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CASP-9 gene functional polymorphisms and cancer risk: a large-scale association study plus meta-analysis

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ABSTRACT. We investigated the association between CASP-9 polymorphisms and susceptibility to neoplasm. Fourteen studies with a total of 2733 neoplasm cases and 3352 healthy controls were included. Meta-analysis showed that the rs4645981*T allele and the rs4645981*T allele carrier were positively associated with neoplasm susceptibility [odds ratio (OR) = 1.43, 95% confidence interval (95%CI) = 1.12-1.81, P = 0.004; OR = 1.46, 95%CI = 1.10-1.93, P = 0.009, respectively]. However, the rs1052576*A allele, rs1052576*A carrier, rs2308941*T allele, and rs2308941*T carrier might decrease the risk of cancer (OR = 0.72, 95%CI = 0.58-0.89, P = 0.003; OR = 0.76, 95%CI = 0.63-0.92, P = 0.004; OR = 0.20, 95%CI = 0.09-0.45, P < 0.0001; OR = 0.21, 95%CI = 0.06-0.75, P = 0.02, respectively). There was no significant association between rs1263, rs1052571, rs2308950, rs4645978, rs4645980, rs4645982, and rs4646018 and cancer risk (all P > 0.05). In conclusion, this meta-analysis suggests that CASP-9 gene polymorphisms are involved in the pathogenesis of various cancers. The rs4645981*T allele and the rs4645981*T allele carrier might increase the risk of cancer, but the rs1052576*A allele, rs1052576*A carrier, rs2308941*T allele, and rs2308941*T carrier might be protective.

Key words: CASP-9; Gene polymorphisms; Cancer; Meta-analysis

INTRODUCTION

Caspase-9 is a cysteine protease encoded by the CASP-9 gene (Thornberry, 1997; Shiozaki et al., 2003) located on chromosome 1p36.1 (Bian et al., 2004). A member of the caspase gene family, caspase-9, plays an important role in the mitochondrial death pathway. In this pathway, cell death signals lead to mitochondrial release of cytochrome *c*, which binds and facilitates formation of the heptameric apoptosome that recruits and activates caspase-9. During apoptosis, the extrinsic and intrinsic pathways in humans use the caspase enzyme cascade; the extrinsic pathway utilizes caspase-8 and -10, while the intrinsic pathway employs caspase-9 (Kesarwani et al., 2011). Complex recruitment of caspase-9 leads to activation through formation of the apoptosome (Gil et al., 2002). Many studies have identified significant associations between the caspase gene cluster and cancer susceptibility, particularly for CASP-7, -8, and -10 (Oliveira et al., 2004; De Vecchi et al., 2009; Liu et al., 2010). However, Catchpoole and Lock (2001) found that CASP-9 is also strongly associated with neuroblastoma. Liamarkopoulos et al. (2011) confirmed that CASP-9 genetic polymorphisms influence the risk of gastric cancer. Moreover, Choi et al. (2012) demonstrated CASP-9 involvement in the pathogenesis of lung cancer. Seo et al. (2011) suggested that ovarian cancer susceptibility is correlated with CASP-9. However, these studies did not characterize the precise relationship between CASP-9 and cancer risk, and uncertainty remains. We performed this study to describe the overall associations between CASP-9 and cancer risk.

MATERIAL AND METHODS

Literature search

PubMed, Cochrane library, Embase, Web of Science, Springerlink, CNKI, and CBM databases were searched (last search was updated on May 10, 2012) extensively to identify relevant studies. The search terms included ["Caspase-9" or "ICE-Like Apoptotic Protease 6" or "Procaspase-9" or "Caspase 9" (Mesh)] and ["SNPs" or "SNP" or "polymorphism, genetic" (Mesh)] and ["cancer" or "tumor" or "Neoplasms" (Mesh)]. References in eligible studies or textbooks were also reviewed.

Inclusion and exclusion criteria

The studies included had to meet the following criteria: case-control study; focused on associations between CASP-9 polymorphisms and cancer susceptibility; all patients with the diagnosis of cancer confirmed by pathological examination of surgical specimens; the frequencies of alleles or genotypes in case and control groups could be determined; and the publication was in English or Chinese. Studies were excluded when they were not case-control studies about CASP-9 gene polymorphisms and cancer susceptibility; if they were based on incomplete data; or if useless or overlapping data were reported.

Data extraction

Using a standardized form, data from the studies published were extracted independently by 2 reviewers (Z.Y.Z. and Y.X.). The following information was extracted from each article: first author, year of publication, country, language, ethnicity, study design, diagnostic criteria, source of cases and controls, number of cases and controls, mean age, sample, pathological types, detection methods, polymorphism genotype frequency, and evidence of Hardy-Weinberg equilibrium (HWE) in controls. In case of conflicting evaluations, an agreement was reached following discussion with a third reviewer (R.W.).

Quality assessment

Two reviewers (X.Y.J. and X.T.) independently assessed the quality of the papers according to modified STROBE quality score systems (Son et al., 2006; Zhang et al., 2011). Forty quality appraisal assessment items were used in this meta-analysis, with scores ranging from 0 to 40. Scores of 0-20, 20-30, and 30-40 were defined as low, moderate, and high quality, respectively. Disagreement was resolved by discussion with a third reviewer (R.W.).

Statistical analysis

Allele or genotype frequencies of CASP-9 SNPs were determined by allele counting. The odds ratio (OR) and 95% confidence interval (95%CI) were calculated using Review Manager version 5.1.6 (provided by the Cochrane Collaboration, available at: http://ims.cochrane.org/revman/download) and STATA version 12.0 (Stata Corp., College Station, TX, USA). Between-study variation and heterogeneity were estimated using the Cochrane Q-test (Higgins and Thompson, 2002; Zintzaras and Ioannidis, 2005) ($P \leq 0.05$ indicated statistically significant heterogeneity). We also quantified the effect of heterogeneity by using the I^2 test. I^2 ranges between 0 and 100% and represents the proportion of inter-study 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, the random-effect model was used for meta-analysis, or the fixed-effect model was used. To establish the effect of heterogeneity on the meta-analysis conclusions, subgroup analysis was performed. We determined whether the genotype frequencies of the controls were in HWE using the χ^2 test. Subgroup analysis based on nationality was used to explore and explain diversity among the results of different studies. Sensitivity analysis was performed by sequential omission of individual studies. Publication bias was investigated by Begger's funnel plot, and funnel plot asymmetry was assessed by the Egger linear regression test (Peters et al., 2006); statistical significance was indicated by the Egger test ($P < 0.05$). All P values were two-sided. To ensure reliability and accuracy, two reviewers (Z.Y.Z. and Y.X.) independently populated the data in the statistical software programs and obtained the same results.

RESULTS

Characteristics of the studies included

Fourteen studies (Park et al., 2006; Fang et al., 2007; Lan et al., 2007; Lou et al., 2007; He et al., 2008; Hosgood et al., 2008; Ye et al., 2008; Gangwar et al., 2009; Ulybina et al., 2009;

Wu, 2009; Kesarwani et al., 2011; Ni et al., 2011; Theodoropoulos et al., 2010, 2011) were included and 80 were excluded, based on the inclusion and exclusion criteria. A flow chart representing study selection is shown in Figure 1. The total numbers of cancer cases and healthy controls were 2733 and 3352 in 14 case-control studies, which evaluated the relationship between CASP-9 gene polymorphisms and susceptibility to cancer. Publication year ranged from 2005 to 2011. All patients fulfilled the diagnosis criteria of malignant neoplasm confirmed by pathological examination of the surgical specimen. The source of controls was based on a healthy population. Ten SNPs in CASP-9 were addressed, including rs1263, rs1052571, rs1052576, rs2308941, rs2308950, rs4645978, rs4645980, rs4645981, rs4645982, and rs4646018. HWE tests were performed on the genotype distribution of controls in all the studies included. We found that 4 studies mainly from Asian populations were in non-HWE ($P < 0.05$), while all others were in HWE ($P > 0.05$). All quality scores were >20 (moderate to high quality). The characteristics and methodological quality of the studies included are summarized in Table 1.

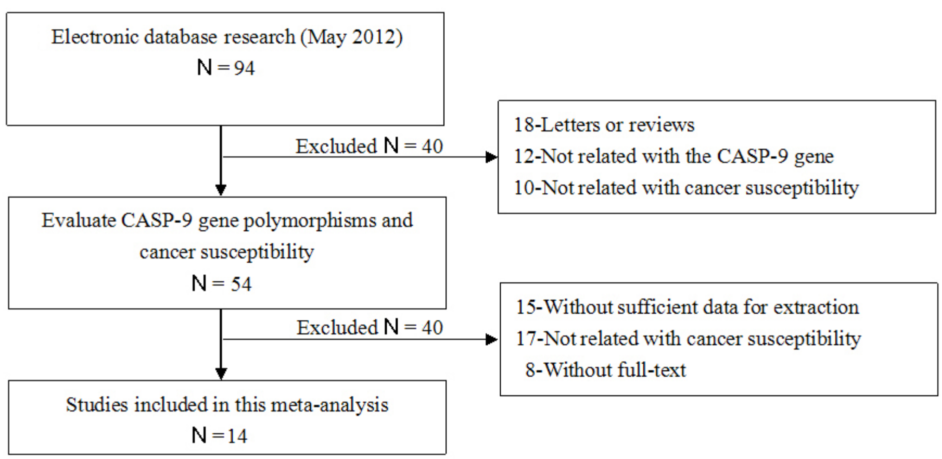

Figure 1. Flow chart shows the study selection procedure.

Association between CASP-9 gene polymorphisms and cancer risk

A summary of the meta-analysis of the association between CASP-9 gene polymorphisms and cancer susceptibility is provided in Table 2. The meta-analysis showed that rs4645981, including the rs4645981*T allele and the rs4645981*T allele carrier, was positively associated with cancer susceptibility (OR = 1.43, 95%CI = 1.12-1.81, P = 0.004; OR = 1.46, 95%CI = 1.10-1.93, P = 0.009, respectively). However, there were negative associations between rs1052576, rs2308941, and cancer susceptibility. The rs1052576*A allele, rs1052576*A carrier, rs2308941*T allele, and rs2308941*T carrier might decrease the risk of cancer (OR = 0.72, 95%CI = 0.58-0.89, P = 0.003; OR = 0.76, 95%CI = 0.63-0.92, P = 0.004; OR = 0.20, 95%CI = 0.09-0.45, $P < 0.0001$; OR = 0.21, 95%CI = 0.06-0.75, P = 0.02, respectively). In addition, there were no significant associations for rs1263, rs1052571, rs2308950, rs4645978, rs4645980, rs4645982, and rs4646018 (all $P > 0.05$). The significance of pooled OR in all individual and subgroup analyses was not excessively influenced by omitting any single study or the non-HWE studies. The positive associations between CASP-9 gene polymorphisms and cancer susceptibility are shown in Figure 2.

Table 1. Characteristics of individual studies included in the meta-analysis.

Reference	Country	Ethnicity	Number		Detection	Disease	SNP	HWE	
			Case	Control				P	Test
Park et al., 2006	Korea	Asian	432	432	PCR-RFLP	Lung cancer	rs4645978 (A/G)	0.77	HWE
							rs4645980 (T/G)	0.77	HWE
							rs4645981 (C/T)	0.69	HWE
							rs4645982 (del/ins)	0.59	HWE
Fang et al., 2007	China	Asian	70	100	PCR-RFLP	Gastric cancer	rs1052576 (G/A)	0.52	HWE
Lan et al., 2007	USA	Caucasian	461	535	DNA sequencing	Lymphoma	rs1052576 (G/A)	0.67	HWE
						Lymphoma	rs1052576 (G/A)	0.67	HWE
						Lymphoma	rs1052576 (G/A)	0.67	HWE
Lou et al., 2007	China	Asian	81	100	PCR-RFLP	Lung cancer	rs1052571 (C/T)	0.80	HWE
							rs1052576 (G/A)	0.52	HWE
He et al., 2008	China	Asian	170	100	PCR-RFLP	Colon cancer	rs1052576 (G/A)	0.52	HWE
Hosgood et al., 2008	USA	Caucasian	128	516	DNA sequencing	Multiple myeloma	rs1052576 (G/A)	0.76	HWE
Ye et al., 2008	China	Asian	33	33	DNA microarray	Variant cancer	rs2308941 (C/T)	<0.05	non-HWE
Gangwar et al., 2009	India	Asian	212	250	PCR-RFLP	Bladder cancer	rs4645978 (A/G)	<0.05	non-HWE
							rs4645982 (del/ins)	0.60	HWE
Ulybina et al., 2009	Russia	Caucasian	111	110	AS-PCR	Lung cancer	rs1052571 (C/T)	0.77	HWE
							rs2308950 (A/G)	0.69	HWE
							rs1052576 (G/A)	0.89	HWE
Wu, 2009	China	Asian	100	60	PCR-RFLP	Liver cancer	rs1052576 (G/A)	0.84	HWE
Theodoropoulos et al., 2010	Greece	Caucasian	80	160	PCR-RFLP	Pancreatic cancer	rs1263 (A/G)	0.08	HWE
Kesarwani et al., 2011	India	Asian	175	198	PCR-RFLP	Prostate cancer	rs4645978 (A/G)	<0.05	non-HWE
							rs4645982 (del/ins)	<0.05	non-HWE
Ni et al., 2011	China	Asian	278	278	PCR-RFLP	Gastric cancer	rs4646018 (G/A)	0.52	HWE
Theodoropoulos et al., 2011	Greece	Caucasian	402	480	PCR-RFLP	Colorectal cancer	rs1263 (A/G)	0.93	HWE

SNP = single nucleotide polymorphisms; HWE = Hardy-Weinberg equilibrium; PCR = polymerase chain reaction; RFLP = restriction fragment length polymorphism; AS = allele specific.

Table 2. Meta-analysis of the association between CASP-9 gene polymorphisms and cancer risk.

SNPs		Cases (n/N)	Controls (n/N)	OR (95%CI)	P	Heterogeneity test	Effect model
Rs1263	G allele	436/964	646/1280	1.44 (0.26-7.84)	0.67	P < 0.00001, I^2 = 98%	Random
	G carrier	324/482	488/640	1.82 (0.12-26.97)	0.66	P < 0.00001, I^2 = 95%	Random
Rs1052571	T allele	113/384	130/420	0.87 (0.64-1.19)	0.39	P = 0.93, I^2 = 0%	Fixed
	T carrier	97/192	106/210	0.93 (0.61-1.40)	0.72	P = 0.96, I^2 = 0%	Fixed
Rs1052576	A allele	1047/2226	1601/3022	0.72 (0.58-0.89)	0.003	P = 0.009, I^2 = 65%	Random
	A carrier	806/1113	1160/1511	0.76 (0.63-0.92)	0.004	P = 0.41, I^2 = 3%	Fixed
Rs2308941	T allele	33/66	55/66	0.20 (0.09-0.45)	<0.0001	-	Fixed
	T carrier	20/33	29/33	0.21 (0.06-0.75)	0.02	-	Fixed
Rs2308950	G allele	3/222	8/220	0.36 (0.10-1.39)	0.14	-	Fixed
	G carrier	3/111	8/110	0.35 (0.09-1.37)	0.13	-	Fixed
Rs4645978	G allele	642/1634	771/1760	0.83 (0.72-0.95)	0.008	P = 0.64, I^2 = 0%	Fixed
	G carrier	506/817	583/880	0.82 (0.67-1.00)	0.05	P = 0.27, I^2 = 24%	Fixed
Rs4645980	G allele	367/864	354/864	1.06 (0.88-1.29)	0.53	-	Fixed
	G carrier	289/432	280/432	1.10 (0.83-1.45)	0.52	-	Fixed
Rs4645981	T allele	193/864	145/864	1.43 (1.12-1.81)	0.004	-	Fixed
	T carrier	171/432	134/432	1.46 (1.10-1.93)	0.009	-	Fixed
Rs4645982	T allele	666/1628	768/1760	0.90 (0.79-1.04)	0.14	P = 0.57, I^2 = 0%	Fixed
	T carrier	541/814	609/880	0.90 (0.73-1.10)	0.29	P = 0.38, I^2 = 0%	Fixed
Rs4646018	A allele	233/556	251/556	0.88 (0.69-1.11)	0.28	-	Fixed
	A carrier	189/278	197/278	0.87 (0.61-1.25)	0.46	-	Fixed

OR = odds ratio; 95%CI = 95% confidence interval.

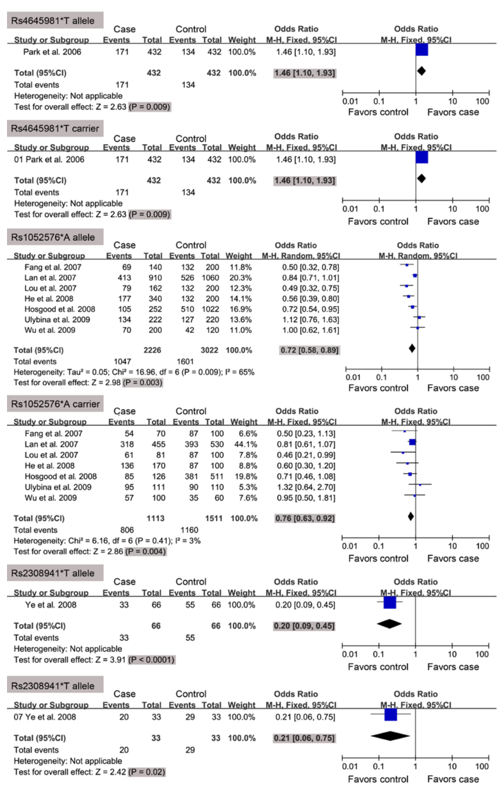

Figure 2. Association of the rs4645981*T allele and the rs4645981*T carrier with susceptibility to neoplasm. The squares and horizontal lines correspond to the study-specific odds ratio (OR) and 95% confidence interval (95%CI). The diamond represents the summary OR and 95%CI. M.-H. = Mantel-Haenszel estimator.

Publication bias

Publication bias of the literatures was accessed by Begger's funnel plot and the Egger linear regression test. The Egger linear regression test was used to measure the asymmetry of the funnel plot. All graphical funnel plots appeared to be symmetrical (Figure 3). The Egger test also showed no statistically significant publication bias (all P > 0.05). Findings of the Egger publication bias test are shown in Table 3.

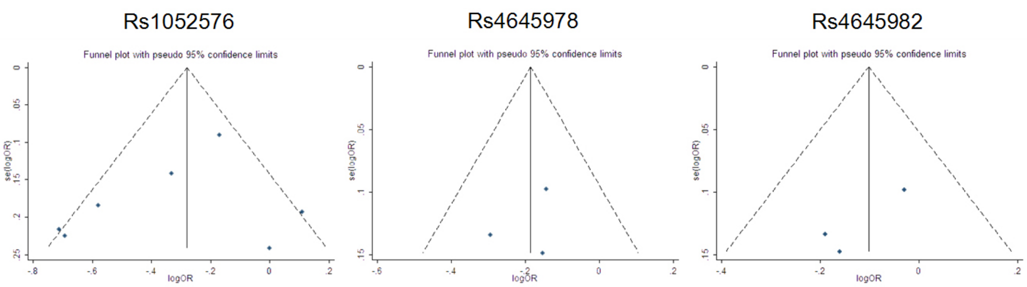

Figure 3. Begger's funnel plot of publication bias for the association between rs1052576, rs4645978, rs4645982, and susceptibility to lung cancer.

Table 3. Evaluation of publication bias by the Egger linear regression test.

SNPs	Coefficient	SE	*t*	P	95%CI
rs4645978 (A/G)	-1.416	2.584	-0.550	0.681	(-34.248-31.416)
rs4645982 (del/ins)	-3.228	1.284	-2.510	0.241	(-19.537-13.081)
rs1052576 (G/A)	-1.633	1.838	-0.890	0.415	(-6.359-3.092)

SE = standard error; 95%CI = 95% confidence interval.

DISCUSSION

Caspase-9 may cause aberrant apoptosis inhibition, and the relevance of this process has been demonstrated in a number of cancer types (Kelly et al., 2010). Caspase-9 is a member of the Caspase family of cysteine proteases that have been implicated in apoptosis and cytokine processing (Bian et al., 2004). As a central initiator caspase, caspase-9 can be triggered in a response to stimuli that damage mitochondria directly or by signals originating in other parts of the cell (Potokar et al., 2003). Although many studies have evaluated the association between CASP-9 gene polymorphisms and cancer risk, the results remain controversial.

In this meta-analysis, we examined 10 SNPs in the CASP-9 gene, including rs1263, rs1052571, rs1052576, rs2308941, rs2308950, rs4645978, rs4645980, rs4645981, rs4645982, and rs4646018. Our study showed that the rs4645981*T allele and the rs4645981*T allele carrier had significant associations with cancer risk after adjustment for multiple testing. However, the rs1052576*A allele, rs1052576*A carrier, rs2308941*T allele, and rs2308941*T carrier might decrease the risk of cancer. There was no association between rs1263, rs1052571, rs2308950, rs4645978, rs4645980, rs4645982, and rs4646018 and cancer risk (all P > 0.05). Although a recent collaborative study found an association for other SNPs of the CASP-9 gene and their haplotypes, there has been no pooled analysis of rs1263, rs1052571, rs2308950, rs4645978, rs4645980, rs4645982, and rs4646018 and cancer risk. Some studies have shown that ethnicity may influence cancer susceptibility through variations in genetic background and environmental exposure leading to various gene-gene and gene-environmental interactions. Sensitivity analysis was performed by omitting any single study and non-HWE studies; no influence was found.

The many limitations of our meta-analysis should be addressed. First, the relevant research articles are few and the sample size of this meta-analysis was not large. In addition, some relevant studies could not be included in our analysis due to incomplete raw data. Third, we were not able to address the sources of heterogeneity in all studies. Fourth, although all cases and controls were well defined with similar inclusion criteria, there may be factors not taken into account that may have influenced our results. Most important, our meta-analysis was based on unadjusted OR estimates because not all publications presented adjusted OR; when they did, the OR were not adjusted by the same potential confounders, such as ethnicity, gender, geographic distribution, etc. Given these results, additional investigation in these areas is needed, and our conclusions should be interpreted cautiously.

In conclusion, this meta-analysis of 14 case-control studies demonstrated that CASP-9 gene polymorphisms are involved in the pathogenesis of various cancer. The rs4645981*T allele and the rs4645981*T allele carrier might increase the risk of cancer, but the rs1052576*A allele, rs1052576*A carrier, rs2308941*T allele, and rs2308941*T carrier might be protective. As few studies are available in this field and evidence remains limited, we emphasize the necessity to conduct large studies with adequate methodological quality and proper control of confounding factors in order to obtain valid results.

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