Risk of Breast Cancer in Association with the Use of Second-generation Antipsychotics

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Objective: Previous studies regarding the relationship between the risk of breast cancer (BC) and antipsychotics use have reported inconsistent findings. Insufficient sample size and/or observation period may have hindered revealing the risk of BC associated with antipsychotics use. We aimed to investigate whether the use of second-generation antipsychotics (SGA) is associated with increased risk of BC.

Methods: We used the Health Insurance Review Agency database in South Korea between 2008 and 2018. The index date was determined as the date of the first antipsychotic prescription. We selected women prescribed SGAs for more than 30 days within a year from the index date and age-matched controls, yielding 498,970 cases and 997,940 controls. The Cox proportional hazards regression model was used for estimating the risk.

Results: The incidence rates of BC were 109.74 and 101.51 per 100,000 person-years in the case and control groups, respectively. There was an increased risk of BC in the case group (hazard ratio [HR] = 1.08, 95% confidence interval [CI] 1.04−1.13). There was a higher risk of BC in subjects prescribed with ≥ 10,000 mg of olanzapine equivalent dose (HR = 1.29, 95% CI 1.14−1.46) than those with < 10,000 mg (HR = 1.05, 95% CI 1.00−1.11). The increased risk of BC in the case group became significant after six years of the observation period (≥ 6 years: HR = 1.24, 95% CI 1.14−1.35, 3 to < 6 years: HR = 1.06, 95% CI 0.97−1.15, < 3 years: HR = 1.02, 95% CI 0.95−1.09).

Conclusion: This study indicated that the use of SGAs is associated with increased risk of BC in a long-term relationship with a dose-response pattern.

KEY WORDS: Antipsychotic drug; Breast cancer; Pharmacoepidemiology.

INTRODUCTION

Antipsychotic drugs have been used for the treatment of several psychiatric disorders, including schizophrenia spectrum disorder, dementia, obsessive-compulsive disorder, and generalized anxiety disorder [1]. Despite various differences in receptor profiles between antipsychotics, dopamine receptor antagonism, a common pharmacodynamic of antipsychotics, has been acknowledged as a key mechanism in exerting clinical effectiveness [2]. Hyperprolactinemia, one of the adverse effects owing to dopamine receptor antagonism, is associated with infertility, galactorrhea, gynecomastia, sexual dysfunction, and osteoporosis [3]. In association with the risk of breast cancer, it has been demonstrated in experimental studies that prolactin is involved in the proliferation of breast epithelial cells and tumor vascularization [4]. A meta-analysis reported a positive association between plasma prolactin and breast cancer [5]. These previous findings and hyperprolactinemia induced by the use of antipsychotics have raised a question about the relationship between the use of antipsychotics and the risk of breast cancer.

Several studies have been conducted to evaluate the risk of breast cancer in association with the use of anti-
psychotics. Experimental studies have reported inconsistent findings, with individual studies reporting the impact of antipsychotics on mammary tumorigenesis [6] or antiproliferative effects of antipsychotics [7]. So far, there is no evidence reporting association between the use of first-generation antipsychotics and the risk of breast cancer, except for a previous study by Wang et al. [8]. In 2002, Wang et al. [9] observed a 16% increased risk of breast cancer in patients exposed to typical antipsychotics, compared to those not exposed to them. A dose-response relationship between greater risk and larger cumulative dosage of the antipsychotics was also found, but the clinical implication of the findings was limited in light of the small hazards and the possibility of residual confounding. Among second-generation antipsychotics, risperidone has been examined as a possible risk factor for developing breast cancer because of its strong anti-dopaminergic profile which increases the risk of hyperprolactinemia [10]. In two previous nationwide population-based studies, there was no increased risk of breast cancer in risperidone users compared to individuals prescribed another atypical antipsychotics or a typical antipsychotic [11,12]. Contrary to the negative findings, in 2018, Pottegard et al. [13] used Danish nationwide population data to show a higher risk of breast cancer in subjects exposed to the long-term antipsychotics, along with a weak dose-response pattern. The authors also found that non-prolactin inducing-antipsychotics increase the risk of breast cancer, raising a question of the role of prolactin in the relationship between antipsychotics and breast cancer.

As the aforementioned studies showed, the relationship between the use of antipsychotics and the risk of breast cancer remains unclear regardless of the type of antipsychotics and their property for inducing hyperprolactinemia. A relatively short observation duration and/or insufficient sample size of previous studies may have hindered the discovery of long-term risk of breast cancer associated with antipsychotics use. With regard to a previous study by Dalton et al. [14], it has been pointed out that the negative finding may be owing to the inclusion criteria which was so broad that most of the included patients had not been exposed to high and/or chronic doses of antipsychotics, which indicated the need for enough large sample size exposed to the long-term antipsychotics for evaluating the risk of breast cancer associated with the use of antipsychotics. As typical antipsychotics have been mainly examined as exposure variables in previous studies, the number of studies regarding the role of second-generation antipsychotics as the risk factors for breast cancer is relatively small. Furthermore, to date, the comparative risk of breast cancer between second-generation antipsychotics has not been examined though of a wide variety of receptor profiles between second-generation antipsychotics.

The goal of the present study was to investigate the risk of breast cancer associated with the use of second-generation antipsychotics, and the comparative risk of breast cancer between different antipsychotics, which were categorized by their properties for inducing hyperprolactinemia. We also examined the time point at which the subjects exposed to these antipsychotics had a significantly higher incidence of breast cancer compared to control subjects and whether the risk of breast cancer had a relationship with the cumulative antipsychotic dose. A nationwide population database between 2008 and 2018 in South Korea was utilized for this study, yielding a total of 1,496,910 subjects as the study population.

METHODS

Data Sources

We obtained nationwide claim data from the Health Insurance Review Agency (HIRA) database in South Korea, which included information on medical service use such as diagnoses, interventions, and drug prescriptions as well as demographic characteristics [15]. Due to the compulsory health insurance system in South Korea, the HIRA database includes the claim data of the whole South Korean population, which makes it possible to reflect a pattern of medical service use by the entire population. The diagnosis in the claim data is based on the International Classification of Diseases, 10th revision (ICD-10). The claim data used in the current study was anonymized and provided only for the purpose of research.

This study was conducted following the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008 and approved by the Institutional Review Board of the HIRA (No. 2020-095). Informed consent was exempted owing to the use of anonymous data.
**Study Population**

The study period started from January 1, 2007 to December 31, 2019. The index date was determined as the date of the first antipsychotic prescription from January 1, 2008, to December 31, 2018. The case group was identified by the following criteria: 1) female, 2) prescribed second-generation antipsychotics for more than 30 days within a year from the index date, 3) aged between 18 and 79 years at the index date. From the 577,865 subjects who met the above-mentioned criteria, we excluded the subjects using the following exclusion criteria: 1) prescribed second-generation antipsychotics in 2007 (n = 66,667), 2) the diagnosis of breast cancer from January 1, 2007, to the index date (n = 4,847), 3) the diagnosis of breast cancer or death within 30 days following the index date (n = 909), resulting in a total of 505,442 case subjects. With a ratio of case and control as 1:2, we selected 1,155,730 age-matched controls who had not been prescribed second-generation antipsychotics from January 1, 2007 to December 31, 2019. The following exclusion criteria were implemented next: 1) the diagnosis of breast cancer from January 1, 2007 to the index date (n = 5,618), 2) the diagnosis of breast cancer or death within 30 days of the index date (n = 1,817), yielding a total of 1,148,295 control subjects. The final study population consisted of subjects whose matched cases or controls were not removed by the above exclusion procedures, resulting in 498,970 cases and 997,940 controls (Fig. 1). For identifying psychiatric diagnosis of the case group, we categorized psychiatric diagnoses into four groups which were F00-09 (Organic, including symptomatic, mental disorders), F10-19 (Mental and behavioral disorders due to psychoactive substance use), F20-29 (Schizophrenia, schizotypal and delusional disorders), and F30-39 (Mood disorders). We regarded that a case subject had been diagnosed with a psychiatric disorder if the corresponding diagnostic code existed at least once during the observation period.

**Exposure and Outcome**

The following second-generation antipsychotics were used in the selection of the study population and later analysis steps: amisulpride, aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone, and zotepine. Among second-generation antipsychotics, clozapine was not included in the current study because it is usually prescribed for specific circumstances such as treatment-resistant schizophrenia and psychotic symptoms in idiopathic Parkinson’s disease. We categorized the antipsychotics into three groups according to their...
properties for inducing hyperprolactinemia [16]: 1) group A for high risk; amisulpride, risperidone, paliperidone, and zotepine, 2) group B for moderate risk; olanzapine and ziprasidone, and 3) the group C for low risk; aripiprazole and quetiapine. If a case subject had been prescribed antipsychotic drugs solely within a certain antipsychotic group during the observation period, then the subject was included in the corresponding antipsychotic group. If a case subject had been prescribed antipsychotics in more than two antipsychotic groups throughout the observation period, we excluded the case subject in the subgroup analysis about the differential risk of breast cancer by the risk of hyperprolactinemia of antipsychotic drugs.

For both case and control groups, the follow-up time was defined from 30 days following the index date to the occurrence of breast cancer, death, or the end of the study period (December 31, 2019), whichever occurred first. The diagnosis of breast cancer was identified based on the primary ICD diagnostic code of C50 when the subject was discharged from a medical institution. The observational period was categorized into three groups as three-year intervals for evaluating the time point from which the increased risk of breast cancer in the case group became significant. We converted the dose of antipsychotics into an olanzapine equivalent using equations adopted from a previous study [17]. The cumulative antipsychotic dose was also categorized by a criterion of 10,000 mg olanzapine equivalent dose.

Statistical Analysis

Continuous and categorical variables were presented as mean (standard deviation) or median (interquartile range) and number (%). We estimated the incidence rate of breast cancer in the case and control groups, and presented as the number of subjects with breast cancer per 100,000 person-years. Cox proportional hazards regression model was used for calculating hazard ratio (HR) and 95% confidence interval (CI) of the association between breast cancer and second-generation antipsychotics. For the antipsychotic group categorized by the risk for hyperprolactinemia, the risk of breast cancer was estimated compared to the corresponding matched controls. We divided the case group into three subgroups based on their age at the index date (18–44 years, 45–64 years, 65–79 years) and calculated the risk of breast cancer compared to their matched controls. Regarding the relationship between the risk of breast cancer, and the observational period and cumulative antipsychotic dose, we calculated the risk using person-years of all subjects whose observational period or cumulative antipsychotic dose met a certain criterion, i.e., for the observational period, < 3, 3 to < 6, or ≥ 6 years, and for the cumulative antipsychotic dose, more or less than 10,000 mg of olanzapine equivalent dose. Statistical significance was determined based on a two-tailed p value of < 0.05. All statistical analyses were performed using the R program (ver. 4.0.2; R Development Core Team, Vienna, Austria).

RESULTS

The demographic and clinical characteristics of the study population are presented in Table 1. The mean age of the case and control groups was 52.6 ± 18.3 years, and the mean observation periods were 64.9 ± 40.1 and 69.9 ± 39.6 months, respectively. The median of total duration of antipsychotic prescription and total olanzapine equivalent dose in the case group were 330 (99–1,140) days and 445 (107–2,261) mg. The number of case subjects that had less than 10,000 mg of the total olanzapine equivalent dose were 446,298 (89.4%). In the case group, 461,189 (92.4%) subjects had been diagnosed with mood disorders (F30-39) at least once during the observation period. The percentage of case subjects having the diagnostic code of organic, including symptomatic, mental disorders (F00-09), mental and behavioral disorders due to psychoactive substance use (F10-19), or schizophrenia, schizotypal and delusional disorders (F20-29) at least once during the observation period were 43.1%, 10.2%, and 47.9%, respectively.

We calculated the incidence rate of breast cancer in the case and control groups, and the HR and 95% CI for risk of breast cancer in association with the use of second-generation antipsychotics (Table 2). The incidence rates of breast cancer were 109.74 (105.79–113.80) and 101.51 (97.86–105.27) per 100,000 person-years in the case and control groups. The case group showed a significantly increased risk of breast cancer compared to the control group (HR = 1.08, 95% CI 1.04–1.13, p < 0.001). The incidence rates of breast cancer were 165.45 (152.31–179.43), 148.94 (121.18–181.15), and 108.84 (102.76–115.19) per 100,000 person-years in the groups A, B, and C, respectively. All antipsychotic groups showed...
Table 1. Demographic and clinical characteristics of the study population

| Variable                              | Total         | Cases<sup>a</sup> | Controls     |
|---------------------------------------|---------------|-------------------|--------------|
|                                       | All           | Group A           | Group B      | Group C      |               |
| Number of subjects                    | 1,496,910     | 498,970           | 56,742       | 13,085       | 249,973       | 997,940       |
| Age (yr)                              | 52.6 ± 18.3   | 52.6 ± 18.3       | 54.6 ± 17.3  | 55.1 ± 15.9  | 53.4 ± 18.5   | 52.6 ± 18.3   |
| Age group (yr)                        |               |                   |              |              |               |               |
| 18−44                                 | 535,308 (35.8)| 178,436 (35.8)    | 17,155 (30.2)| 3,399 (26.0) | 86,498 (34.6) | 356,872 (35.8)|
| 45−64                                 | 457,575 (30.6)| 152,525 (30.6)    | 19,539 (34.4)| 5,338 (40.8) | 73,797 (29.5) | 305,050 (30.6)|
| 65−79                                 | 504,027 (33.7)| 168,009 (33.7)    | 20,048 (35.3)| 4,348 (33.2) | 89,678 (35.9) | 336,018 (33.7)|
| Observation period (mo)               | 68.2 ± 39.9   | 64.9 ± 40.1       | 74.6 ± 43.9  | 61.6 ± 40.4  | 52.8 ± 34.8   | 69.9 ± 39.6   |
| Total duration of antipsychotic       | 330 (99−1,140)| 224 (73−984)      | 128 (58−390) | 195 (74−578) |               |               |
| prescription (mo)                     |               |                   |              |              |               |               |
| Total olanzapine equivalent dose (mg) | 445 (107−2,261)| 445 (126−2,516)   | 380 (150−1,225)| 175 (56−621)|               |               |
| Total olanzapine equivalent dose      |               |                   |              |              |               |               |
| < 10,000 mg                           | 446,298 (89.4)| 49,723 (87.6)     | 12,461 (95.2)| 246,299 (98.5)|               |               |
| ≥ 10,000 mg                           | 52,672 (10.6) | 7,019 (12.4)      | 624 (4.8)    | 3,674 (1.5)  |               |               |
| Diagnosis of psychiatric disorder     |               |                   |              |              |               |               |
| Organic, including symptomatic,       | 214,986 (43.1)| 24,786 (43.7)     | 4,506 (34.4) | 104,537 (41.8)|               |               |
| mental disorders (F00-09)             |               |                   |              |              |               |               |
| Mental and behavioral disorders due to| 50,786 (10.2) | 3,070 (5.4)       | 672 (5.1)    | 26,838 (10.7)|               |               |
| psychoactive substance use (F10-19)   |               |                   |              |              |               |               |
| Schizophrenia, schizotypal and delusional disorders (F20-29) | 239,083 (47.9)| 31,488 (55.5)     | 5,414 (41.4) | 72,421 (29.0)|               |               |
| Mood disorders (F30-39)               | 461,189 (92.4)| 43,386 (76.5)     | 11,869 (90.7)| 241,192 (96.5)|               |               |

Values are presented as mean ± standard deviation, number (%), or median (interquartile range).

<sup>a</sup>Antipsychotic group was categorized based on the risk for hyperprolactinemia. Group A for high risk included amisulpride, paliperidone, risperidone, and zotepine. Group B for moderate risk included olanzapine and ziprasidone. Group C for low risk included aripiprazole and quetiapine.
Table 2. Risk of breast cancer in association with the use of second-generation antipsychotica

|      | Number of subjects | Events | Person-Years | Incidence rate (per 100,000 person-years) | HR (95% CI) | p value |
|------|--------------------|--------|--------------|------------------------------------------|------------|---------|
| All  |                   |        |              |                                          |            |         |
| Cases| 498,970            | 2,914  | 2,655,393    | 109.74 (105.79 – 113.80)                 | 1.08 (1.04 – 1.13) | < 0.001 |
| Controls | 997,940   | 5,819  | 7,33,256     | 101.51 (97.86 – 105.27)                 | 1.00 (ref.) |         |
| Group A |                  |        |              |                                          |            |         |
| Cases | 56,742             | 584    | 352,967      | 165.45 (152.31 – 179.43)                | 1.65 (1.49 – 1.84) | < 0.001 |
| Controls | 113,484   | 808    | 804,608      | 100.42 (93.62 – 107.59)                | 1.00 (ref.) |         |
| Group B |                  |        |              |                                          |            |         |
| Cases | 13,085             | 100    | 67,142       | 148.94 (121.18 – 181.15)                | 1.29 (1.01 – 1.65) | 0.04    |
| Controls | 26,170   | 167    | 144,685      | 115.42 (98.58 – 134.32)                | 1.00 (ref.) |         |
| Group C |                  |        |              |                                          |            |         |
| Cases | 249,973            | 1,196  | 1,098,848    | 108.84 (102.76 – 115.19)                | 1.10 (1.02 – 1.18) | 0.01    |
| Controls | 499,946   | 2,368  | 2,381,803    | 99.42 (95.46 – 103.51)                | 1.00 (ref.) |         |

HR, hazard ratio; CI, confidence interval Ref., reference.

Antipsychotic group was categorized based on the risk for hyperprolactinemia. Group A for high risk included amisulpride, paliperidone, risperidone, and zotepine. Group B for moderate risk included olanzapine and ziprasidone. Group C for low risk included aripiprazole and quetiapine.

Figure 2. The cumulative incidence rate of breast cancer according to the observation period. x-axis indicates the observation period from the index date, which is the date of the first antipsychotic prescription.

Fig. 2. The cumulative incidence rate of breast cancer according to the observation period. x-axis indicates the observation period from the index date, which is the date of the first antipsychotic prescription.

a significantly increased risk of breast cancer compared to their matched controls (group A: HR = 1.65, 95% CI 1.49 – 1.84, \( p < 0.001 \), group B: HR = 1.29, 95% CI 1.01 – 1.65, \( p = 0.04 \), group C: HR = 1.10, 95% CI 1.02 – 1.18, \( p = 0.01 \)).

Figure 2 and Table 3 show the risk of breast cancer according to the age group, observation period and cumulative olanzapine equivalent dose. The case subjects aged between 45 and 64 years at the index date had a significantly increased risk of breast cancer compared to the control subjects (HR = 1.17, 95% CI 1.09 – 1.24, \( p < 0.001 \)). While less than six years of the observation period showed no significantly increased risk of breast cancer (\(< 3\) years: HR = 1.02, 95% CI 0.95 – 1.09, \( 3 \) to \(< 6 \) years: HR = 1.06, 95% CI 0.97 – 1.15), more than six years of the observation period showed otherwise (HR = 1.24, 95% CI 1.14 – 1.35, \( p < 0.001 \)). A higher risk of breast cancer was observed in the subjects prescribed with \( \geq 10,000 \) mg of total olanzapine equivalent dose (HR = 1.29, 95% CI 1.14 – 1.46, \( p < 0.001 \)) compared to those with \(< 10,000 \) mg of total olanzapine equivalent dose (HR = 1.05, 95% CI 1.00 – 1.11, \( p = 0.031 \)).
Table 3. Risk of breast cancer by the age group, observation period and cumulative olanzapine equivalent dose

| Age group (yr) | Events | Person-Years | Incidence rate (per 100,000 person-years) | HR (95% CI) | p value |
|----------------|--------|--------------|------------------------------------------|-------------|---------|
| 18−44          | 861    | 1,035,905    | 83.12 (77.66−88.86)                      | 1.03 (0.95−1.12) | 0.43    |
| 45−64          | 1,509  | 886,104      | 170.30 (161.81−179.11)                   | 1.17 (1.09−1.24) | < 0.001 |
| 65−79          | 544    | 733,384      | 74.18 (68.07−80.68)                      | 0.93 (0.85−1.03) | 0.18    |

| Observation period (yr) | Events | Person-Years | Incidence rate (per 100,000 person-years) | HR (95% CI) | p value |
|-------------------------|--------|--------------|------------------------------------------|-------------|---------|
| < 3                     | 1,240  | 1,262,169    | 98.24 (92.85−103.87)                     | 1.02 (0.95−1.09) | 0.66    |
| 3 to < 6                | 848    | 799,583      | 106.06 (99.04−113.44)                    | 1.06 (0.97−1.15) | 0.18    |
| ≥ 6                     | 826    | 593,641      | 139.14 (129.81−148.96)                   | 1.24 (1.14−1.35) | < 0.001 |

| Cumulative olanzapine equivalent dose (mg) | Events | Person-Years | Incidence rate (per 100,000 person-years) | HR (95% CI) | p value |
|-------------------------------------------|--------|--------------|------------------------------------------|-------------|---------|
| < 10,000                                  | 2,496  | 2,394,130    | 104.25 (100.20−108.43)                   | 1.05 (1.00−1.11) | 0.03    |
| ≥ 10,000                                  | 418    | 261,263      | 155.99 (145.02−176.09)                   | 1.29 (1.14−1.46) | < 0.001 |

DISCUSSION

In this study, we used nationwide claim database to include a population-based cohort of about 1.5 million subjects for examining the association between the risk of breast cancer and the use of second-generation antipsychotics. An 8% increased risk of breast cancer was found in the subjects exposed to the second-generation antipsychotics. All antipsychotic groups showed a significantly higher risk of breast cancer compared with the matched control groups. The increased risk of breast cancer in the case group became statistically significant after six years of the observation period. There was a dose-response pattern showing a higher risk of breast cancer in the subjects with ≥ 10,000 mg of cumulative olanzapine equivalent dose than those with < 10,000 mg.

Compared to previous studies reporting an increased risk of breast cancer in subjects having antipsychotics [9,13], the current study showed a slightly lower increase in the risk of breast cancer associated with the use of antipsychotic dopamine antagonists. Pottegard et al. [13] found an 11% increased risk of breast cancer in the subjects exposed to second-generation antipsychotics. In the previous study by Pottegard et al. [13], the authors found the increased risk in the subjects with more than 10,000 mg of cumulative olanzapine equivalent dose. In our study, a 29% increased risk of breast cancer was observed in the subjects with more than 10,000 mg of the total olanzapine equivalent dose. Contrary to the previous studies, we found a higher risk of breast cancer even in the subjects with less than 10,000 mg of cumulative olanzapine equivalent dose, with a dose-response relationship between higher risk and larger cumulative dose of the antipsychotics. A comparatively larger sample size of the present study may contribute to these notable findings of a higher risk of breast cancer in the subjects with relatively low-dose antipsychotics and a clear dose-response pattern.

We observed that after six years of the observation period, the increased risk of breast cancer related to the use of second-generation antipsychotics became statistically significant. The results indicated that the subjects cumulatively exposed to the second-generation antipsychotics could be at higher risk of breast cancer. In other words, short-term exposure to the antipsychotics may not significantly contribute to the risk of breast cancer. With regard to previous studies [14,18-20] reporting no association between the use of antipsychotics and the occurrence of breast cancer, some had a much longer observation period than the present study. Even though the current study had a short observation duration compared to the previous studies, a larger number of subjects with the long-term follow-up duration might have contributed to the positive findings about the time point after which the increased risk of breast cancer became statistically significant. It could be also postulated that the null results from the previous studies may be owing to a lack of adequate sample size and/or observation period to reveal a slight but significantly increased risk of breast cancer related to the use of antipsychotics.

Despite the somewhat arbitrary aspect in the methodology for grouping the antipsychotics, the current study...
showed that as the risk of hyperprolactinemia of antipsychotics increased, an increasing trend was observed in the risk of breast cancer in the case group. However, the results should be considered exploratory because confounding variables for the risk of breast cancer were not evenly distributed among the three antipsychotic groups at a reasonable level. Previous studies on the association of antipsychotics use with the risk of breast cancer have mainly focused on the influence of hyperprolactinemia induced by the use of antipsychotics, however, there was no differential association of the risk of breast cancer stratified by the risk of hyperprolactinemia of antipsychotics [9,11-13,21]. Although it has been reported that more than 95% of breast cancer cells overexpress prolactin receptors which are closely related to tumorigenesis and cell proliferation [22,23], it is still obscure how the increased prolactin by antipsychotics use is associated with the occurrence of breast cancer. Previous experimental studies have reported inconsistent findings regarding the effect of antipsychotics on the proliferation of breast cancer cells, where some antipsychotic drugs suppress the growth and proliferation of breast cancer cells [7,24-26], while hyperprolactinemia-inducing antipsychotics promote breast cancer by activating JAK-STAT5 in precancerous lesions [6]. The current study showed that antipsychotics having a low risk of hyperprolactinemia were also associated with a higher risk of breast cancer, which suggests that the effect of hyperprolactinemia is not sufficient to comprehensively elucidate the relationship between antipsychotics use and the development of breast cancer. Further research is needed to reveal underpinning mechanisms for the relationship between them.

This study used nationwide claim data, which provided a very large sample size and aided in revealing a slight but significantly increased risk of breast cancer in the case subjects prescribed with second-generation antipsychotics. However, there are some limitations that should be considered. First, we did not investigate whether the subjects were exposed to antipsychotics a few years before the index date. Although we used a window period of one year to exclude the effect of previous exposure to antipsychotics, it could not be disregarded that exposure to antipsychotics from few years prior might have affected the development of breast cancer during the study period. However, there was no significant difference in the risk of breast cancer between the case and control groups in the early phase of the observation period, i.e., less than six years. Second, we did not consider confounding variables known as the risk factors for breast cancer, including smoking, alcohol use, diabetes mellitus, lack of breast-feeding, family history of breast cancer, nulliparity, and obesity [8]. Owing to the inherent limitation of the HIRA database, it was not possible to consider these variables in the analysis in an appropriate manner. According to previous studies [11,21], among several possible confounding variables, age was the only variable affecting the association between antipsychotics use and the risk of breast cancer. As we used age-matched controls in the current study, the confounding effect of age was adjusted in the analysis. It has been acknowledged that several drugs are associated with the risk of breast cancer, including aspirin, statin, insulin, metformin and other oral hypoglycemic agents, oral contraceptive, estrogen, and progesterone [27]. Although it would seem to be better to include these concomitant medications as covariates, because of an arbitrary aspect in how to retrieve information on these risk factors from the HIRA database and include these variables in a statistical model, we did not consider these variables in the current study. Third, although we aimed to investigate the risk of breast cancer associated with the use of antipsychotic drugs, specifically in relation to the risk of hyperprolactinemia of antipsychotics, the actual occurrence of hyperprolactinemia could not be determined because of the inherent limitation of the HIRA database. Fourth, it would be possible that patients with schizophrenia in the case group could affect the association of the risk of breast cancer with a longer duration and cumulative dose of antipsychotic use. We showed that a majority of subjects in the case group had been diagnosed with F20-29 at least once during the observation period. The disorder of schizophrenia itself rather than antipsychotics use could affect the risk of breast cancer based on previous reports of difficulty in marrying and nulliparity in schizophrenia patients [28]. It was also possible that the long-term use of antipsychotics reflected the chronicity of schizophrenia. The association of antipsychotics use with the risk of breast cancer in a psychiatric disorder, especially in schizophrenia, should be elucidated in future research. Fifth, the current result did not indicate the causal relationship between the use of second-generation antipsychotics and the occurrence of breast cancer. The present findings only indicated that at
the population level, there was a significantly increased risk of breast cancer in subjects exposed to second-generation antipsychotics than in those not exposed to them. Further research is needed to clarify how these atypical antipsychotics are implicated in the increased risk of breast cancer.

There was an 8% increased risk of breast cancer in case subjects exposed to second-generation antipsychotics. All antipsychotic groups showed a significantly increased risk of breast cancer. With regard to the observation period, the increased risk of breast cancer became statistically significant after six years of the observation period. There was a much higher incidence rate and risk of breast cancer in subjects with higher cumulative olanzapine equivalent dose than those with lower dose, indicating a dose-response relationship. Further studies are needed to clarify how the use of second-generation antipsychotics is involved in the increased risk of breast cancer. Underlying contributing factors for the relationship between the use of second-generation antipsychotics and the risk of breast cancer should be identified and utilized in clinical practice for early cancer detection and an increase in life expectancy.

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