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A Nationwide Study on the Incidence of Breast Cancer in Korean Women with Osteoporosis Receiving Raloxifene Treatment

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ABSTRACT

Purpose: Raloxifene is a selective estrogen receptor modulator (SERM), and raloxifene treatment for osteoporosis is reimbursable under the Korean National Health Insurance. Evidence suggests that SERMs use reduces the risk of breast cancer in Asian population. Herein, we retrospectively investigated the protective effect of raloxifene on breast cancer rates in Korean population.

Methods: Using the Health Insurance Review and Assessment Service database, we selected women with osteoporosis aged 50 years and above. Patients treated for at least 2 years with raloxifene were assigned to the user group, whereas the remaining patients were assigned to the non-user group. The effect on breast cancer risk was assessed using the Cox proportional-hazards model with a time-dependent covariate to adjust for immortal time bias.

Results: A total of 322,870 women who were registered between 2010 and 2011 were included. The user group comprised 0.7% (n = 2,307) of the total population. The mean age was 65.7 ± 8.0 years and 67.2 ± 8.6 years in the user and non-user groups, respectively (p < 0.001). There was no difference in the previous use of estrogen replacement between the 2 groups (p = 0.087). The incidence of breast cancer per 1,000 person-years was 0.49 (n = 8) and 0.68 (n = 1,714) in the user and non-user groups, respectively (hazard ratio [HR], 0.63, 95% confidence interval [CI], 0.32–1.27). HR decreased with increase in the treatment duration, but this change was not statistically significant (HR, 1.00, 95% CI, 0.32–3.11 in 2–3 years; HR, 0.63, 95% CI, 0.20–1.94 in 3–4 years; and HR, 0.41, 95% CI, 0.10–1.65 in 4–5 years).

Conclusion: Long-term treatment with raloxifene in women with osteoporosis was not significantly associated with a reduction in breast cancer rates. However, further investigation is required for a conclusive proof.

Keywords: Breast neoplasms; Chemoprevention; Osteoporosis; Postmenopause; Raloxifene hydrochloride

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Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

Formal analysis: Lee JS; Funding acquisition: Park S; Methodology: Lee JS; Resources: Lee JS, Park S; Supervision: Lee JE, Kim Z, Han SW, Hur SM, Choi YJ; Writing - original draft: Lee J, Park S; Writing - review & editing: Lee J, Lee JS, Park S.

INTRODUCTION

A large clinical trial have shown that tamoxifen can reduce the risk of breast cancer; hence, most guidelines recommend the use of risk-reducing agents in women with a high risk of breast cancer development [1-4]. Along with lifestyle modification, risk-reducing agents are recommended for women at advanced age and having unfavorable histology such as lobular carcinoma *in situ* or atypical hyperplasia in the breast biopsy, or based on the risk prediction models.

Besides tamoxifen, other selective estrogen receptor modulators (SERMs) have also been evaluated for their efficacy in reducing the risk of breast cancer [5-7]. Raloxifene acts as an estrogen agonist in bone and lipids, and Cauley et al. [8] evaluated its use as a risk-reducing agent in a clinical trial involving patients with osteoporosis. During the four years of observation in this trial, a 72% reduction in the risk of developing breast cancer was observed in the raloxifene group. In another trial involving patients with congestive heart failure (RUTH trial) [7], raloxifene treatment was found to be associated with decreased breast cancer incidence. Moreover, in a head-to-head comparison of tamoxifen and raloxifene, raloxifene showed comparable efficacy at an estimated 50% risk reduction, but the toxicity profiles differed between the two drugs [9]. Tamoxifen was associated with an increased risk of endometrial cancer, uterine sarcoma, cataracts, deep vein thrombosis, and stroke. Although raloxifene was also associated with an increased risk of endometrial cancer, thromboembolic events, and cataracts, the incidence of developing these conditions was lower.

Despite the robust efficacy of risk-reducing agents, there is limited data on Asian population, and therefore, the use of these agents is not yet widely accepted in Asian countries [10]. Currently, raloxifene treatment in patients with osteoporosis has been approved for reimbursement under the Korean National Health Insurance. Therefore, we conducted a retrospective analysis using the nationwide healthcare claims data to investigate the risk reduction effect of raloxifene on breast cancer development.

METHODS

The Health Insurance Review and Assessment Service (HIRA) database records reimbursement information from national health insurance claims in Korea. Almost all individuals in Korea are insured by the Korean National Health Insurance; therefore, the HIRA database can be used to design a nationwide cohort study. HIRA claims data include age, sex, diagnoses, medical costs claimed, procedures, prescribed drugs, and a unique anonymous number for each patient [11]. Using the HIRA database, female osteoporotic patients aged 50 years or above who received raloxifene prescriptions were identified. Considering that the observation period is expected to be more than five years, osteoporosis patients newly diagnosed between January 1, 2010 and December 31, 2011, were included in this study, and observation data were obtained until July 31, 2019. Osteoporosis was defined using the diagnostic code from claim data, which was based on the International Classification of Diseases 10th revision (ICD-10), and was categorized as M80, M81, and M82. Osteoporosis treatment (bisphosphonate or raloxifene) records were also collected. We also reviewed the diagnostic codes and prescriptions of patients enrolled between January 1, 2009 and December 31, 2009, and removed the subjects who had already been treated for osteoporosis or had a history of any malignancy, including invasive or noninvasive breast cancer. Based on economic status, the subjects were divided into the low-income group from

the Medical Aid Program or the lower rank in the National Health Insurance and the high-income group. The Charlson Comorbidity Index (CCI) was calculated using ICD-10 diagnosis claim records within one year before the osteoporosis diagnosis to assess comorbidities.

Raloxifene prescription records were retrieved using the drug code, and individuals whose prescriptions were maintained for more than two years were assigned to the raloxifene user group, whereas others were assigned to the non-user group. New claim records with a diagnosis code of C50 (invasive cancer) or D05 (noninvasive cancer) were considered as new diagnoses of breast cancer. Noninvasive cancer was defined as newly created D05 code claims with V193 code. To remove cases that were upstaged from noninvasive cancer to invasive cancer after surgery and to prevent duplication of enrollment, new C50 claims within six months from the first claim of D05 were removed from the D05 population. These data were again screened to find whether the individuals were given another claim code of V193, which indicates patients with malignant neoplasm. If C50 or D05 codes were found within two years of raloxifene treatment, it was considered as an outcome in the non-user group. Since information regarding the date of death cannot be obtained from the HIRA database, we defined surrogate censoring or date of death as the last claim date among those who did not have claim records between July 31, 2017, and the final observation date. Endocrine treatment (SERMs or aromatase inhibitors) records within one year of breast cancer diagnosis were also reviewed to indirectly screen for hormone receptor-positive tumors.

Baseline characteristics are expressed as mean (\pm standard deviation) or percentage (%). Differences in the distribution of baseline characteristics between raloxifene user and non-user groups were identified using the Student's *t*-test or χ^2 test, as appropriate. The study exposure was the use of raloxifene, considered as a time-varying variable. We then compared the incidence of breast cancer between raloxifene user and non-user groups. The person-years (PY) for each patient in both groups were calculated from the index date to the end of follow-up. The crude incidence rates (IRs) of breast cancer were calculated as the number of breast cancer cases per 1,000 PY. We calculated hazard ratios (HRs) for developing breast cancer with 95% confidence interval (CI) using the Cox proportional hazard model with time-dependent covariates adjusted for age, previous use of hormone therapy, economic status, and CCI (0, 1, 2, 3, 4, \geq 5). To account for competing risks due to mortality, we fitted a proportional sub-distribution hazards regression model with death as the competing event. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, USA) and *p*-values < 0.05 were considered statistically significant.

Ethical approval

This study was performed with approval from the institutional review board of Chungbuk National University Hospital (approval number: 2020-04-014). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

RESULTS

Baseline characteristics

Of the 333,781 patients who had been newly diagnosed with osteoporosis between 2010 and 2011, 322,870 were enrolled in this study with an observation period of more than two years.

Among all patients, 2,307 (0.7%) were raloxifene users, whereas 320,563 (99.3%) were non-users. **Figure 1** shows the patient enrollment criteria and the follow-up period. Raloxifene users were younger than non-users (mean age = 65.7 ± 8.0 years vs. 67.2 ± 8.6 years, $p < 0.001$), and the proportion of patients aged 50 to 69 years was high among raloxifene users. There was no difference between the two groups in terms of previous estrogen replacement use ($p = 0.087$). The proportion of subjects in the low-income group from the Medical Aid Program or those in the lower rank of the National Health Insurance was lower among raloxifene users. Moreover, raloxifene users had fewer comorbidities than non-users (CCI 2.7 ± 2.1 vs. 2.8 ± 2.2; $p = 0.004$). The baseline characteristics are shown in **Table 1**. The median duration of follow-up was 8.1 years (interquartile range = 7.5–8.6 years) in both groups (the total patient-years of follow-up are presented by treatment group in **Supplementary Table 1**).

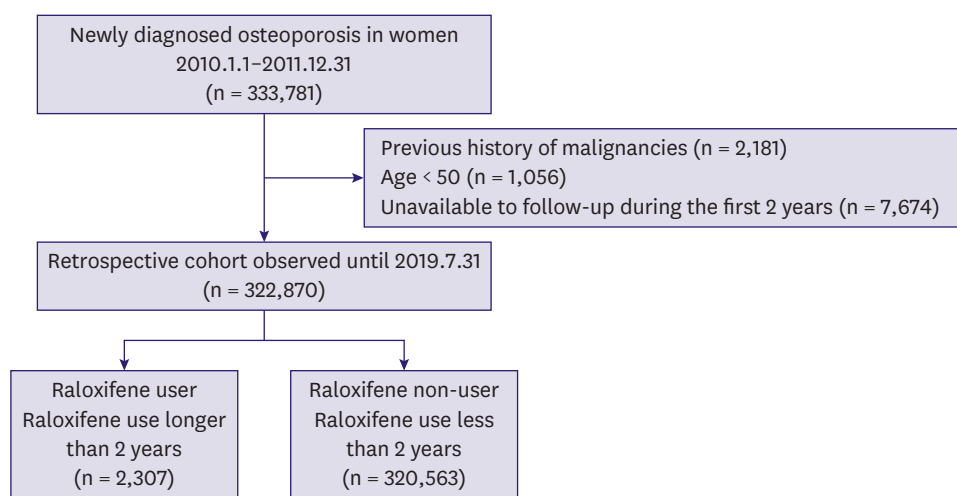


Figure 1. Enrollment, treatment, and grouping of the study population.

Table 1. Baseline characteristics

Characteristics	Raloxifene user	Non-user	<i>p</i>
No. of patients	2,307	320,563	
Age (yr)			< 0.001
Mean ± SD	65.7 ± 8.0	67.2 ± 8.6	
Median (range)	66 (50–92)	67 (50–112)	
Age group (yr)			< 0.001
50–59	555 (24.1)	67,452 (21.0)	
60–69	1,003 (43.5)	124,895 (39.0)	
≥ 70	749 (32.5)	128,216 (40.0)	
Previous use of hormone therapy	130 (5.6)	15,593 (4.9)	0.087
Economic status			< 0.001
High	2,149 (93.2)	290,780 (90.7)	
Low	158 (6.8)	29,783 (9.3)	
Charlson Comorbidity Index			0.025
Mean ± SD	2.7 ± 2.1	2.8 ± 2.2	0.004
0	284 (12.3)	39,577 (12.3)	
1	514 (22.3)	63,488 (19.8)	
2	452 (19.6)	64,947 (20.3)	
3	381 (16.5)	52,386 (16.3)	
4	275 (11.9)	37,705 (11.8)	
≥ 5	401 (17.4)	62,460 (19.5)	

Values are presented as number (%).
SD = standard deviation.

Breast cancer incidence

During the follow-up period, nine raloxifene users and 1,714 non-users were diagnosed with breast cancer. The IR per 1,000 PY for invasive and non-invasive cancer among raloxifene users was 0.43 (0.20–0.89) and 0.06 (0.01–0.43), respectively. Among non-users, the IR for invasive and non-invasive cancer per 1,000 PY was 0.64 (0.61–0.67) and 0.05 (0.04–0.06), respectively. There was no significant difference in the incidence of invasive breast cancer between the two groups when competing risk was considered (adjusted HR, 0.63, 95% CI, 0.32–1.27, $p = 0.198$; **Table 2, Figure 2A**). Lower incidence of breast cancer was observed in patients with longer treatment duration; however, the difference was not statistically significant (**Table 3, Figure 2B**). In the 2–3 years, 3–4 years, and 4–5 years treatment durations, the adjusted HR was 1.00 (95% CI, 0.32–3.11, $p = 0.997$), 0.63 (95% CI, 0.20–1.94, $p = 0.418$), and 0.41 (0.10–1.65) (95% CI, 0.10–1.65, $p = 0.212$), respectively.

Among raloxifene users, 37.5% of patients underwent endocrine treatment compared to 62.0% in the non-user group; however, the difference was not statistically significant ($p = 0.272$; **Supplementary Table 2**).

Table 2. Incidence of breast cancer by treatment group

Breast cancer type	Raloxifene			Control			Unadjusted		Adjusted*	
	No. of events	Follow-up duration (yr)	IR per 1,000 PY	No. of events	Follow-up duration (yr)	IR per 1,000 PY	HR (95% CI)	p	HR (95% CI)	p
All breast cancer	8	16,441	0.49 (0.24–0.97)	1,714	2,502,569	0.68 (0.65–0.72)	0.67 (0.34–1.34)	0.261	0.63 (0.32–1.27)	0.198
Invasive breast cancer	7	16,441	0.43 (0.20–0.89)	1,591	2,502,569	0.64 (0.61–0.67)	0.63 (0.30–1.33)	0.228	0.60 (0.29–1.26)	0.177
Noninvasive breast cancer	1	16,441	0.06 (0.01–0.43)	123	2,502,569	0.05 (0.04–0.06)	1.17 (0.16–8.38)	0.874	1.07 (0.15–7.68)	0.948

IR = incidence rate; PY = person-years; HR = hazard ratio; CI = confidence interval.

*Adjusted by age, previous use of hormone therapy, economic status, and Charlson Comorbidity Index.

Table 3. Incidence of breast cancer by duration of treatment (type: all breast cancer)

Duration of treatment (yr)	No. of events	Rate per 1,000	Unadjusted		Adjusted*	
			HR (95% CI)	p	HR (95% CI)	p
Control	1,714	0.68 (0.65–0.72)	1.00 (Ref.)		1.00 (Ref.)	
2–3	3	0.90 (0.29–2.80)	1.03 (0.33–3.18)	0.966	1.00 (0.32–3.11)	0.997
3–4	3	0.48 (0.15–1.49)	0.68 (0.22–2.10)	0.499	0.63 (0.20–1.94)	0.418
4–5	2	0.29 (0.07–1.16)	0.44 (0.11–1.75)	0.243	0.41 (0.10–1.65)	0.212

HR = hazard ratio; CI = confidence interval.

*Adjusted by age, previous use of hormone therapy, economic status, and Charlson Comorbidity Index.

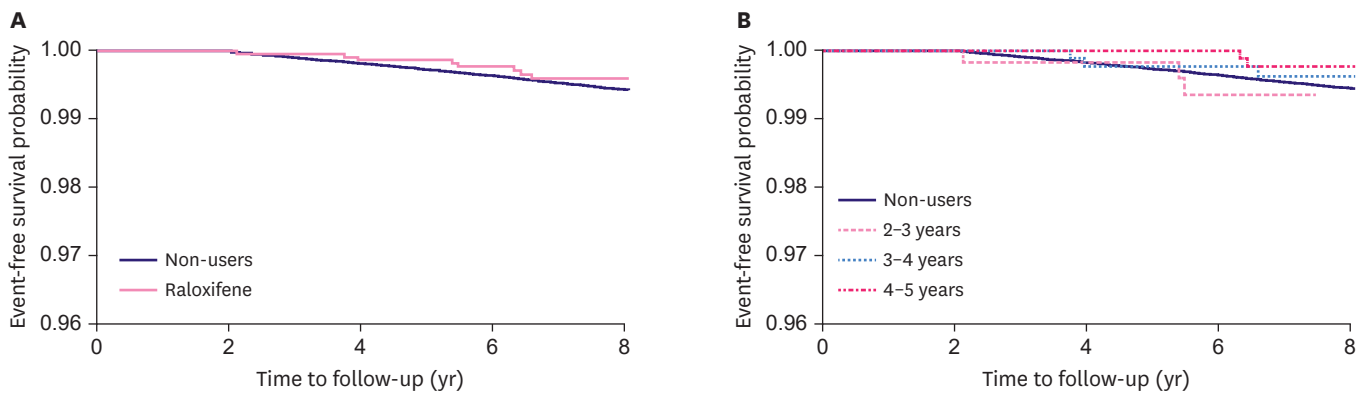


Figure 2. Breast cancer development in the study groups. (A) Event-free survival probability in raloxifene users and non-users; (B) Event-free survival probability following different treatment periods.

DISCUSSION

In this study, we retrospectively reviewed the effect of raloxifene on reducing the risk of breast cancer in women with osteoporosis. Although we observed that the incidence of breast cancer was lower in patients treated with raloxifene for longer durations, the difference was not statistically significant.

Raloxifene has been approved for the treatment of postmenopausal osteoporosis under the Korean National Health Insurance. However, a previous study showed that in Korea, the use of raloxifene is lower compared to that of bisphosphonates (3.2% vs. 96.8% of osteoporosis patients) [11]. In this previous study, the authors also observed that raloxifene users had more comorbidities including chronic gastritis or gastroesophageal reflux disease, lipid disorders, rheumatic diseases, hot flashes, and coronary artery diseases, suggesting that the adverse effect profiles of raloxifene users might affect the choice of drugs for osteoporosis treatment. Herein, we found that only 0.7% of patients with osteoporosis received raloxifene treatment during the study period. Moreover, the prescription rate of raloxifene was higher in the US claims data (17,983 received raloxifene, whereas 79,891 received bisphosphonate under Medicare from 2003 to 2004) [12] and in the Taiwan claim data (9,534 raloxifene users vs. 19,840 alendronate users from 2003 to 2007) [13]. Contrary to the American or European guidelines, the use of raloxifene is not approved for breast cancer risk reduction in Korea, which might be one of the reasons why clinicians are reluctant to prescribe raloxifene instead of bisphosphonates.

In the RUTH trial, it was observed that raloxifene treatment reduced the risk of breast cancer, and only 1.2 cases of invasive breast cancer were found out of 1,000 women treated for one year [7]. In the present study, the HR was 0.41 in patients treated with raloxifene for 4–5 years; however, compared to groups with lower treatment duration, the difference in HR was not statistically significant. Despite a sufficient number of cases and long follow-up period, we could not draw a robust conclusion regarding the effect of raloxifene on breast cancer development because of the low incidence of this cancer in our study cohort. Females with osteoporosis or low bone mineral density are at a lower risk of breast cancer than those with high bone mineral density, possibly because bone mineral density directly reflects the duration of exposure to estrogen during the patients' lifetime [14-17]. Our study included patients with osteoporosis, which might explain the low incidence of breast cancer in these subjects.

A previous study showed that the incidence of invasive breast cancer is significantly reduced in females taking raloxifene for two or more years. However, the interaction between the treatment duration and the effect of treatment on invasive breast cancer incidence was not statistically significant [18]. Considering the risk-reducing effects of raloxifene, we included patients who were taking raloxifene for more than two years. Although we observed that the incidence of breast cancer decreased with longer raloxifene treatment duration, this finding was not statistically significant.

Another study on chemoprevention showed that only 23% of women who were at a high risk of breast cancer used risk-reducing agents [19], and the fear of adverse effects was the greatest concern among the study participants. The use of chemopreventive drugs is low in both trial and non-trial settings. However, a systemic review highlighted that factors including abnormal biopsy, physicians' recommendation, and advanced age affected the use of chemopreventive agents, highlighting the importance of communication with patients [20]. In the Korean guidelines, there is no definite recommendation regarding the use of

tamoxifen or aromatase inhibitors for breast cancer risk reduction, and the guidelines only allow tamoxifen use as a risk-reducing agent in *BRCA* mutation carriers. The present study did not have any clinical data because we used the insurance claims database to evaluate the actual risk in individuals. However, if physicians consider adverse effects and patient comorbidities when choosing agents for osteoporosis management, breast cancer risk should also be considered.

Several studies have confirmed that raloxifene reduces the risk of invasive breast cancer in postmenopausal women with osteoporosis [8,18,21]. Although there is clear evidence regarding the benefits of raloxifene use, only a few patients with osteoporosis have used raloxifene in Korea because of clinicians' preference or due to paucity of evidence in Korean population. Nevertheless, we may consider using raloxifene in postmenopausal women with osteoporosis.

The limitations of this study include small sample size in the raloxifene user group. Since raloxifene treatment for breast cancer risk reduction is not reimbursable in Korea, the use of chemopreventive agents is low. Second, fewer cancer events in the study population that prevented us from drawing a statistically significant conclusion. Third, we could not ascertain the menopausal status of the patients based on the information present in the database. In the absence of detailed information, we considered age alone as a crude proxy for menopausal status based on an epidemiologic study [22]. HIRA is a claims database that does not contain clinical data; hence, we were unable to consider other factors that could influence the risk of breast cancer development such as a family history or previous biopsy results.

Despite its limitations, this study is a rare overview on the use of raloxifene for breast cancer risk reduction in Korean population. Our nationwide analysis showed no significant association between the use of raloxifene in women with osteoporosis and reduction of the breast cancer risk. Further observational studies are required to determine the protective effects of SERMs on breast cancer development in Asian women.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

The patient-years of follow-up

[Click here to view](#)

Supplementary Table 2

Use of endocrine treatment

[Click here to view](#)

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