakoshi A, Hamajim N. Association of XRCC1 Arg399Gln and OGG1 Ser326Cys polymorphisms with the risk of cervical cancer in Japanese subjects. Gynecologic Oncology, 2005; 99: 43 – 49.
23. Zhang J, Dhakal IB, Greene G, Lang NP, Kadlubar FF. Polymorphisms in hOGG1 and XRCC1 and risk of prostate cancer: effects modified by plasma antioxidants. Urology, 2010; 75: 779–85.
24. Gangwar R, Ahirwar D, Mandhani A, Mittal RD. Do DNA repair genes OGG1, XRCC3 and XRCC7 have an impact on susceptibility to bladder cancer in the North Indian population? Mutat Res, 2009; 680: 56–63.
25. Mandal RK, Gangwar R, Kapur R, Mittal RD. Polymorphisms in base-excision & nucleotide-excision repair genes & prostate cancer risk in north

Indian population. Indian J Med Res, 2012; 135: 64-71.
26. Datkhile KD, Patil MN, Khamkar TS, Vhaval RD, Durgawale PP, Chougule PG, Gudur A, Kakade SV. Genetic polymorphisms in DNA repair genes (hOGG1 & APE1) and their association with oral cancer susceptibility in rural Indian population: A hospital based case-control study. Int J Med Sci Phy Heal, 2016; 6(1): 23-28.
27. Datkhile KD, Bhosale SJ, Patil MN, Durgawale PP, Kakade SV. Association of Genetic Variants in hOGG1 and APE1 Genes with Breast Cancer Risk in a Rural Population: A Hospital Based Case-Control Study. J Krish Inst Med Sci Uni, 2017; 6(4): 18-27.