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Research report

Adjuvant treatments of breast cancer increase the risk of depressive disorders: A population-based study

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ABSTRACT

Background: Previous studies have posited conflicting results regarding depressive disorders among breast cancer survivors who received adjuvant therapies including chemotherapy, radiotherapy, selective estrogen receptor modulator (e.g. tamoxifen), third-generation aromatase inhibitors (AIs; e.g. anastrozole, letrozole or exemestane), and monoclonal antibody (e.g. trastuzumab). We therefore performed a population-based study with a defined breast cancer cohort to investigate the risk of depressive disorders in breast cancer patients who received adjuvant therapies.

Methods: We conducted a retrospective study of a breast cancer cohort of 36,586 participants who were selected from the National Health Insurance Research Database(NHIRD) in Taiwan. Patients were observed for a maximum of 6 years to determine the incidences of newly onset depressive disorders. Kaplan–Meier and Cox regression analyses were used to identify the risk factors associated with depressive disorders in breast cancer patients who underwent adjuvant therapies

Results: Of the total 36,586 patients, 1342 (3.7%) were ascertained with depressive disorders. The Cox multivariate proportional hazards analysis showed that age of 40–59 (adjusted hazard ratio (aHR) 1.327, 95% CI 1.123–1.567, $p=0.001$), chemotherapy (aHR 1.555, 95% CI 1.387–1.743, $p<0.001$), radiotherapy (aHR 1.385 95% CI 1.220–1.571, $p<0.001$), tamoxifen (aHR 1.458, 95% CI 1.110–1.914, $p=0.007$), AIs (aHR 1.360, 95% CI 1.193–1.550, $p<0.001$), and trastuzumab (aHR 1.458, 95% CI 1.110–1.914, $p=0.007$) were independent risk factors for developing depressive disorders.

Limitations: The dosage effect of adjuvant treatments, cancer staging, genetic or environmental confounders associated with the risk of depressive disorders were not comprehensively evaluated.

Conclusion: Developing depressive disorders are at higher risk in breast cancer survivors aged 40–59 who received adjuvant treatments including chemotherapy, radiotherapy, tamoxifen, AIs or trastuzumab. Psychological evaluation and support are necessarily needed in breast cancer survivors who received adjuvant therapies.

1. Introduction

Breast cancer is the most prevalent malignancy in women worldwide and the most common cause of death from cancer (Benson et al., 2009; DeSantis et al., 2014). In recent years, 5 years survival rates have increased to the extent about 77.5–90.3% survive (DeSantis et al., 2011), which can be resulted from successful early screening or detection interventions (Warner, 2011), surgery, and adjuvant treatments including chemotherapy (Berry et al., 2005), radiotherapy (Buchholz, 2009), selective estrogen receptor modulator (e.g. tamoxifen) (Early Breast Cancer Trialists' Collaborative Group et al., 2011), third-generation aromatase inhibitors (AIs; e.g. anastrozole, letrozole or exemestane), or monoclonal antibody (e.g. trastuzumab) (Benson et al., 2009; Hudis, 2007).

Depressive disorder (DD) is characterized by sadness or irritability and accompanied by at least several psychophysiological changes (Belmaker and Agam, 2008). DD is a widespread chronic disease and associated with substantial mortality, comorbidities,

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and disabilities (Kessler et al., 2003; Lepine and Briley, 2011). Previous studies have reported that there existed an increased risk of depression among breast cancer survivors (Aukst-Margetic et al., 2005; Burgess et al., 2005; Christensen et al., 2009; Hopwood et al., 1991; Hung et al., 2013). However, breast cancer patients receive different adjuvant regimens according to factors like menopause or age (Benson et al., 2009). No studies investigate the incidence of depressive disorders in different age group.

Moreover, adjuvant treatments including chemotherapy (Hwang et al., 2013; van Dam et al., 1998), radiotherapy (Hess and Chen, 2014), and tamoxifen (Breuer and Anderson, 2000; Cathcart et al., 1993; McMichael et al., 2013; Thompson et al., 1999) have been reported to have association with depression in breast cancer survivors, but other studies show conflict results (Day et al., 2001; Day et al., 1999; Lee et al., 2007; Schilder et al., 2009). Besides, AIs (Coombes et al., 2007; Goss et al., 2011; Pagani et al., 2014) have been found depression during treatment, but these trials were not designed to address risk of depressive disorders among breast cancer patients. Furthermore, trastuzumab, a new adjuvant therapy, has not been evaluated the risk of depressive disorder before.

This study was aimed to investigate the risk of depressive disorders among breast cancer survivors who received adjuvant treatments by using the population-based retrospective database which was retrieved from the National Health Insurance Research Database (NHIRD) in Taiwan.

2. Methods

2.1. Data

The National Health Insurance (NHI) program was launched by the Taiwan government in 1995 and provides comprehensive health care for 98.29% of its citizens in 2006 (Cheng et al., 2011). The NHI research database (NHIRD) contains comprehensive information including outpatient, inpatient, prescription drugs, and traditional Chinese medicine services. The diagnostic and procedure codes are based on the International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) and Procedure Coding System (ICD-9-PCS). This study retrieved the breast cancer (ICD-9-CM: 174.XX) outpatient and inpatient care database to define the study cohort of breast cancer survivors from January 1 2000 to December 31 2007 ($n=36,586$).

2.2. Ethics statement

The Institutional Review Board of the China Medical University Hospital approved this study (CMUH103-REC3-077). Due to the nature of secondary data analysis, all information potentially identifying any individual patient was encrypted, written consent from study patients was not obtained. The Bureau of NHI and Institutional Review Board of China Medical University Hospital guarantee the data regulations of the patients' confidentiality.

2.3. Study population

We identified adult women (age ≥ 20 years old) with a primary diagnosis of breast cancer (ICD-9-CM code = 174.XX) for the first time between January 1, 2002, and December 31, 2007 from NHIRD. We excluded subjects diagnosed with depressive disorders (ICD-9-CM code: 296.2X-296.3X, 300.4, and 311.X) (Chen et al., 2014), bipolar disorders (ICD-9-CM code: 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8, 296.80, and 296.89) (Hu et al., 2013), or alcohol-use disorders (ICD-9-CM codes: V113, 9800, 2650, 2651, 3575, 4255, 3050, 291, 303, and 571.0–571.3) (Hu et al., 2013) before enrollment and excluded death or withdrawal from the NHI system during the study period. All patients who survived from January 1 2002 to December 31 2007 with breast cancer were observed to investigate if they were diagnosed with depressive disorders according to ICD-9-CM codes (ICD-9-CM code: 296.2X-296.3X, 300.4, and 311.XX).

2.4. Covariate assessment

We identified adjuvant therapies including chemotherapy, radiotherapy, tamoxifen, AIs, and trastuzumab. Patients who received chemotherapy (ICD-9-PCS code: V581 and 992.5), or radiotherapy (ICD-9-PCS code: 922 and V580) were identified based on diagnostic and procedure codes. Tamoxifen, AIs including anastrozole, letrozole or exemestane, and trastuzumab prescribed to the study cohort for each patient were calculated (Hsieh et al., 2014). Comorbidity diseases were assessed using the Charlson Comorbidity Index (CCI) (Charlson et al., 1987).

2.5. Statistical analysis

Descriptive statistics were used to investigate demographic characteristics, disease- and treatment-related characteristics, and depressive disorders. To identify the risk factors of treatment options associated with depressive disorders, the patients were divided into two groups, subjects with depressive disorders and subjects without depressive disorders. Cox regression was used to identify factors associated with depressive disorders or non-depressive disorders (dependent variable). Independent variables included surgery, chemotherapy, radiotherapy, tomaxifen, AIs, and trastuzumab. Regarding database processing, MY Structured Query Language (MySQL) was used for extraction, linkage, and processing of the data. All statistical analyses were performed using IBM SPSS statistical software (version 20.0 for Windows; IBM Corp., New York, NY, USA). The two-tailed p-value < 0.05 was considered to be statistically significant (Fig. 1).

3. Results

3.1. Clinical characteristics of the study population

From January 1 2002 to December 31 2007, a total of 36,586 breast cancer survivors were enrolled. The mean age at enrollment was 52.1 ± 11.8 years, and the mean follow up period was 2.7 ± 1.7 years. The most common adjuvant treatments were tamoxifen (63.0%), and chemotherapy (45.8%). The most common underlying diseases were hypertension (19.3%), and diabetes (11.1%) (Table 1). The comparisons of the treatments and clinical variables between the breast cancer patients without depressive disorders and with depressive disorders are presented in Table 2.

3.2. Incidence rate of depressive disorders

During the study period, 1342 patients (3.67%) were diagnosed with depressive disorders. Among those who developed depressive disorder, 164 (12.2%) were 20–39 years of age, 946 (70.5%) 40–59 years of age, 224 (16.7%) 60–79 years of age, and 8 (0.6%) ≥ 80 years of age (Table 2). Kaplan–Meier estimates of the cumulative incidence of depressive disorders in the breast cancer patients at four age groups are shown in Fig. 2. The cumulative incidence of depressive disorders was significantly highest for 40–59 years of age ($p < 0.05$).