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Original Article

Breast cancer risk among women with schizophrenia and association with duration of antipsychotic use: population-based cohort study in South Korea

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Background

Breast cancer is a major global health issue, especially among women. Previous research has indicated a possible association between psychiatric conditions, particularly schizophrenia, and an increased risk of breast cancer. However, the specific risk of breast cancer in women with schizophrenia, compared with those with other psychiatric disorders and the general population, remains controversial and needs further clarification.

Aims

To estimate the risk of breast cancer among people with schizophrenia compared with people with other psychiatric disorders and people in the general population.

Method

We utilised medical claims data of women aged 18 to 80 years in the Korean National Health Information Database from 2007 to 2018. Individuals with schizophrenia were defined as women with ICD-10 codes F20 or F25 ($n = 224\,612$). The control groups were defined as women with other psychiatric disorders ($n = 224\,612$) and women in the general Korean population ($n = 449\,224$). Cases and controls were matched by index date and age, in a 1:1:2 ratio. We estimated the hazard of breast cancer using the Cox proportional hazards model, adjusting for insurance premiums and medical comorbidities. Among the people with schizophrenia, we used the landmark method to estimate the association between duration of antipsychotic medication use and the incidence of breast cancer.

Results

In multivariable Cox regression models, the hazard rate of breast cancer was 1.26 times higher in the people with schizophrenia than in the general population (95% CI: 1.20–1.32). In comparison with the psychiatric patient group, the hazard ratio was 1.17 (95% CI: 1.11–1.28). 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.

Conclusions

Women with schizophrenia have an elevated risk of breast cancer, and long-term use of antipsychotics is associated with an increased risk of breast cancer.

Keywords

Psychotic disorders/schizophrenia; antipsychotics; epidemiology; survival analysis; breast cancer.

People with schizophrenia are at increased risk of developing multiple comorbidities, including anxiety disorders, depression, cardiovascular disease and diabetes.[1–3] This results in a 15-year lower life expectancy than the general population[4] that is attributed to many factors, such as 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 behaviours (e.g. cigarette smoking and cancer screening).[5]

The risk of breast cancer among individuals with schizophrenia has also been studied.[6] Although this remains an inconclusive topic, many studies have suggested an increased risk of breast cancer among women with schizophrenia. In a Swedish population-based cohort study, individuals with schizophrenia had a significantly higher incidence of breast cancer than the general population.[7] These findings are consistent with those of a recent meta-analysis, although substantial between-study variance existed.[8] Other studies have shown a null or even an inverse association between schizophrenia and breast cancer,[9–11] with significant heterogeneity across populations.[12] Notably, studies from Asian populations have produced inconsistent results.[9,10,13,14] Additionally, many previous studies have focused solely on people with schizophrenia or made comparisons only with the general population. There is a need for studies that also compare people with schizophrenia with people with other psychiatric conditions to gain a clearer understanding.

To address these discrepancies, we conducted this study to estimate the risk of breast cancer among individuals with schizophrenia in Korea. We sought to extend this literature by employing two populations of controls (the general Korean population and people with other severe psychiatric disorders) and conducting analyses stratified by age and antipsychotic treatment duration.

The rationale for the two control group designs was that some studies have shown that people with bipolar disorder or post-traumatic stress disorder have a higher risk of developing breast cancer than the general population.[15,16] In addition, individuals with schizophrenia and other psychiatric disorders may share observed or unobserved behavioural or structural characteristics that could contribute to an increased risk of breast cancer, including smoking, stress and obesity.[17,18] Thus, if we were to find that people with schizophrenia have a higher risk of breast cancer than people with other psychiatric disorders, this finding could support a schizophrenia-specific cause.

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Antipsychotic medications are a mainstay of treatment for schizophrenia and are used to reduce symptom intensity and frequency;[19] however, many antipsychotic medications have been known to cause hyperprolactinemia,[20,21] which has been a topic of investigation in the development of breast cancer. The association between hyperprolactinemia and breast cancer is still controversial, with some studies suggesting a potential risk[22,23] while others do not support this association.[24,25] Consequently, our study also sought to explore the role of antipsychotic medication use in influencing breast cancer risk among people with schizophrenia.

Method

Data source

The Korean National Health Information Database (NHID) is a public database of medical services organised using the National Health Insurance System (NHIS) of South Korea, a universal health insurance system that covers approximately 98% of the medical expenses of the Korean population.[26] The database contains information on medical utilisation, including insurance eligibility, diagnostic codes, prescribed medications, and procedures and claims records. Diagnoses are coded according to the 10th revision of the International Classification of Diseases (ICD-10).

Study population, exposures and outcome

For this analysis, we used the NHID data for 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.

We used a matched cohort design to compare outcomes between women with schizophrenia, women with other psychiatric disorders and women in the general population. The first control group (control 1) consisted of women 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 women in the general Korean population, defined as those without any ICD-10 diagnostic codes for psychiatric diseases or dementia (F00–F99, G30, F31.8 and G31.00) within the same period.

The earliest diagnosis date of schizophrenia during the follow-up period was set as the index date, and two control groups were matched with women with schizophrenia based on the exact age at the index date. The index dates of two control groups were randomly selected. Women with schizophrenia were matched in a 1:1 ratio with women in the 'other psychiatric disorders' control group and in a 1:2 ratio with women in the general Korean population control group. Women with 'other psychiatric disorders' who had been diagnosed with psychiatric disorders on or before the index date were included in the matching process. Preliminary screening initially identified 234 718 women with schizophrenia who were initially matched with 234 718 women with other psychiatric disorders and 469 436 women 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 1 year after the index date), all four individuals in that group were excluded. We excluded 10 106 individuals with schizophrenia, 10 106 with other psychiatric disorders, and 20 212 from the general population control group. The final sample included 224 612 individuals with schizophrenia, 224 612 with other psychiatric disorders and 449 224 individuals from the general Korean population (Supplementary Figure 1 available at https://doi.org/10.1192/bjp.2024.170).

Breast cancer was 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 at any time during the first year of follow-up. The 1-year lag time was used to minimise the possibility of reverse causality. The NHID ICD-10 codes for the diagnosis of schizophrenia, other psychiatric disorders and breast cancer have been previously validated.[27,28]

Covariates

We sought to adjust our estimates for potential confounders according to socioeconomic status and medical comorbidities. Medical insurance premium payments in the index year were used as proxy variables for socioeconomic status.[29] Insurance premiums were categorised into five groups as follows: medical aid (for socioeconomically disadvantaged individuals who do not pay insurance premiums), Q1 (lowest), Q2, Q3 and Q4 (highest). The Charlson Comorbidity Index (CCI) was used to adjust for comorbidities.[30] CCI values were based on the appearance of corresponding ICD-10 diagnostic codes for each comorbidity before the index date (Supplementary Table 1). As a variable representing medical utilisation, the number of out-patient visits (per year) excluding psychiatric visits was adjusted.

Statistical analysis

To assess baseline differences in covariates between the schizophrenia group and the two control groups, we used repeated-measures analysis of variance for continuous variables and McNemar's test for categorical variables. Using the Cox proportional hazards model stratified on matched sets, we estimated the hazard ratio (conditional on matched sets) and 95% confidence interval for breast cancer in the schizophrenia and other psychiatric disorder groups (Control 1), with the general population group (Control 2) as a reference. To confirm the difference in breast cancer risk between women with schizophrenia and those with other psychiatric disorders, we conducted the same analysis with the other psychiatric disorder group as a reference. In the crude model, the schizophrenia group and the two control groups were matched by index date and age in the index year with no covariate adjustment. In the adjusted model, we included insurance premiums, CCI and the number of out-patient visits as covariates. We checked for violations of the proportional hazards assumption by fitting a regression model of the Schoenfeld residuals against time and testing for a non-zero slope.[31] In the sensitivity analysis, we used Fine and Gray's competing risk survival analysis model in which mortality was considered a competing risk.[32] Additionally, for another sensitivity analysis, we used the first 2 years (2007–2008) as a washout period and only included individuals who were diagnosed with schizophrenia for the first time in the data-set after this period, considering them as incident cases of schizophrenia.

We considered the following two extensions: First, we conducted analyses stratified by age, specifying age categories as <40 years, 40–64 years and ≥65 years. The objective of this analysis was to estimate the hazard ratio of breast cancer differentiating perimenopausal or menopausal women from women of other age groups.[33]

Second, we used landmark analysis to estimate the hazard ratio for breast cancer according to the duration of antipsychotic medication treatment. For our landmark analysis, only those who had been followed up for at least 5 years were included in the analytic sample. Of the 224 612 women with schizophrenia included in the primary analysis, 143 778 were included in the landmark analysis (Supplementary Figure 1). The landmark method was used to

control for immortal time bias when estimating the risk of breast cancer based on the duration of antipsychotic medication treatment.[34] When events occurred prior to the landmark point, those participants were excluded from the 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 analysed. The landmark point was designated 5 years after the index date. We probed the robustness of our findings by setting alternative landmark points at 4 and 6 years. The duration of antipsychotic medication use was calculated by adding the duration of prescribed medication to the record. The NHID holds information about prescribed medications, including the prescription date and duration of prescribed medications. Instances with overlap between separate antipsychotic prescriptions were combined to form a single episode of antipsychotic use. Treatment duration was specified as a five-level categorical variable: <0.5 year, 0.5–1 year, 1–3 years, 3–4 years and ≥4 years. Additionally, we performed the same landmark analysis after stratification by the generation of antipsychotics (first-generation antipsychotics (FGA) versus second-generation antipsychotics (SGA)).

The antipsychotic medications were reviewed by qualified psychiatrists (C.-H.C. and S.K.). The ATC codes for the antipsychotic medications are listed in Supplementary Table 2. All statistical analyses were conducted using SAS software (version 9.4 for Windows; SAS Institute Inc., Cary, NC, USA).

Ethical approval

This study was approved by the Institutional Review Board of the Yonsei University College of Medicine (4–2022-0711) and the Korea NHIS Medical Information Disclosure Committee (NHIS-2021-1-146). Informed consent for the present study was waived because of its use of deidentified NHID data. All procedures in this study complied with the ethical standards of the relevant national and institutional committees on human experimentation and the Declaration of Helsinki of 1975, as revised in 2008.

Results

Demographic and clinical characteristics

Consistent with our matching procedure, the average age was the same across all three groups (48.12 years; standard deviation (s.d.), 16.81). The mean (s.d.) follow-up years for people with schizophrenia was 7.10 (4.03), while the group with other psychiatric disorders and the general population group had mean (s.d.) follow-up years of 7.51 (3.91) and 7.27 (3.92), respectively. The CCI score indicating comorbidity was higher among women with schizophrenia and other psychiatric disorders than among women in the general population; 27% of women in the schizophrenia group had a CCI score of 3 or higher (indicating moderate to severe comorbidity[35]), compared with 18% in the other psychiatric disorders group and 11% in the general population group. In the schizophrenia group, the proportion of women in the highest insurance group (Q4) was the lowest (26.63%), followed by women with other psychiatric disorders (30.70%) and women in the general population (32.86%). (Table 1)

Incidence of breast cancer compared with control groups

The incidence of breast cancer was 1.49 per 1000 person-years among women with schizophrenia, 1.38 per 1000 person-years among women with other psychiatric disorders and 1.17 per 1000 person-years among women in the general population (Table 1). These differential incidence rates translated into an increased hazard of breast cancer among women with schizophrenia compared with women in the general Korean population (hazard ratio = 1.27; 95% CI: 1.20–1.33). After adjusting for comorbidity, socioeconomic status and medical utilisation, the estimated hazard remained similar (hazard ratio = 1.26; 95% CI: 1.20–1.32). Women with other psychiatric disorders (control 1) also had an elevated hazard of breast cancer, compared with women in the general population (hazard ratio = 1.17; 95% CI: 1.11–1.28). When other psychiatric disorders were used as the reference in the adjusted

Table 1 Characteristics of people with schizophrenia and two control groups (1:1:2 matched)

	People with schizophrenia	People with other psychiatric disorders	General population group
N	224 612	224 612	449 224
Person-years	1 594 933.48	1 686 403.07	3 264 211.33
Follow-up years, mean (s.d.)	7.10 (4.03)	7.51 (3.91)	7.27 (3.92)
Age, mean (s.d.)	48.12 (16.81)	48.12 (16.81)	48.12 (16.81)
Charlson Comorbidity Index, *N* (%)			
0	105 540 (46.99)	99 393 (44.25)	256 674 (57.14)
1, 2	59 346 (26.42)	85 120 (37.90)	145 353 (32.36)
≥3	59 726 (26.59)	40 099 (17.85)	47 197 (10.51)
Insurance premium quartile, *N* (%)			
Medical aid[a]	48 981 (21.96)	9927 (4.47)	10 630 (2.39)
Q1(lowest)	37 682 (16.89)	44 764 (20.14)	87 059 (19.58)
Q2	34 819 (15.61)	45 637 (20.53)	90 509 (20.35)
Q3	42 181 (18.91)	53 690 (24.16)	110 406 (24.83)
Q4(highest)	59 398 (26.63)	68 225 (30.70)	146 114 (32.86)
Out-patient visits, day/year			
0–7	72 801 (32.41)	33 113 (14.74)	173 347 (38.59)
7–14	51 888 (23.10)	61 166 (27.23)	141 802 (31.57)
14–21	34 624 (15.42)	47 279 (21.05)	69 280 (15.42)
≥21	65 299 (29.07)	83 054 (36.98)	64 795 (14.42)
Death, *N* (%)	4684 (2.09)	1120 (0.50)	2319 (0.52)
Breast cancer, *N* (%)	2381 (1.06)	2323 (1.03)	3824 (0.85)
Incidence rate of breast cancer, *N*/1000 person-years	1.49	1.38	1.17

People with schizophrenia: persons diagnosed with schizophrenia. People with other psychiatric disorders: 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, excluding the case group and control 1 group (diagnosis codes F00–F99, G30, G31.8, G31.00).
a. Medical aid group consists of socioeconomically disadvantaged individuals who do not pay medical insurance premiums.

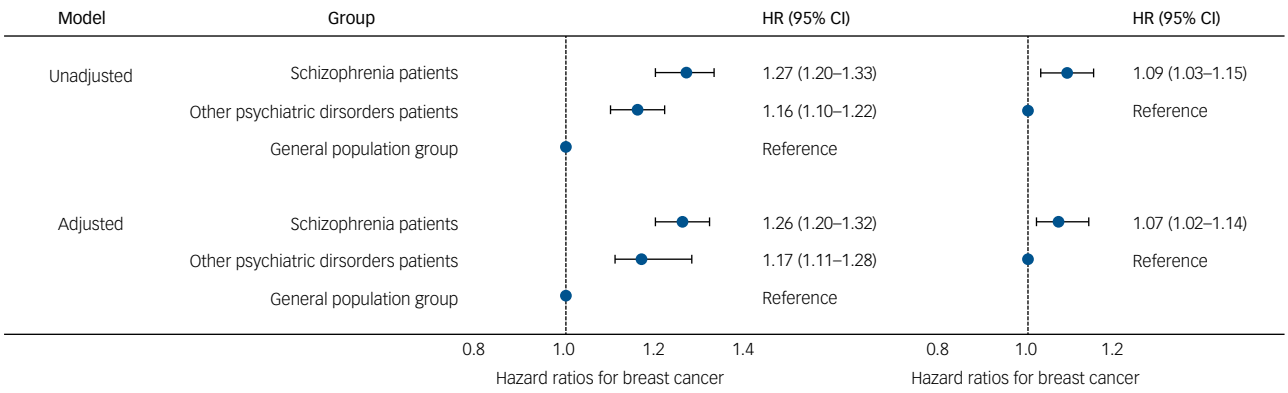

Fig. 1 Hazard ratios (HR) for breast cancer among people with schizophrenia and two control groups (1:1:2 matched). Schizophrenia: people diagnosed with schizophrenia and prescribed antipsychotics. People with other psychiatric disorders: persons who have been diagnosed with psychiatric disorders, excluding the case group (diagnosis codes F10–F19, F30–F69) general population: persons who have never been diagnosed with psychiatric disorders or dementia, excluding the case group and control 1 group (diagnosis codes F00–F99, G30, G31.8, G31.00). Unadjusted: crude model (matched by age), adjusted: Charlson Comorbidity Index, insurance premiums and the number of out-patient visits per year adjusted.

model, the risk of breast cancer remained significantly higher among women with schizophrenia (hazard ratio = 1.07; 95% CI: 1.02–1.14) (Fig. 1).

Competing risks analysis

In subdistributional hazard models accounting for competing risks, the estimated hazard ratios were 1.24 (95% CI: 1.18–1.31) for women with schizophrenia and 1.17 (95% CI: 1.12–1.23) for women with other psychiatric disorders, compared with the general population. Compared with those of women with other psychiatric disorders, the estimated hazard ratio was 1.06 (95% CI: 1.01–1.12) for women with schizophrenia (Supplementary Table 3).

Analysis with 2-year washout period

When analysing the risk of breast cancer using only incident cases of schizophrenia with a 2-year washout period, no significant results were observed. Compared with the general population group, the hazard ratio was 1.05 (95% CI: 0.96–1.15), indicating no significant increase in breast cancer risk. Similarly, no significant difference was found when comparing to the other psychiatric disorders group (hazard ratio = 0.97, 95% CI: 0.88–1.07) (Supplementary Table 4).

Age-stratified analysis

In the age-stratified analysis, women with schizophrenia (compared with women in the general population) between the ages of 40 and 64 years had the highest relative risk of breast cancer (hazard ratio = 1.36 (95% CI: 1.26–1.46)). The hazard ratio of breast cancer for those younger than 40 years was 1.07 (95% CI: 0.95–1.20); among those ≥ 65 years of age, the hazard ratio was 1.14 (95% CI: 0.94–1.38). However, compared with those with other psychiatric disorders, no significant results were observed in any subgroup, but women with schizophrenia who were ≥ 65 years of age had the highest relative risk of breast cancer (hazard ratio = 1.18 (95% CI: 0.96–1.46)) (Supplementary Table 5).

Landmark analysis with antipsychotic medication

In a landmark analysis limited to women with schizophrenia, the risk of breast cancer increased with increasing duration of antipsychotic treatment, after adjusting for comorbidities and socioeconomic status. Compared with women on treatment for <0.5 years, women on treatment for 0.5–1 year did not have an elevated hazard of breast cancer (hazard ratio = 0.95 (95% CI: 0.68–1.33)). Women on treatment for 1–3 years had a hazard ratio of 1.23 (95% CI: 1.00–1.51), women on treatment for 3–4 years had a hazard ratio of 1.21 (95% CI: 0.96–1.52) and women on treatment for ≥4 years had a hazard ratio of 1.36 (95% CI: 1.12–1.66) (P = 0.001) (Table 2). Similar findings were obtained in landmark analyses specifying landmark time points of 4 and 6 years (Supplementary Table 6).

Antipsychotic generation stratification

When stratified by generation of antipsychotics FGA versus SGA, the estimated association between treatment duration and breast cancer risk was not statistically significant for SGAs (P = 0.147). For FGAs, women with schizophrenia who received treatment for

Table 2 Landmark analysis of breast cancer incidence in individuals with schizophrenia with different duration of antipsychotics use

Antipsychotics duration	*N*	(Case)	Incidence rate (*N*/1000 py)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	*P* for trend
<0.5 year	24 360	(136)	0.63	Ref	Ref	0.001
0.5–1 year	8801	(47)	0.60	0.97 (0.70–1.36)	0.95 (0.68–1.33)	
1–3 years	40 342	(375)	0.92	1.68 (1.38–2.04)	1.23 (1.00–1.51)	
3–4 years	21 249	(179)	0.84	1.51 (1.21–1.89)	1.21 (0.96–1.52)	
≥4 years	49 026	(431)	0.90	1.55 (1.28–1.89)	1.36 (1.12–1.66)	

Model 1: age adjusted.
Model 2: (model 1) + Charlson Comorbidity Index, insurance premiums and the number of out-patient visits per year adjusted.
Landmark time: 5 years after index date.
py, person-years; HR, hazard ratio.

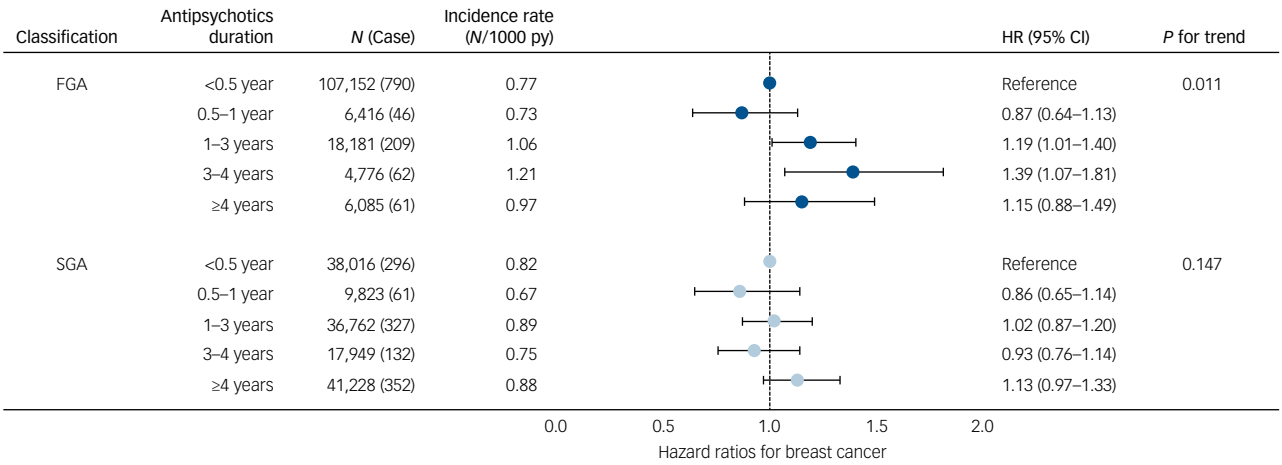

Fig. 2 Landmark analysis of breast cancer incidence by duration of antipsychotics use by generation. Model: age, Charlson Comorbidity Index, insurance premiums and the number of out-patient visits per year adjusted. Landmark time: 5 years after index date. FGA, first-generation antipsychotics; SGA, second generation antipsychotics; py, person-years, HR, hazard ratio.

1–3 years had a hazard ratio of 1.19 (95% CI: 1.01–1.40), while women who received treatment for 3–4 years had a hazard ratio of 1.39 (95% CI: 1.07–1.81). Although the test for trend was statistically significant ($P = 0.011$), no statistically significant association was found for women who received treatment for more than 4 years (hazard ratio = 1.15 (95% CI: 0.88–1.49)) (Fig. 2, Supplementary Table 7). As some people with other psychiatric disorders may also take antipsychotics, we examined the distribution of antipsychotic treatment durations. However, the majority of individuals in the 'other psychiatric disorders' group did not take antipsychotics (91.34%), and among those who took antipsychotics, a significant portion had a treatment duration of less than 1 year (7.02%) (Supplementary Table 8).

Discussion

In this South Korean population-based cohort study, with over 6 545 547 person-years of follow-up, we found that women with schizophrenia had a higher risk of breast cancer than women in the general Korean population. The elevated risk compared with women with other psychiatric disorders suggests that the estimated association is due to factors specific to schizophrenia rather than unmeasured behavioural or structural characteristics shared by women with other psychiatric disorders. Consistent with the prevailing models of biological plausibility, the risks were highest for middle-aged women between the ages of 40 and 64 years, and for women treated with first-generation antipsychotic medications.

The higher risk of breast cancer among middle-aged women with schizophrenia could be consistent with a model based on 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. Similar to our findings, a Swedish population-based cohort study of 111 306 people with schizophrenia found an elevated incidence of breast cancer among women with schizophrenia aged 40–65 years (incidence rate ratio = 1.19 (95% CI: 1.09–1.29)).[7]

Findings from our landmark analysis supported the hypothesis that antipsychotic medications increase the risk of breast cancer, and this needs to be interpreted in relation to hyperprolactinemia. Although hyperprolactinemia is a general feature of most antipsychotic medications, large differences have been observed within this class of medications.[36,37] The highest rates of hyperprolactinemia are consistently reported in association with amisulpride, risperidone and paliperidone, while the aripiprazole and quetiapine have the most favourable profile with regard to the outcome.[36,37] Our finding that breast cancer risk was associated only with the use of FGAs could potentially be explained by the fact that SGAs include both prolactin-preserving antipsychotics and prolactin-raising antipsychotics. Similar to our findings, 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.[14] A Taiwanese study also observed that among SGAs, exposure to 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.[14] These findings highlight the necessity of investigating the mediating effect of hyperprolactinemia on the risk of breast cancer linked to specific antipsychotics.

The current study has a few limitations. First, we did not have access to information regarding the specific antipsychotic medication used. Because of 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 versus SGA) was provided. Moreover, without specific medication names and dosage information (e.g. olanzapine 5 mg/10 mg), it was not possible to calculate defined daily doses (DDD) or cumulative doses.

Second, we lacked information on menopausal status and age at menopause. We inferred perimenopausal and postmenopausal statuses based on age. However, there was significant heterogeneity in menopausal onset across age groups. More detailed data (e.g. gathered using surveys) could help resolve this uncertainty.

Third, our landmark analysis included only individuals who had been followed up to the landmark point, which may have caused selection bias. In addition, although the period of antipsychotic treatment was calculated from the index date to the landmark point, no treatment was considered after the landmark point. Therefore, it is difficult to ascribe clinical meaning to duration thresholds because the actual duration of antipsychotic medication use may be longer. It is clear from our analysis that longer treatment duration is associated with a higher risk of breast cancer.

Fourth, our study includes both incident and prevalent cases of schizophrenia due to the left-censored nature of our data. We conducted an additional analysis using the first 2 years (2007–2008) as a

washout period and analysed only those who were first diagnosed with schizophrenia within the data-set after this period. However, this approach yielded non-significant results across all outcomes. Analysing only incident cases would predominantly include younger individuals, as schizophrenia typically manifests in early adulthood, thus complicating breast cancer observation within the 12-year follow-up. Thus, confirming the risk of breast cancer development requires sufficient observation periods for incident cases of people with schizophrenia.

Fifth, we lacked information on genetic predisposition factors, such as family history of breast cancer. Breast cancer is strongly influenced by genetic factors.[38] Therefore, further research evaluating both the genetic and environmental factors of breast cancer is necessary. Additionally, because of lack of data, other potential confounding factors such as obesity, diet, substance use, smoking, alcohol, parity (nulliparity) and breastfeeding were not accounted for in our study. These factors are known to influence breast cancer risk and may vary between the schizophrenia group and the control groups.[21,39] Including these variables in subsequent analyses would provide a more comprehensive understanding.

Sixth, in the analysis of breast cancer risk based on the duration of antipsychotic use among people with schizophrenia, confounding by indication may still be present. There may be differences in disease characteristics, such as severity, between individuals with shorter and longer medication durations. However, the severity of schizophrenia is not directly linked to breast cancer risk, and there may be complex mechanisms involved that are not fully understood.

Despite these limitations, our study has several strengths. First, using two control groups, we confirmed the risk of breast cancer among women with schizophrenia, not only compared with women in the general population but also women with other psychiatric disorders. The results of this study support 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 our knowledge, this is the first Korean study to use national data to investigate the association between schizophrenia and breast cancer. Therefore, the findings of this study can be extrapolated to the entire population of Korea. This study serves as a foundation for the development of new clinical guidelines. As one aspect of the patient treatment guidelines, healthcare providers should recommend breast cancer screening for postmenopausal women with schizophrenia. Although additional medication research is required, it might be possible to establish medication selection guidelines that suggest the use of SGAs rather than FGAs for individuals with schizophrenia and confirmed breast cancer risk factors such as a family history of breast cancer.

Our findings suggest the need for further studies to understand the mechanisms underlying the observed association, as well as to support enhanced surveillance efforts for breast cancer prevention in this key population.[40]

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Supplementary material

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Data availability

Data cannot be shared publicly because of the regulations of the National Health Insurance Sharing Service.

Author contributions

Study design and concept: J.S.Y., S.K., C.-H.C. and S.J.J. Data acquisition, analysis and interpretation: J.S.Y., S.K., C.-H.C. and S.J.J. Drafting of the manuscript: J.S.Y. Critical revision of the manuscript for intellectual content: S.K., K.K., A.C.T., C.-H.C. and S.J.J. Statistical analysis: J.S.Y. and S.K. Obtained funding: S.J.J. Study supervision: S.J.J. and C.-H.C.

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Declaration of interest

A.C.T. receives an honorarium from Elevier for his work as Co-editor in Chief of the Elsevier-owned journal *SSM – Mental Health*. The other authors declare no competing interests related to this study.

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