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Association between Benzodiazepine and Dementia Risk in Treating Depression after Breast Cancer Diagnosis: A Nationwide Population-Based Cohort Study

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Purpose: This study investigates the risk of developing dementia in breast cancer patients diagnosed with depression within 2 years of their cancer diagnosis, comparing those taking antidepressants alone versus those taking both antidepressants and benzodiazepines.

Materials and Methods: Utilizing data from the Korean National Health Insurance claims database collected over 14 years, we included a cohort of 197917 breast cancer patients. Among them, 19170 were diagnosed with depression within 2 years of their cancer diagnosis. After matching for comorbidities and age, we included 1376 patients in each group for 1:1 matching, and 1326 patients taking only antidepressants and 5304 patients taking both antidepressants and benzodiazepines for 1:4 matching.

Results: In the initial 1:1 matched analysis, no significant difference in dementia incidence was observed between the group taking only antidepressants and the group taking both antidepressants and benzodiazepines. However, further detailed analysis revealed that patients taking higher doses or using benzodiazepines for longer durations had an increased risk of dementia. In the 1:4 matched analysis, the group taking both medications exhibited a significantly higher incidence of dementia compared to those taking only antidepressants (hazard ratio, 1.807; 95% confidence interval, 1.263–2.583; p=0.0012).

Conclusion: This study underscores the importance of cautious benzodiazepine use in breast cancer patients diagnosed with depression, given its potential to significantly increase dementia risk.

Key Words: Breast cancer, depression, benzodiazepines, dementia, cognitive impairment

INTRODUCTION

Depression is a common psychiatric disorder that affects many cancer patients, increasing their overall burden and impairing their quality of life.[1] The prevalence of major depressive disorder in cancer patients is two to three times higher than in the general population, suggesting that approximately 14.9% of cancer patients are diagnosed with major depressive disorder.[2] Depression has psychological and biological effects related to inflammatory responses and inflammation-related chemokines in cancer patients. It can influence the progression of cancer, leading to poor prognosis.[3] Therefore, it is important not to overlook depression in cancer patients and to actively treat it using various psychological and medical methods.[1]

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Breast cancer significantly affects the quality of life of patients, both physically and psychologically, which can lead to reduced treatment compliance, ultimately increasing mortality rates.[4] The worldwide prevalence of depression among patients with breast cancer is 32.2%.[5] Antidepressants or benzodiazepines are commonly used to treat depression in patients with breast cancer and other types of cancer. These medications aim to improve overall mental well-being by alleviating depressive symptoms, anxiety, insomnia, and other depression-related symptoms.[6,7] However, benzodiazepines are associated with an increased incidence of dementia and cognitive impairment.[8] Therefore, benzodiazepines must only be used for short-term periods and discontinued thereafter.

Previously, we found an inverse association between breast cancer and the occurrence of dementia, even when considering the impact of the adverse effects of cancer treatments on cognitive function.[9] Our finding aligned with earlier research indicating that cancer patients have a reduced risk of developing dementia.[10] The results of our previous study, indicating an inverse association between breast cancer and the occurrence of dementia[9] present an intriguing question for physicians treating depression in cancer patients, particularly given concerns about benzodiazepines potentially impairing cognitive function.[8] If the protective effect against cognitive decline associated with cancer outweighs the cognitive decline effect induced by benzodiazepines, physicians may feel less concerned about cognitive side effects related to medication. This would enable them to more actively manage symptoms such as depressed mood, anxiety, and insomnia in cancer patients diagnosed with depression through the use of benzodiazepines. To resolve this question, we decided to investigate the impact on cognitive function when cancer patients diagnosed with depression were taking antidepressants with benzodiazepines.

To our knowledge, no study has compared the cognitive impairment caused by the use of benzodiazepines in patients with cancer, especially breast cancer. Therefore, we compared the risk of developing dementia in patients with breast cancer who were diagnosed with depression within 2 years of cancer diagnosis when taking antidepressants alone versus when taking antidepressants with benzodiazepines, using a nationwide population-based cohort registry. Our research may guide physicians on how to use benzodiazepines for patients with breast cancer diagnosed with depression.

MATERIALS AND METHODS

Study design and database

This retrospective observational cohort study used nationally representative data collected from the Korean National Health Insurance (NHI) claims database over 14 years, from January 2007 to December 2021. The NHI database includes all medical data, such as personal information, date of disease registry, diagnostic codes, procedure information, and prescription information. The disease codes specified in the International Classification of Diseases, 10th revision (ICD-10), were used to record diagnoses.

All individual information was anonymized before data processing to comply with the privacy guidelines of the Health Insurance Portability and Accountability Act. The study protocol was approved by the Institutional Review Board (IRB) of Gangnam Severance Hospital (local IRB number: 3-2019-0425), which waived the need for informed consent based on the retrospective cohort design. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

We included patients who had been diagnosed with breast cancer (ICD-10 code; C50) between 2008 and 2013 and who had not seen a physician for any type of cancer (ICD-10 code; C code) during the preceding 2-year period (2-year washout period before the study period). We selected patients who were newly diagnosed with depression within 2 years of their breast cancer diagnosis. The study enrollment date for patients was defined as the date they were first prescribed antidepressants following their diagnosis of depression. Follow-up duration (in months) was calculated from the date of enrollment. Participants were monitored for the development of dementia until 2021. Patients without an event were censored on December 31, 2021. The overall risk of any type of dementia was compared between the group taking only antidepressants and the group taking both antidepressants and benzodiazepines.

Predictor and outcome variables

The main outcomes of interest were whether benzodiazepine use increased the risk of all types of dementia (ICD-10 codes F00.0, F00.1, F00.2, F00.9, F01.0, F01.1, F01.2, F01.3, F01.8, F01.9, F02.0, F02.1, F02.2, F02.3, F02.8, F03, G30.0, G30.1, G30.8, G30.9, G31.0, G31.01, G31.02, G31.03, G31.04, G31.08, and G31.82) in patients with breast cancer who had been diagnosed with depression (ICD-10 codes F32, F33) within 2 years after cancer diagnosis. These codes include Alzheimer's disease, vascular dementia, dementia with Lewy bodies, frontotemporal dementia, Parkinson's disease, and other types of dementia. When entering the diagnosis code for dementia into a patient's medical record, a Korean clinician usually makes a diagnosis based on both diagnostic impressions and test results, such as the Mini-Mental State Examination,[11] Clinical Dementia Rating,[12] and Global Deterioration Scale.[13] Magnetic resonance imaging scans or neuropsychological tests are also often performed. However, that information could not be obtained from the NHI. In this context, considering the medical environment in Korea, with the relative ease of visiting a physician, to increase the diagnostic validity of neurodegenerative diseases, dementia was defined as at least 10 contacts with a physician resulting in a corresponding diagnostic code between 2014 and 2021.

To analyze the relationship between benzodiazepines and dementia, we investigated the doses of benzodiazepines used (dosage of benzodiazepine) and the number of days they were used (duration of benzodiazepine use). The dosage of benzodiazepine (mg/day) was calculated by converting all used benzodiazepines to diazepam, considering benzodiazepine equivalent doses (10 mg of diazepam=1 mg of lorazepam=0.5 mg of clonazepam=0.5 mg of alprazolam=1 mg of etizolam=12.5 mg of chlordiazepoxide=10 mg of clobazam), summing the total prescribed doses, and then dividing by the follow-up duration.[14-16] The duration of benzodiazepine use (in months) was calculated by summing all the prescribed days. If there were multiple prescriptions on the same prescription record, the duration was calculated using the maximum number of days from those prescriptions. We analyzed the median values for the dosage of benzodiazepine and the duration of benzodiazepine use before matching, after 1:1 matching, and after 1:4 matching for each case. We analyzed the risk of developing dementia when the dosage of benzodiazepine or the duration of benzodiazepine use was either less or greater than the median.

Study population

In total, 197917 patients with breast cancer were included in this study (Fig. 1). Among them, 19170 patients who were diagnosed with depression within 2 years of cancer diagnosis were included. Patients who were diagnosed with breast cancer or depression before 2008, as well as those who were diagnosed with other cancers before the diagnosis of breast cancer or depression, were excluded. We also excluded patients who were diagnosed with dementia before their breast cancer or depression diagnosis, as well as those diagnosed with dementia before taking antidepressants or benzodiazepines. To minimize misclassification errors, patients diagnosed with depression and those with mental retardation (ICD-10 code: F7), schizophrenia (ICD-10 code: F2), bipolar disorder (ICD-10 codes: F30 and F31), and epilepsy (ICD-10 codes: G40 and G41) were excluded from the analysis. Lastly, we excluded patients who were diagnosed with depression within 2 years after a breast cancer diagnosis but were not prescribed antidepressants. To minimize potential confounding and ensure comparability between groups, we performed 1:1 propensity score matching, which resulted in 1376 patients in both the group taking only antidepressants and the group taking both antidepressants and benzodiazepines. Recognizing that the group taking both medications was larger, we also conducted 1:4 matching to leverage the larger sample size, thereby increasing the statistical power of our analysis while maintaining bal-

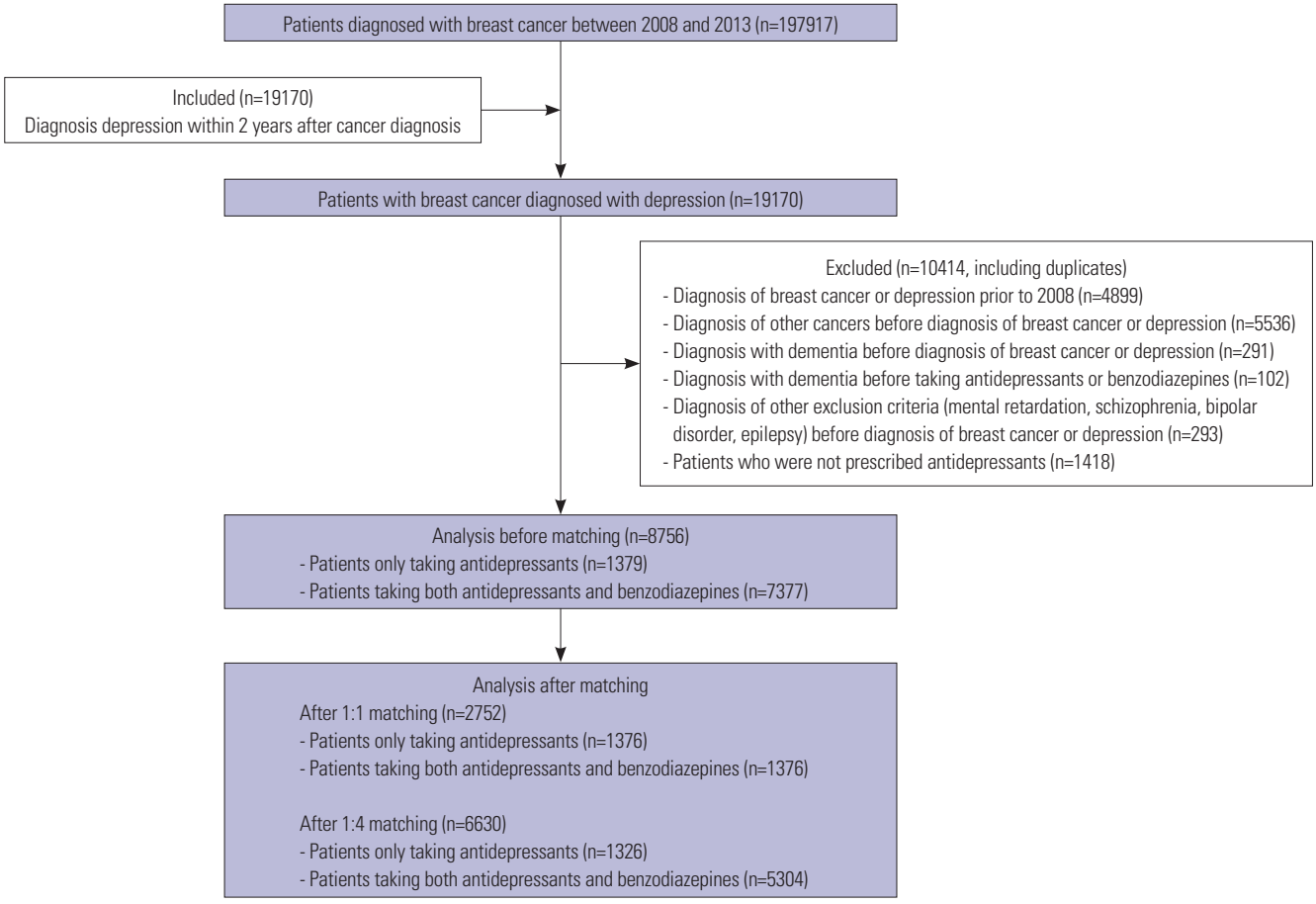

Fig. 1. Flowdiagram for the selection and enrollment of eligible participants in this study.

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ance. This approach yielded 1326 patients in the antidepressant-only group and 5304 patients in the group taking both antidepressants and benzodiazepines, allowing for a more robust comparison.

Confounding variables

Confounding variables included several comorbidities and age. This study defined confounding variables related to the development of dementia as follows: diabetes (ICD-10 codes E10, E11, E12, E13, and E14), hypertension (ICD-10 code I10), hyperlipidemia (ICD-10 code E78), chronic obstructive pulmonary disease (COPD; ICD-10 code J44), chronic kidney disease (CKD; ICD-10 code N18), liver cirrhosis (LC; ICD-10 codes K74 and K703), and heart failure (ICD-10 code I50). Furthermore, we defined the presence of comorbidities as any diagnosis of the aforementioned codes within the 2 years preceding the enrollment date.

To reduce selection bias, we estimated propensity scores for each of the participants to match the subjects who took only antidepressants to those who took both antidepressants and benzodiazepines. This was calculated for each participant using logistic regression analysis, including variables of comorbidities and age. A nearest neighbor-matching algorithm with a "greedy" approach was performed to match the subjects using propensity scores.[17,18] Randomization was performed using an algorithm in the SAS software program (ver. 9.4, SAS Institute Inc., Cary, NC, USA). We tested the proportional hazards assumption by including an interaction term between variables and natural-log-transformed follow-up time. We also checked the log-minus-log survival plots.

Statistical analysis

The primary endpoint was the overall risk of dementia in patients with breast cancer who were taking antidepressants or benzodiazepines compared to the comorbidities- and age-matched control group. To compare the characteristics between the two groups, the Student's t-test was used to analyze continuous variables, and the chi-square test or Fisher's exact test was used to analyze categorical variables. The cumulative dementia incidence rates for the two groups were estimated using Kaplan–Meier curves and compared with the log-rank test. Cox proportional hazard models were used to determine the hazard ratios (HRs) and 95% confidence intervals (CIs) to investigate dementia onset after adjusting for confounding variables. We applied the backward likelihood method (entry effects: p=0.05; removal effects: p=0.05). Statistical significance was set at a two-sided p<0.05. Statistical analyses were performed using SAS software (ver. 9.4, SAS Institute Inc.).

Table 1. Comparison of Clinical Characteristics of Patients Taking Antidepressants with and without Benzodiazepines

Dementia	Before matching				After matching (1:1 matching)				After matching (1:4 matching)			
	Total	Antidepressants (n=1379)	Antidepressants with benzodiazepines (n=7377)	p	Total	Antidepressants (n=1376)	Antidepressants with benzodiazepines (n=1376)	p	Total	Antidepressants (n=1326)	Antidepressants with benzodiazepines (n=5304)	p
No	8219 (93.87)	1345 (97.53)	6874 (93.18)	<0.0001	2649 (96.26)	1342 (97.53)	1307 (94.99)	0.0004	6277 (94.68)	1293 (97.51)	4984 (93.97)	<0.0001
Yes	537 (6.13)	34 (2.47)	503 (6.82)		103 (3.74)	34 (2.47)	69 (5.01)		353 (5.32)	33 (2.49)	320 (6.03)	

Values are presented as number (%).

RESULTS

Characteristics of the subjects

Table 1 shows the between-group differences in developing dementia. Before matching, the difference in dementia incidence between the group of patients taking antidepressants and the group taking antidepressants with benzodiazepines was significant (p<0.0001). After 1:1 matching (p=0.0004) and 1:4 matching (p<0.0001), the difference in dementia incidence between the two groups remained significant. Supplementary Table 1 (only online) shows the between-group differences in comorbidities and ages. Before matching, the mean ages (± standard deviation, SD) of patients taking antidepressants and those taking antidepressants with benzodiazepines were 49.96±10.10 and 51.70±10.26 years, respectively [standardized mean difference (SMD)=0.171]. After 1:1 matching, the mean ages (±SD) of patients taking antidepressants and those taking antidepressants with benzodiazepines were 50.00±10.07 and 49.88±10.09 years, respectively (SMD=0.012); and after 1:4 matching, the mean ages (±SD) of patients taking antidepressants and those taking antidepressants with benzodiazepines were 50.37±9.88 and 50.20±9.74 years, respectively (SMD=0.017). Not only for ages but also for all other comorbidities such as diabetes, hypertension, hyperlipidemia, COPD, CKD, LC, and heart failure, the SMD values were below 0.1 in both 1:1 matching and 1:4 matching. This demonstrates that matching between the group of patients taking antidepressants and the group taking antidepressants with benzodiazepines was successfully achieved. During the matching process, all variables met the proportional hazard assumption.

Risk analysis of dementia

Before matching, the median follow-up duration was 95.48±28.99 months. Patients taking only antidepressants had a significantly lower incidence of dementia (p=0.0001). After 1:1 matching, benzodiazepines did not significantly affect the incidence of dementia (p=0.0850). After 1:4 matching, the patients taking only antidepressants had a significantly lower incidence of dementia compared to those taking antidepressants with benzodiazepines (p=0.0045) (Fig. 2).

Next, we analyzed the cumulative incidence of dementia when the use of benzodiazepines was either less or greater than the median. Before matching, after 1:1 matching, and after 1:4 matching, the median values for the dosage of benzodiazepine (mg/day) were 0.316, 0.265, and 0.295, respectively. Before matching, an increased dosage of benzodiazepine was associated with an increased risk of dementia (p<0.0001), which persisted even after 1:1 matching (p<0.0001) and after 1:4 matching (p<0.0001) (Supplementary Fig. 1, only online).

Furthermore, we analyzed the cumulative incidence of dementia when the duration of benzodiazepine use was either less or greater than the median. Before matching, after 1:1 matching, and after 1:4 matching, the median values for the duration of benzodiazepine use (in months) were 2.066, 1.672, and 1.967, respectively. Before matching, long-term benzodiazepine use was associated with an increased risk of dementia (p<0.0001), which persisted even after 1:1 matching (p<0.0001) and after 1:4 matching (p<0.0001) (Supplementary Fig. 2, only online).

In the univariate Cox proportional hazard analyses of the unmatched cohorts, diabetes, hypertension, COPD, LC, age, taking antidepressants with benzodiazepines, taking more benzodiazepines over median, and taking them for a longer duration over the median were significantly positively associated with the incidence of dementia (Table 2). In the multivariate analysis of the unmatched cohort, LC, age, and taking antidepressants with benzodiazepines were significantly positively associated with the incidence of dementia (Table 3). After 1:1 matching for comorbidities and age in the univariate Cox proportional hazard analyses, the results showed that hyperten-

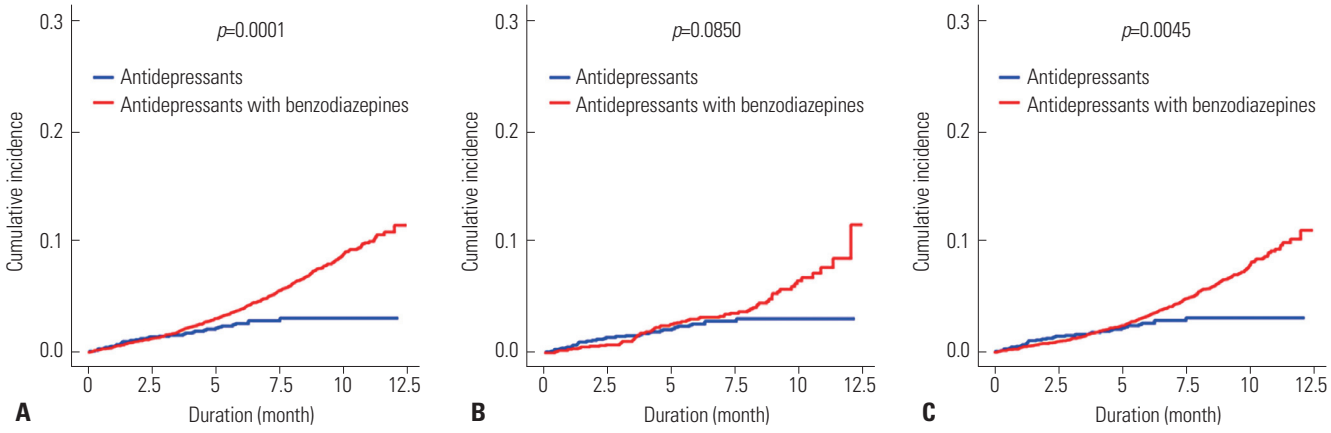

Fig. 2. Kaplan–Meier analysis of the incidence of dementia between patients with breast cancer taking antidepressants with or without benzodiazepines. (A) Before matching, patients taking antidepressants with benzodiazepines exhibited a higher incidence of dementia than those taking antidepressants without benzodiazepines (p=0.0001, log-rank test). (B) After matching (1:1 matching), benzodiazepines did not significantly affect the incidence of dementia (p=0.0850, log-rank test). (C) After matching (1:4 matching), patients taking antidepressants with benzodiazepines exhibited a higher incidence of dementia than those taking antidepressants without benzodiazepines (p=0.0045, log-rank test).

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Table 2. Risk of Developing Dementia from Analyses Using Cox Proportional Hazard Models, Univariable Model

Variable	Univariable model					
	Before matching		After matching (1:1 matching)		After matching (1:4 matching)	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Group						
Antidepressants	Ref		Ref		Ref	
Antidepressants with benzodiazepines	1.949 (1.376–2.761)	0.0002	1.439 (0.949–2.182)	0.0867	1.675 (1.169–2.401)	0.0049
Dosage of benzodiazepine (mg/day)	1.010 (1.009–1.011)	<0.0001	1.019 (1.014–1.023)	<0.0001	1.023 (1.021–1.026)	<0.0001
Duration of benzodiazepine use (month)	1.008 (1.005–1.011)	<0.0001	1.009 (1.001–1.017)	<0.0001	1.009 (1.005–1.013)	<0.0001
Dosage of benzodiazepine (mg/day)						
None	Ref					
<Median	0.904 (0.617–1.326)	0.6057	0.676 (0.372–1.228)	0.1987	0.744 (0.492–1.126)	0.1615
≥Median	3.008 (2.116–4.275)	<0.0001	2.198 (1.420–3.402)	0.0004	2.613 (1.815–3.762)	<0.0001
Duration of benzodiazepine use (month)						
None	Ref					
<Median	1.108 (0.762–1.613)	0.5909	0.656 (0.356–1.207)	0.1749	0.882 (0.588–1.323)	0.5441
≥Median	2.770 (1.947–3.940)	<0.0001	2.182 (1.411–3.375)	0.0004	2.429 (1.685–3.502)	<0.0001
Diabetes						
No	Ref		Ref		Ref	
Yes	2.211 (1.101–4.442)	0.0258	1.508 (0.210–10.812)	0.6827	0.558 (0.078–3.974)	0.5605
Hypertension						
No	Ref		Ref		Ref	
Yes	2.826 (1.630–4.901)	0.0002	8.471 (2.685–26.729)	0.0003	4.649 (2.201–9.820)	<0.0001
Hyperlipidemia						
No	Ref		Ref		Ref	
Yes	0.984 (0.440–2.202)	0.9690	0.490 (0.068–3.513)	0.4774	0.238 (0.015–3.826)	0.3109
COPD						
No	Ref		Ref		Ref	
Yes	3.484 (1.558–7.791)	0.0024	4.207 (0.586–30.185)	0.1531	2.936 (0.731–11.788)	0.1289
CKD						
No	Ref					
Yes	7.731 (0.485–123.322)	0.1478				
LC						
No	Ref					
Yes	968.600 (168.697–561.363)	<0.0001				
Heart failure						
No	Ref					
Yes	4.721 (0.293–76.013)	0.2737				
Age (yr)	1.110 (1.101–1.118)	<0.0001	1.117 (1.100–1.134)	<0.0001	1.112 (1.103–1.121)	<0.0001

CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstruction pulmonary disease; HR, hazard ratio; LC, liver cirrhosis.

sion, age, taking more benzodiazepines over median (HR, 2.198; 95% CI, 1.420–3.402; p=0.0004), and taking them for a longer duration over the median were significantly associated with a higher incidence of dementia (HR, 2.182; 95% CI, 1.411–3.375; p=0.0004). After 1:4 matching for comorbidities and age in the univariate Cox proportional hazard analyses, taking antidepressants with benzodiazepines (HR, 1.675; 95% CI, 1.169–2.401; p=0.0049), taking more benzodiazepines over median (HR, 2.613; 95% CI, 1.815–3.762; p<0.0001), and taking them for a longer duration over the median were significantly associated with a higher incidence of dementia (HR, 2.429; 95% CI, 1.685–3.502; p<0.0001). In the multivariate analysis, taking antidepressants with benzodiazepines was associated with a higher incidence of dementia in the 1:1 matched cohort (HR, 1.532; 95% CI, 1.012–2.321; p=0.0440) and 1:4 matched cohort (HR, 1.807; 95% CI, 1.263–2.583; p=0.0012).

In the multivariate analysis of dosage of benzodiazepine of the unmatched cohorts, taking benzodiazepines was associated with a higher incidence of dementia (HR, 1.009; 95% CI, 1.008–1.01; p<0.0001), and taking more benzodiazepines over the median was significantly associated with a higher incidence of dementia (HR, 2.347; 95% CI, 1.654–3.331; p<0.0001)

Table 3. Risk of Developing Dementia from Analyses Using Cox Proportional Hazard Models, Multivariable Model

Variables	Multivariable model (antidepressants vs. antidepressants with benzodiazepines)					
	Before matching		After matching (1:1 matching)		After matching (1:4 matching)	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Group						
Antidepressants	Ref		Ref		Ref	
Antidepressants with benzodiazepines	1.681 (1.189–2.378)	0.0033	1.532 (1.012–2.321)	0.0440	1.807 (1.263–2.583)	0.0012
Diabetes						
No	Ref		Ref		Ref	
Yes	1.295 (0.655–2.560)	0.4566	0.780 (0.109–5.599)	0.8052	0.631 (0.126–3.159)	0.5757
Hypertension						
No	Ref		Ref		Ref	
Yes	1.480 (0.859–2.548)	0.1576	3.093 (0.973–9.831)	0.0557	1.686 (0.812–3.500)	0.1610
Hyperlipidemia						
No	Ref		Ref		Ref	
Yes	1.241 (0.570–2.700)	0.5869	0.672 (0.093–4.840)	0.6929	0.227 (0.014–3.683)	0.2970
COPD						
No	Ref		Ref		Ref	
Yes	1.683 (0.773–3.663)	0.1897	1.919 (0.266–13.823)	0.5177	2.544 (0.729–8.879)	0.1432
CKD						
No	Ref					
Yes	7.587 (0.473–121.631)	0.1523				
LC						
No	Ref					
Yes	394.208 (68.403–2271.840)	<0.0001				
Heart failure						
No	Ref					
Yes	9.401 (0.577–153.083)	0.1155				
Age (yr)	1.109 (1.101–1.117)	<0.0001	1.117 (1.099–1.134)	<0.0001	1.112 (1.103–1.122)	<0.0001

CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstruction pulmonary disease; HR, hazard ratio; LC, liver cirrhosis.

(Supplementary Tables 2 and 3, only online). After matching, taking benzodiazepines was associated with a higher incidence of dementia in the 1:1 matched cohorts (HR, 1.010; 95% CI, 1.006–1.015; $p<0.0001$) and 1:4 matched cohorts (HR, 1.016; 95% CI, 1.013–1.018; $p<0.0001$). Also, taking more benzodiazepines over the median was significantly associated with a higher incidence of dementia in the 1:1 matched cohorts (HR, 2.135; 95% CI, 1.381–3.300; $p=0.0006$) and 1:4 matched cohorts (HR, 2.566; 95% CI, 1.785–3.688; $p<0.0001$).

In the multivariate analysis of the duration of benzodiazepine use of the unmatched cohorts, taking benzodiazepines was associated with a higher incidence of dementia (HR, 1.004; 95% CI, 1.001–1.008; $p=0.0105$), and taking benzodiazepines longer over the median was significantly associated with a higher incidence of dementia (HR, 2.128; 95% CI, 1.498–3.023; $p<0.0001$) (Supplementary Tables 4 and 5, only online). After matching, taking benzodiazepines was associated with a higher incidence of dementia in the 1:4 matched cohorts (HR, 1.006; 95% CI, 1.002–1.010; $p=0.0038$). Also, taking benzodiazepines longer over median was significantly associated with a higher incidence of dementia in the 1:1 matched cohorts (HR, 2.110; 95% CI, 1.366–3.258; $p=0.0008$) and 1:4 matched cohorts (HR, 2.344; 95% CI, 1.629–3.371; $p<0.0001$). Detailed information regarding the dosage and duration of benzodiazepine use, as well as patient follow-up times, is available in Supplementary Tables 6, 7, and 8 (only online).

DISCUSSION

This study compared the risk of dementia between patients with breast cancer diagnosed with depression who were taking antidepressants alone and those taking antidepressants with benzodiazepines. It is the first nationwide longitudinal cohort study focusing specifically on patients with breast cancer diagnosed with depression and receiving medication for psychiatric symptoms. Our study used real-world data from the Korean NHI claims database to ensure the validity and representativeness of the findings. To enhance the accuracy of the causal relationships, we adjusted for comorbidities and age, which could influence interpretation, and minimized selection bias through propensity score matching. Additionally,

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to thoroughly analyze the relationship between the risk of dementia and the use of benzodiazepines, we conducted separate analyses based on both the dosage and duration of benzodiazepine use.

Patients with breast cancer diagnosed with depression taking antidepressants alone or antidepressants with benzodiazepines were followed for over 14 years. After matching the cohorts for confounders, such as medical comorbidities and age, patients taking antidepressants with benzodiazepines exhibited a higher risk of dementia. The risk of dementia increased with more and longer use of benzodiazepines, significantly in patients taking benzodiazepines over the median values of the dosage of benzodiazepine and the duration of benzodiazepine use. These findings align with a previous hypothesis that the use of benzodiazepines could lead to cognitive impairment.[19]

While the exact mechanism by which benzodiazepines contribute to cognitive decline is not yet fully understood, it is known that prolonged use of benzodiazepines could impair the body's ability to cope with early-phase brain lesions by interfering with excitatory synapses and decreasing cognitive reserve, a phenomenon referred to as the "limitation in cognitive reserve capacity."[20] Furthermore, benzodiazepines decrease brain-derived neurotrophic factor[21] while concurrently increasing the levels of β-amyloid precursor protein mRNA and tau protein phosphorylation.[22] All these alterations could heighten the risk of cognitive decline by promoting neuroinflammation, reducing synaptic plasticity and the effectiveness of brain insulin signaling, and increasing the accumulation of Aβ plaques and neurofibrillary tangles.[20]

In our previous study, we revealed an inverse relationship between cancer and neurodegeneration.[9] Based on our previous findings and several other studies, we focused on several proteins suspected to be related to the unique association between cancer and dementia. Pin1 (peptidylprolyl cis/trans isomerase, never in mitosis gene A-interacting 1) is a potential explanation for the inverse relationship between cancer and dementia.[23] Pin1, an enzyme critical for protein folding and cell cycle regulation, is overexpressed in many human tumors but exhibits diminished function in the brain tissues of patients with Alzheimer's disease. In mouse models of Alzheimer's disease, enhancing Pin1 expression in postnatal neurons reverses neurodegeneration,[24] while single nucleotide polymorphisms in the Pin1 promoter that suppress Pin1 expression have been linked to a higher risk of Alzheimer's disease[25] and a lower risk of cancer.[26] High levels of PVRIG (poliovirus receptor-related immunoglobulin domain-containing protein), an immune checkpoint receptor, can also reduce the occurrence of cancer but are simultaneously associated with a higher risk of dementia.[27] Furthermore, levels of very low-density lipoprotein (VLDL) are significant variables in this inverse relationship between cancer and dementia. Patients with dementia typically have higher VLDL levels,[28] while those with cancer generally have lower VLDL levels.[29]

However, in this study, our recent findings challenge the prevailing notion of an inverse relationship between cancer and dementia. This is why our study warrants significant attention. In our previous cohort study, we discovered that breast cancer was a predictor of a lower risk for dementia (HR, 0.091; 95% CI, 0.075–0.111; $p<0.001$).[9] This finding confirmed that cancer has a protective effect against cognitive decline, consistent with what has been reported in several prior studies.[23,27] However, in the current study, we analyzed data using the same methodology to investigate how cognitive function is affected when breast cancer patients, diagnosed in the same country and during the same time frame, receive pharmacological treatment for depression. The results demonstrated that breast cancer patients undergoing treatment for depression had a significantly increased risk of developing dementia. Notably, the likelihood of dementia increased significantly with the use of higher doses and longer durations of medication. This discovery led us to consider that certain factors may outweigh the protective effect of breast cancer on cognitive function. By comparing our previous research[9] with the current study, we inferred that the newly identified factor contributing to cognitive impairment is the use of benzodiazepines, an element added in the present study and one that has been reported in various prior studies as a potential contributor to cognitive decline.[8] This highlights the complexity of the relationship between cancer, dementia, and medication effects.

This study has several limitations. First, the diagnosis of dementia may not be objective. Contrary to the diagnosis process of breast cancer, which is highly definitive owing to its pathological confirmation, assessing cognitive problems primarily depends on the doctor's clinical experience and subjective judgment. To overcome this, we enrolled patients who had made more than 10 hospital visits due to cognitive decline and were subsequently diagnosed with dementia. Nonetheless, despite these efforts, if a patient had inherently high levels of anxiety, particularly excessive anxiety regarding their perceived cognitive decline, the criterion of "more than 10 hospital visits," established to enhance the objectivity of dementia diagnosis, could be compromised by repeated visits driven by anxiety. Furthermore, high anxiety in patients could also lead to secondary cognitive decline, which may further undermine the objectivity of the dementia diagnosis. If we had reviewed the neuropsychological tests or neuroimaging data of patients from an insurance claims database, a more precise analysis might have been possible. However, this was not feasible due to practical constraints. Second, this study did not take into account that depressive symptoms themselves can affect cognitive function. If patients who were taking benzodiazepines for simple insomnia, anxiety, or phobias without depressive symptoms had been properly selected and included in the study, it would have been possible to more accurately analyze the impact of benzodiazepines on cognitive function in pa-

tients with breast cancer. In the same context, this study did not consider the treatment progress of depression in patients taking psychiatric medications. Even though psychiatric medication was administered, if symptoms accompanying depression, such as depressed mood, anxiety, and insomnia, did not improve, these depressive symptoms could have affected cognitive function.[30] Third, although our sample size was large and the follow-up period was relatively long, we used longitudinal data from the South Korean population. Thus, the findings may not be generalizable to patients from other countries or different ethnicities. Fourth, while this study is meaningful in that it revealed a significant association between benzodiazepine use and cognitive decline in breast cancer patients, it only demonstrated that increased dosage and duration of benzodiazepine use, particularly at levels exceeding the median values among the patients included in this study, were significantly linked to cognitive impairment. However, it did not identify more specific or absolute thresholds for the dosage and duration of benzodiazepine use that would impact cognitive function. Fifth, this study utilized information recorded in the Korean NHI claims database, which does not include health checkup variables such as body mass index, smoking, alcohol consumption, or exercise, nor does it contain data on patient mortality. Due to these inherent limitations of the database, we were unable to analyze the potential effects of these variables on dementia incidence. Lastly, we did not explicitly consider the potential negative impact of cancer treatments such as chemotherapy and endocrine therapy on cognitive function, commonly referred to as "chemobrain."[31] However, our previous study using a comparable cohort found that the impact of cancer treatment on the occurrence of dementia in patients with breast cancer was not significant.[9] Therefore, it is unlikely that this limitation had a notable effect on the results. It is also important to note that this study did not account for potential interactions with medications used for the management of other medical conditions, which could have influences the results.

In conclusion, our findings suggest that the risk of dementia may be higher in patients with breast cancer diagnosed with depression who take both antidepressants and benzodiazepines, compared to those who take antidepressants alone. Additionally, the likelihood of dementia appears to increase with higher doses and longer use of benzodiazepines. Therefore, it may be advisable to use benzodiazepines at the lowest effective dose and for the shortest duration possible in these patients to help reduce the risk of cognitive impairment. Furthermore, considering appropriate nonpharmacological interventions, such as mindfulness meditation, cognitive behavioral therapy, and neuromodulation techniques, alongside medication therapy could also be beneficial.

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