Schizophrenia Research xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Risk of breast cancer in risperidone users: A nationwide cohort study

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ARTICLE INFO

Article history:
Received 13 April 2016
Received in revised form 26 October 2016
Accepted 26 October 2016
Available online xxxx

Keywords:
Risperidone
Breast cancer
Cohort study
Antipsychotics
Atypical antipsychotics

ABSTRACT

Background: Several antipsychotics, especially risperidone, are known to increase serum prolactin. Hyperprolactinemia has been linked to the development of mammary gland tumors in animal studies. We therefore investigated the risk of breast cancer in a nationwide cohort of women using risperidone or other antipsychotics.

Methods: All women, 18 years or older, who initiated treatment with risperidone or any other antipsychotic between 2006 and 2012 were identified in Swedish nationwide registers. Patients with two consecutive dispensations of the same antipsychotic within 3 months, no previous cancer diagnosis, and no previous dispensations of paliperidone were included. The final cohort consisted of 55976 women of whom 22908, 24524, and 8544 were exposed to risperidone, other atypical antipsychotics, and typical antipsychotics, respectively. A Cox regression model was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the association between antipsychotics and breast cancer.

Results: Patients were followed prospectively, the mean follow-up time ranging from 2.4 to 2.8 years between treatment groups. After adjusting for age, there was no increased risk for breast cancer among risperidone users compared to patients exposed to another atypical antipsychotic (HR 0.94, 95% CI 0.72–1.22) or a typical antipsychotic (HR 1.25, 95% CI 0.94–1.66). Analyses stratified by tumor stage, using active treatment follow-up time, or including only treatment naïve patients did not reveal any noteworthy change in the results.

Conclusion: Risperidone use does not confer an increased short-term risk of breast cancer compared to other antipsychotic agents.

1. Introduction

Risperidone is a widely used atypical antipsychotic and a potent dopamine antagonist. Its strong *anti*-dopaminergic profile increases the risk of hyperprolactinemia (Haddad and Wieck, 2004), which can cause menstrual irregularities, galactorrhea, gynecomastia, reduced libido, sexual dysfunction, infertility, and decreased bone mineral density (Ajmal et al., 2014; Biller et al., 1992).

Although animal studies show that risperidone induces hyperprolactinemia in rodents and that rodents exposed to risperidone have an increased risk of mammary gland tumors (Harvey, 2005, 2012), results of studies in humans have so far been inconclusive. Two nested case-control studies have indicated a modest association between hyperprolactinemia and subsequent breast cancer, especially in postmenopausal women (Tikk et al., 2014; Tworoger et al., 2013), whereas several other studies have failed to identify any significant association between higher prolactin levels and breast cancer risk (Manjer et al., 2003; Helzlsouer et al., 1994; Kabuto et al., 2000; Wang et al., 1992). As for the role of antipsychotics, a large retrospective study of > 100,000 US women found that previous use of antipsychotics was associated with a 16% increased risk of breast cancer (Wang et al., 2002). However, a recent review article looking into the potential risks with psychotropic medication in breast cancer patients concluded that the current data on prolactin and breast cancer are insufficient to deprive patients potentially effective treatment for psychiatric conditions and that further research is needed to clarify the relation between hyperprolactinemia caused by psychiatric medication and the risk of breast cancer (Froes Brandao et al., 2016).

We conducted a nationwide cohort study using data from national population based registers in Sweden to assess the association between risperidone use and development of breast cancer in women.

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http://dx.doi.org/10.1016/j.schres.2016.10.035
0920-9964/

2. Methods

2.1. Data sources

Eligible patients were identified in the Prescribed Drug Register, to which all prescription drugs dispensed by Swedish pharmacies have been reported since July 1, 2005 (Wettermark et al., 2007). The register holds information on the name of the dispensed drug, its classification code according to the World Health Organization Anatomical Therapeutic Chemical System (ATC), prescribed dose, amount, and date of dispensing. In addition, each dispensing can be linked to an individual through the unique personal registration number assigned to all Swedish residents at birth or immigration. We then collected information on breast cancer diagnoses and other cancer diagnoses for all eligible patients from the Swedish Cancer Registry. All cancers in Sweden have been mandatorily reported to this register upon detection since 1958, including information on the primary site of the tumor, its malignancy, histology, stage, and the date of diagnosis (Mattsson and Rutqvist, 1985).

Data on psychiatric diagnoses and somatic comorbidities were obtained from the Swedish National Patient Register. This register includes information on all hospitalizations and outpatient visits in specialized care in Sweden since 1964, with full national coverage of inpatient care and specialized outpatient care since 1987 and 2001, respectively (Ludvigsson et al., 2011). Recorded information includes hospital admission and discharge dates and registered discharge diagnoses according to the International Classification of Diseases (ICD, 7th edition for 1964–1967, 8th edition for 1968–1986, 9th edition for 1987–1996, and 10th edition afterwards) system. We further obtained information on deaths and migration from the Causes of Death Register and the Register of Population and Population Changes. In addition, we collected information on child birth and parity from The Swedish Multi-Generation Register.

2.2. Study population

We identified all women, 18 years or older, who had filled a first prescription of risperidone or any other antipsychotic between 2006 and 2012. All patients with two recorded consecutive dispensations of the same antipsychotic within 3 months, no history of malignancy (other than non-melanoma skin cancer) prior to the start of follow-up, and no recorded dispensations of paliperidone (Park et al., 2016) were included in the study.

2.3. Exposure and follow-up time

Patients were classified as exposed to 1) risperidone, 2) any other atypical antipsychotic, or 3) a typical antipsychotic, depending on the two recorded consecutive dispensations. Patients had to be new users of risperidone, another atypical antipsychotic, or a typical antipsychotic, defined as having no recorded dispensations of that specific drug within 6 months prior to the first prescription fill during the study period. Exposure group assignments were made in the following hierarchical order: women with dispensations of antipsychotics during the study period were assessed for eligibility to be included in the risperidone cohort. If not eligible due to no dispensations of risperidone or due to failing other eligibility criteria, women with dispensations of any other atypical antipsychotic drug were assessed for eligibility to be included in the other atypical antipsychotic cohort. If not eligible, remaining women were assessed for eligibility to be included in the typical antipsychotic cohort. While risperidone users were allowed to have a prior exposure to other atypical or typical antipsychotic drugs, patients in the other atypical antipsychotic group were not allowed to have any prior risperidone use, and typical antipsychotic drug users were not allowed to have any prior atypical antipsychotic drug (including risperidone) use. Patients were considered treatment naïve if they had no recorded prescription fill for any antipsychotic in the 6-months prior to the first dispensation of the antipsychotic under study.

Follow-up time was calculated in two different ways for each patient: 1) total cohort follow-up time and 2) active treatment follow-up time. The total cohort follow-up time extended from 365 days following the exposure index date (the second dispensation of an antipsychotic during the study period) until occurrence of breast cancer (ICD-9 code 174 and ICD-10 code C50), emigration, death, or the end of the study period (December 31, 2012), whichever occurred first. The active treatment follow-up time extended from 365 days following the second dispensation of an antipsychotic after which the patients were included until discontinuation of the treatment regimen + 1 year, occurrence of breast cancer, emigration, death, or the end of the study period, whichever occurred first. A gap of 1 year or more between two consecutive dispensations was considered as discontinuation of active treatment, the date for treatment discontinuation being defined as the date of the last dispensation plus days of drug supply.

2.4. Statistical analysis

Overall and stage-specific incidence rates of breast cancer were estimated for each of the three exposure groups. Rates were calculated based on the total cohort follow-up time and active treatment follow-up time, respectively, and reported as number of cases per 100,000 person-years. The stage of the tumor was categorized into three groups: stage 0–1, 2, and 3–4 (Edge and Carlson, 2011).

We used Cox proportional hazards regression models to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between each of the studied exposures and breast cancer. Possible confounding factors, including age, parity, clinic of the prescriber, hospitalizations due to psychiatric or somatic disorders, comorbidities and comedications, were assessed by introducing the covariates in the crude model, one by one. Our a priori decision was that covariates would be retained in the final adjusted model only if the covariate in question changed the HR for the antipsychotic exposure variable by 10% or more, compared with the unadjusted HR for the same exposure (ie, adjusted HR/unadjusted HR is either >1.10 or <0.90). In total, we assessed 23 potential confounding variables of which only age changed the HR for any antipsychotic exposure by 10% or more, and thus was included in the final adjusted model (Supplement A). The proportional hazards assumption was investigated using a proportionality test and "log(-log(survival)) versus log of survival time" plots. In addition, graphical assessment of time trends was conducted by "log(-log(survival) versus log of survival time" plots, scaled Schoenfeld residual plots, and Kaplan-Meier survival curves. The analyses confirmed that the proportional hazard assumption was met when data was stratified by category of age (18–49, 50–59, 60–69, 70–79, and ≥80 years).

2.5. Ethics

The study was approved by the regional ethical review board in Stockholm.

3. Results

Information on eligible and excluded patients is shown in Fig. 1. The final study cohort included a total of 55,976 women, of whom 22,908 were exposed to risperidone, 24,524 were exposed to another atypical antipsychotic, and 8544 were exposed to a typical antipsychotic. Patients were followed for up to 6 years with a mean follow-up time ranging from 2.4 years in the risperidone group to 2.8 years in the typical antipsychotics group.

Table 1 shows baseline characteristics of the patients in each treatment group. Mean age at treatment initiation differed considerably between the groups, ranging from 46.2 years (SD = 18.1) for new users of atypical antipsychotics other than risperidone to 71.3 years (SD = 20.9)

Please cite this article as: Reutfors, J., et al., Risk of breast cancer in risperidone users: A nationwide cohort study, Schizophr. Res. (2016), http://dx.doi.org/10.1016/j.schres.2016.10.035