Relationship of Programmed Death-1 (PD-1) and Programmed Death Ligand-1 (PD-L1) Polymorphisms with Overall Cancer Susceptibility: An Updated Meta-Analysis of 28 Studies with 60,612 Subjects

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Background:
Programmed death-1 and its ligand-1 (PD-1/PD-L1) regulate tumor immunotherapy. A large number of studies have explored the relationship between PD-1, PD-L1, and different tumor susceptibility. However, these conclusions are not always consistent. Therefore, we updated this meta-analysis.

Material/Methods:
MEDLINE, Web of Science, EMBASE and other databases were searched systematically to obtain related research. Then, we used STATA15.0 software to carry out the final meta-analysis. The computational advantage is better than OR to evaluate this relationship.

Results:
A total of a total of 28 related studies were involved in our meta-analysis. It was found that PD-1 rs11568821 and rs7421861 increased the overall cancer probability in the allelic genetic model, while PD-1 rs36084323 effectively reduced the risk of cancer in the dominant genetic model. In the homozygous genetic model, PD-L1 rs17718883 effectively increased the probability of tumorigenesis. PD-L1 rs4143815 is associated with a reduced incidence of cancer in heterozygote, homozygote and dominant genetic patterns. Subgroup analysis showed that PD-1 rs2227981 can promote the susceptibility to breast cancer, while PD-1 rs2227982 can reduce the susceptibility to breast cancer. PD-L1 rs2890658 can significantly reduce the risk of lung and liver cancer.

Conclusions:
PD-1 rs11568821, rs36084323, rs7421861, PD-L1 rs17718883, and rs4143815 are associated with tumor susceptibility. However, a review based on more experimental evidence is needed to verify our findings.

Keywords:
Disease Susceptibility • Genes, Neoplasm • Meta-Analysis • PDCD1 Protein, Human

Abbreviations:
PD-1 – programmed cell death-1; PD-L1 – programmed cell death ligand-1; CNKI – China National Knowledge Infrastructure; ORs – odds ratios; CIs – confidence intervals; TME – the tumor microenvironment; APCs – antigen-presenting cells; ICB – immune checkpoint blockade; SNPs – single-nucleotide polymorphisms; HWE – Hardy-Weinberg equilibrium; CTLA-4 – cytotoxic T lymphocyte-associated protein 4; FDA – Food and Drug Administration; NOS – Newcastle-Ottawa Scale; PCR – polymerase chain reaction; LDR – ligase detection reaction; qRT – quantitative real time; RFLP – restriction fragment length polymorphism

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**Background**

Cancer is a serious global problem. According to the American Cancer Society (ACS), there were more than 1.8 million new cancer cases and 606,520 cancer-related deaths in the United States last year [1]. In the past few decades, considerable progress has been made in understanding how cancer successfully escapes from the immune system and survives, and these advances provide an active way to overcome tumor immune escape and may help to eliminate cancer cells [2]. As a preliminary study, immunotherapy is mainly concentrated in immune checkpoints [3]. Programmed cell death protein 1 and its ligand (PD-1/PD-L1) pathway play an important role in the induction and maintenance of immune tolerance in the tumor microenvironment [4]. Early studies have shown that several IgG4 antibodies point to PD-1/PD-L1 in some solid tumors. These studies have helped to improve the first round of PD-1 inhibitors, such as nivolumab, which were approved by the U.S. Food and Drug Administration (FDA) in 2014 [5]. PD-L1, pointing to PD-1, on T cells helps to destroy cancer cells. However, tumor cells show immune escape through the expression of PD-L1 [6]. The overexpression of PD-L1 in many kinds of cells, such as cancer cells and antigen-presenting cell (APC), is considered to be the key factor for maintaining anti-tumor immunity in the tumor microenvironment (TME) and tumor draining lymph nodes. The increase of PD-L1 level is related to the enhancement of (ICB) response blocked by immune checkpoints against PD-1/PD-L1 [7]. Due to the complexity of tumor immunity, there is no definite biomarker to evaluate the results of PD-1/PD-L1 targeted therapy [8]. It is very important to identify the single-nucleotide polymorphism (SNP) that affects expression of the PD-1 gene and participates in tumor susceptibility. Therefore, it will help to predict potential individuals and clarify the pathophysiological mechanism of cancer [9]. A growing number of studies have explored the relationship between PD-1 and PD-L1 single-nucleotide polymorphisms and multiple cancer susceptibility. However, their results are not consistent, and the same location has different effects in different studies [10-19]. More systematic reviews are needed to support the evidence of these results. To address this problem, we propose a new meta-analysis to assess the relationship between PD-1 and PD-L1 and cancer susceptibility.

**Material and Methods**

**Literature Search**

The related literatures in the databases of PubMed, Web of Science, EMBASE, and China National knowledge Infrastructure (CNKI) and Wanfang data information Service platform were searched by computer, and the related research was carried out. To determine the relationship between PD-1/PD-L1 mutations and cancer susceptibility, we used the following keywords: (programmed cell death 1 or programmed cell death ligand1 or PD-1 or PDCD1 or PD-L1 or CD274 or B7-H1) and (polymorphism or genotype or variant or SNP) and (cancer or carcinoma or neoplasm).

We searched for relevant published research until March 28, 2019, and also searched the literature for relevant dissertations. **Figure 1** shows a flowchart of search strategies that illustrate PD-1 and PD-L1 variants and cancer predisposition.

**Inclusion and Exclusion Criteria**

The process of retrieving studies is shown in **Figure 1**. We list the inclusion and exclusion standards below.

**Inclusion Criteria**

The inclusion criteria were: (1) Case-control studies on the relationship of PD-1 and PD-L1 variant with cancer predisposition; (2) The genotypes of control groups were in Hardy-Weinberg equilibrium (HWE); (3) Allele frequencies in studies were shown; (4) English and Chinese articles; and (5) Studies with human subjects.

**Exclusion Criteria**

The exclusion criteria were as follows: (1) genotypes in the control group did not conform to HWE; (2) studies of genotype frequency estimates of odds ratio (OR) and 95% confidence interval (CI) could not be obtained; (3) useful data or results could not be extracted; (4) the results were not related to cancer susceptibility; (5) the article was a duplicate publication or existed only as an abstract.

**Data Extraction**

The data were extracted independently by 2 authors. If necessary, the differences between the 2 authors were resolved through discussion with a third investigator. All valid data are shown in **Table 1**: author’s name, year, country, nationality, cancer type, number of groups, P value of HWE, and genotype method.

**Trials Quality Assessment**

The quality of the selected articles was evaluated with the Ottawa Newcastle scale (NOS). The NOS score was ranged from 0 to 9. Scores greater than 5 indicate high-quality articles. **Table 2** lists the quality of all selected studies. The assessment includes the following 3 parts: (1) selection of subjects; (2) comparability between groups; and (3) exposure assessment.
Statistical Analyses

STATA15.0 software was used for statistical analysis. Q test and heterogeneity coefficient $I^2$ were used to evaluate the heterogeneity of the study. If there was no statistical heterogeneity ($I^2 < 50\%$), our meta-analysis used a fixed-effect model, as well as random effects. The combined OR value and its 95% CI were evaluated to assess the relationship. We include 5 genetic models: (1) allele, (2) heterozygote, (3) homozygote, (4) dominance, and (5) recessive model, and studies the relationship between them. If it was indispensable, we analyzed the relevant causes that may have led to heterogeneity in groups. We used the funnel chart and the P value of Egger’s and Begg’s test to judge the publication deviation.

Results

Based on our search strategy, a total of 476 appropriate and related articles were identified. In the end, 28 articles were screened out for analysis.
### Table 1. Characteristics of the selected articles.

| Genotype | n | First author | Year | Country | Ethnicity | Cancer type | Case | Control | HWE | Genotype methods |
|----------|---|---------------|------|---------|-----------|-------------|------|---------|-----|-----------------|
| PD-1 rs10204525 | 6 | Zhou R-M | 2016 | China | Asian | Esophageal cancer | 33 | 226 325 | 51 | 238 296 0.748 | PCR–LDR |
|            |    | Zang B | 2019 | China | Asian | Esophageal cancer | 63 | 329 420 | 50 | 359 551 0.388 | qRT-PCR |
|            |    | Ren H-T | 2016 | China | Asian | Breast cancer | 54 | 248 257 | 51 | 240 291 0.879 | PCR |
|            |    | Tang WF | 2015 | China | Asian | Gastric cancer | 21 | 123 169 | 53 | 219 309 0.119 | PCR–LDR |
|            |    | Qiu H | 2014 | China | Asian | Esophageal cancer | 43 | 240 317 | 63 | 243 345 0.038 | PCR–LDR |
|            |    | Tang WF | 2017 | China | Asian | Esophageal cancer | 544 | 397 98 | 870 | 672 132 0.887 | PCR–LDR |
| PD-1 rs11568821 | 5 | Fathi F | 2019 | Iran | Asian | Basal cell cancer | 3 | 183 24 | 7 | 58 255 0.099 | PCR-RFLP |
|            |    | Bayram S | 2012 | Turkey | Asian | Hepatocellular carcinoma | 0 | 191 45 | 0 | 56 180 0.038 | PCR-RFLP |
|            |    | Haghsenas MR | 2011 | Iran | Asian | Breast cancer | 8 | 365 63 | 4 | 55 231 0.725 | PCR-RFLP |
|            |    | Ma Y | 2015 | China | Asian | Non-small cell lung cancer | 0 | 426 102 | 2 | 142 456 0.009 | PCR-RFLP |
|            |    | Fathi F | 2018 | Iran | Asian | Carcinomas of head and neck | 4 | 119 27 | 5 | 32 113 0.162 | PCR-RFLP |
| PD-1 rs17718883 | 3 | Xie Q | 2018 | China | Asian | Hepatocellular carcinoma | 215 | 8 2 | 108 69 | 23 0.025 | PCR-RFLP |
|            |    | Li Q | 2018 | China | Asian | Gastric cancer | 87 | 13 1 | 77 | 48 16 0.054 | PCR |
|            |    | Chen S | 2017 | China | Asian | Hepatocellular carcinoma | 122 | 1 0 | 77 | 48 16 0.054 | PCR |
| PD-1 rs2227981 | 11 | Fathi F | 2019 | Iran | Asian | Basal cell carcinoma | 30 | 87 93 | 150 134 | 36 0.466 | PCR-RFLP |
|            |    | Zhou R-M | 2016 | China | Asian | Esophageal cancer | 52 | 241 291 | 46 | 229 310 0.683 | PCR–LDR |
|            |    | Li XF | 2016 | China | Asian | Cervical cancer | 44 | 167 45 | 87 | 101 62 0.004 | PCR-RFLP |
|            |    | Ma Y | 2015 | China | Asian | Non-small cell lung cancer | 68 | 216 244 | 98 | 246 256 0.004 | PCR-RFLP |
|            |    | Fathi F | 2018 | Iran | Asian | Carcinomas of head and neck | 16 | 69 65 | 13 | 71 66 0.317 | PCR-RFLP |
|            |    | Hua Z | 2011 | China | Asian | Breast cancer | 22 | 169 295 | 24 | 210 244 0.012 | PCR-RFLP |
|            |    | Mojtabehed Z | 2012 | Iran | Asian | Colorectal cancer | 32 | 109 59 | 36 | 89 75 0.290 | PCR-RFLP |
|            |    | Li Y | 2016 | China | Asian | Ovarian cancer | 351 | 233 351 | 51 | 250 319 0.837 | PCR–LDR |
|            |    | We L | 2017 | China | Asian | Ovarian cancer | 7 | 42 67 | 6 | 44 60 0.571 | RT-PCR |
|            |    | Haghsenas MR | 2010 | Iran | Asian | Breast cancer | 50 | 191 194 | 46 | 145 137 0.445 | PCR-RFLP |
|            |    | Sanaz Savabkar | 2013 | Iran | Asian | Gastric cancer | 6 | 66 50 | 7 | 70 89 0.136 | PCR-RFLP |
Table 1 continued. Characteristics of the selected articles.

| Genotype | n | First author | Year | Country | Ethnicity | Cancer type | Case | Control | HWE | Genotype methods |
|----------|---|--------------|------|---------|-----------|-------------|------|---------|-----|-----------------|
| PD-1     |    |              |      |         |           |             |      |         |     |                 |
| rs2227982| 10| Zhou R-M     | 2016 | China   | Asian     | esophageal cancer | 149 305 130 | 150 297 138 | 0.702 | PCR-LDR         |
|          |    | Tan D        | 2017 | China   | Asian     | ovarian cancer    | 87 60 17 | 111 48 11 | 0.075 | qRT-PCR         |
|          |    | Ma Y         | 2015 | China   | Asian     | non-small cell lung cancer | 343 148 37 | 404 168 28 | 0.056 | PCR-RFLP        |
|          |    | Hua Z        | 2011 | China   | Asian     | breast cancer     | 111 249 127 | 95 268 143 | 0.121 | PCR-RFLP        |
|          |    | Kasamatsu T  | 2019 | Japan   | Asian     | multiple myeloma  | 55 116 40 | 43 55 26 | 0.285 | PCR-RFLP        |
|          |    | Tang WF      | 2015 | China   | Asian     | gastric cancer    | 75 168 87 | 163 292 148 | 0.448 | PCR-LDR         |
|          |    | Qiu H        | 2014 | China   | Asian     | esophageal cancer  | 159 303 154 | 189 325 167 | 0.245 | PCR-LDR         |
|          |    | Tang WF      | 2017 | China   | Asian     | esophageal cancer  | 220 549 272 | 416 816 442 | 0.309 | PCR-LDR         |
|          |    | Tang WF      | 2017 | China   | Asian     | esophageal cancer  | 87 168 75 | 148 292 163 | 0.448 | PCR-LDR         |
|          |    | Ren H-T      | 2016 | China   | Asian     | breast Cancer     | 172 257 128 | 137 299 146 | 0.503 | PCR             |
| PD-1     |    |              |      |         |           |              |      |         |     |                 |
| rs2890658| 6 | Chen Y-B     | 2014 | China   | Asian     | non-small cell lung cancer | 242 48 3 | 266 26 1 | 0.671 | PCR-RFLP        |
|          |    | Xie Q        | 2018 | China   | Asian     | hepatocellular carcinoma | 170 49 6 | 139 55 6 | 0.844 | PCR-RFLP        |
|          |    | Zhou R-M     | 2017 | China   | Asian     | esophageal cancer  | 18 161 396 | 15 144 418 | 0.541 | PCR-LDR         |
|          |    | Li Q         | 2016 | China   | Asian     | gastric cancer    | 79 20 2 | 98 39 4 | 0.959 | PCR             |
|          |    | Ma Y         | 2015 | China   | Asian     | non-small cell lung cancer | 416 106 6 | 512 84 4 | 0.785 | PCR-RFLP        |
|          |    | Chen S       | 2017 | China   | Asian     | hepatocellular carcinoma | 95 27 1 | 98 39 4 | 0.959 | PCR             |
| PD-1     |    |              |      |         |           |              |      |         |     |                 |
| rs3608432| 10| Zhou R-M     | 2016 | China   | Asian     | esophageal cancer  | 134 303 147 | 142 298 145 | 0.649 | PCR-LDR         |
|          |    | Zang B       | 2019 | China   | Asian     | esophageal cancer  | 8 132 673 | 12 188 761 | 0.919 | qRT-PCR         |
|          |    | Hua Z        | 2011 | China   | Asian     | esophageal cancer  | 116 271 103 | 112 260 140 | 0.673 | PCR             |
|          |    | Kasamatsu T  | 2019 | Japan   | Asian     | multiple myeloma  | 50 110 51 | 33 54 37 | 0.154 | PCR-RFLP        |
|          |    | Bôas Gomez GV| 2018 | Brazil  | Caucasian | Cutaneous Melanoma | 6 18 226 | 0 25 225 | 0.405 | qRT-PCR         |
|          |    | Ma Y         | 2015 | China   | Asian     | non-small cell lung cancer | 138 246 144 | 148 296 156 | 0.747 | PCR-RFLP        |
|          |    | Li Y         | 2016 | China   | Asian     | ovarian cancer    | 169 301 150 | 129 323 168 | 0.251 | PCR-RFLP        |
|          |    | We L         | 2017 | China   | Asian     | ovarian cancer    | 37 57 22 | 21 53 36 | 0.849 | PCR-LDR         |
|          |    | Zhao Y       | 2018 | China   | Asian     | colorectal cancer  | 116 207 96 | 123 253 121 | 0.686 | PCR-RFLP        |
|          |    | Tang WF      | 2017 | China   | Asian     | esophageal cancer  | 282 521 238 | 444 800 430 | <0.001 | PCR-LDR         |
mutations and cancer susceptibility. Six trials involving 3797 subjects confirmed the relationship between PD-L1 rs2890658 and cancer susceptibility. Six studies, including 3015 subjects, estimated the relationship between PD-L1 rs4143815 and cancer susceptibility.

Meta-analysis Results

Table 3 contains our meta-analysis summary of PD-1 and PD-L1 variants and cancer susceptibility. Table 4 lists the subgroup analyses based on cancer type.

ORs of PD-1 SNPs and Cancer Predisposition

As regards PD-1 rs11568821 polymorphism, we revealed the variant increased the cancer predisposition in the allele genetic model (OR=1.314, 95% CI=1.116-1.547, P=0.001, G vs A). PD-1 rs36084323 variant was proved to decrease the cancer risk in dominant genetic model (OR=0.903, 95% CI =0.819-0.995, P=0.038, GG+GA vs AA). PD-1 rs7421861 variant was found to enhance cancer predisposition in the heterozygote model (OR=1.202, 95% CI=1.031-1.402, P=0.0019, TT vs CC) and dominant genetic model (OR=1.181, 95% CI=1.020-1.368, P=0.026, TT+CT vs CC). No clear relationship was found between rs2227981, rs227982, and rs10204525 variants and cancer susceptibility. Forest plots of meta-analysis of PD-1 rs11568821 and rs10204525 in the allele model are demonstrated in Figure 2. Forest plots of meta-analysis on PD-1 rs36084323 and rs2227981 in the dominant model are shown in Figure 3. Forest plots of the meta-analysis of PD-1 rs7421861 in the heterozygote model and dominant model are presented in Figure 4.

Subgroup Analysis of PD-1 SNPs and the Cancer Predisposition

We conducted some subgroup analyses that were based on cancer types. We detected PD-1 rs2227981 promoted the predisposition of breast cancer (OR=1.219, 95% CI=1.045-1.422, p=0.012, C vs T, Figure 5). PD-1 rs2227982 variant was

Table 1 continued. Characteristics of the selected articles.

| Genotype | n  | First author | Year | Country | Ethnicity | Cancer type                  | Case | Control | HWE     | Genotype methods |
|----------|----|--------------|------|---------|-----------|-------------------------------|------|---------|---------|-----------------|
| PD-L1    |    |              |      |         |           |                               |      |         |         |                 |
| rs4143815| 6  | Wang W       | 2013 | China   | Asian     | Gastric cancer                | 45   | 72      | 88      | 135 188 79 0.746 | PCR             |
|          |    | Tan D        | 2017 | China   | Asian     | Ovarian cancer                | 31   | 82      | 51      | 54 78 38 0.334 | qRT-PCR         |
|          |    | Xie Q        | 2018 | China   | Asian     | Hepatocellular carcinoma      | 50   | 101     | 74      | 65 104 31 0.316 | PCR-RFLP        |
|          |    | Zhou R-M     | 2017 | China   | Asian     | Esophageal cancer             | 211  | 277     | 87      | 203 289 85 0.275 | PCR-LDR         |
|          |    | Li Q         | 2016 | China   | Asian     | Gastric cancer                | 41   | 47      | 13      | 49 76 16 0.09   | PCR              |
|          |    | Chen S       | 2017 | China   | Asian     | Hepatocellular carcinoma      | 50   | 50      | 23      | 49 76 16 0.09   | PCR              |
| PD-1     | 8  |              |      |         |           |                               |      |         |         |                 |
| rs7421861|    | Tang WF      | 2017 | China   | Asian     | Esophageal cancer             | 7    | 91      | 226     | 22 168 408 0.368 | PCR-LDR         |
|          |    | Zang B       | 2019 | China   | Asian     | Esophageal cancer             | 343  | 370     | 100     | 457 411 92 0.977 | PCR-RFLP        |
|          |    | Hua Z        | 2011 | China   | Asian     | Breast cancer                 | 11   | 146     | 333     | 12 130 370 0.884 | PCR-RFLP        |
|          |    | Tang WF      | 2015 | China   | Asian     | Gastric cancer                | 7    | 91      | 226     | 22 168 408 0.367 | PCR-LDR         |
|          |    | Qiu H        | 2014 | China   | Asian     | Esophageal cancer             | 21   | 168     | 411     | 25 188 460 0.295 | PCR-LDR         |
|          |    | Jie Ge       | 2015 | China   | Asian     | Colorectal cancer             | 14   | 187     | 395     | 17 163 440 0.684 | PCR-RFLP        |
|          |    | Tang WF      | 2017 | China   | Asian     | Esophageal cancer             | 41   | 358     | 642     | 54 454 1166 0.232 | PCR-LDR         |
|          |    | Ren H-T      | 2016 | China   | Asian     | Breast cancer                 | 23   | 196     | 341     | 28 205 347 0.746 | PCR              |
Table 2. Quality assessment based on the Newcastle-Ottawa Scale of trials included in this meta-analysis.

| Items            | Adequacy of case definition | Representativeness of the cases | Selection of controls | Definition of controls | Comparability | Ascertained of exposure | Same method of ascertainment | Non-response rate | Total scores |
|------------------|-----------------------------|--------------------------------|-----------------------|------------------------|---------------|-------------------------|-------------------------------|------------------|--------------|
| Tao, 2017        | ◆                           | ◆                              | NA                    | NA                     | NA            | ◆                       | ◆                             | NA               | 4            |
| Cheng, 2017      | NA                          | ◆                              | NA                    | ◆                      | ◆             | ◆                       | ◆                             | NA               | 7            |
| Zhou, 2017       | ◆                           | ◆                              | NA                    | ◆                      | ◆             | ◆                       | ◆                             | ◆                | 8            |
| Li, 2016         | ◆                           | ◆                              | NA                    | NA                     | ◆             | ◆                       | ◆                             | ◆                | 6            |
| Mojtabahi, 2012  | ◆                           | NA                             | NA                    | ◆                      | ◆             | ◆                       | ◆                             | ◆                | 6            |
| Qiu, 2014        | ◆                           | ◆                              | NA                    | ◆                      | ◆             | ◆                       | ◆                             | ◆                | 8            |
| Tang, 2015       | ◆                           | ◆                              | NA                    | NA                     | ◆             | ◆                       | ◆                             | ◆                | 7            |
| Haghshenas, 2011 | ◆                           | NA                             | NA                    | ◆                      | ◆             | ◆                       | ◆                             | ◆                | 6            |
| Li, 2016         | ◆                           | ◆                              | NA                    | ◆                      | ◆             | ◆                       | ◆                             | ◆                | 8            |
| Kasamatsu, 2019  | ◆                           | ◆                              | NA                    | NA                     | NA            | ◆                       | ◆                             | ◆                | 5            |
| Boas, 2018       | NA                          | ◆                              | NA                    | NA                     | ◆             | ◆                       | ◆                             | ◆                | 5            |
| Wei, 2017        | ◆                           | ◆                              | NA                    | ◆                      | ◆             | ◆                       | ◆                             | ◆                | 8            |
| Fathi, 2018      | ◆                           | NA                             | NA                    | ◆                      | ◆             | ◆                       | ◆                             | ◆                | 6            |
| Xie, 2018        | ◆                           | ◆                              | NA                    | ◆                      | ◆             | ◆                       | ◆                             | ◆                | 8            |
| Emma, 2010       | NA                          | ◆                              | NA                    | ◆                      | ◆             | ◆                       | ◆                             | ◆                | 4            |
| Bay, 2012        | ◆                           | ◆                              | NA                    | ◆                      | ◆             | ◆                       | ◆                             | ◆                | 8            |
| Zhou, 2016       | ◆                           | ◆                              | NA                    | ◆                      | ◆             | ◆                       | ◆                             | ◆                | 7            |
| Li, 2016         | ◆                           | ◆                              | NA                    | ◆                      | ◆             | ◆                       | ◆                             | ◆                | 8            |
| Haghshenas, 2016 | NA                          | NA                             | NA                    | ◆                      | NA            | ◆                       | ◆                             | ◆                | 3            |
| Namavar, 2017    | ◆                           | NA                             | NA                    | ◆                      | ◆             | ◆                       | ◆                             | ◆                | 6            |
| Ge, 2015         | ◆                           | ◆                              | NA                    | ◆                      | ◆             | ◆                       | ◆                             | ◆                | 6            |
| Wang, 2013       | ◆                           | ◆                              | NA                    | ◆                      | ◆             | ◆                       | ◆                             | ◆                | 7            |
| Chen, 2014       | NA                          | ◆                              | NA                    | ◆                      | ◆             | ◆                       | ◆                             | ◆                | 6            |
| Tan, 2017        | ◆                           | ◆                              | NA                    | ◆                      | ◆             | ◆                       | ◆                             | ◆                | 7            |
| Zang, 2020       | NA                          | NA                             | NA                    | NA                     | NA            | ◆                       | ◆                             | ◆                | 5            |
| Ren, 2016        | ◆                           | ◆                              | NA                    | ◆                      | ◆             | ◆                       | ◆                             | ◆                | 6            |
| Ma, 2015         | ◆                           | ◆                              | NA                    | ◆                      | ◆             | ◆                       | ◆                             | ◆                | 7            |
| Hua, 2011        | ◆                           | ◆                              | NA                    | ◆                      | ◆             | ◆                       | ◆                             | ◆                | 7            |
| Tang, 2017       | ◆                           | ◆                              | NA                    | ◆                      | ◆             | ◆                       | ◆                             | ◆                | 6            |
| Fathi, 2019      | ◆                           | ◆                              | NA                    | ◆                      | ◆             | ◆                       | ◆                             | ◆                | 7            |
| Zhao, 2018       | ◆                           | ◆                              | NA                    | ◆                      | ◆             | ◆                       | ◆                             | ◆                | 5            |
| Genotype         | Contrast model          | OR (95%CI)     | P      | Test for heterogeneity | L² (%) | P      | Analysis model |
|------------------|-------------------------|----------------|--------|------------------------|--------|--------|----------------|
| rs10204525       | A vs G                  | 1.002 (0.889-1.129) | 0.976  | 67.50                  | 0.009  | R      |                |
|                  | AA vs GG                | 1.073 (0.866-1.331) | 0.517  | 49.00                  | 0.081  | R      |                |
|                  | AA+GA vs GG             | 1.068 (0.843-1.354) | 0.586  | 61.80                  | 0.023  | R      |                |
|                  | AA vs AG+GG             | 0.995 (0.856-1.599) | 0.943  | 59.40                  | 0.031  | R      |                |
| rs11568821       | G vs A                  | 1.314 (1.116-1.547) | 0.001  | 0.00                   | 0.609  | T      |                |
|                  | AG vs AA                | 0.911 (0.437-1.898) | 0.803  | 0.00                   | 0.716  | F      |                |
|                  | GG vs AA                | 1.298 (0.644-2.618) | 0.466  | 0.00                   | 0.691  | F      |                |
|                  | GG+GA vs AA             | 1.221 (0.606-2.459) | 0.576  | 0.00                   | 0.698  | T      |                |
|                  | GG vs GA+AA             | 1.061 (0.955-1.180) | 0.270  | 0.00                   | 1.000  | F      |                |
| rs17718883       | C vs G                  | 14.156 (4.024-49.805) | <0.001 | 85.10                  | 0.001  | R      |                |
|                  | GC vs GG                | 2.077 (0.645-6.691) | 0.221  | 0.00                   | 0.626  | F      |                |
|                  | CC vs GG                | 25.488 (8.494-76.481) | <0.001 | 0.00                   | 0.829  | F      |                |
|                  | CC+CG vs GG             | 16.615 (5.365-49.609) | <0.001 | 0.00                   | 0.869  | F      |                |
|                  | CC vs CG+GG             | 16.361 (4.203-63.685) | <0.001 | 84.60                  | 0.001  | R      |                |
|                  | C vs T                  | 1.077 (0.753-1.539) | 0.686  | 96.20                  | <0.001 | R      |                |
|                  | TC vs TT                | 1.054 (0.542-2.058) | 0.873  | 0.00                   | 0.036  | F      |                |
| rs2227981        | CC vs TT                | 1.095 (0.531-2.260) | 0.805  | 95.20                  | <0.001 | R      |                |
|                  | CC+CT vs TT             | 1.085 (0.548-2.146) | 0.815  | 95.50                  | <0.001 | R      |                |
|                  | CC vs CT+TT             | 1.059 (0.759-1.464) | 0.771  | 91.60                  | <0.001 | R      |                |
| rs2227982        | C vs T                  | 0.981 (0.898-1.071) | 0.665  | 56.00                  | 0.015  | R      |                |
|                  | TC vs TT                | 1.050 (0.952-1.158) | 0.330  | 0.00                   | 0.773  | F      |                |
|                  | CC vs TT                | 0.977 (0.824-1.157) | 0.787  | 50.20                  | 0.034  | R      |                |
|                  | CC+CT vs TT             | 1.028 (0.938-1.127) | 0.555  | 0.00                   | 0.498  | F      |                |
|                  | CC vs CT+TT             | 0.942 (0.809-1.096) | 0.437  | 64.30                  | 0.003  | R      |                |
| rs2890658        | A vs C                  | 1.002 (0.718-1.400) | 0.989  | 79.80                  | <0.001 | R      |                |
|                  | CA vs CC                | 1.154 (0.902-1.476) | 0.254  | 0.00                   | 0.933  | F      |                |
|                  | AA vs CC                | 1.121 (0.596-1.806) | 0.638  | 0.00                   | 0.036  | F      |                |
|                  | AA+AC vs CC             | 1.159 (0.915-1.469) | 0.220  | 0.00                   | 0.640  | F      |                |
|                  | AA vs AC+CC             | 1.002 (0.662-1.515) | 0.994  | 76.90                  | 0.001  | R      |                |
|                  | G vs A                  | 0.930 (0.862-1.000) | 0.106  | 49.80                  | 0.036  | F      |                |
| rs36084323       | AG vs AA                | 0.933 (0.842-1.034) | 0.189  | 31.30                  | 0.158  | F      |                |
|                  | GG vs AA                | 0.829 (0.701-0.981) | 0.029  | 38.80                  | 0.099  | R      |                |
|                  | GG+GA vs AA             | 0.903 (0.819-0.995) | 0.038  | 35.10                  | 0.127  | T      |                |
|                  | GG vs GA+AA             | 0.913 (0.798-1.044) | 0.183  | 49.00                  | 0.039  | R      |                |
|                  | C vs G                  | 0.752 (0.555-1.019) | 0.066  | 86.90                  | <0.001 | R      |                |
| rs4143815        | GC vs GG                | 0.560 (0.365-0.860) | 0.008  | 76.00                  | 0.001  | R      |                |
|                  | CC vs GG                | 0.537 (0.315-0.918) | 0.023  | 82.00                  | <0.001 | R      |                |
|                  | CC+CG vs GG             | 0.555 (0.351-0.877) | 0.012  | 81.50                  | <0.001 | R      |                |
|                  | CC vs CG+GG             | 0.809 (0.575-1.138) | 0.223  | 75.70                  | 0.001  | R      |                |

Table 3. Meta-analyses on PD-1 and PD-L1 variants and cancer susceptibility.
confirmed to decrease breast cancer risk in the allele model (OR=1.173, 95% CI=1.040-1.322, P=0.010, C vs T, Figure 5); homozygote model (OR=1.379, 95% CI=1.081-1.758, P=0.010, CC vs TT) and recessive genetic model (OR=1.375, 95% CI=1.126-1.679, P=0.002, CC vs TT). As regards the PD-1 rs36084323, our analyses results showed this polymorphism lowered the ovarian cancer predisposition in the heterozygote model (OR=0.695, 95% CI=0.538-0.897, P=0.005, AG vs AA); homozygote model (OR=0.615, 95% CI=0.459-0.823, P=0.001, GG vs AA, Figure 6) and dominant genetic model (OR=0.666, 95% CI=0.523-0.847, P=0.001, GG+GA vs AA, Figure 6).

**Meta-analyses on PD-1 and PD-L1 variants and cancer susceptibility.**

| Genotype | Contrast model | OR (95%) | P       | Test for heterogeneity | Analysis model |
|----------|----------------|----------|---------|------------------------|----------------|
|          |                |          |         | I² (%)                 |                |
| rs7421861| T vs C         | 0.980    | 0.855-1.124 | 0.777 | 74.20 | <0.001 | R |
|          | TC vs CC       | 1.202    | 1.031-1.402 | 0.019 | 0.00 | 0.963 | F |
|          | TT vs CC       | 1.171    | 0.969-1.416 | 0.102 | 19.80 | 0.272 | F |
|          | TT+CT vs CC    | 1.181    | 1.020-1.368 | 0.026 | 0.00 | 0.642 | F |
|          | TT vs CT+CC    | 0.947    | 0.811-1.106 | 0.492 | 68.10 | 0.003 | R |

**Discussion**

It has recently been confirmed that checkpoint blockade immunotherapy is one of the reasons for the continued decline in cancer mortality [1]. Single-nucleotide polymorphisms are expected to become biomarkers to help scientists classify tumors and will allow patients to be assigned to the most appropriate treatment [42]. PD-1 and PD-L1 play an indispensable role in immune tolerance, and they have become key targets in cancer therapy [43]. Some articles have discussed the relationship between PD-1 and PD-L1 mutations and different cancer susceptibility, but the conclusions are still inconsistent. Our study estimated the relationship between 9
Table 4. Subgroup analyses based on cancer type.

| Genotype | Subgroup | n | Contrast model | OR (95% CI) | P  | Test for heterogeneity | Analysis model |
|----------|----------|---|----------------|-------------|----|------------------------|----------------|
|          |          |   | A vs G         | 1.015 (0.862-1.195) | 0.859 | 77.40 | 0.004 | R |
| rs10204525 | Breast cancer | 4 | GA vs GG       | 1.063 (0.796-1.419) | 0.679 | 63.70 | 0.041 | R |
|          |          |   | AA vs GG       | 1.122 (0.749-1.681) | 0.576 | 77.70 | 0.004 | R |
| rs10204525 | Gastric cancer | 1 | AA vs AG+GG    | 1.030 (0.832-1.274) | 0.787 | 71.90 | 0.014 | R |
| rs10204525 | Breast cancer | 1 | A vs G         | 0.891 (0.745-1.064) | 0.202 | -   | -    | R |
| rs2227981  |          |   | GA vs GG       | 0.976 (0.640-1.488) | 0.910 | -   | -    | R |
|          |          |   | AA vs GG       | 0.834 (0.549-1.267) | 0.395 | -   | -    | R |
| rs2227981  | Gastric cancer | 1 | AA vs AG+GG    | 0.898 (0.601-1.342) | 0.600 | -   | -    | R |
| rs2227981  | Breast cancer | 2 | A vs G         | 1.085 (0.871-1.351) | 0.021 | -   | -    | R |
| rs2227981  |            |   | GA vs GG       | 1.417 (0.817-2.461) | 0.215 | -   | -    | R |
| rs2227981  |            |   | AA vs GG       | 1.380 (0.805-2.366) | 0.241 | -   | -    | R |
| rs2227981  |            |   | AA+GA vs GG    | 1.396 (0.825-2.360) | 0.213 | -   | -    | R |
| rs2227981  |            |   | AA vs AG+GG    | 0.851 (0.674-1.074) | 0.174 | -   | -    | R |
| rs2227982  |            |   | C vs T         | 1.219 (1.045-1.422) | 0.012 | 6.70 | 0.301 | R |
| rs2227982  |            |   | TC vs TT       | 1.081 (0.750-1.557) | 0.677 | 0.00 | 0.408 | R |
| rs2227982  |            |   | CC vs TT       | 1.309 (0.910-1.883) | 0.147 | 0.00 | 0.975 | R |
| rs2227982  |            |   | CC+CT vs TT    | 1.206 (0.852-1.707) | 0.291 | 0.00 | 0.750 | R |
| rs2227982  |            |   | CC vs CT+TT    | 1.301 (0.991-1.706) | 0.058 | 49.60 | 0.159 | R |
| rs2227982  |            |   | C vs T         | 0.639 (0.241-1.694) | 0.368 | 94.60 | <0.001 | R |
| rs2227982  |            |   | CC+CT vs TT    | 0.336 (0.058-1.942) | 0.223 | 89.00 | <0.003 | R |
| rs2227982  |            |   | CC vs CT+TT    | 0.769 (0.390-1.516) | 0.449 | 82.90 | 0.015 | R |
| rs2227982  | Esophageal cancer | 4 | C vs T         | 0.982 (0.914-1.056) | 0.623 | 10.20 | 0.342 | F |
| rs2227982  | Esophageal cancer | 4 | CC vs TT       | 1.095 (0.966-1.241) | 0.154 | 0.00 | 0.813 | F |
| rs2227982  | Esophageal cancer | 4 | CC+CT vs TT    | 0.961 (0.831-1.112) | 0.592 | 15.10 | 0.316 | F |
| rs2227982  | Breast cancer | 2 | C vs T         | 1.173 (1.040-1.322) | 0.010 | 0.00 | 0.599 | F |
| rs2227982  | Breast cancer | 2 | TC vs TT       | 1.012 (0.823-1.245) | 0.908 | 0.00 | 0.758 | F |
| rs2227982  | Breast cancer | 2 | CC vs TT       | 1.079 (1.081-1.758) | 0.010 | 0.00 | 0.734 | F |
| rs2227982  | Breast cancer | 2 | CC+CT vs TT    | 1.120 (0.921-1.361) | 0.257 | 0.00 | 0.980 | F |
| rs2227982  | Breast cancer | 2 | CC vs CT+TT    | 1.375 (1.126-1.679) | 0.002 | 0.00 | 0.536 | F |
Table 4 continued. Subgroup analyses based on cancer type.

| Genotype  | Subgroup       | n | Contrast model       | OR (95% CI) | P     | Test for heterogeneity | Analysis model |
|-----------|----------------|---|----------------------|-------------|-------|------------------------|----------------|
| rs2890658 | Non-small cell lung | 2 | A vs C               | 0.609 (0.477-0.777) | 0.000 | 5.20                   | 0.304 | F |
|           |                 |   | CA vs CC             | 0.777 (0.252-2.398) | 0.661 | 0.00                  | 0.817 | F |
|           |                 |   | AA vs CC             | 0.465 (0.155-1.397) | 0.172 |                      |      |   |
|           |                 |   | AA+AC vs CC          | 0.503 (0.167-1.510) | 0.221 | 0.00                  | 0.668 | F |
|           |                 |   | AA vs AC+CC          | 0.589 (0.454-0.765) | 0.000 | 0.00                  | 0.345 | F |
|           | Hepato-cellular carcinoma | 2 | CA vs CC             | 1.195 (0.430-3.323) | 0.733 | 0.00                  | 0.380 | F |
|           |                 |   | AA vs CC             | 1.648 (0.612-4.436) | 0.323 | 0.00                  | 0.361 | F |
|           |                 |   | AA+AC vs CC          | 1.516 (0.566-4.065) | 0.408 | 0.00                  | 0.362 | F |
|           |                 |   | AA vs AC+CC          | 1.405 (1.002-1.970) | 0.049 | 0.00                  | 0.794 | F |
| rs36094323 | Esophageal cancer | 3 | G vs A               | 1.036 (0.893-1.202) | 0.639 | 0.00                  | 0.629 | F |
|           |                 |   | AG vs AA             | 1.041 (0.893-1.214) | 0.608 | 0.00                  | 0.960 | F |
|           |                 |   | GG vs AA             | 0.942 (0.789-1.125) | 0.510 | 0.00                  | 0.436 | F |
|           |                 |   | GG+GA vs AA          | 0.908 (0.872-1.165) | 0.317 | 0.00                  |      |   |
|           |                 |   | GG vs GA+AA          | 1.024 (0.810-1.295) | 0.843 | 68.90                 | 0.040 | R |
|           |                 |   | G vs A               | 0.727 (0.523-1.012) | 0.059 | 64.70                 | 0.092 | R |
|           | Ovarian cancer  | 2 | A vs G               | 1.065 (0.538-0.897) | 0.005 | 0.00                  |      |   |
|           |                 |   | AG vs AA             | 0.615 (0.459-0.823) | 0.001 | 61.80                 | 0.106 | F |
|           |                 |   | GG vs AA             | 0.666 (0.523-0.847) | 0.001 | 0.00                  | 0.333 | F |
|           |                 |   | GG+GA vs AA          | 0.645 (0.197-1.196) | 0.085 | 30.00                 | 0.092 | R |
| rs4143815 | Gastric cancer | 2 | C vs G               | 0.708 (0.307-1.630) | 0.417 | 92.90                 | <0.001 | R |
|           |                 |   | GC vs GG             | 0.449 (0.185-1.089) | 0.077 | 73.90                 | 0.050 | R |
|           | Hepato-cellular carcinoma | 2 | C vs G               | 0.736 (0.440-1.233) | 0.245 | 81.50                 | 0.200 | R |
|           |                 |   | GC vs GG             | 0.422 (0.279-0.639) | 0.000 | 0.00                  | 0.795 | R |
|           |                 |   | CC vs GG             | 0.498 (0.132-1.878) | 0.303 | 87.00                 | 0.006 | R |
|           |                 |   | CC+CG vs GG          | 0.473 (0.162-1.384) | 0.172 | 83.80                 | 0.013 | R |
|           |                 |   | CC vs CG+GG          | 0.815 (0.348-1.911) | 0.638 | 85.20                 | 0.009 | R |
|           | Esophageal cancer | 4 | C vs G               | 0.708 (0.307-1.630) | 0.417 | 92.90                 | <0.001 | R |
|           |                 |   | GC vs GG             | 0.449 (0.185-1.089) | 0.077 | 73.90                 | 0.050 | R |
|           |                 |   | CC vs GG             | 0.498 (0.132-1.878) | 0.303 | 87.00                 | 0.006 | R |
|           |                 |   | CC+CG vs GG          | 0.473 (0.162-1.384) | 0.172 | 83.80                 | 0.013 | R |
|           |                 |   | CC vs CG+GG          | 0.815 (0.348-1.911) | 0.638 | 85.20                 | 0.009 | R |
|           | Breast cancer   | 2 | C vs G               | 0.708 (0.307-1.630) | 0.417 | 92.90                 | <0.001 | R |
|           |                 |   | GC vs GG             | 0.449 (0.185-1.089) | 0.077 | 73.90                 | 0.050 | R |
|           |                 |   | CC vs GG             | 0.498 (0.132-1.878) | 0.303 | 87.00                 | 0.006 | R |
|           |                 |   | CC+CG vs GG          | 0.473 (0.162-1.384) | 0.172 | 83.80                 | 0.013 | R |
|           |                 |   | CC vs CG+GG          | 0.815 (0.348-1.911) | 0.638 | 85.20                 | 0.009 | R |

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FAHDI F (2019)  
BAHAM S (2012)  
HAHSHENAS MR (2011)  
MA Y (2015)  
FAHDI F (2018)  
OVERALL (I-squared=0.0%, p=0.869)

Study ID  OR (95% CI)  % weight
Fahdi F (2019) 1.65 (1.06, 2.57) 12.68
Bayram S (2012) 1.28 (0.84, 1.93) 15.65
Haghshenas MR (2011) 1.22 (0.86, 1.73) 22.19
Mai Y (2015) 1.30 (0.99, 1.69) 37.60
Fahdi F (2018) 1.23 (0.76, 1.99) 11.87
OVERALL (I-squared=0.0%, p=0.869) 1.31 (1.12, 1.55) 100.00

Zhou R-M (2016)  
ZANG B (2019)  
REN H-T (2016)  
TANG W (2015)  
QIU H (2014)  
TANG W (2017)  
OVERALL (I-squared=67.5%, p=0.009)

Study ID  OR (95% CI)  % weight
Zhou R-M (2016) 1.23 (1.02, 1.48) 15.85
Zang B (2019) 0.81 (0.69, 0.94) 17.99
Ren H-T (2016) 0.89 (0.75, 1.06) 16.16
Tang W (2015) 1.08 (0.87, 1.35) 13.65
Qiu H (2014) 1.06 (0.89, 1.26) 16.35
Tang W (2017) 1.03 (0.91, 1.16) 19.99
OVERALL (I-squared=67.5%, p=0.009) 1.00 (0.89, 1.13) 100.00

Note: Weights are from random effects analysis

Figure 2. Forest plots of meta-analysis. (A) PD-1 rs11568821 in allele model (B) PD-1 rs10204525 in allele model.

Zhou R-M (2016)  
ZANG B (2019)  
HAHSHENAS MR (2011)  
MA Y (2015)  
LI Y (2016)  
WEI L (2017)  
ZHAO Y (2018)  
TANG W (2017)  
OVERALL (I-squared=35.1%, p=0.127)

Study ID  OR (95% CI)  % weight
Zhou R-M (2016) 1.08 (0.82, 1.41) 11.81
Zang B (2019) 1.27 (0.52, 3.13) 1.00
Hua Z (2011) 0.90 (0.67, 1.21) 10.77
Kasamatsu T (2019) 1.17 (0.70, 1.94) 3.16
Boas Gomez GV (2018) 0.08 (0.00, 1.34) 0.75
Ma Y (2015) 0.93 (0.71, 1.23) 12.86
Li Y (2016) 0.70 (0.54, 0.91) 15.56
Wei (2017) 0.50 (0.27, 0.93) 3.39
Zhan (2018) 0.86 (0.64, 1.15) 11.01
Tang W (2017) 0.97 (0.82, 1.16) 29.70
OVERALL (I-squared=35.1%, p=0.127) 0.90 (0.82, 0.99) 100.00

Note: Weights are from random effects analysis

Figure 3. Forest plots of meta-analysis. (A) PD-1 rs36084323 in dominant model (B) PD-1 rs2227981 in dominant model.

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Figure 5. Forest plots of Subgroup analysis. (A) breast cancer (PD-1 rs2227981 in allele model); (B) breast cancer (PD-1 rs2227982 in allele model).

Figure 6. Forest plots of Subgroup analysis. (A) ovarian cancer (PD-1 rs36084323 in homozygote model); (B) ovarian cancer (PD-1 rs36084323 in homozygote model).

Figure 7. Forest plots of meta-analysis. (A) PD-L1 rs17718883 in homozygote model; (B) PD-L1 rs2890658 in homozygote model.
| Study ID  | OR (95% CI) | % weight |
|----------|-------------|----------|
| Wang W (2013) | 0.30 (0.20, 0.46) | 18.93 |
| Tan D (2017)  | 0.78 (0.46, 1.32) | 17.16 |
| Xie Q (2018) | 0.41 (0.25, 0.67) | 17.51 |
| Zhou R-M (2017) | 0.94 (0.67, 1.32) | 20.08 |
| Li Q (2016) | 0.76 (0.34, 1.72) | 12.54 |
| Cheng S (2017) | 0.46 (0.22, 0.95) | 13.79 |
| Overall | 0.56 (0.36, 0.86) | 100.00 |

Note: Weights are from random effects analysis.

| Study ID  | OR (95% CI) | % weight |
|----------|-------------|----------|
| Wang W (2013) | 0.30 (0.17, 0.42) | 18.23 |
| Tan D (2017) | 0.78 (0.46, 1.32) | 17.16 |
| Xie Q (2018) | 0.41 (0.25, 0.67) | 17.51 |
| Zhou R-M (2017) | 0.94 (0.67, 1.32) | 20.08 |
| Li Q (2016) | 0.76 (0.34, 1.72) | 12.54 |
| Cheng S (2017) | 0.46 (0.22, 0.95) | 13.79 |
| Overall | 0.56 (0.36, 0.86) | 100.00 |

Note: Weights are from random effects analysis.

Figure 8. Forest plots of meta-analysis. (A) PD-L1 rs4143815 in heterozygote model; (B) PD-L1 rs4143815 in homozygote model.

| Study ID  | OR (95% CI) | % weight |
|----------|-------------|----------|
| Non-small cell lung cancer | Non-small cell lung cancer | Non-small cell lung cancer |
| Chen Y-B (2014) | 0.49 (0.31, 0.79) | 21.34 |
| Ma Y (2015) | 0.66 (0.50, 0.88) | 48.11 |
| Subtotal (I-squared=5.2%, p=0.304) | Subtotal (I-squared=5.2%, p=0.304) | Subtotal (I-squared=5.2%, p=0.304) |
| Xie Q (2018) | 1.28 (0.88, 1.87) | 17.57 |
| Cheng S (2017) | 1.50 (0.91, 2.46) | 10.71 |
| Subtotal (I-squared=0.0%, p=0.629) | Subtotal (I-squared=0.0%, p=0.629) | Subtotal (I-squared=0.0%, p=0.629) |
| Overall (I-squared=83.0%, p=0.001) | Overall (I-squared=83.0%, p=0.001) | Overall (I-squared=83.0%, p=0.001) |
| 0.84 (0.70, 1.01) | 100.00 |

Note: Weights are from random effects analysis.

| Study ID  | OR (95% CI) | % weight |
|----------|-------------|----------|
| Non-small cell lung cancer | Non-small cell lung cancer | Non-small cell lung cancer |
| Chen Y-B (2014) | 0.48 (0.29, 0.79) | 22.61 |
| Ma Y (2015) | 0.64 (0.47, 0.87) | 49.66 |
| Subtotal (I-squared=0.0%, p=0.345) | Subtotal (I-squared=0.0%, p=0.345) | Subtotal (I-squared=0.0%, p=0.345) |
| Xie Q (2018) | 1.36 (0.88, 2.08) | 17.57 |
| Cheng S (2017) | 1.49 (0.86, 2.59) | 10.15 |
| Subtotal (I-squared=0.0%, p=0.794) | Subtotal (I-squared=0.0%, p=0.794) | Subtotal (I-squared=0.0%, p=0.794) |
| Overall (I-squared=82.0%, p=0.001) | Overall (I-squared=82.0%, p=0.001) | Overall (I-squared=82.0%, p=0.001) |
| 0.82 (0.66, 1.00) | 100.00 |

Note: Weights are from random effects analysis.

Figure 9. Forest plots of Subgroup analysis. (A) hepatocellular cancer (PD-L1 rs2890658 in allele model); (B) hepatocellular cancer (PD-L1 rs2890658 in recessive model).

| Study ID  | OR (95% CI) | % weight |
|----------|-------------|----------|
| Gastric cancer | Gastric cancer | Gastric cancer |
| Wang W (2013) | 0.30 (0.20, 0.46) | 38.13 |
| Li Q (2016) | 0.76 (0.34, 1.72) | 14.38 |
| Subtotal (I-squared=73.9%, p=0.050) | Subtotal (I-squared=73.9%, p=0.050) | Subtotal (I-squared=73.9%, p=0.050) |
| Xie Q (2018) | 0.41 (0.25, 0.67) | 30.22 |
| Cheng S (2017) | 0.46 (0.22, 0.95) | 17.27 |
| Subtotal (I-squared=0.0%, p=0.993) | Subtotal (I-squared=0.0%, p=0.993) | Subtotal (I-squared=0.0%, p=0.993) |
| Overall (I-squared=27.6%, p=0.013) | Overall (I-squared=27.6%, p=0.013) | Overall (I-squared=27.6%, p=0.013) |
| 0.41 (0.29, 0.57) | 100.00 |

Note: Weights are from random effects analysis.

| Study ID  | OR (95% CI) | % weight |
|----------|-------------|----------|
| Gastric cancer | Gastric cancer | Gastric cancer |
| Wang W (2013) | 0.40 (0.17, 0.42) | 29.33 |
| Li Q (2016) | 1.03 (0.44, 2.39) | 20.82 |
| Subtotal (I-squared=63.5%, p=0.098) | Subtotal (I-squared=63.5%, p=0.098) | Subtotal (I-squared=63.5%, p=0.098) |
| Xie Q (2018) | 0.32 (0.18, 0.56) | 27.10 |
| Cheng S (2017) | 0.71 (0.34, 1.50) | 22.75 |
| Subtotal (I-squared=72.6%, p=0.013) | Subtotal (I-squared=72.6%, p=0.013) | Subtotal (I-squared=72.6%, p=0.013) |
| Overall (I-squared=76.0%, p=0.001) | Overall (I-squared=76.0%, p=0.001) | Overall (I-squared=76.0%, p=0.001) |
| 0.46 (0.26, 0.84) | 100.00 |

Note: Weights are from random effects analysis.

Figure 10. Forest plots of Subgroup analysis. (A) PD-L1 rs4143815 in heterozygote model (B) PD-L1 rs4143815 in homozygote model.
Table 5. Publication bias consequences.

| Genotype       | Contrast model | Publication bias (Egger’s test) | Publication bias (Begg’s test) |
|----------------|----------------|-------------------------------|--------------------------------|
|                |                | t    | P     | Z    | P    |
| rs11568821     | G>A            | 0.52 | 0.642 | -0.24| 1.000|
| rs17718883     | C>G            | 1.03 | 0.49  | 1.04 | 0.296|
| rs36094323     | G>A            | -0.61| 0.557 | 0.36 | 0.721|
| rs4143815      | C>G            | -0.45| 0.676 | 0.75 | 0.452|
| rs7421861      | T>C            | -0.62| 0.71  | 0.49 | 0.621|

Figure 11. Publication bias. (A) Begg’s funnel plot for PD-1 rs11568821 in allele model; (B) Begg’s funnel plot for PD-1 rs36094323 in allele model.

Figure 12. Publication bias. (A) Begg’s funnel plot for PD-L1 rs4143815; (B) Begg’s funnel plot for PD-1 rs7421861 in allele model.
variants of PD-1 and PD-L1 and cancer susceptibility. Our results suggest that PD-1 rs36084323 and PD-L1 rs4143815 are significantly associated with decreased cancer susceptibility, while PD-1 rs7421861, rs11568821, and PD-L1 rs17718883 variants increase overall cancer susceptibility. We found that there was no clear relationship between PD-1 rs2227981, rs2227982, rs10204525, and PD-L1 rs2890658 mutations and cancer susceptibility.

Subgroup analysis showed that PD-1 rs2227981 increased the susceptibility to breast cancer. In addition, PD-1 rs2227982 is associated with reduced susceptibility to breast cancer. However, PD-1 rs36084323 is associated with reduced susceptibility to ovarian cancer. In addition, our results suggest that the PD-L1 rs4143815 mutation significantly reduces the susceptibility to liver cancer. There was a negative correlation between PD-L1 rs2890658 and susceptibility to non-small cell lung cancer.

Recently, Hashemi et al. [44] conducted a meta-analysis of 27 case-control studies to explore the relationship between PD-1 genes rs11568821, rs2227981, rs2227982, and rs7421861 and tumor susceptibility. The results showed that the mutations of PD-1 rs2227981, rs11568821, rs7421861, and PD-L1 rs4143815 were related to the overall susceptibility to cancer. However, Hashemi et al. did not include Chinese studies, nor did they rule out low-quality studies based on NOS scores. Shan et al. [10] conducted a meta-analysis of 10 studies (9571 subjects) and found that PD-1 rs36084323 was associated with reduced susceptibility to cancer in Asians, which is consistent with our findings. Compared with the meta-analysis of Shan et al., the genetic polymorphism studied in this paper is more comprehensive and includes more recent research results. However, a study by Zhou et al. [14] showed that PD-L1 rs1771883 polymorphism may have led to a lack of statistical ability to study this relationship. Secondly, there is obvious heterogeneity in several polymorphisms; therefore, we conducted a subgroup analysis to find out the causes of heterogeneity. Finally, we inferred that the type of cancer and the country of residence of the participants may lead to heterogeneity. These mean that our results should be interpreted carefully.

Tumor immunotherapy targeting PD-1 and PD-L1 immune checkpoint pathways has begun in the field of oncology. The combination of anti-PD-1 and anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) has produced an effective pathological response rate in the treatment of breast and lung cancer [45]. At present, 3 PD-L1 inhibitors have been approved for non-small cell lung cancer [46]. Aaron et al confirmed that the effective rate of blocking PD-1 with nivolumab was more than half in unselected patients with Hodgkin’s lymphoma [47]. Melanoma patients with other types of cancer showed the best response [48]. Our meta-analysis includes more case and control samples than previous studies, and we also included Chinese studies. In addition, we evaluated the quality of NOS research, including high-quality research and excluding low-quality articles. Last but not least, in our study, 26 of the 27 trials were conducted in Asians and only 1 in Whites, which could reduce the potential effects of different races on genetic susceptibility. Therefore, our meta-analysis makes a more convincing assessment than previous studies.

However, this study also has some limitations. First of all, the small number of participants with the PD-L1 rs1771883 polymorphism may have led to a lack of statistical ability to study this relationship. Secondly, there is obvious heterogeneity in several polymorphisms; therefore, we conducted a subgroup analysis to find out the causes of heterogeneity. Finally, we inferred that the type of cancer and the country of residence of the participants may lead to heterogeneity. These mean that our results should be interpreted carefully.

Conclusions

In conclusion, our results suggest that both PD-1 rs36084323 and PD-L1 rs4143815 variants decrease cancer predisposition, while PD-1 rs7421861, rs11568821, and PD-L1 rs17718883 polymorphisms significantly increase the risk of cancer.

Conflicts of Interest

None.
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