RESEARCH ARTICLE

XRCC1 Arg399Gln Gene Polymorphism and Hepatocellular Carcinoma Risk in the Chinese Han Population: A Meta-analysis

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Abstract

Purpose: Numerous studies have evaluated the association between XRCC1 Arg399Gln gene polymorphism and hepatocellular carcinoma risk in the Chinese Han population. However, the results have been inconsistent. We therefore here examined whether the XRCC1 Arg399Gln gene polymorphism confers hepatocellular carcinoma risk by conducting a meta-analysis. Methods: PubMed, Google scholar and China National Knowledge Infrastructure databases were searched for eligible articles in English and Chinese that were published before April 2012. Results: 6 studies involving 1,246 patients with hepatocellular carcinoma and 1,953 controls were included. The association between XRCC1 Arg399Gln gene polymorphism and hepatocellular carcinoma in the Chinese Han population was significant under GG vs AA (OR = 1.48, 95% CI = 1.13 to 1.94). Limiting the analysis to the studies with controls in the Hardy-Weinberg equilibrium, the results were persistent and robust. Conclusions: In the Chinese Han population, the XRCC1 Arg399Gln gene polymorphism is associated with an increased hepatocellular carcinoma risk.

Keywords: Arg399Gln - gene polymorphism - meta-analysis - hepatocellular carcinoma - risk

Asian Pacific J Cancer Prev, **13**, 3601-3604

Introduction

Hepatocellular carcinoma is the sixth most common cancer worldwide and the third most frequent cause of cancer death.More than 700 000 cases of this malignant disease were diagnosed in 2008, with an age-adjusted worldwide incidence of 16 cases per 100 000 inhabitants (Ferlay et al., 2012). Risk factors increase a person's chance of getting this disease. The classic risk factors for hepatocellular carcinoma include: chronic hepatitis B or C; excessive alcohol consumption; obesity; diabetes; pre-existing liver cirrhosis (Forner et al., 2012).In addition, genetic factors also play impor¬tant role in the pathogenesis of Hepatocarcinogenesis.

The encoded protein of X-ray repair cross-complementing group 1 (XRCC1) is scaffolding protein directly associated with polymerase beta (pol β), DNA ligase III (lig III), poly (ADP-ribose), polymerase (PARP) and functions in complex to facilitate the base excision repair and single-strand break repair (Thompson et al., 2000). The human XRCC1 gene is located on chromosome 19q13.2 containing 17 exons and it encodes a protein of 633 amino acids (Lindahl et al., 1999). A number of single nucleotide polymorphisms (SNP) have been reported in the Ensembl database. Among them, Arg194Trp(rs1799782), Arg280His (rs25489) and Arg399Gln (rs25487) are highly studied and caused nonconservative changes (Shen et al., 1998). These nonconservative amino acid changes may alter XRCC1 function. This change in protein biochemistry leads to the supposition that variant alleles may diminish repair kinetics, thereby influencing susceptibility to adverse health effects, including cancer (Geng et al., 2008).

To date, XRCC1 Arg399Gln gene polymorphism has been shown to be linked to susceptibility to gastric cancer,colorectal cancer, lung cancer and breast cancer (Dufloth et al., 2005; Geng et al., 2008; Wu et al., 2011; Cui et al., 2012; Liu et al., 2012), and several case-control studies have inves¬tigated the association between XRCC1 Arg399Gln gene polymorphism and hepatocellular carcinoma risk. How¬ever, with relatively small sample sizes, these former studies provided limited informa¬tion and could not draw a convincing conclusion. Hence, we performed a meta-analysis based on 6 eligible studies (1246 cases and 1953 controls), with the intention of obtaining a more reliable hepatocellular carcinoma risk assessment in association with XRCC1 Arg399Gln gene polymorphism in the Chinese Han population.

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Materials and Methods

Literature review

We performed an electronic search of the PubMed, google scholar and China National Knowledge Infrastructure database to retrieve papers linking XRCC1 Arg399Gln gene polymorphism and susceptibility to hepatocellular carcinoma available until April 2012 in English and Chinese, using the following key words: "XRCC1", "Arg399Gln", "gene polymorphism", "hepatocellular carcinoma" and "single nucleotide polymorphism". The reference lists of major textbooks, reviews and included articles were identified through manual searches to find potentially eligible studies. Studies reported by the same authors were checked for possible overlapping participant groups.

Inclusion and exclusion criteria

Studies were included in this meta-analysis if they met the following criteria: i) case-control studies that addressed hepatocellular carcinoma cases and healthy controls; ii) studies that evaluated the association between XRCC1 Arg399Gln gene polymorphism and hepatocellular carcinoma risk and iii) studies that included sufficient genotype data for extraction. Studies were excluded when: i) not case-control studies that evaluated the association between XRCC1 Arg399Gln gene polymorphism and hepatocellular carcinoma risk; ii) case reports, letters, reviews, meta-analysis, and editorial articles; iii) studies that were based on incomplete data and those with no usable data reported; iv) duplicate data were contained and v) family-based design.

Data extraction

Using a standardized form, data from published studies were extracted independently by two reviewers to acquire the necessary information (Weihong Duan and Zhenyu Zhu). From each of the included articles the following information was retrieved: first author, year of publica¬tion, Area, study design, source of cases and con¬trols, number of cases and controls, sample, detection methods, polymorphisms, genotypes frequency and evidence of Hardy-Weinberg equilibrium (HWE) in controls. For conflicting evaluations, an agreement was reached following a discussion.

Statistical analysis

Meta-analysis was performed using the STATA package version 12.0 (Stata Corporation, College Station, Texas). The strength of the associations between XRCC1 Arg399Gln gene polymorphism and susceptibility to hepatocellular carcinoma were estimated by odds ratio (OR) and 95% confidence interval (95%CI) under co-dominant model (GG vs AA, GG vs AG), dominant model (AA+AG vs GG) and recessive model (GG+AG vs AA) were all calculated by the fixed-effects model or random-effects model. Between-study heterogeneities were estimated using the Q-test and the I^2 test (Higgins and Thompson, 2002; Zintzaras and Loannidis, 2005). I^2 represents the variability that can be attributed to heterogeneity rather than chance. I^2 values of 25, 50 and 75% were defined as low, moderate and high estimates, respectively. When a significant Q-test ($P<0.10$) or $I^2>50\%$ indicated heterogeneity across studies. When a significant Q-test ($P < 0.10$) or $I^2>50\%$ indicated heterogeneity across studies,the random effects model was used for meta-analysis, or else the fixed effects model was used. We tested whether genotype frequencies of controls were in HWE using the χ^2 test.Publication bias was investigated by Begg's funnel plot, and $P<0.05$ was considered as statistically significant publication bias.Sensitivity analysis was performed by removing the studies in the meta-analysis due to the genotype distribution in the control groups of the study deviating from HWE.

Results

Eligible studies

After searching, 168 candidate studies were collected and 6 eligible studies were eventually determined for meta-analysis (Yu et al., 2003; Yang et al., 2004; Long et al., 2005; Long et al., 2006; Ren et al., 2008; Tang et al., 2011). The flow chart for the study selection is summarized in Figure 1. These 6 case-control studies selected included a total of 1246 cases and 1953 healthy controls. All studies were case-control studies that evaluated the association of XRCC1 Arg399Gln gene polymorphism and susceptibility to hepatocellular carcinoma. The publication year of the included studies ranged from 2003 to 2011. The HWE

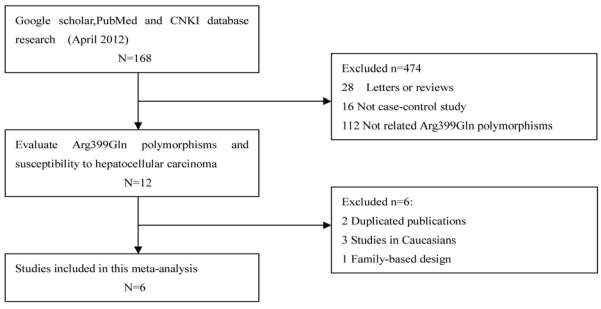

Figure 1. Flow Diagram of Study Selection Procedure

Table 1. Flow Diagram of Study Selection Procedure

Study included	Year	Area	Source of controls	Detection method	cases	controls	Genotypes for cases			Genotypes for controls			HWE test
							AA	AG	GG	AA	AG	GG	
Yu et al1	2003	Taiwan	population-based	PCR-RFLP	577	389	301	223	53	218	143	28	0.18
Yang et al2	2004	Jiangsu	population-based	PCR-RFLP	72	137	34	7	28	58	15	63	0
Long et al3	2005	Guangxi	hospital-based	PCR-RFLP	140	536	72	63	5	362	159	15	0.62
Long et al4	2006	Guangxi	hospital-based	PCR-RFLP	257	649	131	95	31	439	162	48	0
Ren et al5	2008	Beijing	hospital-based	PCR-RFLP	50	92	32	14	4	46	41	5	0.28
Tang et al6	2011	Guangxi	population-based	PCR-RFLP	150	150	41	94	15	84	54	12	0.43

Table 2. Summary ORs and 95%CI of RCC1 Arg399Gln Gene Polymorphism and Hepatocellular Carcinoma Risk

Subgroup	Genetic model	Sample size		Type of model	Test of heterogeneity		Test of association		Test of publication bias	
		Case	Control		I^2	P	OR	95% CI	z	P
Overall	GG vs AA	1246	1953	Fixed	42.8%	0.12	1.48	1.13-1.94	0.00	1.00
	GG vs AG			Fixed	0%	0.77	1.07	0.80-1.44	0.00	1.00
	Dominant model			Fixed	0%	0.53	0.78	0.60-1.02	0.00	1.00
	Recessive model			Random	84.7%	0.00	1.44	0.95-2.19	0.00	1.00
consistent with	GG vs AA	917	1167	Fixed	0%	0.62	1.56	1.07-2.29	0.34	1.00
HWE	GG vs AG			Fixed	0%	0.48	1.08	0.74-1.58	0.34	1.00
	Dominant model			Fixed	0%	1.00	0.76	0.53-1.10	0.34	1.00
	Recessive model			Random	87.4%	0.00	1.50	0.83-2.70	0.34	1.00

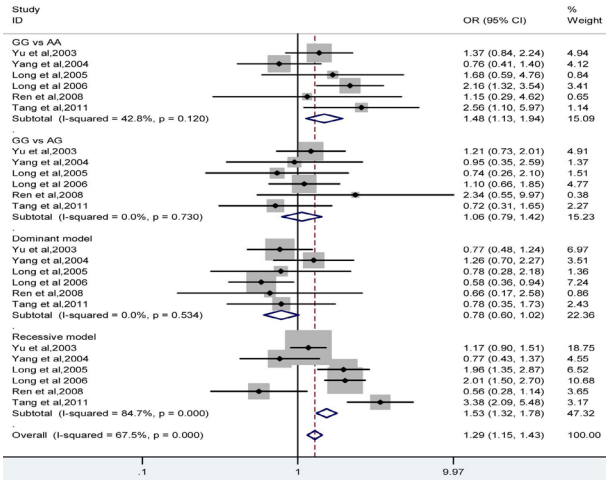

Figure 2. Forest Plot of Hepatocellular Carcinoma Risk Associated with XRCC1 Arg399Gln Gene Polymorphism

test was per¬formed on the genotype distribution of the controls in all studies included, all of them showed to be in HWE (P>0.05) except Yang et al (P<0.001) and Long et al (P<0.001). The information from these 6 studies and the numbers of cases and controls with AA, AG and GG genotypes reported in each study are all presented in Table 1.

Meta-analysis

A summary of the meta-analysis findings of the association between XRCC1 Arg399Gln gene polymorphism and hepatocellular carcinoma risk is provided in Table 2. The association between XRCC1 Arg399Gln gene polymorphism and hepatocellular carcinoma in the Chinese Han population was significant under GG vs AA (OR = 1.48, 95% CI = 1.13 to 1.94). Sensitivity analysis was performed with controls in the Hardy-Weinberg equilibrium and the result was not altered, indicating the result of meta-analysis was statis¬tically significant (Table 2).

Publication bias

Publication bias of the literature was accessed by Begg's funnel plot and the Egger linear regression test. The Egger linear regression test was used to measure the asymmetry of the funnel plot. The results of the Egger linear regression test are shown in Table 2. Results showed that there was no publication bias (all P>0.05).

Discussion

Genetic susceptibility to cancer has been a focus in scientific research. In recent years, the association between XRCC1 Arg399Gln gene polymorphism and several cancers has attracted growing attention. Many research studies have evaluated the association of XRCC1 Arg399Gln gene polymorphism and hepatocellular carcinoma risk,but the results are controversial. Our meta-analysis quantitatively assessed the association between XRCC1 Arg399Gln gene polymorphism and susceptibility to hepatocellular carcinoma in the Chinese Han population. Finally, 6 case-control studies were included and assessed, involving a total of 1246 psoriasis cases and 1953 healthy controls. The results strongly suggested that there was significant association between XRCC1 Arg399Gln gene polymorphism and hepatocellular carcinoma risk in the Chinese Han population (GG vs AA:OR = 1.48, 95% CI = 1.13-1.94). Deviation of allelic distributions from HWE may contribute to between-study heterogeneity,sensitivity analysis by limiting this meta-analysis to those studies that are consistent with HWE revealed that this meta-analysis was realistic and believable. There was no evi¬dence of publication bias in this meta-analysis. As the eligible study number was small in this meta-analysis of XRCC1 Arg399Gln gene polymorphism, these results still need further investigation.

The mechanism of how XRCC1 Arg399Gln gene polymorphism relates to hepatocellular carcinoma risk is still unclear. Some epidemiological studies have recently shown a positive association between the XRCC1 399 Gln allele and cancer (Yu et al., 2004; Kirk et al., 2005). And these studies suggest that this polymorphism may alter the normal protein function, and consequently may be associated with a reduction in DNA-repair capacity (Li et al., 2003; Wang et al., 2003). As is known, genetic polymorphisms altering the level of protein expressed would be anticipated to have a substantial influence on disease activity (Tahara et al., 2009). Those evidences sug¬gested that Arg399Gln polymorphism might play an important role in the development of hepatocellular carcinoma.

There were also some limitations in our meta-analysis. First, with the merely published studies included in our meta-analysis, publication bias is very likely to occur, though no statistically significant publication bias is found in our metaanalysis. Secondly, our results were

based on unadjusted estimates, while a more precise analysis should be conducted adjusted by other factors like smoking, drinking status and environmental factors. Thirdly, our analysis did not consider the possibility of gene-gene or SNP-SNP interactions or the possibility of linkage disequilibrium between polymorphisms. Further investigations of the haplotypic effect of a gene and the study of multiple polymorphisms in different genes are needed.

In conclusion, our meta-analysis of 6 case-control studies demonstrated that there was an association between XRCC1 Arg399Gln gene polymorphism and hepatocellular carcinoma risk in the Chinese Han population. Due to limitations showed above in this analysis, it is critical that larger and well-designed multicenter studies are needed to confirm our results.

Acknowledgements

The author(s) declare that they have no competing interests.

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