Chinese Journal of Physiology 50(6): 294-300, 2007

Relationship between Polymorphisms of Nucleotide Excision Repair Genes and Oral Cancer Risk in Taiwan: Evidence for Modification of Smoking Habit

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Abstract

Inherited polymorphisms in DNA repair genes may be associated with differences in the repair capacity and contribute to individual's susceptibility to smoking-related cancers. Both *XPA* and *XPD* encode proteins that are part of the nucleotide excision repair (NER) pathway. In a hospital-based case-control study, we have investigated the influence of *XPA* A-23G and *XPD* Lys751Gln polymorphisms on oral cancer risk in a Taiwanese population. In total, 154 patients with oral cancer, and 105 age-matched controls recruited from the Chinese Medical Hospital in Central Taiwan were genotyped. No significant association was found between the heterozygous variant allele (AG), the homozygous variant allele (AA) at *XPA* A-23G, the heterozygous variant allele (AC), the homozygous variant allele (CC) at *XPD* Lys751Gln, and oral cancer risk. There was no significant joint effect of *XPA* A-23G and *XPD* Lys751Gln on oral cancer risk either. Since *XPA* and *XPD* are both NER genes, which are very important in removing tobacco-induced DNA adducts, further stratified analyses of both genotype and smoking habit were performed. We found a synergistic effect of variant genotypes of both *XPA* and *XPD,* and smoking status on oral cancer risk. Our results suggest that the genetic polymorphisms are modified by environmental carcinogen exposure status, and combined analyses of both genotype and personal habit record are a better access to know the development of oral cancer and useful for primary prevention and early intervention.

Key Words: XPA, XPD, nucleotide excision repair, polymorphism, oral cancer

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Received: October 13, 2006; Revised: March 16, 2007; Accepted: May 11, 2007.
 ISSN : 0304-4920. http://www.cps.org.tw

Introduction

Oral cancer is one of the most commonly diagnosed cancers in the world, and is the fourth most common cause of cancer in Taiwan. Its rising incidence and mortality during the last two decades poses a formidable challenge to oncologists. Early premalignant oral lesions, such as leukoplakia, appear as a white patch in the oral cavity of betel and tobacco consumers; five to ten percent of them progress toward malignancy (11). Therefore, the identification of biomarkers for screening the high-risk population for increased predisposition to cancer is of utmost importance for primary prevention and early intervention.

The various DNA repair pathways constitute a first line caretaking the genomic stability, thus defending against carcinogenesis. Molecular epidemiological studies have shown considerable individual variation in DNA repair capacity in the general population. Individuals with suboptimal DNA repair capacity are at increased risk of smoking-related cancers, such as lung cancer and squamous cell carcinoma of the head and neck (6, 27). The variation in DNA repair capacity may be the result of functional polymorphisms in those DNA repair genes. Tobacco-induced DNA adducts are primarily removed by nucleotide excision repair (NER) pathway. It is reported that lung cancer patients have lower capacity to repair benzo[a]pyrene diol epoxide DNA adducts (15), and they have lower expression level of the two genes involved in NER, *XPG* and *CSB*, compared to the healthy controls (7). The role of DNA repair capacity has also been investigated in studies of the association between polymorphisms in DNA repair genes and the carcinogenesis (10).

XPA protein is involved in a step of damage recognition after the initial damage recognition by XPC-hHR23B (21, 24, 30), and XPA is reported to interact with replication protein A, transcription factor IIH, and ERCC1-XPF (1, 26). Several polymorphism hot spots have been described in this gene (16). The polymorphism *XPA* A-23G is a G/A transversion four nucleotides upstream of the start codon of XPA possibly improving the Kozak sequence (18). There are several indications that the G-allele is protective against risk of lung cancer. Homozygous carriers of the G-allele had 0.58-fold risk of lung cancer compared with homozygous carriers of the A-allele in a study of Korean lung cancer patients and healthy volunteers (18). In another study including three different ethnic groups, carriers of the G-allele also had a lower risk of lung cancer development than homozygous carriers of the A-allele (28). Caucasian homozygous carriers of the G-allele had a 0.69-fold risk of lung cancer. Similar results were found for the much smaller groups of Mexican-Americans and African-Americans. Furthermore, individuals who were homozygotes of the G-allele had 13% higher DNA repair capacity than homozygous A-allele carriers as estimated by host cell reactivation assay (28).

XPD encodes a helicase that participates in the opening of the damaged DNA after the damage recognition step in NER repair system. Two single nucleotide polymorphisms (SNP) in the *XPD* gene have been extensively studied (10). *XPD* Asp321Asn in exon 10 causes an amino acid substitution in a conserved region of *XPD*. *XPD* Lys751Gln in exon 23 causes an amino acid substitution in the C-terminal part of the protein. The presence of the variant allele *XPD* exon23C has been associated with relatively high risk of lung cancer (12, 29), while other studies fail to find statistically significant associations (4, 8, 18). The variant allele of *XPD* exon 10 has also been associated with relatively high risk of lung cancer (4, 12, 29). The variant alleles of the two polymorphisms co-segregate closely. The variant alleles of the *XPD* Asp312Asn and Lys751Gln have been associated with higher DNA adduct levels than the wild type alleles indicating suboptimal damage removal (12) and the presence of variant alleles in *XPD* Asp312Asn and Lys751Gln is associated with relatively low DNA repair capacity (20, 22). It has been recently reported that the associated between *XPD* polymorphisms in Asp312Asn and Lys751Gln with lung cancer risk and heterozygous or homozygous carriers of the variant allele of *XPD* A751C were at 1.64- or 2.01-fold higher risk of lung cancer, respectively (25). Carriers of the variant allele of *XPD* Asp312Asn were also at higher risk of lung cancer than homozygous carriers of the wild type allele (25).

The above-mentioned polymorphisms have all been associated with low NER capacity. Carriers of risk alleles in two or more of these SNPs are likely to be at elevated risk of smoking-related cancer, because several partial deficiencies in the same repair pathway may severely compromise the repair of bulky adducts. Thus, we were interested to check susceptible sites in *XPA* and *XPD* genes together in Taiwanese population, especially in oral cancer patients. Interaction between the polymorphisms in relation to risk of oral cancer, which is highly related to tobacco smoking, may therefore occur. In the present study, we aimed at determining whether the polymorphisms in *XPA* and *XPD* are risk factors for Taiwanese oral cancer and whether the polymorphisms *XPA* A-23G and *XPD* Lys751Gln have joint effect on oral cancer risk in Central Taiwan population.

Materials and Methods

Study Population and Sample Collection

We recruited 154 subjects diagnosed with oral

cancer at the outpatient clinics of general surgery between 1997-2005 at the China Medical University Hospital, Taichung, Taiwan, Republic of China. All subjects voluntarily participated, completed a self-administered questionnaire and provided their peripheral blood. One hundred and five non-oral cancer healthy people as controls were selected by matching for age and gender after initial random sampling from the Health Examine Cohort, which consisted of subjects who voluntarily visited the health-screening clinic at the same hospital. A questionnaire administered to the subjects included questions on smoking habit and history and frequency. Self-reported smoking habits were evaluated and classified as categorical variables. Information on smoking habits was obtained as more than twice a week for years. Smokers were defined as an individual who had smoked at least once a day for more than 1 year in his or her lifetime. Our study was approved by the Institutional Review Board of China Medical University Hospital and written informed consent was obtained from all participants.

Genotyping Assays

The genomic DNA was prepared from peripheral blood leucocytes using a QIAamp Blood Mini Kit. Briefly, as for *XPA* A-23G, the primers 5'-TTAACTGCGCAGGCGCTCACTC-3' and 5'-AAAGCCCCGTCGGCCGCCGCCAT-3' were used. The PCR conditions was set as: 1 cycle at 95°C for 5 min, 35 cycles at 95°C for 40 s, 55°C for 40 s, and 72°C for 40 s, and 1 final cycle of extension at 72°C for 7 min. The polymorphisms were analyzed by PCR amplification followed by further restriction enzyme digestion with MspI, breaking the PCR products of 158 bp (A allele) into 132 and 26 bp (G allele) (18). As for *XPD* Lys751Gln, the primers 5'-GCCCGCTCTGGATTATACG-3' and 5'-CTATCATCTCCTGGCCCCC-3' were used. The PCR conditions was set as: 1 cycle at 95°C for 5 min, 35 cycles at 95°C for 40 s, 58°C for 40 s, and 72°C for 40 s, and 1 final cycle of extension at 72°C for 7 min. The polymorphisms were analyzed by PCR amplification followed by further restriction enzyme BlpI, breaking them into 290 and 146 bp (A allele) or 227, 146 and 63 bp (C allele) (4).

Statistical Analyses

To ensure that the controls used were representative in the general population and to exclude the possibility of genotyping error, deviation of the genotype frequencies of *XPA* A-23G or *XPD* Lys751Gln SNP in the control subjects from those expected under the Hardy-Weinberg equilibrium was assessed using the goodness-of-fit test. On the basis of the observed frequencies of the selected SNPs, we estimated global haplotype frequencies by using the expectation-maximization algorithm (9). Pearson's χ^2 test or Fisher's exact test (when the expected number in any cell was less than five) was used to compare the distribution of the *XPA* and *XPD* genotypes and haplotypes between cases and controls. Data was recognized as significant when the statistical *P* value is less than 0.05.

To analyze the association between genotype and oral cancer risk after stratification into genetic alterations and smoking status, multiple logistic regression analyses were performed. All analyses were performed based on two-sided probabilities using SAS, version 8.2 (SAS Institute, Cary, NC, USA).

Table 1. Allele frequencies for *XPA* A-23G and *XPD* Lys751Gln polymorphisms in the oral cancer and control groups

Allele	Cases (%) N = 308	Controls (%) N = 210	*P* value[a]
XPA A-23G			
Allele A	160 (51.9)	111 (52.9)	0.9094
Allele G	148 (48.1)	99 (47.1)	
XPD Lys751Gln			
Allele A (Lys)	286 (92.9)	193 (91.9)	0.9177
Allele C (Gln)	22 (7.1)	17 (8.1)	

[a] the *P* value was based on χ^2 test.

Results

The mean ages of the oral cancer patients and the controls were 54.39 (SD = 12.08) and 53.02 (SD = 10.08) years, respectively. The majority of the cases were men, and the proportion of men and women were of almost the same ratio in the patient and control groups (i.e., 129 men and 25 women). Characteristically, the most common sites of primary tumor were tongue and buccal mucosa in this Central Taiwan population we surveyed. Approximately 39% (60 of 154) of the study cohort consisted of patients diagnosed with TNM late stage (III and IV) oral cancer (data not shown), and about 89% of them (137 of 154) were cigarette-smokers. The frequency of the alleles for the *XPA* A-23G and *XPD* Lys751Gln between oral cancer and control groups was shown in Table 1. The distribution of the *XPA* and *XPD* genotypes in controls was in Hardy-Weinberg equilibrium. Genotypes containing the A allele at *XPA* A-23G were of the same proportion compared to controls, which means that the G or A allele at *XPA* A-23G was not significantly associated with oral cancer risk ($P > 0.05$). Similarly, either Lys

Table 2. Association of *XPA* A-23G and *XPD* Lys751Gln polymorphisms and oral cancer risk

Genotype	Cases (%)	Controls (%)	Crude OR (95% CI)[a]
XPA			
A/A	38 (24.7)	29 (27.6)	1.00 (ref)
A/G	84 (54.5)	53 (50.5)	1.21 (0.69~2.19)
G/G	32 (20.8)	23 (21.9)	1.06 (0.52~2.19)
A/G or G/G	116 (75.3)	76 (72.4)	1.17 (0.66~2.05)
XPD			
Lys/Lys	134 (87.0)	89 (84.8)	1.00 (ref)
Lys/Gln	18 (11.7)	15 (14.2)	0.80 (0.38~1.66)
Gln/Gln	2 (1.3)	1 (1.0)	1.33 (0.12~14.87)
with Gln	20 (13.0)	16 (15.2)	0.83 (0.41~1.69)

[a] OR, odds ratio; CI, confidence interval.

or Gln at *XPD* Lys751Gln, was not differently distributed in the oral cancer patients and control groups ($P > 0.05$).

The frequency of the genotype of *XPA* A-23G and *XPD* Lys751Gln polymorphisms in the oral cancer and control groups was shown in Table 2. The odds ratios (ORs) for heterozygotes, homozygotes, a combination of hetero- and homozygotes for A-23G G-allele of *XPA* were 1.21, 1.06, and 1.17 (95% CI = 0.69-2.19, 1.06-2.19, 1.17-2.05), respectively, using A-23G A-allele homozygotes as the reference group. Thus, neither hetero- nor homozygotes of A-23G G-allele of XPA seemed to be risky genotypes for oral cancer (Table 2). The finding is different to that of previous report that A-23G A-allele of *XPA* was a protective factor of basal and squamous cell carcinoma (17). Similarly in the case of *XPD*, the ORs for heterozygotes, homozygotes, a combination of hetero- and homozygotes for 751Gln of *XPD* were 0.80, 1.33, and 0.83 (95% CI = 0.38-1.66, 0.12-14.87, 0.41-1.69), respectively, using Lys/Lys homozygotes as the reference group. The data showed that neither hetero- nor homozygotes of 751Gln of *XPD* seemed to be risky or protective genotypes, taking homozygous 751Lys as reference, for oral cancer (Table 2).

Since *XPA* and *XPD* are two proteins important to the same NER system, the gene-gene interaction was also investigated. The result of analysis of the combination of *XPA* A-23G and *XPD* Lys751Gln was shown in Table 3, and there was not a significant difference between oral cancer and control groups ($P > 0.05$). The results in Table 3 showed that there is no joint effect of *XPA* A-23G and *XPD* Lys751Gln in oral carcinogenesis.

Since tobacco-induced DNA adducts are primarily removed by NER DNA repair pathway, in which XPA and XPD are two of the key proteins, we were also interested in the interaction of genetic (*XPA* and *XPD*) and environmental (smoking) factors. About

Table 3. Distribution of combination of *XPA* A-23G and *XPD* Lys751Gln polymorphisms in the oral cancer and control groups

Genotype	Cases (%) N = 154	Controls (%) N = 105	*P* value[a]
XPA/XPD			0.7954
AA/AA	33 (21.4)	27 (25.7)	
AA/AC or CC	5 (3.2)	2 (1.9)	
AG/AA	73 (47.4)	44 (41.9)	
AG/AC or CC	11 (7.2)	9 (8.6)	
GG/AA	28 (18.2)	18 (17.1)	
GG/AC or CC	4 (2.6)	5 (4.8)	

[a] the *P* value was based on χ^2 test.

89% of the case (137 of 154) and 14% of the control (15 of 105) groups were cigarette-smokers. In Table 4, the "common" group with putative low-risk *XPA* A/A genotype, and without smoking habit ("no"= nonsmoker), was used as reference. The crude OR of the stratification with either harboring variant *XPA* genotype (A/G or G/G, "variant") or with smoking habit ("yes"=smoker) was 3.52 (95% CI = 1.26-9.84), and the crude OR of that with both harboring variant *XPA* genotype and smoking habit was increased to 47.7 (95% CI = 15.48-147.01) (Table 4). By the same analyzing strategy, the same trend and joint effect of *XPD* genotype and smoking habit on oral cancer were also significant (Table 5). In Table 5, the "common" group with putative low-risk *XPD* A/A genotype, and without smoking habit ("no"= nonsmoker), was used as reference. The crude OR of the stratification with either harboring variant *XPD* genotype (A/C or C/C, "variant") or with smoking habit ("yes"=smoker) was 28.48 (95% CI = 13.93-58.23), and the crude OR of that with both harboring variant *XPD* genotype and smoking habit was 26.33 (95% CI = 7.87-88.04)

Table 4. The interaction of *XPA* A-23G genotype and smoking habit in oral cancer risk

XPA genotype	Smoking	Case (%)	Control (%)	OR
Common	No	5 (3.25)	27 (25.71)	1 (reference)
Variant Common	No Yes	43 (27.92)	66 (62.86)	3.52 (1.26-9.84)
Variant	Yes	106 (68.83)	12 (11.43)	47.7 (15.48-147.01)
Common = AA Variant = AG/GG	No = nonsmoker Yes = smoker			*P* for trend < 0.0001

Table 5. The interaction of *XPD* Lys751Gln genotype and smoking habit in oral cancer risk

XPA genotype	Smoking	Case (%)	Control (%)	OR
Common	No	15 (9.74)	79 (75.24)	1 (reference)
Variant Common	No Yes	119 (77.27)	22 (20.95)	28.48 (13.93-58.23)
Variant	Yes	20 (12.99)	4 (3.81)	26.33 (7.87-88.04)
Common = AA Variant = AG/GG	No = nonsmoker Yes = smoker			*P* for trend < 0.0001

Table 6. The joint effect of *XPA* A-23G, *XPD* Lys751Gln genotypes, and smoking habit on oral cancer risk

XPA	XPD	Smoking	Case (%)	Control (%)	OR
Common	Common	No	5 (3.25)	26 (24.76)	1 (reference)
Common Common Variant	Common Variant Common	Yes No No	38 (24.68)	55 (52.38)	3.59 (1.27-10.19)
Variant Variant Common Variant	Variant Common Variant Variant	No Yes Yes Yes	111 (72.08)	24 (22.86)	24.05 (8.38-68.95)
Common = AA Variant = AG/GG	Common = AC Variant = AC/CC	No = nonsmoker Yes = smoker			*P* for trend < 0.0001

(Table 5).

In Table 6, the joint effect of the three factors, genotyping of *XPA*, *XPD* and smoking habit was investigated altogether. The "common" group with putative low-risk *XPA* (A/A), *XPD* (A/A) genotype, and without smoking habit ("no"=nonsmoker), were used as reference. The crude ORs of the stratification with one of the three factors, variant *XPA* (A/G or G/G), variant *XPD* (A/C or C/C) genotype, or smoking habit was 3.59 (95% CI = 1.27-10.19), and the crude ORs of the stratification with two or all of the three factors were significantly increased to 24.05 (95% CI = 8.38-68.95). The 7-fold synergistic increase from 3.59 to 24.05 suggested that genetic factors (*XPA* and *XPD*), modified by the environmental factor (smoking), may also contribute to oral cancer risk.

Discussion

The XPA protein seems to play a central role in NER through its interaction with several proteins, such as replication protein A, TFIIH, and ERCC1-XPF. Thus, we hypothesized that genetic polymorphisms of XPA may modulate the susceptibility to oral cancer. The frequency of the *XPA* -23G allele among the healthy controls in this study was 0.47, similar to that (0.52) observed in Korean population (18) and a less than those (0.57 and 0.66) in Polish and Caucasian populations

(5, 17). We have found that the allele frequency of A and G at *XPA* A-23G was almost equally distributed in both case and control groups (Table 1), and the associations between that of *XPA* A-23G and oral cancer risk were not statistically significant (Table 2). In the literature, there was mounting evidence showing different role of this polymorphism in different smoking-related cancers. It has been recently reported that AG and GG genetypes of *XPA* A-23G increased oral cancer risk in Japanese. However, the *XPA* A-23G polymorphism had no interactions with smoking habit (23). Using GG at *XPA* A-23G as the reference, the A-allele was less frequent among cases of both basal and squamous cell carcinoma than the controls (17). On the contrary, the AA genotype leads to an increased risk of lung cancer in the previous studies (3, 18, 19, 28). This was probably because different samples were under investigations, and as mentioned previously, the allele frequency varies among different ethnicities and sub-populations. Moreover, it is possible that the association between *XPA* A-23G and risk of oral cancer was dependent on other factors, such as other genotypes and environmental factors. In this paper, we have proposed a hypothesis that the variation in *XPA* genotype may seem important when *XPD* also harboring genetic variations. In our data, the polymorphism of *XPD* Lys751Gln was not associated to oral cancer, either (Table 2). This finding is consistent with a literature reporting that oral cancer risk was increased with inheritance of *XPD* exon 6 polymorphism, but not *XPD* Lys751Gln in Thai population (14). The C-terminal of XPA interacts physically with TFIIH (which *XPD* is part of) during the NER process (30). It is possible that the amino acid substitution in position 751 of *XPD* could modify the interaction between XPA and TFIIH either directly or indirectly. Up to now, more studies about the role of *XPA* in oral cancer are still needed, and there is controversy about the role of the *XPA* in smoking-related cancers. Possibly, the variation in *XPA* genotype may seem important when other gene(s), not *XPD*, also harboring genetic variations. For instance, it is reported that p53 haplo-insufficiency profoundly accelerates the onset of tongue tumors in mice lacking the *XPA* gene (13).

We did not find any risky, protective, or joint effects of *XPA* A-23G or *XPD* Lys751Gln in the Central Taiwan population. It is possible that our findings are limited for relatively small numbers investigated. Therefore, the functional relevance of the *XPA* and *XPD* polymorphisms and their role in oral cancer susceptibility remain to be determined in larger epidemiological studies. Moreover, it is very possible that the association between *XPA* A-23G and *XPD* Lys751Gln and risk of oral cancer was dependent on other factors, such as other genotypes and environmental factors. We hypothesized that the genetic and functional polymorphisms of these DNA repair genes, were modified by the environmental factor, to precede carcinogenesis.

There is accumulating evidence showing that some environmental factors, such as smoking, alcohol drinking, and betel chewing are closely associated with oral carcinogenesis. Since tobacco induced a various type of DNA adducts, there is abundant evidence showing that the tobacco-induced DNA adducts are primarily removed from our genome by NER DNA repair pathway, in which XPA and XPD are two of the key proteins. Thus, smoking is possibly the most important environmental factor that may modulate the genetic effect of *XPA* and *XPD* on oral cancer susceptibility. Although after analyzing the polymorphisms of *XPA* and *XPD*, and their joint effect, there was no association between each of them and oral cancer susceptibility (Table 1-3), it was very interesting to know that they were modified by the smoking habit to be related to oral cancer (Table 4-6). Therefore, the DNA repair pathway-based analysis, using both genotyping and personal habit recording, is much more promising in finding predictive markers of clinical outcomes, comparing with simple genotyping or haplotyping.

The relatively low influence of single or few variant alleles on cancer risk contrasts the markedly increased risk associated with a reduced phenotypic DNA repair capacity (2, 6, 27). It is agreed that the complex environmental carcinogens may generate various types of DNA damage, activate their responsible DNA proteins in different DNA repair pathways to remove them. In this case, further investigations of other SNPs in NER genes, and the NER capacity determined in tobacco-treated human lymphocytes can provide integrative understanding about the smoking-related oral carcinogenesis. In the future, a detailed personal "DNA repairing genotype" coupled with "DNA repairing phenotype", can help individuals to prevent themselves from specific environmental carcinogen exposures, and lower the risk of oral cancer.

Acknowledgments

We thank Dr. WK Yang for his critical review of the manuscript and his precious scientific advice and English editing, and CW Tsai, SY Lin and YA Hsu for their technical assistance. This study was supported by National Science Council 95-2320-B-039 -014 - MY3 and China Medical University CMU95-269.

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