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Impact of DNA polymorphisms in key DNA base excision repair proteins on cancer risk

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Abstract

Genetic variation in DNA repair genes can modulate DNA repair capacity and may be related to cancer risk. However, study findings have been inconsistent. Inheritance of variant DNA repair genes is believed to influence individual susceptibility to the development of environmental cancer. Reliable knowledge on which the base excision repair (BER) sequence variants are associated with cancer risk would help elucidate the mechanism of cancer. Given that most of the previous studies had inadequate statistical power, we have conducted a systematic review on sequence variants in three important BER proteins. Here, we review published studies on the association between polymorphism in candidate BER genes and cancer risk. We focused on three key BER genes: 8-oxoguanine DNA glycosylase (*OGGI*), apurinic/apyrimidinic endonuclease (*APE1/APEX1*) and x-ray repair cross-complementing group 1 (*XRCC1*). These specific DNA repair genes were selected because of their critical role in maintaining genome integrity and, based on previous studies, suggesting that single-nucleotide polymorphisms (SNPs) in these genes have protective or deleterious effects on cancer risk. A total of 136 articles in the December 13, 2010 MEDLINE database (National Center for Biotechnology Information, <http://www.ncbi.nlm.nih.gov/pubmed/>) reporting polymorphism in *OGGI*, *XRCC1* or *APE1* genes were analyzed. Many of the reported SNPs had diverse association with specific human cancers. For example, there was a positive association between the *OGGI Ser326Cys* variant and gastric and lung cancer, while the *XRCC1 Arg399Gln* variant was associated with reduced cancer risk. Gene–environment interactions have been noted and may be important for colorectal and lung cancer risk and possibly other human cancers.

Keywords

OGGI; *XRCC1*; *APE1*; cancer; gene polymorphism; DNA repair; DNA damage

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Introduction

There are two main types of DNA damages, endogenous and exogenous. Endogenous DNA damage is primarily caused by reactive oxygen species (ROS), which are the by-products of normal cellular metabolism. Exogenous DNA damage is caused by the environmental agents such as ultraviolet light, ionizing radiation and chemicals.¹ Some oxidative DNA lesions form at a high rate. For example, it is estimated that 100–500 8-hydroxyguanine (8-oxoG) lesions are formed per day in a human cell,² and formamidopyrimidine lesions (2,6-diamino-4-hydroxy-5-formamidopyrimidine and 4,6-diamino-5-formamidopyrimidine) form at a similar or higher rate in cells exposed to oxidative stress.³ Oxidative damage to DNA, which also includes sugar modifications and strand breaks, can lead to transcription or replication defects, mutations, genomic instability and ultimately cellular dysfunction. In turn, cell stress pathways can induce apoptosis or support unregulated cell growth^{4,5} (Figure 1) through the activation of oncogenes or inactivation of tumor suppressor genes.⁶

Environmental chemicals and cancer; tobacco smoke as a model compound

Most cancers are the result of the interactions of multiple genes and environmental factors. Tobacco smoke is a good example of an environmental risk factor for lung and other cancers.^{7–9} Tobacco use is by far the most recognized link between exposure to known carcinogens and death from cancer, and like the aflatoxin–hepatocellular carcinoma relationship, can be considered a model for understanding mechanisms of cancer induction by exogenous chemical carcinogens.^{10,11} Tobacco smoke consists of at least 3800 chemical constituents,¹² including benzo[*a*]pyrene (BaP) and small chemical carcinogens, such as formaldehyde, ethylene oxide, benzene, 1,3-butadiene and many others. After biotransformation, the metabolites can induce oxidative stress or can covalently bind to DNA, leading to DNA modifications that can promote mutagenic bypass if unrepaired.¹³ Tobacco smoke-induced DNA damage is repaired predominantly by base excision repair (BER, see more in The BER Pathway section) and nucleotide excision repair (NER).

In addition to DNA repair, xenobiotic metabolizing enzymes, that is, cytochromes, glutathione-*S*-transferase (*GST*) and *N*-acetyl-transferase, can modify the risk of exposure. However, in the absence of exposure, the presence or absence of these genetic risk factors is irrelevant. For example, both *GSTM1* and *GSTT1* genes can be deleted and their corresponding conjugating activity is absent without increased cancer risk, whereas functional polymorphisms in these genes may play a significant role in tobacco-related cancer susceptibility.¹⁴ There are also associations between DNA repair gene polymorphism and lung cancer, presumably because the genetic defects decrease capacity to remove potentially mutagenic BaP DNA adducts or other DNA lesions introduced by tobacco smoke.^{15–21} Antioxidant defense systems and multiple DNA repair pathways have evolved to protect cells from oxidative stress and oxidative DNA damaging agents, acting as first and second lines of defense, respectively.^{22,23}

The BER pathway

BER is critical for genome maintenance, and defects in BER are related to cancer risk and premature aging.²⁴ BER is the main pathway for the repair of apurinic and apyrimidinic

(AP) sites.²⁵ DNA single-strand breaks as well as 8-oxoG, Fapy lesions or other base or sugar modifications arise via oxidation, alkylation or spontaneous decay.²⁶ BER is classically initiated by a DNA glycosylase, which cleaves the *N*-glycosyl bond, releasing the substrate base and generating an abasic site. The abasic site is then cleaved by an AP lyase or AP endonuclease and, at instances when repair is successfully executed, the one base gap in the cleaved DNA strand is filled-in by a DNA polymerase and ligated by a DNA ligase.^{1,27}

Genetic susceptibility to cancer and DNA repair

Single-nucleotide polymorphisms (SNPs) are the DNA base variants present in the human population at a frequency >1%.^{28,29} The nonsynonymous coding SNPs (nsSNPs) and SNPs in regulatory regions are believed to have the highest impact on phenotype. Both nsSNPs and regulatory SNPs in DNA repair genes can result in reduced DNA repair capacity, which can underlie a higher mutation rate and increased cancer risk.³⁰ If a polymorphism is in a repair gene that plays a pivotal role in the removal of oxidative DNA damage, for instance, the resulting reduced repair activity will increase the possibility of disease, particularly in the face of oxidative stress. Studies on polymorphisms, therefore, provide an opportunity to discover candidate susceptibility alleles. However, the functional outcome and phenotypic effect of some polymorphisms are unknown. This review focuses on the phenotypic effects of variants in three genes, which have important roles in BER, in the development of carcinogenesis.

This review examines possible effects on cancer risk from polymorphisms in three BER proteins: 8-oxoguanine DNA glycosylase 1 (*OGG1*), AP endonuclease 1 (*APE1*), and x-ray repair cross complementing group 1 (*XRCC1*). The *OGG1* gene is located at 3p25 and encodes the major repair enzyme for 8-oxoG. 1245C>G is a well-characterized *OGG1* polymorphism that results in substitution of serine with cysteine at codon 326.³¹ Molecular epidemiologic case-control studies suggest that the *hOGG1*Cys326 allele is associated with a higher risk of developing several types of cancers.³²⁻³⁶ In addition to catalyzing excision of 8-oxoG from DNA, *OGG1* possesses the ability to incise at abasic sites via an AP lyase activity. It has been demonstrated that the *OGG1* Cys326 protein repairs 8-oxoG inefficiently, leading to the hypothesis that this variant may contribute to a higher cellular mutation rate.³⁷

APE1 (also known as *APE*, *APEX*, *HAP1* and *REF-1*) plays an essential role in BER. *APE1* initiates repair of abasic sites in DNA by hydrolyzing the phosphodiester backbone 5' to an AP site.³⁸ Known sequence variants in *APE1* include an amino acid change from aspartic acid to glutamic acid (Asp148Glu) in exon 5 that may be associated with hypersensitivity to ionizing radiation and cancer risk.³⁸⁻⁴⁰ However, the Asp148Glu substitution did not alter *APE1* AP site incision activity in vitro.⁴¹ *APE1* also plays a role in regulating the DNA binding capacity of several transcription factors and thus gene expression efficiency. As will be discussed further below, some studies show an influence of *APE1* polymorphism on the prognosis of ovarian, gastroesophageal and pancreatico-biliary cancer.⁴²

XRCC1 is an important scaffold protein that interacts with the enzymatic factors such as polyadenosine diphosphate (ADP)-ribose polymerase, DNA ligase III and DNA polymerase

β to facilitate efficient repair of DNA single-strand breaks.⁴³ *XRCCI* is located at 19q13.2 and consists of 17 exons encoding a 633 amino acid protein. A common genetic variant in *XRCCI* (C>T) in exon 6 results in an Arg to Trp (rs25487) substitution at codon 194, while another polymorphism (G>A) in exon 10 changes amino acid Arg to Gln in codon 399⁴⁴ and yet another polymorphism (G>A) in exon 9 changes amino acid Arg to His (rs25489) in codon 280.⁴⁵

A variant *XRCCI* gene may alter protein function and repair capacity, thus leading to genetic instability and carcinogenesis. However, the current data on the consequences of the 194 and 399 amino acid variants on *XRCC1* function are complex.³⁷ Nevertheless, since any of the nsSNPs described above may represent functional polymorphisms, the possible influence of the polymorphic variants in *OGGI*, *XRCCI* and *APE1* on cancer risk is reviewed in further detail herein (Figure 2).

Materials and methods

As will be discussed in much detail later, SNPs in some BER genes appear to confer greater susceptibility to environmentally induced cancers. While recent studies have begun to evaluate the effect of SNPs on the DNA repair and metabolizing genes on the treatment outcome, such analyses have not been included in this review. In this review, we conducted a PubMed search of published articles using the keywords ‘*OGGI*, Ser326Cys or *APE1*, Asp148Glu or *XRCCI*, Arg399Gln, Arg194Trp, Arg280His and cancer’. A total of 136 articles were identified in the December 13, 2010 MEDLINE database (National Center for Biotechnology Information, PubMed database: <http://www.ncbi.nlm.nih.gov/pubmed/>). These specific gene polymorphisms were selected because of their high frequency and because of the large number of epidemiological studies examining their association with multiple cancers. Only quantitative studies were considered. Abstracts from scientific meetings were not reviewed. Studies with a sample size of <100 were excluded. There was no selection for specific cancer types. Odds ratios (ORs) for selected polymorphisms were tabulated and compared, primarily from case-control studies. Figure 3 presents inclusion/exclusion criteria. Forty-one articles did not meet the inclusion criteria (such as, studies on disease polymorphism, response to drug therapy polymorphism, occupational exposure to chemical polymorphisms, genotoxicity assays-polymorphism associations, etc.). Of the 136 articles, 76 met inclusion criteria. The articles included studies on 15 types of cancer (Figure 4) and their association with *OGGI*, *APE1* or *XRCCI* gene polymorphisms. Of all the studies, 55% were conducted in Asian populations and 45% were conducted in Caucasian populations. Most of the studies were hospital-based. Some cancer types were pooled and defined as one cancer type: oral/pharyngeal cancers and laryngeal cancers were pooled and defined as upper aerodigestive cancer (UADC); colon and colorectal cancer were pooled and defined as colon cancer; biliary tract and gallbladder cancer were pooled and defined as biliary tract cancer; mesothelioma, lung and non-small-cell lung carcinoma (NSCLC) were pooled and defined as lung cancer; precancerous gastric lesions, gastric cancer and gastric cardiac adenocarcinoma (ADC) were pooled and defined as gastric cancer; cervix, endometriosis and uterine leiomyoma were pooled and defined as gynecological cancer. In some articles, many different gene polymorphisms (more than 15 gene polymorphisms) and one cancer type association were studied. For these articles, only data relevant to *OGGI*,

APE1 and *XRCC1* SNPs are discussed in detail herein. Results of each study are given in Tables 1 to 8 and are discussed below.

Results

Colorectal cancers

Table 1 summarizes the associations of gene polymorphisms (*OGGI* Ser326Cys, *APE1* Asp148Glu, *XRCC1* Arg399Gln, Arg280His and Arg194Trp) and colorectal cancer. Gu et al. conducted a meta-analysis of 27 published studies that included 12,432 cancer cases and 17,349 controls. Their overall results suggested that the variant genotypes were associated with a moderately increased risk of all cancer types (OR = 1.09, 95% CI = 1.01–1.18 for TG vs. TT; OR = 1.08, 95% CI = 1.00–1.18 for GG/TG vs. TT). The meta-analysis also supported that the *APE1* Asp148Glu polymorphism is a low-penetrance risk factor for cancer development.⁴³ Curtin et al. genotyped colon cancer cases and matched population-based controls for BER variants in *OGGI* (Ser326Cys) and *XRCC1* (Arg399Gln, Arg280His and Arg194Trp). No association was found between the selected polymorphisms and overall colon cancer susceptibility. However, a twofold increased risk of carrying the proto-oncogene serine/threonine protein kinase *BRAF* V600E allele was observed in current and former cigarette smokers for the *OGGI* Cys326Cys polymorphism (OR = 2.2; 95% CI = 1.02–4.9). *XRCC1* Arg194Trp gene polymorphism was associated with a modestly increased risk of *TP53* mutations in smokers (OR = 1.4; 95% CI = 1.02–1.9). Collectively, these findings suggest that *OGGI* Ser326Cys and Arg194Trp cosegregate with other colon cancer-associated mutations.⁴⁶

Kim et al. investigated the effect of *OGGI* on the risk of colon cancer in the Korean population and found that the *OGGI* Ser326Cys polymorphism did not alter the overall OR for colon cancer. However, subgroup analysis revealed a trend for increased OR with smoking or frequent meat intake in the Cys/Cys carriers.⁴⁷

The study of Hansen et al. did not support Kim et al.'s results. Hansen et al. found no association between *OGGI* Ser326Cys polymorphism and the risk of colorectal adenomas, regardless of the degree of dysplasia in a Norwegian population. Furthermore, *OGGI* Ser326Cys gene polymorphism had a protective effect (OR = 0.56; 95% CI = 0.32–0.97 Ser/Ser vs. Ser/Cys) against the risk of colorectal cancer. Since meat consumption and smoking are frequent in the Norwegian population, different gene–environment interactions are likely in both the types of population.⁴⁸ In another cohort study, in a Norwegian population, the association between *XRCC1* gene polymorphisms (Arg194Trp, Arg280His and Arg399Gln) and the risk of colorectal adenomas and carcinomas was examined. This study demonstrated increased risk of advanced colorectal neoplasia in individuals with the *XRCC1* Arg280His gene polymorphism and a reduced risk associated with the Arg399Gln gene polymorphism.⁴⁹

Moreno et al. investigated whether common polymorphisms in DNA repair genes correlate with colorectal cancer risk or patient prognosis and response to chemotherapy. In fact, adjuvant chemotherapy causes an acute increase in DNA damage, suggesting that the DNA repair capacity in specific cancer cells, tumors or individuals may influence the therapeutic

efficacy of the selected DNA-interactive drugs. In the study, the incidence of 28 common SNPs in 15 DNA repair genes was determined in DNA from colorectal cancer patients. SNPs were examined in the following genes: BER (*OGG1*, *LIG3*, *APE*, *POLB*, *XRCC1*, *PCNA* and *MUTYH*), NER (*ERCC1*, *ERCC4* and *ERCC5*), double-strand break repair (*XRCC2*, *XRCC3* and *XRCC9*) and direct reversal repair (*MGMT*). The findings suggest that, among the BER genes, in contrast to the results of Hansen et al., homozygous carriers of *OGG1* Ser/Cys had a statistically significant twofold higher risk of colorectal cancer than the carriers of the wild type allele (OR = 2.31; 95%CI = 1.05–5.09). The *APE1* Asp148Glu variant was also associated with an increased risk of colorectal cancer (OR = 3.04; 95% CI = 1.38–6.71 for *APE1* Asp148Glu).⁵⁰

In a subsequent study, no association was found with *APE1* in colorectal cancer, but the risk was increased in colon cancer for the Glu/Glu genotype. For *OGG1* Ser326Cys, a significantly increased risk was observed in smokers. Interestingly, the joint effect of variant alleles of *APE1* Asp/Glu and *hOGG1* Ser/Cys showed increased colorectal cancer risk (OR = 6.37; 95% CI = 1.40–29.02).⁵¹ However, different results were obtained in Korean (OR = 1.72; 95% CI = 1.12–2.76 Ser/Cys, only meat intake),⁴⁷ Japanese (OR = 1.43; 95% CI = 0.69–2.95 for Ser/Cys + Cys/Cys) and Chinese populations (OR = 1.4; 95% CI = 0.9–2.2 for Ser/Cys; OR = 1.4; 95% CI = 0.9–2.1 for Cys/Cys).^{52,53} Another study in a Caucasian population showed no association of the *OGG1* Cys/Cys genotype (OR = 0.963; 95% CI = 0.446–2.079) with the risk of cancer progression, despite the elevated oxidative stress in these cancer patients.⁵⁴

Wang et al. analyzed the distributions of three SNPs (*XRCC1* Arg399Gln, *XRCC3* Thr241Met and *XPD* Lys751Gln) in DNA repair genes, assessed the association of these genetic polymorphisms with colon and rectal cancer susceptibility, as well as evaluated the interactions of gene–gene and gene–environment in a case-control study of an Indian population. No association was observed between the *XRCC1* Arg399Gln gene polymorphism and cancer risk (OR = 1.44; 95% CI = 0.76–2.75 for colon; OR = 1.40; 95% CI = 0.96–2.06 for rectal; OR = 1.41; 95% CI = 0.99–2.03 colorectal cancer). However, the *XRCC1* Gln399 allele was associated with a significantly increased rectal cancer risk among men (OR = 1.65; 95% CI = 1.04–2.64), indicating a gender effect of this allele on colorectal cancer. Furthermore, individuals carrying *XRCC1* Gln399, *XRCC3* Thr/Thr (double-strand break repair) and *XPD* Gln751 demonstrated the highest colorectal cancer risk (OR = 3.52; 95% CI = 1.43–9.44).⁵⁵

Environmental factors, such as diet, lifestyle and environmental pollution, have important impact on the development of colorectal cancer. Thus, Wang et al. also evaluated the interaction of gene–smoking or gene–alcohol on rectal or colorectal cancer risk. The *XRCC1* Arg399Gln gene polymorphism was not found to be interacting significantly with tobacco consumption on cancer susceptibility (interaction $p > 0.05$, respectively). Conversely, there was a positive association of the *XRCC1* Gln399 allele with rectal (OR = 1.56; 95% CI = 1.05–2.33) and colorectal (OR = 1.61; 95% CI = 1.11–2.34) cancer among non-drinkers, and there was a weak evidence that *XRCC1* Arg/Arg genotype increased the risk of rectal (OR = 1.93; 95% CI = 0.94–4.04) or colorectal (OR = 1.91; 95% CI = 0.96–3.86) cancer among drinkers ($p = 0.05$ for rectal cancer and 0.03 for colorectal cancer). Alcohol intake did not

affect the results of the other genetic polymorphisms, that is, *XRCC3* Thr241Met and *XPB* Lys715Gln (interaction $p > 0.05$, respectively). Finally, based on a small proportion of vegetarians in their study group, Wang et al. argued that the insufficient nutrition may explain some of the increased risk of rectal cancer (OR = 1.83; 95% CI = 1.04–3.26). Meta-analysis with a large population confirmed the previous studies, showing no association between *XRCC1* gene polymorphisms and colorectal cancer.⁵⁶ Additional studies similarly found no association between *XRCC1* Arg399Gln gene polymorphism and colorectal cancer risk.^{46,50,52,53}

Lung cancer

Table 2 summarizes the associations of gene polymorphisms and lung cancer. Lung cancer is one of the most common cancers and is the leading cause of cancer death worldwide. In 2006, there were an estimated 1,352,000 new lung cancer cases and 1,179,000 lung cancer deaths. The main types of lung cancer are small-cell lung carcinoma and NSCLC. There are three main subtypes: squamous cell lung carcinoma (SCLC), ADC and large-cell lung carcinoma. This distinction is important for therapy. SCLC is most strongly associated with smoking, while ADC is least strongly associated with smoking and the most common lung cancer in nonsmokers. Thus, genetic as well as environmental factors should be considered in developing and applying interventions.³³

The International Lung Cancer Consortium analyzed the correlation between DNA repair gene variants and lung cancer susceptibility using the data from 14 studies for 18 sequence variants in 12 DNA repair genes (*APE1*, *OGG1*, *XRCC1*, *XRCC2*, *XRCC3*, *ERCC1*, *XPB*, *XPF*, *XPA*, *XPG*, *MGMT* and *TP53*). Six studies were conducted in European countries, four in the United States and four in Asia or the Pacific Islands. Seven studies used hospital-based controls, seven studies used population-based controls and one study used a nested cohort study design. The number of subjects in these studies ranged from 2073 to 13,955. Relevant to the review here, we focused on the BER variants in *OGG1*, *APE1* and *XRCC1*. *OGG1* Ser326Cys homozygous variant individuals were associated with lung cancer risk in Caucasians (OR = 1.34; 95% CI = 1.01–1.79) based on 2569 cases and 4178 controls in four studies; however, this association was lacking in Asian populations.^{18,32,57,58} *OGG1* Ser326Cys also showed a differential effect in non-Hispanic Whites in one study.³² Popanda et al. found reduced risk of lung cancer associated with *APE1* Glu148Glu in Caucasians. When *APE1* Glu148Glu and *XRCC1* Gln399Gln were combined, ORs were reduced (OR = 0.69; 95% CI = 0.28–1.73), especially in the SCLC group (OR = 0.39; 95% CI = 0.10–1.53). For homozygous individuals carrying the Glu variant of *APE1*, a protective effect was found (OR = 0.77; 95% CI = 0.51–1.16). Popanda et al. found that *XRCC1* Arg/Gln and Gln/Gln genotypes, when pooled and considered together, had higher lung cancer risk (adjusted OR = 2.15; CI 95% = 1.08–4.28) than *XRCC1* Arg/Arg homozygotes in an Italian population.⁵⁹ Similar observations were made in a Chinese hospital based case-control study.⁸ In this study, individuals with a homozygous *XRCC1* Gln/Gln genotype (OR = 1.75; 95% CI = 1.02–3.01) exhibited a slightly higher risk of lung cancer overall and the adjusted OR was increased in the cases with ADC (OR = 2.62; 95% CI = 1.44–4.79). No joint effect of cooking oil fume and Gln399 was observed on lung cancer risk in women nonsmokers.⁸ No significant association was reported between *OGG1* Ser326Cys and lung cancer risk.

In the first prospective population-based study of Danes, there were no associations between *XRCC1* Arg280His and Arg399Gln or *OGG1* Ser326Cys gene polymorphisms and risk of lung cancer.⁶⁰ Miyaishi et al. also did not find a significantly increased risk of lung ADC or SCLC with respect to *OGG1* genotype (OR = 1.39; 95% CI = 0.61–3.19; Ser/Ser vs. Cys/Cys for ADC and OR = 1.22; 95% CI = 0.40–3.75; Ser/Ser vs. Cys/Cys for SCLC).¹⁹ A larger hospital-based study performed in Turkey generally supported these results, although the *OGG1* Ser326Cys polymorphism had a reduced lung cancer risk in smokers (Cys/Cys vs. Ser/Ser; adjusted OR = 0.62; 95% CI = 0.26–1.43).⁶¹ Kohno et al. found that the effect of the *OGG1* Ser326Cys gene polymorphism on lung ADC risk was not modified by smoking in this study population.³³ However, some lung cancer studies have suggested higher lung cancer risk associated with *OGG1* Cys/Cys vs. Ser/Ser,^{33,62,63} yet did not find an association between the *XRCC1* Arg399Gln gene polymorphism and lung cancer risk. These inconsistencies highlight the difficulties associated with comparing different genotypes and different cancer subtypes.⁶⁴

Nonsmokers who develop lung cancer provide a good model for investigating the effects of genetic polymorphisms. A hospital-based case-control ($n = 55$ lung cancers and $n = 74$ controls) study was conducted to evaluate the impact of polymorphisms on lung cancer risk in nonsmoking Chinese women. Although the sample size was small, this study was valuable because it only involved nonsmokers. A significant protective effect of the variant T allele of *XRCC1* (Trp194) was observed (T vs. C, OR = 0.51; 95% CI = 0.29–0.90, $p = 0.02$). Women carrying at least one variant T allele of *XRCC1* had a decreased risk of lung cancer compared with homozygous Arg194 wild type carriers (OR = 0.46; 95% CI = 0.22–0.96, $p = 0.04$).⁶⁵ Protective effects of the variant T allele of *XRCC1* Trp194 have been observed by De Ruyck et al. among Caucasian Belgians, and they reported that *XRCC1* Arg/Trp heterozygotes have a significantly reduced risk of lung cancer (OR = 0.32, $p = 0.024$).⁶⁶

Yin et al. found a significantly decreased risk of lung cancer associated with the Arg/His or His/His genotype of *XRCC1* at position 280 (OR = 0.38; 95% CI = 0.19–0.75, Arg/His + His/His vs. Arg/Arg, $p = 0.005$) in a larger population of ‘never-smokers’, while there was no interaction between Arg/His genotype and smoking.⁶⁷ In a population-based cohort of 57,053 Danes, messenger RNA (mRNA) levels of *OGG1*, *NEIL1* (nei endonuclease VIII-like 1 (*Escherichia coli*)), *MUTYH* (mutY Homolog (*E. coli*)) and *NUDT* and subsequent lung cancer risk was evaluated. Overall, mRNA levels of BER genes were not predictors of lung cancer risk. However, subjects with the *OGG1* Cys/Cys genotype had a reduced expression level of *OGG1* mRNA, and there was a positive association between the level and risk of lung cancer. Assuming that the amino acid substitution reduces repair capacity, as has been demonstrated in several independent studies,^{68,69} this observation might indicate that the expression of *OGG1* is regulated by the level of oxidative DNA damage. Finally, the intracellular level of *OGG1* Cys326 protein was directly correlated with urinary excretion of 8-oxoG, which could be interpreted as a biomarker of exposure to oxidative stress.⁹

Gastrointestinal cancer

Table 3 summarizes the associations of gene polymorphisms and gastrointestinal cancer. Gastric cancer is the second leading cause of cancer death and the fourth most common epithelial neoplasia worldwide, with the highest incidence in China, Japan and Eastern European countries.⁷⁰ According to the GLOBOCAN 2008 data, summary statistics indicate that the gastric cancer is fifth in males among the five most frequent cancers (prostate, lung, colorectal, bladder and stomach), whereas no gastric cancer is observed in females.⁷¹ A variety of factors including sodium intake, *Helicobacter pylori* infection and smoking induce inflammation in the stomach. An inflammatory cell infiltrate in the gastric mucosa increases the production of ROS, which causes potentially mutagenic 8-oxoG lesions in the DNA. In mammalian cells, 8-oxoG is repaired by BER enzymes such as *OGG1*, *MYH* and *NEIL1*. In addition, *MTH1*, a part of the defense system against oxidative damage, removes 8-oxo-dGTP from the nucleotide pool, thus preventing incorporation of the base lesion into DNA during replication. *OGG1*-c.977C>G (Ser326Cys) was associated with a difference in 8-oxoG repair capacity, and *MTH1*-c.247G>A (Val83Met) has been reported to be associated with increased risk of gastric cancer. These results suggest that SNPs *OGG1*-c.977C>G (Ser326Cys) and *MTH1*-c.247G>A (Val83Met) may lead to the accumulation of 8-oxoG in the gastric mucosa.⁷²

Li et al. conducted a population-based cohort study in China to evaluate the association between *H. pylori*-associated precancerous gastric lesions and the following polymorphisms: *XRCC1*, Arg399Gln and Arg194Trp; poly-ADP-ribose polymerase, Val762Ala; *OGG1* Ser326Cys and *APE1* Asp148Glu. An inverse association was found between *XRCC1* Arg/Trp + Trp/Trp and progression of gastric lesions, suggesting that Trp194 allele may play a protective role in this population. The *OGG1* Ser/Cys + Cys/Cys genotype was associated with an increased risk of progression in subjects with intestinal metaplasia or dysplasia at baseline, indicating that the Cys326 allele was a deleterious allele in this high-risk population.⁷³ In the Korean population, a similar protective effect of Trp194 was observed.⁷⁴ In particular, the frequencies of Trp194 or Gln399 homozygotes were similar in the cases and controls and were not associated with a risk of gastric cancer upon adjustment for age and sex. However, with the Arg194Arg genotype as the reference group, the combined genotype (Arg/Trp and Trp/Trp) specific OR was 0.66 (95%CI = 0.44–1.00, $p = 0.052$), indicative of the 194Trp allele operating as a protective allele for gastric cancer.⁷⁶

Malik et al. assessed the role of *OGG1* Ser326Cys in susceptibility to gastric cancer in Kashmir valley, where the incidence is three to six times higher than various metropolis cancer registries in India. No association was observed. However, smoking habit showed significantly higher risk in gastric cancer patients harboring the *OGG1* Ser/Cys genotype (OR = 8.975; 95% CI = 5.156–15.622; $p = 0.0001$), suggesting that the gene–environment interactions are more important in the development of gastrointestinal cancer compared with colorectal cancer. Higher consumption of salted tea was also found to be associated with increased risk of gastric cancer. Individuals that consumed salted tea in a range of two to eight cups per day and individuals that consumed salted tea of more than four cups per day were regarded as high salted tea consumers. However, when taking potential gene–environment interactions into account, there was no association of *OGG1* Ser326Cys gene

polymorphism with smoking and salted tea consumption. Therefore, the authors concluded that although the *OGGI* Ser326Cys gene polymorphism is reported to be a risk factor in some cancers, it does not appear to play a major role in gastric cancer development in Kashmir valley.⁷⁵

Yan et al. did not find any significant difference in allele and genotype distributions of *XRCCI* Arg/Trp or Arg/Gln genotypes between gastric cardia adenocarcinoma (GCA) and controls. However, smokers with the His allele at codon 280 had a significantly increased risk of GCA.⁷⁶ Since the Arg280His variant occurs in the proliferating cell nuclear antigen binding region,⁷⁷ the transition from a positively charged Arg to His within the conserved region could alter specific *XRCCI* functions. For the *XRCCI* Arg194Trp gene polymorphism, no association was found for the risk of GCA,⁷⁶ consistent with previous results conducted in China and Korean.^{73,74} In contrast, Yuan et al. found that the *XRCCI* Trp194 allele significantly increased the risk of gastric cancer and also associated with the risk of gastric cardia carcinoma and promoted distant metastasis of gastric cancer.⁷⁸ Thus, there are conflicting results on the association between gastric cancer and *XRCCI* or *OGGI* gene polymorphisms. These discrepancies may reflect differences in the study population or cancer location. Indeed, noncardia gastric cancer risk is positively associated with *H. pylori* infection, but cardia cancer is not. Ethnic differences may also influence gastric cancer risk. Palli et al. carried out a multigenic study on gastric cancer with polymorphic DNA repair and metabolic genes. A significant interaction of the *APE1* wild type genotype was observed with either the single *GSTT1* or double *GSTM1*–*GSTT1* null genotype or the *XPA* mutant allele, with *APE1* being protective for cancer susceptibility.⁷⁹

Bladder cancer

Table 4 summarizes the associations of gene polymorphisms and bladder cancer. In our previous work, we found the *OGGI* Cys/Cys genotype to be more frequent among bladder cancer patients (OR = 2.41; 95% CI = 1.36–4.25). However, no association was observed in the Arg399Gln gene polymorphism and the risk of bladder cancer (OR = 0.72; 95% CI = 0.41–1.26).⁸⁰ Huang et al. observed similar results regarding the *XRCCI* Arg399Gln gene polymorphism, but did not find any association with the *OGGI* Ser326Cys gene polymorphism and bladder cancer risk.⁶⁴

Breast cancer

Table 5 summarizes the associations of gene polymorphisms and breast cancer. Studies suggest that breast cancer is initiated by somatic mutations that may have been introduced during error-prone repair of estrogen-induced abasic sites.⁸¹ However, SNPs may modulate breast cancer risk, including *XRCCI* Arg194Trp and Arg399Gln, *APE1* Asp148Glu and *OGGI* Ser326Cys. Sigurdson et al. evaluated 19 SNPs in eight genes involved in BER (e.g. *XRCCI* and *APE1*), interactions with *BRCA1* (*BRIPI*, *ZNF350* and *BRCA2*) or growth regulation (*TGFβ1* and *IGFBP3*). *XRCCI* Arg194Trp and Arg399Gln polymorphisms were associated with increased breast cancer risk (*XRCCI* Arg/Arg vs. Arg/Trp + Trp/Trp, cumulative risk up to age 70 years, risk ratio (RR) = 2.3, 95% CI = 1.3–3.8; Arg/Arg vs. Gln/Gln, RR = 1.9, 95% CI = 1.1–3.9, respectively). However, *APE1* Asp148Glu was associated with a significantly lower risk than the homozygous genotype (RR = 0.2, 95% CI

= 0.1–0.5, *Asp/Asp* vs. *Glu/Glu*, cumulative risk up to age 70 years, $p < 0.001$). No associations were observed for the polymorphisms in the other genes noted above. Moreover, the study indicated that some *XRCC1* variants in combination with *BRCA1* are low penetrance breast cancer risk alleles.⁸² Recently, a study was conducted by Ali et al. on US women who carried *XRCC1* Arg399Gln variant, but not the commonly reported *APE1* Glu148 variant. This study reported that *XRCC1* Gln399 may enhance the risk of breast cancer.⁸¹

Although individual DNA repair genotypes might have a small effect, combined nsSNPs in multiple DNA repair pathways may have a larger effect on cancer risk. Smith et al. analyzed 18 nsSNPs in four DNA repair pathways in Caucasians and African Americans to evaluate potential associations with breast cancer risk. Their data suggested that in Caucasians, breast cancer risk was significantly associated with *APE1* Asp/Glu genotype (OR = 1.44; 95% CI = 1.03–2.00, Asp/Glu + Glu/Glu); this association was not observed in African Americans due to limited sample size.⁸³

Two large population-based studies (one in the United States and one in Poland), a hospital-based cohort study in Denmark and one hospital-based study in Taiwan found no significant association between *OGGI* Cys/Cys (*Cys/Cys* vs. *Ser/Ser*; adjusted OR = 1.00; 95% CI = 0.7–1.4 and OR = 0.98; 95% CI = 0.52–1.86; *Ser/Ser* vs. *Cys/Cys* for cohort study) or *XRCC1* Gln/Gln (*Gln/Gln* vs. *Arg/Arg*, adjusted OR = 0.8; 95% CI = 0.7–1.109) and breast cancer risk.⁸⁴ A smaller Taiwan hospital-based breast cancer study concurred with this result⁸³ data were adjusted for age, body mass index (BMI), family history of breast cancer in first-degree relatives, age at menarche, age at first full-term pregnancy, parity, age at menopause, menopausal status, hormone replacement therapy and highest level of education. In the Taiwan population, a significantly increased breast cancer risk was found for the *Cys/Cys* genotype (*Cys/Cys* vs. *Ser/Ser*; OR = 2.05; 95% CI = 1.14–3.69) in postmenopausal women.^{84–86} Yuan et al. investigated the effect of *OGGI* Ser326Cys gene polymorphism on the susceptibility to breast cancer with data collected in a meta-study, since the published studies on *OGGI* Ser326Cys polymorphism and breast cancer risk had inconsistent conclusions. The meta-analysis suggested that the *hOGGI* Cys326 allele is associated with significant protection against breast cancer in European women.⁸⁷

Gynecologic cancers and disorders

Table 6 summarizes the associations of gene polymorphisms and gynecologic cancers and/or disorders. Cervical cancer, including squamous cell carcinoma (SCC), ADC and adenosquamous cell carcinoma (ADSC) subtypes, is the third most common cancer worldwide. Cervical cancer is associated with persistent human papillomavirus infection in the minority of cases. Polymorphisms in the *OGGI* and *XRCC1* genes were not associated with cervical cancer risk.⁸⁸ In a hospital-based epidemiologic study conducted in Japan, there was no significant association between the *XRCC1* Arg399Gln gene polymorphism and risk of cervical cancer, when all histologic subtypes were included.⁸⁸ However, ADC/ADSC was associated with Arg/Gln (OR = 2.98; 95% CI = 1.11–8.01 for Gln/Gln and OR = 2.18; 95% CI = 1.11–4.26 for Arg/Gln + Gln/Gln in ADC and ADSC), whereas SCC was

not. Similar data for Gln/Gln were observed in never smokers (OR = 3.85; 95% CI = 1.28–11.59, $p = 0.017$), but not among smokers.⁸⁸

Endometriosis is a common, benign, estrogen-dependent, chronic gynecological disorder. Although multiple theories exist regarding the etiology of endometriosis, the exact pathogenesis remains uncertain. A recent study on a Turkish population showed no association between *XRCC1* Arg399Gln, *XRCC3* Thr241Met, *XPB* Lys751Gln, *XPD* Asp104His, *APE1* Asp148Glu and *hOGG1* Ser326Cys and endometriosis risk.⁴² However, the study sample size was very small (52 patients and 110 controls).

Uterine leiomyoma is the most common gynecological benign tumor of the myometrium. It is a significant cause of pelvic pain, abnormal uterine bleeding, infertility and pregnancy complications. Many factors including age, family genetics, emotional status, hormone levels and environmental factors may contribute to the development of this disease. One study investigated whether the different *XRCC1* codon polymorphisms were related to the occurrence of uterine leiomyoma in a Chinese population.⁸⁹ These investigators found a significant risk associated with codon 280 (OR = 3.633; 95% CI = 2.147–6.148; Arg/Arg vs. Arg/His), but no association with codons 399 and 194. However, the sample size again was small ($n = 136$), and further studies are therefore needed.⁸⁹

Upper aerodigestive cancer

Table 7 summarizes the associations of gene polymorphisms and UADC. Elahi et al. measured *OGG1* expression and the association between *OGG1* polymorphism and aerodigestive tract cancer. Significantly increased risk of orolaryngeal cancer was observed with decreased *hOGG1* expression in all the tissues (tongue, tonsil, mouth, larynx and esophagus).³⁶ Furthermore, although no association between *OGG1* genotype and orolaryngeal cancer risk was found in never smokers, significantly increased risk was observed in Cys/Cys smokers.³⁶ Hashimoto et al. confirmed this latter observation regarding the relationship of Cys326 and smoking status with cancer susceptibility (OR = 8.10; 95% CI = 1.06–61.73 for *OGG1* Cys/Cys).⁹⁰ For *XRCC1*, the polymorphic variants at codons 399, 194 and 280 were associated with increased risk of oral cancer in an Indian population. Moreover, smokers and betel quid chewers with the variant allele of *XRCC1* at position 399 also exhibited increased risk of oral cancer.⁹¹ The *XRCC1* Arg194Trp gene polymorphism was associated with increased risk of head and neck cancer in Korean and Hungarian populations,^{92–94} whereas no associations were reported for the other *XRCC1* polymorphisms. In a separate study, Kowalski et al. observed an increase risk with only Arg/Trp plus Trp/Trp genotypes at codon 194.⁹³ In the US population, no association was found with *APE1* Asp148Glu and *XRCC1* Arg399Gln, Arg280Trp and Arg194Trp gene polymorphisms and head and neck cancer risk.⁹⁴

The others

Table 8 summarizes the associations of gene polymorphisms and different cancer types (skin, acute lymphoblastic leukemia (ALL), head and neck, prostate, non-Hodgkin Lymphoma (NHL), brain, lung and UADC), with further discussion in each of the sections to follow.

Skin cancer—Sun exposure, but not history of sunburn, is recognized as an important risk factor for skin cancer development. Kang et al. found lower risk of SCC associated with *XRCCI* Arg194Trp and higher risk of basal cell carcinoma (BCC) associated with the Arg399Gln variant.⁴ Another study suggests that *XRCCI* Arg280His and Arg399Gln genotypes are risk factors for skin cancer.⁹⁵ A well-designed nested case-control study undertaken by the Danish prospective cohort ‘Diet, Cancer and Health’ involved 319 cases carefully matched with 319 controls recruited from a cohort of 57,053 Danes. However, no association was found between the *OGGI* Ser326Cys and risk of BCC (OR = 0.98, 95% CI = 0.70–1.37; for Ser326Cys, OR = 1.09; 95% CI = 0.59–2.03 for Cys/Cys). The lack of association may reflect low environmental exposure to sunlight in Denmark or selection of the *OGGI* SNP and this skin cancer subtype.⁶⁰

Acute lymphoblastic leukemia—ALL is characterized by improper development and differentiation of lymphoid progenitor cells. It is the most common childhood cancer with a peak at 2 ± 5 years of age.⁹⁶ The influence of the Arg194Trp, Arg280His and Arg399Gln polymorphisms of *XRCCI* on the development of childhood ALL was investigated in 120 patients and 120 controls in Mexico. No significant difference was observed between patients and controls (OR = 1.71, 95% CI = 0.65–4.48 for Arg/Arg vs. Gln/Gln, OR = 2.15; 95% CI = 0.52–8.89 for Arg/Arg vs. Trp/Trp and OR = 2.02; 95% CI = 0.18–22.72 for Arg/Arg vs. His/His).⁹⁷ The lack of association for the *XRCCI* Trp194 and Gln399 variants with ALL was similarly observed in Turkish children.⁹⁸ However, Matullo et al. found a 2.5-fold increased risk of ALL in patients carrying the Gln/Gln genotype.⁹⁹

Prostate cancer—Prostate cancer (PCa) is one of the most common malignancies in men in the Western countries and accounts for 31% of new annual cancer cases in men. The incidence of PCa varies greatly with race and geography.¹⁰⁰ Xu et al. investigated individual and joint effects of the three polymorphisms in *XRCCI* on PCa risk. The 194 Arg/Trp genotype was associated with lower risk of PCa than wild type, while Arg280His had no impact on PCa risk. Compared with wild type, Arg399Gln variant alone was associated with a statistically significant increased risk of PCa (adjusted OR: 3.19; 95% CI = 1.48–6.88). When the three polymorphisms (Arg194Trp, Arg280His and Arg399Gln) were evaluated in combination, subjects with a Arg/Arg, Arg/His and Arg/Gln genotype had a significantly higher risk of PCa (adjusted OR = 4.31; 95% CI = 1.24–14.99).¹⁰¹

Non-Hodgkin lymphoma—NHL represents a heterogeneous group of lymphocytic disorders ranging in aggressiveness from indolent to highly aggressive and rapidly proliferative. Although it is the fifth cause of cancer mortality in the United States, NHL remains poorly understood and is largely incurable.¹⁰² Well-known risk factors include family history, immune dysfunction (e.g. autoimmune diseases, immune deficiency syndromes and iatrogenic immunosuppression after organ transplant), immune stimulation and infection (e.g. human T-lymphotrophic virus type I and human immunodeficiency virus). Occupational and environmental exposures have also been proposed as risk factors for NHL.¹⁰³ SNP variants of *XRCCI* Arg399Gln, Arg194Trp and Arg280His were not significantly related to the risk of NHL subtypes, including diffuse large B cell lymphoma or follicular lymphoma. However, two combinations of SNP variants (Arg/Gln + Gln/Gln or

Arg/Trp + Trp/Trp or Arg/His + His/His vs. wild genotype) showed a trend of increased risk, suggesting an 'additive' effect. Regarding smoking status, individuals with at least one Arg399Gln variant allele have a threefold increase in follicular lymphoma risk (adjusted OR = 3.01; 95% CI = 1.16–7.82) compared with heavy smokers with the wild type genotype.¹⁰⁴ However, as these past studies involved about 200 cases and controls, larger scale studies are needed.

Hepatocellular carcinoma—Hepatitis B virus (HBV) and hepatitis C virus (HCV) increase chromosomal instability and insertional mutagenesis and are primary risk factors for hepatocellular carcinoma (HCC). Approximately 30–50% of HBV-related deaths are attributable to HCC; however, only 2.5% of HCV-infected individuals develop HCC. The association between *XRCCI* (codons 194, 280 and 399) and hepatitis virus-related HCC was investigated in an Indian population. The homozygous variant genotypes at codons 194 and 399 were protective for HCC risk (OR = 0.78 and 0.33, respectively). Arg/Trp and Arg/His heterozygosity at positions 194 and 399 increased risk to approximately twofold (OR = 2.27; 95% CI = 1.01–5.08; $p < 0.001$) or fivefold (OR = 4.95; 95% CI = 2.48–9.89; $p < 0.001$), respectively, for HCC, and twofold (OR = 2.25; 95% CI = 1.02–5.00; $p < 0.05$) and sixfold (OR = 6.27; 95% CI = 3.13–12.58), respectively, for viral hepatitis in healthy subjects. The Arg280His variant genotype had a twofold increased risk of HCC. Arg/Trp + Arg/His and Arg/Gln + Arg/His combinations were 35.96- and 5.28-fold more frequently associated with HCC, respectively. Gln/Gln at codon 399 was negatively associated with HCC. No association was observed for the risk of HCC and chronic viral hepatitis B and C.¹⁰⁵

Gall bladder tract cancers—The gallbladder is susceptible to ROS-induced DNA damage, lipid peroxidation and biliary stasis. Since *XRCCI* and *OGGI* play important roles in the repair of oxidative DNA damage. Srivastava et al. investigated the role of *OGGI* Ser326Cys and *XRCCI* Arg399Gln gene polymorphisms in gallbladder cancer (GBC) susceptibility. The frequency of the variant *OGGI* Cys/Cys genotype in female GBC patients was significantly higher than in controls (OR = 5.92; 95% CI = 1.20–29.13). However, this significance vanished when Ser/Cys + Cys/Cys genotypes were combined and compared with wild type. Disease risk due to the *OGGI* Ser326Cys polymorphism in female GBC patients may be due to gallstone complications, which are more predominant in females, or may reflect the larger sample size of this group. In GBC, the Cys allele may be recessive, so that homozygote carriers could potentially have increased risk of the disease.⁴⁴ The frequency of *XRCCI* Arg/Gln and Gln/Gln genotypes for codon 399 was significantly different from controls ($p = 0.039$ and 0.003 , respectively) and conferred low risk of GBC; a trend test was also significant ($p = 0.001$ for trend). Another study on biliary system cancer was performed by Huang et al. They found that *XRCCI* Arg/Gln and *OGGI* Cys/Cys genotypes were unrelated to GBC risk and suggested that the replication in future epidemiological studies is required to confirm the association of biliary tract cancer with the polymorphisms in *OGGI* and *XRCCI* genes.¹⁰⁶

Brain tumors—*XRCCI* Arg399Gln, Arg194Trp and Arg280His gene polymorphisms were not significantly associated with the risk of brain tumors; however, homozygous Gln/Gln showed a nearly statistically significant association with risk of all brain tumor

types (i.e. glioma, glioblastoma and meningioma; OR = 1.32; 95% CI = 0.97–1.81; OR = 1.48; 95% CI = 0.98–2.24 and OR = 1.34; 95% CI, 0.96–1.86, respectively). There was no significant difference in the risk of brain tumors between carriers and noncarriers of the variant *XRCC1* alleles Trp194 and His280.¹⁰⁷

Thyroid carcinoma—Thyroid cancer is the most prevalent endocrine malignancy, and the incidence rate has increased in recent decades. The relationship between Arg399Gln, Arg280His, Arg194Trp in *XRCC1* or Asp148Glu in *APE1* and the risk of differentiated thyroid carcinoma and regional lymph node (LN) metastasis was examined. Only *XRCC1* Arg194Trp was identified as having a possible association with the risk of thyroid cancer and LN, which may be increased by SNPs in other DNA repair genes.¹⁰⁸

Discussion

DNA damage is generated by a variety of endogenous and exogenous chemical and physical agents. To prevent the potentially mutagenic or lethal consequences of DNA modifications, cells have evolved a series of complementary yet distinct DNA repair processes. The BER pathway copes with most spontaneous forms of DNA damage, including oxidative lesions such as base modifications, abasic sites and single-strand breaks. Not surprisingly, there is evidence that deficiencies in BER are associated with elevated risk of cancer, neurodegenerative disease and premature aging phenotypes. Thus, for the past decade or more, epidemiologists have determined the association of specific SNPs in BER genes with susceptibility to a range of cancer types, with or without a relevant exposure. We present in this review a summary of several key molecular epidemiology studies focused on the *OGG1* Ser326Cys, *APE1* Asp148Glu and *XRCC1* Arg399Gln, Arg280His and Arg194Trp polymorphic variants. Based on the articles reviewed herein, we conclude the following.

1. No association was observed between *XRCC1* Arg399Gln, Arg280His and Arg194Trp gene polymorphisms and colorectal cancer risk; however, *OGG1* Ser326Cys and *APE1* Asp148Glu increased colorectal cancer risk in some instances. Smoking and red meat consumption modifies the increased risk of colorectal cancer associated with the *OGG1* Cys/Cys genotype. The gene–environment interaction between current smoking and *APE1* (Glu/Glu and Asp/Glu + Glu/Glu) and *XRCC1* (Arg/Trp) gene polymorphisms was statistically significant for colorectal cancer risk. Smoking is associated with significantly increased cancer risk in subjects with *XRCC1* Arg399Gln genotype when combined with *XRCC3* Thr241Thr and *XPB* 751Gln allele. The intake of meat and animal fat was consistently associated with the increased risk of large-bowel cancer. It was suggested that the abundant iron after red meat intake and inadequate activity of bile pigments to act as iron chelators would stimulate the Fenton reaction, which produces superoxide radicals. In addition, excessive fat intake increases the concentration of bile acids, which act as cytotoxic surfactants and can damage the colon.
2. Gene–environment interactions are much more important in the development of gastrointestinal cancer than colorectal cancer. While no association was reported between BER gene polymorphisms (i.e. *OGG1* Ser326Cys, *APE1* Asp148Glu and

XRCCI Arg399Gln, Arg194Trp and Arg280His) and gastrointestinal cancer, when adjusted for smoking status, alcohol and red meat, the interaction of genotypes with lifestyle factors (such as environmental risks, dietary habits and cigarette smoking) significantly increased the risk of development of gastrointestinal cancer. However, there are conflicting results on the association between gastrointestinal cancer and these gene polymorphisms due to the differences in the study population or cancer location.

3. The effect of *OGGI* polymorphism on lung cancer risk differs in Caucasian and Asian individuals. *OGGI* polymorphism has a significant impact on lung cancer risk in Caucasians, yet not in Asians. *OGGI* Ser/Cys polymorphism is protective in smokers in a few studies, but not in all studies performed to date. One possible explanation for the protective effect is that the cells carrying the protective allele incur more DNA damage and undergo apoptosis more frequently than cells with the nonprotective allele. Some *XRCCI* gene polymorphisms have a protective effect in nonsmokers in comparison with smokers.
4. Bladder and lung cancers are smoking-related cancers. Strong associations were reported between *OGGI* Cys/Cys genotype and bladder cancer in smoker subjects. Conversely, no association was reported with nonsmokers and the *APE1* Asp148Glu gene polymorphism. These conclusions are, however, based on a limited number of studies.
5. *OGGI* Ser326Cys polymorphism and breast cancer risk had an inconsistent relationship. The risk of breast cancer was increased when the *XRCCI* Arg/Gln and Arg/Trp genotypes were combined with *BRCA1*. Similarly, the risk of gynecological cancer increased with the *XRCCI* Arg399Gln gene polymorphism. Notably, the codon 399 variant of *XRCCI* lies near the BRCT-1 domain, a region that facilitates a biologically relevant interaction with PARP-1 with extensive homology to BRCA1.¹⁰⁹ The conclusions regarding breast cancer risk and BER polymorphisms are also based on a limited number of studies.
6. UADC is another smoking related cancer type. Thus, smoking interacts strongly the risk of UADC in individuals with *OGGI* Ser326Cys and *XRCCI* Arg399Gln or Arg194Trp polymorphism.
7. For skin cancer and other cancers (Table 8), the most studied polymorphisms are *XRCCI* Arg399Gln, Arg194Trp and Arg280His. A two-to fourfold increased cancer risk has been observed with these polymorphisms and each of these cancer types. Cancer subtypes are important and modulate the risk of cancer. For example, while Arg/Trp genotype reduces the risk of SCC, Arg/Gln genotype increases the risk of BCC. For GBC, a strong association with *OGGI* Cys/Cys in females was reported. However, this association disappeared when genotypes were combined (Ser/Cys + Cys/Cys).

It still remains somewhat unclear whether the polymorphisms in *OGGI* Ser326Cys, *APE1* Asp148Glu or *XRCCI* Arg399Gln, Arg280His and Arg194Trp directly or indirectly affect either protein levels or activities, which would be instrumental in modifying risk of different

cancer types³⁷ (see further discussion in the study by Wilson et al.³⁷). However, while we advocate prospective examination of the associations between polymorphisms and cancer risk, it is always difficult to unambiguously incorporate environmental risk factor data (smoking, drinking, diet, etc.) into gene polymorphism–cancer association analysis due to uncertainties about the past. Thus, in some studies, alternative definitions for the environmental risk factors were used to try to resolve this problem. Nevertheless, simple and common study designs to evaluate gene polymorphism–cancer association have been the case-control approach. This method is easier and cheaper than other alternative protocols, although it may cause substantial bias and spurious associations as most required expectations cannot be met. Also, case-control studies on genetically homogenous or heterogenous populations may modify the results of the analysis.

Epidemiological investigations of DNA repair polymorphisms must be adequately designed with respect to sample size and the selection of polymorphisms and due to the small sample size of most of the studies to date, inconsistent results can be expected. Only six studies considered in this review had a sample size more than 1000,^{12,33,46,62,84} and these studies would be expected to give more accurate results with greater statistical power. In general, a large sample size reduces false-positive and false-negative results and provides more reliable data. It can, however, be very difficult to enroll enough patients for comprehensive association studies. Moreover, it is difficult to carry out multicentric hospital- and population-based studies in some countries. Furthermore, in most developing countries, follow-up studies and use of survey instruments are difficult. This leads to a small sample size in studies that are performed in developing countries. For example, in Turkey, it is very hard to get enough samples to carry out Genome Wide Association Studies (GWAS) or to obtain good statistics showing cancer frequencies.

In addition to the rationale, targeted SNP association studies described herein, GWAS are an important approach for discovering genetic variants influencing cancer risk. GWAS permits interrogation of the entire human genome at levels of resolution previously unattainable, in thousands of unrelated individuals, while many other approaches are biased by specific hypotheses regarding disease mechanism. On the other hand, to rule out false positive GWAS results, statistical analyses must be held to very high stringency and study replication is essential to account for biased representation in the study population and/or genotyping errors. For this reason, meta-analyses may be more valuable. However, meta-analyses also has limitations, such as (a) eligibility criteria for inclusion of subjects and sources of controls may differ among studies; (b) it is difficult to rule out incipient cancer in the controls and (c) gene–gene and gene–environment interactions may not be addressed because of the lack of sufficient data. Another weak aspect of GWAS is that many polymorphisms have different distributions and frequencies in different populations or geographic regions and consequently, association studies in mixed populations may produce false positive results. Confounding factors such as diet, smoking status, hormonal status and BMI should be considered in all GWAS studies. The selection of gene variants is also important and should consider functional outcome and phenotypic effect. Gene–gene interactions and their synergistic or additive effects should be considered as well as cancer type, stage or grade, patient ethnicity and population structure. DNA repair activity, when considered, should be quantified using the most accurate available methods, and/or multiple

methods, where possible. mRNA or protein levels can also be used for additional evidence of DNA repair capacity.

Conclusion

In conclusion, to fully understand the role of DNA damage and DNA repair in the carcinogenesis, prospective studies are needed and additional genes should be analyzed. Such studies should investigate mRNA expression, DNA damage levels and DNA repair capacity and should consider gene–environment and gene–gene interactions.

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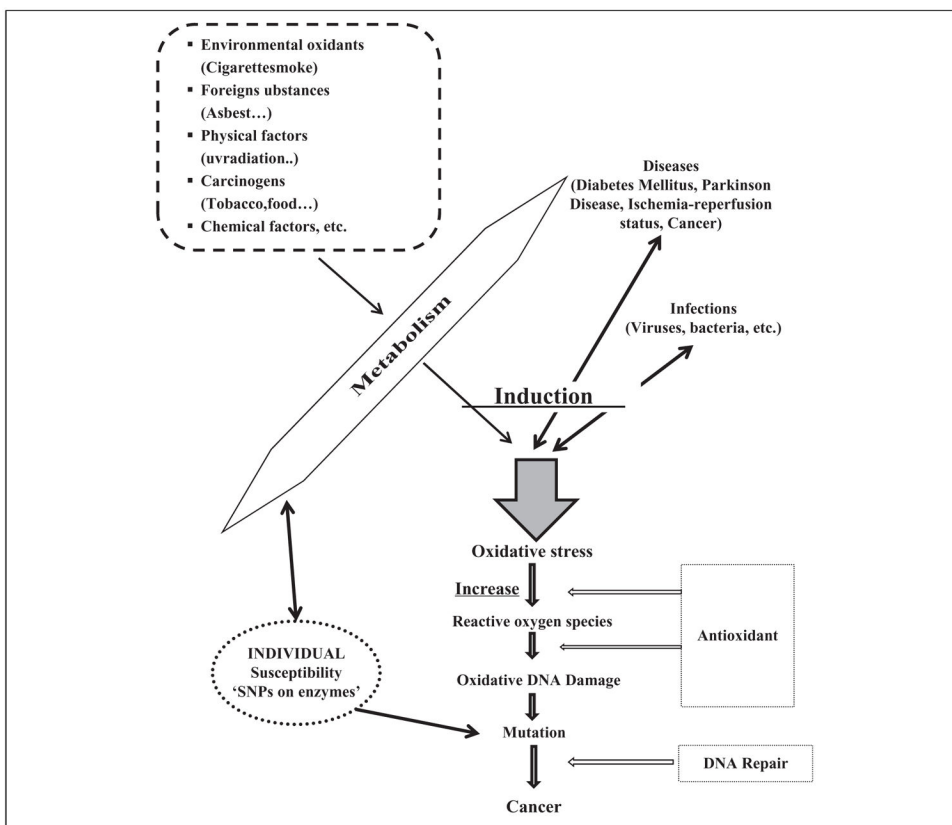


Figure 1. The relationship between oxidative DNA damage, carcinogenesis and environmental factors and their link with individual susceptibility.

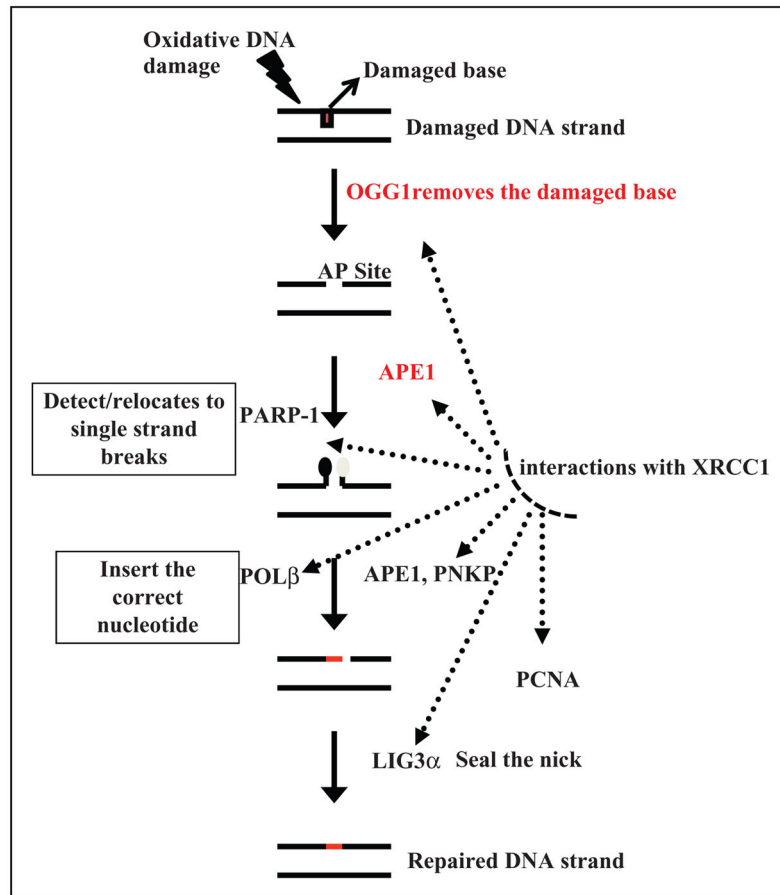


Figure 2.
The roles of OGG1, XRCC1 and APE1 protein in base excision repair.

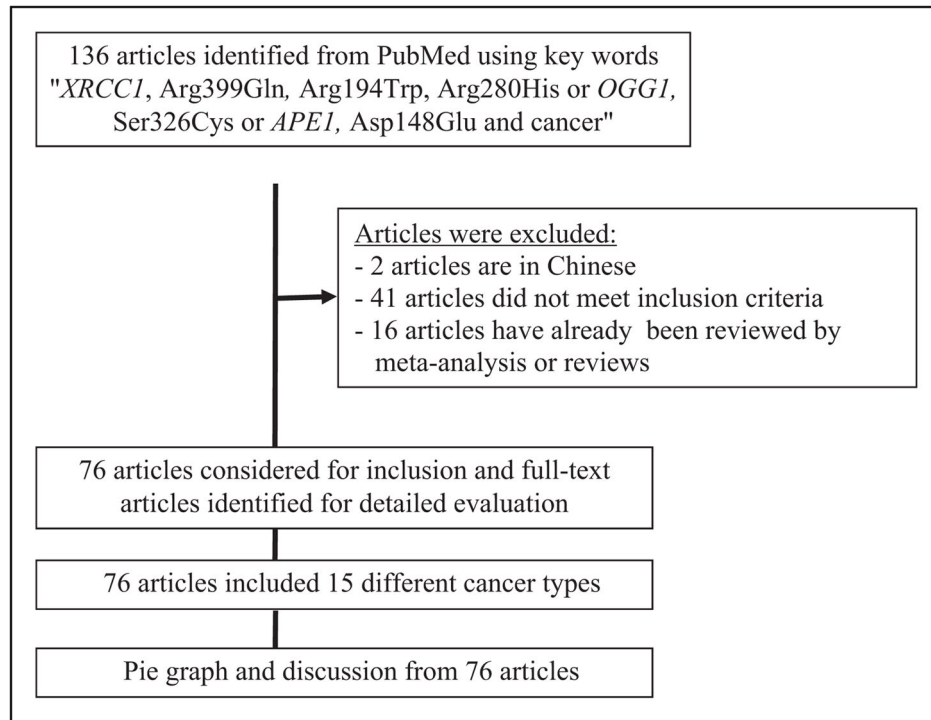


Figure 3.
Flow chart of selection of studies.

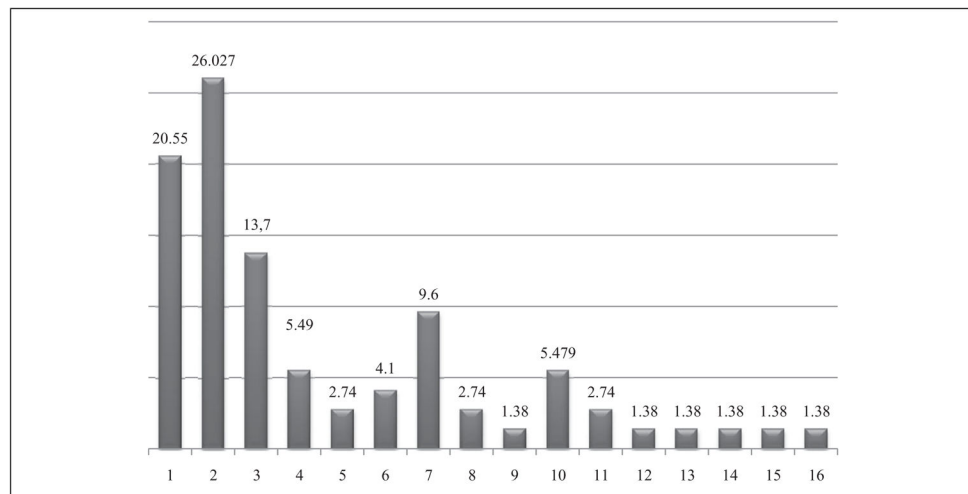


Figure 4. Distribution in cancer types (%) among individuals in the population discussed in this review. 1. Colon cancer; 2. Lung cancer; 3. Gastric cancer; 4. Bladder cancer; 5. Biliary tract cancer; 6. Upper aerodigestive cancer; 7. Breast cancer; 8. ALL; 9. Head and neck cancer; 10. Gynecological cancers; 11. Skin cancer; 12. Hepatocarcinoma; 13. Thyroid cancer; 14. Brain cancer; 15. Prostate cancer; 16. Non-Hodgkin lymphoma. Oral/pharyngeal cancers and laryngeal cancers were pooled and defined as upper aerodigestive cancer. Colon and colorectal cancer were pooled and defined as colon cancer. Biliary tract and gallbladder cancer were pooled and defined as biliary tract cancer. Mesothelioma, lung and non-small-cell lung carcinoma were pooled and defined as lung cancer. Precancerous gastric lesions, gastric cancer and gastric cardiac adenocarcinoma were pooled and defined as gastric cancer. Cervix, endometriosis and uterine leiomyoma were pooled and defined as gynecological cancer.

Table 1
 Summary of findings from case-control studies of genetic polymorphisms in DNA repair genes (*OGG1*, *APE1* and *XRCC1*) and their interactions with environmental factors and colorectal cancers including colon, rectum and colorectal

Study population	No. of cases/controls	Main effects of polymorphisms			Gene-environment interaction	References
		OGG1 Ser326Cys	XRCC1 (Arg399Gln, Arg194Trp, Arg280His)	APE1Asp148Glu		
American (H)	1582/1951	1.3-fold IR (Cys/Cys and Ser/Cys + Cys/Cys)	NA (Arg/Gln) 1.2-fold IR (Arg/Trp + Trp/Trp) - (Arg/His)	-	-	Curtin et al. ⁴⁶
Korean (H)	125/247	NA	-	-	S: 2.5- to 3-fold IR (Cys/Cys) RM: 4.5-fold IR (2 times/week)	Kim et al. ⁴⁷
Norwegian (H)	166/974	RR (Cys/Cys) (adenoma, ADC)	-	-	-	Hansen et al. ⁴⁸
Norwegian (H)	1100/399	-	NA (C, ADC)	RR (Arg/Gln) IR (Arg/His)	-	Skjelbred et al. ⁴⁹
Spanish (H)	377/329	2-fold IR (Cys/Cys)	NA (Arg/Trp)	3-fold IR (Asp/Glu)	-	Moreno et al. ⁵⁰
Czech Republic (H)	532/532	6- to 7-fold IR (OGG1 Cys/Cys + APE1 Glu + Glu)	NA (Arg/Gln, Arg/Trp) - (Arg/His)	IR (Colon, colorectal) (Asp/Glu)	S: 4- and 5-fold IR (Cys/Cys)	Pardini et al. ⁵¹
Japanese (H)	68/121	NA	NA	2.3-fold IR (Asp/Glu + Glu/Glu)	S: 5-fold IR (Asp/Glu + Glu/Glu)	Kasahara et al. ⁵²
Chinese (P)	303/1159 294/1120	NA	NA (Arg/Gln, Arg/Trp) - (Arg/His)	-	S:1.5- to 2-fold IR (Arg/Trp, Trp/Trp)	Stern et al. ⁵³
Turkish (H)	110/116	NA	-	-	NA	Engin et al. ⁵⁴
Indian (H)	302/291	-	1.6-fold IR (Rectal Cancer in males, Gln399 allele) - (Arg/His, Arg/Trp)	-	S:1- to 1.5-fold IR (Arg/Arg) 2-fold IR rectal cancer for vegetarians	Wang et al. ⁵⁵

-: Unreported; NA: no association; IR: increased risk; RR: reduced risk; S: smoking; RM: red meat; H: hospital based study; P: population based study.

Table 2

Summary of findings from case-control studies of genetic polymorphisms in DNA repair genes (*OGG1*, *APE1* and *XRCC1*) and their interactions with environmental factors and lung cancer

Study population	No. of Cases/Controls	OGG1 Ser326Cys	Main effects of polymorphisms			Gene-environment interaction	References
			XRCC1 (Arg399Gln, Arg194Trp, Arg280His)	APE1Asp148Glu	APE1Asp148Glu		
German (H)	463/460	NA	2-fold IR (Arg/Gln + Gln/Gln) -(Arg/His, Arg/Trp)	RR (Glu/Glu)	-	Popanda et al. ⁵⁹	
Chinese (H)	350/350	-	2-fold IR (Arg/Gln, Gln/Gln) NA (Arg/His, Arg/Trp)	-	-	Li et al. ⁸	
Danish(H)	256/269	NA	NA (Arg/Gln, Arg/His);-(Arg/Trp)	-	-	Vogel et al. ⁶⁰	
Japanese (H)	108/121	NA (ADC, SCC)	-	-	-	Miyaishi et al. ¹⁹	
Turkish (H)	165/250	NA	-	-	IE (Cys/Cys) (heavy smokers)	Karahalil et al. ⁶¹	
Japanese (H)	1097/394	IR (Cys/Cys)	-	-	S; 1.5-fold IR (Ser/Cys)	Kohno et al. ³³	
Caucasian Asian (H)	2569/4178	1.5-fold IR (Cys/Cys)	NA	NA	-	Hung et al. ⁶²	
Norwegian (H)	326/386	1.6-fold IR (Cys/Cys)	NA (Arg/Gln, Arg/His, Arg/Trp)	NA	-	Zieboldiny et al. ⁶³	
Chinese (P)	-/1281	NA	1.5-fold IR (Arg/Arg + Trp/Trp) NA (Arg/Gln);-(Arg/His)	NA	-	Li et al. ⁷³	
Belgian (H)	220/350	NA	NA	IR (Asp/Glu Glu/Glu)	-	DeRuyck et al. ⁶⁶	
Chinese (H)	247/253	-	RR (Arg/His + His/His)	-	NA	Yin et al. ⁶⁷	

SCC: squamous cell carcinoma; BCC: basal cell carcinoma; ADC: adenocarcinoma; C: carcinoma; -: unreported; NA: no association; IR: increased risk; RR: reduced risk; S: smoking; D: drinking; RM: red meat; H: hospital based study; P: population based study.

Table 3

Summary of findings from case-control studies of genetic polymorphisms in DNA repair genes (*OGG1*, *APE1* and *XRCC1*) and their interactions with environmental factors and gastrointestinal cancer

Study population	No. of cases/controls	Main effects of polymorphisms				Gene-environment interaction	References
		OGG1 Ser326Cys	XRCC1 (Arg399Gln, Arg194Trp, Arg280His)	APE1 Asp148Glu			
Chinese (H)	1281	IR; (Ser/Cys + Cys/Cys)	PE; (Arg/Trp + Trp/Trp) NA (Arg/Gln), -(Arg/His)	NA	S; 1.5-fold IR (Ser/Cys + Cys/cys)	Li et al. ⁷³	
Korean (H)	190/172		RR; (Arg/Trp + Trp/Trp)			Lee et al. ⁷⁴	
Indian (H)	108/195	NA	-	-	S; 8-fold IR (Ser/Cys); NA, salted tea	Malik et al. ⁷⁵	
Chinese (H)	455/650	-	NA (Arg/Trp), NA (Arg/Gln) -(Arg/His)	-	S; 1.5-fold IR (Arg/His + His/His)	Yan et al. ⁷⁶	
Chinese (H)	190/180	-	IR (Arg/Trp) NA (Arg/His) -(Arg/Gln)	-	S; IR (Arg/His + His/His)	Yuan et al. ⁷⁸	

–: Unreported; NA; no association; IR: increased risk; RR: reduced risk; PE: protective effect; S: smoking; H: hospital based study.

^aGastric Cancer includes gastric cardiac carcinoma.

Table 4

Summary of findings from case-control studies of genetic polymorphisms in DNA repair genes (*OGG1*, *APE1* and *XRCC1*) and their interactions with environmental factors and bladder cancer

Study population	No. of cases/controls	Main effects of polymorphisms			Gene-environment interaction	References
		<i>OGG1</i> Ser326Cys	<i>XRCC1</i> (Arg399Gln, Arg194Trp, Arg280His)	<i>APE1</i> Asp148Glu		
Turkish (H)	100/100	2.5-fold IR (Cys/Cys)	NA	-	Not interaction with smoking	Karahalil et al. ⁸⁰
Caucasian (H)	609/613	NA	PE (Arg/Trp + Trp/Trp)	NA	IR (Cys/Cys) (ever smokers) No interactions (Others)	Huang et al. ⁶⁴
American (H)	539/524	NA	NA (Arg/Gln, Arg/Trp) -(Arg/His)	-	RR (Ser/Cys) (ever smokers)	Huang et al. ⁶⁴

-. Unreported; NA; no association; IR: increased risk; RR: reduced risk; PE: protective effect; S: smoking; RM: red meat; H: hospital based study.

Table 5

Summary of findings from case-control studies of genetic polymorphisms in DNA repair genes (*OGG1*, *APE1* and *XRCC1*) and their interactions with environmental factors and breast cancer

Study population	No. of cases/controls	Main effects of polymorphisms			Gene-environment interaction	References
		OGG1 Ser326Cys	XRCC1 (Arg399Gln, Arg194Trp, Arg280His)	APE1 Asp148Glu		
American (H)	748/2240	-	2.3-fold IR; (Arg/Trp + Trp/Trp) 1.3-fold IR (Gln/Gln)	IE;(Glu/Glu)	-	Sigurdson et al. ⁸²
Caucasian (H)/African-American (AA)(H)	336/416 63/78	-	NA	1.5-fold IR (Asp/Glu + Glu/Glu)	-	Smith et al. ⁸³
USA (P) Poland	1571/1784 1470/1366	NA	NA	NA	No change (Pre and post-menopausal status)	Zhang et al. ⁸⁴
Danish (H)	425/434	NA	-	-	-	Vogel et al. ⁸⁵
Taiwanese (H)	506/424	NA	NA (Arg/Trp, Arg/His) -(Arg/Gln)	NA	-	Sangrajrang et al. ⁸⁶

-: Unreported; NA; no association; IR: increased risk; RR: reduced risk; S: smoking; D: drinking; RM: red meat; H: hospital based study; P: population based study

Table 6

Summary of findings from case-control studies of genetic polymorphisms in DNA repair genes (*OGG1*, *APE1* and *XRCC1*) and their interactions with environmental factors and gynecological (GyC) cancer

Study population	No. of cases/controls	Main effects of polymorphisms				Gene-environment interaction	References
		<i>OGG1</i> Ser326Cys	<i>XRCC1</i> (Arg399Gln, Arg194Trp, Arg280His)	<i>APE1</i> Asp148Glu			
Japanese (H) ^a	131/320	NA	2- to 3-fold IR (Arg/Gln and Arg/Gln + Gln/Gln; ADC/ADSC)-	-	NS; 3.85-fold IR	Niwa et al. ⁸⁸	
Chinese ^b (H)	136/140	-	2-fold IR (Arg/His) NA; (Arg/Gln, Arg/Trp)	-	-	Yang et al. ⁸⁹	

ADC: adenocarcinoma; ADSC: adenosquamous cell carcinoma; -: Unreported; NA: no association; IR: increased risk; RR: reduced risk; S: smoking; NS: never smoker; H: hospital based study.

^a Cervical cancer.

^b Uterine leiomyoma.

Table 7

Summary of findings from case-control studies of genetic polymorphisms in DNA repair genes (*OGG1*, *APE1* and *XRCC1*) and their interactions with environmental factors and upper aero digestive cancer (UADC^a)

Study population	No. of cases/controls	Main effects of polymorphisms			Gene-environment interaction	References
		<i>OGG1</i> Ser326Cys	<i>XRCC1</i> (Arg399Gln, Arg194Trp, Arg280His)	<i>APE1</i> Asp148Glu		
Japanese (H)	192 ^a	NA	-	-	S; 8-fold IR (Cys/Cys); D; NA	Hashimoto et al. ⁹⁰
Indian (H)	200/110	-	2- to 13-fold IR (Gln/Gln, Arg/Gln + Gln/Gln, Arg/Trp, Arg/Trp + Trp/Trp)	-	S; IR (Arg/Gln + Gln/Gln)	Ramachandran et al. ⁹¹
Korean (H)	147/168	-	2.6-fold IR (Arg/Trp, Trp/Trp)	-	-	Tae et al. ⁹²
Polish (H)	92/124	-	IR (Arg194Trp + Arg399Arg) NA others	-	NA	Kowalski et al. ⁹³
American (H)	830/854	-	NA (Arg/Gln)	NA (Asp/Glu)	NA	Li et al. ⁹⁴

UADC: upper aero digestive cancer including oral, pharynx, laryngeal, esophageal, head and neck; -: unreported; NA: no association; IR: increased risk; S: smoking; D: drinking; H: hospital based study.

^a Case only design.

Table 8

Summary of findings from case-control studies of genetic polymorphisms in DNA repair genes (*OGG1*, *APE1* and *XRCC1*) and their interactions with environmental factors and different cancer types (skin, ALL, prostate, NHL, brain, lung, UADC, ALL)

cancer Type	Study population	No. of cases/controls	Main effects of polymorphisms			Gene-environment interaction	References
			OGG1 Ser/Cys	XRCC1 (Arg/Gln, Arg/Trp, Arg/His)	APE1Asp/Glu		
Skin	Korean (H)	212/207	-	RR (Trp/Trp) SCC IR (Arg/Gln, Arg/Gln + Gln/Gln) BCC	-	-	Kang et al. ⁴
ALL	Mexican (H)	120/120	-	NA	-	-	Meza-Espinoza et al. ⁹⁷
Brain, lung, UADC, ALL	European (H)	567/1094	-	2.5-fold IR (Gln/Gln) (ALL), NA; Others	-	-	Miatullo et al. ⁹⁹
Prostate	Korean (H)	207/235	-	4-fold IR (Arg/Gln, Arg/Gln + Gln/Gln)	-	-	Xu et al. ¹⁰¹
NHL	Chinese (H)	221/254	-	3-fold IR (Arg/Gln + Gln/Gln, Arg/Trp + Trp/Trp, Arg/His + His/His)	-	-	Liu et al. ¹⁰⁵
HCC	Indian (H)	-	-	2.27- and 4.95-fold IR (Arg/Trp and Arg/His)	-	-	Kiran et al. ¹⁰⁶
Brain	Caucasian (H)	1225/1560	-	NA (Arg/Gln, Arg/Trp, Arg/His)	-	-	Kituru et al. ¹⁰⁸
DTC	Caucasian (H)	-	-	IR (Trp/Trp) DTC 4.5-fold IR LN	NA	-	Chiang et al. ¹⁰⁹

ALL: acute lymphoblastic leukemia; NHL: non-Hodgkin lymphoma; HCC: hepatocellular carcinoma; GBC: gall bladder cancer; DTC: differentiated thyroid carcinoma; LN⁶: regional lymph node; SCC: squamous cell carcinoma; BCC: basal cell carcinoma; -: unreported; NA: no association; IR: increased risk; RR: reduced risk; S: smoking; RM: red meat; H: hospital based study; P: population based study.