RESEARCH COMMUNICATION

XRCC1-77T>C Polymorphism and Cancer Risk: A Meta-analysis

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Abstract

Variants of X-ray repair cross-complementing group 1 (XRCC1) are involved in the development of cancer, but studies investigating the association of XRCC1-77T>C polymorphism with cancer risk have reported conflicting results. To clarify the effect of the XRCC1 -77T>C polymorphism on cancer risk, we performed a meta-analysis by conducting searches of the published literature in PubMed, Embase and CBM databases. Finally, 13 studies were included into our meta-analysis, involving a total of 11, 678 individuals. Subgroup analyses were performed by ethnicity and cancer type. The results of this meta-analysis showed that there was significant association between the C variant of XRCC1-77T>C polymorphism and cancer risk in all four genetic comparison models (ORC vs. T =1.19, 95% CI 1.07-1.31, P = 0.001; OR homozygote model =1.28, 95% CI 1.07-1.52, P = 0.007; OR recessive genetic model =1.22, 95% CI 1.04-1.44, P = 0.015; OR dominant model =1.21, 95% CI 1.07-1.35, P = 0.001). In the subgroup analyses based on ethnicity, the association was still significant in the Asian population (all p values<0.001), but not in the Caucasian population (all p values > 0.05). Thus, the XRCC1 -77T>C polymorphism is associated with cancer risk, and individuals with XRCC1 -77C variant have a significantly higher cancer risk, particularly in the Asian population.

Keywords: XRCC1 - cancer - genetic polymorphism - meta-analysis

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Introduction

Certain genetic variants associated with repair of DNA substantially increase the risk of cancer in carriers because of defined biochemical alterations caused by the polymorphisms. Base excision repair (BER) is the predominant DNA damage repair pathway for the processing of small base lesions, derived from oxidation and alkylation damage (Almeidaet al., 2007). One of the most important proteins is X-ray repair cross-complementation group 1 (XRCC1), a scaffold protein closely associated with BER pathway coordination by interacting with most components of the BER short-patch pathway (Vidalet al., 2001; Campalanset al., 2005; Daset al., 2006). The XRCC1 gene is 33 kb in length, and is located on chromosome 19q13.2-13.3. More than 60 validated single nucleotide polymorphisms in XRCC1 gene are listed in Ensemble database, and most extensively studied are genetic changes Arg194Trp, Arg280His, Arg399Gln and -77T>C (Ginsberget al., 2011).

Recently, a variant in the 5'untranslated region (UTR) of XRCC1 (-77 T>C, rs3213245) has been identified, which appeared to lower XRCC1 levels by decreasing gene expression and was shown to be significantly associated with risks of esophageal squamous cell carcinoma and lung cancer in a Chinese population . Mutations of XRCC1 may increase the risk of cancers by impairing the interaction of XRCC1 with the other enzymatic proteins and consequently altering DNA repair activity (Tudek, 2007). Previous studies investigating the association between XRCC1 -77T>C polymorphism and risk of different cancers have provided inconsistent results (Haoet al., 2004; Haoet al., 2006; Bassoet al., 2007). Most of those studies involved no more than a few hundred cancer cases, which is too few to assess reliably any genetic effects. Furthermore, the interpretation of available studies may be complicated by different ethnicities, different population sampling strategies or different genotyping procedures. Therefore, there was a role for meta-analysis in pooling these studies, particularly to clarify the effect of XRCC1 -77T>C genotype on cancer risk. Hence, we carried out a meta-analysis of available data from all relevant studies.

Materials and Methods

Search strategy and selection criteria

Computer searches of PubMed, Embase and Chinese Bio-medicine Database (CBM) used the following search criterion: ("cancer" or "carcinoma" or "tumor") and ("polymorphism" or "polymorphisms") and ("XRCC1" or "X-ray repair cross-complementation group 1") without language restriction. All eligible articles were retrieved and their references were checked for other relevant articles. When the same patient population was included

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Table 1. Characteristics of Studies Included in this Meta-analysis

Reference	Ethnicity (country)	Characteristics of cases	Characteristics of controls	HWE‡
Betti et al., 2011	Caucasians(Italy)	109 histologically confirmed malignant mesothelioma cases	252 population controls	Yes
Liu et al., 2011	Asians(China)	995 histologically confirmed breast cancer cases	1004 cancer-free controls	Yes
Wang et al., 2010	Asians(China)	234 bladder cancer patients	253 cancer-free controls	Yes
Sterpone et al., 2010	Caucasians(Italy)	43 histologically confirmed breast cancer cases	31 healthy volunteers	Yes
Corso et al., 2009	Caucasians(Italy)	456 histologically confirmed gastric cancer patients	507 healthy controls	Yes
Hsieh et al., 2009	Asians(China)	294 histologically confirmed lung cancer cases	288 cancer-free controls	Yes
Li et al., 2008	Asians(China)	350 histologically confirmed lung cancer cases	350 cancer-free controls	Yes
De et al., 2007	Caucasians(Belgium)	109 histologically confirmed lung cancer cases	110 cancer-free controls	Yes
Sak et al., 2007	Caucasians(UK)	530 bladder cancer patients	556 healthy controls	Yes
Brem et al., 2006	Caucasians(France)	247 breast cancer cases	380 healthy controls	Yes
Hao et al., 2006	Asians(China)	1024 histologically confirmed lung cancer cases	1118 cancer-free controls	Yes
Hu et al., 2005	Asians(China)	710 lung cancer patients	710 cancer-free controls	Yes
Hao et al., 2004	Asians(China)	405 histologically confirmed ESCC cases†	478 cancer-free controls	Yes

†ESCC, esophageal squamous cell carcinoma; ‡HWE, Hardy-Weinberg equilibrium

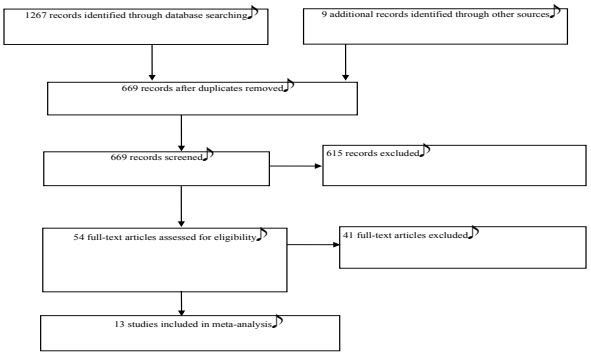

Figure 1. Flowchart of Selection of Studies for Inclusion in the Meta-analysis

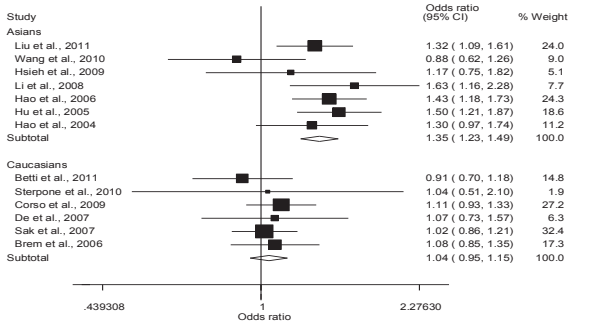

Figure 2. Forest Plots of Pooled OR with 95% CI for Associations Between XRCC1 -77T>C Polymorphism and Cancer Risk. (The size of the data markers is inversely proportional to the variance of the log ORs; horizontal lines represent the 95% CIs. The pooled ORs and the subtotals for each region and their 95% CIs are indicated by the squares; A. C vs. T; B. Homozygote comparison model; C. Recessive genetic comparison model)

in different articles, only the most recent or complete study was used in this meta-analysis. The inclusion criteria were: (1) case-control studies which evaluated the association of XRCC1 -77T>C polymorphism with cancer risk; (2) based on unrelated cancer individuals; (3) sufficient published genotype data for estimating an odds ratio (OR) with 95% confidence interval (CI); (4) genotype distribution of the control population reported was in Hardy-Weinberg equilibrium (HWE).

Data extraction

The following information was extracted from each study, according to a fixed protocol: study design, ethnicity of participants, numbers of cases and controls, DNA extraction and genotyping methods and frequency of genotypes. Confirmation of the extracted information was sought by correspondence with investigators.

Statistical Analysis

A chi-square test (http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl) was used to determine if genotype distribution of the control population reported conformed to HWE ($P < 0.05$ was considered significant). Statistical heterogeneity across the various trials was tested with the use of Cochran's Q statistic (Cochran, 1954). A P value of more than the nominal level of 0.10 for the Q statistic indicated a lack of heterogeneity across trials, allowing for the use of a fixed-effects model (the Mantel-Haenszel method) (Mantelet al., 1959); otherwise, the random-effects model (the DerSimonian and Laird method) was used (DerSimonianet al., 1986). The pooled ORs were performed on the Allele gene model (C vs. T), homozygote model (CC vs. TT), dominant model (CC+TC vs. TT), and recessive model (CC vs. TC+TT) respectively. The significance of pooled OR was tested by Z test ($P < 0.05$ was considered significant). Subgroup analyses were performed by ethnicity, cancer type and sample size. Ethnic group was defined as Caucasian, Asian, African or others. An estimate of potential publication bias was carried out using funnel plot and Egger's linear regression test. The significance of the intercept was determined by the t test suggested by Egger, and $P < 0.05$ was considered representative of a statistically significant publication bias (Eggeret al., 1997). Data were analyzed with the use of STATA (version 10.0; Stata Corporation, College Station, TX) and Review Manager (version 5.0; Oxford, England). All the P values were two-sided.

Results

Characteristics of Identified Studies

A flow diagram illustrating the study selection process was shown in Figure 1. The search strategy generated 669 studies, of which 54 RCTs with full-text were further assessed for eligibility. Studies provide genotyping data of mixed population indicated as "mixed" ethnicity. At last, 13 relevant case-control genetic association articles were finally identified, involving a total of 5598 cancer cases

Table 2. Distribution of XRCC1 -77T>C Genotypes and Alleles Among Cancer Cases and Controls in the Meta-analysis

Reference	Genotype						Allele				P HWE†
	T/T (n)		T/C (n)		C/C (n)		T (n)		C (n)		
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	
Betti et al., 2011	75	104	99	144	27	47	249	352	153	238	0.81
Liu et al., 2011	766	817	210	179	19	8	1742	1813	248	195	0.6
Wang et al., 2010	174	178	56	73	4	2	404	429	64	77	0.06
Sterpone et al., 2010	20	15	19	13	4	3	59	43	27	19	0.94
Corso et al., 2009	155	188	219	238	82	81	529	614	383	400	0.7
Hsieh et al., 2009	251	250	40	37	3	1	542	537	46	39	0.76
Li et al., 2008	264	291	75	55	11	4	603	637	97	63	0.45
De et al., 2007	37	40	53	52	19	18	127	132	91	88	0.87
Sak et al., 2007	174	187	266	275	90	94	614	649	446	463	0.68
Brem et al., 2006	90	134	107	187	50	59	287	455	207	305	0.64
Hao et al., 2006	783	924	223	182	18	12	1789	2030	259	206	0.37
Hu et al., 2005	500	558	198	148	12	4	1198	1264	222	156	0.08
Hao et al., 2004	305	384	94	89	6	5	704	857	106	99	0.95
Caucasians	551	668	763	909	272	302	1865	2245	1307	1513	0.81
Asians	3043	3402	896	763	73	36	6982	7567	1042	835	0.34
Total	3594	4070	1659	1672	345	338	8847	9812	2349	2348	<0.01

†P HWE, P values for Hardy-Weinberg equilibrium

Table 3. Summary of Pooled Odds Ratios (OR) with Confidence Interval (CI) in the Meta-analysis

Results before adjustment for heterogeneity Comparison	Model	Studies (No. of cases / controls)	Odds Ratio OR[95%CI]	M*	Heterogeneity P I^2 (%)	Egger's test
Total studies	C vs. T	13(5,598/6,080)	1.19(1.07-1.31)	R	50.4	0.871
	Homozygote comparison model	13(5,598/6,080)	1.28(1.07-1.52)	F	11.3	0.018
	Recessive genetic comparison model	13(5,598/6,080)	1.22(1.04-1.44)	F	9.5	0.013
	Dominant genetic comparison model	13(5,598/6,080)	1.21(1.07-1.35)	R	39.1	0.176
Caucasians	C vs. T	6(1586/1879)	1.04(0.95-1.15)	F	0	0.801
	Homozygote comparison model	6(1586/1879)	1.09(0.90-1.34)	F	0	0.715
	Recessive genetic comparison model	6(1586/1879)	1.08(0.91-1.30)	F	0	0.79
	Dominant genetic comparison model	6(1586/1879)	1.04(0.90-1.19)	F	0	0.838
Asians	C vs. T	7(4012/4201)	1.35(1.23-1.49)	F	27.7	0.342
	Homozygote comparison model	7(4012/4201)	2.28(1.52-3.42)	F	0	0.511
	Recessive genetic comparison model	7(4012/4201)	2.15(1.44-3.22)	F	0	0.403
	Dominant genetic comparison model	7(4012/4201)	1.36(1.22-1.51)	F	35.4	0.276
Lung cancer	C vs. T	5(2487/2576)	1.41(1.25- 1.59)	F	0	0.366
	Homozygote comparison model	5(2487/2576)	1.91(1.24-2.94)	F	0	0.214
	Recessive genetic comparison model	5(2487/2576)	1.73(1.14- 2.62)	F	0	0.133
	Dominant genetic comparison model	5(2487/2576)	1.45(1.27-1.66)	F	0	0.211
Breast cancer	C vs. T	3(1285/1415)	1.20(1.04-1.39)	F	0	0.713
	Homozygote comparison model	3(1285/1415)	1.47(1.00-2.17)	F	12.2	0.81
	Recessive genetic comparison model	3(1285/1415)	1.52(1.06-2.18)	F	0	0.837
	Dominant genetic comparison model	3(1285/1415)	1.18(0.99-1.42)	F	19.8	0.66

*M, model of meta-analysis; R, random-effects model; F, Fixed-effects model; †PH, the P value of heterogeneity test

and 6080 controls (Table 1) (Huet al., 2005; Bremet al., 2006; De Ruycket al., 2007; Saket al., 2007; Liet al., 2008; Corsoet al., 2009; Hsiehet al., 2009; Sterponeet al., 2010; Wanget al., 2010; Bettiet al., 2011; Liuet al., 2011). Table 2 showed the distribution of XRCC1 -77T>C genotypes and alleles among cancer cases and controls in the meta-analysis.

Results of Meta-analysis

Table 3 listed the main results of this meta-analysis. Overall, statistically significant association between XRCC1 -77C polymorphism and cancer risk was found in total population analyses in all four genetic comparison models(ORC vs. T =1.19, 95%CI 1.07-1.31, P = 0.001; OR Homozygote model =1.28, 95%CI 1.07-1.52, P = 0.007; OR Recessive genetic model =1.22, 95%CI 1.04-1.44, P = 0.015; OR Dominant model =1.21, 95%CI 1.07-1.35, P = 0.001) (Figure 2).

In subgroup analyses based on ethnicity, the association was still significant in the Asian population (All p values < 0.001) but not in Caucasians (All p values > 0.05). Subgroup analyses based on cancer type showed XRCC1 -77C variant was significantly associated with increased risk of breast cancer and lung cancer (Table 3). Subgroup analyses of other kinds of cancers were not performed owing to the lack of relevant studies.

The between-study heterogeneity was not obvious in most comparisons except the Allele gene model (C vs. T)

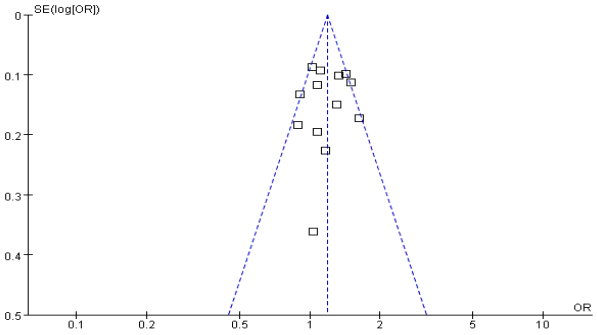

Figure 3. Funnel Plot for Publication Bias Test in the Meta-analysis Investigating for Associations Between XRCC1 -77T>C Polymorphism and Cancer Risk. (C vs. T, Each point represents a separate study for the indicated association. LogOR, natural logarithm of odds ratio; Horizontal line, mean effect size)

comparison analysis based on total studies (I^2=50.4%). Interestingly, the heterogeneity remarkably decreased in subgroup analyses based on ethnicity (I^2=0.0% in Caucasians and 27.7% in Asians), indicating the difference between various ethnicities led to the between-study heterogeneity (Table 3).

Publication Bias

Funnel plot and Egger's test were both performed to assess the publication bias of this meta-analysis. The shape of the funnel plots for most genetic contrast models seemed symmetrical, and most P values of Egger's tests were more than 0.05 (Table 3, Figure 3), providing statistical evidence of funnel plot symmetry. The results above suggested that publication bias was not evident in our meta-analyses.

Discussion

The present meta-analysis of 13 case-control studies, involving a total of 5,898 cancer cases and 6,080 controls, provides the most comprehensive assessment so far of the association between XRCC1 -77T>C polymorphism and cancer risk. The findings of this meta-analysis indicate that variant homozygote CC of XRCC1 -77T>C is significantly associated with increased cancer risk (OR=1.28, 95%CI 1.07-1.52; P = 0.007). Particularly, individuals with the CC genotype has a 128% higher odd of cancer risk compared with individuals with TT carriers in Asians (OR (95%CI) =2.28(1.52-3.42); P < 0.001). In the subgroup analysis by ethnicity, the association is still significant in the Asian population (All p values < 0.001) but not in the Caucasian population (All p values > 0.05), suggesting a possible role of ethnic differences in genetic backgrounds and the environment (Table 3). Therefore, those gene-variant associations vary in different ethnicities and the reason may be different genetic backgrounds among various ethnicities.

Heterogeneity is a potential problem when interpreting the results of all meta-analyses, and finding of the source of heterogeneity is one of the most important goals of meta-analysis. The present meta-analysis showed that there was strong heterogeneity between studies in the Allele gene model (C vs. T) comparison analysis based on total studies (I^2=50.4%). Therefore, we first stratified studies according to ethnicity. Heterogeneity between studies remarkably decreased or removed in subgroup analyses by ethnicity (I^2=0.0% in Caucasians and 27.7% in Asians; Table 3), which indicated between-study heterogeneity mainly come from ethnic differences in genetic backgrounds and also further indicated differences of genetic backgrounds among different ethnicities in mechanisms of carcinogenesis.

Our results show that the association between XRCC1 -77T>C polymorphism and cancer risk are obvious in lung cancer and breast cancer but not in the others, indicating that XRCC -77T>C polymorphism may exert different effects in different kinds of cancer. However, it also likely that the observed different effects may be due to chances because studies with small sample size may have insufficient statistical power to detect a slight effect or may have generated a fluctuated risk estimate. For example, the sample size of gastric cancer in this meta-analysis was only 456 individuals which were too small to generate an acceptable risk estimate. Thus, large and carefully designed case-control studies among other kinds of cancers are needed to provide the best evidence for such a possible association in other ethnicity or cancers.

Efficient DNA repair represents an important defense mechanism in neutralizing mutagenic damage, and XRCC1 supports DNA repair by binding to the site where damaged bases have been removed or where single strand breaks (SSBs) have occurred for other reasons, which facilitates the activity of polymerase and ligase enzymes and so is central to the proper functioning of BER (Ginsberg and Angle, 2011). XRCC1 gene variants, which appeared to influence XRCC1 levels by decreasing gene expression, might be significantly associated with cancer risk. A variety of cancer outcomes have been evaluated according to XRCC1 polymorphism, and several large-scale meta-analyses combining data from multiple studies have been published to investigate the association between XRCC1 polymorphism and various cancers, such as cervical cancer, gastric cancer, lung cancer and breast cancer. Huang Y et al suggested obvious association was found between breast cancer and XRCC1 Arg399Gln polymorphism (Huanget al., 2009). Dai L et al found that Gln/Gln genotype might be associated with esophageal squamous cell carcinoma risk in Asians, while Lao T et al found that Gln variant of XRCC1 Arg399Gln might decrease the risk of bladder cancer among ever-smokers (Laoet al., 2008; Daiet al., 2009). But there were no large-scale meta-analyses combining data from multiple studies published to investigate the association between XRCC1 -77T/C polymorphism and cancer risk. Thus, this present meta-analysis is the fist meta-analysis assessing the association between XRCC1 -77T/C polymorphism and cancer risk, and suggests that C variant of XRCC1 -77T/C is an important genetic hallmark contributing to cancer susceptibility.

However, there are still some limitations in this meta-analysis. First, misclassification bias was possible. For example, most studies could not exclude latent cancer cases in the control group. The controls in some studies were selected from non-cancer patients, while

the controls in other several studies were just selected from asymptomatic individuals. Second, the eligibility criteria for inclusion of subjects and sources of controls were different from each other. For example, some studies were population-based, and some were hospital-based. The allele distribution in the hospital control groups might not have been representative of the general population. Therefore, using a proper and representative population-based control subjects is very important to reduce biases in such genetic association studies. Third, gene-gene and gene-environmental interactions were not addressed in this meta-analysis. As we know, aside from genetic factor, smoking is a major risk factor for cancer; however we didn't perform subgroup analyses in smokers or nonsmokers owing to the limited reported information on such associations in the included studies. Considering these limitations, our results should be interpreted with caution.

Despite of those limitations, this meta-analysis suggests the C variant of XRCC1 -77T>C is an important genetic hallmark contributing to cancer risk, but these gene-variant associations vary in different ethnicities. Besides, large and carefully designed case-control studies among other kinds of cancers need performing to provide the best evidence for such a possible association in other ethnicity or cancers.

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The authors declare that they have no competing interests.

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