Programmed Cell Death-1 Polymorphisms Decrease the Cancer Risk: A Meta-Analysis Involving Twelve Case-Control Studies

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Abstract

Programmed cell death-1 (PD-1) plays an important inhibitory role in anti-tumor responses, so it is considered as a powerful candidate gene for individual’s genetic susceptibility to cancer. Recently, some epidemiological studies have evaluated the association between PD-1 polymorphisms and cancer risk. However, the results of the studies are conflicting. Therefore, a meta-analysis was performed. We identified all studies reporting the relationship between PD-1 polymorphisms and cancers by electronically searches. According to the inclusion criteria and the quality assessment of Newcastle-Ottawa Scale (NOS), only high quality studies were included. A total of twelve relevant studies involving 5,206 cases and 5,174 controls were recruited. For PD-1.5 (rs2227981) polymorphism, significantly decreased cancer risks were obtained among overall population, Asians subgroup and population-based subgroup both in TT vs. CC and TT vs. CT+CC genetic models. In addition, a similar result was also found in T vs. C allele for overall population. However, there were no significant associations between either PD-1.9 (rs2227982) or PD-1 rs7421861 polymorphisms and cancer risks in all genetic models and alleles. For PD-1.3 (rs11568821) polymorphism, we found different cancer susceptibilities between GA vs. GG and AA vs. AG +GG genetic models, and no associations between AA vs. GG, AA+AG vs. GG genetic models or A vs. G allele and cancer risks. In general, our results firstly indicated that PD-1.5 (rs2227981) polymorphism is associated a strongly decreased risk of cancers. Additional epidemiological studies are needed to confirm our findings.

Introduction

Programmed cell death-1 (PD-1), a member of the CD28/B7 superfamily of costimulatory molecules, is expressed on activated CD4+ and CD8+ T cells, natural killer T (NKT) cells, B cells, activated monocytes and some dendritic cell (DC) [1]. The human gene encoding PD-1 is
located on chromosome 2q37.3, which encodes a 50–55 kD type I transmembrane glycoprotein protein \([2, 3]\). The PD-1 is consisted of an immunoglobulin-like extracellular domain, and a cytoplasmic domain containing an immunoreceptor tyrosine-based inhibitory motif (ITIM) and immunoreceptor tyrosine-based switch motif (ITSM) \([4]\). PD-1 has been well characterized as a negative regulator of T cells, and when interacts with its two ligands PD-L1 (B7-H1) and PD-L2 (B7-DC), it can strongly inhibit both proliferation and cytokine production by CD4 and CD8 T lymphocytes \([5, 6]\). PD-L1 has been reported to be expressed on a variety of tumor tissues or cell lines, including breast cancer, cervical cancer, gastric carcinoma, esophageal cancer and laryngocarcinoma \([7–11]\). In addition, PD-1 is importantly involved in the regulation of regulatory T-cells (Treg) function in cancer patients. Recently, some studies have revealed a direct relation between PD-1 blockade and down-regulation of intracellular FoxP3 expression by Treg to correct immune escape in various types of tumors \([12–14]\). Based on the inhibitory role of PD-1 in anti-tumor responses, we considered the PD-1 gene (Gene bank ID: 5133) as a powerful candidate for genetic susceptibilities of individuals to cancers. Previous, most studies researched about the association between the PD-1 polymorphisms and several autoimmune diseases, including type 1 diabetes (T1D), ankylosing spondylitis (AS), SLE and rheumatoid arthritis (RA) \([15–18]\). In recent years, some studies have been changed the focus on the role of PD-1 polymorphisms in various types of cancer patients. To date, several single nucleotide polymorphisms (SNPs) have been reported for the PD-1 susceptibility of cancers in literature, such as PD-1.5 (rs2227981), PD-1.9 (rs2227982), PD-1 rs7421861 and PD-1.3 (rs11568821) et al. However, the association between the PD-1 polymorphisms and cancer risk is inconsistent. To clarify this issue, we performed a meta-analysis from all eligible studies, to assess the association of the PD-1 polymorphism with cancer risk.

**Materials and Methods**

**Primary search strategy and Inclusion Criteria**

We identified all studies reporting the relationship between PD-1 polymorphisms and cancers published before December 22, 2015 by electronically searches. The databases include Pubmed, EMBASE, the Cochrane Library database, Google Scholar, China National Knowledge Infrastructure (CNKI) and Wan Fang. The search strategies were based on combinations of the following key words: (“Programmed death-1” or “PD-1”) and (“cancer” or “carcinoma”) and (“gene” or “allele” or “genotype” or “mutation” or “variant” or “polymorphism”), without any restriction on language. The reference lists of reviews and retrieved articles were also searched by hand for additional articles. We did not enroll abstracts or unpublished studies. For inclusion, the studies must have met the following criteria: (1) studied on human beings; (2) clear objective in the relation between PD-1 polymorphisms and cancer; (3) case-control study, regardless of sample size, using a hospital-based or a population-based design; (4) sufficient published data about the size of the sample, odds ratio (OR), and their 95% confidence intervals (CIs).

**Data Extraction**

Data were carefully and independently extracted from all eligible publications by three of the authors (Wenjing Dong, Zhirong Shi and Jianjun Xiao). Any disagreement was resolved by discussion among the authors. All eligible data were listed in Table 1: the surname of the first author, date of publication, quality scores, ethnicity, sources of controls, number of cases and controls and the P value of Hardy-Weinberg Equilibrium (HWE). Different ethnicities were categorized as Asian and Caucasian. Study designs were stratified to population-based studies and hospital-based studies.
Quality assessment

Three authors (Wenjing Dong, Zhirong Shi and Jianjun Xiao) assessed the study quality independently using the Newcastle-Ottawa Scale which is a star rating system [19]. Nine stars are defined as the full score, and 5 to 9 stars are usually considered to be a high methodological quality while 0 to 4 stars are considered to be a poor quality [20]. The quality of all enrolled studies was showed in Table 2. Any disagreements on the NOS score of the studies were resolved by discussion between the authors and our meta-analysis only enrolled high quality studies.

Statistical Analysis

Crude ORs with corresponding 95% CIs were used to estimate the strength of the association between the PD-1 polymorphisms and cancer risk. The significance of the pooled OR was determined by the Z test and \( P \) (two-tailed) \(<0.05\) was considered statistically significant. Hardy-Weinberg equilibrium (HWE) in controls was calculated by chi-square test and \( P<0.05\)
signified a departure from HWE. Between-study heterogeneity was calculated by the I² test. If the heterogeneity was statistically significant (I² > 50%) [21], a random effect model (the DerSimonian and Laird method) [22] was used; otherwise, a fixed effect model (the Mantel-Haenszel method) [23] was applied. Subgroup analyses were performed by ethnicity and the control sources. The funnel plot and Egger’s test were both used to examine the publication bias. For the interpretation of Egger’s test, statistical significance was defined as P < 0.05 [24]. The statistical analysis was performed with STATA statistical software (Version 12.0; Stata Corporation, College Station, TX, USA).

Results

Study characteristics

Five hundred and sixty-eight studies were retrieved after searching and screening based on our literature search strategy. There were 18 studies left when the irrelevant studies were excluded. Out of these, 14 studies had analyzed the association between the PD-1 polymorphisms and cancers. After data extraction, one article [25] was excluded because of without control group while another one [26] was excluded as discussed about the gestational trophoblastic neoplasms, which contain both benign and malignant tumors. Hence we obtained 12 relevant studies that examined the association between the PD-1 polymorphisms and cancer risk (Fig 1) [27–38]. All of them were evaluated by Newcastle-Ottawa Scale and met the high quality (Table 2). Overall, the meta-analysis included 5,206 cancer patients and 5,174 controls from 12 articles. The information extracted from all eligible articles was summarized in Table 1. All articles we included were case-control studies. Among them, breast cancer, gastric cancer, colorectal cancer and lung cancer are studied by two articles, respectively. The rest four studies are colon, esophageal, cervical and liver cancer study, respectively. Out of the 12 studies, 7 studies focused on the PD-1.5 (rs2227981), while the PD-1.9 (rs2227982), PD-1 rs7421861 and PD-1.3
(rs11568821) were all discussed in 4 studies, respectively. Among the 12 studies included in the meta-analysis, there were 11 studies of Asians and 1 study of Caucasians. According to the control source, only 4 were hospital-based researches, the rest 8 were population-based researches.

**PD-1.5 (rs2227981)**

Data from seven studies which including 3,395 cases and 2,912 controls researched about the 
PD-1.5 (rs2227981) were pooled together. Six of the studies were population-based and only one study was hospital-based. According to the ethnicity, six articles were researched about Asians and one study was about Caucasians. We conducted analyses for all genetic models and allele in overall group, Asians subgroup and population-based subgroup. Overall, we obtained significantly decreased cancer risks both in TT vs. CC (OR = 0.72, 95% CIs: 0.62–0.85, 
P = 0.000, $I^2 = 14.0\%$), TT vs. CT+CC (OR = 0.75, 95% CIs: 0.65–0.87, P = 0.000, $I^2 = 0.0\%$) genetic models and T vs. C (OR = 0.88, 95% CIs: 0.78–0.99, P = 0.04, $I^2 = 53.6\%$) allele. However, no dramatic associations were found in the other genetic models (TT+CT vs. CC: 
OR = 0.91, 95% CIs: 0.75–1.10, P = 0.343, $I^2 = 65.6\%$; TC vs. CC: OR = 0.97, 95% CIs: 0.78–1.19, P = 0.759, $I^2 = 68.2\%$) (Fig 2). When stratified by ethnicity, similar results were obtained in Asians subgroup. Cancer risks were remarkably reduced in TT vs. CC (OR = 0.75, 95% CIs: 0.61–0.92, P = 0.006, $I^2 = 24.1\%$) and TT vs. CT+CC (OR = 0.75, 95% CIs: 0.62–0.92, P = 0.005, 
$I^2 = 10.8\%$) genetic models. There were no significant associations in TT+CT vs. CC 
(OR = 0.94, 95% CIs: 0.74–1.20 P = 0.625, $I^2 = 69.9\%$), TC vs. CC (OR = 0.99, 95% CIs: 0.76–1.30, P = 0.959, $I^2 = 72.4\%$) and T vs. C (OR = 0.90, 95% CIs: 0.77–1.05, P = 0.190, $I^2 = 59.1\%$)
Fig 2. Forest plots of the PD-1.5 (rs2227981) polymorphism and cancer risk for overall populations (A for TT vs. CC; B for TT vs. CT+CC; C for TT+CT vs. CC; D for TC vs. CC and E for T vs. C). The squares and horizontal lines correspond to the study-specific ORs and 95% CIs. The areas of the squares reflect the study-specific weights (which was the inverse of the variance). The diamonds represent the pooled ORs and 95% CIs.

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When considered the source of the control groups, we conducted analysis in population-based subgroup. Also, decreased cancer risks were found in TT vs. CC (OR = 0.71, 95% CIs: 0.61–0.84, P = 0.000, \(I^2 = 7.5\%\)), TT vs. CT + CC (OR = 0.74, 95% CIs: 0.64–0.86, P = 0.000, \(I^2 = 1.9\%\)) and T vs. C (OR = 0.84, 95% CIs: 0.78–0.91, P = 0.000, \(I^2 = 26.5\%\)). However, still we had observed no significant associations in TT + CT vs. CC (OR = 0.85, 95% CIs: 0.72–1.00, P = 0.054, \(I^2 = 52.0\%\)) and TC vs. CC (OR = 0.91, 95% CIs: 0.75–1.10, P = 0.335, \(I^2 = 61.5\%\)) (Fig 4).

**PD-1.9 (rs2227982) and PD-1 rs7421861**

The PD-1.9 (rs2227982) and PD-1 rs7421861 polymorphisms were both discussed in four studies, which including 1,961 and 1,975 cases, and 2,390 and 2,403 controls, respectively. Overall, there were no significant associations between either PD-1.9 (rs2227982) (Fig 5) or PD-1 rs7421861 (Fig 6) and cancers in all genetic models and allele (PD-1.9: TT vs. CC: OR = 1.10, 95% CIs: 0.84–1.45, P = 0.487, \(I^2 = 52.4\%\); TT vs. CT + CC: OR = 1.04, 95% CIs: 0.89–1.21, P = 0.609, \(I^2 = 15.5\%\); TT + CT vs. CC: OR = 1.06, 95% CIs: 0.93–1.22, P = 0.399, \(I^2 = 41.6\%\); TC vs. CC: OR = 1.04, 95% CIs: 0.90–1.20, P = 0.595, \(I^2 = 25.8\%\); T vs. C: OR = 1.04, 95% CIs: 0.95–1.14, P = 0.393, \(I^2 = 41.5\%\); PD-1 rs7421861: CC vs. TT: OR = 0.86, 95% CIs: 0.61–1.23, P = 0.419, \(I^2 = 0.0\%\); CC vs. CT + TT: OR = 0.84, 95% CIs: 0.59–1.19, P = 0.331, \(I^2 = 0.0\%\); CC + CT vs. TT: OR = 1.10, 95% CIs: 0.97–1.24, P = 0.137, \(I^2 = 0.0\%\); CT vs. TT: OR = 1.13, 95% CIs: 0.99–1.28, P = 0.072, \(I^2 = 0.0\%\); C vs. T: OR = 1.06, 95% CIs: 0.95–1.18, P = 0.322, \(I^2 = 0.0\%\)). All the studies about these two polymorphisms are conducted in Asians. When concerning the control sources, there are two hospital-based and two population-based articles studied about the PD-1.9 (rs2227982) polymorphism, while three hospital-based and one population-based article studied about the PD-1 rs7421861 polymorphism.

**PD-1.3 (rs11568821)**

There are four studies containing 1,280 cases and 1,236 controls discussed this polymorphism. All of these studies are population-based and conducted in Asians. Overall, a significantly decreased cancer risk was found in AG vs. GG genetic model (OR = 0.79, 95% CIs: 0.65–0.96, P = 0.021, \(I^2 = 0.0\%\)). Interestingly, an increased cancer risk was found in AA vs. AG + GG genetic model (OR = 2.25, 95% CIs: 1.30–3.87, P = 0.004, \(I^2 = 48.5\%\)). In addition, there were no associations between cancer risk and AA vs. GG (OR = 1.72, 95% CIs: 0.50–5.94, P = 0.394, \(I^2 = 59.4\%\)), AA + AG (OR = 0.92, 95% CIs: 0.63–1.32, P = 0.638, \(I^2 = 68.4\%\)) vs. GG or A vs. G (OR = 1.02, 95% CIs: 0.64–1.62, P = 0.945, \(I^2 = 85.5\%\)) (Fig 7).

**Publication bias**

We performed both funnel plots and Egger’s tests for all genetic models and allele to assess the publication bias. Our results showed all the funnel plots were symmetrical distribution that suggested absence of publication bias (S1–S6 Figs). Also the results were supported by the Egger’s tests (S1 Table).

**Discussion**

It is known to us that PD-1 is an immune gene with potent inhibitory effects on immune cells. As an important gene for the “fine turning” of T lymphocyte activation and proliferation to affect host anti-tumor immunity, PD-1 merits more investigations. Many studies have reported that over expression of PD-1 is associated with poor prognosis in several tumors, which including breast, cervical, gastric, esophageal cancers and non-small cell lung cancer.
Fig 3. Forest plots of the PD-1.5 (rs2227981) polymorphism and cancer risk for Asians subgroup (A for TT vs. CC; B for TT vs. CT+CC; C for TT+CT vs. CC; D for TC vs. CC and E for T vs. C). The squares and horizontal lines correspond to the study-specific ORs and 95% CIs. The areas of the squares reflect the study-specific weights (which was the inverse of the variance). The diamonds represent the pooled ORs and 95% CIs.

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Fig 4. Forest plots of the PD-1.5 (rs2227981) polymorphism and cancer risk for population-based subgroup (A for TT vs. CC; B for TT vs. CT+CC; C for TT+CT vs. CC; D for TC vs. CC and E for T vs. C). The squares and horizontal lines correspond to the study-specific ORs and 95% CIs. The areas of the squares reflect the study-specific weights (which was the inverse of the variance). The diamonds represent the pooled ORs and 95% CIs.

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Fig 5. Forest plots of the PD-1.9 (rs2227982) polymorphism and cancer risk for overall populations (A for TT vs. CC; B for TT vs. CT+CC; C for TT +CT vs. CC; D for TC vs. CC and E for T vs. C). The squares and horizontal lines correspond to the study-specific ORs and 95% CIs. The areas of the squares reflect the study-specific weights (which was the inverse of the variance). The diamonds represent the pooled ORs and 95% CIs.

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Fig 6. Forest plots of the PD-1 rs7421861 polymorphism and cancer risk for overall populations (A for CC vs. TT; B for CC vs. CT+TT; C for CC+CT vs. TT; D for CT vs. TT and E for C vs. T). The squares and horizontal lines correspond to the study-specific ORs and 95% CIs. The areas of the squares reflect the study-specific weights (which was the inverse of the variance). The diamonds represent the pooled ORs and 95% CIs.

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PD-1 is expressed on tumor specific T cells, when interacts with PD-Ls, expressed on tumor and immune cells, could extensively restricts host anti-tumor immunity and creates antitumor suppressive milieu [40, 41]. Accordingly, it has been considered that blockade of PD-1-PDLs interaction as an immunotherapy procedure to conquer immune-
suppression associated with cancer condition [41]. Recently, some studies had investigated the relationship between PD-1 polymorphisms and various cancers including breast, gastric, colorectal, lung and liver cancer, et al. However, the results are controversial. So we performed this meta-analysis to discuss the associations between PD-1 polymorphisms and cancer risk.

Previously, Mamat U et al. performed a meta-analysis [42] discussed the association between PD-1.5 (rs2227981) polymorphism and cancer risks. Their results showed no association between PD-1.5 (rs2227981) polymorphism and total cancer risk, but revealed an increased digestive system tumor risk. However, we found that they wrongly included one study researched about the PD-1.3 (rs11568821) polymorphism and colon cancer risk [43] in their meta-analysis. Hence, it may significantly affect their total results and digestive system tumor subgroup results. In addition, they only enrolled six studies which including a wrong one and discussed the cancer risks with one polymorphism. By contrast, our meta-analysis included 12 relevant published studies and discussed the cancer risks with four polymorphisms. Moreover, our meta-analysis included higher numbers of the cases and controls than the prior one. In addition, we evaluated the quality of studies by Newcastle-Ottawa Scale and all the studies we included were met high quality, while the prior meta-analysis did not conduct any study quality assessment. So, our meta-analysis made a more convincing and detailed evaluation than the prior study did. All the characteristics and results of the present study for PD-1.5 (rs2227981) polymorphism compared with the prior meta-analysis were summarized in Table 3.

In recent years, the application of the genome-wide association study (GWAS) in many types of diseases has exploded and lots of the GWASs about cancer risk were published. However, there is no GWAS focused on the PD-1 polymorphisms and cancer risk. Therefore, our research mainly concerned on the case-control studies. In this study, association between PD-1.5 (rs2227981), PD-1.9 (rs2227982), PD-1 rs7421861 or PD-1.3 (rs11568821) and cancers risk were examined in all genetic models and allele, and all the results were summarized in Table 4. Concerning PD-1.5, our results showed a significant decreased cancer risks both in TT vs. CC.

Table 3. Characteristics and results of the present study compared with the previous meta-analysis.

| Polymorphism       | Contrast          | No. of studies | No. of cases | No. of controls | Overall results |
|--------------------|-------------------|----------------|-------------|-----------------|----------------|
| PD-1.5 (rs2227981) | TT vs. CC         | 6              | 1,415       | 1,611           | –              |
|                    | TT vs. CT+CC      | –              | –           | –               | –              |
|                    | TT+CT vs. CC      | –              | –           | –               | –              |
|                    | TC vs. CC         | –              | –           | –               | –              |
|                    | T vs. C           | –              | –           | –               | –              |
| Asians Subgroup    | TT vs. CC         | NA             | 2,095       | 2,102           | NA             |
|                    | TT vs. CT+CC      | NA             | –           | –               | –              |
|                    | TT+CT vs. CC      | NA             | –           | –               | –              |
|                    | TC vs. CC         | NA             | –           | –               | –              |
|                    | T vs. C           | NA             | –           | –               | –              |
| Population-based Subgroup | TT vs. CC | NA             | 3,273       | 2,746           | NA             |
|                    | TT vs. CT+CC      | NA             | –           | –               | –              |
|                    | TT+CT vs. CC      | NA             | –           | –               | –              |
|                    | TC vs. CC         | NA             | –           | –               | –              |
|                    | T vs. C           | NA             | –           | –               | –              |

+, positive result; –, negative result; NA, not available
and TT vs. CT+CC genetic models for overall population, Asians and population-based controls, also significant decreased cancer risk was found in T vs. C allele for overall population. PD-1.5 located in exon 5, is a synonymous polymorphism that does not change final amino acid sequence of the protein. Thus these significant associations between PD-1.5 and cancers probably may be PD-1.5 variation linkage disequilibrium with other PD-1 gene polymorphisms that may lead to alter the PD-1 expression level [44]. Recently, Zhang Hua et al. [29] reported that the frequencies of CC genotype and C allele were higher in breast cancer patients than those in control individuals in Chinese population, and CC genotype and C allele may play a potential risk role in breast cancer. Consistently, our results indicated that in PD-1.5, TT genotype may reduce the cancers risk.

We also investigated the PD-1.9 (rs2227982) and PD-1 rs7421861 polymorphisms. It has been identified that PD-1.9, located in exon 5, is a non-synonymous SNP of PD-1, resulting the amino acid substitution from valine to alanine during protein synthesis, which probably lead to different structures and different functions of PD-1. As for PD-1 rs7421861, it is situated in intron 1 where a number of regulatory elements and splicing control elements exist [45, 46]. Therefore, due to the disruption of the splice site or alteration of the mRNA secondary structure, PD-1 rs7421861 may induce aberrant splicing, and further result in translational prevention [47–49]. However, we failed to find the associations between cancer risk and the PD-1.9 (rs2227982) or PD-1 rs7421861 in all genetic models and alleles. The limited sample size may be an important reason of the results, and we should treat the results with caution. Further studies are also needed to determine the function of these two polymorphisms.

In addition, we discussed the PD-1.3 (rs11568821) polymorphism in our meta-analysis. The PD-1.3 polymorphism was a guanine (G) to adenine (A) single nucleotide polymorphism (SNP) at nucleotide +7146 in the PD-1 intron 4. A region of PD-1 intron 4 was described as an enhancer-like structure containing binding sites for several transcription factors [50]. Existing study has shown that the PD-1.3 polymorphism in this region may affect the binding of the runt-related transcription factor 1 (RUNX1) and alter the transcriptional regulation and the efficiency of PD-1 gene [51]. Moreover, the research indicated that the presence of A allele of PD-1.3 polymorphism disrupted the binding site for RUNX1 transcription factors and resulted the impairment of PD-1 inhibitory effect and higher lymphocyte activity [50]. Hence, the A allele of PD-1.3 polymorphism may have increased tumor immunity capacity and decreased the susceptibility of cancers. Consistently, our results of PD-1.3 (rs11568821) polymorphism showed a decreased cancer risk in GA vs. GG, but an increased cancer risk was found in AA vs. AG+GG. Besides, no dramatic associations were found between AA vs. GG, AA+AG vs. GG genetic models or A vs. G allele and cancer risk. However, large scale and more rigorous analytical studies will be required to confirm the association between PD-1.3 polymorphism and cancer risk.

There are some limitations should be addressed in this meta-analysis. First of all, the limited number of participants for PD-1.3 (rs11568821) polymorphism may lead to insufficient statistical power to explore the real association. Secondly, the heterogeneities were significant in some genetic models and alleles for PD-1.5 (rs2227981) and PD-1.3 (rs11568821) polymorphisms. When we performed subgroup analyses stratified by ethnicity and control source, the heterogeneities in some subgroups were decreased or removed while in some subgroups were still existed. Thirdly, lacking of the original data limited our further evaluation of potential gene-gene, gene-environment, or even different polymorphism loci of the same gene, which all may affect cancer risk.

In summary, our meta-analysis suggested that the PD-1.5 (rs2227981) polymorphism is associated with significantly decreased cancer risks both in TT vs. CC and TT vs. CT+CC genetic models, no matter for overall population, Asians subgroup or population-based...
subgroup, also the decreased cancer risk was found in T vs. C allele for overall population. No associations were found between the cancer risks and PD-1 rs2227982 or PD-1 rs7421861 in all genetic models and allele. In addition, for PD-1 rs11568821 polymorphism, we found different cancer susceptibility between GA vs. GG and AA vs. AG+GG genetic models, and no associations between AA vs. GG, AA+AG vs. GG genetic models or A vs. G allele and cancer risk. However, our results firstly revealed a significantly decreased risk between PD-1 polymorphisms and cancers, even though the data may be limited. Hence, large scale, well-designed epidemiological studies will be required to confirm our findings in the future.

**Supporting Information**

S1 Fig. Funnel plot for publication bias of the PD-1.5 (rs2227981) polymorphism and cancer risk for overall populations (A for TT vs. CC; B for TT vs. CT+CC; C for TT+CT vs. CC; D for TC vs. CC and E for T vs. C).

(TIF)
S2 Fig. Funnel plot for publication bias of the PD-1.5 (rs2227981) polymorphism and cancer risk for Asians subgroup (A for TT vs. CC; B for TT vs. CT+CC; C for TT+CT vs. CC; D for TC vs. CC and E for T vs. C).

(SIF)

S3 Fig. Funnel plot for publication bias of the PD-1.5 (rs2227981) polymorphism and cancer risk for population-based subgroup (A for TT vs. CC; B for TT vs. CT+CC; C for TT+CT vs. CC; D for TC vs. CC and E for T vs. C).

(SIF)

S4 Fig. Funnel plot for publication bias of the PD-1.9 (rs2227982) polymorphism and cancer risk for overall populations (A for TT vs. CC; B for TT vs. CT+CC; C for TT+CT vs. CC; D for TC vs. CC and E for T vs. C).

(SIF)

S5 Fig. Funnel plot for publication bias of the PD-1 rs7421861 polymorphism and cancer risk for overall populations (A for CC vs. TT; B for CC vs. CT+TT; C for CC+CT vs. TT; D for CT vs. TT and E for C vs. T).

(SIF)

S6 Fig. Funnel plot for publication bias of the PD-1.3 (rs11568821) polymorphism and cancer risk for overall populations (A for AA vs. GG; B for AA vs. AG+GG; C for AA+AG vs. GG; D for AG vs. GG and E for A vs. G).

(SIF)

S1 Meta-Analysis on Genetic Association Studies Form.

(DOCX)

S1 Table. Summary of the Egger's test P-value

(DOCX)

Author Contributions

Conceived and designed the experiments: JWP. Performed the experiments: WJD. Analyzed the data: MCG ZRS. Contributed reagents/materials/analysis tools: ZRS JJX JKZ. Wrote the paper: WJD MCG.

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