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HuGE systematic review and meta-analysis demonstrate association of CASP-3 and CASP-7 genetic polymorphisms with cancer risk

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ABSTRACT. Genetic variations in the caspase genes CASP-3 and CASP-7 are known to be involved in apoptosis, cytokine maturation, cell growth and differentiation. Polymorphisms of CASP-3 and CASP-7 genes have been increasingly recognized as important regulators in the development of cancer. However, whether there is a specific association is still controversial. Therefore, we made a Human Genome Epidemiology review and meta-analysis to explore the association between polymorphisms of CASP-3 and CASP-7 genes and cancer risk. Based on the inclusion criteria, we examined 9 case-control studies, with a total of 3142 cancer cases and 3670 healthy controls. Meta-analysis results showed that the homozygote (CC) of rs2705897 in the CASP-3 gene is positively associated with cancer susceptibility [odds ratio (OR) = 4.36, 95% confidence interval (CI) = 1.26-15.11, P = 0.02], while the C allele and C carrier (TC+CC) of rs1049216 are negatively associated with cancer risk (OR = 0.81, 95%CI = 0.69-0.95, P = 0.01; OR = 0.78,

95%CI = 0.63-0.97, P = 0.02, respectively). The G allele and G carrier of rs4647603 (A/G) in CASP-3 had positive associations with cancer susceptibility (OR = 1.69, 95%CI = 1.37-2.09, P < 0.001; OR = 1.93, 95%CI = 1.26-2.93, P = 0.002, respectively). The T allele of rs12415607, the G allele and homozygote (GG) of rs2227310, and homozygote (CC) of rs3124740 also had positive associations with cancer risk (OR = 1.18, 95%CI = 1.02-1.37, P = 0.03; OR = 1.17, 95%CI = 1.01-1.34, P = 0.03; OR = 1.34, 95%CI = 1.04-1.74, P = 0.03; OR = 1.30, 95%CI = 1.04-1.63, P = 0.02, respectively). In addition, homozygote (AA) of rs11196418 showed a significant negative association with cancer risk (OR = 0.36, 95%CI = 0.14-0.93, P = 0.03). These meta-analysis results demonstrated that CASP-3 and CASP-7 genetic polymorphisms are involved in the pathogenesis of cancer.

Key words: Caspase 3; Genetic polymorphism; Susceptibility; Cancer; Meta-analysis

INTRODUCTION

Cancers occur in numerous tissues with multiple etiologies and varying tumor progression (Evan and Vousden, 2001) and is one of the greatest threats to human health (He et al., 2008). The number of people who die from cancer increases annually. Cell apoptosis (programmed cell death) is a rather significant biological process that maintains the integrity and homeostasis of multicellular organisms (Thompson, 1995). During the process of cell apoptosis, abnormal cell death or maturation might cause cancer. Previous studies have suggested that caspases (cysteinyl aspartate-specific proteinases) may be responsible for some of the cellular changes associated with apoptosis (Cohen, 1997; Budihardjo et al., 1999).

Caspases are important mediators of apoptosis. Caspase-3 (also known as CPP32, SCA-1, and CPP32B) is a cysteine protease encoded by the CASP-3 gene located at chromosome 4q34 (Lakhani et al., 2006). Caspase-7, an apoptosis-related cysteine peptidase, is encoded by the CASP-7 gene located at chromosome 10q25.1-10q25.2 (Teixeira et al., 2008). Caspase-3 and caspase-7 are executioner caspases (Yu et al., 2009). Caspase-3 plays a central role in the execution phase of cell apoptosis, cleaving and activating caspases 6, 7, and 9 (Lakhani et al., 2006).

Single nucleotide polymorphisms (SNPs) are the most common form of human genetic variation and may contribute to individual susceptibility to cancer (Son et al., 2006). In recent years, many studies have been conducted to investigate the associations between CASP-3 and CASP-7 genes and cancer susceptibility. Several reports have shown that CASP-3 is mutated in various types of cancers, such as pediatric neuroblastoma (Wang and Zheng, 2004), breast cancer (Devarajan et al., 2002), and gastric carcinoma (Isobe et al., 2004). However, these studies have not determined the exact role of CASP-3 and CASP-7 genetic polymorphisms in cancer risk, and conclusions about this link remain controversial. Therefore, we performed a Human Genome Epidemiology (HuGE) review and meta-analysis by including the most recent and relevant publications to gather statistical evidence of the associations that have been investigated.

MATERIAL AND METHODS

Identification of eligible studies

PubMed, Cochrane Library, Embase, Web of Science, Springerlink, China National Knowledge Infrastructure, and the Chinese Biomedical Database were extensively searched to identify relevant studies published by May 10, 2012. The search terms included ("caspase-3" or "CASP 3" or "Caspase 3" [Mesh] or "caspase-7" or "CASP 7" or "Caspase 7" [Mesh]), ("SNPs" or "SNP" or "polymorphism, genetic" [Mesh]), and ("cancer" or "tumor" or "Neoplasms" [Mesh]). The references in eligible studies and textbooks were also manually reviewed to find potentially eligible studies. The included studies had to meet the following criteria: 1) studies used a case-control design to examine associations between CASP-3 or CASP-7 genetic polymorphisms and cancer risk; 2) all patients had a diagnosis of a malignant tumor confirmed by pathological examination of a surgical specimen; 3) the frequencies of alleles or genotypes in case and control groups could be extracted; and 4) the language of publication was English or Chinese. Studies were excluded when they were 1) not case-control studies about CASP-3 or CASP-7 genetic polymorphisms and cancer risk; 2) based on incomplete data; 3) reporting irrelevant or overlapping data; and 4) meta-analyses, letters, reviews, or editorials.

Data extraction

Using a standardized form, 2 reviewers (S. Yan and Y.Z. Li) extracted data from published studies independently to obtain the necessary information. The following information was extracted from each of the articles included: 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, cancer types, genotype methods, polymorphism genotype frequency, and evidence of Hardy-Weinberg equilibrium (HWE) in controls. In cases of conflicting evaluations, an agreement was reached after a discussion with a third reviewer (Y.L. Liu).

Quality assessment of included studies

Two reviewers (J.W. Zhu and C.L. Liu) independently assessed the quality of selected papers according to a modified Strengthening the Reporting of Observational Studies in Epidemiology quality score system (von Elm et al., 2007; Zhang et al., 2011). Forty assessment items related to the quality appraisal were rated in this meta-analysis with a scale 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 through discussion with a third reviewer (Y.L. Liu).

Statistical analysis

The odds ratio (OR) and 95% confidence interval (95%CI) were calculated using Review Manager Version 5.1.6 [provided by Cochrane Collaboration; http://ims.cochrane.org/revman/download (accessed August 9, 2012)] and STATA Version 12.0 (Stata Corp., College Station, TX, USA). Between-study variations and heterogeneities were estimated using the Cochran Q statistic (Higgins and Thompson, 2002; Zintzaras and Ionnidis, 2005). A P value of ≤ 0.05 was considered a manifestation of statistically significant heterogeneity.

We also quantified the effect of heterogeneity using the I^2 test. I^2 represents the proportion of inter-study variability that can be attributed to heterogeneity rather than to chance with a range of 0 and 100%. 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 an I^2 of >50% indicated heterogeneity across studies, the random-effect model was used for meta-analysis or the fixed-effect model was used. We tested whether genotype frequencies of controls were in HWE using the chi-square test. Sensitivity analysis was mainly performed through sequential omission of individual studies.

Publication bias was investigated using the Begger funnel plot, and the funnel plot asymmetry was assessed with the Egger linear regression test (Peters et al., 2006). Statistical significance was reached when the P value of the Egger test was <0.05. All P values were two-sided. To ensure the reliability and accuracy of the results, 2 reviewers (S. Yan and Y.Z. Li) populated the data in the statistical software programs independently and obtained the same results.

RESULTS

Characteristics of the studies included

The search strategy retrieved 105 potentially relevant studies. According to the inclusion criteria, 9 studies (Xie, 2004; Lan et al., 2007; Hosgood et al., 2008; Lee et al., 2009; Ulybina et al., 2009; Xu et al., 2009; Lei, 2010; Ni et al., 2011; Mittal et al., 2012) were included in the meta-analysis and 96 were excluded. The flow chart of study selection is shown in Figure 1. The 9 case-control studies selected included 3142 cases and 3670 healthy controls, which evaluated the relationship between CASP-3 or CASP-7 genetic polymorphisms and cancer risk. The publication year of the studies involved ranged from 2004 to 2012. All patients fulfilled the diagnostic criteria of malignant neoplasm confirmed by pathological examination of a surgical specimen. The source of controls was a healthy population. Five SNPs in the CASP-3 gene and 6 SNPs in the CASP-7 gene were addressed. The HWE test was performed on the genotype distribution of the controls in all the studies included and all were in HWE ($P > 0.05$). All quality scores of the studies included were >20 (moderate-high quality). The characteristics and methodological quality of the studies included are summarized in Table 1. The genotype distributions of CASP-3 and CASP-7 genetic polymorphisms in case and control groups are shown in Table 2.

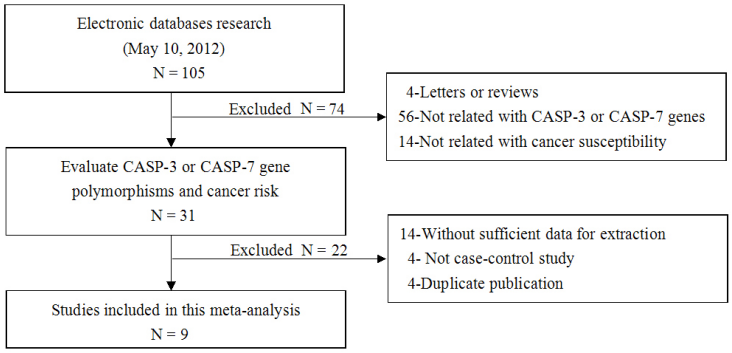

Figure 1. Flow chart shows the study selection procedure.

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

First author	Year	Country	Ethnicity	Number		Genotype method	Cancer type	Gene	SNP	HWE		Quality score
				Case	Control					χ^2	P	
Xie	2004	China	Asian	63	124	PCR-DHPLC	Lymphoma	CASP-3	rs4647602 (C/A)	1.65	0.20	20
									rs2705897 (A/C)	1.42	0.23	
									rs1049216 (T/C)	1.42	0.23	
Lan et al.	2007	USA	Caucasian	461	535	DNA Sequencing	Lymphoma	CASP-3	rs6948 (C/A)	0.23	0.63	22
									rs1049216 (T/C)	0.59	0.44	
Hosgood et al.	2008	USA	Caucasian	128	516	DNA Sequencing	Myeloma	CASP-3	rs6948 (C/A)	0.13	0.71	22
									rs1049216 (T/C)	0.85	0.36	
Lee et al.	2009	Korea	Asian	720	720	High resolution melting	Lung cancer	CASP-7	rs12415607 (G/T)	0.33	0.57	27
									rs11593766 (A/G)	0.02	0.90	
									rs2227310 (C/G)	0.46	0.50	
									rs10787498 (G/T)	0.45	0.50	
Ulybina et al.	2009	Russia	Caucasian	111	110	AS-PCR	Lung cancer	CASP-7	rs2227310 (C/G)	0.20	0.65	24
Xu et al.	2009	China	Asian	1028	1003	DNA probe	Endometrial cancer	CASP-7	rs11196418 (G/A)	0.02	0.90	24
									rs11593766 (T/G)	2.04	0.15	
									rs3124740 (G/C)	0.04	0.84	
									rs11196445 (G/A)	0.92	0.34	
									rs10787498 (T/G)	0.40	0.53	
Lei et al.	2010	China	Asian	161	159	PCR-RFLP	Colorectal cancer	CASP-3	rs12108497 (A/G)	3.24	0.07	28
Ni et al.	2011	China	Asian	278	278	PCR-RFLP	Gastric cancer	CASP-3	rs12108497 (T/C)	3.84	0.05	20
Mittal et al.	2012	India	Asian	192	225	PCR-RFLP	Prostate cancer	CASP-3	rs4647603 (A/G)	0.02	0.88	21

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

Table 2. Genotype distribution of CASP-3 or CASP-7 genetic polymorphisms in case and control groups.

First author	Year	SNP	Case group									Control group								
			Total	1	2	1/1	1/2	2/2	1/2+2/2	TA	MAF	Total	1	2	1/1	1/2	2/2	1/2+2/2	TA	MAF
Xie	2004	rs4647602 (C/A)	63	73	53	22	29	12	41	126	0.42	124	140	108	36	68	20	88	248	0.44
		rs2705897 (A/C)	63	93	33	38	17	8	25	126	0.26	124	192	56	72	48	4	52	248	0.23
		rs1049216 (C/T)	63	99	27	38	23	2	25	126	0.21	124	192	56	72	48	4	52	248	0.23
Lan et al.	2007	rs6948 (C/A)	450	499	401	135	229	86	315	900	0.45	531	539	523	134	271	126	397	1062	0.49
		rs1049216 (T/C)	451	696	206	266	164	21	185	902	0.23	525	762	288	273	216	36	252	1050	0.27
Hosgood et al.	2008	rs6948 (C/A)	123	128	118	36	56	31	87	246	0.48	512	524	500	132	260	120	380	1024	0.49
		rs1049216 (T/C)	122	189	55	69	51	2	53	244	0.23	506	738	274	265	208	33	241	1012	0.27
Lee et al.	2009	rs12415607 (G/T)	720	856	584	260	336	124	460	1440	0.41	720	913	527	293	327	100	427	1440	0.37
		rs1593766 (A/G)	720	1279	161	565	149	6	155	1440	0.11	720	1295	145	582	131	7	138	1440	0.10
		rs2227310 (C/G)	720	813	627	246	321	153	474	1440	0.44	720	878	562	272	334	114	448	1440	0.39
		rs10787498 (G/T)	720	1150	290	467	216	37	253	1440	0.20	720	1141	299	455	231	34	265	1440	0.21
Ulybina et al.	2009	rs4647297 (C/G)	111	213	9	102	9	0	9	222	0.04	110	211	9	101	9	0	9	220	0.04
		rs2227310 (C/G)	111	164	58	57	50	4	54	222	0.26	110	158	62	57	44	9	53	220	0.28
Xu et al.	2009	rs11196418 (G/A)	1028	1847	209	825	197	6	203	2056	0.10	1001	1786	216	801	184	16	200	2002	0.11
		rs11593766 (T/G)	1025	1902	148	883	136	6	142	2050	0.07	1001	1817	185	824	169	8	177	2002	0.09
		rs3124740 (G/C)	1027	1138	916	326	486	215	701	2054	0.45	984	1142	826	324	494	166	660	1968	0.42
		rs11196445 (G/A)	1018	1686	350	702	282	34	316	2036	0.17	998	1696	300	718	260	20	280	1996	0.15
		rs10787498 (T/G)	1028	1654	402	675	304	49	353	2056	0.20	1002	1630	374	653	324	25	349	2004	0.19
Lei et al.	2010	rs12108497 (A/G)	161	233	89	80	73	8	81	322	0.28	159	187	131	49	89	21	110	318	0.41
Ni et al.	2011	rs12108497 (T/C)	278	364	192	119	126	33	159	556	0.35	277	407	147	149	109	19	128	554	0.27
Mittal et al.	2012	rs4647603 (A/G)	192	254	130	89	76	27	103	384	0.34	225	338	112	129	80	16	96	450	0.25

SNP = single nucleotide polymorphism; 1 = wild allele; 2 = variant allele; 1/1 = wild homozygote; 1/2 = heterozygote; 2/2 = variant homozygote; TA = total number of alleles; MAF = minor allele frequency.

Association between CASP-3 gene polymorphisms and cancer risk

A summary of the meta-analysis findings of the association between CASP-3 gene polymorphisms and cancer risk is provided in Table 3. The meta-analysis result showed that the homozygote (CC) of rs2705897 in the CASP-3 gene had a positive association with cancer susceptibility (OR = 4.36, 95%CI = 1.26-15.11, P = 0.02), whereas the C allele and C carrier (TC + CC) of rs1049216 showed negative associations with cancer risk (OR = 0.81, 95%CI = 0.69-0.95, P = 0.01, and OR = 0.78, 95%CI = 0.63-0.97, P = 0.02, respectively), suggesting that the C allele and C carrier (TC + CC) of rs1049216 might decrease the risk of cancer (see Figure 2). However, no significant connection was found in rs4647602, rs6948, or rs12108497 (all P > 0.05). The significance of the pooled OR in all individual analyses was not influenced excessively by omitting any single study.

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

Polymorphisms		Cancer	Control	OR (95%CI)	P value	Heterogeneity		Effect model
						P	I^2	
rs4647602 (C/A)	A allele	53/126	108/248	0.94 (0.61-1.45)	0.78	-	-	Fixed
	CA+AA	41/63	88/124	0.76 (0.40-1.46)	0.41	-	-	
	AA	12/63	20/124	1.22 (0.56-2.70)	0.62	-	-	
	CA	29/63	68/124	0.70 (0.38-1.29)	0.26	-	-	
rs2705897 (A/C)	C allele	33/126	56/248	1.22 (0.74-2.00)	0.44	-	-	Fixed
	AC+CC	25/63	52/124	0.91 (0.49-1.69)	0.77	-	-	
	CC	8/63	4/124	4.36 (1.26-15.11)	0.02	-	-	
	AC	17/63	48/124	0.59 (0.30-1.14)	0.11	-	-	
rs1049216 (T/C)	C allele	360/1272	754/2310	0.81 (0.69-0.95)	0.01	0.54	0%	Fixed
	TC+CC	299/636	613/1155	0.78 (0.63-0.97)	0.02	0.85	0%	
	CC	61/636	141/1155	0.71 (0.48-1.04)	0.08	0.13	52%	
	TC	238/636	472/1155	0.88 (0.72-1.08)	0.22	0.64	0%	
rs6948 (C/A)	A allele	519/1146	1023/2086	0.87 (0.75-1.01)	0.06	0.36	0%	Fixed
	CA+AA	402/573	777/1043	0.80 (0.63-1.02)	0.07	0.81	0%	
	AA	117/573	246/1043	0.85 (0.66-1.10)	0.22	0.19	43%	
	CA	285/573	531/1043	0.94 (0.76-1.16)	0.55	0.39	0%	
rs12108497 (A/G)	G allele	281/878	278/872	0.90 (0.34-2.36)	0.83	<0.001	95%	Random
	AG+GG	240/439	238/436	0.85 (0.25-2.85)	0.79	<0.001	95%	
	GG	41/439	40/436	0.82 (0.16-4.20)	0.81	0.001	90%	
	AG	199/439	198/436	0.93 (0.48-1.79)	0.82	0.02	82%	

Cases and controls are reported as number of individuals/total individuals. OR = odds ratio; 95%CI = 95% confidence interval.

Association between CASP-7 gene polymorphisms and cancer risk

Associations between CASP-7 gene polymorphisms and cancer risk are shown in Table 4. The pooled analysis showed that the T allele of rs12415607, G allele and homozygote (GG) of rs2227310, and homozygote (CC) of rs3124740 had positive associations with cancer risk (OR = 1.18, 95%CI = 1.02-1.37, P = 0.03; OR = 1.17, 95%CI = 1.01-1.34, P = 0.03; OR = 1.34, 95%CI = 1.04-1.74, P = 0.03; and OR = 1.30, 95%CI = 1.04-1.63, P = 0.02, respectively). In addition, homozygote AA of rs11196418 showed a significant negative association with cancer risk (OR = 0.36, 95%CI = 0.14-0.93, P = 0.03; Figure 3). Nevertheless, no significant associations were found between rs10787498 and rs11593766 and cancer risk (all P > 0.05). Sensitivity analysis was conducted by omitting single studies, and no influence was found in the significance of the pooled OR.

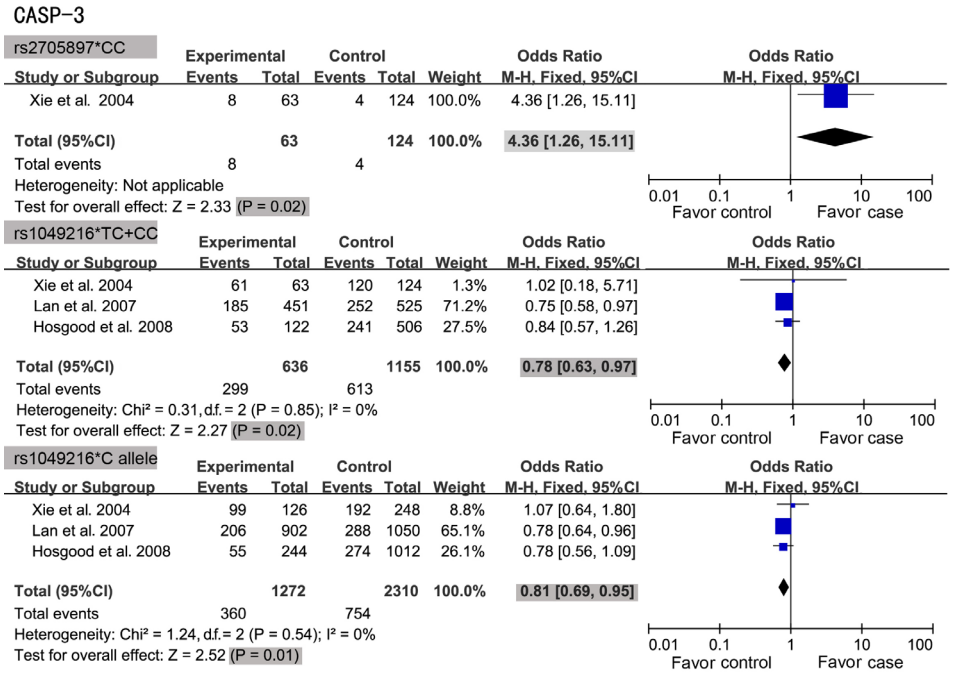

Figure 2. Association between CASP-3 gene polymorphisms and cancer risk.

Table 4. Meta-analysis of the association between CASP-7 polymorphisms and cancer risk.

Polymorphisms		Cancer	Control	OR (95%CI)	P value	Heterogeneity		Effect model
						P	I^2	
rs12415607 (G/T)	T allele	584/1440	527/1440	1.18 (1.02-1.37)	0.03	-	-	Fixed
	GT+TT	460/720	427/720	1.21 (0.98-1.50)	0.07	-	-	
	TT	124/720	100/720	1.29 (0.97-1.72)	0.08	-	-	
	GT	336/720	327/720	1.05 (0.85-1.29)	0.63	-	-	
rs10787498 (G/T)	T allele	2804/3496	2771/3444	0.98 (0.87-1.11)	0.78	0.43	0%	Fixed
	GT+TT	1662/1748	1663/1722	0.69 (0.39-1.21)	0.19	0.10	64%	
	TT	1142/1748	1108/1722	1.04 (0.91-1.20)	0.55	0.73	0%	
	GT	520/1748	555/1722	0.89 (0.77-1.03)	0.11	0.83	0%	
rs2227310 (C/G)	G allele	685/1662	624/1660	1.17 (1.01-1.34)	0.03	0.20	39%	Fixed
	CG+GG	528/831	501/830	1.15 (0.94-1.40)	0.18	0.63	0%	
	GG	157/831	123/830	1.34 (1.04-1.74)	0.03	0.15	14%	
	CG	371/831	378/830	0.96 (0.80-1.17)	0.71	0.34	0%	
rs11196418 (G/A)	A allele	209/2056	216/2002	0.94 (0.77-1.14)	0.52	-	-	Fixed
	GA+AA	203/1028	200/1001	0.99 (0.79-1.23)	0.90	-	-	
	AA	6/1028	16/1001	0.36 (0.14-0.93)	0.03	-	-	
	GA	197/1028	184/1001	1.05 (0.84-1.32)	0.65	-	-	
rs11593766 (T/G)	G allele	309/3490	330/3442	0.93 (0.63-1.35)	0.69	0.02	81%	Random
	TG+GG	297/1745	315/1721	0.93 (0.61-1.42)	0.73	0.02	83%	
	GG	12/1745	15/1721	0.79 (0.37-1.69)	0.54	0.84	0%	
	TG	285/1745	300/1721	0.94 (0.61-1.45)	0.77	0.02	83%	
rs3124740 (G/C)	C allele	916/2054	826/1968	1.11 (0.98-1.26)	0.09	-	-	Fixed
	GC+CC	701/1027	660/984	1.06 (0.88-1.27)	0.57	-	-	
	CC	215/1027	166/984	1.30 (1.04-1.63)	0.02	-	-	
	GC	486/1027	494/984	0.89 (0.75-1.06)	0.20	-	-	

Cases and controls are reported as number of individuals/total individuals. OR = odds ratio; 95%CI = 95% confidence interval.

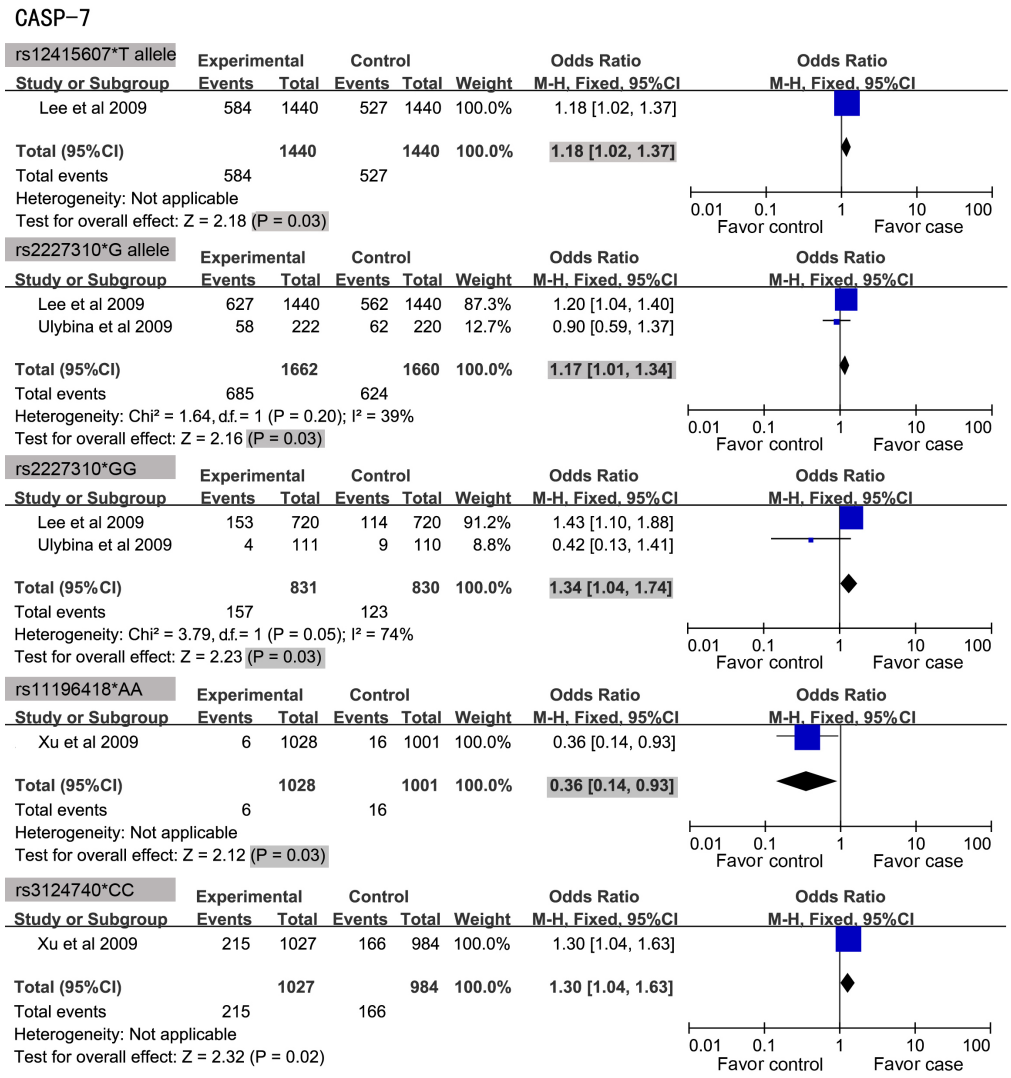

Figure 3. Association between CASP-7 gene polymorphisms and cancer risk.

Publication bias

Publication bias was assessed based on rs1049216 in CASP-3 using the Begger funnel plot and the Egger linear regression test, which was used to measure the asymmetry of the funnel plot. All graphical funnel plots of the studies included appeared to be symmetrical (Figure 4). The Egger test also revealed no statistical significance for all evaluations of publication bias (all $P > 0.05$). The findings of the Egger publication bias test are shown in Table 5.

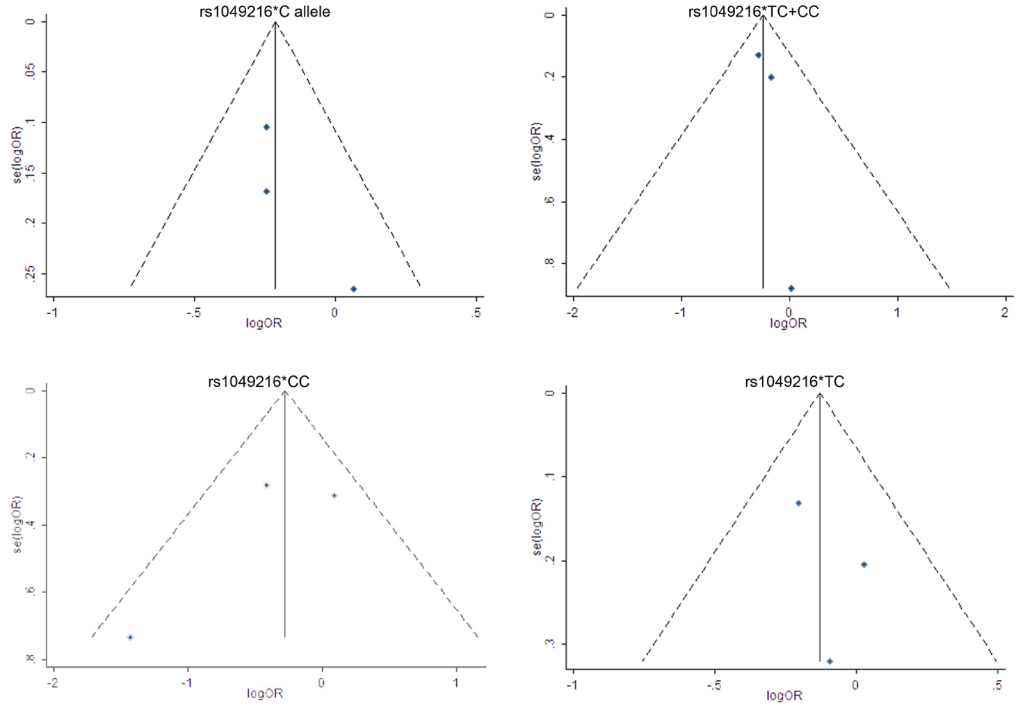

Figure 4. Begger funnel plot of publication bias based on rs1049216 in the CASP-3 gene.

Table 5. Evaluation of publication bias based on rs1049216 by the Egger linear regression test.

Comparison	Coefficient	SE	*t*	P	95%CI
T allele	1.576	0.982	1.600	0.355	(-10.908, 14.059)
TC + CC	0.509	0.387	1.320	0.414	(-4.411, 5.430)
CC	-2.514	2.418	-1.040	0.488	(-33.231, 28.203)
TC	1.027	1.301	0.790	0.575	(-15.499, 17.552)

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

DISCUSSION

Apoptosis plays an important role in protecting hosts from cancer development by eliminating DNA-damaged cells (Mittal et al., 2012). An imbalance between cell death and proliferation may lead to cancer. Two main apoptotic pathways occur in humans: extrinsic and intrinsic (Theodoropoulos et al., 2011). During the apoptotic process, both of these pathways use the caspase enzyme cascade: the extrinsic pathway includes caspase-8 and -10, whereas the intrinsic pathway includes caspase-9, and they converge to use caspase-3, -6, and -7 as effector caspases (Nicholson and Thornberry, 1997; Hajra and Liu, 2004; Kesarwani et al., 2011).

Caspase-3 is one of the key actors in apoptosis, being responsible either partially or totally for the proteolytic cleavage of many key proteins. CASP-3 mutation has been reported in

the MCF-7 breast cancer cell line (Kurokawa et al., 1999), suggesting the presence of CASP-3 mutation in human cancer tissues. Soung et al. (2004) detected CASP-3 mutations in several types of tumors, including 4 of 98 colon carcinomas (4.1%), 4 of 181 non-small cell lung cancers (2.2%), 2 of 129 non-Hodgkin lymphomas (1.6%), 2 of 165 stomach carcinomas (1.2%), 1 of 80 hepatocellular carcinomas (1.3%), and 1 of 28 multiple myelomas (3.6%). This presence indicates that the CASP-3 gene occasionally mutates in human tumors. Caspase-7 is another effector caspase that is comparatively important to caspase-3 in apoptosis execution, especially in cells with deficient or underexpressed caspase-3. Caspase-7, which is an important intracellular effector of granzyme B-mediated apoptosis and cytotoxic T-lymphocyte-induced cell killing, might act as a negative regulator of apoptosis.

An immunohistochemical study has revealed a downregulation of caspase-7 in colon cancer samples compared with that in normal colon mucosa (Palmerini et al., 2001). Soung et al. (2003) also observed CASP-7 gene mutations in several types of human solid cancers, including 2 of 98 colon carcinomas (2.0%), 1 of 50 esophageal carcinomas (2.0%), and 1 of 33 head and neck carcinomas (3.0%). To assess the role of CASP-3 and CASP-7 genetic polymorphisms in cancer susceptibility, we conducted a HuGE review and meta-analysis to clarify these associations.

Overall, our fixed-effect model analysis showed that the homozygote of rs2705897 in the CASP-3 gene might increase the risk of cancer. Similarly, the T allele of rs12415607, G allele and homozygote of rs2227310, and homozygote (CC) of rs3124740 in the CASP-7 gene were also risk factors for susceptibility to cancer. Interestingly, we identified protective roles for the C allele and C carrier (TC + CC) of rs1049216 in the development of carcinogenesis, which is consistent with the results of previous studies (Lan et al., 2007; Hosgood et al., 2008). In addition, the homozygote of rs11196418 in the CASP-7 gene is also a protective factor for cancer risk.

Given that the eligible number of studies in this meta-analysis was small, these results require further investigation. Furthermore, some limitations in this meta-analysis should be addressed: 1) the analysis was based on unadjusted OR estimates because not all published studies presented adjusted ORs or presented ORs that were not adjusted by the same potential confounders, such as age, gender, ethnicity, and exposure; 2) significant between-study heterogeneity was present in studies of the caspase-3 polymorphism, and the genotype distribution also showed deviation from HWE in one study; 3) the number of studies and number of subjects in the studies included in the meta-analysis were small, and some relevant studies were excluded from our analysis owing to incomplete raw data; 4) although the cases and controls of each study were well defined with similar inclusion criteria, factors that were not taken into account may have influenced our results; and 5) meta-analysis is a retrospective research that is subject to methodological limitations.

In conclusion, this meta-analysis of 9 case-control studies demonstrated that CASP-3 and CASP-7 genetic polymorphisms are involved in the pathogenesis of variant cancer. Because few studies are available in this field, current evidence remains limited. Therefore, we emphasize the necessity of conducting large studies with adequate methodological quality and proper control of confounds to obtain valid results.

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