Association between PD-1 and PD-L1 Polymorphisms and the Risk of Cancer: A Meta-Analysis of Case-Control Studies

Mohammad Hashemi 1,2,*, Shima Karami 2, Sahel Sarabandi 2, Abdolkarim Moazeni-Roodi 3, Andrzej Malecki 4, Saeid Ghavami 5,6,*, and Emilia Wiechec 7,*

1 Genetics of Non-communicable Disease Research Center, Zahedan University of Medical Sciences, Zahedan 9816743463, Iran
2 Department of Clinical Biochemistry, School of Medicine, Zahedan University of Medical Sciences, Zahedan 9816743175, Iran
3 Department of Clinical Biochemistry, Iranshahr University of Medical Sciences, Iranshahr 9916643535, Iran
4 Institute of Physiotherapy and Health Sciences, The Jerzy Kukuczka Academy of Physical Education in Katowice, 40-065 Katowice, Poland
5 Department of Human Anatomy and Cell Science, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB R3E 0J9, Canada
6 Research Institute in Oncology and Hematology, CancerCare Manitoba, University of Manitoba, Winnipeg, MB R3E 3P5, Canada
7 Department of Clinical and Experimental Medicine, Linköping University, 58183 Linköping, Sweden
* Correspondence: mhd.hashemi@gmail.com or hashemim@zaums.ac.ir (M.H.); saeid.ghavami@umanitoba.ca (S.G.); emilia.wiechec@liu.se (E.W.)

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Abstract: A number of case-control studies regarding the association of the polymorphisms in the programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) genes with the risk of cancer have yielded inconsistent findings. Therefore, we have conducted a comprehensive, updated meta-analysis study to identify the impact of PD-1 and PD-L1 polymorphisms on overall cancer susceptibility. The findings revealed that PD-1 rs2227981 and rs11568821 polymorphisms significantly decreased the overall cancer risk (Odds Ratio (OR) = 0.82, 95% CI = 0.68–0.99, p = 0.04, TT vs. CT+CC; OR = 0.79, 95% CI = 0.67–0.94, p = 0.006, AG vs. GG, and OR = 0.82, 95% CI = 0.70–0.96, p = 0.020, AG+AA vs. GG, respectively), while PD-1 rs7421861 polymorphism significantly increased the risk of developing cancer (OR = 1.16, 95% CI = 1.02–1.33, p = 0.03, CT vs. TT). The PD-L1 rs4143815 variant significantly decreased the risk of cancer in homozygous (OR = 0.62, 95% CI = 0.41–0.94, p = 0.02), dominant (OR = 0.70, 95% CI = 0.50–0.97, p = 0.03), recessive (OR = 0.76, 95% CI = 0.60–0.96, p = 0.02), and allele (OR = 0.78, 95% CI = 0.63–0.96, p = 0.02) genetic models. No significant association between rs2227982, rs36084323, rs10204525, and rs2890658 polymorphisms and overall cancer risk has been found. In conclusions, the results of this meta-analysis have revealed an association between PD-1 rs2227981, rs11568821, rs7421861, as well as PD-L1 rs4143815 polymorphisms and overall cancer susceptibility.

Keywords: apoptosis; PD-1; PD-L1; polymorphism; cancer; meta-analysis

1. Introduction
Cancer, a main public health issue is the leading cause of death globally. It was estimated that there will be about 18.1 million new cases of cancer and 9.6 million cancer deaths in 2018 [1]. Thus, the etiology and pathogenesis of cancer has not been elucidated completely and their understanding is
decisive. Genome-wide association studies (GWAS) have simplified the search for potential genetic variants that are implicated in many diseases including cancer and single nucleotide polymorphisms (SNPs) are well studied genetic variations found in human genome. The number of SNPs that have so far been identified to play an important role in cancer susceptibility is significant [2]. It has been proposed that the immune system plays a key role in resisting and eliminating cancer cells and can affect cancer susceptibility. One of the main hallmarks of cancer cells is the immune suppression and evasion [3].

Tumor cells express the programmed death-1-ligand 1 (PD-L1) as an adaptive, resistant mechanism to suppress the inhibitory receptor, namely programmed cell death-1 (PD-1) in order to evade host immunosurveillance [4]. PD-1, also known as PD1 and CD279, is a cell surface immunosuppressive receptor belonging to immunoglobulin superfamily and is encoded by the PDCD1 gene [5–7]. PD-1, is a negative regulator of the immune system and is expressed on CD4⁺ T cells, CD8⁺ T cells, NKT cells, B cells, and monocytes [8,9]. The antitumor CD8⁺ T cells exhibit preferential expression of PD-1 leading to their exhaustion and functional impairment, which in turns lead to attenuated tumor-specific immunity disseminating tumor progression [10,11]. The PD-1 blockade elevates the magnitude of T cell response such as proliferation of T cells and production of effector cytokines [12]. Additionally, PD-L1 signaling through conserved sequence motifs confers resistance of cancer cells towards proapoptotic interferon (IFN)-mediated cytotoxicity [13].

PD-1/PD-L1 axis is an important pathway to maintain immune tolerance and prevent autoimmune diseases in the evolution of immunity [14–16]. Furthermore, it influences the balance between tumor immune surveillance and immune resistance [17,18]. Elevated PD-L1 expression in tumor cells or tumor-infiltrating lymphocytes (TILs) leads to the exhaustion of T cells [19], and hence attenuated tumor-specific immunity disseminating tumor progression [20]. Gene polymorphisms might affect the normal process of gene activation and transcriptional initiation, hence influence the quantity of mRNA and encoded protein [21]. Both PD-1 and PD-L1 are polymorphic. Several studies investigated the association between genetic polymorphisms of PD-1 and PD-L1 genes and the risk of various cancers, but the finding are still inconclusive [5–7,22–52]. Thus, we performed a comprehensive meta-analysis in order to study the association of polymorphisms in PD-1 and PD-L1 genes with the risk of cancer. The locations and base pair positions of single nucleotide polymorphisms (SNPs) in PD-1 and PD-L1 genes are presented in Table 1.

### Table 1. Locations and base pair positions of single nucleotide polymorphisms (SNPs) in PD-1 and PD-L1 genes.

| Gene Name | db SNP rs # ID * | Chromosome Position | Location | Base Change | Amino Acid Change |
|-----------|-----------------|---------------------|----------|-------------|------------------|
| PD-1      | rs2227981       | chr2:241851121      | Upstream | C/T         |                  |
|           | rs2227982       | chr2:241851281      | Exon     | C/T         | Ala215Val        |
|           | rs7421861       | chr2:241853198      | Intron   | G/A         |                  |
|           | rs11568821      | chr2:241851760      | Intron   | G/A         | -                |
|           | rs36084323      | chr2:241859444      | Upstream | G/A         |                  |
|           | rs10204525      | chr2:241850169      | 3'UTR    | A/G         |                  |
|           | rs4143815       | chr9:5468257        | 3'UTR    | G/C         | -                |
|           | rs2890658       | chr9:5465130        | Intron   | A/C         | -                |

* db = databases; rs # = reference SNP #; UTR: untranslated region.

### 2. Results

#### 2.1. Study Characteristics

A flow diagram of the study selection process is shown in Figure 1. For PD-1 polymorphisms, 54 case-control studies from a total of 26 articles [5–7, 22–43, 52] examining the associations of 6 widely
studied polymorphisms in PD-1 gene and cancer risk were included in this meta-analysis. There were 16 studies involving 5622 cases and 5450 controls that reported the association between PD-1 rs2227981 polymorphism and cancer. Eleven studies including 4766 cases and 5839 controls investigated the relationship between PD-1 rs2227982 polymorphism and cancer. Nine studies with 1846 cases and 1907 cases reported the association between PD-1 rs11568821 variant and cancer risk. Seven studies including 3576 cancer cases and 5277 controls studied the correlation between PD-1 rs7421861 polymorphism and cancer. Seven studies involving 3589 cases and 4314 controls examined the association between PD-1 rs36084323 polymorphism and cancer risk. Six studies including 3366 cancer cases and 4391 controls studied the relationship between PD-1 rs10204525 polymorphism and cancer.

**Figure 1.** Flow diagram of study selection for this meta-analysis.

For PD-L1 polymorphisms, 13 case-control studies from 10 articles [27,38,44–51] that assessed the impact of two polymorphisms of PD-L1 were included in the pooled analysis. Eight studies including 3030 cases and 4145 controls evaluated the association between PD-L1 rs4143815 polymorphism and cancer risk. Five studies with 1909 cases and 1970 controls assessed the correlation between PD-L1 rs2890658 variant and cancer risk. The characteristics of all these studies are shown in Table 2.
Table 2. Characteristics of the studies eligible for meta-analysis.

| First Author | Year | Country | Ethnicity | Cancer Type | Source of Control | Genotyping Method | Case/Control | Cases | Controls | HWE |
|--------------|------|---------|-----------|-------------|------------------|-------------------|-------------|-------|----------|-----|
| PD-1 rs2227981 |      |         |           |             |                  |                   |             |       |          |     |
| Fathi        | 2019 | Iran    | Asian     | Squamous Cell Carcinomas of Head and Neck | HB | PCR-RFLP | 150/150 | 65  | 69  | 16  | 199 | 101 | 66  | 71  | 13 | 203 | 97  | 0.317 |
| Gomez        | 2018 | Brazil  | South American | Cutaneous Melanoma | PB | RT-PCR | 250/250 | 87 | 126 | 37  | 300 | 200 | 85  | 130 | 35 | 300 | 200 | 0.188 |
| Haghshenas   | 2011 | Iran    | Asian     | Breast cancer | PB | PCR-RFLP | 435/328 | 194 | 191 | 50  | 579 | 291 | 137 | 145 | 46 | 419 | 237 | 0.446 |
| Haghshenas   | 2017 | Iran    | Asian     | Thyroid cancer | PB | PCR-RFLP | 105/160 | 40 | 51  | 14  | 131 | 79  | 99  | 51  | 13 | 249 | 71  | 0.331 |
| Hu            | 2011 | China   | Asian     | Breast cancer | PB | PCR-RFLP | 486/478 | 295 | 169 | 22  | 759 | 213 | 244 | 210 | 24 | 698 | 258 | 0.012 |
| Ivansson     | 2010 | Sweden  | Caucasian | Cervical cancer | PB | TaqMan | 1300/810 | 471 | 603 | 226 | 1545 | 1055 | 257 | 375 | 178 | 889 | 731 | 0.064 |
| Li            | 2016 | China   | Asian     | Cervical cancer | PB | PCR-RFLP | 256/250 | 45  | 167 | 44  | 257 | 253 | 62  | 101 | 87  | 225 | 275 | 0.004 |
| Li            | 2017 | China   | Asian     | Ovarian cancer | HB | PCR-LDR | 620/620 | 351 | 233 | 36  | 935 | 305 | 137 | 257 | 89  | 36  | 239 | 161 | 0.837 |
| Ma            | 2015 | China   | Asian     | Lung cancer | PB | PCR-RFLP | 528/600 | 244 | 216 | 68  | 704 | 352 | 256 | 246 | 98  | 758 | 442 | 0.004 |
| Mojtabehdi   | 2012 | Iran    | Asian     | Color cancer | PB | PCR-RFLP | 175/200 | 47  | 102 | 26  | 196 | 154 | 75  | 89  | 36  | 239 | 161 | 0.290 |
| Mojtabehdi   | 2012 | Iran    | Asian     | Rectal cancer | PB | PCR-RFLP | 25/200 | 12  | 7   | 6   | 31  | 19  | 75  | 89  | 36  | 239 | 161 | 0.290 |
| Namavar Jahromi | 2017 | Iran    | Asian     | Malignant Brain tumor | PB | PCR-RFLP | 56/150 | 22  | 31  | 3   | 75  | 37  | 94  | 47  | 9   | 235 | 65  | 0.346 |
| Pirdelkhosh  | 2018 | Iran    | Asian     | NSCLC       | PB | PCR-RFLP | 206/173 | 78  | 100 | 28  | 256 | 156 | 60  | 89  | 24  | 209 | 137 | 0.321 |
| Savabkar     | 2013 | Iran    | Asian     | Gastric cancer | HB | PCR-RFLP | 122/166 | 50  | 66  | 6   | 166 | 78  | 89  | 70  | 7   | 248 | 84  | 0.136 |
| Yin          | 2014 | China   | Asian     | Lung cancer | PB | PCR-LDR | 324/330 | 198 | 106 | 20  | 502 | 146 | 181 | 105 | 44  | 467 | 193 | 0.001 |
| Zhou         | 2016 | China   | Asian     | ESCC        | PB | PCR-LDR | 584/585 | 291 | 241 | 52  | 823 | 345 | 310 | 229 | 46  | 849 | 321 | 0.683 |
| PD-1 rs2227982 |      |         |           |             |                  |                   |             |       |       |      |     |
| Fathi        | 2019 | Iran    | Asian     | Squamous Cell Carcinomas of Head and Neck | HB | PCR-RFLP | 150/150 | 146 | 4   | 0   | 296 | 4   | 146 | 4   | 0  | 296 | 4   | 0.868 |
| Gomez        | 2018 | Brazil  | South American | Cutaneous Melanoma | PB | RT-PCR | 250/250 | 227 | 21  | 2   | 475 | 25  | 225 | 25  | 0  | 475 | 25  | 0.405 |
| Hua          | 2011 | China   | Asian     | breast cancer | PB | PCR-RFLP | 487/306 | 111 | 249 | 127 | 471 | 503 | 95  | 268 | 143 | 458 | 554 | 0.121 |
| Ma           | 2015 | China   | Asian     | Lung cancer | PB | PCR-RFLP | 528/600 | 343 | 148 | 37  | 834 | 222 | 404 | 168 | 28  | 976 | 224 | 0.056 |
| Qiu          | 2014 | China   | Asian     | esophageal cancer | HB | PCR-LDR | 616/681 | 159 | 303 | 154 | 621 | 611 | 189 | 325 | 167 | 703 | 659 | 0.245 |
| Ramzi        | 2018 | Iran    | Asian     | Leukemia    | PB | PCR-RFLP | 59/38  | 38  | 18  | 3   | 94  | 24  | 17  | 19  | 2   | 53  | 23  | 0.255 |
| Ren          | 2016 | China   | Asian     | Breast Cancer | PB | MassARRAY | 557/582 | 172 | 257 | 128 | 601 | 513 | 137 | 299 | 146 | 573 | 591 | 0.503 |
| Tan          | 2018 | China   | Asian     | Ovarian cancer | PB | PCR-RFLP | 164/170 | 87  | 60  | 17  | 234 | 94  | 111 | 48  | 11 | 270 | 70  | 0.075 |
| Tang         | 2015 | China   | Asian     | Gastric cardia adenocarcinoma | HB | PCR-LDR | 336/603 | 75  | 168 | 87  | 318 | 342 | 163 | 292 | 148 | 618 | 588 | 0.448 |
| Tang         | 2017 | China   | Asian     | Esophagogastric junction adenocarcinoma | HB | SNPscan | 1041/1674 | 220 | 549 | 272 | 989 | 1093 | 416 | 816 | 442 | 1648 | 1700 | 0.309 |
| Zhou         | 2016 | China   | Asian     | ESCC        | PB | PCR-LDR | 584/585 | 149 | 305 | 130 | 603 | 565 | 150 | 297 | 138 | 597 | 573 | 0.702 |
### Table 2. Cont.

| First Author | Year | Country | Ethnicity | Cancer Type | Source of Control | Genotyping Method | Case/Control | Cases | Controls | HWE |
|--------------|------|---------|-----------|-------------|------------------|------------------|-------------|-------|----------|-----|
| **PD-1 rs7421861** |      |         |           |             |                  |                  |             |       |          |     |
| Ge           | 2015 | China   | Asian     | Colon cancer | HB               | PCR-RFLP         | 199/620      | 133   | 60       | 163 | 1043 | 197 | 0.685 |
| Ge           | 2015 | China   | Asian     | Rectal cancer | HB               | PCR-RFLP         | 362/620      | 241   | 114      | 128 | 440  | 163 | 1043 | 197 | 0.685 |
| Hua          | 2011 | China   | Asian     | Breast cancer | PB               | PCR-RFLP         | 490/512      | 333   | 146      | 186 | 370  | 130 | 870  | 154 | 0.885 |
| Qiu          | 2014 | China   | Asian     | esophageal cancer | HB               | PCR-LDR         | 603/673      | 411   | 168      | 21  | 990  | 210 | 460  | 188 | 25  | 1108 | 238 | 0.295 |
| Ren          | 2016 | China   | Asian     | Breast Cancer | PB               | MassARRAY        | 560/580      | 341   | 196      | 23  | 878  | 242 | 347  | 205 | 28  | 899  | 261 | 0.746 |
| Tang         | 2015 | China   | Asian     | Gastric cardia adenocarcinoma | HB               | PCR-LDR         | 324/598      | 226   | 91       | 7   | 543  | 105 | 408  | 168 | 22  | 984  | 212 | 0.368 |
| Tang         | 2017 | China   | Asian     | esophageogastric junction adenocarcinoma | HB               | SNPscan         | 1041/1674    | 642   | 358      | 41  | 1642 | 440 | 1166 | 454 | 54  | 2786 | 562 | 0.232 |
| **PD-1 rs11568821** |      |         |           |             |                  |                  |             |       |          |     |
| Bayram       | 2012 | Turkey  | Asian     | liver cancer | HB               | PCR-RFLP         | 236/236      | 191   | 45       | 42  | 45   | 180 | 56   | 0   | 416 | 56   | 0.039 |
| Fathi        | 2019 | Iran    | Asian     | Squamous-Cell Carcinomas of Head and Neck | HB               | PCR-RFLP         | 150/150      | 119   | 27       | 4   | 265  | 35  | 113  | 32  | 5   | 258  | 42  | 0.162 |
| Haghbezas    | 2011 | Iran    | Asian     | Breast cancer | PB               | PCR-RFLP         | 436/290      | 365   | 63       | 8   | 793  | 79  | 231  | 55  | 4   | 517  | 63  | 0.726 |
| Haghbezas    | 2017 | Iran    | Asian     | Thyroid cancer | PB               | PCR-RFLP         | 95/160       | 82    | 13       | 0   | 177  | 13  | 127  | 30  | 3   | 284  | 36  | 0.440 |
| Ma           | 2015 | China   | Asian     | lung cancer | PB               | PCR-RFLP         | 528/600      | 426   | 102      | 0   | 954  | 102 | 456  | 142 | 2   | 1054 | 146 | 0.009 |
| Namavar Jahromi | 2017 | Iran    | Asian     | Malignant Brain tumor | PB               | PCR-RFLP         | 56/150       | 47    | 8        | 1   | 102  | 10  | 116  | 30  | 4   | 262  | 38  | 0.240 |
| Pirdelkhoosh | 2018 | Iran    | Asian     | NSCLC      | PB               | PCR-RFLP         | 206/173      | 171   | 31       | 4   | 373  | 39  | 144  | 26  | 3   | 314  | 32  | 0.168 |
| Ramzi        | 2018 | Iran    | Asian     | Leukemia   | PB               | PCR-RFLP         | 59/38        | 38    | 18       | 3   | 94   | 24  | 21   | 13  | 4   | 55   | 21  | 0.373 |
| Yousefi      | 2013 | Asian   | Asian     | colon cancer | PB               | PCR-LDR         | 80/110       | 18    | 27       | 35  | 63   | 97  | 43   | 45  | 22  | 131  | 89  | 0.114 |
| **PD-1 rs36084323** |      |         |           |             |                  |                  |             |       |          |     |
| Gomez        | 2018 | Brazil  | South American | Cutaneous-Melanoma | PB               | RT-PCR         | 230/250      | 226   | 18       | 6   | 470  | 30  | 225  | 25  | 0   | 475  | 25  | 0.405 |
| Hua          | 2011 | China   | Asian     | Breast cancer | PB               | PCR-RFLP         | 490/512      | 103   | 271      | 116 | 477  | 503 | 140  | 260 | 112 | 540  | 484 | 0.673 |
| Li           | 2017 | China   | Asian     | Ovarian cancer | HB               | PCR-LDR         | 620/620      | 150   | 305      | 169 | 601  | 639 | 168  | 323 | 129 | 659  | 581 | 0.251 |
| Ma           | 2015 | China   | Asian     | lung cancer | PB               | PCR-RFLP         | 528/600      | 144   | 246      | 138 | 534  | 522 | 156  | 296 | 148 | 608  | 592 | 0.747 |
| Shamsdin     | 2018 | Iran    | Asian     | Colon cancer | PB               | PCR-RFLP         | 76/73        | 60    | 15       | 1   | 135  | 17  | 18   | 28  | 27  | 84   | 82  | 0.059 |
| Tang         | 2017 | China   | Asian     | esophageogastric junction adenocarcinoma | HB               | SNPscan         | 1041/1674    | 238   | 521      | 282 | 997  | 1085| 430  | 800 | 444 | 1660 | 1688 | 0.071 |
| Zhou         | 2016 | China   | Asian     | ESCC       | PB               | PCR-LDR         | 584/585      | 147   | 303      | 134 | 597  | 571 | 145  | 298 | 142 | 588  | 582 | 0.649 |
| First Author | Year | Country | Ethnicity | Cancer Type | Source of Control | Genotyping Method | Case/Control | Cases | Controls | HWE |
|--------------|------|---------|-----------|-------------|------------------|------------------|--------------|-------|-----------|-----|
| PD-1 rs10204525 |      |         |           |             |                  |                  | AA AG GG A G | AA AG GG A G |       |
| Li           | 2013 | China   | Asian     | HCC         | PB               | TIANamp          | 271 318      | 80 83 8 443 99 160 130 28 450 186 | 0.828 |
| Qiu          | 2014 | China   | Asian     | esophageal cancer | HB               | PCR-LDR         | 600 651     | 317 240 43 874 326 345 243 63 933 369 | 0.039 |
| Ren          | 2016 | China   | Asian     | Breast Cancer | PB               | MassARRAY       | 559 582     | 257 248 54 762 356 291 240 51 822 342 | 0.880 |
| Tang         | 2015 | China   | Asian     | Gastric cardia adenocarcinoma | HB               | PCR-LDR        | 313 581     | 169 123 21 461 165 309 219 53 837 325 | 0.120 |
| Tang         | 2017 | China   | Asian     | esophagogastric junction adenocarcinoma | HB               | SNPscan       | 1039 1674   | 544 397 98 1485 593 870 672 132 2412 936 | 0.888 |
| Zhou         | 2016 | China   | Asian     | ESCC        | PB               | PCR-LDR     | 584 585     | 325 226 33 876 292 296 238 51 830 340 | 0.749 |
| PD-L1 rs1413815 |      |         |           |             |                  |                  | AA AG GG A G | AA AG GG A G |       |
| Catalano     | 2018 | Czech   | Caucasian | Colon cancer | HB               | TaqMan        | 824 1103    | 388 345 91 1121 527 514 467 122 1495 711 | 0.306 |
| Catalano     | 2018 | Czech   | Caucasian | Rectal cancer | HB               | TaqMan        | 371 1103    | 167 162 42 496 246 514 467 122 1495 711 | 0.306 |
| Du           | 2017 | China   | Asian     | NSCLC       | HB               | sequencing    | 320 199     | 52 145 123 249 391 40 80 79 160 238 | 0.021 |
| Tan          | 2018 | China   | Asian     | Ovarian cancer | PB               | PCR-RFLP     | 164 170     | 51 82 31 184 144 38 78 54 154 186 | 0.334 |
| Tao          | 2017 | China   | Asian     | Gastric cancer | HB               | Sequencing    | 346 300     | 123 153 70 399 293 317 117 223 160 457 | 0.543 |
| Wang         | 2013 | China   | Asian     | Gastric cancer | HB               | sequencing    | 205 393     | 88 72 45 248 162 70 188 135 326 458 | 0.746 |
| Xie          | 2018 | China   | Asian     | HCC         | HB               | sequencing    | 225 200     | 74 101 50 249 201 31 104 65 166 234 | 0.316 |
| Zhou         | 2017 | China   | Asian     | ESCC        | PB               | PCR-LDR     | 575 577     | 87 277 211 451 699 85 289 203 459 695 | 0.275 |
| PD-L1 rs2808038 |      |         |           |             |                  |                  | AA AG GG A G | AA AG GG A G |       |
| Chen         | 2014 | China   | Asian     | NSCLC       | HB               | PCR-RFLP     | 292 293     | 242 48 3 532 54 266 26 1 538 28 0.671 |
| Cheng        | 2015 | China   | Asian     | NSCLC       | HB               | PCR-RFLP     | 288 300     | 233 51 4 517 59 269 30 1 569 32 0.867 |
| Ma           | 2015 | China   | Asian     | lung cancer | PB               | PCR-RFLP     | 529 600     | 416 106 6 938 318 512 84 4 1108 92 0.785 |
| Xie          | 2018 | China   | Asian     | HCC         | HB               | sequencing    | 225 200     | 170 49 6 389 61 129 55 6 333 67 0.844 |
| Zhou         | 2017 | China   | Asian     | ESCC        | PB               | PCR-LDR     | 575 577     | 18 165 296 197 953 15 144 435 174 980 | 0.541 |

List of Abbreviations: HCC: Hepatocellular carcinoma; PB: Population-based; HB: Hospital-based; ESCC: Esophageal squamous cell carcinoma; LDR: Ligase Detection Reaction; NSCLC: non-small cell lung cancer; PCR-RFLP: PCR-Restriction fragment length polymorphism; HWE: Hardy-Weinberg equilibrium; MassARRAY® System: Nonfluorescent detection platform utilizing mass spectrometry to accurately measure PCR-derived amplicons.
2.2. Main Analysis Results

2.2.1. Association of PD-1 Polymorphisms with Cancer Risk

The pooled analysis involving PD-1 rs2227981 polymorphism revealed that this variant significantly decreased the overall cancer risk in recessive (OR = 0.82, 95% CI = 0.68–0.99, p = 0.04, TT vs. CT+CC) genetic models (Table 3 and Figure 2).

![Figure 2](image-url)

**Figure 2.** Forest plot for the association between PD-1 rs2227981 polymorphism and cancer susceptibility for CT vs. CC (A), TT vs. CC (B), CT+TT vs. CC (C), TT vs. CT+TT (D), and T vs. C (E).
Table 3. The pooled ORs and 95% CIs for the association between PD-1 and PD-L1 polymorphisms and cancer susceptibility.

| Polymorphism     | n   | Genetic Model     | Association Test | Heterogeneity Test | Publication Bias Test |
|------------------|-----|-------------------|------------------|-------------------|----------------------|
|                  |     |                   | OR (95% CI)      | Z                 | χ² (%)               | p        | Egger’s Test p | Begg’s Test p |
| PD-1 rs2227981   | 16  | CT vs. CC         | 1.11 (0.93–1.33) | 1.16              | 61.22 75            | <0.00001 | 0.032       | 0.031       |
|                  |     | TT vs. CC         | 0.86 (0.72–1.04) | 1.51              | 27.39 45            | 0.03     | 0.034       | 0.024       |
|                  |     | CT+TT vs. CC      | 1.05 (0.89–1.24) | 0.64              | 58.58 74            | <0.00001 | 0.019       | 0.005       |
|                  |     | TT vs. CT+CC      | 0.82 (0.68–0.99) | 2.04              | 31.12 52            | 0.008    | 0.155       | 0.150       |
|                  |     | T vs. C           | 0.98 (0.87–1.09) | 0.43              | 51.48 71            | <0.00001 | 0.020       | 0.012       |
| PD-1 rs2227982   | 11  | CT vs. CC         | 1.01 (0.85–1.19) | 0.09              | 24.53 59            | 0.006    | 0.359       | 0.186       |
|                  |     | TT vs. CC         | 1.05 (0.87–1.26) | 0.51              | 17.10 47            | 0.050    | 0.288       | 0.180       |
|                  |     | CT+TT vs. CC      | 1.02 (0.86–1.20) | 0.22              | 26.49 62            | 0.003    | 0.469       | 0.484       |
|                  |     | TT vs. CT+CC      | 1.00 (0.90–1.10) | 0.04              | 7.52 0              | 0.581    | 0.184       | 0.211       |
|                  |     | T vs. C           | 1.02 (0.92–1.12) | 0.38              | 20.50 51            | 0.025    | 0.927       | 0.715       |
| PD-1 rs11568821  | 9   | AG vs. GG         | 0.79 (0.67–0.94) | 2.73              | 3.89 0              | 0.87     | 0.499       | 0.409       |
|                  |     | AA vs. GG         | 1.01 (0.47–2.14) | 0.01              | 13.19 47            | 0.07     | 0.015       | 0.091       |
|                  |     | AG+AA vs. GG      | 0.82 (0.70–0.96) | 0.24              | 11.30 29            | 0.19     | 0.613       | 0.835       |
|                  |     | AA vs. AG+GG      | 1.07 (0.54–2.13) | 0.19              | 11.79 41            | 0.11     | 0.010       | 0.095       |
|                  |     | A vs. G           | 0.88 (0.68–1.15) | 0.92              | 24.39 67            | 0.002    | 0.822       | 0.835       |
| PD-1 rs7421861   | 7   | CT vs. TT         | 1.16 (1.02–1.33) | 2.20              | 0.01 46             | 0.09     | 0.215       | 0.881       |
|                  |     | CC vs. TT         | 1.00 (0.79–1.28) | 0.03              | 4.76 0              | 0.57     | 0.116       | 0.881       |
|                  |     | CT+CC vs. TT      | 1.14 (0.99–1.31) | 1.81              | 12.93 54            | 0.04     | 0.196       | 0.453       |
|                  |     | CC vs. CT+TT      | 0.96 (0.75–1.22) | 0.37              | 3.49 0              | 0.75     | 0.101       | 0.652       |
|                  |     | C vs. T           | 1.09 (0.97–1.23) | 1.42              | 13.02 54            | 0.04     | 0.200       | 0.652       |
| PD-1 rs36084323  | 7   | AG vs. GG         | 0.92 (0.71–1.20) | 0.60              | 27.83 78            | 0.0001   | 0.042       | 0.051       |
|                  |     | AA vs. GG         | 1.08 (0.77–1.52) | 0.45              | 28.21 79            | <0.0001  | 0.079       | 0.188       |
|                  |     | AG+AA vs. GG      | 0.88 (0.64–1.21) | 0.79              | 47.46 87            | <0.0001  | 0.081       | 0.293       |
|                  |     | AA vs. AG+GG      | 1.06 (0.83–1.36) | 0.46              | 22.86 74            | 0.0008   | 0.137       | 0.348       |
|                  |     | A vs. G           | 0.89 (0.70–1.14) | 0.92              | 66.01 91            | <0.00001 | 0.160       | 0.453       |
| Polymorphism     | n | Genetic Model | OR (95% CI) | Z     | p     | χ²   | I² (%) | p     | Egger’s Test | Begg’s Test |
|------------------|---|---------------|-------------|-------|-------|------|--------|-------|-------------|------------|
| **PD-1 rs10204525** | 6 | AG vs. AA     | 0.94 (0.80–1.10) | 0.76  | 0.45  | 13.13 | 62     | 0.02 | 0.640       | 0.851       |
|                  |   | GG vs. AA     | 0.76 (0.53–1.09) | 1.48  | 0.14  | 19.40 | 74     | 0.002| 0.031       | 0.091       |
|                  |   | AG+GG vs. AA  | 0.90 (0.75–1.08) | 1.10  | 0.27  | 18.41 | 73     | 0.002| 0.399       | 0.188       |
|                  |   | GG vs. AG+AA  | 0.78 (0.57–1.09) | 1.46  | 0.14  | 16.64 | 70     | 0.005| 0.020       | 0.039       |
|                  |   | G vs. A       | 0.89 (0.76–1.05) | 1.38  | 0.17  | 23.71 | 79     | 0.0002| 0.172       | 0.091       |
| **PD-L1 rs4143815** | 8 | CG vs. GG     | 0.75 (0.55–1.01) | 1.89  | 0.06  | 43.76 | 84     | <0.0001 | 0.230       | 0.322       |
|                  |   | CC vs. GG     | 0.62 (0.41–0.94) | 2.28  | 0.02  | 52.19 | 87     | <0.00001| 0.188       | 0.138       |
|                  |   | CG+CC vs. GG  | 0.70 (0.50–0.97) | 2.15  | 0.03  | 43.20 | 84     | <0.00001| 0.184       | 0.138       |
|                  |   | CC vs. CG+GG  | 0.76 (0.60–0.96) | 2.30  | 0.02  | 25.19 | 72     | 0.0007 | 0.070       | 0.138       |
|                  |   | C vs. G       | 0.78 (0.63–0.96) | 2.33  | 0.02  | 61.68 | 89     | <0.00001| 0.100       | 0.138       |
| **PD-L1 rs2890658** | 5 | AC vs. AA     | 1.36 (0.92–2.01) | 1.53  | 0.13  | 13.83 | 71     | 0.008 | 0.757       | 0.624       |
|                  |   | CC vs. AA     | 1.12 (0.68–1.84) | 0.45  | 0.65  | 4.31  | 7      | 0.37  | 0.032       | 0.050       |
|                  |   | AC+CC vs. AA  | 1.35 (0.89–2.04) | 1.43  | 0.15  | 16.24 | 75     | 0.003 | 0.736       | 1.000       |
|                  |   | CC vs. AC+AA  | 0.90 (0.71–1.15) | 0.83  | 0.41  | 4.25  | 6      | 0.37  | 0.041       | 0.050       |
|                  |   | C vs. A       | 1.30 (0.88–1.91) | 1.32  | 0.19  | 25.96 | 85     | <0.0001| 0.248       | 0.142       |
In regard to PD-1 rs11568821 polymorphism, the findings indicated that this variant significantly decreased the overall cancer risk in heterozygous (OR = 0.79, 95% CI = 0.67–0.94, p = 0.006, AG vs. GG) and dominant (OR = 0.82, 95% CI = 0.70–0.96, p = 0.020, AG+AA vs. GG) genetic models (Table 3).

The pooled analysis proposed that PD-1 rs7421861 polymorphism significantly increased the risk of overall cancer in heterozygous (OR = 1.16, 95% CI = 1.02–1.33, p = 0.03, CT vs. TT) genetic models (Table 3).

No significant association was found between PD-1 rs2227982, rs36084323, and rs10204525 polymorphisms and cancer susceptibility (Table 3).

We performed stratified analyses and the findings are summarized in Table 4. We observed that PD-1 rs2227981 significantly decreased the risk of gastrointestinal (GI) cancer (OR = 0.68, 95% CI = 0.56–0.84, p = 0.000, TT vs. CC; OR = 0.60, 95% CI = 0.40–0.89, p = 0.011, TT vs. CT+CC; OR = 0.83, 95% CI = 0.75–0.91, p = 0.000, T vs. C), lung cancer (OR = 0.65, 95% CI = 0.44–0.97, p = 0.030, TT vs. CC; OR = 0.84, 95% CI = 0.71–0.99, p = 0.043, CT+TT vs. CC; OR = 0.83, 95% CI = 0.72–0.95, p = 0.009, T vs. C), and breast cancer (OR = 0.82, 95% CI = 0.70–0.96, p = 0.012, T vs. C).

Furthermore, we found that the PD-1 rs2227982 was associated with an increased risk of cancer in hospital based studies (OR = 1.22, 95% CI = 1.06–1.40, p = 0.006, CT vs. CC; OR = 1.20, 95% CI = 1.05–1.37, p = 0.008, CT+TT vs. CC). We also found a negative correlation between the PD-1 rs2227982 polymorphism and the risk of gastrointestinal cancer (OR = 1.18, 95% CI = 1.04–1.34, p = 0.011, CT vs. CC; OR = 1.16 (95% CI = 1.03–1.30, p = 0.017, CT+TT vs. CC) and breast cancer risk (OR = 0.73, 95% CI = 0.59–0.90, p = 0.004, CT vs. CC; OR = 0.73, 95% CI = 0.57–0.93, p = 0.010, TT vs. CC; OR = 0.73, 95% CI = 0.60–0.89, p = 0.002, CT+TT vs. CC; OR = 0.85, 95% CI = 0.76–0.96, p = 0.010, T vs. C). With reference to the PD-1 rs7421861, our finding proposed that this variant significantly increased the risk of cancer in hospital based studies (OR = 1.89, 95% CI = 1.01–1.40, p = 0.042, CT vs. TT) as well as gastrointestinal cancer (OR = 1.19, 95% CI = 1.01–1.40, p = 0.042, CT vs. CC). Moreover, a significantly reduce cancer risk in population-based studies (OR = 0.80, 95% CI = 0.66–0.97, p = 0.020, AG vs. GG) was observed regarding PD-1 rs11568821 variant. The PD-1 rs36084323 variant was however associated with an increased risk of cancer in hospital-based studies (OR = 1.17, 95% CI = 1.01–1.35, p = 0.042, AG+AA vs. GG).
| Variable | No. | CT vs. CC | TT vs. CC | CT+TT vs. CC | TT vs. CT+CC | T vs. C |
|----------|-----|-----------|-----------|-------------|-------------|--------|
| PD-1 rs227961 | 14  | 1.16 (0.94–1.43) | 0.173 | 0.89 (0.71–1.12) | 0.312 | 1.09 (0.98–1.32) | 0.393 | 0.83 (0.66–1.04) | 0.106 | 1.00 (0.87–1.14) | 0.953 |
| Population-based | 13  | 1.12 (0.91–1.39) | 0.276 | 0.88 (0.80–1.07) | 0.175 | 1.08 (0.87–1.38) | 0.571 | 0.81 (0.66–1.01) | 0.060 | 0.97 (0.85–1.10) | 0.611 |
| Hospital-based | 3   | 1.06 (0.72–1.61) | 0.714 | 0.91 (0.53–1.59) | 0.749 | 1.04 (0.68–1.57) | 0.875 | 0.85 (0.57–1.26) | 0.421 | 1.03 (0.76–1.41) | 0.839 |
| Gastrointestinal cancer | 3   | 1.13 (0.73–1.76) | 0.588 | 0.68 (0.56–0.84) | 0.000 | 0.95 (0.71–1.27) | 0.713 | 0.60 (0.40–0.99) | 0.011 | 0.83 (0.75–0.91) | 0.000 |
| Lung cancer | 3   | 0.91 (0.76–1.10) | 0.324 | 0.65 (0.44–0.97) | 0.020 | 0.84 (0.71–0.99) | 0.043 | 0.69 (0.45–1.04) | 0.079 | 0.83 (0.72–0.95) | 0.009 |
| Breast cancer | 2   | 0.78 (0.56–1.08) | 0.136 | 0.76 (0.53–1.10) | 0.147 | 0.80 (0.59–1.08) | 0.058 | 0.83 (0.59–1.17) | 0.291 | 0.82 (0.76–0.89) | 0.012 |

| PD-1 rs2227962 | CT vs. CC | TT vs. CC | CT+TT vs. CC | TT vs. CT+CC | T vs. C |
|----------------|-----------|-----------|-------------|-------------|--------|
| Population-based | 10  | 1.02 (0.85–1.21) | 0.845 | 1.04 (0.87–1.26) | 0.655 | 1.02 (0.86–1.22) | 0.790 | 1.00 (0.90–1.10) | 0.921 | 1.02 (0.92–1.22) | 0.708 |

| PD-1 rs7421861 | CT vs. TT | CC vs. TT | CT+CC vs. TT | CC vs. CT+TT | C vs. T |
|----------------|-----------|-----------|-------------|-------------|--------|
| Hospital-based | 5   | 1.89 (1.01–1.40) | 0.042 | 1.05 (0.79–1.39) | 0.745 | 1.16 (0.98–1.38) | 0.096 | 0.99 (0.74–1.31) | 0.916 | 1.11 (0.95–1.29) | 0.192 |
| Population-based | 2   | 1.09 (0.86–1.39) | 0.478 | 0.89 (0.56–1.43) | 0.630 | 1.07 (0.84–1.37) | 0.565 | 0.88 (0.55–1.40) | 0.586 | 1.04 (0.85–1.28) | 0.692 |
| Gastrointestinal cancer | 5   | 1.19 (1.01–1.40) | 0.042 | 1.05 (0.79–1.39) | 0.745 | 1.16 (0.97–1.38) | 0.096 | 1.00 (0.75–1.32) | 0.979 | 1.11 (0.95–1.29) | 0.192 |
| Breast cancer | 2   | 1.09 (0.86–1.39) | 0.478 | 0.89 (0.56–1.43) | 0.630 | 1.07 (0.84–1.37) | 0.565 | 0.88 (0.55–1.40) | 0.586 | 1.04 (0.85–1.28) | 0.692 |

Table 4. Stratified analysis of PD-1 and PD-L1 polymorphisms with cancer susceptibility.
2.2.2. *PD-L1* Polymorphisms and Cancer Risk

The pooled ORs results for the relationship between the *PD-L1* rs4143815 and rs2890658 polymorphisms and the risk of cancer are shown in Table 3. The *PD-L1* rs4143815 variant significantly decreased the risk of cancer in homozygous (OR = 0.62, 95% CI = 0.41–0.94, *p* = 0.02), dominant (OR = 0.70, 95% CI = 0.50–0.97, *p* = 0.03), recessive (OR = 0.76, 95% CI = 0.60–0.96, *p* = 0.02), and allele (OR = 0.78, 95% CI = 0.63–0.96, *p* = 0.02) genetic models (Table 3 and Figure 3). The pooled analysis did not support an association between *PD-L1* rs2890658 polymorphism and risk of cancer susceptibility (Table 3).

We did stratified analysis (Table 4) and the findings revealed that *PD-L1* rs4143815 polymorphism significantly reduced the risk of gastrointestinal cancer (OR = 0.68, 95% CI = 0.48–0.97, *p* = 0.032, CC vs. GG; OR = 0.64, 95% CI = 0.53–0.76, *p* = 0.003, CC vs. GG; OR = 0.95, 95% CI = 0.76–1.18, *p* = 0.58, CC vs. GG; OR = 0.64, 95% CI = 0.43–0.95, *p* = 0.028, CG+CC vs. GG; OR = 0.76, 95% CI = 0.59–0.98, *p* = 0.034, C vs. G) and hospital-based studies (OR = 0.75, 95% CI = 0.58–0.97, *p* = 0.030, CC vs. CG+GG; OR = 0.76, 95% CI = 0.58–0.99, *p* = 0.043, C vs. G). In regard to *PD-L1* rs2890658, a positive correlation between this variant and the risk of lung cancer (OR = 1.74, 95% CI = 1.37–2.19, *p* = 0.000, AC vs. AA; OR = 1.77, 95% CI = 1.41–2.23, *p* = 0.000, AC+CC vs. AA; OR = 1.72, 95% CI = 1.39–2.13, *p* = 0.000 C vs. A) was observed (Table 4).

We did stratified analysis (Table 4) and the findings revealed that *PD-L1* rs4143815 polymorphism significantly reduced the risk of gastrointestinal cancer (OR = 0.68, 95% CI = 0.48–0.97, *p* = 0.032, CC vs. GG; OR = 0.64, 95% CI = 0.53–0.76, *p* = 0.003, CC vs. GG; OR = 0.95, 95% CI = 0.76–1.18, *p* = 0.58, CC vs. GG; OR = 0.64, 95% CI = 0.43–0.95, *p* = 0.028, CG+CC vs. GG; OR = 0.76, 95% CI = 0.59–0.98, *p* = 0.034, C vs. G) and hospital-based studies (OR = 0.75, 95% CI = 0.58–0.97, *p* = 0.030, CC vs. CG+GG; OR = 0.76, 95% CI = 0.58–0.99, *p* = 0.043, C vs. G). In regard to *PD-L1* rs2890658, a positive correlation between this variant and the risk of lung cancer (OR = 1.74, 95% CI = 1.37–2.19, *p* = 0.000, AC vs. AA; OR = 1.77, 95% CI = 1.41–2.23, *p* = 0.000, AC+CC vs. AA; OR = 1.72, 95% CI = 1.39–2.13, *p* = 0.000 C vs. A) was observed (Table 4).

Figure 3. Forest plot of the relationship between *PD-L1* rs4143815 polymorphism and cancer susceptibility for CG vs. GG (A), CC vs. GG (B), CG+CC vs. GG (C), CC vs. CG+GG (D), and C vs. G (E).
2.3. Heterogeneity

As shown in Table 3, heterogeneity between the studies regarding the PD-1 rs2227981, PD-1 rs36084323, PD-1 rs10204525, and PD-L1 rs4143815 was observed in all genetic models. For PD-1 rs2227982 polymorphism, our results showed no evidence of heterogeneity in the recessive model (TT vs. CT+CC). Regarding PD-1 rs11568821, heterogeneity was not observed in the heterozygous, homozygous, dominant, and recessive genetic models. Similarly, no evidence of heterogeneity in the heterozygous, homozygous, and recessive genetic models of PD-1 rs7421861 was found. Heterogeneity was not detected in the homozygous and recessive genetic models of the PD-L1 rs2890658.

2.4. Publication Bias

The potential publication bias of the studies included in the present meta-analysis was examined by Begg’s funnel plot and Egger’s test. The results of publication bias are summarized in Table 3. Based on the above analysis, no publication bias for the association of PD-1 rs2227982, PD-1 rs7421861, and PD-L1 rs4143815 variants in all genetic models and cancer risk was demonstrated (Table 3 and Figure 4).

Figure 4. The funnel plot of PD-L1 rs4143815 for the test of publication bias for CG vs. GG (A), CC vs. GG (B), CG+CC vs. GG (C), CC vs. CG+GG (D), and C vs. G (E).
As presented in Table 3 and Figure 5, no publication bias was observed in recessive genetic model of PD-1 rs2227981. Obvious publication bias was not found in the heterozygous, dominant, and allele genetic models of the PD-1 rs11568821 and PD-L1 rs2890658 (Table 3). Moreover, the publication bias was not observed in heterozygous, dominant, recessive, and allele genetic models of the PD-1 rs36084323 and PD-1 rs10204525. (Table 3).

**Figure 5.** The funnel plot of PD-1 rs2227981 polymorphism for the test of publication bias for CT vs. CC (A), TT vs. CC (B), CT+TT vs. CC (C), TT vs. CT+TT (D), and T vs. C (E).

### 2.5. Sensitivity Analysis

Sensitivity analysis was conducted by replicating analysis after neglecting one study at a time to estimate the effect of quality of studies on the final findings. Taken together, our findings from the meta-analysis of the correlation between analyzed polymorphisms and cancer susceptibility remained unchanged in the heterozygous (PD-1 rs2227982, PD-1 rs36084323 and PD-1 rs10204525), homozygous (PD-1 rs2227982, PD-1 rs7421861, PD-1 rs36084323, PD-1 rs10204525 and PD-L1 rs2890658), dominant (PD-1 rs36084323 and PD-1 rs10204525), recessive (PD-1 rs2227982, PD-1 rs7421861, PD-1 rs10204525, and PD-L1 rs2890658).
rs36084323 and PD-L1 rs2890658), and allele (PD-1 rs2227982, PD-1 rs7421861 PD-1 rs10204525 and PD-L1 rs2890658) genetic models (Figure 6). In regard to PD-L1 rs4143815, the findings changed in the heterozygous, homozygous, dominant, recessive, and allele genetics models (Figure 7).

![Figure 6. Sensitivity analyses for studies on PD-1 rs2227981 polymorphism and cancer susceptibility for CG vs. GG (A), CC vs. GG (B), CG+CC vs. GG (C), CC vs. CG+GG (D), and C vs. G (E).]
3. Discussion

It has been proposed that environmental and genetic factors contribute to cancer development [53,54]. Single nucleotide polymorphisms (SNPs) can be considered as biological markers that help scientists to recognize genes that are related to cancer [55]. PD-1 and PD-L1 are involved in the regulation of programmed cell death, which is the regulator of cancer cell proliferation as well as primary response in many cancer therapy strategies. Several studies have investigated the association between PD-1 as well as PD-L1 polymorphisms and the risk of various types of cancers; however, the findings remain discrepant. This meta-analysis provides, for the first time a quantitative estimated of the association between six SNPs of PD-1 and two SNPs of PD-L1 gene and cancer susceptibility. The findings indicated that PD-1 rs2227981 and rs11568821 polymorphisms as well as PDL-1 rs4143815 variant significantly decreased the overall cancer risk, while PD-1 rs7421861 polymorphism significantly increased the risk of overall cancer. Our findings revealed no significant association between PD-1 rs2227982, PD-1 rs36084323, PD-1 rs10204525, and PD-L1 rs2890658 polymorphisms and overall cancer risk.
We performed stratified analyses and our findings indicate that PD-1 rs2227981 significantly decreased the risk of gastrointestinal cancer, lung cancer and breast cancer. The PD-1 rs2227982 was associated with increased risk of cancer in hospital-based studies and lower risk of gastrointestinal and breast cancer. Similarly to PD-1 rs7421861, the PD-1 rs7421861 and PD-1 rs36084323 variants significantly increased the risk of cancer in hospital-based studies. The PD-1 rs11568821 was linked to reduce risk of cancer in population-based studies. Moreover, our findings revealed that PD-L1 rs4143815 polymorphism significantly reduced the risk of gastrointestinal cancer and hospital-based studies. A positive correlation between PD-L1 rs2890658 variant and the risk of lung cancer was observed.

Recently, Zou et al. [56] performed a meta-analysis of the association between PD-L1 rs4143815 polymorphism and the risk of cancer and found also a significant association between this variant and cancer risk, which is in line with our findings. Like our results, a meta-analysis conducted by Da et al. [57] revealed no significant association between PD-1 rs36084323 polymorphism and overall cancer susceptibility. Similar to previous meta-analysis conducted by Zhang et al. [58], we have also found that PD-1 rs2227981 and rs11568821 polymorphisms were associated with decreased cancer susceptibility. In another study, Dong et al. [59] conducted a meta-analysis aimed to inspect the associations between PD-1 rs2227981, rs2227982, rs7421861, and rs11568821 polymorphisms and cancer risk. There were seven studies involving 3395 cases and 2912 controls for PD-1 rs2227981, four studies including 1961 cases and 2390 controls for PD-1 rs2227982, four studies with 1975 cases and 2403 controls for PD-1 rs7421861, and four studies for PD-1 rs11568821 variant and cancer risk. They have found that rs2227981 and rs11568821 polymorphisms significantly decreased the risk of cancer. Mamat et al. [60] conducted a meta-analysis of six studies involving 1427 cases and 1811 controls and have observed no significant association between PD-1 rs2227981 polymorphism and the risk of cancer.

Nevertheless, the number of cases and controls as well as the number of polymorphisms in our meta-analysis is higher than in those previously published meta-analysis studies.

It has been proposed that gene expression could be potentially affected by genetic polymorphisms [21,61–63]. Alterations in the expression of PD-1 and PD-L1 were detected in many cancer types including gastric cancer, lung cancer, thyroid cancer, laryngeal carcinoma, extrapulmonary small cell carcinoma, and breast cancer [63–69].

PD-1/PD-L1 axis impairs T cell activation by preventing Ras-Raf-MEK-ERK and PI3K-AKT signaling pathways, which are mainly believed to promote proliferation and differentiation of T cell [70]. The inhibitory regulation of PD-1/PD-L1 is typically compared to a brake in T cell activation [71]. PD-L1 is exerted by tumors to escape from immune system. Tumor-specific PD-L1-expression was not prognostic in colorectal cancer, while high immune cell-specific PD-1 expression was associated with a prolonged overall survival [72]. It has been revealed that high expression of PD-1 on peripheral blood T cell subsets is correlated with poor prognosis of metastatic gastric cancer [73]. Fang et al. [74] reported that the peripheral blood PD-1 expression was significantly higher in breast cancer patients than benign breast tumors. PD-1 and PD-L1 expression have been shown to be associated with adverse clinicopathological features in clear cell renal carcinoma [75].

This meta-analysis has however several limitations. Firstly, there are relatively small sample sizes of studies for some polymorphisms that should be expanded. Secondly, we have included in this meta-analysis only studies published in English, thus publication bias may have occurred. Thirdly, obvious heterogeneities were found in certain polymorphisms. Differences in ethnic background, type of cancer, and other baseline characteristics of participants may contribute to between-study heterogeneities. Lastly, gene-gene and gene-environment interactions which may affect cancer susceptibility were not evaluated in this meta-analysis due to lack of sufficient data. Therefore, the results of this meta-analysis should be cautiously interpreted.

In conclusion, the current meta-analysis suggests that rs2227981 and rs11568821 polymorphisms of PD-1 and the rs4143815 polymorphism of PD-L1 were associated with protection against cancer, while PD-1 rs7421861 polymorphism significantly increased cancer risk.
4. Methods

4.1. Literature Search

We searched PubMed, Web of Science, Scopus, and Google Scholar databases for publications that studied the association between PD-1 and PD-L1 polymorphisms and cancer risk. The last search was updated on 18 December 2019. The following search terms were used: “programmed cell death 1 or PDCD1 or PD-1, or CD279, or programmed death-1-ligand 1 or CD274 or B7-H1” and “polymorphism or single nucleotide polymorphism or SNP or variation” and “cancer or carcinoma, or tumor”.

The process of recognizing eligible studies is presented in Figure 1. The inclusion and exclusion criteria were as follows. (1) The studies evaluated the association between the PD-1 and PD-L1 polymorphisms and cancer risk, (2) studies with necessary information on genotype or allele frequencies to estimate ORs and 95% CIs, (3) studies with human subjects, and (4) case-control design. We excluded reviews, conference papers, and other studies that were published as abstracts only.

4.2. Data Extraction

The data were recovered from eligible articles independently by two authors. Disagreements were discussed with the third investigator. The following information was recorded for each study: first author’s name, publication year, patient’s nationality, genotypes, and allele frequencies.

4.3. Statistical Analysis

We performed a meta-analysis to assess the association between PD-1 and PD-L1 polymorphisms and cancer susceptibility. The observed genotype frequencies in the controls were tested for Hardy-Weinberg equilibrium (HWE) using the chi-squared test.

Odds ratio (OR) and 95% confidence interval (CI) were calculated to evaluate the association between PD-1 and PD-L1 polymorphisms and cancer risk in five genetic models, which were heterozygous, homozygous, dominant, recessive, and allele. The strength of the association between each polymorphism and cancer risk was assessed by pooled odds ratios (ORs) and their 95% confidence intervals (CIs). The Z-test was used for statistical significance of the pooled OR. We estimated the between-study heterogeneity by the Q-test and I² test: if I² < 50% and P > 0.1, the fixed effects model was used to estimate the ORs and the 95% CI; otherwise, the random effects model was applied.

We evaluated publication bias using funnel plots for visual inspection and conducting quantitative estimations with Egger’s test.

Sensitivity analysis was achieved by excluding each study in turn to assess the stability of the results. All analyses were achieved by STATA 14.1 software (Stata Corporation, College Station, TX, USA).

5. Conclusions

The findings of our meta-analysis proposed that PD-1 rs2227981, rs11568821, rs7421861, as well as PD-L1 rs4143815 polymorphisms associated with overall cancer susceptibility. Further well-designed studies with large sample sizes are warranted to confirm our findings.

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