

## Association of PDCD6 polymorphisms with the risk of cancer: Evidence from a meta-analysis

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### ABSTRACT

**This study was designed to evaluate the relationship between Programmed cell death protein 6 (PDCD6) polymorphisms and cancer susceptibility. The online databases were searched for relevant case-control studies published up to November 2017. Review Manage (RevMan) 5.3 was used to conduct the statistical analysis. The pooled odds ratio (OR) with its 95% confidence interval (CI) was employed to calculate the strength of association. Overall, our results indicate that PDCD6 rs3756712 T>G polymorphism was significantly associated with decreased risk of cancer under codominant (OR = 0.82, 95%CI = 0.70–0.96,  $p = 0.01$ , TG vs TT; OR = 0.53, 95%CI = 0.39–0.72,  $p < 0.0001$ , GG vs TT), dominant (OR = 0.76, 95%CI = 0.66–0.89,  $p = 0.0004$ , TG+GG vs TT), recessive (OR = 0.57, 95%CI = 0.43–0.78,  $p = 0.0003$ , GG vs TT+TG), and allele (OR = 0.76, 95%CI = 0.67–0.86,  $p < 0.00001$ , G vs T) genetic model. The finding did not support an association between rs4957014 T>G polymorphism of PDCD6, and different cancers risk.**

### INTRODUCTION

Cancer is a major public health burden, with an estimate of 14.1 million new cancer cases and 8.2 million cancer-related deaths occurred globally in 2012 [3]. In 2018, 1,735,350 new cancer cases and 609,640 cancer deaths are projected to occur in the United States. It has been reported that over the past decade, the rate of incidence (2005–2014) was nearly linear and without any

changes in women, and declined by approximately 2% annually in men, while the rate of cancer death (2006–2015) was declined by about 1.5% annually in both men and women [32]. It is estimated that in 2017, 1,688,780 new cancer cases was diagnosed and 600,920 cancer deaths are estimated to occurred in the United States [31]. Although significant progress has been reached in understanding the mechanism and pathogenesis of different types of cancers, the exact etiology is still not completely

understood. Growing evidences indicate that cancer is a multifactorial disease caused by genetic background and environmental interactions [4, 8].

Apoptosis, also known as programmed cell death, is involved in physiological cell death [11]. Many factors contribute in the apoptotic pathway, including caspases, pro- and anti-apoptotic Bcl2 family members, and mitochondrial pro-apoptotic proteins [5, 6, 22]. Defects in the apoptosis machinery may lead to serious disease including cancer, autoimmune disease and drug resistance in tumors [5, 7, 26].

Programmed cell death protein 6 (*PDCD6*), located on chromosome 5p15.33 contains 43351 bp, is also known as apoptosis-linked gene-2 (*ALG-2*). *PDCD6* gene encodes a 22 kDa calcium-binding protein comprising five serially repetitive EF-hand structures. This protein is one of the prototypic members of the penta-EF-hand protein family. Initially, *PDCD6* was considered as a pro-apoptotic protein contributing to T-cell receptor-, Fas-, and glucocorticoid- induced programmed cell death [30, 12], as well as endoplasmic reticulum stress induced apoptosis during organ formation [25, 18]. In recent years, some *PDCD6*-interacting proteins have been identified, including Peflin [14], Alix [21], Fas [12] and Annexin XI [28]. However none of them regulates *PDCD6* activity, and such factor yet awaits to be identified. Alix and *PDCD6* interaction with procaspase-8 potentiated cell death induction via tumor necrosis factor receptor 1 (TNFR1) [19]. Several studies have examined the expression of *PDCD6* in clinical tumor tissues or cell lines, and found that *PDCD6* has opposing effects in different tumors. *PDCD6* expression was upregulated in tumor tissue samples from lung, breast, colon cancer, and ovarian cancer, which suggested that *PDCD6* might be involved in maintenance of cellular viability [15, 10, 17, 33, 24]. In contrast, decreased *PDCD6* expression was detected in non-small cell lung cancer (NSCLC), gastric cancer and HeLa cells [38, 40].

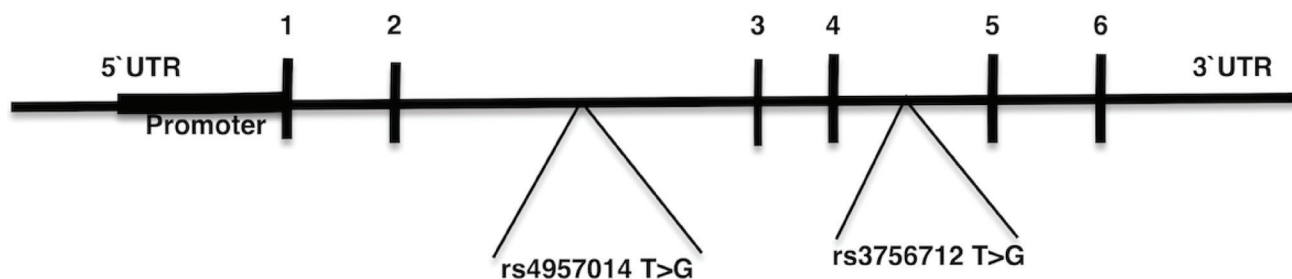
Recently, it has been shown that that miR-124-3p attenuated tumor metastasis by inhibiting *PDCD6* expression, and that the miR-124-3p/*PDCD6* signaling

axis could potentially be a therapeutic target for patients with advanced breast cancer [43]. Another study showed that the over-expression of miR-124 suppressed *PDCD6* expression, inhibited cell proliferation, migration and invasion, and induced apoptosis in SKOV3 and OCVAR3 cells *in vitro* [41]. Furthermore it has been proposed that miR-183 may function as an oncogene that may increase childhood acute myeloid leukemia (AML) cell proliferation by targeting *PDCD6* [37].

Previous studies inspecting the association between *PDCD6* gene polymorphisms and cancer indicated inconclusive and contradictory results [9, 45, 44, 42]. Hence, we have performed a meta-analysis on all the published case-control studies to evaluate the association of *PDCD6* rs3756712 T>G and rs4957014 T>G gene polymorphisms with the risk of cancer. Maps of the human *PDCD6* gene with polymorphisms positions is illustrated in Figure 1.

## METHODOLOGY

A comprehensive search in PubMed, Web of Science, Scopus, and Google Scholar databases was performed for all articles describing an association between *PDCD6* polymorphism and cancer risk published up to November 2017 without language restriction. The search strategy was “cancer, carcinoma, tumor, neoplasm”, “*PDCD6*, programmed cell death 6”, and “polymorphism, mutation, variant”. Figure 2 summarized the process of identifying eligible studies. Relevant studies, eligible for the meta-analysis must meet the following criteria: 1) Original case-control studies of the correlation between the *PDCD6* polymorphism and cancer; 2) studies provided sufficient information of the genotype frequencies of *PDCD6* polymorphism in both cases and controls; 3) the studies have not repeated reports in the same population. The criteria for exclusion were: 1) the articles that describe case reports, reviews, overlapped data, animal or mechanism studies for *PDCD6* polymorphism and cancer; 2) no genotype frequency or genotype information were provided for *PDCD6* polymorphism and cancer; 3) insufficient information for data extraction.



**Figure 1: Map of the human *PDCD6* gene with polymorphisms positions indicated.** Exons 1–6 are numbered and represented by black boxes. Both of the rs3756712 T>G and rs4957014 T>G variants positioned in intron region.

## Data extraction

Extraction of the data has been conducted by two independent scientists. The data were collected from each study including the first author's name, publication year, ethnicity of participants, the sample size, and the genotype and allele frequencies of cases and controls.

## Statistical analysis

Meta-analysis was carried out using Revman 5.3 software, which was provided by the Cochrane Collaboration (Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014) and STATA 14.1 software (Stata Corporation, College Station, TX, USA). All of the data in the studies are dichotomous data, which has been expressed as odds ratios (ORs) with 95% confidence intervals (CIs) to assess the association between the polymorphisms and cancer. Hardy-Weinberg equilibrium (HWE) for each study was determined by the chi-square tests of control group data. Odds ratios (ORs) and 95% confidence intervals (CIs) were pooled to evaluate the association between the polymorphisms and risk of cancer. For each polymorphism the ORs were calculated for dominant, codominant, recessive, over-dominant, and allele genetic models. Heterogeneity

also assessed using the  $I^2$  statistic, interpreted as the proportion of the total variation contributed by inter-study variation, and the Cochran chi-square  $Q$ -test, with a significance level of  $P < 0.10$  and  $I^2 > 50\%$ . When significant heterogeneity values were returned, the random-effects model (the DerSimonian and Laird method) was used to estimate pooled ORs. Otherwise, the fixed-effects model (the Mantel-Haenszel method) was employed. The significance of the pooled OR was assessed by the  $Z$ -test, and  $P < 0.05$  was considered to be statistically significant.

Publication bias was evaluated by funnel plot. The degree of asymmetry was measured using Egger's linear regression test;  $p < 0.05$  was considered significant publication bias [2]. The characteristics and relevant data of the included studies are shown in Table 1. The genotypes of *PDCD6* polymorphisms in controls were all in accordance with HWE ( $P > 0.05$ ) except for Zhou *et al.* [45] (Table 1).

## RESULTS

### Association of *PDCD6* rs3756712 T>G and rs4957014 T>G polymorphisms and cancer risk

Four studies [42, 45, 44, 9] reported the association between rs3756712 and rs4957014 polymorphisms and

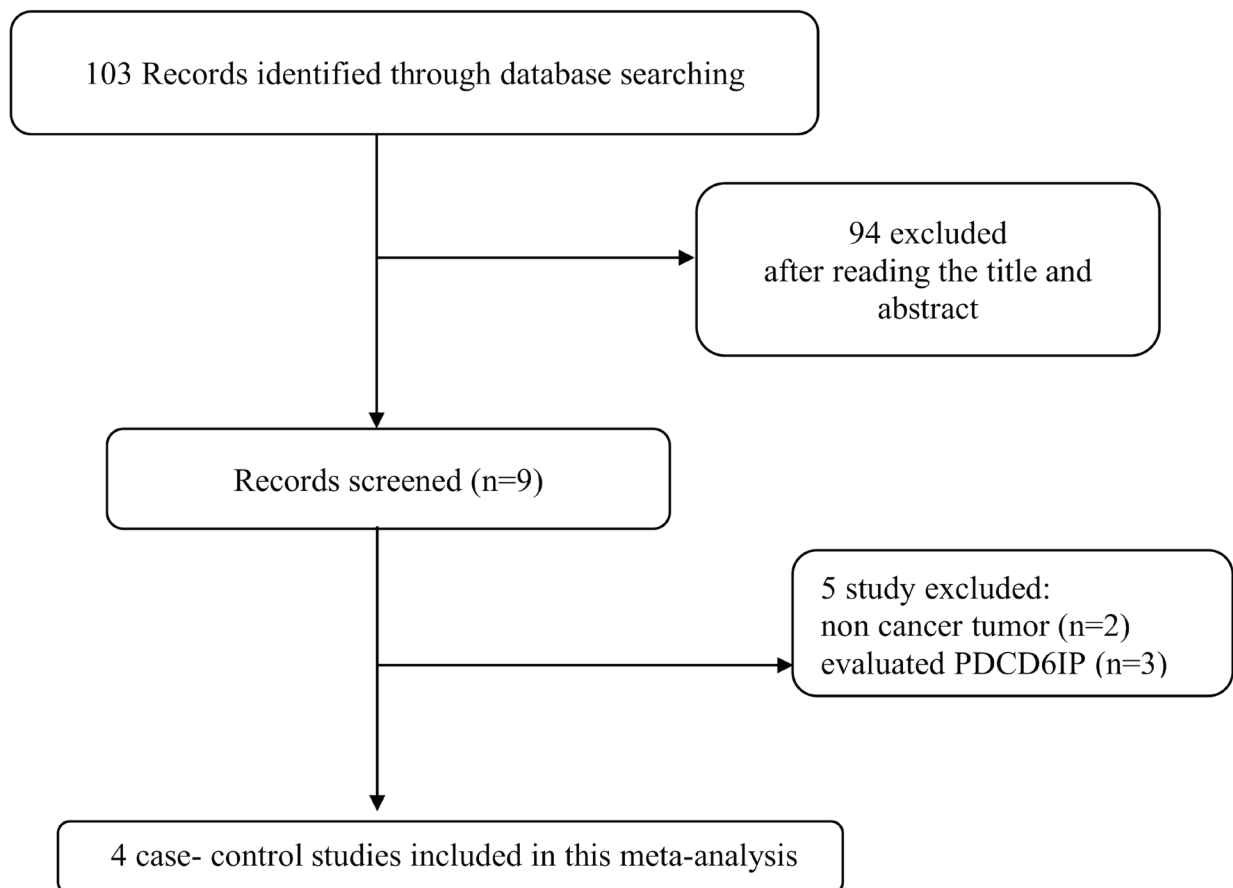


Figure 2: Flow chart of literature screening and selection in the meta-analysis.

**Table 1: Distribution information of genotypes and alleles of all studies included in the meta-analysis for rs3756712 T>G and rs4957014 T>G polymorphisms of programmed cell death 6 (PDCD6)**

Author	Year	Country	Ethnicity	Cancer type	Source of control	Genotyping method	Case/control	cases					Controls					HWE
								TT	GT	GG	T	G	TT	GT	GG	T	G	
rs3756712								TT	GT	GG	T	G	TT	GT	GG	T	G	
Yuan	2017	China	Asian	Endometrial Cancer	HB	PCR-RFLP	238/518	153	70	15	376	100	290	184	44	764	272	0.060
Zhou	2015	China	Asian	Cervical squamous cell carcinoma	HB	PCR-RFLP	328/541	202	109	17	513	143	298	195	48	791	291	0.053
Zhou	2014	China	Asian	Bladder cancer	HB	PCR-RFLP	332/509	214	101	17	529	135	279	183	47	741	277	0.037
He	2012	China	Asian	Lung cancer	HB	PCR-RFLP	302/306	168	120	14	456	148	168	111	27	447	165	0.167
rs4957014								TT	GT	GG	T	G	TT	GT	GG	T	G	
Yuan	2017	China	Asian	Endometrial Cancer	HB	PCR-RFLP	238/518	83	131	24	297	179	234	231	53	699	337	0.720
Zhou	2015	China	Asian	Cervical squamous cell carcinoma	HB	PCR-RFLP	328/541	130	142	56	402	254	243	246	52	732	350	0.365
Zhou	2014	China	Asian	Bladder cancer	HB	PCR-RFLP	332/509	170	125	37	465	199	229	232	48	690	328	0.325
He	2012	China	Asian	Lung cancer	HB	PCR-RFLP	302/306	155	124	23	434	170	134	136	36	404	208	0.868

HB, hospital based.

**Table 2: Meta-analysis of the association between PDCD6 rs3756712 T>G and rs4957014 T>G polymorphisms and cancer risk**

SNP	Genetic model	OR	95%CI	<i>p</i>	Heterogeneity I <sup>2</sup> (%)	Egger's test <i>P</i>	Begg's test <i>P</i>
rs3756712							
	TG vs TT	0.82	0.70–0.96	0.01	23	0.656	1.00
	GG vs TT	0.53	0.39–0.72	<0.0001	0	0.759	1.00
	TG+GG vs TT	0.76	0.66–0.89	0.0004	7	0.477	0.497
	GG vs TT+TG	0.57	0.43–0.78	0.0003	0	0.877	0.497
	TG vs TT+GG	0.88	0.75–1.02	0.09	28	0.729	0.497
	G vs T	0.76	0.67–0.86	<0.00001	0	0.448	1.00
rs4957014							
	TG vs TT	0.99	0.70–1.40	0.97	79	0.661	0.497
	GG vs TT	1.12	0.67–1.89	0.66	77	0.190	0.174
	TG+GG vs TT	1.02	0.73–1.44	0.90	81	0.865	0.497
	GG vs TT+TG	1.12	0.70–1.78	0.64	74	0.018	0.042
	TG vs TT+GG	0.96	0.71–1.31	0.82	77	0.570	1.00
	G vs T	1.04	0.80–1.34	0.79	81	0.373	0.174

cancer. As shown in Figure 3 and Table 2, the results showed that *PDCD6* rs3756712 T>G polymorphism was significantly associated with decreased risk of cancer under codominant (OR = 0.82, 95%CI = 0.70–0.96, *p* = 0.01, TG vs TT; OR = 0.53, 95%CI = 0.39–0.72, *p* < 0.0001, GG vs TT), dominant (OR = 0.76, 95%CI = 0.66–0.89, *p* = 0.0004, TG+GG vs TT), recessive (OR = 0.57, 95%CI = 0.43–0.78, *p* = 0.0003, GG vs TT+TG), and allele (OR = 0.76, 95%CI = 0.67–0.86, *p* < 0.00001,

G vs T) genetic model. Regarding rs4957014 T>G polymorphism of *PDCD6*, the finding did not support an association between rs4957014 T>G polymorphism and cancer risk (Figure 4 and Table 2).

### Heterogeneity and publication bias

Heterogeneity of the included studies concerning each polymorphism is shown in Table 2. A funnel plot was



PDCD6 rs3756712

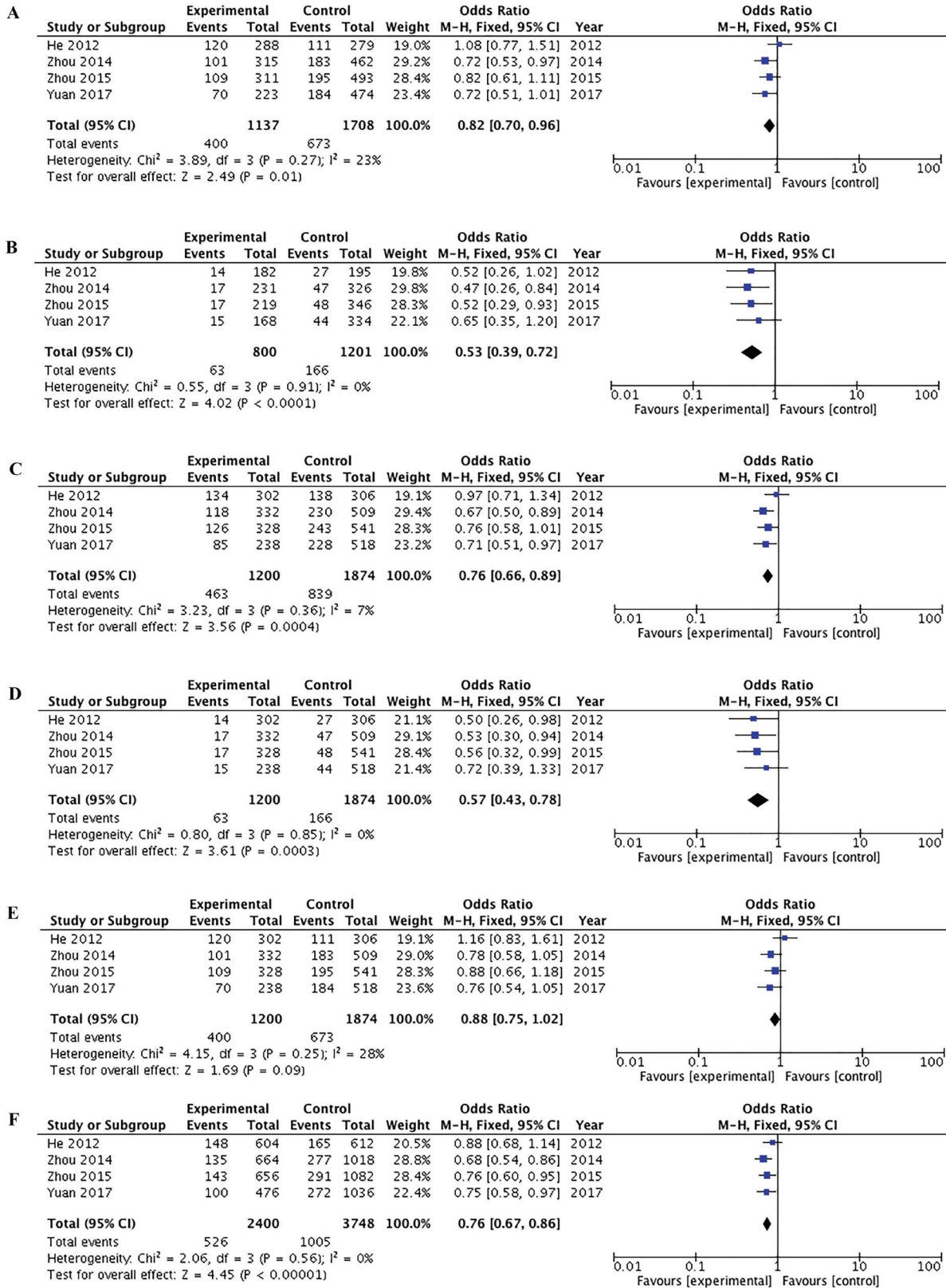
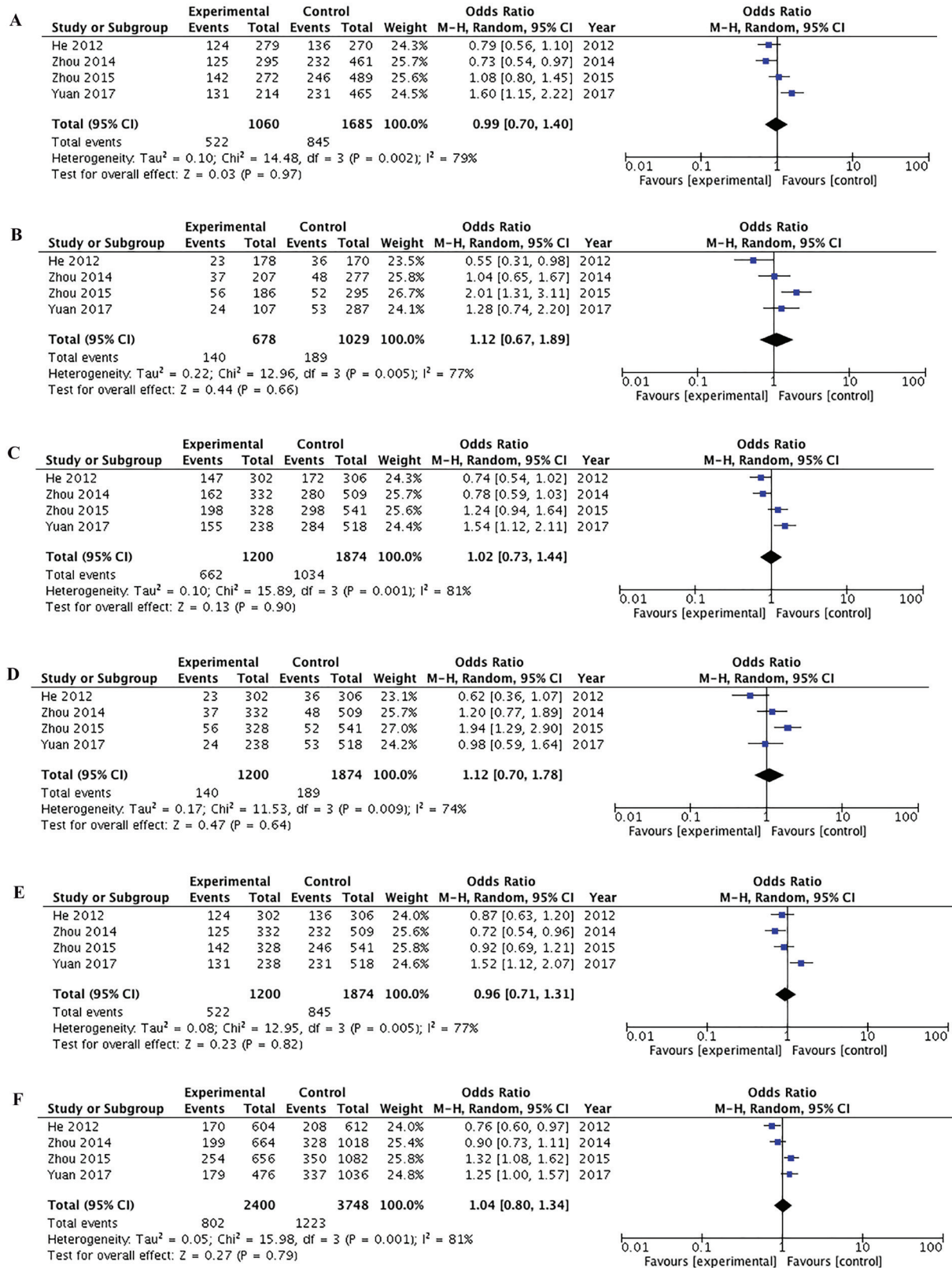


Figure 3: Forest plots of the association between cancer risk and the rs3756712 T>G polymorphism in the overall study population under the following models. (A) TG vs TT, (B) GG vs TT, (C) TG+GG vs TT, (D) GG vs TT+TG, (E) TG vs TT+GG, and (F) G vs T.

## PDCD6 rs4957014



**Figure 4: Forest plots of the association between cancer risk and the rs4957014 T>G polymorphism in the overall study population under the following models. (A) TG vs TT, (B) GG vs TT, (C) TG+GG vs TT, (D) GG vs TT+TG, (E) TG vs TT+GG, and (F) G vs T.**

generated as a visual aid to detect risk of publication bias (Figures 5 and 6). Regarding rs3756712 variant, Egger's linear regression analysis suggested no publication bias for this meta-analysis of the codominant, dominant, recessive, overdominant and allele model (all *P*-values for bias > 0.05). For rs4957014 polymorphism, the findings indicated that the publication bias exist only for recessive model (Table 2).

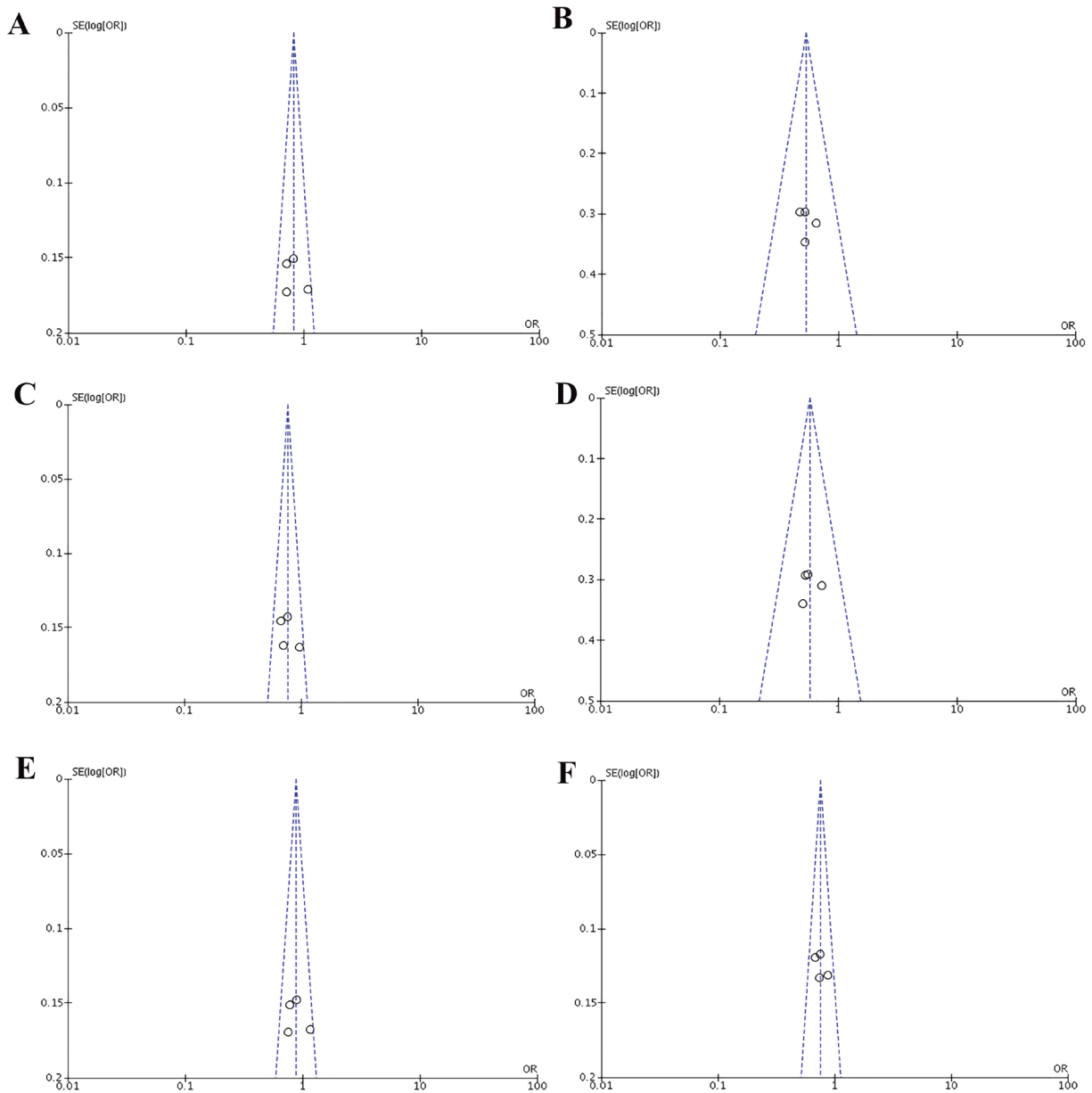
### Sensitivity analysis

Sensitivity analysis was done using the method of eliminating studies one by one to verify whether our results

were influenced by each included study. For rs3756712 variant, the pooled ORs were not considerably altered except in codominant heterozygous model (TG vs TT) and overdominant (TG vs TT+GG) model (Figure 7). Regarding rs4957014 variant, the pooled ORs altered only in overdominant model (Figure 8). Therefore, the results confirmed that the present meta-analysis was relatively stable and reliable.

### DISCUSSION

PDCD6, a proapoptotic protein, is a Ca<sup>2+</sup> binding protein of the EF-hand type belonging to the subfamily

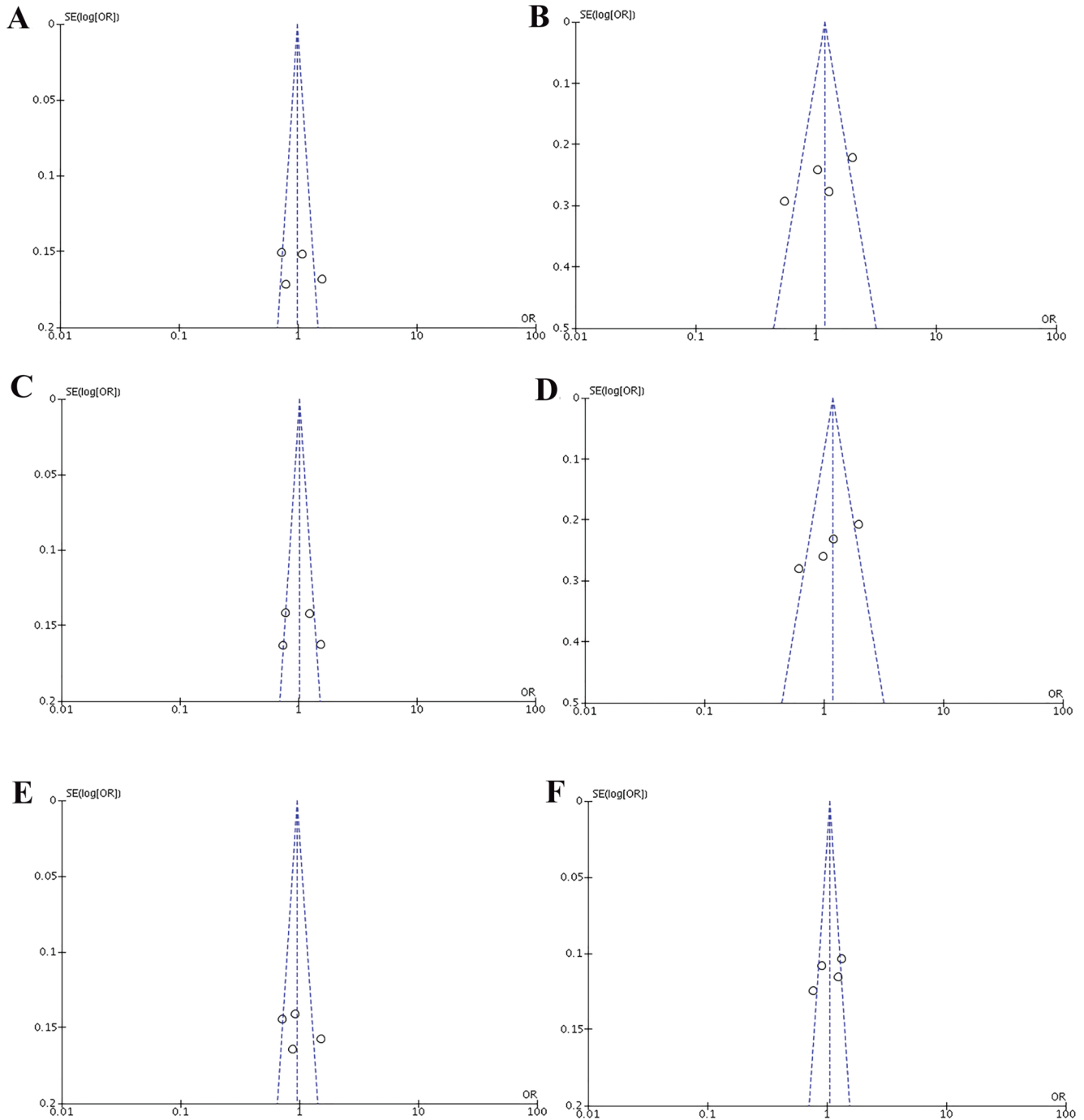


**Figure 5: Funnel plots of the association between cancer risk and the rs3756712 T>G polymorphism in the overall study population under the following models. (A) TG vs TT, (B) GG vs TT, (C) TG+GG vs TT, (D) GG vs TT+TG, (E) TG vs TT+GG, and (F) G vs T.**

of penta-EF-hand (PEF) protein that is required for the induction of apoptosis by a variety of stimuli [35, 20]. Binding of  $\text{Ca}^{2+}$  to PDCD6 induces a conformational change [34], which enables the interaction with several proteins, including ALG-2-interacting protein X (ALIX) [36], Sec31A [39, 16], and annexin A11 [28, 29]. Several lines of evidence suggest that interacting

partner of PDCD6 is ALIX/AIP1, an adaptor protein, which has been implicated in apoptotic signaling [23, 13].

The pathogenesis of carcinogenesis involves environmental factors, molecular signaling pathways, and host genetic factors [1, 6]. Since single nucleotide polymorphism (SNP) is the main cause of human genetic

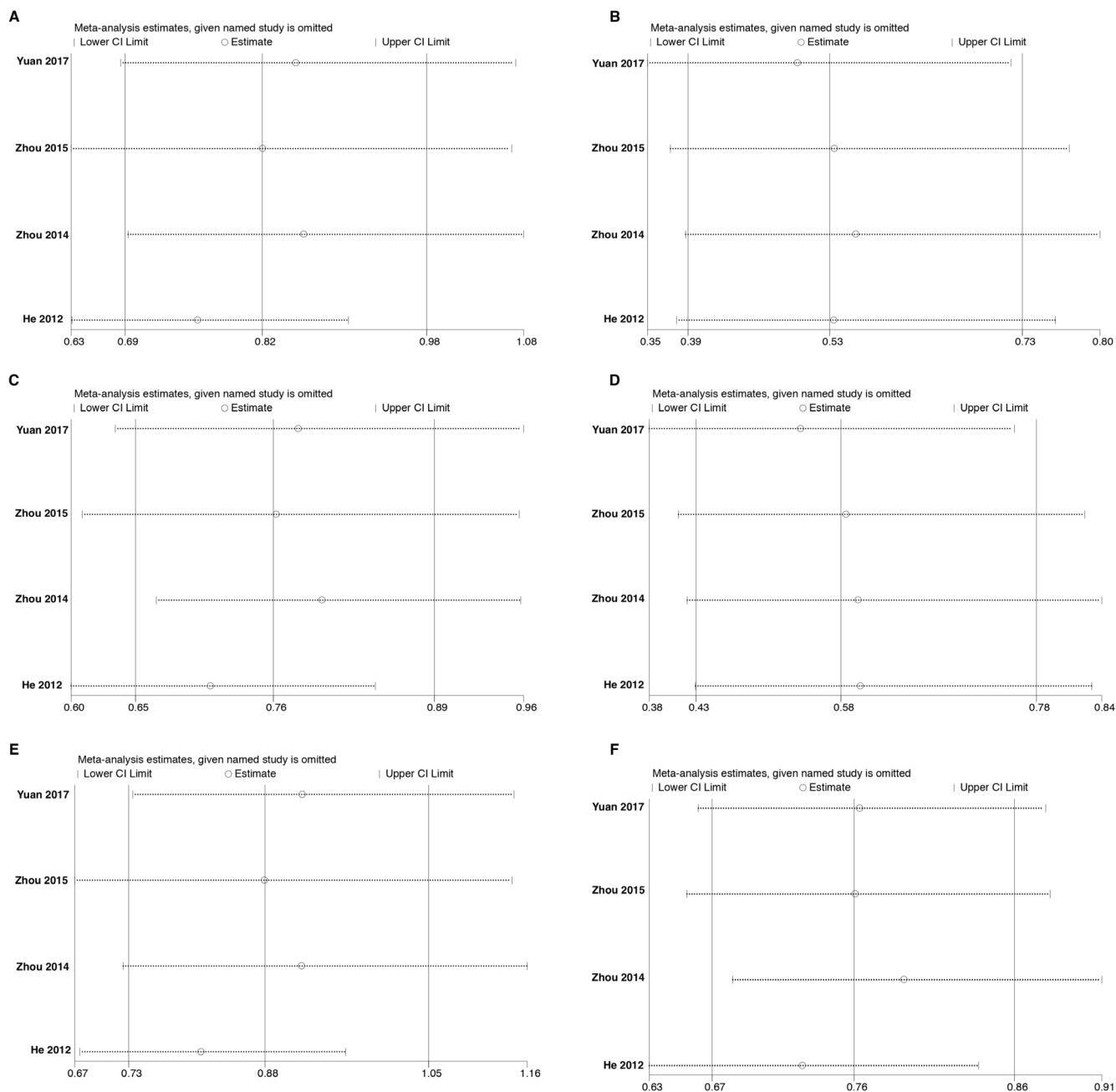


**Figure 6: Funnel plots of the association between cancer risk and the rs4957014 T>G polymorphism in the overall study population under the following models. (A) TG vs TT, (B) GG vs TT, (C) TG+GG vs TT, (D) GG vs TT+TG, (E) TG vs TT+GG, and (F) G vs T.**



variation, the connection between SNPs and individual risk of cancer has drawn considerable attention [27, 8]. As we know, limited polymorphisms have been reported about *PDCD6* gene. Several investigations have been done to find the possible association between two tag SNPs of *PDCD6*, rs3756712 and rs4957014 polymorphisms, and various cancer risk [45, 9, 44, 42]. Zhou *et al.* [45] reported that rs3756712 and rs4957014 polymorphisms of *PDCD6* significantly decreased the risk of bladder cancer. He *et al.* [9] have found no significant association between *PDCD6* rs3756712 variant and risk of Non-small cell lung cancer

(NSCLC). Their findings proposed that rs4957014 variant of *PDCD6* significantly decreased the risk of NSCLC. On the other hand, it has been revealed that rs3756712 and rs4957014 polymorphisms of *PDCD6* significantly increased the risk of cervical squamous cell carcinoma (CSCC) [44]. Recently, Yuan *et al.* [42] investigated the association between rs3756712 and rs4957014 polymorphisms of *PDCD6* and risk of CSCC. Their findings suggested that both of the variants significantly increased the risk of CSCC.

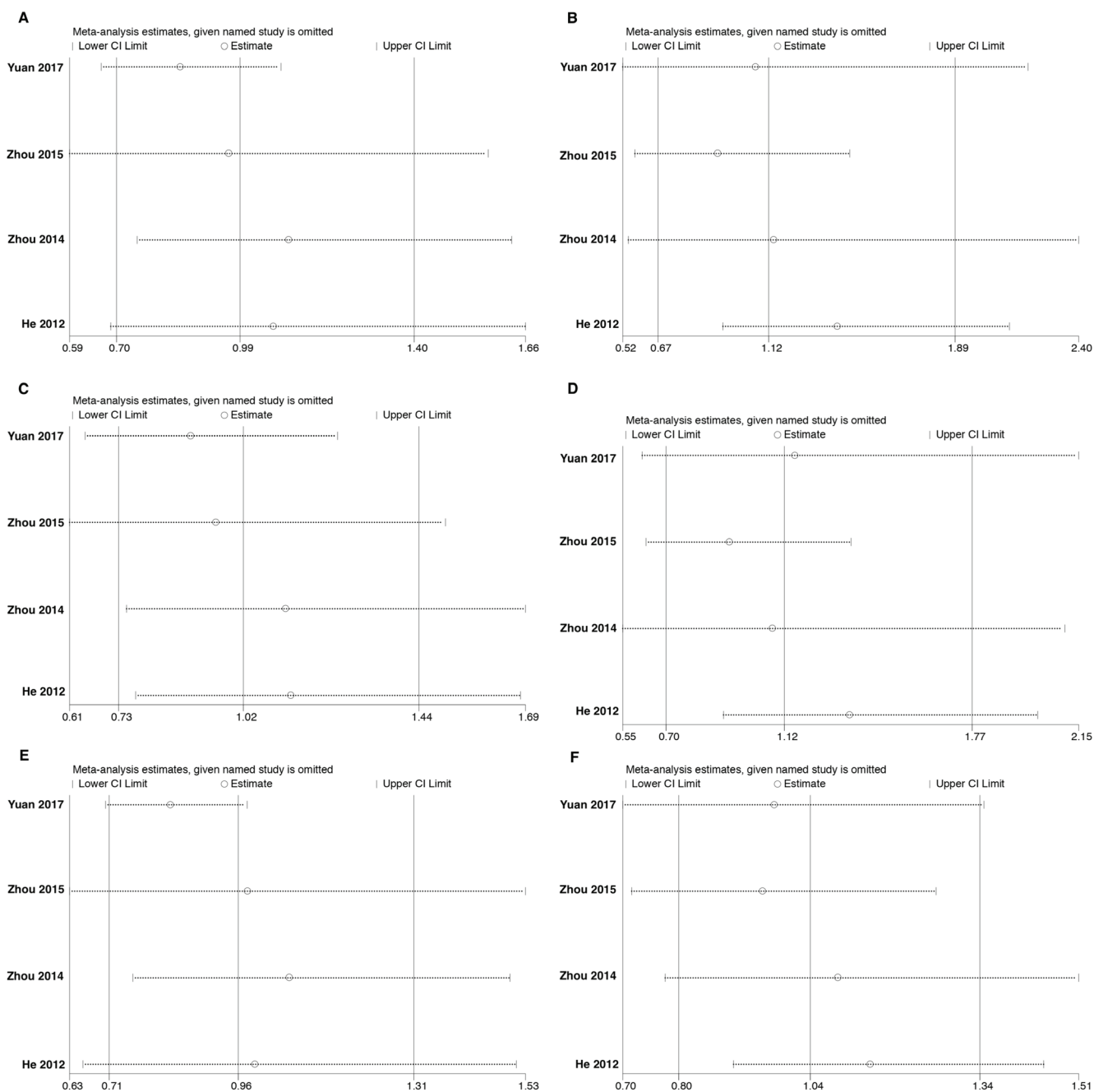


**Figure 7: Sensitivity analyses for studies on *PDCD6* rs3756712 T>G using different genetic models. (A) TG vs TT, (B) GG vs TT, (C) TG+GG vs TT, (D) GG vs TT+TG, (E) TG vs TT+GG, and (F) G vs T.**

Due to contrasting findings about *PDCD6* polymorphism in certain types of cancers, the present meta-analysis was performed to evaluate the impact of two SNPs of *PDCD6* on cancer risk. To our knowledge, this is the first meta-analysis evaluating the impact of *PDCD6* polymorphisms on cancer. The attained results suggest that the *PDCD6* rs3756712 T>G polymorphism significantly decreased the risk of cancer under codominant, dominant, recessive, and allele genetic model. The findings did

not support an association between rs4957014 T>G polymorphism of *PDCD6* and cancer risk.

In conclusion, to our knowledge, this is the first present study suggested that there is an association between the *PDCD6* rs3756712 T>G polymorphism and cancer. The rs3756712 T>G variant may be a potential marker for cancer. Further well-designed case-control studies with a larger sample size and different ethnicities should be done to confirm the findings.



**Figure 8: Sensitivity analyses for studies on *PDCD6* rs4957014 T>G using different genetic models. (A) TG vs TT, (B) GG vs TT, (C) TG+GG vs TT, (D) GG vs TT+TG, (E) TG vs TT+GG, and (F) G vs T.**

## Abbreviations

ALG-2: apoptosis-linked gene-2; AIP1: ALG-2-interacting protein 1; ALIX: ALG-2-interacting protein X; CSCC: cervical squamous cell carcinoma; CI: confidence interval; HWE: Hardy-Weinberg equilibrium; NSCLC: non-small cell lung cancer; OR: odds ratio; PEF: penta-EF-hand; PDCD6: Programmed cell death protein 6; RevMan: Review Manager; SNP: single nucleotide polymorphism.

## CONFLICTS OF INTEREST

The authors have declared that no competing interests exist.

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