REVIEW ARTICLE

Polymorphisms in human DNA repair genes and head and neck squamous cell carcinoma

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Abstract

Genetic polymorphisms in some DNA repair proteins are associated with a number of malignant transformations like head and neck squamous cell carcinoma (HNSCC). Xeroderma pigmentosum group D (*XPD*) and X-ray repair cross-complementing proteins 1 (*XRCC1*) and 3 (*XRCC3*) genes are involved in DNA repair and were found to be associated with HNSCC in numerous studies. To establish our overall understanding of possible relationships between DNA repair gene polymorphisms and development of HNSCC, we surveyed the literature on epidemiological studies that assessed potential associations with HNSCC risk in terms of gene–environment interactions, genotype-induced functional defects in enzyme activity and/or protein expression, and the influence of ethnic origin on these associations. We conclude that large, well-designed studies of common polymorphisms in DNA repair genes are needed. Such studies may benefit from analysis of multiple genes or polymorphisms and from the consideration of relevant exposures that may influence the likelihood of HNSCC when DNA repair capacity is reduced.

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Introduction

DNA in most cells is regularly damaged by endogenous and exogenous mutagens. Unrepaired damage can result in apoptosis or may lead to unregulated cell growth and cancer (Cao *et al.* 2011). If DNA damage is recognized by cell machinery, several responses may occur to prevent replication in the presence of genetic errors. At the cellular level, checkpoints can be activated to arrest the cell cycle, transcription can be upregulated to compensate for the damage, or the cell can undergo apoptosis (Vispe *et al.* 2000). Alternatively, the damage can be repaired at the DNA level enabling the cell to replicate. Complex pathways involving numerous molecules have evolved to perform such repair (Knudson 1989; Shields and Harris 1991). Because of the importance of maintaining genomic integrity in the general and specialized functions of cells, as well as in the prevention of carcinogenesis, genes coding for DNA repair enzymes have been proposed as candidate cancer-susceptibility genes (Knudson 1989; Shields and Harris 1991).

Head and neck squamous cell carcinoma (HNSCC) is the fifth most common cancer worldwide and is associated with low survival and high morbidity when diagnosed in advanced stage (Gallegos-Hernández 2006; Penel *et al.* 2007) accounting for nearly 500,000 newly diagnosed cancer cases per year (Parkin *et al.* 1992; Mao *et al.* 2004; Sturgis *et al.* 2004). Epidemiological studies have shown that HNSCC occurs through a complex multistage process that may involve exposure to a combination of carcinogens from cigarette smoking (Frank 2004; Vineis *et al.* 2004), alcohol consumption (Viswanathan and Wilson 2004) or tobacco chewing (Brennan and Boffetta 2004). Individuals differ widely in their capacity to repair DNA damage on exposure to exogenous sources like tobacco smoke, smokeless tobacco and alcohol, and to endogenous reactions involving oxidants (Valko *et al.* 2006). Previous results from case–control studies of several phenotypic and genotypic assays support the hypothesis that genetic susceptibility or predisposition plays an important role in HNSCC aetiology (Ingelman-Sundberg 2001; Garavello *et al.* 2008). It has been hypothesized that susceptibility to disease development is based on inherited differences in the efficiencies of DNA repair and cell cycle control, or a combination of these. The major research focus in the area of gene–environment interactions in relation to HNSCC has been involved on genes in repair enzymes for

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alcohol and tobacco smoke constituents (Báez 2008). Polymorphisms in the genes encoding these enzymes may modulate DNA repair (Matullo *et al.* 2001) by altering their expression and function, leading to variation in cancer risk.

To maintain integrity of the genome, mammalian cells have developed several DNA-repair mechanisms that each deal with a specific type of DNA damage. DNA-repair genes, like detoxification enzymes, are responsible for preventing cancer by protecting the integrity of the genome and are therefore considered as cancer-susceptibility genes (Hu *et al.* 2002; Kotnis *et al.* 2005). The association between defective DNA-repair caused by highly penetrant mutations in DNA-repair genes on one hand, and chromosomal instability and cancer predisposition on the other, is well documented for rare familial cancer syndromes like xeroderma pigmentosum (XP) (Hu *et al.* 2002). Many studies have been claiming links between the XP group D (*XPD*) single-nucleotide polymorphisms (SNPs) and cancers of various kinds (Sturgis *et al.* 2000; Stern *et al.* 2002; Vogel *et al.* 2001; Butkiewicz *et al.* 2001; Rybicki *et al.* 2004).

The aim of these studies has been to identify high-risk individuals or populations that can be targeted by chemoprevention strategies to reduce cancer burden. In this paper, we review those studies (published up to March 2011) that examined the association between variations in genes coding for enzymes that are important in DNA repair (*XRCC1*, *ERCC2* and *XRCC3*) and increased risk for HNSCC.

DNA repair genes

The genetic alterations associated with HNSCC are numerous and involve a variety of different pathways. Involvement of a particular pathway and accumulation of aberrant pathways can sometimes be due to random chance, but more commonly, they are due to a lifetime of environmental exposure. Thus, the opportunity for DNA damage is high, and there is often a multistep accumulation of genetic events that leads to development of HNSCC. Several polymorphisms in DNA double-strand-break-repair genes and their association with susceptibility to different types of cancer have already been studied.

XRCC1

The human *XRCC1* gene is located at 19q13.2, spans 32 kb, and has 17 exons (Thompson and West 2000; Sterpone and Cozzi 2010). More than 60 SNPs have been identified with the most extensively investigated coding region SNPs: rs25487 in exon 10 (G to A; Arg399Gln), rs1799782 in exon 6 (C to T; Arg194Trp), and rs25489 in exon 9 (G to A; Arg280His) (Hung *et al.* 2005; Laczmanska *et al.* 2006). Figure 1 (Sterpone and Cozzi 2010) shows the locations of these coding region SNPs within the functional domains outlined above. The Arg399Gln mutation has been a particular research focus owing to its location within the BRCT I binding domain (Shen *et al.* 1998). Mutations in the BRCT I domain of BRCA1 have been implicated in altered function of this tumour suppressor protein; however, the effect of this domain within the XRCC1 protein has yet to be completely elucidated.

The promoter binding site polymorphism, −77T→C, appears to be an important determinant of gene expression as it has been associated with a 2–6-fold decrease in transcription in two *in vitro* expression systems, and with increased DNA damage and cancer risk in several epidemiology

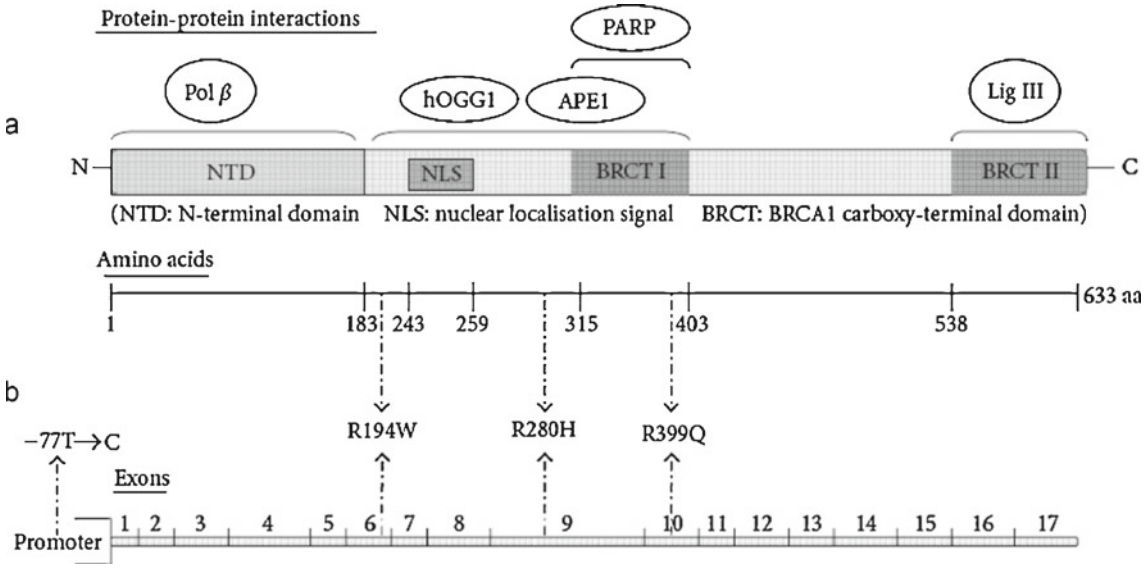

Figure 1. Human XRCC1 protein and gene structure showing protein domains known to interact with other components of base excision repair and the locations of key polymorphisms. Interacting proteins are defined in the text. (Reprinted with permission from Sage-Hindawi Publishers from Sterpone and Cozzi (2010)).

studies (Ginsberg *et al.* 2011). Figure 2 presents a summary model of the potential interactive effects of SNPs in *XRCC1* if they should occur in the same individual. The upstream −77T→C SNP has the potential to reduce XRCC1 function induced by the coding region SNP (Arg399Gln) or offset the increased function due to the Arg194Trp SNP. The net effect on XRCC1 function needs to be evaluated within the broader context of SNPs in other base excision repair (BER) enzymes to understand the overall effect on DNA repair. Research that explores haplotype effects on DNA repair in recombinant systems will be helpful to better understand the net effect of multiple SNPs. Probabilistic models can also be useful in exploring the interaction among multiple SNPs on DNA repair (Olshan *et al.* 2002).

The two polymorphisms C→T substitution (Arg194Trp) in exon 6 and a G→A substitution (Arg399Gln) in exon 10, were investigated in several HNSCC studies. Sturgis *et al.* (1999) and Olshan *et al.* (2002) reported the results of case–control analyses, finding an association between the XRCC1 Arg194Trp and Arg399Gln polymorphisms and the risk of HNSCC. The direction of the association with the Arg399Gln polymorphism was different between the two studies. Sturgis *et al.* (1999) found an elevated risk for the less common genotype in Texas population (USA) (Gln/Gln vs Arg/Gln or Arg/Arg; odds ratio = 1.5; confidence intravel = 0.9–2.6). However, Olshan *et al.* (2002) observed a decreased risk of HNSCC for the 399Gln homozygous genotype among whites American (Carolina, USA) (Gln/Gln vs Arg/Arg; OR = 0.1 among whites). The prevalence of the polymorphism among controls was very similar in the two studies (Sturgis *et al.* 1999; Olshan *et al.* 2002) (Gln/Gln, Sturgis study = 10.8%; whites in Olsham study = 10.6%), but the case distributions were clearly discordant (Gln/Gln, Sturgis study = 15.8%; whites in Olsham study = 3.1%). Despite a large number of studies in well-characterized populations, results from HNSCC patients are still confusing. There was a marginally significant risk of HNSCC observed in variants of *XRCC1* genotype with 194Trp allele in a Thailand population (Kietthubthew *et al.* 2006). Moreover, in a recent study, a statistically significant association was found for *XRCC1* codon 399 (for Caucasians only) and *XRCC1* codon 194 variants and HNSCC American (New York) population (Flores-Obando *et al.* 2010). No significant difference was found between patients and controls with

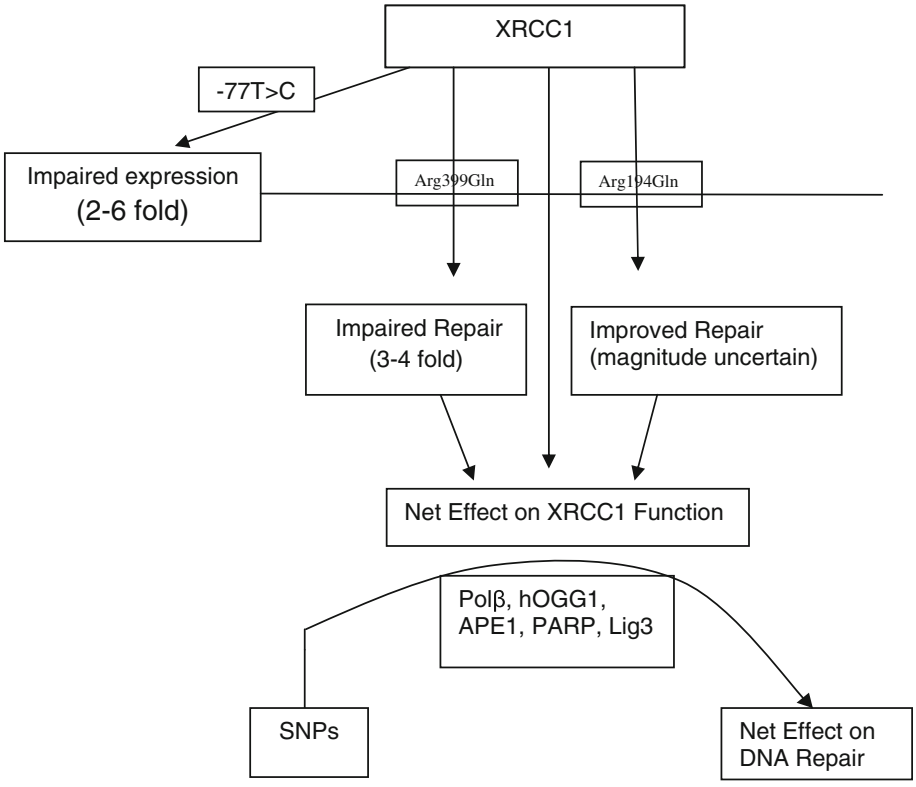

Figure 2. Summary model of *XRCC1* polymorphism influence on DNA repair. Coding-region SNPs can increase or decrease XRCC1 function while regulatory-sequence SNP decreases gene expression. Multiple SNPs within same individual may interact and produce a net effect on *XRCC1*. This combines with modulating SNPs in other base excision repair enzymes to lead to an overall effect on DNA repair.

respect to the investigated polymorphisms of *XRCC1* (Arg194Trp and Arg399Gln) in a Hungarian population; whereas a significant difference was found between patients with different *XRCC1* codones 194 polymorph status in clinical stage III (Csejtei *et al.* 2009). Further, no altered risk of HNSCC was associated with the *XRCC1* Arg399Gln genotype in non-Hispanic white population (Li *et al.* 2007) and in a Polish population (Jelonek *et al.* 2010). However, in a study of populations from eastern India, smokers carrying risk genotype of *XRCC1* with dominant 399Gln allele were overrepresented in HNSCC patients (Majumder *et al.* 2005). Other recent reports showed an association of the 399Arg variant with HNSCC (Kowalski *et al.* 2009); moreover, Yang Y. *et al.* (2008) found that there was a 3.37-fold increased risk of laryngeal carcinoma for individuals carrying *XRCC1* Arg/Gln+ and Gln/Gln genotypes, at codon 399 compared with subjects carrying *XRCC1* Arg/Arg genotype. The amino acid replacement Arg to Gln at position 399 might lead to increased risk of laryngeal carcinoma (Yang Y. *et al.* 2008).

Recently, Gugatschka *et al.* (2011) studied the genetic variants *XRCC1* Arg194Trp, *XRCC1* Gln399Arg and *XRCC1* Arg280His in an HNSCC case–control study. They found no significant difference between patients and controls in respect of the investigated polymorphisms in an Austrian Caucasian population. However, Kumar *et al.* (2012) found significant difference between patients and controls in respect of *XRCC1* Arg194Trp and *XRCC1* Gln399Arg SNPs in an Indian population, but no significant difference for *XRCC1* Arg280His. To investigate the effect of *XRCC1* polymorphisms, including codon 194 (Arg–Trp), 280 (Arg–His) and 399 (Arg–Gln), on risk of oral cancer, Zhou *et al.* (2009) performed a systematic review and meta-analysis of all the available published case–control studies from January 1966 to 2008. Both fixed-effect and random-effects model were used to pool the OR. The various OR comparisons showed that oral cancer risk was not associated with the three *XRCC1* polymorphisms. However, after stratification, significant association was found between the *XRCC1* Arg194Trp polymorphism and oral cancer among Asians, with an OR of 1.34 (95% CI = 1.00–1.81) for allele comparison, 1.37 (95% CI = 1.07–1.77) for TT homozygotes versus CC homozygotes, and 1.42 (95% CI = 1.04–1.93) for comparison under the dominant model. ORs among these three polymorphisms all yielded significant between-study heterogeneity and a part of the heterogeneity was due to ethnic differences. They found that the Arg194Trp polymorphism in *XRCC1* gene may be a biomarker of oral cancer susceptibility among Asian populations (Zhou *et al.* 2009).

Smoking, alcohol consumption and chewing of betel quid are associated with production of free-radical intermediates that induce base damage and single-strand breaker in DNA. Matullo *et al.* (2006) reported that *XRCC1* Arg399Gln genotype modified the effects of smoking and betel quid chewing but not consumption of alcohol. They showed that the *XRCC1* Arg399Gln exhibited a risk of 3.9 (95% CI = 1.76–9.05) for smoking and 4.62 (95%, CI = 1.24–17.2) for betel quid chewing. These results were consistent with an earlier report (Werbrouck *et al.* 2008), which showed that there was a modest positive association with smoking and betel quid chewing for subjects with *XRCC1* 399 codon variant genotypes. A two-fold increase in risk was associated with almost all genotypes studied (Ramachandran *et al.* 2006). However, Krupa *et al.* (2011) showed that Arg399Gln polymorphism of *XRCC1* gene and Arg415Gln polymorphism of *ERCC4* gene may not be associated with smoking-related and drinking-related laryngeal cancer.

Polymorphisms *N*-acetyl transferase 2 locus lead to rapid acetylation property of the enzyme. Improper acetylation of heterocyclic and aromatic amines present in tobacco might cause DNA adduct formation while accumulation of these adducts can cause cancer (Majumder *et al.* 2007). Majumder *et al.* (2005) reported that acetylation status could modify the risk of cancer for *XRCC1* genotypes variant at codon 399 (Gln/Gln, i.e. A/A) among slow-acetylator genotypes. So smoking and its carcinogen component could be interaction factors of risk of oral cancer affected by *XRCC1* genotype (Zhou *et al.* 2009). The 399Gln polymorphism in the DNA repair gene *XRCC1* has been indicated to have a contributive role in DNA adduct formation, sister chromatid exchange and increased risk of cancer development (Hsieh *et al.* 2003). Two hundred and thirty-seven male oral squamous cell carcinomas (OSCCs) were included in a study (Hsieh *et al.* 2003) to investigate the role of *XRCC1* 194Trp, 280His and 399Gln polymorphisms in p53 gene mutation. They observed that OSCC patients with Gln/Gln genotype exhibited a significantly higher frequency of p53 mutation than those with Arg/Gln and Arg/Arg genotypes. After adjusting for age, cigarette smoking, betel chewing, and alcohol consumption, the Gln/Gln genotype still showed an independent association with frequency of p53 mutation (OR = 4.50; 95% CI = 1.52–13.36). The findings support the hypothesis that *XRCC1* Arg399Gln amino acid change may alter the phenotype of the XRCC1 protein, resulting in a DNA repair deficiency. This study also suggests an important role for *XRCC1* 399Gln polymorphism in p53 gene mutation in Taiwanese OSCCs (Hsieh *et al.* 2003).

Alcohol-related cancers and genetic susceptibility in Europe (ARCAGE) is a multicentre case–control study conducted in 14 centres within 10 European countries. The International Agency for Research on Cancer (IARC) was responsible for the overall coordination of the study. One thousand five hundred and eleven cases and 1457 controls (ARCAGE study), and 115 SNPs from 62 a priori selected genes were studied in relation to upper aerodigestive tract (UADT) cancer (Canova *et al.* 2009). Eleven SNPs were statistically associated with UADT cancer (5.75 expected). Among the DNA repair genes, two SNPs involved in nucleotide excision repair (NER) were associated with reduced UADT cancer risk: *ERCC1* IVS5+33A→C (OR = 0.45; 95% CI = 0.23–0.90) and *ERCC4* S835S (OR = 0.83; 95% CI = 0.70–0.98). For two SNPs, involved in the *BER* gene, *XRCC1* P206P

(rs915927) and *XRCC3* IVS5-571A>G (rs861530), the corresponding rare alleles were associated with reduced UADT cancer risk ($P = 0.04$ for both) (Canova *et al.* 2009).

Nasopharyngeal cancer (NPC) (Chen *et al.* 1989) has a striking geographic and ethnic distribution, with particularly high rates observed among southeast Chinese and other individuals of Chinese descent (Parkin 1992; Hildesheim and Levin 1993). Aetiological factors include Epstein–Barr virus infection, tobacco smoking, and consumption of salted fish (Yuan *et al.* 2000a,b). To date, there are only a few published studies on nasopharyngeal carcinoma reporting associations between NPC risk and *XRCC1* polymorphisms. Recently, Laantri *et al.* (2011) genotyped three SNPs in *XRCC1* in 598 NPC cases from Morocco, Algeria and Tunisia and 545 controls. They found that the genotype and allele distributions for *XRCC1* 399Arg/Trp, 280Arg/His, and 194Arg/Trp SNPs did not differ significantly among NPC cases and controls. Moreover, they observed that *XRCC1* 194Trp allele frequency was significantly lower in a North African population than in Asian populations (frequencies = 0.04 in North African versus 0.31 in Cantonese Chinese and 0.21 in Han Chinese). No association was found between polymorphisms at codon 399 of *XRCC1* and NPC (Cho *et al.* 2003; Cao *et al.* 2006). In contrast, a significant protective influence of the *XRCC1* 194Trp/Trp genotype (OR = 0.34, 95% CI = 0.14–0.82) was observed on NPC risk in smokers, suggesting effect modification by tobacco smoking (Cao *et al.* 2006). Pan *et al.* (2007) reported an association between *XRCC1* gene polymorphisms and susceptibility to NPC in Cantonese nuclear families through a family-based association study and found no evidence of association (Pan *et al.* 2007).

Studies implicating genetic polymorphisms as prognostic factors for HNSCC are now increasingly available. Candidate polymorphisms have been evaluated in DNA repair, cell cycle, xenobiotic metabolism, and growth factor pathways. This review has focussed on three polymorphisms located in the coding region of *XRCC1* gene that might influence DNA repair capacity, thus explaining their association with HNSCC risk. Arg399Gln is the most widely studied variant with evidence supporting a quantitative effect of genotype on phenotype. The Arg399Gln increases the risk of HNSCC by 3–4 fold. The Arg194Trp variant may also be a biomarker of HNSCC susceptibility. A third coding region polymorphism, at codon 280, appears to decrease repair function.

XRCC3

The *XRCC3* gene is located in the 14q32.3 chromosome region. XRCC3 protein participates in DNA double-strand break / recombinational repair and is a member of a family of Rad-51-related proteins that probably participate in homologous recombination to maintain chromosome stability and repair DNA damage (Tebbs *et al.* 1995).

The *XRCC3* 241Met variation is a nonconservative change, but it does not reside in the ATP-binding domain, the only functional domain identified in the protein. In a study of 133 nonsmokers, 93 former smokers and 82 current smokers, the *XRCC3* 241Met variant was significantly associated with increased bulky DNA adduct levels among all volunteers as a group and among nonsmokers (Matullo *et al.* 2001). The C722T substitution is the most thoroughly investigated polymorphism in *XRCC3* gene resulting from a (C-to-T) transition in exon 7 (722 C>T, Thr241Met, rs861539). Although the functional relevance of this polymorphism is unknown, some studies have reported that 722 TT genotype is associated with increased risk of cancer (Shen *et al.* 2002). Significant association was found between the *XRCC3* 722C>T polymorphism, present in the coding region of the gene, and increased risk of OSCC in a Thai population (Broughton *et al.* 1996). On the other hand, no consistent results were reported for this SNP in American HNSCC populations (Shen *et al.* 2002; Huang *et al.* 2005). Werbrouck *et al.* (2008) found that *XRCC3* 722C>T variant allele significantly increased the risk of HNSCC. The strongest association was found for the heterozygous genotype (adjusted OR = 2.05, $P = 0.02$). For the homozygous variant genotype, an adjusted OR of 1.77 was obtained, but this was not statistically significant ($P = 0.13$). In contrast, the distribution of the genotypes did not differ between cases and controls for the polymorphisms 1843A>G and 562A>G (Werbrouck *et al.* 2008).

Sliwinski *et al.* (2010) performed a case–control study to search for association between HNSCC and/or precancerous hyperplastic laryngeal lesions (PHLL) occurrence and the 3429G>C (G135C) polymorphism in *RAD51* and C722T (Thr241Met) in *XRCC3*. They found association between PHLL and the 722CT (OR = 6.67; 95% CI = 3.02–14.74) as well as 722TT (OR = 4.65; 95% CI = 2.30–9.43) variants of the *XRCC3* gene. Similar relation was observed between these genotypes and HNSCC (OR = 2.59; 95% CI = 1.61–4.16; and OR = 5.54, 95% CI = 3.22–9.52, respectively). Moreover, they also observed association between PHLL (OR = 6.04; 95% CI = 3.69–9.90) and HNSCC (OR = 6.04; 95% CI = 3.69–9.90) and the 135GC variant of the *RAD51* gene. They also found association between these *XRCC3* or *RAD51* polymorphic variants and smoking status in PHLL (ORs 2.85–10.28 and 1.82–7.35, respectively) and HNSCC patients (ORs 2.94–13.93 and 1.36–3.94, respectively) as well as alcohol intake among PHLL (ORs 3.44–6.12 and 3.52–8.43, respectively) and HNSCC subjects (ORs 2.71–7.01 and 2.33–4.62, respectively). The C722T polymorphism of *XRCC3* and the G135C polymorphism of *RAD51* might be associated with HNSCC and might be used as predictive factor of precancerous lesion for HNSCC in a Polish population (Sliwinski *et al.* 2010). Little data evidenced an association between HNSCC and this polymorphism, but no one linked it to PHLL. Sliwinski *et al.* (2010) data did provide evidence to support the reports of Kiethubthew *et al.* (2006) that 241TT variant of the *XRCC3* polymorphism caused more than 3-fold higher risk of OSCC in a Thailand population. A significant increased risk of

second neoplasms (sites for the UADT and for HNSCC) was also observed among *XRCC3* 241TT homozygotes in Americans (Gal *et al.* 2005). In contrast to these results, no association between HNSCC or oral leukoplakia could be detected with the C722T polymorphism of *XRCC3* gene in an American population (Broughton *et al.* 1996; Majumder *et al.* 2005). This research was actually performed on a population with mixed ethnicity (Caucasian, Hispanic and African-American), and that may be the reason for the lack of any association (Broughton *et al.* 1996).

Oral premalignant lesions (OPLs) are early genetic events en route to oral cancer. Identification of individuals susceptible to OPL is critical to prevention of oral cancer. Yang H. *et al.* (2008) evaluated the associations of 10 genetic variants in nine genes of the double-strand break DNA repair pathway with OPL risk. The most notable finding was an intronic polymorphism (A17893G) in *XRCC3*. They compared the polymorphism A17893G with the homozygous wildtype AA genotype and they found that the OR for the heterozygous AG and homozygous variant GG genotypes were 0.85 (0.49–1.48) and 0.18 (0.07–0.47), respectively ($P = 0.002$). Further, they found that *XRCC3*, G–C haplotype was associated with a significantly decreased risk of OPL (OR = 0.40, 95% CI = 0.23–0.68). When A17893G-T241M was compared with the most common A–C haplotype of *XRCC3*. Moreover in comparison of A17893G polymorphism with individuals without the G–C haplotype, the odds ratio were 1.04 (95% CI = 0.56–1.95) and 0.20 (95% CI = 0.08–0.51) for subjects with one copy and two copies of the G–C haplotype, respectively ($P = 0.005$) (Yang H. *et al.* 2008). In keeping with these results showing a protective role for the variant allele in *XRCC3* A17893G in OPL development, a meta-analysis of a total of 24,795 cancer patients and 34,209 controls reported a significantly reduced cancer risk associated with this allele under a dominant genetic model (OR = 0.92, 95% CI = 0.87–0.96, $P = 0.0004$) (Han *et al.* 2006). Whether this intronic SNP has any functional impact on the splicing of the *XRCC3* transcript should be further evaluated through assessment of *XRCC3* mRNA levels in subjects with different genotypes. Until that is done, the possibility that the reduced OPL risk is due to other variants that are in linkage disequilibrium with this SNP cannot be ruled out (Yang H. *et al.* 2008). Further, the presence of complex interactions between *DSB* gene variations and smoking was demonstrated that influenced OPL susceptibility.

Despite a large number of studies, results from HNSCC patients in well-characterized populations are still confusing. There was a marginally significant risk of HNSCC associated with polymorphisms of the *XRCC3* gene.

ERCC2

The gene *ERCC2* (located at 19q13.3) encodes the ERCC2 protein. ERCC2 is one of the seven genetic complementation groups that forms an essential component of the NER pathway, a major DNA repair pathway that removes photoproducts from UV radiation and bulky adducts from a huge number of chemicals, cross-links and oxidative damage through the action of 20 proteins and several multiprotein complexes (Ma *et al.* 1995; Sancar 1995). The ERCC2 protein functions as an ATP-dependent 5′–3′ helicase joined to the basal transcription factor II H (TFIIH) complex and participates in the local unwinding of DNA to allow RNA transcription machinery to access the promoter and to permit the NER machinery to access the lesion (Egly 2001; Friedberg 2001).

Several studies suggest that *ERCC2* is a highly polymorphic gene and correlation of its polymorphisms and cancer risk have been extensively studied (Benhamou and Sarasin 2005; Clarkson and Wood 2005). Among the genetic polymorphisms in *ERCC2*, the SNP causing amino acid change in codon 751 (Lys to Gln) (rs13181) has been considered very important and there is evidence that subjects homozygous for the variant genotype have suboptimal DNA repair capacity for benzo[a]pyrene adducts and UV-induced DNA damage (Spitz *et al.* 2001; Qiao *et al.* 2002). The rs13181 polymorphism, located in exon 23, is an A-to-C substitution that results in a Lys751Gln substitution in the important domain of interaction between ERCC2 protein and its helicase activator inside the TFIIH complex (Coin *et al.* 1998), which is indicative of possible involvement of this SNP in defective activity of the protein.

A statistically significant association was found between *ERCC2* Asp312Asn polymorphism and HNSCC (Flores-Obando *et al.* 2010). In a study to assess relevant main and interactive effects of polymorphisms in DNA repair genes on susceptibility to HNSCC, Harth *et al.* (2008) found that in subgroup analysis of nonsmokers, main effects in *ERCC2* C/C genotype in Lys751Gln and combined *ERCC2* C/A and A/A genotypes in Arg156Arg were predominant. Gugatschka *et al.* (2011) studied genetic variants *ERCC2* Lys751Gln (rs13181), *ERCC2* Asp312Asn (rs1799793) and *XRCC3* Thr241Met (rs861539) in a primary study group comprising 169 patients (HNSCC) and 463 healthy control subjects. Polymorphisms associated with HNSCC were further analysed in an independent replication study including 125 HNSCC patients. They found that only *ERCC2* (Lys751Gln) Gln/Gln genotype was associated with HNSCC in the primary study ($P = 0.033$) and in the replication study ($P = 0.023$), resulting in an overall OR of 0.54 (95% CI = 0.35–0.92; $P = 0.006$). Another recent study (Kumar *et al.* 2012) demonstrated positive association of *ERCC2* Lys751Gln polymorphism with increased risk of HNSCC; *ERCC2* Lys751Gln variants exhibited two-fold increase in HNSCC risk.

Two other studies (Sturgis *et al.* 2000; Ramachandran *et al.* 2006) on assessment of risk of HNSCC associated with rs13181 polymorphism mutant genotypes reported significant positive association with HNSCC risk among non-Hispanic white subjects and a South Indian population, respectively. Correspondingly, Mitra *et al.* (2009) found that a statistically significant 1.5-fold or more increase in HNSCC risk was associated with the mutant genotypes of rs13181

Table 1. Summary of studies on genes status on HNSCC.

Gene	Population	*N* (case/control)	SNP	OR	95% CI	*P* value	Reference
XRCC1	American (USA)	203/424	28152A	1.59	0.97–2.61	–	Sturgis *et al.* (1999)
	Thailand	112/192	Arg399Gln (AA)	0.3	0.10–0.88	0.03	Kietthubthew *et al.* (2006)
			Arg399Gln (CT)	2.26	1.20–4.28	0.01	
	Meta-analysis: Asian (five studies) European (three studies)	1326/3130	Arg149Trp				Zhou *et al.* (2009)
			T vs. C	1.20	0.91–1.59	0.004	
			TC vs. CC	1.22	0.90–1.64	0.014	
			(TT+TC) vs. CC	1.23	0.90–1.68	0.005	
			Arg339Gln				
			A vs. G	1.07	0.86–1.33	0.001	
			AA vs. GG	1.15	0.75–1.78	0.009	
			(AA+AG) vs. GG	1.06	0.83–1.36	0.009	
	Fourteen centres (meta-analysis)	1511/1457	P206P (rs915927)	0.83	0.69–0.99	0.04	Hsieh *et al.* (2003)
XRCC3	Thailand	112/192	241 Met	3.3	1.31–8.36	0.01	Kietthubthew *et al.* (2006)
	Polish	288/353	C722T	2.27	1.82–2.85	<0.0001	Sliwinski *et al.* (2010)
			C722CT	3.31	2.17–5.09	<0.0001	
			C722TT	6.14	3.79–10.11	<0.0001	
			C722CT/TT	4.03	2.66–6.01	<0.0001	
	Fourteen centres (meta-analysis)	1511/1457	IV55-571A>G (rs861530)	0.89	0.75–1.05	0.04	Hsieh *et al.* (2003)
ERCC2	Australian	169/463	751 Gln/Gln (rs13181)	0.54	0.35–0.92	0.033	Gugatschka *et al.* (2011)
	Indian	278/ 278	751 Gln/Gln	2.19	1.36–3.55	0.002	Kumar *et al.* (2012)
	Indian	285/400	Lys751Gln/A18911C (rs13181)				Coin *et al.* (1998)
			CC	1.68	1.01–2.78	0.049	
			AC	1.53	1.09–2.14	0.016	

–Undefined.

(*ERCC2*), namely homozygous mutant (CC) (OR = 1.680, 95% CI = 1.014–2.784, $P = 0.0497$) and heterozygote (AC) (OR = 1.531, 95% CI = 1.092–2.149, $P = 0.0167$).

ERCC2 codes for a DNA helicase that is a component of the NER pathway, which is responsible for removal of DNA adducts induced by tobacco smoke (Sturgis *et al.* 1998). Polymorphisms in DNA-repair genes could contribute to interindividual differences in cancer susceptibility in smokers. By reducing DNA-repair capacity, these polymorphisms may influence the net level of smoking-induced genetic damage significantly, a critical step in the cascade of events leading to cancer. Affatato *et al.* (2004) studied the effect of *ERCC2* polymorphisms on chromosome aberration frequencies in smokers. They found that the risk was more pronounced in smokers (OR = 4.67; 95% CI = 1.04–20.90; $P = 0.04$) and in all subjects >48 years old (OR = 7.33; 95% CI = 1.53–35.10; $P = 0.01$). Previously, Sturgis *et al.* (2000) had hypothesized that such genetic variants in *ERCC2* are markers for susceptibility to HNSCC, alcohol-related and smoking-related cancer, and therefore would exist in different frequencies in individuals with and without HNSCC. They reported an association between polymorphisms in *ERCC2* exons 6 (C22541A) and 23 (A35931C) and risk of HNSCC (Sturgis *et al.* 2000). The finding that 35931CC is a potential risk genotype is consistent with the reported polymorphic site that causes amino acid substitution (Shen *et al.* 1998) and may affect the protein function (Broughton *et al.* 1996).

Cheng *et al.* (1998) reported that HNSCC patients had a reduced repair capacity for tobacco carcinogen benzo[a]pyrenediol-epoxide-induced DNA damage in a reporter gene, suggesting that an inefficient nucleotide excision repair may be involved in the aetiology of HNSCC. In contrast, Sturgis *et al.* (2002a) found that the 23047 and 23051 variants of *ERCC2* were extremely rare and did not contribute significantly to risk of HNSCC in a non-Hispanic white population. In another study Sturgis *et al.* (2002b) showed that the *ERCC1* 8092CC genotype and the *ERCC2* 23591A allele were associated with nonsignificantly increased risk of HNSCC: OR = 1.15 (95% CI = 0.84–1.59)

and 1.28 (95% CI = 0.93–1.76), respectively, whereas having both risk genotypes was associated with an even higher risk of HNSCC: OR = 1.78 (95% CI = 0.99–3.17). These two polymorphisms may contribute to risk of HNSCC, but more studies are needed to confirm their role in HNSCC.

HNSCC is primarily a disease of smokers and drinkers and rarely occurs in nonsmokers and nondrinkers. Theoretically, HNSCC patients are genetically more susceptible to carcinogenesis in the mucosa of the upper aerodigestive tract. According to this hypothesis, cancer occurs in these individuals after relatively minor environmental exposures to carcinogens because of a less efficient DNA repair system. However, several studies suggest that current and cumulative exposure to tobacco (and other environmental agents) might be more relevant in individuals carrying polymorphisms in *ERCC2* gene. It is also possible that these polymorphisms might result in suboptimal DNA repair capacity, which is overwhelmed only by expressive DNA damages induced by smoking.

Conclusion

The studies reviewed here demonstrate that polymorphisms in three DNA repair genes (*XRCC1*, *XRCC3* and *ERCC2*) are involved in HNSCC susceptibility. The interesting point is that the proteins encoded by these genes are known to participate in different DNA repair pathways. This observation is consistent with the induction of multiple DNA lesions by tobacco smoke and by other environmental agents that require involvement of different DNA repair system. Polymorphisms in these DNA repair genes might confer small but significant increase in HNSCC risk. This risk is often linked to the level of carcinogen exposure, and may differ between ethnic and/or racial groups. Various polymorphisms in these genes are summarized in table 1. Several of these studies described above discuss HNSCC risk for a mixed racial and/or ethnic cohort. As cited above, several genotypes appear to play differential roles in cancer susceptibility for different racial groups. Thus, even if cases and controls are matched by race, potential genotype-associated risks attributable to a specific population may be overlooked when different racial and/or ethnic groups are combined.

It is acknowledged that there is real logistical difficulty in combating some of the potential biases listed above. However, attempts should be made to conduct carefully designed studies of sufficient size to detect small but significant effects. Such studies will enable us to better understand the role of DNA repair enzymes in HNSCC development and may be crucial in establishing the value of potentially ‘high-risk’ genotypes in HNSCC prevention strategies.

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