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REVIEW ARTICLE

Relationship Between CASP9 and CASP10 Gene Polymorphisms and Cancer Susceptibility: Evidence from an Updated Meta-analysis

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Abstract

Caspase-9 (*CASP9*) and caspase-10 (*CASP10*) polymorphisms were associated with human cancers; however, the results remain controversial. In this meta-analysis, we aimed to estimate the relationship among *CASP9* (rs1052576, rs1052571, rs4645978, rs4645981, rs4645982, rs2308950) and *CASP10* (rs13006529, rs13010627, rs3900115) polymorphisms and the overall risk of cancers. Relevant studies were obtained from Web of Science, MEDLINE, PubMed, Scopus, and Google scholar databases (updated January 1, 2021). Odds ratio (OR) and 95% confidence intervals (CIs) were measured to estimate the strength of association. Our meta-analysis included 40 studies. The rs4645981 significantly enhanced the risk of cancer under TT vs. CC (OR = 2.42), TC vs. CC (OR = 1.55), TT+ TC vs. CC (OR = 1.66), TT vs. TC + CC (OR = 1.91), and T vs. C (OR = 1.57) inheritance models. As for the rs1052571 variant, increased risk of cancer was observed under TT vs. CC (OR =1.22), TC vs. CC (OR = 1.17), and TT+ TC vs. CC (OR = 1.18) models. The stratified analysis showed a significant correlation between rs4645978 or rs4645981 polymorphisms and cancer risk, while in Asians rs4645978 conferred an increased risk of colorectal, lung, and prostate cancer. Both rs4645981 and rs1052576 polymorphisms were correlated with an enhanced risk of lung cancer. In conclusion, our meta-analysis suggested that *CASP9* rs4645981 and rs1052571 polymorphisms are associated with overall cancer risk. More studies on larger populations are warranted to validate these associations.

Keywords Cancer · Caspase-9 · Caspase-10 · Meta-analysis · Polymorphism

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Introduction

Cancer is ranked as the second leading cause of death among adults in the USA and is considered a global public health concern with great importance [1]. Only in the USA, a total of 1,806,590 new cancer cases and more than six hundred thousand cancer-related deaths are projected to occur in 2020 [2]. Moreover, it has been approximated that the worldwide incidence of cancer will exceed 25 million by 2032 [3]. As a multifactorial disease, genetics and environmental factors serve pivotal roles in cancer etiology [4].

Apoptosis is a programmed cell death mechanism that modulates tissue hemostasis in different organisms [5]. The escape from apoptosis is known to be a hallmark of malignancy, and it regulates the development and progression of tumors [5–7]. Historically, major pathways of apoptosis have been characterized that lead to activation of effector caspases and cell death: the intrinsic (mitochondrial) pathway and the extrinsic (receptor-mediated) pathway. Apoptotic pathways converge at the activation of effector caspases (CASP-3, -6, and -7) [5, 8]. CASP 8 and 10 are initiator caspases activated after ligand binding to death receptors (i.e., tumor necrosis factor receptor superfamily) [9]. Downregulation of *CASP9* and *CASP10* is frequently observed in cancer patients and correlates with resistance to chemotherapy and/or poor clinical outcome [10, 11].

The gene encoding human *CASP9* is mapped on chromosome 1p36.2, spans ~33 kb in length, and consists of 8 introns and 9 exons. The human *CASP10* gene resides on chromosome 2q33.1 with ~46 kb length, 13 exons, and 11 introns and located approximately 20–30 kb to the 5′ untranslated region of the *CASP8* gene [12]. Genomic mutations in *CASP10* and allelic imbalance and epigenetic modifications in the *CASP9* gene have been reported in multiple human tumors [13, 14]. Single-nucleotide polymorphisms (SNPs) are the most common type of single-base variations that predicts the risk of multiple diseases, including cancer [15]. Among the candidate SNPs, variations mapped in the promoteric regions of genes are well-studied because they most probably influence gene expression and might affect cancer susceptibility [5]. Figure 1 and Table 1 illustrate the genetic location of *CASP9* and *CASP10* polymorphisms.

Several reports have studied the relationship between *CASP9* and *CASP10* polymorphisms and cancer [5, 15–53]. However, the implication of these two initiator caspases and the risk of developing human cancers remains ill-defined. Hence, gaining a better understanding of the role of *CASP9* and *CASP10* variations in cancer incidence will expand our horizons for designing such curative strategies. Therefore, given the amount of accumulated data, we conducted a comprehensive meta-analysis by including the most relevant and recent publications (updated January 1, 2021) to identify statistical evidence.

Methods

Literature Search

We retrieved a list of the case–control studies through a comprehensive Internet-based literature search of Web of Knowledge, PubMed, Scopus, Google Scholar, and

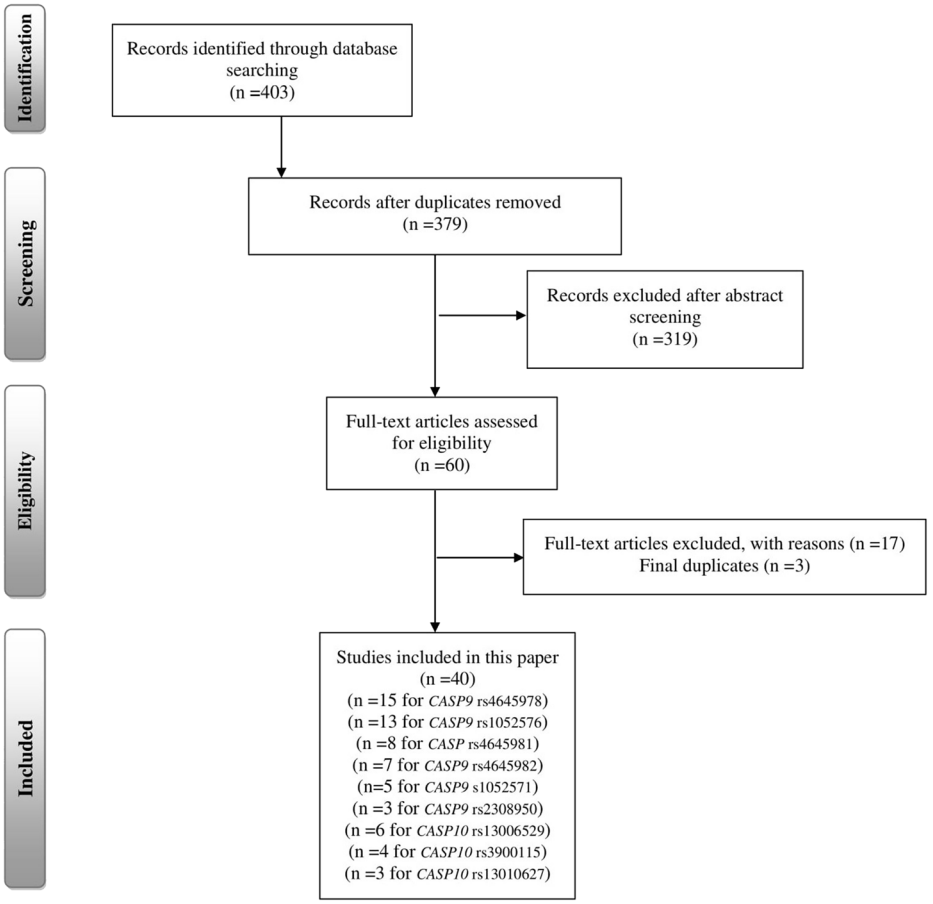

Fig. 1 Flow diagram of selecting studies for the meta-analysis

Embase databases. The used keywords were as follows: ("cancer" OR "carcinoma" OR "tumor" OR "neoplasm" OR "neoplasia") AND ("caspase-10" OR "caspase-9" OR "CASP 10" OR "CASP 9" OR "caspase10" OR "caspase9" OR "CASP10" OR "CASP9" OR "caspase 10" OR "caspase 9" OR "CASP-10" OR "CASP-9") AND ("gene polymorphism" OR "polymorphism" OR "SNP" OR "gene mutation" OR "gene variant" OR "mutation" OR "variant"). No language, country, or ethnicity restrictions were imposed. Additional publications were retrieved using a hand search. If the results of studies on different tumors or gene polymorphisms were reported in the same literature, they were regarded as a separate study to report. The included studies met the following criteria; [1] original case–control study about *CASP9* and *CASP10* polymorphisms and cancer susceptibility; [2] studies with sufficient published data to enable the estimation of odds ratios (ORs) with confidence intervals (CIs); [3] the frequency distribution of genotypes in the control group conformed to Hardy–Weinberg equilibrium (HWE). Review articles, case reports, duplicate publications, and studies with too little information were excluded.

Table 1 Main characteristics of the studies included in the meta-analysis

Study (year)/SNP	Case/control	Cases (n, %)					Controls (n, %)					P_{HWE}	P_{HWE*}
		GG	GA	AA	G	A	GG	GA	AA	G	A		
CASP9, rs4645978													
Park (2006)	432/432	59	225	148	343	521	79	215	138	373	491	0.766	0.931
Gangwar (2009)	212/250	28	103	81	159	265	62	99	89	223	277	0.002	0.010
Theodoropoulos (2010)	79/160	46	3	30	95	63	33	91	36	157	163	0.081	0.125
Kesarwani (2010)	173/198	49	42	82	140	206	47	81	70	175	221	0.016	0.056
Lee (2010)	720/720	111	349	260	571	869	126	325	269	577	863	0.106	0.151
Liamarkopoulos (2011)	88/480	10	34	44	54	122	125	239	116	489	471	0.933	0.910
Theodoropoulos (2011)	402/480	66	181	155	313	491	125	239	116	489	471	0.933	0.910
George (2012)	165/205	48	40	77	136	194	47	83	75	177	233	0.012	0.052
Theodoropoulos (2012)	261/480	109	111	41	329	193	130	240	110	500	460	0.910	0.910
Wang (2012)	118/213	15	62	41	92	144	51	93	69	195	231	0.079	0.125
Wu (2013)	450/631	53	216	181	322	578	94	322	215	510	752	0.135	0.176
Cingeetham (2014)	179/297	59	80	40	198	160	91	118	88	300	294	<0.001	0.003
Edathara (2019)	483/510	175	229	79	579	387	145	214	151	504	516	<0.001	0.003
Costa (2019)_1	438/350	60	204	174	324	552	50	143	157	243	457	0.065	0.123
Costa (2019)_2	178/350	32	46	100	110	246	50	143	157	243	457	0.065	0.123
Costa (2019)_3	172/350	28	70	74	126	218	50	143	157	243	457	0.065	0.123
Altamemi (2020)	50/50	12	22	16	46	54	5	12	33	22	78	0.033	0.095
CASP9, rs1052576	**AA**	**AG**	**GG**	**A**	**G**	**AA**	**AG**	**GG**	**A**	**G**			
Fang (2007)	70/100	15	39	16	69	71	45	42	13	132	68	0.521	0.811
Lan (2007)	530/455	133	260	137	526	534	95	223	137	413	497	0.809	0.893
Lou (2007)	81/100	18	43	20	79	83	45	42	13	132	68	0.521	0.811
Hosgood (2008)	126/511	20	65	41	105	147	129	252	130	510	512	0.757	0.893
He (2008)	170/100	41	95	34	177	163	45	42	13	132	68	0.521	0.811
Ulybina (2009)	111/110	16	56	39	88	134	20	53	37	93	127	0.893	0.893
Wu (2009)	100/60	13	44	43	70	130	7	28	25	42	78	0.843	0.893
Ulybina (2011)	121/142	29	50	42	108	34	26	62	54	114	170	0.276	0.784
Cingeetham (2014)	179/303	36	92	51	164	194	46	156	101	248	358	0.259	0.784
Ozdogan (2017)_1	43/75	7	28	8	42	44	14	32	29	60	90	0.336	0.783
Ozdogan (2017)_2	27/75	6	14	7	26	28	14	32	29	60	90	0.336	0.783
Yilmaz (2017)	69/76	15	38	16	68	70	23	37	16	83	69	0.875	0.893

Table 1 (continued)

Study (year)/SNP	Case/control	Cases (n, %)					Controls (n, %)					P_{HWE}	P_{HWE*}
		GG	GA	AA	G	A	GG	GA	AA	G	A		
Ercan (2019)	96/67	30	36	30	96	96	18	40	9	76	58	0.077	0.784
Edathara (2019)	474/506	152	244	78	548	400	162	261	83	585	427	0.197	0.784
CASP9, rs4645981	**CC**	**CT**	**TT**	**C**	**T**	**CC**	**CT**	**TT**	**C**	**T**			
Park (2006)	432/432	261	149	22	671	193	298	123	11	719	145	0.688	0.802
Lee (2010)	720/720	438	251	31	1127	313	482	209	29	1173	267	0.295	0.786
Theodoropoulos (2012)	261/480	137	112	12	386	136	361	111	8	833	127	0.873	0.873
Cao (2013)	565/311	414	141	13	963	167	239	69	3	547	75	0.416	0.802
Javid (2013)	160/160	33	75	52	141	179	60	78	22	198	122	0.674	0.802
Shokrzadeh (2013)	100/100	56	37	7	149	51	67	29	4	163	37	0.702	0.802
Cingeetham (2014)	178/301	72	93	13	237	119	194	79	28	467	135	0	0
Edathara (2019)	482/508	432	27	23	891	73	407	69	32	883	133	0	0
CASP9, rs4645982	**D/D**	**D/I**	**I/I**	**D**	**I**	**D/D**	**D/I**	**I/I**	**D**	**I**			
Park (2006)	432/432	159	211	62	529	335	161	201	70	523	341	0.585	0.695
Gangwar (2009)	212/250	74	104	34	252	172	73	128	49	274	226	0.596	0.695
Kesarwani (2010)	170/198	40	101	29	181	159	37	121	40	195	201	0.002	0.012
George (2012)	171/205	49	95	27	193	149	44	121	40	209	201	0.010	0.034
Cingeetham (2014)	172/300	49	79	44	177	167	93	149	58	335	265	0.903	0.903
Edathara (2019)	432/432	158	180	140	496	460	155	231	121	541	473	0.057	0.099
Cavalcante (2020)	81/58	16	24	41	56	106	13	20	25	46	70	0.033	0.077
CASP9, rs1052571	**CC**	**CT**	**TT**	**C**	**T**	**CC**	**CT**	**TT**	**C**	**T**			
Lou (2007)	81/100	55	24	2	134	28	66	30	4	162	38	0.800	0.800
Ulybina (2009)	111/110	14	57	40	85	137	20	52	38	92	128	0.765	0.800
Ulybina (2011)	121/142	25	52	44	102	140	25	57	60	107	177	0.084	0.417
Lavender (2012)	1162/1111	320	589	253	1229	1095	348	553	210	1249	973	0.711	0.800
Azevedo (2019)	133/279	25	74	34	124	142	70	129	80	269	289	0.216	0.540
CASP9, rs2308950	**GG**	**GA**	**AA**	**G**	**A**	**GG**	**GA**	**AA**	**G**	**A**			
Ulybina (2009)	111/110	108	3	0	219	3	102	8	0	212	8	0.692	0.928
Ulybina (2011)	121/142	117	3	1	237	5	139	3	0	281	3	0.899	0.928
Azevedo (2019)	133/279	129	3	1	261	5	276	3	0	555	3	0.928	0.928
CASP10, rs3900115	**AA**	**AG**	**GG**	**A**	**G**	**AA**	**AG**	**GG**	**A**	**G**			
Ye (2004)	84/140	59	21	4	139	29	91	46	3	228	52	0.307	0.614

Table 1 (continued)

Study (year)/SNP	Case/control	Cases (n, %)					Controls (n, %)					P_{HWE}	P_{HWE*}
		GG	GA	AA	G	A	GG	GA	AA	G	A		
Lan (2007)	522/446	129	264	129	522	522	126	203	117	455	437	0.059	0.237
Hosgood (2008)	121/503	28	61	32	117	125	122	256	125	500	506	0.688	0.816
Liu (2013)	300/296	172	118	10	462	138	168	109	19	445	147	0.815	0.816
CASP10, rs13010627	**GG**	**GA**	**AA**	**G**	**A**	**GG**	**GA**	**AA**	**G**	**A**			
Frank (2006)	511/547	455	55	1	965	57	456	85	6	997	97	0.368	0.904
Gaudet (2009)	26917/30429	23456	3352	109	50264	3570	26597	3706	126	56900	3958	0.798	0.905
Meyer (2013)	507/488	459	47	1	965	49	425	61	2	911	65	0.905	0.905
CASP10, rs130106529	**AA**	**AT**	**TT**	**A**	**T**	**AA**	**AT**	**TT**	**A**	**T**			
MacPherson (2004)	935/955	217	481	237	915	955	256	484	215	996	914	0.632	0.948
Li (2008)	805/835	206	418	181	830	780	239	415	181	893	777	0.973	0.981
Ulybina (2009)	111/110	26	52	33	104	118	24	43	43	91	129	0.042	0.156
Lee (2010)	716/718	41	219	456	310	1131	43	227	448	313	1123	0.052	0.156
Ulybina (2011)	121/142	31	55	35	117	125	27	70	45	124	160	0.981	0.981
Arnaout (2012)	100/100	9	43	48	61	139	14	41	45	69	131	0.353	0.707

D deletion, *I* insertion, P_{HWE} the *P* value of chi-square test for Hardy–Weinberg equilibrium (HWE) for the control data, P_{HWE*} PHWE corrected for multiple testing by FDR method

Document Quality Assessment

Quality assessment (QA) of the included publications was carried out by two researchers as described previously [54]. Each publication was scored carefully. Low-quality studies were scored equal to or less than 9, while high-quality studies were scored more than 9 (Table 1). In case of disagreement, the two researchers would settle through information exchange and ultimately reached an agreement.

Data Extraction

Two independent researchers (S.S and A.Z.A) abstracted the relevant data according to the standard protocol and the study's criteria. A third author (H.S) joined the study later to settle possible discrepancies. The following information were extracted from each included study: the first author's name, publication date, ethnicity, country, cancer type, the method for genotyping of *CASP9* and *CASP10* polymorphisms, allele, and genotype distribution in the studied groups, and results of the HWE test (Table 1).

Statistical Analysis

Data analysis was carried out by both Stata15.0 statistical software and MetaGenyo web tool [55]. Deviation from HWE was examined in controls via a χ^2 test. Pooled ORs with 95% CIs were calculated to estimate the strength of association between *CASP9* and *CASP10* variants and susceptibility to cancer under allelic, homozygous/heterozygous codominant, dominant, and recessive contrasted genetic models. $P < 0.05$ was considered statistically significant. Heterogeneity between-studies was evaluated via I^2 statistics. We applied a fixed-effects model if $I^2 < 50\%$, and if heterogeneity was present ($I^2 > 50\%$), analyses were repeated using a random-effects model. Publication bias was determined via Egger's test and visual inspection of funnel plots. The sensitivity analysis was done by sequentially omitting each study and calculating the pooled OR to investigate the effect of each study on overall estimates.

TSA and FPRP Analyses

In this study, trial sequential analysis (TSA) was used to enhance the robustness of the conclusion and decrease the random errors caused by sparse data and repetitive testing. We used the TSA software version 0.9.5.10 (http://www.ctu.dk/tsa/) to calculate the required information size (RIS) (meta-analysis sample size) [56] under the assumption of a plausible relative risk of 10% with low-risk bias, and the significance of 5% for type I error and 20% for type II error (power 80%). The TSA monitoring boundaries were plotted based on the required information size and the risk for type I and type II errors. The robustness of the conclusion is confirmed when the cumulative Z-curve (blue line) passes the TSA monitoring boundary (dotted red lines sloping inward) before the required information size is obtained. Otherwise, the data is insufficient to get a robust conclusion, and more trials are required. False-positive report probability (FPRP) values were assessed with different prior probabilities (0.25, 0.1, 0.01, 0.001, and 0.0001) [57]. An FPRP value < 0.2 indicated a significant correlation.

Result

Basic Information of Research Data

A total of 40 articles published between 2004 and 2020, including 15 case–control studies on *CASP9* rs4645978, 13 studies on *CASP9* rs1052576, 8 studies on *CASP* rs4645981, 7 studies on *CASP9* rs4645982 and *CASP10* rs13006529, 5 studies on *CASP9* s1052571, 4 studies on *CASP10* rs3900115, and 3 studies on either *CASP9* rs2308950 or *CASP10* rs13010627 were included in this study (Table 1). Figure 1 illustrates the specific screening process of the retrieved studies. Figure 2 and Supplementary Table 1 show the position of analyzed SNPs within the *CASP9* and *CASP10* genes. The basic information of the included studies and their QA scores are represented in Supplementary Table 2.

Main Analysis Results

Table 2 demonstrates the main results of the meta-analysis on the association of *CASP9* and *CASP10* variants with cancer susceptibility. Our pooled analysis revealed no significant association between *CASP9* rs4645978, rs1052576, rs4645982, and rs2308950 polymorphisms and cancer incidence under different inheritance patterns. However, the pooled OR from 6 studies showed that *CASP9* rs4645981 enhanced the risk of developing cancer under allelic [OR = 1.57; 95% CI, 1.25–1.97; $P < 0.001$, T vs. C], codominant homozygous [OR = 2.42; 95% CI, 1.46–4.00; $P < 0.001$, TT vs. CC], codominant heterozygous [OR =1.56; 95% CI, 1.21–2.00; $P < 0.001$, TC vs. CC], dominant [OR = 1.66; 95% CI, 1.26–2.17; $P < 0.001$, TT+ TC vs. CC], and recessive [OR = 1.92; 95% CI,

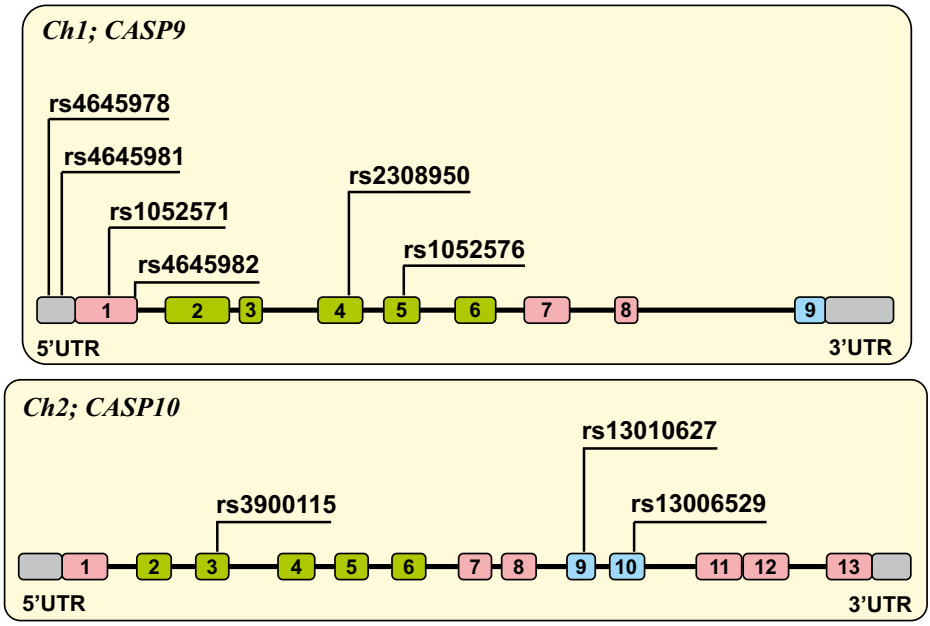

Fig. 2 Schematic representation and information of the examined variants on 1p36.2 and 2q33.1

Table 2 The pooled ORs and 95% CIs for the association between *CASP9* and *CASP10* polymorphisms and overall risk of cancer

Polymorphism	No.	Genetic model	Association test		Heterogeneity			Egger's test
			OR (95% CI)	*P*	Model	I^2 (%)	P_h	*P*
CASP9 rs4645978	14	AA vs. GG	1.31 (0.92-1.8)	0.1320	Random	86.32	0.000	0.912
		AG vs. GG	0.83(0.59; 1.15)	0.276	Random	84.65	0.000	0.151
		AA+ AG vs. GG	1.10(0.85; 1.41)	0.445	Random	78.1	0.000	0.923
		AA vs. AG + GG	1.40(0.96; 2.03)	0.076	Random	93.77	0.000	0.437
		A vs. G	1.21(0.94; 1.55)	0.131	Random	93.48	0.000	0.649
CASP9 rs1052576	14	GG vs. AA	0.79(0.56; 1.10)	0.172	Random	67.74	0.000	0.143
		GA vs. AA	1.00(0.87; 1.16)	0.908	Fixed	34.24	0.101	0.571
		GG+ GA vs. AA	0.92(0.73; 1.14)	0.468	Random	53.78	0.008	0.239
		GG vs. GA + AA	0.80 (0.61;1.06)	0.122	Random	69.34	0.000	0.230
		G vs. A	0.88 (0.7;1.05)	0.176	Random	71.9	0.000	0.199
CASP9 rs4645981	6	TT vs. CC	2.42(1.46; 4.00)	**<0.001**	Random	55.16	0.048	0.433
		TC vs. CC	1.56(1.21; 2.00)	**<0.001**	Random	67.92	0.008	0.593
		TT+ TC vs. CC	1.66(1.26; 2.17)	**<0.001**	Random	74.13	0.001	0.384
		TT vs. TC + CC	1.92(1.42; 2.58)	**<0.001**	Fixed	39.65	0.141	0.561
		T vs. C	1.57(1.25; 1.97)	**<0.001**	Random	75.25	0.001	0.375
CASP9 rs4645982	5	II vs. DD	1.04(0.84; 1.27)	0.707	Fixed	17.4	0.303	0.942
		ID vs. DD	0.90(0.76; 1.06)	0.227	Fixed	0	0.558	0.897
		II + ID vs. DD	0.95(0.81; 1.11)	0.521	Fixed	0	0.644	0.664
		II vs. ID + DD	1.13(0.94; 1.35)	0.178	Fixed	40.45	0.151	0.789
		I vs. D	1.01(0.91; 1.13)	0.722	Fixed	17.29	0.304	0.698
CASP9 rs1052571	5	TT vs. CC	1.22(1.00; 1.50)	**0.046**	Fixed	0	0.491	0.289
		TC vs. CC	1.17(1.00; 1.38)	**0.049**	Fixed	0	0.598	0.816
		TT+ TC vs. CC	1.18(1.00; 1.38)	**0.032**	Fixed	0	0.542	0.776
		TT vs. TC + CC	1.07(0.90; 1.26)	0.403	Fixed	0	0.414	0.107
		T vs. C	1.09(0.99; 1.21)	0.062	Fixed	0	0.460	0.189
CASP9 rs2308950	3	AA vs. GG	4.77(0.49; 46.19)	0.176	Fixed	0	0.799	0.218
		AG vs. GG	0.85(0.35; 2.04)	0.721	Fixed	33.92	0.220	0.197
		AA+ AG vs. GG	1.06(0.46; 2.47)	0.878	Fixed	54.9	0.108	0.182
		AA vs. AG + GG	4.73(0.49; 45.81)	0.178	Fixed	0	0.802	0.223
		A vs. G	1.33(0.34; 5.23)	0.678	Random	64.72	0.058	0.166
CASP10 rs3900115	4	GG vs. AA	1.01(0.77; 1.33)	0.914	Fixed	22.02	0.278	0.932
		AG vs. AA	1.08(0.89; 1.32)	0.387	Fixed	0	0.393	0.127
		GG + AG vs. AA	1.05(0.87; 1.26)	0.569	Fixed	0	0.580	0.264
		GG vs. AG + AA	0.93(0.74; 1.17)	0.555	Fixed	28.03	0.243	0.900
		G vs. A	1.00(0.88; 1.13)	0.965	Fixed	0	0.799	0.459
CASP10 rs13010627	3	AA vs. GG	0.94(0.73; 1.22)	0.682	Fixed	32.96	0.225	0.280
		AG vs. GG	0.81(0.57; 1.13)	0.229	Random	77.63	0.011	0.111
		AA+ AG vs. GG	0.79(0.54; 1.14)	0.210	Random	81.39	0.004	0.136
		AA vs. AG + GG	0.94(0.73; 1.22)	0.672	Fixed	27.87	0.25	0.284
		A vs. G	0.78(0.54; 1.13)	0.200	Random	83.44	0.002	0.156
CASP10 rs13006529	6	AA vs. TT	1.14 (0.97; 1.34)	0.095	Fixed	0.340	11.71	0.272
		AT vs. TT	1.12 (0.98; 1.30)	0.091	Fixed	0	0.629	0.547
		AA+ AT vs. TT	1.137(0.99; 1.29)	0.060	Fixed	0	0.465	0.379
		AA vs. AT + TT	1.05(0.94; 1.19)	0.340	Fixed	0	0.529	0.145
		A vs. T	1.07 (0.99; 1.15)	0.086	Fixed	11.66	0.340	0.163

CI confidence interval, *OR* odds ratio, P_h *P* value from the heterogeneity test

1.42–2.58; $P < 0.001$, TT vs. TC + CC] genetic patterns. Figure 3 demonstrates the forest plot for the relationship between *CASP9* rs4645981 polymorphism and cancer risk using different genetic contrasted models. Regarding *CASP9* rs1052571, an increased risk of developing cancer was observed under codominant homozygous [OR = 1.22; 95% CI, 1.00–1.50; $P = 0.046$, TT vs. CC], codominant heterozygous [OR = 1.17; 95% CI, 1.00–1.38; $P = 0.049$, TC vs. CC], and dominant [OR = 1.18; 95% CI, 1.00–1.38; $P = 0.032$, TT+ TC vs. CC] modes of inheritance. No significant association was found between *CASP10* SNPs and overall risk of cancer.

Stratified Analysis Results

The subgroup analyses of *CASP9* and *CASP10* variants on risk of cancer are shown in Tables 3 and 4. Regarding ethnicity of cancer patients, the *CASP9* rs4645978 variant conferred an increased risk of cancer in Asians, under codominant homozygous [OR = 1.26; 95% CI, 1.06–1.50; $P = 0.008$, AA vs. GG], recessive [OR = 1.16; 95% CI, 1.02–1.31; $P = 0.015$, AA vs. AG + GG], and allelic [OR = 1.12; 95% CI, 1.03–1.23; $P = 0.006$, A vs. G] genetic patterns. With respect to *CASP9* rs4645981, the findings from five studies suggested a noteworthy

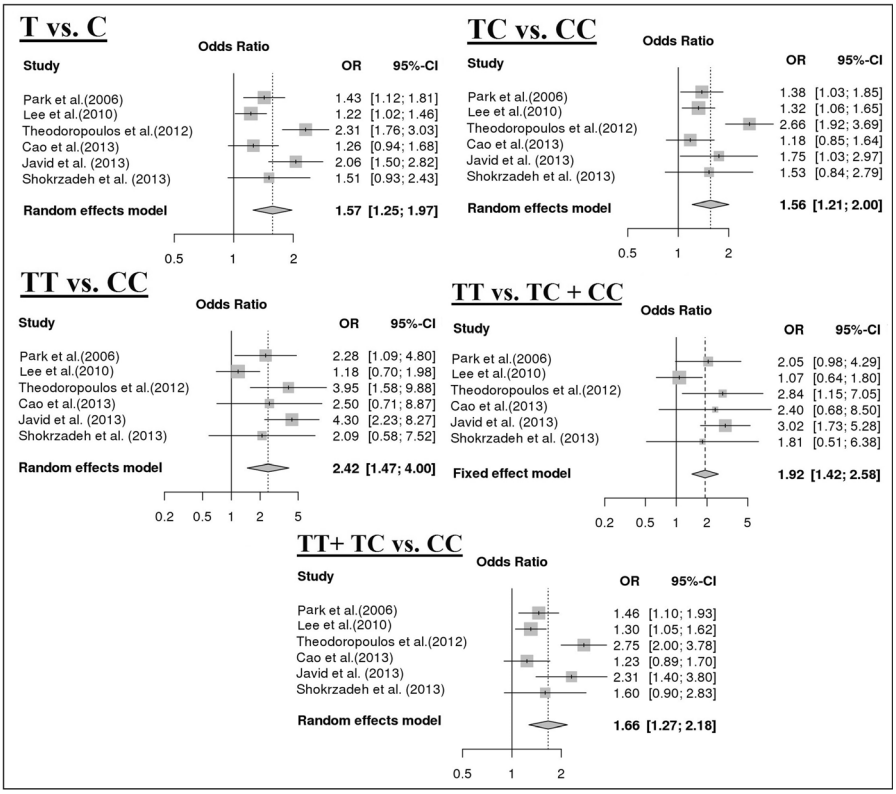

Fig. 3 The forest plot for the association between *CASP9* rs4645981 polymorphism and cancer risk using different genetic contrasted models

association between this variant and increased risk of cancer in the Asian population ($P < 0.001$ for all the assessed genetic models) (Table 3).

Stratifying according to cancer type indicated that *CASP9* rs4645978 significantly enhanced the risk of developing colorectal cancer (under all examined genetic models), and lung and prostate cancer (under codominant heterozygous and dominant genetic patterns). We also observed an enhanced risk of lung cancer ($n = 4$ studies) regarding codominant homozygous (OR = 2.25), codominant heterozygous (OR = 1.34), dominant (OR = 1.39), and recessive (OR = 1.92) models of *CASP9* rs4645981 polymorphism. The T allele of this polymorphism increased susceptibility to lung cancer by 1.43-fold. Interestingly, the G allele of *CASP9* rs1052576 was associated with a diminished risk of developing lung cancer [OR = 0.70; 95% CI, 0.56–0.90; $P = 0.004$] (Table 4).

Heterogeneity and Publication Bias

The heterogeneity results of all the studied polymorphisms are summarized in Tables 2 and 3. As shown in Fig. 4, a symmetrical-shaped funnel plot was generated for the association between *CASP9* rs4645981 polymorphism and cancer risk, which indicates no publication bias. Regarding *CASP9* rs4645981 and rs1052571 polymorphisms, Egger's linear regression analysis detected no publication bias for the current meta-analysis under different genetic models (P values for bias > 0.05). No publication bias was also detected for significant findings of the stratified analysis, except for the relationship between three high-quality studies on *CASP9* rs4645981 and cancer susceptibility under the codominant homozygous model (P value for bias = 0.008).

Sensitivity Analysis

Regarding TT vs. CC and TT vs. TC + CC models of *CASP9* rs4645981, Lee et al.'s study had the most profound impact on pooled ORs (Fig. 5); thus, these findings should be interpreted carefully. As for the other significant results of this meta-analysis, the relevant pooled ORs indicated no significant change in the assessed genetic models (data not shown). Except for TT vs. CC and TT vs. TC + CC models of *CASP9* rs4645981, the final summary ORs are reliable and stable.

Results of TSA and FPRP Analyses

Our meta-analysis indicated a significant association between CASP9 polymorphisms (rs4645981 and rs1052571) and overall cancer risk. For rs1052571, rs4645978, and rs1052576, the cumulative Z-curve did not pass the TSA boundary lines illustrating that the cumulative evidence is insufficient. More trials are warranted to confirm the effect of these SNPs on cancer susceptibility. However, the TSA analysis of rs4645981 indicated the crossing of cumulative Z-curve (blue line) over the trial sequential monitoring boundary (dotted red line) ($P < 0.05$), suggesting reliable evidence for the rs4645981 effect on cancer risk.

Table 5 represents the calculated FPRP values regarding the main significant findings in the present meta-analysis. With the assumption of a prior probability of 0.25, most FPRP values were less than 0.2, indicating the observed significant associations were notable.

Table 3 Stratified analysis of the *CASP9* and *CASP10* polymorphisms on cancer risk by ethnicity and quality

SNP	Ethnicity	No.	Genetic model	Association test		Heterogeneity			Egger's test
				OR (95% CI)	*P*	Model	I^2 (%)	P_h	*P*
CASP9 rs4645978	Asian	6	AA vs. GG	1.26(1.06; 1.50)	**0.008**	Fixed	0	0.464	0.412
.			AG vs. GG	1.01(0.68; 1.51)	0.922	Random	79.06	0.000	0.526
			AA+ AG vs. GG	1.15(0.89; 1.49)	0.260	Random	57.95	0.036	0.987
			AA vs. AG + GG	1.16(1.02; 1.31)	**0.015**	Fixed	42.27	0.123	0.163
			A vs. G	1.12(1.03; 1.23)	**0.006**	Fixed	0	0.603	0.291
	Caucasian	4	AA vs. GG	2.34(0.71; 7.69	0.158	Random	95.48	0.000	0.555
			AG vs. GG	0.50(0.17; 1.47)	0.208	Random	94.08	0.000	0.525
			AA+ AG vs. GG	1.41(0.65; 3.05)	0.379	Random	92.47	0.000	0.407
			AA vs. AG + GG	3.00(0.82;10.96)	0.097	Random	97.65	0.000	0.533
			A vs. G	1.96(0.80; 4.76)	0.136	Random	97.97	0.000	0.414
	Hispanic	3	AA vs. GG	0.92(0.70; 1.22)	0.568	Fixed	0	0.910	0.820
			AG vs. GG	0.82(0.50; 1.35)	0.445	Random	65.33	0.056	0.353
			AA+ AG vs. GG	0.90(0.69; 1.17)	0.446	Fixed	0	0.590	0.307
			AA vs. AG + GG	1.04(0.70; 1.56)	0.816	Random	75.80	0.020	0.519
			A vs. G	0.98(0.85; 1.13)	0.755	Fixed	25.53	0.261	0.558
	QA>9	4	AA vs. GG	1.02(0.62; 1.67)	0.939	Random	85.09	0.000	0.660
			AG vs. GG	1.03(0.68; 1.55)	0.905	Random	82.57	0.000	0.885
			AA+ AG vs. GG	1.02(0.65; 1.61)	0.919	Random	87.06	0.000	0.746
			AA vs. AG + GG	0.99(0.78; 1.28)	0.945	Random	70.78	0.016	0.465
			A vs. G	0.98(0.76; 1.26)	0.894	Random	87.08	0.000	0.474
CASP9 rs1052576	Asian	6	GG vs. AA	0.62(0.33; 1.14)	0.123	Random	78.24	0.000	0.177
			GA vs. AA	0.97(0.78; 1.21)	0.782	Fixed	0	0.845	0.058
			GG+ GA vs. AA	0.82(0.60; 1.13)	0.238	Random	46.17	0.098	0.039
			GG vs. GA + AA	0.65(0.39; 1.09)	0.103	Random	82.08	0.000	0.307
			G vs. A	0.76(0.55; 1.04)	0.088	Random	81.95	0.000	0.148
	Caucasian	6	GG vs. AA	0.98(0.68; 1.43)	0.946	Fixed	18.82	0.291	0.898
			GA vs. AA	1.06(0.61; 1.85)	0.837	Random	68.41	0.007	0.771
			GG+ GA vs. AA	1.05(0.65; 1.70)	0.832	Random	62.21	0.021	0.814
			GG vs. GA + AA	1.01(0.74; 1.37)	0.951	Fixed	0	0.578	0.579
			G vs. A	1.01(0.84; 1.21)	0.861	Fixed	22.16	0.267	0.616
	QA>9	3	GG vs. AA	0.92(0.54; 1.56)	0.770	Random	77.78	0.011	0.188

Table 3 (continued)

SNP	Ethnicity	No.	Genetic model	Association test		Heterogeneity			Egger's test
				OR (95% CI)	*P*	Model	I^2 (%)	P_h	*P*
			GA vs. AA	1.03(0.84; 1.26)	0.786	Fixed	0	0.419	0.042
			GG+ GA vs. AA	0.99(0.72; 1.34)	0.931	Random	57.55	0.095	0.019
			GG vs. GA + AA	0.94(0.64; 1.37)	0.763	Random	72.44	0.000	0.395
			G vs. A	0.96(0.75; 1.24)	0.794	Random	77.59	0.012	0.278
CASP9 rs4645981	Asian	5	TT vs. CC	2.22(1.27; 3.86)	**<0.001**	Random	57.55	0.051	0.594
			TC vs. CC	1.34(1.16; 1.56)	**<0.001**	Fixed	0	0.776	0.280
			TT+ TC vs. CC	1.40 (1.22; 1.61)	**<0.001**	Fixed	22.14	0.274	0.186
			TT vs. TC + CC	1.82 (1.33; 2.50)	**<0.001**	Fixed	46.46	0.113	0.717
			T vs. C	1.43 (1.19; 1.72)	**<0.001**	Random	53.15	0.074	0.323
			T vs. C	1.57(1.14; 2.18)	**0.006**	Random	60.83	0.078	0.944
	QA>9	3	TT vs. CC	2.03(1.01; 4.09)	**0.047**	Random	65.23	0.056	0.008
			TC vs. CC	1.67(1.11; 2.52)	**0.013**	Random	84.49	0.002	0.408
			TT+ TC vs. CC	1.71(1.12; 2.62)	**0.013**	Random	86.55	0.000	0.341
			TT vs. TC + CC	1.52(1.04; 2.23)	**0.032**	Fixed	52.61	0.121	0.067
			T vs. C	1.57(1.09; 2.25)	**0.014**	Random	86.51	0.000	0.286
CASP9 rs4645982	Asian	4	II vs. DD	1.02(0.83; 1.27)	0.8155	Fixed	33.69	0.210	0.739
			ID vs. DD	0.89(0.76; 1.07)	0.224	Fixed	0	0.396	0.995
			II + ID vs. DD	0.94(0.80; 1.10)	0.468	Fixed	0	0.524	0.985
			II vs. ID + DD	1.08(0.82; 1.44)	0.570	Random	53.33	0.092	0.524
			I vs. D	1.01(0.91; 1.12)	0.861	Fixed	28.22	0.243	0.855
	QA>9	2	II vs. DD	1.03(0.80; 1.33)	0.798	Fixed	0	0.377	NA
			ID vs. DD	1.13(0.65; 1.97)	0.656	Random	79.52	0.027	NA
			II + ID vs. DD	0.9(0.78; 1.15)	0.616	Fixed	0	0.494	NA
			II vs. ID + DD	1.09(0.72; 1.64)	0.684	Random	68.06	0.077	NA
			I vs. D	1.02(0.89; 1.16)	0.778	Fixed	0	0.510	NA
CASP9 rs1052571	Caucasian	3	TT vs. CC	1.07(0.72; 1.58)	0.751	Fixed	0	0.371	0.775
			TC vs. CC	1.34(0.92; 1.94)	0.117	Fixed	0	0.395	0.813
			TT+ TC vs. CC	1.22(0.86; 1.73)	0.254	Fixed	16.47	0.302	0.955
			TT vs. TC + CC	0.88(0.66; 1.18)	0.393	Fixed	0	0.702	0.445
			T vs. C	0.38(0.83; 1.22)	0.928	Fixed	0	0.399	0.962
CASP10 rs3900115	Asian	2	GG vs. AA	0.69(0.34; 1.40)	0.302	Fixed	59.64	0.115	NA

Table 3 (continued)

SNP	Ethnicity	No.	Genetic model	Association test		Heterogeneity			Egger's test
				OR (95% CI)	*P*	Model	I^2 (%)	P_h	*P*
			AG vs. AA	0.99(0.74; 1.33)	0.968	Fixed	48.29	0.164	NA
			GG + AG vs. AA	0.92(0.70; 1.23)	0.605	Fixed	0	0.525	NA
			GG vs. AG + AA	0.92(0.22; 3.96)	0.917	Random	66.69	0.083	NA
			G vs. A	0.91(0.72; 1.15)	0.413	Fixed	0	0.968	NA
	QA>9	3	GG vs. AA	0.99(0.75; 1.31)	0.953	Fixed	33.44	0.223	0.432
			AG vs. AA	1.14(0.93; 1.41)	0.197	Fixed	0	0.668	0.558
			GG + AG vs. AA	1.09(0.90; 1.32)	0.384	Fixed	0	0.644	0.752
			GG vs. AG + AA	0.91(0.72; 1.15)	0.447	Fixed	28.81	0.245	0.554
			G vs. A	1.00(0.88; 1.15)	0.891	Fixed	0	0.647	0.703
CASP10 rs13010627	QA>9	2	AA vs. GG	0.97(0.75; 1.25)	0.831	Fixed	0	0.543	NA
			AG vs. GG	0.90(0.64; 1.27)	0.565	Random	67.47	0.079	NA
			AA+ AG vs. GG	0.90(0.63; 1.27)	0.544	Random	69.86	0.068	NA
			AA vs. AG + GG	0.97(0.75; 1.25)	0.815	Fixed	0	0.564	NA
			A vs. G	0.89(0.63; 1.25)	0.532	Random	70.46	0.066	NA
CASP10 rs13010629	Caucasian	4	AA vs. TT	1.14(0.96; 1.36)	0.133	Fixed	39.51	0.175	0.025
			AT vs. TT	1.13(0.97; 1.31)	0.107	Fixed	0	0.447	0.276
			AA+ AT vs. TT	1.13(0.98; 1.31)	0.079	Fixed	21.37	0.282	0.087
			AA vs. AT + TT	1.05(0.91; 1.22)	0.470	Fixed	26.63	0.252	0.086
			A vs. T	1.07(0.98; 1.16)	0.129	Fixed	43.57	0.150	0.016
	QA>9	3	AA vs. TT	1.20(1.01; 1.43)	**0.035**	Fixed	0	0.709	0.416
			AT vs. TT	1.15(0.99; 1.34)	0.064	Fixed	0	0.845	0.019
			AA+ AT vs. TT	1.17(1.01; 1.35)	**0.027**	Fixed	0	0.842	0.240
			AA vs. AT + TT	1.09(0.96; 1.24)	0.169	Fixed	0	0.74	0.554
			A vs. T	1.09(1.01; 1.19)	**0.029**	Fixed	0	0.735	0.346

CI confidence interval, *OR* odds ratio, *NA* not applicable, *QA* quality assessment

Table 4 Stratified analysis of the *CASP9* and *CASP10* polymorphisms on cancer risk by cancer type

SNP	Ethnicity	No.	Genetic model	Association test		Heterogeneity			Egger's test
				OR (95% CI)	*P*	Model	I^2 (%)	P_h	*P*
CASP9 rs4645978	Colorectal cancer	2	AA vs. GG	1.95(1.16; 3.26)	**0.012**	Random	72.02	0.059	NA
			AG vs. GG	1.31(1.01; 1.70)	**0.039**	Fixed	0	0.480	NA
			AA+ AG vs. GG	1.55(1.21; 1.98)	**<0.001**	Fixed	35.75	0.212	NA
			AA vs. AG + GG	1.59(1.06; 2.38)	**0.025**	Random	77.71	0.034	NA
			A vs. G	1.40(1.06; 1.87)	**0.019**	Random	79.31	0.028	NA
	Lung cancer	2	AA vs. GG	1.20(0.94; 1.54)	0.130	Fixed	5.96	0.302	NA
			AG vs. GG	1.28(1.01; 1.62)	**0.037**	Fixed	0	0.574	NA
			AA+ AG vs. GG	1.25(1.00; 1.56)	**0.049**	Fixed	0	0.407	NA
			AA vs. AG + GG	1.00(0.84; 1.19)	0.965	Fixed	0	0.383	NA
			A vs. G	1.06(0.95; 1.20)	0.280	Fixed	2.99	0.310	NA
	Prostate cancer	3	AA vs. GG	0.75(0.37; 1.54)	0.439	Random	70.63	0.033	0.072
			AG vs. GG	0.50(0.35; 0.73)	**<0.001**	Fixed	0	0.788	0.130
			AA+ AG vs. GG	0.71(0.52; 0.98)	**0.035**	Fixed	0	0.431	0.117
			AA vs. AG + GG	0.92(0.38; 2.22)	0.857	Random	88.46	0.000	0.041
			A vs. G	0.80(0.46; 1.41)	0.450	Random	85.44	0.001	0.055
CASP9 rs1052576	Lung cancer	3	GG vs. AA	0.81(0.33; 1.99)	0.651	Random	78.04	0.011	0.552
			GA vs. AA	0.59(0.28; 1.26)	0.175	Random	66.69	0.050	0.322
			GG+ GA vs. AA	0.56(0.30; 1.04)	0.070	Random	57.75	0.094	0.051
			GG vs. GA + AA	0.69(0.33; 1.43)	0.314	Random	71.16	0.031	0.507
			G vs. A	0.70(0.56; 0.90)	**0.004**	Fixed	55.30	0.107	0.635
CASP9 rs4645981	Lung cancer	4	TT vs. CC	2.25(1.17; 4.32)	**0.015**	Random	68.16	0.024	0.585
			TC vs. CC	1.34(1.15; 1.55)	**<0.001**	Fixed	0	0.659	0.440
			TT+ TC vs. CC	1.39(1.20; 1.61)	**<0.001**	Fixed	39.24	0.176	0.213
			TT vs. TC + CC	1.92(1.10; 3.33)	**0.021**	Random	59.85	0.058	0.701
			T vs. C	1.43(1.16; 1.76)	**<0.001**	Random	64.31	0.038	0.282
CASP9 rs1052571	Lung cancer	2	TT vs. CC	1.27(0.61; 2.66)	0.520	Fixed	0	0.347	NA
			TC vs. CC	1.17(0.71; 1.92)	0.533	Fixed	0	0.343	NA
			TT+ TC vs. CC	1.13(0.70; 1.83)	0.597	Fixed	8.88	0.295	NA
			TT vs. TC + CC	1.01(0.60; 1.71)	0.968	Fixed	0	0.542	NA
			T vs. C	1.06(0.78; 1.45)	0.707	Fixed	0	0.435	NA
CASP10 rs3900115	Non-Hodgkin lymphoma	2	GG vs. AA	1.11(0.79; 1.56)	0.541	Fixed	0	0.420	NA

Table 4 (continued)

SNP	Ethnicity	No.	Genetic model	Association test		Heterogeneity			Egger's test
				OR (95% CI)	*P*	Model	I^2 (%)	P_h	*P*
			AG vs. AA	1.01(0.57; 1.77)	0.983	Random	65.04	0.091	NA
			GG + AG vs. AA	1.10(0.85; 1.43)	0.446	Fixed	38.27	0.203	NA
			GG vs. AG + AA	0.95(0.71; 1.27)	0.739	Fixed	23.81	0.252	NA
			G vs. A	1.03(0.88; 1.21)	0.764	Fixed	0	0.633	NA
CASP10 rs13010627	Breast cancer	2	AA vs. GG	0.95(0.74; 1.23)	0.730	Fixed	62.08	0.104	NA
			AG vs. GG	0.85(0.54; 1.31)	0.460	Random	83.35	0.014	NA
			AA+ AG vs. GG	0.82(0.50; 1.34)	0.432	Random	86.83	0.006	NA
			AA vs. AG + GG	0.95(0.73; 1.23)	0.717	Fixed	59.40	0.116	NA
			A vs. G	0.81(0.48; 1.34)	0.414	Random	88.73	0.003	NA
CASP10 rs13010629	Breast cancer	2	AA vs. TT	1.01(0.55; 1.88)	0.961	Random	67.68	0.079	NA
			AT vs. TT	1.10(0.89; 1.36)	0.348	Fixed	60.52	0.111	NA
			AA+ AT vs. TT	0.12 (0.56; 1.68)	0.920	Random	69.66	0.069	NA
			AA vs. AT + TT	1.12(0.92; 1.36)	0.246	Fixed	0	0.323	NA
			A vs. T	1.01(0.75; 1.36)	0.938	Random	65.17	0.090	NA
	Lung cancer	2	AA vs. TT	0.95(0.65; 1.39)	0.798	Fixed	0	0.341	NA
			AT vs. TT	1.04(0.70; 1.53)	0.828	Fixed	0	0.816	NA
			AA+ AT vs. TT	1.00(0.70; 1.43)	0.992	Fixed	0	0.723	NA
			AA vs. AT + TT	0.99(0.81; 1.21)	0.960	Fixed	58.16	0.122	NA
			A vs. T	1.00(0.84; 1.17)	0.969	Fixed	37.57	0.206	NA

CI confidence interval, *OR* odds ratio, *NA* not applicable

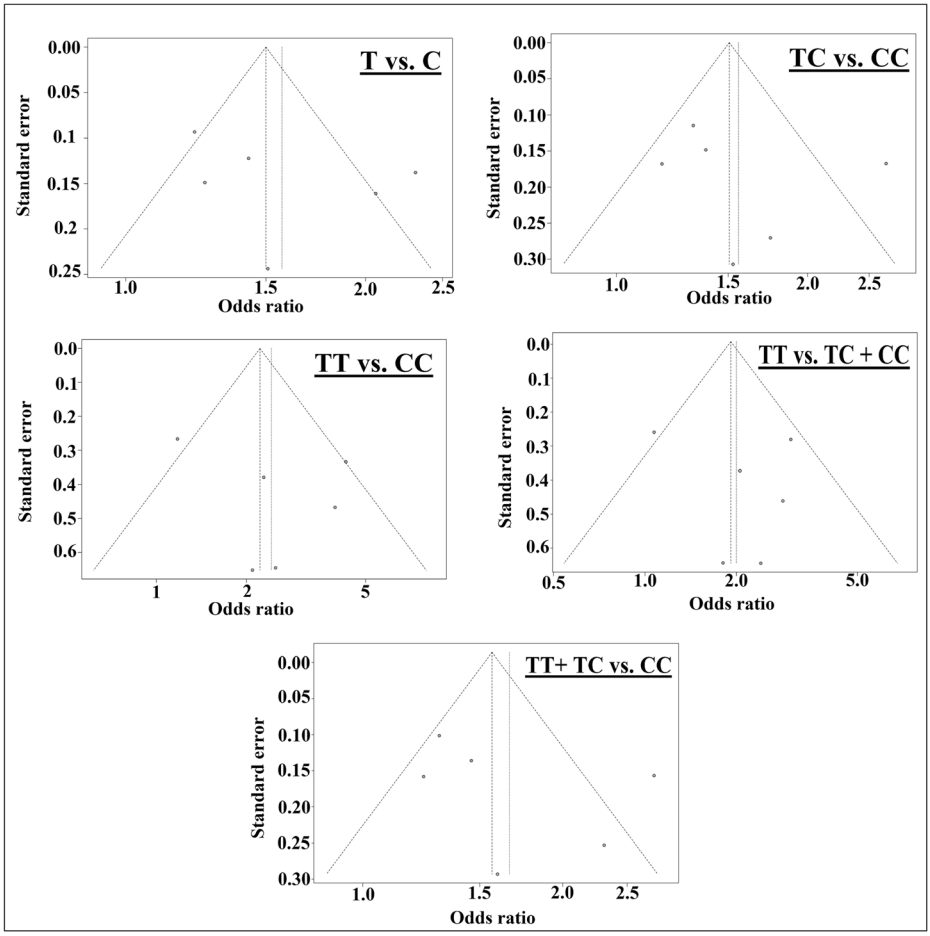

Fig. 4 Funnel plot for the association between *CASP9* rs4645981 polymorphism and cancer risk using different genetic contrasted models

Discussion

As the role of cell death in the pathophysiology of cancer is gaining ground, it appears crucial to study the genetic variations of the apoptosis-associated gene in human malignancies. For example, variations in apoptosis-related genes (i.e., death receptors and TNF superfamily ligands) have been investigated in hematological malignancies as well as solid tumors [58, 59]. Apoptosis, a genetically mediated cell suicide program and an essential physiological response, serves an indispensable role in maintaining tissue hemostasis and discarding harmful and/or unnecessary cells [60]. Characterization of the intrinsic and extrinsic pathways of apoptosis has straightened out how apoptosis is deregulated in most human malignancies [61]. Some studies have recommended that restoring the function of these caspases by overexpressing them could be a beneficial curative approach toward cancer [62, 63].

It has been shown that CASP9 is necessary for p53-dependent apoptosis [64]. Failure of CASP9 activation also induced a higher threshold for apoptotic cell death [65]. Horn and

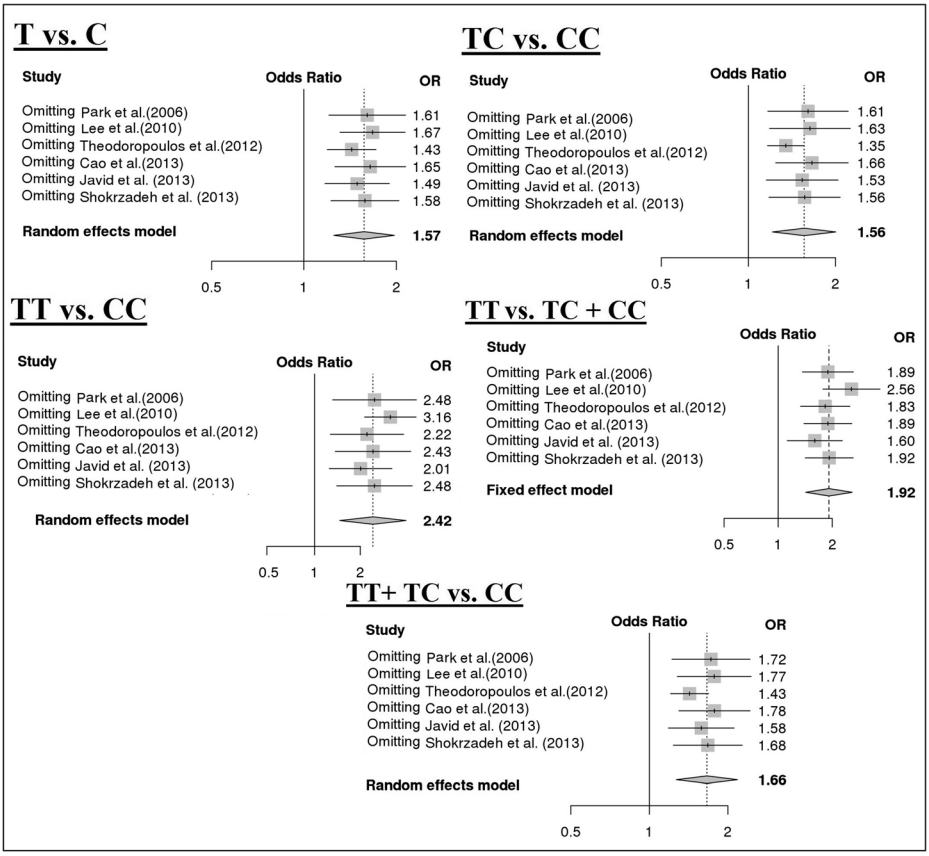

Fig. 5 Sensitivity analysis for studies on *CASP9* rs4645981 using different genetic contrasted models

coworkers have shown that CASP10 negatively regulates death receptor-mediated activation of CASP8, and therefore perturbing cell death [66]. Based on another hypothesis, CASP10 makes cancer cells more susceptible to TRAIL-induced apoptosis following a CASP3-dependent fashion [67]. It is assumed that any alteration in the genetic formation of caspases could potentially impact the rate of apoptosis [68]. Nevertheless, the mechanisms by which caspases, including CASP9 and 10, get regulated are not fully understood. Moreover, *CASP10* mutations have been associated with impaired apoptotic function, suggesting that *CASP10* deficiency might be the reason why cancer cells evade apoptosis [13].

Few SNPs (i.e., rs1052576, rs1052571, and rs2308950) are mapped within the coding region of *CASP9* gene. Ulybina et al. had suggested that genetic variations in this region might not be linked to the risk of developing breast cancer [23]. Instead, most studied SNPs in the *CASP9* gene have resided in non-coding regions, i.e., promoter site and intronic regions. The rs4661636, rs6685648, and rs2020902 polymorphisms (located within introns of *CASP9*) or rs4645982 (an insertion/deletion SNP situated in a splice donor site) were shown to be functional and with the potential to alter *CASP9* mRNA splicing patterns [69, 70]. Besides, alternative splicing of *CASP9* might have different impacts on apoptosis and affect cancer cells' tumorigenicity, as this gene produces two protein isoforms (CASP9a and CASP9b)

Table 5 False-positive report probability analysis of the noteworthy results for *CASP9* rs4645981 and rs1052571 polymorphisms

SNP	Genetic model	Subgroup	OR (95% CI)	*P*	Power	Prior probability				
						0.25	0.1	0.01	0.001	0.0001
CASP9 rs4645981	Codominant (TT vs. CC)	Overall	2.42(1.46; 4.00)	<0.001	0.938	**<0.001**	**0.001**	**0.010**	**0.096**	0.516
		Asians	2.22(1.27; 3.86)	<0.001	0.661	**<0.001**	**0.001**	**0.015**	**0.131**	0.602
		QA>9	2.03(1.01; 4.09)	0.047	0.610	**0.188**	0.409	0.884	0.987	0.999
		Lung cancer	2.25(1.17; 4.32)	0.015	0.983	**0.044**	**0.121**	0.602	0.938	0.993
	Codominant (TC vs. CC)	Overall	1.56(1.21; 2.00)	<0.001	0.998	**0.001**	**0.002**	**0.019**	**0.167**	0.667
		Asians	1.34(1.16; 1.56)	<0.001	0.815	**0.002**	**0.004**	**0.057**	0.380	0.860
		QA>9	1.67(1.11; 2.52)	0.013	0.109	0.264	0.518	0.922	0.992	0.999
		Lung cancer	1.34(1.15; 1.55)	<0.001	0.740	**0.001**	**0.004**	**0.041**	0.302	0.812
	Dominant (TT+ TC vs. CC)	Overall	1.66(1.26; 2.17)	<0.001	0.999	**0.001**	**0.003**	**0.029**	**0.231**	0.750
		Asians	1.40 (1.22; 1.61)	<0.001	0.902	**0.002**	**0.005**	**0.052**	0.356	0.847
		QA>9	1.71(1.12; 2.62)	0.013	0.916	**0.041**	**0.113**	0.584	0.934	0.993
		Lung cancer	1.39(1.20; 1.61)	<0.001	0.461	**0.002**	**0.006**	**0.064**	0.409	0.874
	Recessive (TT vs. TC + CC)	Overall	1.92(1.42; 2.58)	<0.001	0.658	**0.001**	**0.003**	**0.043**	**0.313**	0.820
		Asians	1.82 (1.33; 2.50)	<0.001	0.323	**0.005**	**0.014**	**0.133**	0.607	0.939
		QA>9	1.52(1.04; 2.23)	0.032	0.914	**0.095**	**0.240**	0.776	0.972	0.997
		Lung cancer	1.92(1.10; 3.33)	0.021	0.818	**0.072**	**0.188**	0.718	0.962	0.996
	Allelic (T vs. C)	Overall	1.57(1.25; 1.97)	<0.001	0.972	**0.001**	**0.003**	**0.030**	**0.236**	0.755
		Asians	1.43 (1.19; 1.72)	<0.001	0.677	**0.003**	**0.008**	**0.081**	0.470	0.899
		QA>9	1.57(1.09; 2.25)	0.014	0.219	**0.161**	0.365	0.864	0.985	0.998
		Lung cancer	1.43(1.16; 1.76)	<0.001	0.999	**0.001**	**0.002**	**0.020**	**0.174**	0.678
CASP9 rs1052571	Codominant (TT vs. CC)	Overall	1.22(1.00; 1.50)	0.046	0.554	**0.199**	0.428	0.892	0.988	0.999
	Codominant (TC vs. CC)	Overall	1.17(1.00; 1.38)	0.049	0.650	**0.184**	0.404	0.882	0.987	0.999
	Dominant (TT+ TC vs. CC)	Overall	1.18(1.00; 1.38)	0.032	0.818	**0.105**	0.260	0.795	0.975	0.997

CI confidence interval, *OR* odds ratio, *QA* quality assessment. FPRP values < 0.2 were considered significant

through inclusion/exclusion of four exons [71, 72]. Promoteric SNPs of *CASP9* (e.g., rs4645981 and rs4645978) were more intensively studied. This evidence shed light on the relevance of transcriptional regulation of this gene [31, 33] since the $G_{rs4645978}$ $C_{rs4645981}$ haplotype showed an elevated promoter activity compared with $G_{rs4645978}$ $T_{rs4645981}$ and $A_{rs4645978}$ $C_{rs4645981}$ combinations [5]. We then pursued the hypothesis suggesting the SNPs within the *CASP10* gene might affect overall cancer susceptibility. It has been shown that the rs13006529 polymorphism impacts the very last amino acid of the protein [73]. However, this SNP was not correlated with breast cancer incidence [48]. The rs13010627 resides 5 amino acids upstream of the cleavage site of mature CASP10; hence, this variation could impact CASP10 activation and disrupt its function [45, 74].

In 2012, a meta-analysis was carried out by Yan and coworkers on 7 case–control studies, including 3962 subjects. They reported a positive association between the A allele carriers of *CASP9* rs1052576 polymorphism and cancer incidence in American and Chinese populations (OR = 0.63); thus, A allele and A allele carriers of this polymorphism had established protective roles against cancer [75]. In our study, we included 14 studies and enrolled 4877 subjects to enhance statistical power. In contrast, we found no relationship between this variant and the overall risk of cancer in Asians or Caucasians. In the same year, another comprehensive meta-analysis was performed by Xu et al. on 9 studies with 5528 subjects for rs4645978, 6 studies with 2403 subjects for rs105276, and 2 studies with 2304 subjects for rs4645981. By pooling the results of included studies, they observed a protective effect for *CASP9* rs1052576 under AA vs. GG (OR = 0.75) and A vs. G models (OR = 0.85) against cancer susceptibility. As for *CASP9* rs4645981, they found an increased incidence of lung cancer among Asians under allelic (OR = 1.23, T vs. C) and recessive (OR = 1.22, CC vs. CT+TT) contrasted genetic models. However, they found no evidence of the association between *CASP9* rs4645978 and overall cancer incidence [76]. In our updated meta-analysis, we enrolled 5910 subjects for examining the link between *CASP9* rs4645981 polymorphism and cancer risk and observed significant results under different contrasted models. Still, by including 14 studies for each SNP, we found no association between *CASP9* rs1052576 and rs4645978 and the overall risk of cancer.

In 2012, Yan and colleagues reviewed and conducted a meta-analysis on the relationship between *CASP10* variants and cancer incidence. They pooled the results from 8 studies with 29,936 cases of cancer and 34,041 healthy subjects. Concerning *CASP10* rs13006529, they included 3751 subjects and found that the T allele was associated with a 1.17-fold increased risk of cancer. Simultaneously, the other two *CASP10* polymorphisms, rs3900115 and rs13010627, were not associated with cancer risk. Moreover, by performing a stratified analysis, they observed a positive association of *CASP10* rs13006529*T carriers with breast cancer incidence (OR=1.17) [77]. In our study, we enrolled 5648 subjects and found no noteworthy association between this variant and cancer incidence.

Dysregulated apoptosis might lead to tumorigenesis [78]. In this respect, somatic or non-somatic mutations within caspase genes are frequent in a wide range of malignancies [79]. In 2019, Hashemi et al. showed that *CASP3* polymorphisms are associated with the overall risk of cancer [80]. One year later, Hashemi and colleagues performed a meta-analysis and showed that common SNPs within *CASP8*, including rs3769818, rs3769821, rs3769825, rs3834129, and rs1045485, are also correlated with susceptibility to cancer [68]. In 2013, Yan and colleagues reported that variations in *CASP7*, another caspase that contributed to cell proliferation and cytokine maturation, are involved in the pathogenesis of cancer [81]. The possible association between variations in other caspases and cancer risk is currently being investigated.

Heterogeneity partly determines the difficulty in drawing overall conclusions, and it might affect the results of our meta-analysis. Hence, our results should be interpreted with attention because of some limitations. This might happen because of differences in the genetic background of the subjects or allele frequencies between the studied populations. Moreover, the observed heterogeneity might be due to the lifestyle and age of cancer patients, dissimilar methods of diagnosis, and cancer types. On the other hand, most of the included studies were conducted on a limited number of populations. Cancer is a multifactorial disorder, and environmental factors play crucial roles in its susceptibility. Despite these limitations, the findings of the pooled analysis provided a conclusive estimate for the impact of *CASP9* and *CASP10* polymorphisms on cancer susceptibility.

Conclusion

In conclusion, our meta-analysis suggested that *CASP9* rs4645981 and rs1052571 polymorphisms are associated with overall cancer risk. However, more studies on larger populations are warranted to validate these associations.

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Declarations

Conflict of Interest The authors declare no competing interests.

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