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Depression risk among breast cancer survivors: a nationwide cohort study in South Korea

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Abstract

Background Depression among breast cancer survivors is a significant concern affecting their long-term survivorship and quality of life. This study investigates the incidence of depression among breast cancer survivors and identifies associated risk factors.

Methods This retrospective cohort study used data from the Korean National Health Insurance Service database and included 59,340 breast cancer patients without a history of depression who underwent surgery between January 1, 2010, and December 31, 2016. They were individually matched 1:2 by age with a general population without cancer ($n = 99,834$). The mean follow-up period was 6.4 ± 2.6 years. Sub-distribution hazard ratios (sHRs) and 95% confidence intervals (CIs) were calculated considering death as a competing risk and adjusting for sociodemographic factors and comorbidities.

Results Breast cancer survivors with a mean (standard deviation) age of 51.5 (9.2) years had a 39% increased risk of depression compared to non-cancer controls (sHR 1.39, 95% CI 1.36–1.42). During the first year post-diagnosis, breast cancer survivors across all ages exhibited a significantly elevated risk of depression, with a sHR of 3.23 (95% CI 3.08–3.37). Notably, younger survivors had a sHR of 4.51 (95% CI 4.19–4.85), and older survivors had a sHR of 2.56 (95% CI 2.42–2.71). One year post-surgery, younger survivors (age ≤ 50 years) showed a 1.16-fold increase in depression risk (sHR 1.16, 95% CI 1.11–1.20), while older survivors (age > 50 years) showed no significant change in risk, which decreased over time. Use of anthracycline, taxane, or endocrine therapy was associated with an increased depression risk (sHR 1.17, 95% CI 1.13–1.22; sHR 1.12, 95% CI 1.07–1.16; and sHR 1.27, 95% CI 1.14–1.41, respectively), with endocrine therapy showing a 41% increased depression risk in older survivors (sHR 1.41, 95% CI 1.23–1.61).

Conclusion This study demonstrates a significant association between breast cancer and depression, with a particularly heightened risk in younger survivors within the first year post-diagnosis. Special attention is needed to meticulously screen for depressive symptoms during the early follow-up years for breast cancer survivors who are premenopausal or have undergone chemotherapy and endocrine therapy.

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Keywords breast cancer, depression, cancer survivorship

Background

Breast cancer is the most prevalent cancer among women globally [1] and the fifth leading cause of cancer-related deaths, with approximately 2.3 million new cases annually [2]. Advances in medical technology have increased survival rates, leading to a growing population of breast cancer survivors [3].

Breast cancer survivors face an elevated risk of depression [4], affecting their long-term well-being and quality of life. This condition has multifaceted consequences, impacting mental health, emotional resilience, physical recovery, and social interactions [5–7], and can worsen treatment outcomes [8, 9]. Most previous studies on this topic have been cross-sectional and based on outdated data from Western countries, with few cohort studies available **(Additional file 1: Tables S1).** These cohort studies have limitations such as small sample sizes [7, 10], short follow-ups [7, 10–12], or inadequate control for covariates [10, 11, 13, 14]. A recent cohort study provides valuable insights into the trajectories of depressive symptoms among breast cancer survivors [12] but differential patterns by age remains inconclusive and require further investigation. Additionally, most studies compared breast cancer patients within their own cancer groups, limited comparisons to non-cancer controls [10, 12, 13]. Moreover, few studies have explored adjuvant treatments as risk factors for depression typically investigating each treatment modality individually with small participant numbers [15–18].

Our study aims to investigate the risk of depression among breast cancer survivors compared to a non-cancer general population in South Korea and to identify different patterns of depression by age and adjuvant treatments using data from the Korean National Health Insurance Service (NHIS) [19].

Methods

Data source and study setting

The Korean NHIS functions as the primary insurer for the entirety of South Korea's population, extending medical coverage to around 97% of citizens and providing medical assistance to the remaining 3% with lower incomes. Its database encompasses information regarding sociodemographic and health information such as diagnoses, treatments, and prescriptions. The NHIS conducts a comprehensive health screening program every two years. This program targets individuals aged 40 or older and all employees, regardless of age. The program involves a series of assessments, including body measurements, questions about past health and lifestyle habits (smoking, alcohol consumption, and physical activity), and lab tests [20]. The use of resources from the NHIS has been validated by various epidemiologic studies [21, 22].

This study was approved by the Institutional Review Board of Samsung Medical Center (NHIS-2023-1-212). Due to the anonymized nature of the data, the requirement for informed consent from participants was waived.

Study population

This retrospective cohort study analyzed 126,566 women who were first diagnosed with breast cancer and underwent breast cancer surgery between January 1, 2010, and December 31, 2016. Those who were younger than 18 years (n=43), had a history of other cancer diagnosis (n=5,514), were diagnosed with depression prior to breast cancer diagnosis (n=24,592), or had missing values (n=2,596) were excluded, leaving 91,851 breast cancer survivors. Finally, breast cancer survivors were matched 1:2 to the general female population without cancer based on birth year at baseline. We excluded those who had not undergone health screening within 2 years prior to breast cancer diagnosis (n=31,889) or within the corresponding index date in the control group (n=82,679) and those with any missing information (n=622 and 1,189, respectively) to ensure all the necessary variables were obtained. Finally, 59,340 breast cancer individuals and 99,834 matched controls were selected for this study (Fig. 1) [23].

Definition of breast cancer

In this study, breast cancer cases were validated through the concurrent presence of two primary markers in patient records: the International Classification of Diseases, Tenth Revision (ICD-10) code (C50) and a distinctive cancer-specific identifier for insurance claims (V193) code. In accordance with the NHIS policy in Korea, individuals diagnosed with cancer receive significant reductions in medical expenses, bearing only 5% of the total costs associated with treatment. This reduction is facilitated by application of a specific code (V193), which mandates official medical certification by a licensed healthcare professional.

Study outcomes and follow-up

We defined the primary outcome as the incidence of newly diagnosed depression, identified by ICD-10 codes F32 (depressive episode) and F33 (recurrent depressive disorder) [24, 25]. The subjects were followed from the date of breast cancer diagnosis or corresponding index date (for controls) to the date of depression diagnosis;

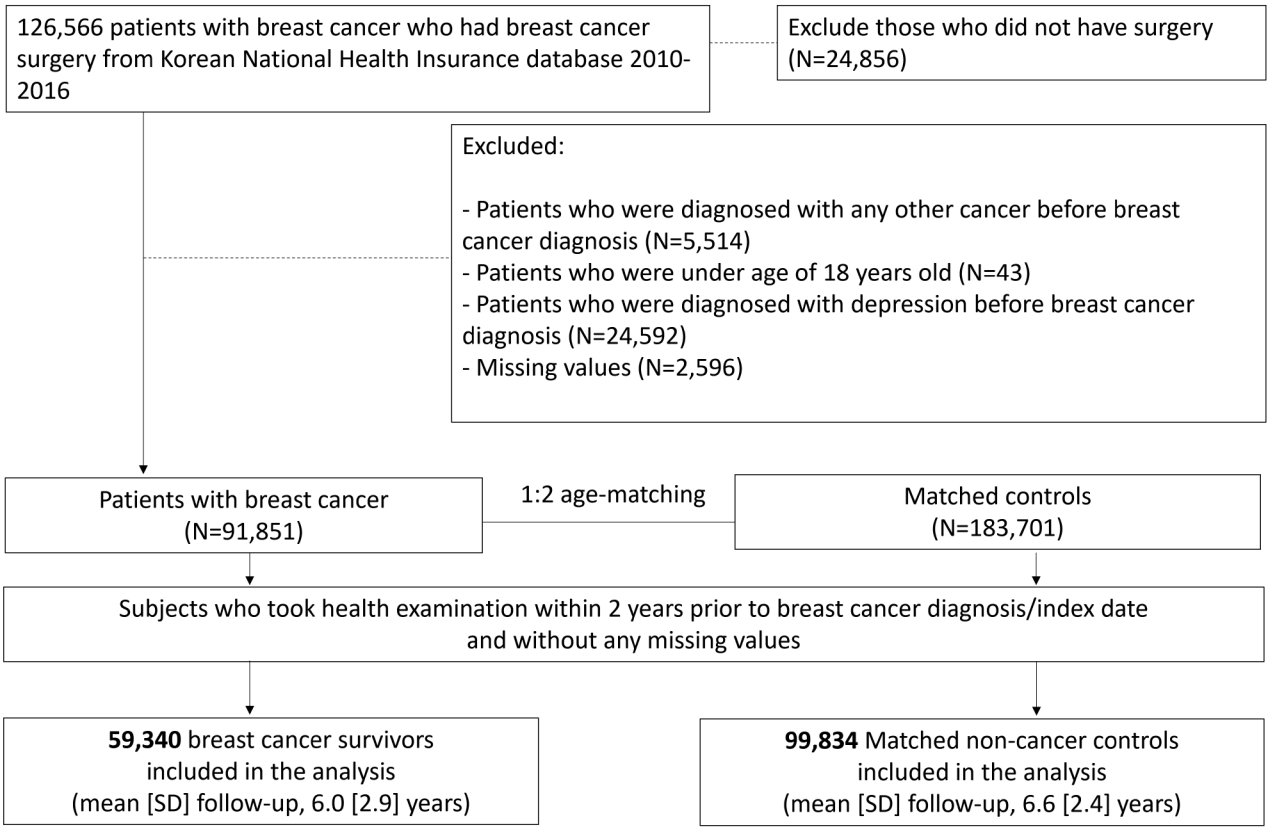

Fig. 1 Flowchart showing study population selection

the end of the follow-up period, December 31, 2020; or death, whichever came first.

Covariates

Participants' demographics (age, income, and residential location) were determined from the insurance eligibility database and collected as of the date of breast cancer diagnosis. Low-income individuals were defined as those in the lowest 25% of insurance premium payments, using this as a proxy for their income status. The health screening database contained information on health behaviors collected via a self-administered questionnaire. Smoking status was categorized as individuals who have never smoked (never), individuals who previously smoked (former), or individuals who currently smoke (current), while alcohol consumption was classified as individuals who do not drink (0 g/day) or individuals who drink (>0 g/day). Regular exercise was defined as engaging in over 30 min of moderate physical activity at least five times per week or over 20 min of vigorous physical activity at least three times per week, following criteria from previous studies [26]. Body mass index (BMI) is calculated by dividing an individual's weight in kilograms by their height in meters squared. Obesity was defined using the Asian-Pacific criteria, wherein a BMI exceeding 25 kg/m^2 indicates obesity.

Baseline covariates for concurrent medical conditions were measured using a combination of laboratory tests, insurance records, and prescription data collected one year prior to breast cancer diagnosis. Hypertension was diagnosed based on specific ICD-10 codes, the use of antihypertensive medications, or recorded blood pressure readings equal to or exceeding 140/90 mmHg. Diabetes mellitus was identified by the presence of specific ICD-10 codes along with antidiabetic medications or fasting glucose levels equal to or greater than 126 mg/dL. Dyslipidemia was identified using the specific ICD-10 code along with the use of lipid-lowering medications or a total cholesterol level exceeding 240 mg/dL. Chronic kidney disease (CKD) was diagnosed when the estimated glomerular filtration rate, calculated using the Modification of Diet in Renal Disease formula, fell below 60 mL/min/1.73 m^2. Information regarding cancer treatments was gathered within one year after breast cancer diagnosis.

Statistical analysis

Descriptive statistics were conducted using means and standard deviations for continuous variables, and

numbers and percentages for categorical variables. Sub-distribution hazards ratios (sHRs) and 95% confidence intervals for the incidence of depression were estimated by conducting the Fine-Gray proportional sub-distribution hazards model. This model accounts for death as a competing risk [27]. We used Schoenfeld's residuals to assess the proportional hazards assumption and found no statistically significant deviations. The reference group was a 1:2 age-matched control group selected from the general population without cancer, and sHRs and 95% CIs were calculated for breast cancer survivors and age groups relative to the reference group. In the initial model (Model 1), sHRs were unadjusted. Model 2 was adjusted for age, income, and residential area, and Model 3 was further adjusted for BMI, hypertension, diabetes mellitus, dyslipidemia, CKD, smoking status, alcohol consumption, and physical activity. These covariates were selected based on a literature review. All the analyses were stratified by age groups (age ≤ 50 years and age > 50 years) considering the average age of menopause in Korea [28].

Table 1 Baseline characteristics of study participants

	Control	Breast cancer	*P*-value
	N = 99,834	*N* = 59,340	
Mean age, years	51.6 ± 9.3	51.5 ± 9.2	0.008
Income status, low 25%	24,355 (24.4)	13,532 (22.8)	< 0.001
Residual location, urban	47,455 (47.5)	29,869 (50.3)	< 0.001
Smoking status			0.10
Never /former	96,456 (96.6)	57,241 (96.5)	
Current	3,378 (3.4)	2,099 (3.54)	
Alcohol consumption			0.24
None	74,136 (74.3)	44,225 (74.5)	
>0 g/day	25,698 (25.7)	15,115 (25.5)	
Physical activity			0.06
None	81,253 (81.4)	48,517 (81.8)	
Regular exercise	18,581 (18.6)	10,823 (18.2)	
Obesity (BMI ≥ 25, kg/m^2)	28,868 (28.9)	17,379 (29.3)	0.13
Comorbidity			
Diabetes mellitus	5,321 (5.3)	3,342 (5.63)	0.01
Hypertension	18,404 (18.4)	11,325 (19.1)	0.001
Dyslipidemia	14,263 (14.3)	8,959 (15.1)	< 0.001
Chronic kidney disease	259 (0.3)	166 (0.3)	0.45
Cancer treatment type			
Anthracycline	-	30,547 (51.5)	-
Cyclophosphamide	-	34,043 (57.4)	-
Fluorouracil	-	8397 (14.2)	-
Trastuzumab	-	8570 (14.4)	-
Methotrexate or cisplatin	-	4036 (6.8)	-
Tamoxifen	-	29,460 (49.7)	-
Taxane	-	16,453 (27.7)	-
Aromatase inhibitor	-	16,273 (27.4)	-
Radiation therapy	-	42,703 (72.0)	-

Data are expressed as mean ± SD or number (%)

Abbreviations: SD, standard deviation; BMI, body mass index

We conducted landmark analyses at 1, 3 and 5 years post-breast cancer diagnosis to estimate the risk of depression for individuals who were event-free at each point. This method allowed us to illustrate the changes in depression risk over time and assess the long-term impacts of breast cancer and its treatments on depression incidence [29]. We conducted a sensitivity analysis comprising only the breast cancer survivors to examine the risk factors of depression. Different cancer adjuvant treatments, such as anthracyclines, taxanes, trastuzumab, endocrine treatment, and radiation therapy, were included in the sensitivity analysis. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). The P-values reported in this analysis are two-tailed, and the level of significance was set at 0.05.

Results

Baseline characteristics

The study included 59,340 breast cancer survivors with a mean (standard deviation [SD]) age of 51.5 (9.2) years. Comorbidities like hypertension, diabetes, and dyslipidemia were more prevalent among survivors. Among the breast cancer survivors, 72% underwent radiation therapy, with the majority receiving anthracycline (51.5%), cyclophosphamide (57.4%), and/ or tamoxifen (49.7%) (Table 1).

Depression risk among breast cancer survivors

During a mean (SD) follow-up period of 6.0 (2.9) years, breast cancer survivors had a 39% higher risk of depression compared to controls (sHR 1.39; 95% CI, 1.36–1.42). Younger survivors (age ≤ 50 years) had a 64% increased risk, while older survivors (age > 50 years) had a 23% increased risk (adjusted hazard ratio [aHR] 1.64; 95% CI 1.58–1.80 and aHR 1.23; 95% CI 1.20–1.27, respectively) (Table 2).

Changes in the risk of depression over time

The depression risk within the first year of diagnosis and the landmark analyses demonstrating changes in depression risk over time are provided in Table 3. During the first year post-diagnosis, breast cancer survivors of all ages exhibited a significantly elevated risk of depression, with a sHR of 3.23 (95% CI 3.08–3.37). Notably, younger survivors had a sHR of 4.51 (95% CI 4.19–4.85), and older survivors had a sHR of 2.56 (95% CI 2.42–2.71). At the 1-year landmark period, the risk of depression was increased by 4% in breast cancer survivors compared to controls (Model 3: sHR 1.04, 95% CI 1.01–1.07). This association differed by age group: younger survivors exhibited a 1.16-fold increased risk of depression (sHR 1.16, 95% CI 1.11–1.20), whereas older survivors exhibited an insignificant change in the risk of depression (sHR

Table 2 Adjusted sub-distribution hazard ratios for developing depression in breast cancer survivors compared to noncancer control group by age categories

Age group		Subjects, No.	Case, No.	Duration, PY	Incidence rate (per 1,000 PY)	sHR (95% CI)		
						Model 1	Model 2	Model 3
All ages	Control	99,834	18,696	655078.6	28.5	1 (ref.)	1 (ref.)	1 (ref.)
	Breast cancer	59,340	14,492	357111.2	40.6	1.39 (1.36–1.42)	1.39 (1.36–1.42)	1.39 (1.36–1.42)
Age ≤ 50	Control	49,312	7,039	333091.1	21.1	1 (ref.)	1 (ref.)	1 (ref.)
	Breast cancer	29,922	6,516	183835.9	35.4	1.64 (1.58–1.69)	1.69 (1.58–1.69)	1.64 (1.58–1.70)
Age > 50	Control	50,522	11,657	321987.4	36.2	1 (ref.)	1 (ref.)	1 (ref.)
	Breast cancer	29,418	7,976	173275.3	46	1.24 (1.20–1.27)	1.24 (1.21–1.28)	1.23 (1.20–1.27)
P for interaction						< 0.001	< 0.001	< 0.001

Abbreviations: PY, person-years; sHR, sub-distribution hazard ratio; CI, confidence interval

Model 1 : Unadjusted

Model 2 : Age, income, residual location

Model 3 : Age, income, residual location, diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, smoking status, alcohol drinking, physical activity, body mass index

0.97, 95% CI 0.94-1.00). At the 3-year landmark period, the risk of depression decreased in all ages of breast cancer survivors (sHR 0.93, 95% CI 0.90–0.96). Depression risk didn't differ in younger survivors, but decreased in older ones (sHR 0.89, 95% CI 0.85–0.93). The 5-year landmark analysis yielded similar results to the 3-year landmark analysis.

Risk factors of depression among breast cancer survivors

Smoking (aHR 1.41, 95% CI 1.30–1.53) and dyslipidemia (aHR 1.10, 95% CI 1.05–1.16) increased the risk of depression by 41% and 10%, respectively, among breast cancer survivors, regardless of age group (Table 4). Regarding treatment, the use of anthracycline (aHR 1.17, 95% CI 1.13–1.22), taxane (aHR 1.12, 95% CI 1.07–1.16), and both tamoxifen and aromatase inhibitor (aHR 1.27, 95% CI 1.14–1.41) were potential risk factors for depression across the overall sample of breast cancer survivors (Table 4 and Fig. 2). In the age-specific analysis, endocrine therapy was not significantly linked to the risk of depression in those younger than 50 years.

Discussion

This nationwide population-based cohort study reports that 59,340 breast cancer survivors exhibited an increased risk of depression compared to the age-matched control group. Notably, different patterns emerged by age group: survivors younger than 50 years had a 1.16-fold higher risk of depression at 1-year post-surgery, while older survivors had a decreased risk. Additionally, current smoking, dyslipidemia, and chemotherapy and endocrine therapy were potential risk factors.

Our findings align with prior research showing a higher risk of depression in breast cancer survivors compared to healthy controls. However, our study offers several improvements on previous work. We followed participants over a long time period (maximum follow-up = 11 years), demonstrating the temporal change in depression risk through landmark analysis. Most previous studies were of a cross-sectional or had a short follow-up unable to show a developmental trajectory of depression risk. We also observed different patterns of risk according to age of menopause, considering BMI, lifestyle habits, and existing health conditions, which increased the reliability of our results. Finally, this study is the largest of its kind to examine depression risk in breast cancer survivors in relation to specific treatment methods like chemotherapy and radiation therapy.

Our results indicate that the risk of depression is highest during the first year following diagnosis and then decreases. This concurs with existing literature, such as a Danish cohort study [14] reporting a relative ratio of 1.70 (95% CI 1.41–2.05) for depression in women with breast cancer, which diminished afterward. A recent cohort study conducted in France showed a variety of trajectories for depressive symptoms in breast cancer patients, including remission of depressive symptoms [12]. Other cohort studies [7, 10] have also reported increased depression prevalence in the year after diagnosis and a decrease thereafter, but were insufficient to delineate the actual risk compared to the non-cancer population. Our findings provide valuable information to the risk of clinically significant depression beyond the first year after diagnosis. One possible explanation for this decrease over time is that the initial depression could be primarily due to the distress of the cancer diagnosis itself, with gradual adaptation occurring in subsequent years [30]. The increased availability of psychological support for breast cancer survivors might also help mitigate the long-term risk of depression [44]. Although our study could not directly assess access to or use of psychological support, we acknowledge that such interventions might help explain the decreased depression risk observed in breast cancer survivors as time passes.

We demonstrated that the risk for depression was significantly higher in breast cancer survivors younger than

Table 3 Adjusted sub-distribution hazard ratios for depression during the first year post-diagnosis, and at the 1-year, 3-year, and 5-year landmark periods in breast cancer survivors compared to non-cancer control group

Age group		Subjects, *N*	Case, *N*	Duration, PY	Incidence rate (per 1,000 PY)	sHR (95% CI)		
						Model 1	Model 2	Model 3
During the first year post-diagnosis								
All ages	Control	99,834	2,826	98,440.30	28.7	1 (ref.)	1 (ref.)	1 (ref.)
	Breast cancer	59,340	5,304	55,866.60	94.9	3.22 (3.08–3.37)	3.23 (3.09–3.38)	3.23 (3.08–3.37)
Age ≤ 50	Control	49,312	952	48,849.20	19.5	1 (ref.)	1 (ref.)	1 (ref.)
	Breast cancer	29,922	2,567	28,275.50	90.8	4.51 (4.19–4.84)	4.51 (4.19–4.85)	4.51 (4.19–4.85)
Age > 50	Control	50,522	1,874	49,591.20	37.8	1 (ref.)	1 (ref.)	1 (ref.)
	Breast cancer	29,418	2,737	27,591.10	99.2	2.57 (2.42–2.72)	2.57 (2.43–2.72)	2.56 (2.42–2.71)
P for interaction						< 0.001	< 0.001	< 0.001
1-year landmark								
All ages	Control	97,006	15,870	556,638.2	28.5	1 (ref.)	1 (ref.)	1 (ref .)
	Breast cancer	53,879	9,188	301,244.6	30.5	1.04 (1.01–1.07)	1.04 (1.02–1.07)	1.04 (1.01–1.07)
Age ≤ 50	Control	48,359	6,087	284,242	21.4	1 (ref.)	1 (ref.)	1 (ref.)
	Breast cancer	27,293	3,949	155,560.4	25.4	1.15 (1.11–1.20)	1.15 (1.11–1.2)	1.16 (1.11–1.2)
Age > 50	Control	48,647	9,783	272,396.2	35.9	1 (ref.)	1 (ref.)	1 (ref.)
	Breast cancer	26,586	5,239	145,684.2	36	0.97 (0.94–1.01)	0.98 (0.94–1.01)	0.97 (0.94-1.00)
P for interaction						< 0.001	< 0.001	< 0.001
3-year landmark								
All ages	Control	91,513	10,458	368,191.9	28.4	1 (ref.)	1 (ref.)	1 (ref.)
	Breast cancer	49,209	5,310	198,522.7	26.7	0.93 (0.90–0.96)	0.93 (0.90–0.96)	0.93 (0.90–0.96)
Age ≤ 50	Control	46,394	4,135	189,479.3	21.8	1 (ref.)	1 (ref.)	1 (ref.)
	Breast cancer	25,241	2,251	103,251.1	21.8	0.99 (0.90–1.04)	0.99 (0.94–1.04)	0.99 (0.94–1.04)
Age > 50	Control	45,119	6,323	178,712.6	35.3	1 (ref.)	1 (ref.)	1 (ref.)
	Breast cancer	23,968	3,059	95,271.6	32.1	0.89 (0.85–0.93)	0.89 (0.85–0.93)	0.89 (0.85–0.93)
P for interaction						0.002	0.003	0.002
5-year landmark								
All ages	Control	76,469	5,521	194,148.2	28.4	1 (ref.)	1 (ref.)	1 (ref.)
	Breast cancer	40,972	2,802	105,234	26.6	0.92 (0.88–0.97)	0.93 (0.89–0.97)	0.93 (0.88–0.97)
Age ≤ 50	Control	39,485	2,232	100,639.4	22.2	1 (ref.)	1 (ref.)	1 (ref.)
	Breast cancer	21,342	1,163	55,131.1	21.1	0.98 (0.87–1.01)	0.94 (0.87–1.01)	0.94 (0.87–1.01)
Age > 50	Control	36,984	3,289	93,508.8	35.2	1 (ref.)	1 (ref.)	1 (ref.)
	Breast cancer	19,630	1,639	50,102.9	32.7	0.92 (0.86–0.97)	0.92 (0.88–0.98)	0.92 (0.86–0.97)
P for interaction						0.63	0.73	0.66

Abbreviations: PY, person-years; sHR, sub-distribution hazard ratio; CI, confidence interval

Model 1 : Unadjusted

Model 2 : Age, income, residential location

Model 3 : Age, income, residential location, diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, smoking status, alcohol drinking, physical activity, body mass index

Table 4 Sensitivity analysis to identify risk factors for developing depression among breast cancer survivors

	All age				Age ≤ 50				Age > 50			
	Subjects, *N*	Case, *N*	IR (per 1,000 PY)	Adjusted sHR* (95% CI)	Subjects, *N*	Case, *N*	IR (per 1,000 PY)	Adjusted sHR* (95% CI)	Subjects, *N*	Case, *N*	IR (per 1,000 PY)	Adjusted sHR* (95% CI)
Place												
Urban	29,869	7213	40	1 (ref.)	14,774	3156	34.6	1 (ref.)	15,095	4057	45.5	1 (ref.)
Rural	29,471	7279	41.2	1.03 (0.99–1.06)	15,148	3360	36.3	1.03 (0.98–1.08)	14,323	3919	46.6	1.02 (0.98–1.09)
Income												
High	45,808	11,048	39.9	1 (ref.)	23,209	4955	34.7	1 (ref.)	22,599	6093	45.5	1 (ref.)
Low 25%	13,532	3444	43	1.06 (1.02–1.10)	6713	1561	38.2	**1.07 (1.01–1.14)**	6819	1883	47.9	1.04 (0.99–1.09)
BMI												
< 25 kg/m^2	41,961	10,085	39.8	1 (ref.)	23,541	5102	35.2	1 (ref.)	18,420	4983	46	1 (ref.)
≥ 25 kg/m^2	17,379	4407	42.5	0.98 (0.92–1.03)	6381	1414	36.4	1.01 (0.92–1.11)	10,998	2993	46.1	0.96 (0.89–1.03)
Smoking status												
Never/former	57,241	13,814	40	1 (ref.)	28,715	6140	34.7	1 (ref.)	28,526	7674	45.6	1 (ref.)
Current	2099	678	58.1	**1.41 (1.30–1.53)**	1207	376	54.8	**1.50 (1.35–1.67)**	892	302	62.7	**1.31 (1.16–1.47)**
Alcohol consumption												
None	44,225	10,877	40.6	1 (ref.)	19,974	4312	34.7	1 (ref.)	24,251	6565	45.7	1 (ref.)
>0 g/day	15,115	3615	40.5	1.06 (1.01–1.10)	9948	2204	36.9	1.04 (0.98–1.10)	5167	1411	47.6	1.06 (1.00–1.12)
Physical activity												
None	48,517	11,797	40.3	1 (ref.)	25,132	5459	35.3	1 (ref.)	23,385	6338	45.9	1 (ref.)
Regular exercise	10,823	2695	42	1.02 (0.98–1.07)	4790	1057	36.5	1.02 (0.96–1.09)	6033	1638	46.6	1.02 (0.96–1.07)
Hypertension												
No	48,015	11,252	38.7	1 (ref.)	28,016	6049	35.1	1 (ref.)	19,999	5203	44	1 (ref.)
Yes	11,325	3240	48.7	1.05 (1.00–1.10)	1906	467	40.2	1.013 (0.92–1.12)	9419	2773	50.5	**1.06 (1.01–1.12)**
Diabetes												
No	55,998	13,505	40	1 (ref.)	29,413	6373	35.2	1 (ref.)	26,585	7132	45.4	1 (ref.)
Yes	3342	987	51.3	1.03(0.97–1.11)	509	143	48.7	1.87 (0.99–1.40)	2833	844	51.7	1.02 (0.95–1.10)
Dyslipidemia												
No	50,381	11,910	38.9	1 (ref.)	28,643	6166	35	1 (ref.)	21,738	5744	44.4	1 (ref.)
Yes	8959	2582	50.4	**1.10 (1.05–1.16)**	1279	350	47.4	**1.24 (1.10–1.40)**	7680	2232	50.9	**1.08 (1.03–1.14)**
Chronic kidney disease												
No	59,174	14,441	40.5	1 (ref.)	29,871	6505	35.4	1 (ref.)	29,303	7936	45.9	1 (ref.)
Yes	166	51	58.2	1.23 (0.94–1.62)	51	11	34.6	0.98 (0.54–1.79)	115	40	71.8	1.32 (0.97–1.80)
Anthracycline												
No	28,793	6488	36.6	1 (ref.)	13,875	2612	29.9	1 (ref.)	14,918	3876	43.2	1 (ref.)
Yes	30,547	8004	44.5	**1.17 (1.13–1.22)**	16,047	3904	40.5	**1.26 (1.18–1.34)**	14,500	4100	49.1	**1.10 (1.05–1.16)**
Taxane												
No	42,887	10,086	38.1	1 (ref.)	21,112	4332	32.6	1 (ref.)	21,775	5754	43.7	1 (ref.)
Yes	16,453	4406	47.6	**1.12 (1.07–1.16)**	8810	2184	42.9	**1.11 (1.04–1.18)**	7643	2222	53.4	**1.12 (1.06–1.19)**

Table 4 (continued)

	All age				Age ≤ 50				Age > 50			
	Subjects, *N*	**Case, *N***	**IR (per 1,000 PY)**	**Adjusted sHR* (95% CI)**	**Subjects, *N***	**Case, *N***	**IR (per 1,000 PY)**	**Adjusted sHR* (95% CI)**	**Subjects, *N***	**Case, *N***	**IR (per 1,000 PY)**	**Adjusted sHR* (95% CI)**
Trastuzumab												
No	50,770	12,235	39.7	1 (ref.)	26,150	5574	34.4	1 (ref.)	24,620	6661	45.6	1 (ref.)
Yes	8570	2257	46	1.03 (0.98–1.08)	3772	942	43.1	**1.08 (1.01–1.17)**	4798	1315	48.4	0.99 (0.93–1.06)
Endocrine therapy												
No	15,011	3830	43.5	1 (ref.)	6377	1450	38.2	1 (ref.)	8634	2380	47.6	1 (ref.)
Tamoxifen	28,056	6267	35.9	0.98 (0.94–1.03)	21,400	4532	33.8	0.96 (0.90–1.02)	6656	1735	42.7	1.00 (0.94–1.07)
Aromatase inhibitor	14,869	4007	45.9	0.99 (0.94–1.03)	1407	375	46.2	1.08 (0.96–1.21)	13,462	3632	45.9	0.98 (0.93–1.04)
Tamoxifen and Aromatase inhibitor	1404	388	55.5	**1.27 (1.14–1.41)**	738	159	44.5	1.08 (0.92–1.28)	666	229	66.8	**1.41 (1.23–1.61)**
Radiation therapy												
No	16,637	4125	41.6	1 (ref.)	7991	1696	34.8	1 (ref.)	8646	2429	48.3	1 (ref.)
Yes	42,703	10,367	40.2	0.97 (0.94–1.01)	21,931	4820	35.7	0.99 (0.94–1.05)	20,772	5547	45.1	0.96 (0.91–1.00)

Abbreviations: PY, person-years; sHR, sub-distribution hazard ratio; CI, confidence interval

* adjusted for all variables listed in the Table 4

50 years, which aligns with prior studies reporting greater prevalence of psychological distress and depressive symptoms in this population compare to older patients [7, 31, 32]. Given the higher likelihood of young women being diagnosed with a more aggressive form of breast cancer [33], it is reasonable to assume that they may experience elevated psychological distress, potentially placing them at a greater risk of depression compared to older women. Additionally, several studies have documented the increased susceptibility of younger women with breast cancer to psychological distress [34–36] and pain [37, 38] compared to their older counterparts. Overall, the challenges young breast cancer patients face during diagnosis (potentially dealing with a more aggressive cancer type [39]), treatment (facing menopausal side-effects [40]), and post-treatment (such as extended medication use, difficulties in sex life [10], or concern about fertility [41]) lead to a heightened risk of depression. Furthermore, younger women may experience a greater sense of frustration as their expectations for health or femininity are higher, further exacerbating their psychological distress [42].

Our study also showed that the increased risk of depression among younger breast cancer survivors persists longer than among older breast cancer survivors. Younger survivors had a 16% higher risk than matched controls after 1 year, which decreased to similar levels as the controls after 3 years. Older survivors showed no increased risk after 1 year and a decreased risk compared to controls after 3 years. An observational study conducted in the USA found that depressive symptoms in younger women with breast cancer decrease significantly after the first year but remain slightly higher than those in older women over a 26-month period [43]. Similarly, a German study found a higher prevalence of depression among younger patients even after 5 years [44]. While our study concurs with previous studies showing that younger patients are at higher risk, we also found that their depression risk eventually decrease to levels similar to the control group, which we believe is a novel finding.

Interestingly, we found that survivors older than 50 years had a lower risk of depression compared to matched controls after 3 and 5 years. To the best of our knowledge, only one German study has shown a lower prevalence of severe depression in breast cancer survivors older than 80 compared to non-cancer controls [45]. Most prior research has either compared depression symptoms across age groups [46–48] or investigated the prevalence of depressive symptoms in older patients exclusively [49–52], showing that older women with breast cancer experience subsequent depression to a lesser extent than younger counterpart. Contrary to studies reporting high levels of psychological depression or anxiety within 1 year after diagnosis or surgery in older

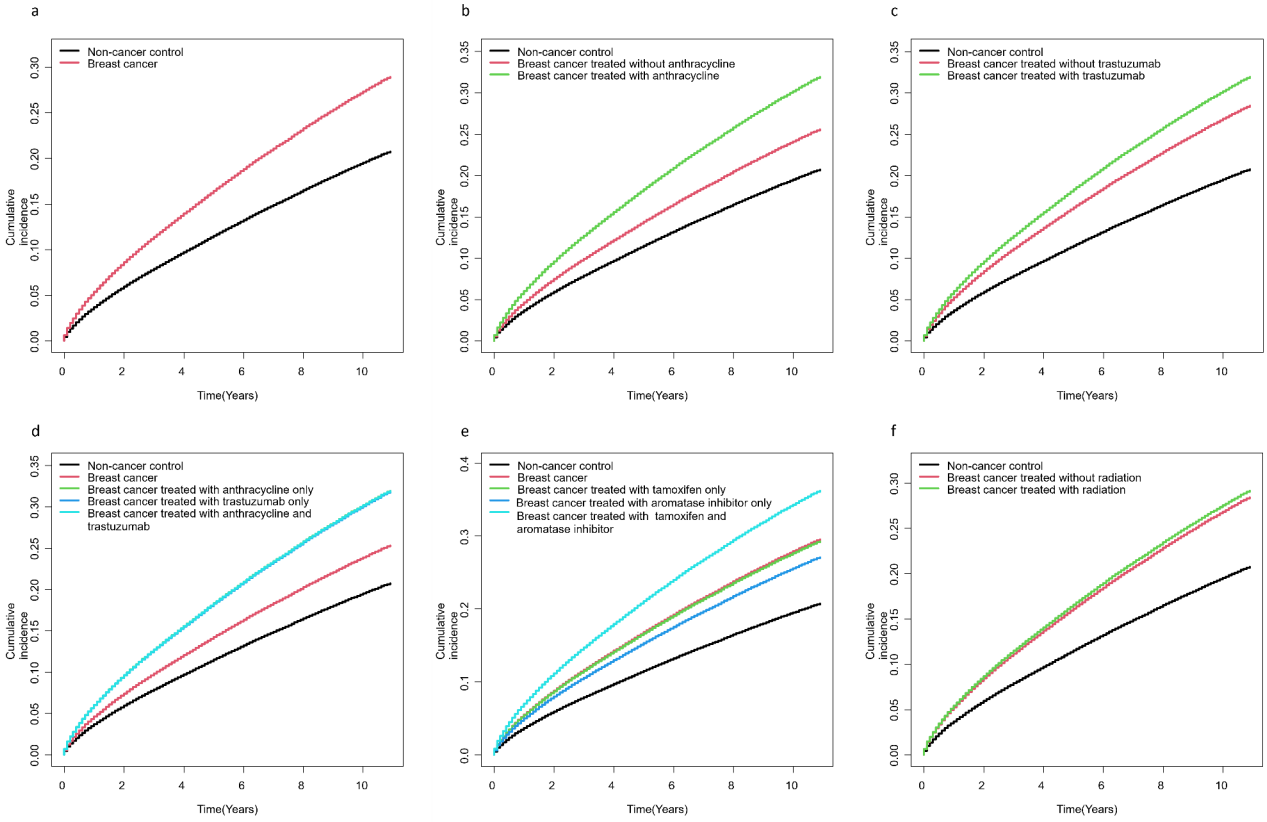

Fig. 2 Cumulative incidence of depression according to treatment type. Overall (**a**), anthracycline (**b**), trastuzumab (**c**), anthracycline and trastuzumab (**d**), tamoxifen and aromatase inhibitor (**e**), radiation therapy (**f**)

breast cancer patients [51, 52], we did not show a significant increase in depression risk compared to controls in the first year, and the risk decreased over time.

The decreased risk of depression among older breast cancer survivors can be attributed to several factors. Older women tend to have a greater mental capacity to adapt to their situation after a cancer diagnosis [47, 53]. Their passive and introverted coping strategies help them maintain high functioning in familiar environments under threatening conditions [53], effectively managing health outcomes using realistic coping methods from their life experiences and problem-solving skills [54]. Some older women exhibit post-traumatic growth, experiencing positive psychological change after overcoming significant challenges like cancer. This growth can include a greater appreciation for life, enhanced personal strength, improved relationships, and a reevaluation of priorities [55]. Lastly, social adaptation related to family and work situations might positively affect older survivors, leading to decreased depression risk [56]. Increased attention and care from family members and minimal work-related distress due to retirement may contribute to this decreased risk.

We found that the use of anthracycline and taxane was associated with an increased depression risk in breast cancer survivors. Chemotherapy-related depression is well-documented, with previous studies showing a two-fold increase in depressive symptoms among patients with breast cancer undergoing chemotherapy [15, 16]. A Taiwanese cohort study reported a higher risk depressive disorders with chemotherapy (adjusted HR 1.56; 95% CI 1.39–1.74) [13]. A randomized controlled study found that anthracycline-based chemotherapy increased depression rates by 23.9% [57]. The mechanism behind chemotherapy-induced depression includes side effects such as interference with daily life, body image issues, sexual dysfunction, and persistent tiredness and joint pain. Additionally, taxane-based drugs may damage nerve cell structures and functions in the brain, potentially leading to depression [58].

We also found that treatment with aromatase inhibitors and tamoxifen was associated with a higher risk of depression in older breast cancer survivors. While research on tamoxifen and depression is inconclusive, some studies report depression as a side effect leading to its discontinuation [17, 59], while others find no association [18, 60] or even fewer depressive symptoms

with tamoxifen use [61]. Aromatase inhibitors alone have been linked to an increased depression risk (adjusted HR 1.46; 95% CI 1.11–1.91) [13]. One study noted worsened depressive symptoms in postmenopausal women using aromatase inhibitors [62]. Our results indicate that breast cancer survivors older than 50 who underwent treatment with both tamoxifen and aromatase inhibitors had a 41% increased risk of depression. This highlights the need for close monitoring of depressive symptoms in post-menopausal patients switching between these treatments.

Limitations

Our study has some limitations. First, as this study is based on claims data, clinical information such as cancer stage and BRCA mutation was not available. Second, there is the possibility of under-detection of depression by clinical diagnosis. This may be attributed to the characteristics of depressive patients in Asian countries, who may be hesitant to seek healthcare due to social stigma [63, 64]. Third, data on certain types of surgery and treatments associated with increased risk of depression, such as gonadotropin-releasing hormone agonist (GnRHa), were unavailable for our study period (2010−2016). This limits the applicability of our findings in the context of contemporary breast cancer care for premenopausal women, where the risk of depression can be higher with either radical surgery or GnRHa use [65–67]. Last, caution should be exercised when generalizing our findings, as we only included data from the Korean population.

Conclusion

Our study found that breast cancer survivors have a 39% increased risk of depression compared to non-cancer controls. Survivors younger than 50 years faced a higher risk in the first year after diagnosis, while those older than 50 years showed a decreased risk at 3 and 5 years. Adjuvant treatments like chemotherapy and endocrine therapy were identified as contributing factors. These findings highlight the need for targeted screenings and interventions, especially for younger survivors and those undergoing chemotherapy and endocrine therapy.

Abbreviations

sHR	sub-distribution hazard ratio
aHR	adjusted hazard ratio
CI	confidence intervals
NHIS	National Health Insurance Service
ICD-10	International Classification of Diseases, Tenth Revision
BMI	body mass index
CKD	chronic kidney disease

Supplementary Information

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Supplementary Material 1: Additional file 1: Table S1. Selected previous studies on depression and breast cancer

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Author contributions

Conceptualization: HLC, BSK, KH, DWS. Resources: BSK, KH, DWS. Data Curation: HLC, BSK, KH, DWS. Methodology and Formal Analysis: BSK, KH. Investigation: HLC, BSK, KH, DWS. Interpretation: All authors. Writing-Original draft: HLC. Writing-Review and Editing: All authors. Supervision: KH, DWS. All authors read and approved by the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Samsung Medical Center (approval no. NHIS-2023-1-212). The NHIS granted permission to use the NHIS database. Informed consent was waived because all screened populations agreed to transfer their screening results to the NHIS, and the NHIS database was constructed after anonymization of individual identities.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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