

The Risk of Antipsychotic Drugs on Breast Cancer: A Systematic Review and Meta-analysis

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ABSTRACT

Objectives: To investigate the association between the consumption of antipsychotic drugs and breast cancer. **Methods:** In this systematic review and meta-analysis study, relevant studies were extracted from different databases including PubMed, ScienceDirect, Cochrane, Medline, and additional sources. The selected studies were statistically analyzed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. **Results:** Of a total of 11 studies selected, five were case-control type and six were cohort type. The overall study quality was 6.7. Meta-analysis of the five case-control studies (which together had 81 766 breast cancer patients and 1 150 316 control participants) showed no significant association between the overall use of antipsychotic drugs and the incidence of breast cancer (odds ratio = 1.06; 95% CI: 0.94–1.19; $p = 0.36$). Q-test results showed evidence of heterogeneity ($p < 0.10$) in the overall analysis. The I^2 statistical assessment also show evidence of heterogeneity ($I^2 > 75\%$). **Conclusions:** The use of antipsychotic drugs does not significantly increase the risk of breast cancer.

According to the Global Cancer Observatory, breast cancer comprises approximately 25% of all cancers in women and was ranked in 2020 as the cancer with the highest incidence, prevalence, and mortality.¹

The causative risk factors for breast cancer are broadly classified as modifiable and nonmodifiable. Genetic disposition is the prime nonmodifiable risk factor. Women with mutations in the *BRCA1* and *BRCA2* genes have a higher risk for breast cancer in the postmenopausal period.² In these women, if the menopause phase is acquired with a long onset, the consequent longer-term estrogen exposure might also be a risk factor. Family history with one or both factors increases the overall risk of breast cancer.³

Meanwhile, modifiable risk factors of breast cancer are diverse and often lifestyle-related, such as obesity, excessive alcohol consumption, hormone replacement therapy, and the use of certain drugs.⁴

Among the drugs under the scanner are antipsychotics which are often used together with antidepressants by the Asian geriatric population.⁵ Excessive use of antipsychotics has been suggested to be a risk factor for breast cancer through hormonal modulation. The rising tendency to

overprescribe antipsychotics (often without valid diagnosis of mental illness) is reported to have led to their overconsumption.⁶

Antipsychotics function as dopamine antagonists in the body through post-synaptic D2 receptor blockade in the pituitary gland. Dopamine is a natural inhibitor of prolactin, a hormone that regulates breast development and several physiological functions. Reduced dopamine availability in the system increases the levels of plasma prolactin, causing lactotrophic cells to become more active than normal, raising the risk of breast cancer.⁷

The question of whether antipsychotics increase the risk of breast cancer is still not settled. While several studies reported a significant correlation between antipsychotic drug use and breast cancer risk,^{8–10} others found it non-significant.^{11–13} Therefore, we launched the current systematic review and meta-analysis to evaluate the relationship, if any, between antipsychotic drugs and breast cancer incidence.

METHODS

We searched medical databases such as PubMed, ScienceDirect, Cochrane, Medline, and other

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appropriate sources for research papers containing the keywords 'antipsychotic', 'breast cancer', and 'risk.' Google Scholar was excluded to avoid grey literature.

The inclusion criteria were the following: (1) the study should report an association between the use of antipsychotic agents and breast cancer incidence in a patient group; (2) the study should report the relative risk of breast cancer among patient groups both qualitatively and quantitatively using the odds ratio (OR) with 95% CI; (3) the study should have a non-randomized controlled design, either case-control or cohort; and (4) the study should be published in either English or Indonesian language.

Two authors independently conducted the study selection, quality assessment, and data extraction. Differences of opinion between them were resolved through consideration and discussion with the third author. All protocols in this study's writing were developed based on the standards of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [Figure 1].¹⁴

For the quality assessment of the selected studies, we used the Newcastle-Ottawa Scale adaptation. To evaluate the case-control studies, we used the following assessment criteria, with maximum points given in parentheses: selection (4 points), comparability (2 points), and exposure (2 points). For cohort studies, the factors assessed included selection (4 points), comparability (1 point), and outcomes (3 points). The total points earned ranged from 0 indicating the worst quality to 8 indicating the best quality. Based on the above, each paper was classified as good (total points > 7), moderate (5–6), or poor (< 4).

Two authors independently extracted data on baseline characteristics, exposures, and outcomes from the selected studies. Also extracted were the author identity, publication year, study design, country, and the number of participants in both the case and control groups. Studies without sufficient data were excluded from the quantitative analysis (meta-analysis).

The main intended outcome of this systematic review was the estimation of the risk of breast cancer from the use of antipsychotic drugs. We employed the OR parameter with a 95% CI using a random effect model in view of the expected diversities in the numbers and characteristics of participants between different studies. The heterogeneity level

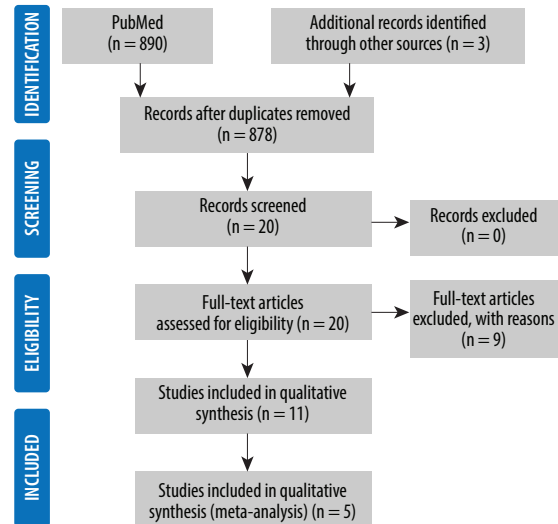


Figure 1: Diagram depicting the selection process of the study.

was assessed using the Q-test with a significance value at $p < 0.10$ and an assessment of the I^2 statistic. The higher significance (p -value) threshold was given because the statistical tests for heterogeneity were not particularly potent. Quantitative analysis of each group of antipsychotic drugs was conducted to determine the OR for each sub-group.

RESULTS

The literature search process is depicted in the PRISMA flow diagram [Figure 1]. The initial search yielded 890 studies, and manual review yielded three more. After excluding duplicates and screening titles and abstracts, 20 studies were shortlisted for feasibility assessment, nine of which were excluded. Finally $n = 11$ studies were chosen to be eligible for qualitative synthesis out of which five were also suitable for meta-analysis.

All the 11 selected studies were written in English. Five were case-control type and six were cohort type. The studies emerged from five countries: USA (four studies), UK (two), Denmark (two), Taiwan (two), and Sweden (one). The cohort sizes (including controls) ranged from 256 to 663 960, with a total of 1 419 997 participants. The number of breast cancer patients per study ranged from 91 to 60 360 with an overall total of 97 566. Five studies classified antipsychotic use into two types: typical (first generation) and atypical (second generation). Most studies were retrospective, based on past patient data from medical records. The study quality ranged

Table 1: The characteristics and results of the 11 studies that evaluated breast cancer risks of antipsychotics.

Author and year	Antipsychotic drug users (n)		Country	Study design	Drug type	Result	Study quality
	Case*	Total**					
Kanhouwa, ¹⁵ 1984	121	65 555	US	Case-control	Neuroleptic	Neuroleptics had no significant effect on breast cancer.	Moderate
Kelly, ¹⁶ 1999	91	256	US	Case-control	Neuroleptic	There was no significantly increased risk of breast cancer.	Good
Wang, ⁸ 2002	2467	52 819	US	Cohort	Dopamine antagonist	Antipsychotic dopamine antagonists could slightly increase (with statistical significance) the risk of breast cancer.	Good
Dalton, ¹⁷ 2006	341	25 264	Denmark	Cohort	Neuroleptic	There was no increased risk of breast cancer.	Good
Hippisley-Cox, ⁹ 2007	1478	8121	UK	Nested case-control	Conventional antipsychotics, atypical antipsychotics, and lithium	There was an increased risk of breast cancer in schizophrenics.	Moderate
Azoulay, ¹⁸ 2011	1237	106 362	UK	Nested case-control	Atypical and typical antipsychotics	When compared with typical antipsychotics, atypical antipsychotics did not appear to increase the risk of breast cancer.	Moderate
Reutfors, ¹⁹ 2017	348	55 976	Sweden	Cohort	Risperidone, other atypical antipsychotics, and typical antipsychotics	Risperidone use did not increase the short-term risk of breast cancer compared with other antipsychotic agents.	Good
Chou, ¹⁰ 2017	29 641	88 923	Taiwan	Cohort	First-generation antipsychotics (FGA), risperidone, paliperidone, amisulpride, and other second-generation antipsychotics (SGA)	Schizophrenic patients who consumed both FGA and SGA had slightly higher risk of breast cancer than non-schizophrenic patients.	Good
Pottgard, ¹¹ 2018	60 360	663 960	Denmark	Case-control	Single antipsychotic	Overall, there was no clinically important association between antipsychotic use and breast cancer risk.	Moderate
Tsai, ¹³ 2018	1449	233 237	Taiwan	Cohort	Risperidone, other atypical antipsychotics, and conventional antipsychotics.	There was no evidence of an increased risk of breast cancer associated with risperidone compared to other atypical or conventional antipsychotics.	Good
George, ¹² 2019	33	119 524	US	Cohort	Atypical and typical antipsychotics	The use of antipsychotic drugs did not increase the overall risk of breast cancer. However, the relationship between antipsychotics and breast cancer in situ has the potential for further investigation.	Good

*The number of patients who took antipsychotics and developed breast cancer.

**The total number of patients in the study.

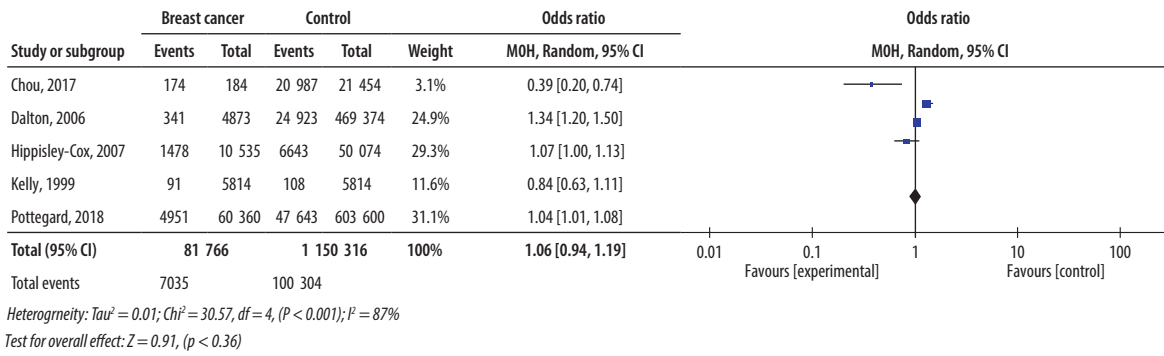


Figure 2: Forest plot regarding the overall use of antipsychotic drugs against breast cancer.

from 5 points (moderate) to 8 points (high) with an average of 6.7 points, indicating that the overall quality was suitable for meta-analysis. The summaries of the included studies are presented in Table 1.

Meta-analysis (quantitative synthesis) of five studies (9–11, 15, 16) with 81 766 breast cancer patients and 1 150 316 controls demonstrated a lack of significant association between the overall use of antipsychotics and breast cancer incidence (OR = 1.06, 95% CI: 0.94–1.19; $p = 0.36$) [Figure 2]. The relationships of distinct subgroups of antipsychotic drugs on breast cancer could not be analyzed due to inadequate subgroup-wise data.

The heterogeneity of the studies was assessed using the Q-test. The results of the analysis show evidence of heterogeneity ($p < 0.10$) in the overall analysis. The I^2 statistical assessment also demonstrates heterogeneity ($I^2 > 75\%$). Therefore, this finding supports using a random effect model to determine the correlation and effect estimation on data synthesis. The risk of publication bias was evaluated using the Egger's test and funnel plot symmetry assessment. The Egger's test revealed significant

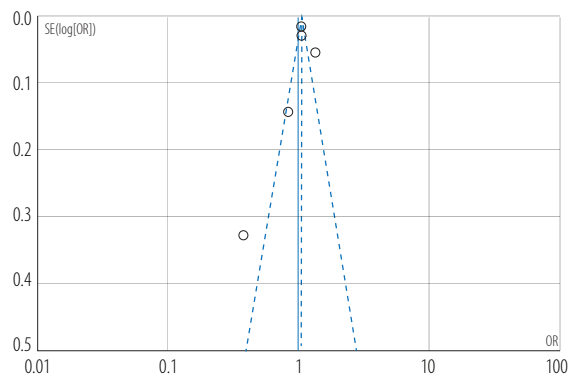


Figure 3: Funnel plot regarding the overall use of antipsychotic drugs against breast cancer. (Each circle represents one study.)

publication bias in the results of quantitative analysis ($p < 0.05$). The funnel plot [Figure 3] indicates a small possibility of publication bias.

DISCUSSION

Typical antipsychotic drugs, especially phenothiazines, have antiproliferative effects on the breast cancer MCF-7 cell line. Among the phenothiazines, perphenazine and chlorpromazine have the best cytotoxic activity,²⁰ though the pharmacological mechanism remains unclear. The result of cytotoxicity may not be associated with ligand-based antipsychotics at dopamine and serotonin receptors because the concentrations required to induce cytotoxicity are many times greater than those required to satisfy these receptors.²¹

Antipsychotics may be inducing cytotoxicity to cancer cells by chemically interacting with the cell membrane. This may be facilitated by the drug's amphiphilic properties, thereby upsetting the cell's cholesterol homeostasis, leading to its apoptosis.²² In addition, phenothiazines at pharmacological doses are known to increase the body's natural killer cell activity, mitogen-induced activation, and human T-cell proliferation. Thus, the ability of phenothiazines to stimulate the immune system may boost the natural resistance against tumor cells.²⁰

Meanwhile, atypical antipsychotics such as clozapine with its main metabolite N-desmethylozapine, have toxic effects on normal cells on myeloid maturation and myeloid mitotic components. This effect is implicated in agranulocytosis which occurs in approximately 1% of patients treated with clozapine.²⁰

Another atypical antipsychotic, sertindole, is known to cause cell apoptosis by directly inducing autophagy and inhibiting 5-HT₆ receptors. The

administration of sertindole near the maximum therapeutic dose weakens breast tumor growth by 22.7% in xenotransplant mice. However, the mechanism of this inhibition remains unclear. The most likely explanation is the inhibition of the dopamine and serotonin receptors.²³

Several previous studies have also demonstrated antipsychotic drugs as having no significant association with the incidence of breast cancer in both men and women, thus supporting our findings.^{24,25} On the other hand, in-vitro and in-vivo studies on antipsychotic drugs such as the pimozide, chlorpromazine, and piperidine classes have indicated their therapeutic potential for several types of cancer including breast cancer.^{26–28} Besides, atypical antipsychotic drugs such as olanzapine are known to reduce cancer-related symptoms and side effects of chemotherapy such as nausea and vomiting.²⁹ However, others such as clozapine in conjunction with chemotherapy might increase cancer-related complications such as neutropenia.³⁰

Despite our comprehensive literature search, only a few studies of sufficient specificity and quality could be identified. Even these had insufficient data on the antipsychotic subclasses. Therefore our meta-analysis could not evaluate the impact of individual antipsychotic subclasses on breast cancer.

CONCLUSION

This systematic review and meta-analysis found that antipsychotic drug usage did not significantly increase breast cancer risk. Further studies are needed regarding the relationship between subclass-wise antipsychotic usage and breast cancer risk in the long term. More randomized controlled trials, cohort, or case-control studies need to be conducted on the relationship between the usage of various antipsychotic subclasses and the risk of developing breast cancer.

Based on such studies, updated information on each antipsychotic subclass and their risk potential for breast cancer should be made available to clinicians.

Disclosure

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