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Association between depressive disorders and risk of breast cancer recurrence after curative surgery

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Abstract

The aim of the study was to investigate the association between depressive disorders and risk of tumor recurrence in patients with breast cancer after curative surgery.

A nationwide cohort study between January 2001 and December 2007 was conducted. Data were taken from the Taiwan National Health Insurance Research Database. Among 30,659 newly diagnosed breast cancer patients, we identified 1147 breast cancer patients with depressive disorders and 2294 matched breast cancer patients without depressive disorders, both of whom received curative breast surgery between January 2003 and December 2007.

The risk of first tumor recurrence was compared between patients who developed depressive disorders after breast surgery (depressive disorder cohort, n = 1147) and matched patients who did not develop depressive disorders (matched nondepressive disorder cohort, n = 2294). Cumulative incidences and hazard ratios (HRs) were calculated after adjusting for competing mortality.

The depressive disorder cohort had a higher rate of recurrence when compared with the matched nondepressive disorder cohort (17.1% vs 12.5%; $P < .001$). The Kaplan–Meier analysis revealed a predisposition of patients with depressive disorders to suffer from recurrence (log-rank test, $P < .001$). After multivariate adjustment, the HR for subsequent recurrence among the depressive disorder cohort was 1.373 (95% confidence interval 1.098–1.716, $P = 0.005$). Moreover, the depressive disorder cohort had higher risk of overall mortality even though not significant after adjusted (adjusted HR 1.271, 95% confidence interval 0.930–1.737, $P = 0.132$).

Depressive disorder was associated with a higher risk of breast cancer recurrence among patients after curative breast surgery.

Abbreviations: AIs = aromatase inhibitors, CCI = Charlson Comorbidity Index, CI = confidence interval, DD = depressive disorder, HPA = hypothalamic-pituitary-adrenal, HR = hazard ratio, ICD-9-CM = International Classification of Disease, 9th Revision, Clinical Modification, ICD-9-PCS = International Classification of Disease, 9th Revision, Procedure Coding System, MySQL = MY Structured Query Language, NDRIs = norepinephrine and dopamine reuptake inhibitors, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institute, SARIs = serotonin receptor antagonists and reuptake inhibitors, SNRIs = serotonin–norepinephrine reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.

Keywords: breast cancer, depressive disorders, recurrence

1. Introduction

Breast cancer is the most prevalent malignancy in women and the leading cause of death from cancer.[3,12] In recent years, because of successful early screening or detection interventions,[37] surgery, and adjuvant therapies including radiotherapy,[5] chemotherapy,[4] selective oestrogen receptor modulator (e.g., tamoxifen),[14] third-generation aromatase inhibitors (AIs) (e.g., anastrozole, letrozole, or exemestane), or monoclonal antibody (e.g., trastuzumab),[3,22] 5 years survival rates have increased to 77.5% to 90.3%.[13]

Depressive disorder (DD) is a widespread chronic disease, characterized by sadness or irritability and accompanied by several psychophysiological symptoms.[2] Evidence has shown that DD is associated with substantial mortality, comorbidities, and disabilities.[24,26] Previous studies have indicated an increasing risk of depression among breast cancer survivors.[1,6,11,21,23]

Animal models have clearly shown the effect of stress on metastasis and tumor growth.[36] A recent meta-analysis of 31 prospective studies found a 25% higher mortality rate for patients with cancer with depressive symptoms.[33] However, whether depression can predict breast cancer recurrence is conflicting because of limited numbers of studies, different population, or assessment instruments.[20]

This study was aimed to investigate the risk of breast cancer recurrence among patients who developed DDs after receiving curative surgery by using the population-based retrospective

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database which was retrieved from the National Health Insurance Research Database (NHIRD) in Taiwan.

2. Methods

2.1. Database

The National Health Insurance (NHI) is a mandatory universal health insurance program launched by the Taiwan government to provide comprehensive medical service to almost all Taiwanese residents since 1995. The National Health Research Institute (http://nhird.nhri.org.tw/en) is in charge of the Taiwan NHI program and maintains the entire insurance claims database, namely, the NHIRD. The NHIRD consists of detailed healthcare data covering 98.29% of the entire Taiwan's 23 million population. The data used in this study were retrieved from the population-based Cancer Database, comprised of patients with 5 major cancer diagnoses including breast cancer, liver cancer, gastric cancer, colon cancer, and lung cancer; all the registration files and medical claims for the reimbursement of these individuals were collected from 2001 to 2007. The National Health Research Institute has validated the released database which is representative of the whole Taiwanese population. 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).

2.2. Study sample and control

The study was exempt from full review by the Institutional Review Board of China Medical University Hospital because the data sets consisted of de-identified secondary data (CMUH103-REC3–077). In this study, we enrolled adult patients (aged 20 years and older) who had newly diagnosed breast cancer (ICD-9-CM codes 174.XX) and received curative surgery for the first time from 2003 to 2007. Breast cancer patients who developed DDs (ICD-9-CM code: 296.2X-296.3X, 300.4, and 311.X) after curative surgery were enrolled as the study cohort (DD cohort). We excluded subjects diagnosed with DDs before breast surgery.

2.3. Matching

The control group of breast cancer patients who did not develop DDs after curative surgery was selected at a ratio of 2 control patients per 1 patient with DD. The control group was matched for each individual's age, sex, index year, breast surgery, chemotherapy, and radiotherapy. Matching for the age and year of enrollment was allowed within a tolerance range (± 5 years). For the control group, the start date of follow-up was defined as the first date of admission for first-time breast surgery (ICD-9-CM code: 85.2X-85.4X) in the enrollment year.

2.4. Main outcome measures

Breast cancer recurrence was defined as a claim for chemotherapy administration, radiation, or surgery 3 months or more after the end of initial primary surgery.[9] Both cohorts were followed up until the date of breast cancer recurrence, death, or the end of 2007. Death was defined as death during hospitalization, or withdrawal of the patient from the NHI program.[40]

2.5. Covariate assessment

We identified patients who received chemotherapy (ICD-9-PCS code: V581 and 992.5) or radiotherapy (ICD-9-PCS code: 922 and V580) based on diagnostic and procedure codes. Adjuvant therapies included chemotherapy, radiotherapy, selective oestrogen receptor modulator (e.g., tamoxifen), AIs, and monoclonal antibody (e.g., trastuzumab). We used the Charlson Comorbidity Index (CCI) to evaluate comorbidity diseases.[8]

2.6. Antidepressant use or psychotherapy

We further evaluated the cancer recurrence risk among breast cancer patients who developed DDs and received treatments including antidepressants or psychotherapy. In our study, antidepressants were classified into selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine, fluvoxamine, paroxetine, citalopram, escitalopram, and sertraline), serotonin–norepinephrine reuptake inhibitors (SNRIs) (e.g., duloxetine and venlafaxine), norepinephrine and dopamine reuptake inhibitors (NDRIs) (e.g., bupropion), serotonin receptor antagonists and reuptake inhibitors (SARI) (e.g., trazodone), and tricyclic antidepressants (TCAs) (e.g.,amitriptyline, clomipramine, imipramine, dothiepin, doxepin, maprotilinem, and melitracen). Information on receipt of psychotherapy was based on the treatment code of NHIRD claims (45010C, 45087C, 45013C).

2.7. Statistical analysis

We used descriptive statistics to investigate demographic characteristics, disease and treatment-related characteristics, and DDs. To identify the risk factors of recurrence and mortality associated with DDs, the patients were divided into 2 groups—subjects who developed DDs and subjects who did not. Cox regression was used to identify factors associated with DDs or non-DDs (dependent variable). Independent variables included surgery, chemotherapy, radiotherapy, tomaxifen, AIs, and trastuzumab, outpatient visits, major coexisting diseases, and propensity. We used MY Structured Query Language (MySQL) 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). The 2-tailed P value <0.05 was considered to be statistically significant.

3. Results

3.1. Demographic characteristics of the breast cancer cohort

From January 1, 2002 to December 31, 2007, a total of 30,659 breast cancer patients admitted for the first time with primary diagnosis of breast cancer and received curative surgery were enrolled. Figure 1 shows a flowchart of enrollment and follow-up. During a mean follow-up period of 2.53 years, 1147 patients (3.74%) were newly diagnosed with DDs.

For each of the DD patients, we randomly selected 2 patients from the same period without DD under the same exclusion criteria and frequency-matched them with the case cohort for sex, age, index year, breast surgery, chemotherapy, and radiotherapy to establish a non-DD cohort. Finally, 1147 breast cancer patients with DDs and 2294 breast cancer patients without DDs were included in this study. The basic characteristics of the DD cohort and the matched control group are shown in Table 1.

3.2. Five-year cumulative incidences of breast cancer recurrence and overall mortality

During a mean follow-up period of 2.53 years, there were higher rates of recurrence among the DD cohort as compared

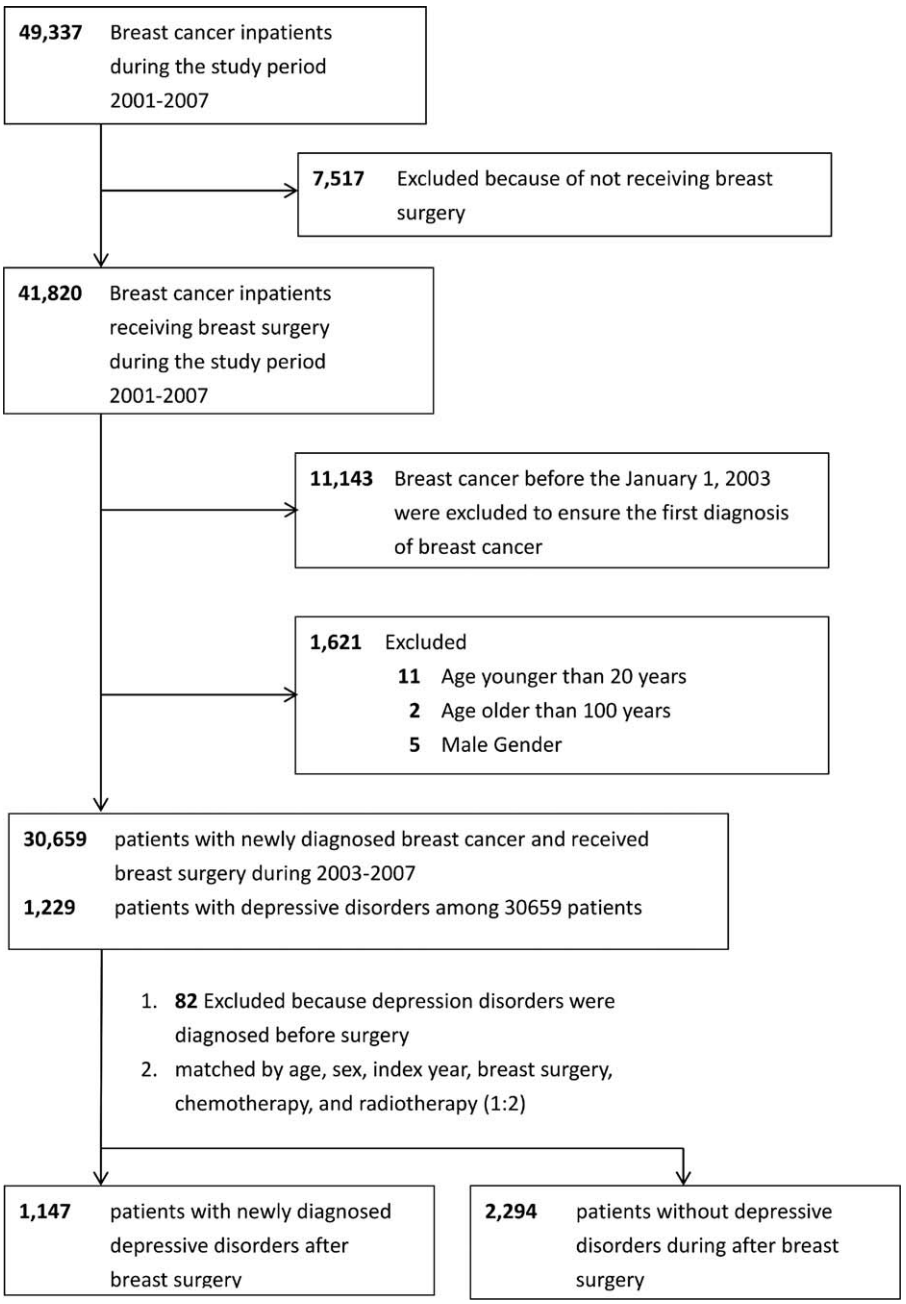

Figure 1. Selection of study patients.

with the control group (17.1% vs 12.5%; $P=0.0088$). Breast cancer patients who developed DDs after curative surgery had a significantly higher risk for incident recurrence than the comparison group (log-rank test, $P=0.0088$; Fig. 2). Multivariate analysis in 4 different models consistently indicated that DDs were independently associated with incident recurrence (Table 2A). The fully adjusted hazard ratio (HR) in the model 4 was 1.373 (95% confidence interval [CI] 1.098–1.716, $P=0.005$). Death before the recurrence of breast cancer was defined as competing mortality. During the follow-up period, overall deaths for the DD cohort and matched control cohort were 70 (6.10%) and 103 (4.49%), respectively. The risk of overall mortality was higher in DD cohort (5-year cumulative incidence 10.2%) than in matched control cohort (8.5%), although it was not significant after being adjusted (adjusted HR [aHR] 1.271, 95% CI 0.930–1.737, $P=0.132$) (Table 2B).

Among breast cancer patients with DDs, SSRI is the most common antidepressant (35.7%). The Cox univariate proportional-hazards analysis showed that patients with DDs receiving SSRI, SNRI, NDRI, SARI, or psychotherapy had lower risks of cancer recurrence. In the Cox multivariate proportional-hazards analysis, depressed patients with SSRI treatment had the significantly lowest risk of recurrence (aHR 0.581, 95% CI 0.395 to 0.856, $P=0.006$) (Table 3).

4. Discussion

To the best of our knowledge, this is the first study to investigate risk of tumor recurrence in breast cancer patients who developed

Table 1

Demographic profile of study patients (N = 3441).

	Nondepressive (n = 2294)	Depressive (n = 1147)		
	M ± SD, n (%)	M ± SD, n (%)	t/χ^2	*P*
Age, y	50.91 ± 10.09	51.03 ± 10.15	0.036	0.850
20–39	272 (11.9)	136 (11.9)	0.00	1.00
40–59	1608 (70.1)	804 (70.1)		
60–79	400 (17.4)	200 (17.4)		
80	14 (0.6)	7 (0.6)		
Follow-up, y	2.54 ± 1.37	2.50 ± 1.38	0.239	0.625
Type of adjuvant therapies				
Chemotherapy	1348 (58.8)	674 (58.8)	0.000	1.000
Radiotherapy	600 (26.2)	300 (26.2)	0.000	1.000
Tamoxifen	1474 (64.3)	722 (64.3)	0.566	0.452
AIs	405 (17.7)	258 (22.5)	11.509	0.001
Trastuzumab	70 (3.1)	56 (4.9)	7.266	0.007
Charlson Comorbidity Index, no. (%)				
0	2096 (91.4)	1048 (91.4)	4.736	0.315
1	56 (2.4)	37 (3.2)		
2	109 (4.8)	53 (4.6)		
3	11 (0.5)	4 (0.3)		
≥4	22 (1.0)	5 (0.4)		
Outpatient visits per person per y				
>0 and ≤10	445 (19.4)	122 (10.6)	120.882	<0.001
>10 and ≤20	1142 (49.8)	471 (41.1)		
>20 and ≤30	469 (20.4)	324 (28.2)		
>30	238 (10.4)	230 (20.1)		
Major coexisting diseases				
Hypertension	246 (10.7)	119 (10.4)	0.098	0.754
Diabetes	133 (5.8)	58 (5.1)	0.801	0.371
Coronary disease	19 (0.8)	11 (1.0)	0.151	0.697
COPD	19 (0.8)	12 (1.0)	0.407	0.524
Autoimmune diseases	15 (0.7)	8 (0.7)	0.022	0.882
Cerebrovascular disease	14 (0.6)	4 (0.3)	1.005	0.316
Cirrhosis	12 (0.5)	5 (0.4)	0.118	0.731
Chronic kidney disease	9 (0.4)	6 (0.5)	0.301	0.583
Propensity score	0.331 ± 0.037	0.338 ± 0.045	24.83	<0.001

AIs = aromatase inhibitors, COPD = chronic obstructive pulmonary disease, SD = standard deviation.

DDs after receiving curative surgery using the population-based retrospective database. The results of this nationwide, population-based cohort study shows that the incidence rate of DDs in breast cancer survivors after curative surgery was 3.74%; there were higher rates of recurrence among the DD cohort as compared with the control group (17.1% vs 12.5%; $P = 0.0088$); the risk of overall mortality was higher in DD cohort (5-year cumulative incidence 10.2%) than in matched control cohort (8.5%).

Our study agreed with previous studies which have reported that there existed an increased risk of depression among breast cancer survivors.[1,6,11,21,23] In our study, the incidence of DD is 16.72 per 1000 per year, whereas Hung et al reported 14.55 per 1000 per year of 26,629 breast cancer patients.[23] These incidences are higher than the incidence of women in Taiwan (3.04 per 1000 per year).[10] A review of 36 studies found the rate of depression cited in these studies was about 10% to 25%, because the data from these studies were largely stemming from differences in study population, study design, and choice of depression measure.[15]

Moreover, our results found that there were higher rates of recurrence among breast cancer patients who developed DDs compared with those who did not (17.1% vs 12.5%; $P = 0.0088$). A trial of 1588 newly diagnosed breast cancer patients showed that fatigue remained a significant predictor of recurrence-free survival ($P = 0.0004$; risk ratio [RR] 1.32 [1.13–1.54]).[20] A meta-analysis found that depressive symptoms are associated with poor progression, although not significant (RR unadjusted 1.23, 95% CI 0.85–1.77, $P = 0.28$).[19,28,33,38]

The results of this study showed the DD cohort had higher risk of overall mortality (although not statistically significant, aHR = 1.271, 95% CI 0.930–1.737, $P = 0.132$). However, one published meta-analysis including 25 studies showed that mortality rates were up to 25% higher in patients with depressive symptoms (unadjusted RR = 1.25, 95% CI 1.12–1.40, $P < 0.001$), and up to 39% higher in patients diagnosed with major or minor depression (unadjusted RR = 1.39, 95% CI 1.10–1.89, $P < 0.03$).[33]

How might depression affect the progression of breast cancer? Potential mechanisms may be related to the endocrine effects and hypothalamic-pituitary-adrenal (HPA) dysfunction.[35] Stress hormones may suppress immune resistance to cancer cells[7,25,35] or different effects on gluconeogenesis in healthy versus tumor cells.[31,32] Apart from this, strong evidence shows that cortisol dysregulation is common in depression.[17,29] The HPA axis dysregulation associated with depression may worse the cortisol dysregulation and result in shorter survival.[34] Animal models have shown chronic stress promotes tumor growth and angiogenesis primarily through activation of the tumor cell cyclic AMP (cAMP)–protein kinase A (PKA) signaling pathway

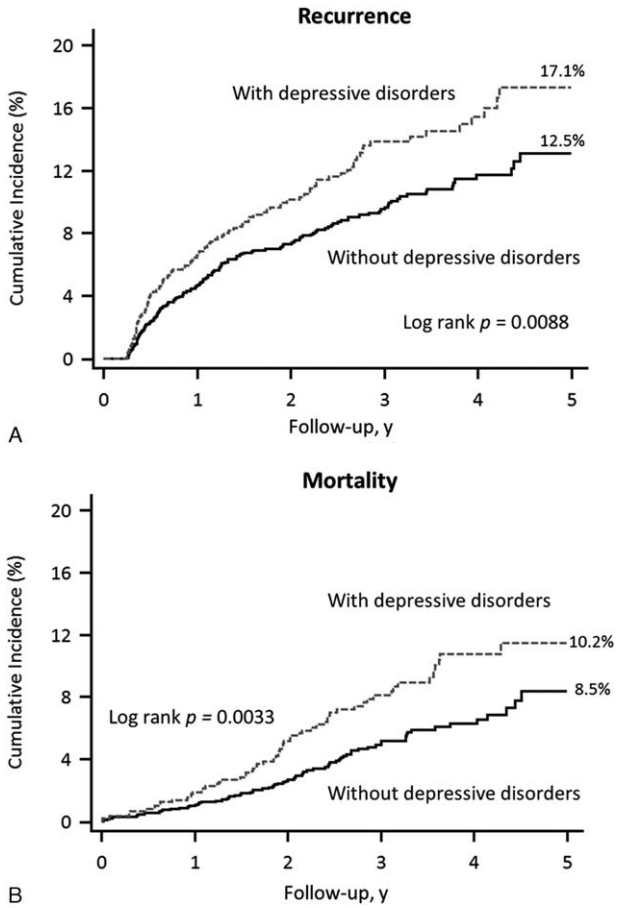

Figure 2. Cumulative incidence of breast cancer recurrence and overall mortality after curative surgery.

Table 2

(A) Serial multivariate adjustment showing depressive disorders as a risk factor for recurrence incidence.

Adjustment model	Hazard ratio	95% CI	*P*
Crude, unadjusted	1.459	1.173–1.815	0.001
Model 1*	1.265	1.012–1.580	0.039
Model 2†	1.362	1.090–1.702	0.006
Model 3‡	1.363	1.090–1.703	0.007
Model 4§	1.373	1.098–1.716	0.005

(B) Serial multivariate adjustment showing depressive disorders as a risk factor for mortality.

Adjustment model	Hazard ratio	95% CI	*P*
Crude, unadjusted	1.354	0.999–1.834	0.050
Model 1*	1.211	0.887–1.652	0.228
Model 2†	1.277	0.973–1.742	0.122
Model 3‡	1.275	0.933–1.741	0.128
Model 4§	1.271	0.930–1.737	0.132

CI = confidence interval.
* Adjusted for age, outpatient visits.
† Adjusted for variables in model 1 plus adjuvant therapies in Table 1.
‡ Adjusted for variables in model 2 plus all comorbidities in Table 1.
§ Adjusted for variables in model 3 plus Charlson Comorbidity Index.

by the β2adrenergic receptor.[36] Stress-related pathways have been directly involved in the pathophysiology and treatment of DDs.[18,39] Further studies will need to investigate the possible mechanisms between the tumor recurrence and DDs in breast cancer patients after curative surgery.

Two important clinical implications of our study should be noted. First, intensive or more frequent monitoring schemes of DDs and related symptoms should be taken into account for breast cancer patients who received curative surgeries. Second, specific management programs which were aimed to relieve DDs among breast cancer patients receiving curative surgeries should be further developed. One previous study has proposed decreased depressive symptoms were significantly associated with longer survival.[16] Based on the finding of this study, breast cancer patients receiving curative surgeries are strongly suggested to receive psychological or psychiatrical assessments for preventing further development of DDs. In conclusion, we strongly suggest that a psychiatrist should be invited as 1 team member of the treatment team of breast cancer patients who are scheduled to receive surgery, which may help prevent the onset of DDs and may further help prolong survival of breast cancer patients.

The present study has some limitations. First, the NHIRD could not provide data of possible confounding variables, including cancer staging, physical symptoms, genetic factors,[15,27] patients' coping skills,[30,35] and so on, which may be associated with the risk of developing DDs. Second, we assumed the recurrence is close to the re-surgery, chemotherapy, or radiotherapy.[9] Further study will be needed to clarify more accurate date of relapse. Third, there is no biomedical laboratory

Table 3

Cox regression analysis of cancer recurrence risk among breast cancer survivors with depressive disorders receiving antidepressants and psychotherapy (N = 1147).

Variables	Number (%)	Univariate analysis			Multivariate analysis		
		HR	95% CI of HR	*P*	aHR	95% CI of aHR	*P*
Type of antidepressants							
SSRI	409 (35.7)	0.563*	0.386–0.821	0.003	0.581*	0.395–0.856	0.006
SNRI	138 (12.0)	0.601	0.324–1.112	0.105	0.631	0.339–1.177	0.148
NDRI	48 (4.2)	0.611	0.226–1.651	0.331	0.654	0.240–1.781	0.406
SARI	272 (23.7)	0.730	0.482–1.105	0.137	0.756	0.495–1.153	0.194
TCA	269 (23.5)	1.334	0.933–1.908	0.115	1.401	0.976–2.011	0.067
Psychotherapy	266 (31.9)	0.705	0.479–1.038	0.077	0.869	0.580–1.302	0.497

Multivariable analysis including SSRI, SNRI, NDRI, SARI, TCA and psychotherapy.
aHR = adjusted hazard ratio, HR = hazard ratio, NDRI = norepinephrine and dopamine reuptake inhibitors, SARI = serotonin receptor antagonists and reuptake inhibitors, SNRI = serotonin–norepinephrine reuptake inhibitors, SSRI = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.
* $P < 0.01$.

test that is diagnostic for DDs. Physicians diagnose based on the observation of a number of depressive symptoms over a certain period. There is a concern of the association of valid and reliable measures of DDs. In Taiwan, a diagnosis of DDs was made according to ICD-9 CM code by board-certified psychiatrists and physicians.

In conclusion, this study found a subsequent risk of DDs in breast cancer patients after curative surgery, and those who developed DDs had higher risk of recurrence and mortality. Our findings suggest breast cancer receiving operation may need more psychological evaluation and treatment.

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