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Female schizophrenia patients and risk of breast cancer: A population-based cohort study

Ana Isabel Wu Chou [a], Yu-Chiao Wang [b,c], Cheng-Li Lin [b,c], Chia-Hung Kao [d,e,f,*]

[a] Department of Psychiatry, Wan-Fang Hospital, Taipei Medical University, Taipei, Taiwan
[b] Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan
[c] College of Medicine, China Medical University, Taichung, Taiwan
[d] Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan
[e] Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan
[f] Department of Bioinformatics and Medical Engineering, Asia University, Taichung, Taiwan

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ABSTRACT

Objective: Breast cancer is the most common type of cancer in women. This population-based cohort study aimed to examine the association between breast cancer in female schizophrenia patients and its association with the use of antipsychotics drugs.

Methods: All study subjects were selected from the Taiwan Insurance Claims Data (1998–2008). We compared the risk for breast cancer between female schizophrenia patients receiving antipsychotics ($n = 29{,}641$) with female patients without any serious mental illnesses nor receiving antipsychotic drugs ($n = 59{,}282$). We also compared between patients on 1) first-generation antipsychotics (FGAs) alone; 2) combination of first and second generation antipsychotics (SGAs); and 3) SGAs alone. We then stratified those on SGAs into two subgroups according to their prolactin-elevating properties: risperidone (RIS), paliperidone (PAL) or amisulpride (AMI) and all other SGAs.

Results: After adjusting for confounding factors, the risk of breast cancer in female schizophrenia patients was 1.94 higher than the non-schizophrenia cohort (aHR: 1.94, 95% CI: 1.43–2.63). Schizophrenia patients receiving a combination of FGAs and SGAs had a slightly higher risk of breast cancer than non-schizophrenic patients (aHR: 2.17, 95% CI: 1.56–3.01). Patients on RIS, PAL, and AMI had a 1.96-fold risk of breast cancer compared to the non-schizophrenic cohort (95% CI: 1.36–2.82).

Conclusions: This study raises awareness among both clinicians and patients about the importance of breast cancer screening and the promotion of healthy lifestyle choices. Due to the nature of our database, confounding factors – such as parity, obesity, hormone therapy, and smoking - could not be controlled for.

1. Introduction

Schizophrenia patients have a life expectancy of 15–20 years shorter than the general population (Hennekens et al., 2005) despite advances in modern medicine to improve mental health care. In order to decrease mortality rates in schizophrenia patients, many treatment guidelines in recent years have recommended the monitoring of cardiovascular and metabolic health (Lehman et al., 2004; Taylor et al., 2015) whereas comparatively, no clear recommendations have been given for the screening of cancer. Breast cancer in particular, is the most common type of cancer in women around the world, with a lifetime risk of 1 in 9 women in the general population. Since women with schizophrenia have higher prevalence of well-known breast cancer risk factors, such as unhealthy lifestyle behaviors (McCreadie et al., 1998), obesity (Coodin, 2001), diabetes mellitus (DM) (Bai et al., 2013) and lower number of parity (Power et al., 2013), they may be more prone to developing breast cancer than the general population. But study results across the literature are conflicting. Some studies have found an increased risk (Ji et al., 2013; Catalá-López et al., 2014), while others found either a non-statistically significant increase or a decreased risk (Chou et al., 2011). In an 11-year prospective study, Tram et al. showed that breast cancer was the most common type of cancer among female schizophrenia patients and that it carried higher standardized mortality rates (SMR) than the

Abbreviations: PRL, prolactin; HTN, hypertension; DM, diabetes mellitus; NHI, National Health Insurance; ICD-9-CM, International Classification of Diseases Ninth Revision Clinical Modification; NHIRD, National Health Insurance Research Database; LHID2000, Longitudinal Health Insurance Database 2000; RCIPD, Registry for Catastrophic Illness Patient Database released by the National Health.

* Corresponding author at: Graduate Institute of Clinical Medicine Science and School of Medicine, College of Medicine, China Medical University, No. 2, Yuh-Deh Road, Taichung 404, Taiwan.
E-mail address: d10040@mail.cmuh.org.tw (C.-H. Kao).

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general population (Tran et al., 2009). This study aimed to investigate the association of breast cancer and schizophrenia patients in Han Chinese women.

2. Materials and methods

2.1. Data sources

The National Health Insurance (NHI) program has been implemented in Taiwan since 1995 and covers >99% of the Taiwanese population. We used two databases from the Health Insurance Research Database (NHIRD) between the years 1997 and 2011: the Longitudinal Health Insurance Database 2000 (LHID2000) and the Registry for Catastrophic Illness Patient Database (RCIPD) released by the National Health Research Institutes (NHRI). Patients with severe mental illness and cancer are eligible for the application of a catastrophic illness. These include our study subjects: schizophrenia patients and patients of breast cancer. The LHID2000 was a database containing the claims data for one million people randomly sampled from 2000 NHIRD enrollment records. To safeguard the confidentiality of the insured patients, scrambled identification numbers were used to link datasets. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH104-REC2-115). The IRB also specifically waived the consent requirement.

2.2. Study subjects

Fig. 1 shows the procedure of selecting study subjects, from two data sets of the NHIRD. Diagnoses associated with medical service were coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). We identified female schizophrenia patients who had newly diagnosed schizophrenia (ICD-9-CM: 295) and been prescribed antipsychotic medications between the years 1998 and 2008. The schizophrenia patients were divided into three groups based on their antipsychotic prescription: a first-generation sub-cohort for patients taking only FGAs, a second-generation sub-cohort for patients taking only SGAs, and a FGA/SGA sub-cohort for those taking a combination of both FGAs and SGAs. The index date was defined as the time they were first diagnosed with schizophrenia. The comparison subjects were selected from women without mental illnesses (ICD-9CM: 290–319) and had not used antipsychotic drugs, using the ratio of 1:1 matching on a propensity score (Parsons, 2001). The propensity score was calculated by a logistic regression to estimate the probability of the disease status given the baseline variables including age, occupation, monthly income, medications and comorbidities listed in Table 1. In both cohorts, we excluded subjects who had breast cancer (ICD-9-CM: 174) before the index date and follow-up time of one year. The follow-up person-years at the end of 2011 was calculated for each subject until they received a diagnosis of breast cancer, or withdrew from the insurance system, either due to death or loss to follow-up.

2.3. Statistical analysis

The standardized difference was used to quantify differences in mean or prevalence between the schizophrenia and non-schizophrenia cohorts for all variables, respectively (Austin, 2009). A value of standardized mean differences equals 0.01 or less, which indicates a negligible difference in means between schizophrenia and non-schizophrenia cohorts. The breast cancer incidence was estimated and stratified by antipsychotic drug types, age, occupation, income, comorbidity and medication for both cohorts. The crude hazard ratios (cHRs) and adjusted hazard ratios (aHRs) of breast cancer in the schizophrenia and non-schizophrenia cohorts were measured for these variables by using Cox proportional hazards model analysis. Multivariable model was controlled for, age, occupation, monthly income, comorbidities and four types of medication (including lithium, valproate sodium, antidepressants, and anxiolytics and hypnotics) for adjustment. The FGA and SGA exposure histories of schizophrenia patients were measured according to categorized exposure dose (none, <306, 306–2575, or ≥2575 g/year; <28, 28–245, or ≥245 g/year) based on tertile method, to estimate the dose-response relationship between the antipsychotic drug levels and the risk of breast cancer. Statistical significance was considered set at 0.05 and *p*-values are two-sided. All analyses were performed using SAS statistical software (version 9.4 for Windows; SAS Institute, Inc., Cary, NC, USA).

3. Results

The distribution of demographic characteristics, mental illness medication states and comorbid conditions between the schizophrenia and non-schizophrenia cohorts are similar as shown in Table 1. The mean ages in the schizophrenia cohort and the non-schizophrenia cohort were 41.4 (SD = 14.3) and 42.0 (SD = 15.3) years, respectively. Most schizophrenic patients were working white-collar jobs (45.6% compared to 34.2% blue collar and 20.3% others) but it is less likely compared to non-schizophrenic patients with 44.2% working white collar jobs. Both cohorts have less low income (53.7% vs. 53.9%). The major

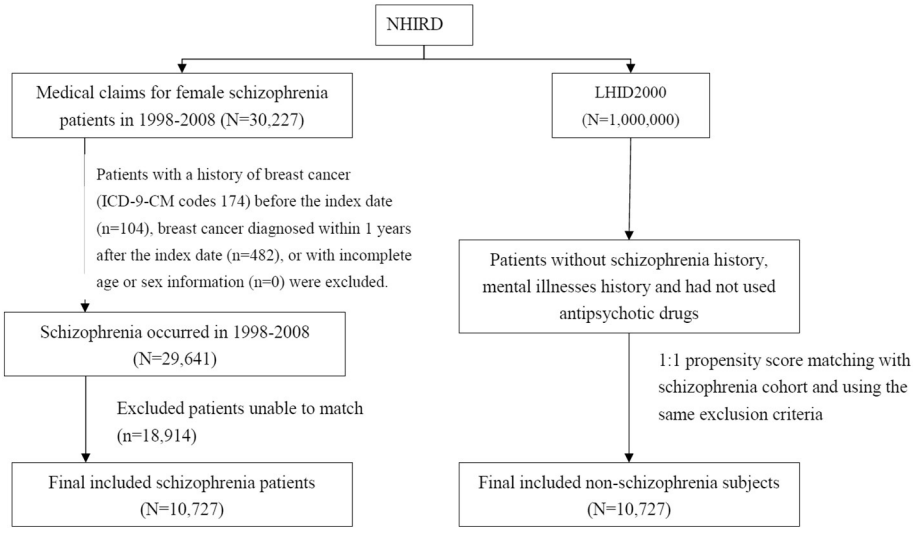

Fig. 1. The procedure of selecting study subjects, from two data sets of the NHIRD.

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