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

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Received: 17 May 2021

Accepted: 4 January 2022

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DOI 10.5001/omj.2022.71

ABSTRACT

Objectives: Breast cancer ranked first as cancer in women, with the highest incidence, mortality, and prevalence globally. Various factors can cause breast cancer. Excessive use of psychotropic drugs such as antipsychotics can be a risk factor for breast cancer. However, there are different results in several studies related to the effect of the use of antipsychotic drugs on the incidence of breast cancer. This study aims to investigate the association between the risk of using antipsychotic drugs on breast cancer.

Methods: Data were extracted from different databases including PubMed, ScienceDirect, Cochrane, MEDLINE, and other appropriate additional sources. Data were reported according to the PRISMA guidelines.

Results: Eleven studies were included in qualitative synthesis and five studies in the quantitative synthesis. All studies were written in English, five case-control studies, and six cohort studies with a study quality average of 6.7 points. There were five studies

with 81,766 breast cancer patients and 1,150,316 control participants on quantitative synthesis that showed no significant association between overall use of antipsychotic drugs and the incidence of breast cancer in general (OR = 1.06; 95% CI = 0.94-1.19; p = 0.36). The Q-test analysis results show evidence of heterogeneity (p <0.10) in the overall analysis. The I^2 statistical assessment also shows evidence of heterogeneity (I^2> 75%).

Conclusion: The use of antipsychotic drugs does not significantly increase the risk of breast cancer.

Keywords: antipsychotic, breast cancer, risk

INTRODUCTION

The diagnosis of breast cancer dominates the diagnosis of cancer in women. According to The Global Cancer Observatory (GLOBOCAN), this cancer has been diagnosed in approximately 25% of all cancer cases in women. Breast cancer is frequently included in the top 10 most common cancers and ranked first as cancer with the highest incidence, mortality, and prevalence in 2020.[1]

Various factors can cause breast cancer, broadly classified as modifiable and nonmodifiable risk factors. One of the nonmodifiable risk factors is genetic factors. Women with mutations in the BRCA1 and BRCA2 genes have a higher risk to develop breast cancer in the postmenopausal period.[2] Besides, the risk of postmenopausal breast cancer is also experienced by women with slow onset. If the menopause phase is acquired with a long onset, then estrogen exposure will also be longer. Family history with one or both of the factors mentioned will increase the risk of breast cancer.[3] Meanwhile, modifiable risk factors in breast cancer are quite diverse, such as obesity,

excessive alcohol consumption, hormone replacement therapy, and the use of special drugs.[4]

Excessive use of psychotropic drugs such as antipsychotics can be a risk factor for breast cancer. Antipsychotics tend to be used repeatedly with antidepressants in the Asian geriatric population.[5] Furthermore, an estimated 7.04 million antipsychotics are prescribed to children, adults, and adolescents, with 56.7-67.0% having no mental illness diagnosis.[6] Thus, it illustrates the potential of overusing antipsychotic drugs.

Antipsychotic drugs, particularly when overused, have been shown to affect breast cancer risk through hormonal modulation. Antipsychotics will act as dopamine antagonists in the body through post-synaptic D2 receptor blockade in the pituitary gland. The nature of dopamine, a natural inhibitor of prolactin, a hormone that regulates woman breasts development and physiological function, makes the antidopamine effect triggered by external drugs, e.g., antipsychotics, will suppress the normal function of dopamine. With the decreased normal activity of dopamine due to overuse of antipsychotics, plasma prolactin levels will increase, causing lactotrophic cells to become more active than normal and lead to the incidence of breast cancer.[7]

Several studies have shown a significant correlation between the use of antipsychotic drugs and breast cancer risk.[8–10] Meanwhile, other studies have found no significant differences between those two.[11–13] Therefore, the authors were interested in raising this topic in a systematic review and meta-analysis to deeply review the risk of using antipsychotic drugs on breast cancer incidence.

METHODS

Literature Study

The literature study search used several databases, i.e., PubMed, ScienceDirect, Cochrane, MEDLINE, and other appropriate additional sources. A search on Google Scholar was not carried out to avoid the use of grey literature. The study search protocol used Boolean operators, i.e., "AND" and "OR" with keywords of "antipsychotic", "breast cancer", and "risk".

Study Selection

All studies to be included in this study had to meet several criteria, i.e., (1) the study reported an association between the use of antipsychotic agents and breast cancer incidence in a patient group; (2) the study reported the relative risk of breast cancer among patient groups both qualitatively and quantitatively using the odds ratio (OR 95% CI) parameter; (3) the study design was a non-randomized controlled study, either case-control or cohort; (4) the study was written either in Indonesian or English. Two authors independently conducted study selection, study quality assessment, and data extraction (IS, AI). The differences of opinion between the two authors were resolved through consideration and discussion with the third author (IK). 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) guideline.[14]

Study Quality Assessment

The study quality assessment method used the Newcastle Ottawa Scale (NOS) adaptation. In a case-control study, the assessment criteria include several factors, i.e., selection (maximum 4 points), comparability (maximum 2 points), and exposure (maximum 2 points). Meanwhile, the cohort study includes several factors, i.e., selection (maximum 4 points), comparability (maximum 1 point), and outcomes (maximum 3 points). The total points range from 0 indicating the worst quality to 8

indicating the best quality. Interpretation of study quality was classified as good (total points >7), moderate (total points 5 or 6), and poor (total points <4).

Data Extraction

Two authors independently extracted data of baseline characteristics, exposures, and outcomes from previously inclusion studies. Furthermore, data extraction was carried out related to the author's identity, publication year, study design, country, the number of participants in both the case and control groups. Studies without sufficient data were excluded from the quantitative analysis.

Data Analysis

The main outcome of this systematic review was the estimation of breast cancer risk for the use of antipsychotic drugs. The author utilized the odds ratio parameter with a 95% confidence interval using a random effect model since the number of populations between studies is likely to be diverse. The heterogeneity level was assessed using the Q-test with a significance value at $p < 0.10$ and an assessment of the I^2 statistic. Quantitative analysis on each group of antipsychotic drugs was carried out to determine the odds ratio for each sub-group.

RESULTS

Literature Search

A total of 890 studies were identified during the initial search on several databases and three additional studies originating from the literature review. Fifteen duplicate articles were identified and excluded. Furthermore, the title and abstract were screened, excluding 858 studies, while 20 studies were accepted for further feasibility assessment. Nine studies were excluded, thus the remaining 11 studies were eligible for inclusion in

the qualitative synthesis and five studies for the quantitative synthesis. The entire literature search process was developed based on the PRISMA flow diagram (**Figure 1**).

Study Characteristics

All studies were written in English. Five studies were case-control and six were cohort studies. Four studies were conducted in the United States, two studies in the United Kingdom, two studies in Denmark, two studies in Taiwan, and one study in Sweden. The population size ranged from 256 to 663,960 participants with a total population of 1,419,997 participants. The number of breast cancer patients ranged from 91 to 60,360 participants with a total of 97,566 participants. Five studies classified drug use into two groups: typical (first generation) and atypical (second generation) antipsychotics. Most studies employed patient data obtained through the medical records of cancer patients. The study quality ranged from 5 to 8 points (moderate-high) with an average of 6.7 points, indicating that the study quality was relatively suitable for quantitative synthesis. All summaries of the included studies are presented in **Table 1**.

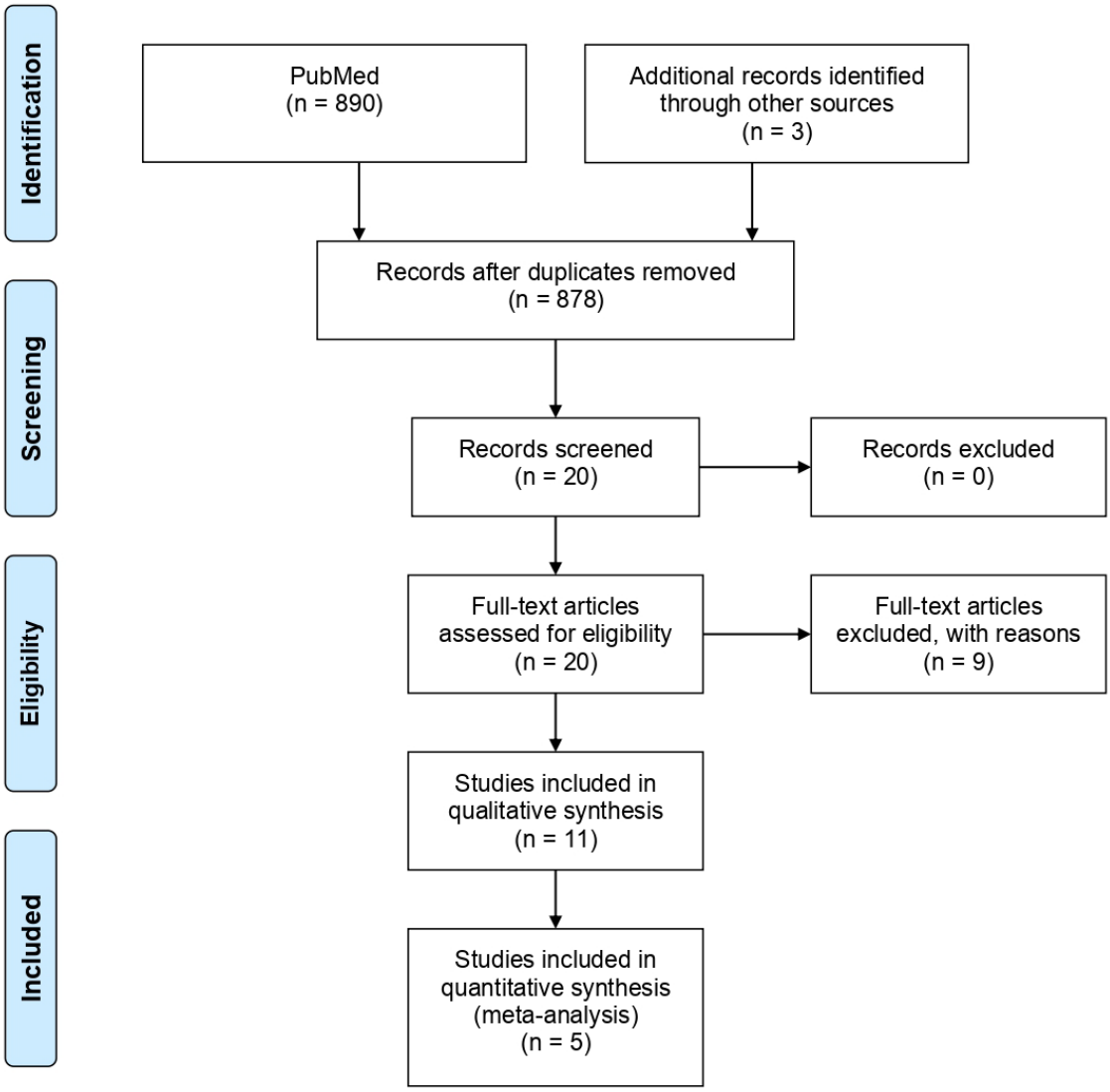
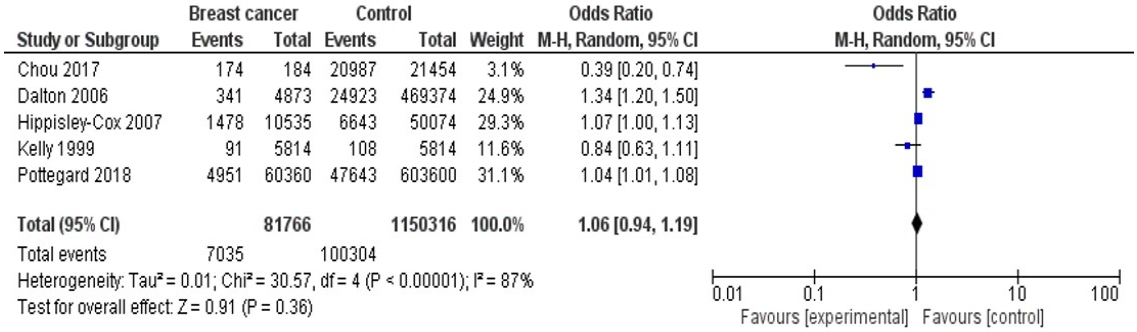


Figure 1. PRISMA Diagram

Data Synthesis

Five studies[9–11,15,16] with 81,766 breast cancer patients and 1,150,316 control participants in the quantitative synthesis demonstrated zero significant association between the overall use of antipsychotics and breast cancer incidence (OR = 1.06; 95%CI = 0.94-1.19; p = 0.36) in **Figure 2**. The quantitative analysis on each

antipsychotic drug group was not performed due to the inadequate study data of each sub-group.



Study Heterogeneity Analysis and Publication Bias Risk

The heterogeneity assessment 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 assessed using the Egger test with a significance value of $p<0.05$ and funnel plot symmetry assessment. The Egger test results show significant results; hence, publication bias in the results of quantitative analysis was discovered. In the funnel plot's qualitative analysis, a symmetrical graph is shown in **Figure 3**, indicating a small possibility of publication bias.

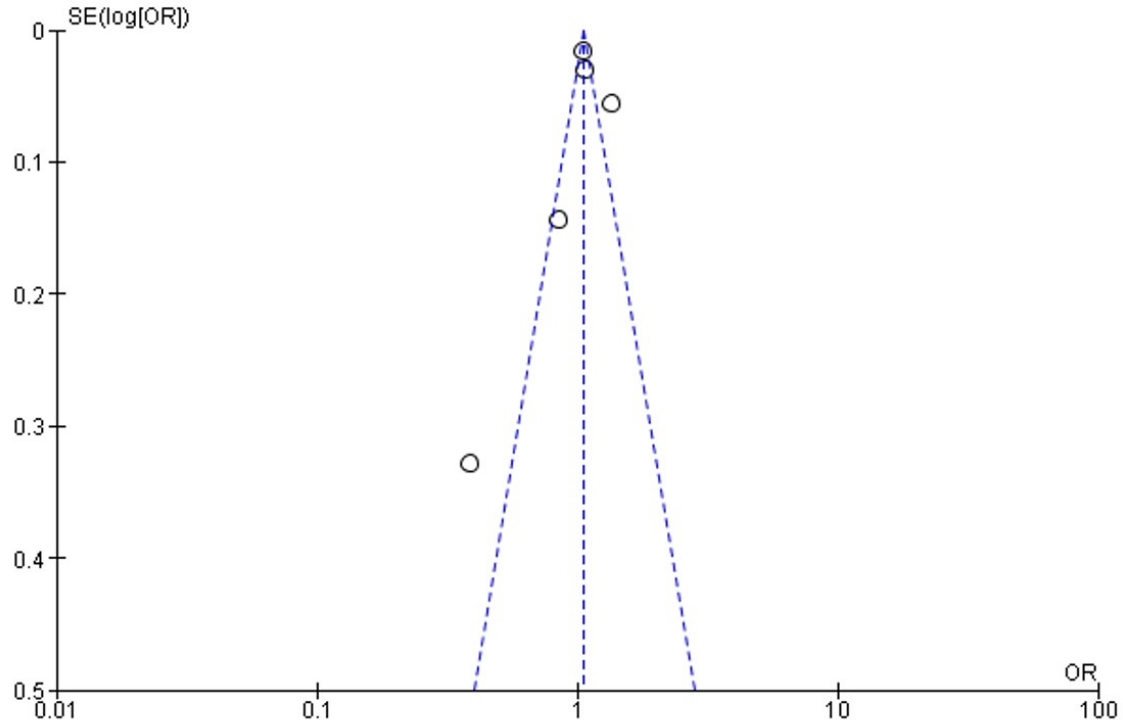


Figure 3. Funnel plot regarding the overall use of antipsychotic drugs against breast cancer.

Table 1. Study characteristic results

Author and Year	Antipsychotic Drug Users (n)		Country	Study Design	Drug Type	Result	Study Quality	Reference No.
	Case	Total						
Kanhouwa, 1984	121	65,555	United States	Case-control	Neuroleptic	Neuroleptics had no significant effect on breast cancer	Moderate	[17]
Kelly, 1999	91	256	United States	Case-control	Neuroleptic	There was no significantly increased risk of breast cancer	Good	[15]
Wang, 2002	2.467	52,819	United States	Cohort	Dopamine antagonist	Antipsychotic dopamine antagonists could slightly increase the risk of breast cancer significantly	Good	[8]
Dalton, 2006	341	25,264	Denmark	Cohort	Neuroleptic	There was no increased risk of breast cancer	Good	[16]
Hippisley-Cox, 2007	1,478	8,121	United Kingdom	Nested-case-control	Conventional antipsychotics, atypical antipsychotics, and lithium	There was an increased risk of breast cancer in schizophrenics. The increased risk of marginal breast cancer was due to the residual fusion by lower parity than the increased risk.	Moderate	[9]
Azoulay, 2011	1,237	106,362	United Kingdom	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	[18]
Reutfors, 2016	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	[19]

Chou, 2017	29,641	88,923	Taiwan	Cohort	First Generation Antipsychotics (FGA), risperidone, paliperidone, amisulpride, and other Second Generation Antipsychotics (SGA)	Schizophrenic patients with the combination of FGA and SGA had a slightly higher risk of breast cancer compared to non-schizophrenic patients	Good	[10]
Pottegard, 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	[11]
Tsai, 2018	1,449	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	[13]
George, 2019	33	119,524	United States	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 is potential for further investigation.	Good	[12]

DISCUSSION

Typical antipsychotic drugs, especially phenothiazines, have antiproliferative properties in the MCF-7 cell line of breast adenocarcinoma. Perphenazine and chlorpromazine are phenothiazine group drugs that have the best cytotoxic activity.[20] However, the pharmacological mechanism of the cytotoxicity of antipsychotic drugs against cancer cell development 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]

Antipsychotic cytotoxicity to cancer cells may involve direct interaction between the drug and cell membrane. This interaction can be partly explained by the drug's amphiphilic properties, thereby affecting cholesterol homeostasis and cell apoptosis.[22] Also, phenothiazines are known to increase natural killer (NK) cell activity and inhibit mitogen-induced activation and human T-cell proliferation at pharmacological doses. Phenothiazine is also able to stimulate the immune system, impacting the resistance to tumor cells.[20]

Meanwhile, atypical antipsychotics such as clozapine with its main metabolite, i.e., N-desmethyl clozapine, show a toxic effect 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 inhibition of the dopamine and serotonin receptors.[23]

In several previous studies, the use of antipsychotic drugs demonstrated no significant association with the incidence of breast cancer in both men and women.[24,25] These findings are suitable with the results of this study, which reported no significant association between antipsychotic drug usage and breast cancer incidence. On the other hand, several psychotic drugs, such as the pimozide, chlorpromazine, and piperidine classes are also known to have potential as new therapies for several types of cancer, including breast cancer through in vitro and in vivo studies.[26–28] Besides, atypical antipsychotic drugs such as olanzapine are known to reduce symptomatic cancer-related symptoms and side effects of chemotherapy, e.g., nausea and vomiting.[29] However, other studies have reported that the use of atypical antipsychotic drugs such as clozapine in conjunction with chemotherapy can increase cancer-related complications such as neutropenia.[30]

CONCLUSION

This systematic review and meta-analysis found that antipsychotic drug usage did not significantly increase breast cancer risk. The limitation in this study is the lack of recent studies on the antipsychotic subclass, thus the meta-analysis results can only be analyzed in the overall use of antipsychotic drugs and not specific. Further studies are needed regarding the relationship between antipsychotic usage and breast cancer risk as a long-term evaluation complemented by the type of antipsychotic drug used for each patient. Hence, subclass analysis can be carried out and determine its significance in more detail. Therefore, randomized controlled trial (RCT), cohort, or case-control

studies on the relationship between antipsychotic drug usage and the risk of developing breast cancer need to be performed to obtain more complete and recent data.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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