Am J Transl Res 2024;16(6):2699-2710
www.ajtr.org /ISSN:1943-8141/AJTR0157922

Original Article

Causal effect analysis of estrogen receptor associated breast cancer and clear cell ovarian cancer

Li Ji[1*], Yanbo Liu[2*], Zihan Wang[1*], Qiuru Huang[1*], Jiaying Cai[1], Han Gu[1], Jiaxin Li[1], Xia Chen[3], Chenrui Feng[1], Xuxin He[1], Xiaonan Deng[1], Xinmeng Cheng[1], Xiuwen Kong[1], Xiaoqi Zhu[1], Tong Wu[1], Binbin Yang[1], Ziwen Lin[1], Xiaoqing Yang[4], Guannan Feng[2], Jun Yu[1]

[1]Institute of Reproductive Medicine, School of Medicine, Nantong University, Nantong 226001, Jiangsu, China; [2]Department of Obstetrics and Gynecology, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Gusu School, Nanjing Medical University, Suzhou 215000, Jiangsu, China; [3]Department of Obstetrics and Gynecology, Nantong First People's Hospital, Affiliated Hospital 2 of Nantong University, Nantong University, Nantong 226001, Jiangsu, China; [4]Department of Obstetrics and Gynecology, The Affiliated Hospital of Nantong University, Nantong University, Nantong 226001, Jiangsu, China. [*]Equal contributors.

Received May 20, 2024; Accepted June 4, 2024; Epub June 15, 2024; Published June 30, 2024

Abstract: Background: Evidence indicates that the risk of developing a secondary ovarian cancer (OC) is correlated with estrogen receptor (ER) status. However, the clinical significance of the relationship between ER-associated breast cancer (BC) and clear cell ovarian cancer (CCOC) remains elusive. Methods: Independent single nucleotide polymorphisms (SNPs) strongly correlated with exposure were extracted, and those associated with confounders and outcomes were removed using the PhenoScanner database. SNP effects were extracted from the outcome datasets with minor allele frequency > 0.01 as the filtration criterion. Next, valid instrumental variables (IVs) were obtained by harmonizing exposure and outcome effects and further filtered based on F-statistics (> 10). Mendelian randomization (MR) assessment of valid IVs was carried out using inverse variance weighted (IVW), MR Egger (ME), weighted median (WM), and multiplicative random effects-inverse variance weighted (MRE-IVW) methods. For sensitivity analysis and visualization of MR findings, a heterogeneity test, a pleiotropy test, a leave-one-out test, scatter plots, forest plots, and funnel plots were employed. Results: MR analyses with all four methods revealed that CCOC was not causally associated with ER-negative BC (IVW results: odds ratio (OR) = 0.89, 95% confidence interval (CI) = 0.66-1.20, P = 0.431) or ER-positive BC (IVW results: OR = 0.99, 95% CI = 0.88-1.12, P = 0.901). F-statistics were computed for each valid IV, all of which exceeded 10. The stability and reliability of the results were confirmed by sensitivity analysis. Conclusions: Our findings indicated that CCOC dids not have a causal association with ER-associated BC. The absence of a definitive causal link between ER-associated BC and CCOC suggested a minimal true causal influence of ER-associated BC exposure factors on CCOC. These results indicated that individuals afflicted by ER-associated BC could alleviate concerns regarding the developing of CCOC, thereby aiding in preserving their mental well-being stability and optimizing the efficacy of primary disease treatment.

Keywords: Clear cell ovarian cancer, estrogen receptor, breast cancer, Mendelian randomization, single nucleotide polymorphisms, instrumental variables

Introduction

Ovarian and breast malignancies exhibit significant similarities, and thus prompted researchers to investigate a potential correlation between these two kinds of female cancers [1, 2]. It has been demonstrated that both breast and ovarian tissues show positive immunohistochemical staining for estrogen receptor (ER), and this has led to the incorporation of ovarian cancer (OC) with breast cancer (BC) in research studies [3, 4]. In fact, there is some evidence to suggest that elevated estrogen levels can lead to an increase in the prevalence of both ovarian and ER-positive BC [5, 6]. However, it has also been reported that while oral contraceptives act as protective factors against OC, particularly their prolonged use, they may increase the risk of BC [7]. Thus, the causal link between these female cancers and the role of ER signal-

https://doi.org/10.62347/EC009552

Table 1. GWAS datasets for ER-negative BC, ER-positive BC and CCOC

	ER-negative BC	ER-positive BC	CCOC
Year	2015	2015	2017
Population	European	European	European
Ncase	3,611	4,202	1,366
Ncontrol	18,084	18,084	40,941
Total sample size	21,695	22,286	42,307
Author	Michailidou K	Michailidou K	Phelan
GWAS ID	ieu-a-1166	ieu-a-1167	ieu-a-1124
PMID	25751625	25751625	28346442

GWAS, genome-wide association studies; Ncase, number of cases; Ncontrol, number of controls; SNPs, single-nucleotide polymorphisms; ER, estrogen receptor; BC, breast cancer; CCOC, clear cell ovarian cancer.

ing is a topic that requires further in-depth investigation.

Annually, approximately 240,000 women worldwide are diagnosed with OC [8-10]. With a five-year survival rate below 45%, it is the seventh leading cause of mortality among women [11-13]. OC encompasses a diverse array of subtypes [14, 15]. One of these is clear-cell ovarian cancer (CCOC), which is widely acknowledged for its enhanced aggressiveness [16] and is a distinct histological type of epithelial ovarian cancer [17, 18]. CCOC has a median overall survival of 24 months, which is half that of patients who have epithelial OC with a serious and endometrioid histology [19, 20]. A population-based study on the theory of reciprocal associations among breast, ovarian, and uterine corpus cancers revealed that the collective risk of secondary cancers was most pronounced during the initial 5 years following diagnosis of the primary cancer [21]. These bidirectional connections imply shared risk factors among these three types of female cancers. However, there is little documentation of ethnic differences in these risk factors. Diagnosis of BC at a young age has been linked to a heightened likelihood of developing subsequent malignancies [22], and these secondary cancers have been shown to negatively impact the survival rates of individuals who have already overcome BC [22]. Another study suggested that the risk of developing a secondary OC was positively correlated with age but inversely linked to race and ER status [23]. Furthermore, advanced age and a lack of ER expression imply a increased possibility of subsequent OCs [23]. Unfortunately, the clinical significance of the relationship between ER-associated BC and CCOC remains uncertain. The present study tries to address this research gap by using several Mendelian randomization (MR) methods to explore the potential causal association between these two kinds of female cancers.

Methods

Collection of data from the genome-wide association study (GWAS) database

To ensure analytical accuracy and mitigate the influence of environmental variables and gender disparities, we meticulously curated data from identical population origins and gender sources available on the official open GWAS website. Specifically, we selected the GWAS dataset pertaining to ER-negative BC and ER-positive BC from IEU OPEN GWAS (https://gwas.mrcieu.ac.uk/), deposited under IDs ieu-a-1166 and ieu-a-1167 containing 21,695 and 22,286 samples, respectively [24]. Additionally, the GWAS dataset for CCOC, deposited under ID ieu-a-1124, consisted of 42,307 samples [25]. Detailed information regarding these three GWAS datasets is provided in **Table 1**.

Extraction of instrumental variables (IVs)

A two-step univariate two-sample MR analysis was conducted to explore ER-associated BC exposure and CCOC. A schematic diagram of the study is presented in **Figure 1**. The analysis was executed using the R software, following a structured procedure: Initially, single nucleotide polymorphisms (SNPs) associated with exposure in the exposed dataset were extracted (*P* value < 5e-08). Subsequently, SNPs exhibiting negligible linkage disequilibrium effects within a 10,000-kb window (r^2 < 0.001) were confirmed. These SNPs were cross-referenced in PhenoScanner (www.phenoscanner.medschl.cam.ac.uk) to eliminate those linked to confounding variables and outcomes [26]. Confounding factors for CCOC encompass well-established risk elements such as smoking [27]. The effects of SNPs were extracted from the outcome datasets by setting minor allele frequency > 0.01 as the filtration criterion.

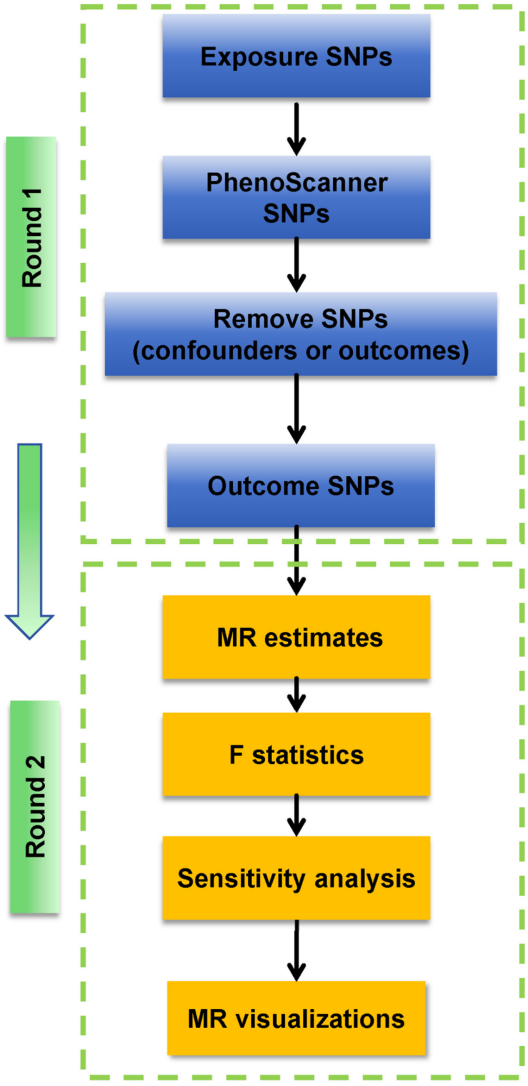

Figure 1. Flow chart depicting the MR analysis conducted in this study. MR, Mendelian randomization; SNPs, single-nucleotide polymorphisms.

MR analysis and visualizations

All statistical analyses for this study were performed using the TwoSampleMR package. MR assessment of valid IVs was conducted through inverse variance weighted (IVW), MR Egger (ME), weighted median (WM), and multiplicative random effects-inverse variance weighted (MRE-IVW) regression methods. The IVW methodology assessed the magnitude of the therapeutic impact through the computation of inverse variance weighting for individual IVs. In the event of the absence of heterogeneity and pleiotropy, IVW could furnish compelling evidence of a causal association between exposure and the resultant effect [28]. The WM approach exhibited relative insensitivity to outliers and was often the preferred choice in the presence of heterogeneity during analysis. However, the WM technique was inherently proficient in the analysis of IVs. If this assumption was invalid, the WM estimations might display bias [29]. Consequently, in scenarios of heterogeneity, the outcomes of MRE-IVW for comparative analysis could yield more resilient evidence [30]. ME methodology offered evidence about the validity of IVs and the causal hypothesis by assuming that there was a linear relationship between the residual of the IV and the outcome variable [31]. The outcomes of the MR analysis were visually represented through funnel plots, scatter plots, and forest plots. The funnel plot served to ascertain the presence of heterogeneity in the findings by assessing the symmetry of IVs with IVW lines. Concurrently, the scatter plot could elucidate the gradient of the outcomes scrutinized through IVW, MRE-IVW, WM, and ME methodologies, aiding in the evaluation of the relationship between exposure and the resultant outcome.

F-statistics

Statistical strength was calculated using the equation $F = R^2(n - 1 - k)/(1 - R^2)k$. F values > 10 meant that rare mutations had been averted and the results of the study were generalizable [32].

Sensitivity analysis

For sensitivity analysis and visualization of the MR findings, the heterogeneity test, pleiotropy test, and leave-one-out test were applied. The Q-test was utilized for heterogeneity assessment by using the IVW and ME methods, and the results were considered reliable when the *P*-value was > 0.05 [33]. Subsequently, the ME intercept test was employed for pleiotropy evaluation. The presence of an intercept suggests the presence of additional factors that influence the outcome, and a *P*-value < 0.05 in the ME test signifies the existence of pleiotropy [34]. In this case, the MRE-IVW method was used to detect a potential causal relationship between exposure and outcome [35]. Sensitivity analysis was then further conducted by iteratively removing SNPs in the leave-one-out test; consistent results after SNP removal would indicate the reliability of the study [36].

Table 2. Two-sample univariable MR analysis between ER-positive/negative BC and CCOC

Exposure	Outcome	Method	nSNP	OR	95% CI	*P*-value
ER-negative BC	CCOC	IVW	6	0.89	0.66 to 1.20	0.431
		ME		2.99	0.40 to 22.27	0.345
		WM		1.04	0.74 to 1.46	0.813
		MRE-IVW		0.89	0.66 to 1.20	0.431
ER-positive BC	CCOC	IVW	41	0.99	0.88 to 1.12	0.901
		ME		0.69	0.53 to 0.90	0.009
		WM		0.96	0.80 to 1.15	0.636
		MRE-IVW		0.99	0.88 to 1.12	0.901

IVW, inverse variance weighted; ME, MR Egger; WM, weighted median; MRE-IVW, multiplicative random effects inverse variance weighting; ER, estrogen receptor; BC, breast cancer; CCOC, clear cell ovarian cancer; SNPs, single-nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; MR, Mendelian randomization.

Table 3. Heterogeneity tests in univariable MR analysis

Exposure	Outcome	Method	Cochran's Q	Q_df	Q-*P*-value
ER-negative BC	CCOC	ME	5.397	4	0.249
		IVW	7.336	5	0.197
ER-positive BC		ME	33.851	39	0.703
		IVW	42.954	40	0.346

ME, MR-Egger; IVW, Inverse variance weighted; ER, estrogen receptor; BC, breast cancer; CCOC, clear cell ovarian cancer; MR, Mendelian randomization.

Table 4. Pleiotropy tests in univariable MR analysis

Exposure	Outcome	ME-intercept	SE	*P*-value
ER-negative BC	CCOC	-0.179	0.149	0.297
ER-positive BC		0.048	0.016	0.004

ER, estrogen receptor; BC, breast cancer; CCOC, clear cell ovarian cancer; ME, MR-Egger; MR, Mendelian randomization; SE, standard error.

Results

Causal effects of ER-associated BC exposure on CCOC

After SNP screening, 6 SNPs were identified for assessing the causal impact of ER-negative BC on CCOC and 41 SNPs were identified for evaluating the causal effect of ER-positive BC on CCOC (Supplementary Tables 1 and 2). The MR analysis results for ER-negative BC versus CCOC using the IVW (odds ratio (OR): 0.89; 95% confidence interval (CI): 0.66-1.20), ME (OR: 2.99; 95% CI: 0.40-22.27), WM (OR: 1.04; 95% CI: 0.74-1.46), and MRE-IVW (OR: 0.89; 95% CI: 0.66-1.20) methods had *P* values exceeding 0.05, which indicates the absence of a causal link between ER-negative BC and CCOC (**Table 2**). Conversely, in the MR analysis of the causal impact of ER-positive BC on CCOC, a *P* value below 0.05 was observed for ME (OR: 0.69; 95% CI: 0.53-0.90; P = 0.009). This is indicative of the presence of horizontal pleiotropy. In the case of such analyses, MRE-IVW can provide a more precise estimation of the overall effect magnitude. However, the MRE-IVW results (OR: 0.99; 95% CI: 0.88-1.12; P = 0.901) implied lack of a causal relationship between ER-positive BC and CCOC (**Table 2**).

F-statistics and sensitivity analysis

F-statistics were computed for each valid IV, all of which exceeded 10 (Supplementary Tables 1 and 2). Cochran's Q statistics calculated via the ME and IVW methods to assess heterogeneity revealed that there was no heterogeneity (*P*-value > 0.05) among the IVs employed in the MR analysis (**Table 3**). In pleiotropy analysis, horizontal pleiotropy was not detected in the valid IVs in terms of the impact of ER-negative BC on CCOC, while ME analysis demonstrated the presence of pleiotropy in the impact of ER-positive BC on CCOC (**Table 4**). However, the existence of pleiotropy did not alter the causal effect, since the MRE-IVW outcome for the impact of ER-positive BC on CCOC had a *P*-value > 0.05. In the leave-one-out test, the removal of valid IVs did not change the effect of either ER-negative BC or ER-positive BC on CCOC (Supplementary Tables 3 and 4).

MR visualization

Scatter plots were drawn to illustrate the estimated causal effects of valid IVs for the impact of ER-negative and ER-positive BC on CCOC (**Figure 2**). Each point in the scatter plot represents a genetic variation, but the points in the

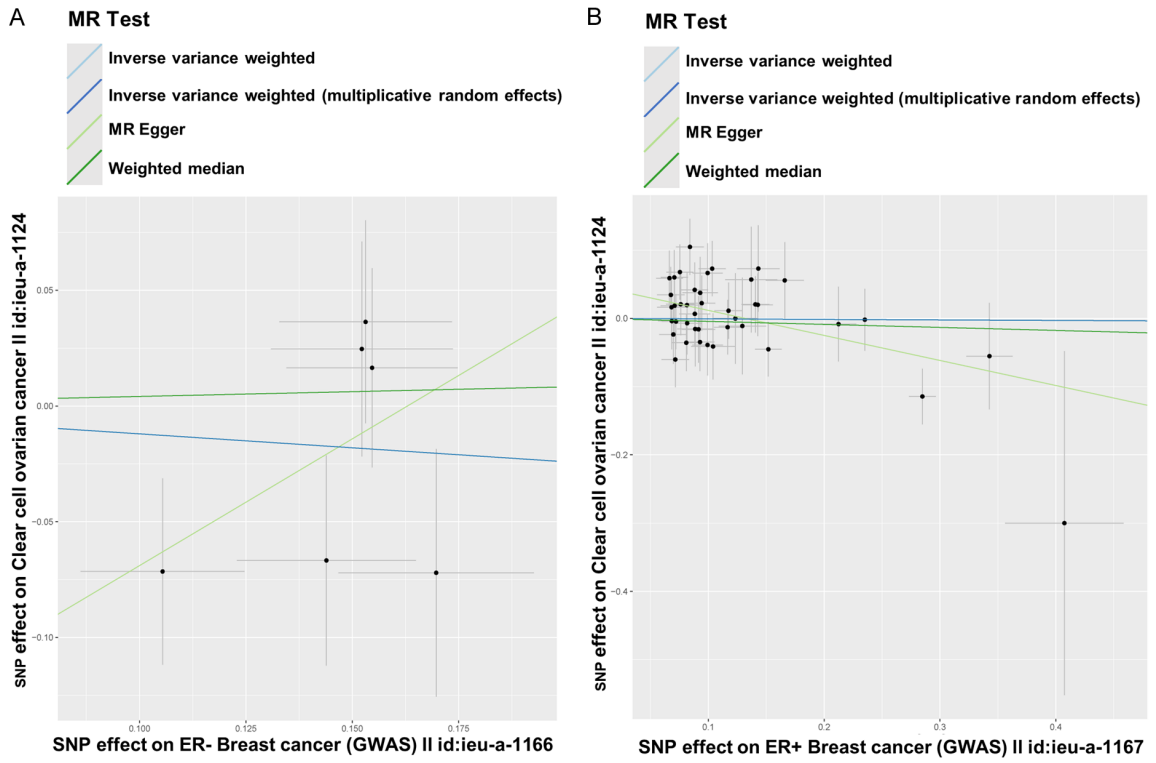

Figure 2. Scatter plots of causal effect estimations. A. Scatter plots depicting the effect of ER-negative BC on CCOC. B. Scatter plots depicting the effect of ER-positive BC on CCOC. ER, estrogen receptor; BC, breast cancer; CCOC, clear cell ovarian cancer.

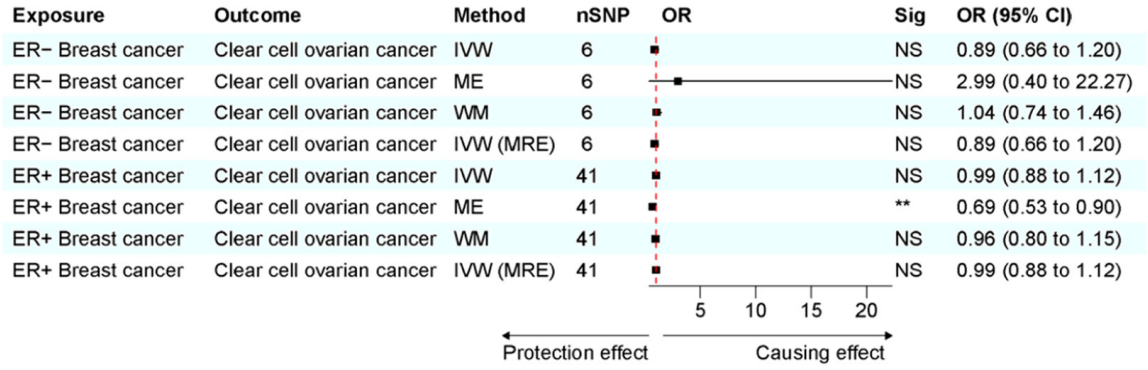

Figure 3. Forest plots depicting the causal effect estimations of the association between ER-associated BC and CCOC in univariable MR analysis. IVW, inverse variance weighted; ME, MR Egger; WM, weighted median; MRE-IVW, multiplicative random effects inverse variance weighting; ER, estrogen receptor; BC, breast cancer; CCOC, clear cell ovarian cancer.

graph do not show a strong correlation overall. The forest plot was visualized based on estimations derived from the IVW, ME, WM, MRE-IVW methods, and the results revealed that genetic variations of CCOC were not associated with the risk of either ER-negative BC or ER-positive BC (**Figure 3**). The results of MR leave-one-out sensitivity analysis are presented in **Figure 4**; The results of heterogeneity testing were visualized through the funnel plot (**Figure 5**). With IVW as the axis of symmetry, the SNPs in this study were found to be roughly symmetrically distributed along this axis, without exhibiting heterogeneity.

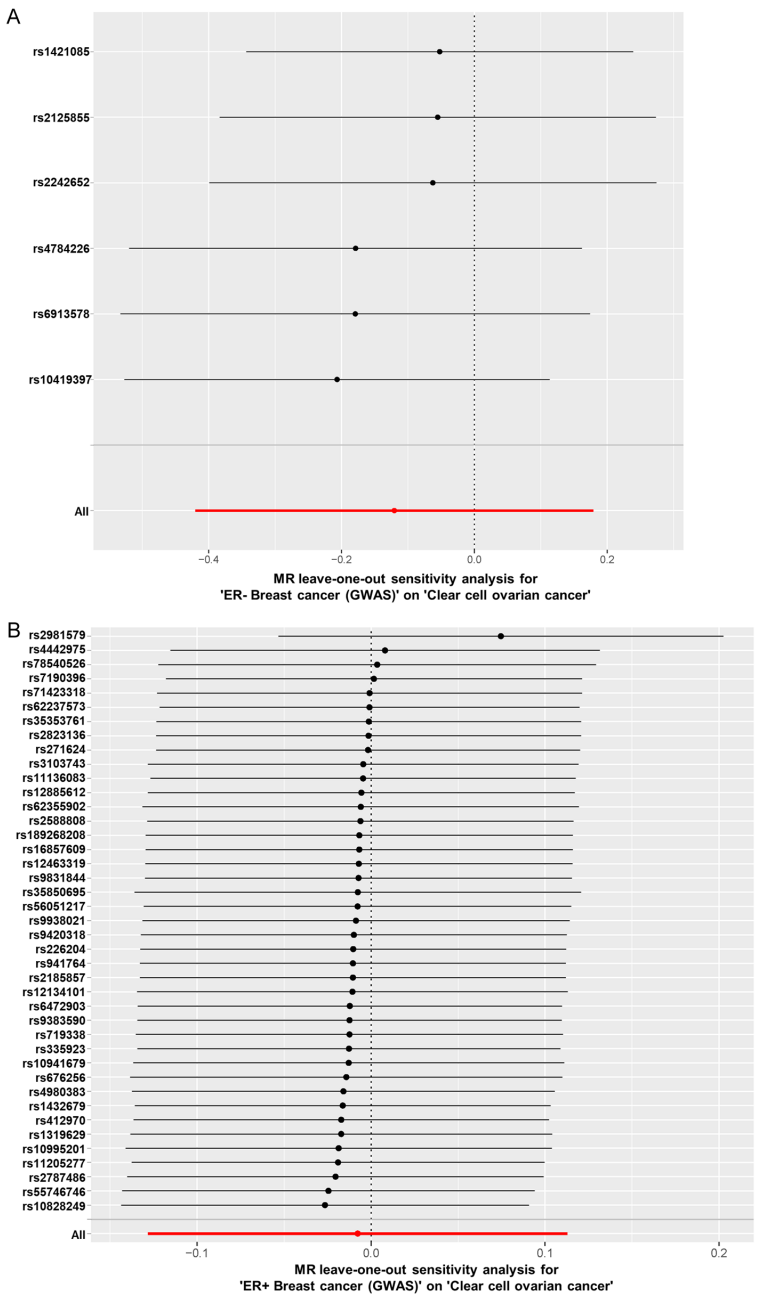

Figure 4. MR leave-one-out sensitivity analysis. A. Leave-one-out estimation for ER-negative BC on CCOC. B. Leave-one-out estimation for ER-positive BC on CCOC. ER, estrogen receptor; BC, breast cancer; CCOC, clear cell ovarian cancer.

Discussion

OC stands as one of the top five leading causes of female cancer-related mortality worldwide and represents one of the most aggressive gynecological malignancies [37]. While CCOC typically manifests at earlier stages, individuals with advanced disease exhibit a poorer prognosis in comparison to those with other subtypes of epithelial ovarian cancer [18]. Due to its resistance to standard platinum-based chemotherapy regimens, CCOC typically has an unfavorable prognosis [38-40]. This resistance could potentially be attributed to reduced cisplatin sensitivity caused by high expression levels of nuclear 3'-phospoadenosine 5'-phosphosulfate synthase 1 (PAPSS1) in patients undergoing platinum-based chemotherapy that results from diminished ERα signaling [41]. Studies assessing ER content within the context of CCOC have revealed that atypical endometriosis-associated CCOC exhibits lower expression of ERα than endometriosis-associated CCOC, indicating a potential role of ERα loss in the malignant transformation of CCOCs [42]. As mentioned earlier, ER signaling is also intricately linked to BC and poses a substantial threat to women's well-being [43]. Accordingly, BC is categorized into the ER-positive and ER-negative subtypes based on the immunohistochemical profiling of ER [43]. Approximately 80% of individuals diagnosed with BC exhibit ER-positive status [44]. In addition to their ER content, CCOC and BC exhibit similar genetic alterations, including mutations in genes such as *adenine thymine-rich interactive domain 1A* (*ARID1A*). For example, in endometriosis-associated CCOC, there is a high frequency of *ARID1A* mutations [45, 46]. Further, survivors of BC face an elevated risk of developing secondary OC, although the incidence of this form of cancer is relatively low in ER-positive BC patients due to targeted therapies post-diagnosis [47]. Unfortunately, the interconnection between CCOC and ER-associated BC beyond these

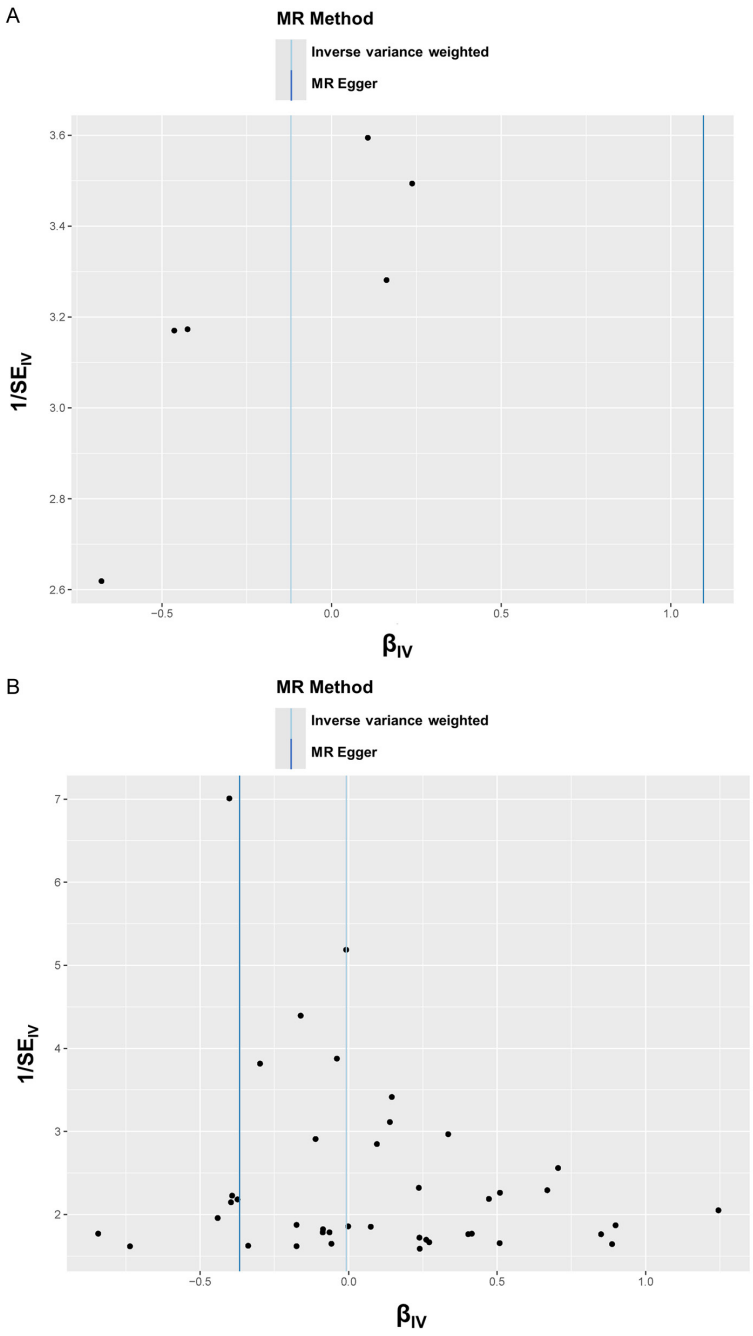

Figure 5. Funnel plot of causal effect estimations. A. Funnel plot for ER-negative BC on CCOC. B. Funnel plot for ER-positive BC on CCOC. ER, estrogen receptor; BC, breast cancer; CCOC, clear cell ovarian cancer.

shared characteristics remains ambiguous. Assessment of ER expression can guide clinical decisions in BC management and may also be promising in terms of targeted therapies for OC, which remains an active area of research. However, there is a scarcity of studies that delve into the causative link between ER-associated BC and the more aggressive CCOC in patients.

This study employed MR to systematically evaluate the causal relationship between ER-associated BC and CCOC. The overarching aim was to establish a robust theoretical framework for understanding the association between these two conditions. MR analysis serves as a valuable tool for addressing confounding variables inherent in observational studies by utilizing genetic variants as IVs for exposure assessment [48]. Specifically, two-sample MR analyses leverage summary statistics from GWAS rather than individual-level data analysis [49]. Unlike observational studies, MR is a statistical method that effectively minimizes the impact of confounding factors, encompassing exposure, confounders, and outcomes [50]. Our results indicate no apparent causal association between ER-associated BC and CCOC - conclusion that is reinforced by sensitivity analysis. This deduction is credible, as SNPs function as IVs in MR analyses to explore potential causal connections between exposure and outcomes, thereby mitigating the impact of confounding variables [51]. The validity of the findings hinges on three key criteria: (1) strong correlation between IVs and exposure factors, (2) absence of correlation between IVs and confounders, and (3) IVs solely influencing outcome variables through exposure factors.

The absence of a definitive causal link between ER-associated BC and CCOC in this study suggests a minimal true causal influence of ER-associated BC exposure factors on CCOC.

This implies that individuals afflicted by ER-associated BC can alleviate concerns regarding the developing of CCOC, thereby aiding in preserving their mental well-being stability and optimizing the efficacy of primary disease treatment [52]. However, this assertion may be somewhat clouded by insufficient statistical power. Additionally, it is plausible that undiscovered SNPs associated with exposure factors exist. However, it is most likely that after accounting for common confounders, no causal relationship exists between ER-associated BC and CCOC. Genetic testing may aid in identifying shared SNPs between ER-associated BC and CCOC, thereby informing the likelihood of secondary CCOC development. Accordingly, future investigations should focus on uncovering common SNPs between ER-associated BC and CCOC to enhance screening methodologies.

A major limitation of the present findings is that the dataset predominantly represents European populations, potentially overlooking genetic disparities among diverse ethnic groups and regions. Furthermore, critical patient information, such as age and cancer stage, was absent in the dataset, hindering a comprehensive analysis.

Conclusions

In summary, this study utilized the two-sample univariable MR analysis to investigate whether there exists a causal link between ER-associated BC and CCOC. Although our current findings did not support a causal association between CCOC and ER-associated BC, future investigations with hitherto unknown SNPs are required to verify these findings and to confirm the absence of such a link.

Acknowledgements

This work was supported partly by Qinglan Project of Jiangsu Province of China, "333 Project" of Jiangsu Province (No. 2022-3-29-061), the 14th Five Year Plan for Leading Talents in Science Education and Health Engineering Medical Innovation Team Leading Talent Program of Nantong City, Research Project of Nantong Health Commission (QA2021016), and the Nantong Key Young Medical Talent Program.

Disclosure of conflict of interest

None.

Address correspondence to: Jun Yu, Institute of Reproductive Medicine, School of Medicine, Nantong University, No. 16, Wenfeng Road, Nantong 226001, Jiangsu, China. E-mail: yujun9117@ntu.edu.cn; Guannan Feng, Department of Obstetrics and Gynecology, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Gusu School, Nanjing Medical University, No. 26, Daoqian Street, Suzhou 215000, Jiangsu, China. E-mail: fengguannan@njmu.edu.cn; Xiaoqing Yang, Department of Obstetrics and Gynecology, The Affiliated Hospital of Nantong University, Nantong University, No. 20, Xisi Road, Nantong 226001, Jiangsu, China. E-mail: ntyxq169@126.com

References

[1] Burgess M and Puhalla S. BRCA 1/2-mutation related and sporadic breast and ovarian cancers: more alike than different. Front Oncol 2014; 4: 19.

[2] Serio PAMP, de Lima Pereira GF, Katayama MLH, Roela RA, Maistro S and Folgueira MAAK. Somatic mutational profile of high-grade serous ovarian carcinoma and triple-negative breast carcinoma in young and elderly patients: similarities and divergences. Cells 2021; 10: 3586.

[3] Diez-Perez A. Selective estrogen receptor modulators (SERMS). Arq Bras Endocrinol Metabol 2006; 50: 720-34.

[4] Rusidzé M, Adlanmérini M, Chantalat E, Raymond-Letron I, Cayre S, Arnal JF, Deugnier MA and Lenfant F. Estrogen receptor-α signaling in post-natal mammary development and breast cancers. Cell Mol Life Sci 2021; 78: 5681-705.

[5] Johansson Å, Schmitz D, Höglund J, Hadizadeh F, Karlsson T and Ek WE. Investigating the effect of estradiol levels on the risk of breast, endometrial, and ovarian cancer. J Endocr Soc 2022; 6: bvac100.

[6] Larsson SC, Kar S, Perry JRB, Carter P, Vithayathil M, Mason AM, Easton DF and Burgess S. Serum estradiol and 20 site-specific cancers in women: Mendelian randomization study. J Clin Endocrinol Metab 2022; 107: e467-e474.

[7] Cibula D, Zikan M, Dusek L and Majek O. Oral contraceptives and risk of ovarian and breast cancers in BRCA mutation carriers: a meta-analysis. Expert Rev Anticancer Ther 2011; 11: 1197-207.

[8] Koren Carmi Y, Mahmoud H, Khamaisi H, Adawi R, Gopas J and Mahajna J. Flavonoids

restore platinum drug sensitivity to ovarian carcinoma cells in a phospho-ERK1/2-dependent fashion. Int J Mol Sci 2020; 21: 6533.
[9] Cole AJ, Iyengar M, Panesso-Gómez S, O'Hayer P, Chan D, Delgoffe GM, Aird KM, Yoon E, Bai S and Buckanovich RJ. NFATC4 promotes quiescence and chemotherapy resistance in ovarian cancer. JCI Insight 2020; 5: e131486.
[10] Zhang H and Zhang Y. Olaparib and paclitaxel in combination with carboplatin in treatment of ovarian cancer: influence on disease control. Am J Transl Res 2022; 14: 468-75.
[11] Webb PM and Jordan SJ. Epidemiology of epithelial ovarian cancer. Best Pract Res Clin Obstet Gynaecol 2017; 41: 3-14.
[12] Hsiao YH, Chen PN, Hsin MC, Wang PH, Huang JY and Yang SF. The risk of distant metastases in patients with gynecologic cancers after surgery: a population-based study. Aging (Albany NY) 2021; 13: 25846-58.
[13] Jiang Q, Qian H, Mei L, Sun Q, Cheng X, Huang W, Xia M, Shao J and Wang J. Effect of bevacizumab plus paclitaxel and carboplatin regimen on prognostic survival of ovarian cancer patients. Am J Transl Res 2022; 14: 8761-7.
[14] Maioru OV, Radoi VE, Coman MC, Hotinceanu IA, Dan A, Eftenoiu AE, Burtavel LM, Bohiltea LC and Severin EM. Developments in genetics: better management of ovarian cancer patients. Int J Mol Sci 2023; 24: 15987.
[15] Barnes BM, Nelson L, Tighe A, Burghel GJ, Lin IH, Desai S, McGrail JC, Morgan RD and Taylor SS. Distinct transcriptional programs stratify ovarian cancer cell lines into the five major histological subtypes. Genome Med 2021; 13: 140.
[16] Atiya HI, Frisbie L, Goldfeld E, Orellana T, Donnellan N, Modugno F, Calderon M, Watkins S, Zhang R, Elishaev E, Soong TR, Vlad A and Coffman L. Endometriosis-associated mesenchymal stem cells support ovarian clear cell carcinoma through iron regulation. Cancer Res 2022; 82: 4680-93.
[17] Gan M, Tai Z, Yu Y, Zhang C and Xu J. Next-generation sequencing shows the genomic features of ovarian clear cell cancer and compares the genetic architectures of high-grade serous ovarian cancer and clear cell carcinoma in ovarian and endometrial tissues. PeerJ 2023; 11: e14653.
[18] Zhou G, Zhu Z, Li L and Ding J. Resibufogenin inhibits ovarian clear cell carcinoma (OCCC) growth *in vivo*, and migration of OCCC cells in vitro, by down-regulating the PI3K/AKT and actin cytoskeleton signaling pathways. Am J Transl Res 2019; 11: 6290-303.
[19] Farley JH, Brady WE, O'Malley D, Fujiwara K, Yonemori K, Bonebrake A, Secord AA, Stephan JM, Walker JL, Nam JH, Birrer MJ and Gershenson DM. A phase II evaluation of temsirolimus with carboplatin and paclitaxel followed by temsirolimus consolidation in clear cell ovarian cancer: an NRG oncology trial. Gynecol Oncol 2022; 167: 423-8.
[20] Winter WE 3rd, Maxwell GL, Tian C, Carlson JW, Ozols RF, Rose PG, Markman M, Armstrong DK, Muggia F and McGuire WP; Gynecologic Oncology Group Study. Prognostic factors for stage III epithelial ovarian cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2007; 25: 3621-7.
[21] Chen MC, Lee KD, Lu CH, Wang TY, Huang SH and Chen CY. The bidirectional association among female hormone-related cancers: breast, ovary, and uterine corpus. Cancer Med 2018; 7: 2299-306.
[22] Lee KD, Chen SC, Chan CH, Lu CH, Chen CC, Lin JT, Chen MF, Huang SH, Yeh CM and Chen MC. Increased risk for second primary malignancies in women with breast cancer diagnosed at young age: a population-based study in Taiwan. Cancer Epidemiol Biomarkers Prev 2008; 17: 2647-55.
[23] Li Z, Wu Q, Song J, Zhang Y, Zhu S and Sun S. Risk of second primary female genital malignancies in women with breast cancer: a SEER analysis. Horm Cancer 2018; 9: 197-204.
[24] Michailidou K, Beesley J, Lindstrom S, Canisius S, Dennis J, Lush MJ, Maranian MJ, Bolla MK, Wang Q, Shah M, Perkins BJ, Czene K, Eriksson M, Darabi H, Brand JS, Bojesen SE, Nordestgaard BG, Flyger H, Nielsen SF, Rahman N, Turnbull C; BOCS, Fletcher O, Peto J, Gibson L, dos-Santos-Silva I, Chang-Claude J, Flesch-Janys D, Rudolph A, Eilber U, Behrens S, Nevanlinna H, Muranen TA, Aittomäki K, Blomqvist C, Khan S, Aaltonen K, Ahsan H, Kibriya MG, Whittemore AS, John EM, Malone KE, Gammon MD, Santella RM, Ursin G, Makalic E, Schmidt DF, Casey G, Hunter DJ, Gapstur SM, Gaudet MM, Diver WR, Haiman CA, Schumacher F, Henderson BE, Le Marchand L, Berg CD, Chanock SJ, Figueroa J, Hoover RN, Lambrechts D, Neven P, Wildiers H, van Limbergen E, Schmidt MK, Broeks A, Verhoef S, Cornelissen S, Couch FJ, Olson JE, Hallberg E, Vachon C, Waisfisz Q, Meijers-Heijboer H, Adank MA, van der Luijt RB, Li J, Liu J, Humphreys K, Kang D, Choi JY, Park SK, Yoo KY, Matsuo K, Ito H, Iwata H, Tajima K, Guénel P, Truong T, Mulot C, Sanchez M, Burwinkel B, Marme F, Surowy H, Sohn C, Wu AH, Tseng CC, Van Den Berg D, Stram DO, González-Neira A, Benitez J, Zamora MP, Perez JIA, Shu XO, Lu W, Gao YT, Cai H, Cox A, Cross SS, Reed MWR, Andrulis IL, Knight JA, Glendon G, Mulligan AM, Sawyer EJ, Tomlinson I, Kerin MJ, Miller N, kConFab I, Group A, Lindblom A, Margolin S, Teo SH, Yip CH, Taib NAM,

Tan GH, Hooning MJ, Hollestelle A, Martens JWM, Collée JM, Blot W, Signorello LB, Cai Q, Hopper JL, Southey MC, Tsimiklis H, Apicella C, Shen CY, Hsiung CN, Wu PE, Hou M-F, Kristensen VN, Nord S, Alnaes GIG, Nbcs, Giles GG, Milne RL, McLean C, Canzian F, Trichopoulos D, Peeters P, Lund E, Sund M, Khaw KT, Gunter MJ, Palli D, Mortensen LM, Dossus L, Huerta JM, Meindl A, Schmutzler RK, Sutter C, Yang R, Muir K, Lophatananon A, Stewart-Brown S, Siriwanarangsan P, Hartman M, Miao H, Chia KS, Chan CW, Fasching PA, Hein A, Beckmann MW, Haeberle L, Brenner H, Dieffenbach AK, Arndt V, Stegmaier C, Ashworth A, Orr N, Schoemaker MJ, Swerdlow AJ, Brinton L, Garcia-Closas M, Zheng W, Halverson SL, Shrubsole M, Long J, Goldberg MS, Labrèche F, Dumont M, Winqvist R, Pylkäs K, Jukkola-Vuorinen A, Grip M, Brauch H, Hamann U, Brüning T, Network G, Radice P, Peterlongo P, Manoukian S, Bernard L, Bogdanova NV, Dörk T, Mannermaa A, Kataja V, Kosma VM, Hartikainen JM, Devilee P, Tollenaar RAEM, Seynaeve C, Van Asperen CJ, Jakubowska A, Lubinski J, Jaworska K, Huzarski T, Sangrajrang S, Gaborieau V, Brennan P, McKay J, Slager S, Toland AE, Ambrosone CB, Yannoukakos D, Kabisch M, Torres D, Neuhausen SL, Anton-Culver H, Luccarini C, Baynes C, Ahmed S, Healey CS, Tessier DC, Vincent D, Bacot F, Pita G, Alonso MR, Álvarez N, Herrero D, Simard J, Pharoah PPDP, Kraft P, Dunning AM, Chenevix-Trench G, Hall P and Easton DF. Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. Nat Genet 2015; 47: 373-80.

[25] Phelan CM, Kuchenbaecker KB, Tyrer JP, Kar SP, Lawrenson K, Winham SJ, Dennis J, Pirie A, Riggan MJ, Chornokur G, Earp MA, Lyra PC Jr, Lee JM, Coetzee S, Beesley J, McGuffog L, Soucy P, Dicks E, Lee A, Barrowdale D, Lecarpentier J, Leslie G, Aalfs CM, Aben KKH, Adams M, Adlard J, Andrulis IL, Anton-Culver H, Antonenkova N; AOCS study group, Aravantinos G, Arnold N, Arun BK, Arver B, Azzollini J, Balmaña J, Banerjee SN, Barjhoux L, Barkardottir RB, Bean Y, Beckmann MW, Beeghly-Fadiel A, Benitez J, Bermisheva M, Bernardini MQ, Birrer MJ, Bjorge L, Black A, Blankstein K, Blok MJ, Bodelon C, Bogdanova N, Bojesen A, Bonanni B, Borg Å, Bradbury AR, Brenton JD, Brewer C, Brinton L, Broberg P, Brooks-Wilson A, Bruinsma F, Brunet J, Buecher B, Butzow R, Buys SS, Caldes T, Caligo MA, Campbell I, Cannioto R, Carney ME, Cescon T, Chan SB, Chang-Claude J, Chanock S, Chen XQ, Chiew YE, Chiquette J, Chung WK, Claes KBM, Conner T, Cook LS, Cook J, Cramer DW, Cunningham JM, D'Aloisio AA, Daly MB, Damiola F, Damirovna SD, Dansonka-Mieszkowska A, Dao F, Davidson R, DeFazio A, Delnatte C, Doheny KF, Diez O, Ding YC, Doherty JA, Domchek SM, Dorfling CM, Dörk T, Dossus L, Duran M, Dürst M, Dworniczak B, Eccles D, Edwards T, Eeles R, Eilber U, Ejlertsen B, Ekici AB, Ellis S, Elvira M, Study E, Eng KH, Engel C, Evans DG, Fasching PA, Ferguson S, Ferrer SF, Flanagan JM, Fogarty ZC, Fortner RT, Fostira F, Foulkes WD, Fountzilas G, Fridley BL, Friebel TM, Friedman E, Frost D, Ganz PA, Garber J, García MJ, Garcia-Barberan V, Gehrig A, Collaborators GS, Gentry-Maharaj A, Gerdes AM, Giles GG, Glasspool R, Glendon G, Godwin AK, Goldgar DE, Goranova T, Gore M, Greene MH, Gronwald J, Gruber S, Hahnen E, Haiman CA, Håkansson N, Hamann U, Hansen TVO, Harrington PA, Harris HR, Hauke J, Study H, Hein A, Henderson A, Hildebrandt MAT, Hillemanns P, Hodgson S, Høgdall CK, Høgdall E, Hogervorst FBL, Holland H, Hooning MJ, Hosking K, Huang RY, Hulick PJ, Hung J, Hunter DJ, Huntsman DG, Huzarski T, Imyanitov EN, Isaacs C, Iversen ES, Izatt L, Izquierdo A, Jakubowska A, James P, Janavicius R, Jernetz M, Jensen A, Jensen UB, John EM, Johnatty S, Jones ME, Kannisto P, Karlan BY, Karnezis A, Kast K, Investigators KC, Kennedy CJ, Khusnutdinova E, Kiemeney LA, Kiiski JI, Kim SW, Kjaer SK, Köbel M, Kopperud RK, Kruse TA, Kupryjanczyk J, Kwong A, Laitman Y, Lambrechts D, Larrañaga N, Larson MC, Lazaro C, Le ND, Le Marchand L, Lee JW, Lele SB, Leminen A, Leroux D, Lester J, Lesueur F, Levine DA, Liang D, Liebrich C, Lilyquist J, Lipworth L, Lissowska J, Lu KH, Lubiński J, Luccarini C, Lundvall L, Mai PL, Mendoza-Fandiño G, Manoukian S, Massuger LFAG, May T, Mazoyer S, McAlpine JN, McGuire V, McLaughlin JR, McNeish I, Meijers-Heijboer H, Meindl A, Menon U, Mensenkamp AR, Merritt MA, Milne RL, Mitchell G, Modugno F, Moes-Sosnowska J, Moffitt M, Montagna M, Moysich KB, Mulligan AM, Musinsky J, Nathanson KL, Nedergaard L, Ness RB, Neuhausen SL, Nevanlinna H, Niederacher D, Nussbaum RL, Odunsi K, Olah E, Olopade OI, Olsson H, Olswold C, O'Malley DM, Ong KR, Onland-Moret NC; OPAL study group, Orr N, Orsulic S, Osorio A, Palli D, Papi L, Park-Simon TW, Paul J, Pearce CL, Pedersen IS, Peeters PHM, Peissel B, Peixoto A, Pejovic T, Pelttari LM, Permuth JB, Peterlongo P, Pezzani L, Pfeiler G, Phillips KA, Piedmonte M, Pike MC, Piskorz AM, Poblete SR, Pocza T, Poole EM, Poppe B, Porteous ME, Prieur F, Prokofyeva D, Pugh E, Pujana MA, Pujol P, Radice P, Rantala J, Rappaport-Fuerhauser C, Rennert G, Rhiem K, Rice P, Richardson A, Robson M, Rodriguez GC, Rodríguez-Antona C, Romm J, Rookus MA, Rossing MA, Rothstein JH, Rudolph A, Run-

nebaum IB, Salvesen HB, Sandler DP, Schoemaker MJ, Senter L, Setiawan VW, Severi G, Sharma P, Shelford T, Siddiqui N, Side LE, Sieh W, Singer CF, Sobol H, Song H, Southey MC, Spurdle AB, Stadler Z, Steinemann D, Stoppa-Lyonnet D, Sucheston-Campbell LE, Sukiennicki G, Sutphen R, Sutter C, Swerdlow AJ, Szabo CI, Szafron L, Tan YY, Taylor JA, Tea MK, Teixeira MR, Teo SH, Terry KL, Thompson PJ, Thomsen LCV, Thull DL, Tihomirova L, Tinker AV, Tischkowitz M, Tognazzo S, Toland AE, Tone A, Trabert B, Travis RC, Trichopoulou A, Tung N, Tworoger SS, van Altena AM, Van Den Berg D, van der Hout AH, van der Luijt RB, Van Heetvelde M, Van Nieuwenhuysen E, van Rensburg EJ, Vanderstichele A, Varon-Mateeva R, Vega A, Edwards DV, Vergote I, Vierkant RA, Vijai J, Vratimos A, Walker L, Walsh C, Wand D, Wang-Gohrke S, Wappenschmidt B, Webb PM, Weinberg CR, Weitzel JN, Wentzensen N, Whittemore AS, Wijnen JT, Wilkens LR, Wolk A, Woo M, Wu X, Wu AH, Yang H, Yannoukakos D, Ziogas A, Zorn KK, Narod SA, Easton DF, Amos CI, Schildkraut JM, Ramus SJ, Ottini L, Goodman MT, Park SK, Kelemen LE, Risch HA, Thomassen M, Offit K, Simard J, Schmutzler RK, Hazelett D, Monteiro AN, Couch FJ, Berchuck A, Chenevix-Trench G, Goode EL, Sellers TA, Gayther SA, Antoniou AC and Pharoah PDP. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet 2017; 49: 680-91.

[26] Staley JR, Blackshaw J, Kamat MA, Ellis S, Surendran P, Sun BB, Paul DS, Freitag D, Burgess S, Danesh J, Young R and Butterworth AS. PhenoScanner: a database of human genotype-phenotype associations. Bioinformatics 2016; 32: 3207-9.

[27] Gram IT, Lukanova A, Brill I, Braaten T, Lund E, Lundin E, Overvad K, Tjønneland A, Clavel-Chapelon F, Chabbert-Buffet N, Bamia C, Trichopoulou A, Zylis D, Masala G, Berrino F, Galasso R, Tumino R, Sacerdote C, Gavrilyuk O, Kristiansen S, Rodríguez L, Bonet C, Huerta JM, Barricarte A, Sánchez MJ, Dorronsoro M, Jirström K, Almquist M, Idahl A, Bueno-de-Mesquita HB, Braem M, Onland-Moret C, Tsilidis KK, Allen NE, Fedirko V, Riboli E and Kaaks R. Cigarette smoking and risk of histological subtypes of epithelial ovarian cancer in the EPIC cohort study. Int J Cancer 2012; 130: 2204-10.

[28] Burgess S, Butterworth A and Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol 2013; 37: 658-65.

[29] Bowden J, Davey Smith G, Haycock PC and Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol 2016; 40: 304-14.

[30] Qin Q, Zhao L, Ren A, Li W, Ma R, Peng Q and Luo S. Systemic lupus erythematosus is causally associated with hypothyroidism, but not hyperthyroidism: a Mendelian randomization study. Front Immunol 2023; 14: 1125415.

[31] Bowden J, Davey Smith G and Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol 2015; 44: 512-25.

[32] Xu Q, Ni JJ, Han BX, Yan SS, Wei XT, Feng GJ, Zhang H, Zhang L, Li B and Pei YF. Causal relationship between gut microbiota and autoimmune diseases: a two-sample Mendelian randomization study. Front Immunol 2022; 12: 746998.

[33] Cohen JF, Chalumeau M, Cohen R, Korevaar DA, Khoshnood B and Bossuyt PM. Cochran's Q test was useful to assess heterogeneity in likelihood ratios in studies of diagnostic accuracy. J Clin Epidemiol 2015; 68: 299-306.

[34] Verbanck M, Chen CY, Neale B and Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat Genet 2018; 50: 693-8.

[35] Burgess S and Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. Eur J Epidemiol 2017; 32: 377-89.

[36] Burgess S, Bowden J, Fall T, Ingelsson E and Thompson SG. Sensitivity analyses for robust causal inference from Mendelian randomization analyses with multiple genetic variants. Epidemiology 2017; 28: 30-42.

[37] Jia YS, Yang L, Zhu YQ and Ma C. Beta-catenin knockdown impairs the viability of ovarian cancer cells by modulating YAP-dependent glycolysis. Am J Transl Res 2023; 15: 982-94.

[38] Kitamura S, Yamaguchi K, Murakami R, Furutake Y, Higasa K, Abiko K, Hamanishi J, Baba T, Matsumura N and Mandai M. PDK2 leads to cisplatin resistance through suppression of mitochondrial function in ovarian clear cell carcinoma. Cancer Sci 2021; 112: 4627-40.

[39] Chen CA, Chiang YC, Chang MC, Hu YH, You SL, Cheng YY, Chou CY and Cheng WF. Gene methylation profiles as prognostic markers in ovarian clear cell and endometrioid adenocarcinomas. Am J Transl Res 2015; 7: 139-52.

[40] DeVorkin L, Hattersley M, Kim P, Ries J, Spowart J, Anglesio MS, Levi SM, Huntsman DG, Amaravadi RK, Winkler JD, Tinker AV and Lum JJ. Autophagy inhibition enhances sunitinib efficacy in clear cell ovarian carcinoma. Mol Cancer Res 2017; 15: 250-8.

[41] Sun L, Ji WX, Li Y, Li ZL, Duan CC, Xia BR and Xiao L. The PAPSS1 gene is a modulator of response to cisplatin by regulating estrogen receptor alpha signaling activity in ovarian cancer cells. J Ovarian Res 2023; 16: 187.
[42] Akahane T, Sekizawa A, Okuda T, Kushima M, Saito H and Okai T. Disappearance of steroid hormone dependency during malignant transformation of ovarian clear cell cancer. Int J Gynecol Pathol 2005; 24: 369-76.
[43] Orrantia-Borunda E, Anchondo-Nuñez P, Acuña-Aguilar LE, Gómez-Valles FO and Ramírez-Valdespino CA. Subtypes of breast cancer. In: Mayrovitz HN, editor. Breast Cancer. Exon Publications; 2022.
[44] Hanker AB, Sudhan DR and Arteaga CL. Overcoming endocrine resistance in breast cancer. Cancer Cell 2020; 37: 496-513.
[45] Itamochi H, Oishi T, Oumi N, Takeuchi S, Yoshihara K, Mikami M, Yaegashi N, Terao Y, Takehara K, Ushijima K, Watari H, Aoki D, Kimura T, Nakamura T, Yokoyama Y, Kigawa J and Sugiyama T. Whole-genome sequencing revealed novel prognostic biomarkers and promising targets for therapy of ovarian clear cell carcinoma. Br J Cancer 2017; 117: 717-24.
[46] Shoji T, Tatsuki S, Abe M, Tomabechi H, Takatori E, Kaido Y, Nagasawa T, Kagabu M, Baba T and Itamochi H. Novel therapeutic strategies for refractory ovarian cancers: clear cell and mucinous carcinomas. Cancers (Basel) 2021; 13: 6120.
[47] Hu ZY, Xiao H, Xiao M, Tang Y, Sun J, Xie ZM and Ouyang Q. Inducing or preventing subsequent malignancies for breast cancer survivors? Double-edged sword of estrogen receptor and progesterone receptor. Clin Breast Cancer 2018; 18: e1149-e1163.
[48] Byrne EM, Yang J and Wray NR. Inference in psychiatry via 2-sample Mendelian randomization-from association to causal pathway? JAMA Psychiatry 2017; 74: 1191-2.
[49] Yarmolinsky J, Wade KH, Richmond RC, Langdon RJ, Bull CJ, Tilling KM, Relton CL, Lewis SJ, Davey Smith G and Martin RM. Causal Inference in cancer epidemiology: what is the role of Mendelian randomization? Cancer Epidemiol Biomarkers Prev 2018; 27: 995-1010.
[50] Hu J, Song J, Chen Z, Yang J, Shi Q, Jin F, Pang Q, Chang X, Tian Y, Luo Y and Chen L. Reverse causal relationship between periodontitis and shortened telomere length: bidirectional two-sample Mendelian random analysis. Front Immunol 2022; 13: 1057602.
[51] Guo JZ, Xiao Q, Gao S, Li XQ, Wu QJ and Gong TT. Review of Mendelian randomization studies on ovarian cancer. Front Oncol 2021; 11: 681396.
[52] Nakata H, Halbach S, Geiser F, Stock S, Kowalski C, Enders A, Pfaff H and Ernstmann N. Health literacy, mental disorders and fear of progression and their association with a need for psycho-oncological care over the course of a breast cancer treatment. Psychol Health Med 2021; 26: 818-31.