Paliperidone and Breast Cancer: A Meta-Analysis to Review the Clinical Correlation of Incidence of Breast Neoplasms

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ABSTRACT

The chronic administration of paliperidone, a prolactin-elevating atypical antipsychotic and active metabolite of risperidone, has elicited clinical concern regarding its possible association with breast cancer, particularly among long-term female users. This comprehensive review synthesizes molecular, preclinical, and epidemiological evidence to investigate whether chronic exposure to paliperidone correlates with an increased incidence of breast cancer. Mechanistically, paliperidone induces prolonged hyperprolactinemia through the blockade of dopamine D_2 receptors in the tuberoinfundibular pathway. Prolactin functions as a mitogen in breast epithelial cells by activating the JAK2/STAT5 signaling cascade, consequently inhibiting apoptosis and facilitating tumorigenesis. Preclinical studies indicate that prolactin-mediated STAT5 activation promotes malignant transformation of precancerous mammary lesions, especially under conditions of prolonged antipsychotic exposure.

Empirical evidence from numerous large-scale epidemiological studies—including nested case–control, retrospective cohort, and claims-based database analyses—demonstrates a modest yet statistically significant elevation in breast cancer risk associated with long-term (>5 years) use of prolactin-elevating antipsychotics, including paliperidone. Adjusted hazard ratios fluctuate between 1. 4 and 1.4. 1.6 across various cohorts, with indications of dose–response and histological specificity (for instance, an increased incidence of lobular carcinoma). Meta-analyses reaffirm this association, particularly among women diagnosed with schizophrenia, although heterogeneity and potential confounding factors (such as nulliparity, obesity, and disparities in screening) complicate causal interpretations. In male patients, the associated risk remains theoretical due to the limited availability of data; however, gynecomastia and sustained hyperprolactinemia have been well documented.

Considering the oncogenic potential of chronic elevation of prolactin, clinicians are recommended to monitor prolactin levels, contemplate the use of prolactin-sparing alternatives when feasible, and ensure adherence to breast cancer screening protocols. While the absolute risk remains low, evolving evidence advocates for a cautious, individualized approach to long-term paliperidone therapy, particularly in patients presenting additional breast cancer risk factors.

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Introduction

PALIPERIDONE is classified as a second-generation (atypical) antipsychotic, primarily indicated for the treatment of schizophrenia and associated psychoses. It serves as the principal active metabolite of risperidone and is recognized for its significant antagonistic properties on dopamine D_2 receptors as well as serotonin 5-HT_2A receptors. A notable consequence of D_2 receptor blockade within the tuberoinfundibular pathway is the development of hyperprolactinemia, which has raised concerns regarding potential endocrine-related adverse effects, including the risk of breast cancer. Breast cancer is hormonally sensitive in nature, and a chronic increase in prolactin levels has been implicated in the process of mammary tumorigenesis across various experimental models. Given that women diagnosed with schizophrenia present with a higher incidence of breast cancer compared to the general population (approximately 25% greater), it is imperative to discern the extent to which chronic antipsychotic treatment—especially with prolactin-raising agents such as paliperidone—contributes to this elevated risk. This review aims to synthesize evidence from clinical and preclinical studies to determine whether the prolonged use of paliperidone correlates with an increased incidence of breast cancer. We will evaluate both female and male populations, scrutinize observational and interventional data, compare the risk profiles of paliperidone with those of other antipsychotic medications (specifically risperidone and olanzapine), and investigate the underlying biological mechanisms at play. Additionally, we will discuss relevant statistical and epidemiologic considerations (such as findings from meta-analyses, effects related to duration of exposure, and the potential for autocorrelation within longitudinal data). Our objective is to deliver a comprehensive, postdoctoral-level analysis intended for an academic medical audience, effectively bridging the disciplines of psychiatric pharmacotherapy and oncologic risk assessment.

Mechanistic Background: Dopaminergic Blockade, Prolactin, and Tumorigenesis

The therapeutic effect of paliperidone is attributed to its antagonism of dopamine D_2 receptors, which reduces psychotic symptoms within the mesolimbic pathway. Conversely, in the tuberoinfundibular pathway, dopamine typically inhibits the release of prolactin; therefore, the blockade of D_2 receptors by paliperidone results in the disinhibition of prolactin secretion by pituitary lactotrophs. Paliperidone ranks among the antipsychotics with the highest propensity to elevate prolactin levels, often resulting in serum prolactin concentrations that exceed those caused by risperidone. Elevated serum prolactin can manifest clinically through symptoms such as galactorrhea, amenorrhea in women, and gynecomastia along with sexual dysfunction in men. Notably, prolactin functions as a hormone with established growth- and differentiation-promoting effects on breast epithelial tissue. Approximately one-third of human breast cancers exhibit responsiveness to prolactin in vitro, indicating that an environment rich in prolactin may potentially facilitate the development or progression of tumors within the breast.

Molecular pathways: Prolactin primarily exerts its effects by binding to prolactin receptors (PRLR) located on breast cells, thereby activating the JAK2-STAT5 signaling cascade. The activation of STAT5 in mammary cells facilitates differentiation and milk production under normal physiological conditions; however, it may also enhance the survival of preneoplastic cells by inhibiting apoptosis. Preclinical research conducted by Johnston et al. (2018) demonstrated that antipsychotics inducing hyperprolactinemia can directly influence this pathway: in mouse models of mammary carcinogenesis, risperidone (a precursor to paliperidone) and pimozide (a first-generation antipsychotic) accelerated the progression of precancerous mammary lesions to invasive cancer, whereas aripiprazole (a prolactin-sparing partial agonist) did not exhibit such effects. Both risperidone and pimozide activated STAT5 in breast tissue and inhibited apoptosis in early lesions; this effect was counteracted by the blockade of the JAK2/STAT5 pathway (e.g., through the use of the JAK inhibitor ruxolitinib). These findings provide support for a biologically plausible mechanism in which chronic elevation of prolactin alleviates an “anticancer” check (apoptosis) and facilitates the survival of nascent tumor cells. In summary, antipsychotic-induced hyperprolactinemia “instigates precancerous cells to progress to cancer via JAK/STAT5 to suppress the apoptosis anticancer barrier.” Moreover, it is noteworthy that prolactin receptors are often overexpressed in breast tumors, and prolactin signaling

has been implicated in the resistance to specific breast cancer therapies.

In addition to prolactin, various other factors and pathways may contribute to this issue. Chronic D_2 blockade can result in hypogonadism (via GnRH suppression) and diminished estrogen levels in premenopausal women. However, the overall impact on breast cancer risk is intricate; while reduced ovarian estrogen may lower the risk, prolactin's direct tumorigenic influence and the lack of cyclic progesterone (another differentiating hormone) could exert detrimental effects. Antipsychotics, such as paliperidone, are also associated with weight gain and insulin resistance, particularly among certain drugs in this class (for instance, olanzapine leads to significant metabolic effects). Weight gain elevates adipose aromatase activity and increases peripheral estrogen levels in postmenopausal women, and obesity itself is a recognized independent risk factor for breast cancer. Consequently, metabolic side effects may indirectly amplify the risk, thereby obscuring the overall picture. Furthermore, individuals with severe mental illness frequently exhibit higher rates of smoking, poor dietary habits, and a sedentary lifestyle, all of which can affect cancer risk or detection. These confounding factors complicate the ability to attribute mechanisms solely to prolactin.

It is also important to highlight that certain studies have paradoxically suggested that specific antipsychotic medications may exhibit anti-tumor properties in vitro or under certain conditions. For instance, phenothiazines and thioxanthenes have been investigated for their potential anti-cancer effects, with proposed mechanisms including dopamine receptor antagonism in tumor cells and effects on the cell cycle. However, it is crucial to acknowledge that these findings are preliminary and frequently drug-specific. The prevailing hypothesis posits that the elevation of prolactin is the principal link between the use of antipsychotic medications and the potential risk of breast carcinogenesis. In light of this hypothesis, medications such as paliperidone, risperidone, haloperidol, and amisulpride—all of which significantly elevate prolactin levels—are currently under scrutiny regarding their association with breast cancer risk. Conversely, prolactin-sparing agents (e.g., aripiprazole, quetiapine, clozapine) are thought to pose a reduced risk. In the subsequent sections, we will review the epidemiological evidence to determine whether clinical data corroborate these biological concerns.

Epidemiological Evidence in Women

Early and Retrospective Studies

Preliminary investigations regarding the connection between antipsychotics and the risk of breast cancer extend back several decades. Hyperprolactinemia has long been acknowledged as a causative factor for mammary tumors in rodent models subjected to chronic antipsychotic exposure. Indeed, studies investigating the carcinogenicity of risperidone in rats and mice indicated an increase in the incidence of pituitary adenomas and mammary gland adenocarcinomas; however, the relevance of these findings to human subjects remained uncertain. By the early 2000 s, epidemiological data began to surface. A substantial retrospective study, encompassing over 108, 108,000 women and published around 2002, revealed that women receiving antipsychotics experienced a modest yet statistically significant increase in breast cancer incidence – approximately 16% higher compared to those not on antipsychotic medications. The risk seemed to be more pronounced in individuals with higher cumulative doses of antipsychotics, suggesting a potential dose- response relationship. This study was among the earliest to issue a cautionary reminder, although its retrospective design left it susceptible to confounding variables.

In the subsequent decade, findings yielded mixed results. Various analyses reported no definitive association between the use of antipsychotics and breast cancer, or generated results that were challenging to interpret due to limited sample sizes. For instance, certain nationwide cohort studies focusing specifically on risperidone did not reveal a short- term increase in breast cancer risk when compared with other antipsychotic medications. This observation was corroborated by a comprehensive review conducted by De Hert and colleagues in 2015, which concluded that the elevation of prolactin levels induced by antipsychotics was of lesser importance in relation to the development of breast cancer than traditional risk factors such as nulliparity, obesity, diabetes, alcohol use, smoking, and physical inactivity. In essence, by 2015, the prevailing consensus suggested that if a connection were to exist, it would likely be relatively

minor and overshadowed by these other risk factors. Consistently, an expert review in endocrinology articulated that there is “no conclusive evidence that antipsychotic medication can increase the risk of breast malignancy, " advocating for caution without inducing alarm (Clevenger et al., 2003; Madhusoodanan et al., 2010).

However, not all early data were negative. A notable Taiwanese cohort study (Chou et al., 2017) examined women diagnosed with schizophrenia who were treated with prolactin-elevating antipsychotics. This investigation involving 88,923 women identified a nearly two-fold increase in the risk of breast cancer among those who had utilized risperidone, paliperidone, or amisulpride, in comparison to those who had not. The hazard ratio (HR) was reported to be approximately 1.94 (95% CI ~1.36–2.82) for that combined group. This significantly elevated relative risk attracted considerable attention; however, it is important to note that the study did not account for numerous breast cancer risk factors (e.g., family history, reproductive history, lifestyle). Therefore, while the findings are suggestive, they leave open the possibility that the observed association may have been influenced by confounding variables (for instance, women with schizophrenia within that cohort may have had higher rates of nulliparity or obesity compared to the general population).

Recent Large-Scale Studies (2018–2022)

In recent years, considerably larger and methodologically rigorous studies have been conducted, utilizing national health registries and big-data methodologies:

Pottegård et al. (2018, Denmark): This investigation was a case–control study employing the Danish Cancer Registry. It included 60,360 women diagnosed with breast cancer from 2000 to 2015 and matched each case to ten controls from the general population. The analysis examined antipsychotic exposure, distinguishing between first-generation and second-generation antipsychotics, classified based on their potential to elevate prolactin levels. Notably, Pottegård et al. indicated no overall association between antipsychotic usage and the risk of developing breast cancer. Neither first-generation (typical) nor second-generation (atypical) antipsychotic usage, categorized broadly, demonstrated significant correlation with breast cancer within this dataset. A subtle hint of a weak dose-response was observed: women with prolonged exposure to high-potency first-generation antipsychotics exhibited a slight increase in risk, and a weak trend with the cumulative dose of second-generation prolactin-elevating antipsychotics was noted. However, the authors warned that these patterns were delicate. Interestingly, the study’s classification of medications revealed certain anomalies – for instance, olanzapine and ziprasidone, which have relatively low prolactin effects, were categorized as “prolactin-sparing,” while asenapine, which has the potential to raise prolactin levels more than olanzapine, was misclassified as prolactin-sparing. Such misclassifications could have attenuated any true difference between prolactin-elevating and prolactin-sparing medications. In conclusion, the Danish study suggests that if there exists an increased risk associated with antipsychotics, it is not substantial at the population level – a reassuring finding, although the authors acknowledged limitations, such as not controlling for parity and body mass index (BMI).

Taipale et al. (2021, Finland): This study concentrated on women diagnosed with schizophrenia, utilizing Finland’s nationwide healthcare registries. It was a nested case–control study within a cohort of 30,785 women diagnosed with schizophrenia, followed from 1972 to 2014. Among these participants, 1,069 developed breast cancer over a follow-up period of up to 17 years. Each case was matched to five controls based on age and illness duration, and importantly, the authors controlled for comorbidities and concomitant medications. Antipsychotic exposure was categorized by cumulative duration in the preceding years. The findings were nuanced: the use of prolactin-sparing antipsychotics (clozapine, quetiapine, aripiprazole) for five or more years did not result in an increased risk of breast cancer (adjusted odds ratio ~0.95–1.19, not significant) when compared to less than one year of usage. In contrast, long-term use of prolactin-increasing antipsychotics, which encompassed all other antipsychotics in that study, demonstrated an association with breast cancer. Specifically, a duration of five or more years of exposure to prolactin-elevating drugs was associated with a 56% increase in the odds of breast cancer (adjusted odds ratio = 1.56, 95% confidence interval 1.27–1.92) when compared to less than one year of exposure. Shorter exposure durations (1–4 years) did not significantly increase risk (odds

ratio ~1.04, confidence interval 0.79–1.36). This suggests a potential time threshold effect, where risk becomes apparent with chronic use over an extended duration. Another noteworthy finding was histologic specificity: long-term use of prolactin-raising antipsychotics was more strongly associated with lobular carcinoma of the breast (odds ratio ~2.36) compared to the more prevalent ductal carcinoma (odds ratio ~1.42). Lobular cancers are often hormone-sensitive, which corresponds with an endocrine-mediated mechanism. One limitation noted was that paliperidone had relatively limited utilization in Finland throughout most of the study time frame (as it was introduced in the late 2000s), leading to essentially absent paliperidone exposure among the cases and controls. Therefore, that study could not directly evaluate paliperidone-specific risk; however, by implication, given that paliperidone is classified as prolactin-elevating, it would be expected to exhibit behavior similar to risperidone, which was prevalent in that cohort.

Rahman et al. (2022, United States): This study constituted a substantial retrospective cohort analysis utilizing U.S. commercial and Medicaid insurance claims, specifically the MarketScan databases. It identified 540,737 women, aged 18 to 64, who were new users of antipsychotics, and compared them to a control group of women who were new users of either mood stabilizers, such as lithium, or anticonvulsants, which were selected as psychiatric comparators known not to elevate prolactin levels. The median follow-up duration was approximately four years, during which roughly 0.2% of the women (914 individuals) developed invasive breast cancer. Antipsychotics were categorized based on their propensity to elevate prolactin: Category 1 includes those with a high propensity (e.g., haloperidol, risperidone, paliperidone); Category 2 comprises those with a moderate propensity (iloperidone, lurasidone, olanzapine); and Category 3 consists of those with low or no propensity (aripiprazole, quetiapine, ziprasidone). Following extensive adjustments for baseline characteristics—including obesity, diabetes, hormone replacement therapy (HRT) use, and benign breast disease—the results indicated that the use of any antipsychotic was associated with a heightened risk of breast cancer compared to the lithium and anticonvulsant group, with an adjusted Hazard Ratio of 1.40 (95% Confidence Interval 1.19 to 1.64). When analyzed by category, Category 1 (high-prolactin drugs such as paliperidone and risperidone) exhibited a Hazard Ratio of 1.50 (1.25 to 1.81), while Category 2 (moderate agents including olanzapine) demonstrated a Hazard Ratio of 1.65 (1.25 to 2.18), both of which were significantly elevated. Category 3 (low prolactin agents) did not reveal a significant increase, with a Hazard Ratio of 1.10 (95% Confidence Interval 0.83 to 1.50). These findings substantiate the hypothesis concerning the prolactin-mediated risk: women on antipsychotics recognized for elevating prolactin levels had an approximately 50% to 65% higher breast cancer risk over a four-year period compared to those on non-prolactin-elevating comparators, whereas women on prolactin-sparing antipsychotics did not exhibit a statistically significant increase in risk. It is noteworthy that the moderate category, which included olanzapine and lurasidone, displayed an elevated risk comparable to that of the high category within this analysis, although the number of users and the duration of follow-up may have varied across categories. Rahman et al. acknowledged that a four-year follow-up period might be insufficient to capture the complete breast cancer risk, particularly given that many individuals in the sample were still under the age of 50, with the median age of cases being 53. Additionally, women over the age of 64 were excluded from this analysis, thereby omitting the age range that typically exhibits peak breast cancer incidence. Nevertheless, this study offers some of the most robust evidence to date regarding the association between the use of prolactin-elevating antipsychotics and breast cancer, independent of significant confounding variables.

Kern et al. (2024, United States): A recent study conducted by Kern and colleagues (published in 2024) employed a distinctive methodology, utilizing a Medicaid population in conjunction with advanced propensity score matching techniques. As detailed in a report by Janssen Medical Information (noting that paliperidone is a product of Janssen), Kern et al. undertook a retrospective cohort study of women diagnosed with schizophrenia, using Medicaid data from 2006 to 2021. They performed a comparative analysis between individuals treated with high-prolactin antipsychotics and those administered low-prolactin antipsychotics, rigorously controlling for over 25,000 covariates through propensity matching. Intriguingly, Kern et al. found no statistically significant difference in breast cancer incidence between the cohort using high-prolactin antipsychotics and those in the low-prolactin group. Additionally, no

significant time-dependent increase in risk was observed when contrasting longer versus shorter durations of high-prolactin drug administration. This finding contrasts with the conclusions drawn by Taipale and Rahman, implying that within a well-matched demographic and health-related context, the isolated impact of prolactin-raising antipsychotics may be more challenging to discern. It is plausible that within the Medicaid population, confounding variables (such as socioeconomic status and access to healthcare) were similarly prevalent across both exposure groups post-matching, thereby minimizing observable differences. Furthermore, it is conceivable that the follow-up duration and case numbers in this study were inadequate to detect a subtle effect. As of 2025, it is imperative to address these discrepancies, noting that findings remain inconsistent; while some large-scale studies indicate a clear association, others do not. Therefore, a consensus on this matter has yet to be fully established, necessitating ongoing analysis.

Meta-Analyses and Pooled Evidence

To synthesize these mixed findings, several **systematic reviews and meta-analyses** have been performed. Two recent ones are particularly informative:

Gao et al. (2022) – published in Frontiers in Oncology conducted a meta-analysis examining twelve observational studies, ultimately encompassing eleven studies with approximately 1.5 million participants. The results of the meta-analysis indicated that exposure to antipsychotics is correlated with a modestly increased risk of breast cancer. Specifically, by pooling cohort and case–control studies, it was found that antipsychotic users exhibit roughly a 23% higher odds of developing breast cancer when compared to non-users (pooled odds ratio ≈ 1.23, 95% confidence interval 1.04–1.47). This moderate positive correlation did not present significant differences when comparing typical versus atypical antipsychotics (odds ratio approximately 1.23 versus 1.0, p = not significant). Notably, Gao et al. also found no significant discrepancy between prolactin-increasing and prolactin-sparing antipsychotics in aggregate (odds ratio approximately 1.13, 95% confidence interval approximately 0.97–1.31). At first glance, this suggests that the risk may not be exclusively attributable to prolactin. However, the authors cautioned that this particular subgroup analysis exhibited very low heterogeneity (which may indicate that few studies distinctly classified drugs by their prolactin effect), and the findings could be influenced by misclassification or limited data regarding truly prolactin-sparing agents. It is noteworthy that the meta-analysis revealed that breast cancer rates were particularly elevated in individuals exposed to paliperidone, risperidone, and sulpiride – all of which are potent prolactin-elevating agents – consistent with previous reports identifying these medications as high-risk. Gao et al. additionally evaluated dose effects; drawing upon data from studies such as Taipale (2021) and Antonova (which stratified by dose), they observed that patients receiving higher cumulative doses of antipsychotics exhibited significantly greater instances of breast cancer compared to those on minimal doses (for example, one analysis indicated odds ratios between approximately 1.33 and 1.39 for maximal dose exposure versus minimal). Furthermore, antipsychotic exposure was associated with poorer breast cancer mortality outcomes (odds ratio approximately 1.54 for cancer patients on antipsychotics versus those not exposed), although this may reflect discrepancies in cancer treatment or overall health. In conclusion, Gao et al. asserted that the utilization of antipsychotics "is an independent risk factor for breast cancer" (with an estimated 20–35% increase in risk) and that a longer duration of use correlates with a higher incidence. They acknowledged considerable heterogeneity (I^2 approximately 89% across studies) and the potential for publication bias, thereby urging caution in the interpretation of results. The absence of any distinction between typical and atypical medications in their analysis may suggest that other factors (such as lifestyle or the underlying mental illness) also contribute to the observed risk. Moreover, they speculated that the role of prolactin is intricately complex – for instance, even "prolactin-sparing" drugs may indirectly affect local prolactin signaling in breast tissue through the autocrine or paracrine production of prolactin by breast cells, a mechanism not captured by measuring serum prolactin levels alone.

Ng et al. (2023) – Published in Epidemiology and Psychiatric Sciences, this meta-analysis encompasses nine observational studies involving over two million individuals. It similarly found that the use of antipsychotics is moderately associated with an elevated risk of breast cancer. In their pooled estimate, there was an increase in risk exceeding 30% associated with antipsychotic use; however, intriguingly, the

combined odds ratio was marginal and "did not reach statistical significance" in one of their models (they reported a pooled hazard ratio of 1.39, 95% confidence interval 1.11–1.73 for cohort studies, and a pooled odds ratio of 1.37 for case–control studies, with a 95% confidence interval overlapping 1). This discrepancy may be attributed to the fact that they did not pool cohorts and case-control studies together or to a conservative analytical approach. Nonetheless, six of the nine individual studies included in their review were categorized as "good quality" and reported a significant association. Consistent with Taipale, the reviewers observed that prolonged exposure (≥5 years) was correlated with an increased risk (odds ratio approximately 1.56), whereas short-term exposure did not exhibit this risk. Additionally, they emphasized the findings from Chou et al. (2017), which indicated that specifically prolactin-elevating antipsychotics (risperidone, paliperidone, amisulpride) were associated with a higher risk (hazard ratio approximately 1.96). Unlike Gao et al., this meta-analysis explicitly concluded that the association may indeed be largely mediated by prolactin, given that the antipsychotics most significantly affecting prolactin levels appear to drive the observed signal. Their overall interpretation was that, despite the evidence remaining inconclusive in absolute terms, the preponderance of data suggests a genuine but moderate increase in breast cancer risk associated with antipsychotic use, particularly for drugs that elevate prolactin levels. They underscored the necessity for clinicians to incorporate this consideration into the risk–benefit assessment of antipsychotic therapy, especially for women presenting with additional risk factors.

In summary, the epidemiological literature on women suggests a pattern: short-term or low-dose use of antipsychotics does not significantly increase breast cancer incidence, but chronic use (especially beyond 5 years or at high cumulative doses) of prolactin-elevating antipsychotics is associated with a modest increase in risk. The relative risk increases reported are between 1.2 and 1.6 in most large studies – for perspective, this is smaller than the risk conferred by factors like obesity or heavy alcohol use, but not negligible. No study indicates an explosive risk (e.g., doubling or more) in the general population of medicated patients, except for the unadjusted Taiwanese study, which likely overestimated due to confounding. It is also clear that results are heterogeneous, with at least one large well-controlled study (Pottegård 2018) finding no significant effect and another (Kern 2024) also observing no difference after matching. This inconsistency highlights that causation is not yet established – women on antipsychotics differ in many ways from those who are not, and despite adjustments, residual confounders may still play a role. Nevertheless, the convergent evidence from several large independent cohorts (Finland, US, etc.), along with mechanistic plausibility, has made this a credible concern in psychiatric pharmacotherapy.

Considerations in Men

While the bulk of research focuses on female patients (for whom breast cancer is much more common), the question of paliperidone and breast cancer risk in **male patients** is Furthermore, male breast cancer remains a rare condition, with a lifetime risk of approximately 0.1% for men as compared to around 12% for women, which presents challenges in conducting epidemiological studies. None of the large cohort studies previously mentioned included a sufficient number of male patients or specific outcomes related to male breast cancer to facilitate definitive conclusions; indeed, many of these studies were predominantly focused on women. For example, the study conducted by Taipale et al. in 2021 examined only female patients with schizophrenia, while Rahman et al. in 2022 explicitly investigated women aged 18 to 64.

Approximately 0.1% for men, compared to approximately 12% for women, presents a significant challenge in conducting studies within epidemiological frameworks. None of the substantial cohort studies aforementioned included a sufficient number of male patients or male breast cancer outcomes to allow for definitive conclusions; a majority of these studies were limited to female subjects. For example, Taipale et al. (2021) focused exclusively on women with schizophrenia, while Rahman et al. (2022) specifically examined women aged 18 to 64.

Notwithstanding, one can draw inferences from pertinent studies conducted on male subjects: Paliperidone and risperidone are frequently associated with gynecomastia (benign enlargement of male breast tissue) as a consequence of hyperprolactinemia. Although gynecomastia is not categorized as cancer, sustained stimulation of estrogen and prolactin in male breast tissue has the potential, theoretically, to

predispose individuals to malignant transformations over time. A study by Etminan et al. (2015) quantified the risk of gynecomastia in adolescent males receiving treatment with risperidone: current users of risperidone exhibited approximately four times the likelihood of developing gynecomastia in comparison to non-users (RR = 3.91, 95% CI 2.01–7.62). Furthermore, adolescent males on risperidone displayed an even greater relative risk, estimated at approximately 5.4-fold. Given that paliperidone shares pharmacological similarities, it is also frequently implicated in cases of gynecomastia as observed in case reports and clinical practice (the paliperidone package insert identifies gynecomastia among common adverse effects and cautions regarding prolactin-mediated consequences in males). It is noteworthy that gynecomastia has been linked to a marginally increased risk of male breast cancer in certain studies, likely due to the fact that conditions leading to gynecomastia—such as hyperestrogenism—may similarly foster carcinogenesis.

Nevertheless, direct evidence that links the use of antipsychotics to male breast cancer is virtually non-existent in the available literature. The infrequency of such cases is so pronounced that even a cohort consisting of half a million patients may only exhibit a limited number of instances of male breast cancer, ultimately resulting in inadequate statistical power. Legal cases and anecdotal reports have suggested a potential connection; for instance, certain claims associated with risperidone litigation have alleged the development of male breast tumors following prolonged usage, in addition to reports of gynecomastia. However, peer- reviewed epidemiological studies have yet to substantiate this association. A Danish registry study examining cancer risk among antipsychotic users (Dalton et al., 2006) did not specifically address male breast cancer; instead, it focused on broader patterns. The study hypothesized in its introduction that some antipsychotics may reduce the risk of certain types of cancer, although this assertion did not pertain to breast cancer specifically.Given the biological context, it can be stated that chronic paliperidone use in men could theoretically increase the risk of breast cancer, but the absolute risk for any individual man remains extremely low. If the relative risk aligns with that observed in women (approximately 1. 3 to 1.3. 5–fold with long-term use), a man' s baseline lifetime risk of 0. 1% may increase to approximately 0. 0.15%, for example – a marginal difference in absolute terms. Clinicians should nonetheless remain vigilant for signs in male patients: persistent unilateral breast enlargement, nipple discharge, or masses in men receiving paliperidone should be evaluated, as male breast cancers, although rare, tend to be hormonally driven when they do occur. In clinical practice, it is advisable to monitor prolactin levels and manage symptomatic hyperprolactinemia in male patients (through dose reduction or switching to a prolactin- sparing antipsychotic) to mitigate any potential risks, including osteoporosis and sexual side effects, with cancer prevention being an additional hypothetical benefit.

Comparative Risk Profiles: Paliperidone vs. Other Antipsychotics

When discussing breast cancer risk, it is useful to contextualize paliperidone against other commonly used antipsychotics:

Paliperidone vs. Risperidone: These two substances are intricately connected; paliperidone is the 9-hydroxyrisperidone, which serves as the active metabolite of risperidone. It is not surprising that their pharmacological profiles and side effects exhibit significant overlap. Both are potent D_2 antagonists and substantially increase prolactin levels. Indeed, among atypical antipsychotics, risperidone has long been recognized as a primary contributor to hyperprolactinemia, while paliperidone appears to be equally potent, if not more so, in elevating prolactin. Clinical data frequently categorize risperidone and paliperidone together. The Taiwanese study conducted by Chou et al. (2017) exemplified this approach, revealing an increased breast cancer risk associated with this combined group (HR ~1. 1.9). In Taipale' s research, the usage of paliperidone was minimal; however, risperidone was included among the “PRL-increasing antipsychotics” that demonstrated a connection with cancer risk. Likewise, the study by Rahman et al. (2022) categorized risperidone and paliperidone within the high- prolactin group and identified a significant increase in risk (HR 1. 50). Conversely, an earlier nationwide cohort study from Denmark that focused on risperidone users (Nielsen et al. 2017, referenced in several reviews) reported no increased short- term breast cancer risk in comparison to other antipsychotics. This finding suggests that over a few years of use, risperidone was not associated with

a greater risk than, for instance, olanzapine or typical antipsychotics concerning breast cancer; however, this study may have been constrained by a limited follow-up period. Overall, considering the high prolactin profile, both risperidone and paliperidone are regarded as antipsychotics warranting considerable concern regarding breast cancer risk, should the association be substantiated. In fact, a psychiatric commentary from 2023 noted that "paliperidone (the first metabolite of risperidone) causes more hyperprolactinemia than any other antipsychotic" and emphasized recent epidemiological reports establishing connections between these prolactin- elevating medications and breast cancer. Therefore, strategies for risk mitigation, such as utilizing the lowest effective dosage, conducting regular screenings, or transitioning to a partial agonist when feasible, are particularly pertinent for patients undergoing long- term treatment with paliperidone or risperidone.

Paliperidone/risperidone vs. Olanzapine: Olanzapine is another frequently utilized atypical antipsychotic; however, it is distinct in that its impact on prolactin levels is negligible. Olanzapine transiently elevates prolactin levels slightly post- dosing, but due to its reduced D_2 occupancy at tuberoinfundibular neurons and potent anticholinergic and antihistaminergic properties, it generally does not induce sustained hyperprolactinemia in the manner that risperidone does. In numerous studies and clinical discussions, olanzapine is classified as a prolactin-sparing antipsychotic. For instance, in the study conducted by Taipale et al., olanzapine was grouped with non- PRL elevating medications (although in Pottegård' s research it was incorrectly classified, as noted). Epidemiologically, one might hypothesize that olanzapine poses a lower risk for breast cancer. The research by Rahman et al. categorized olanzapine as a part of the "moderate PRL" group (alongside lurasidone and iloperidone) and actually discovered a significantly elevated hazard ratio of 1. 65 for that group. This finding was somewhat unexpected and could suggest that factors beyond prolactin are influencing the results, or that the grouping diluted the distinctions (for example, lurasidone does moderately elevate prolactin, while iloperidone' s effect is not well-defined due to infrequent usage). It may also be considered a statistical anomaly or related to the particular comparator group utilized. Other studies, including case–control studies, often did not specifically isolate olanzapine. No compelling evidence implicates olanzapine alone as a contributor to increased breast cancer risk. In fact, it can be noted that quetiapine, clozapine, and aripiprazole – all considered low- prolactin agents like olanzapine – consistently demonstrate no increase in risk within analyses (they frequently serve as reference medications). For example, Taipale observed no increase in risk associated with long- term usage of clozapine/quetiapine (odds ratio approximately 1. 1.0). The implication is that olanzapine is likely more secure from a prolactin/cancer perspective compared to paliperidone or risperidone. However, it does lead to greater weight gain and metabolic syndrome, which could indirectly exacerbate cancer risk over time. Therefore, in patients identified as possessing a high risk for breast cancer (for instance, those with a robust family history or BRCA mutation carriers who also present with psychosis), a psychiatrist may favor olanzapine or quetiapine over paliperidone, specifically to mitigate the hormonal risk. As always, this assessment must be weighed against efficacy requirements and other potential side effects.

First-Generation vs. Second-Generation Antipsychotics: Numerous first-generation antipsychotics (FGAs) exhibit significant activity as D_2 receptor blockers and are associated with elevated levels of prolactin (e.g., haloperidol, fluphenazine). It is noteworthy that FGAs have been utilized for several decades; however, clear epidemiological associations with breast cancer were not established in earlier research, potentially due to the shorter life expectancy of patients or underestimation of the risks involved. Recent studies indicate that there is no substantial difference in risk between FGAs and second-generation antipsychotics (SGAs) categorized as classes. Gao et al. reported no significant difference in risk between typical and atypical antipsychotics overall. Pottegård identified a slight risk associated with long-term use of FGAs, although this effect does not appear to be widespread. Clinically, one particular FGA, pimozide, was linked alongside risperidone in preclinical studies as having the potential to activate STAT5 and promote tumorigenesis in murine models. Additionally, sulpiride, an older atypical antipsychotic utilized in certain countries and noted for its significant elevation of prolactin, was also emphasized by Gao et al. as being associated with increased breast cancer rates. These pharmacological agents are essentially categorized as "high-prolactin" typical or atypical drugs. Meanwhile, chlorpromazine, recognized as a

low-potency FGA, elevates prolactin levels yet possesses complex estrogenic metabolic properties, with no definitive data available regarding its associated cancer risk. In clinical practice, numerous psychiatrists have shifted away from prescribing high doses of FGAs for women who experience hyperprolactinemia, opting instead for atypical antipsychotics such as aripiprazole when feasible.

Other atypicals: Amisulpride, which is utilized in Europe, represents another D_2/D_3 blocker that induces significant hyperprolactinemia. It has been analyzed alongside risperidone and paliperidone in various studies indicating an increased risk (e.g., Chou 2017). Aripiprazole, Brexpiprazole, and Cariprazine are classified as partial agonists and typically reduce prolactin levels or maintain them at normal levels; there is no evidence linking these medications to an elevated risk of breast cancer; in fact, the addition of aripiprazole can effectively address antipsychotic-induced hyperprolactinemia. Quetiapine and Clozapine exhibit minimal effects on prolactin levels and have not been associated with signals of breast cancer in research studies. Therefore, among antipsychotic medications, paliperidone (and its counterpart risperidone) are distinguished by having one of the less favorable profiles concerning potential breast cancer risk, while olanzapine occupies an intermediate position (with metabolic risk but lower prolactin levels) and medications such as aripiprazole or quetiapine are regarded as most favorable in this particular context. This information is receiving increasing recognition in treatment planning; for instance, if a young woman on risperidone experiences elevated prolactin levels and has a family history of breast cancer, a clinician may consider transitioning her to a prolactin-sparing antipsychotic to possibly mitigate long-term risk.

Statistical and Epidemiologic Methodology Considerations

The assessment of the correlation between chronic paliperidone usage and breast cancer necessitates meticulous consideration of both study design and statistical analysis. Breast cancer constitutes a relatively rare outcome within the general populace, particularly for individuals under the age of fifty; therefore, substantial sample sizes and prolonged follow-up periods are requisite. Numerous studies reviewed employed case–control designs, which are efficient for rare outcomes, or retrospective cohorts utilizing administrative databases. Each methodology presents its own strengths and limitations:

Confounding and Bias: Patients who are administered chronic antipsychotic medications exhibit systematic differences compared to those who are not prescribed these drugs. This population frequently presents with severe mental illnesses, which may correlate with lower rates of marriage and childbirth (notably, nulliparity is identified as a risk factor for breast cancer), elevated smoking rates, suboptimal dietary habits and physical health, as well as reduced utilization of preventive health services such as mammograms. These elements can contribute to an increased risk of breast cancer or hinder its timely detection. Without appropriate management, these factors may complicate the assessment of the association. For instance, a particular study highlighted that women diagnosed with schizophrenia experience lower frequencies of breast cancer screening and exhibit higher mortality rates from breast cancer, independent of medication usage. This observation points to a potential detection bias, wherein cancers may be diagnosed at a later stage (or not identified at all) within this demographic. Most contemporary studies have endeavored to account for numerous variables: Rahman et al. adjusted for obesity, diabetes, hormone therapy, benign breast disease, among others, and discovered that the risk linked to antipsychotic medications remained virtually unchanged following these adjustments. Taipale et al. employed a methodology that matched cases and controls based on age and illness duration, and also adjusted for comorbidities, which represents a solid methodological approach. However, certain factors, such as family history of breast cancer, BRCA mutation status, and lifetime estrogen exposure (including the duration from menarche to menopause, breastfeeding patterns, etc.), are generally not included in databases. These could still introduce bias in the results if, for instance, women with schizophrenia possess inherently different reproductive histories. Additionally, the use of antidepressants presents another nuanced factor; there has been speculation regarding whether co-medication, such as selective serotonin reuptake inhibitors (SSRIs), might impact prolactin levels or cancer risk. A study conducted by Kelly et al. (2010) did not account for the impact of antidepressants, which may have implications for the results obtained.

Exposure Definitions: The definition of "chronic use" or high exposure is of fundamental importance. Various studies have employed different cut- off points; for instance, Taipale established a threshold of≥5 years of cumulative exposure, while a cut- off of>1000 defined daily doses (DDD) was utilized, which approximately corresponds to 2. 2.7 years of daily risperidone at a dosage of 5mg, also according to Taipale. Rahman et al. examined both any use compared to none, and they also quantified average daily doses in DDD; however, the primary reporting was conducted by category rather than through a continuous dose- response analysis. Should a study include numerous short- term users within the exposed group, there is a potential that the risk estimate may be diluted. For instance, if paliperidone genuinely increases risk only after a latency period of several years, a cohort with a mean follow- up of approximately 4 years, such as that presented by Rahman et al., may underestimate the long- term effect. This could elucidate why Kern et al. (2024) did not observe a temporal increase; their follow- up period may not have been sufficiently long, or they may have engaged in a broad "ever vs. never" comparison that obscures distinctions in duration. Additionally, the concept of autocorrelation in exposure must be considered: patients who persist in the use of antipsychotics for many years are likely those suffering from chronic illnesses who maintain continuous contact with healthcare services. Their exposure status at different points in time is highly correlated with its prior states (i. e., if an individual utilized paliperidone in year 1, it is likely they continued this usage in year 2, and so forth). This situation necessitates modeling time- dependent confounding and time- dependent exposure, preferably utilizing techniques such as Cox models with time- varying covariates or implementing a lag period; certain studies commenced the "at- risk" clock 180 days subsequent to the initiation of antipsychotics to account for potential latency. In the absence of such adjustments, there exists the risk of either underestimating risk (by incorporating person-time preceding the manifestation of effect) or overestimating it (should incidents of cancer themselves precipitate the discontinuation of antipsychotics, although this scenario is less likely).

Statistical power: The incidence of breast cancer during midlife remains relatively low. For instance, Rahman et al. noted that only 0. 2% of their cohort developed breast cancer over a span of four years. Consequently, despite having a sample size of half a million individuals, approximately 900 cases were recorded in that particular study. Case–control designs, such as those employed by Pottegård, effectively leverage tens of thousands of cases to enhance statistical power. Moreover, meta- analyses contribute to increased power through pooling of data; however, this is often accompanied by a degree of heterogeneity. Indeed, Gao et al. identified significant heterogeneity across various studies, with an I^2 statistic nearing 90%, indicative of population differences- some investigations encompassed all antipsychotic users, whereas others specifically examined patients diagnosed with schizophrenia. Notably, subgroup meta- analyses conducted by Gao et al. indicated that geography may influence outcomes: studies undertaken in Denmark or the United States individually did not demonstrate significant effects (odds ratios of approximately 1. 17 in the U. S. and 1. 1.18 in Denmark, with both 95% confidence intervals overlapping 1). In contrast, studies encompassing Asian populations, specifically in Taiwan, exhibited significant findings, potentially attributable to disparities in antipsychotic prescribing practices or inherent risk profiles. Additionally, another meta-analysis revealed that when concentrating solely on studies involving patients with schizophrenia, the association was markedly stronger (with an odds ratio of approximately 1. 1.84 observed in one analysis). This suggests that the indication for treatment and the characteristics of the population are of paramount importance; including all antipsychotic users- many of whom may consist of older adults prescribed low- dose medications for off- label purposes such as dementia- may dilute the observed effect, while chronic psychiatric patients present a clearer association.

Causality vs. Association: None of these studies can establish causation; they are observational in nature. While it is possible to statistically adjust for known confounders, there may always remain unidentified factors. For instance, is it plausible that characteristics related to schizophrenia or bipolar disorder (independent of medication) could elevate the risk of breast cancer? Some research suggests that chronic psychological stress or immune dysregulation associated with severe mental illness may influence cancer biology, or that certain antipsychotics might, in fact, exhibit protective effects against certain cancers (through dopamine blockade in tumors), resulting in a complex net effect. At least one older hypothesis

proposed that dopamine antagonists might reduce cancer risk through various mechanisms, although evidence did not convincingly support this in the context of breast cancer. Presently, the preponderance of evidence leans toward a genuine medication effect (particularly via prolactin); however, it is prudent to use the term "associated with" instead of "causes" until more prospective data or mechanistic confirmation in human subjects becomes available. It is noteworthy that the FDA and drug manufacturers have refrained from adding a black-box warning or definitive statement indicating that paliperidone or risperidone cause breast cancer; rather, the labels reference hyperprolactinemia, the findings of rodent tumors, and indicate that epidemiologic studies have been inadequate to reach conclusive determinations. This position may evolve should further evidence accumulate.

Meta-analytic nuances: The meta-analyses endeavored to address publication bias; for instance, Gao et al. employed funnel plots and the trim-and-fill method, discovering no significant bias. Additionally, they conducted sensitivity analyses by omitting one study at a time to ascertain the stability of the results. In Gao's study, the exclusion of certain outliers altered the significance of some comparisons, suggesting that the results must be interpreted with caution. The reference to autocorrelation within the context of meta-analysis may pertain to the utilization of certain databases across multiple studies; for example, the same Danish registry data may support two separate publications. Should this not be properly accounted for, it could imply that the meta-analysis is accounting for overlapping populations twice—an instance of data autocorrelation. Although there is no indication that this posed a significant issue, it is a technical aspect worthy of acknowledgment when integrating studies.

In conclusion, the epidemiological methods employed are relatively robust, featuring large samples and the adjustment for numerous confounders; however, inherent limitations persist. The association appears to be statistically significant, albeit modest, and there remains a residual uncertainty regarding true causality and effect size. Subsequent studies could enhance this by undertaking prospective follow-ups of cohorts with systematic prolactin monitoring, which would allow for the direct correlation of prolactin exposure (area-under-the-curve) with cancer outcomes, or by conducting Mendelian randomization studies utilizing genetic proxies for prolactin levels. Thus far, the existing evidence is sufficient to advocate for a cautious approach in clinical settings, yet it is inadequate to definitively assert that "paliperidone will increase a given patient's risk of breast cancer."

Conclusion

Empirical evidence to date suggests that chronic use of paliperidone (and similar prolactin-elevating antipsychotics) may modestly increase the incidence of breast cancer, particularly in female patients following extended periods of therapy. Mechanistically, this is supported by the drug's induction of hyperprolactinemia and the established role of prolactin in breast cell proliferation and tumor progression via the JAK2/STAT5 pathway. Observational studies involving women diagnosed with psychotic disorders have reported odds ratios in the range of approximately 1.2 to 1.6 for breast cancer associated with prolonged exposure to prolactin-raising antipsychotics, although not all studies reach a consensus. The most pronounced signals emerge in individuals with prolonged exposure (≥5 years) or elevated cumulative doses. Shorter-term usage does not appear to notably increase this risk. In comparison, prolactin-sparing medications (e.g., aripiprazole) have not been associated with heightened risk, reinforcing a probable prolactin-mediated effect – notwithstanding some ambiguities in meta-analyses regarding class differences. In male patients, a comparable biological mechanism is present (paliperidone induces marked hyperprolactinemia and gynecomastia in men); however, due to the rarity of male breast cancer, a statistically significant association has not been established—it remains a theoretical concern.

It is essential to emphasize that correlation does not equate to causation. While the associations raise concerns, they have not definitively demonstrated that paliperidone or risperidone induce breast cancer. Confounding factors, ranging from lifestyle choices to parity and the impact of the psychiatric illness itself, complicate interpretation. The current consensus within the literature is cautious: practitioners are advised to remain cognizant of the potential risk, engage in discussions regarding it within the context of treatment decisions, and monitor patients accordingly, while not reflexively avoiding effective antipsychotic therapy out of fear of breast cancer, given the relatively

small absolute risk. The increase in risk, if present, is moderate and must be weighed against the substantial benefits these medications provide in managing psychosis.

Future research should persist in elucidating this issue. Ongoing pharmacovigilance and larger longitudinal cohorts (potentially inclusive of older women, who are at the highest risk for breast cancer, since current studies frequently cap at age 64) will prove beneficial. Translational research into prolactin blockers or dopamine agonists for patients requiring antipsychotics may also reveal whether modulating prolactin can reduce any cancer risk—for instance, could low-dose bromocriptine (a dopamine agonist) counteract antipsychotic-induced hyperprolactinemia without sacrificing psychiatric efficacy, and would that consequently lower breast cancer incidence over time? These remain open questions. Moreover, genetic studies could identify if particular individuals (e.g., those with a high genetic baseline of prolactin or PRLR polymorphisms) are more susceptible to this potential risk.

In conclusion, chronic paliperidone use exemplifies the delicate balance in medicine between attending to serious mental illnesses and managing long-term physical health outcomes. The intersection of psychiatry and oncology emphasized herein necessitates integrated care: ensuring that patients receiving antipsychotics are adequately informed, monitored, and provided with holistic care that addresses both their mental health and cancer prevention. While the incidence of breast cancer may indeed be elevated with long-term paliperidone use, prudent clinical management can help mitigate risks—such as employing the lowest effective doses, contemplating prolactin-sparing alternatives for at-risk individuals, and maintaining vigilance for early signs of malignancy. Patients and healthcare providers should engage in shared decision-making, recognizing that the magnitude of any added risk appears relatively minor in absolute terms, but acknowledging that for individual patients, minimizing all potential risk factors remains ideal. By remaining informed about emerging evidence and employing sound clinical judgment, healthcare providers can continue to safely utilize paliperidone and other antipsychotics while safeguarding patients' endocrine and oncologic health.

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