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Causal relationship between inflammatory factors and gynecological cancer: a Bayesian Mendelian randomization study

Chunxiao Dang[1], Mengmeng Liu[2], Pengfei Liu[1], Jinxing Liu[1], Xiao Yu[3], Yan Dong[4]✉ & Junde Zhao[5]✉

Background: Cervical cancer, ovarian cancer, and endometrial cancer are the three most common cancers in gynecology. Understanding their respective pathology is currently incomplete. Inflammatory factors play an important role in the pathophysiology of these three cancers, but the causal relationship between inflammatory factors and these three cancers is unclear. Methods: Based on publicly available genetic databases, relevant instrumental variables were extracted according to predefined thresholds, and causal analyses of CRP, 41 circulating inflammatory factors, and three gynecological cancers were performed, mainly using the inverse variance weighted method, while bayesian analysis was performed to improve the accuracy of the results. Finally, heterogeneity, horizontal pleiotropy test, and MR Steiger test were carried out to evaluate the reliability of the findings and the causal inference strength. Results: One inflammatory factor (PDGF-BB) and four inflammatory factors (CXCL9, IL-6, CXCL1, and G-CSF) were identified as significantly associated with the risk of ovarian and endometrial cancers, respectively. In comparison, cervical cancer was found to have a negative causal association with one inflammatory factor (G-CSF) and endometrial cancer with two inflammatory factors (CXCL10 and CCL11). Conclusions: Our MR study suggests potential causal relationships between circulating inflammatory regulators and three gynecological cancers from a genetic perspective, which contributes to further understanding of the pathomechanisms of cervical, ovarian and endometrial cancers and highlights the potential of targeting inflammatory factors as therapeutic interventions and predictors

Keywords Circulating inflammatory factors, Cervical cancer, Ovarian cancer, Endometrial cancer, Mendelian randomization

Abbreviations

MR	Mendelian randomization
CC	Cervical cancer
OC	Ovarian cancer
EC	Endometrial cancer
CRP	C-reactive protein
SNP	Single nucleotide polymorphism
IVs	Instrumental variables
GWAS	Genome wide association study
LD	Linkage disequilibrium
IVW	Inverse variance weighted
WME	Weighted median

[1]First Clinical Medical College, Shandong University of Traditional Chinese Medicine, Jinan 250014, China. [2]Dongying People's Hospital (Dongying Hospital of Shandong Provincial Hospital Group), Dongying 257000, China. [3]Department of Gynecology, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan 250014, China. [4]Department of Obstetrics and Gynecology, The Second Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jingba Road No. 1, Jinan 250014, China. [5]Shandong University of Traditional Chinese Medicine, Jingshi Road No. 16369, Jinan 250014, China. ✉email: dongyanfuke@163.com; zhaojunde2020@163.com

WM	Weighted mode
SM	Simple mode
LOO	Leave-one-out
G-CSF	Granulocyte colony-stimulating factor
PDG-BB	Platelet-derived growth factor-BB

Gynecological malignancies are the leading cause of cancer-related deaths in women globally, posing a serious threat to women's health, with approximately 190,000 new diagnoses of cancer and approximately 30,000 deaths from cancer globally, according to the GLOBOCAN 2020 report[1]. Gynecological cancers mainly include cervical, uterine, ovarian, vaginal, and vulvar cancers, among which cervical cancer (CC), endometrial cancer (EC), and ovarian cancer (OC), as the most predominant types of gynecological cancers, are at a high level of morbidity and mortality and have continued to rise over the past decades[1,2].

The link between inflammation and cancer development has attracted considerable interest over the past decades[3]. A growing body of evidence suggests that the activation of inflammation plays a crucial role in the development of cancer, and is closely associated with angiogenesis, proliferation, lymphovascular infiltration, and metastasis[4,5]. Recent studies support the theory that inflammation plays a role in the development and progression of many solid and gynecological tumors[6–8], such as impaired T-lymphocyte function in ovarian cancer patients, elevated levels of IL-6, exacerbation of inflammatory response, inhibition of the body's immune regulatory function along with the high expression of TNF-α, decreased immune levels. In addition, systemic inflammatory biomarkers such as the Systemic Immunoinflammatory Index (SII) have been shown to correlate with the prognosis of cervical and endometrial cancers, among others. However, these studies examined a limited selection of inflammatory factors (IFs) and overlooked the role of other physiological influences. Consequently, it is still unclear whether alterations in inflammatory factors directly contribute to cancer development or if cancer arises from microenvironmental changes that subsequently modify these inflammatory factors. Given the recurrent nature of gynecological cancers and the lack of reliable clinical predictors, it is clinically important to inquire into the exact nature of the interaction between IFs and the three major gynecological cancers.

Mendelian randomization (MR) is a technique that uses single nucleotide polymorphism (SNP) as an instrumental variable (IV) as an alternative to observational studies to mitigate the effects of confounders and bias, thus providing strong evidence of causality[9]. Therefore, we used a two-sample bidirectional Mendelian randomization method to explore the causal associations between C-reactive protein (CRP), IFs, and gynecological cancers to provide fresh perspectives on strategies for treating and preventing gynecological cancers.

Materials and methods

Research design

The bidirectional MR study design is illustrated in Fig. 1, and the MR analysis follows three fundamental assumptions[10]: (1) IVs are closely related to exposure variables. (2) IVs are independent of confounders. (3) IVs affect the outcome solely through their impact on exposure. This study used summary-level data from 41 established genome-wide association studies (GWAS) on circulating inflammatory regulators, CRP, cervical, ovarian, and endometrial cancers. First, we performed causal analyses with CRP and IFs as exposure variables and gynecological cancers as outcomes, followed by reverse causality analyses in which the exposure variables were interchanged with the outcomes.

Data source

Pooled statistics for cervical cancer (N_{case} = 909, $N_{control}$ = 238249), ovarian cancer (N_{case} = 1588, $N_{control}$ = 244932), and endometrial cancer (N_{case} = 2188, $N_{control}$ = 237839) were obtained from a study by Sakaue S et al.[11]. Pooled data for CRPs from two genome-wide association studies (i.e., HapMap and 1000 Genomes interpolated data), which contained data from 88 studies (204,402 European individuals) were included[12]. SNPs for 41 IFs were obtained from the study by Ahola-Olli AV et al.[13], which contained data from the Young Finns Study (YFS) and the "FINRISK" studies (FINRISK1997 and FINRISK2002), which included 8,293 Finnish participants. Univariate associations of 41 moderator concentrations with 10.7 million genetic polymorphisms were performed by adjusting for age, sex, body mass index, and the first 10 genetic principal components. There were no overlapping cohorts and all were of European descent.

Instrumental variable selection

(1) IVs selection: To achieve high accuracy, the IVs of CRP were screened by $P < 5 \times 10^{-8}$, and the IVs of IFs were screened by $P < 5 \times 10^{-6}$ according to a previous study[14]. In the reverse analysis, the IVs of cervical, ovarian, and endometrial cancers were screened by $P < 5 \times 10^{-8}$ because there were relatively fewer SNPs at the $P < 5 \times 10^{-8}$ level. (2) Independence criterion: The linkage disequilibrium (LD) among SNPs for each risk factor was assessed using PLINK clustering. SNPs with LD coefficient r^2 greater than 0.001 and located within a physical distance of less than 10,000 kb were excluded. This step ensured the mutual independence of SNPs to eliminate the influence of genetic pleiotropy on outcomes[15]. (3) Statistical strength criterion: The efficacy of IVs was assessed using the F-statistic, excluding weak IVs with $F < 10$[16]. Additionally, SNPs associated with confounding factors or correlated with outcomes were excluded using the PhenoScanner database (http://www.phenoscanner.medschl.cam.ac.uk/).

Mendelian randomization analysis

The inverse variance weighted (IVW) method[17] served as the primary analytical approach for assessing causality, as it provides the most accurate results when heterogeneity and horizontal pleiotropy are absent. Additionally, we

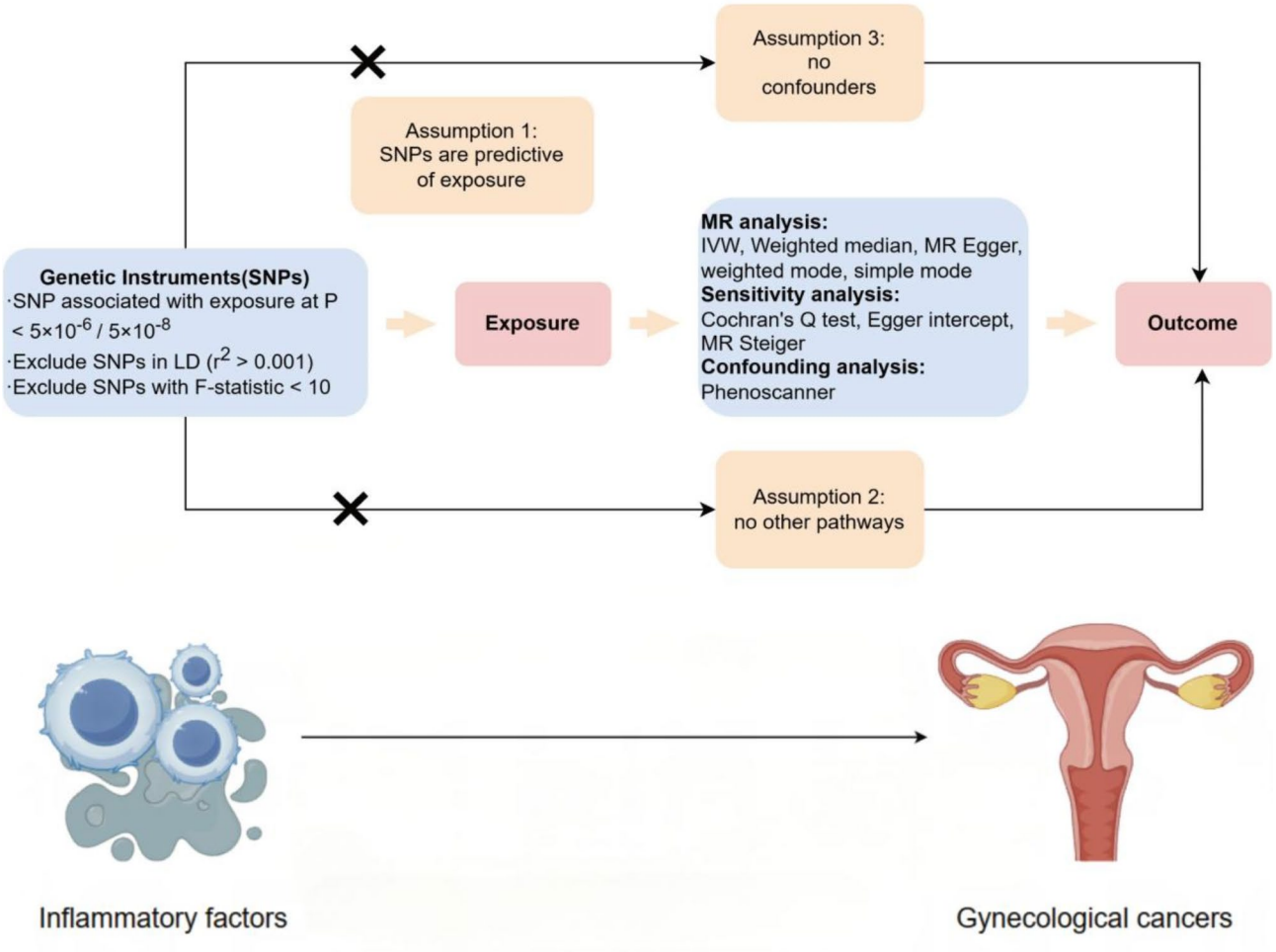

Fig. 1. Flowchart of IVs screening for MR method analysis.

employed several supplementary methods, such as MR-Egger regression, weighted median (WME), simple mode (SM), and weighted mode (WM), to estimate causality under varying conditions. Heterogeneity was assessed using Cochran's Q test, and if heterogeneity was present ($P<0.05$), potential outliers were evaluated using the MR pleiotropy residual sum and outlier (MR-PRESSO) test[18], eliminated, and re-analyzed. Horizontal pleiotropy was detected using the MR-Egger intercept, and the absence of horizontal polytropy ($P>0.05$) indicates that the results of MR analyses are reliable[19]. Multiple corrections using the Bonferroni method ($p<0.0012$, Bonferroni corrected for 41 tests) showed suggestive associations that were significant before multiple corrections ($p<0.05$) but not after multiple corrections ($p>0.0012$), which can be used as a preliminary clue and require further validation[20]. To confirm the stability of effect sizes and eliminate specific SNPs that could affect causal effects, the MR Steiger test was employed to evaluate the directionality of causality. Additionally, a "leave-one-out" (LOO) analysis was conducted as part of the sensitivity analysis to determine the robustness of the results. To improve the accuracy of the results, we performed a Robust Bayesian analysis of the MR results using the RBMR package (https://github.com/AnqiWang2021/RBMR)[21].

Results

Causal relationship between CRP, IFs and gynecological cancer

Before MR analysis, we identified the null variants rs4420638, rs4129267, rs2794520, rs7310409, rs6601302 using PhenoScanner, which are all associated with cholesterol, triglycerides, etc. Cholesterol and triglycerides, as precursors of steroid hormone synthesis, increase the risk of BC, EC, and are therefore excluded[22–24]. Among them, rs4129267 and rs2794520 are associated with inflammatory factors such as IL-6, which promotes the proliferation and migration of ovarian cancer cells[25]. After the selection and coordination of IVs, a total of 49 to 54 SNPs were identified for CRP analysis and 3 to 17 SNPs for the analysis of IFs, with F-statistics ranging from 20.695 to 2408.850, and the results of the major MR analyses of 41 IFs are shown in Supplementary Excel 1.

Using the results of IVW analysis as the primary reference index, it was found that CRP did not have a causal association with cervical cancer (OR = 0.950, 95% CI 0.773–1.168, $P=0.625$), ovarian cancer (OR = 1.114, 95% CI 0.856–1.449, $P=0.422$) and endometrial cancer (OR = 1.067, 95% CI 0.930–1.224, $P=0.357$) and none of these were causally associated. For ovarian cancer, higher blood PDGF-BB (OR = 0.811, 95% CI 0.703–0.934,

IFs	nSNP	OR(95% CI)	Pval	$Pval_{RBMR}$
PDGF-BB	13	0.811(0.703–0.934)	0.004	0.004
CXCL9	14	0.873(0.765–0.997)	0.045	0.020
IL6	5	1.374(1.054–1.791)	0.019	0.025
CXCL1	10	0.923(0.855–0.997)	0.041	0.048
G-CSF	8	0.800(0.642–0.998)	0.048	0.038

Table 1. MR analyses of PDGF-BB in ovarian cancer, and CXCL9, CXCL1, G-CSF, and IL-6 in endometrial cancer.

IFs	nSNP	OR(95% CI)	Pval	$Pval_{RBMR}$
G-CSF	15	0.956(0.915–0.998)	0.040	0.036
CXCL10	12	0.892(0.814–0.979)	0.016	0.020
CCL11	13	0.926(0.870–0.987)	0.018	0.018

Table 2. Results of reverse MR analysis of cervical cancer to G-CSF and endometrial cancer to CXCL10 and CCL11.

$P=0.004$, $P_{RBMR}=0.004$) levels were negatively associated with ovarian cancer, with each increase in the level of PDGF-BB being associated with a reduction in the risk of ovarian cancer by approximately 19%. The weighted median (OR = 0.796, 95% CI 0.667–0.949, $P=0.011$) and weighted mode (OR = 0.797, 95% CI 0.667–0.953, $P=0.029$) provided similar results. In endometrial cancer, higher blood CXCL9 (OR = 0.873, 95% CI 0.765–0.997, $P=0.045$, $P_{RBMR}=0.020$), CXCL1 (OR = 0.923, 95% CI 0.855–0.997, $P=0.041$, $P_{RBMR}=0.048$), and G-CSF (OR = 0.800, 95% CI 0.642–0.998, $P=0.048$, $P_{RBMR}=0.038$) levels were negatively associated with the risk of endometrial cancer. The risk of endometrial cancer decreased by approximately 13%, 8%, and 20% for each increase in the levels of CXCL9, CXCL1, and G-CSF, respectively. In addition, blood IL-6 (OR = 1.374, 95% CI 1.054–1.791, $P=0.019$, $P_{RBMR}=0.025$) levels were positively correlated with the risk of endometrial cancer, with the risk of endometrial cancer increasing by approximately 37% for each increase in IL-6 levels, and similar results were provided by MR-Egger regression (OR = 0.650, 95% CI 0.464–0.911, $P=0.047$). Detailed information is provided in Table 1, and full MR analysis results are provided in Supplementary Excels 2 and 3.

The results of the sensitivity analysis and directionality test are shown in Supplementary Excel 4. Cochran's Q test indicated an absence of heterogeneity among the SNPs. The pleiotropy assessment revealed that the intercepts of the MR-Egger regression terms were all below 0.05, with p-values exceeding 0.05, suggesting no presence of horizontal pleiotropy and confirming that causality was in the anticipated direction. Furthermore, the LOO analyses demonstrated the robustness of the results, as illustrated in Supplementary Fig. 1.

Reverse-direction MR analyses

Three gynecological cancers were used as exposure factors, and CRP and 41 IFs were used as outcome variables for inverse MR analysis. A total of 3–5 SNPs were identified for CRP analysis and 7–16 SNPs for the analysis of IFs, with F-statistics ranging from 20.870 to 49.381. The results of the primary MR analyses of the 41 IFs are shown in Supplementary Excel 5.

IVW analysis showed that cervical cancer (OR = 1.012, 95% CI 0.983–1.043, $P=0.419$), ovarian cancer (OR = 0.969, 95% CI 0.912–1.030, $P=0.316$) and endometrial cancer (OR = 0.988, 95% CI 0.944–1.034, $P=0.607$) had no causal relationship with CRP. Cervical cancer had a negative causal association with G-CSF (OR = 0.956, 95% CI 0.915–0.998, $P=0.040$, $P_{RBMR}=0.036$), while endometrial cancer had a negative causal relationship with CXCL10 (OR = 0.892, 95% CI 0.814–0.979, $P=0.016$, $P_{RBMR}=0.020$), and CCL11 (OR = 0.926, 95% CI 0.870–0.987, $P=0.018$, $P_{RBMR}=0.018$). Cervical and endometrial cancers resulted in decreased levels of the above IFs, as shown in Table 2. The full MR analysis results are provided in Supplementary Excels 6 and 7. Sensitivity analyses showed p-values greater than 0.05 for the Cochran Q test and the MR Egger intercept test, indicating the absence of heterogeneity and horizontal pleiotropy. LOO analyses showed robust results (Supplementary Excel 8, Supplementary Fig. 2).

Discussion

Main findings and interpretation

Based on a large amount of publicly available genetic data, we found no causal associations between serum CRP levels and the three gynecological cancers from a genetic perspective, and there was no inverse causal associations. However, there were several suggestive associations: higher blood levels of PDGF-BB were associated with a decreased risk of ovarian cancer, higher blood levels of CXCL9, CXCL1, and G-CSF were associated with a decreased risk of endometrial cancer, and on the contrary, IL-6 was associated with an increased risk of endometrial cancer. In addition, there were negative causal associations between cervical cancer and G-CSF and endometrial cancer and CXCL10 and CCL11. There was no heterogeneity or horizontal pleiotropy in the results of the MR analysis, so we believe that the conclusion of the study is reliable.

Cervical cancer is the fourth most common cause of cancer morbidity and mortality in women[26]. Despite recent advances in screening tests and treatments, cervical cancer-related mortality remains high. Systemic inflammatory markers are associated with clinical outcomes in patients with cervical cancer and can be used to predict prognosis in various gynecological cancers[27,28]. Granulocyte colony-stimulating factor (G-CSF) is normally produced mainly by fibroblasts, lymphocytes, and macrophages after stimulation with IL-1 and TNF-α[29], but it can also be produced by certain malignant cells[30]. G-CSF is involved in regulating the differentiation and maturation of neutrophils in the microenvironment of chronic inflammatory tumors, increasing the number of PMNs in the peripheral blood[31]. This improves the ability of the immune system to clear HPV infection and reduces virus-induced abnormalities of the cervical epithelium as well as the progression of precancerous lesions. In addition, it has also been found[32] that G-CSF expression is closely related to the degree of tumor differentiation and lymph node metastasis. Cancers accompanied by G-CSF secretion are prone to lymph node metastasis and have a poorer prognosis. We speculate that although G-CSF may promote angiogenesis or immune escape in the advanced stages of tumorigenesis, it may have a protective role in the early stages. In the early stages of cervical cancer, G-CSF may reduce the incidence of cancer by modulating the immune system and suppressing persistent HPV infection and chronic inflammation.

Ovarian cancer is the deadliest gynecological cancer, with 230,000,000 women diagnosed and 150,000,000 dying from the disease each year worldwide[33]. Due to its high metastasis and recurrence rates, the overall prognosis is poor. Platelet-derived growth factor-BB (PDGF-BB) is a peptide growth factor with biological effects such as promoting cell division and proliferation, cell chemotaxis, and vasoconstriction[34]. Existing studies[35] have shown that PDGF-BB promotes the proliferation and migration of ovarian cancer cells through the activation of its receptor PDGFR, as well as angiogenesis in the tumor microenvironment. Ovarian cancer is a highly vascularized cancer, and the angiogenic effect of PDGF-BB helps provide sufficient nutrients and oxygen to the tumor, thus promoting its growth and metastasis[36]. In addition, it has also been shown[37,38] that elevated levels of PDGF-BB correlate with the aggressiveness and poor prognosis of ovarian cancer and can be used as a prognostic reference. Current studies have focused on the pro-cancer role of PDGF-BB, and there is no clear evidence that PDGF-BB has a protective role in cancer. The opposite result was obtained in our study, which may be related to the following reasons: (1) Mendelian randomization analysis uses a genetic variant associated with PDGF-BB to infer an individual's level of PDGF-BBt. Such genetic variants may be associated with changes in PDGF-BB expression levels, but this does not mean that PDGF-BB has the same biological effect in all cases. Certain specific genotypes may result in lower levels of PDGF-BB, thereby reducing the risk of cancer development. (2) PDGF-BB plays an important role in healthy tissue repair, angiogenesis, and matrix remodeling[39], processes that help maintain tissue stability and function under normal physiological conditions. Thus, in the early stages of tumor formation, PDGF-BB may be protective by supporting tissue repair. However, once the tumor enters the progression stage, PDGF-BB may promote the growth, invasion, and metastasis of tumor cells. However, since the data we obtained did not include more detailed cohort information such as age and gender, further subgroup analyses could not be performed.

Endometrial cancer is the most prevalent gynecological cancer globally, with its incidence on the rise[40]. Chemokines are small, molecules secreted proteins whose basic function is to stimulate cell migration, and they are involved in the development of cancers, as well as inflammatory and metabolic diseases, among others[41]. Endometrial cancer, driven by inflammation, involves the activation of complex cytokines and chemokine networks[42]. CXCL1, which exerts pro-inflammatory responses, immunomodulation, and angiogenesis, along with CXCL9 and CXCL10, which share the same receptor (CXCR3), are all induced to recruit Th cells, T cells, and natural killer cells, exerting anti-infective and anti-tumor effects[43,44]. In endometrial cancer, they form a tumor microenvironment that escapes immunity through enrichment and adhesion, thereby affecting the development of endometrial cancer, and they can be used as biomarkers for determining the pathogenesis, early diagnosis, and prognosis of EC. Elevated levels of the cytokine IL-6 are associated with cancer cell proliferation, angiogenesis, and metastasis[45]. Studies have shown[46] that as malignant tumors progress, T-lymphocyte function is impaired, and IL-6 expression can be enhanced, exacerbating the inflammatory response and leading to weakened immune regulation and decreased immune levels. In endometrial cancer studies, IL-6 can promote endometrial cancer progression through mechanisms such as cell proliferation, invasion, migration, adhesion, cell cycle promotion, and induction of epithelial-mesenchymal transition, which are associated with the disease state and poor prognostic factors of endometrial cancer[47]. Chemokine ligand 11 (CCL11) is a powerful, selective eosinophilic chemoattractant that regulates tumor growth by recruiting eosinophilic cells to tumor sites, and down-regulation of its expression may promote tumor growth[48]. In addition, CCL11 promotes the recruitment of myeloid-derived suppressor cells (MDSCs) to the tumor[49], producing inflammatory mediators that enhance the stemness of endometrial cancer cells[50]. The development of endometrial cancer may be associated with chronic inflammation and an imbalance in the immune system[51]. G-CSF plays an important role in regulating immune responses by increasing the activity of immune cells such as neutrophils and macrophages, thereby enhancing immune surveillance of abnormal cells[31]. Therefore, high levels of G-CSF may help reduce the development of precancerous lesions. In addition, G-CSF plays an important role in repairing tissue damage[52], which may contribute to the regeneration of endometrial tissue and reduce the risk of long-term abnormal proliferation. On the other hand, it is well known that tumor-produced G-CSF can cause tumor autocrine stimulation and promote tumor growth[53]. In vitro and in vivo experiments have shown that tumor-derived G-CSF and G-CSF-mediated IL-6 promote the development of a systemic inflammatory response (e.g., leukocytosis, thrombocytosis) in patients with endometrial cancer, which has been associated with aggressive clinical behavior and poor prognosis[50,54]. Therefore, we hypothesize that the role of G-CSF in endometrial cancer is similar to its role in cervical cancer and that it may play a protective role in the early stages of cancer by modulating the immune response, inflammation, and biological processes such as tissue repair.

This study is the first to explore the causal associations between CRP, IFs, and cervical, ovarian, and endometrial cancers using a Mendelian randomization study, which has a large sample size and high statistical efficiency[55], and is more effective than traditional epidemiological methods in controlling for confounding factors as well as reverse causality interference. However, there are several limitations to our study. First, MR analysis relies solely on available genetic data and does not account for non-genetic factors that may affect the occurrence and progression of the disease, including demographics and lifestyle choices. Second, because 16 S sequencing lacks the depth to reliably quantify to the species level, it often relies on extrapolation or the use of higher levels of classification, which can affect the validity of IVs, while alterations in circulating inflammatory factors may also be affected by unpredictable variables in the real-life clinical setting. Third, residual pleiotropy is possible because the exact function of most of these SNPs is unknown. In addition, there may be gene-environment interactions in the effect of SNPs on exposure, implying that SNPs may have a nonlinear effect on outcome risk. Finally, our MR results cannot be generalized to non-Europeans living in different geographic regions because genetic heterogeneity varies by population, environment varies by region, and different living environments and genetic backgrounds lead to differences in the appearance of specific traits in different racial and ethnic groups. Furthermore, although GWAS data for all exposures and outcomes are restricted to participants of European origin, residual confounding from population stratification cannot be completely excluded.

Conclusions

The inflammatory response is an important feature of tumors. Local inflammation promotes tumor progression by creating an inflammatory microenvironment that promotes immune escape and resistance to chemotherapeutic agents, angiogenesis, and metastasis[56]. Laboratory parameters are both inexpensive and simple, and relevant inflammatory indicators may be useful as additional diagnostic and prognostic parameters in gynecological cancers. However, the search for the most reliable pre-treatment prognostic markers of systemic inflammatory response continues due to various factors. In this study, based on large-scale pooled GWAS data, we found potential causal associations between PDGF-BB, CXCL1, CXCL9, CXCL10, IL-6, G-CSF, and CCL11 and gynecological cancers (cervical, ovarian, and endometrial cancers), which enhances current understanding of the role of inflammatory responses in gynecological cancers, and that inflammatory markers could be considered as possible clinical markers and therapeutic targets for gynecological cancers. In particular, our study identified potential protective effects of PDGF-BB and G-CSF against gynecological cancers (cervical, ovarian, and endometrial), especially in the early stages of carcinogenesis or in processes associated with inflammatory regulation. However, the current study only confirmed the pro-cancer role of G-CSF and PDGF-BB in tumor progression and metastasis. This discrepancy may reflect the multifaceted nature of G-CSF, PDGF-BB, and their complex roles in different contexts. To better understand this phenomenon, more studies are needed to integrate the results of Mendelian randomization with the findings of experimental biology studies.

Data availability

Data supporting the findings of this study are available from the paper and its supplementary Information document.

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Author contributions
Pengfei Liu and Chunxiao Dang conceived the study. Chunxiao Dang and Mengmeng Liu provided the design of the study. Mengmeng Liu and Pengfei Liu collected the data. Jinxing Liu, Xiao Yu and Chunxiao Dang conducted the main analyses of the study. Chunxiao Dang and Xiao Yu wrote the body of the manuscript. Junde Zhao and Yan Dong revised the manuscript. All authors reviewed the the manuscript.

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Declarations

Ethics approval and consent to participate
Mendelian randomization analysis was performed using pooled data obtained from GWAS. These data were collected in compliance with the principle of written informed consent and ethical approval was obtained.

Competing interests
The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to Y.D. or J.Z.