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REVIEW ARTICLE

Survivin rs9904341 polymorphism significantly increased the risk of cancer: evidence from an updated meta-analysis of case–control studies

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Abstract

Aims Survivin, a member of inhibitor of apoptosis protein family, is involved in the regulation of cell cycle and apoptosis. Several studies inspected the association between survivin polymorphisms and the risk of various cancers, but the findings remain controversial. We conducted a meta-analysis intending to certify the association between survivin polymorphisms and cancer risk.

Methods All analyses were achieved using RevMan 5.3 software and STATA 14.1 software. Eligible studies were collected by comprehensive literature searching Web of Science, PubMed, Scopus, and Google scholar databases. Pooled estimates of odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the overall impact of survivin polymorphisms on cancer risk.

Results The overall analysis indicates that survivin rs9904341 polymorphism significantly increased the risk of cancer in homozygous codominant (OR 1.41, 95% CI 1.19–1.68, $p=0.0001$, CC vs GG), dominant (OR 1.22, 95% CI 1.07–1.40, $p=0.003$, CG+CC vs GG), recessive (OR 1.34, 95% CI 1.18–1.52, $p<0.0001$, CC vs CG+GG), and allele (OR 1.20, 95% CI 1.09–1.31, $p=0.0001$, C vs G) inheritance models tested. Stratified based on ethnicity revealed that rs9904341 variant significantly increased the risk of cancer in the Asian population. The findings did not support an association between rs1042489, rs2071214, rs8073069, and rs17878467 polymorphisms and risk of cancer.

Conclusions The current study suggests that the survivin rs9904341 polymorphism may be associated with the risk of cancer either overall or in the Asian population. However, further larger and well-designed studies are warranted to evaluate this association in detail.

Keywords Survivin · Polymorphism · Cancer · Meta-analysis

Introduction

Cancer, one of the main leading causes of morbidity and mortality, is a major serious public health problem worldwide [1]. Growing evidence proposed that interaction of various genetic loci and numerous environmental factors plays a role in cancer development [2]. Single nucleotide polymorphisms (SNPs), the common genetic variation in the human genome, are associated with the risk of cancer [3, 4].

The human survivin gene, also called BIRC5, is mapped to the chromosome 17 (17q25.3), encoding survivin [5]. Survivin protein belongs to the human inhibitors of apoptosis proteins (IAPs) family. Survivin, a 16.5 kDa protein, is the smallest member of IAPs [6, 7]. This family of anti-apoptotic proteins includes NAIP, c-IAP1, c-IAP2, XIAP, and survivin [8]. They prevent apoptosis by binding to the

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effector caspases and inhibiting their activities [8, 9]. IAPs are the central regulator of apoptosis [10]. These proteins have a key role in the course of carcinogenesis by increasing cell survival through inhibiting extrinsic and intrinsic apoptosis pathways, promoting accumulation of genetic changes, and increasing resistance to therapy [11]. It has been proposed that unlike other IAP members, survivin is highly expressed in most cancers, although it is rarely expressed in normal adult tissues [12]. As overexpression of survivin is involved in cancer development and metastasis by inhibiting apoptosis [13–15], the survivin polymorphisms may modulate susceptibility to cancer by affecting the survivin expression.

Survivin is polymorphic and several polymorphisms of the survivin gene have been characterized. Some of these are the rs8073069, rs17878467 and rs9904341 variants located in the promoter, the rs2071214 variant that is a missense one located in exon 5, and the rs1042489 variant located in the 3′ untranslated region (3′UTR) (Fig. 1).

Several studies have been conducted to assess the association between survivin polymorphisms and cancer susceptibility in diverse populations [16–55]. But, the findings of these studies are inconsistent. Therefore, we carried out an updated meta-analysis including those newly published articles to find out the impact of survivin rs9904341, rs1042489, rs2071214, rs8073069, and rs17878467 polymorphisms on cancer risk based on all available eligible studies at present.

Methods

Literature search

Relevant publications were identified through a comprehensive search in PubMed, Web of Science, Scopus, and Google Scholar databases using search strategy "cancer, carcinoma, tumor, neoplasms", "survivin or BIRC5" and "polymorphism or mutation or variant or rs9904341 or rs2071214". The last search was up to July 30, 2018.

Inclusion and exclusion criteria

To be eligible for inclusion in the quantitative analysis, the study should meet the following criteria: (1) original case–control studies that assessed the survivin polymorphism and cancer risk; (2) studies providing necessary information about genotype frequencies in both cases and controls. The exclusion criteria were: (1) conference abstract, case reports, reviews, meta-analysis, duplication data; (2) insufficient genotype information provided.

Data extraction

Two investigators independently extracted the relevant data from retrieved articles. The following data were collected from each study such as the first author, publication year, country, ethnicity of the participants, cancer type, source of control, genotyping methods, number of cases and controls, frequencies of genotypes and alleles in case and control groups and result of the HWE test (Table 1).

Statistical analysis

All statistical calculations were conducted by Revman 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and STATA 14.1 software (Stata Corporation, College Station, TX, USA). Hardy–Weinberg equilibrium (HWE) for control groups was tested by Chi square test. Pooled ORs and their 95% CIs for codominant, dominant, recessive, overdominant and the allelic genetic inheritance models were estimated. The *Z* test was employed to determine the significance of the pooled ORs, and a $p < 0.05$ was considered statistically significant.

The *Q*-test was used to evaluate the between-study heterogeneity. When $p > 0.1$ indicating lack of heterogeneity, a fixed-effect model was used; otherwise, the random-effects model was applied.

The potential publication bias was assessed by Begg's funnel plot inspection. The symmetry in plots implied no publication bias. The degree of asymmetry was measured by Egger's test and $p < 0.05$ was considered significant.

Fig. 1 The structure of survivin gene and the positions of polymorphisms analyzed in this meta-analysis

Table 1 Characteristics of the studies eligible for the meta-analysis

First author	Year	Country	Ethnicity	Cancer type	Source of control	Genotyping method	Case/control	Cases					Controls					HWE
								GG	GC	CC	G	C	GG	GC	CC	G	C	
Survivin rs9904341																		
Aminimoghaddam	2015	Iran	Asian	Endometrial cancer	HB	PCR-RFLP	58/55	26	32	0	84	32	38	14	3	90	20	0.284
Antonacopoulou	2010	Greece	Caucasian	Colorectal cancer	HB	TaqMan	163/132	63	84	16	210	116	66	50	16	182	82	0.184
Aynaci	2013	Turkey	Caucasian	Lung cancer	HB	PCR-RFLP	146/98	113	27	6	253	39	56	34	8	146	50	0.388
Bagheri	2017	Iran	Asian	Gastric cancer	HB	PCR-RFLP	101/101	38	42	21	118	84	48	42	11	138	64	0.692
Bayram	2011	Turkey	Caucasian	HCC	HB	PCR-RFLP	160/241	79	70	11	228	92	100	119	22	319	163	0.109
Bogdanovic	2017	Serbia	Caucasian	Urothelial carcinoma	HB	PCR-RFLP	92/82	54	31	7	139	45	26	45	11	97	67	0.220
Borbely	2007	Hungary	Caucasian	Cervical cancer	PB	PCR-RFLP	81/180	29	45	7	103	59	71	85	24	227	133	0.856
Borges	2010	Brazil	Mixed	Gastric cancer	HB	PCR-SSCP	47/57	20	18	9	58	36	21	28	8	70	44	0.784
Chen	2013	China	Asian	Prostate cancer	HB	TaqMan	665/710	150	319	196	619	711	205	331	174	741	679	0.079
Cheng	2008	China	Asian	Gastric cancer	PB	PCR-RFLP	96/67	20	38	38	78	114	31	28	8	90	44	0.667
El-Said	2016	Egypt	African	HCC	HB	TaqMan	60/30	29	19	12	77	43	15	11	4	41	19	0.403
Gazouli	2009	Greece	Caucasian	Colorectal cancer	HB	PCR-RFLP	312/362	68	131	113	267	357	123	163	76	409	315	0.110
Guo	2015	China	Asian	Lung cancer	HB	PCR-RFLP	104/104	20	49	35	89	119	30	51	23	111	97	0.880
Hsieh	2012	Taiwan	Asian	HCC	HB	TaqMan	135/496	37	64	34	138	132	110	242	144	462	530	0.663
Huang	2013	China	Asian	Bladder cancer	HB	PCR-RFLP	200/200	32	102	66	166	234	59	82	59	200	200	0.011
Jaiswal	2012	India	Asian	Bladder cancer	HB	PCR-RFLP	200/200	83	85	32	251	149	98	87	15	283	117	0.471
Jang	2008	Korea	Asian	Lung cancer	HB	FLHP	582/582	139	259	184	537	627	142	293	147	577	587	0.867
Javid	2015	India	Asian	Lung cancer	HB	PCR-RFLP	100/100	22	44	34	88	112	33	51	16	117	83	0.615
Karimian	2018	Iran	Asian	Prostate cancer	HB	PCR-RFLP	157/145	53	67	37	173	141	69	55	21	193	97	0.075
Kawata	2010	Japan	Asian	Bladder cancer	PB	PCR-RFLP	235/346	50	99	86	199	271	75	184	87	334	358	0.228
Kostic	2013	Serbia	Caucasian	Oral SCC	NA	PCR-RFLP	88/111	39	36	13	114	62	45	53	13	143	79	0.662
Kostic	2013	Serbia	Caucasian	Skin BCC	NA	PCR-RFLP	60/111	31	21	8	83	37	45	53	13	143	79	0.662
Li	2012	China	Asian	HCC	PB	PCR-RFLP	178/196	43	100	35	186	170	48	96	52	192	200	0.779
Li	2013	China	Asian	Colorectal cancer	PB	PCR-RFLP	275/270	42	123	110	207	343	55	138	77	248	292	0.633
Li	2018	China	Asian	Acute leukemia	HB	PCR-LDR	182/200	36	76	70	148	216	54	93	53	201	199	0.322
Liarmakopoulos	2013	Greece	Caucasian	Gastric cancer	HB	PCR-RFLP	62/480	18	44	26	80	96	163	216	101	542	418	0.063
Lin	2017	Taiwan	Asian	Urothelial cancer	HB	TaqMan	185/188	43	112	30	198	172	48	99	41	195	181	0.454
Lin	2017	Taiwan	Asian	Bladder cancer	HB	TaqMan	46/188	9	25	12	43	49	48	99	41	195	181	0.454
Ma	2011	China	Asian	Nasopharyngeal carcinoma	PB	TaqMan	844/1021	205	403	236	813	875	273	524	224	1070	972	0.357
Marques	2013	Portugal	Caucasian	Renal cell carcinoma	HB	PCR-RFLP	176/304	78	70	28	226	126	109	160	35	378	230	0.038
Qin	2012	China	Asian	Renal cell carcinoma	HB	TaqMan	710/760	172	345	193	689	731	215	385	160	815	705	0.610
Qin	2015	China	Asian	Pancreatic cancer	HB	PCR-RFLP	224/224	45	106	73	196	252	66	101	57	233	215	0.148
Radojevic-Skodric	2012	Serbia	Caucasian	Wilms tumor	HB	PCR-RFLP	59/82	36	19	4	91	27	26	45	11	97	67	0.220

Table 1 (continued)

First author	Year	Country	Ethnicity	Cancer type	Source of control	Genotyping method	Case/control	Cases					Controls					HWE
								GG	GC	CC	G	C	GG	GC	CC	G	C	
Rasool	2018	India	Asian	Breast cancer	HB	PCR-RFLP	190/200	33	108	49	174	206	55	105	40	215	185	0.429
Theodoropoulos	2010	Greece	Caucasian	Pancreatic cancer	PB	PCR-RFLP	80/160	25	28	27	78	82	57	67	36	181	139	0.062
Upadhyay	2010	India	Asian	Esophageal cancer	HB	PCR-RFLP	250/250	96	110	44	302	198	105	123	22	333	167	0.094
Wang	2009	Taiwan	Asian	Urothelial carcinoma	HB	PCR-RFLP	190/210	33	91	66	157	223	80	86	44	246	174	0.024
Weng	2012	Taiwan	Asian	Oral cancer	HB	TaqMan	439/424	119	218	102	456	422	94	204	126	392	456	0.507
Yamak	2014	Turkey	Caucasian	Colon cancer	HB	PCR-RFLP	60/45	16	35	9	67	53	25	16	4	66	24	0.542
Yang	2009	China	Asian	Esophageal SCC	HB	PCR-RFLP	221/268	55	108	58	218	224	63	124	81	250	286	0.249
Yang	2009	China	Asian	Gastric cancer	HB	PCR-RFLP	220/220	46	110	64	202	238	47	122	51	216	224	0.104
Yazdani	2012	Iran	Asian	PTC	HB	PCR-RFLP	123/131	48	56	19	152	94	70	54	7	194	68	0.407
Zahedi	2012	Iran	Asian	Endometrial cancer	HB	PCR-RFLP	31/30	10	21	0	41	21	19	9	2	47	13	0.524
First author	Year	Country	Ethnicity	Cancer type	Source of control	Genotyping method	Case/control	Cases					Controls					HWE
								TT	CT	CC	T	C	TT	CT	CC	T	C	
Survivin rs1042489																		
El-Said	2016	Egypt	African	HCC	HB	TaqMan	60/30	28	18	14	74	46	15	10	5	40	20	0.171
Guo	2015	China	Asian	Lung cancer	HB	PCR-RFLP	104/104	20	52	32	92	116	17	54	33	88	120	0.516
Hsieh	2012	Taiwan	Asian	HCC	HB	TaqMan	135/496	42	70	23	154	116	124	245	127	493	499	0.788
Jang	2008	Korea	Asian	Lung cancer	HB	FLHP	582/582	197	277	108	671	493	190	291	101	671	493	0.563
Karimian	2018	Iran	Asian	Prostate cancer	HB	PCR-RFLP	157/145	88	53	16	229	85	91	43	11	225	65	0.076
Li	2012	China	Asian	HCC	PB	PCR-RFLP	178/196	48	99	31	195	161	67	102	27	236	156	0.228
Weng	2012	Taiwan	Asian	Oral cancer	HB	TaqMan	439/424	156	204	79	516	362	109	208	107	426	422	0.698
First author	Year	Country	Ethnicity	Cancer type	Source of control	Genotyping method	Case/control	Cases					Controls					HWE
								AA	AG	GG	A	G	AA	AG	GG	A	G	
Survivin rs2071214																		
Guo	2015	China	Asian	Lung cancer	HB	PCR-RFLP	104/104	44	42	18	130	78	56	40	8	152	56	0.818
Hsieh	2012	Taiwan	Asian	HCC	HB	TaqMan	135/496	97	34	4	228	42	364	125	7	853	139	0.307
Jang	2008	Korea	Asian	Lung cancer	HB	FLHP	582/582	351	189	42	891	273	350	205	27	905	259	0.664
Karimian	2018	Iran	Asian	Prostate cancer	HB	PCR-RFLP	157/145	128	28	1	284	30	130	14	1	274	16	0.374
Kawata	2010	Japan	Asian	Bladder cancer	PB	PCR-RFLP	235/346	150	78	7	378	92	196	135	15	527	165	0.167
Wang	2013	China	Asian	PTC	HB	Sequencing	122/193	80	32	10	192	52	96	70	27	262	124	0.019
Weng	2012	Taiwan	Asian	Oral cancer	HB	TaqMan	439/424	285	137	17	707	171	304	114	6	722	126	0.197

Table 1 (continued)

First author	Year	Country	Ethnicity	Cancer type	Source of control	Genotyping method	Case/control	Cases					Controls					HWE
								GG	GC	CC	G	C	GG	GC	CC	G	C	
Survivin rs8073069																		
Guo	2015	China	Asian	Lung cancer	HB	PCR-RFLP	104/104	54	39	11	147	61	57	39	8	153	55	0.713
Jang	2008	Korea	Asian	Lung cancer	HB	FLHP	582/582	314	215	53	843	321	300	231	51	831	333	0.494
Li	2012	China	Asian	HCC	PB	PCR-RFLP	178/196	101	61	16	263	93	107	77	12	291	101	0.706
Li	2018	China	Asian	Acute leukemia	HB	PCR-LDR	182/200	91	71	20	253	111	107	75	18	289	111	0.359
Yamak	2014	Turkey	Caucasian	Colon cancer	HB	PCR-RFLP	67/45	38	29	0	105	29	13	18	14	44	46	0.181
Yang	2009	China	Asian	Esophageal SCC	HB	PCR-RFLP	221/268	81	102	38	264	178	123	121	24	367	169	0.455
First author	Year	Country	Ethnicity	Cancer type	Source of control	Genotyping method	Case/control	Cases					Controls					HWE
								CC	CT	TT	C	T	CC	CT	TT	C	T	
Survivin rs17878467																		
Hsieh	2012	Taiwan	Asian	HCC	HB	TaqMan	135/496	134	1	0	269	1	496	0	0	992	0	1.0
Jaiswal	2012	India	Asian	Bladder cancer	HB	PCR-RFLP	200/200	10	46	144	66	334	15	64	121	94	306	0.120
Li	2013	China	Asian	CRC	PB	PCR-RFLP	275/270	17	92	166	126	424	17	88	165	122	418	0.263
Radojevic-Skodric	2012	Serbia	Caucasian	Wilms tumor	HB	PCR-RFLP	59/82	37	18	4	92	26	41	37	4	119	45	0.228
Yamak	2014	Turkey	Caucasian	Colon cancer	HB	PCR-RFLP	68/45	21	39	8	81	55	35	7	3	77	13	0.013

Sensitivity analyses were executed by excluding a single study at a time to assess the relative influence on pooled estimate.

Results

Study characteristics

Overall, 42 articles met the selection criteria for quantitative data analysis [16–55]. The screening process is presented in detail in Fig. 2. Table 1 shows the characteristics and relevant data of the included studies.

Quantitative synthesis

For rs9904341, 43 case–control studies from 40 articles including 8,613 cancer cases and 10,361 controls were enrolled in the analysis. The findings revealed that rs9904341 variant significantly increased the risk of cancer in homozygous codominant (OR 1.40, 95% CI 1.17–1.67, $p = 0.0002$, CC vs GG), dominant (OR 1.22, 95% CI 1.07–1.40, $p = 0.003$, CG+CC vs GG), recessive (OR 1.34, 95% CI 1.18–1.52, $p < 0.0001$, CC vs CG+GG), and allele models (OR 1.20, 95% CI 1.09–1.31, vs G) (Table 2; Fig. 3).

Regarding rs1042489 variant, 7 studies including 1655 cases and 1977 controls proposed no significant association between the variant and risk of cancer. For rs2071214, the findings from 7 studies involving 1774 cases and 2290 controls showed that this variant was not associated with cancer risk. For rs8073069, the data from 6 studies including 1334 cases and 1395 controls suggested no significant association between this polymorphism and cancer risk. Concerning rs17878467 variant, the findings from 5 studies (737 cases and 1093 controls) did not support an association between this polymorphism and cancer risk (Table 2).

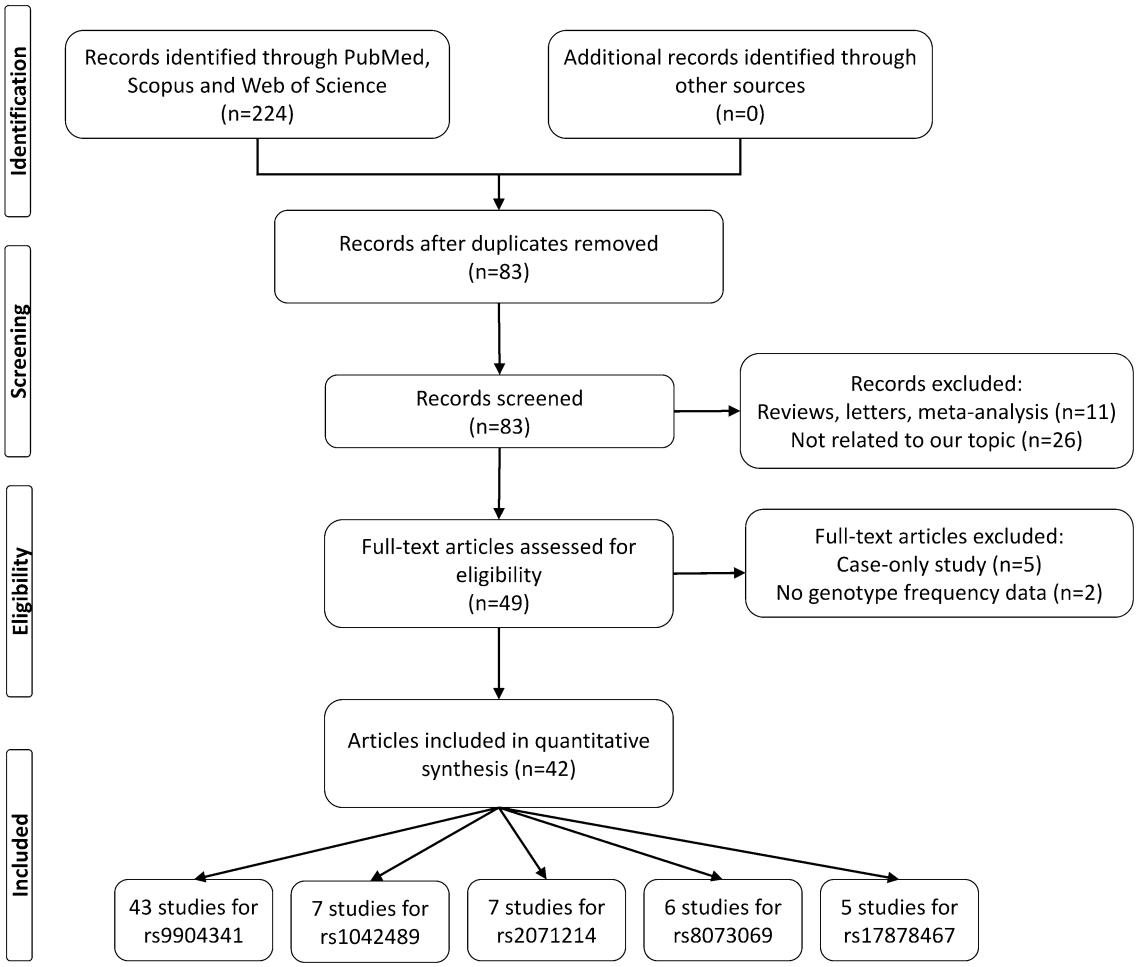

Fig. 2 Flow chart illustrating the article screening and selection process for this meta-analysis

Table 2 The pooled ORs and 95% CIs for the association between survivin polymorphisms and cancer susceptibility

Polymorphism	No.	Genetic model	Association test			Heterogeneity			Egger's test *p* value	Begg's test *p* value
			OR (95% CI)	*Z*	*p*	χ^2	I^2 (%)	*p*		
rs9904341	43	CG vs GG	1.13 (0.99–1.29)	1.87	0.06	126.25	68	< 0.00001	0.397	0.146
		CC vs GG	1.41 (1.19–1.68)	3.96	0.0001	133.83	69	< 0.00001	0.983	0.981
		CG+CC vs GG	1.22 (1.07–1.40)	2.96	0.003	155.08	73	< 0.00001	0.502	0.213
		CC vs CG+GG	1.34 (1.18–1.52)	4.55	< 0.0001	105.15	60	< 0.00001	0.969	0.875
		CG vs CC+GG	0.96 (0.87–1.06)	0.82	0.41	99.48	58	< 0.00001	0.385	0.457
		C vs G	1.20 (1.09–1.31)	3.89	0.0001	173.86	76	< 0.00001	0.937	0.762
rs1042489	7	CT vs TT	0.91 (0.78–1.06)	1.22	0.22	7.99	25	0.24	0.507	0.453
		CC vs TT	0.90 (0.62–1.31)	0.53	0.59	17.00	65	0.009	0.419	0.652
		CT+CC vs TT	0.93 (0.73–1.19)	0.57	0.57	13.76	56	0.03	0.493	0.652
		CC vs CT+TT	0.93 (0.71–1.21)	0.56	0.58	11.72	49	0.07	0.414	0.881
		CT vs CC+TT	0.98 (0.85–1.2)	0.36	0.72	2.62	0	0.85	0.351	0.293
		C vs T	0.96 (0.79–1.16)	0.44	0.66	18.78	68	0.005	0.402	0.652
rs2071214	7	AG vs AA	1.00 (0.78–1.29	0.030	0.98	15.89	62	0.01	0.683	0.453
		GG vs AA	1.35 (0.74–2.44)	0.98	0.33	16.78	64	0.01	0.959	0.652
		AG+GG vs AA	1.05 (0.79–1.38)	0.33	0.74	21.69	72	0.001	0.762	0.652
		GG vs AG+AA	1.37 (0.83–2.28)	1.22	0.22	12.77	53	0.05	0.979	0.881
		AG vs GG+AA	0.98 (0.79–1.21)	0.21	0.84	12.30	51	0.06	0.601	0.453
		G vs A	1.09 (0.84–1.40)	0.63	0.528	26.26	77	0.000	0.799	0.652
rs8073069	6	CG vs GG	0.97 (0.82–1.14)	0.41	0.68	5.04	1	0.41	0.829	0.348
		CC vs GG	1.22 (0.69–2.16)	0.69	0.49	16.87	70	0.005	0.489	0.327
		CG+CC vs GG	0.98 (0.74–1.29)	0.16	0.87	13.85	64	0.02	0.583	0.348
		CC vs CG+GG	1.25 (0.75–2.07)	0.85	0.39	14.32	65	0.01	0.513	0.624
		CG vs CC+GG	0.95 (0.81–1.10)	0.72	0.47	1.68	0	0.891	0.312	0.851
		G vs C	0.95 (0.70–1.29)	0.34	0.74	29.24	83	< 0.0001	0.436	0.348
rs17878467	5	CT vs CC	1.75 (0.60–5.10)	1.02	0.31	23.92	83	< 0.0001	0.153	0.042
		TT vs CC	1.46 (0.92–2.34)	1.60	0.11	3.75	20	0.29	0.424	0.497
		CT+TT vs CC	1.84 (0.68–4.99)	1.20	0.23	23.54	83	< 0.0001	0.108	0.042
		TT vs CT+CC	1.24 (0.96–1.60)	1.62	0.10	4.35	31	0.23	0.600	1.00
		CT vs CC+TT	1.30 (0.60–2.83)	0.66	0.51	26.94	85	< 0.00001	0.539	0.497
		T vs C	1.48 (0.86–2.54)	1.42	0.16	20.72	81	< 0.00001	0.508	0.174

Subgroup analysis results

Stratified analysis of survivin rs9904341 polymorphism was achieved by ethnicity and cancer type (Table 3). The subgroup analysis by ethnicity indicated that rs9904341 polymorphism significantly increased the risk of cancer in the Asian population but not in Caucasians. Also, the findings suggested that this variant significantly increased the risk of gastrointestinal cancer, digestive tract cancer, gastric cancer, colorectal cancer, bladder cancer, pancreatic cancer, renal cancer, prostate cancer, endometrial cancer, papillary thyroid carcinoma, nasopharyngeal carcinoma, breast cancer, and acute leukemia. While, rs9904341 variant was associated with protection against oral cancer, lung cancer and Wilms' tumor. No significant association was found between rs9904341 variant and risk of hepatocellular carcinoma, urothelial cancer, esophageal carcinoma, skin cancer, and cervical cancer (Table 3).

Heterogeneity and publication bias

Heterogeneity among the studies included in the meta-analysis is shown in Table 2. The findings showed that heterogeneity existed between some studies.

The potential publication bias was assessed using a Begg's funnel plot and Egger's linear regression test. As shown in Fig. 4, the shape of funnel plots was symmetrical and no publication bias was observed. The Egger's test also indicated that publication bias was not evident (Table 2).

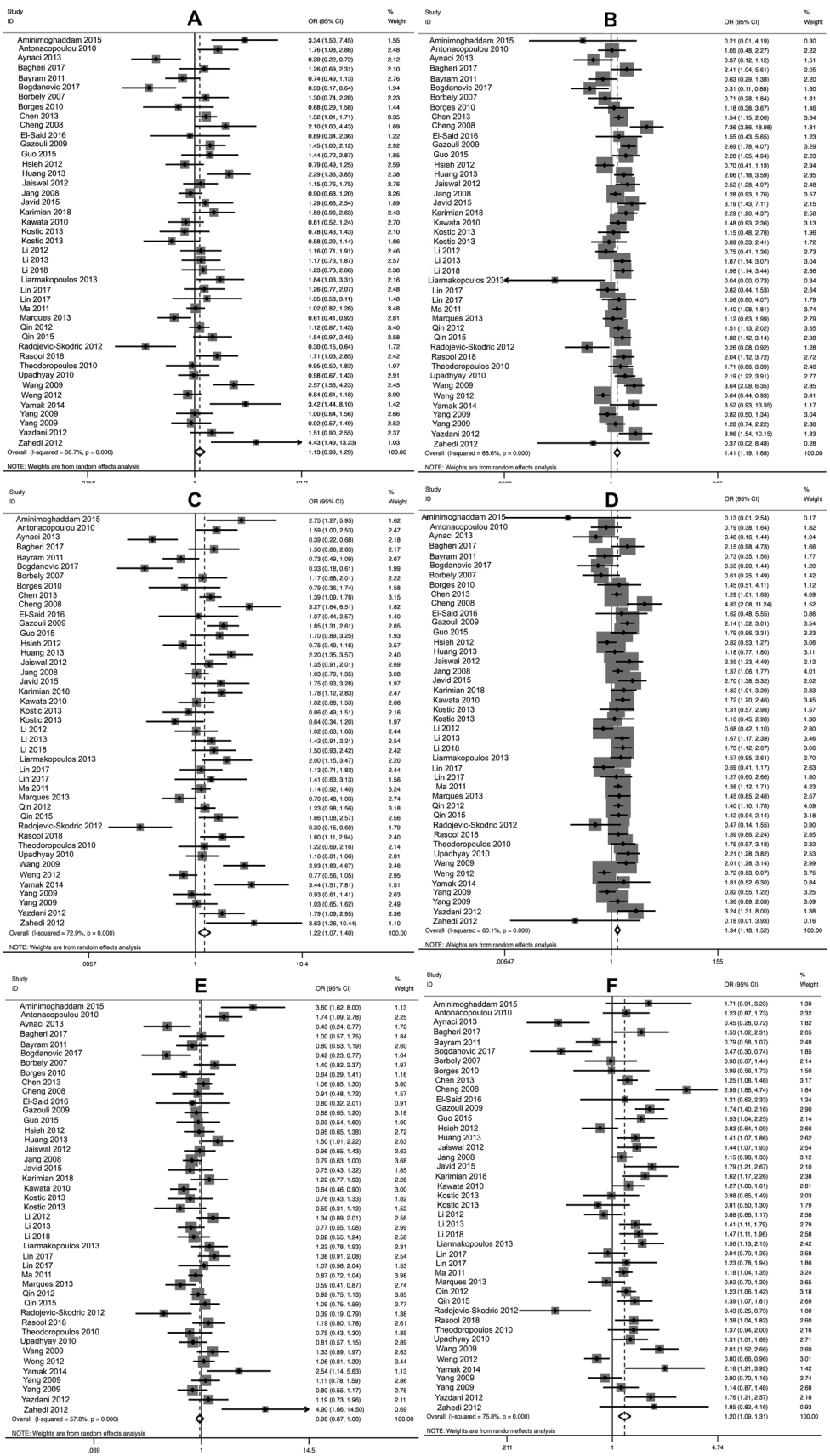

Fig. 3 The pooled ORs and 95% CIs for the association between survivin rs9904341 polymorphism and cancer susceptibility. The forest plot for relationship between survivin rs9904341 polymorphism and cancer susceptibility for CG vs GG **a**, CC vs GG **b**, CG+CC vs GG **c**, CC vs CG+GG **d**, CG vs CC+GG **e**, and C vs G **f**

Table 3 Stratified analysis of survivin rs9904341 polymorphism on cancer susceptibility

Parameters	No.	CG vs GG		CC vs GG		CG+CC vs GG		CC vs CG+GG		CG vs CC+GG		C vs G	
		OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Ethnicity													
Asian	28	1.24 (1.10–1.41)	0.0004	1.59 (1.33–1.91)	< 0.00001	1.37 (1.21–1.55)	< 0.00001	1.40 (1.21–1.61)	< 0.00001	1.01 (0.92–1.11)	0.83	1.29 (1.18–1.42	< 0.00001
Caucasian	13	0.87 (0.62–1.23)	0.43	0.88 (0.56–1.40)	0.59	0.91 (0.64–1.30)	0.62	1.12 (0.83–1.51)	0.44	0.82 (0.63–1.07)	0.14	0.96 (0.74–1.24)	0.76
Cancer type													
Gastrointestinal cancer	17	1.18 (1.00–1.40)	0.060	1.46 (1.06–1.99)	0.020	1.30 (1.07–1.56)	0.008	1.39 (1.10–1.75)	0.005	0.98 (0.86–1.12)	0.79	1.27 (1.09–1.48)	0.002
Digestive tract system	11	1.30 (1.05–1.61)	0.010	1.76 (1.17–2.62)	0.006	1.48 (1.18–1.87)	0.0007	1.62 (1.23–2.13)	0.0006	1.00 (0.83–1.20)	0.97	1.42 (1.19–1.69)	0.0001
Gastric cancer	5	0.78 (0.31–1.93)	0.59	1.12 (0.27–4.59)	0.87	1.52 (0.97–2.36)	0.07	1.87 (1.24–2.80)	0.003	1.04 (0.83–1.30)	0.71	1.51 (1.09–2.10)	0.01
Hepatocellular carcinoma	4	0.86 (0.67–1.11)	0.25	0.75 (0.53–1.04)	0.09	0.85 (0.65–1.05)	0.12	0.78 (0.59–1.05)	0.1	0.98 (0.77–1.25)	0.90	0.85 (0.73-1.00)	0.05
Lung cancer	4	0.89 (0.54–1.46)	0.63	1.46 (0.74–2.89)	0.28	1.03 (0.57–1.86)	0.93	1.49 (0.93–2.40)	0.1	0.73 (0.56–0.95)	0.02	1.11 (0.70–1.75)	0.65
Colorectal cancer	4	1.59 (1.15–2.21)	0.005	2.02 (1.33–3.08)	0.001	1.75 (1.35–2.27)	< 0.0001	1.62 (1.11–2.35)	0.01	1.20 (0.76–1.90)	0.43	1.54 (1.27–1.86)	< 0.0001
Bladder cancer	4	1.28 (0.81–2.02)	0.30	1.82 (1.35–2.46)	< 0.0001	1.41 (1.01–1.97)	0.04	1.54 (1.17–2.04)	0.002	0.98 (0.66–1.46)	0.93	1.12 (0.81–1.54)	0.49
Urothelial cancer	3	1.04 (0.35–3.08)	0.94	1.02 (0.26–3.99)	0.97	1.04 (0.32–3.35)	0.94	0.96 (041-2.26)	0.93	0.90 (0.52–1.54)	0.70	0.98 (0.46–2.09)	0.95
Oral cancer	2	0.83 (0.62–1.11)	0.83	0.67 (0.47–0.95)	0.02	0.79 (0.60–1.03)	0.08	0.85 (0.50–1.45)	0.56	0.99 (0.75–1.30)	0.93	0.83 (0.69–0.98)	0.03
Esophageal carcinoma	2	0.99 (0.74–132)	0.93	1.32 (0.51–3.46)	0.57	1.06 (0.80–1.38)	0.70	1.32 (0.50–3.5)	0.57	0.95 (0.70–1.29)	0.73	1.08 (0.75–1.56)	0.67
Panceatic cancer	2	1.28 (0.81–2.02)	0.29	1.82 (1.20–2.74)	0.004	1.48 (1.05–2.10)	0.03	1.52 (1.08–2.13)	0.02	0.96 (0.67–1.37)	0.82	1.39 (1.12–1.72)	0.003
Renal cancer	2	0.85 (0.47–1.53)	0.58	1.42 (1.10–1.84)	0.008	0.95 (0.55–1.65)	0.18	1.48 (1.07–2.05)	0.02	0.76 (0.50–1.17)	0.21	1.09 (0.82–1.44)	0.57
Prostate cancer	2	1.37 (1.09–1.73)	0.008	1.69 (1.21–2.35)	0.002	1.47 (1.18–1.82)	0.0005	1.37 (1.05–1.78)	0.02	1.08 (0.89–1.31)	0.42	1.25 (1.08–1.44)	0.002
Endometrial cancer	2	3.69 (1.93–7.04)	< 0.0001	0.27 (0.03–2.40)	0.24	1.95 (0.80–4.76)	0.14	0.15 (0.02–1.29)	0.08	4.01 (2.11–7.63)	< 0.0001	1.77 (1.07–2.91)	0.03
Skin cancer	1	0.58 (0.29–1.14)	0.11	1.15 (0.48–1.78)	0.75	0.64 (0.34–1.20)	0.16	1.16 (0.45–2.98)	0.76	0.59 (0.31–1.33)	0.11	0.97 (0.61–1.03)	0.08
PTC	1	1.51 (0.90–2.55)	0.12	3.96 (1.54–10.15)	0.004	1.79 (1.09–2.95)	0.02	0.18 (0.01–3.930	0.28	1.19 (0.73–1.96)	0.49	1.17 (0.53–2.57)	0.69

Table 3 (continued)

Parameters	No.	CG vs GG		CC vs GG		CG+CC vs GG		CC vs CG+GG		CG vs CC+GG		C vs G	
		OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Nasopharyngeal carcinoma	1	1.02 (0.82–1.28)	0.83	1.40 (1.08–1.81)	0.01	1.14 (0.92–1.40)	0.23	1.38 (1.12–1.71)	0.003	0.87 (0.72–1.02)	0.12	0.99 (0.67–1.47)	0.97
Wilms tumor	1	0.30 (0.15–0.64)	0.002	0.26 (0.08–0.92)	0.04	0.30 (0.15–0.60)	0.0007	1.35 (0.94–1.93)	0.10	0.39 (0.19–0.79)	0.008	0.43 (0.25–0.73)	0.002
Cervical cancer	1	1.26 (0.69–2.31)	0.45	0.71 (0.28–1.84)	0.49	1.17 (0.68–2.01)	0.58	0.61 (0.25–1.49)	0.28	1.40 (0.82–2.37)	0.21	0.98 (0.67–1.44)	0.91
Breast cancer	1	1.71 (1.03–2.85)	0.04	2.04 (1.12–3.72)	0.02	1.80 (1.11–2.94)	0.02	1.39 (0.86–2.240)	0.17	1.19 (0.80–1.78)	0.39	1.37 (0.94–2.00)	0.11
Acute leukemia	1	1.23 (0.73–2.06)	0.44	1.98 (1.14–3.44)	0.02	1.50 (0.93–2.42)	0.10	1.73 (1.12–2.67)	0.01	0.82 (0.55–1.24)	0.35	1.47 (1.11–1.96)	0.008

Sensitivity analysis

We performed a sensitivity analysis to assess the effect of a specific publication on the overall estimate. The sensitivity analysis revealed that the elimination of an individual study in turn did not change the OR effect of the combined effect, which suggested that the pooled results was stable and reliable in the meta-analysis (Fig. 5).

Discussion

Apoptosis or programmed cell death is a physiological mechanism of cell death. The regulation of apoptosis is critical for proper development and function of multicellular organisms. Defects in the apoptosis machinery may lead to various diseases, including cancer [56]. Survivin, a potent anti-apoptosis factor, is a member of the IAPs [57]. Survivin plays a role in cancer cell survival and is overexpressed in most common types of cancers [58]. It has been proposed that mutation in the promoter region of survivin gene may lead to the overexpression of survivin in cancer cells [59]. It has been shown that the −31G>C polymorphism (rs9904341) located in the promoter region of survivin gene correlated with gene expression. The −31C allele has significantly high activity compared to − 31G allele [60].

In the present meta-analysis, we estimated the association between the survivin gene polymorphisms and cancer risk based on 43 eligible case–control studies [16–55]. Pooled risk estimates revealed that survivin rs9904341 polymorphism was significantly associated with an increased risk of overall cancer. Stratified analysis proposed that this variant significantly increased the risk of gastric cancer, colorectal cancer, bladder cancer, pancreatic cancer, renal cancer, prostate cancer, endometrial cancer, papillary thyroid carcinoma, nasopharyngeal carcinoma, breast cancer, and acute leukemia. While, the variant was associated with protection against oral cancer, lung cancer and Wilms' tumor. The variant was not associated with the risk of hepatocellular carcinoma, urothelial cancer, esophageal carcinoma, skin cancer, and cervical cancer. A met-analysis performed by Zhu et al. [61] aimed to determine the relationship between survivin polymorphisms and the cancer susceptibility. In agreement to our findings, the data from 26 studies proposed that rs9904341 variant significantly increased the risk of cancer. Stratified analysis by cancer types revealed that the variant increased the risk of colorectal cancer, while there was no significant association between this variant and esophageal cancer risk. The variant significantly decreased the risk of hepatocellular carcinoma.

For the survivin rs2071214, pooled analysis from five studies indicated a significant association between this variant and an increased cancer risk [61]. Our meta-analysis

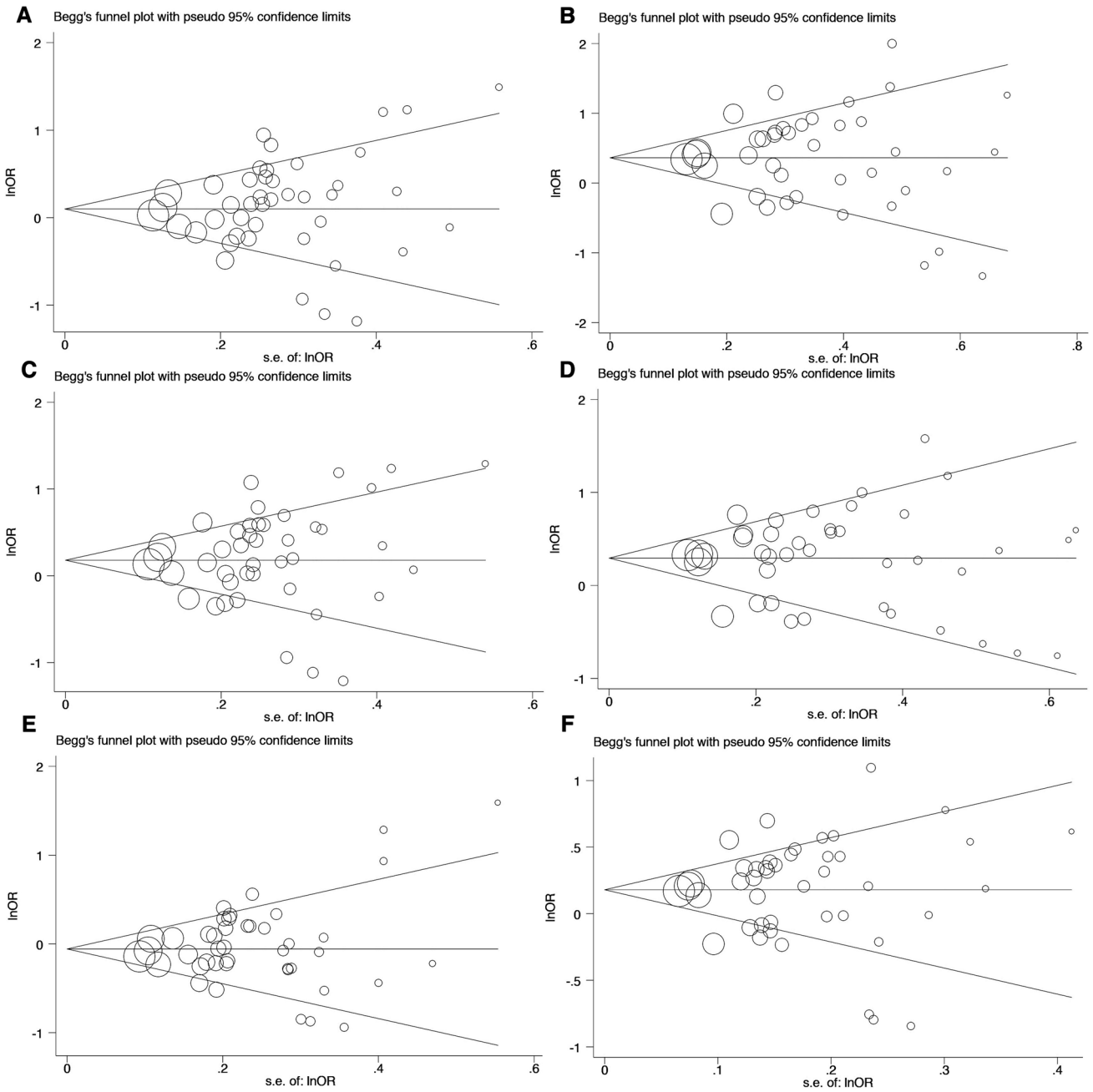

Fig. 4 The funnel plot for the test of publication bias for survivin rs9904341 polymorphism. The funnel plot for CG vs GG **a**, CC vs GG **b**, CG+CC vs GG **c**, CC vs CG+GG **d**, CG vs CC+GG **e**, and C vs G **f**

from seven studies did not support an association between rs2071214 variant and cancer risk. For the survivin rs17878467, they found that this variant significantly decreased the risk of cancer [61]. While our data from five studies did not support an association between the variant and risk of cancer. Regarding rs8073069 variant, they observed that this variant significantly increased the risk of cancer ($n=3$) [61]. In contrast, we found no significant association between the variant and risk of cancer ($n=6$).

In a meta-analysis from 13 studies, Srivastava et al. [62] have found that rs9904341 variant significantly increased the risk of overall cancer. Quin et al. [63] performed a meta-analysis to examine the relationship between rs9904341variant and the risk of overall cancer. They enrolled 29 studies with 7,473 cancer cases and 9086 controls and found that this variant significantly increased the risk of overall cancer.

Zhou et al. [64] conducted a meta-analysis of the association between survivin rs9904341 (− 31 G/C)

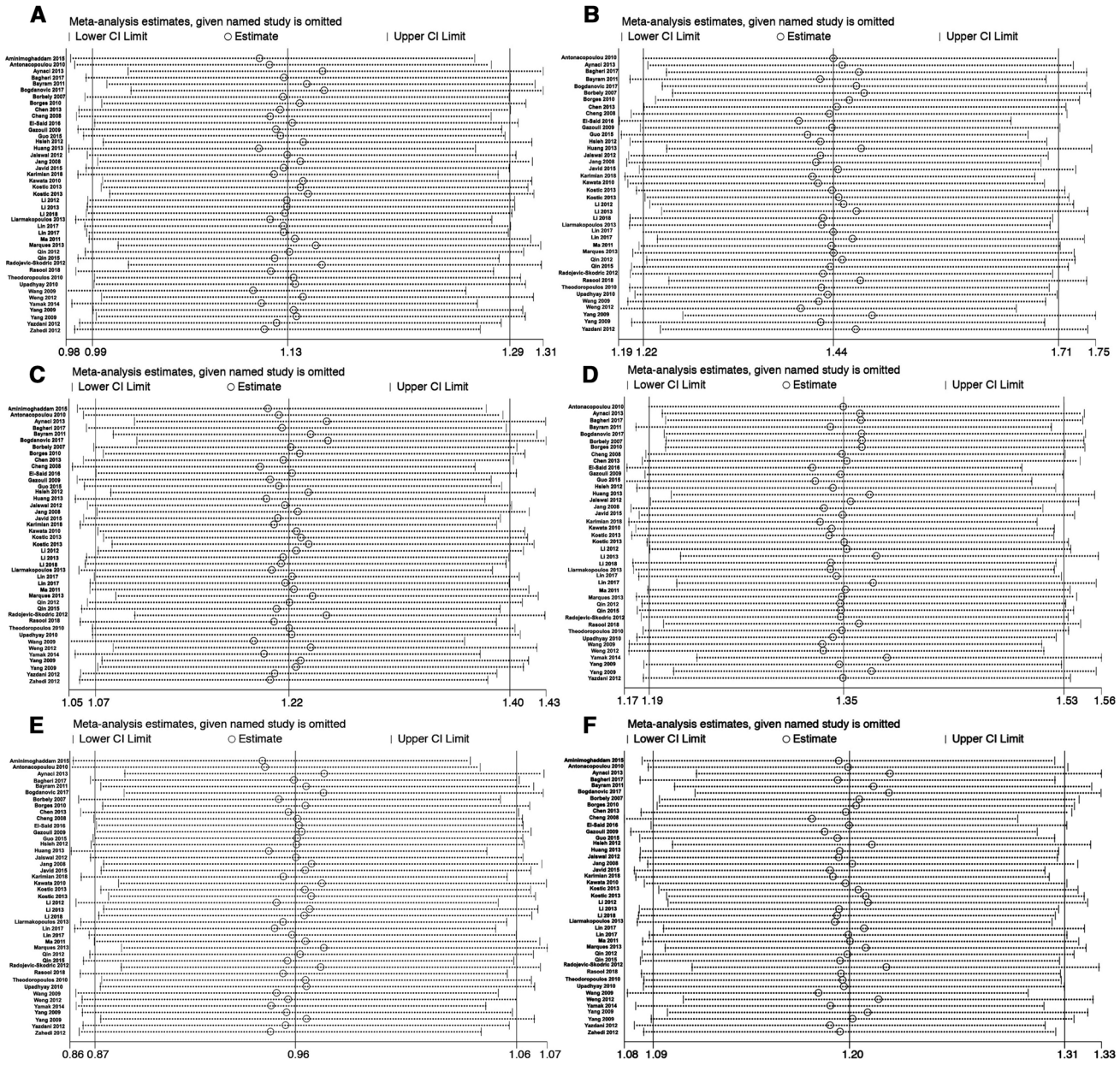

Fig. 5 Sensitivity analyses for studies on survivin rs9904341 polymorphism using different genetic models. Sensitivity analyses for CG vs GG **a**, CC vs GG **b**, CG+CC vs GG **c**, CC vs CG+GG **d**, CG vs CC+GG **e**, and C vs G **f**

polymorphism and risk of colorectal cancer. They enrolled six case–control studies and found that the variant significantly increased the risk of colorectal cancer. The findings is agreement with our stratified analysis by cancer types.

The meta-analysis performed by Liu et al. [65] from nine studies revealed that survivin rs9904341 polymorphism significantly increased the risk of gastrointestinal tract cancer. Our findings from 11 studies are in agreement with this finding. Relative larger sample sizes in our meta-analysis compared to polished meta-analysis increase statistical power.

Survivin, a member of IAP family, is implicated in inhibiting apoptosis and promoting cell proliferation and cancer development. Overexpression of survivin has been reported to be related with a poor prognosis of several cancers including glioma [66], renal cell cancer [67], esophageal cancer [68], breast cancer [69], gastric cancer [70, 71], ovarian cancer [72], laryngeal cancer [73], and colorectal cancer [74–76].

There are some limitations that need to be noted in our meta-analysis. First, heterogeneity existed among studies. The heterogeneity maybe derived from the difference

of ethnicity, cancer type and source of control. Second, gene–environmental interactions were not evaluated due to the lack of relevant data across the comprised studies. Gene–environmental interactions may alter cancer risk. Finally, the small sample sizes of studies for rs1042489, rs2071214, rs8073069, rs17878467 variants as well as subgroup analysis cause low power of data, though we have pooled all published studies.

In summary, our meta-analysis provided an evidence of the association between survivin rs9904341polymorphism and increased risk of cancer. Concurrently, the same results were obtained in stratified analysis of ethnicity in the Asian population, which suggests that the increased risk might be ethnicity specific. Further studies with larger sample sizes focusing on cancer types or ethnicities should be done to confirm the findings.

Compliance with ethical standards

Conflict of interest The authors have declared that no competing interests exist.

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