Nasopharyngeal Carcinoma and Genetic Polymorphisms of DNA Repair Enzymes *XRCC1* and *hOGG1*[1]

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Abstract

Nitrosamine consumption and polymorphisms in CYP2E1, the product of which is involved in the activation of nitrosamines into reactive intermediates, have been shown to be associated with nasopharyngeal carcinoma (NPC) risk. Given that reactive intermediates created during nitrosamine metabolism are capable of DNA damage, we further hypothesized that differences between individuals in their ability to repair DNA damage might be important in NPC pathogenesis. To evaluate this hypothesis, this study focused on effects of genetic polymorphisms of DNA repair genes *hOGG1* and *XRCC1* on the development of NPC. We conducted a case-control study to investigate the genotypes of 334 patients with NPC and 283 healthy community controls matched by sex, age, and residence. The PCR-based RFLP assay was used to identify genetic polymorphisms. After adjustment for sex, age, and ethnicity, the odds ratio (OR) of developing NPC for *hOGG1* codon 326 genotypes of *Ser*/*Cys* and *Cys*/*Cys* compared with the *Ser*/*Ser* genotype was 1.6 (95% CI, 1.0–2.6). For *XRCC1* codon 280 genotypes of *Arg*/*His* and *His*/*His* compared with the *Arg*/*Arg* genotype, the OR was 0.64 (95% CI, 0.43–0.96). Among subjects with putative high-risk genotypes for both *hOGG1* and *XRCC1*, the OR was 3.0 (95% CI, 1.0–8.8). Furthermore, subjects with putative high-risk genotypes for *hOGG1*, *XRCC1*, and *CYP2E1* had an OR of disease of 25 (95% CI, 3.5–177). Polymorphisms of the DNA repair genes *hOGG1* (codon 326) and *XRCC1* (codon 280) are associated with an altered risk of NPC. Carriers of multiple putative high-risk genotypes have the highest risk of developing NPC.

Introduction

NPC[3] has a striking geographic and ethnic distribution, with particularly high rates observed among southeast Chinese and other individuals of Chinese descent (1, 2). NPC is linked to EBV infection (3–7). In addition to EBV, numerous other environmental and host factors have been shown to be associated with the development of NPC (8–15). In particular, long-term cigarette smoking, consumption of salted fish and foods containing nitrosamine or nitrosamine precursors at an early age, and occupational exposure to wood dust have been shown to be consistently associated with this disease. Host factors previously shown to be associated with NPC development include *HLA* class I and II alleles (likely involved via their regulation of the immunological response to EBV infection) and *CYP2E1* gene polymorphisms (likely involved via its modulation of the activation of environmental procarcinogens, including nitrosamines, into reactive intermediates capable of DNA damage; Refs. 2, 16).

Various cellular metabolic processes result in the formation of hydroxyl radicals that can cause oxidative damage to DNA (17). This damage often results in single base changes that can be reversed by BER mechanisms (18, 19). *hOGG1* and *XRCC1* are two of the enzymes participating in the BER pathway, the DNA repair system involved in the repair of damage resultant from oxidative stress. *hOGG1* can recognize and excise oh8Gua, the major form of oxidative DNA damage induced by reactive free radicals (20, 21). *XRCC1* complexes with DNA polymerase β via the NH_2 terminus domain and with DNA ligase III via a blue ribbon commission on transportation (BRCT) domain to repair nicks or gaps left in the BER pathway (22, 23). *XRCC1* has also been shown to be involved in the detection of single strand breaks between incision and ligation, an effect that likely occurs via poly(ADP-ribose) polymerase-dependent and poly(ADP-ribose) polymerase-independent mechanisms (24–26).

Genetic polymorphisms of DNA repair genes have been reported to determine susceptibility to several cancers, including lung, esophageal, bladder, and nonmelanoma skin cancers (19, 27–31). No studies, to date, have examined the association between genetic polymorphisms in DNA repair genes and NPC. In this study, we describe results from a case-control study (334 NPC cases; 283 community controls) conducted in Taiwan in which polymorphisms in the *hOGG1* (codon 326) and *XRCC1* (codons 280 and 399) genes are investigated. We were moti-

Received 1/27/03; revised 6/13/03; accepted 6/23/03.
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[1] Supported by the National Science Council Grant NSC89-2314-B-002-427.
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[3] The abbreviations used are: NPC, nasopharyngeal carcinoma; hOGG1, human 8-oxoguanine DNA glycosylase 1; XRCC1, X-ray repair cross-complementing 1; BER, base excision repair; oh8Gua, 8-hydroxyguanine; OR, odds ratio; CI, confidence interval.

vated to evaluate DNA repair mechanisms by previous results from our case-control study, suggesting that exposure to nitrosamines and nitrosamine precursors from various sources (diet and cigarette smoking) is associated with NPC development and that polymorphisms in the *CYP2E1* gene (a gene responsible for the activation of nitrosamines and other procarcinogens into reactive intermediates capable of inducing DNA damage) were also associated with disease development (10, 14, 16). We hypothesize that if DNA damage induced via activation by *CYP2E1* of nitrosamines and other procarcinogens is important in the development of NPC, DNA repair mechanisms should also play an important role in the development of this tumor.

Materials and Methods

The methods for case ascertainment and control selection were described in detail previously (10, 16). In brief, 378 eligible NPC cases were recruited from July 15, 1991, through December 31, 1994, at two large referral hospitals in Taipei, Taiwan. For each eligible case subject, we attempted to match one community control subject by age (5-year groups), sex, and residence (the same district/township). Ninety-nine percent of eligible cases ($n = 375$) and 87% of eligible controls ($n = 327$) agreed to a detailed risk factor interview administered by a trained nurse-interviewer. Blood specimens were obtained from 367 cases and 321 controls. In this study, 334 cases (88% of eligibles) and 283 controls (75% of eligibles) were included because DNA from the remaining subjects was exhausted by previous testing for other factors. No differences were noted between the 617 subjects included in the present analysis and the 71 subjects for whom DNA was unavailable for testing, with respect to gender, ethnicity, education, and smoking. The 71 untested subjects were slightly older than the 617 subjects included in our study (mean age = 48.5 *versus* 45.4 years; $P = 0.04$). This study was reviewed and approved by the Institutional Review Boards at the National Cancer Institute and the National Taiwan University. All participants provided informed consent.

hOGG1 genotyping was performed using a PCR-RFLP technique. The primers used to identify the polymorphism at codon 326 of *hOGG1* were as follows: forward, 5′-ACTGTCACTAGTCTCACCAG-3′ and reverse, 5′-GGAAGGTGCTTGGGGAAT-3′. A 40-μl reaction mixture containing 29.71 μl of double-distilled water, 10× PCR buffer (4 μl), 1 μl of each primer (5 mM/μl), 1 μl of the mixture of deoxynucleoside triphosphates (2.5 mM/μl), 1.2 μl of $MgCl_2$ (50 mM/μl), and 0.45 unit of (5 unit/μl) TaqDNA polymerase (Amersham Pharmacia Biotech) was used. The PCR condition was initiated by a 4-min denaturation step at 94°C, followed by 35 cycles at 94°C for 40 s, 55°C for 30 s, 72°C for 40 s, and a final step at 72°C for 10 min. The PCR products were subjected to restriction digestion overnight at 37°C by *Fnu*4HI. The digestion products were resolved on 2% agarose gels. A single band at 200 bp characterizes the wild-type *Ser* allele at codon 326; a band at 100 bp characterizes the variant type *Cys* allele.

XRCC1 genotyping was performed using a PCR-RFLP technique. The primers used to identify the polymorphism of *XRCC1* at codon 280 and codon 399 were as follows: forward, 5′-TTGACCCCCAGTGGTGCT-3′ and reverse, 5′-CCCTGAAGGATCTTCCCCAGC-3′ for codon280; forward, 5′-GGACTGTCACCGCATGCGTCGG-3′ and reverse, 5′-GGCTGGGACCACCTGTGTT-3′ for codon 399. A 40-μl reaction mixture containing 29.71 μl double-distilled water, 10× PCR buffer (4 μl), 1 μl of each primer (5 mM/μl), 1 μl of the mixture of deoxynucleoside triphosphates (2.5 mM/μl), 1.2 μl of $MgCl_2$ (50 mM/μl), and 0.45 unit (5 unit/μl) of *Taq*DNA polymerase (Amersham Pharmacia Biotech) was used. The PCR condition was initiated by a 4-min denaturation step at 94°C, followed by 35 cycles at 94°C for 40 s, 55/57°C for 30 s, 72°C for 40 s, and a final step at 72°C for 10 min. The PCR products were subjected to restriction digestion overnight at 37°C by *Rsa*I for codon 280 and by *Msp*I for codon 399. The digestion products were resolved on 2.5% agarose gels. Two bands at 126 and 62 bp characterize the wild-type *Arg* allele for codon 280; a single band at 188 bp characterizes the variant type *His* allele. Two bands at 115 and 34 bp characterize the wild-type *Arg* allele for codon 399; a single band at 149 bp characterizes the variant type *Gln* allele.

An 8% masked, random sample ($n = 51$) of subjects was tested in replicate. Three (6%) masked duplicates had discordant results after genotyping; these discrepancies were resolved by repeat testing. The statistical analysis of our data were performed using the SAS statistical software (SAS, Cary, NC). The ethnic-specific genotype distribution for each of the polymorphisms evaluated was compared using Pearson's χ^2 test (32). Using a goodness-of-fit test, we compared the observed and expected genotype counts and computed the χ^2 statistic as a measure of the deviation from Hardy-Weinberg equilibrium (33). Unconditional logistic regression models were used to estimate the OR and 95% CI of disease associated with genetic polymorphisms (32, 34, 35). Unconditional logistic regression was chosen over conditional logistic regression to avoid losses of cases and controls without a matched pair. Both unadjusted OR estimates and OR estimates adjusted for age, gender, and ethnicity are presented. Additional adjustment for other risk factors associated with NPC in our population (*e.g.*, cigarette smoking, family history of NPC, dietary nitrosamine consumption during childhood, HLA alleles, and occupational exposure to wood dust) did not affect the results (data not shown). Trend tests were performed by including the categorical variable of interest as a continuous variable in the logistic variable and assessing departure of the resultant β coefficient from 0.

Results

Three-hundred thirty-four cases and 283 controls are included in this analysis. The average age of cases and controls was 45.3 and 45.6, respectively. The gender ratio for both cases and controls was ~2:1. Ethnically, 81.7% of cases and 70.9% of controls were of Fukienese origin; 8.4% of cases and 6.4% of controls were of Hakka origin; the remaining 9.9% of cases and 22.7% of controls were of Cantonese, Aboriginal, or other Han origin ($P = 0.001$). A total of 42.2% of cases and 30.1% of controls reported less than a junior high school education; 41.1% of cases and 51.1% of controls reported higher than a senior high school education ($P = 0.04$). Other relevant risk factors reported from this population include most notably ≥25 years of cigarette smoking (OR, 1.7; 95% CI, 1.1–2.9) and homozygosity for the *CYP2E1 Rsa*I *c2* variant allele (OR, 2.6; 95% CI, 1.2–5.7; Refs. 10, 16).

We first investigated whether there was evidence for heterogeneity in genotype distributions or allele frequencies by ethnicity in our study (Table 1). All distributions were in Hardy-Weinberg equilibrium. No significant differences were noted for the three polymorphisms examined when individuals of Fukienese, Hakka, and other ethnic origins were compared among our community controls. For *XRCC1* codon 280, however, there was a suggestion that the *His* variant allele fre-

Table 1 Distribution of *hOGG1* codon 326, *XRCC1* codon 280, and *XRCC1* codon 399 in different ethnic groups among 283 community controls

Grouping of DNA repair genes	Fukien no. (%)	Hakka no. (%)	Other no. (%)	Hardy-Weinberg equilibrium χ^2 P
hOGG1 codon 326				
Ser/Ser	33 (16.5)	3 (16.7)	10 (15.4)	
Ser/Cys	89 (44.5)	10 (55.6)	30 (46.2)	
Cys/Cys	78 (39.0)	5 (27.8)	25 (38.5)	>0.05
Cys allele frequency	0.61	0.56	0.62	
XRCC1 codon 280				
Arg/Arg	147 (73.5)	17 (94.4)	51 (78.5)	
Arg/His	51 (25.5)	1 (5.6)	14 (21.5)	
His/His	2 (1.0)	0 (0.0)	0 (0.0)	>0.05
His allele frequency	0.14	0.03	0.11	
XRCC1 codon 399[b]				
Arg/Arg	109 (54.8)	8 (44.4)	35 (53.9)	
Arg/Gln	74 (37.2)	9 (50.0)	26 (40.0)	
Gln/Gln	16 (8.0)	1 (5.6)	4 (6.2)	>0.05
Gln allele frequency	0.27	0.31	0.26	

[a] 'Other' included the aboriginal, Cantonese, and other Han origins.
[b] The genotype of one subject couldn't be identified.

Table 2 Association between *hOGG1* and *XRCC1* genotypes and NPC

Grouping the DNA repair genes	NPC case patients No. (%)	Community control subjects No. (%)	Unadjusted OR	Adjusted[a] OR_1(95% CI)	Adjusted[a] OR_2 (95% CI)
hOGG1 codon 326					
Ser/Ser	36 (10.8)	46 (16.3)	1.0	1.0	1.0
Ser/Cys	175 (52.6)	129 (45.6)	1.7[b]	1.8 (1.1–2.9)	1.6 (1.0–2.6)
Cys/Cys	122 (36.6)	108 (38.2)	1.4	1.4 (0.86–2.4)	
Unknown	1	0			
XRCC1 codon 280					
Arg/Arg	275 (82.8)	215 (76.0)	1.0	1.0	1.0
Arg/His	55 (16.6)	66 (23.3)	0.65[b]	0.64 (0.43–0.97)	0.64 (0.43–0.96)
His/His	2 (0.6)	2 (0.7)	0.78	0.66 (0.09–4.7)	
Unknown	2	0			
XRCC1 codon 399					
Arg/Arg	174 (52.1)	152 (54.0)	1.0	1.0	1.0
Arg/Gln	128 (38.3)	109 (38.7)	1.0	1.0 (0.74–1.5)	
Gln/Gln	32 (9.6)	21 (7.5)	1.3	1.3 (0.72–2.4)	1.3 (0.68–2.2)
Unknown	0	1			

[a] OR estimates adjusted for age, gender, and ethnicity.
[b] Indicates unadjusted ORs in which 95% CI excludes 1.0.

quency was lower (0.03) among the small group ($n = 18$) of individuals of Hakka descent compared with Fukienese or other Chinese ethnic groups (0.14 and 0.11, respectively). Because no significant differences were noted between ethnic groups and because the vast majority of individuals in our study (77%) were of Fukienese descent, herein we report results of analyses that combined across ethnic groups. However, ethnicity was included in multivariate models to control for possible population stratification. In addition, analyses restricted to individuals of Fukienese origin (the only group with sufficiently large numbers) yielded similar results to those reported herein (data not shown).

Next, we examined the association between *hOGG1* and *XRCC1* polymorphisms and NPC (Table 2). After adjusting for gender, age, and ethnicity, the OR for NPC associated with the *Cys*/*Cys* or *Ser*/*Cys* genotypes combined compared with the *Ser*/*Ser* genotype was 1.6 (95% CI, 1.0–2.6). The adjusted OR for NPC associated with *XRCC1* codon 280 genotypes *His*/*His* or *Arg*/*His* combined compared with the *Arg*/*Arg* genotype was 0.64 (95% CI, 0.43–0.96). No significant association was observed between *XRCC1* codon 399 polymorphism and NPC.

Table 3 presents results of the analysis that evaluated the joint effect of polymorphisms at *hOGG1* codon 326 and *XRCC1* codon 280. For simplicity, we considered as the referent group for this analysis carriers of the genotypes found to be at lowest risk of disease (*i.e.*, *Ser*/*Ser* for *hOGG1* and *Arg*/*His-His*/*His* for *XRCC1*). As shown in the table, individuals who carried only one of the two polymorphisms associated with NPC risk (*i.e.*, *hOGG1 Ser*/*Cys-Cys*/*Cys* or *XRCC1 Arg*/*Arg*) were at an ~2-fold increased risk of NPC, whereas individuals who carried both putative risk genes had an OR of 3.0 (95% CI, 1.0–8.8).

Because individuals homozygous for an allele of the *CYP2E1* gene that is detected by *Rsa*I digestion (*c2* allele) were previously found to have an increased risk of NPC in our study (OR, 2.6; 95% CI, 1.2–5.7; Ref. 16), we next examined the joint effect of polymorphisms in the *CYP2E1*, *hOGG1*, and *XRCC1* genes on NPC risk. A clear dose response of increasing risk with increasing number of putative genes was observed ($P_{trend} = 0.001$). Relative to carriers of none of the three putative high-risk genes, carriers of one putative high-risk gene had an OR of 3.0 (95% CI, 0.78–11.1), carriers of two putative high-

Table 3 Joint effect of *hOGG1* codon 326 and *XRCC1* codon 280 and NPC risk

Gene-gene grouping *hOGG1* codon 326	*XRCC1* codon 280	NPC case patients	Community control subjects	Unadjusted OR	Adjusted[a] OR (95% CI)
Ser/Ser	*Arg/His + His/His*	5	11	1.0	1.0
Ser/Ser	*Arg/Arg*	31	35	1.9	1.9 (0.59–6.2)
Ser/Cys + Cys/Cys	*Arg/His + His/His*	52	57	2.0	2.0 (0.63–6.1)
Ser/Cys + Cys/Cys	*Arg/Arg*	243	180	3.0[b]	3.0 (1.0–8.8)

[a] OR estimates adjusted for age, gender, and ethnicity.
[b] Indicates unadjusted ORs in which 95% CI excludes 1.0.

risk alleles had an OR of 4.3 (95% CI, 1.2–16.0), and carriers of all three putative high-risk genotypes had an OR of 25 (95% CI, 3.5–177). Adjustment for age, gender, and ethnicity did not materially alter these estimates.

Discussion

Limitations of the present study include the modest sample size that reduced our ability to evaluate gene-gene interactions and the 6% genotyping error rate observed among the 8% random sample selected for blind duplicate testing. Despite these limitations, results from this study support a role of DNA repair enzymes in the etiology of NPC. In our study of 334 patients diagnosed with NPC and 283 health community controls, we observed associations with NPC for polymorphisms in both the *hOGG1* and *XRCC1* DNA repair genes. For the *hOGG1* gene, an OR of 1.6 was observed among individuals with *Cys*/*Cys* or *Ser*/*Cys* genotypes. For the *XRCC1* gene, an OR of 0.64 was observed among individuals with *Arg*/*His* or *His*/*His* genotypes, whereas no association with disease was noted for polymorphisms at codon 399 of *XRCC1*. Interestingly, individuals with putative risk genes for both *hOGG1* (*Cys*/*Cys* or *Ser*/*Cys*) and *XRCC1* (*Arg*/*Arg*) were at 3-fold increased risk of NPC. Furthermore, when we evaluated individuals who had both putative DNA repair risk genes and who were also carriers of the *c2*/*c2* allele of *CYP2E1* (an allele previously shown to be associated with increased risk of NPC, presumably because of its increased ability to activate nitrosamines into reactive intermediates capable of DNA damage), we observed a 25-fold increased risk of NPC when compared with individuals who were carriers of none of the three putative risk genes. Although intriguing, these gene-gene joint effect findings should be interpreted with caution, given the modest size of the present study to evaluate joint effects.

Our findings are the first to suggest an association between polymorphisms in DNA repair genes and risk of developing NPC. At least one other study has observed an association between the Cys^{326} form of the *hOGG1* gene and risk of other cancers such as esophageal cancer and lung cancer (29, 36). Furthermore, some evidence exists suggesting decreased *hOGG1* activity in the repair of oh8Gua by the Cys^{326} form compared with the Ser^{326} form of this gene (37). However, not all evidence points to functional differences between these two forms of *hOGG1*. Some studies that have evaluated the possibility that the Cys^{326} form of *hOGG1* has a lower ability to repair oh8Gua failed to detect such a difference (38–40).

With regard to polymorphisms in the *XRCC1* gene, evidence suggests that variability at codon 399 correlate with differences in DNA repair ability (41). However, in our study, we observed no significant association between *XRCC1* codon 399 polymorphisms and NPC risk, whereas differences in codon 280 did correlate with disease risk. To our knowledge, no studies have evaluated biological differences in the DNA repair ability of the Arg^{280} and His^{280} forms of the *XRCC1* gene, and epidemiological studies that have evaluated the association between polymorphisms at this codon of *XRCC1* and disease for tumors other than NPC have had conflicting results (28, 30, 42). The results from our study should therefore be interpreted with caution until our findings are reproduced and/or biological support for the observed association is obtained.

In summary, we observe associations between polymorphisms in two DNA repair genes, *hOGG1* and *XRCC1*, and NPC risk. The association was stronger for individuals who carried both putative risk genes (OR, 3) and strongest for the subset of individuals who also were carriers of the high-risk *c2*/*c2* allele of *CYP2E1*. This is the first study to focus on the association between genetic polymorphisms in DNA repair genes and NPC risk. In the future, polymorphisms in this and other DNA repair genes should be studied to confirm or to refute the involvement of DNA repair mechanisms in the etiology of NPC.

Acknowledgments

We thank the efforts of the study nurses, technicians and coordinators in Taiwan (Pei-Ling Chan, Hsiu-Yen Chang, Ya-Ting Chang, Shu-I Chao, Ching-Fen Chen, Hsiu-Chien Chen, Hsiu-Ling Chen, Kuo-Szu Chiang, Yin-Chu Chien, Hsiu-Mei Cho, Ching-Chi Chu, Tuen-Tze Dan, Fung-Yuan Hsu, Hsue-Rhu Hsu, Yun-Ping Huang, Jih-Huei Lin, Pei-Hsu Lin, Yu-Shum Lin, De-Hwei Liu, Wen-Ling Liu, Shu-Mei Peng, Hwei-Chen Teng, Cher-Tsung Wu, Shi-Yi Yang, and Pei-Chen Yen) and the contribution made by individuals from Westat, Inc. (David Downes, Brenda Sun, Jeanne Rosenthal and Erika Wilson) and Winnie Rickert of Information Management Services, Inc. We also thank Dr. Hon-Hsin Lee for support throughout the project.

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