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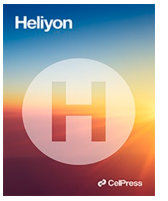

Research article

Causal relationship between cancer and immune cell traits: A two-sample mendelian randomization study

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ABSTRACT

Background: Observational studies provide evidence of correlations between cancer and the immune system. Previous research has established associations between immune traits and the propensity for developing certain cancers. However, a systematic exploration of these connections remains largely uncharted. Therefore, further investigation is needed to examine the causal association between cancer and immune cell traits using Mendelian randomization (MR) approach.
Methods: We identified genetic instruments for breast cancer (BC), lung cancer (LC), endometrial cancer (EC), ovarian cancer (OC), prostate cancer (PC), and their subtype cancers to investigate their potential causal impact on immune traits. Data on cancer and immune cell traits were obtained from the IEU Open GWAS project. To assess whether these five cancer types and subtype cancers have a causal association with immune cell traits, we conducted two-sample MR analyses. Additionally, we conducted bidirectional MR analyses to examine the direction of causal relationships and adjusted for potentially related pleiotropy through multivariable MR analysis.
Results: We have identified several causal relationships between different types of cancer and immune traits. We found that breast cancer may influence 49 immune cell traits, endometrial cancer may influence 38, lung cancer may influence 25, ovarian cancer may influence 19, and prostate cancer may influence 28. Among these, breast cancer and lung cancer were associated with four common immune traits: CD25 on IgD^{-} $CD38^{dim}$, CD25 on sw mem, CD24 on IgD^{-} $CD38^{-}$, and CD25 on IgD^{-} $CD38^{-}$. Lung cancer and prostate cancer shared four immune traits: CD25 on IgD^{+} $CD24^{+}$, CD25 on IgD^{+} $CD38^{-}$, CD66b on $CD66b^{++}$ myeloid cell, DN ($CD4^{-}CD8^{-}$) AC. Endometrial cancer and ovarian cancer shared two immune traits: TD DN ($CD4^{-}CD8^{-}$) %DN, EM DN ($CD4^{-}CD8^{-}$) %DN. Breast cancer and endometrial cancer shared one immune trait: CD20 on IgD^{-} $CD38^{dim}$. Endometrial cancer and prostate cancer shared one immune trait: CCR2 on myeloid DC. Lastly, breast cancer, lung cancer, and prostate cancer shared one immune trait: CD25 on $CD24^{+}$ $CD27^{+}$. Additionally, we identified specific immune traits that may serve as protective or risk factors for cancers. We found 14 immune traits may influence breast cancer, 9

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immune traits may influence endometrial cancer, 22 immune traits may influence lung cancer, 9 immune traits may influence ovarian cancer, and 14 immune traits may influence prostate cancer. Among these, breast cancer and prostate cancer shared three immune traits: HLA DR^{++} monocyte %monocyte, HLA DR on plasmacytoid DC, and HLA DR on DC. Lung cancer and ovarian cancer shared one immune trait: $CD62L^{-}$ monocyte %monocyte. Prostate cancer and endometrial cancer shared one immune trait: HLA DR on $CD33^{dim}$ HLA DR^{+} $CD11b^{+}$. Lastly, ovarian cancer and prostate cancer shared one immune trait: CD3 on resting Treg.

Conclusions: Our MR study suggests a potential relationship between immune traits and cancers, particularly highlighting 14 immune traits that are simultaneously influenced by two or three of five cancer types, while also indicating that 6 immune traits may simultaneously contribute to the development of two of the cancers. This elucidation enables us to reveal a significant involvement of immune traits in cancer progression, providing critical insights into how immune traits affect cancer susceptibility.

1. Introduction

The development, recurrence, and metastasis of tumors have long been known to be closely correlated with the immunological components [1]. The inflammatory immune response plays a pivotal role in the tumor microenvironment (TME) and correlates with unfavorable outcomes in cancer prognosis [2]. In the TME, cancer cells produce substances that hinder the function of immune cells or influence metabolic interplay between tumor cells and immune cells, impairing system's ability to combat the cancer [3–5]. For example, extracellular vesicles encourage the exhaustion of $CD8^{+}$ T cells by deubiquitinating the TGF-β receptor [6]. Recent research demonstrated that cancer cells have the ability to limit the availability of glucose to effector T cells, which in turn diminishes the effectiveness of T cell function by upregulating specific microRNAs [7]. Identifying the impact of tumors on various immune cell characteristics is instrumental in the discovery of oncological biomarkers and in elucidating the mechanisms underlying the immunological imbalances associated with cancer.

Immune cells can embody complex, dichotomous functions, serving as pivotal agents in both pro-tumor and anti-tumor effects. In typical conditions, immune cells demonstrate anti-tumor effects through immune surveillance and immune cytotoxicity. Nevertheless, under specific circumstances, certain immune cells may inadvertently contribute to the progression of tumors [8]. The infiltration of immunosuppressive cells, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), into the tumor microenvironment impedes the activity of effector immune cells, thereby hindering an effective anti-tumor immune response [9]. In BC models, decreasing the number of Tregs leads to the upregulation of PD-L1 expression on tumor cells and alters the composition of tumor-infiltrating lymphocytes (TILs), which results in the activation of $CD8^{+}$ T cells [10]. MDSCs are a heterogeneous population and the accumulation of myeloid cells that are often immunosuppressive [11]. Blocking the accumulation of MDSCs in tumors increases the infiltration, activation, and therapeutic effectiveness of murine natural killer (NK) cells that were transferred into the tumor [12]. While immunotherapy research has predominantly concentrated on T cells, growing evidence suggests that tumor-infiltrating B cells and plasma cells play a critical and synergistic role in tumor control [13]. In addition, the low expression of human leukocyte antigen DR (HLA DR) on the monocyte subset might exert immunosuppressive function [14]. All in all, exposing impact of immune traits on cancer is significant for developing antitumor immunotherapies and cancer individualized screening and prevention [15].

Observational evidence has indicated that diseases characterized by chronic inflammation are linked to a higher risk of various cancers [16,17]. Moreover, the use of anti-inflammatory drugs, may play a preventive role in several types of cancer, including colorectal, endometrial, lung, breast, prostate, and ovarian cancers [18]. Given the close association between immune cells and inflammatory responses, we have conducted a Mendelian randomization study on the tumor and immune cell characteristics in breast cancer, lung cancer, endometrial cancer, ovarian cancer, prostate cancer, and the their subtype cancers.

Previous MR analyses have explored the correlation between immune cell characteristics and cancer [19–21]. For example, Xu et al. found that elevated levels of $CD14^{-}$ $CD16^{+}$ monocytes is a protective factor, CD27 on $CD24^{+}$ $CD27^{+}$ B cell is a risk factor, and IgD^{+} $CD24^{+}$ B cells and CD27 on class-switched memory B cells are potential risk factors in lung cancer [22]. After the Bonferroni method, Wang et al. found the $CD45RA^{-}$ $CD4^{+}$ $\%CD4^{+}$, $CD8^{dim}$ %T cell, BAFF-R on IgD^{+} $CD38^{-}$ unsw mem, CD27 on PB/PC lowered the risk of ER^{+} breast cancer; CD19 on IgD^{-} $CD38^{br}$, CD25 on IgD $^{+}$ $CD38^{dim}$ were associated with a higher risk of ER $^{+}$ breast cancer; CX3CR1 on $CD14^{+}$ $CD16^{-}$ monocyte has a protective effect against ER^{-} breast cancer [19]. However, these studies predominantly emphasize the impact of immune traits on cancer and subtype cancers, leaving the reciprocal influence of cancer and subtype cancers on immune traits less understood. Additionally, the same immune cell traits affected by different tumors have not been explored, and these immune cell traits may play a more significant role in the occurrence and progression of tumors.

Therefore, our aim was to conduct a comprehensive two-sample MR analysis to investigate the causal relationships between five cancers (breast, endometrial, lung, ovarian and prostate cancer) and a broad range of immune cell traits, including B cell panel, T cell panel, cDC (circulating dendritic cells) panel, maturation stages of T cell panel, monocyte panel, myeloid cell panel, TBNK (T, B and NK cells) panel, Treg panel. These analyses were selected to explore the controversy and uncertainty of the role of immune cells in cancer, eventually helping to develop anti-tumor strategies.

2. Material and methods

2.1. Study design

Fig. 1 provides an overview of the analytical approach. To qualify as valid instrumental variables (IVs), three basic assumptions must be met: (1) the genetic variants should have a strong association with the exposure; (2) the genetic variants should not be associated with any potential confounding variables that might affect the exposure-outcome relationship; and (3) the genetic variants should not have any effect on the outcome other than through the exposure [23].

To ensure the credibility and precision of the conclusions regarding the causal connection between cancer and immune cells, we established strict criteria for selecting single nucleotide polymorphisms (SNP) [24]. These criteria included: 1) Genome-wide significance with cancer or immune traits ($p < 5 \times 10^{-8}$) for each SNP; 2) Ensuring the independence of each SNP by limiting the linkage disequilibrium (LD) among SNPs associated with cancer or immune traits to $r^2 < 0.001$ within a window size of 10,000 kb; and 3) Using F-statistics (F-statistics = $(\beta/SE)^2$) to verify the strength of the correlation between instrumental variables (IVs) and exposure factors [25].

2.2. Cancer data

We have obtained the complete dataset of cancer from the IEU Open GWAS project https://gwas.mrcieu.ac.uk/. Descriptive statistics for the phenotypic characteristics included in the genome-wide association studies (GWAS) of cancer data were available in Table S1. The genetic association summary statistics for breast cancer risk were acquired from two sources: the Breast Cancer Association Consortium (BCAC), which is comprised of 68 studies, and the Discovery, Biology, and Risk of Inherited Variants in Breast Cancer Consortium (DRIVE). The combined sample size for these studies was 122,977 breast cancer cases and 105,974 controls. When stratified by estrogen receptor (ER) expression, there were 69,501 ER^+ BC cases and 21,468 ER^- BC cases included in the analysis [26].

The associations between SNPs and the risks of overall endometrial cancer, as well as endometrioid and non-endometrioid histological subtypes, were obtained from a meta-analysis of 17 studies conducted by the Endometrial Cancer Association Consortium (ECAC), the Epidemiology of Endometrial Cancer Consortium (E2C2), and the UK Biobank. The total sample size included 12,906 endometrial cancer cases and 108,979 country-matched controls of European ancestry. Within the sample, there were 8758 cases of endometrioid histological subtype and 1230 cases of non-endometrioid histological subtype [27].

Genetic associations between SNPs and the risk of developing lung cancer were obtained from the International Lung Cancer

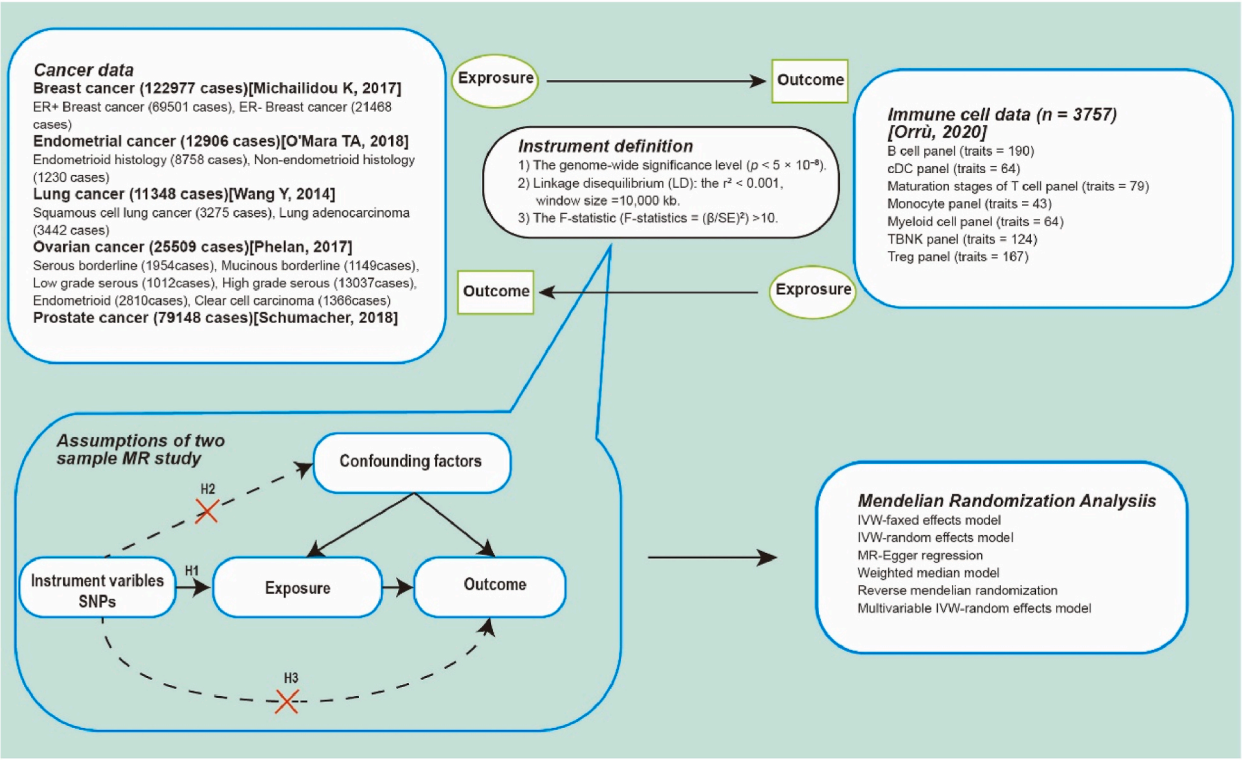

Fig. 1. Overview of the analytical plan. MR: Mendelian randomization; SNP: Single nucleotide polymorphism; IVW: Inverse-variance weighted; ER: Estrogen receptor; cDC: Circulating dendritic cells; TBNK: T, B and NK cells.

Consortium (ILCCO) consisting of 11,348 patients and 15,861 controls of European descent. The study included 3442 cases of lung adenocarcinoma and 3275 cases of squamous cell lung cancer (SCLC) [28].

The Ovarian Cancer Association Consortium (OCAC) and the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) conducted a meta-analysis to investigate the associations between SNPs and the risk of overall invasive epithelial ovarian cancer, as well as its histological subtypes. The study included up to 25,509 cases of epithelial ovarian cancer and 40,941 controls. The number of ovarian cancer cases by histotype was serous borderline (1954cases), mucinous borderline (1149cases), low grade serous (LGSOC, 1012cases), high grade serous (HGSOC, 13037cases), endometrioid (ENOC, 2810cases), and clear cell carcinoma (CCOC, 1366cases) [29].

The Prostate Cancer Association Group to Investigate Cancer-Associated Alterations in the Genome (PRACTICAL) consortium conducted a study to investigate the associations between SNPs and the risk of developing cancer. The study included 79,148 cases of prostate cancer and 61,106 controls of European descent [30].

2.3. Immune traits data

We have obtained the complete dataset of immune cell traits from the IEU Open GWAS project. Valeria et al. conducted a study utilizing flow cytometry to profile a broad range of 539 immune traits, encompassing 118 absolute cell counts, 389 mean fluorescence intensities (MFIs) of surface antigens, and 32 morphological parameters. Additionally, they considered 192 relative counts, which are ratios between cell levels. Overall, a total of 731 cell traits were assessed in a population cohort consisting of 3757 individuals from European descent. Descriptive statistics for the phenotypic characteristics included in the GWAS of immune traits were provided in Table S2. The immune traits were identified by seven panels, including B cell, myeloid cell, monocyte, TBNK cell, Treg, maturation stages of T cell, and cDC in their study, and the classification approaches for seven panel in our analysis align with those [31]. Here, we describe the classification approaches for B cell, myeloid cell and monocyte panel.

For B cell panel, CD19 positive cells were identified as total B cells and were further classified using various approaches. The classification approaches used in B cell panel include CD24 versus CD38, CD27 versus IgD, IgD versus CD38, CD24 versus CD27, IgD versus CD24, and CD20 versus CD38 (Fig. 2A). For monocyte panel, monocytes were identified based on morphological parameters and HLA DR positivity. The monocyte population was further subdivided into three subsets: classical, non-classical, and intermediate (Fig. 2B). For myeloid cell panel, the myeloid-enriched cells were subdivided based on CD14 high positivity and further classified into

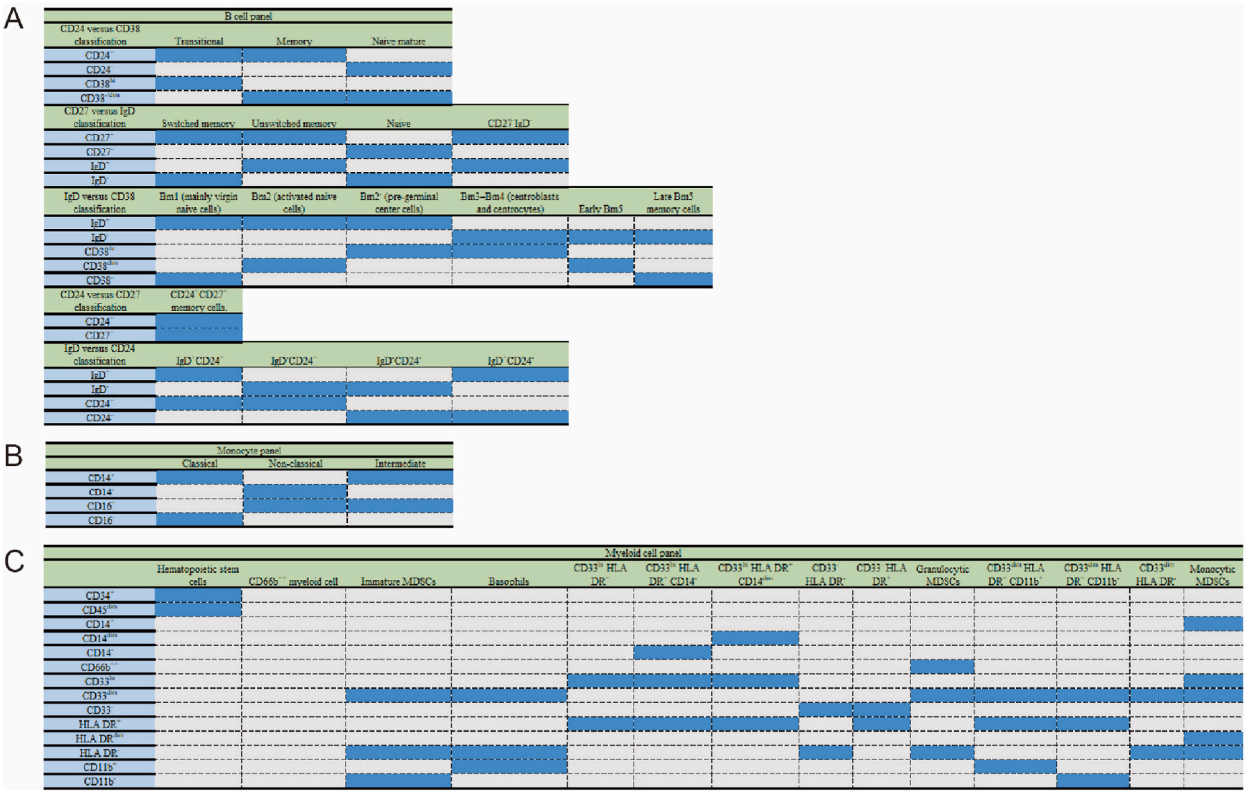

Fig. 2. The classification approaches for B cells (A), monocytes (B) and myeloid cells (C) panel. Different immune cells are distinguished by the presence of specific antibodies, denoted by the color blue. HLA DR: human leukocyte antigen DR; MDSCs: myeloid-derived suppressor cells. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

five subsets based on CD33 and HLA DR expression. Additional sub-characterization was done using CD11b and CD66b antibodies: granulocytic myeloid-derived suppressor cells (MDSCs); immature MDSCs; and basophils. Monocytic MDSCs were identified based on high positivity for CD14 and CD33, and weak positivity for HLA DR. Finally, hematopoietic stem cells were identified as $CD34^{+}$ $CD45^{dim}$ cells (Fig. 2C). The specific classification can be found in Table S2.

2.4. Other factors

To meet the second condition of MR analysis, we searched for potential instrumental variable selection confounding factors in the PhenoScanner database [32]. If there were existing relationships between confounders and immune traits, we conducted multivariable MR analyses. When the breast cancer as exposure, the PhenoScanner database search revealed associations of instruments with obesity-related and basal metabolic rate traits. Therefore, we chose SNPs for body mass index (BMI) from a GWAS [33] of 694,649 participants and basal metabolic rate (BMR) [34] for the multivariable MR analyses. For endometrial cancer, we chose SNPs for BMI, systolic blood pressure [35], diastolic blood pressure [35], and coronary heart disease [36] for the multivariable MR analyses. For ovarian cancer, we chose SNPs for BMI for the multivariable MR analyses. For prostate cancer, we chose SNPs for BMI, rheumatoid arthritis [37], coronary heart disease for the multivariable MR analyses via the inverse-variance method. Other confounders are detailed in Table S3.

2.5. Statistical analyses

Given that we have established a stringent threshold of $P < 1 \times 10^{-8}$ for SNPs associated with cancer or immune cell characteristics. This stringent threshold occasionally resulted in a limited number of instrumental variables available for analysis. To ensure the reliability of our results, we excluded traits from the analysis if they had fewer than three instrumental variables. For traits that had multiple instrumental variables, the inverse-variance weighted (IVW) test [38], MR-Egger regression [39] and weighted median (WM) [40] were used. IVW relies on the premise of no horizontal pleiotropy across all SNPs, under which it offers the most precise evaluation of causal effects. In contrast, the other two methodologies may yield more resilient estimates under less stringent circumstances. Specifically, WM permits the inclusion of up to 50 % ineffective SNPs, while MR-Egger detects horizontal pleiotropy and heterogeneity, particularly when such pleiotropy is present across all SNPs [20]. Given certain conditions, the IVW method was found to be marginally more effective than the other methods, and therefore the results were predominantly based on the IVW method, while the remaining three methods were utilized as supplementary analyses [41]. To assess the third MR assumption, we evaluated the heterogeneity of independent SNP effects using Cochran's Q statistics, and employed the MR-PRESSO and MR-Egger regression tests to monitor and detect any potential horizontal pleiotropy effect [32,42]. If the P-value of heterogeneity was less than 0.05, we utilized the random effects IVW method as the primary statistical analysis approach. Otherwise, we used the fixed effect IVW method. Furthermore, we calculated the P-value of the MR-Egger intercept and the P-value of the MR-PRESSO global test to evaluate potential horizontal pleiotropy effects. If the P-value of the MR-Egger intercept or the MR-PRESSO global test was less than 0.05, it indicated the presence of horizontal pleiotropy. To account for confounding factors in our models, we conducted a multivariable IVW MR analysis. The multivariable IVW approach simultaneously considers multiple exposure factors, thereby minimizing the potential impact of SNP-exposure effects on other assumed risk factors along an indirect pathway [43]. To investigate whether the identified significant cancer genera have any causal impact on immune traits, we conducted a reverse MR analysis [44]. This entailed using SNPs associated with immune traits as instrumental variables and the identified causal cancer genus as the outcome.

All statistical analyses were conducted using R version 4.3.0. For MR analysis, we utilized the MendelianRandomization package (version 0.7.0) [45] and TwoSampleMR package (version 0.5.6). In addition, for MR-PRESSO analysis, we employed the MRPRESSO package (version 1.0) [42].

3. Results

3.1. Genetic instrument selection and F-statistics

We identified a total of 142, 16, 5, 12, and 137 SNPs significantly associated with breast, endometrial, lung, ovarian, and prostate cancer, respectively, at a significance level of $p < 5 \times 10^{-8}$. The minimum F-statistics for these SNPs were 29.72, 30.37, 15.69, 29.98, and 29.57, respectively. Additional information on the significant SNPs and F-statistics for cancer and immune traits can be found in Tables S4 and S5. The findings suggest that any potential bias stemming from weak instruments (F-statistics <10) has been effectively addressed.

3.2. The detection of heterogeneity and directional pleiotropy

To evaluate the heterogeneity of independent SNP effects, we employed Cochran's Q statistics. To examine the potential influence of horizontal pleiotropy, we utilized MR-Egger regression tests and MR-PRESSO (Tables S6 and Table S7). For certain MR-PRESSO analyses where there were insufficient instrumental variables ($n < 4$), the global test was not computed. If the P-value of the MR-Egger intercept or the MR-PRESSO global test for horizontal pleiotropy was less than 0.05, we removed the results between cancer and immune traits. These results of Cochran Q Test and MR-Egger intercept test both indicate the absence of heterogeneity or pleiotropy in relation to these cancer and immune cell traits.

3.3. Causal effects of five cancers on seven panels immune traits

In our analysis of the causal effects of five cancers on immune traits, we identified several significant associations. Specifically, breast cancer was found to influence 49 immune cell traits, endometrial cancer may influence 38, lung cancer may influence 25, ovarian cancer may influence 19, and prostate cancer may influence 28. Among these, breast cancer and lung cancer were associated with four common immune traits: CD25 on IgD$^-$ CD38^{dim} (CD25 expression on IgD$^-$ CD38^{dim} B cell), CD25 on sw mem (CD25 expression on switched memory B cell), CD24 on IgD$^-$ CD38$^-$(CD24 expression on IgD$^-$ CD38$^-$ B cell), and CD25 on IgD$^-$ CD38$^-$(CD25 expression on IgD$^-$ CD38$^-$ B cell). Lung cancer and prostate cancer shared four immune traits: CD25 on IgD$^+$ CD24$^+$ (CD25 expression on IgD$^+$ CD24$^+$ B cell), CD25 on IgD$^+$ CD38$^-$ (CD25 expression on IgD$^+$ CD38$^-$ B cell), CD66b on CD66b^{++} myeloid cell (CD66b expression on CD66b^{++} myeloid cell), and DN (CD4$^-$CD8$^-$) AC (Central Memory CD4$^-$CD8$^-$ T cell Absolute Count). Endometrial cancer and ovarian cancer shared two immune traits: TD DN (CD4$^-$CD8$^-$) %DN (Terminally Differentiated CD4$^-$CD8$^-$ T cell % CD4$^-$CD8$^-$ T cell), EM DN (CD4$^-$CD8$^-$) %DN (Effector Memory CD4$^-$CD8$^-$ T cell %CD4$^-$CD8$^-$ T cell). Breast cancer and endometrial cancer shared one immune trait: CD20 on IgD$^-$ CD38dim (CD20 on IgD$^-$ CD38^{dim} B cell). Endometrial cancer and prostate cancer shared one immune trait: CCR2 on myeloid DC (CCR2 on myeloid Dendritic Cell). Lastly, breast cancer, lung cancer, and prostate cancer shared one immune trait: CD25 on CD24$^+$ CD27$^+$ (CD25 expression on CD24$^+$ CD27$^+$ B cell) (Fig. 3). Together, these results suggest that cancers can influence immune cell traits, and some immune cell traits can be influenced by different cancers.

3.4. Causal effects of five cancers on three panels (B cell, monocyte and myeloid cell panel) immune traits

3.4.1. Breast cancer

Breast cancer has been found to influence the traits in B cells, monocytes, and myeloid cells (Fig. 4). Specifically, in relation to B cells, breast cancer was causally associated with IgD$^-$ CD27$^-$ %B cell (IgD$^-$ CD27$^-$ B cell/B cell ratio, $\beta = 0.117$, 95%CI = 0.042 to 0.191, P = 0.002, IVW), IgD$^-$ CD24$^-$ %B cell (IgD$^-$ CD24$^-$ B cell/B cell ratio, $\beta = 0.099$, 95%CI = 0.025 to 0.174, P = 0.009, IVW), and so on. Regarding monocytes, breast cancer was associated with CD14 on CD14$^+$ CD16$^+$ monocyte (CD14 expression on CD14$^+$ CD16$^+$ monocyte, $\beta = -0.079$, 95%CI = −0.152 to −0.006, P = 0.035, IVW), CCR2 on CD14$^+$ CD16$^-$ monocyte (CCR2 expression on CD14$^+$ CD16$^-$ monocyte, $\beta = -0.092$, 95%CI = −0.165 to −0.02, P = 0.013, IVW), and so on. For myeloid cell, breast cancer was causally associated with CD14 on CD33^{br} HLA DR $^+$ CD14^{dim} (CD14 expression on CD33^{br} HLA DR $^+$ CD14^{dim} myeloid cell, $\beta = -0.151$, 95%CI = −0.259 to −0.042, P = 0.006, IVW). These findings shed light on the potential impact of breast cancer on the immune system within these cell populations.

3.4.2. Endometrial cancer

Endometrial cancer has been found to influence the traits of B cell and myeloid cell (Fig. 5). For B cell, endometrial cancers were causally associated with BAFF-R on CD24$^+$ CD27$^+$ (BAFF-R expression on CD24$^+$ CD27$^+$ B cell, $\beta = -0.132$, 95%CI = −0.254 to −0.009, P = 0.035, IVW), BAFF-R on IgD$^+$ CD24$^+$ (BAFF-R expression on IgD$^+$ CD24$^+$ B cell, $\beta = -0.14$, 95%CI = −0.263 to −0.018, P = 0.025, IVW), and so on. For myeloid cell, endometrial cancers were causally associated with CD45 on CD33^{dim} HLA DR$^-$ (CD45 expression on CD33^{dim} HLA DR$^-$ myeloid cell, $\beta = -0.216$, 95%CI = −0.397 to −0.036, P = 0.019, IVW) and CD45 on basophil (CD45 expression on basophil, $\beta = -0.223$, 95%CI = −0.403 to −0.042, P = 0.015, IVW). These results suggest that endometrial cancer can affect immune cell traits.

3.4.3. Lung cancer

Lung cancer has been found to influence the traits of B cell and myeloid cell (Fig. 6). For B cell, lung cancers were causally associated with IgD $^+$ CD38^{br} AC (IgD$^+$ CD38$^+$ B cell absolute count, $\beta = -0.144$, 95%CI = −0.269 to −0.02, P = 0.023, IVW), IgD $^+$ CD38^{br} %lymphocyte (IgD $^+$ CD38^{br} B cell/lymphocyte ratio, $\beta = -0.158$, 95%CI = −0.285 to −0.031, P = 0.015, IVW) and so on. For myeloid cell, endometrial cancers were causally associated with CD66b on CD66b^{++} myeloid cell (CD66b expression on CD66b^{++}

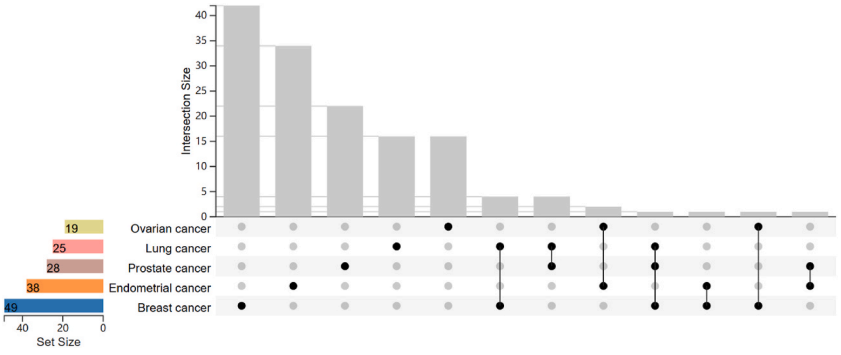

Fig. 3. The causal relationships between different types of cancer and immune traits. Set Size: the number of immune cell characteristics that are influenced by different types of cancer. Intersection Size: distribution of immune cell characteristics in different tumors.

Exposure(ID)	Outcome(Immune traits)	Immune trait ID	Method	nSNP	β(95%CI)	P
Breast cancer	B cell	B cell				
ieu-a-1126	IgD- CD27- %B cell	ebi-a-GCST90001399	IVW	130	0.117(0.042 to 0.191)	0.002
ieu-a-1126	IgD- CD24- %B cell	ebi-a-GCST90001413	IVW	130	0.099(0.025 to 0.174)	0.009
ieu-a-1126	CD20- %B cell	ebi-a-GCST90001419	IVW	130	0.092(0.019 to 0.165)	0.014
ieu-a-1126	Unsw Mem %lymphocyte	ebi-a-GCST90001432	IVW	130	-0.077(-0.151 to -0.003)	0.04
ieu-a-1126	CD20 on B cell	ebi-a-GCST90001743	IVW	130	-0.079(-0.153 to -0.005)	0.037
ieu-a-1126	CD20 on IgD- CD38dim	ebi-a-GCST90001757	IVW	130	-0.092(-0.166 to -0.019)	0.014
ieu-a-1126	CD20 on memory B cell	ebi-a-GCST90001758	IVW	130	-0.086(-0.159 to -0.012)	0.022
ieu-a-1126	CD20 on sw mem	ebi-a-GCST90001761	IVW	130	-0.092(-0.166 to -0.018)	0.015
ieu-a-1126	CD20 on IgD+	ebi-a-GCST90001762	IVW	130	-0.082(-0.156 to -0.009)	0.029
ieu-a-1126	CD24 on IgD- CD38-	ebi-a-GCST90001769	IVW	130	-0.09(-0.165 to -0.015)	0.018
ieu-a-1126	CD24 on sw mem	ebi-a-GCST90001773	IVW	130	-0.083(-0.157 to -0.008)	0.03
ieu-a-1126	CD25 on CD24+ CD27+	ebi-a-GCST90001777	IVW	130	-0.074(-0.147 to -0.002)	0.045
ieu-a-1126	CD25 on IgD- CD38-	ebi-a-GCST90001787	IVW	130	-0.084(-0.158 to -0.011)	0.025
ieu-a-1126	CD25 on IgD- CD38dim	ebi-a-GCST90001789	IVW	130	-0.076(-0.148 to -0.003)	0.041
ieu-a-1126	CD25 on sw mem	ebi-a-GCST90001793	IVW	130	-0.085(-0.159 to -0.011)	0.024
ieu-a-1126	CD27 on CD24+ CD27+	ebi-a-GCST90001798	IVW	130	-0.094(-0.168 to -0.02)	0.013
ieu-a-1126	CD27 on IgD- CD38-	ebi-a-GCST90001802	IVW	130	-0.097(-0.172 to -0.023)	0.011
ieu-a-1126	CD27 on IgD- CD38dim	ebi-a-GCST90001804	IVW	130	-0.108(-0.182 to -0.035)	0.004
ieu-a-1126	CD27 on memory B cell	ebi-a-GCST90001805	IVW	130	-0.088(-0.163 to -0.014)	0.02
ieu-a-1126	CD27 on unsw mem	ebi-a-GCST90001806	IVW	130	-0.103(-0.178 to -0.029)	0.007
ieu-a-1126	CD27 on sw mem	ebi-a-GCST90001808	IVW	130	-0.113(-0.188 to -0.039)	0.003
Breast cancer	Monocyte	Monocyte				
ieu-a-1126	CD14 on CD14+ CD16+ monocyte	ebi-a-GCST90001983	IVW	130	-0.079(-0.152 to -0.006)	0.035
ieu-a-1126	CD14 on CD14+ CD16- monocyte	ebi-a-GCST90001986	IVW	130	-0.078(-0.15 to -0.005)	0.036
ieu-a-1126	CCR2 on CD14- CD16-	ebi-a-GCST90002003	IVW	130	-0.103(-0.176 to -0.029)	0.006
ieu-a-1126	CCR2 on CD14+ CD16- monocyte	ebi-a-GCST90002004	IVW	130	-0.092(-0.165 to -0.02)	0.013
ieu-a-1126	CD16 on CD14+ CD16+ monocyte	ebi-a-GCST90002005	IVW	130	-0.077(-0.152 to -0.002)	0.045
Breast cancer	Myeloid cell	Myeloid cell				
ieu-a-1126	CD14 on CD33br HLA DR+ CD14dim	ebi-a-GCST90002020	IVW	130	-0.151(-0.259 to -0.042)	0.006

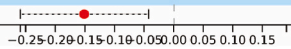

Fig. 4. The specific associations between breast cancer and immune cell traits. SNP: Single nucleotide polymorphism; IVW: Inverse-variance weighted.

Exposure(ID)	Outcome(Immune traits)	Immune trait ID	Method	nSNP	β(95%CI)	P
Endometrial cancer	B cell	B cell				
ebi-a-GCST006464	BAFF-R on CD24+ CD27+	ebi-a-GCST90001702	IVW	15	-0.132(-0.254 to -0.009)	0.035
ebi-a-GCST006464	BAFF-R on IgD+ CD24+	ebi-a-GCST90001703	IVW	15	-0.14(-0.263 to -0.018)	0.025
ebi-a-GCST006464	BAFF-R on IgD+ CD24-	ebi-a-GCST90001704	IVW	15	-0.135(-0.257 to -0.013)	0.031
ebi-a-GCST006464	BAFF-R on IgD+ CD38-	ebi-a-GCST90001705	IVW	15	-0.153(-0.275 to -0.03)	0.015
ebi-a-GCST006464	BAFF-R on IgD+ CD38br	ebi-a-GCST90001708	IVW	15	-0.132(-0.255 to -0.009)	0.035
ebi-a-GCST006464	BAFF-R on IgD+ CD38dim	ebi-a-GCST90001709	IVW	15	-0.142(-0.265 to -0.02)	0.023
ebi-a-GCST006464	BAFF-R on IgD- CD24-	ebi-a-GCST90001710	IVW	15	-0.123(-0.245 to -0.001)	0.048
ebi-a-GCST006464	BAFF-R on IgD- CD27-	ebi-a-GCST90001711	IVW	15	-0.145(-0.267 to -0.023)	0.02
ebi-a-GCST006464	BAFF-R on IgD- CD38-	ebi-a-GCST90001712	IVW	15	-0.137(-0.259 to -0.015)	0.028
ebi-a-GCST006464	BAFF-R on memory B cell	ebi-a-GCST90001715	IVW	15	-0.142(-0.264 to -0.02)	0.023
ebi-a-GCST006464	BAFF-R on naive-mature B cell	ebi-a-GCST90001716	IVW	15	-0.132(-0.255 to -0.01)	0.034
ebi-a-GCST006464	BAFF-R on unsw mem	ebi-a-GCST90001717	IVW	15	-0.135(-0.257 to -0.012)	0.031
ebi-a-GCST006464	BAFF-R on sw mem	ebi-a-GCST90001718	IVW	15	-0.132(-0.255 to -0.01)	0.034
ebi-a-GCST006464	BAFF-R on IgD+	ebi-a-GCST90001719	IVW	15	-0.146(-0.269 to -0.024)	0.019
ebi-a-GCST006464	CD20 on IgD+ CD38- naive	ebi-a-GCST90001749	IVW	15	-0.225(-0.39 to -0.059)	0.008
ebi-a-GCST006464	CD20 on IgD+ CD38- unsw mem	ebi-a-GCST90001750	IVW	15	-0.169(-0.334 to -0.004)	0.044
ebi-a-GCST006464	CD20 on IgD- CD38dim	ebi-a-GCST90001757	IVW	15	-0.132(-0.252 to -0.012)	0.03
ebi-a-GCST006464	BAFF-R on B cell	ebi-a-GCST90001829	IVW	15	-0.14(-0.263 to -0.018)	0.025
Endometrial cancer	Myeloid cell	Myeloid cell				
ebi-a-GCST006464	CD45 on CD33dim HLA DR-	ebi-a-GCST90002050	IVW	15	-0.216(-0.397 to -0.036)	0.019
ebi-a-GCST006464	CD45 on basophil	ebi-a-GCST90002051	IVW	15	-0.223(-0.403 to -0.042)	0.015

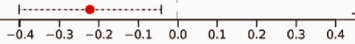

Fig. 5. The specific associations between endometrial cancer and immune cell traits. SNP: Single nucleotide polymorphism; IVW: Inverse-variance weighted.

myeloid cell, β = −0.23, 95%CI = −0.421 to −0.039, P = 0.018, IVW). These findings indicate that lung cancer may impact the characteristics of immune cells.

3.4.4. Ovarian cancer

Ovarian cancer has been found to the traits of B cell and myeloid cell (Fig. 7). For B cell, ovarian cancers were causally associated with $CD20^{-}$ $CD38^{-}$ AC ($CD20^{-}$ $CD38^{-}$ B cell absolute count, β = −0.162, 95%CI = −0.307 to −0.018, P = 0.028, IVW), IgD^{-} $CD38^{dim}$ AC (IgD^{-} $CD38^{dim}$ B cell absolute count, β = −0.152, 95%CI = −0.297 to −0.008, P = 0.039, IVW) and so on. For myeloid cell, ovarian cancers were causally associated with CD11b on $CD33^{br}$ HLA DR^{+} $CD14^{dim}$ (CD11b expression on $CD33^{br}$ HLA DR^{+} $CD14^{dim}$ myeloid cell, β = 0.214, 95%CI = 0.002 to 0.425, P = 0.048, IVW). These results suggest that ovarian cancer can influence immune cell traits.

Exposure(ID)	Outcome(Immune traits)	Immune trait ID	Method	nSNP	β(95%CI)	P
Lung cancer	B cell	B cell				
ieu-a-966	IgD+ CD38br AC	ebi-a-GCST90001392	IVW	5	-0.144(-0.269 to -0.02)	0.023
ieu-a-966	IgD+ CD38br %lymphocyte	ebi-a-GCST90001429	IVW	5	-0.158(-0.285 to -0.031)	0.015
ieu-a-966	Transitional %lymphocyte	ebi-a-GCST90001578	IVW	5	-0.132(-0.258 to -0.006)	0.04
ieu-a-966	CD24 on IgD- CD38-	ebi-a-GCST90001769	IVW	5	0.184(0.055 to 0.313)	0.005
ieu-a-966	CD25 on B cell	ebi-a-GCST90001775	IVW	5	0.15(0.021 to 0.278)	0.022
ieu-a-966	CD25 on CD24+ CD27+	ebi-a-GCST90001777	IVW	5	0.196(0.071 to 0.322)	0.002
ieu-a-966	CD25 on IgD+ CD24+	ebi-a-GCST90001778	IVW	5	0.188(0.062 to 0.314)	0.003
ieu-a-966	CD25 on IgD+ CD38-	ebi-a-GCST90001780	IVW	5	0.129(0.002 to 0.256)	0.047
ieu-a-966	CD25 on IgD+ CD38dim	ebi-a-GCST90001784	IVW	5	0.142(0.013 to 0.27)	0.031
ieu-a-966	CD25 on IgD- CD24-	ebi-a-GCST90001785	IVW	5	0.132(0.004 to 0.26)	0.043
ieu-a-966	CD25 on IgD- CD27-	ebi-a-GCST90001786	IVW	5	0.135(0.009 to 0.261)	0.036
ieu-a-966	CD25 on IgD- CD38-	ebi-a-GCST90001787	IVW	5	0.192(0.065 to 0.318)	0.003
ieu-a-966	CD25 on IgD- CD38dim	ebi-a-GCST90001789	IVW	5	0.189(0.065 to 0.314)	0.003
ieu-a-966	CD25 on memory B cell	ebi-a-GCST90001790	IVW	5	0.182(0.057 to 0.308)	0.004
ieu-a-966	CD25 on unsw mem	ebi-a-GCST90001792	IVW	5	0.176(0.05 to 0.302)	0.006
ieu-a-966	CD25 on sw mem	ebi-a-GCST90001793	IVW	5	0.206(0.079 to 0.332)	0.001
ieu-a-966	CD27 on IgD+ CD38- unsw mem	ebi-a-GCST90001801	IVW	5	0.219(0.045 to 0.394)	0.014
ieu-a-966	CD38 on PB/PC	ebi-a-GCST90001817	IVW	5	0.126(0.004 to 0.249)	0.043
ieu-a-966	IgD on unsw mem	ebi-a-GCST90001826	IVW	5	-0.146(-0.275 to -0.018)	0.026
Lung cancer	Myeloid cell	Myeloid cell				
ieu-a-966	CD66b on CD66b++ myeloid cell	ebi-a-GCST90001836	IVW	5	-0.23(-0.421 to -0.039)	0.018

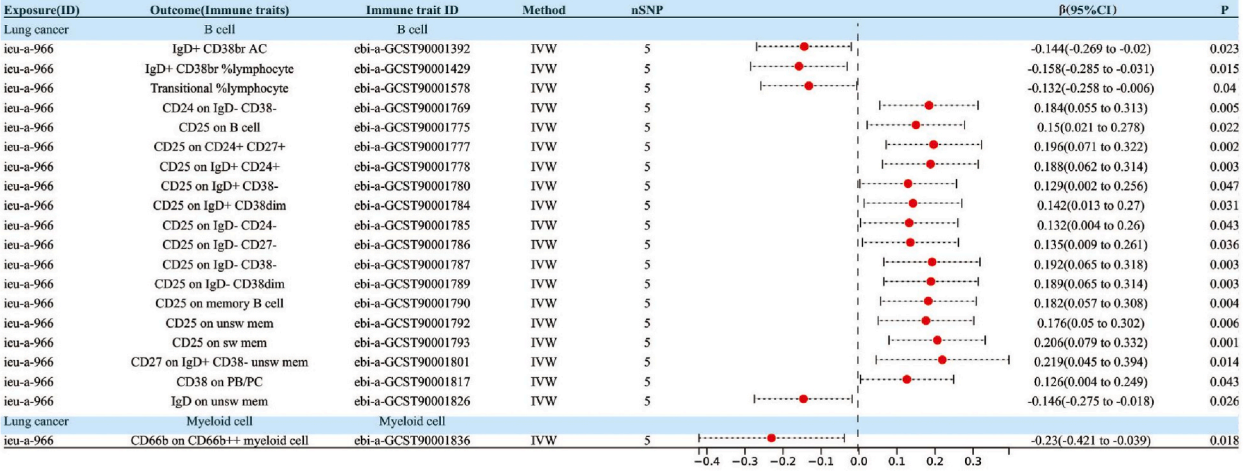

Fig. 6. The specific associations between lung cancer and immune cell traits. SNP: Single nucleotide polymorphism; IVW: Inverse-variance weighted.

Exposure(ID)	Outcome(Immune traits)	Immune trait ID	Method	nSNP	β(95%CI)	P
Ovarian cancer	B cell	B cell				
ieu-a-1120	CD20- CD38- AC	ebi-a-GCST90001423	IVW	10	-0.162(-0.307 to -0.018)	0.028
ieu-a-1120	IgD- CD38dim AC	ebi-a-GCST90001438	IVW	10	-0.152(-0.297 to -0.008)	0.039
ieu-a-1120	CD20- CD38- %lymphocyte	ebi-a-GCST90001444	IVW	10	-0.147(-0.291 to -0.003)	0.046
Ovarian cancer	Myeloid cell	Myeloid cell				
ieu-a-1120	CD11b on CD33br HLA DR+ CD14dim	ebi-a-GCST90002097	IVW	10	0.214(0.002 to 0.425)	0.048

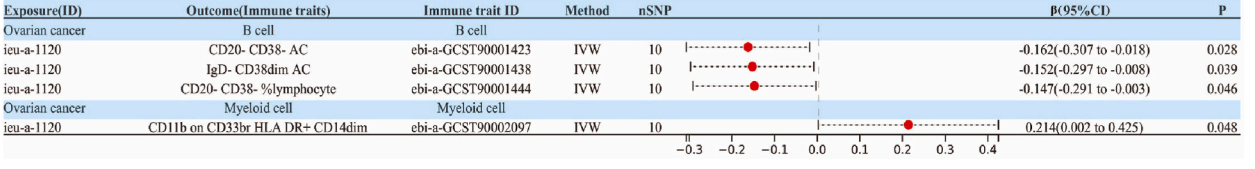

Fig. 7. The specific associations between ovarian cancer and immune cell traits. SNP: Single nucleotide polymorphism; IVW: Inverse-variance weighted.

3.4.5. *Prostate cancer*

Prostate cancer has been found to influence the traits of traits of B cell, monocyte, myeloid cell (Fig. 8). For B cell, breast cancer was causally associated with CD25 on $CD24^+$ $CD27^+$ (CD25 expression on $CD24^+$ $CD27^+$ B cell, $\beta = -0.067$, 95%CI = −0.127 to −0.006, P = 0.031, IVW), CD25 on IgD^+ $CD24^+$ (CD25 expression on IgD^+ $CD24^+$ B cell, $\beta = -0.069$, 95%CI = −0.13 to −0.008, P = 0.026, IVW), and so on. For monocyte, breast cancer was associated with PDL-1 on $CD14^+$ $CD16^-$ monocyte (PDL-1 expression on $CD14^+$ $CD16^-$ monocyte, $\beta = 0.076$, 95%CI = 0.015 to 0.137, P = 0.015, IVW) and CD64 on $CD14^-$ $CD16^-$ (CD64 expression on $CD14^-$ $CD16^-$ monocyte, $\beta = 0.069$, 95%CI = 0.009 to 0.129, P = 0.024, IVW). For myeloid cell, breast cancer was causally associated with CD66b on $CD66b^{++}$ myeloid cell (CD66b expression on $CD66b^{++}$ myeloid cell, $\beta = 0.102$, 95%CI = 0.009 to 0.195, P = 0.031, IVW), CD45 on $CD66b^{++}$ myeloid cell (CD45 expression on $CD66b^{++}$ myeloid cell, $\beta = 0.123$, 95%CI = 0.032 to 0.215, P = 0.008, IVW), and so on. These findings indicate that prostate cancer may impact the characteristics of immune cells.

3.5. *Causal effects of subtype cancers on panels (B cell, monocyte and myeloid cell panel) immune traits*

We identified causal relationships between breast subtype (ER^+ and ER^- breast cancer), endometrial subtype (endometrioid

Exposure(ID)	Outcome(Immune traits)	Immune trait ID	Method	nSNP	β(95%CI)	P
Prostate cancer	B cell	B cell				
ieu-b-85	CD25 on CD24+ CD27+	ebi-a-GCST90001777	IVW	115	-0.067(-0.127 to -0.006)	0.031
ieu-b-85	CD25 on IgD+ CD24+	ebi-a-GCST90001778	IVW	115	-0.069(-0.13 to -0.008)	0.026
ieu-b-85	CD25 on IgD+ CD38-	ebi-a-GCST90001780	IVW	115	-0.086(-0.147 to -0.025)	0.006
ieu-b-85	CD27 on T cell	ebi-a-GCST90001799	IVW	115	0.1(0.021 to 0.179)	0.013
Prostate cancer	Monocyte	Monocyte				
ieu-b-85	PDL-1 on CD14+ CD16- monocyte	ebi-a-GCST90001993	IVW	115	0.076(0.015 to 0.137)	0.015
ieu-b-85	CD64 on CD14- CD16-	ebi-a-GCST90002001	IVW	115	0.069(0.009 to 0.129)	0.024
Prostate cancer	Myeloid cell	Myeloid cell				
ieu-b-85	CD66b on CD66b++ myeloid cell	ebi-a-GCST90001836	IVW	115	0.102(0.009 to 0.195)	0.031
ieu-b-85	CD45 on CD66b++ myelod cell	ebi-a-GCST90002048	IVW	115	0.123(0.032 to 0.215)	0.008
ieu-b-85	CD11b on CD33dim HLA DR-	ebi-a-GCST90002095	IVW	115	-0.135(-0.227 to -0.043)	0.004
ieu-b-85	CD11b on basophil	ebi-a-GCST90002096	IVW	115	-0.123(-0.214 to -0.031)	0.009

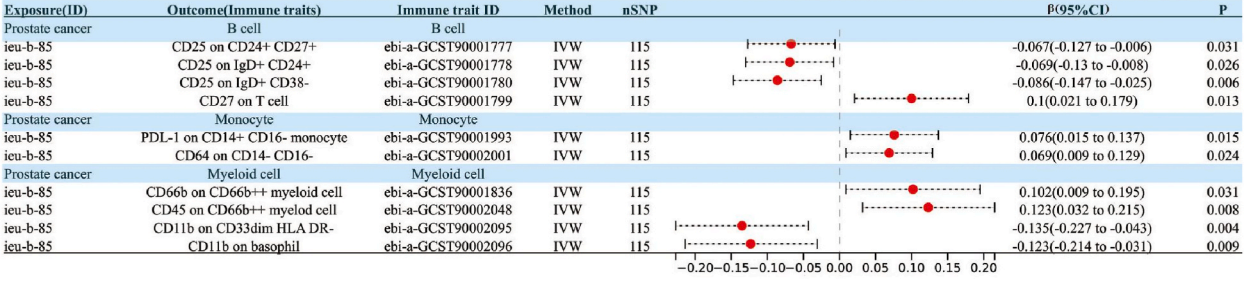

Fig. 8. The specific associations between prostate cancer and immune cell traits. SNP: Single nucleotide polymorphism; IVW: Inverse-variance weighted.

histology), lung subtype (SCLC) and ovarian subtype (HGSOC, serous borderline and mucinous borderline) cancer and immune traits. The results can be found in Fig. S1. No relationship was found between immune traits and the following subtype cancers: non-endometrioid histology endometrial cancer, lung adenocarcinoma, LGSOC, ENOC, and CCOC. These findings indicate that cancer subtypes may affect the traits of immune cells.

3.6. Causal effects of five cancers and their subtype on other four panels (TBNK, Treg, maturation stages of T cell and DC panel) immune traits

The complex interplay of specialized cells and molecules within the immune system plays a pivotal role in cancer [46]. By categorizing immune cells into four additional panels, we expanded our analysis to explore the relationship between different types of cancers and immune traits. The casual associations between cancer and immune traits are presented in Table S8. These results indicate that the interaction between cancers and immune cell characteristics is a widespread occurrence.

3.7. Multivariable MR analysis

The PhenoScanner search revealed connections between instrumental variables for cancer and associated traits. However, when

Exposure	Exposure(ID)	Outcome	Outcome(ID)	Method	nSNP	β(95%CI)	P
Breast cancer	ieu-a-1126	IgD- CD27- %B cell	ebi-a-GCST90001399	SVMR IVW	130	0.117(0.042 to 0.191)	0.002
Body mass index	ieu-b-40	IgD- CD27- %B cell	ebi-a-GCST90001399	SVMR IVW	385	-0.243(-0.427 to -0.059)	0.010
Breast cancer	ieu-a-1126	IgD- CD27- %B cell	ebi-a-GCST90001399	MVMR IVW	419	0.065(-0.047 to 0.178)	0.256
body mass index	ieu-b-40	IgD- CD27- %B cell	ebi-a-GCST90001399	MVMR IVW	419	-0.17(-0.339 to -0.002)	0.048
Breast cancer	ieu-a-1126	IgD- CD24- %B cell	ebi-a-GCST90001413	SVMR IVW	130	0.099(0.025 to 0.174)	0.009
Coronary heart disease	ieu-a-7	IgD- CD24- %B cell	ebi-a-GCST90001413	SVMR IVW	37	-0.175(-0.282 to -0.068)	0.001
Breast cancer	ieu-a-1126	IgD- CD24- %B cell	ebi-a-GCST90001413	MVMR IVW	149	0.089(0.021 to 0.157)	0.011
Coronary heart disease	ieu-a-7	IgD- CD24- %B cell	ebi-a-GCST90001413	MVMR IVW	149	-0.157(-0.261 to -0.053)	0.003
Breast cancer	ieu-a-1126	CD20- %B cell	ebi-a-GCST90001419	SVMR IVW	130	0.092(0.019 to 0.165)	0.014
Body mass index	ieu-b-40	CD20- %B cell	ebi-a-GCST90001419	SVMR IVW	384	-0.177(-0.355 to 0)	0.049
Breast cancer	ieu-a-1126	CD20- %B cell	ebi-a-GCST90001419	MVMR IVW	419	0.056(-0.06 to 0.172)	0.343
body mass index	ieu-b-40	CD20- %B cell	ebi-a-GCST90001419	MVMR IVW	419	-0.204(-0.376 to -0.033)	0.020
Breast cancer	ieu-a-1126	CD80 on CD62L+ plasmacytoid DC	ebi-a-GCST90002038	SVMR IVW	130	-0.121(-0.204 to -0.037)	0.005
Body mass index	ieu-b-40	CD80 on CD62L+ plasmacytoid DC	ebi-a-GCST90002038	SVMR IVW	376	-0.261(-0.469 to -0.053)	0.014
Breast cancer	ieu-a-1126	CD80 on CD62L+ plasmacytoid DC	ebi-a-GCST90002038	MVMR IVW	419	-0.14(-0.275 to -0.005)	0.043
body mass index	ieu-b-40	CD80 on CD62L+ plasmacytoid DC	ebi-a-GCST90002038	MVMR IVW	419	-0.203(-0.403 to -0.003)	0.046
Ovarian cancer	ieu-a-1120	Naive CD8br %CD8br	ebi-a-GCST90001552	SVMR IVW	10	0.131(0.019 to 0.243)	0.022
Body mass index	ieu-b-40	Naive CD8br %CD8br	ebi-a-GCST90001552	SVMR IVW	309	-0.239(-0.394 to -0.084)	0.002
Ovarian cancer	ieu-a-1120	Naive CD8br %CD8br	ebi-a-GCST90001552	MVMR IVW	460	0.136(0.03 to 0.242)	0.012
body mass index	ieu-b-40	Naive CD8br %CD8br	ebi-a-GCST90001552	MVMR IVW	460	-0.151(-0.278 to -0.023)	0.021
Prostate cancer	ieu-b-85	CD8dim NKT AC	ebi-a-GCST90001633	SVMR IVW	116	-0.072(-0.133 to -0.011)	0.020
Coronary heart disease	ieu-a-7	CD8dim NKT AC	ebi-a-GCST90001633	SVMR IVW	37	0.108(0.004 to 0.213)	0.042
Prostate cancer	ieu-b-85	CD8dim NKT AC	ebi-a-GCST90001633	MVMR IVW	133	-0.091(-0.156 to -0.027)	0.005
Coronary heart disease	ieu-a-7	CD8dim NKT AC	ebi-a-GCST90001633	MVMR IVW	133	0.096(-0.013 to 0.206)	0.085
Prostate cancer	ieu-b-85	CD8dim NKT %T cell	ebi-a-GCST90001634	SVMR IVW	116	-0.071(-0.132 to -0.01)	0.022
Coronary heart disease	ieu-a-7	CD8dim NKT %T cell	ebi-a-GCST90001634	SVMR IVW	37	0.114(0.008 to 0.219)	0.035
Prostate cancer	ieu-b-85	CD8dim NKT %T cell	ebi-a-GCST90001634	MVMR IVW	133	-0.085(-0.149 to -0.021)	0.009
Coronary heart disease	ieu-a-7	CD8dim NKT %T cell	ebi-a-GCST90001634	MVMR IVW	133	0.095(-0.014 to 0.204)	0.088
Prostate cancer	ieu-b-85	CD8dim NKT %lymphocyte	ebi-a-GCST90001635	SVMR IVW	116	-0.07(-0.131 to -0.009)	0.025
Coronary heart disease	ieu-a-7	CD8dim NKT %lymphocyte	ebi-a-GCST90001635	SVMR IVW	37	0.114(0.009 to 0.219)	0.033
Prostate cancer	ieu-b-85	CD8dim NKT %lymphocyte	ebi-a-GCST90001635	MVMR IVW	133	-0.084(-0.148 to -0.019)	0.011
Coronary heart disease	ieu-a-7	CD8dim NKT %lymphocyte	ebi-a-GCST90001635	MVMR IVW	133	0.094(-0.016 to 0.204)	0.093
Prostate cancer	ieu-b-85	CD28- CD8dim %T cell	ebi-a-GCST90001661	SVMR IVW	116	-0.08(-0.143 to -0.017)	0.013
Coronary heart disease	ieu-a-7	CD28- CD8dim %T cell	ebi-a-GCST90001661	SVMR IVW	37	0.157(0.048 to 0.265)	0.005
Prostate cancer	ieu-b-85	CD28- CD8dim %T cell	ebi-a-GCST90001661	MVMR IVW	133	-0.09(-0.159 to -0.022)	0.010
Coronary heart disease	ieu-a-7	CD28- CD8dim %T cell	ebi-a-GCST90001661	MVMR IVW	133	0.121(0.005 to 0.237)	0.041
Prostate cancer	ieu-b-85	CD28- CD8dim AC	ebi-a-GCST90001663	SVMR IVW	116	-0.066(-0.129 to -0.003)	0.042
Coronary heart disease	ieu-a-7	CD28- CD8dim AC	ebi-a-GCST90001663	SVMR IVW	37	0.144(0.035 to 0.253)	0.010
Prostate cancer	ieu-b-85	CD28- CD8dim AC	ebi-a-GCST90001663	MVMR IVW	133	-0.083(-0.153 to -0.013)	0.021
Coronary heart disease	ieu-a-7	CD28- CD8dim AC	ebi-a-GCST90001663	MVMR IVW	133	0.121(0.002 to 0.239)	0.046
Prostate cancer	ieu-b-85	CD64 on CD14- CD16-	ebi-a-GCST90002001	SVMR IVW	115	0.069(0.009 to 0.129)	0.024
Rheumatoid arthritis	ieu-a-832	CD64 on CD14- CD16-	ebi-a-GCST90002001	SVMR IVW	38	0.089(0.032 to 0.146)	0.002
Prostate cancer	ieu-b-85	CD64 on CD14- CD16-	ebi-a-GCST90002001	MVMR IVW	119	0.051(-0.024 to 0.125)	0.183
Rheumatoid arthritis	ieu-a-832	CD64 on CD14- CD16-	ebi-a-GCST90002001	MVMR IVW	119	0.113(0.049 to 0.177)	0.001
Prostate cancer	ieu-b-85	Activated Treg AC	ebi-a-GCST90001486	SVMR IVW	116	0.065(0.002 to 0.128)	0.044
Coronary heart disease	ieu-a-7	Activated Treg AC	ebi-a-GCST90001486	SVMR IVW	37	-0.148(-0.257 to -0.039)	0.008
Prostate cancer	ieu-b-85	Activated Treg AC	ebi-a-GCST90001486	MVMR IVW	133	0.063(-0.006 to 0.132)	0.075
Coronary heart disease	ieu-a-7	Activated Treg AC	ebi-a-GCST90001486	MVMR IVW	133	-0.097(-0.215 to 0.021)	0.107
Endometrial cancer	ebi-a-GCST006464	CD3 on CD28+ DN (CD4-CD8-)	ebi-a-GCST90001862	SVMR IVW	15	-0.143(-0.276 to -0.011)	0.034
Coronary heart disease	ieu-a-7	CD3 on CD28+ DN (CD4-CD8-)	ebi-a-GCST90001862	SVMR IVW	37	0.129(0.014 to 0.243)	0.028
Endometrial cancer	ebi-a-GCST006464	CD3 on CD28+ DN (CD4-CD8-)	ebi-a-GCST90001862	MVMR IVW	51	-0.108(-0.244 to 0.027)	0.117
Coronary heart disease	ieu-a-7	CD3 on CD28+ DN (CD4-CD8-)	ebi-a-GCST90001862	MVMR IVW	51	0.11(-0.007 to 0.227)	0.066
Endometrial cancer	ebi-a-GCST006464	HVEM on naive CD8br	ebi-a-GCST90001872	SVMR IVW	15	-0.264(-0.456 to -0.071)	0.007
Body mass index	ieu-b-40	HVEM on naive CD8br	ebi-a-GCST90001872	SVMR IVW	383	-0.371(-0.658 to -0.084)	0.011
Endometrial cancer	ebi-a-GCST006464	HVEM on naive CD8br	ebi-a-GCST90001872	MVMR IVW	486	-0.148(-0.357 to 0.06)	0.163
body mass index	ieu-b-40	HVEM on naive CD8br	ebi-a-GCST90001872	MVMR IVW	486	-0.288(-0.581 to 0.006)	0.055
Endometrial cancer	ebi-a-GCST006464	HVEM on CD4+	ebi-a-GCST90001875	SVMR IVW	15	-0.213(-0.405 to -0.02)	0.030
Body mass index	ieu-b-40	HVEM on CD4+	ebi-a-GCST90001875	SVMR IVW*	326	-0.501(-0.836 to -0.165)	0.003
Endometrial cancer	ebi-a-GCST006464	HVEM on CD4+	ebi-a-GCST90001875	MVMR IVW	486	-0.069(-0.287 to 0.149)	0.535
body mass index	ieu-b-40	HVEM on CD4+	ebi-a-GCST90001875	MVMR IVW	486	-0.346(-0.654 to -0.039)	0.027
Endometrial cancer	ebi-a-GCST006464	HVEM on EM CD4+	ebi-a-GCST90001878	SVMR IVW	15	-0.214(-0.409 to -0.019)	0.031
Body mass index	ieu-b-40	HVEM on EM CD4+	ebi-a-GCST90001878	SVMR IVW*	292	-0.384(-0.744 to -0.025)	0.036
Endometrial cancer	ebi-a-GCST006464	HVEM on EM CD4+	ebi-a-GCST90001878	MVMR IVW	486	-0.084(-0.298 to 0.13)	0.441
body mass index	ieu-b-40	HVEM on EM CD4+	ebi-a-GCST90001878	MVMR IVW	486	-0.176(-0.477 to 0.126)	0.253
Endometrial cancer	ebi-a-GCST006464	CD45 on basophil	ebi-a-GCST90002051	SVMR IVW	15	-0.223(-0.403 to -0.042)	0.015
Coronary heart disease	ieu-a-7	CD45 on basophil	ebi-a-GCST90002051	SVMR IVW	37	0.199(0.043 to 0.356)	0.012
Endometrial cancer	ebi-a-GCST006464	CD45 on basophil	ebi-a-GCST90002051	MVMR IVW	51	-0.213(-0.407 to -0.019)	0.032
Coronary heart disease	ieu-a-7	CD45 on basophil	ebi-a-GCST90002051	MVMR IVW	51	0.164(-0.004 to 0.332)	0.055

Fig. 9. Multivariable IVW estimates for adjusted associations between cancers and immune traits. SNP: Single nucleotide polymorphism; IVW: Inverse-variance weighted.

potential pleiotropy was taken into account using a multivariable MR analysis via the inverse-variance method, the combined effect values for these associated traits were modified. For instance, upon considering BMI as a covariate, the previously observed links between breast cancer and immune traits including IgD$^-$ CD27$^-$ %B cell (IgD$^-$ CD27$^-$ B cell/B cell ratio) and CD20$^-$ %B cell (CD20$^-$ B cell/B cell ratio), as well as endometrial cancer and immune traits including HVEM on naive CD8^{br} (HVEM expression on naive CD8$^+$ T cell), HVEM on CD4$^+$ (HVEM expression on CD4$^+$ T cell) and HVEM on EM CD4$^+$ (HVEM expression on effector memory CD4$^+$ T cell) lost their significance. Similarly, adjusting for coronary heart disease revealed that the associations between prostate cancer and immune trait including Activated Treg AC (activated CD4 regulatory T cell absolute count), as well as endometrial cancer and immune trait including CD3 on CD28$^+$ DN (CD3 expression on CD28$^+$ CD4$^-$CD8$^-$ T cell), were no longer statistically significant. Those results were shown in Fig. 9. These results suggest that the majority of findings in our study are minimally influenced by confounding factors.

3.8. Reverse MR analysis

Cancers and immune traits have bidirectional relations. To assess potential reverse causation effects, we utilized a reversed analysis approach by examining the roles of exposure and outcome. We did not find significant bidirectional effects between immune traits and cancer in most of the MR analyses conducted. However, cancer and immune traits have bidirectional relations in certain cases and Fig. 10 presents a summary network to enhance our understanding of complex interplay between immune traits and cancer. The following section demonstrates the impact of immune characteristics on tumor development.

3.8.1. Causal effects of seven immune panels immune traits on five cancers

We identified several causal relationships between immune traits and five cancers risk. Specifically, we found 14 causal relationships with breast cancer, 9 with endometrial cancer, 22 with lung cancer, 9 with ovarian cancer, and 14 with prostate cancer. Among these, breast cancer and prostate cancer shared three immune traits: HLA DR^{++} monocyte %monocyte (HLA DR^{++} monocyte/monocyte ratio), HLA DR on plasmacytoid DC (HLA DR expression on plasmacytoid dendritic cell), and HLA DR on DC (HLA DR expression on dendritic cell). Lung cancer and ovarian cancer shared one immune trait: CD62L$^-$ monocyte %monocyte (CD62L$^-$ monocyte/monocyte ratio). Prostate cancer and endometrial cancer shared one immune trait: HLA DR on CD33^{dim} HLA DR $^+$ CD11b$^+$ (HLA DR expression on CD33^{dim} HLA DR $^+$ CD11b$^+$ myeloid cell). Lastly, ovarian cancer and prostate cancer shared one immune trait: CD3 on resting Treg (CD3 expression on resting CD4 regulatory T cell) (Fig. 11).

In our analysis, immune traits may serve as risk factors for cancer and serve as protective factors against cancer. For B cell panel (Table 1), B cell traits may correlate with the development of breast cancer, lung cancer, endometrial cancer and ovarian cancer. CD20 on IgD$^-$ CD38$^-$ B cell (CD20 expression on IgD$^-$ CD38$^-$ B cell) was a risk factor for breast cancer (OR = 1.058, 95%CI = 1.013–1.106, P = 0.012, IVW), CD25 on IgD $^+$ CD38^{dim} B cell (CD25 expression on IgD $^+$ CD38^{dim} B cell) was risk factor endometrial cancer (OR = 1.108, 95%CI = 1.007–1.218, P = 0.034, IVW). BAFF-R on IgD$^+$ CD24$^+$ B cell (BAFF-R expression on IgD$^+$ CD24$^+$ B cell) was a risk factor for lung cancer (OR = 1.042, 95%CI = 1.004–1.081, P = 0.03, IVW). CD20 on IgD$^+$ CD38$^-$ B cell (CD20 expression on IgD$^+$ CD38$^-$ B cell) was a risk factor for ovarian cancer (OR = 1.118, 95%CI = 1.019–1.226, P = 0.019, IVW). For monocyte panel (Table 1), CD64 on CD14$^-$ CD16$^-$ (CD64 expression on CD14$^-$ CD16$^-$ monocyte) was a protective factor against breast cancer (OR = 0.951, 95% CI = 0.914–0.99, P = 0.014, IVW). HLA DR on CD14$^+$ CD16$^+$ monocyte (HLA DR expression on CD14$^+$ CD16$^+$ monocyte) was a protective factor against prostate cancer (OR = 0.967, 95%CI = 0.941–0.994, P = 0.018, IVW). For myeloid cell panel (Table 1), CD33 on CD33^{dim} HLA DR $^+$ CD11b$^+$ (CD33 expression on CD33^{dim} HLA DR $^+$ myeloid cell) was a protective factor against breast cancer (OR = 0.989, 95%CI = 0.979–0.999, P = 0.028, IVW). HLA DR on CD33^{dim} HLA DR $^+$ CD11b$^+$ (HLA DR expression on CD33^{dim} HLA DR $^+$ CD11b$^+$ myeloid cell) was a protective factor against endometrial cancer (OR = 0.944, 95%CI = 0.902–0.988, P = 0.013, IVW). Basophil %CD33^{dim} HLA DR$^-$ CD66b$^-$ (Basophil/CD33^{dim} HLA DR$^-$ CD66b$^-$ myeloid cell ratio) was a protective factor against prostate cancer (OR = 0.972, 95%CI = 0.945–0.999, P = 0.045, IVW). To gain a deeper understanding of the relationship between immune traits and cancers, we conducted MR analysis to include four additional panels (TBNK, Treg, maturation stages of T cells, and DC panels) (Table 2). The field of cancer immunology focuses on studying how the immune system interacts with cancer cells and how this interaction can be harnessed for therapeutic purposes [47]. Categorizing cancers based on specific characteristics has indeed been

	Cancers-Immune traits				Immune traits-Cancers			
Exposure‖Outcome	Method	nSNP	β (95%CI)	P	Method	nSNP	OR (95%CI)	P
BC‖CD20 on sw mem	IVW	130	-0.092(-0.166 to -0.018)	0.015	IVW	7	1.034(1.004 to 1.065)	0.025
BC‖CD8 on EM CD8br	IVW	130	-0.105(-0.187 to -0.023)	0.012	IVW	3	1.047(1.019 to 1.076)	0.001
ER+ BC‖CD27 on CD24+ CD27+	IVW	91	-0.09(-0.164 to -0.016)	0.018	IVW	8	0.977(0.955 to 1)	0.048
ER+ BC‖CD27 on IgD- CD38dim	IVW	91	-0.095(-0.169 to -0.021)	0.012	IVW	7	0.976(0.954 to 0.998)	0.032
ER+ BC‖CD27 on sw mem	IVW	91	-0.125(-0.2 to -0.05)	0.001	IVW	8	0.977(0.955 to 0.999)	0.037
SCLC‖CD25 on CD24+ CD27+	IVW	3	0.24(0.098 to 0.382)	0.001	IVW	4	0.879(0.777 to 0.995)	0.042
SCLC‖CD25 on memory B cell	IVW	3	0.224(0.081 to 0.366)	0.002	IVW	4	0.875(0.772 to 0.992)	0.038
SCLC‖CD25 on unsw mem	IVW	3	0.219(0.077 to 0.361)	0.003	IVW	4	0.872(0.765 to 0.993)	0.039
SCLC‖CD27 on IgD- CD38-	IVW	3	0.146(0.001 to 0.291)	0.048	IVW	7	1.109(1.011 to 1.217)	0.028

Fig. 10. Summarized results of bidirectional MR study on cancers and immune traits. SNP: Single nucleotide polymorphism; IVW: Inverse-variance weighted.

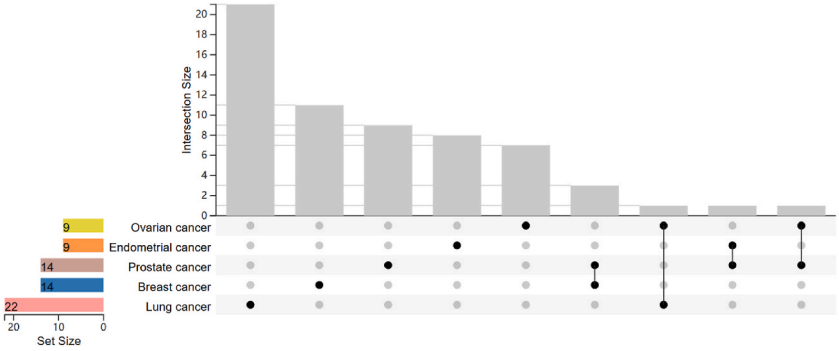

Fig. 11. The causal relationships between different types of cancer and immune traits. Set Size: the number of immune cell characteristics that influence different types of cancer. Intersection Size: distribution of immune cell characteristics in different tumors.

Table 1
Causal effects of three immune panels (B cell, monocyte and myeloid cell panel) immune traits on five cancers.

Exposure	Outcome (ID)	Method	Nsnp	OR(95%CI)	P
B cell	Breast cancer				
CD20 on sw mem	ieu-a-1126	IVW	7	1.034(1.004–1.065)	0.025
CD20 on IgD- $CD38^{-}$	ieu-a-1126	IVW	4	1.058(1.013–1.106)	0.012
B cell	Endometrial cancer				
CD25 on IgD + CD38dim	ebi-a-GCST006464	IVW	3	1.108(1.007–1.218)	0.034
B cell	Lung cancer				
BAFF-R on $CD24^{+}$ $CD27^{+}$	ieu-a-966	IVW	6	1.038(1.001–1.077)	0.046
BAFF-R on IgD + $CD24^{+}$	ieu-a-966	IVW	5	1.042(1.004–1.081)	0.03
BAFF-R on IgD + $CD24^{-}$	ieu-a-966	IVW	10	1.041(1.006–1.078)	0.02
BAFF-R on IgD + $CD38^{-}$	ieu-a-966	IVW	9	1.045(1.009–1.083)	0.014
BAFF-R on IgD + $CD38^{-}$ naive	ieu-a-966	IVW	8	1.044(1.009–1.08)	0.012
BAFF-R on IgD + $CD38^{-}$ unsw mem	ieu-a-966	IVW	7	1.038(1.001–1.077)	0.045
BAFF-R on IgD + CD38br	ieu-a-966	IVW	10	1.042(1.006–1.079)	0.022
BAFF-R on IgD + CD38dim	ieu-a-966	IVW	10	1.039(1.005–1.075)	0.025
BAFF-R on IgD- $CD27^{-}$	ieu-a-966	IVW	8	1.039(1–1.078)	0.048
BAFF-R on IgD- $CD38^{-}$	ieu-a-966	IVW	6	1.041(1.003–1.081)	0.033
BAFF-R on IgD- CD38br	ieu-a-966	IVW	3	1.11(1.006–1.226)	0.038
BAFF-R on memory B cell	ieu-a-966	IVW	5	1.039(1.001–1.078)	0.044
BAFF-R on naive-mature B cell	ieu-a-966	IVW	10	1.042(1.006–1.078)	0.02
BAFF-R on unsw mem	ieu-a-966	IVW	5	1.039(1.001–1.078)	0.045
BAFF-R on IgD+	ieu-a-966	IVW	10	1.039(1.004–1.075)	0.028
BAFF-R on transitional	ieu-a-966	IVW	8	1.046(1.008–1.086)	0.018
BAFF-R on B cell	ieu-a-966	IVW	10	1.039(1.004–1.075)	0.027
B cell	Ovarian cancer				
CD20 on IgD + $CD38^{-}$	ieu-a-1120	IVW	4	1.118(1.019–1.226)	0.019
Monocyte	Breast cancer				
CD64 on $CD14^{-}$ $CD16^{-}$	ieu-a-1126	IVW	3	0.951(0.914–0.99)	0.014
HLA DR on $CD14^{-}$ $CD16^{-}$	ieu-a-1126	IVW	5	0.978(0.962–0.996)	0.014
Monocyte	Prostate cancer				
HLA DR on $CD14^{+}$ $CD16^{+}$ monocyte	ieu-b-85	IVW	4	0.967(0.941–0.994)	0.018
HLA DR on monocyte	ieu-b-85	IVW	4	1.047(1.021–1.073)	0
Myeloid cell	Breast cancer				
CD33 on CD33dim HLA DR + CD11b+	ieu-a-1126	IVW	7	0.989(0.979–0.999)	0.028
CD33 on CD33dim HLA DR + CD11b-	ieu-a-1126	IVW	7	0.989(0.979–0.999)	0.03
HLA DR on $CD33^{-}$ HLA DR+	ieu-a-1126	IVW	3	0.976(0.962–0.991)	0.002
Myeloid cell	Endometrial cancer				
HLA DR on CD33dim HLA DR + CD11b+	ebi-a-GCST006464	IVW	4	0.944(0.902–0.988)	0.013
HLA DR on CD33dim HLA DR + CD11b-	ebi-a-GCST006464	IVW	5	0.943(0.904–0.985)	0.008
Myeloid cell	Prostate cancer				
Basophil %CD33dim HLA DR- CD66b-	ieu-b-85	IVW	3	0.972(0.945–0.999)	0.045
HLA DR on CD33br HLA DR + $CD14^{-}$	ieu-b-85	IVW	3	1.05(1.026–1.075)	0
HLA DR on CD33br HLA DR + CD14dim	ieu-b-85	IVW	3	1.07(1.036–1.105)	0
HLA DR on CD33dim HLA DR + CD11b+	ieu-b-85	IVW	4	0.955(0.933–0.978)	0

valuable in understanding the relationship between immune traits and cancer. The casual associations between seven panels immune traits and cancer subtypes are presented in Table S9. Together, these findings imply that various immune cell traits can influence cancer development.

Table 2
Causal effects of four immune panels (TBNK, Treg, maturation stages of T cells, and DC panels) immune traits on five cancers.

Exposure	Outcome (ID)	Method	Nsnp	OR(95%CI)	P
cDC	Breast cancer				
CD11c on granulocyte	ieu-a-1126	IVW	4	1.039(1.006–1.074)	0.022
HLA DR on myeloid DC	ieu-a-1126	IVW	7	0.978(0.964–0.993)	0.003
HLA DR on plasmacytoid DC	ieu-a-1126	IVW	9	0.984(0.973–0.995)	0.004
HLA DR on DC	ieu-a-1126	IVW	7	0.982(0.969–0.995)	0.005
cDC	Lung cancer				
CD62L- monocyte %monocyte	ieu-a-966	IVW	4	0.919(0.845–0.999)	0.046
cDC	Ovarian cancer				
CD62L- monocyte %monocyte	ieu-a-1120	IVW	4	0.937(0.88–0.998)	0.042
cDC	Prostate cancer				
HLA DR on plasmacytoid DC	ieu-b-85	IVW	9	1.045(1.031–1.06)	0
HLA DR on DC	ieu-b-85	IVW	7	1.051(1.034–1.068)	0
Maturation stages of T cell	Breast cancer				
CD8 on EM CD8br	ieu-a-1126	IVW	3	1.047(1.019–1.076)	0.001
CD45RA + CD8br %CD8br	ieu-a-1126	IVW	5	0.985(0.973–0.997)	0.015
Maturation stages of T cell	Lung cancer				
CD4 on naive $CD4^+$	ieu-a-966	IVW*	4	0.813(0.671–0.985)	0.034
CD4RA on TD $CD4^+$	ieu-a-966	IVW	3	1.083(1.015–1.155)	0.015
Maturation stages of T cell	Ovarian cancer				
CD45RA on naive $CD4^+$	ieu-a-1120	IVW	10	0.962(0.934–0.99)	0.009
Maturation stages of T cell	Prostate cancer				
Naive CD8br %T cell	ieu-b-85	IVW	3	0.992(0.986–0.998)	0.009
TBNK	Breast cancer				
HLA DR++ monocyte %monocyte	ieu-a-1126	IVW	3	0.958(0.926–0.991)	0.013
TBNK	Prostate cancer				
HLA DR++ monocyte %monocyte	ieu-b-85	IVW	3	1.057(1.014–1.103)	0.009
HLA DR + NK %NK	ieu-b-85	IVW	7	1.039(1.009–1.069)	0.01
FSC-A on NK	ieu-b-85	IVW	3	1.079(1.027–1.134)	0.002
HLA DR on B cell	ieu-b-85	IVW	8	1.02(1–1.041)	0.048
Treg	Endometrial cancer				
$CD39^+$ $CD4^+$ AC	ebi-a-GCST006464	IVW	6	0.943(0.9–0.988)	0.014
$CD39^+$ CD8br %T cell	ebi-a-GCST006464	IVW	7	1.027(1–1.055)	0.047
$CD39^+$ CD8br AC	ebi-a-GCST006464	IVW	6	1.031(1.003–1.059)	0.028
CD45RA- $CD28^-$ CD8br AC	ebi-a-GCST006464	IVW	116	1(1–1)	0.007
CD25 on $CD39^+$ $CD4^+$	ebi-a-GCST006464	IVW	5	0.958(0.921–0.996)	0.032
CD4 on $CD39^+$ secreting Treg	ebi-a-GCST006464	IVW	3	1.116(1.032–1.207)	0.006
Treg	Lung cancer				
CD25hi CD45RA- CD4 not Treg %T cell	ieu-a-966	IVW	3	0.939(0.884–0.997)	0.041
$CD28^+$ CD45RA + CD8dim AC	ieu-a-966	IVW	6	0.975(0.953–0.997)	0.026
Treg	Ovarian cancer				
Resting Treg % CD4 Treg	ieu-a-1120	IVW	11	0.968(0.944–0.992)	0.01
Resting Treg %CD4	ieu-a-1120	IVW	6	0.957(0.928–0.987)	0.006
Activated Treg %CD4 Treg	ieu-a-1120	IVW	4	1.059(1.011–1.109)	0.016
CD25++ CD8br AC	ieu-a-1120	IVW	3	1.092(1.012–1.178)	0.023
CD3 on resting Treg	ieu-a-1120	IVW	5	0.952(0.91–0.997)	0.036
CD127 on $CD28^+$ $CD4^+$	ieu-a-1120	IVW	3	1.111(1.02–1.211)	0.016
Treg	Prostate cancer				
CD3 on resting Treg	ieu-b-85	IVW	5	0.968(0.941–0.995)	0.021

4. Discussion

Cancer employs diverse mechanisms to disrupt the normal functioning of immune cells, thereby promoting tumor growth and advancement. By employing a two-sample MR, we examined potential associations of cancers and their subtypes with immune cell traits, including associations between absolute cell counts, proportions of cells, and the levels of cell surface antigens.

We identified SNPs that demonstrated a significant association with breast, endometrial, lung, ovarian, and prostate cancers, using a significance threshold of $P < 5 \times 10^{-8}$. The selected single instrumental variables (IVs) exhibited an F-statistic greater than 10 and an r^2 value less than 0.001, indicating that none of the SNPs were weak instrumental variables. Among these SNPs, we found the rs4784227 (P = 1E-200) in FPXA1 and rs11379664 (P = 1E-200) in FGFR2 were strongly associated with overall breast cancer. rs11651052 (P = 4.00037E-20) in HNF1B was strongly associated with overall endometrial cancer. rs8040868 (P = 4.9705E-60) in CHRNA3 was strongly associated with overall lung cancer. rs62276619 (P = 5.53478E-39) in TIPARP was strongly associated with overall ovarian cancer. rs11986220 (P = 1.09901E-187) was strongly associated with overall prostate cancer. The rs11986220 variant is located within a FoxA1 binding site, where the prostate cancer risk allele enhances both FoxA1 binding affinity and androgen responsiveness [48]. Additionally, genetic variants associated with BMI consistently appear as a variable across various cancer types in our study, suggesting a potential relationship between cancer incidence and BMI. Recent studies underscore the significance of BMI as a contributing risk factor across a spectrum of cancers [49,50].

Our discovery regarding the link between cancer and immune traits aligns with previous observational studies, which have demonstrated that cancer contributes to the dysregulation of immune cells. Tregs inhibit the immune response against tumors, and their infiltration into tumor tissues is often linked to a poor prognosis. Depletion of Tregs was able to improve the antitumor response [51]. Examination of the tumor microenvironment in prostate cancer underscores the role of infiltrating Tregs and macrophages as pivotal indicators of unfavorable prognosis [52]. Consistent with prior research, our MR analysis suggests that prostate cancer is a risk factor for Activated Treg AC (activated Treg cells absolute count, $\beta = 0.065$, 95%CI = 0.002 to 0.128, P = 0.044, IVW). The accumulation of MDSCs that is often immunosuppressive. A recent study reports that the V-domain suppressor of T cell activation (VISTA) deficiency leads to a notable decrease in tumor-associated MDSCs and enhanced T cell-mediated tumor control [53]. In addition, the ovarian cancer microenvironment exerts a significant influence over the metabolism and functionality of MDSCs, thereby intricately tuning the immune microenvironment. Consistent with prior research, our MR analysis suggests that endometrioid histology endometrial cancer ($\beta = 0.213$, 95%CI = 0.045 to 0.381, P = 0.013, IVW) and serous borderline ovarian cancer ($\beta = 0.188$, 95%CI = 0.055 to 0.321, P = 0.006, IVW) are risk factors for Mo MDSC AC (monocytic MDSCs absolute count). The cancer can influence the co-stimulatory molecules and cell surface receptors.

Different cancers can influence the same immune cell traits. In our study, we found that breast cancer and lung cancer were linked to four common immune traits. Similarly, lung cancer and prostate cancer also shared four immune traits. Endometrial cancer and ovarian cancer exhibited two shared immune traits. Additionally, breast cancer and endometrial cancer shared one immune trait. Endometrial cancer and prostate cancer shared one immune trait. Lastly, breast cancer, lung cancer, and prostate cancer shared one immune trait. Different immune characteristics can also affect the same types of cancer. breast cancer and prostate cancer can be influenced by three same immune traits. Lung cancer and ovarian cancer can be influenced by one same immune trait. Prostate cancer and endometrial cancer can be influenced by one same immune trait. Lastly, ovarian cancer and prostate cancer can be influenced by one same immune trait. This implies that research on these immune characteristics may lead to the development of biomarkers and treatment strategies that can simultaneously target different tumors. Transcriptomic analysis reveals four unique TME subtypes consistently identified across a spectrum of 20 distinct cancer types. These TME subtypes exhibit a strong correlation with patient outcomes following immunotherapy treatment in various cancer types, highlighting that individuals with immune-favorable TME subtypes derive the greatest benefit from immunotherapy interventions [54]. This research suggests that immune traits serve as a universal immunotherapy biomarker across a diverse range of cancer categories.

Given the complexity of interactions between tumors and the immune system, different cancers may have divergent effects on the same immune traits. The CD25 and CD24 on IgD^- $CD38^-$ B cell surface, CD25 on switched memory B cell surface and CD25 on IgD^- $CD38^{dim}$ B cell surface tends to decrease in expression in breast cancer and increase in expression in lung cancer in our analysis. The CD25 on IgD^- $CD38^{dim}$ B cell tends to decrease in expression in prostate cancer and increase in expression in lung cancer in our analysis. The CD25 on IgD^- $CD38^{dim}$ B cell surface tends to increase in expression in prostate cancer and decrease in expression in lung cancer in our analysis. In addition, the regulation of immune cells involves complex genetic mechanisms that exhibit highly selective effects on cancer risk. It is also important to note that the same immune traits may have divergent effects on different types of cancer. For example, HLA DR expression on plasmacytoid DC is a protective factor against breast cancer, but a risk factor for prostate cancer. In reverse MR analysis, the same immune traits may be different in the different stage of cancer development. The higher expression of CD20 on switched memory tends to be a risk factor for breast cancer development, but the breast cancer tends to induce the lower expression of CD20 on switched memory. The higher expression of CD25 on memory B cell tends to a protective factor against SCLC, but the SCLC tends to induce the higher express of CD25 on memory B cell.

Experimental research have suggested that cancer can influence the immune system of cancer patients through multiple mechanisms. Nevertheless, the precise mechanism through cancer induce immune system dysregulation has yet to be determined. Hence, a mechanistic analysis of our findings is necessary for further investigation. Cytokines are potent secreted regulators of diverse cell types and cellular activities, especially in the immune system [55]. Dysregulated cytokine production by malignant cells is involved in the dysregulated immune cells. For example, Interleukin-10 (IL-10) stimulates the expression of CD39 on $CD8^+$ T cells, thereby enhancing the effectiveness of anti-PD1 therapy in EGFR-mutated non-small cell lung cancer [55]. A recent study has proposed that tumor-derived immunoglobulin-like transcript 4 (ILT4) is directly implicated in inducing cell senescence in naive/effector T cells [56]. Given the complex connections among cancer, circulating inflammatory cytokines, and immune traits, further studies and mediation MR analysis are needed to explore the detailed associations and underlying mechanisms.

Apart from the factors related to inflammation, tumor metabolism factors may also have an impact on immune cell characteristics. The metabolically adverse tumor microenvironment creates obstacles for tumor-infiltrating immune cells, hindering sustained clinical remission post-immunotherapy. The metabolic interaction between cancer cells and adjacent immune cells may influence the magnitude and type of immune responses, underscoring the potential role of metabolic crosstalk in immune surveillance and evasion [57]. Increased levels of lipoprotein lipase in radiation-induced thymic lymphomas result in elevated serum triacylglycerol (TAG) levels, subsequently causing dysfunction in dendritic cells (DCs) [58]. Moreover, within the tumor microenvironment, the competitive uptake of glucose is accountable for impairing T cell function. Additionally, the competitive uptake of amino acids, glutamine, fatty acids, and other metabolites or growth factors by both tumor cells and immune cells, along with the expression of corresponding transporters on their surfaces, are pivotal factors influencing immune cell functionality [59]. These interplay may change the immune cells traits. Therefore, exploring the correlation among tumors, metabolic reactions, and immune cell characteristics holds great promise for investigating tumor immune mechanisms.

Similar effects also exist between tumors, extracellular vesicles, and immune cell characteristics. The tumor-induced systemic environment affects both the frequency and phenotype of monocytes, leading them to acquire immunosuppressive functions [60]. To some extent, this imbalance in immune cell activity within the tumor microenvironment is mediated by tumor-derived extracellular

vesicles (EVs). For instance, in cases of melanoma and colon cancer, tumor-derived exosomes inhibit the differentiation of peripheral inflammatory monocytes into dendritic cells, instead promoting their polarization into the monocytic MDSC phenotype, which is marked by reduced expression of HLA-DR [61]. In addition, stimulation of monocytes with pancreatic cancer-derived EVs led to distinctive alterations in the expression of HLA-DR, PD-L1, CD86, and CD64 [62]. Collectively, cancer can impact the immune system of patients through various mechanisms. Further investigation, including MR analysis, is necessary to delve into the correlation between cancers and immune characteristics.

The impact of cancer on immune cell traits offers significant potential for future research and clinical practice. Tumor-associated immune cell characteristics may influence the tumor microenvironment, which in turn can impact immunotherapy strategies. Research indicates that a significant proportion of patients do not benefit from immune checkpoint inhibitors (ICIs) due to resistance or relapse, which is likely caused by the presence of various immunosuppressive cells, such as MDSCs, in the TME. These cells strongly inhibit T-cell activity, facilitating the immune escape of malignant tumors [63]. Recent discoveries suggest that targeting MDSCs could be a promising alternative approach for immunotherapy, reshaping the immunosuppressive microenvironment and enhancing the effectiveness of cancer immunotherapy [64]. Together, further exploration into the role of immune cells can inform the development of targeted immunotherapies.

In our MR results, the ovarian cancer-associated immune traits are significantly fewer than other cancer-associated immune traits. The phenomenon could be attributed to the low tumor mutational burden (TMB) characteristic of ovarian cancer. TMB quantifies the number of nonsynonymous mutations present in a tumor sample, reflecting both genomic instability and the probability of neoepitope emergence on the cell surface [65,66]. Neoepitopes are unique proteins displayed on the exterior of cancer cells, making them recognizable by the immune system. Ovarian cancer is typically classified as a "cold tumor", exhibiting a low TMB phenotype [67]. Consequently, its responsiveness to immunotherapy has traditionally been constrained. In addition, lung cancer is intimately linked to immune responses and tends to exhibit a favorable response to immunotherapy. However, in our study, we observed a limited association between lung cancer and immune cell traits, such as dmonocyte traits or myeloid cells traits. This may be attributable to the stringent criteria we applied in selecting instrumental variables, which may have precluded the identification of associations between lung cancer and immune cell traits. The same influence potentially extends to other cancers as well.

Our study has some limitations. Firstly, the GWAS of cancers and immune traits are from European populations. As linkage disequilibrium patterns vary across ethnic groups, our study is not suitable for non-European populations [68,69]. It is crucial to exercise caution when extrapolating our findings to other populations. Secondly, we employed multivariate MR to explore the potential presence of horizontal pleiotropy resulting from confounding factors. However, despite employing multivariate MR analysis, it was challenging to mitigate bias caused by pleiotropic effects that is beyond the ones examined in our analysis. Thirdly, it is important to note that our study focused on only five types of cancers, and it is necessary to investigate potential associations between immune traits and other types of cancer. Notably, leukemia and lymphoma directly impact immune cells, which are vital for maintaining a functional immune system [70]. For the relationship between pancreatic cancer and immune system, the effectiveness of immunotherapy has been limited so far, although multiple clinical trials of immunotherapy have been launched as treatments with promising clinical results.

5. Conclusions

Our MR estimates reveal potential contributions of various cancers and their subtypes to the immune cell traits, such as breast and lung cancer-associated CD25 on IgD^{-} CD38^{dim}, CD25 on sw mem, CD24 on IgD^{-} CD38^{-}, and CD25 on IgD^{-} CD38^{-} immune cell traits; lung and prostate cancer-associated CD25 on IgD^{+} CD24^{+}, CD25 on IgD^{+} CD38^{-}, CD66b on CD66b^{++} myeloid cell, DN (CD4^{-}CD8^{-}) AC immune cell traits; endometrial and ovarian cancer-associated TD DN (CD4^{-}CD8^{-}) %DN, EM DN (CD4^{-}CD8^{-}) %DN immune cell traits; breast and endometrial cancer-associated CD20 on IgD^{-} CD38^{dim} immune cell traits; endometrial and prostate cancer-associated CCR2 on myeloid DC immune cell traits; breast cancer, lung cancer, and prostate cancer-associated CD25 on CD24^{+} CD27^{+} immune cell traits. Furthermore, our findings highlight the complex regulation of cancer risk by immune cells, such as HLA DR^{++} monocyte % monocyte, HLA DR on plasmacytoid DC, and HLA DR on DC (breast cancer and prostate cancer); CD62L^{-} monocyte %monocyte (lung and ovarian cancer); HLA DR on CD33dim HLA DR^{+} CD11b^{+} (prostate cancer and endometrial cancer); CD3 on resting Treg (ovarian and prostate cancer). The impact of various types of cancer on the same immune cell traits, as well as the influence of different immune characteristics on the same type of cancer, is highlighted by this research. It demonstrates that immune traits can act as universal biomarkers and targets for immunotherapy across a diverse range of cancer types. Altogether, our findings are crucial for cancer immunotherapy, as they enhance our understanding of the dysregulation mechanisms in immune cells and have significant implications for public health strategies aimed at reducing cancer risk.

CRediT authorship contribution statement

Zejing Qiu: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jingjing Fan:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jun He:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Xingxing Huang:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Zuyi Yang:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Qinsong Sheng:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation,

Conceptualization. **Lijun Jin:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Statements

During the preparation of this work the authors used ChatGPT 4o mini in order to improve readability and language of the work. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Availability of data and materials

The summary data of cancer and immune traits can be downloaded from the IEU Open GWAS project https://gwas.mrcieu.ac.uk/.

Ethics approval and consent to participate

Our analysis used publicly available genome-wide association study (GWAS) summary statistics. No new data were collected, and no new ethical approval was required.

Consent for publication

Not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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