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Role of *CASP-10* gene polymorphisms in cancer susceptibility: a HuGE review and meta-analysis

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ABSTRACT. We investigated a possible association between *CASP-10* gene polymorphisms and susceptibility to cancer through a meta-analysis. Eight studies with a total of 29,936 cancer cases and 34,041 healthy controls were included. Meta-analysis results showed that the rs13006529*T carrier was significantly associated with increased cancer risk (OR = 1.17, 95%CI = 1.01-1.36, P = 0.03). However, rs3900115 and rs13010627 showed no association with cancer susceptibility (all P > 0.05). In the subgroup analysis by cancer type, we found that the rs13006529*T carrier was a risk factor for breast cancer (OR = 1.17, 95%CI = 1.01-1.36, P = 0.03). Similarly, no association was found between *CASP-10* polymorphisms and susceptibility to lymphoma, myeloma, melanoma, or lung cancer (all P > 0.05). This meta-analysis suggests that the rs13006529*T carrier in the *CASP-10* gene might be a risk factor for cancer susceptibility, especially for breast cancer.

Key words: *CASP-10*; Genetic polymorphisms; Cancer; Susceptibility; Meta-analysis

INTRODUCTION

Apoptosis is a particular type of programmed cell death that commonly occurs in the developing embryo, normal healthy adult tissues, and many pathological settings (Alison and Sarraf, 1992). The morphological features of apoptosis include changes in plasma membrane asymmetry and attachment, cytoplasm condensation, and nucleus and internucleosomal DNA cleavage (Doonan and Cotter, 2008). Dysregulation of apoptosis, resulting in too little or excessive cell death is implicated in the pathogenesis of stroke, myocardial infarction, neurodegenerative diseases, cancer, and autoimmune disorders (Rupinder et al., 2007). Among the 14 mammalian caspases identified thus far, only caspase-10 shares homologous death-effector domains with caspase-8, suggesting that caspase-10 may also interact with death receptors (Wang et al., 2001; Ghavami et al., 2009). Dysregulation of apoptosis is one of the hallmarks of cancers (Kim et al., 2009). Caspase-10 is an initiation-phase caspase, and somatic mutations of the *CASP-10* gene have been reported in many cancers (Oh et al., 2010). Park et al. (2002) confirmed that somatic alterations of the *CASP-10* gene might contribute to pathogenesis in a subset of gastric cancers through the loss of their apoptotic function. Kim et al. (2009) also found that *CASP-10* mutation might contribute to the pathogenesis of acute leukemias and multiple myelomas. Moreover, Shin et al. (2002) analyzed the entire coding region and all splice sites of the *CASP-10* gene to detect somatic mutations in 117 cases of human non-Hodgkin's lymphoma. They suggested that apoptotic dysregulation due to *CASP-10* mutation may mediate lymphomatogenesis. However, Oh et al. (2010) found that mutation of *CASP-10* is rare in colon, breast, lung, and hepatocellular carcinomas. To address the inconsistencies in these studies and assess the association between *CASP-10* gene polymorphisms and cancer susceptibility, we performed a Human Genome Epidemiology (HuGE) review and meta-analysis based on published case-control studies.

MATERIAL AND METHODS

Literature search

We extensively searched PubMed, Cochrane Library, Embase, Web of Science, Springerlink, CNKI, and CBM databases (last search was updated on May 10, 2012) to identify relevant studies. Search terms included ["Caspase-10" or "Caspase-10" or "Caspase 10" (Mesh)] and ["SNPs" or "SNP" or "polymorphism" 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 included studies had to meet the following criteria: the type of study should be a case-control study; the study must be focused on associations between *CASP-10* gene polymorphisms and cancer susceptibility; all patients must have the diagnosis of malignant tumor confirmed by pathological examination of the surgical specimen; the frequencies of alleles or genotypes in case and control groups should be capable of extraction,

and the publication should be in English or Chinese. Studies were excluded when they were not case-control studies of *CASP-10* gene polymorphisms, and cancer risk; if they were based on incomplete data; if useless or overlapping data were reported, or if it were meta-analyses, letters, reviews, or editorial articles.

Data extraction

Using a standardized form, data from published studies were extracted independently by two reviewers (Yan S and Li YZ) to collect information including: first author, year of publication, country, language, ethnicity, study design, diagnostic criteria, source of cases and controls, number of cases and controls, sample, cancer types, genotype methods, allele or genotype frequency, and evidence of Hardy-Weinberg equilibrium (HWE) in controls. In cases of conflicting evaluations, an agreement was reached following a discussion with a third reviewer (Liu YL).

Quality assessment of the studies included

Two reviewers (Zhu JW and Liu CL) independently assessed the quality of the papers according to modified STROBE quality score systems (von Elm et al., 2007; Zhang et al., 2011). Forty quality appraisal 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 (Liu YL).

Statistical analysis

The odds ratio (OR) and 95% confidence interval (95%CI) were calculated in 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 variations and heterogeneities were estimated using Cochran's Q-statistic (Higgins and Thompson, 2002; Zintzaras and Ioannidis, 2005) ($P \leq 0.05$ was considered to represent 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 effects model was generated for meta-analysis, or the fixed effects model was used. We tested whether the genotype frequencies of controls were in HWE using the χ^2 test. Subgroup analysis based on country was used to explore and explain the diversity of results from the selected studies. Sensitivity analysis was mainly performed by sequential omission of individual studies. Publication bias was investigated by the Begger funnel plot, and funnel plot asymmetry was assessed by the Egger linear regression test (Peters et al., 2006); statistical significance was indicated when the P value of the Egger test was <0.05. All P values were two-sided. To ensure reliability and accuracy, two reviewers (Yan S and Li YZ) independently populated the data in the statistics software programs and obtained the same results.

RESULTS

The characteristics of the studies included

According to the inclusion criteria, 8 studies (MacPherson et al., 2004; Ye, 2004; Frank et al., 2006; Lan et al., 2007; Hosgood et al., 2008; Li et al., 2008; Gaudet et al., 2009; Ulybina et al., 2009) were included and 97 were excluded. A flow chart of the study selection process is shown in Figure 1. The total number of cancer cases and healthy controls were 29,936 and 34,041 in these 8 case-control studies, which evaluated the relationship between *CASP-10* polymorphisms and cancer susceptibility. Publication year ranged from 2004 to 2009. All patients fulfilled the diagnosis criteria of malignant tumor confirmed by pathological examination of a surgical specimen. The source of controls was based on a healthy population. Three polymorphisms in the *CASP-10* gene were addressed, including rs13006529 (I522L) A>T in exon 10, rs13010627 (V410I) G>A in exon 9 and rs3900115 (A2823G) A>G in exon 3. Overall, there were 3 breast studies, 2 lymphoma studies, and 3 others including myeloma, melanoma, and lung cancer. Seven of these studies were conducted in a Caucasian population, 1 was in an Asian population. HWE was conducted for the controls in every study. All studies showed HWE except Ulybina et al. ($P < 0.05$). All quality scores were >20 (moderate-high quality). The characteristics and methodological quality of the studies are summarized in Table 1. The genotype distributions of *CASP-10* gene polymorphisms in case and control groups are presented in Table 2.

Association between *CASP-10* polymorphisms and cancer risk

A summary of the meta-analysis findings of the association between *CASP-10* gene polymorphisms and cancer risk is provided in Table 3. The meta-analysis result showed that the rs13006529*T carrier was significantly associated with increased cancer risk (OR = 1.17,

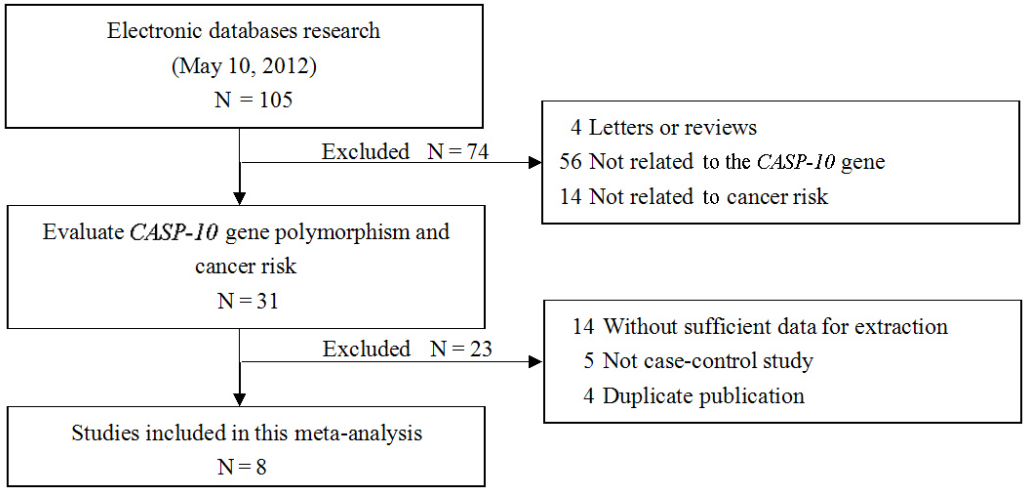

Figure 1. Flow chart of the study selection procedure.

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

Reference	Year	Country	Ethnicity	Number		Genotype method	Cancer type	SNP	HWE		Quality score
				Case	Control				P	Test	
MacPherson et al.	2004	UK	Caucasian	935	955	TaqMan	Breast cancer	rs13006529 (A>T)	0.63	HWE	21
Ye et al.	2004	China	Asian	90	140	PCR-DHPLC	Lymphoma	rs3900115 (A>G)	0.31	HWE	21
Frank et al.	2006	Germany	Caucasian	511	547	TaqMan	Breast cancer	rs13010627 (G>A)	0.37	HWE	26
Lan et al.	2007	USA	Caucasian	446	522	DNA Sequencing	Lymphoma	rs3900115 (A>G)	0.79	HWE	22
Hosgood et al.	2008	USA	Caucasian	121	503	DNA Sequencing	Myeloma	rs3900115 (A>G)	0.69	HWE	22
Li et al.	2008	China	Caucasian	805	835	PCR-RFLP	Melanoma	rs13006529 (A>T)	0.97	HWE	26
Gaudet et al.	2009	Multicenter	Caucasian	26917	30429	TaqMan/Mass-Array	Breast cancer	rs13010627 (G>A)	0.80	HWE	23
Ulybina et al.	2009	Russia	Caucasian	111	110	AS-PCR	Lung cancer	rs13006529 (A>T)	0.04	non-HWE	24

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

Table 2. Genotype distribution of the *CASP-10* gene polymorphism in case and control groups.

Reference	Year	SNP	Case group							Control group						
			Total	1	2	1/1	1/2	2/2	MF	Total	1	2	1/1	1/2	2/2	MF
MacPherson et al.	2004	rs13006529 (A>T)	935	915	955	217	481	237	0.51	955	996	914	256	484	215	0.48
Ye et al.	2004	rs3900115 (A>G)	84	139	29	59	21	4	0.17	140	228	52	91	46	3	0.19
Frank et al.	2006	rs13010627 (G>A)	511	965	57	455	55	1	0.06	547	997	97	456	85	6	0.09
Lan et al.	2007	rs3900115 (A>G)	446	455	437	126	203	117	0.49	522	522	522	129	264	129	0.50
Hosgood et al.	2008	rs3900115 (A>G)	121	117	125	28	61	32	0.52	503	500	506	122	256	125	0.50
Li et al.	2008	rs13006529 (A>T)	805	830	780	206	418	181	0.48	835	893	777	239	415	181	0.47
Gaudet et al.	2009	rs13010627 (G>A)	26917	50264	3570	23456	3352	109	0.07	30429	56900	3958	26597	3706	126	0.07
Ulybina et al.	2009	rs13006529 (A>T)	111	104	118	26	52	33	0.53	110	91	129	24	43	43	0.59

SNP = single nucleotide polymorphism; 1 = wild allele; 2 = variant allele; 1/1 = wild homozygote; 1/2 = heterozygote; 2/2 = variant homozygote; MF = minor allele frequency.

95%CI = 1.01-1.36, P = 0.03) (Figure 2). However, rs3900115 and rs13010627 showed no association with cancer susceptibility (all P > 0.05*)*. In the subgroup analysis by cancer type, we found that the rs13006529*T carrier was a risk factor for breast cancer (OR = 1.17, 95%CI = 1.01-1.36, P = 0.03). Similarly, no association was found between *CASP-10* polymorphisms and susceptibility to lymphoma, myeloma, melanoma, or lung cancer (all P > 0.05). The significance of pooled OR in all individual analyses was not influenced excessively by omitting any single study and non-HWE studies (Ulybina et al., 2009).

Table 3. Meta-analysis of the association between *CASP-10* gene polymorphisms and cancer risk.

Polymorphisms	Cancer (n/N)	Control (n/N)	OR (95%CI)	P	Heterogeneity		Effect model
					P	I^2	
rs13006529 (A>T)							
T allele	1853/3702	1820/3800	1.09 (1.00, 1.19)	0.06	0.22	34%	Fixed
AT + TT	1402/1851	1381/1900	1.17 (1.01, 1.36)	0.03	0.70	0%	
TT	451/1851	439/1900	1.07 (0.92, 1.24)	0.38	0.17	44%	
AT	951/1851	942/1900	1.08 (0.95, 1.22)	0.27	0.59	0%	
rs3900115 (A>G)							
G allele	591/1302	1080/2330	0.98 (0.85, 1.13)	0.79	0.82	0%	Fixed
AG + GG	438/651	823/1165	0.87 (0.70, 1.09)	0.24	0.64	0%	
GG	153/651	257/1165	1.10 (0.87, 1.41)	0.42	0.64	0%	
AG	285/651	566/1165	0.84 (0.69, 1.03)	0.09	0.58	0%	
rs13010627 (G>A)							
A allele	3627/54856	4055/61952	0.81 (0.49, 1.34)	0.41	<0.01	89%	Random
GA + AA	3517/27428	3923/30976	0.82 (0.50, 1.34)	0.43	<0.01	87%	
AA	110/27428	132/30976	0.58 (0.12, 2.73)	0.49	0.12	60%	
GA	3407/27428	3791/30976	0.85 (0.55, 1.31)	0.47	0.02	83%	

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

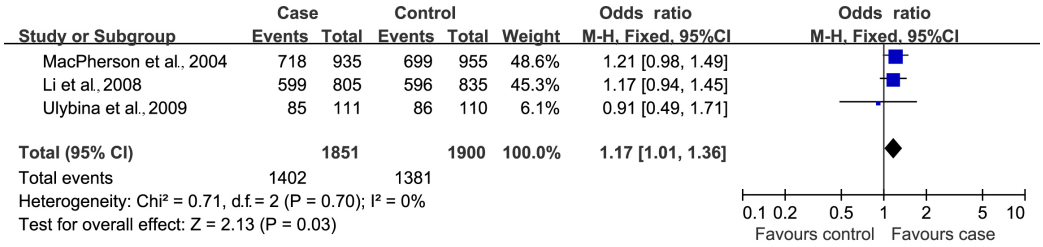

Figure 2. Association between the rs13006529*T carrier and cancer susceptibility. M-H. = Mantel-Haenszel estimator; 95%CI = 95% confidence interval; d.f. = degrees of freedom.

Publication bias

Publication bias of the literatures was assessed based on the rs13006529*T carrier by the Begger 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 statistical significance for all evaluations of publication bias (P > 0.05). Findings of the Egger publication bias test are shown in Table 4.

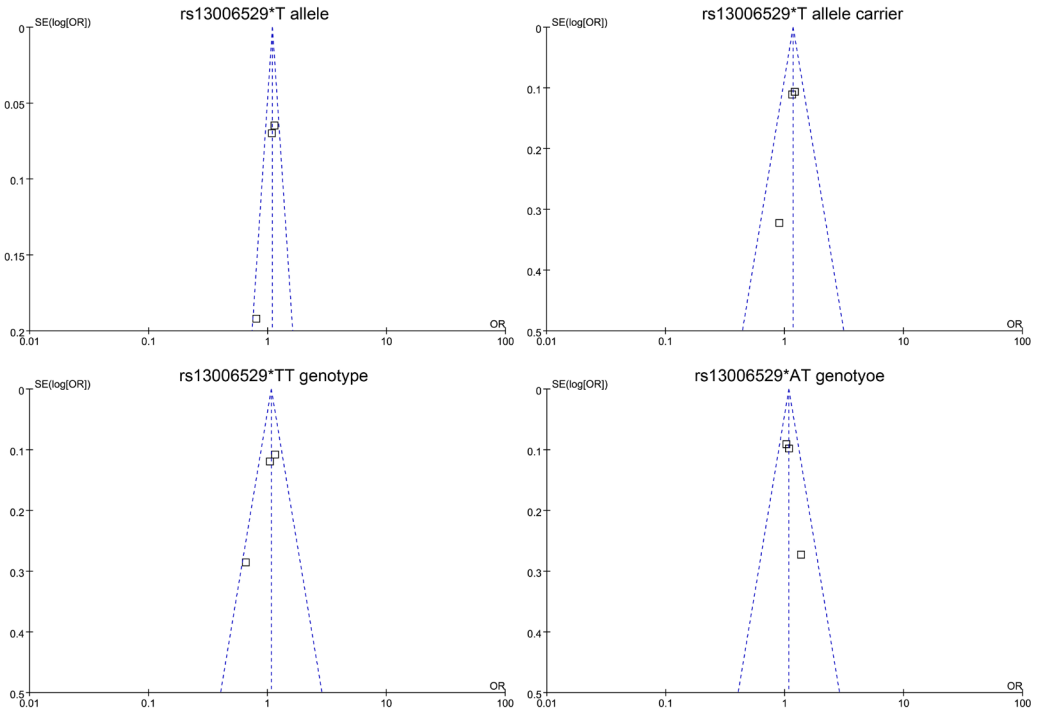

Figure 3. Begger funnel plot of publication bias based on rs13006529. SE = standard error; OR = odds ratio.

Table 4. Evaluation of publication bias based on rs13006529 by the Egger linear regression test.

Comparison	Coefficient	SE	*t*	P	95%CI
T allele	-2.680	0.643	0.643	0.150	(-10.845, 5.485)
AT + TT	-1.262	0.327	-3.860	0.161	(-5.416, 2.892)
TT	-3.135	0.792	-3.960	0.158	(-13.198, 6.929)
AT	1.507	0.565	2.660	0.229	(-5.678, 8.692)

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

DISCUSSION

Caspases mediate highly specific proteolytic cleavage events in dying cells, which collectively manifest the apoptotic phenotype. The key and central role that caspases play in a biochemical cell-suicide pathway has been conserved throughout the evolution of multicellular eukaryotes (Nicholson and Thornberry, 1997). Activation of caspases is of fundamental importance in cell death commitment; thus, substantial efforts have been devoted to understand the mechanisms that underlie this process (Kumar, 2004). The proteolytic activities of the caspases initiate and augment the apoptotic response by maintaining enzymatic cascade in a committed program (Niles et al., 2008). Activated caspases degrade important structural protein elements within cells and RNA splicing or DNA repair-associated proteins (Boatright

and Salvesen, 2003). However, excessive or failed apoptosis is a prominent morphological feature of several human diseases (Nicholson, 1996). These can be divided into disorders of excessive apoptosis (such as neurodegenerative diseases or ischemic damage) and those where insufficient apoptosis occurs (such as autoimmune syndromes, cancers, and sustained pathogenic infections). Caspase 10 is a key regulator of apoptosis or programmed cell death and shares similar functions with caspase-8, as an essential defense mechanism against hyperproliferation and malignancy (Ghavami et al., 2009).

Recent studies have established that *CASP-10* variants may dysregulate apoptosis and thus lead to carcinogenesis. A systematic review of the association of *CASP-10* with cancer risk is statistically more powerful than any single study. In this meta-analysis, including 29,936 cancer cases and 34,041 healthy controls from 8 independent studies, we examined 3 SNPs in the *CASP-10* gene, including rs13006529 (I522L) A>T in exon 10, rs13010627 (V410I) G>A in exon 9, and rs3900115 (A2823G) A>G in exon 3. We demonstrated that the T allele carrier (AT + TT) of rs13006529 was significantly associated with cancer risk after adjustment for multiple testing. However, the T allele, TT and AT genotypes of rs13006529 showed no association with cancer risk. Pooled analysis has revealed no association between rs3900115 and rs13010627 with cancer susceptibility. Subgroup analysis showed that the rs13006529 T allele is a risk factor for breast cancer. Nevertheless, no association was found between *CASP-10* gene polymorphisms and susceptibility to lymphoma, myeloma, melanoma, or lung cancer. Sensitivity analysis was performed by omitting any single study and non-HWE studies: no influence was found. Many limitations of this 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 due to incomplete raw data. Third, we were not able to address the sources of heterogeneity among all studies. Fourth, although all cases and controls were well defined with similar inclusion criteria, there may be factors that were not taken into account and that may have influenced our results. Most important, our meta-analysis was based on unadjusted OR estimates because not all publications presented adjusted ORs and when they did, the ORs 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 8 case-control studies demonstrated that *CASP-10* polymorphisms are associated with the pathogenesis of various cancer. The rs13006529 T allele (AT + TT) might increase the risk of cancer, especially breast cancer. Since only a few studies are available in this field and evidence remains limited, we emphasize the need to conduct large studies with adequate methodological quality, and proper control of confounding factors in order to obtain valid results.

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