The use of atypical antipsychotics and the risk of breast cancer

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Abstract

Purpose: To determine whether atypical antipsychotics, when compared to typical antipsychotics, increase the risk of breast cancer.

Methods: We conducted a retrospective cohort study using a nested case-control analysis within the United Kingdom General Practice Research Database population. We identified all female patients prescribed at least one antipsychotic (either typical or atypical), between January 1, 1988 and December 31, 2007, with follow-up until December 31, 2010. All incident cases of breast cancer were identified and matched up to 10 controls. Adjusted rate ratios (RR) of breast cancer associated with ever use of atypical antipsychotics was compared to ever use of typical antipsychotics.

Results: The cohort included 106,362 patients prescribed antipsychotics during the study period. During a mean follow-up of 5.3 years, 1237 patients were diagnosed with breast cancer (overall rate: 2.7 per 1000/year). Compared to patients who only used typical antipsychotics, exclusive users of atypical antipsychotics were not at increased risk of breast cancer (RR: 0.81, 95% CI: 0.63, 1.05). These results remained consistent after considering specific atypical antipsychotics known to significantly increase prolactin levels such as risperidone (RR: 0.86, 95% CI: 0.60, 1.25). Furthermore, no dose-response was observed in terms of cumulative duration of use and cumulative dose in chlorpromazine equivalents.

Conclusion: The results of this study should provide reassurance that compared to typical antipsychotics, atypical antipsychotics do not increase the risk of breast cancer.

Keywords: Antipsychotics; Breast cancer; Population-based

Introduction

Antipsychotics are now playing important role in the treatment of several psychiatric disorders. In fact, there has been a significant increase in their use, particularly for off-label indications [1,2]. Despite their effectiveness, antipsychotics frequently cause side effects, including hyperprolactinemia [3-5]. High serum prolactin levels are associated with menstrual irregularities, galactorrhea, gynecomastia, sexual dysfunction, infertility and decreased bone mineral density [4]. In addition, some evidence suggests that antipsychotics, via their effects on elevating prolactin levels, may increase the risk of breast cancer [6]. This potential risk was known for first-generation (typical) antipsychotics, as these have been shown to increase prolactin levels in a dose-dependent fashion [7]. While second-generation (atypical) antipsychotics have been associated with less extrapyramidal side effects and prolactin elevations [8], there have been renewed concerns that this may not be necessarily the case, especially for some of the newer atypical antipsychotics such as risperdone and amisulpride which have been associated with a high prevalence of severe hyperprolactinemia [4,7,9].

To date, few observational studies have investigated the association between antipsychotics and the incidence of breast cancer. While most of these studies found null effects [10-14], they had a number of methodological limitations. First, many of these studies were conducted in the late 1970s [10,11], a time that preceded the introduction of atypical antipsychotics in the market. Second, some of these studies were not able to distinguish between the effects of the treatment from that of the underlying disease [10,11,13,15]. Patients with chronic psychiatric disorders are followed more closely than the general population, and it is thus possible that any increased risk is partly due to surveillance bias. In one study, a modest association was observed for antipsychotics in relation to breast cancer risk (HR: 1.16, 95% CI:

1.07, 1.26) [15]. However, antipsychotic users were compared to non-users (mainly non-diseased individuals), raising the possibility that confounding by indication or surveillance bias may affected the results. Furthermore, that study did not differentiate between the use of typical versus atypical antipsychotics, and no analysis was undertaken to assess individual antipsychotics, such as risperidone and amisulpride, as these agents significantly elevate prolactin levels [4,7,9].

Given the increasing use of the newer atypical antipsychotics, and lack of data on their long-term safety, more research is needed to determine whether these agents increase the risk of breast cancer. Thus, the objective of this large population-based study was to determine whether atypical antipsychotics, in comparison to typical antipsychotics, increase the risk of breast cancer.

Methods

Data source

This study was conducted using the General Practice Research Database (GPRD), a primary care database from the United Kingdom (UK) [16]. The GPRD is the world's largest computerized database of longitudinal records from primary care. It contains the complete primary care medical record for more than 10.6 million people (corresponding to around 8% of the UK population) enrolled in more than 600 general practices. The geographic distribution of the practices participating in the GPRD has been shown to be representative of the UK population, and age and sex distributions of patients in the GPRD are similar to those reported by the National Population Census [17]. Participating general practitioners have been trained to record medical information including demographic data, medical diagnoses, and procedures

using a standardized form. Prescriptions dispensed by GPRD physicians are automatically transcribed into the computer record. In addition, the GPRD collects information regarding lifestyle variables such as body mass index (BMI), and quantitative and qualitative data pertaining to smoking and excessive alcohol use. The Read classification is used to enter medical diagnoses and procedures, and a coded drug dictionary based on the UK Prescription Pricing Authority Dictionary is used for recording prescriptions. The recorded information on drug exposures and diagnoses has been validated and proven to be of high quality [18-21]. The study protocol was approved by the Independent Scientific Advisory Committee of the GPRD and the Ethics Committee of the Jewish General Hospital.

Study population & study design

We conducted a population-based cohort study and a nested case-control analysis within the GPRD population. The cohort consisted of all female patients who received at least one prescription for any antipsychotic (either typical or atypical), between January 1, 1988 and December 31, 2007, with follow-up until December 31, 2010.

Cohort entry was the date of a first prescription for an antipsychotic (either typical or atypical) during the study period. Patients were required to have at least one year of up-to-standard medical history in the GPRD at the time of their first prescription. To avoid excluding patients with less than one year of medical history in the GPRD, such patients had their cohort entry moved forward in time after being registered at least one year with their general practice. This cohort entry definition led to the inclusion of both incident and prevalent antipsychotic users. These two groups were differentiated by determining whether there was exposure to antipsychotics in the year prior to cohort entry.

The cohort was restricted to patients at least 18 years of age at the time of cohort entry. Patients with a history of breast cancer at any time prior to cohort entry were excluded (identified using the algorithm described below). The latter criterion was necessary to identify incident cases of breast cancer during follow-up. Thus, all patients in the cohort were followed until a first-ever diagnosis of breast cancer, death from any cause, end of registration with the general practice, or end of the study period (December 31, 2010), whichever came first.

Case-control selection

From the cohort of patients described above, we identified all incident cases of breast cancer using a validated computerized algorithm created within the context a previous study on hormone replacement therapy and the risk of breast cancer [22]. This algorithm includes PEGASUS and Read codes for breast cancer as well as combinations of medical procedures, visits, or treatments related to this outcome. These consist of mastectomies, lumpectomies, axillary node dissections, consultations with oncologists, chemotherapy treatments, radiotherapy and use of postoperative antihormone therapy. Over 95% of breast cancer diagnoses identified with this algorithm were confirmed in a previous review of written records of a random sample of 100 cases [22]. The calendar date of each case's event was defined as the index date.

Up to 10 controls were randomly selected from the case's risk set, after matching on year of birth, year of cohort entry, prevalent use of antipsychotics, and duration of follow-up. To avoid excluding cases, we relaxed the matching criteria for 8 cases to year of birth ± 1 year and year of cohort entry ± 1 year. By definition, all controls were alive, never diagnosed with breast cancer, and were registered with their general practice when matched to a given case, and thus

had equal duration of medical history information at the risk set date. The date of the risk set was the index date for the controls.

Exposure to antipsychotics

We considered all antipsychotics on the UK market during the study period. The typical antipsychotics that were considered consisted of benperidol, chlorpromazine, droperidol, flupentixol, fluphenazine, fluspirilene, haloperidol, levomepromazine, loxapine, oxypertine, pericyazine, perphenazine, pimozide, pipotiazine, promazine, sulpiride, thioridazine, trifluoperazine, trifluperidol, and zuclopenthixol. Prochlorperazine, a typical antipsychotic, was not included since it is used as a treatment for migraines, nausea and morning sickness in the UK. However, patients who used prochlorperazine together with another antipsychotic at cohort entry were included in the cohort. The atypical antipsychotics that were considered consisted of amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, remoxipride, risperidone, sertindole, and zotepine.

The primary analysis consisted of comparing patients who were only prescribed atypical antipsychotics to patients only prescribed typical antipsychotics between cohort entry and index date. Thus, the following three mutually exclusive groups were created: *ever exposed* to 1) atypical antipsychotics only; 2) typical antipsychotics only; and 3) both atypical and typical antipsychotics. Patients who were *ever exposed* to typical antipsychotics only served as the reference category.

In a subsequent analysis, we determined whether specific atypical antipsychotics, particularly risperidone (the most frequently prescribed atypical antipsychotic in our population), increased the risk of breast cancer. Therefore, patients *ever exposed* to atypical antipsychotics

only were further categorized into one of the following mutually exclusive categories: 1) risperidone only, 2) risperidone and other atypical antipsychotics, and 3) other atypical antipsychotics.

Finally, we conducted two dose-response analyses among patients *ever exposed* to atypical antipsychotics only: *cumulative duration of use* and *cumulative dose*. *Cumulative duration of use* was calculated by summing the durations of all atypical antipsychotic prescriptions up until the index date for each patient. As for *cumulative dose*, we first converted all atypical antipsychotic prescriptions to olanzapine milligram equivalents [21]. These equivalents were then summed for each patient up until the index date. Both *cumulative duration of use* and *cumulative dose* were entered in tertiles in the models based on the distribution in the controls. For all exposure definitions above, we excluded the year prior to index date to account for a biologically meaningful latency time window.

Antipsychotics with prolactin or warning labels

There are a number of antipsychotics known to increase prolactin levels, as indicated on their warning labels. These consist of amisulpiride, benperidol, chlorpromazine, fluphenazine, haloperidol, olanzapine, perphenazine, pericyazine, pimozide, pipotiazine, risperidone, sulpiride, trifluoperazine and zuclopenthixol. Therefore, it was of interest to determine whether such antipsychotics increased the risk of breast cancer, compared to antipsychotics with no such warning labels. Thus, patients were categorized into one of the following three mutually exclusive groups: *ever use* of 1) antipsychotics with warning labels only, 2) both antipsychotics with and without warning labels, and 3) antipsychotics with no warning labels only. The latter group served as the reference category for this analysis.

Potential confounders

The risk estimates were adjusted for co-morbid clinical conditions and exposures, measured at index date, known to be associated with breast cancer that might also influence the choice of antipsychotic therapy. These consisted of excessive alcohol use, obesity (BMI ≥ 30), smoking status, aspirin use, selective serotonin reuptake inhibitors, statins, previous cancer (other than non-melanoma skin cancer and breast cancer), hypertension, insulin, metformin, other oral hypoglycaemic agents, prior oophorectomy, prior use of hormone replacement therapy (HRT), and prior use of oral contraceptives. Finally, in order to minimize any potential effect of confounding by indication, we adjusted the models for known antipsychotic indications. These consisted of schizophrenia and related disorders, bipolar disorder, other psychotic disorders, dementia, major depression with or without psychotic features, and others.

Statistical analysis

Descriptive statistics were used to summarize the characteristics of the cohort, cases and matched controls. Person-time at risk was measured from cohort entry to time of event or end of follow-up. Conditional logistic regression was used to estimate RRs, along with 95% confidence intervals (CI). In addition to year of birth, year of cohort entry, prevalent antipsychotic use and duration of follow-up on which the logistic regression was conditioned, the models were adjusted for the potential confounders described above.

The primary analysis determined the RR of breast cancer associated with *ever use* of atypical antipsychotics only when compared to *ever use* of typical antipsychotics only. Since our cohort also included prevalent users, we conducted a sensitivity analyses by stratifying cases and matched controls on the prevalent use of antipsychotics prior to cohort entry.

We conducted three secondary analyses among patients ever exposed to atypical antipsychotics, one of which determined whether the risk of breast cancer was increased in patients exposed to risperidone, and two others to evaluate whether the risk increased in a dose-dependent fashion according to *cumulative duration of use* and *cumulative dose*.

We also conducted two exploratory analyses to determine whether breast cancer risk varied between different patient groups. In the first analysis, we assessed whether peri-menopausal status modified the association between atypical antipsychotics and breast cancer. This analysis was performed because several epidemiologic studies have shown an association between serum prolactin levels and breast cancer risk in pre- and peri-menopausal women [24-27]. Thus, we stratified cases and matched controls based on age at cohort entry (≥ 50 versus < 50) as a proxy for menopausal status. In the second analysis, we stratified cases and matched controls based on their history of HRT use, on the grounds that this therapy has been shown to increase prolactin levels [24].

Finally, we conducted another analysis to determine whether patients prescribed antipsychotics (either typical or atypical) with known effects on prolactin levels are at an increased risk compared to patients who did not use such drugs. All analyses were conducted with SAS version 9.2 (SAS Institute, Cary, NC).

Results

Of the 139,863 female patients using antipsychotics during the study period, 106,362 met the inclusion criteria (Figure 1). The mean (SD) age at cohort entry was 63 (21.6) years, and the mean duration of follow-up was 5.3 (4.8) years. At cohort entry, 85,142 (80.0%) were prescribed typical antipsychotics, 20,800 (19.6%) were prescribed atypical antipsychotics, while 430 (0.4%) were using both concomitantly. Of patients prescribed typical antipsychotics at cohort entry, thioridazine (36.4%) was the most frequently prescribed, while risperidone was the most frequently prescribed (47.3%) atypical antipsychotic.

At the time of cohort entry, 20,241 (19.0%) patients were diagnosed with major depression with or without psychotic features, 9646 (9.1%) with dementia, 7472 (7.0%) with psychotic disorders, 5683 (5.3%) with schizophrenia and related disorders, 1689 (1.6%) with bipolar disorder, while 61,641 (58.0%) had other undocumented conditions.

During the 560,661 person-years of follow-up, a total of 1237 patients were diagnosed with breast cancer, yielding an overall rate of 2.7/1000 persons per year (95% CI: 2.5, 2.8). Table 1 presents the characteristics of cases and of the 11,625 matched controls. Compared to controls, cases were more likely to have been diagnosed with cancer (other than non-melanoma skin cancer and breast cancer), have hypertension, and used anti-diabetic agents and HRT, while being less likely to have had an oophorectomy.

Table 2 presents the results of the primary analysis. Overall, exclusive users of atypical antipsychotics were not at an increased risk of breast cancer when compared to exclusive users of typical antipsychotics (adjusted RR: 0.81, 95% CI: 0.63, 1.05). These results did not differ between incident and prevalent users (adjusted RR: 0.87, 95% CI: 0.63, 1.21 and adjusted RR: 0.75, 95% CI: 0.48, 1.17, respectively). When atypical antipsychotic users were further

categorized by drug type, no increased risk was found among those prescribed risperidone (Table 2). With respect to cumulative duration of use and cumulative dosage of atypical antipsychotics, there were no statistically significant associations, although the point estimates were lower than one in the former (Table 3).

The results of the secondary analyses indicated that breast cancer risk did not differ significantly between pre- and post-menopausal patients. Similarly, past use of HRT did not appear to modify the risk, although the adjusted RR for HRT users was higher than for non-users (adjusted RR: 0.99, 95% CI: 0.56, 1.75 and adjusted RR: 0.76, 95% CI: 0.57, 1.03, respectively) (Figure 2). Finally, patients exclusively prescribed antipsychotics known to increase prolactin levels were not an increased risk of breast cancer, compared to those who were not prescribed such drugs (adjusted RR: 1.06, 95% CI: 0.92,1.22).

Discussion

The results of this study indicate that atypical antipsychotics do not increase the risk of breast cancer compared to typical antipsychotics. This finding was strengthened by the lack of any dose-response association, which considered both cumulative duration of use and cumulative dose. Furthermore, no increased risk was observed in high risk groups, such as in post-menopausal women and in those with a history of HRT use. Finally, no increased risk was observed with antipsychotics known to increase prolactin levels, suggesting that these elevations do not translate into an increased breast cancer risk, compared to other antipsychotics.

To our knowledge, this is the first study to investigate whether atypical antipsychotic agents increase the risk of breast cancer. Our study provides reassuring evidence that compared to typical antipsychotics, atypical antipsychotics do not increase this risk in patients exposed for up to 23 years. In fact, although not statistically significant, the point estimates in the different analyses were all under unity, suggesting that atypical antipsychotics, when compared to typical antipsychotics, might be associated with a lower risk of breast cancer. Whether these effects are due to the anti-tumour properties of certain atypical antipsychotics, or by a higher carcinogenicity of typical antipsychotics remains to be determined. Thus, these results need to be confirmed in large, carefully designed studies.

This population-based study has a number of strengths. First, we assembled a large population-based cohort of patients prescribed antipsychotic agents, followed for up to 23 years. Thus, the size and long-term follow-up of the cohort enabled the identification of a significant number of breast cancer cases. Second, because the GPRD uses pre-recorded exposure histories, the possibility of recall bias was eliminated. Third, our exposure and covariates were time-dependent, thus taking into account changes in these variables over time. Finally, the GPRD

database contains information on a number of important confounders, such as BMI, excessive alcohol use, and smoking. Therefore, we were able to adjust for a number of important confounders often absent in administrative databases.

This study does have some limitations. First, drug information in the GPRD represents prescriptions written by general practitioners. As such, it is unknown whether prescriptions were actually filled at the pharmacy. Second, as with any observational study, confounding by indication is always a concern. However, this potential bias was minimized by using a reference group consisting of antipsychotic users. Furthermore, we adjusted the models for the most common indications of antipsychotic use, to further reduce any residual confounding by indication. We were not able to adjust for certain breast cancer risk factors, such as family history of breast cancer, parity, and age at menarche, but it is unlikely however, that these variables were differentially distributed between atypical and typical antipsychotic users, lowering the possibility that these unmeasured variables biased the results. Finally, it is possible that some physicians concerned with the prolactin-elevating potential of atypical antipsychotics preferentially prescribed typical antipsychotics to patients at high risk of breast cancer, which would have diluted the point estimate to the null. Although this is a possibility, it is unlikely as atypical antipsychotics were introduced in the market in the 1990s on the premise that they would be more effective while producing less adverse effects than typical antipsychotics, although this view has been challenged [28,29].

In conclusion, the results of this study indicate that atypical antipsychotics, when compared to typical antipsychotics, do not appear to increase the risk of breast cancer. These results remained consistent after considering duration of use and dose, and different subgroups of

patients at an inherently increased risk of breast cancer. These results should provide reassurance to both physicians and patients on the long-term safety of these agents.

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Conflicts of interest

The authors report no conflicts of interest.

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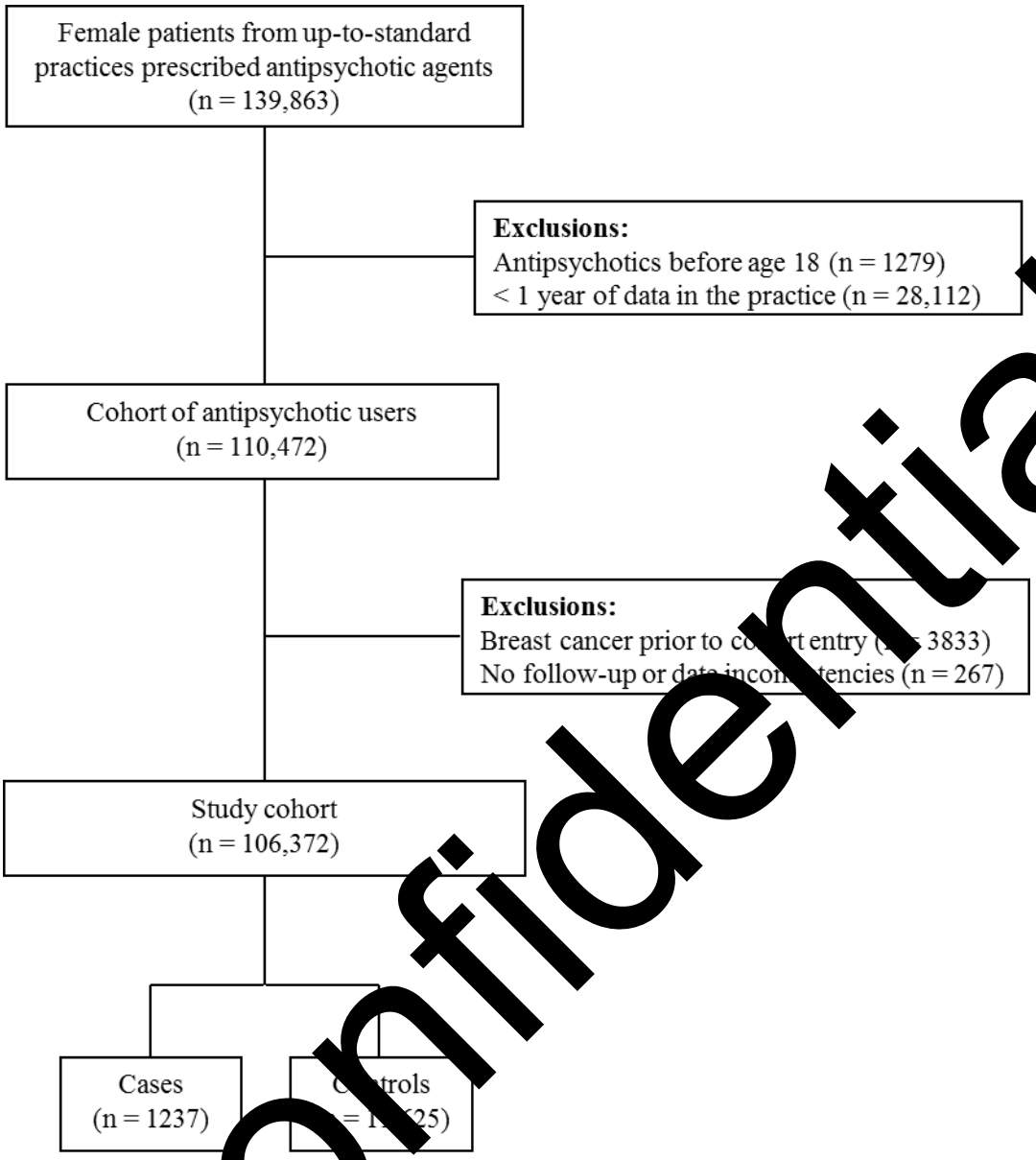

Figure 1. Study flow chart

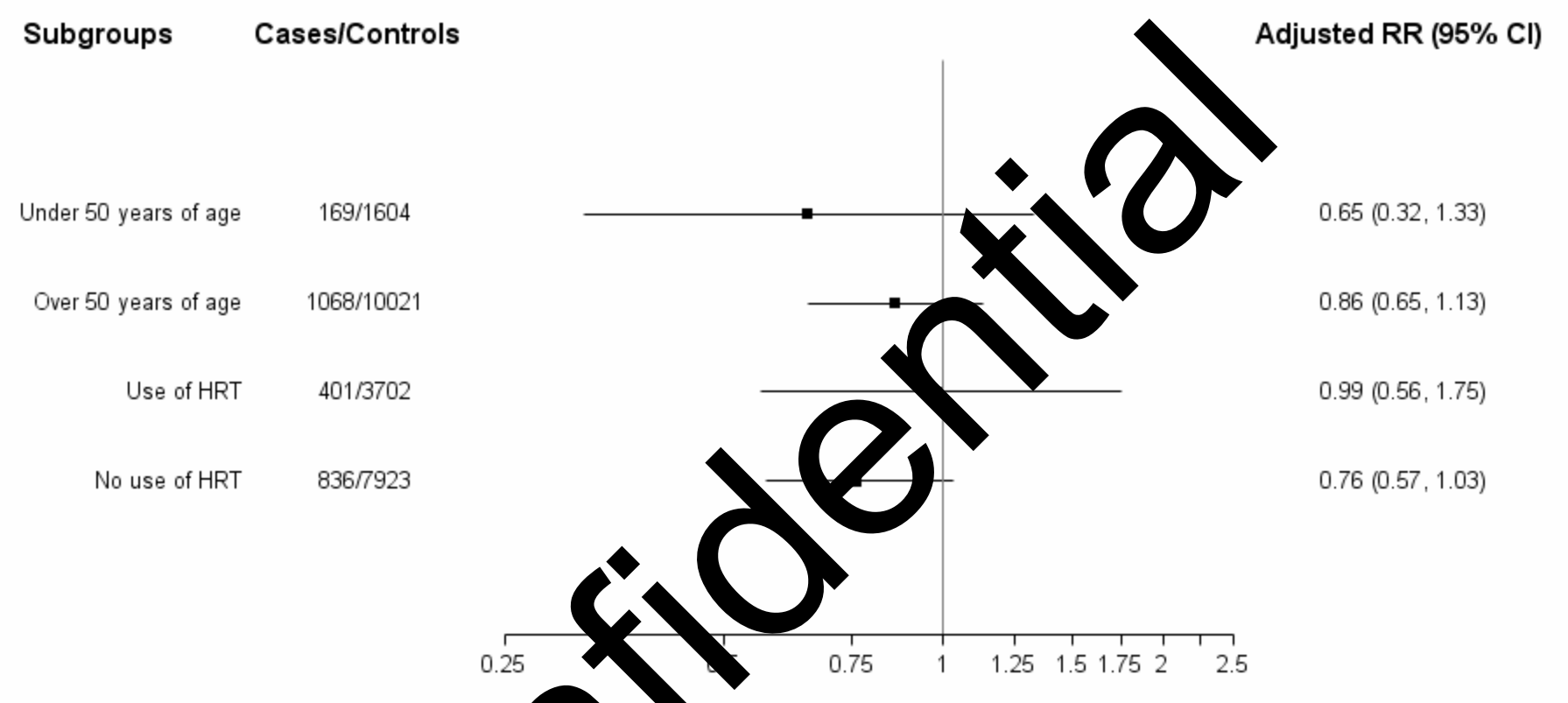

Figure 2. Breast cancer risk associated with atypical antipsychotics across different patient subgroups

Table 1. Characteristics of cases and controls at index date

	Cases (n = 1237)	Controls (n = 11,625)
Age (years), mean (SD)*	66.9 (14.3)	66.8 (14.1)
Duration of follow-up (years), mean (SD)*	7.8 (4.8)	7.8 (4.7)
Excessive alcohol use, n (%)	105 (8.5)	1026 (8.8)
Body mass index, n (%)		
< 30	751 (60.7)	7230 (62.2)
≥ 30	265 (21.4)	2503 (21.5)
Unknown	221 (17.9)	1892 (16.3)
Smoking status, n (%)		
Ever	550 (44.5)	5099 (43.9)
Never	557 (45.0)	5281 (45.4)
Unknown	130 (10.5)	1245 (10.7)
Aspirin, n (%)	326 (26.4)	3110 (26.8)
Selective serotonin reuptake inhibitors, n (%)	616 (49.8)	5808 (50.0)
Statins, n (%)	224 (18.1)	1998 (17.2)
Previous cancer, n (%)	194 (15.7)	1259 (10.8)
Hypertension, n (%)	394 (31.9)	3367 (29.0)
Insulin, n (%)	21 (1.8)	194 (1.7)
Metformin, n (%)	78 (6.3)	588 (5.1)
Other oral hypoglycemic agents, n (%)	97 (7.8)	794 (6.8)
Oophorectomy, n (%)	28 (2.3)	354 (3.0)
Hormone replacement therapy, n (%)	401 (32.4)	3702 (31.8)
Oral Contraceptives, n (%)	146 (11.8)	1386 (11.9)

*Cases and controls matched on these variables

Table 2. Atypical antipsychotics and the risk of breast cancer

	Cases (n = 1237)	Controls (n = 11,625)	Crude RR	Adjusted RR (95% CI)‡
Typical antipsychotics only, n (%)	976 (78.9)	9090 (78.2)	1.00	1.00 (Reference)
Atypical antipsychotics only, n (%)	96 (7.8)	1078 (9.3)	0.82	0.81 (0.63,1.05)
Risperidone only, n (%)	36 (2.9)	386 (3.3)	0.87	0.86 (0.60, 1.25)
Risperidone and other atypical antipsychotics agents, n (%)	44 (3.6)	479 (4.1)	0.83	0.81 (0.58,1.15)
Other atypical antipsychotic agents, n (%)	16 (1.3)	213 (1.8)	0.69	0.68 (0.39,1.19)
Switches between typical and atypical antipsychotics, n (%)	165 (13.3)	1457 (12.5)	1.04	0.99 (0.82,1.20)

‡Adjusted for the variables listed in Table 1.

Table 3. Cumulative duration and cumulative dose of atypical antipsychotics and the risk of breast cancer

	Cases (n = 1237)	Controls (n = 11,625)	Crude RR	Adjusted RR (95% CI)‡
Typical antipsychotics only, n (%)	976 (78.9)	9090 (78.2)	1.00	1.00 (Reference)
Atypical antipsychotics only				
Cumulative duration of use, n (%)*				
≤ 224 days	36 (2.9)	355 (3.1)	0.95	0.95 (0.65, 1.39)
224 – 687 days	30 (2.4)	366 (3.1)	0.74	0.73 (0.48, 1.11)
≥ 687 days	30 (2.4)	357 (3.1)	0.77	0.75 (0.50, 1.13)
Cumulative dose (in olanzapine equivalents), n (%)*				
≤ 910 mg	32 (2.6)	354 (3.0)	0.84	0.85 (0.57, 1.26)
910 – 3965 mg	31 (2.5)	369 (3.2)	0.77	0.76 (0.51, 1.13)
≥ 3965 mg	33 (2.7)	355 (3.1)	0.84	82 (0.56, 1.20)

‡Adjusted for the variables listed in Table 1.
*Based on tertile categories.