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Risk factors for and incidence of osteoporosis in patients with breast cancer by gender : a nationwide cohort study

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Osteoporosis is common in breast cancer patients, but gender-specific research on its incidence and risk factors is limited. This study examined the incidence and risk of osteoporosis in male and female breast cancer patients and analyzed the risk factors for fractures. This nationwide retrospective cohort study used data from the Korean National Insurance database, identifying invasive breast cancer patients from January 2009 to December 2015.Overall, 80,661 participants (299 males ; 80,362 females) were included. Matching was performed at a 1:5 ratio, based on age, treatment modalities and Charlson Comorbidity Index scores [CCI], resulting in 294 males and 1,470 females.Before and after matching, females consistently showed higher osteoporosis prevalence than males (16.7% vs. 5.0% before, 27.6% vs. 4.8% after, $p < 0.001$). Before matching, hip or vertebral fractures incidence showed no difference (1.2% vs. 1.3%, $p = 0.789$), but after matching, a significant difference was observed. (4.0% vs. 1.0%, $p = 0.011$). Endocrine therapy increased osteoporosis risk, particularly among females (hazard ratio [HR], 6.37; 95% confidence interval [CI], 3.74–10.89; $p < 0.001$). Age, steroid use, and CCI score were significant risk factors for osteoporosis. Adjusting for other variables, females with osteoporosis had a higher hip or vertebral fracture risk than males (HR, 3.96; 95% CI, 1.24–12.64; $p = 0.020$). Our study highlights gender-specific risks for osteoporosis and fractures in breast cancer patients, contributing to a comprehensive understanding for improving long-term outcomes and quality of life in survivors.

Abbreviations

AI	Aromatase inhibitor
NHIS	National Health Insurance Service
IRB	Institutional Review Board
DCIS	Ductal carcinoma in situ
ICD-10	International Classification of Disease,10th revision
CCI	Charlson Comorbidity Index
HR	Hazard ratio
CI	Confidence interval
BMD	Bone mineral density

The incidence of breast cancer is steadily increasing worldwide, with approximately 2.3 million new cases each year, and this number continues to increase[1]. As more patients are diagnosed and treatment modalities advance[2], the number of survivors also increases. Accordingly, physicians should pay more attention to improving the quality of life for breast cancer survivors.

Osteoporosis, a common age-related bone disease that is characterized by reduced bone density and associated with an increased fracture risk, is an important concern. This condition predominantly affects women due to estrogen deficiency[3]. However, it can also impact men. Osteoporotic fracture can result in significant pain,

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functional impairment, decreased quality of life and life expectancy as well as significantly increased healthcare costs[4].

Breast cancer treatments, particularly anti-hormone therapy with aromatase inhibitors (AIs), are common risk factors of osteoporosis[5]. In postmenopausal women, AIs deplete estrogen levels, thereby accelerating bone density loss. Moreover, chemotherapy can induce early menopause in premenopausal females, which exacerbate the risk of osteoporosis due to the rapid decrease in estrogen levels[6]. Further, chemotherapy can have direct toxic effects on bone cells, reducing bone density[7].

While the relationship between breast cancer treatment and osteoporosis in female is well-studied, the data of male breast cancer remains relatively rare, accounting for less than 1% of all breast cancer cases[8]. Data on osteoporosis prevalence and risk factors in male breast cancer patients are particularly limited. Additionally, there is little data on the incidence and risk of osteoporosis and fracture by gender in breast cancer patients.

This study aimed to investigate the incidence of and risk factors for osteoporosis and fracture among breast cancer patients, with a specific focus on differences by gender. By identifying these patterns, the current study aimed to provide valuable insights into improving the management of osteoporosis in this population.

Methods

This retrospective cohort study used data from the Korean National Health Insurance (NHI) claim database of the Health Insurance Review and Assessment Service. The NHI database contains all medical claim data, including personal information, date of disease registry, diagnostic code, procedure behavior code, and prescription data. In this study, variables were defined using diagnostic and procedure codes. Notably, the data used in the analysis were complete and did not have missing values.

Written consent was not required due to the study's retrospective nature; all collected data were managed anonymously according to the privacy guidelines of the Health Insurance Portability and Accountability Act of Korea. The Institutional Review Board (IRB) of Seoul St. Mary's Hospital, Catholic University of Korea approved the study protocol (local IRB number: KC23RISI0200) and waived the need to obtain informed consent for the study.

Study design and study population

As previously described[9], we identified individuals diagnosed with ductal carcinoma in situ (DCIS, International Classification of Disease [ICD]-10 code, D05) or invasive breast cancer (ICD-10 code, C50) in a nationwide population-based cohort. The registration period was from January 2009 to December 2015. Osteoporosis diagnosis was based on the ICD-10 codes (M80, 81, and 82) (Supplementary Table 8), and patients who concurrently received prescriptions for osteoporosis medications including denosumab, romosozumab, risedronate, zoledronic acid, and others were included (Supplementary Table 9).

We extracted data of patients diagnosed with DCIS or breast cancer from the NHI claim database from 2009 to 2015. To minimize misclassification errors, patients with primary DCIS or breast cancer were defined as those who underwent curative surgery within 1 year of their cancer diagnosis. Behavior codes are summarized in Supplementary Table 10. Patients diagnosed with another cancer (ICD-10 code, any C codes) within 2 years before or 6 months after the date of curative surgery were excluded from the analysis. Additionally, patients diagnosed with osteoporosis within 2 years preoperatively, those prescribed with osteoporosis-related medications, or those diagnosed with fractures were excluded. Furthermore, patients who received endocrine therapy, targeted therapy, radiotherapy, or chemotherapy within 1 year preoperatively (neoadjuvant therapy) were excluded from the analysis (Supplementary Fig. 4).

Additionally, a well-known tool for predicting the 10-year survival rate of patients with multiple comorbidities is the Charlson Comorbidity Index (CCI). We here utilized the CCI for forecasting the incidence rate of patients with multiple comorbidities and performed an analysis on the weighted index[10–12] (Supplementary Table 1).

Outcomes

The primary endpoint of this study was to investigate the cumulative incidence and risk of osteoporosis in both male and female breast cancer patients. Secondary endpoints aimed to assess osteoporosis risk according to age, chemotherapy, endocrine therapy, or radiation by gender. Furthermore, we sought to analyze the cumulative incidence of and risk factors for fractures by gender.

Statistical analysis

Using *t*-tests and chi-square tests, baseline demographic and clinical characteristics were compared. The cumulative incidence of osteoporosis between the two groups was shown using Kaplan–Meier curves, and log-rank tests were used for comparisons. Using Cox proportional hazard models, risk factors were determined, confirming hazard ratios (HRs) and 95% confidence intervals (CIs) after adjusting for confounding variables. The Enter method was used for the multivariable Cox proportional hazard model. Statistical significance was determined using two-tailed *p*-values of <0.05. Algorithms from SAS software program (version 9.4, SAS Institute Inc., Cary, NC, USA) were used for performing randomization. Each patient was matched using logistic regression with variables including age, hormone therapy, chemotherapy, radiation therapy, steroid use, and CCI score. Propensity scores were utilized without replacements, employing the nearest neighbor greedy algorithm to match patients at a 1:5 ratio. This ratio was selected based on evidence showing that statistical power improves as the matching ratio increases from 1:1 to 1:5, but stabilized beyond a ratio of 1:5[13]. Therefore, in this study, a PS matching ratio 1:5 was applied, with consideration of statistical power.

Results

Patient cohort

Between 2009 and 2015, 154,111 patients diagnosed with breast cancer or DCIS were initially sorted from the NHI database (Fig. 1). Among them, 25,111 patients who did not undergo curative surgery within 1 year were excluded, leaving 129,000 patients who underwent surgery. Exclusion criteria included patients diagnosed with any other invasive disease within 2 years before or within 6 months after surgery, osteoporosis within 2 years preoperatively or window period, taking osteoporosis medications within 2 years preoperatively or window period, or a history of fracture during the same period. Additionally, patients who received chemotherapy, target therapy, endocrine therapy, or radiation within 1 year preoperatively were excluded. After applying these criteria, 80,661 patients remained for analysis, comprising 299 males and 80,362 female patients. Propensity score matching was performed on the basis of various factors, including age, treatment modalities, past history, and CCI score, resulting in a final cohort of 294 and 1,470 male and female patients, respectively, matched at a 1:5 ratio.

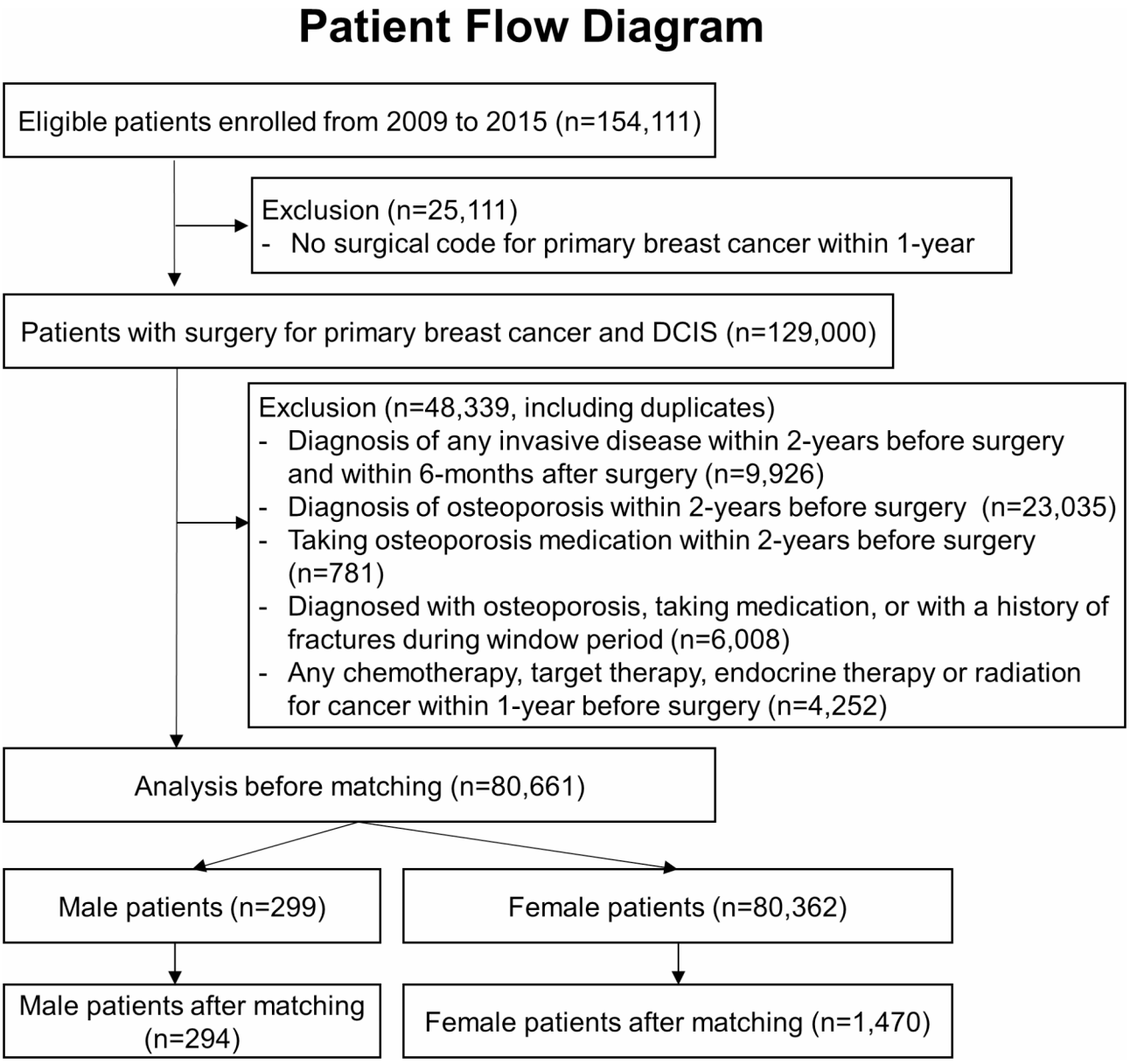

Fig. 1. Flow diagram of patients enrolled in the retrospective cohort study. Between 2009 and 2015, 154,111 patients diagnosed with breast cancer or DCIS were identified from the NHI database. In total, 25,111 patients who did not undergo curative surgery within 1 year were excluded from the study. Finally, 129,000 patients remained. Further exclusions based on additional criteria left 80,661 patients for analysis, including 299 males and 80,362 females. Propensity score matching resulted in a final cohort of 294 male and 1,470 female patients, matched at a 1:5 ratio.

Demographics and incidence of osteoporosis and fracture according to gender

Before matching, 299 males and 80,362 females diagnosed with breast cancer or DCIS who underwent surgery were noted (Table 1). Among those diagnosed with osteoporosis and taking medication, 15 (5.02%) and 13,423 (16.70%) were males and females, respectively ($p < 0.001$). Before matching, the number of patients who developed hip or vertebral fractures following osteoporosis diagnosis was 4 males (1.34%) and 987 females (1.23%). The proportion of female patients receiving endocrine therapy was lower than that of male patients (73.59% vs. 89.97%). Differences were observed between the two groups regarding age, CCI score, receiving target therapy, and radiotherapy. After propensity score matching, all variables were well balanced, resulting in 294 males and 1,470 females (Table 1). Among those diagnosed with osteoporosis and taking osteoporosis medication, 14 (4.76%) and 405 (27.55%) were males and females, respectively ($p < 0.001$). Among patients diagnosed with osteoporosis, 3 males (1.02%) and 59 females (4.01%) developed hip or vertebral fractures after matching, showing a significant difference by gender ($p = 0.011$).

Risk factors for osteoporosis

During a median 9.3-year follow-up before matching, females showed a significantly higher cumulative incidence of osteoporosis than males (Fig. 2(a), $p < 0.001$). During a median 8.9-year follow-up after matching, the cumulative incidence of osteoporosis remained significantly higher in females than in males (Fig. 2(b), $p < 0.001$). Risk factors for developing osteoporosis using the Cox proportional hazard model are presented in

	Before matching			After matching		
	Male, $n = 299$ (%)	Female, $n = 80,362$ (%)	*P* value	Male, $n = 294$ (%)	Female, $n = 1,470$ (%)	*P* value
Osteoporosis			< 0.001			< 0.001
No	284 (94.98)	66,939 (83.30)		280 (95.24)	1,065 (72.45)	
Yes	15 (5.02)	13,423 (16.70)		14 (4.76)	405 (27.55)	
Fracture (at any site)			0.074			0.492
No	209 (69.90)	59,800 (74.41)		206 (70.07)	1,000 (68.03)	
Yes	90 (30.10)	20,562 (25.59)		88 (29.93)	470 (31.97)	
Fracture (Hip or vertebral only)			0.089			0.060
No	284 (94.98)	77,740 (96.74)		281 (95.58)	1,360 (92.52)	
Yes	15 (5.02)	2,622 (3.26)		13 (4.42)	110 (7.48)	
Fracture (Hip or vertebral only) with a diagnosis of osteoporosis			0.789			0.011
No	295 (98.66)	79,375 (98.77)		291 (98.98)	1,411 (95.99)	
Yes	4 (1.34)	987 (1.23)		3 (1.02)	59 (4.01)	
Age (year)			< 0.001			0.996
20–29	5 (1.67)	1,159 (1.44)		5 (1.70)	18 (1.22)	
30–39	16 (5.35)	11,061 (13.76)		16 (5.44)	80 (5.44)	
40–49	50 (16.72)	33,869 (42.15)		50 (17.01)	249 (16.94)	
50–59	68 (22.74)	23,339 (29.04)		68 (23.13)	354 (24.08)	
60–69	84 (28.09)	8,020 (9.98)		84 (28.57)	425 (28.91)	
70–79	59 (19.73)	2,561 (3.19)		59 (20.07)	290 (19.73)	
80-	17 (5.68)	353 (0.44)		12 (4.08)	54 (3.67)	
CCI (Weight number, mean ± SD)	4.57 ± 2.68	3.85 ± 2.28	< 0.001	4.51 ± 2.63	4.46 ± 2.56	0.734
Chemotherapy			0.144			0.847
Not done	133 (44.48)	32,405 (40.32)		129 (43.88)	654 (44.49)	
Done	166 (55.52)	47,957 (59.68)		165 (56.12)	816 (55.51)	
Endocrine therapy			< 0.001			> 0.999
Not done	30 (10.03)	21,224 (26.41)		28 (9.52)	140 (9.52)	
Done	269 (89.97)	59,138 (73.59)		266 (90.48)	1,330 (90.48)	
HER2-target therapy			< 0.001			0.932
Not done	279 (93.31)	68,953 (85.80)		274 (93.20)	1,372 (93.33)	
Done	20 (6.69)	11,409 (14.20)		20 (6.80)	98 (6.67)	
Radiotherapy			< 0.001			0.76
Not done	212 (70.90)	20,738 (25.81)		207 (70.41)	1,048 (71.29)	
Done	87 (29.10)	59,624 (74.19)		87 (29.59)	422 (28.71)	
Steroid medication			0.137			0.730
Not done	176 (58.86)	5,0647 (63.02)		174 (59.18)	854 (58.10)	
Done	123 (41.14)	29,715 (36.98)		120 (40.82)	616 (41.90)	

Table 1. Comparison of clinical characteristics of patients with breast cancer according to gender. *CCI* Charlson Comorbidity index, *SD* standard deviation, *HER2* human epidermal growth factor receptor.

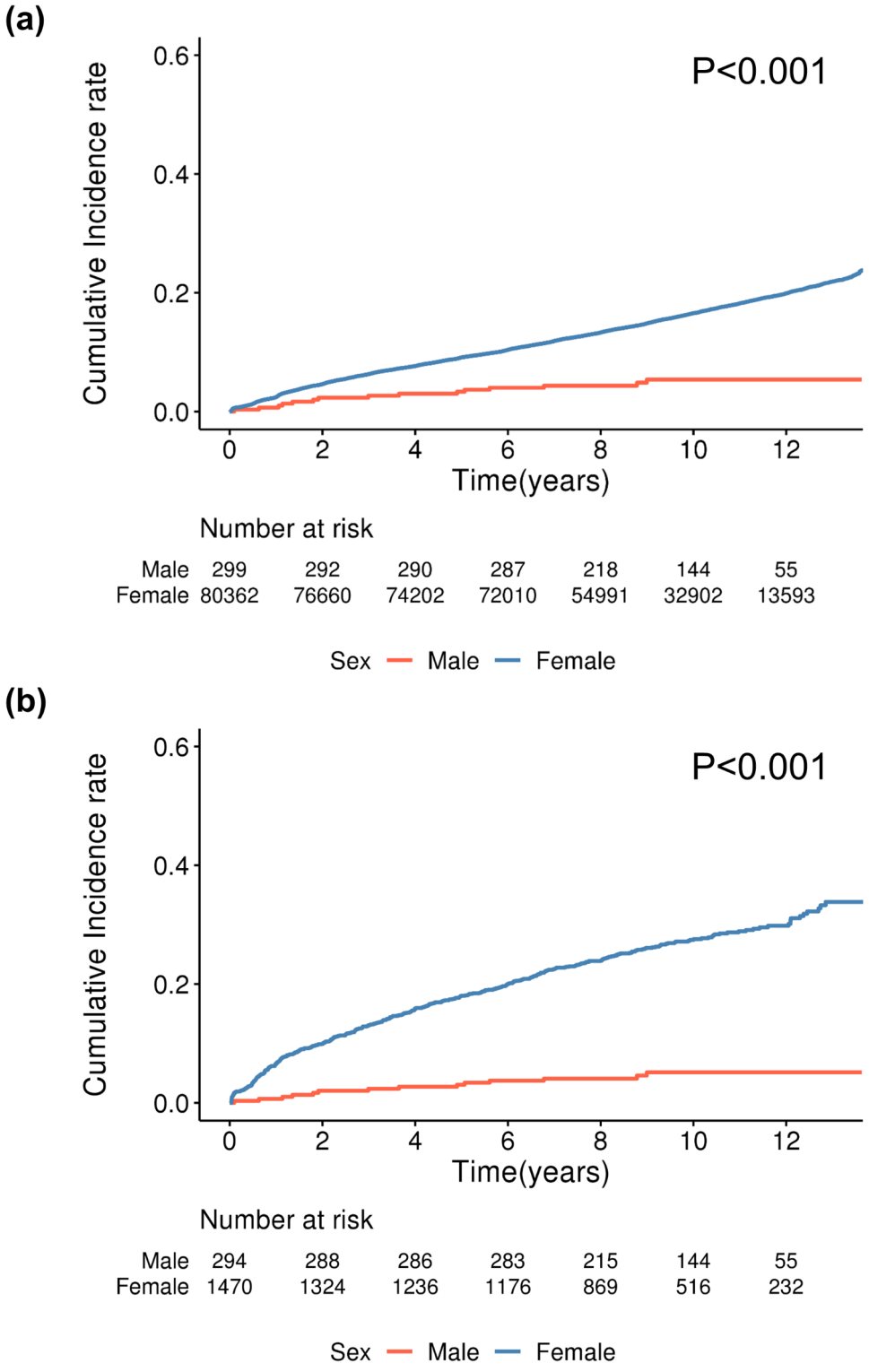

Fig. 2. Kaplan–Meier analysis of osteoporosis incidence in breast cancer patients by gender. (**a**) Before matching, a significant difference in osteoporosis incidence is observed between females and males (a: males, $n = 299$; females, $n = 80{,}362$; $p < 0.001$; log-rank test). (**b**) After matching, osteoporosis incidence in females remains significantly higher than that in males (b: males, $n = 294$; females, $n = 1{,}470$; $p < 0.001$; log-rank test). Median follow up period was 9.32 ± 2.99 years.

Table 2. Before matching, univariate Cox proportional hazard analysis revealed that females had a significantly higher risk of developing osteoporosis than males (Table 2; HR, 3.499; 95% CI, 2.112–5.794; $p < 0.001$) Adjusting for variables including age, treatment modalities, steroid use, and CCI score, females still had a significantly higher risk of developing osteoporosis than males (Table 2; HR, 7.087; 95% CI, 4.269–11.766; $p < 0.001$). In the multivariable analysis, adjuvant therapy, steroid use, age, and CCI score were all associated with osteoporosis development. After matching, univariate and multivariate analyses showed that females had a significantly higher risk of developing osteoporosis than males (Table 2; univariate analysis: HR, 6.592; 95% CI, 3.869–11.230; $p < 0.001$ and multivariate analysis: HR, 6.825; 95% CI, 4.006–11.628; $p < 0.001$). Before matching, the annual incidence of osteoporosis varied by gender (Supplementary Fig. 1(a)). In females, the annual change in osteoporosis incidence temporarily decreased following treatment and subsequently increased over time, whereas in males, little difference was noted. After matching, the increase in annual osteoporosis incidence in females decreased and plateaued for 4 years postoperatively, whereas in males, the annual incidence remained stable (Supplementary Fig. 1(b)).

Risk factors for fractures according to gender

Before matching, males showed a higher cumulative incidence of fractures (at any site) than females (Fig. 3(a), $p = 0.046$). However, after matching, no gender differences were observed (Fig. 3(b), $p = 0.543$). Among osteoporosis patients, no gender difference in the cumulative incidence of hip or vertebral fractures was not noted before matching (Fig. 3(c), $p = 0.868$), but a higher incidence was observed in females after matching (Fig. 3(d), $p = 0.012$).

Furthermore, using the Cox proportional hazard model, we analyzed the risk of fractures (at any site). The analysis of the HRs for fractures (at any site) before and after matching is presented in Supplementary Table 5. Univariate analysis before matching showed that age, gender, endocrine therapy, radiotherapy, steroid use, and CCI score were significant risk factors for fracture. After matching, only age remained a significant risk factor (Supplementary Table 1; HR, 1.276; 95% CI, 1.193–1.365; $p < 0.001$). Multivariable analysis after adjusting variables showed that age and steroid use were as risk factors for fractures (Supplementary Table 1; HR, 1.256; 95% CI, 1.171–1.348; $p < 0.001$ and HR, 1.197; 95% CI, 1.012–1.417; $p = 0.036$, respectively). When analyzing hip or vertebral fracture occurrence only, only age remained significant after matching in the multivariable analysis (Supplementary Table 2; HR, 1.915; 95% CI, 1.607–2.282; $p < 0.001$). The analysis of risk factors for hip or vertebral fractures only among patients diagnosed with osteoporosis is presented in Supplementary Table 3. Before matching, the univariate analysis revealed that age, CCI score, chemotherapy, radiotherapy, and steroid use were risk factors for hip or vertebral fractures only, whereas the multivariable analysis revealed that age, gender, chemotherapy, endocrine therapy, and steroid use were risk factors. Additionally, after matching, age, gender, and chemotherapy were significant risk factors in the univariate analysis, whereas in the multivariable analysis, only age and gender remained significant risk factors (Supplementary Table 3; HR, 2.385; 95% CI, 1.814–3.134; $p < 0.001$ and HR, 3.959; 95% CI, 1.240–12.638; $p = 0.020$, respectively).

	Before matching				After matching			
	Univariate analysis		Multivariable analysis		Univariate analysis		Multivariable analysis	
	HR (95% CIs)	*P*value	HR (95% CIs)	*P*value	HR (95% CIs)	*P*value	HR (95% CIs)	*P*value
Age (per 10-year)	1.74 (1.713–1.763)	< 0.001	1.804 (1.776–1.832)	< 0.001	1.488 (1.374–1.611)	< 0.001	1.579 (1.447–1.722)	< 0.001
Gender		< 0.001		< 0.001		< 0.001		< 0.001
Male	Reference		Reference		Reference		Reference	
Female	3.499 (2.112–5.794)		7.087(4.269–11.766)		6.592 (3.869–11.230)		6.825 (4.006–11.628)	
CCI (Weight number)	1.032 (1.025–1.039)	< 0.001	0.983 (0.975–0.990)	< 0.001	1.003 (0.967–1.040)	0.886	0.964 (0.926–1.004)	0.078
Chemotherapy		< 0.001		< 0.001		0.246		0.967
Not done	Reference		Reference		Reference		Reference	
Done	1.079 (1.042–1.118)		1.216 (1.172–1.262)		0.892 (0.737–1.081)		0.996 (0.807–1.228)	
Endocrine therapy		< 0.001		< 0.001		0.035		< 0.001
Not done	Reference		Reference		Reference		Reference	
Done	1.070 (1.030–1.113)		1.183 (1.137–1.231)		1.501 (1.030–2.189)		2.002 (1.360–2.946)	
HER2-target therapy		< 0.001		< 0.001		0.293		0.032
Not done	Reference		Reference		Reference		Reference	
Done	1.137 (1.085–1.192)		1.112 (1.058–1.168)		1.214 (0.846–1.741)		1.510 (1.036–2.203)	
Radiotherapy		< 0.001		< 0.001		0.503		0.922
Not done	Reference		Reference		Reference		Reference	
Done	0.924 (0.890–0.960)		1.083 (1.041–1.126)		0.929 (0.749–1.152)		0.989 (0.788–1.241)	
Steroid medication		< 0.001		< 0.001		< 0.001		0.013
Not done	Reference		Reference		Reference		Reference	
Done	1.333 (1.288–1.379)		1.266 (1.223–1.310)		1.390 (1.147–1.683)		1.280 (1.054–1.554)	

Table 2. Risk of developing osteoporosis from analyses using Cox proportional hazard models. *CCI* Charlson Comorbidity index, *HER2* human epidermal growth factor receptor.

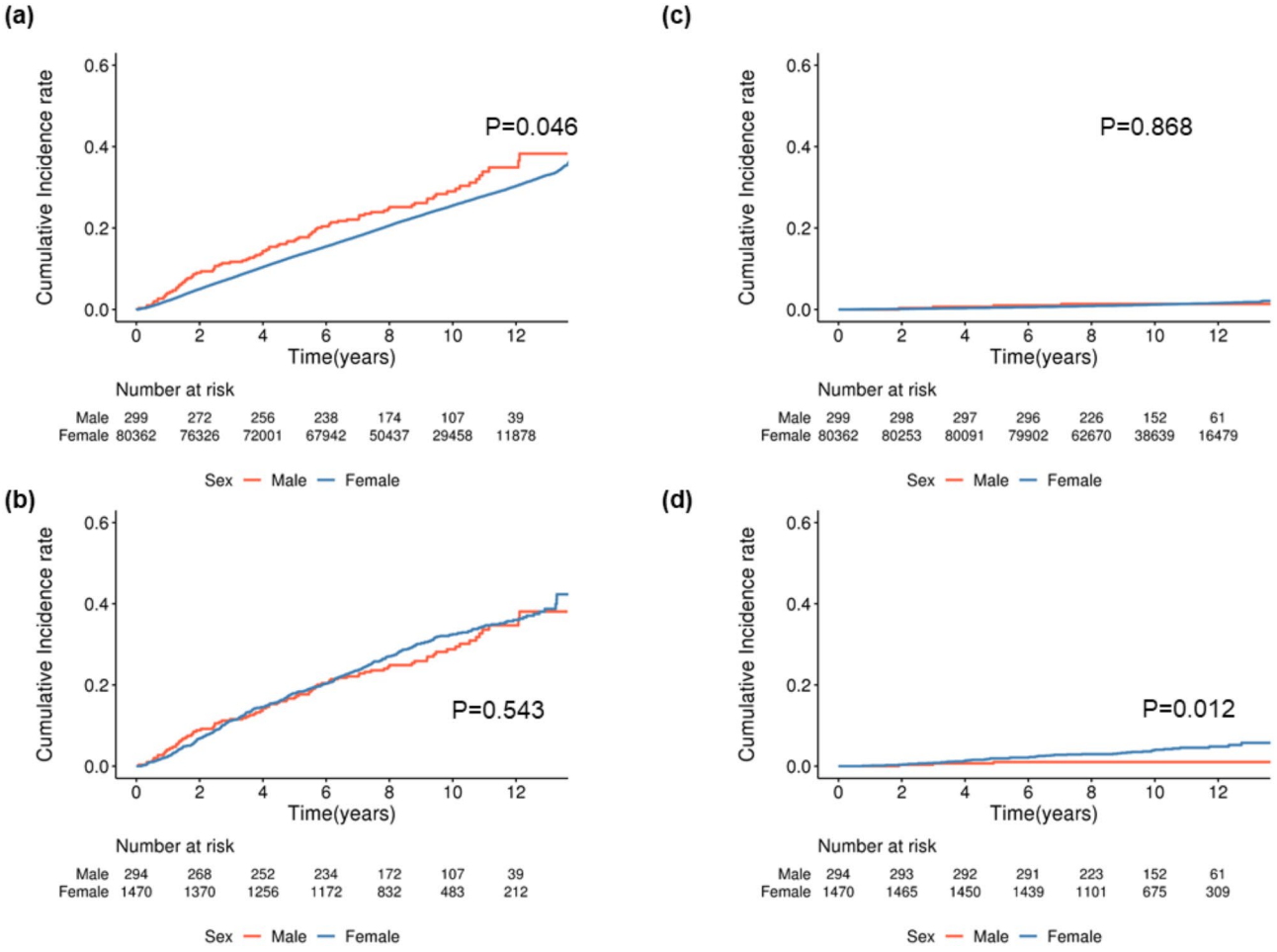

Fig. 3. Kaplan–Meier analysis of hip or vertebral fracture incidence in breast cancer patients by gender. (**a**) Before matching, a significant difference in the incidence of fractures (any site) is observed between females and males (males, $n = 299$; females, $n = 80{,}362$; $p = 0.046$; log-rank test; median follow-up, 8.94 ± 3.13 years). (**b**) After matching, the incidence of fractures (at any site) in females is not significantly higher than that in males (males, $n = 294$; females, $n = 1{,}470$; $p = 0.054$; log-rank test). (**c**) Before matching, no difference in the incidence of fractures (hip or vertebral fractures only) with a diagnosis of osteoporosis is noted between females and males (males, $n = 299$; females, $n = 80{,}362$; $p = 0.868$; log-rank test; median follow-up, 9.87 ± 2.08 years). (**d**) After matching, the incidence of fractures (hip or vertebral fractures only) with a diagnosis of osteoporosis in females is significantly higher than that in males (males, $n = 294$; females, $n = 1{,}470$; $p = 0.012$; log-rank test).

Subgroup analysis of the endocrine treatment group

We conducted a subgroup analysis focusing on postoperative endocrine therapy patients. Overall, 269 males and 59,138 females received endocrine therapy, whereas 30 males and 21,224 females did not. We compared the clinical characteristics in each group (Supplementary Table 4). Osteoporosis incidence was higher in females receiving endocrine treatment than males (16.89% vs. 5.58%, $p < 0.001$). After matching, 266 males and 1,330 females received endocrine therapy (Supplementary Table 5). Among them, 14 males (5.26%) and 376 females (28.27%) were diagnosed with osteoporosis, showing a statistically significant difference ($p < 0.001$). Regarding hip or vertebral fracture occurrence following diagnosis, 3 males (1.13%) and 51 females (3.83%) in the receiving endocrine therapy group were noted ($p = 0.026$).

The cumulative incidence of osteoporosis was higher in females with breast cancer receiving endocrine therapy both before and after matching, while no significant gender difference was observed in the cumulative incidence of fractures at any site (Supplementary Fig. 2(a) and 2(b), $p < 0.001$; Supplementary Fig. 3(a) and 3(b), $p = 0.199$ and $p = 0.501$, respectively). When considering only hip or vertebral fractures, no significant difference was observed between genders before matching, but a significant difference was noted after matching (Supplementary Fig. 3(c) and 3(d), $p = 0.724$ and $p = 0.025$, respectively).

When additional analysis was performed using the Cox proportional hazard model to identify risk factors for osteoporosis in patients receiving endocrine treatment, before matching, all variables showed significant differences in both univariate and multivariate analyses (Supplementary Table 6). After matching, the multivariate analysis revealed that being female was a significant risk factor for developing osteoporosis (Supplementary

Table 9; HR, 6.386; 95% CI, 3.746–10.889; $p < 0.001$). An analysis of risk factors associated with hip or vertebral fractures only occurring after a diagnosis of osteoporosis is provided in Supplementary Table 7.

An analysis based on the type of endocrine therapy regimens (e.g., tamoxifen and AIs) was not performed. For male patients, only three individuals were receiving AIs, rendering the sample size too small for meaningful analysis.

Discussion

The nationwide retrospective cohort study identified the cumulative incidence of and risk factors for osteoporosis in male and female breast cancer patients. Matching and analyzing clinical factors revealed osteoporosis occurred in 27.55% of female and 4.76% of male patients, approximately 5.8-fold more frequent in females. In particular, females showed consistently higher cumulative incidence of osteoporosis than males before and after matching. Although no difference in the incidence of fractures (at any site) was noted between genders, hip or vertebral fractures associated with osteoporosis were significantly higher in females, emphasizing the chronic and progressive nature of osteoporosis. Compared with previously reported studies, our study's extended follow-up periods (9.3 and 8.9 years) allowed a more comprehensively observation of the cumulative incidence between genders. A previous study reported that 2.7% of patients with breast cancer were diagnosed with osteoporosis during a 5-year follow-up period[14]. In contrast, the extended follow-up period in this study allowed us to identify the long-term cumulative incidence in a large number of patients.

The Cox proportional hazard analysis revealed that females consistently exhibited a significantly higher risk of developing osteoporosis compared to males. This higher risk remained significant even after adjusting for other variables and was also associated with a greater likelihood of vertebral or hip fractures. This consistency across different analytical approaches strengthens the evidence that gender is a significant risk factor for the development of osteoporosis and hip or vertebral fractures. Furthermore, the majority of female patients were in a postmenopausal state (76.4% vs. 23.6%), which is consistent with several studies indicating that AI use increases osteoporosis risk[15,16].

Three main reasons account for the higher risk of osteoporosis in females. First, males often use tamoxifen more than AIs in adjuvant endocrine therapy[17,18]. Tamoxifen exhibits an estrogen agonist activity in the bone, suggesting a bone-sparing effect and potentially reducing osteoporosis incidence[16,19,20]. Second, female patients generally receive more adjuvant chemotherapies than male patients. These additional treatments may affect a female's risk of developing osteoporosis. In the case of chemotherapy, when administered to premenopausal female, it can induce early menopause and has a direct toxic effect on bone cells, significantly reducing bone mineral density (BMD) and increasing osteoporosis incidence[21]. Therefore, the higher risk ratio observed in females may be explained by a combination of these factors. Lastly, comparing males and females of the same age showed that males have generally higher bone densities than females.

Previous prospective analyses showed that females with breast cancer experienced an increased fracture incidence, with 68.6 fractures per 10,000 person-years compared with females without breast cancer[22]. However, there have been no reported findings regarding the association between breast cancer and fractures in males. This lack of findings in males may be attributed to the considerably lower breast cancer incidence in males, thereby leading to insufficient study populations. Nonetheless, further research investigating the association between breast cancer and fractures in males could provide valuable insights into post-diagnosis fracture risks and aid in the development of appropriate prevention and treatment strategies.

This study provides a comprehensive analysis of osteoporosis and fracture-associated risk factors in breast cancer patients receiving endocrine therapy. Our subgroup analysis, revealed marked differences in osteoporosis and fracture incidence between genders. Females receiving endocrine therapy showed a significantly higher incidence rate of osteoporosis than males (16.89% vs. 5.58%, $p < 0.001$). This disparity persisted even in the non-endocrine therapy group, where females also showed a higher osteoporosis incidence (16.18% vs. 0%, $p = 0.01$). These findings suggest that gender plays a critical role in osteoporosis development among patients with breast cancer, regardless of endocrine therapy status highlighting the significant need for targeted screening and preventive measures in this population.

This study had several limitations. First, using claim data from the NHI database meant individual patients' medical records cannot be confirmed. The NHI database does not include data on lifestyle, anthropometric data, and socioeconomic status, all of which can impact osteoporosis development. Second, we identified patients diagnosed with osteoporosis by examining ICD codes or osteoporosis medication prescriptions. Currently, in Korea, prescription for osteoporosis medications can be claimed by insurance if the T-score is −2.5 or less; however, in this study, the T-score of each patient could not be confirmed. Lastly, we did not investigate endocrine treatment adherence. Detailed exposure assessment in the NHI database was limited. Nevertheless, we identified the incidence of and risk factors for osteoporosis and fractures by gender in breast cancer patients in Korea using a large-scaled nationwide cohort.

A comparative analysis between women with breast cancer and the general female population in terms of osteoporosis risk provides critical insights into the need for more active interventions in patients with breast cancer[23]. Breast cancer treatments, particularly endocrine therapies and chemotherapy, significantly affect BMD, which accelerates bone loss and increases fracture risk[24,25]. The current study showed that adjuvant therapies are a significant risk factor of osteoporosis in patients with breast cancer. This finding is in accordance with that of previous research highlighting the adverse effect of these therapies on bone health. According to the National Comprehensive Cancer Network guidelines[26], BMD testing is recommended for postmenopausal women or those receiving AI therapy. Further, bisphosphonates or denosumab should be used to maintain or improve BMD and reduce the risk of fractures. Considering these results, implementing early and more frequent osteoporosis screening and treatment strategies individualized to patients receiving adjuvant therapy is essential for reducing long-term skeletal complication in this high-risk population. Furthermore, a gender-

based comparison revealed that female patients with breast cancer exhibited a significantly higher incidence of osteoporosis and hip or vertebral fractures than male patients with breast cancer. These findings underscore the chronic and progressive nature of osteoporosis in female survivors of breast cancer, thereby emphasizing the need for targeted, gender-specific management strategies. Proactive screening, personalized care, and integration of insights from ongoing research into clinical practice are essential to improve long-term outcomes and quality of life. Implementing a multidisciplinary, evidence-based approach to overcome these disparities can enhance the capacity of healthcare systems to deliver comprehensive support to high-risk populations and effectively manage the complex challenges associated with osteoporosis care.

Our retrospective nationwide cohort study showed a significantly higher incidence and risk of osteoporosis and related fractures in female breast cancer patients compared to males, highlighting the chronic and progressive nature of osteoporosis in this population. These findings emphasized the importance of early, gender-specific screening, personalized interventions, and multidisciplinary management strategies to reduce long-term skeletal events and improve overall outcomes.

Data availability

Due to the National Health Insurance (NHI) policy restrictions, the original datasets cannot be exported or shared outside the institution. All data generated or analyzed during this study are included in this research article and supplementary information files. For further inquiries, please contact the corresponding author.

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Author contributions

CY had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization, JL and CY; Data curation, HL, SJ; Funding acquisition, CY; Investigation, JL, DK, HL, SJ, and CY; Methodology, JL, DK, HL, SJ, and CY; Resources, HL, SJ; Formal analysis, JL and CY; Supervision, WP; Writing-original draft, JL and CY; Writing-review & editing, YL, SB and CY.

Declarations

Competing interests

The authors declare no competing interests.

Consent for publication

All authors have given consent for publication.

Institutional review board and informed consent statement

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study protocol was approved by the Institutional Review Board (Local IRB number: KC23RISI0200) of Seoul St. Mary's Hospital, Catholic University of Korea. The need for informed consent was waived by the IRB due to the retrospective study design.

Additional information

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