Antipsychotic use and risk of breast cancer in women with schizophrenia: a nationwide nested case-control study in Finland

Heidi Taipale, Marco Solmi*, Markku Lähteenvuo, Antti Tanskanen, Christoph U Correll, Jari Tiihonen*

Summary

Background Breast cancer is more common in female patients with schizophrenia than in the general population. It is not known whether treatment with prolactin-increasing antipsychotics contributes to increased odds of breast cancer.

Methods We used Finnish nationwide registers of hospital treatment, prescription drug purchases, and cancer diagnoses to do a nested case-control study. Of women with schizophrenia, those with breast cancer (cases) were matched by age and duration of illness with five women without cancer (controls). Cases and controls were aged 18–85 years and exclusion criteria were any previous cancer diagnoses, receipt of organ transplant, mastectomy, or diagnosis of HIV. The main analysis was the association between cumulative exposure to prolactin-increasing drugs and breast cancer. The analyses were done with conditional logistic regression, by adjusting for comorbid conditions and concomitant medications. Ethnicity data were not available.

Findings Of 30 785 women diagnosed with schizophrenia between 1972 and 2014, 1069 were diagnosed with breast cancer between Jan 1, 2000, and Dec 31, 2017. Compared with 5339 matched controls, 1–4 years cumulative exposure (adjusted odds ratio [OR] 0·95, 95% CI 0·73–1·25) or 5 or more years exposure (adjusted OR 1·19, 0·90–1·58) to prolactin-sparing antipsychotics (including clozapine, quetiapine, or aripiprazole) was not associated with an increased risk of breast cancer in comparison with minimal exposure (<1 year). When compared with less than 1 year of exposure to prolactin-increasing antipsychotics (all other antipsychotics), 1–4 years of exposure was not associated with an increased risk, but exposure for 5 or more years was associated with an increased risk (adjusted OR 1·56 [1·27–1·92], p<0·001). The risk for developing lobular adenocarcinoma associated with long-term use of prolactin-increasing antipsychotics (adjusted OR 2·36 [95% CI 1·46–3·82]) was higher than that of developing ductal adenocarcinoma (adjusted OR 1·42 [95% CI 1·12–1·80]).

Interpretation Long-term exposure to prolactin-increasing, but not to prolactin-sparing, antipsychotics is significantly associated with increased odds of breast cancer. Monitoring prolactinemia and addressing hyperprolactinemia is paramount in women with schizophrenia being treated with prolactin-increasing antipsychotics.

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Introduction

Breast cancer is the most common cancer in women. The lifetime prevalence of breast cancer is about 12%,[1] and it is 25% more common in patients with schizophrenia than in the general population.[2,3] Prevalence in this group might be even higher than what is reported in the literature, as according to a meta-analysis pooling data from 47 publications and 4 717 839 individuals, women with schizophrenia have a 48% decreased odds (odds ratio [OR] 0·52 [95% CI 0·43–0·62]) of undergoing screening for breast cancer compared with the general population, suggesting that breast cancer might be underdiagnosed in women with schizophrenia.[4] The disparities in cancer screening might also contribute to the increased mortality due to breast cancer in women with schizophrenia, by delaying diagnosis and interventions.[5]

Women with schizophrenia also have increased rates of risk factors for breast cancer, including higher rates of obesity, diabetes, and smoking, as well as lower rates of parity and breastfeeding, than the general population.[6] Moreover, a high concentration of prolactin is associated with a higher risk for the development of breast cancer.[7,8] Prolactin synthesis is regulated by the dopamine system, and blocking of D2 receptors in the tuberoinfundibular neural path leads to increased prolactin concentrations.[9] Preliminary evidence has shown that prolactin might increase both ductal and lobular cancer cell proliferation,[10,11] but whether the risk is higher for ductal or for lobular cancer is unknown. It has been suspected that antipsychotics blocking D2 receptors and increasing prolactin concentrations could be associated with an increased risk of breast cancer. For example, a US cohort study reported a small (16%) but significant increased

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*Contributed equally

Department of Forensic Psychiatry, University of Eastern Finland, Niuvanniemi Hospital, Kuopio, Finland (H Taipale PhD, M Lähteenvuo PhD, A Tanskanen PhD, Prof J Tiihonen PhD); **Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden** (H Taipale, A Tanskanen, Prof J Tiihonen); **Department of Psychiatry, University of Ottawa, Ottawa, ON, Canada** (M Solmi PhD); **Department of Mental Health, The Ottawa Hospital, Ottawa, ON, Canada** (M Solmi); **Department of Neuroscience, University of Padua, Padua, Italy** (M Solmi); **Padova Neuroscience Center, University of Padua, Padua, Italy** (M Solmi); **Department of Psychiatry, Zucker Hillside Hospital, New York City, NY, USA** (Prof C U Correll PhD); **Department of Psychiatry and Molecular Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, USA** (Prof C U Correll); **Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany** (Prof C U Correll); **Center for Psychiatry Research, Stockholm City Council, Stockholm, Sweden** (H Taipale, A Tanskanen, Prof J Tiihonen); **Neuroscience Center, University of Helsinki, Helsinki, Finland** (Prof J Tiihonen)

Correspondence to:
Prof Heidi Taipale, Department of Forensic Psychiatry, University of Eastern Finland, Niuvanniemi Hospital, 70240 Kuopio, Finland
heidi.taipale@uef.fi

Research in context

Evidence before this study

We searched Pubmed from database inception to March 16, 2021, with search terms "schizophrenia", "antipsychotic", "breast", and "cancer", without any restrictions on language or article type. Breast cancer is more common in women with schizophrenia than in the general population, and high concentrations of prolactin are also associated with a higher risk for the development of breast cancer. Therefore, it has been suspected that antipsychotics blocking dopamine D2 receptors and increasing prolactin concentrations could be associated with an increased risk of breast cancer. Previous studies have reported inconsistent findings regarding the topic. No study with long-term follow-up has been done in women with schizophrenia and by separating prolactin-increasing and prolactin-sparing antipsychotic exposures.

Added value of this study

Using Finnish nationwide register-based data of women with schizophrenia who have been diagnosed with breast cancer compared with age-matched and duration of illness-matched controls with schizophrenia, we found an increased risk of breast cancer associated with long-term (≥5 years) prolactin-increasing antipsychotic exposure compared with minimal (<1 year) exposure. Long-term exposure to prolactin-sparing antipsychotics was not associated with an increased risk. The risk seems to be particularly increased for lobular breast cancer.

Implications of all the available evidence

As long-term exposure to prolactin-increasing antipsychotics might increase the risk of breast cancer in women with schizophrenia, antipsychotics without prolactin-increasing properties should be considered as a first-line long-term treatment for female patients. When using prolactin-increasing antipsychotics, monitoring prolactin concentrations should be considered, and in case of hyperprolactinemia, a switch to a prolactin-sparing antipsychotic or augmentation with prolactin-reducing agents, such as partial dopamine D2 agonists, should be considered. Mental health professionals should work in close collaboration with primary care prevention services and promote proper cancer screening in women with schizophrenia.

risk of breast cancer in women taking antipsychotics (adjusted hazard ratio 1·16; 95% CI 1·07–1·26).[12] However, since a large proportion of the patients apparently had a diagnosis other than schizophrenia, the antipsychotic exposure was modest (median cumulative defined daily doses [DDDs] was 39, corresponding to 39 days of exposure with typical maintenance dose, and the cutoff for the highest quartile was 145 DDDs during the 6·5-year follow-up). Additionally, prolactin-increasing versus prolactin-sparing antipsychotics were not distinguished. A Danish nationwide case-control study with a long follow-up, varying between 5 and 20 years, included people with high (>5000 DDDs) cumulative antipsychotic exposure, and observed a weak dose-response pattern (adjusted OR of up to 1·27) for prolactin-increasing antipsychotics.[13] However, this study did not account for parity, obesity, and substance misuse, which are considered to possibly have a greater association with breast cancer risk than antipsychotic exposure.[14] Also, the low frequency of exposure (only 0·5% of the cases with breast cancer *vs* 0·4% of the controls had schizophrenia) might have affected the results, and the association might have been driven by the genetic link between schizophrenia and breast cancer.[15] A recent Taiwanese study in a cohort of patients with schizophrenia observed that the risk of breast cancer was higher for risperidone, paliperidone, or sulpiride exposure than for aripiprazole, clozapine, quetiapine, olanzapine, or ziprasidone exposure, but no statistical difference was noted, possibly because of insufficient statistical power.[16] Other cohort studies have not found any substantial risk increase in breast cancer associated with antipsychotic use.[17–19] However, these findings are almost self-evident because of small antipsychotic exposure in these studies given that the highest cutoff of classification for cumulative exposure to any patient subgroup was less than 400 DDDs.[19] This low exposure is probably explained by relatively short follow-up periods, and by the fact that a large proportion of patients used medication for an indication other than schizophrenia.

We aimed to investigate the risk of breast cancer in a nationwide cohort of patients with schizophrenia during a maximum follow-up of over 20 years, adjusting for risk factors, such as diabetes, substance misuse, number of children, and use of other medications affecting the risk of breast cancer. Our hypothesis was that in women with schizophrenia prolactin-sparing antipsychotic (aripiprazole, quetiapine, clozapine) exposure is not associated with an increased risk of breast cancer, and that use of prolactin-increasing antipsychotics (all other antipsychotics) is associated with a cumulative dose-dependent risk of breast cancer.

Methods

Study design and participants

We did a nested case-control study. The study database included all 30 785 women aged 16 years or older diagnosed with schizophrenia during the years 1972–2014 in Finland, and cases were the women who developed breast cancer. People with schizophrenia were identified from the hospital discharge register (the ICD codes F20 and F25 [ICD-10] and 295 [ICD-8 and ICD-9]). Data from the hospital discharge register (all hospital care periods with diagnoses between 1972 and 2017),

prescription register (reimbursed prescription drug purchases between 1995 and 2017), and cancer register (all cancer diagnoses between 1972 and 2017) were collected for this base cohort. All registers were linked by personal identification number, which is assigned to each resident in Finland. Ethnicity data were not collected.

The hospital discharge register includes nationwide data on all inpatient care periods in Finnish hospitals since 1969. Outpatient visits to hospitals have been recorded in this register since 1998. Data cover admission and discharge dates and recorded discharge diagnoses using the various ICD classification systems. ICD-8 was used from 1969 to 1986, ICD-9 from 1987 to 1995, and ICD-10 since 1996. The prescription register includes data on all reimbursed prescription drug purchases from Finnish pharmacies with complete coverage since 1995. Data recorded include date of dispensing, the anatomic therapeutic chemical (ATC) code, name of drug product, strength, package size, the number of packages dispensed, and dispensed amount in DDDs as defined by WHO. Information on prescribed dosing or the indication for prescribing are not available. The cancer registry records all cases of cancer diagnoses since 1953 in Finland. Cancers are reported as ICD-10 codes and by the ICD for Oncology (ICD-O 1–3) for topography and morphology codes.

Cases were defined as women with a first-time diagnosis of invasive breast cancer (after their first diagnosis of schizophrenia) between 2000 and 2017 from cancer register data, and the date of their cancer diagnosis was used as the index date (appendix p 1). All cases had at least 5 years of follow-up for medication use before their index date (the prescription register opened in 1995). To ensure validity of the case definition, only histologically verified cancer diagnoses were included, and age range at diagnosis was set to 18–85 years. Exclusion criteria were any previous cancer diagnosis (except non-melanoma skin cancer, to ascertain incident cancer), receipt of organ transplant, mastectomy, or diagnosis of HIV. Mastectomy was an exclusion criterion because women with mastectomy are likely to have an altered risk of developing the outcome of interest. All exclusion criteria were considered only when recorded before breast cancer diagnosis (or the corresponding matching date for controls). After the exclusions, 1069 (3·5%) of the 30785 women]) were identified as cases. Only five (<0·1%) of 31104 male cases had breast cancer and therefore this group could not be analysed further.

For each case and via incidence density sampling,[20] we selected up to five controls without breast cancer from the study database of 30785 women with schizophrenia. The matching criteria were age (±1 year), time since first schizophrenia diagnosis (±1 year), and not having diagnosis of any cancer before the matching. The same exclusion criteria were applied to controls as for the cases, and controls could become cases later (after >1 year). Date of cancer diagnosis of the case was assigned as the index date for the controls.

Procedures

The main exposure measure was exposure to prolactin-increasing antipsychotics. For this measure, antipsychotics (ATC classification code N05A, excluding lithium [N05AN01]) were categorised as prolactin-increasing or prolactin-sparing, or as antipsychotics with non-conclusive effects (which were rarely used in our cohort; appendix p 2). Categorisation was based on a review of previous evidence.[9,21,22] Prolactin-sparing antipsychotic use was restricted to the time when such antipsychotics were used alone, without concomitant prolactin-increasing antipsychotics (ie, exposure time of prolactin-increasing antipsychotic use in combination with prolactin-sparing antipsychotic use was coded as prolactin-increasing antipsychotic use). However, as aripiprazole is a partial D2 agonist and might suppress prolactin increase in a dose-dependent fashion when used concomitantly with prolactin-increasing antipsychotics,[23,24] sensitivity analyses were done for the prolactin-increasing group by excluding time when aripiprazole was used concomitantly.

Prolactin-increasing and prolactin-sparing antipsychotic use was categorised as cumulative duration in terms of days exposed as up to 1 year, 1–4 years, and 5 or more years. For further assessment of dose-response relationship for cumulative exposure, categories 5–9 years, 10–14 years, and 15 or more years were constructed for the main exposure, and for total duration of antipsychotic use. This procedure was not possible for prolactin-sparing antipsychotics because of a substantially lower number of users and shorter cumulative durations than prolactin-increasing antipsychotics. Secondary exposure measures to cumulative duration of antipsychotic use were the cumulative sum of DDDs for all antipsychotics used by a person, and dose as DDDs per day, which was derived as the cumulative sum of DDDs divided by cumulative duration of use. We a priori selected 500, 1000, 2000, and 5000 cumulative sum of DDD as exposure levels. In clinical terms, 1 DDD corresponds to 5 mg of risperidone.[25] Hence, 500 DDD correspond to taking 5 mg of risperidone daily for 1·37 years, 1000 DDD to 2·74 years, 2000 DDD to 5·48 years, and 5000 DDD to 13·70 years. We included all exposure to antipsychotics since 1995 (when the prescription register was founded) until 1 year before an individual's index date, meaning that exposure within 1 year before the index date was disregarded to reduce the possibility of reverse causality and because recent exposure is unlikely to affect cancer development.[26,27] Sensitivity analyses were done with a 3-year lag window and without any lag. Duration of exposure was derived with the PRE2DUP method.[28] This method is based on mathematical modelling of personal drug purchasing behaviour from drug dispensing

See Online for appendix

recorded in the prescription register. On the basis of individual purchase histories (dates and dispensed amounts) and drug package-specific parameters, the method constructs drug use periods that refer to time periods when the medication use started and ended, and the corresponding number of days exposed. The method takes into account variation in purchase histories caused by events, such as stockpiling, and periods in hospital care when drugs are provided by the caring unit and not recorded in the prescription register. Each ATC code was modelled separately and then these periods were processed to larger categories (prolactin-increasing and prolactin-sparing antipsychotic use periods). During, for example, prolactin-increasing antipsychotic use, a person could have used more than one of the mentioned antipsychotics concomitantly or changed from one drug to another if there was no break in drug availability.

	Controls N=5339	Cases N=1069
Age	62·2 (10·3)	62·2 (10·3)
Age categories		
<55 years	1448 (27·1%)	291 (27·2%)
55–69 years	2643 (49·5%)	530 (49·6%)
≥70 years	1248 (23·4%)	248 (23·2%)
Years since schizophrenia diagnosis	23·7 (10·4)	23·7 (10·4)
Type of cancer		
Ductal adenocarcinoma	NA	780 (73·0%)
Lobular adenocarcinoma	NA	214 (20·0%)
Adenocarcinomas NOS	NA	53 (5·0%)
Carcinoma NOS	NA	17 (1·6%)
Other	NA	5 (0·5%)
Stage of cancer		
Localised	NA	417 (39·0%)
Non-localised	NA	515 (48·2%)
Unknown	NA	137 (12·8%)
Number of children		
0	4438 (83·1%)	903 (84·5%)
1	569 (10·7%)	115 (10·8%)
≥2	332 (6·2%)	51 (4·8%)
Somatic comorbidities		
Cardiovascular disease	1142 (21·4%)	242 (22·6%)
Asthma or chronic obstructive pulmonary disease	227 (4·3%)	44 (4·1%)
Diabetes	1088 (20·4%)	220 (20·6%)
Psychiatric comorbidities		
Suicide attempt	588 (11·0%)	125 (11·7%)
Substance misuse	448 (8·4%)	83 (7·8%)
Medication use		
Beta blockers	1658 (31·1%)	380 (35·5%)
Calcium channel blockers, dihydropyridines	604 (11·3%)	129 (12·1%)
Verapamil	42 (0·8%)	17 (1·6%)
Angiotensin system drugs	1194 (22·4%)	284 (26·6%)
Digoxin	133 (2·5%)	33 (3·1%)
Spironolactone	97 (1·8%)	28 (2·6%)
Statins	1092 (20·5%)	240 (22·5%)
Loop diuretics	658 (12·3%)	141 (13·2%)
Opioids	708 (13·3%)	148 (13·8%)
Paracetamol	1280 (24·0%)	274 (25·6%)
NSAID	3363 (63·0%)	688 (64·4%)
Anticholinergic anti-parkinson drugs	1511 (28·3%)	321 (30·0%)
Tricyclic antidepressants	902 (16·9%)	196 (18·3%)
SSRIs	2034 (38·1%)	433 (40·5%)
Systemic hormone replacement therapy, duration of use		
Non-use	3970 (74·4%)	767 (71·7%)
<1 year	573 (10·7%)	124 (11·6%)
1–4 years	414 (7·8%)	80 (7·5%)
≥5 years	382 (7·2%)	98 (9·2%)

(Table 1 continues on next page)

The following covariates were derived on the basis of hospital discharge and prescription register data, and used for adjustments in the statistical analyses: previous diagnoses of cardiovascular disease, diabetes, asthma or chronic obstructive pulmonary disease, substance misuse, or suicide attempt; number of children; use of drugs potentially modifying the risk of breast cancer (beta blockers, calcium channel blockers as dihydropyridines, verapamil, angiotensin system drugs, digoxin, spironolactone, loop diuretics, statins, non-steroidal anti-inflammatory drugs, opioids, paracetamol, anticholinergic antiparkinson drugs, tricyclic antidepressants, selective serotonin reuptake inhibitors, and hormone replacement therapy [systemic preparations with oestrogen, progesterone, or gestagen and their combinations; duration of cumulative use of these drugs was categorised as non-use, less than 1 year, 1–4 years, and 5 or more years]; appendix p 3). Analyses were also adjusted for prolactin-increasing versus prolactin-sparing antipsychotic use in the same exposure categories as the analysis was made (duration, DDD, dose). Covariates were measured with the same lag as antipsychotic exposure, by disregarding 1 year before the index date in the main analyses (and 3 years and without lag window in the sensitivity analyses).

Statistical analyses and outcomes

The analyses were done with conditional logistic regression because of the matched design (matching group as strata). Multivariate models were adjusted for the factors mentioned previously, and factors used in the matching were controlled for in the design. In all analyses, the reference category in the exposure was less than 1 year of use of that particular exposure category, which included never-users and those who had a duration of use less than 1 year, which was unlikely to affect the risk of breast cancer as there is no evidence from randomised controlled trials lasting up to 12 months of any increased risk of breast cancer. The main analysis was the association between cumulative duration of prolactin-increasing drugs with breast cancer. Several sensitivity analyses were done with different exposure categories (prolactin-sparing antipsychotics, all antipsychotics, prolactin-increasing antipsychotic use

when aripiprazole was not used concomitantly, and mutually exclusive exposure of prolactin-increasing *vs* prolactin-sparing antipsychotics), modes of exposure (cumulative sum of DDDs and dose as DDDs per day), and with or without 3-year lag window.

Sensitivity analyses were also done for the main exposure within subgroups of age at index date (aged younger than 55 years, 55–69 years, or 70 years and older), type of breast cancer (ductal adenocarcinoma, lobular adenocarcinoma, adenocarcinomas not specified, carcinoma not specified, and other, of which only ductal adenocarcinoma and lobular adenocarcinoma could be analysed separately due to low sample size in the other categories), and by clinical stage (localised *vs* non-localised disease).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From our study database, we identified 1069 women diagnosed with breast cancer between Jan 1, 2000, and Dec 31, 2017 (cases), and 5339 matched controls. The mean age of cases and controls was 62 years (SD 10) and the mean time since first diagnosis of schizophrenia was 24 years (SD 10; table 1). The three most commonly used antipsychotics were the same in both groups. Ductal adenocarcinoma was the most common type of cancer (780 [73%] of 1069 cases), followed by lobular adenocarcinoma (214 [20%)] cases). A higher proportion of cases used cardiovascular medications (eg, beta blockers and angiotensin system drugs) and hormone replacement therapy than matched controls.

A higher proportion of cases had used prolactin-increasing antipsychotics for 5 or more years (763 [71·4%] of 1069) than controls (3433 [64·3%] of 5339), resulting in an adjusted OR of 1·56 (95% CI 1·27–1·92, p<0·0001) when compared with minimal (<1 year) exposure to prolactin-increasing antipsychotics. A similar proportion of cases used prolactin-sparing antipsychotics for 5 or more years (89 [8·3%]) as controls (436 [8·2%]), with adjusted OR 1·19 (95% CI 0·90–1·58). Adjusted OR for 5 or more years of any antipsychotic use was 1·74 (1·38–2·21; table 2).

Exposure to prolactin-increasing antipsychotics of 5000 or more DDDs was associated with an increased odds of breast cancer (adjusted OR 1·36 [95% CI 1·09–1·70]) compared with exposure of up to up to 500 DDDs. For exposure to prolactin-sparing antipsychotics, the adjusted OR for exposure to 5000 or more DDDs was not significant (adjusted OR 1·15 [95% CI 0·84–1·58]) compared with exposure of up to 500 DDDs exposure (table 3).

When considering the specific type of breast cancer, 5 or more years of exposure to prolactin-increasing antipsychotics was associated with an increased risk of both lobular and ductal adenocarcinoma. The risk was higher for lobular adenocarcinoma (adjusted OR 2·36 [95% CI 1·46–3·82]) than for ductal adenocarcinoma (adjusted OR 1·42 [1·12–1·80]). No material differences were seen regarding the stage of cancer. Finally, no material difference occurred across age groups (table 4).

	Controls N=5339	Cases N=1069
(Continued from previous page)		
Exposure to antipsychotic drugs*†		
Risperidone	1557 (29·2%)	347 (32·5%)
Perphenazine	1573 (29·5%)	340 (31·8%)
Thioridazine	1426 (26·7%)	286 (26·8%)
Olanzapine	1303 (24·4%)	264 (24·7%)
Levomepromazine	1273 (23·8%)	260 (24·3%)
Chlorprothixene	1088 (20·4%)	237 (22·2%)
Chlorpromazine	765 (14·3%)	190 (17·8%)
Quetiapine	860 (16·1%)	170 (15·9%)
Haloperidol	731 (13·7%)	145 (13·6%)
Clozapine	620 (11·6%)	141 (13·2%)
Zuclopenthixol‡	601 (11·3%)	113 (10·6%)

Data are mean (SD) or n (%). Comorbidities and medication use are measured with 1-year lag window. Exposure to antipsychotics measured is since 1995 and until 1-year lag window. NOS=not otherwise specified. NSAID=non-steroidal anti-inflammatory drugs. SSRI=selective serotonin reuptake inhibitor. *Administered orally unless otherwise indicated. †The same person may have used multiple antipsychotics. ‡Administered as a long-acting injectable.

Table 1: **Characteristics of women with schizophrenia and breast cancer (cases) and women with schizophrenia without breast cancer (controls)**

	Control N=5339	Case N=1069	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*
Duration of any antipsychotic use				
<1 year	917 (17·2%)	131 (12·3%)	..	..
1–4 years	646 (12·1%)	108 (10·1%)	1·16 (0·85–1·58)	1·18 (0·86–1·62)
≥5 years	3776 (70·7)	830 (77·6%)	1·75 (1·39–2·19)	1·74 (1·38–2·21)
Duration of prolactin-increasing antipsychotic use†				
<1 year	1134 (21·2%)	179 (16·7%)	..	..
1–4 years	772 (14·5%)	127 (11·9%)	1·03 (0·79–1·35)	1·04 (0·79–1·36)
≥5 years	3433 (64·3%)	763 (71·4%)	1·53 (1·26–1·86)	1·56 (1·27–1·92)
Duration of prolactin-sparing antipsychotic use‡				
<1 year	4521 (84·7%)	907 (84·8%)	..	..
1–4 years	382 (7·2%)	73 (6·8%)	0·95 (0·73–1·24)	0·95 (0·73–1·25)
≥5 years	436 (8·2%)	89 (8·3%)	1·02 (0·79–1·31)	1·19 (0·90–1·58)

Data are n (%) unless otherwise stated. *Adjusted for: substance misuse, previous suicide attempt, cardiovascular disease, asthma or chronic obstructive pulmonary disease, diabetes; number of children; use of opioids, paracetamol, non-steroidal anti-inflammatory drugs, digoxin, spironolactone, statins, loop diuretics, beta blockers, calcium channel blockers, angiotensin system drugs, anti-parkinson drugs, tricyclic antidepressants, selective serotonin reuptake inhibitors, verapamil; and duration of systemic hormone-replacement therapy use. Prolactin-increasing and prolactin-sparing antipsychotics use analyses additionally adjusted for each other. †When excluding time with concomitant use of aripiprazole, additionally adjusted for aripiprazole use time (with and without concomitant prolactin-increasing antipsychotic use). ‡Without concomitant prolactin-increasing antipsychotic use.

Table 2: **Association between duration of exposure to any antipsychotics, prolactin-increasing antipsychotics, and prolactin-sparing antipsychotics and risk of breast cancer with 1-year lag window for exposure**

	Control, N=5339	Case, N=1069	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Cumulative sum of DDDs of any antipsychotics				
<500	1543 (22·9%)	244 (28·8%)	..	..
500–999	454 (8·5%)	91 (8·5%)	1·27 (0·97–1·66)	1·26 (0·96–1·64)
1000–1999	699 (13·1%)	163 (15·2%)	1·51 (1·21–1·89)	1·50 (1·20–1·88)
2000–4999	1292 (24·2%)	274 (25·6%)	1·40 (1·15–1·71)	1·41 (1·15–1·73)
≥5000	1351 (25·3%)	297 (27·8%)	1·50 (1·22–1·85)	1·48 (1·19–1·84)
Cumulative sum DDDs of prolactin-increasing antipsychotics				
<500	1865 (34·9%)	316 (29·6%)	..	..
500–999	510 (9·6%)	94 (8·8%)	1·27 (0·97–1·66)	1·08 (0·83–1·39)
1000–1999	773 (14·5%)	180 (16·8%)	1·51 (1·21–1·89)	1·39 (1·13–1·71)
2000–4999	1228 (23·0%)	266 (24·9%)	1·40 (1·15–1·71)	1·33 (1·10–1·61)
≥5000	963 (18·0%)	213 (19·9%)	1·37 (1·11–1·68)	1·36 (1·09–1·70)
Cumulative sum DDDs of prolactin-sparing antipsychotics				
<500	4292 (80·4%)	855 (80·0%)	..	..
500–999	171 (3·2%)	30 (2·8%)	0·88 (0·60–1·31)	0·83 (0·56–1·24)
1000–1999	246 (4·6%)	49 (4·6%)	1·01 (0·73–1·39)	0·97 (0·70–1·35)
2000–4999	366 (6·9%)	77 (7·2%)	1·07 (0·82–1·39)	1·04 (0·80–1·37)
≥5000	264 (4·9%)	58 (5·4%)	1·12 (0·82–1·53)	1·15 (0·84–1·58)

Data are n (%) unless otherwise stated. Adjusted for: substance misuse, previous suicide attempt, cardiovascular disease, asthma or chronic obstructive pulmonary disease, diabetes; number of children; use of opioids, paracetamol, non-steroidal anti-inflammatory drugs, digoxin, spironolactone, statins, loop diuretics, beta blockers, calcium channel blockers, angiotensin system drugs, anti-parkinson drugs, tricyclic antidepressants, selective serotonin reuptake inhibitors, verapamil; and duration of systemic hormone-replacement therapy use. Prolactin-increasing and prolactin-sparing antipsychotics use analyses additionally adjusted for each other. DDD=defined daily dose.

Table 3: **Association between cumulative dispensed DDD of any antipsychotics, prolactin-increasing antipsychotics, and prolactin-sparing antipsychotics and risk of breast cancer with 1-year lag window for exposure**

In sensitivity analyses, prolactin-increasing antipsychotic use from 5 to 9 years (adjusted OR 1·56 [95% CI] 1·24–1·97), 10 to 14 years (adjusted OR 1·51 [1·16–1·95]), and 15 or more years (adjusted OR 1·63 [1·22–2·19]) showed similar results (appendix p 4). When prolactin-increasing antipsychotic use duration was restricted to time when concomitant aripiprazole was not used, the results remained similar for 5–9 years (adjusted OR 1·53 [95% CI 1·22–1·93]), 10–14 years (adjusted OR 1·42 [1·11–1·83]), and 15 or more years use (adjusted OR 1·55 [1·19–2·03]).

No major variation was observed in terms of lag window used. Adjusted OR without lag window was 1·59 (95% CI 1·29–1·95), and was 1·48 (adjusted OR [1·20–1·82]) with a 3-year lag for women with 5 or more years of prolactin-increasing antipsychotic use compared with those with less than 1 year of use (appendix p 5). Prolactin-increasing antipsychotic doses of 1·0–1·4 DDDs per day (adjusted OR 1·31 [95% CI 1·03–1·67]) and 1·5 or more DDDs per day (adjusted OR 1·26 [95% CI 1·00–1·59]) were associated with increased odds of breast cancer compared with less than 0·1 DDDs per day use (appendix p 6).

Finally, when considering mutually exclusive exposure to prolactin-increasing and prolactin-sparing antipsychotics, findings of the main analyses were supported (prolactin-increasing antipsychotics, adjusted OR 1·68 [95% CI 1·30–2·18]; prolactin-sparing antipsychotics, adjusted OR 1·57 [95% CI 0·96–2·58]; appendix p 7). When compared with less than 1 year of use, the adjusted OR for 1–4 years of use of prolactin-increasing antipsychotic use was 1·07 (95% CI 0·68–1·71), and 1·56 (95% CI 1·04–2·34) for 5 or more years of use.

Discussion

To our knowledge, this is the first study on risk of breast cancer within a cohort of patients with schizophrenia including a sufficiently high cumulative antipsychotic exposure to assess the putative increased risk of breast cancer related to use of prolactin-increasing antipsychotics. We were able to adjust for number of children, diabetes, substance misuse, and use of other medications that can affect the risk of breast cancer. Our results showed a greater risk for cumulative exposure to prolactin-increasing antipsychotics in women with 5 or more years of exposure than those with less than 1 year, or 1–4 years, of exposure, but no increased risk for exposure to prolactin-sparing antipsychotics (clozapine, quetiapine, and aripiprazole). Exposure to prolactin-increasing drugs for 5 or more years (adjusted OR 1·56) was associated with 56% higher odds of developing breast cancer than shorter exposure, and no significant association was found with cumulative exposure to prolactin-sparing antipsychotics. Conservatively, if we subtract the 19% non-significantly increased odds with prolactin-sparing antipsychotics from the 56% significantly increased odds with prolactin-increasing antipsychotics, we obtain a 37% relative increase in odds. Using a lifetime incidence of breast cancer in women in the general population of about 12%,[1] with a somewhat higher lifetime incidence in patients with schizophrenia than the general population,[2] this difference between prolactin-increasing versus prolactin-sparing antipsychotics in breast cancer risk upon exposure of 5 or more years would correspond to about a 4% (37%×12%) increase in absolute breast cancer odds with prolactin-increasing antipsychotic treatment. We believe this difference can be considered clinically meaningful. Notably, we showed that the risk is particularly increased for both ductal and lobular cancer, but it is higher for lobular cancer than ductal cancer.

This study complements results from a previous cohort study done in Denmark.[13] In that general population-based study of 60 360 women, a weak association between prolactin-increasing antipsychotics and breast cancer risk (adjusted OR 1·18 [1·06–1·32]) was seen, with a weak dose-response pattern, and similar results also for prolactin-sparing antipsychotics (adjusted OR 1·17). Our study was restricted to women with schizophrenia who share similar risk caused by schizophrenia and related lifestyle behaviours, and thus the effect of the illness on the results is minimised. The findings of the Danish study could have been diluted because only 0·5% of the cases had schizophrenia, and the effects of parity, obesity,

and substance misuse could not be adjusted for. Interestingly, in that study oestrogen receptor status was also accounted for, with a significant association emerging only for oestrogen receptor-positive cancers.[13] Oestrogen receptor status is of particular relevance for lobular cancer cells. Hence, the higher odds for lobular cancer than ductal cancer shown in our study might support the findings from the Danish database that indicated a higher risk of oestrogen receptor-positive cancer than oestrogen receptor-negative cancer.[13]

We interpret our findings to suggest that the increased risk of breast cancer associated with prolactin-increasing antipsychotics might be via hyperprolactinemia. In our study, we could not directly consider prolactin concentrations. Although the association between antipsychotics and hyperprolactinemia is established, the evidence so far on the association between prolactin concentrations and breast cancer is inconclusive, despite plausibility.[29] The role of increased prolactin concentrations on bone health is established, as prolactin decreases oestrogen concentrations, and low oestrogen concentrations affect bone health.[30] Hence, international guidelines recommend normalising elevated prolactin concentrations[30] in patients treated with antipsychotics. In addition to selecting prolactin-sparing antipsychotics as otherwise clinically appropriate (aripiprazole, brexpiprazole, cariprazine, lumateperone, quetiapine, or clozapine),[31,32] several strategies are available to reduce prolactin concentrations, mainly treatment with cabergoline or concomitant administration of D2 partial agonists such as aripiprazole (and possibly cariprazine or brexpiprazole, for which no data are available yet).[30,33]

Strengths of this study include the cohort, which was nationwide and included all people diagnosed with schizophrenia in inpatient care over four decades. We were able to assess exposure to prolactin-increasing antipsychotics for over 20 years in some instances. This study has several limitations. First, we were not able to adjust for obesity and smoking status, as no information on body mass index or smoking was available in considered registries. Second, we could not assess the risk by oestrogen-receptor status, again due to an absence of that information in the cancer register. Third, we were not able to assess family history of breast cancer or genetic mutations, which are also an established risk factor for breast cancer. Fourth, we were unable to adjust the analyses for illness severity, oral contraceptive use, and lifestyle factors. However, since the significantly increased cancer risk upon long-term exposure with prolactin-increasing antipsychotics was not observed with prolactin-sparing antipsychotics, of which clozapine was one, illness severity was unlikely a significant remaining confounder. Fifth, we could not analyse risk of breast cancer specifically associated with aripiprazole use because there were not long enough exposure times in our dataset, likely due to aripiprazole's relatively recent introduction into the Finnish market in 2004. Finally, more recent antipsychotics than the ones studied, such as brexpiprazole, cariprazine and lumateperone, were not yet marketed during the study period.

Further studies are needed to replicate these findings in different countries, and to assess the possible confounding role of cancer screening rates and cancer mortality in people prescribed prolactin-increasing antipsychotics, and ideally adjusted for prolactin concentrations, as well as body mass index and smoking, in the analyses.

In conclusion, long-lasting exposure to prolactin-increasing antipsychotics might increase the risk of breast cancer in women in schizophrenia. Therefore, antipsychotics without prolactin-increasing properties

	Control, N=5339	Case, N=1069	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Years of exposure to prolactin-increasing antipsychotics by type of cancer				
Ductal adenocarcinoma	..	..	..	..
<1 year	828/3899 (21·2%)	137/780 (17·6%)	..	..
1–4 years	596/3899 (15·3%)	88/780 (11·3%)	0·87 (0·64–1·18)	0·82 (0·60–1·12)
≥5 years	2475/3899 (63·5%)	555/780 (71·2%)	1·48 (1·18–1·85)	1·42 (1·12–1·80)
Lobular adenocarcinoma	..	..	..	..
<1 year	226/1066 (21·2%)	31/214 (14·5%)	..	..
1–4 years	123/1066 (11·5%)	25/214 (11·7%)	1·52 (0·82–2·81)	2·00 (1·04–3·83)
≥5 years	717/1066 (67·3%)	158/214 (73·8%)	1·72 (1·10–2·70)	2·36 (1·46–3·82)
Years of exposure to prolactin-increasing antipsychotics by stage of cancer				
Localised	..	..	..	..
<1 year	124/681 (18·2%)	20/137 (14·6%)	..	..
1–4 years	73/681 (10·7%)	13/137 (9·5%)	0·83 (0·54–1·29)	0·87 (0·56–1·37)
≥5 years	484/681 (71·1%)	104/137 (75·9%)	1·73 (1·26–2·38)	1·88 (1·34–2·63)
Non-localised	..	..	..	..
<1 year	446/2085 (21·4%)	68/417 (16·3%)	..	..
1–4 years	326/2085 (15·6%)	44/417 (10·6%)	1·19 (0·83–1·72)	1·26 (0·87–1·84)
≥5 years	1313/2085 (63·0%)	305/417 (73·1%)	1·44 (1·09–1·90)	1·51 (1·13–2·02)
Years of exposure to prolactin-increasing antipsychotics by age				
Aged <55 years	..	..	..	..
<1 year	354/1448 (24·4%)	56/291 (19·2%)	..	..
1–4 years	276/1448 (19·1%)	42/291 (14·4%)	0·94 (0·59–1·49)	0·91 (0·57–1·47)
≥5 years	818/1448 (56·5%)	193/291 (66·3%)	1·62 (1·13–2·31)	1·59 (1·08–2·35)
Aged 55–69 years	..	..	..	..
<1 year	493/2643 (18·7%)	78/530 (14·7%)	..	..
1–4 years	301/2643 (11·4%)	55/530 (10·4%)	1·15 (0·78–1·71)	1·15 (0·76–1·72)
≥5 years	1849/2643 (70·0%)	397/530 (74·9%)	1·43 (1·08–1·90)	1·49 (1·10–2·00)
Aged ≥70 years	..	..	..	..
<1 year	287/1248 (23·0%)	45/248 (18·1%)	..	..
1–4 years	195/1248 (15·6%)	30/248 (12·1%)	0·96 (0·55–1·67)	0·98 (0·55–1·74)
≥5 years	766/1248 (61·4%)	173/248 (69·8%)	1·62 (1·07–2·45)	1·69 (1·08–2·64)

Data are n (%) unless otherwise stated. Adjusted for: substance misuse, previous suicide attempt, cardiovascular disease, asthma or chronic obstructive pulmonary disease, diabetes; number of children; use of opioids, paracetamol, non-steroidal anti-inflammatory drugs, digoxin, spironolactone, statins, loop diuretics, beta blockers, calcium channel blockers, angiotensin system drugs, anti-parkinson drugs, tricyclic antidepressants, selective serotonin reuptake inhibitors, verapamil; duration of systemic hormone-replacement therapy use; and prolactin-sparing antipsychotic use.

Table 4: **Association between duration of prolactin-increasing antipsychotic use and risk of breast cancer stratified by type and stage of cancer and age at diagnosis, with 1-year lag window for exposure**

should be considered as a first-line long-term treatment for women with schizophrenia.[31,32] When using prolactin-increasing antipsychotics, baseline and target dose steady-state monitoring of prolactin concentrations should be considered and, in case of hyperprolactinemia, a switch to a prolactin-sparing antipsychotic such as aripiprazole, brexpiprazole, cariprazine, lumateperone, clozapine or quetiapine[22,31,32] or augmentation with prolactin-reducing agents, such as partial D2 agonists or prolactin agonists, should be considered.[30] Finally, mental health professionals should work in close collaboration with primary care prevention services and promote proper cancer screening in women with schizophrenia.[6]

Contributors

HT, JT, MS, and CUC were responsible for the concept. HT, JT, AT, and ML did the analytic design. HT and AT did the data analysis and had access to, and validated, the data. HT and MS wrote the first draft. HT, ML, MS, AT, CUC, and JT interpreted the results. All authors had the final responsibility for the decision to submit for publication.

Declaration of interests

MS has received fees or honoraria from Angelini, Lundbeck. JT, HT, and AT have participated in research projects funded by grants from Janssen-Cilag and Eli Lilly to their employing institution. HT reports personal fees from Janssen-Cilag and Otsuka. JT reports personal fees from Eli Lilly, Janssen-Cilag, Lundbeck, and Otsuka; is a member of an advisory board for Lundbeck, and is a consultant to Orion. ML is a board member of Genomi Solutions and Nursie Health, has received honoraria from Sunovion, Orion Pharma, Lunbdbeck, Otsuka Pharma, and Janssen-Cilag, and research funding from the Finnish Cultural Foundation and the Emil Aaltonen Foundation. CUC has been a consultant or advisor to, or has received honoraria from, AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Axsome, Damitsa, Gedeon Richter, Hikma, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Medscape, Merck, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Servier, Sumitomo Dainippon, Sunovion, Supernus, Takeda, Teva, and Viatris. CUC provided expert testimony for Janssen and Otsuka, served on a data safety monitoring board for Lundbeck, Rovi, Supernus, and Teva, and received grant support from Janssen and Takeda. CUC received royalties from UpToDate and is also a stock option holder of LB Pharma.

Data sharing

Data collected for this study are proprietary of the Finnish government agencies Social Insurance Institution of Finland, National Institute for Health and Welfare, and Finnish cancer registry, which granted researchers permission and access to the data. The data that support findings of this study are available from these authorities, but restrictions apply to the availability of these data. The code used to analyse these data is available upon request from the corresponding author, for purposes of reproducing the results.

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