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Original Article

Association of programmed death-1 gene polymorphism rs2227981 with tumor: evidence from a meta analysis

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Abstract: To investigate the association of programmed death-1 gene polymorphism rs2227981 with tumor risk. The PubMed, Medline, Ovid Medline, EMBASE, Web of Knowledge were searched. Meta-analyses were conducted using RevMan 5.2.2 software. Total six researches involving in a total of 1427 tumor patients and 1811 healthy control people were included into this meta analysis. There was no association of PD-1 gene polymorphism with total tumor risk under four genetic models. (CT+TT vs CC, OR=1.09, 95% CI=0.80-1.49, P=0.59; CT+CC vs TT, OR=0.93, 95% CI=0.52-1.66, P=0.61; TT vs CC, OR=0.99, 95% CI=0.57-1.72, P=0.97; CT vs CC, OR=1.16, 95% CI=0.80-1.70, P=0.43). The sub-group analysis shown there were a significantly difference on association of PD-1 gene polymorphism with digestive system tumor risk between tumor patients and healthy control people, except recessive model. (CT+TT vs CC, OR=1.57, 95% CI=1.20-2.07, P=0.001; TT vs CC, OR=1.67, 95% CI=1.12-2.49, P=0.01; CT vs CC, OR=1.51, 95% CI=1.13-2.01, P=0.005). Moreover, the meta analysis results shown that there were association of PD-1 gene polymorphism with tumor risk under two models for the tumor specific occurring only in women. (CT+TT vs CC, OR=0.80, 95% CI=0.67-0.95, P=0.01; TT vs CC, OR=0.61, 95% CI=0.44-0.83, P=0.002). This study suggests that PD-1 gene polymorphism rs2227981 is associated with specific tumor types, including digestive system tumor and tumor specific occurring in woman.

Keywords: Programmed death-1, polymorphism, tumor, genetic models, RevMan, meta analysis

Introduction

Lots of factors involves in cause of tumor, including infectious aspects, environment factors, and genetic factors [1-3]. Human immune system plays an important role in resisting tumors, of which the T lymphocyte is the most important anti-tumor immune regulator. Therefore, it is suggest that some immune response-related genes polymorphisms may contribute to tumor pathogenesis.

Programmed death-1 (PD-1), a 55 KDa type I transmembrane glycoprotein, is a potent immunoregulatory molecule expressed on lots of cells, including natural killer T cells (NKTs), monocytes, activated T and B lymphocytes [4]. As we know, PD-1 plays a crucial role in assisting cancer cell to escape the host immune system. Inhibition of PD-1 can improve the anti-tumor activity of immune system [5]. Other study reported that PD-1 is involved in the arthritis, which indicated that PD-1 may play a center role in development of autoimmune disease [6]. Moreover, there was a evidence that PD-1 gene polymorphism is associated with susceptibility of systemic lupus erythematosus [7]. Moreover, more and more studies have focus on the rheumatoid arthritis [8], type 1 diabetes [9] and ankylosing spondylitis [10], however, little is known the relationship between PD-1 gene polymorphism with tumor susceptibility, especially PD-1 rs2227981 (+7785).

The aim of this meta analysis was to comprehensively and quantitatively summarize the all world results to evaluated PD-1 gene polymorphism rs2227981 with tumor risk.

Methods

Lots of databases included PubMed, Medline, Ovid Medline, EMBASE, Web of Knowledge were searched form 1990 to present. The main

Table 1. Charateristics of Studies Included in the Meta-analysis

Study	Year	Ethnicity	Tumor type	Case							Control						
				CC	CT	TT	CC+CT	CC+TT	CT+TT	N	CC	CT	TT	CC+CT	CC+TT	CT+TT	N
Dehaghani	2009	Iran	gestational trophoblastic neoplasms	42	37	13	79	55	50	92	118	56	121	174	239	177	295
Haghshenas	2011	Iran	breast cancer	194	191	50	385	244	241	443	137	145	46	282	183	191	328
Hua	2011	China	breast cancer	295	169	22	464	317	191	490	244	210	24	454	268	234	512
Mojtahedi	2012a*	Iran	colon cancer	47	102	26	149	73	128	175	75	89	36	164	111	125	200
	2012b*		Rectal cancer	12	7	6	19	18	13	25	75	89	36	164	111	125	200
Savabkar	2013	Iran	gastric cancer	50	66	6	116	56	72	122	89	70	7	159	96	77	166
Yousefi	2013	Iran	Colorectal Cancer	18	27	35	45	53	62	80	43	45	22	88	65	67	110

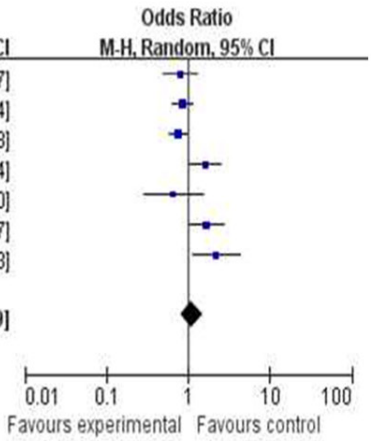
*from the same study.

A

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Dehaghani et al.,2009	50	92	177	295	14.4%	0.79 [0.50, 1.27]
Haghshenas et al.,2011	241	443	191	328	18.0%	0.86 [0.64, 1.14]
Hua et al.,2011	191	490	234	512	18.7%	0.76 [0.59, 0.98]
Mojtahedi et al.,2012a	128	175	125	200	15.0%	1.63 [1.05, 2.54]
Mojtahedi et al.,2012b	13	25	125	200	8.5%	0.65 [0.28, 1.50]
Savabkar et al.,2013	72	122	77	166	14.3%	1.66 [1.04, 2.67]
Yousefi et al.,2013	62	80	67	110	11.1%	2.21 [1.15, 4.23]
Total (95% CI)		**1427**		**1811**	**100.0%**	**1.09 [0.80, 1.49]**
Total events	757		996			

Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 22.55$, df = 6 (P = 0.0010); $I^2 = 73\%$

Test for overall effect: Z = 0.53 (P = 0.59)

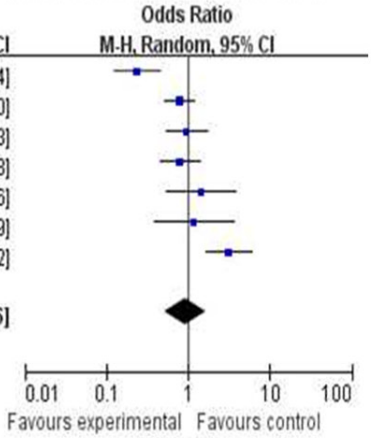


B

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Dehaghani et al.,2009	13	92	121	295	15.0%	0.24 [0.13, 0.44]
Haghshenas et al.,2011	50	443	46	328	16.6%	0.78 [0.51, 1.20]
Hua et al.,2011	22	490	24	512	15.3%	0.96 [0.53, 1.73]
Mojtahedi et al.,2012a	26	175	36	200	15.6%	0.79 [0.46, 1.38]
Mojtahedi et al.,2012b	6	25	36	200	11.9%	1.44 [0.54, 3.86]
Savabkar et al.,2013	6	122	7	166	10.8%	1.17 [0.38, 3.59]
Yousefi et al.,2013	35	80	22	110	14.9%	3.11 [1.64, 5.92]
Total (95% CI)		**1427**		**1811**	**100.0%**	**0.93 [0.52, 1.66]**
Total events	158		292			

Heterogeneity: $Tau^2 = 0.48$; $Chi^2 = 33.33$, df = 6 (P < 0.00001); $I^2 = 82\%$

Test for overall effect: Z = 0.24 (P = 0.81)

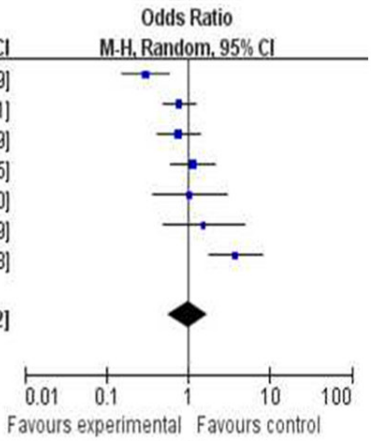


C

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Dehaghani et al.,2009	13	55	121	239	15.1%	0.30 [0.15, 0.59]
Haghshenas et al.,2011	50	244	46	183	17.2%	0.77 [0.49, 1.21]
Hua et al.,2011	22	317	24	268	15.8%	0.76 [0.41, 1.39]
Mojtahedi et al.,2012a	26	73	36	111	15.6%	1.15 [0.62, 2.15]
Mojtahedi et al.,2012b	6	18	36	111	11.4%	1.04 [0.36, 3.00]
Savabkar et al.,2013	6	56	7	96	10.6%	1.53 [0.49, 4.79]
Yousefi et al.,2013	35	53	22	65	14.2%	3.80 [1.77, 8.18]
Total (95% CI)		**816**		**1073**	**100.0%**	**0.99 [0.57, 1.72]**
Total events	158		292			

Heterogeneity: $Tau^2 = 0.41$; $Chi^2 = 26.02$, df = 6 (P = 0.0002); $I^2 = 77\%$

Test for overall effect: Z = 0.03 (P = 0.97)



D

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Dehaghani et al.,2009	37	79	56	174	14.1%	1.86 [1.08, 3.20]
Haghshenas et al.,2011	191	385	145	282	17.6%	0.93 [0.68, 1.26]
Hua et al.,2011	169	464	210	454	18.1%	0.67 [0.51, 0.87]
Mojtahedi et al.,2012a	102	149	89	164	15.3%	1.83 [1.15, 2.90]
Mojtahedi et al.,2012b	7	19	89	164	8.5%	0.49 [0.18, 1.31]
Savabkar et al.,2013	66	116	70	159	15.0%	1.68 [1.04, 2.72]
Yousefi et al.,2013	27	45	45	88	11.4%	1.43 [0.69, 2.97]
Total (95% CI)		**1257**		**1485**	**100.0%**	**1.16 [0.80, 1.70]**
Total events	599		704			

Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 28.19$, df = 6 (P < 0.0001); $I^2 = 79\%$

Test for overall effect: Z = 0.79 (P = 0.43)

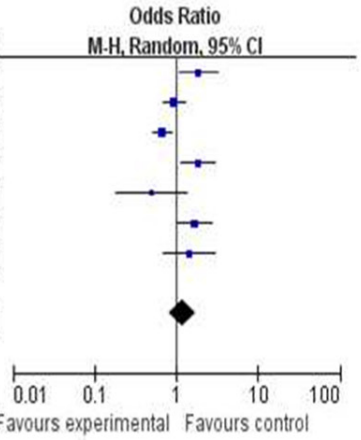


Figure 1. The meta analysis of PD-1 gene polymorphism with total tumor. A. CT+TT vs CC; B. CT+CC vs TT; C. TT vs CC; D. CT vs CC.

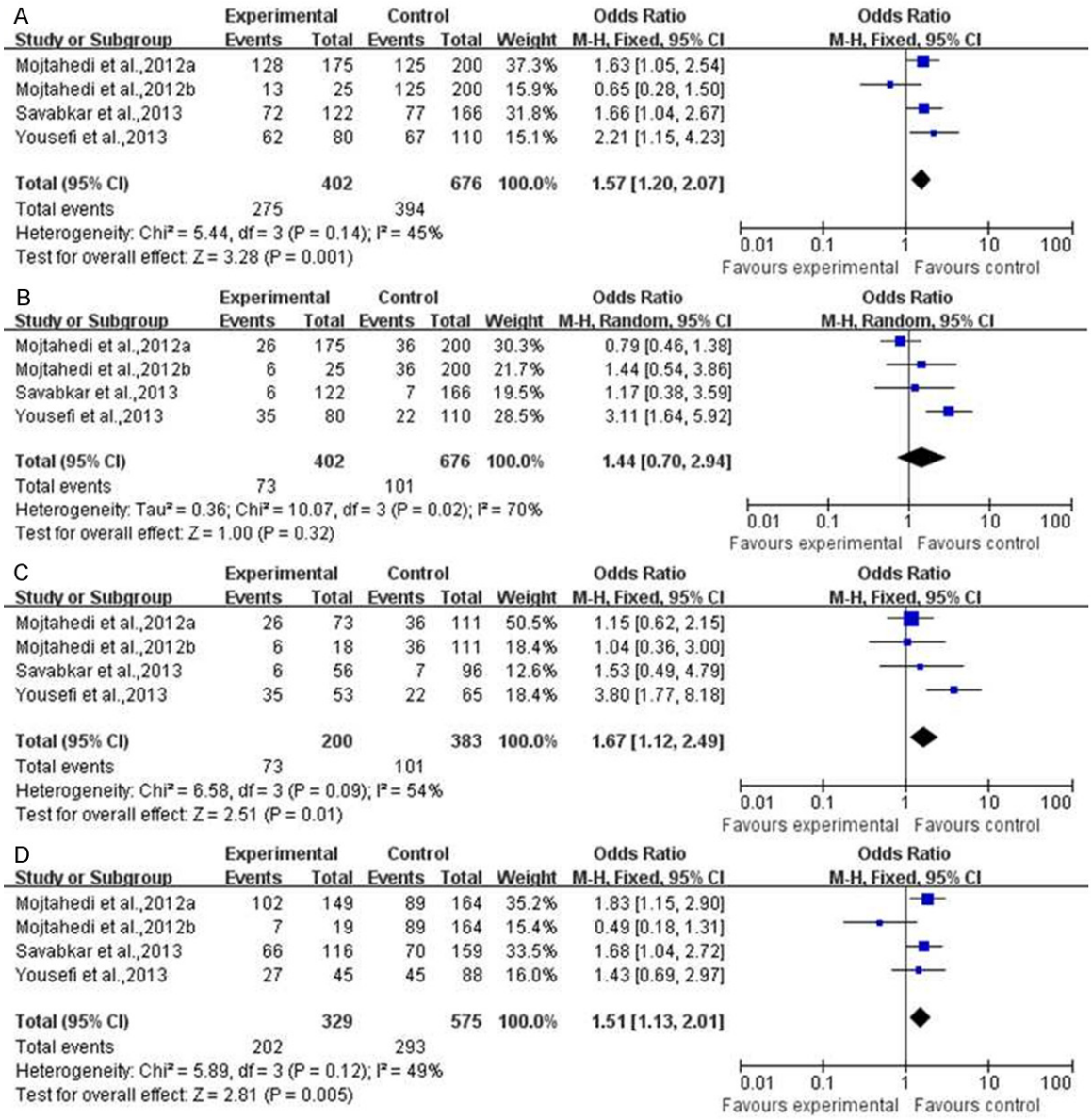


Figure 2. The meta analysis of PD-1 gene polymorphism with digestive system tumor. A. CT+TT vs CC; B. CT+CC vs TT; C. TT vs CC; D. CT vs CC.

terms "programmed death-1", "PD-1", "polymorphism", "cancer", "tumor", "carcinoma" in the title and/or abstract were used. References cited in the retrieved articles were also searched for relevant titles.

Data extraction and quality assessment

Two investigators independently reviewed all potentially eligible studies and collected data. The discussion and consensus were considered if the there were discrepancies. The quality of all collected data was ranked in accordance with the score of the non-randomized controlled clinical trial quality evaluation standard.

Statistical methods

The all collected data were included into Review Manager software (5.2.2). Heterogeneity was evaluated by X^2 and I^2. The dichotomous vari-

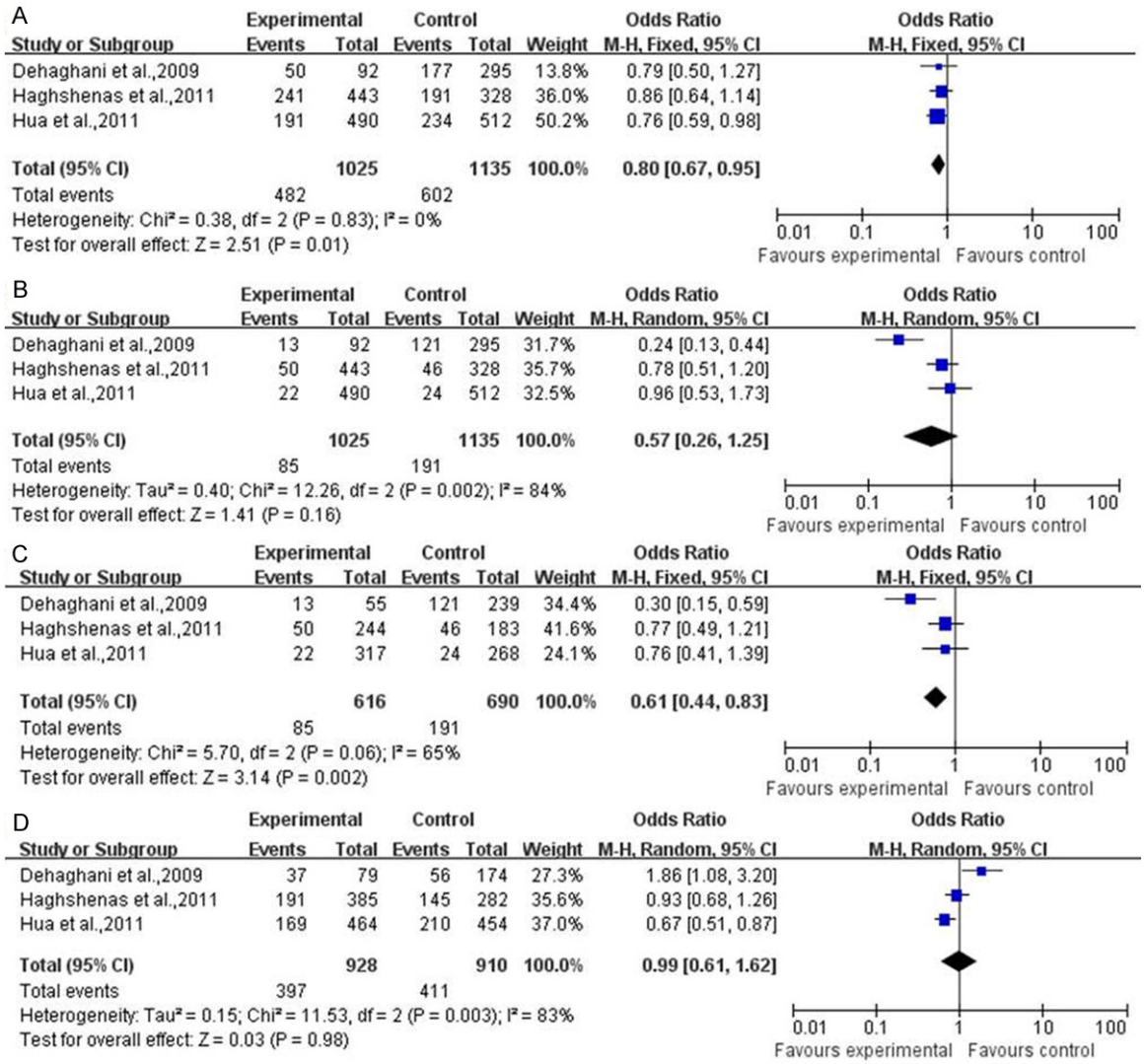


Figure 3. The meta analysis of PD-1 gene polymorphism with tumor specific occurring in woman. A. CT+TT vs CC; B. CT+CC vs TT; C. TT vs CC; D. CT vs CC.

ables was analyzed via estimation of odds ratios (OR) with 95% confidence interval (95% CI). Heterogeneity was considered if the I^2 statistic was >50% or P<0.05.

Results

Study characteristics

The characteristics of all included studies were summarized in **Table 1**. We collected the data from six studies [11-16], involving in a total of 1427 tumor patients and 1811 healthy control people. Two studies involved in colorectal cancer [14, 16], of which one study involved in rectal cancer [14], one research involved in gastric cancer [15], two papers involved in breast cancer [12, 13], and one article involved in gestational trophoblastic neoplasms [11]. Five studies were from Iran [11, 13-16], only on from China [13]. More detail can be found in **Table 1**.

No association of PD-1 gene polymorphism with tumor risk

As shown in **Figure 1**, the meta analysis results shown that there was no association of PD-1 gene polymorphism with tumor risk under four genetic models. (CT+TT vs CC, OR=1.09, 95% CI=0.80-1.49, P=0.59; CT+CC vs TT, OR=0.93, 95% CI=0.52-1.66, P=0.61; TT vs CC, OR=0.99, 95% CI=0.57-1.72, P=0.97; CT vs CC, OR=1.16, 95% CI=0.80-1.70, P=0.43).

Sub-group analysis

We further explored potential causes of the PD-1 gene polymorphism with different tumors. As shown in **Figure 2**, there were a significantly difference on association of PD-1 gene polymorphism with digestive system tumor risk between tumor patients and healthy control people, except recessive model. (CT+TT vs CC, OR=1.57, 95% CI=1.20-2.07, P=0.001; TT vs CC, OR=1.67, 95% CI=1.12-2.49, P=0.01; CT vs CC, OR=1.51, 95% CI=1.13-2.01, P=0.005).

For the tumor occurring only in women, the meta analysis results shown that there were association of PD-1 gene polymorphism with tumor risk under two models. (CT+TT vs CC, OR=0.80, 95% CI=0.67-0.95, P=0.01; TT vs CC, OR=0.61, 95% CI=0.44-0.83, P=0.002) However, the results under other two models indicated there were no correlation. (CT+CC vs TT, OR=0.57, 95% CI=0.26-1.25, P=0.16; CT vs CC, OR=0.99, 95% CI=0.61-1.62, P=0.98) (**Figure 3**).

Discussion

In this meta analysis, the results shown that there were significantly difference on association of PD-1 rs2227981 gene polymorphism with special tumor type, including digestive system tumor and tumor occurring in woman under specific genetic models.

Human tumors have lots of genetic and epigenetic changes, which can produce some immune system-recognizing tumor antigens [17]. PD-1, liking CTLA-4, is a member of the B7-CD28 family and is potential therapeutic anticancer target based on its role of regulating T cell activation. PD-1 is a key immune-checkpoint receptor, which regulates immunosuppression by expression on activated T cell. Therefore, the PD-1 maybe a potential molecular target for tumor progression in tumors. The relative studies revealed that the association of CD28 and CTLA-4 gene polymorphisms with tumor risk is present [18-20]. Compared to the CTLA-4, the PD-1 is involve in the later of a T cell response in order to limit the T cell activity in the tumor microenvironment [21].

In our study, we demonstrated that PD-1 gene polymorphism rs2227981 is not relevant to total tumor types risk. So, we performed a subgroup analysis. The meta analysis results shown that an association of PD-1 gene polymorphism rs2227981 with digestive system tumors or tumors only occurring in woman under specific genetic models. Savabkar et al. [15] and Mojtahedi et al. [14] reported that significant association in CT genotype and gastric cancer and colon cancer risk. Similarly, other study demonstrated association of CT genotype of the PD-1 gene polymorphism and rheumatoid arthritis [22]. Moreover, PD-1 gene polymorphism CC genotype and C allele may play a potential risk in tumor specific occurring in woman, including breast cancer [13], which all are consistent with our results.

In here, five studies involved in Iran, only research is from China, which limited the meta analysis results. Moreover, other limitation in this meta analysis should be addressed. Firstly, a relatively small number of studies and sample size were included into this study, which may influence the statistical power of the analysis. Secondly, our meta analysis results were based on unadjusted estimates, while a more precise analysis could be conducted if individual data were available.

In conclusion, this study suggested that PD-1 gene polymorphism rs2227981 is associated with specific tumor types, including digestive system tumor and tumor specific occurring in woman. However, more studies needed to be included into this meta analysis.

Disclosure of conflict of interest

None.

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