Do Psychiatric Disorders Influence the Risk of Female Cancer? Results From a Genetic Study

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Abstract

**Background:** Depression and anxiety contribute to an increased global burden of disease and affect women more often than men. Despite evidence from experimental data showing a shared biological mechanism involved in both mental health disorders and female hormone-dependent cancers, results from epidemiological investigations remain inconsistent.

**Methods:** We aim to understand a putative causal relationship between psychological distress and female malignancy by conducting a two-sample Mendelian randomization (MR) analysis. We used summary statistics from the hitherto largest genome-wide association studies (GWAS) performed in depression ($N_{\text{case}}=246,363$), anxiety ($N_{\text{case}}=44,465$), breast ($N_{\text{case}}=122,977$) and ovarian ($N_{\text{case}}=25,509$) cancer. We constructed strong instruments using the 102 depression-associated SNPs, the 6 anxiety-associated SNPs, and applied several MR approaches.

**Results:** We found that genetic predisposition to depression significantly increased the risk of both overall breast cancer (OR [95%CI] = 1.10 [1.03-1.18]) and its estrogen receptor (ER)- subtype (1.12 [1.01-1.24]), while a borderline significance was observed for ER+ subtype (1.08 [0.99-1.18]). These findings were corroborated by our genetic correlation analysis where a significantly shared genetic basis was observed for depression and breast cancer. On the contrary, we did not identify any causal association of anxiety with breast cancer. None of the mental health traits were associated with the onset of ovarian cancer or its serous subtype. Sensitivity analyses using different sets of instruments revealed consistent results.

**Conclusions:** Our findings suggest that poor mental health condition such as major depression disorder is likely to be causally associated with the development of breast cancer, providing evidence supporting for the potential deleterious consequence of mental illness on cancer onset.

Introduction

Depression and anxiety are the two most frequently diagnosed mental health disorders which contribute to an increased burden of morbidity and disability worldwide.[1, 2] According to results from the Global Burden of Disease Study 2017, both depression and anxiety appear in the top 20 causes of years lived with disability (YLDs) and rank particularly high among women (the 3rd and 8th leading causes). [3]

It has been speculated that vulnerability to stress, especially the presence of mental health disorders, are likely to increase the susceptibility to subsequent cancer onset, in particular, hormone-driven cancers. Several hypothesized physiological mechanisms have been proposed including inflammation and oxidative stress, a decreased immune surveillance, as well as a dysfunctional activation of the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis.[4] Indeed, a large number of epidemiological studies have explored a link between poor mental health and the development of female hormone-related cancers. For example, a meta-analysis aggregating data from 11 cohort studies totaling 182,241 participants found a pooled relative risk (RR) of breast cancer as 1.13 with confidence intervals including 1.00 (95%CI: 0.94–1.36), indicating a nonsignificant association between depression and breast cancer. [5] Nevertheless, another meta-analysis performed subgroup analysis on studies with a follow-up period of more than 10 years and identified a statistically significant pooled RR of 2.50 (95%CI: 1.06–5.91) for breast cancer among depressed patients. [6] As for ovarian cancer, the current epidemiological evidence are insufficient to demonstrate any association where results from a meta-analysis of 3 studies reported a pooled RR of 1.08 (95%CI: 0.93–1.24) for depression and anxiety patients. [7]

Nevertheless, epidemiological design can hardly determine whether an association is causal or as a result of confounding,[8] since the observed relationship could be mediated via the shared poor lifestyles including active smoking[9–13], excessive alcohol consumption,[10, 11, 14–16] obesity,[9, 17–19] and nonadherence to medical appointments (screening). Furthermore, observational studies cannot identify reverse causality, meaning there is likely a bidirectional relationship between cancer and depression.[20] It may take a long time to validate associations as a stronger increase of breast cancer
risk with longer follow-up period (e.g. > 10 years[6]) may be needed due to the length of carcinogenesis.[21] Finally, inconsistency may also arise from differed definitions and misclassifications of mental health disorder.

Mendelian randomization (MR) uses genetic variants (single nucleotide polymorphisms, SNPs) associated with exposure as instrumental variables (IVs) to estimate a causal effect between exposures and outcomes.[8] Since genetic variants are randomly assigned at conception and largely independent of confounders, MR estimates are less susceptible to reverse causality and confounding inherent in conventional epidemiological designs.[22–24] The application of MR remains limited in the field of psychiatric disorder and malignancy – the only available studies were all restricted to schizophrenia and reported a shared genetic component as well as a causal relationship between schizophrenia and breast cancer. [25–27]

Therefore, we aim to conduct a two-sample MR to understand a putative causal relationship between common psychiatric disorders and female hormone-driven cancers. Summary statistics for the exposures were extracted from the largest genome-wide association studies (GWAS) of anxiety (44,465 cases / 58,113 controls) and depression (246,363 cases / 561,190 controls) conducted by the Psychiatric Genomic Consortium (PGC).[28, 29] Summary statistics for the outcomes were extracted from the largest GWAS of breast (122,977 cases / 105,974 controls) and endothelia ovarian cancer (25,509 cases / 40,941 controls) conducted by the OncoArray network.[30, 31]

**Materials And Methods**

We applied a standard two-sample MR framework where the IV-exposure and IV-outcome associations were from two independent non-overlapping populations.

**IV-exposure** For anxiety, GWAS summary data were obtained from the UK biobank (UKB) where participants involving 44,465 cases and 58,113 controls (all European ancestry) took part in an online mental health follow-up questionnaire. We incorporated 6 IVs associated with two anxiety-related phenotypes (lifetime anxiety disorder and current anxiety symptoms) derived from electronic health records. Lifetime anxiety disorder combined self-reported clinical lifetime diagnosis of an anxiety disorder and probable generalized anxiety disorder; while current anxiety symptoms counted as cases anyone who reported at least moderate symptoms of generalized anxiety disorder in the two weeks preceding assessment.[28]

For depression, GWAS summary data were obtained from a meta-analysis of 246,363 cases and 561,190 controls (all European ancestry) combining three largest previous studies of depression (23andMe, UKB and PGC). The phenotypes ranged self-reported help-seeking for problems with nerves, tension or depression (termed broad depression). A total of 102 independent variants associated with depression were identified, including genes and pathways associated with synaptic structure and neurotransmission.[29]

In both exposure GWAS, quality control for post-imputation data of a minor allele frequency (MAF) > 0.01 and a Hardy-Weinberg equilibrium (HWE) > $1 \times 10^{-6}$ were applied. Population stratification was controlled by adjusting for principal components.[28, 29] We only included biallelic common genetic variants reaching genome-wide significance as our IVs, that is, 6 anxiety-associated SNPs and 102 depression-associated SNPs.

**IV-outcome** For the outcome breast cancer, GWAS summary data from the Breast Cancer Association Consortium (BCAC) on 122,977 breast cancer cases (of which, 69,501 estrogen receptor (ER) + breast cancer and 21,468 ER− breast cancer) and 105,974 controls were used, all European ancestry.[30] For ovarian cancer, GWAS summary data from the Ovarian Cancer Association Consortium (OCAC) on 25,509 epithelial ovarian cancer (EOC) cases (of which, 14,049 serous subtype, a subtype that is part of the surface epithelial-stromal tumor group which derives from Mullerian epithelium) and 40,941 controls were retrieved, all European ancestry.[31]

In both outcome GWAS, approximately 10 million SNPs were imputed to the 1000 Genome Project reference panel and filtered by stringent quality control procedures (call rate > 95%, MAF > 0.001, HWE > $1 \times 10^{-7}$ in controls and > $1 \times 10^{-12}$ in cases).[30, 31] IV-outcome associations were extracted from cancer GWAS summary data.
**Statistical methods** We performed a standard two-sample MR to evaluate a causal relationship between exposures (anxiety and depression) and outcomes (risk of breast and ovarian cancer) applying several MR approaches and sensitivity analyses.

The inverse-variance weighted (IVW) approach is a commonly used method [22] which implements an inverse-weighted meta-analysis regressing the outcome effect coefficient on the exposure effect coefficient with intercept term zero. To reduce biased estimate leading to causality at the circumstance that an IV has pleiotropic effect, we adopted two additional methods, MR-Egger regression [23] and weighted median approach.[24] The MR-Egger can be used to detect and correct for bias due to directional pleiotropy. Complementary to MR-Egger, the weighted median method can provide a consistent causal estimation with even ≥ 50% invalid IVs.

Complementary to the primary analyses, several important sensitivity analyses were conducted to guarantee the validity of findings. Firstly, to detect the influence of outlier SNPs on the estimate, we conducted a leave-one-out analysis excluding one SNP at-a-time to evaluate the impact of single SNP on MR estimate. Secondly, we estimated the causal association excluding pleiotropic SNPs, that is, SNPs significantly associated with confounding traits such as BMI, smoking and education as confirmed by NHGRI-EBI Catalog of published GWAS (Supplementary Table 1). High prevalence of mental health disorders is frequently observed among cancer patients, to largely minimize reverse causality,[20] we also applied a bidirectional MR analysis where we assessed the effect of cancer status on mental health conditions.

Finally, MR analysis used only a few instrumental SNPs to interrogate a putative causal relationship. With the availability of full set GWAS summary data, we were able to calculate genetic correlation leveraging SNPs all over the genome, which measures the intrinsic average genome-wide sharing between traits that is due to genetic effects independent of environmental factors. We carried out this analysis using an algorithm implemented in statistical software linkage disequilibrium score regression (LDSC) which leverages the relationship between association statistics and linkage disequilibrium patterns across the genome and estimates genetic correlation with only GWAS summary data.[32]

We calculated statistical power using the non-centrality parameter (NCP) of the test statistic as suggested by Brion et al. (http://cns-genomics.com/shiny/mRnd/). All analyses were conducted using package “TwoSampleMR” in R v3.6.3.

**Results**

The number of overall breast cancer cases was 122,977, of which 69,501 were ER+ cases and 21,468 were ER- cases. The number of overall ovarian cancer cases was 22,406, of which 14,049 were serous ovarian cancer cases. According to the exposure GWAS, 1.37% and 8.9% of the phenotypic variance can be explained by the 6 anxiety-associated SNPs and the 102 depression-associated SNPs. With such amount of variance explained and under current sample size, for anxiety, our study had 80% power to detect a causal effect of a relative 10.5% (i.e. ORs of 1.105 or more) increase in overall breast cancer risk and 21% increase in overall ovarian cancer. The corresponding estimates for ER+, ER- and serous subtypes were 12.5%, 18.2% and 21.0%. For depression, the minimal detectable effects in overall breast and ovarian cancer were 8.0% and 4.8% increase, and the relevant estimates in ER+, ER- and serous subtypes were 9.4%, 4.0% and 7.1% increase (Table 1).

Supplementary Table 2 presents the associations of index SNPs (IVs) with cancers.

As shown in Figure 1, we found a significantly shared genetic basis between anxiety and breast cancer (overall =0.10, P=6.0 \( \cdot 10^{-3} \); ER+ =0.15, P=5.0 \( \cdot 10^{-3} \)) as well as between depression and breast cancer (overall =0.09, P=1.6 \( \cdot 10^{-5} \); ER+ =0.08, P=1.5 \( \cdot 10^{-3} \); ER- =0.10, P=2.9 \( \cdot 10^{-3} \)), all P-values passed Bonferroni correction (P < 0.05/5). On the contrary, we did not observe significant genetic correlation of anxiety or depression with ovarian cancer.

Motivated by these findings, we continued to performed MR analysis. As shown in Table 2, for anxiety, we did not find convincing evidence in support for a causal effect with overall breast cancer (OR [95%CI] 0.99 [0.94-1.04]) or its subsets (ER+ 0.97 [0.92-1.03]; ER- 1.05 [0.92-1.19]) using the IVW approach. Consistently, no significant result was revealed from the MR-
Egger regression (0.96 [0.80-1.15]) or the weighted median approach (0.99 [0.93-1.05]). We did not observe apparent signs of horizontal pleiotropy (P for MR-Egger intercept = 0.79, 0.95 and 0.38 for overall, ER+ and ER– breast cancer).

However, we found genetic predisposition to depression was significantly associated with an increased risk of both overall breast cancer (1.10 [1.03-1.18], P = 6.0 \times 10^{-5}) and ER– subtype (1.12 [1.01-1.24], P = 0.04) using IVW. The effects remained consistent using weighted median approach (overall 1.09 [1.00-1.19], P = 0.04; ER– 1.17 [1.01-1.36], P = 0.03). The estimates remained directional consistent in MR-Egger although we observed larger statistically uncertainties, which was not surprising given MR-Egger provides twice larger standard errors compared to IVW. We did not observe horizontal pleiotropy (P for MR-Egger intercept = 0.87 and 0.82 or overall and ER– breast cancer). No significant finding was identified for depression with ER+ subset (1.08 [0.99-1.18], P = 0.07).

On the contrary, neither anxiety nor depression appeared to influence the risk of ovarian cancer. Using IVW, the associations for anxiety (0.98 [0.86-1.12], P = 0.78) and depression (1.05 [0.93-1.17], P = 0.43) with overall ovarian cancer was not significant. The relevant risk in serous subtype was 0.93 with anxiety 1.00 with depression (Table 2). All estimates remained consistent in MR-Egger regression (overall: anxiety 0.80 [0.48-1.35], depression 1.65 [0.84-3.25]; serous subtype: anxiety 0.76 [0.42-1.37], depression 1.26 [0.55-2.89]) or weighted median approach (overall: anxiety 0.95 [0.83-1.09], depression 1.10 [0.93-1.29]; serous subtype: anxiety 0.85 [0.73-0.99], depression 1.03 [0.85-1.26]).

Since we observed a putative causal link between depression and breast cancer, to guarantee the validity of results, we performed several sensitivity analyses. In the leave-one-out analysis, the depression-breast cancer association remained consistent when we iteratively excluded one SNP at a time and performed IVW using the remaining SNPs (Supplementary Table 3). We also controlled for the influence from confounders such as obesity, smoking and education by excluding pleiotropic SNPs. Using the 73 depression-associated IVs that are not associated with confounding traits, we detected consistent significant causal effects of depression with breast cancer (overall 1.12 [1.02-1.22], P = 0.01; ER– 1.16 [1.02-1.31], P = 0.02), corroborating our primary finding (Table 3).

Malignant diseases and mental health conditions often co-occur. To understand if cancer status would affect mental health, we implemented a bidirectional MR analysis. Genetic predisposition to cancer was neither associated with the risk of depression (breast cancer 1.00 [0.99-1.02]; ER+ 1.00 [0.99-1.02]; ER– 1.07 [0.97-1.17]; ovarian cancer 1.00 [0.98-1.02]) nor associated with the risk of anxiety (breast cancer 0.98 [0.94-1.03]; ER+ 0.99 [0.94-1.04]; ER– 0.99 [0.97-1.02]; ovarian cancer 0.94 [0.85-1.05]). We identified similar null effects using the MR-Egger regression and the weighted median approach (Table 4). We did not perform bidirectional MR analysis for serous ovarian cancer due to limited availability of IVs in this cancer subset.

**Discussion**

Mendelian randomization (MR) is an elegant statistical tool which leverages large-scale GWAS summary data to understand a putative causal relationship between exposures and outcomes. This approach has been successfully applied to schizophrenia where three studies independently yet consistently demonstrated a causal role of schizophrenia in breast cancer – each SD increment in liability to schizophrenia increases risk of breast cancer by 1.04 to 1.09-fold; while in contrast, the estimated causal effect of breast cancer on schizophrenia was not significantly different from zero. [25–27] These genetic results provide an avenue to elucidating the biological mechanisms underpinning the observed relationship as well as treatment strategies to both diseases. Unlike the case of schizophrenia, no MR design has been performed for depression and anxiety with cancer risk, despite the fact that they are the two most common psychiatric conditions that have been studied in relation to cancer in general. We for the first time demonstrate that genetic predisposition to depression significantly increases cancer risk by 10–15% in overall breast cancer and its ER– subtype. Moreover, we found a small but significant genetic correlation between the two disorders, indicating a shared genetic origin.
Epidemiological evidence regarding the depression-cancer relationship remains inconsistent, yet our findings are largely supported by prospective studies with longer follow-up times, which tend to identify stronger associations between depression and cancer. [21, 33, 34] For example, results from a large-scale cohort study with 24 years of follow-up showed that major depression disorder was associated with an increased risk of subsequent breast cancer (hazard ratio, HR = 4.4, 95%CI: 1.08–17.6). [33] In addition, our findings are also supported by a few small-scale case-control designs. For example, a study aggregated data from 582 cases and 540 controls and reported a risk factor of frequent depression (OR = 1.32, 95%CI: 1.00-1.75) with breast cancer onset in young women. [35] Similarly, a cross-sectional study involving 54 cases and 1,106 controls supported a risk effect of depression on breast cancer (OR = 4.50, 95%CI: 1.64–12.31). [34] Biological mechanisms underlying depression and breast cancer remains unclear, most likely involving both genetic susceptibility and environmental triggers. One hypothesis is that persistent activation of HPA axis in depression impairs immune response, which contributes to the development and progression of cancer. [36, 37] Our findings also suggest a genetic overlap between the two traits, where we estimated that around one-tenth of the genetic contribution to breast cancer is shared with genetic contribution to depression. In fact, the genetic correlation of 0.10 between depression and breast cancer (as a somatic disease) is noteworthy in comparison with genetic correlation between some psychiatric disorders, for example, between depression and anxiety (r_g = 0.15). [38] On the contrary, our MR study did not reveal evidence for a link between anxiety and breast cancer despite a significant genetic correlation. With limited availabilities of instrumental variables in anxiety (N = 6), our MR results may be underpowered and should be interpreted with caution.

Evidence regarding the association between psychiatric disorders and subsequent onset of ovarian cancer remains controversial. A recent meta-analysis aggregating 3 cohorts reported a null association of depression and anxiety with ovarian cancer incidence (RR = 1.08, 95%CI: 0.93–1.24); [39] while a prospective study aggregating two US cohorts identified depression assessed 2–4 years before cancer diagnosis is associated with an increased risk of ovarian cancer (HR = 1.30, 95%CI: 1.05–1.60). [40] Our MR found no evidence for an association of depression/anxiety with risk of either overall or serous ovarian cancer. We performed several sensitivity analyses to support the validity of our primary findings. For example, we conducted MR-Egger regression to detect horizontal pleiotropy; we checked each instrument in GWAS catalogue and performed sensitivity analysis removing pleiotropic IVs (IVs associated with traits other than exposure and outcome of interest). The consistent results across different analyses lend supports to the validity of our findings.

The diagnosis and treatment of female cancer are frequently accompanied by changes in physical status and function, unpleasant side effects, decline in quality of life, and impaired social relationships. Therefore, unlike the sparsity of studies regarding cancer incidence, psychological distress among cancer patients have been extensively investigated. For breast cancer, some studies reported the prevalence of depression and anxiety were the highest shortly after diagnosis (< 6 months) but declined afterwards [41] and the long-term (> 1 year) risk of depression and anxiety was not significantly heightened among patients compared to the general population; [42] while other studies reported inconsistent results. [43–45] For ovarian cancer, a prospective study found the level of anxiety was the highest prior to surgery and gradually decreased thereafter; [46] yet a retrospective study found women diagnosed with ovarian cancer had an increased risk for depression compared to their controls. [47] The associations may differ by treatment measures, cancer sites and follow-up period. Our bidirectional MR results provide evidence for the direction of this relationship, in which genetically instrumented hormone-dependent cancer did not appear to have a reverse impact on depression or anxiety. These negative emotions that are often observed in clinical settings could therefore likely be consequences secondary to cancer diagnosis.

To the best of our knowledge, this is the first study using genetic instruments to assess a relationship between common mental health disorders (depression and anxiety) and female hormonal cancer. A fundamental assumption of MR is that the genetic variants do not influence outcome via a different biological pathway from the exposures (horizontal pleiotropy). Violation of these assumptions could bring bias into the causal estimates. We used MR-Egger regression and median weighted approach as complimentary analysis to minimize such confounding. We also performed sensitivity analyses to ensure the validity of IVs. People under psychiatric distress tend to have poorer health behaviors including higher prevalence of smoking and drinking, inactivity and poor diet. We capitalized on the 73 SNPs strongly associated with depression at
genome-wide significance and free from associations with confounding traits as confirmed by GWAS Catalog. The pattern of results remained unchanged as compared to the primary analysis guaranteed the robustness of our MR estimates and suggested negligible bias from pleiotropy.

Several limitations need to be acknowledged. First, our analysis was performed among the European population limiting its generalizability. Moreover, it can be argued that not all our depression-breast cancer causal associations survived Bonferroni correction (P < 0.05/5), however, results were consistent in terms of both direction and effect size across different statistical approaches and sensitivity analyses, all pointing towards a role of depression in breast cancer. Last but not least, although we constructed a strong IV for depression using the 102 depression-associated SNPs, the effect size was minimal (12% in the flagship relationship) and the phenotypic variance explained by those GWAS-identified depression-associated SNPs was still modest (~ 9%), future studies should be conducted to replicate our findings.

Conclusions

To conclude, our study, based on data from the most recently published also the largest breast cancer GWAS, provides evidence on that the reported association between depression and breast cancer is likely to be causal. Our results highlight the important role of early screening and effective intervention of depression in cancer prevention. Future studies are needed to explore the anxiety-cancer relationship when large-scale GWAS results of anxiety are released into public domain.

Abbreviations

MDD major depression disorder
MR Mendelian randomization
SNPs single nucleotide polymorphisms
IV instrumental variable
GWAS genome-wide association studies
UKB UK biobank
MAF minor allele frequency
HWE Hardy-Weinberg equilibrium
BCAC the Breast Cancer Association Consortium
OCAC the Ovarian Cancer Association Consortium
EOC epithelial ovarian cancer
IVW inverse-variance weighted method
LDSC linkage disequilibrium score regression

Declarations

Ethics approval and consent to participate

The summary statistics used in the present study are aggregated level of data which do not contain any personal information. The original GWAS have obtained ethical approval from relevant ethics review committees.
Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Nothing declared

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Authors’ contributions

JJZ and XJ designed the study, analyzed the data, interpreted the results and wrote the manuscript. HYZ, ZN and JS interpreted the results and revised the manuscript. All authors provided the corresponding author with permission to be named in the manuscript. XJ is the guarantor of this study

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### Table 1. Number of cancer cases, controls and statistical power in Mendelian randomization study of anxiety, depression and risk of breast and ovarian cancer.

| Cancer type      | Cases  | Controls | Total   | Proportion of cases | Minimum detectable odds ratio |
|------------------|--------|----------|---------|---------------------|-------------------------------|
|                  |        |          |         |                     | anxiety $(R^2=0.014)$          | depression $(R^2=0.089)$       |
| Breast cancer    |        |          |         |                     |                               |                               |
| Overall          | 122977 | 105974   | 228951  | 0.54                | 0.906/1.105                   | 0.925/1.080                   |
| ER-positive      | 69501  | 95042    | 164543  | 0.42                | 0.887/1.125                   | 0.910/1.094                   |
| ER-negative      | 21468  | 100594   | 122062  | 0.18                | 0.830/1.182                   | 0.961/1.040                   |
| Ovarian cancer   |        |          |         |                     |                               |                               |
| Overall          | 22406  | 40941    | 63347   | 0.35                | 0.817/1.210                   | 0.954/1.048                   |
| Serous           | 14049  | 40941    | 54990   | 0.25                | 0.782/1.246                   | 0.931/1.071                   |

ER, oestrogen receptor; assume 80% power, 5% alpha level; $R^2$: phenotypic variance explained by the index SNPs.
Table 2. Mendelian randomization estimates of anxiety and depression with risk of breast and ovarian cancer using multiple GWAS-identified variants.

| Cancer type (Outcome) | Method        | Anxiety (Exposure) | Depression (Exposure) |
|-----------------------|---------------|--------------------|-----------------------|
|                       |               | OR (95% CI)        | P-value               | OR (95% CI)              | P-value | P-value for intercept |
| **Overall Breast Cancer** | Inverse variance weighted | 0.99(0.94-1.04) | 0.58                  | 1.10(1.03-1.18)          | 6 \times 10^{-3} |
|                       | MR-Egger      | 0.96(0.80-1.15)    | 0.69                  | 1.07(0.70-1.63)          | 0.77    | 0.87 |
|                       | Weighted median | 0.99(0.93-1.05)   | 0.76                  | 1.09(1.00-1.19)          | 0.04    |
| **ER-positive Breast** | Inverse variance weighted | 0.97(0.92-1.03) | 0.34                  | 1.08(0.99-1.18)          | 0.07    |
| Cancer                | MR-Egger      | 0.98(0.79-1.22)    | 0.87                  | 1.13(0.68-1.90)          | 0.63    | 0.86 |
|                       | Weighted median | 0.97(0.91-1.04)   | 0.45                  | 1.07(0.96-1.18)          | 0.23    |
| **ER-negative Breast** | Inverse variance weighted | 1.05(0.92-1.19) | 0.49                  | 1.12(1.01-1.24)          | 0.04    |
| **Cancer**            | MR-Egger      | 0.83(0.51-1.34)    | 0.48                  | 1.04(0.56-1.94)          | 0.90    | 0.82 |
|                       | Weighted median | 1.07(0.94-1.20)   | 0.32                  | 1.17(1.01-1.36)          | 0.03    |
| **Overall Ovarian**   | Inverse variance weighted | 0.98(0.86-1.12) | 0.78                  | 1.05(0.93-1.17)          | 0.43    |
| **Cancer**            | MR-Egger      | 0.80(0.48-1.35)    | 0.45                  | 1.65(0.84-3.25)          | 0.15    | 0.18 |
|                       | Weighted median | 0.95(0.83-1.09)   | 0.48                  | 1.10(0.93-1.29)          | 0.28    |
| **Serous Ovarian**    | Inverse variance weighted | 0.93(0.80-1.07) | 0.30                  | 1.00(0.87-1.14)          | 0.95    |
| Cancer                | MR-Egger      | 0.76(0.42-1.37)    | 0.41                  | 1.26(0.55-2.89)          | 0.58    | 0.57 |
|                       | Weighted median | 0.85(0.73-0.99)   | 0.04                  | 1.03(0.85-1.26)          | 0.75    |
Table 3. Mendelian randomization estimates of depression with risk of breast and ovarian cancer using multiple GWAS-identified variants excluding confounders.

| Method                    | Overall breast cancer | ER-positive breast cancer | ER-negative breast cancer | Overall ovarian cancer | Serous ovarian cancer |
|---------------------------|-----------------------|---------------------------|---------------------------|------------------------|-----------------------|
|                           | OR (95% CI)           | P-value                   | OR (95% CI)               | P-value                | OR (95% CI)           | P-value               |
| Inverse variance weighted | 1.12 (1.02-1.22)      | 0.01                      | 1.11 (1.00-1.24)          | 0.06                   | 1.16 (1.02-1.31)      | 0.02                   |
| MR-Egger                  | 1.29 (0.75-2.22)      | 0.36                      | 1.35 (0.70-2.60)          | 0.37                   | 1.56 (0.74-3.33)      | 0.25                   |
| MR-Egger intercept        | 0.60                  | 0.56                      |                           | 0.43                   | 0.31                  | 0.66                   |
| Weighted median           | 1.09 (0.98-1.20)      | 0.11                      | 1.07 (0.94-1.20)          | 0.31                   | 1.18 (0.99-1.41)      | 0.06                   |
|                           |                       |                           |                           |                        | 1.13 (0.92-1.38)      | 0.25                   |
|                           |                       |                           |                           |                        | 1.04 (0.83-1.30)      | 0.72                   |
Table 4. Bidirectional mendelian randomization estimates of genetic predisposition to cancer with risk of anxiety and depression using multiple cancer GWAS-identified variants.

| Cancer type (Exposure) | Method              | Anxiety (Outcome) | Depression (Outcome) |
|------------------------|---------------------|-------------------|----------------------|
|                        | OR (95% CI)         | P-value           | P-value for intercept| OR (95% CI)         | P-value | P-value for intercept |
| Overall Breast Cancer  | Inverse variance    | 0.98 (0.94-1.03)  | 0.45                 | 1.00 (0.99-1.02)    | 0.63    |                     |
|                        | weighted            |                   |                      |                     |         |                      |
| MR-Egger               | 0.98 (0.90-1.06)    | 0.59              | 0.61                 | 0.98 (0.95-1.01)    | 0.11    | 0.03                 |
| Weighted median        | 0.96 (0.90-1.02)    | 0.18              |                      | 1.00 (0.98-1.03)    | 0.71    |                      |
| ER-positive Breast Cancer | Inverse variance    | 0.99 (0.94-1.04)  | 0.65                 | 1.00 (0.99-1.02)    | 0.70    |                     |
|                        | weighted            |                   |                      |                     |         |                      |
| MR-Egger               | 0.96 (0.86-1.07)    | 0.46              | 0.65                 | 0.98 (0.95-1.00)    | 0.07    | 0.02                 |
| Weighted median        | 0.99 (0.92-1.06)    | 0.76              |                      | 1.01 (0.98-1.03)    | 0.65    |                      |
| ER-negative Breast Cancer | Inverse variance    | 1.07 (0.97-1.17)  | 0.18                 | 0.99 (0.97-1.02)    | 0.65    |                     |
|                        | weighted            |                   |                      |                     |         |                      |
| MR-Egger               | 0.92 (0.67-1.24)    | 0.58              | 0.67                 | 0.96 (0.87-1.05)    | 0.36    | 0.41                 |
| Weighted median        | 1.06 (0.93-1.22)    | 0.36              |                      | 0.99 (0.96-1.03)    | 0.57    |                      |
| Overall Ovarian Cancer | Inverse variance    | 0.94 (0.85-1.05)  | 0.28                 | 1.00 (0.98-1.02)    | 0.75    |                     |
|                        | weighted            |                   |                      |                     |         |                      |
| MR-Egger               | 1.00 (0.84-1.18)    | 0.99              | **0.002**            | 1.01 (0.98-1.05)    | 0.57    | 0.35                 |
| Weighted median        | 0.97 (0.87-1.09)    | 0.64              |                      | 1.00 (0.97-1.02)    | 0.40    |                      |

Figures
Figure 1

Genetic correlation between anxiety and depression and cancers. a, genetic correlation between anxiety and cancers. b, genetic correlation between depression and cancers. blue square: genetic correlation, grey bars: confidence interval.

Supplementary Files

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