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Causal effect between breast cancer and ovarian cancer: a two-sample mendelian randomization study

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Abstract

Objectives Improved breast cancer (BC) outcomes highlight the importance of secondary primary cancers (SPCs) on survivor prognosis. The objective of this study was to investigate the potential genetic association between primary BC and ovarian cancer (OC), laying the groundwork for the development of preventive strategies for SPC-OC following BC surgery.

Methods This study aimed to assess the connection between BC and OC using a two sample Mendelian randomization (MR) approach, exclusively employing aggregate level data from publicly available genome wide association studies (GWASs). Finally, the Genetic Risk Scores (GRS) method was used for secondary analysis to verify the results robustness further.

Results The IVW method revealed a genetic correlation between Overall BC and ER + BC with Serous borderline tumors, while ER-BC exhibited genetic correlation with Mucinous borderline tumors and high-grade serous ovarian cancer. The findings from the GRS method aligned with those of the primary analysis, reinforcing the study's robustness.

Conclusion Our MR Study identifies an association between BC and OC, highlighting the importance of increased vigilance in clinical practice for individuals with a history of BC. Timely intervention and treatment measures should be taken when necessary.

Keywords Mendelian randomization, Breast cancer, Ovarian cancer, Genetic association, Causal relationship

Introduction

In the United States, according to the 2022 statistics on breast cancer among women by the American Cancer Society, the incidence of breast cancer (BC) has steadily increased over most of the past four decades. In 2022, an estimated 287,850 new cases of invasive BC and 51,400 cases of ductal carcinoma in situ are expected to be diagnosed among American women, and an estimated 43,250 deaths [1]. According to data compiled by the National Cancer Institute, the 5-year survival rate for breast cancer patients in the United States improved significantly, with an overall rate of 91% [2]. However, as breast cancer patients survive longer, the incidence of second primary cancers (SPCs) has increased [3]. According to data provided by the American Cancer Society, a considerable number of individuals in the United States have successfully overcome BC, indicating the importance of screening for SPCs. Regular screening for ovarian cancer (OC), which is associated with women's health, is crucial to ensure the ongoing health of this diverse patient population within these SPCs.

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OC, the most common gynecological tumor, carries a high mortality rate, ranking as the seventh most common cause of cancer-related deaths in women, with the majority occurring in postmenopausal women over 50 years old [4]. The disease typically remains asymptomatic in its early stages, with 75% of cases diagnosed at an advanced clinical stage [5]. Survival rates for OC patients are closely associated with staging. For instance, in the United States, the 5-year survival rate exceeds 90% for stage I ovarian cancer patients, while it drops to only 25% for patients with distant metastases. Despite favorable prognosis for early stage OC, the overall 5-year survival rate stands at 48.6%. Hence, there is an urgent need to devise effective prevention strategies to alleviate the public health burden of OC [6]. Factors influencing OC risk recently identified include genetic predisposition, smoking, and benign gynecological diseases, among others [7]. Observational studies indicate that ovarian cancer is one of the main types of SPCs after breast cancer surgery, with a higher incidence of ovarian cancer in breast cancer patients with BRCA1/2 gene mutations [8]. Nevertheless, the potential association between specific pathological types of breast cancer and ovarian cancer at the genetic level remains to be observed.

Mendelian randomization (MR) is a method that uses genetic variations as instrumental variables to evaluate the causal effect of exposures on outcomes. Due to the fortuitous allocation of alleles during conception, this approach mitigates the influence of confounding environmental factors, effectively addressing inherent confounds often present in observational investigations [9, 10]. Simultaneously, it effectively avoids the pitfalls of reverse causality, as the genotype remains unaffected by the condition under investigation [11]. Additionally, unlike randomized controlled trials (RCTs), MR can be conducted using pre-existing open-access data from comprehensive genome wide association studies (GWASs), significantly broadens its investigative scope and enhances its statistical robustness [12]. In this study, we conducted a two sample Mendelian randomization analysis to evaluate the causal relationship between BC and OC.

Materials and methods

Study design and assumption

This study utilized data from published research, employing the two-sample MR Method to assess the causal relationship between BC and OC. Relevant single nucleotide polymorphisms (SNPs) were extracted from GWAS summary results as instrumental variables (IVs) for estimating causal effects, following a quality control procedure. Mendelian randomization studies must adhere to three fundamental assumptions: (i) the correlation hypothesis (instrumental variables are associated with the exposure); (ii) the Independence hypothesis (instrumental variables are independent of potential confounders); (iii) the Exclusion Restriction assumption (instrumental variables influence outcomes solely through exposure) [13]. The study design and flow chart of the present MR study, Fig. 1.

Data sources and single nucleotide polymorphisms selection

GWAS of OC

The cohort from Ovarian Cancer Association Consortium (OCAC) included 40,941 controls and 25,509 epithelial OC cases of European ancestry [14]. From them, 3103 cases were borderline tumors and 22,406 malignant OC cases. The summary level statistics for OC GWAS were accessed using the R package "Two Sample MR" (v0.5.7) and GWAS IDs from the IEU Open GWAS database (https://gwas.mrcieu.ac.uk/). The borderline tumors comprised serous borderline tumors (GWAS ID: ieu-a-1230; $n=1954$) and mucinous borderline tumors (GWAS ID: ieu-a-1232; $n=1149$). The malignant OC cases include LGSOC (GWAS ID: ieu-a-1122; $n=1012$), HGSOC (GWAS ID: ieu-a-1121; $n=13{,}037$), mucinous OC (GWAS ID: ieu-a-1123; $n=1417$), endometrioid OC (GWAS ID: ieu-a-1125; $n=2810$), clear cell carcinoma (GWAS ID: ieu-a-1124; $n=1366$).

GWAS of BC

IVs associated with BC were obtained from the largest GWAS conducted to date, published by Kyriaki et al. in 2017. This study consisted of a large sample size, comprising 122,977 BC cases and 105,974 controls [15]. The BC include Overall BC (GWAS ID: ieu-a-1126), ER + BC (GWAS ID: ieu-a-1127), and ER-BC (GWAS ID: ieu-a-1128). GWAS IDs from the IEU Open GWAS database https://gwas.mrcieu.ac.uk/.

Genetic instruments

A clumping process ($r^2<0.001$, clumping distance = 10,000 kb) was employed to ensure no linkage disequilibrium (LD) between SNPs. Palindromic alleles were excluded. The strength of the IV exposure correlation was assessed using the F-statistic, with an F-statistic > 10 considered sufficient to mitigate bias from weak IVs. SNPs associated with confounding factors, such as smoking, BRCA1/2, and body mass index, were removed by examining PhenoScannerV2 (http://www.phenoscanner.medschl.cam.ac.uk/) for suspected links, to fulfill the second assumption of MR. SNPs from exposure and outcome datasets underwent harmonization after quality control to ensure consistent directions of SNP effects in the TSMR analyses.

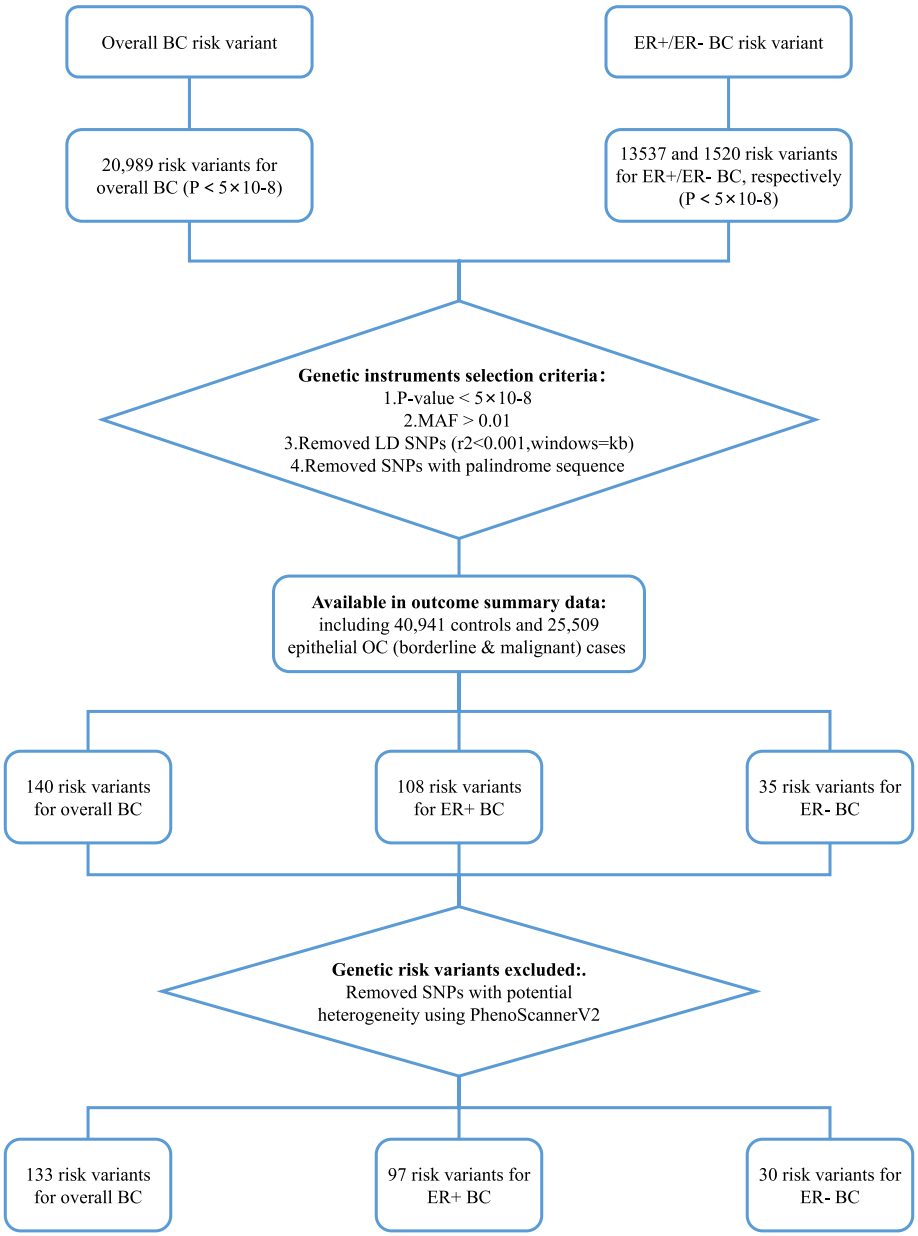

Fig. 1 The study design and flow chart of the present MR study

Statistical analyses

Five MR methods utilized included: Weighted median regression, Inverse variance weighting (IVW), Mendelian randomization Egger (MR Egger), Simple mode and Weighted mode. The primary statistical model utilized was IVW with random effects. Potential horizontal pleiotropy of IVs was assessed through MR-Egger regression and the MR pleiotropy residual sum and outlier (MR-PRESSO) method [16]. MR-PRESSO also identifies outliers within the IVs. After removing outliers, we iteratively reconducted the MR-Egger and MR-PRESSO tests. Heterogeneity among IVs was identified and quantified using Cochran's Q statistic. To ensure the reliability and stability of causal effect estimates, we performed a leave-one-out sensitivity analysis to identify and exclude SNPs with a substantial impact on the results. All MR analyses used the R package "Two Sample MR" (version 4.1.3) [17]. In addition, to confirm the aforementioned MR Results, a secondary analysis was performed using the GRS method. The analysis used R software (version 3.5.3) and the "gtx" R package (windows version 0.0.8) [18].

Result

Instrumental variable selection

In the MR analysis, 20,989 overall BC, 13,537 ER + BC, and 1,520 ER- BC IVs showed significant differences ($p < 5 \times 10^{-8}$) from the BC GWAS data. Following the clumping process, we selected 140 SNPs of overall BC, 108 SNPs of ER + BC and 35 SNPs of ER- BC with no LD. None of these SNPs had minor allele frequencies (MAFs) less than 0.01. We collected essential information about these SNPs, including the effect allele, other alleles, beta coefficient, standard error of beta (SE), and p-value. To eliminate confounding factors and palindromic sequences, we utilized PhenoscannerV2, which confirmed the absence of associations between these SNPs and the mentioned confounders. Ultimately, we identified 133 genetic IVs for overall BC, 97 IVs specifically associated with ER + BC, and 30 IVs specifically linked to ER- BC. Basic characteristics along with summary effect estimates of included IVs on BC are presented in the Supplementary Table 1.

Causal relationship between BC and OC

MR and GRS analysis results of Overall BC to OC

For our investigation, IVW served as the principal analytical approach to examine the correlation between BC and OC. In general, we found evidence of correlation effects of overall BC on Serous borderline tumors at the genetic level (IVW: OR = 1.14, 95% CI: 1.01–1.30, $P = 0.04$, Supplementary Table 2; Figs. 2 and 3C). The IVW method did not indicate any causal effect of overall BC on other OC (LGSOC: OR = 0.91, 95% CI: 0.77–1.07, $P = 0.26$; HGSOC: OR = 1.00, 95% CI: 0.93–1.08, $P = 0.97$; Mucinous borderline tumors: OR = 1.07, 95% CI: 0.94–1.21, $P = 0.32$; Clear cell OC: OR = 0.97, 95% CI: 0.87–1.09, $P = 0.65$; Mucinous OC: OR = 1.11, 95% CI: 0.97–1.28, $P = 0.13$; Endometrioid OC: OR = 1.05, 95% CI: 0.95–1.16, $P = 0.31$, Supplementary Table 2; Fig. 3A, B, D, E, F, G). The result of MR Egger regression was inconsistent with those findings from IVW at Clear cell OC, Supplementary Table 2.

To validate the outcomes of the preceding Mendelian randomization (MR) analysis, we conducted an

Exposure	Outcome	Method	nSNP	OR(95%CI)	P.value
Overall BC	Serous borderline tumors	IVW	133	1.14(1.01 to 1.30)	0.04
	Mucinous borderline tumors	IVW	133	1.07(0.94 to 1.21)	0.32
	LGSOC	IVW	133	0.91(0.77 to 1.07)	0.26
	HGSOC	IVW	133	1.00(0.93 to 1.08)	0.97
	Mucinous OC	IVW	133	1.11(0.97 to 1.28)	0.13
	Endometiioid OC	IVW	133	1.05(0.95 to 1.16)	0.31
	Clear cell OC	IVW	133	0.97(0.87 to 1.09)	0.65
ER+ BC	Serous borderline tumors	IVW	97	1.14(1.01 to 1.29)	0.04
	Mucinous borderline tumors	IVW	97	1.03(0.89 to 1.18)	0.71
	LGSOC	IVW	97	1.03(0.87 to 1.22)	0.76
	HGSOC	IVW	97	1.02(0.95 to 1.10)	0.56
	Mucinous OC	IVW	97	1.12(0.97 to 1.29)	0.12
	Endometiioid OC	IVW	97	1.09(0.99 to 1.19)	0.06
	Clear cell OC	IVW	97	1.07(0.95 to 1.20)	0.29
ER− BC	Serous borderline tumors	IVW	30	0.92(0.76 to 1.11)	0.36
	Mucinous borderline tumors	IVW	30	0.81(0.66 to 0.98)	0.03
	LGSOC	IVW	30	1.17(0.93 to 1.47)	0.19
	HGSOC	IVW	30	1.19(1.03 to 1.38)	0.02
	Mucinous OC	IVW	30	1.02(0.83 to 1.25)	0.84
	Endometiioid OC	IVW	30	0.95(0.81 to 1.10)	0.48
	Clear cell OC	IVW	30	1.02(0.85 to 1.21)	0.86

P<0.05 was considered statistically significant

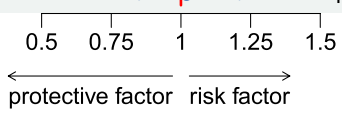

Fig. 2 Forest plot of our Two Sample Mendelian Randomization study based on the IVW method

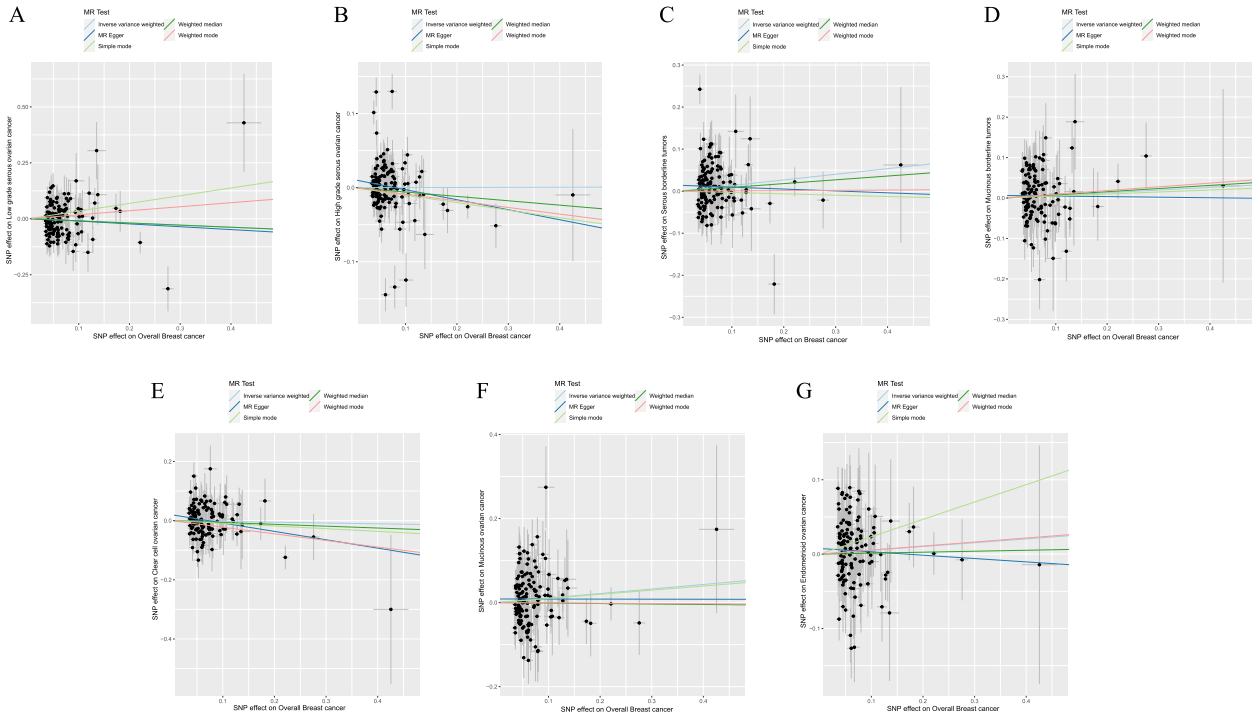

Fig. 3 The scatter plots represent genetic IVs association between Overall BC and OC. Scatter plots for MR analysis methods highlighting the effect of Overall BC genetic liability effects on LGSOC (**A**), HGSOC (**B**), Serous borderline tumors (**C**), Mucinous borderline tumors (**D**), Clear cell OC (**E**), Mucinous OC (**F**) and Endometrioid OC (**G**)

additional MR analysis using the GRS. This subsequent examination corroborated the initial MR findings linking Overall BC to OC, demonstrating that the GRS_{BC} indicated a genetic association between overall BC and Serous borderline tumors (OR = 1.14, 95% CI: 1.03–1.26, $P = 0.01$, Table 1). The GRS_{BC} indicated no causal effect of overall BC on Other pathological types of OC (Mucinous borderline tumors: OR = 1.06, 95% CI: 0.93–1.20, $P = 0.37$; LGSOC: OR = 0.90, 95% CI: 0.79–1.04, $P = 0.15$; HGSOC: OR = 1.00, 95% CI: 0.96–1.05, $P = 0.92$; Mucinous OC: OR = 1.13, 95% CI: 1.00–1.26, $P = 0.05$; Endometrioid OC: OR = 1.05, 95% CI: 0.97–1.15, $P = 0.20$; Clear cell OC: OR = 0.98, 95% CI: 0.87–1.10, $P = 0.73$, Table 1).

MR and GRS analysis results of ER + BC to OC

In ER + BC to OC MR study, the application of the IVW method revealed a genetic connection between ER + BC and Serous borderline tumors (IVW: OR = 1.14, 95% CI: 1.01–1.29, $P = 0.04$, Supplementary Table 2; Figs. 2 and 4C). There was no indication of a genetic relationship between ER + BC and other pathological types of OC by using the IVW approach (LGSOC: OR = 1.03, 95% CI: 0.87–1.22, $P = 0.76$; HGSOC: OR = 1.02, 95% CI: 0.95–1.10, $P = 0.56$; Mucinous borderline tumors: OR = 1.03, 95% CI: 0.89–1.18, $P = 0.71$; Clear cell OC:

Table 1 The effects of the GRS_{BC} on OC

Exposure	Outcome	OR (95%CI)	*P* value
Overall BC	Serous borderline tumors	1.14(1.03 to 1.26)	0.01
	Mucinous borderline tumors	1.06(0.93 to 1.20)	0.37
	LGSOC	0.90(0.79 to 1.04)	0.15
	HGSOC	1.00(0.96 to 1.05)	0.92
	Mucinous OC	1.13(1.00 to 1.26)	0.05
	Endometrioid OC	1.05(0.97 to 1.15)	0.20
	Clear cell OC	0.98(0.87 to 1.10)	0.73
ER + BC	Serous borderline tumors	1.11(1.01 to 1.22)	0.04
	Mucinous borderline tumors	1.05(0.93 to 1.19)	0.41
	LGSOC	0.97(0.85 to 1.11)	0.63
	HGSOC	1.00(0.96 to 1.05)	0.91
	Mucinous OC	1.11(1.00 to 1.25)	0.05
	Endometrioid OC	1.08(1.00 to 1.17)	0.06
	Clear cell OC	1.01(0.90 to 1.13)	0.83
ER- BC	Serous borderline tumors	0.92(0.80 to 1.07)	0.30
	Mucinous borderline tumors	0.89(0.68 to 0.99)	0.04
	LGSOC	1.12(0.91 to 1.37)	0.27
	HGSOC	1.19(1.11 to 1.27)	3.34E-07
	Mucinous OC	1.06(0.90 to 1.26)	0.47
	Endometrioid OC	0.92(0.82 to 1.04)	0.19
	Clear cell OC	1.00(0.85 to 1.19)	0.97

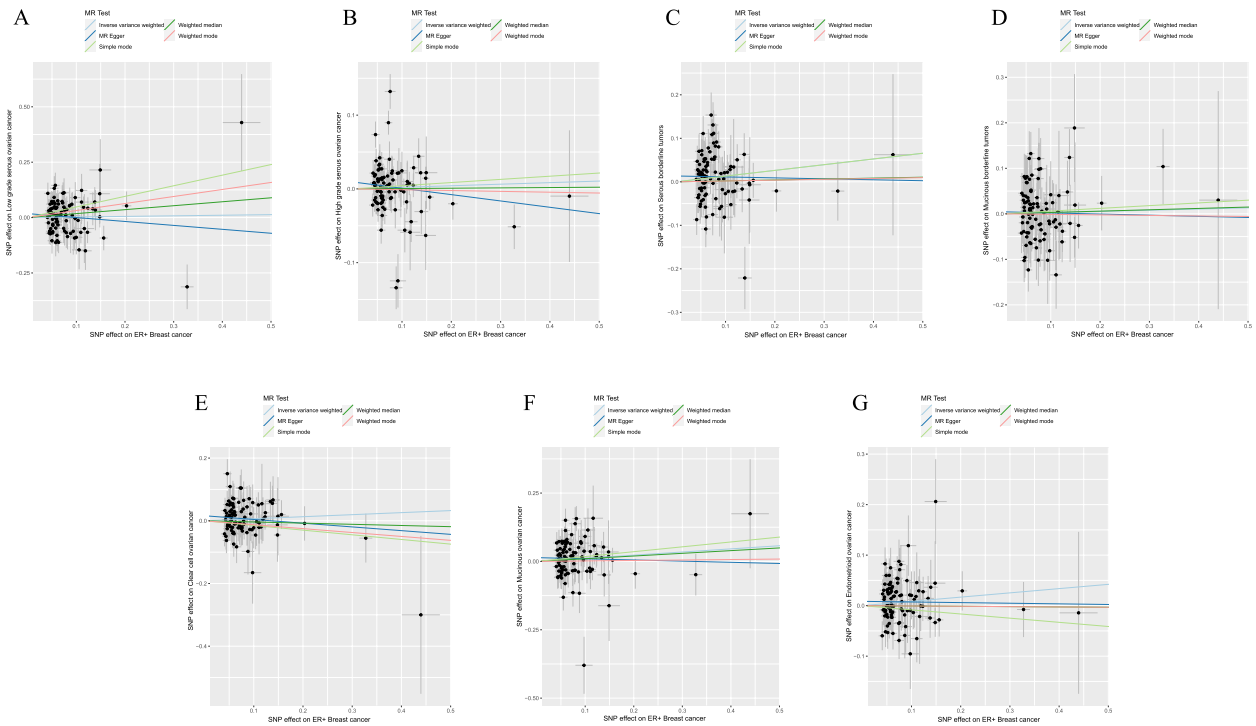

Fig. 4 The scatter plots represent genetic IVs association between ER+ BC and OC. Scatter plots for MR analysis methods highlighting the effect of ER+ BC genetic liability effects on LGSOC (**A**), HGSOC (**B**), Serous borderline tumors (**C**), Mucinous borderline tumors (**D**), Clear cell OC (**E**), Mucinous OC (**F**) and Endometrioid OC (**G**)

OR = 1.07, 95% CI: 0.95–1.20, $P = 0.29$; Mucinous OC: OR = 1.12, 95% CI: 0.97–1.29, $P = 0.12$; Endometrioid OC: OR = 1.09, 95% CI: 0.99–1.19, $P = 0.06$, Supplementary Table 2; Figs. 2 and 4A, B, D, E, F, G). Comparable outcomes have been detected through diverse MR methods, such as weighted median, simple median, weighted median regression, and MR Egger, suggesting the absence of a genetic connection between ER + BC and other pathological types of OC, Supplementary Table 2.

The GRS_{ER+BC} associated with ER + BC indicated a genetic linkage with serous borderline tumors, which consistent with the previously mentioned MR results (OR = 1.11, 95% CI: 1.01–1.22, $P = 0.04$, Table 1). No potential association was observed between ER + BC and various other pathological types of OC, as indicated by the GRS_{ER+BC} (Mucinous borderline tumors: OR = 1.05, 95% CI: 0.93–1.19, $P = 0.41$; LGSOC: OR = 0.97, 95% CI: 0.85–1.11, $P = 0.63$; HGSOC: OR = 1.00, 95% CI: 0.96–1.05, $P = 0.91$; Mucinous OC: OR = 1.11, 95% CI: 1.00–1.25, $P = 0.05$; Endometrioid OC: OR = 1.08, 95% CI: 1.00–1.25, $P = 0.06$; Clear cell OC: OR = 1.01, 95% CI: 0.90–1.13, $P = 0.83$, Table 1).

MR and GRS analysis results of ER- BC to OC

In ER- BC to OC MR study, IVW analysis revealed an association between ER- BC and HGSOC: (OR = 1.19; 95% CI: 1.03–1.38, $P = 0.02$, Supplementary Table 2; Figs. 2 and 5B) and Mucinous borderline tumors (OR = 0.81; 95% CI: 0.66–0.98, $P = 0.03$; Supplementary Table 2, Figs. 2 and 5D) at the genetic level. However, the IVW method lacks a genetic relationship between ER- BC and Other pathological types of OC (LGSOC: OR = 1.17, 95% CI: 0.93–1.47, $P = 0.19$; Serous borderline tumors: OR = 0.92, 95% CI: 0.76–1.11, $P = 0.36$; Mucinous OC: OR = 1.02, 95% CI: 0.83–1.25, $P = 0.84$; Endometrioid OC: OR = 0.95, 95% CI: 0.81–1.10, $P = 0.48$; Clear cell OC: OR = 1.02, 95% CI: 0.85–1.21, $P = 0.86$, Supplementary Table 2; Figs. 2 and 5A, C, E, F, G). Comparable outcomes have been observed across various MR methods, including weighted median, simple median, weighted median regression, and MR Egger, suggesting the absence of a genetic connection between ER- BC and other pathological types of OC, Supplementary Table 2.

The $GRS_{ER\text{-}BC}$ revealed a genetic level association between ER- BC and Mucinous borderline tumors in accordance with MR result (OR = 0.89, 95% CI: 0.68–0.99, $P = 0.04$, Table 1) and HGSOC (OR = 1.19, 95% CI: 1.11–1.27, $P = 3.34E\text{-}07$, Table 1). The $GRS_{ER\text{-}BC}$ showed no

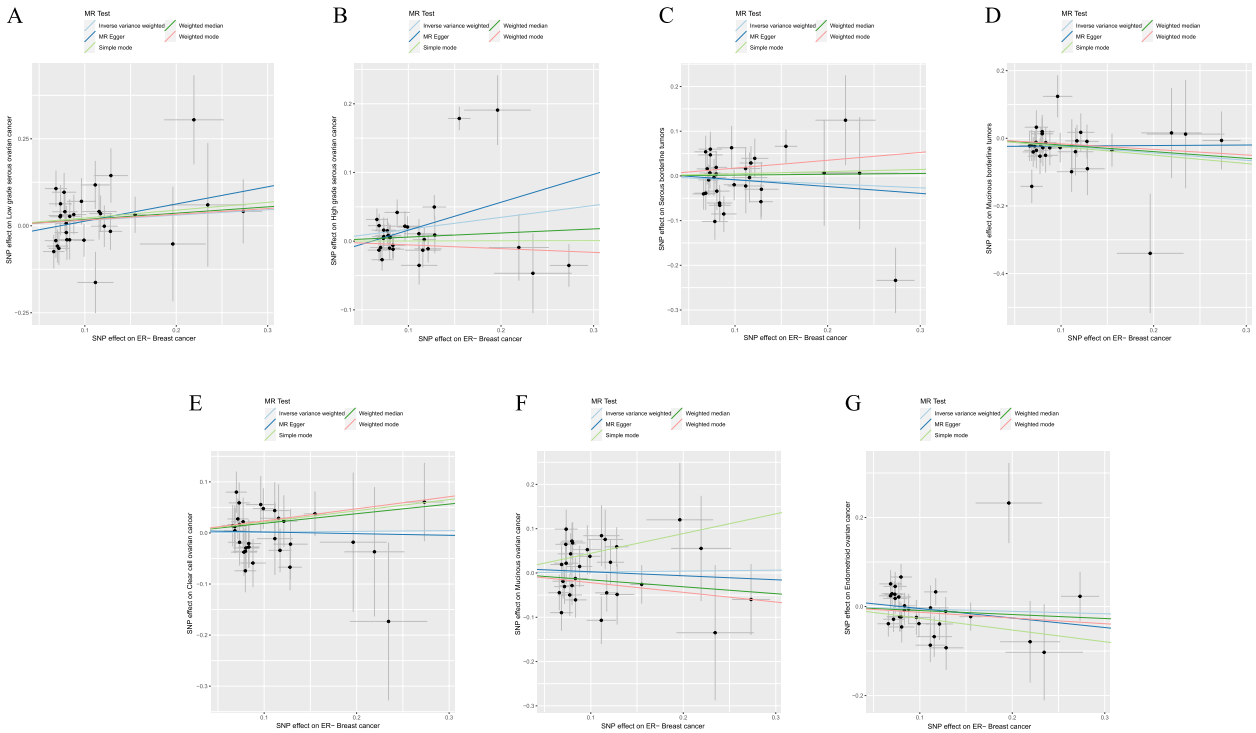

Fig. 5 The scatter plots represent genetic IVs association between ER- BC and OC. Scatter plots for MR analysis methods highlighting the effect of ER- BC genetic liability effects on LGSOC (**A**), HGSOC (**B**), Serous borderline tumors (**C**), Mucinous borderline tumors (**D**), Clear cell OC (**E**), Mucinous OC (**F**) and Endometrioid OC (**G**)

potential association between ER- BC and Other pathological types of OC (Serous borderline tumors: OR = 0.92, 95% CI: 0.80–1.07, $P = 0.30$; LGSOC: OR = 1.12, 95% CI: 0.91–1.37, $P = 0.27$; Mucinous OC: OR = 1.06, 95% CI: 0.90–1.26, $P = 0.47$; Endometrioid OC: OR = 0.92, 95% CI: 0.82–1.04, $P = 0.19$; Clear cell OC: OR = 1.00, 95% CI: 0.85–1.19, $P = 0.97$, Table 1).

Pleiotropy and sensitivity analysis

MR-Egger intercept estimates did not significantly deviate from zero, offering limited evidence of directional pleiotropy in the analyzed associations. Moreover, Cochran's Q test results also showed no signs of heterogeneity among the chosen SNPs in Table 2. Additionally, the leave-one-out analysis indicated that no single SNP disproportionately influenced the results. The results of the pleiotropic and sensitivity analyses are presented in Supplementary Figs. 1, 2, 3.

Discussion

In analyzing invasive epithelial OC subtypes and borderline tumors, encouraging evidence suggests a positive correlation between the genetic susceptibility of Overall BC and ER + BC with Serous borderline tumors, similarly, a positive correlation exists between the genetic susceptibility of ER- BC and the occurrence of HGSOC. However, the genetic predisposition to ER-BC is negatively associated with the risk of Mucinous borderline tumors.

Previous research has suggested a notably higher occurrence of SPCs among cancer patients compared to the general population, and tends to increase over time [19]. Moreover, it has been observed that more than 19% of patients undergoing follow-up periods exceeding 20 years might develop SPCs [20]. Research has shown that patients diagnosed with breast cancer after the age of 50 have a significantly increased risk of developing ovarian cancer within five years [21]. Conversely, patients diagnosed with breast cancer before the age of 50 have a 4.3 times higher risk of ovarian cancer recurrence compared to those diagnosed after the age of 50 [3]. With the gradual rise in the proportion of SPCs following BC, there has been a notable surge in research interest regarding the occurrence, treatment, and prognosis of SPCs. Unfortunately, few previous studies have stratified the link between breast and ovarian cancer. In our investigation, we performed a stratified analysis of breast cancer and ovarian cancer using summary statistics derived from large-scale GWAS studies of European ancestry, incorporating datasets such as Finn Gen and OCAC, employing

Table 2 Heterogeneity and Horizontal pleiotropy analysis

Exposure	Outcome	Cochran's Q statistic	Cochran's Q P	MR-Egger intercept P
Overall BC	Serous borderline tumors	212.52	0.001	0.16
	Mucinous borderline tumors	133.53	0.45	0.53
	LGSOC	180.92	0.003	0.84
	HGSOC	351.13	0.001	0.06
	Mucinous OC	191.45	0.001	0.42
	Endometrioid OC	189.02	0.001	0.32
	Clear cell OC	125.89	0.63	0.03
ER + BC	Serous borderline tumors	138.85	0.003	0.26
	Mucinous borderline tumors	105.63	0.24	0.73
	LGSOC	133.88	0.006	0.27
	HGSOC	216.11	0.001	0.16
	Mucinous OC	140.82	0.002	0.31
	Endometrioid OC	104.53	0.26	0.31
	Clear cell OC	82.57	0.83	0.16
ER- BC	Serous borderline tumors	45.45	0.03	0.82
	Mucinous borderline tumors	22.26	0.81	0.32
	LGSOC	34.69	0.22	0.29
	HGSOC	133.87	0.001	0.27
	Mucinous OC	39.82	0.09	0.71
	Endometrioid OC	42.06	0.06	0.46
	Clear cell OC	23.29	0.76	0.85

the two-sample MR method. Our conclusions are similar to those of previous studies, but it is worth noting that our study shows that there are different pathologic types of ovarian cancer risk with different ER levels.

The etiology of SPC remains unclear. Potential connections between genetic elements, environmental factors, and lifestyle practices with the incidence of SPC have been proposed by earlier observational research [22, 23]. Research indicates that 5% to 10% of breast cancer patients have identifiable genetic mutations, known as hereditary BC, with BRCA1/2 gene mutations representing 15%. Women with BRCA1/2 mutations not only face a higher risk of breast cancer but also of other cancers including ovarian, fallopian tube, pancreatic, gastrointestinal, and melanoma. Similarly, men with these mutations have an elevated risk of breast and prostate cancer [24]. For BRCA mutation carriers, prophylactic salpingectomy with delayed oophorectomy (PSDO) is the most effective method to reduce the risk of fallopian tube and ovarian cancer occurrence, consistently recommended in guidelines [25, 26]. Whether prophylactic surgery is necessary for carriers of other inherited ovarian cancer-related genetic mutations remains controversial. In this study, even after adjusting for BRCA-related SNPs, risk factors associated with subtypes of breast cancer and ovarian cancer were identified. Therefore, the PSDO should be carried out scientifically, reasonably and in a standardized manner. Love et al. concluded in a review that bilateral oophorectomy combined with tamoxifen is an effective treatment for ER + premenopausal breast cancer, and considering the social determinants of health, it should be incorporated into treatment decisions to provide equitable care [27]. This conclusion is further supported by the elevated risk of ovarian cancer observed among ER + BC patients in this study. Although the US Preventive Services Task Force (USPSTF) continues to advise against ovarian cancer screening for asymptomatic women without hereditary cancer syndromes, it recommends regular screening for high-risk women who have not undergone PSDO, with the hope of early detection of ovarian cancer [28]. However, there is currently a lack of evidence showing clinical benefits of ovarian cancer screening for high-risk women [29]. Therefore, in clinical practice, for patients with non-BRCA gene mutations, individual treatment should be combined with the patient's genetic mutation, personal history, family history and surgical intention.

Our MR study has several advantages. Firstly, to our knowledge, this is the first study to evaluate the genetic associations between BC and OC using a two-sample MR analysis and large-scale GWAS data. Secondly, the use of GWAS datasets for BC and OC primarily based

on European ancestry populations minimizes the impact of population stratification. Additionally, we systematically screened confounding factors associated with BC and OC using the PhenoScanner database and eliminated IVs associated with confounding factors to avoid potential pleiotropy of genetic IVs. Furthermore, the influence of pleiotropy was further examined using the MR-Egger and MR-PRESSO (outlier-corrected) methods, ensuring the reliability of the results [30]. Finally, in addition to using the IVW method as the primary analysis approach, this study also employed the GRS method as a secondary analysis method. However, there are some shortcomings in our research. Firstly, all the GWAS data incorporated herein exclusively pertained to European cohorts, thus the generalizability of the findings to the wider populace warrants further scrutiny. Furthermore, removing the possibility of pleiotropy effects entirely in any MR study is challenging, which may introduce bias in assessing causal effects [31]. Finally, studies of clinical data and basic experiments are imperative to foster a deeper comprehension of the intricate mechanisms and underlying pathogenesis of BC on OC.

Conclusions

The causal relationship between breast cancer and ovarian cancer risk was analyzed using MR Analysis, which indicated that breast cancer is associated with an increased risk of ovarian cancer. The results of this study may provide a basis for the prevention and management of ovarian cancer after breast cancer surgery.

Abbreviations

OC	Ovarian cancer
BC	breast cancer
ER+	estrogen receptor-positive
ER-	estrogen receptor-negative
GWAS	genome-wide association study
SPC	second primary cancer
GRS	Genetic risk score
MR	mendelian randomization
SNP	single-nucleotide polymorphism
MAF	minor allele frequency
IVW	inverse variance weighting
IVs	instrumental variables
MR-PRESSO	mendelian randomization pleiotropy residual sum and outlier
LGSOC	Low grade serous ovarian cancer
HGSOC	high grade serous ovarian cancer

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-13033-8.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Supplementary Material 5.

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Authors' contributions

QC wrote the main manuscript text and prepared Figs. 3, 4 and 5, Tables 1, 2 and supplementary material. XY prepared Figs. 1–2 and revision and review. CWJ performs article design and revision and review. All authors reviewed the manuscript. All authors significantly contributed to this work, participating in conception, study design, data acquisition, analysis, interpretation, drafting, revising, and critically reviewing the article.

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Data availability

Data is provided within the manuscript. The data sets used or analyzed in this study are included in the article/Supplementary Material and IEU Open GWAS database (https://gwas.mrcieu.ac.uk/).

Declarations

Ethics approval and consent to participate

We adopted an MR approach by using publicly accessible summary level statistics of published GWASs, which did not require ethical approval.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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