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ORIGINAL ARTICLE

Immune Cells and Risk of Cervical Cancer: Evidence from a Mendelian Randomization Study

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SUMMARY

Background: **Immune dysfunction is involved in the development of cervical cancer. There is lack of causal evidence presenting the effects of immune cells on the risk of cervical cancer (CC).**
Methods: **The genetic information of single nucleotide polymorphisms (SNPs) from European descents was employed and a two-sample Mendelian randomization (MR) strategy was designed. In total, 731 kinds of immune cells were included as the exposures. For cervical cancer, the data was from the cohort involving almost 24,0000 participants. The inverse variance weighted (IVW) approach served as the main strategy for causality inference. MR-Egger and weighted median were the alternative methods for comparison. Sensitivity analyses focusing on heterogeneity and pleiotropy were then carried out to verify the estimated effects.**
Results: **After selecting eligible SNPs for MR analysis, the IVW approach identified a total of 24 immune cell characteristics which were causally correlated with CC at $p < 0.05$. Among them, six immune cell phenotypes are confirmed to be related to an elevated risk of CC, while the remaining eighteen immune cell characteristics demonstrate protective effects against CC. MR-Egger and weighted median showed comparable results, and the detected associations passed the heterogeneity and pleiotropy tests.**
Conclusions: **This Mendelian randomization study demonstrated causal associations between immune cells and CC, underscoring the intricate interactions of the immune system with CC. The results also provide insights into the mechanisms of CC development attributed to immunological regulation and highlight potential therapeutic targets for improving immune responses in patients with CC.**
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KEYWORDS

cervical cancer, immune cells, Mendelian randomization study, immunity, single nucleotide polymorphisms

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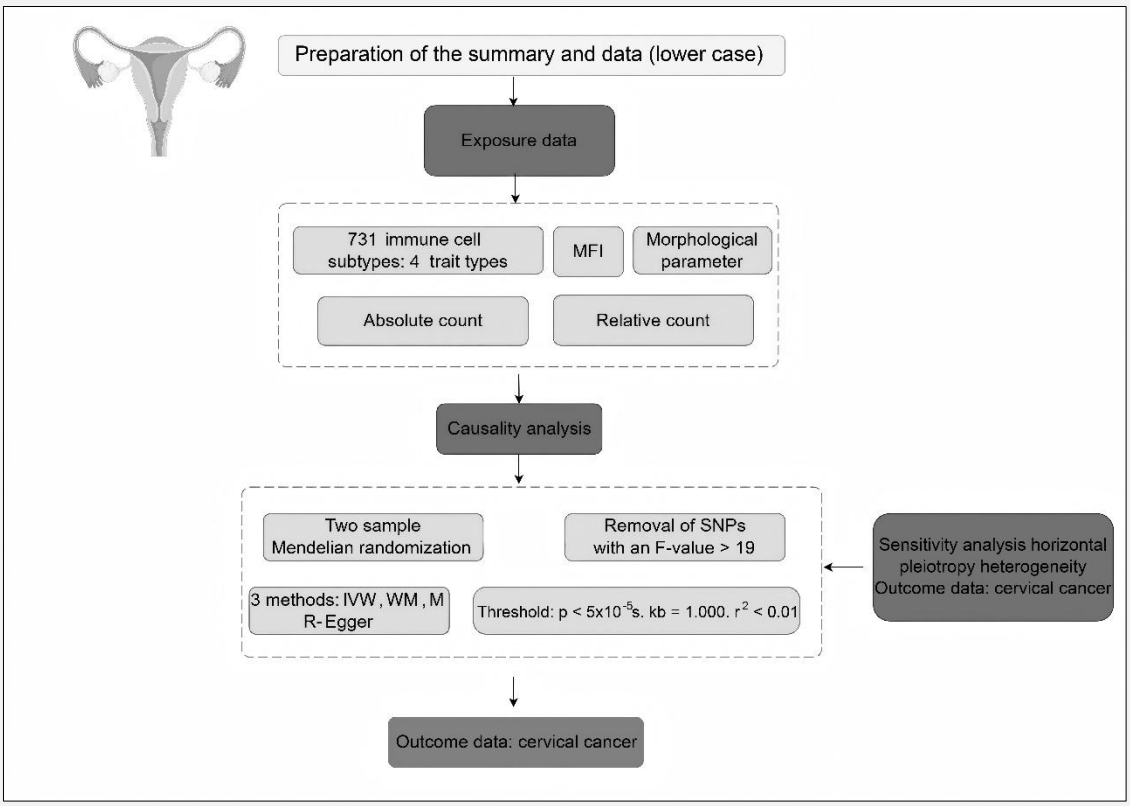
Graphical Abstract



INTRODUCTION

Cervical cancer (CC) is the fourth most common cancer in terms of both incidence and mortality in women, with an estimated 660,000 new cases and 350,000 deaths, according to the global cancer (GLOBOCAN) statistics from the International Agency for Research on Cancer (IARC) in 2022 [1]. It is also the second leading cause of cancer-related mortality in younger women (aged 20 to 39 years) globally [2]. During the period 1990 to 2019, China experienced 1,145,534 fatalities attributable to CC [3], and the situation of CC prevention and control is still not optimistic. Therefore, it is necessary and urgent to seek effective strategies for disease prevention.

Immunotherapy has emerged as one of the promising approaches to enhance treatment outcomes, given that CC is largely linked to persistent human papillomavirus (HPV) infection. Recent advancements in immunotherapy have focused on various strategies, including immune checkpoint inhibitors (ICIs), therapeutic vaccines, and novel combinatorial approaches. For instance, studies have shown that ICIs, like PD-1 or PD-L1 inhibitors, are effective in treating advanced CC [4]. Besides, research of therapeutic vaccines aimed at HPV E6 and E7 antigens is underway, with the potential to enhance cell-mediated immunity and improve patient outcomes [5]. In addition, personalized immunotherapy is prospective by identifying neoantigens derived from tumor-specific mutations and targeting them to further elicit a robust immune response to improve the treatment effectiveness [6]. The integration of biomarker-driven strategies, such as assessing PD-L1 expression and tumor-infiltrating lymphocytes, has also been shown to predict responses to immunotherapy, allowing for more tailored treatment plans [4,7]. Taken together, the results of the studies mentioned above indicate the involvement of immune dysregulation in CC.

However, implementation of immunotherapy still remains challenging for CC, especially in low-resource settings which lack effective disease screening and vaccination programs. Furthermore, ongoing research is essential to understand the mechanisms of immunotherapy resistance and to develop strategies to overcome the barrier to improve the efficacy of these promising therapeutic options [8]. Studying the connection between im-

mune cells and CC will contribute to exploring the immune mechanisms of CC. Currently, there is still limited research on the association between immune cells and the risk of CC in a causal way. Although the majority of studies have characterized immune infiltration in CC, the causal impact of immune cell traits on CC risk has not been well established.

A statistical strategy, named Mendelian randomization (MR), is employed to figure out associations between exposures and health-related outcomes in a causal way [9]. To simulate the conditions of random allocation in randomized controlled traits (RCTs), the MR technique exploits single nucleotide polymorphisms (SNPs) known as genetic variants tightly related to the exposure level as instrumental variables (IVs). This technique enables the inference of causalities free from confounding factors and refrains from reverse causation [10]. Therefore, by using MR restricted to European populations, this study aimed to explore the causalities between different types of immune cells and CC. The results might add evidence on the immune mechanisms of CC.

MATERIALS AND METHODS

Study design

The design of the study was a two-sample MR framework to systematically investigate causations between 731 kinds of immune cells and the risk of CC with the use of genome-wide association studies (GWAS). Three principal presumptions lay the foundation for the validity of Mendelian randomization (Figure 1): 1) Relevance: IVs are tightly linked to the exposure; 2) Independence: IVs are not linked to confounders related to the exposure or outcome; 3) Exclusion restriction: The outcome should be affected by the IVs only through the exposure. We conducted and reported the MR study with the standard of Strengthening the Reporting of Observational Studies in Epidemiology using MR (STROBE-MR) [11,12]. There was no need for ethical clearance or informed consent as they have been disclosed in the primary GWAS.

Data sources

GWAS data of circulating 731 immune cells

This study utilized the GWAS information of 731 immune cells from the research undertaken by Zhao and colleagues, with 3,757 European participants included [13]. In this GWAS, all the 731 immune cells were grouped into seven categories, including B cells, mature T cells, regulatory T cells (Treg cells), monocytes, conventional dendritic cells, myeloid cells, TBNK cells. Specifically, the genetic information could be retrieved in the GWAS Catalog database (ID: GCST90001391-GCST90002121) and the University of Bristol (https://data.bris.ac.uk/data/dataset).

Detailed information on the immune cells is shown in Supplementary Table 1.

GWAS data of CC

A comprehensive investigation of over 1,000,000 individuals yielded summary GWAS data for CC, comprising 909 cases diagnosed with CC and 238,249 controls (ID: ebi-a-GCST90018817) [14]. This study performed GWAS analysis on over 200 phenotypes across distinct races including Europe and East Asia. By meta-analyzing data from the United Kingdom Biobank (UKB) and the FinnGen databases, this GWAS study revealed about 5,000 novel loci. To avoid population heterogeneity, only data derived from European descent was used in our study.

Selection of IVs

The SNPs used as IVs were selected at $p < 5 \times 10^{-5}$ to satisfy the first MR assumption, which requires a significant correlation between SNPs and the immune cell phenotypes [15]. To make sure that the SNPs were independent of each other, we then conducted clumping at linkage disequilibrium (LD) of $r^2 < 0.01$ within the genetic distance of 1,000 kb. Following earlier studies, the R^2 values representing the degree of explanation and F statistics representing the statistical strength for each of the SNPs were computed in the exposure cohort [16]. The formula for calculating r^2 is as follows: $r^2 = 2 \times maf \times (1\text{-}maf) \times beta^2$, where "maf" refers to minor allele frequency and "beta" refers to the GWAS estimate for single SNP exerted on exposures. The formula for the calculation of F-statistics is $F = beta^2/se^2$, where "se" refers to the standard error for the beta value [17].

Statistical analysis

A common reliable MR analysis technique used for our primary study was the inverse variance-weighted (IVW) method [18]. Specifically, the random-effects model of the IVW method was adopted as it balances heterogeneity to some extent. Additionally, we carried out secondary analyses utilizing the Egger regression model [19] and the weighted median approach [20]. Excepting for various MR models utilized, we also performed sensitivity analyses using different methods. We assessed the possible influence of horizontal pleiotropy by examining the MR-Egger regression's intercept value [19]. We also evaluated heterogeneity utilizing Cochran's Q test [21]. At a significance threshold of a two-tailed $\alpha = 0.05$, the MR analysis results were displayed as odds ratios (ORs) with their matching 95% confidence intervals (CIs). The "TwoSampleMR" package was utilized to undertake all MR analyses within the R software (version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Overview of the IVs

After filtering, 18,521 SNPs for 731 immune cells were utilized for the ultimate MR analysis (Supplementary Table 2), with the F-statistics varying from 19.548 to

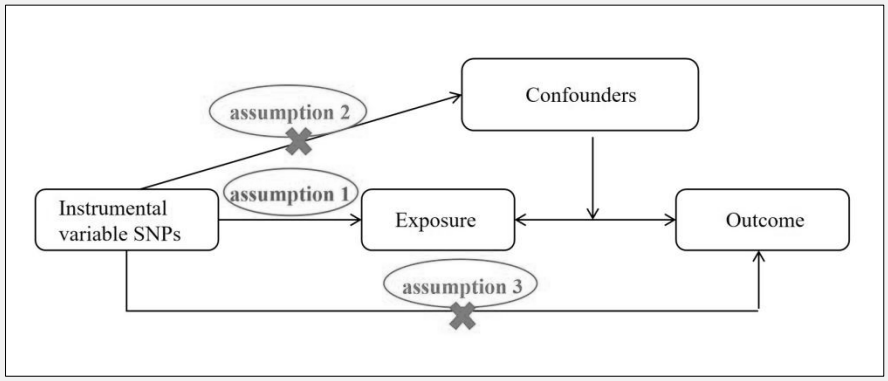


Figure 1. The three key assumptions of MR. MR Mendelian randomization.

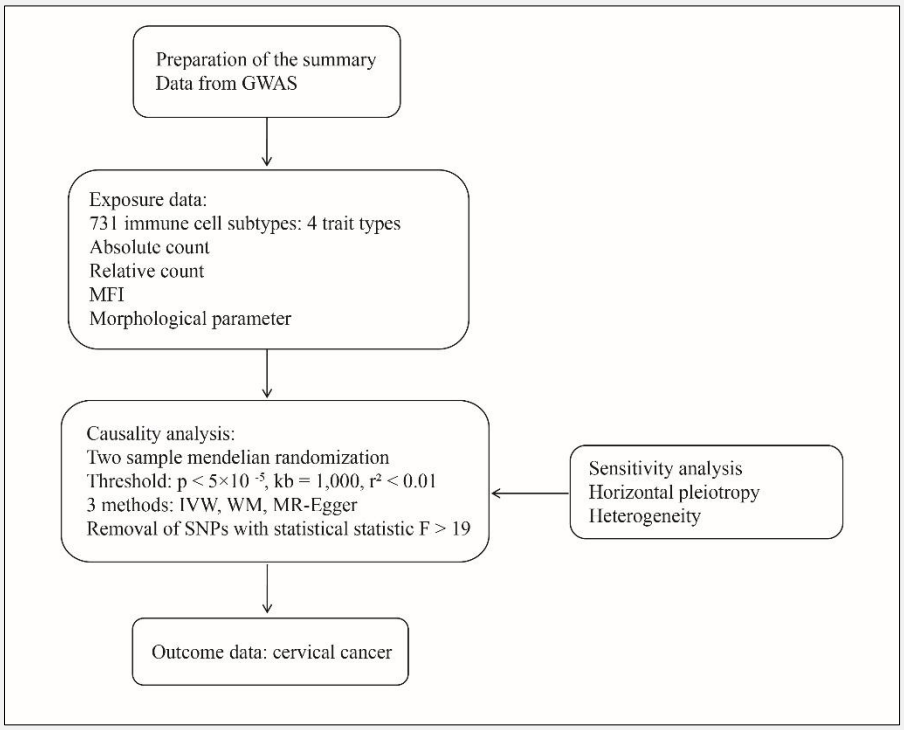


Figure 2. The flowchart graph of our study.

3,161.455, suggesting all the IVs were sufficient in statistical strength. The research design workflow is shown in Figure 2 and all the results are presented in Figure 3 and Supplementary Table 3.

Immune cells and an increased risk of CC

At the significance of $p < 0.05$ for the IVW method, we detected that CD66b on CD66b++ myeloid cell (OR: 1.111, 95% CI: 1.038 - 1.190, p = 0.002), CD39+ acti-

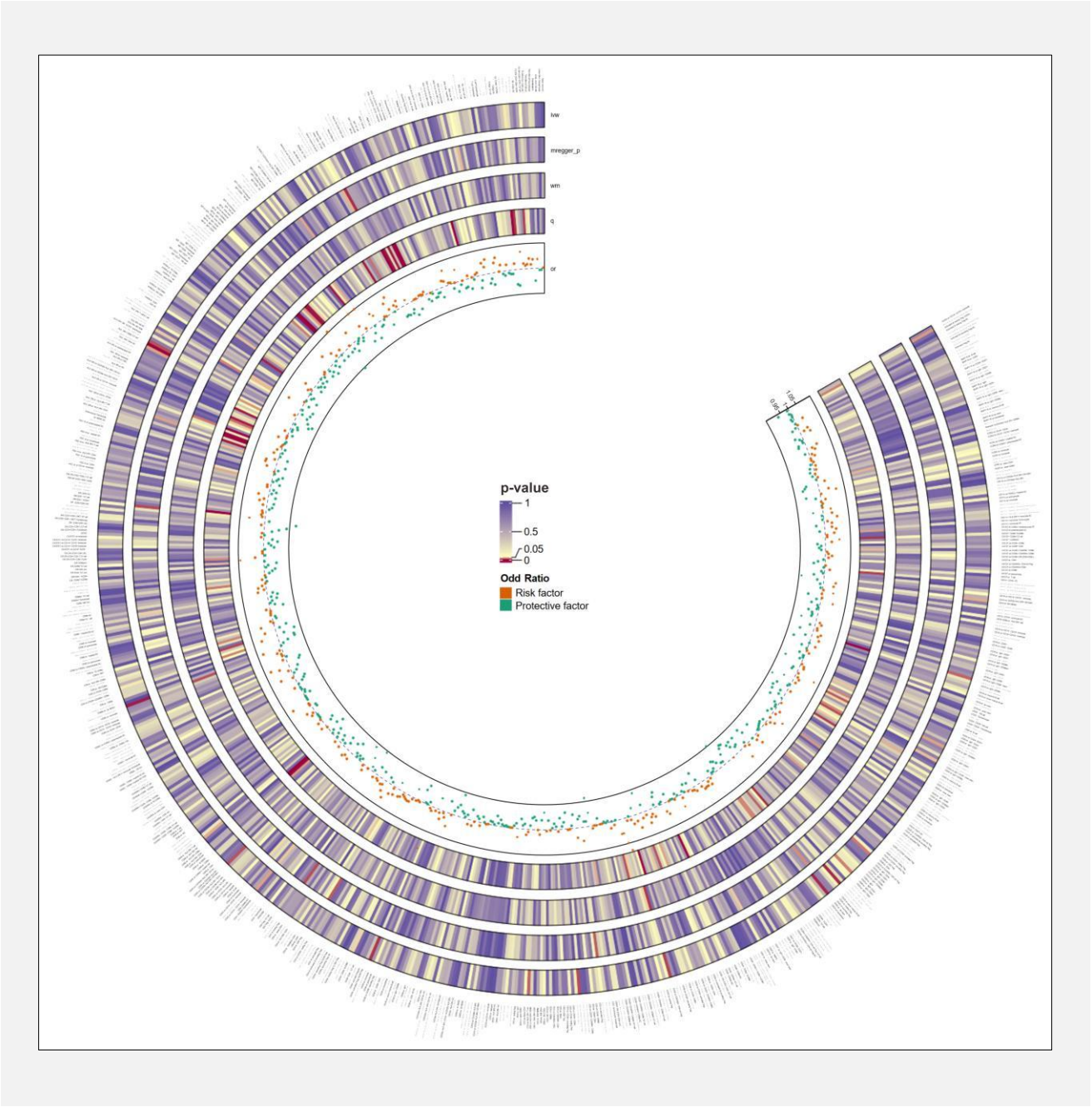


Figure 3. MR analysis results with IVW, MR Egger, and WM methods indicated a causal association between 731 immune cells and CC.

IVW inverse variance weighting, WM weighted median, OR odds ratio.

vated Treg %activated Treg (OR: 1.246, 95% CI: 1.065 - 1.458, p = 0.006), CD28 on CD45RA- CD4 not Treg (OR: 1.182 , 95% CI: 1.043 - 1.340, p = 0.009), CD20 on IgD+ (OR: 1.109, 95% CI: 1.010 - 1.218, p = 0.030), CD14 on Mo MDSC (OR: 1.068, 95% CI: 1.006 - 1.134, p = 0.032), and CD8 on CD28+ CD45RA+ CD8br (OR: 1.095, 95% CI: 1.002 - 1.197, p = 0.045) showed a significant association with an elevated CC risk and MR Egger approach also showed analogous results (Figure 4).

Immune cells and a decreased risk of CC

At the significance of $p < 0.05$ for the IVW method, we detected HLA DR+ CD8br %T cell (OR: 0.893, 95% CI: 0.838 - 0.952, p = 0.0005), CD25 on sw mem (OR: 0.855, 95% CI: 0.768 - 0.952, p = 0.004), CD25 on

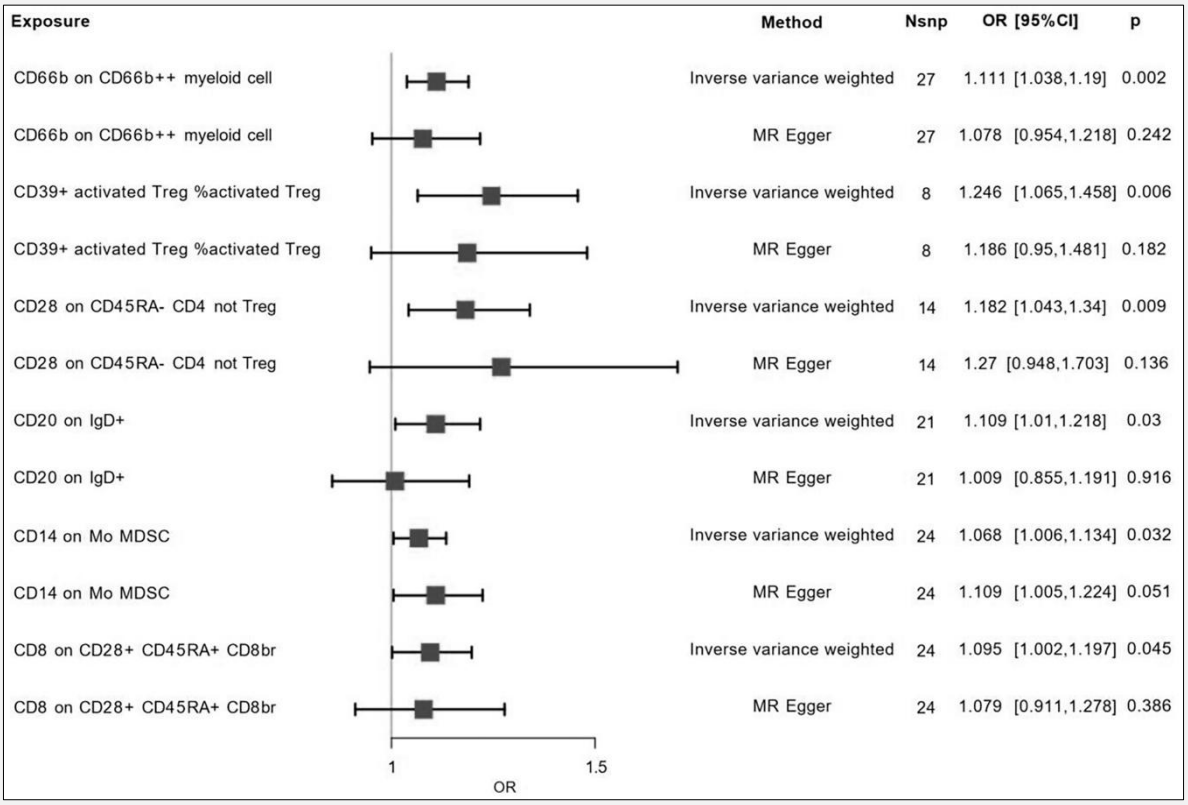


Figure 4. The forest plot demonstrated causal associations between six identified immune phenotypes and the risk of CC incidence with IVW and MR Egger methods.

IgD+ CD38dim (OR: 0.897, 95% CI: 0.832 - 0.966, p = 0.004), CD3 on CD39+ activated Treg (OR: 0.907, 95% CI: 0.842 - 0.978, p = 0.011), HLA DR+ CD8br AC (OR: 0.926, 95% CI: 0.873 - 0.983, p = 0.011), CD45 on CD33br HLA DR+ CD14dim (OR: 0.933, 95% CI: 0.884 - 0.985, p = 0.012), CD3 on HLA DR+ T cell (OR: 0.929, 95% CI: 0.876 - 0.986, p = 0.015), CD19 on IgD+ CD38- unsw mem (OR: 0.923, 95% CI: 0.865 - 0.985, p = 0.016), CD25 on CD45RA+ CD4 not Treg (OR: 0.908, 95% CI: 0.838 - 0.985, p = 0.020), CD25 on IgD+ CD24+ (OR: 0.919, 95% CI: 0.855 - 0.988, p = 0.022), Activated & resting Treg % CD4 Treg (OR: 0.929, 95% CI: 0.870 - 0.992, p = 0.028), CD4+ CD8dim AC (OR: 0.882, 95% CI: 0.789 - 0.987, p = 0.029), HLA DR+ CD8br %lymphocyte (OR: 0.912, 95% CI: 0.839 - 0.991, p = 0.030), CD45 on HLA DR+ T cell (OR: 0.905, 95% CI: 0.826 - 0.992, p = 0.032), CD20 on IgD+ CD38- unsw mem (OR: 0.880, 95% CI: 0.781 - 0.992, p = 0.036), HLA DR+ T cell AC (OR: 0.934, 95% CI: 0.876 - 0.996, p = 0.039), CD39+ CD8br %CD8br (OR: 0.897, 95% CI: 0.809 - 0.996, p = 0.041), TD CD4+ %T cell (OR: 0.911, 95% CI: 0.831 - 0.998, p = 0.045) presented a significant relationship with a reduced CC risk (Figure 5). The MR-Egger regression model and the weighted median model also produced comparable estimates (Supplementary Table 3).

Sensitivity analysis

No evidence of heterogeneity or directional pleiotropy in the relationships of immunophenotypes with CC was detected by the results observed in the Cochran's Q-test of the IVW model and MR-Egger regression, as well as the intercept test results of the Egger regression model. These results are presented in Supplementary Table 4 and Table 5.

DISCUSSION

In this study, we found that in three immune traits (MFI, relative count, and absolute count), a total of 24 immune cell characteristics were causally correlated with CC. Among them, six immune cell phenotypes are

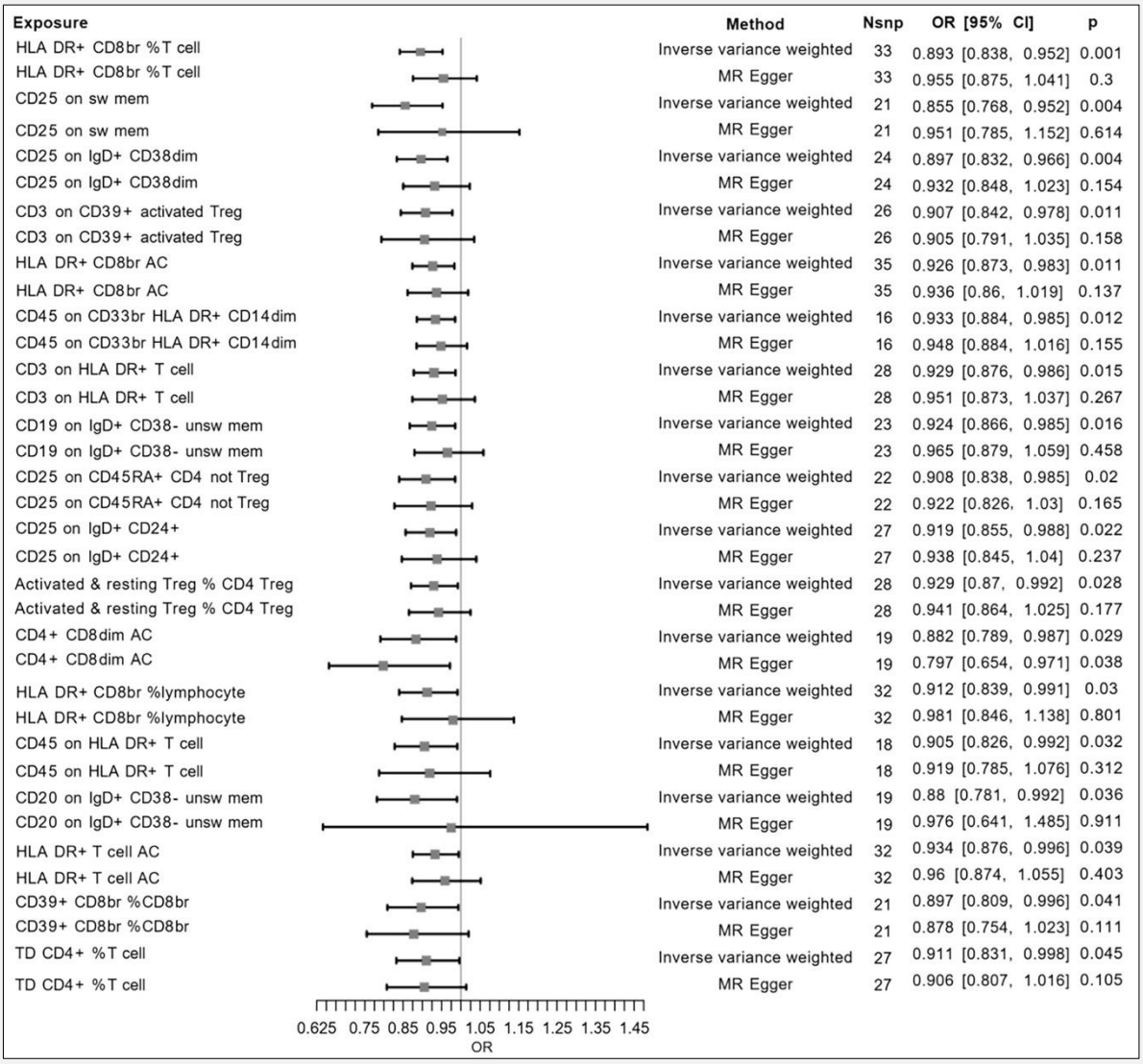


Figure 5. After using the IVW and MR Egger approaches, the forest plot illustrated that eighteen immune phenotypes showed a significant relationship with a reduced CC risk.

confirmed to be related to an elevated risk of CC, and eighteen immune cell characteristics demonstrate protective effects against CC.

It has been reported that in the CC development and progression, circulating immune cells occupy a critical part, especially involved in the immune evasion mechanisms linked with human papillomavirus (HPV) infection. Prior studies have reported that various subsets of immune cells, including natural killer (NK) cells and regulatory T cells (Tregs), are remarkably altered in CC patients, influencing tumor behavior and patient outcomes [22-24].

For Treg cells, CD25 is currently a widely recognized marker [25]. Sakaguchi and colleagues first reported the immunosuppressive and immune-regulatory functions of Treg cells [26]. In regulatory CD4+T cells, CD25 primarily participates in the process of differentiation and proliferation. In Treg cells that simultaneously express CD4 and CD25, CD25 is an essential ingredient of the IL-2 receptor that holds the functions of immunity regulation. Specifically, the structure of IL-2 changes when it binds to the receptor to prepare for formatting the IL2Rα/β/γ and IL-2 tetramer, thereby inducing the downstream reactions, including MAPK, PI3K/Akt/

mTOR, and JAK/STAT5 signaling pathways [27]. Besides, Shang et al. reported that in different types of tumor microenvironments (TME) the Treg cell numbers were elevated and demonstrated a positive association with poor tumor prognosis [28]. Though CD25 is predominantly presented on activated T cells, some B cell subgroups also express it for distinct functions. The expression of CD25 marks that B cells have been stimulated and activated to produce IL-2 or other particular antibodies. In addition, the activated B cells in TME play an anti-cancer role by facilitating M1 polarization of macrophages and recruitment of effector T cells [29]. Our MR analysis showed a negative correlation between CD25 on sw mem, CD25 on IgD+ CD38dim, and CD25 on IgD+ CD24+, and the CC risk. However, detailed mechanisms for the anti-cancer efficacy of CD25-marked B cells remain blank. Therefore, the observed results in the current research furnish a theoretical foundation for future investigations.

HLA-DR is predominantly expressed on antigen-presenting cells like macrophages, B cells, and dendritic cells. It pertains to the class II major histocompatibility complex (MHC II) and is a part of the human leukocyte antigen system. The HLA-DR molecules are involved in immune response with the critical feature of presenting the T cells with antigenic peptide fragments [30]. The association between HLA-DR and CC has been the subject of extensive research. Several studies have identified specific HLA-DR alleles that contribute to the development of CC, particularly in populations with varying genetic backgrounds. For instance, a meta-analysis concluded that certain HLA-DRB1 haplotypes are significantly related to CC risk in Chinese. Moreover, a systematic investigation of the HLA-DP region also revealed associations with CC susceptibility, suggesting that HLA-DP polymorphisms might contribute to the pathogenesis of this disease [31]. In addition, HLA-DR also influences the effectiveness of immune surveillance against tumor cells in TME [32]. The above-mentioned contents suggest HLA-DR as a biomarker for predicting CC progression and response to therapies. Our work further suggests an impeding impact of HLA-DR on CC development by targeting the TBNK panel. In the conditions of chronic inflammation, the expression of HLA-DR on monocytes was decreased, indicating its potential for immunosuppression that enhances the current results [33].

In immune response, TBNK (T cell, B cell, and Natural Killer cell) cells play a crucial part, and their interaction with tumor cells can significantly influence cancer development and progression. Prior research showed that the activity of TBNK cells in TME can influence the behavior of CC cells, particularly if they are infected by human papillomavirus (HPV). The capabilities of T cells depend on the molecules expressed in them. In detail, CD4+T cells mainly participate in generating cytokines, whereas the CD8+T cell subset directly eradicates target cells. To this end, increased CD4+CD8+T cell levels are expected to hinder tumor development and exacerbation. This is in line with the results of the current study. In addition, B cells play an intricate role in the development and progression of CC. Specifically, B cells influence both tumor immunity and TME with their capabilities to produce cytokines, interact with Tregs, and function as antigen-presenting cells, which underscores their potential as targets for tumor immunotherapy. Understanding the dual roles of B cells in CC would help facilitate novel strategies for enhancing anti-tumor immunity to achieve more favorable outcomes for patients.

Our findings indicate that CD39+ activated Treg % activated Treg augments the risk of CC, whereas the CD3 on CD39+ activated Treg phenotype manifests a prevention efficacy. The two kinds of immune cells presented divergent impacts though they belong to the same cellular subgroup, which we consider to be attributed to distinct markers on the cells. In patients with CC, expression of CD3 might afford a protective role as it engages in signaling pathways and mediates the response to inflammation. This observation aligns with results from recent explorations showing improved overall survival in patients diagnosed with CC benefiting from a higher density of CD3+ tumor-infiltrating lymphocytes (TILs) [34]. This suggests that CD3+ T cell infiltration might be a hallmark of activated immune response which consequently protects against tumor progression. Besides, the reduction of CD3+ T cells might also partially contribute to the immune evasion mechanisms in which Tregs suppress the activity of effector T cells including those expressing CD3 [35]. In addition, a study reported that closer distance between CD3+ cell and PD-L1+ tumor cell might enhance the effectiveness of ICIs in CC treatment [36]. In line with the existing literature, the current findings enhance evidence for promising therapeutic strategies focusing on the modulation of CD3+ T cell responses to improve anti-tumor immunity in CC patients.

We noticed in our MR analysis that CD20 on IgD+ exerted a detrimental impact, while CD20 on IgD+ CD38-unsw mem displayed a protective effect. CD38 is expressed on various immune cells including TBNK cells, and is involved in the activation and regulation of immune responses [37]. It is a glycoprotein serving as an enzyme and receptor that plays a critical role in various cellular processes containing calcium influx regulation, cell signaling, immune response, and so on. Its role in the cancer biology, especially in CC, is complicated and multifaceted. Studies have shown that the immune microenvironment in tumors could be influenced by CD38. For instance, the high level of CD38 in TME has been linked to immunosuppressive conditions, which might promote tumor progression by impeding efficient anti-tumor immunity [38]. Deshpande et al. also observed that the presence of CD38+ immune cells in TME was correlated with a poor prognosis in patients with CC, and the immune evasion mechanism is the possible explanation [39]. Moreover, Liao and colleagues have demonstrated CD38 promoted the proliferation and in-

hibited the apoptosis of cervical cancer cells through affecting the mitochondria functions [40].

Taken together, these results are concordant with our results showing that CD38-negative immune cells predicted a lower risk of CC. Notably, recent research has also emphasized the potential of targeting CD38 for cancer immunotherapy. Specifically, inhibitors of CD38 are now being studied for their ability to enhance anti-tumor immunity and improve therapeutic outcomes in various cancers, including CC [41].

The study has several limitations. First, the results reported in this work mainly come from genetic data of European populations, which might limit their generalizability to other ethnic groups. Thereby, the scope of cases and populations covered should be expanded to verify the generalizability of the conclusions in future studies. Second, owing to the data availability, stratified analyses were unable to be conducted, potentially neglecting variations in different gender or age subgroups. Finally, while the two-sample MR design would help a lot in addressing the issue of causation [42], the underlying biological mechanisms should be taken into consideration when interpreting MR results. To this end, the substantial causal relationships between immune features and CC require further triangulation validations in cell lines, animal models, and clinical trials.

In conclusion, this Mendelian randomization study demonstrated causal associations between immune cells and CC, underscoring the intricate interactions of the immune system with CC. The results also provide insights into the mechanisms of CC development attributed to immunological regulation and highlight potential therapeutic targets for improving immune responses in patients with CC.

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Availability of Data and Materials:
The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate:
According to the guidance received from our research ethics board, no ethics review is required for studies utilizing public data sets.

Declaration of Interest:
The authors have no conflicts of interest to declare.

References:

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024; 74(3):229-63. (PMID: 38572751)

2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin 2022;72(1):7-33. (PMID: 35020204)

3. Wang Z, Guo E, Yang B, et al. Trends and age-period-cohort effects on mortality of the three major gynecologic cancers in China from 1990 to 2019: Cervical, ovarian and uterine cancer. Gynecol Oncol 2021;163(2):358-63. (PMID: 34507827)

4. D'Alessandris N, Palaia I, Pernazza A, et al. PD-L1 expression is associated with tumor infiltrating lymphocytes that predict response to NACT in squamous cell cervical cancer. Virchows Arch 2021;478(3):517-25. (PMID: 32915266)

5. Dyer BA, Zamarin D, Eskandar RN, Mayadev JM. Role of Immunotherapy in the Management of Locally Advanced and Recurrent/Metastatic Cervical Cancer. J Natl Compr Canc Netw 2019;17(1):91-7. (PMID: 30659133)

6. Bao C, An N, Xie H, et al. Identifying Potential Neoantigens for Cervical Cancer Immunotherapy Using Comprehensive Genomic Variation Profiling of Cervical Intraepithelial Neoplasia and Cervical Cancer. Front Oncol 2021;11:672386. (PMID: 34221990)

7. Ping Q, Chen Q, Li N. Identification of m(6)A-related lncRNAs prognostic signature for predicting immunotherapy response in cervical cancer. SLAS Technol 2024;29(6):100210. (PMID: 39490531)

8. Ge Y, Zhang Y, Zhao KN, Zhu H. Emerging Therapeutic Strategies of Different Immunotherapy Approaches Combined with PD-1/PD-L1 Blockade in Cervical Cancer. Drug Des Devel Ther 2022;16:3055-70. (PMID: 36110399)

9. Sanderson E. Multivariable Mendelian Randomization and Mediation. Cold Spring Harb Perspect Med 2021;11(2):a038984. (PMID: 32341063)

10. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. Hum Mol Genet 2014;23(R1):R89-98. (PMID: 25064373)

11. Skrivankova VW, Richmond RC, Woolf BAR, et al. Strengthening the reporting of observational studies in epidemiology using mendelian randomisation (STROBE-MR): explanation and elaboration. BMJ 2021;375:n2233. (PMID: 34702754)

12. Au Yeung SL, Gill D. Standardizing the reporting of Mendelian randomization studies. BMC Med 2023 May 18;21(1):187. (PMID: 37198682)

13. Zhao JH, Stacey D, Eriksson N, et al. Genetics of circulating inflammatory proteins identifies drivers of immune-mediated disease risk and therapeutic targets. Nat Immunol 2023;24(9):1540-51. (PMID: 37563310)

14. Sakaue S, Kanai M, Tanigawa Y, et al. A cross-population atlas of genetic associations for 220 human phenotypes. Nat Genet 2021;53(10):1415-24. (PMID: 34594039)

15. Wu K, Luo Q, Liu Y, Li A, Xia D, Sun X. Causal relationship between gut microbiota and gastrointestinal diseases: a mendelian randomization study. J Transl Med 2024 Jan 23;22(1):92. (PMID: 38263233)

16. Chen L, Peters JE, Prins B, et al. Systematic Mendelian randomization using the human plasma proteome to discover potential therapeutic targets for stroke. Nat Commun 2022;13(1):6143. (PMID: 36253349)

17. Bowden J, Holmes MV. Meta-analysis and Mendelian randomization: A review. Res Synth Methods 2019;10(4):486-96. (PMID: 30861319)

18. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. Genet Epidemiol 2016;40(4):304-14. (PMID: 27061298)

19. Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. Eur J Epidemiol 2017;32(5):377-89. (PMID: 28527048)

20. Kulinskaya E, Dollinger MB. An accurate test for homogeneity of odds ratios based on Cochran's Q-statistic. BMC Med Res Methodol 2015;15:49. (PMID: 26054650)

21. Hemani G, Zheng J, Elsworth B, et al. The MR-Base platform supports systematic causal inference across the human phenome. Elife 2018;7:e34408. (PMID: 29846171)

22. Heeren AM, Kenter GG, Jordanova ES, de Gruijl TD. CD14(+) macrophage-like cells as the linchpin of cervical cancer perpetrated immune suppression and early metastatic spread: A new therapeutic lead? Oncoimmunology 2015;4(6):e1009296. (PMID: 26155430)

23. Zou R, Gu R, Yu X, et al. Characteristics of Infiltrating Immune Cells and a Predictive Immune Model for Cervical Cancer. J Cancer 2021;12(12):3501-14. (PMID: 33995627)

24. Liang Y, Lü B, Zhao P, Lü W. Increased circulating GrMyeloid-derived suppressor cells correlated with tumor burden and survival in locally advanced cervical cancer patient. J Cancer 2019; 10(6):1341-8. (PMID: 31031843)

25. Flynn MJ, Hartley JA. The emerging role of anti-CD25 directed therapies as both immune modulators and targeted agents in cancer. Br J Haematol 2017;179(1):20-35. (PMID: 28556984)

26. Sakaguchi S, Sakaguchi N, Asano M, Itoh M, Toda M. Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. J Immunol 1995;155(3):1151-64. (PMID: 7636184)

27. Wang X, Rickert M, Garcia KC. Structure of the quaternary complex of interleukin-2 with its alpha, beta, and gammac receptors. Science 2005;310(5751):1159-63. (PMID: 16293754)

28. Shang B, Liu Y, Jiang SJ, Liu Y. Prognostic value of tumor-infiltrating FoxP3+ regulatory T cells in cancers: a systematic review and meta-analysis. Sci Rep 2015;5:15179. (PMID: 26462617)

29. Jiang T, Zhou C, Ren S. Role of IL-2 in cancer immunotherapy. Oncoimmunology 2016;5(6):e1163462. (PMID: 27471638)

30. Newman AM, Steen CB, Liu CL, et al. Determining cell type abundance and expression from bulk tissues with digital cytometry. Nat Biotechnol 2019;37(7):773-82. (PMID: 31061481)

31. Chen D, Gyllensten U. Systematic investigation of contribution of genetic variation in the HLA-DP region to cervical cancer susceptibility. Carcinogenesis 2014;35(8):1765-9. (PMID: 24743517)

32. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71(3): 209-49. (PMID: 33538338)

33. Wang C, Zhu D, Zhang D, et al. Causal role of immune cells in schizophrenia: Mendelian randomization (MR) study. BMC Psychiatry 2023;23(1):590. (PMID: 37582716)

34. Shah W, Yan X, Jing L, Zhou Y, Chen H, Wang Y. A reversed CD4/CD8 ratio of tumor-infiltrating lymphocytes and a high percentage of CD4(+)FOXP3(+) regulatory T cells are significantly associated with clinical outcome in squamous cell carcinoma of the cervix. Cell Mol Immunol 2011;8(1):59-66. (PMID: 21200385)

35. Zhang Y, Li J, Yang F, Zhang X, Ren X, Wei F. Relationship and prognostic significance of IL-33, PD-1/PD-L1, and tertiary lymphoid structures in cervical cancer. J Leukoc Biol 2022;112(6): 1591-603. (PMID: 35501298)

36. Rodrigues M, Vanoni G, Loap P, et al. Nivolumab plus chemoradiotherapy in locally-advanced cervical cancer: the NICOL phase 1 trial. Nat Commun 2023;14(1):3698. (PMID: 37349318)

37. Henderson SA, Tetzlaff MT, Pattanaprichakul P, et al. Detection of mitotic figures and G2+ tumor nuclei with histone markers correlates with worse overall survival in patients with Merkel cell carcinoma. J Cutan Pathol 2014;41(11):846-52. (PMID: 25263506)

38. Shen-Gunther J, Wang CM, Poage GM, et al. Molecular Pap smear: HPV genotype and DNA methylation of ADCY8, CDH8, and ZNF582 as an integrated biomarker for high-grade cervical cytology. Clin Epigenetics 2016;8(1):96. (PMID: 27651839)

39. Matsuo K, Huang Y, Matsuzaki S, et al. Association between hysterectomy wait-time and all-cause mortality for micro-invasive cervical cancer: treatment implications during the coronavirus pandemic. Arch Gynecol Obstet 2022;306(1):283-7. (PMID: 34302197)

40. Liao S, Xiao S, Chen H, et al. CD38 enhances the proliferation and inhibits the apoptosis of cervical cancer cells by affecting the mitochondria functions. Mol Carcinog 2017;56(10):2245-57. (PMID: 28544069)

41. Ouh YT, Park JJ, Kang M, et al. Discrepancy between Cytology and Histology in Cervical Cancer Screening: a Multicenter Retrospective Study (KGOG 1040). J Korean Med Sci 2021;36(24): e164. (PMID: 34155836)

42. Neto EC, Keller MP, Attie AD, Yandell BS. Causal graphical models in systems genetics: a unified framework for joint inference of causal network and genetic architecture for correlated phenotypes. Ann Appl Stat 2010;4(1):320-39. (PMID: 21218138)

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