Examining the causal relationship between schizophrenia and breast cancer: survival analysis and Mendelian randomization

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GLOSSARY OF ABBREVIATIONS

CCI	Charlson comorbidity index
CI	Confidence interval
ER	Estrogen receptor
FGA	First generation antipsychotics
GP	General population group
GSMR	Generalized summary-based Mendelian randomization
GWAS	Genome-wide association study
HER2	Human growth factor receptor 2
HEXA	Health examinee cohort
HR	Hazard ratio
ICD-10	International classification of diseases
IRR	Incidence rate ratio
IVW	Inverse variance weighted
KoGES	Korea genome epidemiology study
LD	Linkage disequilibrium
MR	Mendelian randomization
NHID	National health information database
NHIS	National health insurance system
OP	Other psychiatric disorders patients
OR	Odds ratio
PTSD	Post-traumatic stress disorder
PRS	Polygenic risk score
SeBCS	Seoul breast cancer study
SGA	Second generation antipsychotics
SNP	Single nucleotide polymorphism
SP	Schizophrenia patients

ABSTRACT

Examining the causal relationship between schizophrenia and breast cancer: survival analysis and Mendelian randomization

Introduction

Epidemiological observational research has identified a link between schizophrenia and breast cancer, but findings in Asian contexts show variations. The underlying cause of the higher breast cancer incidence among individuals with schizophrenia remains unclear. A central query revolves around whether this association is attributed to genetic or lifestyle risk factors or if it arises from factors related to the disease itself, such as the disease process or its treatment.

Therefore, this study aimed to investigate the association between schizophrenia and breast cancer separately in two main parts. First, the current study aimed to examine whether schizophrenia patients have increased breast cancer risk than the general population and other psychiatric disorders and further identify the effect of antipsychotic medication. Second, the study aimed to investigate the causal relationship between schizophrenia and breast cancer by conducting a two-sample Mendelian randomization analysis.

PART I. Association between schizophrenia and breast cancer: survival analysis

Medical claims data of women aged 18 to 80 years in the Korean National Health Information Database from 2007 to 2018 were employed. Schizophrenia cases were defined as women with ICD-10 codes F20 or F25 and who had been prescribed antipsychotic medication (n=224,743). The first control group was defined as women with other psychiatric disorders (ICD-10 codes F10-F19 or F30-F69) (n=224,743). The second control group was defined as women in the general Korean population (n=449,486). Cases and controls were matched by index date (date of the first diagnosis of schizophrenia during the follow-up period) and age at the index date, in a 1:1:2 ratio. The hazard of breast cancer was estimated using the Cox proportional hazards model, adjusting for insurance premiums, residential region, and medical comorbidities. Among schizophrenia cases, the landmark method was used to estimate the association between the duration of antipsychotic medication use and the incidence of breast cancer. In multivariable Cox regression models, these rates corresponded to an increased hazard of breast cancer among women with schizophrenia compared with women in the general Korean population (Hazard Ratio (HR)=1.26; 95% CI, 1.12-1.33) and compared with women with other psychiatric disorders (HR=1.08; 95% CI, 1.02-1.14). Among women with schizophrenia, the hazard of breast cancer was greater among those who took antipsychotic medications for 1 year or more compared with those who took antipsychotics for less than 6 months (0.5-1 year: HR=0.95, 95% CI [0.68-1.33];1-3 years: HR=1.28, 95% CI [1.04-1.56]; 3-4 years: HR=1.20, 95% CI [0.96-1.50]; ≥4 years: HR=1.32, 95% CI [1.09-1.61]).

PART II. Causal relationship between schizophrenia and breast cancer: two-sample Mendelian randomization and polygenic risk score

A two-sample Mendelian randomization was performed to identify the causal association between schizophrenia and breast cancer. Genetic variants significantly associated with schizophrenia were obtained from the NHGRI-EBI GWAS Catalog. The study population was 2,165 patients with breast cancer from the Seoul Breast Cancer Study (SeBCS) and 2,046 healthy controls from a large urban cohort that is part of the Korea Genome Epidemiology Study (KoGES). A candidate gene association analysis was conducted for both breast cancer cases and controls, followed by a two-sample MR. For MR methods, inverse variance weighting (IVW), weighted median, and MR-Egger approaches were used to estimate the effect of schizophrenia on breast cancer risk. Radial MR methods were applied to remove outliers subject to pleiotropic bias. A causal association between schizophrenia and breast cancer was observed in the IVW method of MR analysis (OR=1.14; 95% CI, 1.01-1.28). The Radial MR analysis detected outliers and consistent effect estimates were observed after removing the outliers (OR=1.14, 95% CI 1.01-1.28). A polygenic risk score (PRS) was created with SNPs that showed a positive direction in the MR results of individual SNPs and compared in the breast cancer group and the control group. A significant association was observed between schizophrenia PRS (per 1SD) and breast cancer (Odds Ratio (OR)=1.18; 95% CI, 1.12-1.26).

CONCLUSION

The phenotypic association analysis demonstrated that women with schizophrenia have an elevated risk of breast cancer compared to women with other psychiatric disorders and women in the general Korean population. Among women with schizophrenia, breast cancer risk is associated with increasing duration of treatment with antipsychotic medications. The Mendelian randomization study corroborated the findings, which suggested a causal relationship between schizophrenia and breast cancer.

Keywords: schizophrenia, breast cancer, antipsychotic medication, landmark analysis, two-sample Mendelian randomization

I. INTRODUCTION

1. Backgrounds

Schizophrenia and breast cancer risk

Schizophrenia is a severe mental disorder causing significant personal and social burden due to severe and long-term disability.[1] Globally, the age-standardized (based on the Global Burden of Disease 2016 reference population) point prevalence of schizophrenia is estimated to be 0.28%, and the number of prevalent cases was 20.9 million in 2016.[2] Schizophrenia is characterized by positive (e.g. hallucinations, delusions), negative (e.g. avolition, anhedonia), and disorganized symptoms, and is also associated with cognitive impairment.[1,3]

People with schizophrenia are known to be at increased risk for multiple comorbidities, including anxiety disorders, depression, cardiovascular disease, and diabetes.[4-7] The cumulative result over the life course, at a population level, is that people with schizophrenia have a 15-year lower life expectancy compared with the general population.[8] The decrement in life expectancy is thought to have multifactorial causes, including the illness itself (e.g., suicide), adverse effects of medical comorbidities (e.g., acute myocardial infarction), adverse effects of medications (e.g., cardiometabolic effects of long-term antipsychotic treatment), and differences in health and preventive behaviors (e.g., cigarette smoking, cancer screening).[9]

The risk of cancer among people with schizophrenia has also been studied, including breast cancer, which is the most commonly diagnosed cancer in women.[10] While this is still an inconclusive topic, there have been many studies that suggest an increased risk of breast cancer among women with schizophrenia.

Review of previous studies

In a population-based cohort study in Sweden followed up from 1990 to 2013, people with schizophrenia had a significantly higher incidence of breast cancer compared with the general population (IRR=1.19, 95% confidence interval (CI) [1.12-1.26]).[11] . In that study, schizophrenia patients were defined using the National Patient Register, and 59,262 schizophrenia patients were obtained, analyzing a larger number of study subjects and incident cases than previous studies. In an Asian context, a retrospective cohort study from Taiwan, examining follow-up data from 1998 to 2008 involving 10,727 patients with schizophrenia, found a significantly higher risk of breast cancer compared to the general population (HR=1.94, 95% CI 1.43-2.63).[12] The hazard ratio was obtained after adjusting for age, occupation, income, morbidity, and medication use. These findings were consistent with a recent meta-analysis[13], although substantial between-study variance existed.[14-29] Other studies have shown a null or even inverse association between schizophrenia and breast cancer,[15,17,18,20,23,24,29] with significant heterogeneity observed across populations.[30] In particular, a retrospective cohort study conducted in Israel, one of the Asian countries, reported a very low breast cancer incidence rate in patients with schizophrenia compared to the general population (SIR=0.63, 95% CI 0.47-0.83)[23] (Appendix Table 1).

In order to address these discrepancies in the literature, this study was conducted to estimate the risk of breast cancer among people with schizophrenia in the Korean national population.

Comparison with other psychiatric disorders patients

Previous studies assessing the incidence of breast cancer in schizophrenia patients have exclusively used the general population, or individuals without schizophrenia or psychiatric disorders, as a comparative reference group. However, it is also necessary to investigate whether patients with schizophrenia have a higher risk of breast cancer, not only compared to the general population but also compared to patients with other psychiatric diseases. Although still controversial, studies have shown that people with bipolar disorder or PTSD also have a higher risk of breast cancer than the general population.[31-33] In addition, people with schizophrenia and those with other psychiatric diseases share several characteristics that may contribute to an increased risk of breast cancer, including smoking, stress, and obesity.[23,34] Therefore, if schizophrenia patients have a higher risk of breast cancer compared to other psychiatric patients, it can be expected that there is a schizophrenia-specific cause.

Hormonal factors and antipsychotic implications

Moreover, the disturbances of endogenous hormones have been implicated as a common risk factor for schizophrenia and breast cancer.[35] Previous studies have shown that estrogen levels decrease during certain periods, such as menopause, which can often lead to

exacerbation of schizophrenic symptoms in schizophrenia patients.[36,37] Also, hyperprolactinemia has been found in many patients with schizophrenia, even in antipsychotic-naïve patients with first-episode psychosis.[38-40] In addition, many studies have shown that high prolactin in postmenopausal women is associated with breast cancer.[41] Accordingly, it can be predicted that the association between schizophrenia and breast cancer will be higher in women during perimenopause, when endogenous hormones such as estrogen and prolactin change significantly, than in women in other age groups. Therefore, it is necessary to compare the associations between schizophrenia and breast cancer in subgroups after stratification by age.

Finally, antipsychotics are an important factor among the proposed causes of the increased risk of breast cancer in patients with schizophrenia. Antipsychotic medications are used as a fundamental element of treatment to reduce the symptoms' intensity and frequency[42]. However, many types of antipsychotics have been known to cause hyperprolactinemia[43,44], and hyperprolactinemia has been implicated as a risk factor for breast cancer.[45,46] However, there is still a lack of research on the extent to which the risk of breast cancer increases depending on the type and duration of the antipsychotics.

Causality between schizophrenia and breast cancer revealed through genetic information

On the other hand, epidemiological observational studies face limitations in establishing causal relationships due to unobserved confounding and reverse causality. To address these

limitations, this study aimed to employ two methods with genetic information to evaluate whether genetic susceptibility to schizophrenia is associated with breast cancer risk. First, it was necessary to obtain the schizophrenia-related PRS, a continuous score that reflects an individual's genetic susceptibility to the disease, and confirm its association with breast cancer. Second, it was imperative to confirm causality by performing Mendelian randomization. Mendelian randomization (MR) offers a solution by employing genome-wide significant genetic variants as instrumental variables (IVs) to accurately determine a specific exposure's causal impact and direction on an outcome, theoretically eliminating unobserved confounders. By conducting 2 sample MR, in which IV and the estimation of the IV with breast cancer were derived from independent populations, bias in the causal estimate can be further reduced.[47]

While recent research indicates a connection between genetic markers linked to schizophrenia and an increased breast cancer risk, the potential genetic overlap between these conditions has not been thoroughly investigated.[48,49] Furthermore, genetic analyses are scarce to explore the association between schizophrenia and breast cancer within the East Asian population.

Implications for Prevention and Treatment

Schizophrenia and breast cancer, respectively representing mental and cancerous diseases, impose significant burdens on individuals and society. Investigating the association between these two diseases offers insight into whether patients with schizophrenia have a

heightened risk for breast cancer and the biological mechanisms underlying this potential risk. Such comprehension is vital for devising strategies for the prevention, detection, and treatment of breast cancer in those with schizophrenia. Moreover, focusing on the Korean population in this study ensures insights that cater to the unique characteristics of East Asians.

2. Objectives of the study

The research questions deal with two main parts regarding schizophrenia and breast cancer; analysis using epidemiological data and analysis using genetic data. More specifically, in the first part, the current study aimed to

1) compare the risk of breast cancer in patients with schizophrenia and other psychiatric disorders, and the general population by using Asian national data,

2) further stratify by age to compare the magnitude of the association between schizophrenia and breast cancer in postmenopausal women with other age groups,

3) determine the exact effect of taking antipsychotics on breast cancer in patients with schizophrenia.

In the latter part, the study aimed to determine whether a causal relationship between schizophrenia and breast cancer is established by using

1) a two-sample Mendelian randomization analysis and

2) a polygenic risk score analysis.

PART I. Association between schizophrenia and breast cancer: survival analysis

II. MATERIALS AND METHODS

1. Data source and study population

The Korea National Health Information Database (NHID) is a public database on medical services organized using the National Health Insurance System (NHIS) of South Korea. This universal health insurance system covers the medical expenses of approximately 98% of the Korean population.[50] The database includes information on medical utilization, insurance eligibility, diagnostic codes, prescribed medications and procedures, and claims records. Diagnoses were coded according to the 10th International Classification of Diseases (ICD-10) revision.

This analysis used NHID data on women aged 18-80 years from 2007 to 2018. The schizophrenia group was defined as those with ICD-10 diagnostic codes for schizophrenia or schizoaffective disorder (F20, F25) between 2007 and 2018 and who had been prescribed antipsychotic medications within the same time frame. ICD-10 diagnostic codes and antipsychotic medications were reviewed by a qualified psychiatrist (CHC, SK). The list of ATC codes for antipsychotic medications is presented in Appendix Table 2.

A retrospective matched cohort design was used to compare outcomes among people with schizophrenia vs. people with other psychiatric disorders and people in the general population. The first control group (control 1) consisted of people with ICD-10 diagnostic codes for psychiatric disorders between 2007 and 2018, excluding schizophrenia and

schizoaffective disorder (F10-F19, F30-F69). The second control group (control 2) consisted of people in the general Korean population, defined as those without any ICD-10 diagnostic codes for psychiatric diseases or dementia (F00-F99, G30, F31.8, G31.00) within the same time frame. The two control group design is that some studies have shown that people with bipolar disorder or PTSD also have a higher risk of breast cancer than the general population.[31,32,51] In addition, people with schizophrenia and other psychiatric disorders may share observed or unobserved behavioral or structural characteristics that could contribute to an increased risk of breast cancer, including smoking, stress, obesity, or reduced preventive screening rates.[23,34,52] Thus, if it were found that people with schizophrenia have a higher risk of breast cancer compared to people with other psychiatric disorders, such a finding could support a schizophrenia-specific cause.

The earliest diagnosis date of schizophrenia during the follow-up period was set as the index date, and two control groups with the same age as schizophrenia patients were randomly selected on the index date. People with schizophrenia were matched in a 1:1 ratio with people in the “other psychiatric disorders” control group and a 1:2 ratio with people in the general Korean population control group. Individuals with “other psychiatric disorders” who had not been diagnosed with psychiatric disorders on or before the index date (those diagnosed with other psychiatric disorders between 2007-2018, but after the index date) were excluded from the matching process. The preliminary screening initially identified 234,865 people with schizophrenia, who were matched with 234,865 people with other psychiatric disorders and 469,730 people in the general population. Preliminarily

matched individuals were considered in blocks of four; and if any member of that group was diagnosed with breast cancer before the index date (or within one year after the index date), all four individuals in that group were excluded. On this basis, 10,122 people with schizophrenia, 10,122 people with other psychiatric disorders, and 20,244 people in the general population control group were excluded. The final analytic sample included 224,743 people with schizophrenia, 224,743 people with other psychiatric disorders, and 449,486 people in the general Korean population (Figure 1).

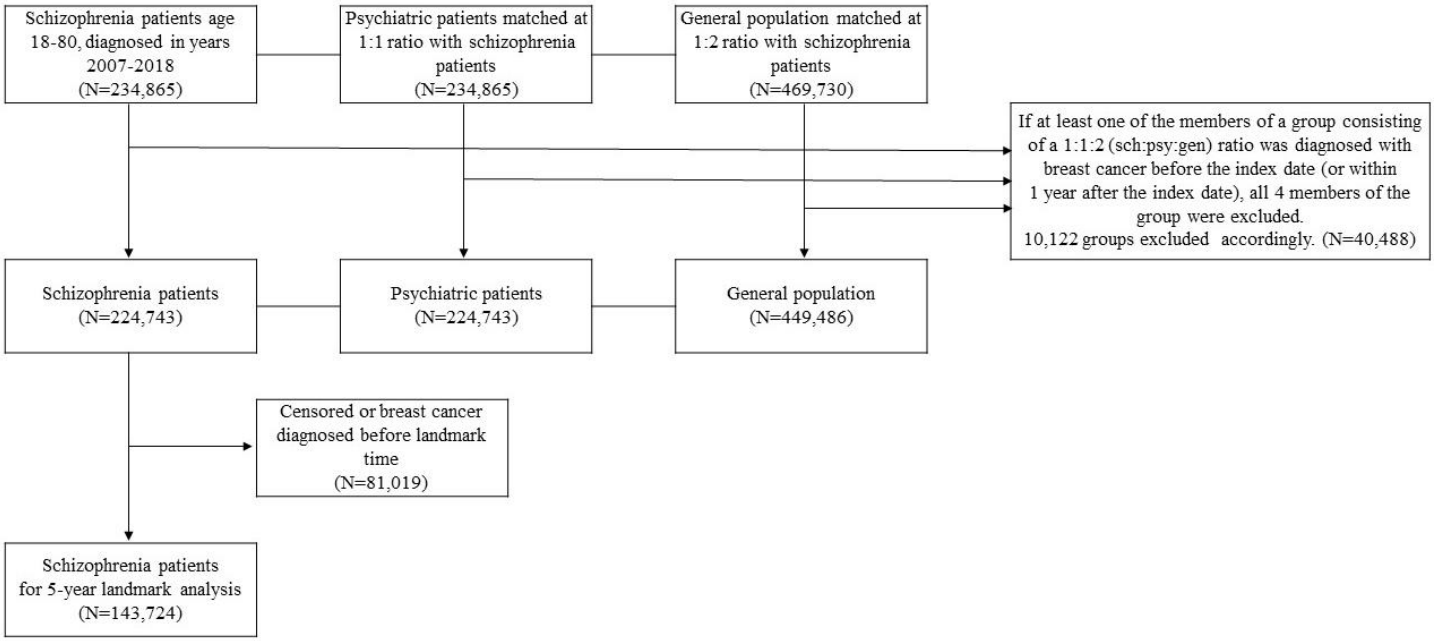

Figure 1. Flow chart of the study population (Part I)

2. Study variables

Breast cancer

Breast cancer cases were defined as having at least one record associated with an ICD-10 diagnostic code for invasive breast cancer (C50) or ductal carcinoma in situ of the breast (D051) observed any time during follow-up beginning 1 year after the index date. The 1 year lag time was used to minimize the possibility of reverse causality and to account for a biologically meaningful latency window, given that a short period of exposure after a diagnosis of schizophrenia is unlikely to be the primary cause of a subsequent cancer diagnosis.[53] The NHID ICD-10 codes for diagnosis of schizophrenia, other psychiatric disorders, and breast cancer have all been previously validated.[54,55]

Covariates

Estimates were sought to be adjusted for potential confounding by socioeconomic status and medical comorbidity. Medical insurance premium payments in the index year served as a proxy variable for socioeconomic status.[56] The insurance premium was categorized into five groups as follows: medical aid (for socioeconomically disadvantaged individuals who do not pay insurance premiums), Q1 (the lowest), Q2, Q3, and Q4 (the highest). Residential regions were classified into metropolitan, urban, and rural. To adjust for medical comorbidities, the Charlson Comorbidity Index (CCI) was utilized.[57] CCI values were based on the appearance of the corresponding ICD-10 diagnostic codes for each comorbidity before the index date. (Appendix Table 3)

3. Statistical analysis

Baseline differences in covariates between the schizophrenia group and the two control groups were assessed using repeated measures analysis of variance (ANOVA) for continuous variables and McNemar's test for categorical variables. Using the Cox proportional hazards model stratified on matched pairs, the hazard ratio (HR) (conditional on matched pairs) and 95% confidence interval (95% CI) were estimated for breast cancer for the schizophrenia group and the other psychiatric disorders group (control 1), specifying the general population group (control 2) as the referent. To confirm the difference in breast cancer risk between patients with schizophrenia and patients with other psychiatric disorders, the same analysis was conducted with the other psychiatric disorders group as the referent. In the crude model, the schizophrenia and the two control groups were matched by index date and age at the index year, with no covariate adjustment. In the adjusted model, insurance premiums and CCI as covariates were included. Violations of the proportional hazards assumption were checked by fitting a regression model of the Schoenfeld residuals against time and testing for a nonzero slope.[58] Fine and Gray's competing risk survival analysis model was used in a sensitivity analysis, where mortality was considered a competing risk.[59] In addition, the E value with the lower confidence limit for the obtained point estimate was calculated as outlined by VanderWeele et al.[60,61] The E value represents the minimum level of association required between an unmeasured confounder and both the exposure and the outcome to completely nullify a specific association between the exposure and the outcome. As the E-value increases, it becomes more challenging to

ascribe the observed outcomes to an unaccounted-for covariate.

The two extensions were considered. First, this study conducted analyses stratified by age, specifying age categories as <40, 40-55, and ≥55. This analysis aimed to estimate the hazard ratio of breast cancer, differentiating perimenopausal or menopausal women from women of other age groups.[62] Additionally, the analysis was stratified by CCI, residential region, and insurance premium levels, to explore whether the association between schizophrenia and breast cancer varies according to the comorbidity or socioeconomic status.

In a second extension, this study used landmark analysis to estimate the hazard ratio of breast cancer according to the duration of antipsychotic medication treatment among schizophrenia patients. Antipsychotic medications are a mainstay of treatment in schizophrenia, used to reduce symptom intensity and frequency[42], but many antipsychotic medications have been known to cause hyperprolactinemia[43,44,63], and hyperprolactinemia has been implicated in the development of breast cancer.[45,46] For our landmark analysis, only those who had been followed for at least 5 years were included in the analytic sample. Of 224,743 people with schizophrenia included in the primary analysis, 143,724 were included in the landmark analysis (Figure 1). The landmark method was used to control for immortal time bias in estimating the risk of breast cancer according to the duration of antipsychotic medication treatment. Landmark analysis is a method of setting arbitrary landmark points, classifying study participants by exposed and unexposed status at the landmark point, and analyzing outcomes occurring in the period after the landmark

point.[64,65] Where events occur prior to the landmark point, those participants are excluded from observation. In this analysis, the duration of antipsychotic medication treatment was calculated as the period from the index date to the landmark point, and only breast cancer cases that occurred at least 1 year after the landmark point were analyzed. The landmark point was designated as 5 years after the index date. The robustness of these findings was probed by setting alternative landmark points at 4 years and 6 years. The duration of antipsychotic medication was calculated by adding the duration of the prescribed medication to the record. The NHID held information about prescribed medications, including prescription dates and the duration of the prescribed medications. Instances where there was an overlap between separate prescriptions for antipsychotics, were combined to form a single episode of antipsychotic use. Treatment duration was specified as a five-level categorical variable: <0.5 years, 0.5-1 year, 1-3 years, 3-4 years, and ≥4 years. Additionally, the same landmark analysis was performed after the stratification by generation of antipsychotics (first-generation antipsychotic [FGA] vs. second-generation antipsychotic [SGA]). In this stratified analysis, antipsychotics of different generations were adjusted to take into account the mutual effects of the two generation antipsychotics in patients taking both antipsychotics concurrently. In other words, the duration of SGA medication was adjusted in the FGA analysis, and the duration of FGA medication was adjusted in the SGA analysis.

The association between antipsychotic use and the risk of breast cancer has also been confirmed in patients with other psychiatric disorders. Using the general Cox proportional

hazard model, hazard ratios and 95% CIs for breast cancer were estimated in patients with other psychiatric disorders who were prescribed antipsychotics compared to those who were not prescribed antipsychotics.

All statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 4.2.2 (R Development Core Team, Vienna, Austria).

III. RESULTS

1. General characteristics of the study population

Consistent with the matching procedure, the average age was the same across all three groups (48.14 years; standard deviation [SD], 16.83). The CCI score indicating comorbidity was higher among people with schizophrenia and other psychiatric disorders compared with people in the general population: 27% of people in the schizophrenia group had a CCI score of 3 or higher (indicating moderate to severe comorbidity[66]), compared to 18% in the other psychiatric disorders group and 11% in the general population group. The proportion of schizophrenia patients residing in metropolitan areas was less (45.01%) compared to other control groups (46.11%, 49.54%), while the proportion of those living in rural areas was higher (11.22%) than in the other control groups (9.76%, 7.01%). The schizophrenia patients In the group of patients with schizophrenia, the proportion of people in the highest insurance group (Q4) was the lowest (26.71%). The psychiatric patient group had a higher percentage, and the general population group had the highest rate (30.78%, 32.88%). (Table1)

Table 1. Characteristics of schizophrenia patients and 2 control groups (1:1:2 matched)

	Schizophrenia patients	Other psychiatric disorders patients	General population group	p-value
N	224,743	224,743	449,486	
Person year	1594069.82	1686889.19	3264077.86	
Age, Mean (SD)	48.14 (16.83)	48.14 (16.83)	48.14 (16.83)	
Insurance premium quartile, N (%)				
Medical aid*	48982 (21.95)	10003 (4.50)	10471 (2.35)	<.0001
Q1(lowest)	37796 (16.93)	44880 (20.18)	87282 (19.62)	
Q2	34855 (15.62)	45499 (20.45)	90805 (20.41)	
Q3	41942 (18.79)	53597 (24.10)	110096 (24.74)	
Q4(highest)	59614 (26.71)	68460 (30.78)	146311 (32.88)	
Region of residence, N(%)				
Metropolitan area	101026 (45.01)	103314 (46.11)	221967 (49.54)	<.0001
Urban area	98241 (43.77)	98878 (44.13)	194688 (43.45)	
Rural area	25189 (11.22)	21864 (9.76)	31417 (7.01)	
Charlson comorbidity index, N (%)				
0	105444 (46.92)	99315 (44.19)	256388 (57.04)	<.0001
1, 2	59432 (26.44)	85395 (38.00)	145682 (32.41)	
≥3	59867 (26.64)	40033 (17.81)	47416 (10.55)	
Death, N(%)	4758 (2.12)	1119 (0.50)	2337 (0.52)	<.0001
Breast cancer, N (%)	2384 (1.06)	2276 (1.01)	3815 (0.85)	<.0001

Notes. Schizophrenia patients: persons diagnosed with schizophrenia and prescribed antipsychotics. Other psychiatric disorders patients: persons who have been diagnosed with psychiatric disorders, excluding the case group (diagnosis codes F10-F19, F30-F69). General population: persons who have never been diagnosed with psychiatric disorders or dementia (diagnosis codes F00-F99, G30, G31.8, G31.00). *Medical aid group consists of socioeconomically disadvantaged individuals who do not pay medical insurance premiums.

2. Association between schizophrenia and breast cancer risk

The incidence of breast cancer was 1.50 per 1,000 person-years among people with schizophrenia, 1.35 per 1,000 person-years among people with other psychiatric disorders, and 1.17 per 1,000 person-years in the general population. These differential incidence rates translated into an increased hazard of breast cancer among people with schizophrenia compared to people in the general Korean population (hazard ratio [HR]=1.27; 95% CI: 1.20-1.34). After adjusting for comorbidity, region of residence, and socioeconomic status, the estimated hazard remained similar (HR=1.26; 95% CI 1.12-1.33). People with other psychiatric disorders (control 1) also had an elevated hazard of breast cancer compared with people in the general population (HR=1.17; 95% CI: 1.12-1.22). When other psychiatric disorders were used as references in the adjusted model, the risk of breast cancer remained significantly higher in patients with schizophrenia (HR=1.08; 95% CI: 1.02-1.14) (Table 2).

Additionally, to evaluate the influence of unaccounted confounders on the study outcomes, E-values were computed. For the HR for breast cancer risk in schizophrenia compared to the general population, this sensitivity analysis yielded an E-value of 1.83, with the lower bound of the 95% CI at 1.49. This indicates the presence of unmeasured confounders that could potentially explain the association between schizophrenia and breast cancer. These confounding factors associated with exposure and outcome would need to have a hazard ratio of at least 1.83 to account for the observed association (Appendix Table 4).

In subdistributional hazard models accounting for competing risks, the estimated hazard ratios were 1.25 (95% CI 1.19-1.32) for people with schizophrenia and 1.17 (95% CI 1.12-1.23) for people with other psychiatric disorders, compared with the general population. Compared with those of people with other psychiatric disorders, the estimated hazard ratios were 1.07 (95% CI 1.01–1.13) for people with schizophrenia (Table 3).

Table 2. Hazard ratios for breast cancer among patients with schizophrenia and 2 control groups (1:1:2 matched)

	N	(case)	Incidence rate (N/1000py)	Unadjusted		Adjusted			
				HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Schizophrenia patients	224,743	(2384)	1.50	1.27 (1.20-1.34)	<.0001	1.26 (1.12-1.33)	<.0001	1.08 (1.02-1.14)	0.006
Other psychiatric disorders patients	224,743	(2276)	1.35	1.16 (1.10-1.22)	<.0001	1.17 (1.12-1.22)	<.0001	Ref	
General population	449,486	(3815)	1.17	Ref		Ref			

Notes. Schizophrenia patients: persons diagnosed with schizophrenia and prescribed antipsychotics. Other psychiatric disorders patients: persons who have been diagnosed with psychiatric disorders, excluding the case group (diagnosis codes F10-F19, F30-F69). General population group: persons who have never been diagnosed with psychiatric disorders or dementia (diagnosis codes F00-F99, G30, G31.8, G31.00).
Unadjusted: crude model (matched by age), Adjusted: insurance premiums, region of residence, Charlson Comorbidity Index (CCI) adjusted

Table 3. Results from the subdistributional hazard model (Fine and Gray model)

	N	(case)	Incidence rate (N/1000py)	Unadjusted		Adjusted			
				HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Schizophrenia patients	224,743	(2384)	1.50	1.26 (1.20-1.31)	<.0001	1.25 (1.19-1.32)	<.0001	1.07 (1.01-1.13)	0.017
Other psychiatric disorders patients	224,743	(2276)	1.35	1.16 (1.11-1.21)	<.0001	1.17 (1.12-1.23)	<.0001	Ref	
General population	449,486	(3815)	1.17	Ref		Ref			

Notes. Schizophrenia patients: persons diagnosed with schizophrenia and prescribed antipsychotics. Other psychiatric disorders patients: persons who have been diagnosed with psychiatric disorders, excluding the case group (diagnosis codes F10-F19, F30-F69). General population group: persons who have never been diagnosed with psychiatric disorders or dementia (diagnosis codes F00-F99, G30, G31.8, G31.00).
Unadjusted: crude model (matched by age), Adjusted: insurance premiums, region of residence, Charlson Comorbidity Index (CCI) adjusted

3. Stratified association between schizophrenia and breast cancer risk

In the age-stratified analysis, people with schizophrenia (compared with the general population) between the ages of 40 and 54 years had the highest risk of breast cancer in the fully adjusted model (HR=1.33, 95% CI [1.24–1.43], p value<.0001). The hazard ratio of breast cancer for those younger than 40 years was 1.12 (95% CI:1.02–1.24); among those ≥55 years of age, the hazard ratio was 1.27 (95% CI:1.15–1.41). However, compared with those with other psychiatric disorders, people with schizophrenia who are ≥55 years of age had a significantly higher risk of breast cancer (HR=1.13, 95% CI [1.02–1.26], p value=0.023). Patients with schizophrenia aged 40-54 years showed a marginally significant association with breast cancer compared to patients with other psychiatric disorders (HR=1.08, 95% CI [1.00-1.147], p-value=0.050) (Table 4).

Following stratification by the Charlson Comorbidity Index (CCI), the highest increase in breast cancer risk among schizophrenia patients, compared to the general population, was observed in those with a CCI score of 0 (HR=1.32, 95% CI [1.24–1.41], p value=<.0001). When compared to patients with other psychiatric disorders, statistically significant results were found only in the group with a CCI of 0 (HR=1.08, 95% CI [1.01–1.16], p value=0.030). In the subset characterized by greater physical frailty, indicated by a CCI of 3 or higher, the risk of breast cancer in schizophrenia patients did not show a significant increase either in comparison to the general population or to patients with other psychiatric disorders.

In addition, the stratification by residential area and insurance premiums revealed that schizophrenia patients residing in metropolitan areas and those belonging to the lower insurance premium group exhibited a heightened risk of breast cancer compared to the general population (Metro: HR=1.32, 95% CI [1.22-1.42], p-value<.0001; insurance premiums 0-5: HR=1.32, 95% CI [1.19-1.47], p-value<0.001). The increased risk was also statistically significant when compared to patients with other psychiatric disorders (Metro: HR=1.13, 95% CI [1.04-1.22], p-value=0.003; insurance premiums 0-5: HR=1.24, 95% CI [1.13-1.38], p-value<0.001) (Appendix Table 5-7).

Table 4. Hazard ratios for breast cancer among patients with schizophrenia and 2 control groups stratified by age at index year (1:1:2 matched)

			N	(case)	Incidence rate (N/1000py)	Unadjusted		Adjusted			
						HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age*	<40	Schizophrenia patients	76,594	(532)	0.93	1.11 (1.00-1.24)	0.052	1.12 (1.02-1.24)	0.024	1.03 (0.92-1.14)	0.657
		Other psychiatric disorders patients	76,594	(537)	0.92	1.10 (0.99-1.23)	0.073	1.10 (1.00-1.20)	0.058	Ref	
		General population	153,188	(936)	0.82	Ref		Ref			
	40-54	Schizophrenia patients	70,293	(1230)	2.14	1.32 (1.23-1.42)	<.0001	1.33 (1.24-1.43)	<.0001	1.08 (1.00-1.17)	0.050
		Other psychiatric disorders patients	70,293	(1164)	1.96	1.20 (1.12-1.30)	<.0001	1.23 (1.15-1.31)	<.0001	Ref	
		General population	140,586	(1879)	1.62	Ref		Ref			
	≥55	Schizophrenia patients	77,856	(622)	1.40	1.32 (1.19-1.46)	<.0001	1.27 (1.15-1.41)	<.001	1.13 (1.02-1.26)	0.023
		Other psychiatric disorders patients	77,856	(575)	1.13	1.11 (1.00-1.23)	0.051	1.13 (1.03-1.24)	0.011	Ref	
		General population	155,712	(1000)	1.03	Ref		Ref			

Notes. Schizophrenia patients: persons diagnosed with schizophrenia and prescribed antipsychotics. Other psychiatric disorders patients: persons who have been diagnosed with psychiatric disorders, excluding the case group (diagnosis codes F10-F19, F30-F69) General population group: persons who have never been diagnosed with psychiatric disorders or dementia (diagnosis codes F00-F99, G30, G31.8, G31.00). *Age at index year. Unadjusted: crude model (matched by age), Adjusted: insurance premiums, region of residence, Charlson Comorbidity Index (CCI) adjusted

4. Association between antipsychotic medication and breast cancer risk

Antipsychotics and breast cancer risk in schizophrenia patients

In the landmark analysis limited to people with schizophrenia, the risk of breast cancer increased with increasing duration of antipsychotic treatment. Compared with people on treatment for <0.5 years, people on treatment for 0.5-1 year did not have an elevated hazard of breast cancer (HR=0.95; 95% CI, 0.68-1.33). People on treatment for 1-3 years had a HR of 1.28 (95% CI: 1.04-1.56), people on treatment for 3-4 years had a HR of 1.20 (95% CI: 0.96-1.50), and people on treatment for ≥4 years had a HR of 1.32 (95% CI: 1.09-1.61) (p-value for trend: 0.005) (Table 5). Similar findings were obtained in landmark analyses specifying landmark time points of 4 and 6 years (Table 6).

When stratified by generation of antipsychotics (first-generation antipsychotic [FGA] vs. second-generation antipsychotic [SGA]), the estimated association between duration of treatment and breast cancer risk was not statistically significant for SGAs (p-value for trend: 0.105). For FGAs, people with schizophrenia who received treatment for 1-3 years had a HR of 1.29 (95% CI: 1.09-1.51), while people who received treatment for 3-4 years had a HR of 1.50 (95% CI: 1.16-1.96). While the test for trend was statistically significant (p=0.005), no statistically significant association was found for people who received treatment for more than 4 years (HR=1.06, 95% CI [0.80-1.40], p value=0.671) (Table 7).

The usage patterns of FGA and SGA were also explored among schizophrenia patients (Appendix Table 8). Given the frequent concurrent use of FGA and SGA by many patients,

and considering the potential mutual influence of these medications, each was incorporated as an adjustment variable in the final landmark analysis model.

Antipsychotics and breast cancer risk in other psychiatric disorders patients

As some patients with other psychiatric disorders may also take antipsychotics, we examined the distribution of antipsychotic treatment duration. However, a majority of individuals in the "other psychiatric disorders" group did not take antipsychotics (91.55%), and among those who did take antipsychotics, a significant portion had a treatment duration of less than one year (6.83%) (Appendix Table 9).

In patients with other psychiatric disorders, when analyzed using the general Cox proportional hazard model, the risk of breast cancer was significantly higher in those who were prescribed antipsychotics compared to those who were not receiving the antipsychotics (HR=1.15, 95% CI [1.00-1.31], p value=0.047) (Table 8).

Table 5. Landmark analysis of breast cancer incidence in schizophrenia patients with different durations of antipsychotic use

Antipsychotics duration	N	(case)	Incidence rate	Model1		Model2		
				HR (95% CI)	p-value	HR (95% CI)	p-value	p for trend
<0.5 year	24,319	(138)	0.64	Ref		Ref		
0.5-1 year	8,813	(48)	0.61	0.98 (0.70-1.36)	0.883	0.95 (0.68-1.33)	0.780	0.005
1-3 years	40,314	(372)	0.91	1.63 (1.34-1.99)	<.0001	1.28 (1.04-1.56)	0.017	
3-4 years	21,256	(177)	0.83	1.47 (1.17-1.83)	0.001	1.20 (0.96-1.50)	0.119	
≥4 years	49,022	(434)	0.91	1.54 (1.27-1.86)	<.0001	1.32 (1.09-1.61)	0.006	

Notes. Landmark time: 5 years after index date,
Incidence rates are expressed in units of N/1000person-year.
Model1: age adjusted, Model2: (model1) + insurance premiums, region of residence, Charlson Comorbidity Index (CCI) adjusted

Table 6. Sensitivity analysis for landmark analysis with different landmark time points

Landmark time	Antipsychotics duration	N	(case)	Incidence rate	Model1		Model2		
					HR (95% CI)	p-value	HR (95% CI)	p-value	p for trend
4-year									
	<0.5 year	30,914	(182)	0.70	Ref		Ref		
	0.5-1 year	11,780	(87)	0.87	1.27 (0.98-1.64)	0.066	1.12 (0.94-1.57)	0.141	0.009
	1-2 years	31,296	(339)	1.09	1.82 (1.52-2.17)	<.0001	1.39 (1.15-1.67)	0.001	
	2-3 years	25,816	(235)	0.95	1.52 (1.26-1.85)	<.0001	1.27 (1.04-1.55)	0.017	
	≥3 years	58,833	(530)	0.97	1.49 (1.26-1.77)	<.0001	1.32 (1.11-1.56)	0.002	
6-year									
	<0.5 year	19,113	(104)	0.58	Ref		Ref		
	0.5-1 year	6,978	(36)	0.54	0.96 (0.66-1.40)	0.832	0.92 (0.63-1.36)	0.683	0.030
	1-3 years	19,847	(118)	0.60	1.10 (0.85-1.43)	0.478	0.98 (0.75-1.28)	0.902	
	3-4 years	24,329	(249)	0.93	1.88 (1.50-2.37)	<.0001	1.37 (1.07-1.74)	0.011	
	≥4 years	59,268	(461)	0.76	1.42 (1.14-1.75)	0.002	1.18 (0.95-1.47)	0.134	

Notes. Incidence rates are expressed in units of N/1000person-year.
Model1: age adjusted, Model2: (model1) + insurance premiums, region of residence, Charlson Comorbidity Index (CCI) adjusted

Table 7. Landmark analysis of breast cancer incidence by duration of antipsychotics use by generation

Class	Antipsychotics duration	N	(case)	Incidence rate	Model1		Model2		
					HR (95% CI)	p-value	HR (95% CI)	p-value	p for trend
FGA									
	<0.5 year	107,828	(789)	0.77	Ref		Ref		
	0.5-1 year	6,469	(51)	0.79	1.08 (0.81-1.43)	0.603	0.99 (0.75-1.32)	0.952	0.005
	1-3 years	18,393	(210)	1.07	1.55 (1.34-1.81)	<.0001	1.29 (1.09-1.51)	0.002	
	3-4 years	4,882	(63)	1.22	1.75 (1.35-2.26)	<.0001	1.50 (1.16-1.96)	0.002	
	≥4 years	6,152	(56)	0.89	1.21 (0.92-1.59)	0.165	1.06 (0.80-1.40)	0.671	
SGA									
	<0.5 year	38,044	(301)	0.83	Ref		Ref		
	0.5-1 year	9,829	(60)	0.66	0.79 (0.60-1.04)	0.087	0.85 (0.64-1.12)	0.240	0.105
	1-3 years	36,751	(319)	0.87	1.11 (0.95-1.30)	0.201	1.04 (0.89-1.23)	0.601	
	3-4 years	17,873	(129)	0.73	0.92 (0.74-1.13)	0.402	0.92 (0.74-1.13)	0.421	
	≥4 years	41,227	(360)	0.90	1.09 (0.93-1.27)	0.274	1.15 (0.98-1.35)	0.094	

Notes. Landmark time: 5 years after index date.
Incidence rates are expressed in units of N/1000person-year.
FGA(first generation antipsychotics), SGA(second generation antipsychotics)
Model1: age adjusted, Model2: (model1) + insurance premiums, region of residence, Charlson Comorbidity Index (CCI), duration of SGA/FGA use adjusted (The SGA use was adjusted in the FGA analysis, and vice versa.)

Table 8. Hazard ratios of breast cancer incidence by antipsychotic use in other psychiatric patients

Antipsychotics	N	(case)	Incidence rate	Model1		Model2	
				HR (95% CI)	p-value	HR (95% CI)	p-value
No	205,613	(2025)	1.33	Ref		Ref	
Yes	19,130	(251)	1.52	1.17 (1.03-1.34)	0.018	1.15 (1.00-1.31)	0.047

Notes. Incidence rates are expressed in units of N/1000person-year.
Model1: age adjusted, Model2: (model1) + insurance premiums, region of residence, Charlson Comorbidity Index (CCI) adjusted

PART II. Causal relationship between schizophrenia and breast cancer: two sample Mendelian Randomization and polygenic risk score

II. MATERIALS AND METHODS

1. Selection of the Genetic Instrumental Variables

Summary-level genetic data for schizophrenia were obtained from the NHGRI-EBI Catalog of human genome-wide association studies (GWAS, http://www.ebi.ac.uk/gwas/). A search for "schizophrenia" in the NHGRI-EBI Catalog yielded 137 studies and 3851 SNPs as of January 25, 2022 (Figure 2). Included were studies that focused solely on schizophrenia as a trait, resulting in 70 studies with 2561 SNPs. Studies identifying SNPs related not only to schizophrenia but also to other psychiatric disorders (such as bipolar disorder and autism spectrum disorders) were excluded. From the included studies, only those studies with East Asian populations were selected, resulting in 18 studies and 550 SNPs left. Finally, after excluding SNPs, those with missing effect size or variance of the SNP, as well as those with p-values greater than 5×10^{-8} and duplicated SNPs (published in different studies), a total of 249 SNPs were selected.

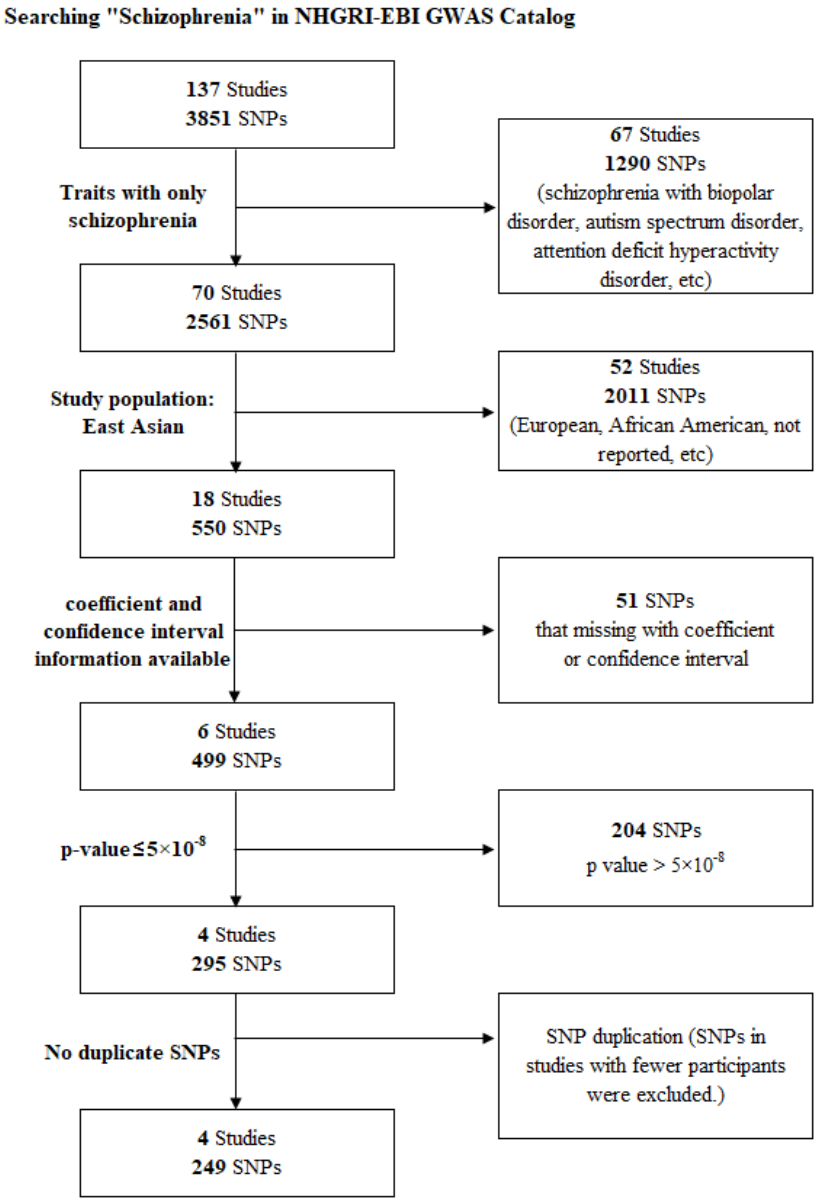

Figure 2. Flow chart of SNPs selection from NHGRI-EBI GWAS Catalog (Part II)

2. Data source and study population for outcome

A candidate gene association analysis was conducted with 2,165 patients with breast cancer from the Seoul Breast Cancer Study (SeBCS) and 2,046 healthy controls from a large urban cohort that is part of the Korea Genome Epidemiology Study (KoGES).

Seoul Breast Cancer Study (SeBCS)

The SeBCS recruited breast cancer cases and controls to conduct a hospital-based case-control study of female breast cancer in Seoul, Korea, since 1995.[67] The Seoul National University and ASAN Medical Center recruited controls and cases of historically confirmed incident breast cancer. As part of SeBCS, a genotyping of 2,165 breast cancer patients who visited Seoul National University Hospital was conducted in 2008. The genotyping method was Affymetrix Genome-Wide Human SNP array 6.0(Affymetrix, Inc. Santa Clara, CA, USA), which identified 555,117 SNPs.

Koreas Genome Epidemiology Study (KoGES)

KoGES is an ongoing population-based cohort study that has been investigating major genetic and environmental factors for common diseases in the Korean population since 2001.[68] The control group was selected from the health examinee cohort (HEXA), which is a subset of KoGES. Among the 173,195 subjects who participated in the HEXA baseline survey from 2004 to 2013, 3,693 subjects were genotyped using the Affymetrix 6.0 platform, resulting in the identification of 627,659 SNPs. From this genotyped group, 2,046 women were selected to form the final control group. It was confirmed that none of the

control group had a history of breast cancer diagnosis. The summary of outcome datasets is presented in Appendix Table 10.

3. Gene Extraction from Outcome Data

Among the 249 SNPs identified in the NHGRI-EBI GWAS Catalog, 37 SNPs were commonly extracted from the SNPs of outcome data (SeBCS data for case, KoGES-HEXA data for control) (Figure 3). For the remaining 212 SNPs that could not be extracted, proxy SNPs were found based on R^2>0.8, and it was verified that the proxy SNPs could also be extracted from the SNPs of outcome data. Proxy SNPs were selected using LDlink's LDproxy tool (https://analysistools.nci.nih.gov/LDlink/) and East Asian population data.[69] Where multiple proxy SNPs were identified, the one exhibiting the highest R^2 correlation with the association SNP was chosen. Out of the 212 SNPs, proxy SNPs were determined for 113 SNPs. Combining these with previously extracted 37 SNPs resulted in a final set of 150 SNPs.

Considering that 2-sample Mendelian Randomization (MR) analysis necessitates SNP independence, the LD clumping algorithm was applied using an R^2 threshold of <0.001 within 250kb, to identify independent SNPs. After excluding correlated SNPs by the LD clumping algorithm, a total of 116 SNPs were selected as genetic instruments to genetically determine schizophrenia.

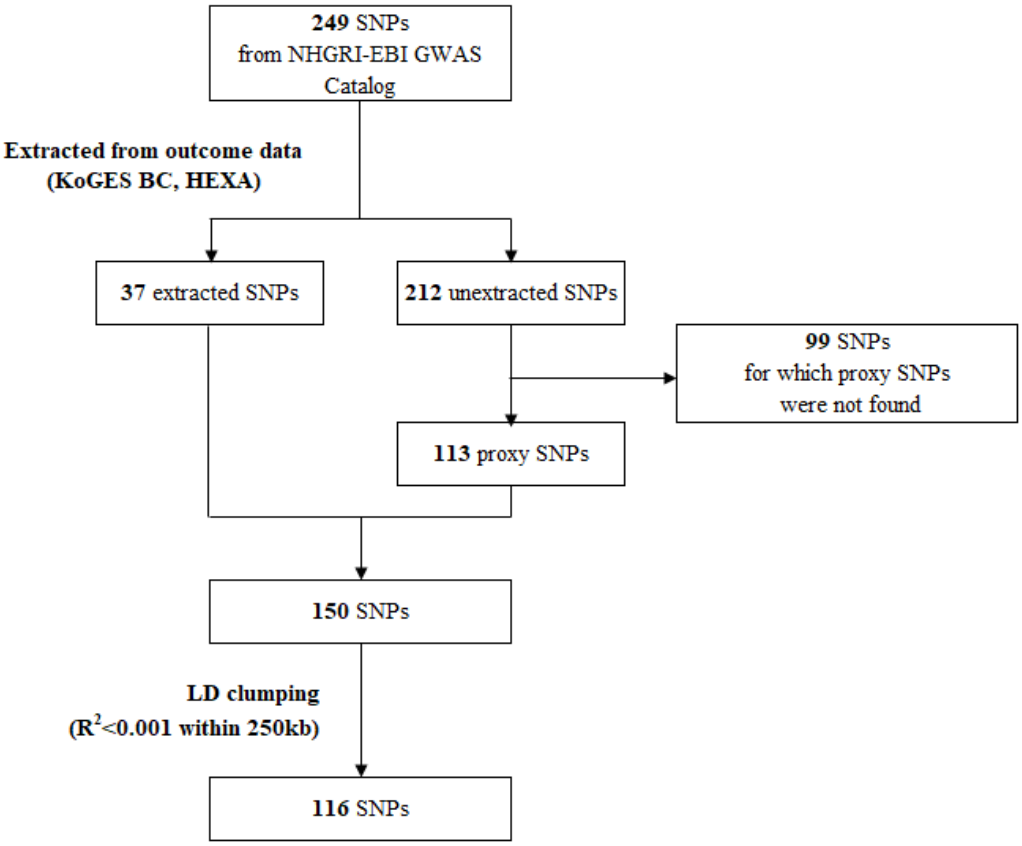

Figure 3. Flow chart of SNPs extraction from outcome data and LD clumping (Part II)

4. Candidate Gene Association Analyses

Association between the candidate SNPs and the breast cancer risk was assessed using the age-adjusted logistic regression in the case–control data (SeBCS, HEXA data). Breast cancer presence was considered as a binary dependent variable, with the number of effect alleles as the independent variable in a test of an additive inheritance model.[70] Age was introduced as a covariate variable in the logistic regression model.

5. Two-sample Mendelian Randomization

For each individual genetic instrument, MR estimates can be derived by dividing the instrument-outcome association (KoGES) by the instrument-exposure association (NHGRI-EBI GWAS Catalog), which is known as Wald ratio estimates. In this study, inverse variance weighted (IVW), MR-Egger, and weighted median regression methods were considered. These approaches leverage Wald ratio estimates to provide more accurate estimates of causal effects and to test and adjust for bias resulting from horizontal pleiotropic pathways.

The IVW estimate is calculated by regressing the set of instrument-outcome associations upon the instrument-exposure associations without including an intercept, and each estimate is weighted by the inverse of the variance of the instrument-outcome association. This means a weighted average of Wald ratio estimates. For MR-Eager regression, an

intercept is added, with the intercept being interpreted as the average horizontal pleiotropic effect and the slope of the regression as the corrected causal effect.[71] MR-Egger is statistically less powerful than IVW as an additional parameter is estimated. Finally, weighted median regression essentially computes the weighted median using the Wald ratio estimates and selects the weights corresponding to the inverse variance weights. If the proportion of non-pleiotropic SNPs surpasses 50% concerning their corresponding weighting, the weighted median has the advantage of being robust to bias due to horizontal pleiotropic bias.

6. Age-stratified Mendelian Randomization

To further examine the effect of breast cancer onset age on the association between the genetic liability of schizophrenia and breast cancer, the candidate gene analysis was performed on the same outcome data (SeBCS, HEXA) but divided into two groups by age (<55 years, ≥55 years). Due to data limitations, the exact onset age of breast cancer was unknown. Thus, the age information at the time the breast cancer was investigated was utilized. It was hypothesized that the proportion of early-onset breast cancer would be higher among younger breast cancer patients. As with the primary analysis, MR analysis was performed using the IVW, MR-Egger, and Weighted Median methods, and MR analysis was also performed before and after removing outliers through radial MR.

7. Polygenic Risk Scores for Schizophrenia

The PRS for each individual was computed by adding up the number of effect alleles (0,1,2) of 63 SNPs, each weighted by its corresponding effect size estimate ($\hat{\beta}_i$). Among the 116 SNPs used in the Mendelian randomization analysis, the PRS was constructed using 63 SNPs. These were selected based on the congruence of the direction of individual SNP MR results (i.e. positive or negative beta estimates) with the overall direction indicated by MR results (beta>0).

$$PRS = \sum_{i}^{I} X_i \hat{\beta}_i$$

These beta coefficients were obtained from the GWAS Catalog, where GWAS studies documented the schizophrenia-related SNPs and their associated effect sizes. The PRS, which is a continuous score, reflects an individual's genetic susceptibility to schizophrenia.

8. Statistical Analysis

Two-sample MR

First, Wald ratio estimates using each of the 116 genetic instruments were calculated by dividing the log odds of breast cancer by the log odds of schizophrenia, obtained from outcome data and NHGRI-EBI GWAS Catalog, respectively. After this, IVW, MR-Egger, and weighted median regression models were used, interpreting the estimated association

as the effect of a genetically determined increase in schizophrenia risk on breast cancer risk. Also, to determine if a single SNP is responsible for the association, leave-one-out analyses were performed by methodically eliminating each SNP in turn and repeating the IVW analysis.

Lastly, the radial variants of the IVW and MR-Egger models were performed. These models are akin to the traditional IVW and MR-Egger regression models, but regress the product of the square root of the weighting for each genetic variant and the Wald ratio estimate upon the square root of the genetic variants' weighting.[72] The radial plot method was used to discover a single outlier SNP that produced substantial disparities. Genetic instruments are judged as outliers depending on how much they deviate from the regression line, and these genetic instruments can be assumed to be subject to pleiotropic bias. The distance between each point and the regression line is proportional to the individual contribution to overall heterogeneity in effect estimates for the genetic instrument.

For the genetic instruments-outcome associations, PLINK2.0 and R version 4.2.2 were employed to conduct gene extraction, LD clumping, and candidate gene association analyses. Additionally, all Mendelian Randomization analyses were executed using the TwoSampleMR[73] and RadialMR[72] R packages, both within the R statistical environment (version 4.2.2, R Development Core Team, Vienna, Austria).

PRS analysis

The association between schizophrenia PRS and breast cancer was calculated by using logistic regression adjusting for age. PRS was modeled in two ways: quartiles (to test for a possible nonlinear relationship) and per standard deviation increase. The PRS quartiles were created and odds ratios were calculated using a logistic regression model for four different categories, and PRS was standardized using Z-scores. Finally, for each SNP, the mean Xiβi value was calculated in both the breast cancer patient group and the control group, and the differences between the means were tested using a Student's t-test.

III. RESULTS

1. Genetic Instrumental Variables for Schizophrenia

As a result of searching for schizophrenia-related SNPs in the NHGRI-EBI GWAS Catalog and selecting/extracting SNPs according to various processes, 116 SNPs were finally determined. The studies in which the 116 SNPs were published were identified as three GWAS studies. Information on each GWAS study is depicted in Table 9.

All 116 SNPs were independent of each other (R^2<0.001). Genetic instruments must be strongly associated with the exposure of interest. The association was quantified using the F-statistic in a regression of exposure on the instrument.[74] The mean F-statistic for the 116 genetic instruments was 41.11, and all genetic instruments met the threshold of F>10, indicating that they were sufficiently powerful instrumental variables (Appendix Table 11).

Table 9. Description of GWAS studies for schizophrenia

No	1st Author	Publication date	Journal	Title	Population	Total Sample Size	Case		Control	
							N	Age (mean±SD)	N	Age (mean±SD)
1	Shi Y	2011-10-30	Nat Genet	Common variants on 8p12 and 1q24.2 confer risk of schizophrenia.*	East Asian	10218	3750		6468	
					Northern Han	3170	1578	36.9±9.3	1592	30.8±11.1
					Central Han	4094	1238	36.2±12.4	2856	60.9±12.2
					Southern Han	2954	934	36.3±16.6	2020	56.1±13.5
2	Yu H	2016-12-06	Mol Psychiatry	Common variants on 2p16.1, 6p22.1 and 10q24.32 are associated with schizophrenia in Han Chinese population.*	East Asian	10154	4384		5769	
					GWAS1 (Northern Han)	2345	746	34.5±8.7	1599	35.8±7.8
					GWAS2 (Northern Han)	3042	1595	30.1±10.7	1447	29.7±9.8
					GWAS3 (Northern Han)	3376	1333	31.3±7.8	2043	31.7±8.9
					GWAS4 (Southern Han)	1390	710	30.2±8.3	680	31.5±9.2
3	Ikeda M	2018-10-03	Schizophr Bull	Genome-Wide Association Study Detected Novel Susceptibility Genes for Schizophrenia and Shared Trans-Populations/Diseases Genetic Effect.*	East Asian	45528	14023		31505	
					Japanese	9348	1940	48.0±14.4	7408	58.7±13.4
					Chinese (GWAS)	26026	7699	-	18327	-
					Chinese (Replication)	10154	4384	-	5770	-
4	Yue WH	2011-10-30	Nat Genet	Genome-wide association study identifies a susceptibility locus for schizophrenia in Han Chinese at 11p11.2.	East Asian (Han Chinese)	2345	746	34.5±8.7	1599	35.8±7.8

Notes. The first three studies are those from which the final 116 SNPs were derived.*

2. Mendelian Randomization Analyses for Breast Cancer Risk

The association for each genetic instrument with schizophrenia and breast cancer risk is presented in Appendix Table 11. IVW, MR-Egger, and weighted median regression were utilized to estimate causal associations between schizophrenia and breast cancer risk (Table 10, Figure 4). Primary MR analysis using the IVW method demonstrated that genetically predicted schizophrenia was positively associated with breast cancer [OR=1.14, 95% confidence interval (CI) 1.01-1.28, p-value=0.029]. A similar observation was obtained using the MR-Egger (OR=1.45, 95% CI 1.06-1.98, p-value=0.020). In contrast, the weighted median method presented a directionally consistent but not significant result, probably caused by the lower statistical power of the method (OR=1.11, 95% CI 0.91-1.34, p-value=0.334). MR Egger intercept test suggested no significant horizontal pleiotropy (p=0.105)[75].

Funnel plots show the individual Wald ratios for each SNP plotted against their precision, with asymmetry indicating directional horizontal pleiotropy. The funnel plot in Figure 5 shows that there is no strong pattern of asymmetry, suggesting the absence of an unbalanced, directional pleiotropy that could influence the ultimate estimated effect. The non-significant MR-Egger intercept and the approximately symmetric distribution of individual Wald ratios in the funnel plot can indicate that overall pleiotropic effects are balanced out and are, therefore, unlikely to invalidate the MR results[76].

Table 10. Mendelian randomization for schizophrenia on Breast Cancer Risk

Method	N SNPs	OR	(95% CI)	p-value
IVW	116	1.14	(1.01-1.28)	0.029
MR-Egger regression	116	1.45	(1.06-1.98)	0.020
Intercept				0.105
Weighted Median	116	1.11	(0.91-1.34)	0.334

Notes. IVW indicates inverse-variance weighted; N SNPs, the number of SNPs; and OR, odds ratio.

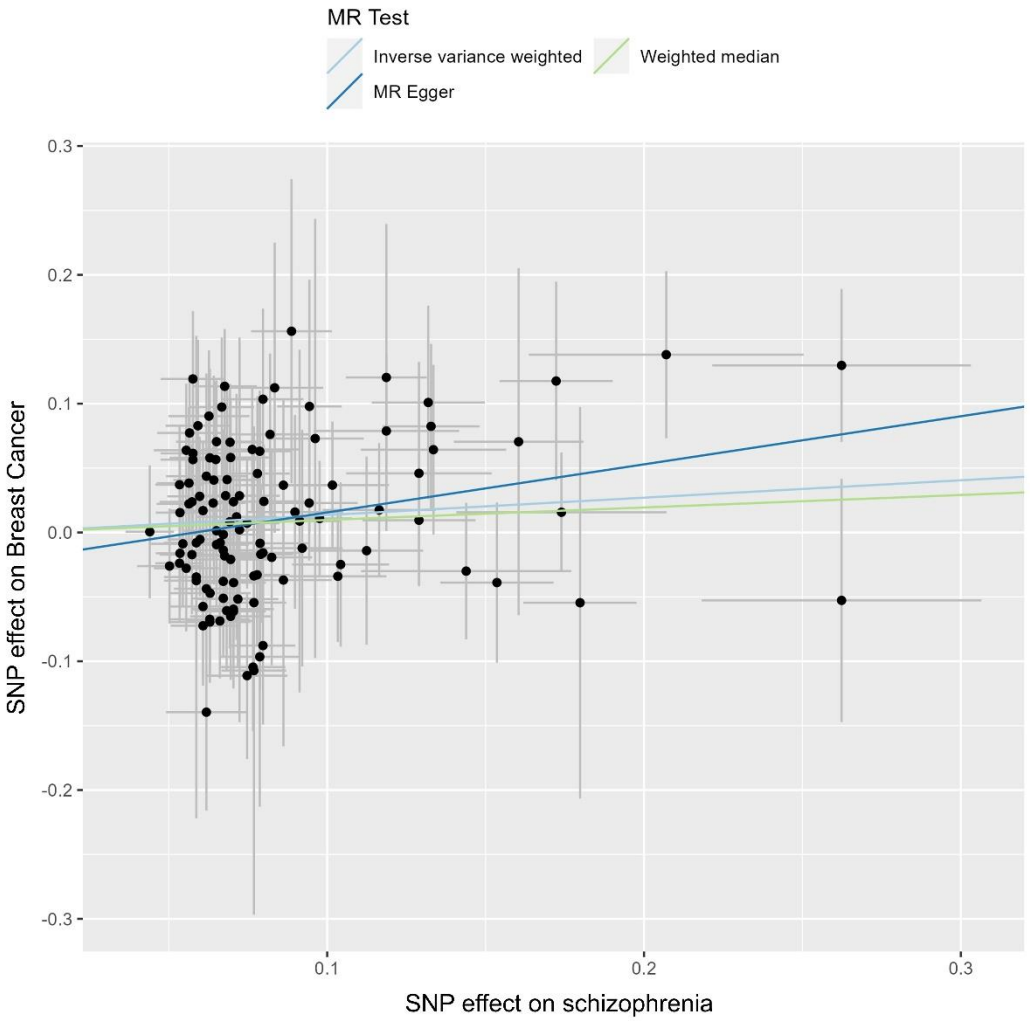

Figure 4. Scatter plot to visualize the causal effect of schizophrenia on breast cancer

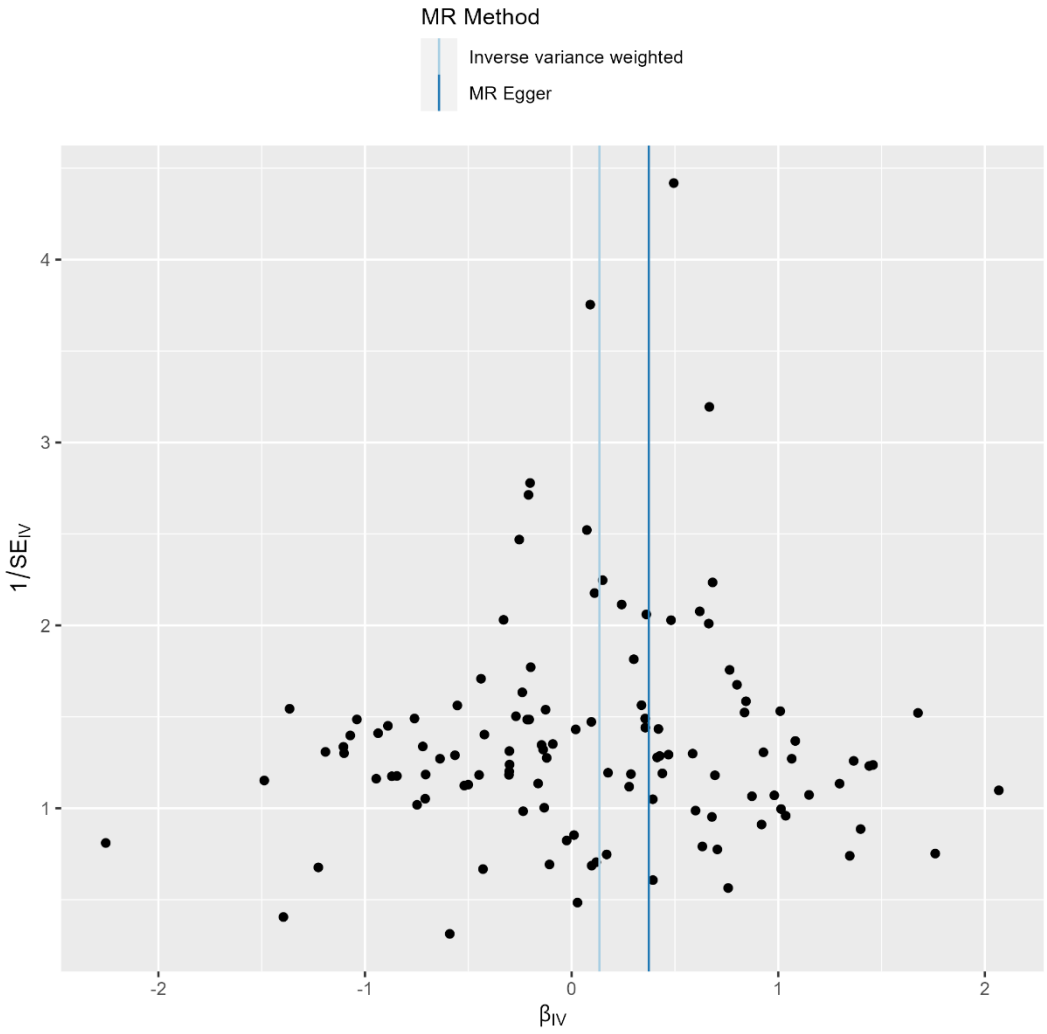

Figure 5. Funnel plot to visualize overall heterogeneity of Mendelian Randomization (MR) estimates for the effect of schizophrenia on breast cancer

3. Effects of Individual Genetic Instruments Concerning Breast Cancer Risk

The causal effects of schizophrenia on breast cancer for each individual genetic tool were presented as a forest plot (Figure 6). Effect estimates (beta) for the 116 SNPs ranged from -2.255 to 2.068 (Appendix Table 12).

Leave-one-out analysis was further performed to explore whether the associations between genetically determined schizophrenia and breast cancer were driven by particular SNPs. Figure 7 and Appendix Table 13 show MR estimates remained relatively stable when sequentially dropping a single SNP out. Compared with the observed results (OR=1.14) from 116 SNPs, the ORs fluctuated from 1.11 to 1.16, and the largest decrease in OR was observed after removing rs1837495, rs17557162, and rs6925744. Removal of rs1837495, rs17557162, or rs6925744 attenuated the association of schizophrenia and breast cancer (p-value=0.051, 0.072, 0.099), suggesting that the three SNPs had a significant impact on the IVW point estimate.

The radial MR analysis was performed with the modified second-order weighting method (Table 11). The radial IVW findings indicated a positive association between schizophrenia and breast cancer (OR=1.14, 95% CI 1.01-1.28, p-value=0.024). The radial MR-Egger analysis, unlike in the conventional setting, did not produce statistically significant results (OR=1.31, 95% CI 0.98-1.76, p-value=0.076). There is little evidence of instrumental heterogeneity for schizophrenia, according to Cochran's Q test (p-value=0.680, 0.712).

However, the IVW Radial MR results and MR-Egger MR results indicated that the three instrumental variables of schizophrenia (rs1837495, rs2250350, rs314263) with substantial effect sizes on breast cancer could be outliers (Figure 8). After the removal of the three outliers, the estimate of schizophrenia's effect on breast cancer remained without large change, but with statistically significant radial MR-Egger results (radial IVW: OR=1.14, 95% CI 1.01-1.28, p-value=0.027; radial MR-Egger OR=1.32, 95% CI 1.01-1.74, p-value=0.046) (Table 11, Figure 9).

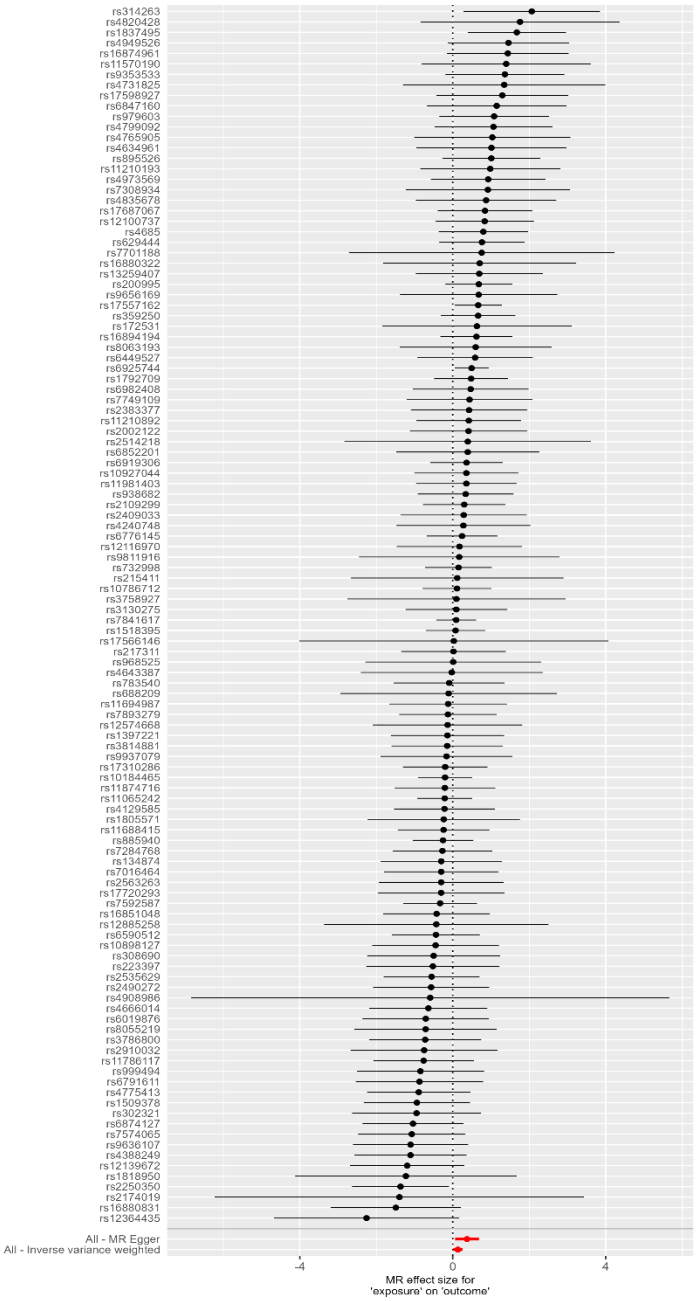

Figure 6. Forest plot to visualize the causal effect of schizophrenia on breast cancer estimated using each SNP singly

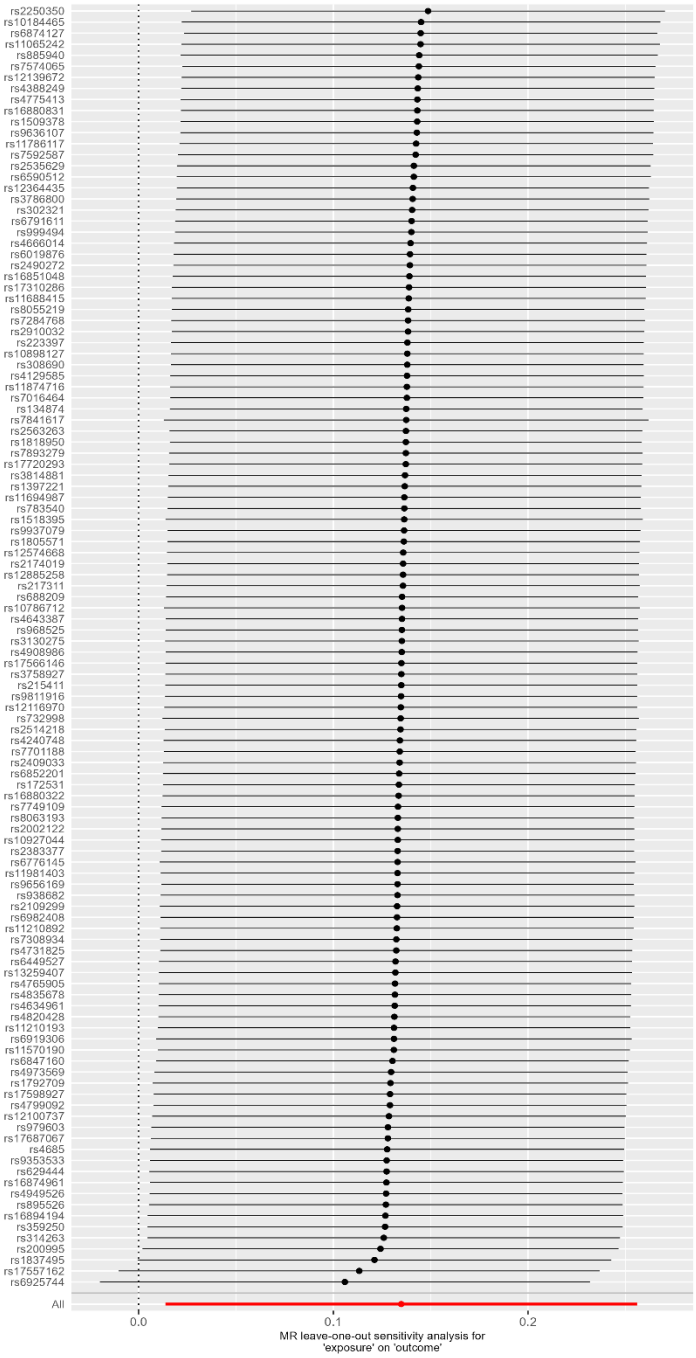

Figure 7. Leave one out plot to identify outlier SNPs

Table 11. Radial MR regression for schizophrenia on Breast Cancer Risk

	Method	N SNPs	OR	(95% CI)	p-value	Q-statistic for heterogeneity	p-value for q statistic
Before removing outliers	Radial IVW	116	1.14	(1.01-1.28)	0.024	107.39	0.680
	Radial MR-Egger	116	1.31	(0.98-1.76)	0.076	106.07	0.712
	Intercept				0.329		
After removing outliers	Radial IVW	113	1.14	(1.01-1.28)	0.027	92.02	0.916
	Radial MR-Egger	113	1.32	(1.01-1.74)	0.046	90.31	0.934
	Intercept				0.218		

Notes. IVW indicates inverse-variance weighted; N SNPs, the number of SNPs; and OR, odds ratio.

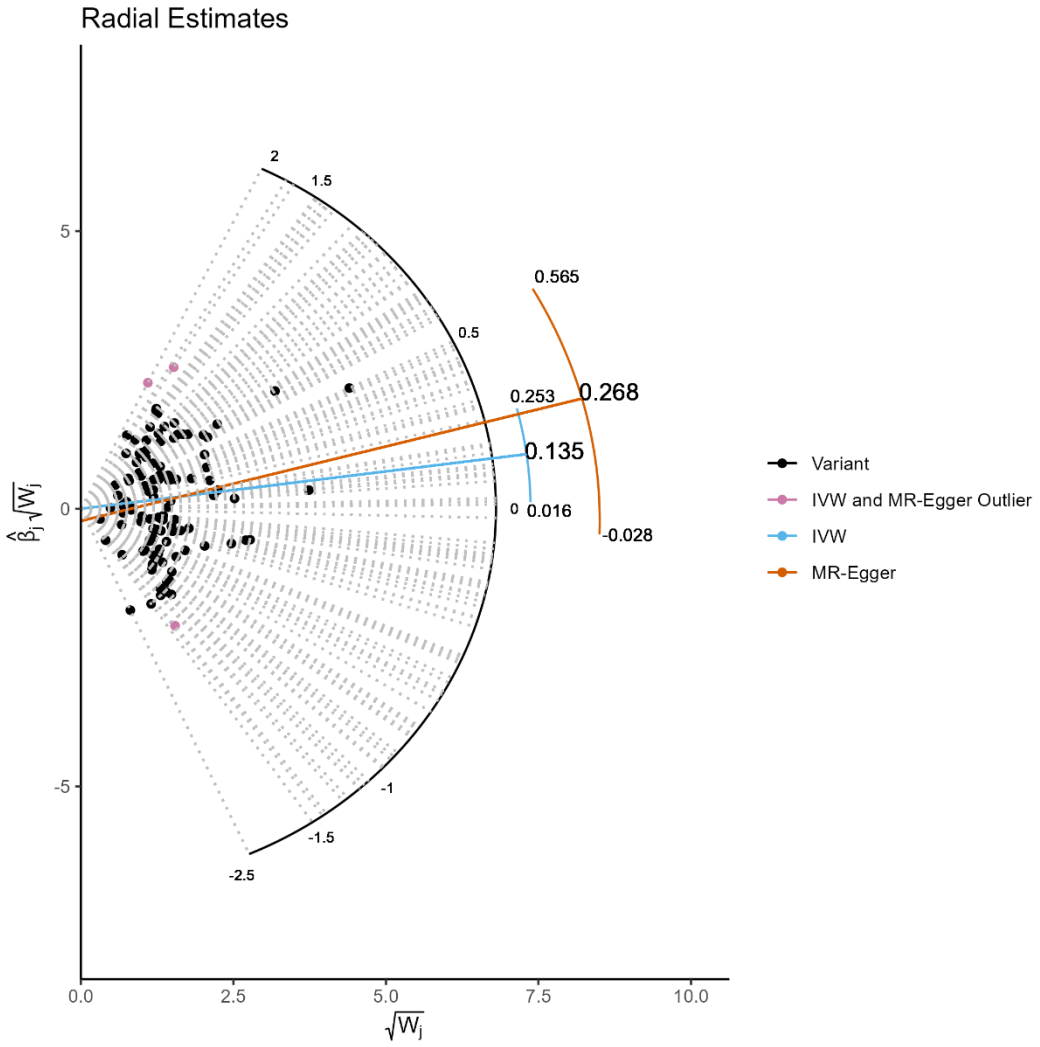

Figure 8. Radial plot to visualize individual outlier single nucleotide polymorphisms (SNPs) in the Mendelian Randomization (MR) estimates for breast cancer

Notes. The radial curve displays the ratio estimate for each SNP. Black dots show valid SNPs. Purple dots show outlier SNPs.

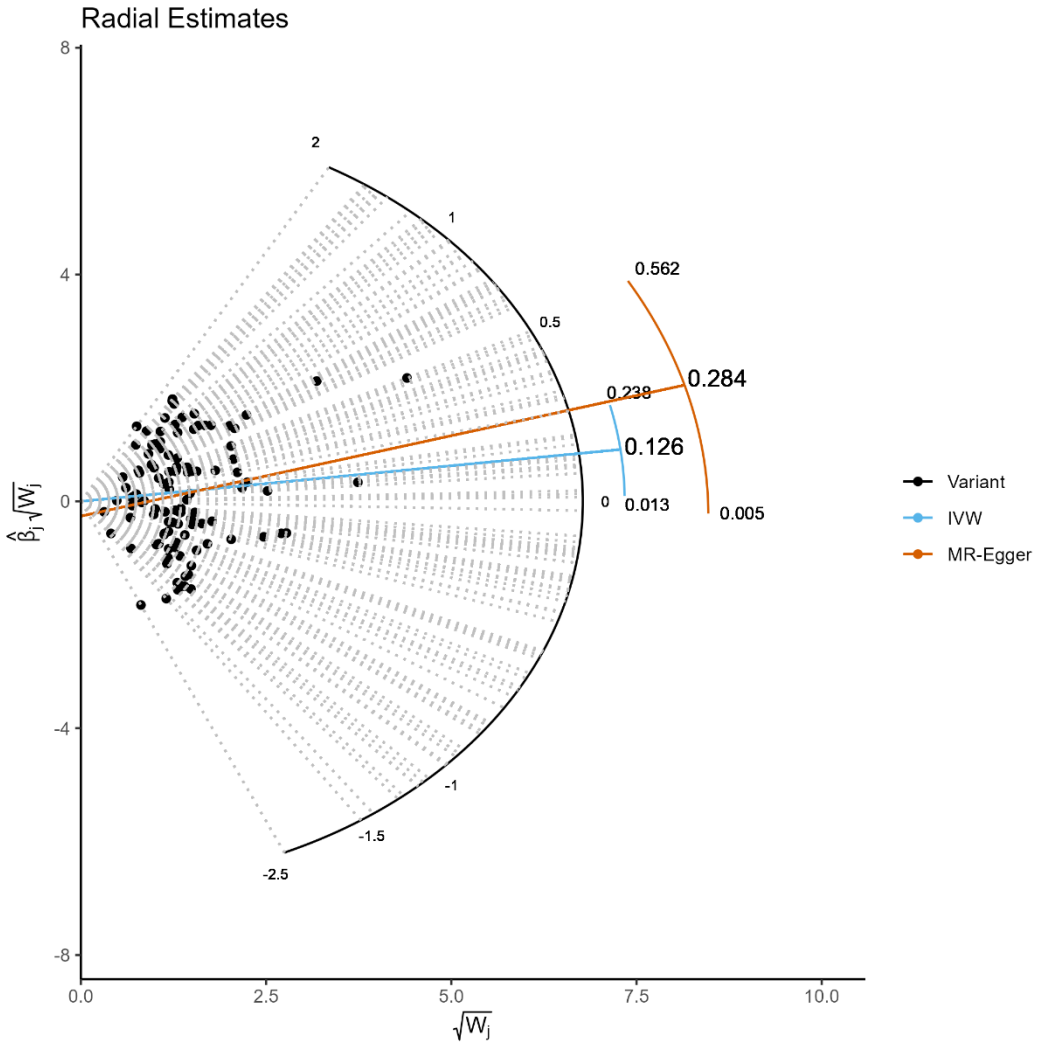

Figure 9. Radial plot of schizophrenia and breast cancer after outliers removed

Notes. The radial curve displays the ratio estimate for each SNP. Black dots show valid SNPs. Purple dots show outlier SNPs.

4. Age-stratified Mendelian Randomization

When stratified based on age of 55, there were 1683 breast cancer patients and 1402 controls in the younger group, and 482 breast cancer patients and 644 controls in the older group. The mean(SD) of age for the younger and older groups was 45.63 (5.33) and 61.40 (5.04), respectively.

After stratification by age 55, the causal association between schizophrenia and breast cancer was estimated using IVW, MR-Egger, and weighted median. MR results from both younger and older groups showed no significant association between genetically determined schizophrenia and breast cancer risk. As a result of IVW, the older group showed a larger effect size than the younger group, but it was not statistically significant (Younger group: OR=1.08, 95% CI [0.93-1.25], p-value=0.313; Older group: OR=1.14, 95% CI [0.90-1.44], p-value=0.258). MR Egger intercept test showed no significant horizontal pleiotropy in both groups (p-value=0.380, 0.683) (Table 12).

Radial MR analysis was performed with a modified second-order weighting method. Radial IVW and Radial MR-Egger results showed no statistically significant association in both the younger and older groups (Table 13). Cochran's Q test showed that there was no severe heterogeneity between the instrumental variables of schizophrenia, but as a result of radial MR, 7 outlier SNPs (rs12364435, rs1837495, rs3786800, rs4775413, rs6874127, rs6925744, rs7308934) were removed from the younger group, and 4 outlier SNPs (rs2250350, rs7308934, rs783540, rs9353533) were removed from the older group. No

statistically significant association was found in both the younger group and the older group even after removing outliers (Younger group: OR=1.10, 95% CI [0.93-1.22], p-value=0.422; Older group: OR=1.20, 95% CI [0.97-1.49], p-value=0.097).

Table 12. Mendelian randomization for schizophrenia on Breast Cancer Risk stratified by age

Age	Method	N SNPs	OR	(95% CI)	p-value
Age<55					
	IVW	116	1.08	(0.93-1.25)	0.313
	MR-Egger regression	116	1.30	(0.88-1.92)	0.184
	Intercept				0.308
	Weighted Median	116	0.98	(0.76-1.26)	0.894
Age≥55					
	IVW	116	1.14	(0.90-1.44)	0.258
	MR-Egger regression	116	1.28	(0.71-2.31)	0.415
	Intercept				0.683
	Weighted Median	116	1.35	(0.93-1.96)	0.116

Notes. IVW indicates inverse-variance weighted; N SNPs, the number of SNPs; and OR, odds ratio.

Table 13. Radial MR regression for schizophrenia on Breast Cancer Risk stratified by age

Age	Method	N SNPs	OR	(95% CI)	p-value	Q-statistic for heterogeneity	p-value for q statistic
Age<55							
Before removing outliers	Radial IVW	116	1.08	(0.93-1.27)	0.313	121.73	0.315
	Radial MR-Egger	116	1.20	(0.82-1.74)	0.345	121.18	0.328
	Intercept				0.553		
After removing outliers	Radial IVW	109	1.10	(0.93-1.22)	0.422	86.70	0.935
	Radial MR-Egger	109	0.94	(0.65-1.37)	0.795	86.34	0.938
	Intercept				0.504		
Age≥55							
Before removing outliers	Radial IVW	116	1.14	(0.90-1.44)	0.249	111.05	0.587
	Radial MR-Egger	116	1.15	(0.65-2.03)	0.623	111.04	0.587
	Intercept				0.978		
After removing outliers	Radial IVW	112	1.20	(0.97-1.49)	0.097	90.08	0.928
	Radial MR-Egger	112	1.12	(0.67-1.86)	0.670	90.05	0.928
	Intercept				0.783		

Notes. IVW indicates inverse-variance weighted; N SNPs, the number of SNPs; and OR, odds ratio. Radial IVW: Mod.2nd

5. Polygenic Risk Score Analysis

The distribution of schizophrenia PRS in the breast cancer patient group and control group is shown in Figure 10. When tested by Student's t-test, the means of PRS between the two groups were significantly different (p-value<.0001).

A significant association between schizophrenia PRS and breast cancer was also observed in the logistic regression model adjusting for age. Compared to the lowest group of PRS (quartile; Q1), the OR (95% CI) of breast cancer was 1.32 (1.11-1.57) for the quartile 3 group and 1.45 (1.22-1.73) for the quartile 4 group (the highest group of PRS). Consistently, a statistically significant association was observed when PRS was defined by per standard deviation increase. The OR (95% CI) of breast cancer was 1.18 (1.12-1.26) per 1SD increase of PRS (Table 14).

For each SNP, when testing whether there was a difference in the mean of Xiβi value between the breast cancer patient group and the control group, significant results were shown for four SNPs; rs1837495, rs6925744, rs17557162, rs314263 (Appendix Table 14).

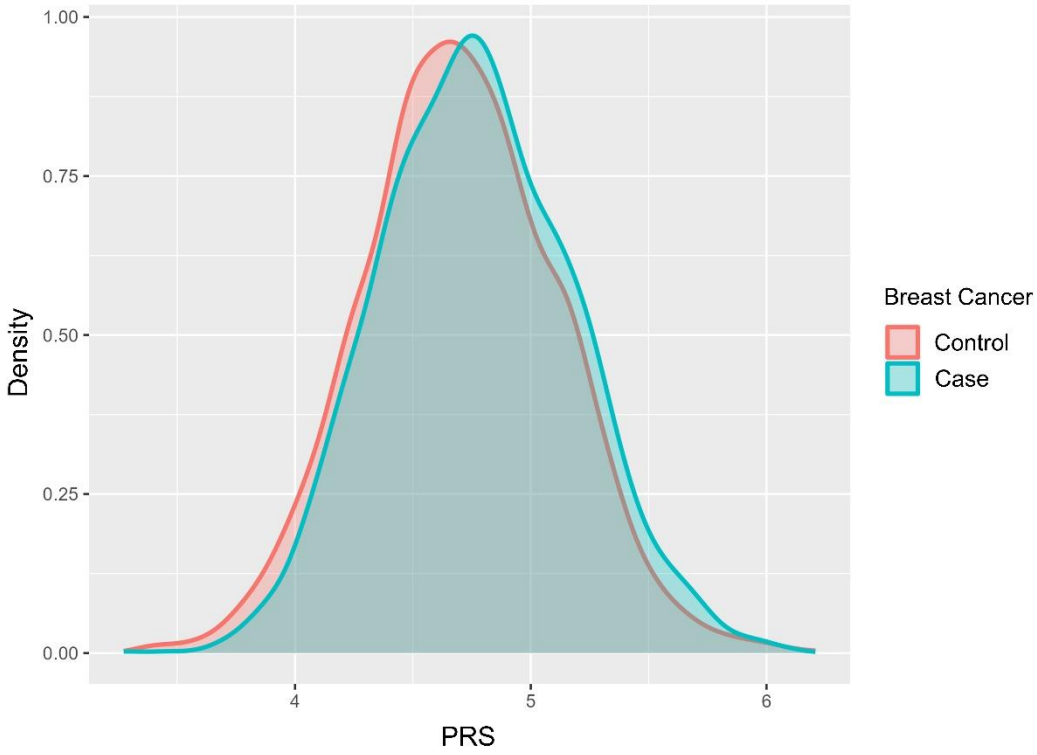

Figure 10. Distribution of schizophrenia PRS in breast cancer cases and healthy controls

Table 14. Association between polygenic risk score of schizophrenia and risk of breast cancer

	Breast cancer				
	N (case/control)	Model 1		Model 2	
Schizophrenia PRS		**OR**	**(95% CI)**	**OR**	**(95% CI)**
Quartile 1	497 / 555	ref		ref	
Quartile 2	512 / 541	1.06	(0.89-1.26)	1.07	(0.90-1.27)
Quartile 3	563 / 489	1.29	(1.08-1.52)	1.32	(1.11-1.57)
Quartile 4	592 / 461	1.43	(1.21-1.70)	1.45	(1.22-1.73)
Per 1 SD increase	2165 / 2046	1.18	(1.11-1.25)	1.18	(1.12-1.26)

Notes. Model1: crude model, model2: age adjusted

IV. DISCUSSION

1. Summary of findings

In this South Korean population-based cohort study with over 6,545,037 person-years of follow-up, it was found that women with schizophrenia had a higher risk of breast cancer compared to women in the general Korean population. The elevated risk observed compared to women with other psychiatric disorders suggests that the estimated association is due to factors specific to schizophrenia rather than unmeasured behavioral or structural characteristics shared by people with other psychiatric disorders. Consistent with prevailing models of biological plausibility, the risks were highest for middle-aged women between the ages of 40 and 54 years and women treated with first-generation antipsychotic medications.

Employing the two-sample Mendelian randomization analysis, the causal relationship between schizophrenia and breast cancer risk was investigated. The MR-Egger estimate reflected the absence of horizontal pleiotropy on breast cancer as its intercept term was statistically not significant. (β=-0.02, SE=0.01, p-value=0.105). Genetically predisposed schizophrenia was significantly related to an increased risk of breast cancer as depicted by the IVW estimation (OR=1.14, 95% CI 1.01-1.28). Although the outliers that appeared due to the radial MR analysis were removed, the correlation between the two disorders consistently showed significant results (OR=1.14, 95% CI 1.01-1.28). In addition, through PRS analysis, a significant association was observed between the schizophrenia PRS (per

1SD) and breast cancer status (OR=1.07; 95% CI, 1.00-1.14). Collectively, it was observed that genetically determined schizophrenia is causally associated with increased breast cancer risk. This finding aligns with the results of the observational study in PART1. When performing MR analysis stratified by age, no significant results were shown even after various MR methods and MR performed after outlier removal in both age groups.

2. Discussion of study findings

The increased risk of breast cancer among women with schizophrenia has been well documented.[11,13] However, substantive heterogeneity has been observed across populations, and many controversial findings have been published based on studies of Asian populations specifically.[30] This study, using national data from Korea, clearly identified an increased risk of breast cancer in women with schizophrenia, which will be important as one of the few studies in Asian populations.

The higher risk of breast cancer among middle-aged women with schizophrenia could be consistent with a model according to the greater influence of schizophrenia or antipsychotic medications on the development of breast cancer during periods in which women experience hormonal changes, such as menopause. Previous studies have shown that the decline in estrogen levels that can occur during specific periods of the life course, such as menopause, can exacerbate positive symptoms among people with schizophrenia.[36,37] Such findings are also consistent with the hyperprolactinemia that has been observed among

people with schizophrenia, even those who are antipsychotic-naïve and experiencing first-episode psychosis.[38-40] Other studies have shown that high prolactin levels during post-menopause are associated with breast cancer.[41] Also, similar to our findings, a Swedish population-based cohort study of 111306 people with schizophrenia found an elevated incidence of breast cancer among women aged 40-65 years with schizophrenia (IRR 1.19, 95% CI 1.09–1.29)[11].

The landmark analysis was also consistent with the hypothesis that antipsychotic medications increase breast cancer risk by causing hyperprolactinemia. While hyperprolactinemia is a general feature of most antipsychotic medications, large differences are observed within this class of medications.[63,77,78] The highest rates of hyperprolactinemia are consistently reported in association with amisulpride, risperidone, and paliperidone, while the aripiprazole and quetiapine have the most favorable profile with regard to the outcome.[77,78] The finding that only treatment with FGAs was associated with breast cancer risk can potentially be explained by the fact that SGAs include prolactin-preserving antipsychotics as well as prolactin-raising antipsychotics. A 2017 study using Taiwan insurance claims data on people with schizophrenia also found that relative to people on FGAs alone, there was no statistically significant elevation of breast cancer among people who used SGAs.[12]

Results regarding the genetic association between schizophrenia and breast cancer have also been confirmed in previous studies. A recent genetic study harnessed summary statistics from genome-wide association studies (GWAS) reported a significant

schizophrenia-breast cancer genetic correlation (r_g=0.14) has been reported.[48] The results are reliable in that they are obtained from extensive genome-wide association studies of schizophrenia (n=40675 cases and 64643 controls) and breast cancer (n=122977 cases and 105974 controls). In addition, in the same study, a bidirectional generalized summary-based Mendelian randomization (GSMR) analysis was conducted, yielding significant findings in only one direction. This outcome supports the presence of a causal relationship between schizophrenia and breast cancer, rather than a relationship driven by pleiotropy. To clarify, when genes associated with schizophrenia were employed as instrumental variables to assess their correlation with breast cancer, a significant result was obtained. Conversely, when genes linked to breast cancer were used as instrumental variables to investigate their association with schizophrenia, no significant result was found.

In addition, three previous studies have consistently identified a significant causal effect (odds ratio) of genetic predisposition to schizophrenia on breast cancer risk by employing Mendelian randomization (MR) analysis to investigate putative causal relationships. (ORs ranging from 1.04 to 1.09)[48,49,79]. All three studies have in common that they were analyzed on the European population and used large-scale GWAS. The current study conducted Mendelian randomization targeting only the Korean population and obtained significant results regarding the causal relationship between schizophrenia and breast cancer. (OR=1.14).

The MR analysis of individual SNPs revealed three significant SNPs (rs314263, rs4820428, and rs1837495) whose results aligned with the overall result's direction. Identified as

schizophrenia-associated SNPs, these three genetic markers are believed to potentially contribute to an increased risk of breast cancer through specific mechanisms. To further understand the genetic context, each of the 116 SNPs used in the MR analysis was examined for gene association using the dbSNP database (https://www.ncbi.nlm.nih.gov/snp/). The genes corresponding to the three significant SNPs are LIN28B (for rs314263), EP300 (for rs4820428), and PLCL1 (for rs1837495) (Appendix Table 15).

The LIN28B gene encodes the lin-28 family of proteins, which are characterized by the presence of a cold-shock domain and a pair of CCHC zinc finger domains.[80] This gene exhibits elevated expression levels in the testis, fetal liver, placenta, as well as in primary human tumors and cancer cell lines.[81,82] The EP300 gene encodes the adenovirus E1A-associated cellular p300 transcriptional co-activator protein.[83] It functions as histone acetyltransferase that regulates transcription via chromatin remodeling and is important in the processes of cell proliferation and differentiation.[84,85] Mutations in this gene are associated with Rubinstein-Taybi syndrome and might also be implicated in the development of epithelial cancer.[86,87] The PLCL1 gene is anticipated to facilitate phospholipase C activity and is predicted to participate in the negative regulation of cold-induced thermogenesis as well as phosphatidylinositol-mediated signaling.[88] There has been no direct link between the PLCL1 gene and cancer. However, there have been a research which shown that the mRNA of PLCL1 gene correlated with the status of PIK3CA, which is frequently somatically mutated oncogene in estrogen receptor (ER)-positive breast

cancer.[89,90 91]

While no direct association with breast cancer has been established for the three genes (LIN28B, EP300, and PLCL1), they have been observed to have connections with cell differentiation or involvement in the regulation of genes associated with breast cancer. As a result, further research is required to elucidate the mechanisms through which these genes might contribute to breast cancer development. This research holds promise from a precision medicine standpoint for predicting and preparing for the risk of breast cancer in individuals with schizophrenia

As a result of the age-stratified MR, the fact that it was not significant in both age groups is expected to be due to low power due to the insufficient number of subjects in each stratum. Each group may suggest a group of early-onset breast cancer and a group of late-onset breast cancer. Prior research has identified distinct developmental mechanisms for early-onset versus late-onset breast cancer.[92] Regarding genetic factors, women with early-onset breast cancer tend to have a pronounced family history of the disease.[93] High-penetrance gene mutations, such as those in BRCA1, BRCA2, TP53, PTEN, and others, are more commonly linked to early-onset cases.[94] Although genetic mutations can influence late-onset breast cancer, they are implicated less often.[95] In terms of hormonal and reproductive factors, increased cumulative lifetime exposure to estrogen is believed to expedite the onset of breast cancer.[96,97] Conversely, late-onset breast cancer might be more influenced by prolonged exposure to carcinogens, whether from environmental sources or lifestyle choices.[98] Given these insights, it might be inferred that genetically determined

schizophrenia has a more pronounced effect on the primary mechanisms of early-onset breast cancer. Therefore, additional research is needed on the association between schizophrenia and age at onset of breast cancer.

3. Limitations and Strengths

There are several limitations in the current study, which consists of two parts. The first limitation of Part I is that access to information on the specific antipsychotic medications was unavailable. Due to heightened safeguards around protecting personal information regarding the use of psychiatric medications, information on specific medication names was not provided -- only information about broad classes (i.e., FGA vs. SGA). Such information would be useful in clarifying the nature of the elevated risk of breast cancer among people on antipsychotic medication treatment. The Taiwanese study referenced earlier also observed that, among SGAs, exposure to the prolactin-raising antipsychotics risperidone, paliperidone, and sulpiride had a larger (but not statistically significant) magnitude of association with breast cancer than exposure to aripiprazole, clozapine, quetiapine, olanzapine, or ziprasidone.[12]

Second, there was lack of information on menopausal status and age of menopause. The perimenopausal and postmenopausal status was inferred strictly based on age. However, there is significant heterogeneity in menopausal onset across ages. More detailed data (e.g., gathered using surveys) could help to resolve this uncertainty.

Third, the landmark analysis included only those who had been followed up to the landmark point, which may cause selection bias. In addition, although the period of antipsychotic medication treatment was calculated from the index date to the landmark point, any treatment after the landmark point was not considered. Therefore, it is challenging to ascribe clinical meaning to the duration thresholds because the actual duration of antipsychotic medication use may be longer. What is clear from the analysis of this study is that a longer duration of treatment is associated with a higher risk of breast cancer.

The latter part also has some limitations that need to be addressed. The first limitation of Part II is, that some SNPs utilized in the two-sample MR analysis were proxy SNPs of original SNPs, found in the NHGRI-EBI GWAS Catalog but could not be extracted from outcome data. It was assumed that SNPs that are very close together would have the same effect size, and $R^2>0.8$ was used as a criterion to replace SNPs.

Second, because of data limitations, the precise age at which breast cancer developed could not be determined. The analysis relied on the age at the time of breast cancer investigation, operating under the assumption that younger breast cancer patients likely have a higher prevalence of early-onset breast cancer. Further research is essential to ascertain if schizophrenia is indeed more strongly associated with early-onset breast cancer.

Third, the subtypes of breast cancer classified by receptor types such as estrogen receptor (ER) and the human growth factor receptor 2 (HER2) were not investigated. It is known that there are differences in heritability or related genetic mutations depending on each

subtype of breast cancer.[99,100] Therefore, the association with genetically determined schizophrenia may differ depending on the breast cancer subtype.

Despite these limitations, this study also had several strengths. One of the strengths of the first part of this study is that by using two control groups, the risk of breast cancer in patients with schizophrenia was confirmed compared not only to the general population but also to people with other psychiatric disorders patients. The results of this study supported the hypothesis that individuals with schizophrenia have an increased risk of breast cancer, that this risk appears to be specific to schizophrenia rather than other psychiatric disorders, and that this risk increases with the duration of antipsychotic medication treatment.

Second, to the best of my knowledge, this study is the first in Korea to investigate the association between schizophrenia and breast cancer using national data. Therefore, it is reasonable to extrapolate the findings of this study to the entire Korean population. Furthermore, this study could serve as a foundation for proposing new clinical guidelines. As one aspect of the patient treatment guidelines, for instance, healthcare providers could emphasize breast cancer screening for postmenopausal women with schizophrenia. Additionally, although additional medication research is required, it might be possible to establish medication selection guidelines that recommend the use of Second-Generation Antipsychotics (SGAs) rather than First-Generation Antipsychotics (FGAs) for schizophrenia patients with confirmed breast cancer risk factors, such as family history of breast cancer.

These findings suggest the need for further study to understand the mechanisms underlying the observed association, as well as the need to support enhanced surveillance efforts for breast cancer prevention in this key population.[101]

The second part of the current study also has several strengths. One of the strengths in the second part of this study is that this is the first study to examine the causal effect of schizophrenia on the risk of breast cancer in a Korean population using two sample MR. Studies targeting European populations have revealed a genetic link between the two disorders, but there have been few studies targeting East Asians and no studies targeting Koreans.

Second, the GWAS datasets for schizophrenia and data for breast cancer are both derived from East Asian people, which avoids the effects of population stratification.

Third, this study used multiple MR methods to conduct sensitivity analyses for different patterns of pleiotropy. Various MR frameworks have demonstrated a causal relationship between genetic predisposition to schizophrenia and breast cancer, and these measures have increased the reliability and validity of the findings.

Two-sample Mendelian Randomization investigated the causal relationship between schizophrenia and breast cancer. This advanced methodology utilizes genetic variants as instrumental variables, offering a more precise and unbiased insight into the causal pathways linking the two conditions. Going beyond observational correlations and leveraging genetic information, this study provides robust and credible evidence on how

schizophrenia may influence the risk of developing breast cancer. The insights gained from this part of the study are instrumental in advancing the field, developing more effective prevention and treatment strategies, and enhancing the overall understanding of the causal mechanisms underlying schizophrenia and breast cancer.

V. CONCLUSIONS

The current study explored the relationship between schizophrenia and breast cancer through analysis using epidemiological data and genetic data. Schizophrenia patients showed significantly increased breast cancer risk compared to the general healthy population and the other psychiatric disorders patients. Schizophrenia-specific breast cancer risk factors were interpreted in two ways in this study. First, taking antipsychotics, especially FGA, in patients with schizophrenia increases the risk of breast cancer. Second, genetically determined schizophrenia increases the risk of breast cancer through a causal relationship. Both pathways were proven to be possible and were robustly analyzed using landmark analysis and two-sample MR analysis, respectively.

Therefore, these findings are appropriate to use as a basis for clinical guidelines regarding the high risk of breast cancer in patients with schizophrenia. There should be guidelines such as recommending breast cancer screening to postmenopausal women with schizophrenia, paying attention to long-term antipsychotic use, and prescribing SGA instead of FGA for schizophrenia patients with a family history of breast cancer.

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APPENDIX

Appendix Table 1. Characteristics of previous studies

No.	Study	Country	Characteristics of patients with schizophrenia	Number of patients with schizophrenia	Comparison population	Follow-up	Number of breast cancer cases	Confirmation of cancer cases	Risk of breast cancer
1	Gulbinat et al, 1992 (Honolulu)[14]	USA	Patients diagnosed with schizophrenia (Hawaii State Psychiatric Case Register)	2779	General population (Honolulu)	1962-1980	NR	NR	RR=1.60 (0.52-3.74)[a]
2	Gulbinat et al, 1992 (Nagasaki)[14]	USA	Patients diagnosed with schizophrenia (All psychiatric institutions in Nagasaki and Nagasaki Mental Health Center)	1388	General population (Nagasaki)	1960-1978	NR	Medical Association Tumor Statistical Committee (ICD-8)	RR=3.23 (1.16-6.78)[a]
3	Lichtermann et al., 2001[16]	Finland	Inpatients or those with disability pension for schizophrenia (National Hospital Discharge and Disability Pension Register)	11418	General Finnish population	1971-1996	152	Finnish Cancer Registry	SIR=1.15 (0.98-1.34)[a]
4	Lawrence et al., 2001[15]	Australia	Patients diagnosed with schizophrenia (Western Australia Health Management database)	1674	General population (Western Australia)	1982-1998	85	Western Australia Cancer Registry	RR=0.97 (0.78-1.22)[a]
5	Dalton, et al., 2003[17]	Denmark	Inpatients with schizophrenia (Danish Psychiatric Central Register)	7541	General Danish population	1943-1997	74	Danish Cancer Registry (ICD-7)	RR=0.97 (0.76-1.20)[b]

6	Goldacre et al., 2005[20]	UK	Inpatients with schizophrenia (National Health Service Center)	9649	General population / Inpatients with various medical and surgical conditions	1963-1999	80	National Health Service-based data (ICD-9)	RR=1.01 (0.80-1.26)[b]
7	Dalton et al., 2005[19]	Denmark	Inpatients with schizophrenia (Danish Psychiatric Central Register)	9743	General Danish population	1969-1995	215	Danish Cancer Registry (ICD-7)	SIR=1.20 (1.05-1.38)[b]
8	Grinshpoon et al., 2005[21]	Israel	Patients diagnosed with schizophrenia (National psychiatric case register)	NR	General population	1962-2001	370	Israeli National Cancer Registry	SIR=1.11 (1.00-1.22)[c]
9	Barak et al., 2005[18]	Israel	Patients diagnosed with schizophrenia (Abarbanel Mental Health Center)	1247	General Jewish population	1993-2003	22	National Cancer Registry of Israel	SIR=0.61 (0.39-0.92)[b]
10	Hippisley-Cox et al., 2007[22]	UK	Patients diagnosed with schizophrenia (QRESEARCH database)	202	General population	1995-2005	49	QRESEARCH database (primary care clinical records)	OR=1.52 (1.10-2.11)[i]
11	Barak et al., 2008[23]	Israel	Patients diagnosed with schizophrenia (Abarbanel Mental Health Center)	2011	General Jewish population	1960-2005	51	National Cancer Registry of Israel	SIR=0.63 (0.47-0.83)[a]
12	Chou et al., 2011[24]	Taiwan	Patients diagnosed with schizophrenia (National Health Research Institute Database)	29196	General population	2000-2008	248	Catastrophic Illness Registration (ICD-9)	HR=1.06 (0.92-1.23)[e]
13	Lin et al., 2011[28]	Taiwan	Patients diagnosed with schizophrenia (National Health Research Institute Database)	33297	General population	1997-2009	215	Catastrophic Illness Registration (ICD-9)	SIR=1.68 (1.35-2.09)[b]

14	McGinty et al., 2012[25]	USA	Patients diagnosed with schizophrenia (Maryland Medicaid database)	1119	General population	1996-2004	42	Medicaid administrative claims data (ICD-9)	SIR=2.90 (2.10-3.90)[d]
15	Ji et al., 2013[26]	Sweden	Inpatients and outpatients with schizophrenia (Swedish Hospital Discharge Register)	27029	General Swedish population	1965-2008	1042	National Cancer Registry of Sweden (ICD-7)	SIR=1.47 (1.38-1.56)[h]
16	Lin et al., 2013[27]	Taiwan	Patients diagnosed with schizophrenia (National Health Insurance Research Database)	46447	General population	1995-2007	341	National Cancer Registry of Taiwan (ICD-9)	SIR=1.50 (1.44-1.60)[b]
17	Osborn et al.,2013[29]	UK	Patients diagnosed with schizophrenia (The Health Improvement Network (THIN) primary care database)	7810	General population	1990-2008	NR	Medical records confirmed cases (ICD-9)	IRR=1.36 (0.96-1.93)[g]
18	Chen et al., 2016[102]	Taiwan	Inpatients with schizophrenia (Psychiatric Inpatient Medical Claims database)	NR	General population	2000-2010	105	Catastrophic illness database (ICD-9)	SIR=1.47 (1.22-1.78)[a]
19	Chou et al., 2017[12]	Taiwan	Patients diagnosed with schizophrenia (National Health Insurance Research Database)	10727	General population	1998-2008	119	Registry for Catastrophic Illness Patient Database (ICD-9)	HR=1.94 (1.43-2.63)[f]
20	Pettersson et al., 2020[11]	Sweden	Patients diagnosed with schizophrenia (National Patient Register)	59262	General population	1990-2013	2189	Cancer Register (ICD-7), National Patient Register (ICD-9,10), and Cause of Death Register (ICD-9,10)	IRR=1.19 (1.12-1.26)[b]

Notes. Only the 10th study (Hippisley-Cox et al, 2007) is a nested case-control study, and the other 19 studies are all retrospective cohort studies.

a: age adjusted, b: age, period of follow-up adjusted, c: age, place of origin adjusted, d: age, race adjusted, e: age, level of urbanization, income and comorbidities adjusted, f: age, occupation, income, comorbidities, and medications adjusted, g: age, period of follow-up, deprivation, smoking, and BMI adjusted, h: age, period of follow-up, residential area, socioeconomic status, comorbidities, parity, and age at first birth adjusted, i: age, socioeconomic status, comorbidities, smoking, obesity, medications, hormone therapy, and oral contraceptive adjusted.

Appendix Table 2. List of antipsychotic medications

Classification	Antipsychotics	ATC code
First Generation Antipsychotics (FGA)		
	haloperidol	N05AD01
	levomepromazine	N05AA02
	perphenazine	N05AB03
	pimozide	N05AG02
	chlorpromazine	N05AA01
Second Generation Antipsychotics (SGA)		
	clozapine	N05AH02
	olanzapine	N05AH03
	risperidone	N05AX08
	sulpiride	N05AL01
	zotepin	N05AX11
	quetiapine	N05AH04
	amisulpride	N05AL05
	aripiprazole	N05AX12
	ziprasidone	N05AE04
	paliperidone	N05AX13
	blonanserin	-

Appendix Table 3. The ICD-10 codes of diseases included in the calculation of the Charlson comorbidity index

Diagnostic categories	Weight	ICD-10 code
Acute myocardial infarction	1	I21, I22, I252
Congestive heart failure	1	I50
Peripheral vascular disease	1	I71, R02, I790, I739, Z958, Z959
Cerebral vascular accident	1	I60, I61, I62, I63, I64, I65, I66, I67, I68, I69, G46, G450, G451, G452, G454, G458, G459
Dementia	1	F00, F01, F02, F051
Pulmonary disease	1	J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67
Connective tissue disorder	1	M32, M33, M34, M35, M050, M052, M051, M053, M058, M059, M060, M063, M069
Peptic ulcer	1	K25, K26, K27, K28
Liver disease	1	K73, K702, K703, K717, K740, K742, K743, K744, K745, K746
Diabetes	1	E101, E105, E109, E111, E115, E119, E131, E135, E139, E141, E145, E149
Diabetes complications	2	E102, E103, E104, E112, E113, E114, E132, E133, E134, E142, E143, E144
Paraplegia	2	G041, G810, G811, G819, G820, G821, G822
Renal disease	2	N01, N03, N18, N19, N25, N052, N053, N054, N055, N056, N072, N073, N074
Cancer	2	C0, C1, C2, C3, C40, C41, C43-C49, C5, C6, C70-C76, C80-C85, C883, C887, C889, C900, C901, C91-C93, C940-C943, C9451, C947, C95, C96
Metastatic cancer	3	C77, C78, C79, C80
Severe liver disease	3	K721, K729, K766, K767
HIV	6	B20, B21, B22, B23, B24

Appendix Table 4. Hazard ratios and E-values for breast cancer among patients with schizophrenia and 2 control groups

	HR (95% CI)	E-value	(lower limit of the 95% CI)	HR (95% CI)	E-value	(lower limit of the 95% CI)
Schizophrenia patients	1.26 (1.12-1.33)	1.83	(1.49)	1.08 (1.02-1.14)	1.37	(1.16)
Other psychiatric disorders patients	1.17 (1.12-1.22)	1.62	(1.49)	Ref		
General population	Ref					

Notes. Schizophrenia patients: persons diagnosed with schizophrenia and prescribed antipsychotics. Other psychiatric disorders patients: persons who have been diagnosed with psychiatric disorders, excluding the case group (diagnosis codes F10-F19, F30-F69). General population group: persons who have never been diagnosed with psychiatric disorders or dementia (diagnosis codes F00-F99, G30, G31.8, G31.00).
Model: insurance premiums, region of residence, Charlson Comorbidity Index (CCI) adjusted

Appendix Table 5. Hazard ratios for breast cancer among patients with schizophrenia and 2 control groups stratified by Charlson comorbidity index

			N	(case)	Incidence rate (N/1000py)	Unadjusted		Adjusted			
						HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
CCI	0	Schizophrenia patients	97,028	(1510)	1.62	1.35 (1.26-1.44)	<.0001	1.32 (1.24-1.41)	<.0001	1.08 (1.01-1.16)	0.030
		Other psychiatric disorders patients	97,028	(1417)	1.46	1.21 (1.13-1.29)	<.0001	1.22 (1.15-1.30)	<.0001	Ref	
		General population	194,056	(2248)	1.21	Ref		Ref			
	1-2	Schizophrenia patients	54,749	(398)	1.32	1.23 (1.08-1.39)	0.002	1.20 (1.07-1.34)	0.003	1.03 (0.91-1.17)	0.618
		Other psychiatric disorders patients	54,749	(390)	0.92	1.14 (1.00-1.30)	0.044	1.16 (1.04-1.29)	0.009	Ref	
		General population	109,498	(664)	1.09	Ref		Ref			
	≥3	Schizophrenia patients	37,846	(194)	1.29	1.05 (0.85-1.30)	0.642	1.05 (0.88-1.25)	0.571	1.09 (0.92-1.29)	0.349
		Other psychiatric disorders patients	37,846	(197)	1.17	0.96 (0.78-1.18)	0.712	0.97 (0.82-1.15)	0.717	Ref	
		General population	37,846	(193)	1.21	Ref		Ref			

Notes. CCI: Charlson Comorbidity Index. Unadjusted: crude model (matched by age), Adjusted: insurance premiums, region of residence, Charlson Comorbidity Index (CCI) adjusted. Schizophrenia and 2 control groups are matched in ratio of 1:1:2 or 1:1:1 in each stratum

Appendix Table 6. Hazard ratios for breast cancer among patients with schizophrenia and 2 control groups stratified by region of residence

			N	(case)	Incidence rate (N/1000py)	Unadjusted		Adjusted			
						HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Resi-dence	Metro	Schizophrenia patients	96,333	(1136)	1.63	1.32 (1.22-1.43)	<.0001	1.32 (1.22-1.42)	<.0001	1.13 (1.04-1.22)	0.003
		Other psychiatric disorders patients	96,333	(1047)	1.43	1.15 (1.07-1.25)	<.001	1.17 (1.09-1.25)	<.0001	Ref	
		General population	192,666	(1761)	1.24	Ref		Ref			
	Urban	Schizophrenia patients	96,125	(916)	1.42	1.25 (1.15-1.36)	<.0001	1.20 (1.10-1.30)	<.0001	1.02 (0.94-1.11)	0.625
		Other psychiatric disorders patients	96,125	(917)	1.35	1.18 (1.08-1.28)	<.001	1.17 (1.09-1.26)	<.0001	Ref	
		General population	184,250	(1493)	1.13	Ref		Ref			
	Rural	Schizophrenia patients	19,435	(175)	1.26	1.43 (1.13-1.82)	0.003	1.31 (1.04-1.63)	0.020	1.12 (0.92-1.38)	0.265
		Other psychiatric disorders patients	19,435	(155)	1.05	1.16 (0.91-1.48)	0.225	1.16 (0.95-1.43)	0.155	Ref	
		General population	19,435	(128)	0.91	Ref		Ref			

Notes. Unadjusted: crude model (matched by age), Adjusted: insurance premiums, region of residence, Charlson Comorbidity Index (CCI) adjusted
Schizophrenia and 2 control groups are matched in a ratio of 1:1:2 or 1:1:1 in each stratum.
Metro presents metropolitan area, urban presents urban area, and rural presents rural area.

Appendix Table 7. Hazard ratios for breast cancer among patients with schizophrenia and 2 control groups stratified by insurance premiums

			N	(case)	Incidence rate (N/1000py)	Unadjusted		Adjusted			
						HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Insurance premiums	0-5	Schizophrenia patients	53,497	(588)	1.53	1.29 (1.14-1.47)	<.0001	1.32 (1.19-1.47)	<.0001	1.24 (1.13-1.38)	<.0001
		Other psychiatric disorders patients	53,497	(507)	1.27	1.04 (0.91-1.19)	0.544	1.06 (0.95-1.18)	0.286	Ref	
		General population	53,497	(455)	1.19	Ref		Ref			
	6-15	Schizophrenia patients	76,040	(709)	1.38	1.25 (1.13-1.37)	<.0001	1.24 (1.14-1.35)	<.0001	1.07 (0.98-1.17)	0.152
		Other psychiatric disorders patients	76,040	(707)	1.27	1.16 (1.05-1.27)	0.003	1.16 (1.07-1.26)	<.001	Ref	
		General population	152,080	(1178)	1.09	Ref		Ref			
	16-20	Schizophrenia patients	54,985	(524)	1.44	1.20 (1.08-1.34)	0.001	1.22 (1.11-1.34)	<.0001	1.05 (0.95-1.17)	0.329
		Other psychiatric disorders patients	54,985	(545)	1.38	1.13 (1.02-1.26)	0.024	1.16 (1.05-1.27)	0.003	Ref	
		General population	109,970	(923)	1.20	Ref		Ref			

Notes. Unadjusted: crude model (matched by age), Adjusted: insurance premiums, region of residence, Charlson Comorbidity Index (CCI) adjusted
Schizophrenia and 2 control groups are matched in a ratio of 1:1:2 or 1:1:1 in each stratum.

Appendix Table 8. Distribution of schizophrenia patients according to the duration of antipsychotic use between the index date and the landmark time (5 years), divided by antipsychotic generation.

		SGA									
		0 year		0-1 year		1-3 years		≥3 years			
		N	(%)	N	(%)	N	(%)	N	(%)	Total	
FGA	0 year	1840	(1.28)	23125	(16.09)	19887	(13.84)	39174	(27.26)	84026	(58.47)
	0-1 year	2585	(1.80)	6325	(4.40)	8788	(6.11)	12573	(8.75)	30271	(21.06)
	1-3 years	4338	(3.02)	3140	(2.18)	6615	(4.60)	4300	(2.99)	18393	(12.79)
	≥3 years	4306	(3.00)	2214	(1.54)	1461	(1.02)	3053	(2.12)	11034	(7.68)
Total		13069	(9.10)	34804	(24.21)	36751	(25.57)	59100	(41.12)	143724	(100.00)

Appendix Table 9. Distribution of antipsychotic treatment duration according to groups (schizophrenia patients vs other psychiatric disorders patients)

	Schizophrenia patients		Other psychiatric disorders patients	
	N	(%)	N	(%)
0 (without antipsychotics)	835	(0.37)	205613	(91.49)
0<year≤1	68893	(30.65)	15490	(6.89)
1<year≤2	24440	(10.87)	1539	(0.68)
2<year≤3	17364	(7.73)	741	(0.33)
3<year≤4	13927	(6.20)	418	(0.19)
4<year≤5	11637	(5.18)	267	(0.12)
5<year≤6	10682	(4.75)	218	(0.10)
6<year≤7	10340	(4.60)	141	(0.06)
7<year≤8	9475	(4.22)	95	(0.04)
8<year≤9	10042	(4.47)	78	(0.03)
9<year≤10	22660	(10.08)	59	(0.03)
10<year≤11	8664	(3.86)	38	(0.02)
11<year≤12	15784	(7.02)	46	(0.02)

Notes. The duration of antipsychotic treatment was calculated between the index date and the earliest of the dates of death, loss to follow-up, or event occurrence.

Appendix Table 10. Summary of Samples in Outcome datasets

	Case	Control
Data source	SeBCS	HEXA baseline
Number of Subjects	2165	2046
Age, mean(SD)	48.16 (9.33)	51.63 (7.66)
Age≥50, N(%)	833 (38.48)	1,097 (53.62)
Genotype Method	Affymetrix 6.0	Affymetrix 6.0

Notes. Affymetrix 6.0 refers to the Affymetrix Genome-Wide Human SNP Array 6.0 chip (Affymetrix, Inc.Santa Clara, CA, USA)

Appendix Table 11. List of Genetic Instruments for Schizophrenia and Log Odds Ratios of Breast Cancer by Each Instrumental SNP

No.	SNP	Chr.	EA	OA	EAF	F statistic	Schizophrenia log_eOR (SE)		Breast cancer log_eOR (SE)	
1	rs10927044	1	A	G	0.569	39.344	0.064	(0.010)	0.023	(0.044)
2	rs11210193	1	A	G	0.206	31.896	0.058	(0.010)	0.057	(0.054)
3	rs11210892	1	G	A	0.305	44.329	0.068	(0.010)	0.029	(0.047)
4	rs12116970	1	C	T	0.923	34.452	0.090	(0.015)	0.016	(0.075)
5	rs12139672	1	G	A	0.392	35.517	0.061	(0.010)	-0.072	(0.046)
6	rs172531	1	G	A	0.098	25.349	0.064	(0.013)	0.041	(0.081)
7	rs4634961	1	A	G	0.980	86.562	0.119	(0.013)	0.120	(0.119)
8	rs4949526	1	T	C	0.257	42.757	0.067	(0.010)	0.097	(0.054)
9	rs16851048	1	C	T	0.120	58.261	0.078	(0.010)	-0.033	(0.056)
10	rs17557162	1	T	A	0.860	22.786	0.207	(0.043)	0.138	(0.065)
11	rs11688415	2	C	T	0.118	46.390	0.104	(0.015)	-0.025	(0.064)
12	rs1509378	2	A	G	0.680	29.712	0.070	(0.013)	-0.065	(0.049)
13	rs1837495	2	G	A	0.468	43.964	0.068	(0.010)	0.113	(0.044)
14	rs359250	2	G	T	0.140	26.717	0.119	(0.023)	0.079	(0.059)
15	rs4973569	2	G	A	0.088	41.299	0.082	(0.013)	0.076	(0.063)
16	rs999494	2	C	T	0.848	30.483	0.070	(0.013)	-0.060	(0.060)
17	rs10184465	2	G	A	0.098	35.342	0.262	(0.044)	-0.053	(0.094)
18	rs11694987	2	C	G	0.670	42.148	0.066	(0.010)	-0.008	(0.052)

19	rs1518395	2	G	A	0.690	52.162	0.129	(0.018)	0.009	(0.051)
20	rs4666014	2	G	A	0.430	33.080	0.059	(0.010)	-0.037	(0.046)
21	rs4685	2	T	C	0.458	59.512	0.079	(0.010)	0.063	(0.047)
22	rs7574065	2	A	T	0.370	24.349	0.063	(0.013)	-0.067	(0.045)
23	rs7592587	2	G	C	0.210	45.603	0.103	(0.015)	-0.034	(0.051)
24	rs895526	2	C	T	0.466	46.190	0.069	(0.010)	0.070	(0.045)
25	rs1397221	3	G	A	0.490	33.080	0.059	(0.010)	-0.008	(0.044)
26	rs1805571	3	G	A	0.843	41.836	0.083	(0.013)	-0.019	(0.084)
27	rs2174019	3	G	A	0.010	56.766	0.077	(0.010)	-0.107	(0.190)
28	rs6776145	3	C	T	0.659	37.966	0.094	(0.015)	0.023	(0.045)
29	rs9811916	3	G	A	0.069	31.326	0.071	(0.013)	0.012	(0.095)
30	rs2535629	3	G	A	0.616	47.678	0.070	(0.010)	-0.039	(0.045)
31	rs308690	3	G	T	0.722	29.596	0.056	(0.010)	-0.028	(0.049)
32	rs4908986	3	G	C	1.000	33.080	0.059	(0.010)	-0.035	(0.187)
33	rs6791611	3	G	C	0.190	47.629	0.070	(0.010)	-0.061	(0.060)
34	rs223397	4	C	T	0.526	24.242	0.050	(0.010)	-0.026	(0.045)
35	rs6852201	4	C	T	0.180	30.529	0.056	(0.010)	0.022	(0.054)
36	rs215411	4	A	T	0.130	46.051	0.069	(0.010)	0.008	(0.098)
37	rs6847160	4	T	A	0.280	29.596	0.056	(0.010)	0.064	(0.052)
38	rs2409033	5	T	C	0.348	48.944	0.054	(0.008)	0.015	(0.045)
39	rs2910032	5	C	T	0.207	24.432	0.063	(0.013)	-0.047	(0.062)
40	rs4388249	5	T	C	0.706	24.376	0.063	(0.013)	-0.070	(0.047)
41	rs4835678	5	C	T	0.154	25.850	0.065	(0.013)	0.057	(0.061)

42	rs6874127	5	G	A	0.438	42.012	0.066	(0.010)	-0.069	(0.045)
43	rs7701188	5	G	A	0.951	39.518	0.096	(0.015)	0.073	(0.170)
44	rs17566146	5	C	G	0.990	32.148	0.072	(0.013)	0.002	(0.149)
45	rs2563263	5	T	C	0.442	48.944	0.054	(0.008)	-0.016	(0.045)
46	rs6449527	5	C	G	0.980	58.399	0.078	(0.010)	0.046	(0.060)
47	rs217311	6	C	T	0.618	40.667	0.065	(0.010)	0.001	(0.045)
48	rs314263	6	C	T	0.279	31.896	0.058	(0.010)	0.119	(0.052)
49	rs6919306	6	T	C	0.216	32.406	0.102	(0.018)	0.037	(0.049)
50	rs7749109	6	A	G	0.986	61.786	0.160	(0.020)	0.070	(0.135)
51	rs9353533	6	C	A	0.190	30.735	0.057	(0.010)	0.077	(0.045)
52	rs16894194	6	T	A	0.810	75.256	0.133	(0.015)	0.082	(0.064)
53	rs17598927	6	C	G	0.880	39.078	0.080	(0.013)	0.103	(0.070)
54	rs17720293	6	C	T	0.979	101.402	0.180	(0.018)	-0.055	(0.152)
55	rs200995	6	T	C	0.921	93.068	0.172	(0.018)	0.118	(0.077)
56	rs2490272	6	C	T	0.360	43.381	0.067	(0.010)	-0.038	(0.052)
57	rs3130275	6	G	A	0.263	53.625	0.075	(0.010)	0.007	(0.051)
58	rs629444	6	C	T	0.890	54.563	0.132	(0.018)	0.101	(0.075)
59	rs688209	6	T	G	0.983	26.512	0.079	(0.015)	-0.008	(0.114)
60	rs6925744	6	C	T	0.840	41.318	0.262	(0.041)	0.130	(0.059)
61	rs885940	6	C	T	0.861	73.967	0.154	(0.018)	-0.039	(0.062)
62	rs11981403	7	C	T	0.945	31.555	0.129	(0.023)	0.046	(0.087)
63	rs4731825	7	T	C	0.931	29.705	0.083	(0.015)	0.112	(0.113)
64	rs9656169	7	C	T	0.824	30.529	0.056	(0.010)	0.038	(0.059)

65	rs16874961	7	A	C	0.676	24.159	0.063	(0.013)	0.090	(0.051)
66	rs2109299	7	G	A	0.820	39.350	0.080	(0.013)	0.024	(0.044)
67	rs13259407	8	C	T	0.632	48.688	0.053	(0.008)	0.037	(0.045)
68	rs16880322	8	T	C	0.075	23.533	0.062	(0.013)	0.044	(0.080)
69	rs16880831	8	G	T	0.163	34.320	0.075	(0.013)	-0.111	(0.065)
70	rs17687067	8	C	A	0.259	24.876	0.076	(0.015)	0.064	(0.048)
71	rs6982408	8	T	G	0.294	34.287	0.060	(0.010)	0.028	(0.046)
72	rs7841617	8	A	G	0.280	27.514	0.174	(0.033)	0.016	(0.046)
73	rs11786117	8	G	A	0.310	43.381	0.067	(0.010)	-0.051	(0.045)
74	rs17310286	8	T	C	0.417	39.078	0.080	(0.013)	-0.016	(0.045)
75	rs4129585	8	A	C	0.218	60.004	0.079	(0.010)	-0.017	(0.053)
76	rs7016464	8	G	C	0.000	29.712	0.070	(0.013)	-0.021	(0.053)
77	rs732998	10	T	C	0.849	42.505	0.116	(0.018)	0.017	(0.052)
78	rs10786712	10	C	T	0.471	91.509	0.098	(0.010)	0.011	(0.045)
79	rs7893279	10	T	G	0.884	39.644	0.112	(0.018)	-0.014	(0.073)
80	rs10898127	11	G	T	0.549	48.688	0.053	(0.008)	-0.024	(0.045)
81	rs11570190	11	C	A	0.108	33.672	0.059	(0.010)	0.083	(0.067)
82	rs12364435	11	C	T	0.127	23.533	0.062	(0.013)	-0.140	(0.076)
83	rs12574668	11	A	C	0.085	52.155	0.092	(0.013)	-0.012	(0.092)
84	rs2514218	11	C	T	0.966	32.148	0.072	(0.013)	0.028	(0.119)
85	rs979603	11	C	T	0.735	26.027	0.065	(0.013)	0.070	(0.048)
86	rs3758927	11	C	G	0.980	51.238	0.091	(0.013)	0.009	(0.133)
87	rs6590512	11	C	T	0.529	56.766	0.077	(0.010)	-0.034	(0.045)

88	rs302321	12	C	A	0.759	35.517	0.061	(0.010)	-0.058	(0.052)
89	rs7308934	12	C	T	0.990	24.376	0.063	(0.013)	0.058	(0.069)
90	rs11065242	12	G	A	1.000	18.820	0.144	(0.033)	-0.030	(0.053)
91	rs4240748	12	G	C	0.720	35.517	0.061	(0.010)	0.017	(0.054)
92	rs4765905	12	C	G	0.054	85.586	0.094	(0.010)	0.098	(0.098)
93	rs12100737	14	A	G	0.560	29.712	0.070	(0.013)	0.058	(0.046)
94	rs2383377	14	A	G	0.167	31.700	0.086	(0.015)	0.037	(0.067)
95	rs12885258	14	A	G	0.039	31.700	0.086	(0.015)	-0.037	(0.129)
96	rs1818950	15	A	G	0.976	38.088	0.079	(0.013)	-0.097	(0.116)
97	rs2002122	15	T	G	0.510	31.560	0.057	(0.010)	0.024	(0.045)
98	rs938682	15	A	G	0.550	30.483	0.070	(0.013)	0.024	(0.045)
99	rs4775413	15	T	C	0.261	44.774	0.068	(0.010)	-0.061	(0.047)
100	rs783540	15	G	A	0.447	34.409	0.060	(0.010)	-0.005	(0.044)
101	rs3814881	16	G	A	0.630	40.667	0.065	(0.010)	-0.009	(0.048)
102	rs8063193	16	C	A	0.098	44.941	0.068	(0.010)	0.041	(0.069)
103	rs9937079	16	G	A	0.588	28.480	0.054	(0.010)	-0.009	(0.048)
104	rs8055219	16	A	G	0.095	56.766	0.077	(0.010)	-0.055	(0.073)
105	rs4643387	17	T	C	0.922	43.381	0.067	(0.010)	-0.002	(0.082)
106	rs11874716	18	T	G	0.480	43.381	0.067	(0.010)	-0.014	(0.045)
107	rs1792709	18	G	A	0.827	33.826	0.134	(0.023)	0.064	(0.066)
108	rs4799092	18	G	C	0.040	31.896	0.058	(0.010)	0.061	(0.045)
109	rs9636107	18	G	A	0.822	61.059	0.080	(0.010)	-0.088	(0.061)
110	rs3786800	19	C	T	0.187	31.703	0.072	(0.013)	-0.052	(0.054)

111	rs968525	19	C	T	0.709	33.080	0.044	(0.008)	0.000	(0.052)
112	rs2250350	20	G	A	0.707	56.338	0.077	(0.010)	-0.105	(0.050)
113	rs6019876	20	C	G	0.000	36.770	0.062	(0.010)	-0.044	(0.052)
114	rs4820428	22	G	A	0.096	48.406	0.089	(0.013)	0.156	(0.118)
115	rs134874	22	G	A	0.656	31.560	0.057	(0.010)	-0.017	(0.046)
116	rs7284768	22	T	C	0.650	43.964	0.068	(0.010)	-0.018	(0.045)

Notes. Chr indicates chromosome; EA, effect allele; OA, other allele; EAF effect allele frequency; and OR, odds ratio

Appendix Table 12. Mendelian randomization results for individual SNPs

SNP	beta	SE	p-value	OR	(95% CI)	
rs314263	2.068	(0.911)	0.023	7.909	(1.326	-47.161)
rs4820428	1.760	(1.329)	0.185	5.812	(0.430	-78.637)
rs1837495	1.677	(0.657)	0.011	5.349	(1.476	-19.389)
rs4949526	1.459	(0.808)	0.071	4.302	(0.883	-20.961)
rs16874961	1.441	(0.812)	0.076	4.225	(0.860	-20.749)
rs11570190	1.399	(1.128)	0.215	4.051	(0.444	-36.962)
rs9353533	1.365	(0.794)	0.086	3.916	(0.826	-18.564)
rs4731825	1.346	(1.351)	0.319	3.842	(0.272	-54.269)
rs17598927	1.297	(0.881)	0.141	3.658	(0.651	-20.568)
rs6847160	1.149	(0.932)	0.217	3.155	(0.508	-19.604)
rs979603	1.083	(0.731)	0.138	2.954	(0.705	-12.376)
rs4799092	1.065	(0.787)	0.176	2.901	(0.620	-13.565)
rs4765905	1.036	(1.042)	0.320	2.818	(0.366	-21.722)
rs4634961	1.014	(1.004)	0.313	2.757	(0.385	-19.724)
rs895526	1.010	(0.653)	0.122	2.746	(0.763	-9.874)
rs11210193	0.981	(0.934)	0.294	2.667	(0.428	-16.637)
rs4973569	0.928	(0.766)	0.225	2.529	(0.564	-11.352)
rs7308934	0.919	(1.097)	0.402	2.507	(0.292	-21.523)
rs4835678	0.873	(0.938)	0.352	2.394	(0.381	-15.052)
rs17687067	0.844	(0.631)	0.181	2.326	(0.675	-8.011)
rs12100737	0.837	(0.656)	0.202	2.309	(0.638	-8.354)
rs4685	0.800	(0.597)	0.180	2.226	(0.691	-7.172)
rs629444	0.765	(0.569)	0.179	2.149	(0.705	-6.555)
rs7701188	0.758	(1.772)	0.669	2.134	(0.066	-68.794)
rs16880322	0.705	(1.290)	0.585	2.024	(0.161	-25.366)
rs13259407	0.694	(0.847)	0.413	2.002	(0.381	-10.529)
rs200995	0.682	(0.447)	0.127	1.978	(0.824	-4.750)
rs9656169	0.679	(1.049)	0.518	1.972	(0.252	-15.410)
rs17557162	0.667	(0.313)	0.033	1.948	(1.055	-3.598)
rs359250	0.664	(0.498)	0.182	1.943	(0.732	-5.156)
rs172531	0.633	(1.264)	0.617	1.883	(0.158	-22.431)
rs16894194	0.620	(0.482)	0.198	1.859	(0.723	-4.781)
rs8063193	0.600	(1.013)	0.554	1.822	(0.250	-13.270)

rs6449527	0.586	(0.770)	0.447	1.797	(0.397	-8.127)
rs6925744	0.494	(0.226)	0.029	1.639	(1.052	-2.552)
rs1792709	0.481	(0.493)	0.329	1.618	(0.616	-4.252)
rs6982408	0.469	(0.773)	0.544	1.598	(0.351	-7.272)
rs7749109	0.439	(0.840)	0.601	1.551	(0.299	-8.048)
rs2383377	0.426	(0.778)	0.584	1.531	(0.333	-7.035)
rs11210892	0.420	(0.697)	0.547	1.522	(0.388	-5.966)
rs2002122	0.414	(0.782)	0.597	1.513	(0.327	-7.006)
rs2514218	0.393	(1.646)	0.811	1.481	(0.059	-37.306)
rs6852201	0.393	(0.953)	0.680	1.481	(0.229	-9.592)
rs6919306	0.361	(0.485)	0.456	1.435	(0.555	-3.712)
rs10927044	0.357	(0.694)	0.607	1.429	(0.367	-5.569)
rs11981403	0.356	(0.671)	0.596	1.428	(0.383	-5.318)
rs938682	0.338	(0.639)	0.597	1.402	(0.401	-4.906)
rs2109299	0.301	(0.551)	0.585	1.351	(0.459	-3.979)
rs2409033	0.287	(0.842)	0.733	1.332	(0.256	-6.940)
rs4240748	0.279	(0.894)	0.755	1.322	(0.229	-7.624)
rs6776145	0.242	(0.473)	0.609	1.274	(0.504	-3.219)
rs12116970	0.176	(0.837)	0.833	1.192	(0.231	-6.150)
rs9811916	0.170	(1.337)	0.899	1.185	(0.086	-16.289)
rs732998	0.150	(0.445)	0.736	1.162	(0.486	-2.779)
rs215411	0.119	(1.418)	0.933	1.126	(0.070	-18.143)
rs10786712	0.111	(0.459)	0.809	1.117	(0.454	-2.747)
rs3758927	0.097	(1.457)	0.947	1.102	(0.063	-19.158)
rs3130275	0.095	(0.679)	0.888	1.100	(0.291	-4.161)
rs7841617	0.090	(0.266)	0.735	1.094	(0.650	-1.843)
rs1518395	0.074	(0.397)	0.853	1.077	(0.495	-2.345)
rs17566146	0.028	(2.064)	0.989	1.028	(0.018	-58.759)
rs217311	0.020	(0.699)	0.978	1.020	(0.259	-4.015)
rs968525	0.011	(1.172)	0.992	1.011	(0.102	-10.056)
rs4643387	-0.024	(1.214)	0.984	0.976	(0.090	-10.543)
rs783540	-0.091	(0.740)	0.902	0.913	(0.214	-3.894)
rs688209	-0.107	(1.443)	0.941	0.899	(0.053	-15.200)
rs11694987	-0.121	(0.784)	0.878	0.886	(0.191	-4.119)
rs7893279	-0.126	(0.650)	0.846	0.882	(0.247	-3.152)
rs12574668	-0.133	(0.997)	0.894	0.875	(0.124	-6.179)

rs1397221	-0.138	(0.757)	0.856	0.871	(0.198	-3.841)
rs3814881	-0.146	(0.743)	0.845	0.864	(0.201	-3.707)
rs9937079	-0.162	(0.881)	0.854	0.850	(0.151	-4.782)
rs17310286	-0.198	(0.565)	0.725	0.820	(0.271	-2.483)
rs10184465	-0.201	(0.360)	0.576	0.818	(0.404	-1.656)
rs11874716	-0.206	(0.673)	0.760	0.814	(0.218	-3.044)
rs11065242	-0.209	(0.369)	0.571	0.811	(0.394	-1.672)
rs4129585	-0.215	(0.673)	0.749	0.807	(0.216	-3.016)
rs1805571	-0.235	(1.016)	0.817	0.791	(0.108	-5.791)
rs11688415	-0.239	(0.612)	0.696	0.787	(0.237	-2.613)
rs885940	-0.253	(0.405)	0.531	0.776	(0.351	-1.717)
rs7284768	-0.270	(0.665)	0.685	0.763	(0.207	-2.811)
rs134874	-0.301	(0.807)	0.710	0.740	(0.152	-3.599)
rs7016464	-0.302	(0.762)	0.692	0.739	(0.166	-3.292)
rs2563263	-0.302	(0.832)	0.716	0.739	(0.145	-3.776)
rs17720293	-0.303	(0.845)	0.720	0.739	(0.141	-3.870)
rs7592587	-0.330	(0.493)	0.503	0.719	(0.274	-1.889)
rs16851048	-0.422	(0.713)	0.554	0.656	(0.162	-2.652)
rs12885258	-0.429	(1.498)	0.774	0.651	(0.035	-12.269)
rs6590512	-0.439	(0.585)	0.454	0.645	(0.205	-2.029)
rs10898127	-0.448	(0.846)	0.596	0.639	(0.122	-3.354)
rs308690	-0.501	(0.886)	0.572	0.606	(0.107	-3.440)
rs223397	-0.520	(0.890)	0.559	0.595	(0.104	-3.402)
rs2535629	-0.553	(0.640)	0.387	0.575	(0.164	-2.017)
rs2490272	-0.565	(0.775)	0.466	0.568	(0.124	-2.596)
rs4908986	-0.590	(3.191)	0.853	0.554	(0.001	-288.403)
rs4666014	-0.637	(0.787)	0.418	0.529	(0.113	-2.473)
rs6019876	-0.707	(0.844)	0.402	0.493	(0.094	-2.579)
rs8055219	-0.709	(0.950)	0.456	0.492	(0.076	-3.168)
rs3786800	-0.720	(0.747)	0.335	0.487	(0.113	-2.105)
rs2910032	-0.748	(0.981)	0.446	0.473	(0.069	-3.237)
rs11786117	-0.761	(0.671)	0.257	0.467	(0.125	-1.740)
rs999494	-0.846	(0.850)	0.320	0.429	(0.081	-2.270)
rs6791611	-0.870	(0.851)	0.306	0.419	(0.079	-2.221)
rs4775413	-0.889	(0.689)	0.197	0.411	(0.107	-1.586)
rs1509378	-0.937	(0.709)	0.186	0.392	(0.098	-1.572)

rs302321	-0.946	(0.861)	0.272	0.388	(0.072	-2.099)
rs6874127	-1.040	(0.673)	0.122	0.353	(0.095	-1.322)
rs7574065	-1.072	(0.715)	0.134	0.342	(0.084	-1.390)
rs9636107	-1.102	(0.768)	0.152	0.332	(0.074	-1.497)
rs4388249	-1.105	(0.748)	0.140	0.331	(0.076	-1.435)
rs12139672	-1.192	(0.764)	0.119	0.304	(0.068	-1.357)
rs1818950	-1.226	(1.478)	0.407	0.293	(0.016	-5.317)
rs2250350	-1.365	(0.648)	0.035	0.255	(0.072	-0.909)
rs2174019	-1.395	(2.465)	0.571	0.248	(0.002	-31.075)
rs16880831	-1.488	(0.868)	0.086	0.226	(0.041	-1.238)
rs12364435	-2.255	(1.234)	0.068	0.105	(0.009	-1.178)
All - Inverse variance weighted	0.135	(0.062)	0.029	1.144	(1.014	-1.292)
All - MR Egger	0.373	(0.158)	0.020	1.452	(1.064	-1.979)

Appendix Table 13. Result of leave-one-out analysis

Excluded SNP	beta	(SE)	p-value	OR	95% CI
rs2250350	0.149	(0.062)	0.017	1.160	(1.027 -1.310)
rs6874127	0.145	(0.062)	0.020	1.156	(1.024 -1.305)
rs7574065	0.144	(0.062)	0.020	1.155	(1.023 -1.304)
rs12139672	0.144	(0.062)	0.020	1.154	(1.022 -1.304)
rs10184465	0.145	(0.063)	0.021	1.156	(1.022 -1.307)
rs4388249	0.143	(0.062)	0.021	1.154	(1.022 -1.303)
rs16880831	0.143	(0.062)	0.021	1.154	(1.022 -1.303)
rs11065242	0.145	(0.063)	0.021	1.156	(1.022 -1.307)
rs4775413	0.143	(0.062)	0.021	1.154	(1.022 -1.303)
rs1509378	0.143	(0.062)	0.021	1.154	(1.022 -1.303)
rs9636107	0.143	(0.062)	0.021	1.154	(1.022 -1.303)
rs885940	0.144	(0.063)	0.021	1.155	(1.022 -1.306)
rs11786117	0.143	(0.062)	0.022	1.153	(1.021 -1.302)
rs7592587	0.142	(0.062)	0.022	1.153	(1.021 -1.303)
rs12364435	0.141	(0.062)	0.023	1.151	(1.020 -1.300)
rs2535629	0.141	(0.062)	0.023	1.152	(1.020 -1.301)
rs6590512	0.141	(0.062)	0.023	1.152	(1.020 -1.301)
rs3786800	0.141	(0.062)	0.023	1.151	(1.019 -1.300)
rs302321	0.141	(0.062)	0.023	1.151	(1.019 -1.299)
rs6791611	0.140	(0.062)	0.024	1.151	(1.019 -1.299)
rs999494	0.140	(0.062)	0.024	1.150	(1.019 -1.299)
rs4666014	0.140	(0.062)	0.024	1.150	(1.018 -1.298)
rs6019876	0.139	(0.062)	0.024	1.150	(1.018 -1.298)
rs2490272	0.139	(0.062)	0.024	1.150	(1.018 -1.298)
rs16851048	0.139	(0.062)	0.025	1.149	(1.018 -1.298)
rs8055219	0.138	(0.062)	0.025	1.149	(1.017 -1.297)
rs2910032	0.138	(0.062)	0.025	1.148	(1.017 -1.297)
rs17310286	0.139	(0.062)	0.025	1.149	(1.017 -1.298)
rs11688415	0.139	(0.062)	0.025	1.149	(1.017 -1.298)
rs7284768	0.138	(0.062)	0.026	1.148	(1.017 -1.297)
rs223397	0.138	(0.062)	0.026	1.148	(1.017 -1.296)
rs308690	0.138	(0.062)	0.026	1.148	(1.017 -1.296)
rs10898127	0.138	(0.062)	0.026	1.148	(1.017 -1.296)

rs7016464	0.138	(0.062)	0.026	1.148	(1.016	-1.296)
rs4129585	0.138	(0.062)	0.026	1.148	(1.016	-1.296)
rs11874716	0.138	(0.062)	0.026	1.148	(1.016	-1.296)
rs1818950	0.137	(0.062)	0.026	1.147	(1.016	-1.295)
rs134874	0.137	(0.062)	0.026	1.147	(1.016	-1.296)
rs2563263	0.137	(0.062)	0.027	1.147	(1.016	-1.295)
rs17720293	0.137	(0.062)	0.027	1.147	(1.016	-1.295)
rs7893279	0.137	(0.062)	0.027	1.147	(1.016	-1.296)
rs3814881	0.137	(0.062)	0.027	1.147	(1.015	-1.295)
rs1397221	0.137	(0.062)	0.027	1.147	(1.015	-1.295)
rs11694987	0.137	(0.062)	0.028	1.146	(1.015	-1.294)
rs9937079	0.136	(0.062)	0.028	1.146	(1.015	-1.294)
rs1805571	0.136	(0.062)	0.028	1.146	(1.015	-1.294)
rs783540	0.136	(0.062)	0.028	1.146	(1.015	-1.294)
rs2174019	0.136	(0.062)	0.028	1.146	(1.015	-1.293)
rs12885258	0.136	(0.062)	0.028	1.146	(1.015	-1.293)
rs12574668	0.136	(0.062)	0.028	1.146	(1.015	-1.293)
rs217311	0.136	(0.062)	0.029	1.145	(1.014	-1.294)
rs688209	0.135	(0.062)	0.029	1.145	(1.014	-1.292)
rs4908986	0.135	(0.062)	0.029	1.145	(1.014	-1.292)
rs4643387	0.135	(0.062)	0.029	1.145	(1.014	-1.292)
rs968525	0.135	(0.062)	0.029	1.145	(1.014	-1.292)
rs17566146	0.135	(0.062)	0.029	1.145	(1.014	-1.292)
rs3758927	0.135	(0.062)	0.029	1.145	(1.014	-1.292)
rs215411	0.135	(0.062)	0.029	1.144	(1.014	-1.292)
rs1518395	0.136	(0.063)	0.029	1.146	(1.014	-1.296)
rs9811916	0.135	(0.062)	0.029	1.144	(1.014	-1.292)
rs3130275	0.135	(0.062)	0.029	1.145	(1.014	-1.293)
rs2514218	0.135	(0.062)	0.030	1.144	(1.013	-1.291)
rs12116970	0.135	(0.062)	0.030	1.144	(1.013	-1.292)
rs10786712	0.135	(0.062)	0.030	1.145	(1.013	-1.294)
rs7701188	0.134	(0.062)	0.030	1.144	(1.013	-1.291)
rs4240748	0.134	(0.062)	0.030	1.144	(1.013	-1.291)
rs2409033	0.134	(0.062)	0.030	1.143	(1.013	-1.291)
rs7841617	0.137	(0.064)	0.030	1.147	(1.013	-1.299)
rs172531	0.134	(0.062)	0.031	1.143	(1.013	-1.290)

rs6852201	0.134	(0.062)	0.031	1.143	(1.013	-1.291)
rs16880322	0.134	(0.062)	0.031	1.143	(1.012	-1.290)
rs732998	0.135	(0.062)	0.031	1.144	(1.012	-1.293)
rs8063193	0.133	(0.062)	0.031	1.142	(1.012	-1.290)
rs7749109	0.133	(0.062)	0.031	1.143	(1.012	-1.290)
rs9656169	0.133	(0.062)	0.032	1.142	(1.012	-1.290)
rs2002122	0.133	(0.062)	0.032	1.142	(1.012	-1.290)
rs2383377	0.133	(0.062)	0.032	1.142	(1.012	-1.290)
rs10927044	0.133	(0.062)	0.032	1.142	(1.012	-1.290)
rs11981403	0.133	(0.062)	0.032	1.142	(1.011	-1.290)
rs938682	0.133	(0.062)	0.032	1.142	(1.011	-1.290)
rs6982408	0.133	(0.062)	0.032	1.142	(1.011	-1.289)
rs4731825	0.132	(0.062)	0.032	1.142	(1.011	-1.289)
rs7308934	0.132	(0.062)	0.032	1.142	(1.011	-1.289)
rs11210892	0.133	(0.062)	0.032	1.142	(1.011	-1.289)
rs2109299	0.133	(0.062)	0.033	1.142	(1.011	-1.290)
rs6776145	0.133	(0.062)	0.033	1.142	(1.011	-1.291)
rs13259407	0.132	(0.062)	0.033	1.141	(1.011	-1.288)
rs6449527	0.132	(0.062)	0.033	1.141	(1.011	-1.288)
rs4765905	0.132	(0.062)	0.033	1.141	(1.011	-1.288)
rs4835678	0.132	(0.062)	0.033	1.141	(1.010	-1.288)
rs4634961	0.132	(0.062)	0.034	1.141	(1.010	-1.288)
rs4820428	0.131	(0.062)	0.034	1.140	(1.010	-1.287)
rs11570190	0.131	(0.062)	0.034	1.140	(1.010	-1.287)
rs11210193	0.131	(0.062)	0.034	1.140	(1.010	-1.287)
rs6847160	0.130	(0.062)	0.035	1.139	(1.009	-1.286)
rs6919306	0.131	(0.062)	0.035	1.140	(1.009	-1.288)
rs4973569	0.130	(0.062)	0.036	1.138	(1.008	-1.286)
rs17598927	0.129	(0.062)	0.037	1.138	(1.008	-1.285)
rs4799092	0.129	(0.062)	0.037	1.138	(1.008	-1.285)
rs1792709	0.129	(0.062)	0.038	1.138	(1.007	-1.286)
rs12100737	0.129	(0.062)	0.038	1.137	(1.007	-1.284)
rs979603	0.128	(0.062)	0.039	1.137	(1.007	-1.284)
rs17687067	0.128	(0.062)	0.039	1.137	(1.006	-1.284)
rs9353533	0.127	(0.062)	0.040	1.136	(1.006	-1.283)
rs4685	0.128	(0.062)	0.040	1.136	(1.006	-1.283)

rs16874961	0.127	(0.062)	0.040	1.136	(1.006	-1.282)
rs4949526	0.127	(0.062)	0.040	1.136	(1.006	-1.282)
rs629444	0.127	(0.062)	0.040	1.136	(1.006	-1.283)
rs895526	0.127	(0.062)	0.041	1.135	(1.005	-1.282)
rs16894194	0.127	(0.062)	0.042	1.135	(1.005	-1.283)
rs314263	0.126	(0.062)	0.042	1.134	(1.005	-1.281)
rs359250	0.127	(0.062)	0.042	1.135	(1.005	-1.282)
rs200995	0.124	(0.062)	0.046	1.132	(1.002	-1.280)
rs1837495	0.121	(0.062)	0.051	1.129	(1.000	-1.275)
rs17557162	0.113	(0.063)	0.072	1.120	(0.990	-1.267)
rs6925744	0.106	(0.064)	0.099	1.112	(0.980	-1.261)
None	0.135	(0.062)	0.029	1.144	(1.014	-1.292)

Appendix Table 14. Comparison of βi*Xi values of each SNP between breast cancer cases and controls

SNP	Case		Control		p-value
	mean	(sd)	mean	(sd)	
rs1837495	0.065	(0.047)	0.062	(0.048)	0.009
rs6925744	0.093	(0.143)	0.085	(0.135)	0.040
rs17557162	0.054	(0.098)	0.060	(0.103)	0.044
rs314263	0.029	(0.035)	0.027	(0.034)	0.050
rs16874961	0.093	(0.039)	0.091	(0.039)	0.067
rs4949526	0.032	(0.040)	0.030	(0.038)	0.076
rs895526	0.064	(0.048)	0.061	(0.048)	0.081
rs200995	0.316	(0.069)	0.312	(0.072)	0.097
rs9353533	0.054	(0.039)	0.052	(0.040)	0.105
rs17598927	0.019	(0.037)	0.017	(0.035)	0.111
rs979603	0.042	(0.043)	0.040	(0.043)	0.137
rs16894194	0.228	(0.065)	0.225	(0.067)	0.142
rs4799092	0.054	(0.040)	0.052	(0.040)	0.152
rs4685	0.060	(0.053)	0.058	(0.053)	0.161
rs11570190	0.015	(0.028)	0.014	(0.027)	0.162
rs4820428	0.007	(0.024)	0.006	(0.023)	0.181
rs6847160	0.085	(0.034)	0.083	(0.034)	0.183
rs359250	0.042	(0.064)	0.040	(0.063)	0.194
rs7308934	0.015	(0.029)	0.014	(0.028)	0.254
rs4835678	0.021	(0.034)	0.020	(0.033)	0.256
rs4765905	0.179	(0.030)	0.178	(0.031)	0.272
rs11981403	0.240	(0.046)	0.239	(0.048)	0.292
rs629444	0.027	(0.057)	0.025	(0.054)	0.295
rs17687067	0.050	(0.051)	0.048	(0.050)	0.298
rs12100737	0.085	(0.047)	0.084	(0.048)	0.312
rs4973569	0.024	(0.042)	0.023	(0.041)	0.315
rs11210193	0.025	(0.034)	0.024	(0.033)	0.317
rs4731825	0.007	(0.024)	0.006	(0.023)	0.369
rs13259407	0.062	(0.037)	0.061	(0.037)	0.371
rs11210892	0.044	(0.045)	0.042	(0.045)	0.394
rs938682	0.075	(0.050)	0.073	(0.049)	0.403
rs9811916	0.009	(0.024)	0.008	(0.023)	0.446

rs6449527	0.026	(0.041)	0.025	(0.041)	0.454
rs2514218	0.005	(0.019)	0.005	(0.019)	0.464
rs7749109	0.312	(0.036)	0.311	(0.039)	0.478
rs172531	0.011	(0.025)	0.010	(0.024)	0.498
rs4634961	0.229	(0.031)	0.229	(0.032)	0.503
rs1792709	0.035	(0.064)	0.034	(0.064)	0.510
rs2002122	0.056	(0.040)	0.055	(0.041)	0.550
rs1518395	0.066	(0.079)	0.065	(0.080)	0.569
rs8063193	0.017	(0.031)	0.016	(0.031)	0.596
rs10927044	0.061	(0.045)	0.060	(0.046)	0.611
rs16880322	0.011	(0.025)	0.010	(0.024)	0.622
rs732998	0.175	(0.071)	0.174	(0.070)	0.643
rs10786712	0.097	(0.069)	0.098	(0.068)	0.644
rs6852201	0.025	(0.033)	0.025	(0.033)	0.679
rs6776145	0.111	(0.066)	0.111	(0.067)	0.695
rs6919306	0.057	(0.065)	0.056	(0.065)	0.715
rs7701188	0.189	(0.017)	0.189	(0.018)	0.730
rs7841617	0.128	(0.119)	0.127	(0.117)	0.758
rs215411	0.131	(0.022)	0.131	(0.022)	0.772
rs4240748	0.027	(0.035)	0.027	(0.035)	0.816
rs9656169	0.094	(0.030)	0.094	(0.030)	0.822
rs2409033	0.051	(0.038)	0.051	(0.037)	0.827
rs968525	0.066	(0.027)	0.066	(0.027)	0.838
rs3130275	0.038	(0.047)	0.038	(0.046)	0.839
rs2109299	0.079	(0.057)	0.079	(0.057)	0.852
rs6982408	0.049	(0.041)	0.048	(0.040)	0.866
rs12116970	0.162	(0.037)	0.162	(0.038)	0.870
rs2383377	0.022	(0.041)	0.022	(0.040)	0.884
rs3758927	0.005	(0.021)	0.005	(0.022)	0.893
rs217311	0.077	(0.045)	0.076	(0.045)	0.929
rs17566146	0.141	(0.015)	0.141	(0.015)	0.960
PRS ($\sum \beta i*Xi$)	4.767	(0.409)	4.700	(0.413)	<.0001

Notes. When PRS=$\sum \beta i*Xi$, the mean of the $\beta i*Xi$ values of each SNP was compared and tested between the breast cancer patient group and the control group. SNPs are shown in ascending order of p value.

Appendix Table 15. SNP-Gene information

SNP	Gene
rs314263	LIN28B : Intron Variant
rs4820428	EP300 : Intron Variant
rs1837495	PLCL1 : Intron Variant
rs4949526	None
rs16874961	DGKI : Intron Variant
rs11570190	CTNND1 : Intron Variant, TMX2-CTNND1 : Intron Variant
rs9353533	EYS : Intron Variant
rs4731825	LOC107986849 : Non Coding Transcript Variant
rs17598927	H2BC6 : 500B Downstream Variant
rs6847160	None
rs979603	None
rs4799092	KCNG2 : Intron Variant
rs4765905	CACNA1C : Intron Variant
rs4634961	MIR137HG : Intron Variant
rs895526	SATB2 : Intron Variant
rs11210193	None
rs4973569	NGEF : Intron Variant
rs7308934	C12orf42 : Intron Variant
rs4835678	KDM3B : Missense Variant
rs17687067	ZDHHC2 : Intron Variant
rs12100737	PCNX1 : Intron Variant
rs4685	SF3B1 : Synonymous Variant
rs629444	None
rs7701188	MEF2C-AS1 : Intron Variant
rs16880322	MMP16 : Intron Variant
rs13259407	PSD3 : Intron Variant
rs200995	None
rs9656169	LOC105375451 : Intron Variant
rs17557162	DCAF6 : Intron Variant
rs359250	None
rs172531	RERE : Intron Variant
rs16894194	None
rs8063193	GRIN2A : Intron Variant

rs6449527	None
rs6925744	LOC105375008 : Intron Variant, LOC124905338 : Intron Variant, LOC124905365 : Intron Variant
rs1792709	LINC01539 : Intron Variant, LOC642484 : Intron Variant
rs6982408	None
rs7749109	None
rs2383377	AKAP6 : Intron Variant
rs11210892	None
rs2002122	None
rs2514218	None
rs6852201	CLCN3 : Intron Variant
rs6919306	FYN : Intron Variant
rs10927044	AKT3 : Intron Variant
rs11981403	DMTF1 : Intron Variant
rs938682	CHRNA3 : Intron Variant
rs2109299	IMMP2L : Intron Variant
rs2409033	CCDC192 : Intron Variant
rs4240748	None
rs6776145	LSMEM2 : Intron Variant
rs12116970	TARS2 : Intron Variant
rs9811916	TRANK1 : Intron Variant
rs732998	NT5C2 : Intron Variant
rs215411	LOC105374524 : Intron Variant
rs10786712	CYP17A1 : Intron Variant
rs3758927	None
rs3130275	None
rs7841617	NSD3 : Intron Variant
rs1518395	VRK2 : Intron Variant
rs17566146	LINC01470 : Intron Variant
rs217311	SNAP91 : Intron Variant
rs968525	MAU2 : Intron Variant
rs4643387	None
rs783540	CPEB1 : Intron Variant
rs688209	IP6K3 : Intron Variant
rs11694987	CUL3 : Intron Variant
rs7893279	CACNB2 : Intron Variant

rs12574668	AMBRA1 : Intron Variant
rs1397221	None
rs3814881	TAOK2 : Intron Variant
rs9937079	None
rs17310286	BNIP3L : 3 Prime UTR Variant
rs10184465	None
rs11874716	LINC03035 : Intron Variant
rs11065242	None
rs4129585	TSNARE1 : Intron Variant
rs1805571	FXR1 : Intron Variant
rs11688415	None
rs885940	None
rs7284768	LOC124905122 : 2KB Upstream Variant
rs134874	TCF20 : Intron Variant
rs7016464	PRDM14 : Intron Variant
rs2563263	LOC105378198 : Non Coding Transcript Variant
rs17720293	ZKSCAN4 : Intron Variant
rs7592587	C2orf69 : Intron Variant
rs16851048	None
rs12885258	RGS6 : Intron Variant
rs6590512	LINC02551 : Intron Variant
rs10898127	DLG2 : Intron Variant
rs308690	None
rs223397	UBE2D3 : Intron Variant
rs2535629	ITIH3 : Intron Variant
rs2490272	FOXO3 : Intron Variant
rs4908986	None
rs4666014	RBKS : Intron Variant
rs6019876	PTGIS : Intron Variant
rs8055219	None
rs3786800	ZNF536 : Intron Variant
rs2910032	None
rs11786117	MSRA : Intron Variant
rs999494	EMX1 : Intron Variant
rs6791611	STAG1 : Intron Variant
rs4775413	LOC107984782 : Intron Variant

rs1509378	LINC01830 : Intron Variant
rs302321	TMTC1 : Intron Variant
rs6874127	HCN1 : Intron Variant
rs7574065	None
rs9636107	TCF4 : Intron Variant
rs4388249	MAN2A1 : Intron Variant
rs12139672	None
rs1818950	None
rs2250350	None
rs2174019	CNTN4 : Intron Variant
rs16880831	None
rs12364435	LOC105376595 : Intron Variant

ABSTRACT (KOREAN)

조현병과 유방암의 인과관계 조사: 생존분석과 멘델리안 무작위배정 분석

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[연구배경 및 목적]

조현병과 유방암에 대하여 기존의 역학 관찰 연구를 통해 그 연관성이 밝혀져 왔지만 아시안인을 대상으로 한 연구 결과에는 이질성이 있다. 또한, 조현병을 가진 개인들 사이에서 유방암 발병률이 높아지는 기본 원인은 아직 명확하지 않다. 이러한 연관성이 공통적인 유전적 위험 요인 또는 생활 습관 위험 요인에 기인한 것인지, 아니면 질병 자체와 관련된 요인, 예를 들어 질병의 진행이나 그 치료에 기인하는 것인지가 중심적인 질문이다.

본 연구에서는 조현병과 유방암 사이의 연관성을 크게 두 파트로 나누어 알아보고자 하였다. 첫째로, 조현병 환자들이 일반 인구 및 다른 정신질환자에 비해 증가된 유방암 위험을 가지고 있는지, 나아가 항정신병 약물의 영향은 무엇인지 조사하고자 하였다. 둘째로, 다유전적 위험점수(PRS) 분석과 2-표본

멘델리안 무작위배정 분석을 통해 조현병과 유방암 사이의 인과관계를 규명하는 것을 목표로 했다.

[파트1. 조현병과 유방암의 연관성: 생존 분석]

2007년부터 2018년까지의 대한민국 국민건강정보 데이터베이스에 있는 18~80세 여성의 의료 청구 데이터를 활용했다. 조현병 환자는 ICD-10 코드 F20 또는 F25를 가지면서 항정신병 약물을 처방 받은 여성을 포함하였다 (n=224,743). 첫 번째 대조군은 다른 정신 질환 (ICD-10 코드 F10-F19 또는 F30-F69)이 있는 여성으로 정의하였고 (n=224,743), 두 번째 대조군은 일반 대한민국 여성 인구로 정의하였다 (n=449,486). 환자와 대조군은 기준 시점 (추적 기간 동안 조현병의 첫 진단 날짜)과 그 시점의 연령을 기준으로 1:1:2 비율로 짝지었으며, 유방암 위험은 보험료와 의학적 동반질환을 조정한 콕스 비례 위험 모델을 사용하여 추정되었다. 또한, 조현병 환자 내에서는 랜드마크 방법을 사용하여 항정신병 약물 사용 기간과 유방암 발생 사이의 연관성을 추정하였다. 다변량 콕스 회귀 모델에서 일반 한국 여성 인구이 비교하여 조현병 여성의 유방암 위험이 유의하게 높았고 (위험비(HR)=1.26; 95% CI, 1.12-1.33), 다른 정신질환을 가진 여성과 비교하여서도 유의하게 높은 유방암 위험을 나타내었다 (HR=1.08; 95% CI, 1.02-1.14). 조현병 환자 중에서

항정신병약물을 6개월 미만 복용한 환자에 비교하여 1년 이상 항정신병약을 복용한 환자에서 유방암 위험이 유의하게 더 높았다 (0.5~1년: HR=0.95, 95% CI [0.68-1.33];1-3년: HR=1.28, 95% CI [1.04-1.56], 3-4년: HR=1.20, 95% CI [0.96-1.50], 4년 이상: HR=1.32, 95% CI [1.09-1.61]).

[파트2. 조현병과 유방암 사이의 인과 관계: 다유전적 위험 점수와 2-표본 멘델리안 무작위배정]

조현병과 유방암 사이의 인과 관계를 확인하기 위해 2-표본 멘델리안 무작위배정을 수행하였다. 조현병과 유의하게 연관된 유전적 변이 (Genetic variants)는 NHGRI-EBI GWAS Catalog 에서 추출되었다. 서울유방암연구(SeBCS)의 유방암 환자 2,165명과 한국유전체역학연구(KoGES)의 일부인 대규모 도시 코호트 (HEXA)의 건강한 대조군 2,046명에서 조현병 다유전적 위험 점수 (PRS)를 계산하고 다유전적 위험 점수와 유방암 사이의 연관성을 조사했다. 또한, 유방암 환자군과 대조군에서 후보 유전자 연관성 분석을 실시하여 2-표본 멘델리안 무작위배정을 수행하였다. 멘델리안 무작위배정 (MR) 방법의 경우, 역분산 가중치(IVW), MR-Egger 및 가중 중앙값 (weighted median) 접근법을 사용하여 유전적으로 결정된 조현병이 유방암 위험에 미치는 영향을 추정하였다. 방사형 MR 방법을 적용하여 다발성 편향

(pleiotropic bias) 의 가능성이 있는 이상값을 제거하였으며, MR 분석의 IVW 방법을 통해 조현병과 유방암 사이의 유의한 인과관계를 확인하였다 (OR=1.14; 95% CI, 1.01-1.28). 방사형 MR 분석에서는 이상값이 발견되었으며, 이상값을 제거한 후 일관적으로 유의한 효과 추정치가 관찰되었다 (OR=1.14, 95% CI 1.01-1.28). 또한, 개별 SNP 의 MR 결과에서 양의 방향을 나타낸 SNP 으로 다유전자 위험 점수(PRS)를 생성하여 유방암군과 대조군에서 비교하였다. 조현병 PRS(1SD 당)와 유방암 사이에 유의한 연관성이 관찰되었다 (OR=1.18, 95% CI 1.12-1.26).

[결론]

표현형으로 나타난 연관성의 분석 결과, 조현병을 가진 여성은 다른 정신질환을 가진 여성 및 일반 한국 여성에 비해 유방암 발생 위험이 더 높은 것으로 나타났다. 조현병이 있는 여성의 경우, 유방암 위험은 항정신병 약물 치료 기간의 증가와 관련이 있었다. 또한, 멘델리안 무작위배정 분석을 통해 조현병과 유방암 사이의 인과관계를 시사하는 결과를 밝혔다.

키워드: 조현병, 유방암, 항정신병 약물, 랜드마크 분석, 2-표본 멘델리안 무작위 배정