# Genetic polymorphisms in key DNA repair genes and risk of head and neck cancer in a Chinese population

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**Abstract.** Although tobacco and alcohol consumption are the major risk factors of head and neck cancer (HNC), genetic variations of genes involved in several biological pathways, such as DNA repair genes, may affect an individual's susceptibility to HNC. However, few studies have investigated the associations between polymorphisms in DNA repair genes and HNC risk in the Chinese population. Thus, we genotyped five common, non-synonymous single-nucleotide polymorphisms (SNPs) [*APEX1* (Asp148Glu), *XRCC1* (Arg399Gln), *ADPRT* (Val762Ala), *XPD* (Lys751Gln) and *XPG* (His1104Asp)] in a hospital-based, case-control study of 397 HNC cases and 900 cancer-free controls in China. The results showed that none of the five SNPs in the DNA repair pathway was significantly associated with HNC risk, suggesting that these polymorphisms may not play a major role in HNC susceptibility in this Chinese population.

## Introduction

The incidence of head and neck cancer (HNC), especially squamous cell carcinoma of the head and neck (SCCHN), has markedly increased in the past 20 years and is now the fifth most common type of cancer worldwide (1). In the United States, it is estimated that there were 48,010 new cases and 11,260 deaths from SCCHN in 2010 (2). Accumulative evidence indicates that exposure to smoking and alcohol consumption are important risk factors of HNC (3); however, only few smokers and drinkers develop HNC, suggesting an individual susceptibility to this cancer in the general population. Most association studies on cancer susceptibility have focused on identifying effects of single-nucleotide polymorphisms (SNPs) in candidate genes of several pathways. Among these, genes involved in the DNA repair pathway are the most investigated due to their vital role in protecting the genome from insults of environmental carcinogens (4,5). Studies have shown inter-individual variations of DNA repair capacity (DRC) in the general population and the effect of a suboptimal DRC on the risk of smoking-related cancers, such as lung cancer and SCCHN (6-8).

Of DNA repair pathways, nucleotide excision repair (NER) is the major repair mechanism for the DNA damage caused by tobacco smoking, which deals with a wide class of DNA damages, including bulky adducts cross-links, oxidative DNA damage, thymidine dimers and alkylating damage (9). NER involves more than 20 proteins whose inactivation may lead to xeroderma pigmentosum (XP) or Cockayne syndrome (CS). For example, rare mutations in xeroderma pigmentosum complementation group D and G (*XPD* and *XPG*) give rise to a combined XP/CS phenotype and are associated with severe neurological abnormalities.

The base excision repair (BER) pathway is another important mechanism that repairs DNA damage resulting from chemical alterations of a single base; a number of proteins are involved in repair steps, such as apurinic/apyrimidinic endonuclease (APE1, also known as APEX1), X-ray repair crosscomplementing 1 (XRCC1) and ADP-ribosyltransferase (ADPRT, also known as PARP1) (10). APE1 is a key member in short-patch BER, which bridges the abasic sites of the damaged base by cleaving the DNA backbone at the 5' side to the abasic site and leaving a 3'-hydroxyl group and a 5'-deoxyribose phosphate group flanking the nucleotide gap (11). ADPRT plays a role in the long-patch BER by specifically binding to DNA strand breaks where it is autoactivated and recruits the XRCC1-Lig3α complex (12). Studies have shown that interactions of ADPRT with XRCC1 as well as other partner proteins, such as Polβ, are critical for stimulating and executing BER processes (13).

Several functional genetic variants, particularly non-synonymous polymorphisms, have been identified in the *XPD*, *XPG*, *APE1*, *XRCC1* and *ADPRT* genes, and have shown a relationship with DRC variation and susceptibility to multiple cancers (14-26). Additionally, several reviews were also published to summarize the associations between functional variants of DNA repair genes and cancer risk, including HNC, and have provided meaningful results (17,20,26). However,

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most published studies on HNC risk and polymorphisms of DNA repair genes were conducted in a Caucasian population, but not in a Chinese population. Therefore, we hypothesize that common, non-synonymous single-nucleotide polymorphisms (nsSNPs) of the above genes may also contribute to the risk of HNC in China. To test this hypothesis, we conducted a case-control study of 397 patients with HNC and 900 cancer-free controls among a Chinese population.

## Patients and methods

*Study population*. Our study was approved by the Institutional Review Board of Nanjing Medical University. All patients with histologically confirmed HNC were recruited from the Jiangsu Stomatological Hospital and the First Affiliated Hospital of Nanjing Medical University, China, from January 2009 to June 2011. Subjects with second HNC primary tumors or metastasized cancer from other organs were excluded from our study. Cancer-free controls were recruited from a cohort of >30,000 participants in a community-based screening program for non-infectious diseases in the Jiangsu Province, China and frequency-matched to the cases according to age (±5 years) and gender. All subjects were genetically unrelated ethnic Han Chinese. All subjects were personally interviewed to collect demographic data (e.g., age and gender) and exposure information (e.g., smoking and drinking status). Each patient donated 5 ml of venous blood after providing a written informed consent. Of all subjects, 397 patients and 900 controls with adequate DNA samples were selected for TaqMan genotyping assay.

*SNP selection and genotyping*. According to the published literature and dbSNP database, we selected five common nsSNPs with minor allele frequency of >0.05 in Chinese Han in Beijing (CHB) [*XPD* Lys751Gln (rs13181), *XPG* His1104Asp (rs17655), *APE1* Asp148Glu (rs1130409), *XRCC1* Arg399Gln (rs25487) and *ADPRT* Val762Ala (rs1136410)] for genotyping, which have been most investigated for their associations with cancer risk in molecular epidemiological studies. Genomic DNA was extracted from the peripheral blood by the standard methods. Genotyping was carried out using the TaqMan allelic discrimination assay on an ABI 7900 system (Applied Biosystems, Foster City, CA, USA). Briefly, PCR primers and Taqman minor groove binder probes were designed and reactions were performed in 384-well microplates with ABI 9700 thermal cyclers (Applied Biosystems). The genotyping results were determined by System SDS software version 2.3. The accordance achieved 100% for the duplicates of 5% of the samples.

*Statistical analysis*. Differences in selected demographic variables, smoking status and drinking status between the cases and controls were evaluated using the Chi-square test. The associations between genotypes of selected polymorphisms and HNC risk were estimated by computing the odds ratios (ORs) and 95% confidence intervals (95% CIs) from both univariate and multivariate logistic regression analyses with adjustment for age, gender, smoking status and drinking status. Homogeneity tests were performed to evaluate the differences in stratum variable-related ORs. All statistical analyses were performed with Statistical Analysis System software (version 9.1.3; SAS Institute Inc., Cary, NC, USA). The significance was established at P<0.05 with a two-side test.

Table I. Distribution of selected variables in HNC cases and cancer-free controls.

| Variables | Cases | | Controls | | P-value[a] |
|---|---|---|---|---|---|
| | No. | % | No. | % | |
| All subjects | 397 | 100 | 900 | 100 | |
| Age (years) | | | | | |
| ≤60 (median) | 209 | 52.6 | 461 | 51.2 | 0.637 |
| >60 (median) | 188 | 47.4 | 439 | 48.8 | |
| Gender | | | | | |
| Female | 136 | 34.3 | 280 | 31.1 | 0.263 |
| Male | 261 | 65.7 | 620 | 68.9 | |
| Smoking status[b] | | | | | |
| No | 212 | 53.7 | 498 | 55.3 | 0.580 |
| Yes | 183 | 46.3 | 402 | 44.7 | |
| Drinking status[b] | | | | | |
| No | 217 | 54.9 | 609 | 67.7 | <0.001 |
| Yes | 178 | 45.1 | 291 | 32.3 | |
| Tumor site | | | | | |
| Oral cavity | 293 | 73.8 | | | |
| Oropharynx | 6 | 1.5 | | | |
| Larynx | 88 | 22.2 | | | |
| Other[c] | 10 | 2.5 | | | |
| Histology | | | | | |
| Squamous | 335 | 84.4 | | | |
| Other[d] | 62 | 15.6 | | | |

[a]Two-sided Chi-square test. [b]Smoking and drinking information was not available for two subjects. [c]Including nasal sinuses, parotid and salivary gland. [d]Including adenocarcinoma, undifferentiated carcinoma and undetermined cancer.

## Results

As shown in Table I, there were no significant differences in the distributions of age and gender between the cases and the controls (P=0.637 and 0.263, respectively), suggesting that the matching for age and gender was satisfactory. Additionally, the difference in smoking status was also non-significant (P=0.580); however, the proportion of drinkers in the cases was significantly higher than that in the controls (45.1 vs. 32.3%, P<0.001). Of the 397 cases, 293 (73.8%) suffered from tumors of the oral cavity, 6 (1.5%) had oropharynx tumors, 88 (22.2%) had larynx tumors and 10 (2.5%) had tumors at other sites. Furthermore, 335 cases (84.4%) presented with squamous cell carcinoma.

The position, minor allele frequency (MAF) and P-values for genotype distributions of the five SNPs in the HapMap database are presented in Table II. The observed genotype frequencies for these five SNPs were all in Hardy-Weinberg equilibrium in the controls (all P>0.05). The single locus analyses revealed that none of the single SNPs were

Table II. Primary information of selected SNPs in DNA repair genes.

| SNP | Gene | Location | Base change | MAF in CHB (HapMap) | MAF in our controls | P-value[a] |
|---|---|---|---|---|---|---|
| rs13181 | *ERCC2/XPD* | chr19 | T>G, Lys751Gln | 0.101 | 0.079 | 0.817 |
| rs17655 | *ERCC5/XPG* | chr13 | G>C, Asp1104His | 0.444 | 0.490 | 0.939 |
| rs1130409 | *APEX1* | chr14 | T>G, Asp148Glu | 0.476 | 0.422 | 0.065 |
| rs25487 | *XRCC1* | chr19 | G>A, Arg399Gln | 0.253 | 0.266 | 0.532 |
| rs1136410 | *ADPRT* | chr1 | T>C, Val762Ala | 0.470 | 0.416 | 0.887 |

[a]Chi-square test for genotyping distributions. MAF, minor allele frequency; CHB, Chinese Han in Beijing.

Table III. Logistic regression analysis for associations between polymorphisms of DNA repair genes and HNC risk.

| Locus | Genotype | Case | | Control | | Crude OR (95% CI) | Adjusted OR (95% CI)[a] | P-value[a] |
|---|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | | | |
| *XPD* | TT | 333 | 84.5 | 752 | 84.8 | 1.00 | 1.00 | |
| rs13181 | TG | 57 | 14.5 | 129 | 14.5 | 1.00 (0.71-1.40) | 0.94 (0.67-1.33) | 0.745 |
| | GG | 4 | 1.0 | 6 | 0.7 | 1.51 (0.42-5.37) | 1.53 (0.42-5.54) | 0.516 |
| | TG/GG | 61 | 15.5 | 135 | 15.2 | 1.02 (0.73-1.42) | 0.97 (0.69-1.35) | 0.857 |
| | Additive | | | | | 1.04 (0.77-1.41) | 1.00 (0.73-1.36) | 0.988 |
| *XPG* | GG | 108 | 27.4 | 234 | 26.5 | 1.00 | 1.00 | |
| rs17655 | CG | 191 | 48.5 | 433 | 49.0 | 0.99 (0.75-1.32) | 0.98 (0.74-1.31) | 0.901 |
| | CC | 95 | 24.1 | 217 | 24.6 | 0.99 (0.71-1.37) | 0.99 (0.71-1.38) | 0.957 |
| | CG/CC | 286 | 72.6 | 650 | 73.5 | 0.95 (0.73-1.25) | 0.95 (0.72-1.24) | 0.685 |
| | Additive | | | | | 0.97 (0.82-1.15) | 0.97 (0.82-1.15) | 0.761 |
| *APE1* | TT | 148 | 37.6 | 304 | 34.2 | 1.00 | 1.00 | |
| rs1130409 | TG | 159 | 40.4 | 420 | 47.2 | 0.78 (0.59-1.02) | 0.77 (0.59-1.02) | 0.065 |
| | GG | 87 | 22.1 | 165 | 18.6 | 1.08 (0.78-1.50) | 1.08 (0.78-1.51) | 0.641 |
| | TG/GG | 246 | 62.4 | 585 | 65.8 | 0.86 (0.68-1.11) | 0.86 (0.67-1.11) | 0.239 |
| | Additive | | | | | 1.00 (0.85-1.18) | 1.00 (0.85-1.18) | 0.982 |
| *XRCC1* | GG | 221 | 56.7 | 481 | 54.3 | 1.00 | 1.00 | |
| rs25487 | GA | 146 | 37.4 | 339 | 38.3 | 0.94 (0.73-1.20) | 0.96 (0.74-1.23) | 0.729 |
| | AA | 23 | 5.9 | 66 | 7.5 | 0.76 (0.46-1.25) | 0.81 (0.49-1.35) | 0.421 |
| | GA/AA | 169 | 43.3 | 405 | 45.7 | 0.91 (0.71-1.15) | 0.93 (0.73-1.19) | 0.578 |
| | Additive | | | | | 0.90 (0.74-1.10) | 0.93 (0.76-1.13) | 0.453 |
| *ADPRT* | TT | 138 | 34.9 | 300 | 34.0 | 1.00 | 1.00 | |
| rs1136410 | TC | 193 | 48.9 | 431 | 48.8 | 0.97 (0.75-1.27) | 0.98 (0.75-1.28) | 0.903 |
| | CC | 64 | 16.2 | 152 | 17.2 | 0.92 (0.64-1.31) | 0.89 (0.62-1.28) | 0.546 |
| | TC/CC | 257 | 65.1 | 583 | 66.0 | 0.96 (0.75-1.23) | 0.96 (0.75-1.24) | 0.752 |
| | Additive | | | | | 0.96 (0.81-1.14) | 0.95 (0.80-1.13) | 0.585 |

significantly associated with HNSCC risk. The genotype distributions of all SNPs in the cases and controls are shown in Table III. Similarly, the multivariate logistic regression analyses also showed that there were no significant associations between these five SNPs and HNSCC risk in different genetic models. For example, the adjusted ORs and 95% CI in the additive model were 1.00 (0.73-1.36) for rs13181, 0.97 (0.82-1.15) for rs17655, 1.00 (0.85-1.18) for rs1130409, 0.93 (0.76-1.13) for rs25487 and 0.95 (0.80-1.13) for rs1136410, respectively.

We further conducted the stratification analyses by age, gender, smoking, drinking, tumor sites and histology, but no significant associations were observed between the genotypes of the five SNPs and HNC risk in every stratum (data not shown). We also analyzed the two-way locus-locus and gene-environment interactions between all five SNPs and environmental factors (i.e., smoking status and alcohol status) using logistic regression models. Only one locus-locus interaction (rs1130409 and rs25487) was statistically significant (adjusted $P_{int}$ 0.036), but changed to non-significant after the multiple test adjustment.

## Discussion

In this case-control study, we assessed the associations of HNC risk with five nsSNPs in key DNA repair genes, which have been most widely studied in a variety of human cancers in other populations. The results showed that none of the five SNPs [*XPD* Lys751Gln (rs13181), *XPG* His1104Asp (rs17655), *APE1* Asp148Glu (rs1130409), *XRCC1* Arg399Gln (rs25487) and *ADPRT* Val762Ala (rs1136410)] were significantly associated with the risk of HNC in China.

*XPD* and *XPG* are two of more than 20 genes involved in NER. *XPD* codes an evolutionarily conserved helicase, a subunit of TFIIH that is essential for transcription and NER. The Lys751Gln (rs13181) polymorphism is located in exon 23 of *XPD* and causes codon 751 Lys (K) to be substituted for Gln (Q) (27). The *XPD* 751Gln allele was reported to be associated with higher DNA adduct levels in non-smokers (28) and phenotypes of repair of BPDE- and UV-induced DNA damage (14).

There have been several studies showing associations between this SNP and risk of multiple cancers, including HNC, but the results from different populations were confusing rather than conclusive (29-39). Recently, a meta-analysis with a total of 12 studies claimed that the *XPD* Lys751Gln polymorphism was not associated with HNC risk (17); however, no genotyping data from the Chinese population was included, with the exception of a Taiwan study with a small sample size of 154 cases and 105 controls (30). Our findings were consistent with those from the meta-analysis, suggesting that the *XPD* Lys751Gln polymorphism may not play a role in the susceptibility to HNC.

*XPG* mainly works as a structure-specific endonuclease that cleaves the damaged DNA strand on the 3' endside (40,41) and stimulates BER of oxidative DNA damage (42,43). The His1104Asp polymorphism (rs17655), located in exon 15 of *XPG*, has been largely investigated in studies on susceptibility to cancers of the breast (44), lung (45), stomach (46), bladder (47), colorectum (48) and head and neck (18,36,49,50). Although it was reported that the His1104Asp polymorphism of *XPG* together with SNPs of several other NER genes jointly contributed to the variability of DRC (16), we found that the His1104Asp polymorphism was not associated with the risk of HNC in China, supporting the results from other published studies for this SNP and HNC risk (18,36,49,50).

*APE1*, *XRCC1* and *ADPRT* are three crucial genes in the BER pathway and genetic variation in these genes may alter BER functions (51,52). In addition to DNA repair activity, *APE1* also regulates the gene expression as a redox co-activator of different transcription factors (11). The Asp148Glu polymorphism (rs3136820) is a T to G transversion at codon 148 of exon 5 in *APE1* and it has been reported to be related to hypersensitivity to ionizing radiation (53). Several studies have investigated the associations between Asp148Glu and cancer risk, but only two from Caucasians focused on HNC risk and neither found significant results (25,54).

Our study also failed to find significant associations between the Asp148Glu polymorphism and HNC risk in China. XRCC1 plays an important role in BER by interacting with a complex of DNA repair proteins, including poly (ADP-ribose) polymerase, DNA ligase 3 and DNA polymerase β (55). The Arg399Gln polymorphism (rs25487) is located at the region of the BRCT-I interaction domain of *XRCC1* and is linked with the reduced DRC (56,57). This polymorphism has been extensively investigated for its associations with cancer risk and the results were conflicting in different types of cancer or different populations (58-61); however, a meta-analysis including 7 studies indicated that Arg399Gln was not significantly associated with SCCHN risk in Caucasians and/or Asians (25), consistent with our findings in this study.

ADPRT is a DNA-dependent chromatin-associated enzyme, activated by DNA damage to catalyze polyADP-ribosylation of various proteins (62). The Val762Ala polymorphism (rs1136410) is located in exon 17 of *ADPRT*, leading to an amino acid exchange of valine to alanine. Although it has been suggested that the Val762Ala polymorphism contributes to altered ADPRT activity and carcinogenesis (63), only one study by Li *et al* has investigated the association of this SNP with SCCHN risk in the Caucasian population and found a protective effect of 762Ala allele on SCCHN risk (25). However, our current data provide evidence that this SNP does not have an effect on susceptibility to HNC risk in the Chinese population. Discrepancies in allele frequency may be a concern for the inconsistence between different studies. In the study by Li *et al*, the Gln allele frequency was 0.160 in Caucasians, while in our group, the Gln allele frequency was 0.416 in our Chinese population.

Several limitations of our study need to be addressed. Firstly, our study was a hospital-based case-control study, and inherent selection bias may lead to spurious findings. Secondly, the sample size of our study was relatively small, which may reduce the statistical power to detect the low penetrance effect of single locus, especially for the stratification and interaction analysis. Thirdly, only five functional SNPs were included in our study, and thus we cannot analyze the association between other SNPs in the DNA repair pathway and HNC risk in China.

In conclusion, this study provided evidence that five SNPs in key DNA repair genes [*XPD* Lys751Gln (rs13181), *XPG* His1104Asp (rs17655), *APE1* Asp148Glu (rs1130409), *XRCC1* Arg399Gln (rs25487) and *ADPRT* Val762Ala (rs1136410)] were not associated with HNC risk in China. The findings need to be validated by larger studies.

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## References

1. Marcu LG and Yeoh E: A review of risk factors and genetic alterations in head and neck carcinogenesis and implications for current and future approaches to treatment. J Cancer Res Clin Oncol 135: 1303-1314, 2009.
2. Jemal A, Siegel R, Xu J and Ward E: Cancer statistics, 2010. CA Cancer J Clin 60: 277-300, 2010.
3. Choi SY and Kahyo H: Effect of cigarette smoking and alcohol consumption in the aetiology of cancer of the oral cavity, pharynx and larynx. Int J Epidemiol 20: 878-885, 1991.
4. Phillips DH: Smoking-related DNA and protein adducts in human tissues. Carcinogenesis 23: 1979-2004, 2002.
5. Stokes MP and Comb MJ: A wide-ranging cellular response to UV damage of DNA. Cell Cycle 7: 2097-2099, 2008.

6. Wei Q, Cheng L, Hong WK and Spitz MR: Reduced DNA repair capacity in lung cancer patients. Cancer Res 56: 4103-4107, 1996.
7. Cheng L, Eicher SA, Guo Z, Hong WK, Spitz MR and Wei Q: Reduced DNA repair capacity in head and neck cancer patients. Cancer Epidemiol Biomarkers Prev 7: 465-468, 1998.
8. Wang LE, Hu Z, Sturgis EM, *et al*: Reduced DNA repair capacity for removing tobacco carcinogen-induced DNA adducts contributes to risk of head and neck cancer but not tumor characteristics. Clin Cancer Res 16: 764-774, 2010.
9. Wood RD: DNA damage recognition during nucleotide excision repair in mammalian cells. Biochimie 81: 39-44, 1999.
10. Hung RJ, Hall J, Brennan P and Boffetta P: Genetic polymorphisms in the base excision repair pathway and cancer risk: a HuGE review. Am J Epidemiol 162: 925-942, 2005.
11. Tell G, Damante G, Caldwell D and Kelley MR: The intracellular localization of APE1/Ref-1: more than a passive phenomenon? Antioxid Redox Signal 7: 367-384, 2005.
12. Caldecott KW: XRCC1 and DNA strand break repair. DNA Repair (Amst) 2: 955-969, 2003.
13. Masson M, Niedergang C, Schreiber V, Muller S, Menissier de Murcia J and de Murcia G: XRCC1 is specifically associated with poly(ADP-ribose) polymerase and negatively regulates its activity following DNA damage. Mol Cell Biol 18: 3563-3571, 1998.
14. Spitz MR, Wu X, Wang Y, *et al*: Modulation of nucleotide excision repair capacity by XPD polymorphisms in lung cancer patients. Cancer Res 61: 1354-1357, 2001.
15. Qiao Y, Spitz MR, Guo Z, *et al*: Rapid assessment of repair of ultraviolet DNA damage with a modified host-cell reactivation assay using a luciferase reporter gene and correlation with polymorphisms of DNA repair genes in normal human lymphocytes. Mutat Res 509: 165-174, 2002.
16. Shen J, Desai M, Agrawal M, *et al*: Polymorphisms in nucleotide excision repair genes and DNA repair capacity phenotype in sisters discordant for breast cancer. Cancer Epidemiol Biomarkers Prev 15: 1614-1619, 2006.
17. Flores-Obando RE, Gollin SM and Ragin CC: Polymorphisms in DNA damage response genes and head and neck cancer risk. Biomarkers 15: 379-399, 2010.
18. Cui Y, Morgenstern H, Greenland S, *et al*: Polymorphism of *Xeroderma pigmentosum* group G and the risk of lung cancer and squamous cell carcinomas of the oropharynx, larynx and esophagus. Int J Cancer 118: 714-720, 2006.
19. Gugatschka M, Dehchamani D, Wascher TC, Friedrich G and Renner W: DNA repair gene ERCC2 polymorphisms and risk of squamous cell carcinoma of the head and neck. Exp Mol Pathol 91: 331-334, 2010.
20. Hiyama T, Yoshihara M, Tanaka S and Chayama K: Genetic polymorphisms and head and neck cancer risk (Review). Int J Oncol 32: 945-973, 2008.
21. Wang Y, Yang H, Li H, *et al*: Association between X-ray repair cross complementing group 1 codon 399 and 194 polymorphisms and lung cancer risk: a meta-analysis. Cancer Lett 285: 134-140, 2009.
22. Yin M, Tan D and Wei Q: Genetic variants of the XRCC1 gene and susceptibility to esophageal cancer: a meta-analysis. Int J Clin Exp Med 2: 26-35, 2009.
23. Wang F, Chang D, Hu FL, *et al*: DNA repair gene XPD polymorphisms and cancer risk: a meta-analysis based on 56 case-control studies. Cancer Epidemiol Biomarkers Prev 17: 507-517, 2008.
24. Hu Z, Wei Q, Wang X and Shen H: DNA repair gene XPD polymorphism and lung cancer risk: a meta-analysis. Lung Cancer 46: 1-10, 2004.
25. Li C, Hu Z, Lu J, *et al*: Genetic polymorphisms in DNA base-excision repair genes ADPRT, XRCC1, and APE1 and the risk of squamous cell carcinoma of the head and neck. Cancer 110: 867-875, 2007.
26. Vineis P, Manuguerra M, Kavvoura FK, *et al*: A field synopsis on low-penetrance variants in DNA repair genes and cancer susceptibility. J Natl Cancer Inst 101: 24-36, 2009.
27. Shen MR, Jones IM and Mohrenweiser H: Nonconservative amino acid substitution variants exist at polymorphic frequency in DNA repair genes in healthy humans. Cancer Res 58: 604-608, 1998.
28. Xing DY, Qi J, Tan W, *et al*: Association of genetic polymorphisms in the DNA repair gene XPD with risk of lung and esophageal cancer in a Chinese population in Beijing. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 20: 35-38, 2003 (In Chinese).
29. An J, Liu Z, Hu Z, *et al*: Potentially functional single nucleotide polymorphisms in the core nucleotide excision repair genes and risk of squamous cell carcinoma of the head and neck. Cancer Epidemiol Biomarkers Prev 16: 1633-1638, 2007.
30. Bau DT, Tsai MH, Huang CY, *et al*: Relationship between polymorphisms of nucleotide excision repair genes and oral cancer risk in Taiwan: evidence for modification of smoking habit. Chin J Physiol 50: 294-300, 2007.
31. Huang WY, Olshan AF, Schwartz SM, *et al*: Selected genetic polymorphisms in MGMT, XRCC1, XPD, and XRCC3 and risk of head and neck cancer: a pooled analysis. Cancer Epidemiol Biomarkers Prev 14: 1747-1753, 2005.
32. Kietthubthew S, Sriplung H, Au WW and Ishida T: Polymorphism in DNA repair genes and oral squamous cell carcinoma in Thailand. Int J Hyg Environ Health 209: 21-29, 2006.
33. Majumder M, Sikdar N, Ghosh S and Roy B: Polymorphisms at XPD and XRCC1 DNA repair loci and increased risk of oral leukoplakia and cancer among NAT2 slow acetylators. Int J Cancer 120: 2148-2156, 2007.
34. Ramachandran S, Ramadas K, Hariharan R, Rejnish Kumar R and Radhakrishna Pillai M: Single nucleotide polymorphisms of DNA repair genes XRCC1 and XPD and its molecular mapping in Indian oral cancer. Oral Oncol 42: 350-362, 2006.
35. Sturgis EM, Zheng R, Li L, *et al*: XPD/ERCC2 polymorphisms and risk of head and neck cancer: a case-control analysis. Carcinogenesis 21: 2219-2223, 2000.
36. Abbasi R, Ramroth H, Becher H, Dietz A, Schmezer P and Popanda O: Laryngeal cancer risk associated with smoking and alcohol consumption is modified by genetic polymorphisms in ERCC5, ERCC6 and RAD23B but not by polymorphisms in five other nucleotide excision repair genes. Int J Cancer 125: 1431-1439, 2009.
37. Matullo G, Dunning AM, Guarrera S, *et al*: DNA repair polymorphisms and cancer risk in non-smokers in a cohort study. Carcinogenesis 27: 997-1007, 2006.
38. Rydzanicz M, Wierzbicka M, Gajecka M, Szyfter W and Szyfter K: The impact of genetic factors on the incidence of multiple primary tumors (MPT) of the head and neck. Cancer Lett 224: 263-278, 2005.
39. Gajecka M, Rydzanicz M, Jaskula-Sztul R, Wierzbicka M, Szyfter W and Szyfter K: Reduced DNA repair capacity in laryngeal cancer subjects. A comparison of phenotypic and genotypic results. Adv Otorhinolaryngol 62: 25-37, 2005.
40. Wakasugi M, Reardon JT and Sancar A: The non-catalytic function of XPG protein during dual incision in human nucleotide excision repair. J Biol Chem 272: 16030-16034, 1997.
41. O'Donovan A, Davies AA, Moggs JG, West SC and Wood RD: XPG endonuclease makes the 3' incision in human DNA nucleotide excision repair. Nature 371: 432-435, 1994.
42. Bessho T: Nucleotide excision repair 3' endonuclease XPG stimulates the activity of base excision repair enzyme thymine glycol DNA glycosylase. Nucleic Acids Res 27: 979-983, 1999.
43. Klungland A, Hoss M, Gunz D, *et al*: Base excision repair of oxidative DNA damage activated by XPG protein. Mol Cell 3: 33-42, 1999.
44. Jorgensen TJ, Visvanathan K, Ruczinski I, Thuita L, Hoffman S and Helzlsouer KJ: Breast cancer risk is not associated with polymorphic forms of xeroderma pigmentosum genes in a cohort of women from Washington County, Maryland. Breast Cancer Res Treat 101: 65-71, 2007.
45. Kiyohara C and Yoshimasu K: Genetic polymorphisms in the nucleotide excision repair pathway and lung cancer risk: a meta-analysis. Int J Med Sci 4: 59-71, 2007.
46. Hussain SK, Mu LN, Cai L, *et al*: Genetic variation in immune regulation and DNA repair pathways and stomach cancer in China. Cancer Epidemiol Biomarkers Prev 18: 2304-2309, 2009.
47. Garcia-Closas M, Malats N, Real FX, *et al*: Genetic variation in the nucleotide excision repair pathway and bladder cancer risk. Cancer Epidemiol Biomarkers Prev 15: 536-542, 2006.
48. Mort R, Mo L, McEwan C and Melton DW: Lack of involvement of nucleotide excision repair gene polymorphisms in colorectal cancer. Br J Cancer 89: 333-337, 2003.
49. Wen SX, Tang PZ, Zhang XM, *et al*: Association between genetic polymorphism in xeroderma pigmentosum G gene and risks of laryngeal and hypopharyngeal carcinomas. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 28: 703-706, 2006 (In Chinese).
50. Manuguerra M, Matullo G, Veglia F, *et al*: Multi-factor dimensionality reduction applied to a large prospective investigation on gene-gene and gene-environment interactions. Carcinogenesis 28: 414-422, 2007.

51. Izumi T, Wiederhold LR, Roy G, *et al*: Mammalian DNA base excision repair proteins: their interactions and role in repair of oxidative DNA damage. Toxicology 193: 43-65, 2003.
52. Dianov GL, Sleeth KM, Dianova II and Allinson SL: Repair of abasic sites in DNA. Mutat Res 531: 157-163, 2003.
53. Hu JJ, Smith TR, Miller MS, Mohrenweiser HW, Golden A and Case LD: Amino acid substitution variants of APE1 and XRCC1 genes associated with ionizing radiation sensitivity. Carcinogenesis 22: 917-922, 2001.
54. Jelonek K, Gdowicz-Klosok A, Pietrowska M, *et al*: Association between single-nucleotide polymorphisms of selected genes involved in the response to DNA damage and risk of colon, head and neck, and breast cancers in a Polish population. J Appl Genet 51: 343-352, 2010.
55. Caldecott KW, Tucker JD, Stanker LH and Thompson LH: Characterization of the XRCC1-DNA ligase III complex in vitro and its absence from mutant hamster cells. Nucleic Acids Res 23: 4836-4843, 1995.
56. Lunn RM, Langlois RG, Hsieh LL, Thompson CL and Bell DA: XRCC1 polymorphisms: effects on aflatoxin B1-DNA adducts and glycophorin A variant frequency. Cancer Res 59: 2557-2561, 1999.
57. Lei YC, Hwang SJ, Chang CC, *et al*: Effects on sister chromatid exchange frequency of polymorphisms in DNA repair gene XRCC1 in smokers. Mutat Res 519: 93-101, 2002.
58. Wei B, Zhou Y, Xu Z, *et al*: XRCC1 Arg399Gln and Arg194Trp polymorphisms in prostate cancer risk: a meta-analysis. Prostate Cancer Prostatic Dis 14: 225-231, 2010.
59. Saadat M: Haplotype analysis of XRCC1 (at codons 194 and 399) and susceptibility to breast cancer, a meta-analysis of the literatures. Breast Cancer Res Treat 124: 785-791, 2010.
60. Zheng H, Wang Z and Shi X: XRCC1 polymorphisms and lung cancer risk in Chinese populations: a meta-analysis. Lung Cancer 65: 268-273, 2009.
61. Hu Z, Ma H, Chen F, Wei Q and Shen H: XRCC1 polymorphisms and cancer risk: a meta-analysis of 38 case-control studies. Cancer Epidemiol Biomarkers Prev 14: 1810-1818, 2005.
62. Kumari SR, Mendoza-Alvarez H and Alvarez-Gonzalez R: Functional interactions of p53 with poly(ADP-ribose) polymerase (PARP) during apoptosis following DNA damage: covalent poly(ADP-ribosyl)ation of p53 by exogenous PARP and noncovalent binding of p53 to the M(r) 85,000 proteolytic fragment. Cancer Res 58: 5075-5078, 1998.
63. Lockett KL, Hall MC, Xu J, *et al*: The ADPRT V762A genetic variant contributes to prostate cancer susceptibility and deficient enzyme function. Cancer Res 64: 6344-6348, 2004.