Pathology - Research and Practice 215 (2019) 229–234

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

Association of PD-L1 gene rs4143815 C > G polymorphism and human cancer susceptibility: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
PD-L1
Cancer
SNP
Meta-analysis

ABSTRACT

Programmed death ligand 1(PD-L1) mediated immune escape play important roles in the development of cancer. The gene polymorphism of PD-L1, in particular rs4143815 C > G, has been associated with the cancer risks, but with conflicting results. Therefore, this meta-analysis was aimed to assess the association between rs4143815 C > G and cancer susceptibility. A systematic literature search was performed to select the studies and the pooled odds ratio (OR) with 95% confidence interval (CI) was used to evaluate the strength of association. Eleven eligible studies containing 3711 cases and 3704 controls were enrolled in the meta-analysis. The results suggested that there is a strong association between rs4143815 C > G and the cancer risks (G vs. C: OR = 1.386, 95% CI: 1.132–1.696, p = 0.002; GG vs. CG + CC: OR = 1.843 95% CI: 1.300–2.613, p = 0.002; GG + CG vs. CC: OR = 1.280, 95% CI: 1.040–1.576, p = 0.020). Subgroup analysis based on cancer type suggested that PD-L1 rs4143815 C > G might increase the susceptibility to gastric cancer (G vs. C: OR = 1.842, 95% CI: 1.403–2.418, p < 0.001) and bladder cancer (G vs. C: OR = 2.015, 95% CI: 1.556–2.608, p < 0.001), and genotype GG carriers of PD-L1 rs4143815 C > G might have higher risks of HCC (GG vs. CG + CC: OR = 2.226 95% CI: 1.562–3.172, p < 0.001). PD-L1 rs4143815 C > G might confer an increased cancer risk, indicating this SNP may contribute to the pathogenesis of cancer and might be used as a potential biomarker to predict the susceptibility to cancer.

1. Introduction

Cancer disease is one of the leading causes of death worldwide, which was responsible for 8.8 million deaths in 2012, and nearly 1 in 6 deaths was due to cancer globally [1]. Although it has been an enormous public health burden worldwide and mounting of investigations have been performed to explore the mechanism of cancer development, the etiology of cancer has not been completely understood. During the past decades, a number of investigations focused on the functional role of the immune system in cancinogenesis, and the results pointed out a critical role of the immune system in cancer development and the gene mutations in immune-related genes may affect the cancer susceptibility [2].

Recent studies have shown that immune escape plays important roles in the development of human cancer disease [3,4]. The cancer cells can suppress the function of immune cells and escape from the immune attack [5]. Particularly, the programmed death ligand 1 (PD-L1, also known as CD274 or B7-H1) has been found to be expressed in a variety of cancers, including the breast cancer, gastric cancer and colorectal cancer [6–8]. It interacts with the programmed cell death 1 (PD-1) and activates the PD-1/PD-L1 immune checkpoints to suppress the immune response of T cells [9]. Although studies on chemical therapy for cancer have generated promising results, major advances have been made by using immunotherapy via blockade of PD-1/PD-L1 checkpoints in the non-small-cell lung cancer and several other cancers recently [10–14]. These inspiring results from clinical trials further highlighted the critical importance of PD-L1-mediated immune escape during the development of cancer.

The human gene PD-L1 (Gene ID: 29,126), encoding a 40 kDa type 1 transmembrane protein, is located at the chromosome 9p24.2. Considering the immune escape role of PD-L1 in the cancer development, genomic variations in PD-L1 might be closely associated with

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https://doi.org/10.1016/j.prp.2018.12.002
Received 27 September 2018; Received in revised form 17 November 2018; Accepted 5 December 2018

cancer risks. The 3'-untranslated region (3'-UTR) of messenger RNA is one of the most important regions in PD-L1 post-transcriptional gene expression regulation because it can be targeted by microRNAs (miRNA), which normally mediates gene translational repression. Structural variations in PD-L1 3'-UTR, including deletions, duplications and translocations, lead to aberrant PD-L1 expression in several cancers [15], supporting the hypothesis that gene variations in PD-L1 3'-UTR may used as useful genetic markers to assess susceptibility to cancer. However, whether gene polymorphisms in the PD-L1 gene are associated with the cancer risks has not been determined.

rs4143815 C > G, a common single nucleotide polymorphism (SNP) and a binding site of miR-570 located at the 3'-UTR of PD-L1, may attenuate the miRNA mediated mRNA degradation and result in up-regulation of PD-L1 expression [16]. Several studies have been performed to investigate the association of rs4143815 C > G with multiple cancer risks, but inconsistent results has been obtained. Some studies found that rs4143815 C > G increased cancer risks whereas other studies found no association between this SNP and cancer risk [17,18]. Given the conflicting results obtained, a meta-analysis on the association between PD-L1 rs4143815 C > G and cancer susceptibility is warranted. Hence, we undertook the first, to the best of our knowledge, meta-analysis to evaluate the rs4143815 C > G gene polymorphism in cancer subjects and health controls. In addition, we performed the subgroup meta-analysis to assess the association between rs4143815 C > G and different type of cancers.

2. Methods

2.1. Literature search and inclusion criteria

A systematic literature search was performed in databases of Medline and China National Knowledge Infrastructure (CNKI). In order to identify studies concerning the PD-L1 polymorphisms and cancer risks, we used the search strategy based on combinations of the following key words: ("PD-L1" or "CD274" or "B7-H1") and ("cancer" or "carcinoma" or "tumor") and ("mutation" or "variation" or "polymorphism"). The entire screening process was conducted according to the PRISMA 2009 statement (*Supplementary file S1*) [19]. The last search was updated on July 31, 2018.

Studies included in the present meta-analysis were selected based on the following criteria: (a) studies evaluating the association between PD-L1 rs4143815 C > G polymorphisms and cancer; (b) case-control studies with unrelated subjects; (c) adequate allelic and genotype frequency data for rs4143815 C > G in case and control groups. Accordingly, studies do not meet our criteria were excluded.

2.2. Data extraction

Two authors screened the included studies and made the data extraction independently. Any disagreements were resolved by discussion with the third author. Qualities of included studies were further assessed by evaluating the sampling and genotyping methods and studies that did not pass the quality control will be excluded. The following characteristics were extracted from each included study: the surname of the first author, year of publication, country of the study, type of cancer, genotype frequencies of the case and controls and P value of Hardy-Weinberg equilibrium (HWE) test for the controls.

2.3. Statistical analysis

Data analysis was performed using STATA statistical software (Version 12.0; Stata Corporation, College Station, TX, USA). We used pooled odds ratios (ORs) with 95% confidence intervals (CIs) to estimate the association between PD-L1 rs4143815 C > G and cancer risk. Pooled ORs were calculated under 4 genetic models, namely additive model (G versus A), recessive model (GG versus CG + CC), homozygotes model (GG versus CC) and dominant model (GG + CG versus CC). The statistical significance of pooled ORs was determined by the Z test and a $p < 0.05$ (two-tailed) was considered statistically significant. The I^2 test was employed to evaluate possible heterogeneity for the included studies. A $p < 0.1$ for the I^2 was considered statistically significant for heterogeneity test and when a $p < 0.1$ for the I^2 test was found, random model was used for the pooled ORs calculation. Publication bias was analyzed using Begg's test and Egger's test, and significant publication bias was indicated by $p < 0.05$. Subgroup meta-analysis was performed based on different cancer types.

3. Results

3.1. Characteristics of included studies

The literature search identified 77 studies relevant to PD-L1 gene and cancer. After reading the title and/or abstract, 54 studies were excluded because these studies were irrelevant. After abstract reading, nine studies were excluded because they were not case control studies. Subsequently, full texts readings were performed on the 14 studies and 3 studies were further excluded due to insufficient data for the meta-analysis. Finally, 11 studies, containing 3711 cases and 3704 controls, investigating the PD-L1 rs4143815 C > G and cancer risks were included in the present meta-analysis (Fig. 1). The characteristics of included studies for the meta-analysis were listed in Table 1. The publication time varied from 2013 to 2018. Genotype The distribution in the controls of included studies was in agreement with Hardy–Weinberg equilibrium, except for 2 studies [20,21]. Out of the 11 included studies, hepatocellular carcinoma (HCC) was studied in 3 articles and gastric and bladder cancer was studied in 2 articles respectively. The rest four studies were esophageal, colorectal, ovarian and lung cancer respectively. Among the 11 studies included in the meta-analysis, there were 10 studies from China and 1 study from Czech Republic.

3.2. Meta-analysis

The results of meta-analysis were listed in Table 2 and a forest plot of ORs under the recessive genetic model was shown in Fig. 2. PD-L1 rs4143815 C > G was significantly associated with overall cancer risks under the 4 genetic models (G vs. C: OR = 1.386, 95% CI: 1.132–1.696, p = 0.002; GG vs. CG + CC: OR = 1.843 95% CI: 1.300–2.613, p = 0.002; GG vs. CC: OR = 1.897 95% CI: 1.300–2.613, p = 0.001; GG + CG vs. CC: OR = 1.280, 95% CI: 1.040–1.576, p = 0.020),

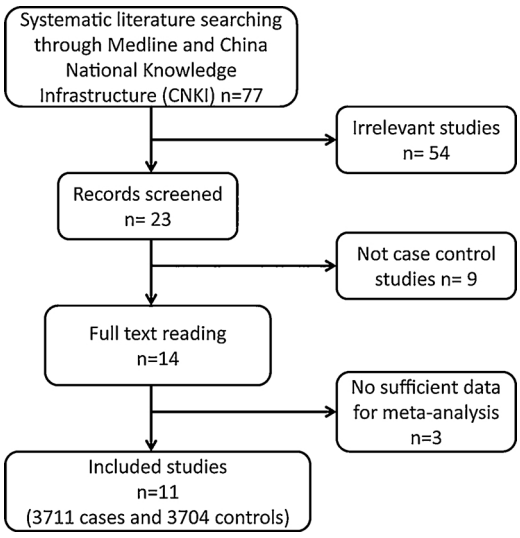

Fig. 1. Flow diagram of article selection process for the meta-analysis.

Table 1
The distribution of the rs4143815 genotypes for case and control.

Author	Year	Country	Cancer type	Case			Control			P HWE
				CC	CG	GG	CC	CG	GG	
Wang	2013	China	Gastric cancer	45	72	88	135	188	70	0.746
Li	2016	China	Bladder cancer	19	21	40	21	41	8	0.074
Cheng	2017	China	HCC	50	50	23	49	76	16	0.095
Du	2017	China	NSCLC	123	145	52	79	80	40	0.021
Liu	2017	China	Bladder cancer	54	71	88	88	112	51	0.164
Tao	2017	China	Gastric cancer	70	153	123	160	223	117	0.023
Catalano	2018	Czech	Colorectal cancer	148	580	632	122	467	514	0.306
Tan	2018	China	Ovarian cancer	31	82	51	54	78	38	0.334
Xie	2018	China	HCC	50	101	74	65	104	31	0.316
Yang	2018	China	HCC	42	42	16	36	54	10	0.113
Zhou	2018	China	ESCC	211	277	87	203	289	85	0.275

Note: NSCLC (Non-small cell lung cancer), HCC (Hepatocellular carcinoma), ESCC (Esophageal squamous cell carcinoma), HWE (Hardy-Weinberg equilibrium).

suggesting the PD-L1 rs4143815 C > G might increased the overall cancer susceptibilities.

Sub-group analysis based on different cancer types revealed that PD-L1 rs4143815 C > G was associated with gastric cancer (G vs. C: $p < 0.001$; GG vs. CG + CC: $p = 0.005$; GG vs. CC: $p < 0.001$; GG + CG vs. CC: $p < 0.001$) and bladder cancer (G vs. C: $p < 0.001$; GG vs. CG + CC: $p = 0.004$; GG + CG vs. CC: $p < 0.017$), suggesting the PD-L1 rs4143815 C > G might increase the gastric and bladder cancer risks. Further, subgroup meta-analysis showed that PD-L1 rs4143815 C > G was associated with HCC under recessive genetic model (OR = 2.226 95% CI: 1.562–3.172, $p < 0.001$) and homozygotes model (OR = 1.953 95% CI: 1.096–3.481, $p = 0.023$), but not additive model ($p = 0.274$) and dominant model ($p = 0.924$), indicating PD-L1 rs4143815 C > G might also increase the HCC susceptibility.

Two included studies deviated from the HWE in controls [20,21], suggesting potential sampling bias and/or genotyping errors. However, when we omitted these two studies, the association between PD-L1 rs4143815 C > G polymorphism and cancer risk was still significant with respect to all the genetic models (G vs. C: OR = 1.377 95% CI: 1.109–1.711, $p = 0.004$; GG vs. CG + CC: OR = 1.808 95% CI: 1.272–2.570, $p = 0.001$; GG vs. CC: OR = 1.920 95% CI: 1.310–2.816, $p = 0.001$; GG + CG vs. CC: OR = 1.305 95% CI: 1.024–1.664, $p = 0.032$) (Table 2).

3.3. Heterogeneity test

P values from I^2 test indicated presence of potential heterogeneity in the meta-analysis of overall cancer types. However, heterogeneity was not found in the sub-group meta-analysis of gastric cancer (dominant model, $p = 0.992$), bladder cancer (additive model, $p = 0.28$; dominant model, $p = 0.733$) and HCC (recessive model, $p = 0.52$).

3.4. Publication bias

Begg's funnel plots and Egger's tests and were employed to assess the potential publication bias and the results were listed in Table 2. Studies in the funnel plots were symmetrical distributed in the overall meta-analysis under all genetic models ($p = 0.187$, 0.428 and 0.187, respectively), suggesting the absence of publication bias for the meta-analysis of overall cancer risks (Fig. 3).

Table 2
Meta-analysis on the association between rs4143815 C > G and cancer risks under different genetic model.

Subgroup	Genetic model	Pooled ORs(95% CI)	P	Heterogeneity (P)	Publication bias (P)	
					Begg's	Egger's
Overall	G vs. C	1.386 (1.132, 1.696)	0.002	0.000	0.187	0.505
	GG vs. CG + CC	1.843 (1.300, 2.613)	0.001	0.000	0.428	0.037
	GG vs. CC	1.897(1.315,2.737)	0.001	0.000	0.428	0.436
	GG + CG vs. CC	1.280 (1.040, 1.576)	0.020	0.001	0.187	0.030
Gastric cancer	G vs. C	1.842 (1.403, 2.418)	0.000	0.081	0.317	N.A.[c]
	GG vs. CG + CC	2.478 (1.306, 4.699)	0.005	0.008	0.317	N.A. [c]
	GG vs. CC	2.951(1.900, 4.581)	0.000	0.138	0.317	N.A. [c]
	GG + CG vs. CC	1.857 (1.448, 2.382)	0.000	0.992	0.317	N.A. [c]
Bladder cancer	G vs. C	2.015 (1.556,2.608)	0.000	0.280	0.317	N.A. [c]
	GG vs. CG + CC	4.307 (1.582, 11.73)	0.004	0.033	0.317	N.A. [c]
	GG vs. CC	3.427 (1.876,6.259)	0.000	0.226	0.317	N.A. [c]
	GG + CG vs. CC	1.536 (1.080, 2.186)	0.017	0.733	0.317	N.A. [c]
HCC[a]	G vs. C	1.241 (0.843,1.827)	0.274	0.021	0.174	0.387
	GG vs. CG + CC	2.226(1.562, 3.172)	0.000	0.520	0.602	0.183
	GG vs. CC	1.953(1.096,3.481)	0.023	0.148	0.602	0.244
	GG + CG vs. CC	1.027 (0.599, 1.760)	0.924	0.030	0.602	0.313
HWE[b]	G vs. C	1.377(1.109,1.711)	0.004	0.000	1.000	0.176
	GG vs. CG + CC	1.808(1.272,2.570)	0.001	0.000	0.835	0.096
	GG vs. CC	1.920(1.310,2.816)	0.001	0.000	0.677	0.240
	GG + CG vs. CC	1.305(1.024,1.664)	0.032	0.000	0.677	0.344

Note: [a]HCC (Hepatocellular carcinoma); [b] the studies derived from Hardy-Weinberg equilibrium (HWE) were excluded for the meta-analysis.[c] p values were not obtained for the Egger's tests because only 2 studies included.

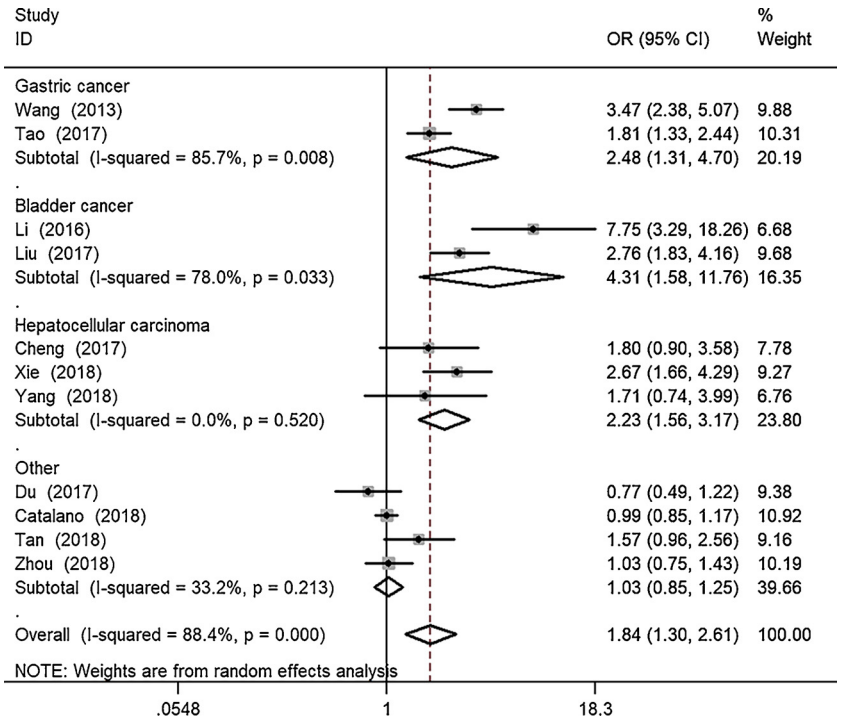

Fig. 2. Forest plot of ORs for rs4143815 C > G in the PD-L1 gene and cancer risk under different genetic models. ORs were estimated under recessive model (GG vs.GC + CC, stratified by cancer type). The circle and horizontal lines correspond to OR and 95% CI and the area of the squares reflects the weight of individual studies included in the meta-analysis. The diamond represents the pooled ORs and 95% CI.

4. Discussion

Programmed death ligand 1(PD-L1) play important roles in cancer development and rs4143815 C > G in the PD-L1 gene might be associated with cancer risk. The goal of the study was to clarify the association between PD-L1 rs4143815 C > G and cancer risks using meta-analysis. Our results showed that PD-L1 rs4143815 C > G increased the overall susceptibility to cancers. Results of subgroup analysis revealed that PD-L1 rs4143815 C > G might increase the gastric and bladder cancer risks, and genotype GG carriers of PD-L1 rs4143815 C > G might have higher risks of HCC based on the available published results. Overall, these findings indicate that the SNP rs4143815 C > G in the PD-L1 3'-UTR might increase the susceptibility to cancer.

PD-L1, an immune checkpoints protein, has been involved in cancer development via promoting T cell apoptosis and facilitating cancer cell escape from immune system [9,22]. The rs4143815 in the 3'-UTR of PD-L1 gene is the binding site of miR-570, and the C > G substitution attenuates the miR-570 mediated mRNA degradation and enhances PD-

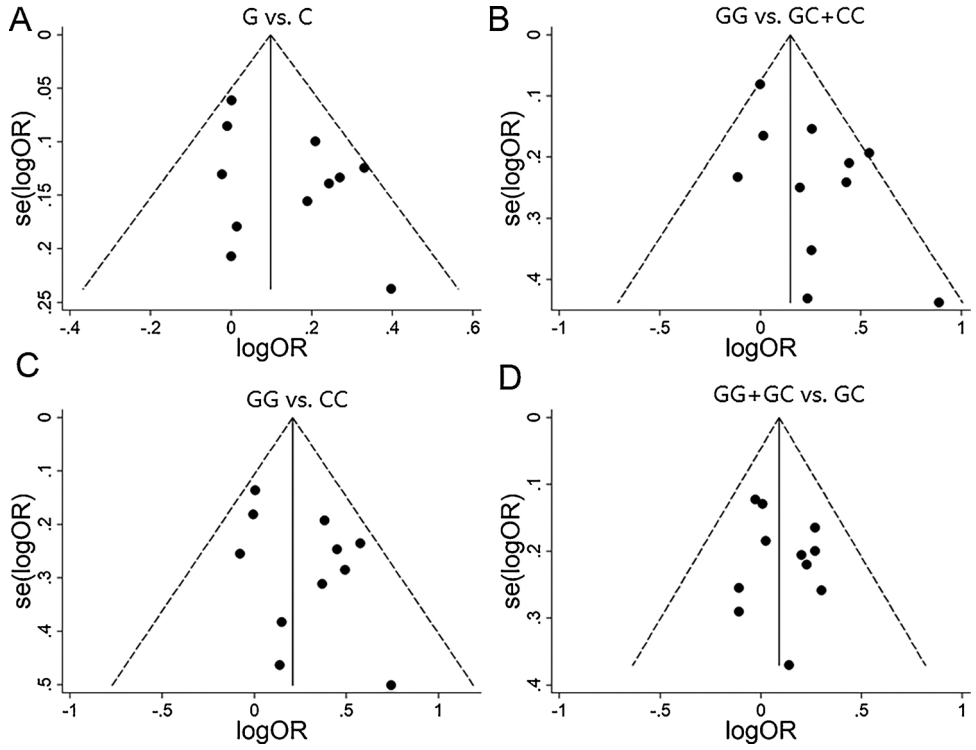

Fig. 3. Begg's funnel plot for association between rs4143815 C > G polymorphism and cancer risk under different genetic models.

L1 expression, thus might increase the cancer risks [16]. A number of case-control studies have been performed to investigate the association between rs4143815 C > G and cancer susceptibility but have yielded controversial results. Some studies reported rs4143815 allele G increased the cancer susceptibilities [16,18,21,23–26]. In contrast, other studies reported insignificant association between rs4143815 C > G and cancer risk [17,20,27,28]. The inconsistent results may be attributed to different study design, limited sample size, different ethnicity groups and potential sampling bias in individual studies, which could be eliminated by using meta-analysis strategy.

In the present meta-analysis, 3711 cases and 3704 controls from 11 studies were included to estimate the association between rs4143815 C > G and cancer susceptibility. To the best of our knowledge, this is the first meta-analysis on the association of PD-L1 gene variations with cancer risks. The results suggested that there is strong association between rs4143815 SNP in the PD-L1 3'-UTR and cancer risks, and the C > G substitution increased overall cancer susceptibilities under all genetic models. Furthermore, the strength of the present meta-analysis was also evidenced by the absence of publication bias, which was demonstrated by the symmetrical distribution of the included studies in the funnel plot (Fig. 3). The genetic susceptibility to disease may vary between ethnicity groups due to different genetic background [29]. In the meta-analysis, 10 out of the 11 studies were performed from China in Asian population and only 1 study from Czech Republic in the Caucasians [17], which could minimize the potential effects of different genetic backgrounds on the results.

We included studies on the association between PD-L1 rs4143815 C > G and different cancers. Although the immune escape has been recognized as a common mechanism in the development of human cancers, the association between PD-L1 gene variations and cancer risks might be vary between different cancers. Hence, we performed subgroup analysis based on the cancer types. The results demonstrated that the PD-L1 rs4143815 C > G increase the gastric and bladder cancer risks under all genetic models while genotype GG increase the HCC susceptibility based on the meta-analysis of available published results, suggesting the development of HCC might be less affected by the rs4143815 C > G than the gastric and bladder cancer. Consistently, Cheng et al. found that only GG genotype in rs4143185 increased the risk of HCC [26]. While Wang et al. have demonstrated that this SNP disrupted the interaction between miR-570 and PD-L1 mRNA and caused aberrant PD-L1 expression in gastric cancer cells, the functional role of PD-L1 rs4143815 C > G in other type of cancers has not been determined [16]. Furthermore, we have also compared the association between PD-L1 rs4143815 C > G and cancer risk with different genetic models, and the ORs in the recessive model and homozygotes model were higher than that of other genetic models for the overall, gastric, bladder cancer and HCC.

In addition to rs4143815 C > G, some other SNPs of PD-L1 have also been associated with the cancer risks, such as the 8923C in the intron 4 of PD-L1 gene was associated with non-small cell lung cancer susceptibility in a Chinese population [30,31]. Although the functional significance of PD-L1 8923 A > C has not been determined, the association has been further confirmed by another study [30]. Meanwhile, the rs10815225 G > C, a SP1 transcript binding site in the promoter of PD-L1, was associated with gastric cancer risk [21]. On the another sides, genomic variations in the PD-1 gene, the receptor of PD-L1, were closely correlated with cancer susceptibilities [32,33]. Our results, together with these studies, further supported the idea that gene variations in the PD-1/PD-L1 checkpoints could affect human cancer risks.

There are some limitations should be addressed in this meta-analysis. First, due to insufficient data, other risk factors such as age, diet habit and body mass, which might also affect cancer risks, were not considered in the meta-analysis. Second, although we have included sufficient cases and controls in the overall meta-analysis, the sample size for the subgroup analysis of individual cancer type is relatively small, which might lead to potential publication bias. In addition, publication bias cannot be fully excluded because positive results are easier to be published than the negative results. Hence, further studies with larger sample sizes for each type of cancer are still required. Importantly, some studies have found that immunotherapy with PD /PD-L1 agents may cause immune-related adverse events (irAEs), it will also be interesting to determine whether PD-L1 gene (rs4143815 C > G) would affect such adverse effects [34]. The last but not the least, most of the studies (10 out of 11) included in the present analysis were from Chinese population and there is not any data regarding the PD-L1 gene polymorphism and lung cancer risk in other Asian population such as the Iranian population [35]. The only study from Caucasians failed to found the association between rs4143815 C > G and cancer susceptibilities[17]. Whether there is such association in the Caucasian population merits further investigations.

5. Conclusion

Our study provided the most comprehensive analysis on the association between PD-L1 gene variations and cancer risk. The results support that rs4143815 C > G in PD-L1 gene 3'UTR is associated with increased cancer susceptibilities, especially for the gastric, bladder cancer and HCC, indicating that this SNP may contribute to the pathogenesis of cancer and might be used as a biomarker to predict the cancer risks. However, due to existed limitations, the results should be interpreted with caution. Future studies with larger sample sizes, and cancer patients and well-matched controls from other populations are still needed.

Acknowledgements

The study was supported by Key Lab for Clinical Anatomy & Reproductive Medicine of Hengyang City (2017KJ182). ST was also partially supported by a grant from University of South China (2014XQD22) and a fellowship from Chinese Scholarship Council (201608430251) while writing this manuscript. TL and XW were supported by a College Students' research learning and innovative experiment program grant from University of South China (No. 2018XJXZ159 and No. 2018XJXZ161).

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