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Association between *IL8RB* C1208T mutation and risk of cancer

A pooled analysis based on 5299 cases and 6899 controls

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Abstract

Introduction: The CXC chemokines are unique cytokines that play a vital role in the progression of many cancers. Association between chemokine (C-X-C motif) receptor 2 (*IL8RB*) C1208T mutation and cancer risk remains incomprehensive.

Methods: We therefore utilized odds ratios and in silico analysis to explore the relationship of *IL8RB* polymorphism on risk to cancer. Furthermore, we adopted gene set enrichment analysis to investigate the *IL8RB* expression in prostate adenocarcinoma.

Results: A total of 14 case-control studies combined with 5299 cases and 6899 controls were included in our analysis. We revealed that individuals carrying TT genotype had an 14% increased cancer risk compared with those with TC + colon cancer (CC) genotype (odds ratio [OR] = 1.14, 95% CI = 1.05–1.25, $P = .003$, $I^2 = 35.6$). Stratification analysis by race showed that East Asians with TT + TC genotype may have a 25% decreased cancer risk compared with control. Stratification analysis by cancer type revealed that individuals with TT genotype were associated with elevated risk of urinary cancer than control. The expression of *IL8RB* was attenuated in prostate adenocarcinoma.

Conclusions: *IL8RB* C1208T may be correlated with the risk of cancer, especially prostate adenocarcinoma.

Abbreviations: BC = breast cancer, CC = colon cancer, CXCR1 = C-X-C chemokine receptor type 1, GSEA = gene set enrichment analysis, HB = hospital-based, HWE = Hardy–Weinberg equilibrium, IL8RB = chemokine (C-X-C motif) receptor 2, LC = lung cancer, MAFs = minor allele frequencies, NCBI = National Center for Biotechnology Information, ORs = odds ratios, TIMER = tumor immune estimation resource, TIMM16 = mitochondrial import inner membrane translocase subunit 16, UC = urinary cancer.

Keywords: analysis, cancer, chemokine (C-X-C motif) receptor 2, mutation

1. Introduction

Malignant tumors remain a global health problem worldwide.[1] The incidence of cancer and the associated mortality are growing in both developing and developed countries.[2] In 2019, approximately 174,650 new prostate adenocarcinoma subjects and 31,620 cancer-related deaths were estimated in the United States.[3] Compared with the western countries, the incidence of cancer in China was lower, but the cancer mortality rate was 30% and 40% higher than that in the United Kingdom and the United States, respectively.[4] Late diagnosis, metastasis, immune escape, and drug resistance are main reasons for the low survival rate of cancer patients.[5] To date, researchers all over the world are trying to discover specific biomarkers for solid tumors. Therefore, it is warranted to develop useful molecular markers to provide targets for the treatments of malignances.[6]

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HP and JO-Y are equal contributors.

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Data accessibility: The data in the current study can be acquired from the corresponding authors upon request.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Chemokines belong to a large family of structurally related small molecules that can participate in the process of cell recruitment and migration.[7,8] CXC chemokines and receptors can also participate in leukocyte migration, embryogenesis, and growth and metastasis of cancer cells.[9–11] CXC chemokine receptor-2 (*IL8RB*) is a major receptor of the CXC superfamily.[12] This 7-transmembrane G protein-coupled receptor has been demonstrated to effect on the endothelial cell membrane, and also in tumor cells. The binding of interleukin-8 (*IL-8*) and C-X-C chemokine receptor type 1 (*CXCR1*) or *IL8RB* can mediates the function of *IL-8*.[13] Other studies have revealed that *IL8RB*, rather than *CXCR1*, is the a vital receptor involved in angiogenesis and chemotaxis induced by chemokine.[14–16] The binding of *IL8RB* can mediate many biological effects including cell proliferation, angiogenesis, and cancer invasion.[17,18]*IL8RB* is considered to participate in the prognosis of many tumors, such as colon cancer, breast cancer (BC), and pancreatic cancer.[19–23]

Studies have revealed that *IL8RB* polymorphisms may have an impact on the development of tumor.[24,25] An et al[26] found that *IL8RB* is correlated with a poor prognosis in urinary cancer (UC) patients. Moreover, *IL8RB* can be served as a potential prognostic factor. However, there were other studies revealed no similar correlation in pancreatic or esophageal cancer.[27,28] The *IL8RB* C1208T polymorphism was evaluated in many cancers, such as urinary, breast, and digestive system. However, the effect of *IL8RB* C1208T polymorphism on cancer remains incomprehensive. Hence, we comprehensively explored the relationship between *IL8RB* C1208T mutation and risk of cancer.[29–39] Furthermore, we employed in silico analysis including gene set enrichment analysis (GSEA) to investigate the expression of *IL8RB* in prostate adenocarcinoma.

2. Materials and methods

2.1. Publication search

An online search of Embase, PubMed, Chinese Wanfang, China national knowledge infrastructure, and Google Scholar. The following keywords were used: ("+1235C/T" OR "C1208T" OR "*IL8RB*" OR "Interleukin-8 receptor") AND ("cancer" OR "tumor" OR "adenocarcinoma") AND ("polymorphism" OR "variation"). The latest search was on September 21, 2021. Extra case-control studies from the references were also screened to increase the number of articles. The PRISMA checklist was shown in Guidelines Checklist.

2.2. Screening criteria

The inclusion criteria were as follows: case-control studies; studies with enough genotype data for assessing the association between *IL8RB* C1208T mutation and cancer risk; and article language used English or Chinese; the diagnostic criteria of cancer in the case group were cancer patients who should be pathologically diagnosed; and the screening criteria of the control group were healthy subjects with no history of cancer or other serious disease. The exclusion criteria were: studies without genetic information on control; data for calculating odds ratios (ORs) were not available; or studies not evaluating the effect of *IL8RB* variation on cancer risk.

2.3. Data collection

The following study characteristics were investigated: the first author's name, year of publication, type of cancer, population ethnicity, control source, genetic data of *IL8RB* C1208T polymorphism, minor allele frequencies (MAFs) in case and control. In a stratified analysis, prostate adenocarcinoma and bladder cancer were classified under the group of urinary system cancer. Esophageal, gastric, liver, colon, and rectal cancers were summarized in cancer of digestive system. The number of cancers <2 was classified into "other cancer." The clinical information and ethical approval were acquired from the reference article. The current study did not involve additional human information.

2.4. Statistical analyses

The effect of *IL8RB* C1208T mutation on cancer risk were measured by ORs and 95% CIs. The evaluation of overall ORs was conducted with 5 genetic models. They were as follows: allelic, heterozygous, homozygous, dominant, and recessive model, which referred to T versus C, TC versus CC, TT versus CC, TT + TC versus CC, and TT versus TC + CC, respectively. The heterogeneity of included studies was evaluated by a Q statistic test. P-value of heterogeneity ($P_{\text{heterogeneity}}$) $<.05$ represents a heterogeneity. Therefore, the random effects method was used. On the other hand, the fixed effects method was selected.[40] The inconsistency of included studies was detected by I^2. The higher the I^2 value, the higher the degree of heterogeneity. P value of the Hardy-Weinberg equilibrium (HWE) (P_{HWE}) was revealed by Fisher exact test. P_{HWE} value of high-quality groups was all more than .05. Conversely, studies with $P_{\text{HWE}} < .05$ were summarized into low-quality groups. The sample size of large sample group should >1000. Hierarchical analysis consisted of cancer type, source of control, ethnicity, sample size, and study quality. Sensitivity analysis was performed by culling single study. The Begg and Egger test were conducted to investigate the publication bias. $P > .05$ represents no significant difference. All statistical analyses were performed with STATA software (version 11.0, Stata Company, College Station, TX).

2.5. In silico analysis of IL8RB

We employed National Center for Biotechnology Information (NCBI) database to investigate the MAFs in various ethnicities (https://www.ncbi.nlm.nih.gov/snp). Additionally, the tumor immune estimation resource (TIMER) database was adopted to explore the gene expression profile of *IL8RB* in different tumors (https://cistrome.shinyapps.io/timer). The Ualcan database was utilized to investigate gene–gene crosstalk and *IL8RB* expression (http://ualcan.path.uab.edu/analysis.html). The protein–protein relationship of IL8RB in *Homo sapiens* was demonstrated by STRING online server database (https://string-db.org/cgi/input.pl). GSEA software was used to explore the potential signaling pathways associated with *IL8RB* in prostate adenocarcinoma samples (http://software.broadinstitute.org/gsea/index.jsp,c2.cp.KEGG.v7.4.symbol.gmt). In the process of GSEA, gene set alignment was carried for 1000 times.[41] Tumor-infiltrating immune cell profile in prostate adenocarcinoma samples was calculated by the CIBERSORT method. In this case, the leukocyte gene signature matrix was performed to demonstrate 22 kinds of immune cells. These 22 immune cell types were identified following the CIBERSORT method (https://cibersort.stanford.edu/). $P < .05$ was considered to be statistically significant.

3. Results

3.1. Main characteristics

A total of 14 case-control studies combined with 5299 patients with cancer and 6899 controls were included (Guidelines Flow Diagram, Table S1, Supplemental Digital Content, http://links.lww.com/MD/G642). In the stratified analysis by cancer type, 5 studies with digestive system cancer, 5 studies focused on both cancers of urinary and lung. Another 2 studies were on BC and only 1 study was on Kaposi sarcoma, which was classified as "other cancer." In the subgroup analysis by ethnicity, there were 7 studies on Europeans, 4 studies focused on East Asian populations, and 2 studies based on West Asian descendants. Only 1 study was on populations with African descent. In the subgroup analysis based on control source, 10 and 4 hospital-based case-control studies were enrolled. In stratified analysis by genotyping method, the number of studies conducted classic polymerase chain reaction, Golden Gate method, TaqMan assay, and iPLEX Gold method was 7, 3, 3, and 1, respectively. In subgroup analysis by quality of study, the number of research with high-quality and low-quality was 10 and 4. Furthermore, we utilized dbSNP according to NCBI database to explore the MAFs of *IL8RB* C1208T mutation in various ethnicities. The distribution frequency of mutated T allele in Africans, Americans, Europeans, South Asians, and East Asians was 0.092, 0.442, 0.493, 0.409, and 0.658, respectively. (Fig. 1).

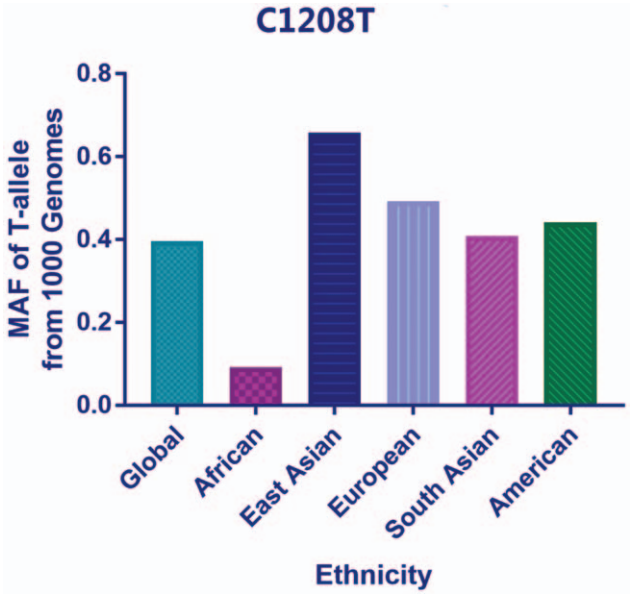

Figure 1. Minor allele frequencies of *IL8RB* in different ethnicities.

3.2. Quantitative synthesis

In the pooled analysis process, ORs combined with 95% CIs were conducted to assess the effect of *IL8RB* C1208T mutation on cancer risk. Overall analysis revealed that individuals with TT genotype could increase 14% of cancer risk than control (OR = 1.14, 95% CI = 1.05–1.25, $P = .003$, $I^2 = 35.6$, Fig. 2A, Table S2, Supplemental Digital Content, http://links.lww.com/MD/G643). Stratified analysis by ethnicity indicated that East Asian individuals carrying TT + TC genotype had a 25% diminished cancer risk (dominant model, 95% CI = 0.59–0.95, $P = .017$, $I^2 = 37.8$). We revealed similar results in heterozygous comparison (95% CI = 0.55–0.92, $P = .010$, $I^2 = 21.9$). However, we found no positive association of *IL8RB* C1208T polymorphism on risk of cancer in European or African populations. In stratification analysis by type of cancer, we observed that individuals with TT genotype could have a 39% augmented UC risk than control (homozygous comparison, 95% CI = 1.06–1.83, $P = .018$, $I^2 = 0$). Similar positive results were obtained in a recessive genetic model (BC: OR = 1.60, 95% CI = 1.08–2.38, $P = .020$, $I^2 = 36.2$, cancers of digestive system: OR = 1.14, 95% CI = 1.01–1.29, $P = .030$, $I^2 = 13.7$, Fig. 2B) and homozygous comparison. For lung cancer

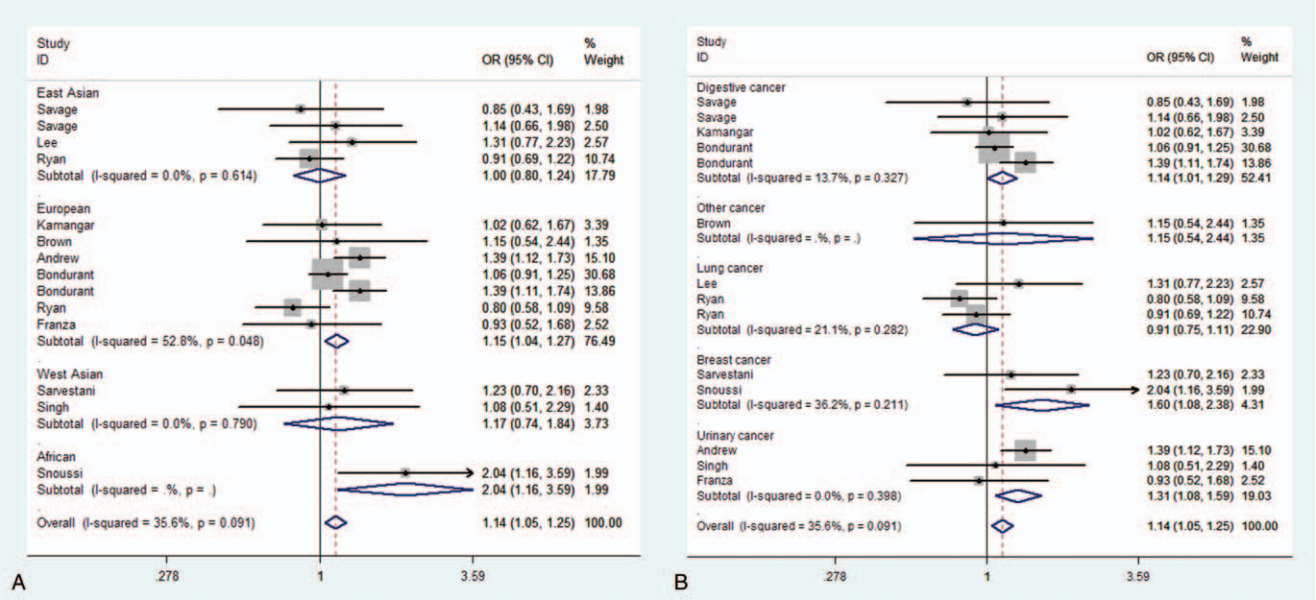

Figure 2. Subgroup analysis of *IL8RB* C1208T variant based on ethnicity (A) and cancer type (B).

(LC), individuals carrying TT genotype had a 30% attenuated cancer risk (95% CI = 0.53–0.92, $P = .010$, $I^2 = 0$). Similar results were obvious in allelic, heterozygous, and dominant genetic models. We obtained different results between large- and small-sample studies in stratification analysis by sample size. Individuals carrying TC genotype had a 17% mitigated cancer risk compared with those carrying CC genotype for small-sample size studies (95% CI = 0.73–0.95, $P = .005$, $I^2 = 28.5$). For studies with large-sample size, individuals with TT genotype had a 22% ameliorated cancer susceptibility compared with control (95% CI = 1.09–1.37, $P < .001$, $I^2 = 63.5$, Fig. 3A). Stratification analysis by control source showed that TT genotype was related to ameliorated cancer risk in population based studies under a recessive model (95% CI = 1.03–1.24, $P = .011$, $I^2 = 42.0$, Fig. 3B). Stratification analysis by study quality revealed no positive association among high-quality studies (homozygous model: 95% CI = 0.89–1.41, $P = .313$, $I^2 = 65.1$, recessive model: 95% CI = 0.99–1.35, $P = .062$, $I^2 = 52.6$). Similar finding was obtained in low-quality studies (homozygous model: 95% CI = 0.70–1.40, $P = .939$, $I^2 = 0$, recessive model: 95% CI = 0.74–1.38, $P = .950$, $I^2 = 0$).

3.3. In silico analysis of IL8RB

We used the TIMER database to evaluate the expression of *IL8RB* in various cancers. *IL8RB* expression was mitigated in patients with prostate adenocarcinoma or bladder cancer (Fig. 4, $P < .001$). The expression of *IL8RB* was also attenuated in BC and LC ($P < .001$). Nevertheless, the *IL8RB* expression was augmented in patients with kidney renal clear cell carcinoma (KIRC, $P < .001$). We further used the Ualcan database to investigate expression of *IL8RB* in UC based on the ethnicity of populations. In the evaluation of *IL8RB* expression in prostate adenocarcinoma, 147 European patients, 6 African American cases, and 52 normal controls were included. Compared with that in normal subjects, the expression of *IL8RB* was down regulated in European patients with prostate adenocarcinoma. No significant difference was revealed in African Americans (Fig. 5A). In the study of *IL8RB* expression in bladder cancer, 320 European patients, 22 African American patients, 44 Asian patients, and 19 normal controls were involved. The expression of *IL8RB* was also restrained in bladder cancer subjects of European, and African American descents. No obvious difference was indicated between the Asian patients and normal controls (Fig. 5B). Expression of *IL8RB* was mitigated in prostate adenocarcinoma patients compared with control ($P < .05$, Fig. 6A). There was no significant correlation between *IL8RB* expression and the age of patients with prostate adenocarcinoma ($P > .05$, Fig. 6B). *IL8RB* expression was diminished in patients with a Gleason score of >8 ($P < .05$, Fig. 6C). Expression of *IL8RB* in patients with advanced prostate adenocarcinoma was lower than that in patients with early-stage prostate adenocarcinoma ($P < .05$, Fig. 6D).

Additionally, gene–gene correlations of *IL8RB* were revealed by the Ualcan database. Twenty-four genes participated in the crosstalk with *IL8RB* in prostate adenocarcinoma (Fig. 7A). The top 3 genes include: mitochondrial import inner membrane translocase subunit 16 (TIMM16, Fig. 7B), nucleoside diphosphate kinase 1 (Fig. 7C), protein phosphatase 1 regulatory inhibitor subunit 14B (PPP1R14B, Fig. 7D). The STRING database was also adopted to demonstrate the protein–protein interaction of IL8RB. Thirty proteins can participate in the crosstalk with IL8RB protein (Fig. 8A). The most related proteins were showed in Fig. 8B). GSEA analysis was additionally conducted to explore the potential pathways related to expression of *IL8RB*. The enrichment heat map was indicated in Fig. 9A. Results from GSEA revealed that the *IL8RB* expression was associated with prostate adenocarcinoma (Fig. 9B, $P < .05$). Signaling pathways, including JAK-STAT signaling (Fig. 9C), aldosterone regulated sodium reabsorption (Fig. 9D), and phosphatidylinositol signaling system (Fig. 9E) were related to high *IL8RB* expression. Moreover, the CIBERSORT method was employed to assess the TICs profile in prostate adenocarcinoma subjects. In CIBERSORT, the leukocyte gene signature matrix (called LM22) was used to distinguish 22 types of immune cells (Fig. 10A). Compared with

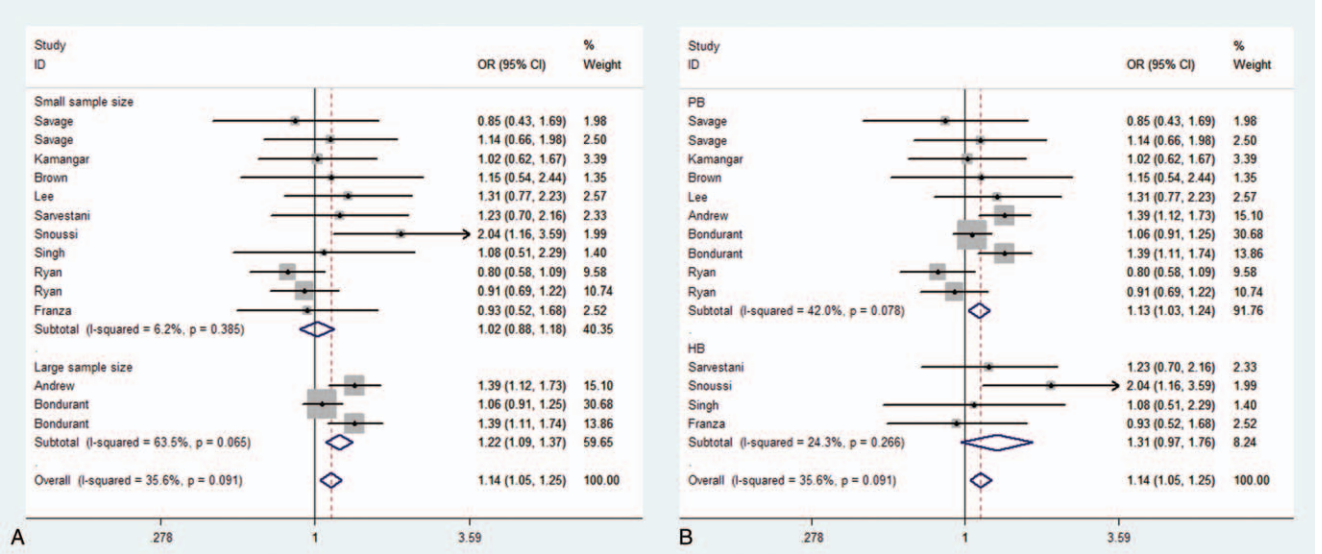

Figure 3. Subgroup analysis of *IL8RB* C1208T polymorphism and likelihood of cancer based on sample size (A) and control source (B).

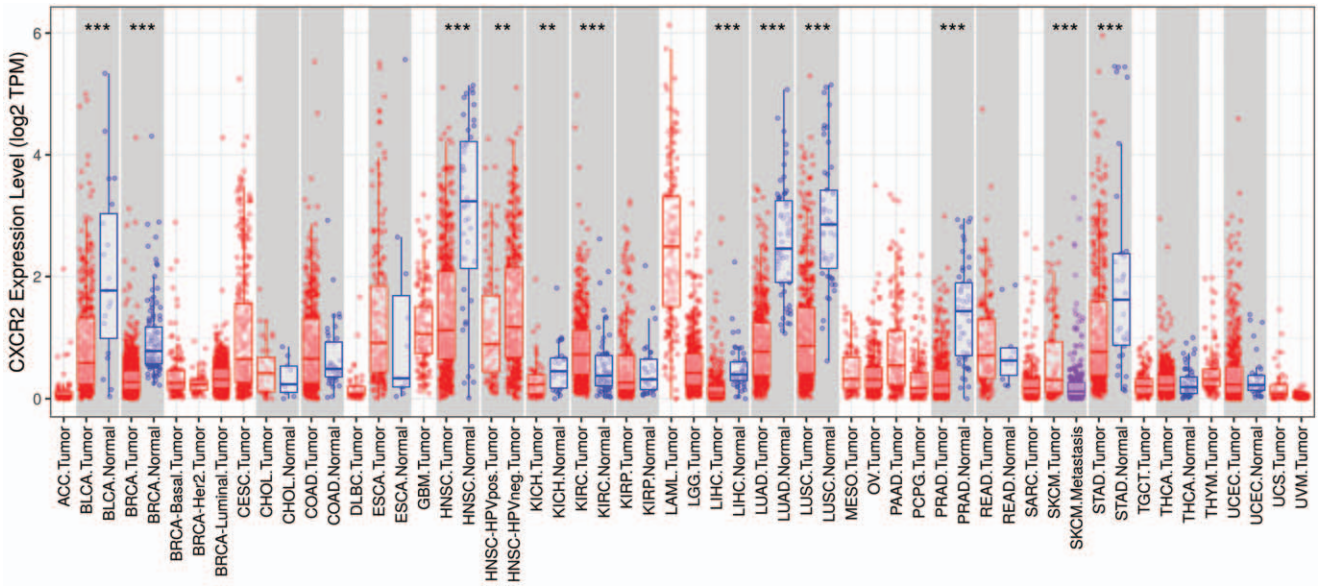

Figure 4. In silico analysis of *IL8RB*. The expression of *IL8RB* was down-regulated in both prostate adenocarcinoma and bladder cancer ($P < .001$) subjects. The expression of *IL8RB* was also attenuated in breast cancer and lung cancer ($P < .001$). Nevertheless, the *IL8RB* expression was augmented in patients with kidney renal clear cell carcinoma (KIRC, $P < .001$).

that in normal tissues, the proportion of macrophage M0 cells was significantly increased in prostate adenocarcinoma samples (Fig. 10B), whereas that of CD4 memory-activated T cells was mitigated (Fig. 10C). The flow chart of in silico analysis was indicated in Fig. 10D.

3.4. Bias diagnostics

Sensitivity analysis was employed to investigate the impact of every single study on the ORs. We further performed the Begg and Egger tests to detect the publication bias. No single study would affect the overall ORs (Fig. 11A). We also obtained no evidence of publication bias according to the Begg (Fig. 11B, $P > .05$) and Egger tests (Fig. 11C, $P > .05$).

4. Discussion

Numerous researchers investigated the risk factors of carcinoma previously. However, they have not been able to identify enough cancer-specific markers to date.[42,43] The development of tumor specific markers plays a notable role in predicting the therapeutic effect of cancer patients. Previous publications have revealed that the expression of *IL8RB* may be related to necrosis and development of carcinomas.[23,44–47] Additionally, *IL8RB* is also a vital autocrine or paracrine growth factor, which participating in inducing tumor invasion and migration.[48] The function of the protein may be realized by gene expression mediated by *IL8RB* gene polymorphism. The correlation between *IL8RB* polymorphism and cancer susceptibility was

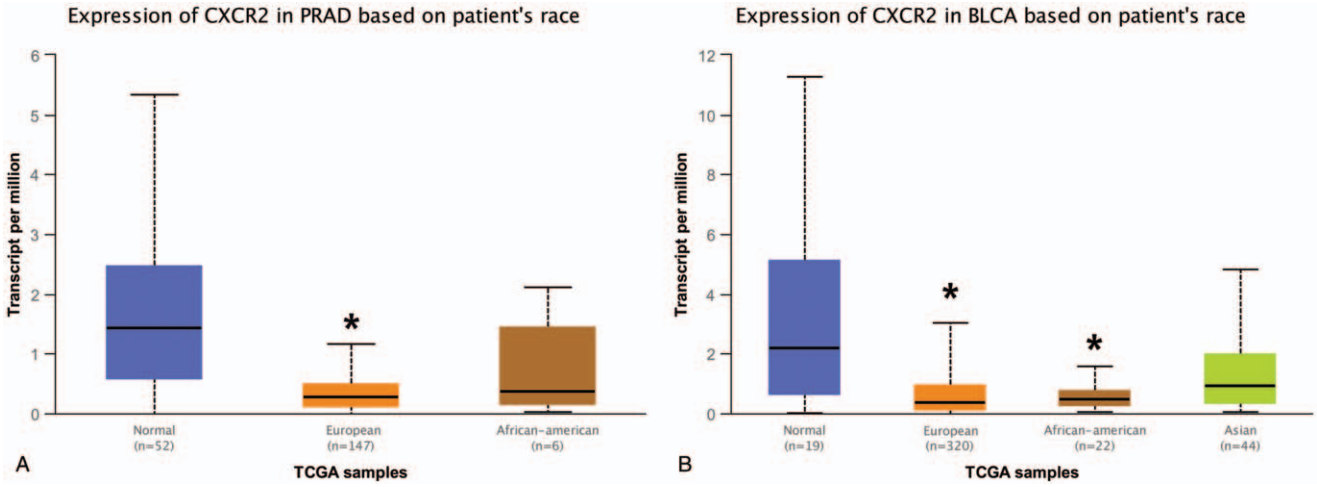

Figure 5. Expression of *IL8RB* in prostate adenocarcinoma and bladder cancer according to the race of participants. Expression of *IL8RB* was attenuated in prostate adenocarcinoma with European descendants (A). The expression of *IL8RB* was also mitigated in bladder cancer patients with European, and African-American descendants (B).

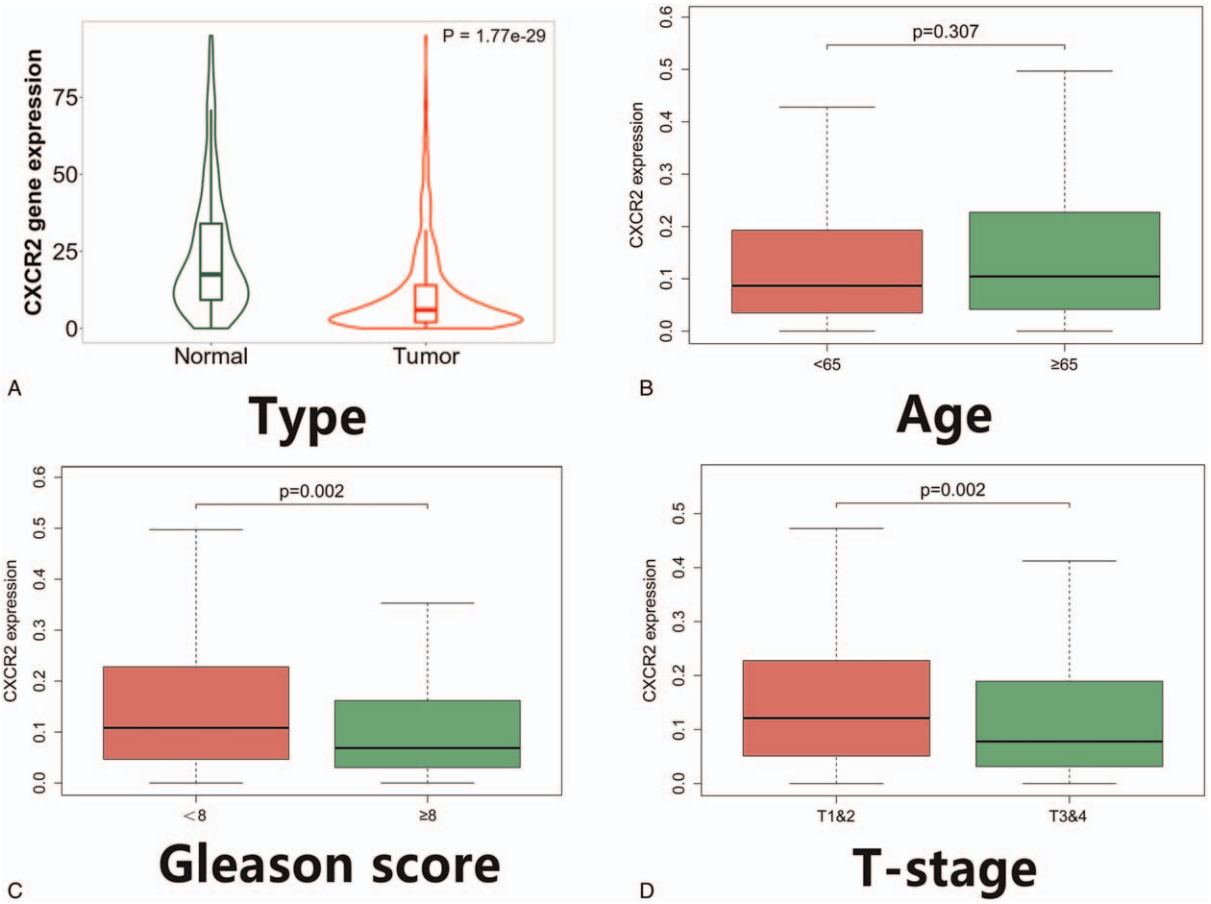

Figure 6. Expression of *IL8RB* in prostate adenocarcinoma patients. The *IL8RB* expression was decreased in prostate adenocarcinoma participants as compared with controls ($P < .05$, A). There was no significant correlation between the *IL8RB* expression and the age of prostate adenocarcinoma patients ($P > .05$, B). The *IL8RB* expression is down-regulated in patients with Gleason score >8 ($P < .05$, C). Patients with Gleason score <8 were considered as early prostate adenocarcinoma. T1 and T2 prostate adenocarcinoma also belong to early stage cancer. T3 and T4 prostate adenocarcinoma belong to advanced cancer. The expression of *IL8RB* in patients with advanced prostate adenocarcinoma was lower than that in patients with early stage ($P < .05$, D).

explored by several previous studies.[32–38] However, there is still no final conclusion so far. Singh et al[36] assessed the *IL8RB* C1208T variation based on Indian patients and indicated that this mutation can increase the bladder cancer susceptibility ($P = .003$, OR = 1.29). Conversely, Ryan et al[37] previously evaluated the *IL8RB* polymorphism based on both European and Asian descendants and revealed that this variant was related to a mitigated LC risk. In 2017, Yang et al[48] summarized the previous literature and conducted a meta-analysis. They revealed that the high *IL8RB* expression in tumor tissue was associated with poor overall survival of cancer patients. In 2018, another meta-analysis performed by Qiao et al[49] showed evidence that *IL8RB* was not a useful predictor of recurrence-free survival for digestive cancer participants. Nevertheless, these 2 studies did not further assess the effect of *IL8RB* C1208T variation on cancer risk. Therefore, a total of 14 studies with 5299 cancer and 6899 controls was summarized in present analysis. Our results showed evidence that *IL8RB* C1208T polymorphism may be correlated with the risk of cancer.

Subgroup analysis by cancer type indicated that C1208T mutation can increase the cancer susceptibility of urinary, breast, and digestive system. Conversely, this C1208T polymorphism was associated with mitigated cancer risk for individuals with LC. This finding was in line with that revealed by Ryan et al.[37] Stratified analysis by ethnicity showed that East Asians with TT + TC genotype had a 25% diminished cancer susceptibility than control. However, we obtained no positive finding for European or African populations. One possible reason might be that most of the authors who performed the pooled analysis were from Asian countries. They tended to publish positive results related to their own ethnicity.[50–53] Moreover, the number of studies based on African populations included in current analysis was fairly few. Different conclusions may be drawn by increasing the sample size. Snoussi et al[34] showed evidence that the *IL8RB* C1208T variation was related to ameliorated BC risk for African patients. Furthermore, stratification analysis by sample size showed evidence that the results between large and small sample size studies might be various. It is warranted that more research combined with large sample sizes should be conducted to further demonstrate the effect of *IL8RB* polymorphism on risk of cancer. Additionally, the in silico analysis was employed to evaluate the *IL8RB* expression on the susceptibility of urinary system cancer. We revealed that the expression of *IL8RB* was diminished in European, and African American bladder cancer patients. Moreover, the *IL8RB* expression was also attenuated in European prostate adenocarcinoma patients. We also found

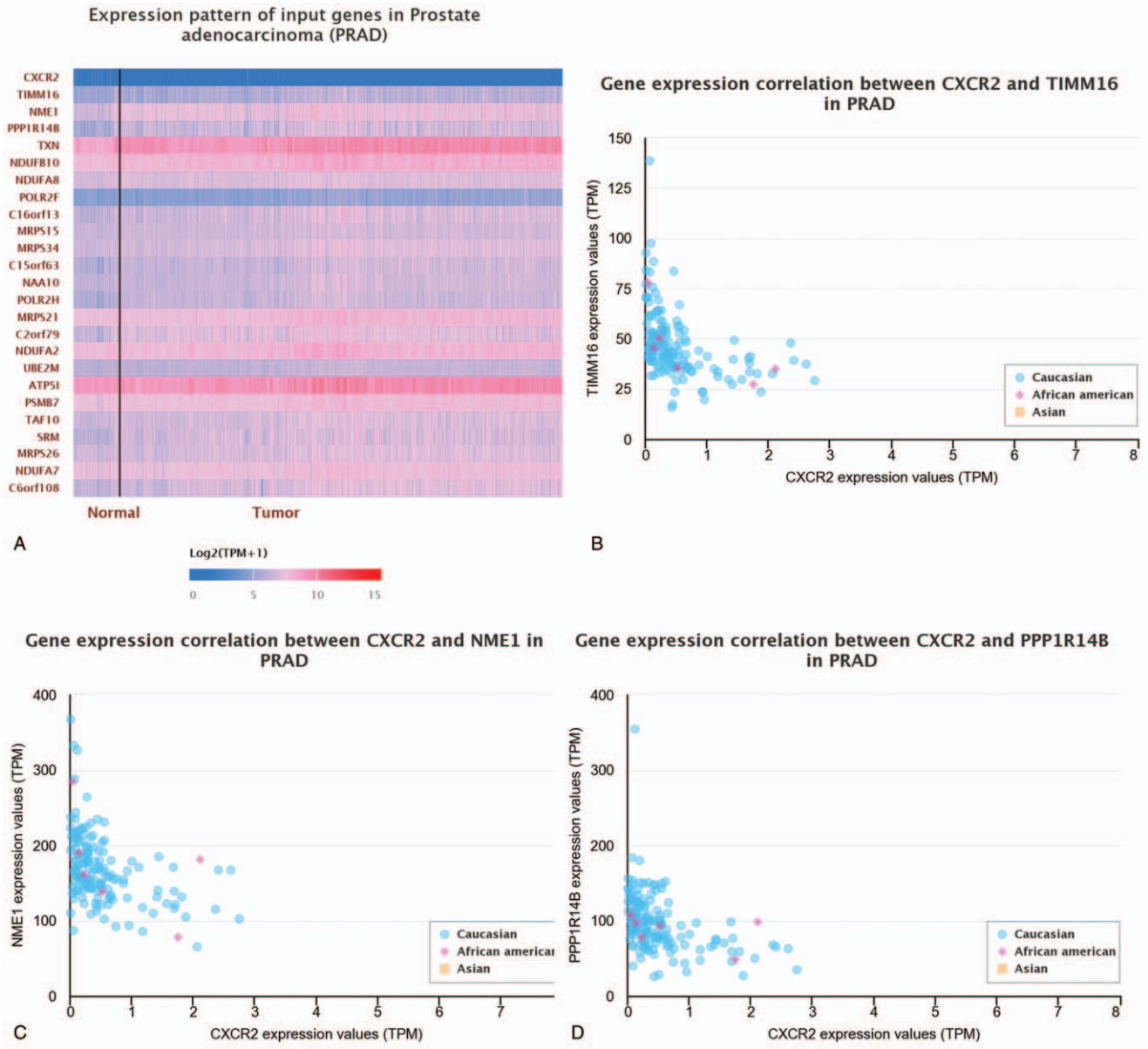

Figure 7. Gene–gene interaction of *IL8RB* in prostate adenocarcinoma patients. Differential expressed genes with *IL8RB* in prostate adenocarcinoma was shown in A. The most correlated gene with *IL8RB* were mitochondrial import inner membrane translocase subunit 16 (TIMM16, B), nucleoside diphosphate kinase 1 (NME1, C), protein phosphatase 1 regulatory inhibitor subunit 14B (PPP1R14B, D).

that the *IL8RB* expression was mitigated in prostate adenocarcinoma patients. Patients with Gleason score <8 were considered as early prostate adenocarcinoma. T1 and T2 prostate adenocarcinoma also belong to early stage cancer. T3 and T4 prostate adenocarcinoma belong to advanced cancer. The expression of *IL8RB* was also attenuated in prostate adenocarcinoma subjects whose Gleason score was higher than 8. The *IL8RB* expression in advanced prostate adenocarcinoma patients was lower than that in early-stage participants.

Furthermore, the GSEA was employed to investigate the potential pathways related to the *IL8RB* expression. We observed that the JAK-STAT signaling, aldosterone regulated sodium re-absorption, and phosphatidylinositol signaling system may be related to high *IL8RB* expression. As *IL8RB* is a 7-transmembrane GPCR highly expressed on the cell membrane of leukocytes, CIBERSORT computational method was utilized to assess the TIC abundance profile in participants with prostate adenocarcinoma. We revealed that the macrophage M0 cells proportion was significantly increased, while the CD4 memory-activated T cells proportion was relatively decreased. There are, however, some drawbacks to the current analysis. Firstly, the number of available study on African populations was relatively small. It is required that more studies based on patients with African descent should be conducted. Second, the number of available studies on carcinomas such as renal cell carcinoma, prostate adenocarcinoma, and bladder cancer was relatively limited. Third, the *IL8RB* C1208T mutation was indicated to be related to increased prostate adenocarcinoma susceptibility.

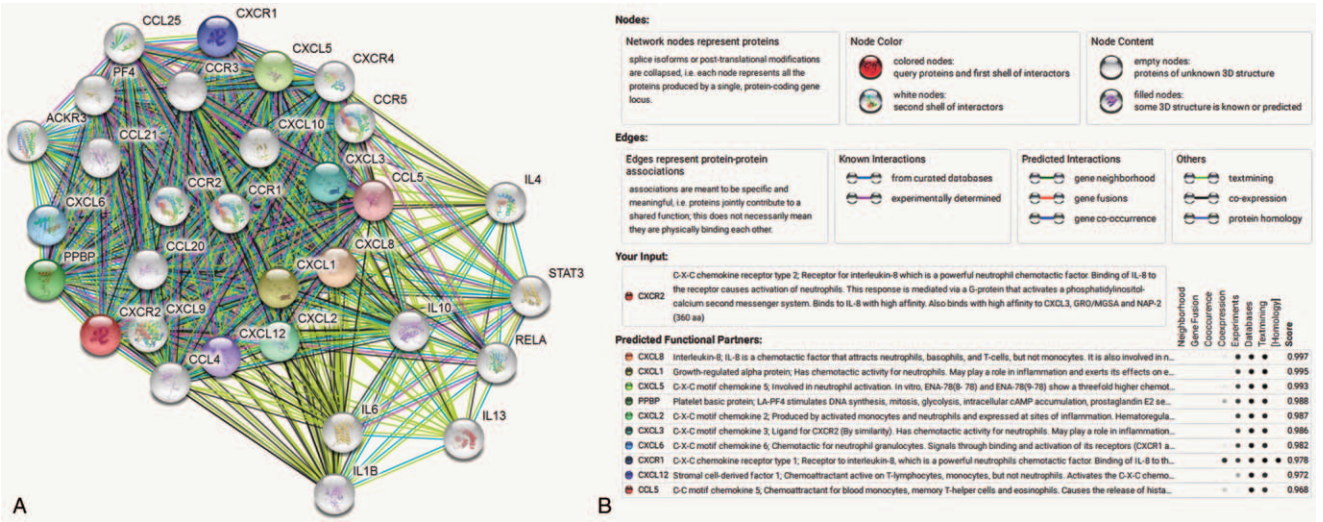

Figure 8. The correlation of IL8RB protein evaluated by the STRING tools. The proteins associated with IL8RB were indicated in A. The top 10 proteins are: CXCL8 (Interleukin-8), CXCL12 (Stromal cell-derived factor 1), CXCL5 (C-X-C motif chemokine 5), CXCR1 (C-X-C chemokine receptor type 1), CXCL6 (C-X-C motif chemokine 6), PPBP (platelet basic protein), CXCL2 (C-X-C motif chemokine 2), CXCL3 (C-X-C motif chemokine 3), CXCL1 (Growth-regulated alpha protein), CCL5 (C-C motif chemokine 5) (B).

More functional experiments are needed to verify whether the variation of *IL8RB* could influence the expression of *IL8RB* in prostate adenocarcinoma. Although a single mutation may not have a large influence on the progression of malignant tumor, more research combined with a gene–gene or gene–environment factor are warranted.

Taken together, we collected all eligible studies according to the inclusion criteria to comprehensively explore the association between *IL8RB* C1208T polymorphism and cancer risk. Our results indicated that *IL8RB* C1208T mutation may be related to augmented cancer risk including urinary, breast, and digestive system. The *IL8RB* C1208T variant can also increase the prostate adenocarcinoma risk, especially for East Asian participants. The *IL8RB* expression of advanced prostate adenocarcinoma cases was lower than that of early stage.

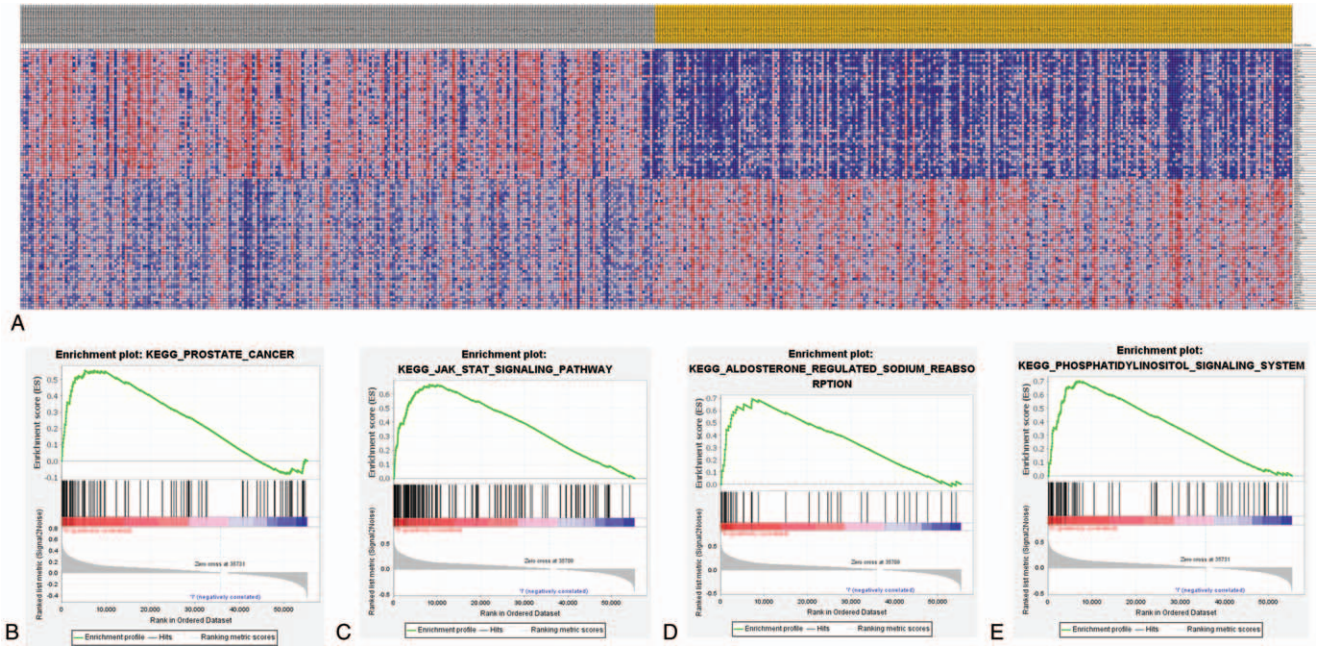

Figure 9. Gene set enrichment analysis (GSEA) for samples with expression of *IL8RB*. The enrichment heat map was indicated in A. GSEA analysis showed evidence that the expression of *IL8RB* is correlated with prostate adenocarcinoma (B, $P < .05$). Signaling pathways, including JAK-STAT signaling (C), aldosterone regulated sodium reabsorption (D), and phosphatidylinositol signaling system (E) were associated with high expression of *IL8RB*.

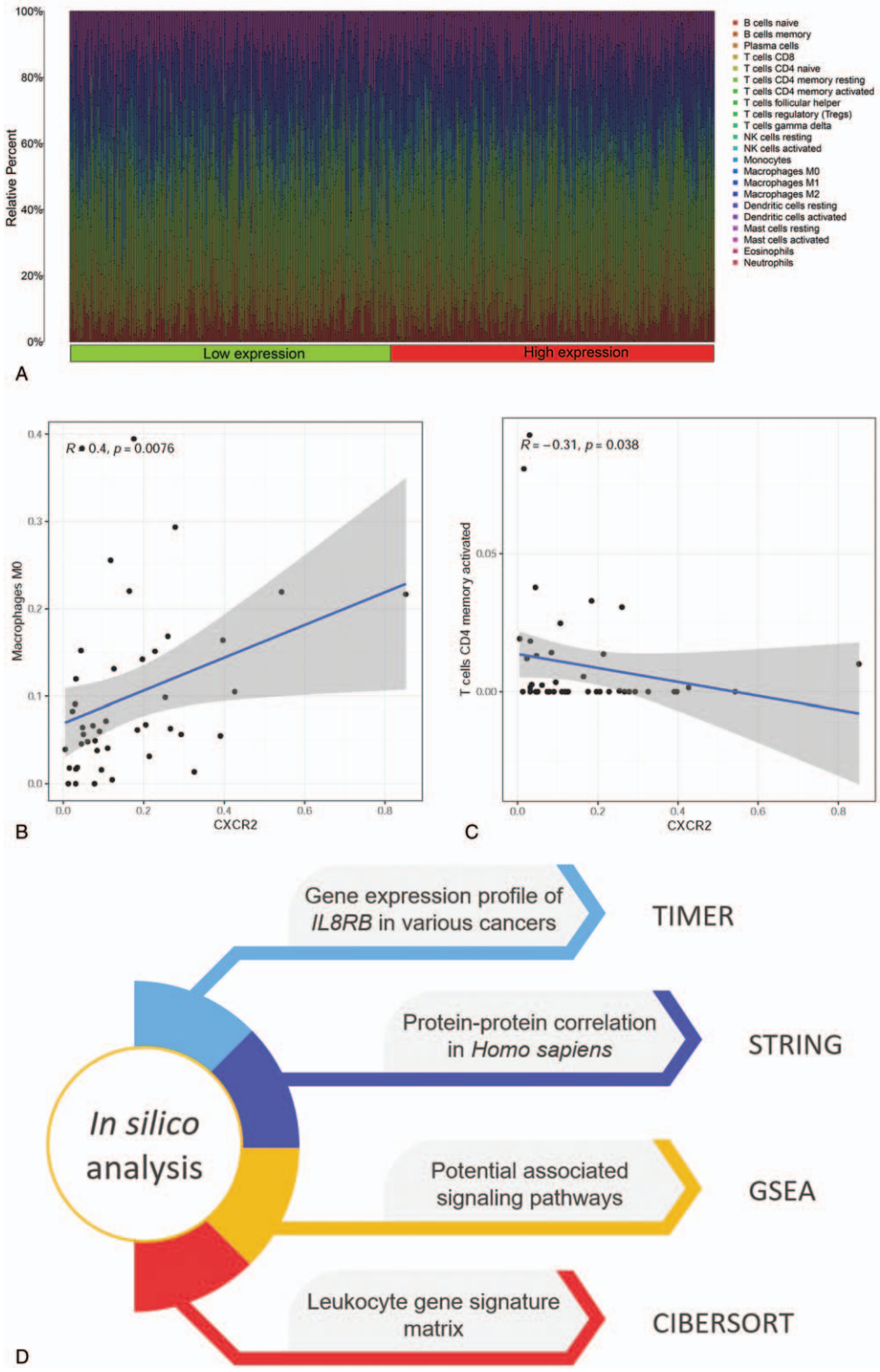

Figure 10. The relationship between the expression of *IL8RB* and the proportion of tumor-infiltrating immune cells (TICs). In CIBERSORT, the leukocyte gene signature matrix (called LM22) was used to distinguish 22 types of immune cells (A). Scatter plots showed that Macrophage M0 cell was the positively correlated TIC with the expression of *IL8RB* ($P = .0076$, B). CD4 memory activated T cell was the negatively correlated TIC with *IL8RB* ($P = .038$, C). The flow chart of in silico analysis was indicated in D.

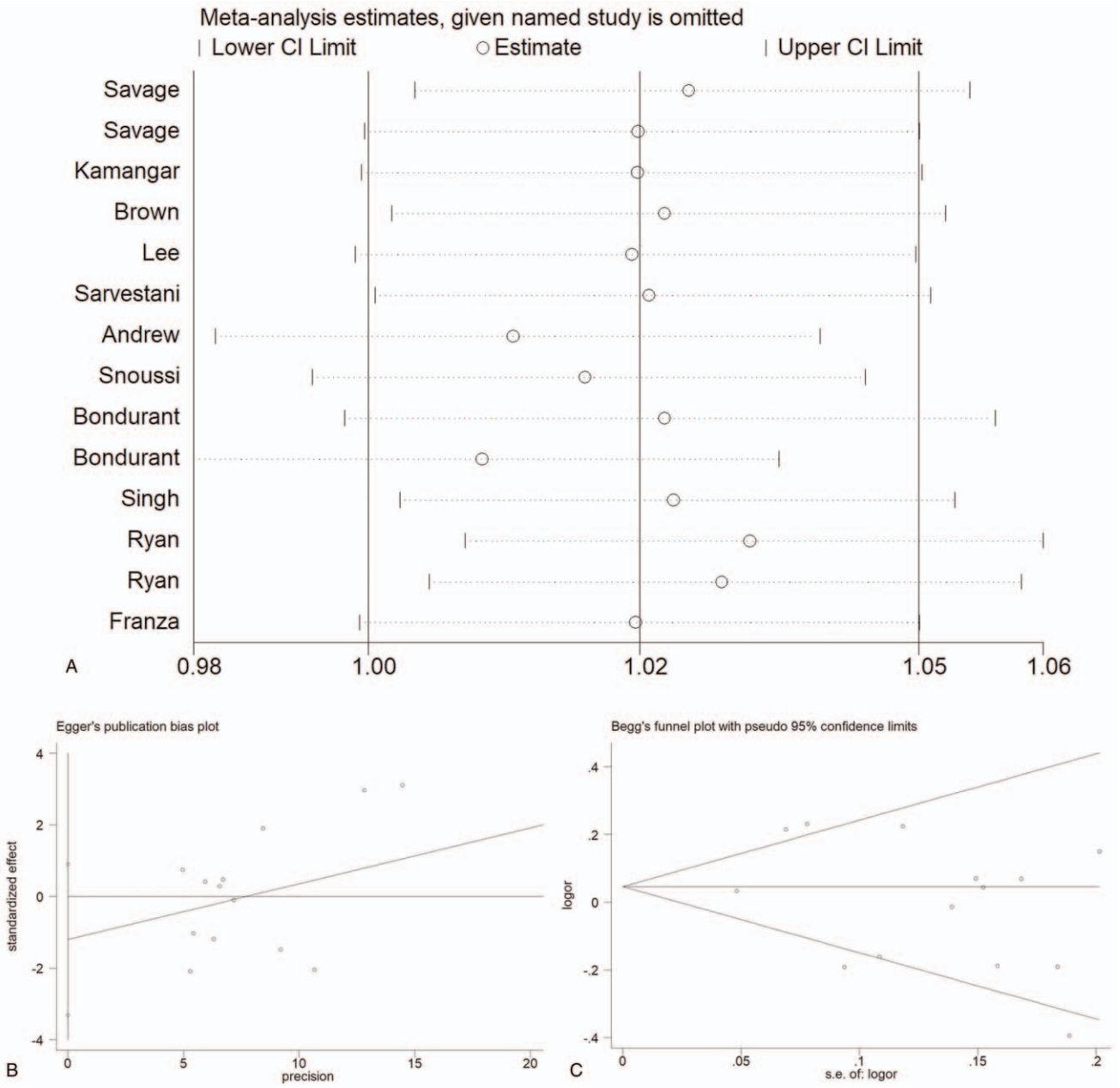

Figure 11. Publication bias of the current study assessed by sensitivity analysis, Begg funnel plot, and Egger test. Sensitivity analysis of *IL8RB* C1208T showed that a single study would not have an impact on the significance of ORs (A). Begg funnel (B) and Egger plot (C) analysis also indicated no evidence of publication bias. ORs = odds ratios.

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