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The association between polymorphisms in the *PDCD1* gene and the risk of cancer

A PRISMA-compliant meta-analysis

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Abstract

Background: The effects of the programed cell death 1 (*PDCD1*) gene polymorphisms on cancer risk have been investigated in some studies; however, the results were conflicting and ambiguous. Therefore, we aimed to do a meta-analysis to investigate the association of PDCD1 polymorphisms with cancer risk from all eligible case–control studies.

Materials and methods: An electronic search of the PubMed, Embase, Chinese National Knowledge Infrastructure, and Wanfang databases was performed. The association between *PDCD1* polymorphisms with cancer risk was calculated with odds ratios (ORs) and their corresponding 95% of confidence intervals (CIs).

Results: A total of 24 case–control studies from 13 articles that investigated the associations of 5 widely studied polymorphisms in *PDCD1* gene and cancer risks were included. The results of meta-analysis: the PDCD-1.5 (rs2227981) and PDCD-1.3 (rs11568821) polymorphisms were associated with decreased risk of cancer (rs2227981: OR = 0.75, 95% CI: 0.64–0.86, $P < 0.0001$ for TT vs TC + CC; rs11568821: OR = 0.79, 95% CI: 0.65–0.96, $P = 0.02$ for TC vs TT), while no significant associations were found for the other 3 polymorphisms (PDCD-1.9 [rs2227982] polymorphism: OR = 1.03, 95% CI: 0.90–1.18, $P = 0.66$ for CC + TC vs TT; *PDCD1* rs7421861 polymorphism: OR = 1.10, 95% CI: 0.96–1.25, $P = 0.16$ for CC + TC vs TT; PDCD-1.6 [rs10204525] polymorphism: OR = 0.93, 95% CI: 0.82–1.05, $P = 0.24$ for GG + GA vs AA).

Conclusion: The meta-analysis suggests that the PDCD-1.5 (rs2227981) and PDCD-1.3 (rs11568821) polymorphisms are associated with susceptibility of cancer. Further studies with larger sample sizes are required to make a better assessment of the above association.

Abbreviations: CI = confidence interval, OR = odds ratio, PDCD1 = programed cell death 1.

Keywords: cancer, meta-analysis, PDCD1, polymorphism

1. Introduction

Programed cell death-1 (*PDCD1*) is an immunoreceptor belonging to the CD28/CTLA-4 family.[1] It is a 55-kd types I transmembrane glycoprotein and a member of the immunoglobulin superfamily B7.[2–4] It is expressed on activated B cells, T cells, and monocytes, and its ligand (PD-L) on immune and nonimmune cells including tumor cells.[5] PD-1 was first identified by Ishida in 1992,[6] its function of negatively regulation in immune response was later found by the generation of *PDCD1*$^{-/-}$ mice.[7] PD-1 is involved in almost every aspect of immune responses including autoimmunity, tumor immunity, infectious immunity, transplantation immunity, allergy, and immunological privilege.[1] The human *PDCD1* gene is located on 2q37.3. In the *PDCD1* gene, several polymorphisms have been identified, such as PDCD-1.1 (rs36084323), PDCD-1.3 (rs11568821), PDCD-1.5 (rs2227981), PDCD-1.9 (rs2227982), and so on.[8–10] The association between polymorphisms in *PDCD1* gene and cancer risk has been studied in many studies. However, these associations were still inconclusive.[8–13] Although a meta-analysis reported the association between PDCD-1.5 (rs2227981) polymorphism and the risk of cancer[14]; however, they only reported 1 polymorphism and did not report the exact search date. The association between other polymorphisms with cancer risk should also be assessed. Thus, we conducted a comprehensive meta-analysis to investigate the association of *PDCD1* gene polymorphisms and cancer risk.

2. Materials and methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement was used in the process of the meta-analysis

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(table S1, http://links.lww.com/MD/B255).[15] The present study is a meta-analysis, and ethical approval was not necessary.

2.1. Literature search

A literature search of the PubMed, EMbase, Chinese National Knowledge Infrastructure, and WanFang databases was carried out to collect the case–control studies that investigated the association between polymorphisms of *PDCD1* gene and the risk of cancer. The date was extended to December 10, 2015. The search words were as follows: polymorphism, variant, cancer, carcinoma, PDCD1, and programed death-1.

2.2. Inclusion and exclusion criteria

We selected eligible studies according to the following criteria: case–control studies, investigating the association between the PDCD1 polymorphisms and cancer risk, detailed genotype data for estimating of odds ratio (OR) and 95% confidence interval (CI), and articles written in English or Chinese. Exclusion criteria were the following: insufficient information on the distribution of *PDCD1* genotypes, case-only studies, and duplicated publications. If multiple studies had overlapping or duplicate data, only those with complete data were included.

2.3. Data extraction

Data extraction was performed independently by 2 of the authors (JZ and TZ) using a standard protocol according to the inclusion criteria. The following data were extracted: the name of the first author, year of publication, country of participants, ethnicity, genotyping methods, and genotype distribution of cases and controls. Disputes were settled by discussion.

2.4. Statistical analysis

Any polymorphism studied in at least 3 case–control studies was included for data analysis. Crude ORs with 95% CIs were

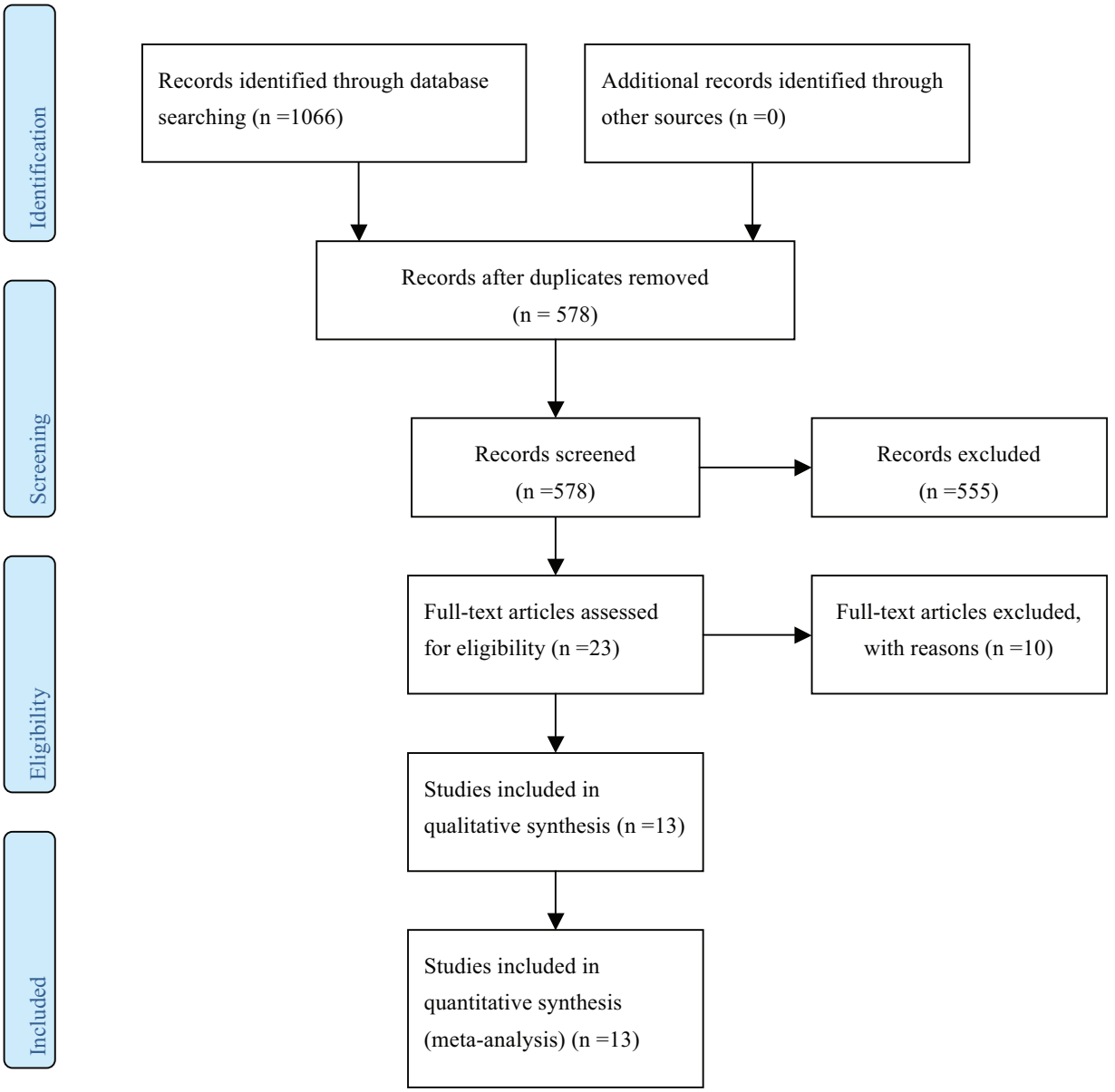

Figure 1. Selection of studies for inclusion in meta-analysis.

Table 1

The characteristics of the included studies.

Reference	Year	Country	Ethnicity	Cancer	Genotyping method	Polymorphisms
Bayram et al[22]	2012	Turkey	European	HCC	PCR-RFLP	rs11568821
Ge et al[24]	2015	China	Asian	Colorectal	PCR-RFLP	rs7421861, rs2227982, and rs10204525
Haghshenas et al[24]	2011	Iran	Asian	Breast	PCR-RFLP	rs2227981 and rs11568821
Hua et al[2]	2011	China	Asian	Breast	PCR-RFLP	rs7421861, rs 2227981, and rs2227982
Ivansson et al[3]	2010	Sweden	European	Cervical	Taqman	rs2227981
Li et al[4]	2013	China	Asian	HCC	PCR-RFLP	rs10204525
Ma et al[5]	2015	China	Asian	Lung	PCR-RFLP	rs11568821, rs2227981, and rs2227982
Mojtahedi et al[8]	2012	Iran	Asian	Colorectal	PCR-RFLP	rs2227981
Qiu et al[9]	2014	China	Asian	Esophageal	PCR-LDR	rs7421861, rs 2227982, and rs10204525
Savabkar et al[10]	2013	Iran	Asian	Gastric	PCR-RFLP	rs2227981
Tang et al[11]	2015	China	Asian	Gastric	PCR-LDR	rs2227982, rs10204525, and rs7421861
Yin et al[12]	2014	China	Asian	Lung	PCR	rs2227981
Yousefi et al[13]	2013	Iran	Asian	Colorectal	PCR-RFLP	rs11568821

HCC = hepatocellular carcinoma.

calculated to evaluate the strength of the association between *PDCD1* polymorphisms and cancer risk.[16,17] All genetic models (additive, dominant, recessive, and codominant) were used to assess the association.[17,18] Take the PDCD-1.9 (rs2227982) polymorphism as an example, the genetic models were as follows: additive model (C vs T), dominant model (CC + CT vs TT), recessive model (CC vs TT + CT), and codominant model (CC vs TT, CT vs TT). A statistical test for heterogeneity was performed based on the Q statistic.[19] If $P < 0.10$ for Q test suggested significant heterogeneity, then the random effects model was conducted to calculate the pooled OR; otherwise, the fixed effects model was selected.[18,20] Sensitivity analysis was performed by omitting each study in turn to assess the quality and consistency of the results. Begg funnel plot and the Egger test were used to evaluate possible publication bias of literatures.[21] All statistical tests were performed by using Revman 5.3 software (The Cochrane Collaboration, UK) and STATA 12.0 software (Stata Corporation, College Station, TX). P values <0.05 were considered statistically significant.

Table 2

The genotypes and alleles distributions of included polymorphisms.

Polymorphism	Reference	Cancer			Control			Cancer		Control	
rs2227981		CC	CT	TT	CC	CT	TT	C	T	C	T
	Haghshenas et al[24]	194	191	50	137	145	46	291	291	419	237
	Hua et al[2]	295	169	22	244	210	24	213	213	698	258
	Ivansson et al[3]	471	603	226	257	375	178	1055	1055	889	731
	Ma et al[5]	244	216	68	256	246	98	352	352	758	442
	Mojtahedi et al[8]	59	109	32	75	89	36	173	173	239	161
	Savabkar et al[10]	50	66	6	89	70	7	78	78	248	84
	Yin et al[12]	198	106	20	181	105	44	146	146	467	193
rs2227982		TT	TC	CC	TT	TC	CC	T	C	T	C
	Ge et al[24]	135	318	145	136	321	168	608	608	593	657
	Hua et al[2]	127	249	111	143	268	95	471	471	554	458
	Ma et al[5]	37	148	343	28	168	404	834	834	224	976
	Qiu et al[9]	159	303	154	189	325	167	611	611	703	659
	Tang et al[11]	75	168	87	148	292	163	342	342	588	618
rs7421861		TT	TC	CC	TT	TC	CC	T	C	T	C
	Ge et al[24]	395	187	14	440	163	17	215	215	1043	197
	Hua et al[2]	333	146	11	370	130	12	168	168	870	154
	Qiu et al[9]	411	168	21	460	188	25	210	210	1108	238
	Tang et al[11]	226	91	7	408	168	22	105	105	984	212
rs11568821		GG	GA	AA	GG	GA	AA	G	A	G	A
	Bayram et al[22]	191	45	0	180	56	0	45	45	416	56
	Haghshenas et al[24]	365	63	8	231	55	4	79	79	517	63
	Ma et al[5]	426	102	0	456	142	2	102	102	1054	146
	Yousefi et al[13]	18	27	35	43	45	22	97	97	131	89
rs10204525		AA	AG	GG	AA	AG	GG	A	G	A	G
	Ge et al[24]	302	257	40	328	259	38	337	337	915	335
	Li et al[4]	180	83	8	160	130	28	99	99	450	186
	Qiu et al[9]	317	240	43	345	243	63	326	326	933	369
	Tang et al[11]	169	123	21	309	219	53	165	165	837	325

Table 3

Summary of results from different comparative genetic models for each polymorphism.

Polymorphism	Genetic model	No. of participants	OR (95% CI)	Z	*P*	I^2 (%)	P_{Het}	Effect model
rs2227981	TT vs TC+CC	6307	0.75 (0.64, 0.86)	3.90	<0.0001	0	0.50	Fixed
	TC+TT vs CC	6307	0.91 (0.76, 1.10)	0.97	0.33	66	0.008	Random
	TT vs CC	3607	0.72 (0.61, 0.84)	4.02	<0.0001	23	0.26	Fixed
	TC vs CC	5450	0.97 (0.80, 1.18)	0.29	0.77	66	0.008	Random
	T vs C	12614	0.88 (0.78, 1.00)	2.02	0.04	59	0.02	Random
rs2227982	CC vs TT+TC	5574	0.98 (0.87, 1.11)	0.28	0.78	6	0.37	Fixed
	CC+TC vs TT	5574	1.03 (0.90, 1.18)	0.44	0.66	7	0.36	Fixed
	CC vs TT	3014	1.01 (0.86, 1.19)	0.13	0.90	35	0.19	Fixed
	CT vs TT	3737	1.03 (0.90, 1.19)	0.47	0.64	0	0.53	Fixed
	C vs T	11148	1.00 (0.93, 1.08)	0.08	0.94	21	0.28	Fixed
rs7421861	CC vs TT+TC	4413	0.84 (0.58, 1.20)	0.96	0.34	0	0.81	Fixed
	CC+TC vs TT	4413	1.10 (0.96, 1.25)	1.40	0.16	16	0.31	Fixed
	CC vs TT	3172	0.86 (0.60, 1.24)	0.80	0.42	0	0.77	Fixed
	CT vs TT	4284	1.12 (0.98, 1.28)	1.71	0.09	7	0.36	Fixed
	C vs T	8826	1.05 (0.94, 1.18)	0.92	0.36	14	0.32	Fixed
rs11568821	AA vs AG+GG	2516	2.25 (1.30, 3.87)	2.91	0.004	49	0.14	Fixed
	AG+AA vs GG	2516	0.92 (0.63, 1.32)	0.47	0.64	68	0.02	Random
	AA vs GG	1981	1.72 (0.50, 5.94)	0.85	0.39	59	0.09	Random
	AG vs GG	2445	0.79 (0.65, 0.96)	2.31	0.02	0	0.42	Fixed
	A vs G	5032	1.02 (0.64, 1.62)	0.07	0.95	85	0.0001	Random
rs10204525	GG vs GA+AA	3958	0.71 (0.47, 1.07)	1.65	0.10	59	0.06	Random
	GA+GG vs AA	3958	0.93 (0.82, 1.05)	1.18	0.24	80	0.002	Random
	GG vs AA	2404	0.68 (0.42, 1.11)	1.53	0.13	70	0.02	Random
	GA vs AA	3664	0.93 (0.72, 1.20)	0.57	0.57	72	0.01	Random
	G vs A	7916	0.86 (0.67, 1.10)	1.23	0.22	82	0.0007	Random

CI = confidence interval; OR = odds ratio.

3. Results

3.1. Eligible studies

We initially identified 1066 potentially relevant studies after searching the databases. After excluding the duplicated records, 578 studies were left for screening. After reading the title and the abstracts of these studies, 555 studies were excluded for not reporting the association between the *PDCD-1* polymorphisms and cancer risks reviews. Thus, 23 studies were left for full-text assessment and data extraction. Among these studies, 2 studies were excluded for not reporting useful data for meta-analysis, 3 were excluded for not being case–control studies, and 5 were excluded for not reporting polymorphism in more than 3 case–control studies. Thus, 13 studies that met the predescribed inclusion criteria were included in the meta-analysis of the association between *PDCD1* polymorphisms and cancer risk (Fig. 1).[2–5,8–13,22–24] Characteristics of all eligible case–control studies are summarized in Table 1. There were 7 case–control studies on PDCD-1.5 (rs2227981) polymorphism,[2,3,5,8,10,12,24] 5 on PDCD-1.9 (rs2227982) polymorphism,[2,5,9,11,23] 4 on rs7421861 polymorphism,[2,9,11,23] 4 on PDCD-1.3 (rs11568821) polymorphism,[5,13,22,24] and 4 on PDCD-1.6 (rs10204525) polymorphism,[4,9,11,23] respectively. Of the 13 included studies, 7 types of cancers including gastric, breast, esophageal, liver (hepatocellular carcinoma), colorectal, cervical, and lung cancer were involved. The genotype distributions in the studies considered in the present meta-analysis are shown in Table 2.

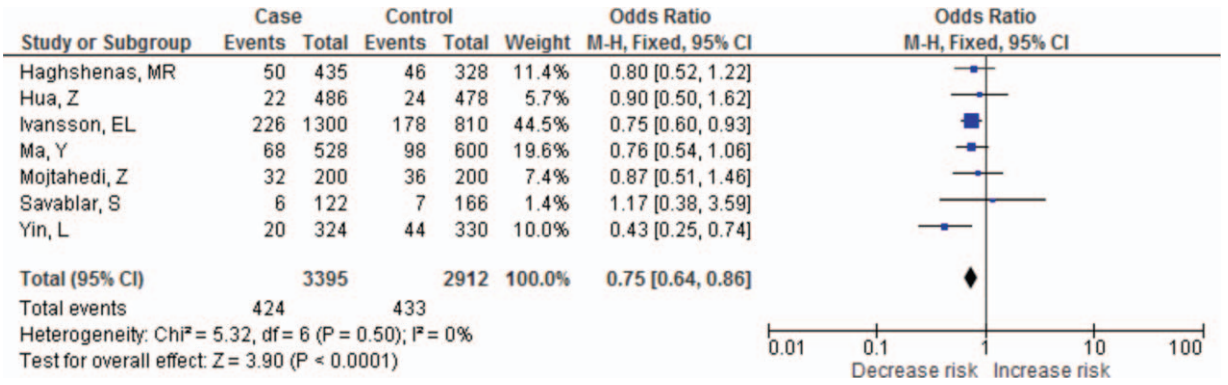

Figure 2. Meta-analysis of programed cell death-1.5 (rs2227981) polymorphism and cancer risk.

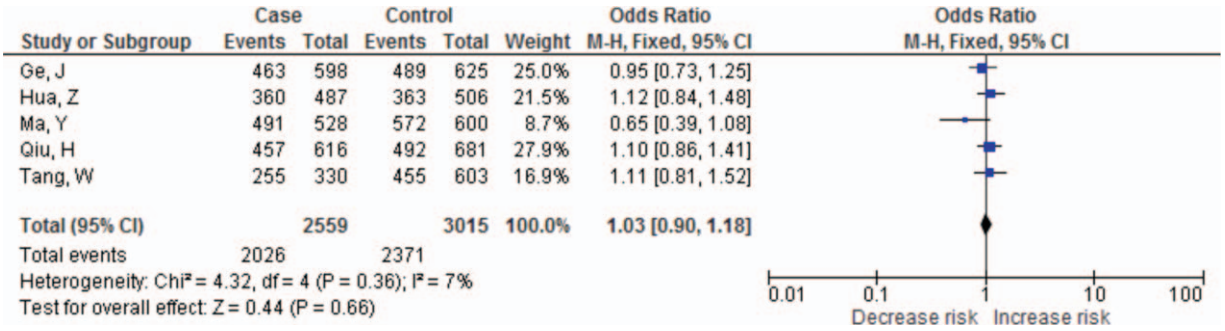

Figure 3. Meta-analysis of programed cell death-1.9 (rs2227982) polymorphism and cancer risk.

3.2. Meta-analysis results

The summary results for the association between *PDCD-1* polymorphisms and the risk of cancer are shown in Table 3. For the PDCD-1.5 (rs2227981) polymorphism, we found a significant association between the polymorphism and overall cancer risk in the recessive genetic model (OR = 0.75, 95% CI: 0.64–0.86, $P < 0.0001$) (Fig. 2). For the PDCD-1.9 (rs2227982) polymorphism, there was no statistical evidence of an association between the polymorphism and overall cancer risk in the dominant genetic model (OR = 1.03, 95% CI: 0.90–1.18, $P = 0.66$) (Fig. 3). For the rs7421861 polymorphism, there was no statistical evidence of an association between the polymorphism and overall cancer risk in the dominant genetic model (OR = 1.10, 95% CI: 0.96–1.25, $P = 0.16$) (Fig. 4). For the PDCD-1.3 (rs11568821) polymorphism, there was statistical evidence of an association between the polymorphism and overall cancer risk in TC versus TT genetic model (OR = 0.79, 95% CI: 0.65–0.96, $P = 0.02$) (Fig. 5). For the PDCD-1.6 (rs10204525) polymorphism, there was no statistical evidence of an association between the polymorphism and overall cancer risk (OR = 0.93, 95% CI: 0.82–1.05, $P = 0.24$) (Fig. 6).

3.3. Publication bias

Publication bias was analyzed by Begg and Egger tests for each polymorphism. No publication bias was detected with either the Begg funnel plot or the Egger test (PDCD-1.5 [rs2227981] polymorphism: Supplement figure 1, http://links.lww.com/MD/B255, t = 0.26 and $P = 0.804$ for Egger test; PDCD-1.9 [rs2227982] polymorphism: Supplement figure 2, http://links.lww.com/MD/B255, t = −2.37 and $P = 0.098$ for Egger test; rs7421861 polymorphism: Supplement figure 3, http://links.lww.com/MD/B255, t = −0.37 and $P = 0.744$ for Egger test; PDCD-1.3 [rs11568821] polymorphism: Supplement figure 4, http://links.lww.com/MD/B255, t = 1.77 and $P = 0.220$ for Egger test; PDCD-1.6 [rs10204525] polymorphism: Supplement figure 5, http://links.lww.com/MD/B255, t = −2.98 and $P = 0.097$ for Egger test).

4. Discussion

Accumulative evidence suggests that PDCD1 is a negative regulator of the immune response.[5,11,23] Genetic variants in *PDCD1* gene have been associated with the pathogenesis of cancers. Several important variants in the gene have been identified, such as the PDCD-1.5 (rs2227981) polymorphism, PDCD-1.9 (rs2227982), and so on.[5,9] Up to now, the associations between polymorphisms in the *PDCD1* gene and the risk of cancer were still inconclusive; thus, we performed the current meta-analysis. To the best of our knowledge, this is the first comprehensive meta-analysis to assess the association of *PDCD1* gene polymorphisms with the risk of cancer.

The current meta-analysis, which included a total of 24 case–control studies from 13 articles, investigated the associations of 5 widely studied polymorphisms in *PDCD1* gene and cancer risk. The results indicated that the variant TT genotype of the rs2227981 polymorphism and TC genotype of the rs11568821 polymorphism were associated with significant decreased risk of cancer, whereas the other 3 polymorphisms (rs2227982, rs7421861, and rs10204525) did not appear to have a significant association with cancer risk. Previous studies reported that the PDCD-1.5 (rs2227981) polymorphism was an asynonymous mutation (C to T, Ala to Ala)[2,24]; it may influence the expression and function of *PDCD1* through linkage disequilibrium with other

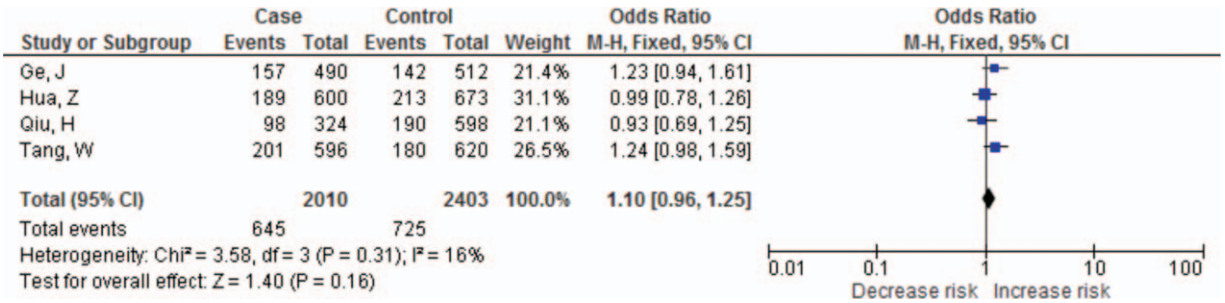

Figure 4. Meta-analysis of *PDCD1* gene rs7421861 polymorphism and cancer risk.

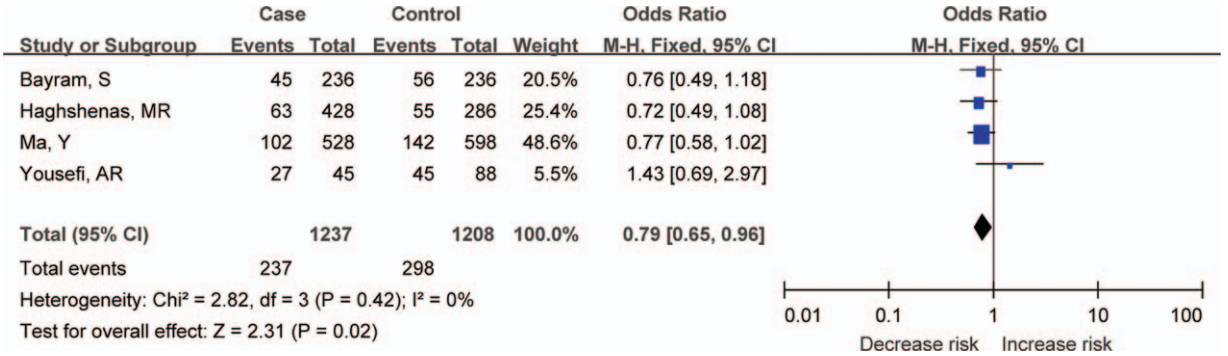

Figure 5. Meta-analysis of programed cell death-1.3 (rs11568821) polymorphism and cancer risk.

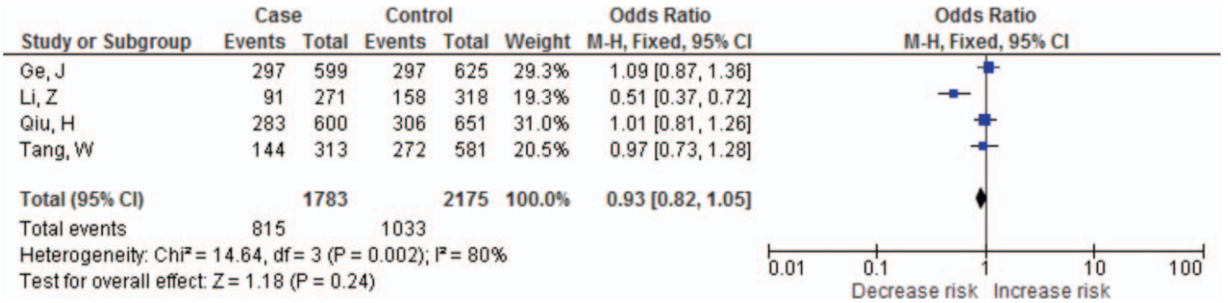

Figure 6. Meta-analysis of programed cell death-1.6 (rs10204525) polymorphism and cancer risk.

nucleotide polymorphisms in *PDCD1* gene or other nearby genes.[2,24] Accordingly, the polymorphism may influence the susceptibility to cancer through these mechanisms.

In this meta-analysis, we also found that the PDCD-1.3 (rs11568821) polymorphism was significantly associated with decreased risk of cancer, and the genotype TC might be a risk factor. A possible reason might be that this polymorphism (T to C) was a polymorphism in the fourth intron of PDCD1,[24] the substitution of T for C in the enhancer within the intron might disrupt the binding site of RUNX1, alter the regulation of gene expression, and influence the PD-1 pathway.[24] PDCD-1.3 (rs11568821) polymorphism may impair the inhibitory effect of PD-1 and thus may lead to positive regulation of cytotoxic lymphocyte activity in T allele carriers.[5,24] Thus, variant TC genotype might contribute to decrease risk of cancer. However, the exact mechanisms are still needed to be analyzed in future studies. However, 11 Asian studies were included in our meta-analysis, and the majority were studies performed in China. Race might play an important role in deriving the conclusions of the current meta-analysis. Some studies have a bigger sample size compared with others within 1 analysis, which might also generate bias. This suggests that the results should be explained with caution.

The problem of heterogeneity and publication bias, which may influence the results of meta-analyses, should also be explained. Significant heterogeneity existed in the analysis among 3 polymorphisms. The heterogeneity might result from cancer types, ethnicity, and the source of controls. However, due to the limited number of studies included, we did not perform analysis of these factors based on subgroups. Publication bias is another important issue in meta-analyses. In the present study, publication bias was analyzed by using Begg funnel plots and the Egger test. We did not detect a significant publication bias for all polymorphisms, suggesting the reliability of our results.

This meta-analysis has pooled the available data from the eligible studies, which has significantly increased the statistical power. However, there are still some weaknesses. First, cancer is a multifactorial disease from complex interactions between environmental exposure and genetic factors. In this meta-analysis, we had insufficient data to conduct an evaluation of such interactions for the role of *PDCD1* polymorphisms and factors in cancer development. Second, numerous present studies are limited for some polymorphisms only. Thus, investigations involving large number of different ethnicities are necessary for a more reliable assessment on their associations. Third, the heterogeneity between studies exists in some polymorphisms, and that may affect the stability of the results.

In conclusion, our meta-analysis suggests that PDCD-1.5 (rs2227981) and PDCD-1.3 (rs11568821) polymorphisms are associated with susceptibility to cancer, while rs2227982, rs7421861, and rs10204525 polymorphism may not be associated with cancer risk. These results should be interpreted cautiously. In order to better understand the potential roles of *PDCD1* polymorphisms in cancer, further studies with larger sample sizes, combining genetic and other environmental risk factors, are needed.

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