RESEARCH COMMUNICATION

HOGG1 Ser326Cys Polymorphism and Susceptibility to Head and Neck Cancer: a Meta-analysis

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Abstract

Purpose: Several research groups have investigated the influence of the human 8-oxoguanine DNA glycosylase 1 (hOGG1) Ser326Cys polymorphism on head and neck cancer (HNC) susceptibility. However, the results remain inconclusive and controversial. We therefore conducted the present meta-analysis. Methods: Relevant studies were identified through a search of PubMed databases until July 2011 and selected on the basis of established inclusion criteria for publications. Results: A total of 8 case-control studies on the association of hOGG1 Ser326Cys polymorphism with HNC risk were included in the present meta-analysis. Overall significant associations were observed (G allele vs. C allele: OR=1.49, 95%CI=1.08-2.05, P<0.01 for heterogeneity; GG vs.CC: OR=2.30, 95%CI=1.05-5.05, P<0.01 for heterogeneity; CG vs. CC: OR=1.40, 95%CI=1.03-1.90, P<0.01 for heterogeneity; dominant model (GG+CG vs. CC): OR=1.52, 95%CI=1.06-2.16, P<0.01 for heterogeneity; recessive model (GG vs. CG+CC): OR=2.04, 95%CI=1.05-3.96, P=0.01 for heterogeneity) after excluding the studies that were not in agreement with HWE. On performance of a subgroup meta-analysis by ethnicity, significant associations were found (G allele vs. C allele: OR=1.40, 95%CI=1.001-1.95, P<0.01 for heterogeneity; GG vs.CC: OR=2.30, 95%CI=1.05-5.05, P<0.01 for heterogeneity; recessive model (GG vs. CG+CC): OR=2.04, 95%CI=1.05-3.96, P=0.01 for heterogeneity) in Caucasian populations after excluding one study not in agreement with HWE. Conclusions: Our results suggested that the G allele might be associated with an increased risk of HNC in Caucasian populations.

Keywords: HOGG1 - polymorphism - head and neck cancer - meta-analysis

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Introduction

Head and neck cancer (HNC; including cancers of the oral cavity, oropharynx, hypopharynx, and larynx) is one of the most common cancers worldwide (Jemal et al., 2005). Various risk factors have been thought to be associated with HNC, including cigarette smoking (Stockwell and Lyman, 1986), heavy alcohol consumption (Pelucchi et al., 2008), and infection with human papillomavirus (HPV) (Fakhry and Gillison, 2006; Lescaille et al., 2011). To our best knowledge, oxidative DNA damage induced by reactive oxygen species is one of the genotoxic effects of tobacco, and as one of the most common forms of oxidative DNA damage, 8-hydroxy-2-deoxyguanosine is an important marker of cellular oxidative stress (Goode et al., 2002). The human 8-oxoguanine DNA glycosylase 1 (hOGG1) gene encodes a DNA glycosylase/AP-lyase, which plays an important role in the base excision repair pathway(BER) (Boiteux and Radicella, 2000). The hOGG1 protein is involved in recognizing the DNA oxidative lesion and catalyzing the removal of 8-hydroxy-2-deoxyguanosine and the cleavage of DNA at AP site during DNA damage repair. Although the hOGG1 gene is expressed as several alternatively-spliced isoforms, only the 1 a-form contains a nuclear localization signal (Shinmura et al., 2000).

Previous studies have revealed the presence of several polymorphisms at the hOGG1 locus. A C>G polymorphism at position 1245 in the 1 a-specific exon 7 of the hOGG1 gene was identified and drew a lot of attention from researchers, and it became the most commonly studied hOGG1 polymorphism. It was reported that this polymorphism results in an amino acid substitution from serine to cysteine in codon 326 (Kohno et al., 1998). In recent years, many epidemiological studies have been carried out to explore the association of the hOGG1 Ser326Cys polymorphism with HNC risk. However, the results remain different or even contradictory partially due to the possible small effect of the genetic polymorphism on HNC risk and the relatively small sample size in each published studies. Therefore, we conducted a meta-analysis of all eligible studies to

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drive a more accurate estimation of the effect of hOGG1 Ser326Cys polymorphism on susceptibility to HNC.

Materials and Methods

Literature review

To identify relevant studies eligible for the meta-analysis, we searched PubMed database up to July 8, 2011, using the following search criteria: head and neck cancer/oral cancer/pharyngeal cancer/oropharyngeal cancer/hypopharyngeal cancer/laryngeal cancer, hOGG1, SNP/polymorphism/variant, without any restriction on language or publication year. The potentially associated studies were read in their entirety to evaluate their appropriateness for inclusion in the analysis. All references cited in the articles were also scanned to identify relevant publications.

Inclusion and Exclusion Criteria

The included studies must meet the following criteria: (1) case-control studies; (2) articles about hOGG1 Ser326Cys polymorphism and risk of HNC; and (3) at least two comparison groups (cancer patients vs. control group); (4) detailed genotyping data.

Data extraction

Two authors (Jun Liu and Zhen Zhang) extracted the data from each article independently to increase objectivity. Discrepancies were not solved until consensus was reached on every item. From each study, the following items were considered: the first author's name, year of publication, country, ethnicity, cancer type, source of the controls, genotyping methods, number of cases and controls, and genotype frequencies for cases and controls.

Statistical analysis

First we evaluated Hardy-Weinberg equilibrium (HWE) for each study using goodness-of-fit test ($\chi 2$ of Fisher's exact test) only in control groups (Zintzaras and Lau, 2008). Crude odds ratios (ORs) with 95% confidence interval (CIs) were calculated to estimate the strength of association between hOGG1 Ser326Cys polymorphism and HNC risk. In the overall and the subgroup meta-analysis, pooled ORs and 95% CIs for G allele vs. C allele, GG vs. CC, CG versus CC, dominant model (GG+CG vs. CC), and recessive model (GG vs. CG+CC) were all calculated. A $\chi 2$–based Q-test was performed to check the heterogeneity of the ORs (Zintzaras and Ioannidis, 2005). If the result of heterogeneity test showed $P>0.1$, ORs were pooled according to the fixed-effects model (Mantel-Haenszel model). Otherwise, the random-effects model (DerSimonian and Laird model) was selected (DerSimonian and Laird, 1986). The Egger regression test and Begg-Mazumdar test were used to measure the potential publication bias(Macaskill et al. 2001) and the results were considered statistically significant for $P<0.05$. All statistical tests were performed with the software STATA v.10.0 (Stata Corporation, College Station, TX, USA).

Results

Eligible studies

A total of 8 case-control studies on the association of hOGG1 Ser326Cys polymorphism with HNC risk were included in the present meta-analysis (Elahi et al., 2002; Zhang et al., 2004; Gorgens et al., 2007; Hall et al., 2007; Yang et al., 2008; Pawlowska et al., 2009; Tsou et

Table 1. Characteristics of StudiesIncluded in the Meta-analysis

First author	Year	Country	Ethnicity	Sample size (case/control)	Source of control	Matching	Genotyping method
Elahi	2002	USA	Caucasian	167/331	Screening	Age, sex, race	RFLP-PCR
Zhang	2004	USA	Caucasian	706/1196	Hospital	Age, sex, smoking	RFLP-PCR
Gorgens	2007	Germany	Caucasian	29/30	Population	Region	Sequencing
Hall	2007	Central and Eastern European countries	Caucasian	579/754	Hospital	Age, sex, region, center	Taqman
Yang	2008	China	Asian	72/72	Hospital	Age, sex	RFLP-PCR
Pawlowska	2009	Poland	Caucasian	253/253	NS	Age, sex	RFLP-PCR
Tsou	2010	China	Asian	620/620	Population	Age, sex, habits	RFLP-PCR
Sliwinski	2011	Poland	Caucasian	265/280	NS	Age, sex	RFLP-PCR

NS, not state; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism

Table 2. HOGG1 Ser326Cys Genotypes Distribution and Allele Frequency in Cases and Controls

Author-Year	Genotype (N)						Allele frequency (N)				
	Cases			Controls			Cases		Controls		HWE(P)Controls
	CC	CG	GG	CC	CG	GG	C	G	C	G	
Elahi (2002)	104	54	9	249	76	6	262	72	574	88	1.00
Zhang (2004)	447	220	39	739	388	69	1114	298	1866	526	0.06
Gorgens (2007)	19	8	2	19	10	1	46	12	48	12	1.00
Hall (2007)	369	185	25	485	253	16	923	235	1223	285	<0.01
Yang (2008)	34	34	4	50	22	0	102	42	122	22	0.35
Pawlowska (2009)	141	91	21	166	77	10	373	133	409	97	0.84
Tsou (2010)	138	252	230	104	251	265	528	712	459	781	<0.01
Sliwinski (2011)	109	128	28	160	111	9	346	184	431	129	0.06

HWE, Hardy-Weinberg equilibrium

Table 3. Summary ORs and 95% CI of hOGG1 Ser326Cys and HNC Risk

Genetic model	Racial descent	OR	95% CI	P*
G allele vs. C allele				
	All	1.29	1.002-1.65	<0.01
	All in HWE	1.49	1.08-2.05	<0.01
	Caucasian	1.24	0.91-1.71	<0.01
	Caucasian in HWE	1.4	1.001-1.95	<0.01
GG vs. CC				
	All	1.78	0.97-3.27	<0.01
	All in HWE	2.3	1.05-5.05	<0.01
	Caucasian	2.21	1.21-4.05	<0.01
	Caucasian in HWE	2.3	1.05-5.05	<0.01
CG vs. CC				
	All	1.2	0.94-1.52	<0.01
	All in HWE	1.4	1.03-1.90	<0.01
	Caucasian	1.22	0.95-1.56	<0.01
	Caucasian in HWE	1.31	0.96-1.79	0.01
GG+CG vs.CC				
	All	1.27	0.96-1.67	<0.01
	All in HWE	1.52	1.06-2.16	<0.01
	Caucasian	1.32	0.995-1.74	<0.01
	Caucasian in HWE	1.41	0.98-2.03	<0.01
GG vs. CG+CC				
	All	1.67	1.01-2.76	<0.01
	All in HWE	2.04	1.05-3.96	0.01
	Caucasian	2.01	1.19-3.38	0.02
	Caucasian in HWE	2.04	1.05-3.96	0.01

*P value for heterogeneity.

al., 2010; Sliwinski et al., 2011), and 2691 HNC cases and 3536 controls were ultimately analyzed. The main characteristics of these studies were summarized in Table1. The sample size ranged from 59 to 1902. Almost all of the cases were confirmed by histological or pathological analysis. There were six studies on Caucasian population and two studies on Asian population. A classic polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay was carried out in 6 of the 8 studies. The hoGG1 Ser326Cys genotype distributions and allele frequencies for cancer cases and controls were presented in Table2. The distribution of genotypes in the controls was consistent with HWE in all but two studies (Hall et al., 2007; Tsou et al., 2010) (P<0.01).

Meta-analysis

Table3 showed the main results of association between the hOGG1 Ser326Cys polymorphism and HNC, and the heterogeneity test. In the overall analysis, significant associations were observed (G allele vs. C allele: OR=1.29, 95%CI=1.002-1.65, P<0.01 for heterogeneity; recessive model (GG vs. CG+CC): OR=1.67, 95%CI=1.01-2.76, P=0.01 for heterogeneity). However, in the pooled results some changes took place after excluding the two studies (Hall et al. 2007; Tsou et al. 2010) that were not in agreement with HWE, and the results showed that there were significant associations in all the genetic models (G allele vs. C allele: OR=1.49, 95%CI=1.08-2.05, P<0.01 for heterogeneity; GG vs.CC: OR=2.30, 95%CI=1.05-5.05, P<0.01 for heterogeneity; CG vs. CC: OR=1.40, 95%CI=1.03-1.90, P<0.01 for heterogeneity; dominant model (GG+CG vs. CC): OR=1.52, 95%CI=1.06-2.16, P<0.01 for heterogeneity; recessive model (GG vs. CG+CC): OR=2.04, 95%CI=1.05-3.96, P=0.01 for heterogeneity). Due to the limited number of studies (Yang et al., 2008; Tsou et al., 2010) from Asian population, we only carried out a subgroup analysis in Caucasian group. In Caucasian population, significant associations were observed (GG vs.CC: OR=2.21, 95%CI=1.21-4.05, P<0.01 for heterogeneity; recessive model (GG vs. CG+CC): OR=2.01, 95%CI=1.19-3.38, P=0.02 for heterogeneity), and exclusion of one study (Hall et al., 2007) that was not consistent with HWE changed the analyzed results slightly. And significant associations were found (G allele vs. C allele: OR=1.40, 95%CI=1.001-1.95, P<0.01 for heterogeneity; GG vs.CC: OR=2.30, 95%CI=1.05-5.05, P<0.01 for heterogeneity; recessive model (GG vs. CG+CC): OR=2.04, 95%CI=1.05-3.96, P=0.01 for heterogeneity) in Caucasian population after excluding one (Hall et al., 2007) studies that was not in agreement with HWE.

Publication Bias

Begg's funnel plot and Egger's test were conducted to evaluate the publication bias of the literature. The contour-enhanced funnel plot for publication bias (data not shown) did not reveal any evidence of obvious asymmetry in the allele contrast (G allele vs. C allele), and as expected, the result of Egger's test provided no obvious evidence of publication bias (t=2.20, P=0.070 for G allele vs. C allele).

Discussion

Genetic susceptibility to cancer has been a focus in scientific research. In recent years, the association between genetic variants of hOGG1 gene and several cancers has attracted growing attention. DNA repair systems play an indispensable role in maintaining genomic integrity and the ability to mediate and repair carcinogen-induced DNA lesion is a key determinant of susceptibility to carcinogenesis. Increasing evidence has demonstrated that reduced DNA repair capacity might play a central role in cancer development (Goode et al., 2002). As a part of the BER pathway, hOGG1 gene might contribute to carcinogenesis. A commonly occurring C-to-G polymorphism at nucleotide 1245 (C1245G) has been the subject of numerous case-control relationship studies of HNC.

Elahi et al. (2002) found that individuals carrying hOGG1 GG/CG genotypes have significantly increased risk for the development of oropharyngeal cancer compared with individuals with CC genotype, and Hall et al. (Hall et al. 2007) observed that the homozygous carriers of the variant alleles of hOGG1 Ser326Cys increased the risk of cancers of the upper aerodigestive tract which comprises the oral cavity, pharynx, larynx and oesophagus. On the contrary, Tsou et al. (Tsou et al., 2010) found that the individuals with GG genotype might have reduced risk of the development of oral cancer. In addition, Zhang et al. (2004) found that the hOGG1 Ser326Cys polymorphism did not have an effect on the genetic susceptibility to HNC. We conducted a meta-analysis by retrieving eligible studies that investigated the association between hOGG1 Ser326Cys polymorphism and HNC risk and the pooled

results demonstrated that the variant G allele of hOGG1 Ser326Cys might increase the risk of HNC, especially in Caucasian population. Considering the limited number of association studies in Asian population, we did not perform the subgroup meta-analysis for Asian population. Therefore, further well-designed and larger case-control studies should be performed for Asian population in future to obtain more accurate estimations of the role of hOGG1 Ser326Cys polymorphism in Asian population.

Many factors may contribute to between-study heterogeneity, such as differences in population characteristics and sample size, and deviation of allelic distributions from HWE. Therefore we performed subgroup analysis and sensitive analysis by limiting the meta-analysis to those studies that are consistent with HWE. Heterogeneity still exists which may be attributed to the different cancer sites of HNC including oral, pharyngeal, laryngeal, oropharyngeal cancer.

Several limitations need to be addressed. First, due to heterogeneity, the results of the present meta-analysis should be interpreted with some extent caution. Second, the current results were based on unadjusted estimates, and lacking of the original data in the included studies limited evaluation of the effect of confounding factors on HNC development. Apparently, some confounding factors (e.g. sex, age, alcohol consumption, smoking, HPV status and socioeconomic status) might affect the association of genetic variants with HNC risk. Third, because of small amount of data, we could not perform a subgroup analysis for Asian population. Fourth, although hOGG1 have several other common single nucleotide polymorphisms identified, we could not obtain more detailed individual data on genotypes of the other polymorphisms to perform linkage disequilibrium and haplotypes analysis.

In conclusion, despite these limitations, the present meta-analysis might provide a more accurate estimation of the association of hOGG1 Ser326Cys polymorphism with HNC risk than individual study. Our results indicated that the hOGG1 Ser326Cys polymorphism was associated with HNC and the G allele might be associated with an increased risk of developing HNC in Caucasian population. The results of our meta-analysis are preliminary and should be treated with cautions. Further well-designed and larger studies should be required to assess haplotypes, gene-gene and gene-environment interactions on hOGG1 polymorphisms and HNC in ethnicity specific populations.

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