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Brief Communication

Characteristics and Prognosis of Breast Cancer Patients With Prior Hormone Replacement Therapy: Insights From the Korean Breast Cancer Society Registry

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ABSTRACT

By investigating the characteristics and prognosis of breast cancer (BC) patients who have undergone hormone replacement therapy (HRT), this study addresses a gap in the existing literature. A total of 17,355 postmenopausal patients with BC were analyzed using data from the Korea Breast Cancer Society database (2000–2014). Among them, 3,585 (20.7%) had a history of HRT before BC diagnosis (HRT group), while 13,770 (79.3%) never received HRT (non-HRT group). The HRT group exhibited an earlier pathologic stage, lower histologic and nuclear grades, and a higher rate of breast conservation surgery compared to the non-HRT group. Furthermore, this group had a higher rate of screening participation and a greater proportion of patients with a normal or overweight body mass index (BMI). The prognosis of the HRT group was better than that of the non-HRT group, with a 5-year overall survival rate of 93.9% versus 91.7% ($p < 0.001$). The hazard ratio for the HRT group was 0.7 (95% confidence interval, 0.608–0.805; $p < 0.001$). Increased screening participation, longer HRT duration, and a normal or overweight BMI were associated with a better prognosis in the HRT group. Patients with BC who underwent HRT showed better clinicopathological characteristics and prognosis than those who did not receive HRT. The results highlighted significant differences in patients who underwent screening and those with a normal or overweight BMI. Furthermore, a longer HRT duration was associated with a better prognosis.

Keywords: Breast Neoplasms; Hormone Replacement Therapy; Prognosis; Survival Rate

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Conflict of Interest

The authors declare that they have no competing interests.

Data Availability

The study used data from the Korean Breast Cancer Society Registry. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Conceptualization: Kim CW, Bae SY; Data curation: Kim CW, Jung Y, Jeong J, Kim HJ, Choi JE, Suh YJ, Kim KS, Park WC, Yoon CI, Lee YJ, Kim D, Bae SY; Formal analysis: Kim CW, Bae SY; Investigation: Kim CW, Jung Y, Jeong J, Kim HJ, Choi JE, Suh YJ, Kim KS, Park WC, Yoon CI, Lee YJ, Kim D, Bae SY; Methodology: Kim CW, Bae SY; Supervision: Bae SY; Writing - original draft: Kim CW, Bae SY; Writing - review & editing: Kim CW, Bae SY.

INTRODUCTION

Breast cancer (BC) is the most common cancer in women, with approximately 1 million new annual cases and a rising incidence rate of about 0.3% per year since 2004 [1-3]. Risk factors for BC include increasing age, early menarche, late menopause, reproductive factors, hormone use, family history, and alcohol and smoking, among other lifestyle factors [4-6].

Hormone replacement therapy (HRT), including estrogen and estrogen–progestin combinations, is linked to BC risk. The Women's Health Initiative trial has demonstrated this association [7-9]. Additionally, the Million Women study found that current postmenopausal HRT users have a slightly higher risk of BC [10]. Despite an ongoing debate, few studies have investigated the prognosis of patients with HRT-related BC. Previous studies found that HRT before diagnosis reduced mortality and recurrence risk [1,11]. Patients with BC with a history of HRT have been found to have less aggressive disease, including a lower histologic grade, smaller size, and lymph node-negative tumors [1,7]. However, for patients with a family history of BC, HRT may slightly worsen prognosis [12,13], and the impact can vary by HRT regimen [1,14]. Given differing opinions on HRT and BC prognosis, assessing BC prognosis considering various factors in HRT patients is crucial.

This study compared the clinicopathological factors and prognosis of BC between HRT-experienced before BC diagnosis and HRT-naïve patients. In addition, how HRT duration, screening, body mass index (BMI), and immunohistochemistry (IHC) subtypes affect prognosis in HRT-experienced BC patients was also evaluated.

METHODS

Material

A cross-sectional design for clinicopathological characteristics (presented as proportions) and a retrospective design for survival analysis were based on data from the Korea Breast Cancer Society database. The data included clinicopathological factors, treatment methods, and the date of death. Further details can be found in a previous study [15].

This study included postmenopausal patients aged 50 to 79 with primary BC who underwent surgery, using the data of 27,560 BC patients collected from 2000 to 2014. Among them, 10,205 were excluded due to pathologic stage IV, unknown stage, having undergone neoadjuvant chemotherapy, or an unclear history of HRT. The final sample included 17,355 patients, of whom 3,585 (20.7%) received HRT before their BC diagnosis (HRT group) and 13,770 (79.3%) did not (non-HRT group).

Patient data included age at diagnosis, surgical method, pathologic and histologic grades, biomarkers, post-surgery treatment, hysterectomy status, family history, and the date of death. Additional variables included BMI, HRT duration, and BC screening status. Estrogen receptor (ER) and progesterone receptor (PR) data were collected based on each hospital's examination methods. Human epidermal growth factor receptor 2 (HER2) data were recorded via IHC staining and fluorescence *in situ* hybridization since 2010. The Ki-67 levels were categorized as low or high using a 20% cut-off. Patients were classified by BMI (kg/m^2) as: < 18.5, underweight; 18.5–22.9, normal; 23–24.9, overweight; 25–29.9, obesity; and ≥ 30, severe obesity. HRT duration was categorized as < 1 year, 1 to < 5 years, 5 to <10 years, and ≥ 10 years.

BC subtypes were classified as follows: Luminal A (ER- and/or PR-positive, HER2-negative, low Ki-67), Luminal B (ER- and/or PR-positive, HER2-negative with high Ki-67 or ER- and/or PR-positive, HER2-positive), HER2 overexpression (ER- and PR-negative, HER2-positive), and triple-negative breast cancer (TNBC) (ER- and PR-negative, HER2-negative). Overall survival (OS) was calculated from diagnosis to death.

Statistical analysis

Clinicopathological data were compared between the HRT and non-HRT groups using the χ^2 test. The OS rates were compared with the Kaplan-Meier method and log-rank test. Prognostic factors were evaluated via univariate and multivariate analysis using the Cox proportional hazards model. A p-value < 0.05 was considered significant. All analyses were conducted with SPSS (version 25.0; IBM Corp., Armonk, USA).

Ethical statement

This is retrospective nature of the study. Approval was granted by the Institutional Review Board of Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea (approval No. KC21ZASI0438). The requirement for informed consent was waived.

RESULTS

Analysis of clinicopathologic characteristics

The clinicopathological characteristics of the two groups are detailed in **Table 1**. Both groups had a median diagnosis age of 58 years. The HRT group had more patients in their 50s (58.8% vs. 55.7%) and fewer patients in their 70s (6.4% vs. 11.1%) than the non-HRT group (p < 0.001). The HRT group had a higher rate of breast-conserving surgery compared to the non-HRT group (60.7% vs. 54.1%, p < 0.001), with no significant difference in axillary lymph node operations (p = 0.304).

The HRT group had a lower Tumor, Node, Metastasis stage than the non-HRT group (stage I: 43.8% vs. 39.0%, p < 0.001; pT1: 59.0% vs. 52.3%, p < 0.001; pN0: 66.1% vs. 65.1%, p = 0.012). The histologic and nuclear grades were also lower in the HRT group compared to the non-HRT group (histological grade G1/G2: 65.2% vs. 61.8%, p = 0.001; nuclear grade G1/G2: 62.0% vs. 59.4%, p = 0.011). The HRT group had a higher proportion of PR-negative (55.6% vs. 53.0%, p = 0.006) and HER2-negative tumors (73.2% vs. 70.6%, p = 0.004) than the non-HRT group. No significant difference was observed in terms of the IHC subtypes (p = 0.279). In the HRT group, 67.4% used HRT for <5 years. The HRT group had a higher BC screening rate (78.4% vs. 59.7%, p < 0.001), more normal BMI (36.8% vs. 31.1%), and fewer obese patients (34.5% vs. 43.1%, p < 0.001). The hysterectomy rates were also higher (18.0% vs. 10.3%, p < 0.001). There was no significant difference in family history (p = 0.913).

Survival analysis

In the Kaplan-Meier analysis, the HRT group had better OS rates than the non-HRT group (5-year OS: 93.9% vs. 91.7%; 10-year OS: 87.1% vs. 82.3%, p < 0.001) (**Figure 1A**). Univariate analysis showed a better prognosis for the HRT group with a hazard ratio (HR) of 0.700 (95% confidence interval [CI], 0.608–0.805; p < 0.001) (**Table 2**). Multivariate analysis, adjusting for age and pathologic staging, indicated a better OS for the HRT group compared to the non-HRT group (HR, 0.804; 95% CI, 0.698–0.925; p = 0.002) (**Table 2**, Model I). Further

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Table 1. Clinicopathologic characteristics of the hormone replacement therapy and non-hormone replacement therapy groups (n = 17,355)

Characteristics	HRT, No. (%)	Non-HRT, No. (%)	*p*-value
No. of patients	3,585 (20.7)	13,770 (79.3)	
Age at diagnosis (yr)			
Mean ± SD	59.2 ± 6.0	59.7 ± 6.8	
Median (range)	58 (50–79)	58 (50–79)	
50–59	2,107 (58.8)	7,666 (55.7)	< 0.001
60–69	1,250 (34.9)	4,569 (33.2)	
70–79	228 (6.4)	1,535 (11.1)	
Breast operation			
Mastectomy	1,395 (39.1)	6,287 (45.8)	< 0.001
BCS	2,167 (60.7)	7,428 (54.1)	
No operation	8 (0.2)	6 (0.0)	
Unknown	15	49	
Axillary lymph node operation			
SLNB	1,388 (38.8)	5,150 (37.5)	0.304
ALND	1,147 (32.1)	4,615 (33.6)	
SLNB + ALND	868 (24.3)	3,290 (23.9)	
No operation	171 (4.8)	684 (5.0)	
Unknown	11	31	
pT			
T0	15 (0.4)	33 (0.2)	< 0.001
Tis	276 (7.7)	1,071 (7.8)	
T1	2,114 (59.0)	7,198 (52.3)	
T2	1,099 (30.7)	4,972 (36.1)	
T3	64 (1.8)	336 (2.4)	
T4	17 (0.5)	160 (1.2)	
pN			
N0	2,370 (66.1)	8,966 (65.1)	0.012
N1mi	45 (1.3)	151 (1.1)	
N1	808 (22.5)	2,989 (21.7)	
N2	224 (6.2)	1,085 (7.9)	
N3	138 (3.8)	579 (4.2)	
Pathologic stage			
Stage 0	274 (7.6)	1,064 (7.7)	< 0.001
Stage I	1,570 (43.8)	5,366 (39.0)	
Stage II	1,350 (37.7)	5,514 (40.0)	
Stage III	391 (10.9)	1,826 (13.3)	
Histologic grade			
G1/G2	1,966 (65.2)	7,233 (61.8)	0.001
G3	1,051 (34.8)	4,470 (38.2)	
Unknown	568	2,067	
Nuclear grade			
G1/G2	1,766 (62.0)	6,293 (59.4)	0.011
G3	1,083 (38.0)	4,308 (40.6)	
Unknown	736	3,169	
ER			
Positive	2,164 (61.4)	8,349 (61.6)	0.802
Negative	1,361 (38.6)	5,200 (38.4)	
Unknown	60	221	
PR			
Positive	1,562 (44.4)	6,353 (47.0)	0.006
Negative	1,959 (55.6)	7,177 (53.0)	
Unknown	64	240	
HER2			
Positive	836 (26.8)	3,442 (29.4)	0.004
Negative	2,288 (73.2)	8,257 (70.6)	
Unknown	461	2,071	

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Table 1. (Continued) Clinicopathologic characteristics of the hormone replacement therapy and non-hormone replacement therapy groups (n = 17,355)

Characteristics	HRT, No. (%)	Non-HRT, No. (%)	*p*-value
Ki-67 level			
< 20%	1,098 (56.8)	4,337 (55.6)	0.333
≥ 20%	835 (43.2)	3,466 (44.4)	
Unknown	1,652	5,967	
IHC subtype			
Luminal A	673 (23.1)	2,562 (23.3)	0.279
Luminal B	1,091 (37.5)	4,213 (38.2)	
HER2 overexpression	514 (17.7)	2,027 (18.4)	
TNBC	631 (21.7)	2,215 (20.1)	
Unknown	676	2,753	
Chemotherapy			
Yes	2,599 (72.5)	9,986 (72.6)	0.943
No	986 (27.5)	3,777 (27.4)	
Unknown	0	7	
Radiation therapy			
Yes	2,293 (67.0)	8,245 (62.7)	< 0.001
No	1,128 (33.0)	4,899 (37.3)	
Unknown	164	626	
Hormonal therapy			
Yes	2,117 (63.7)	8,226 (64.5)	0.369
No	1,209 (36.3)	4,530 (35.5)	
Unknown	259	1,014	
HRT duration (yr)			
No HRT		13,770 (100.0)	
< 1	941 (26.9)		
1 to < 5	1,414 (40.5)		
5 to < 10	761 (21.8)		
≥ 10	378 (10.8)		
Unknown	91		
Breast cancer screening			
Yes	2,161 (78.4)	6,559 (59.7)	< 0.001
No	594 (21.6)	4,426 (40.3)	
Unknown	830	2,785	
BMI (kg/m^2)			
Underweight	46 (1.3)	179 (1.4)	< 0.001
Normal	1,256 (36.8)	4,068 (31.1)	
Overweight	933 (27.3)	3,205 (24.5)	
Obesity	1,050 (30.8)	4,733 (36.2)	
Severe obesity	127 (3.7)	902 (6.9)	
Unknown	173	683	
Hysterectomy			
Yes	647 (18.0)	1,425 (10.3)	< 0.001
No	2,938 (82.0)	12,345 (89.7)	
Family history			
Yes	286 (8.2)	1,117 (8.2)	0.913
No	3,220 (91.8)	12,481 (91.8)	
Unknown	79	172	

Data shown are number (%) not otherwise specified.
HRT = hormone replacement therapy; SD = standard deviation; BCS = breast-conserving surgery; SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; TNBC = triple-negative breast cancer; BMI = body mass index.

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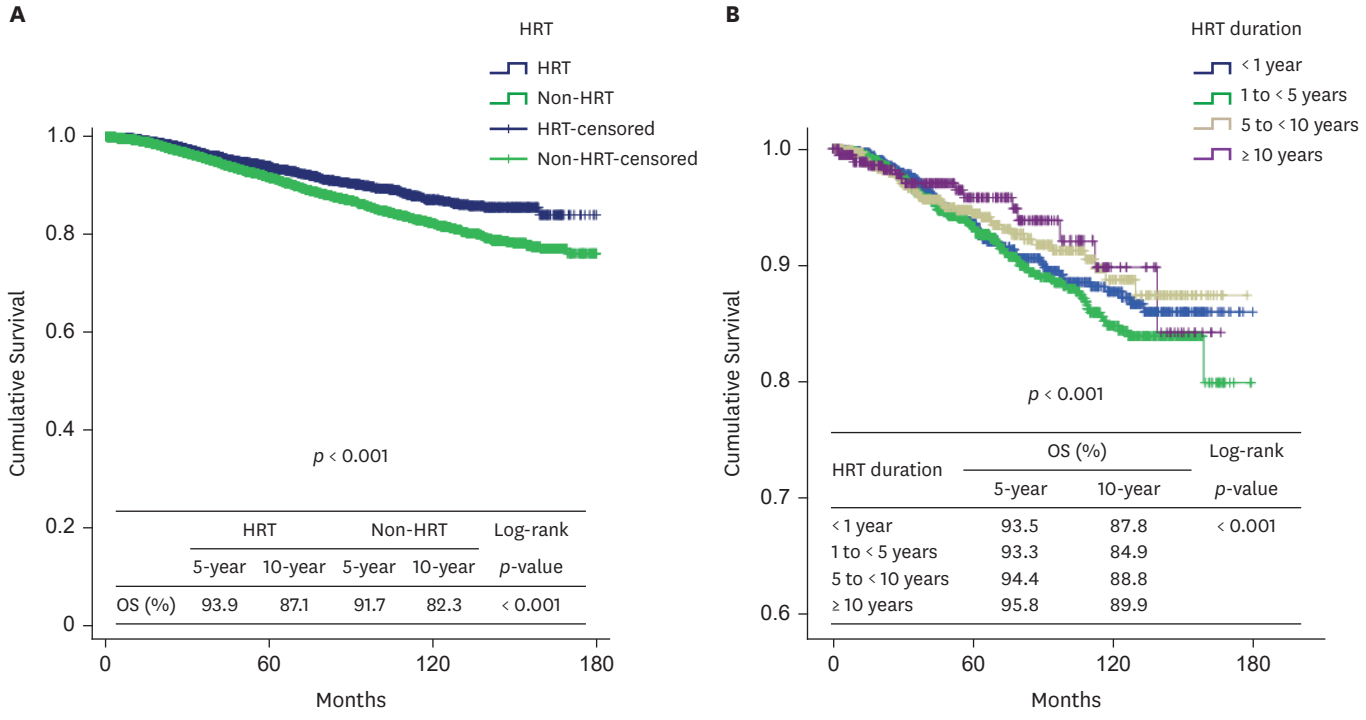

Figure 1. Overall survival of the hormone replacement therapy and non-hormone replacement therapy groups.
(A) OS graph and the 5- and 10-year OS rates of the HRT and non-HRT groups. (B) OS according to HRT duration.
OS = overall survival; HRT = hormone replacement therapy.

adjustment for age, pathologic staging, and BMI yielded similar results (HR, 0.810; 95% CI, 0.701–0.936; $p = 0.004$) (**Table 2**, Model II).

The OS in the HRT group varied with HRT duration. Although an HRT duration of 1 to < 5 years was an exception, it is worth noting that OS rates increased with a longer duration of HRT. In particular, for those with HRT for ≥ 10 years, the 5- and 10-year OS rates were 95.8% and 89.9%, respectively ($p < 0.001$) (**Figure 1B**). Even after adjusting for age and pathologic staging, the ≥ 10 years subgroup was found to have a significantly better OS compared to the non-HRT group (HR, 0.580; 95% CI, 0.354–0.950; $p = 0.030$) (**Table 2**, Model III).

The HRT group (2,159 patients) had a better prognosis than the non-HRT group (6,554 patients) among the 8,713 screened patients (5-year OS: 94.5% vs. 93.2%; 10-year OS: 88.4% vs. 84.7%; $p = 0.017$). However, among 5,017 non-screened patients, OS was not significantly different between the groups ($p = 0.054$) (**Figure 2**). After adjusting for age and pathologic staging, the HRT group demonstrated a better prognosis with screening (HR, 0.789; 95% CI, 0.640–0.973; $p = 0.027$). However, no significant difference was observed for individuals without screening (HR, 0.921; 95% CI, 0.709–1.196; $p = 0.536$) (**Table 2**, Model IV).

In the BMI-based subgroup analysis, the HRT group demonstrated a better prognosis than the non-HRT group among 5,324 patients with normal BMI (5-year OS: 95.2% vs. 91.6%; 10-year OS: 89.3% vs. 81.8%; $p < 0.001$) and 4,138 patients with overweight BMI (5-year OS: 94.4% vs. 92.2%; 10-year OS: 87.4% vs. 82.3%; $p = 0.002$) (**Supplementary Figure 1**).

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Table 2. Analysis of overall survival

Variables	HR	95% CI		*p*-value
		Lower	Upper	
Univariate analysis				
HRT				
No	Reference			
Yes	0.700	0.608	0.805	< 0.001
HRT duration (yr)				
No HRT	Reference			
< 1	0.690	0.540	0.881	0.003
1 to < 5	0.797	0.654	0.971	0.024
5 to < 10	0.625	0.460	0.851	0.003
≥ 10	0.545	0.333	0.892	0.016
BMI (kg/m^2)				
Underweight	1.935	1.326	2.824	0.001
Normal	Reference			
Overweight	1.012	0.872	1.175	0.873
Obesity	1.079	0.944	1.235	0.266
Severe obesity	1.167	0.929	1.466	0.186
Breast cancer screening				
No	Reference			
Yes	0.639	0.568	0.720	< 0.001
Multivariate analysis				
Model I				
Total patients				
Age at diagnosis	1.040	1.032	1.048	< 0.001
Pathologic stage	2.665	2.471	2.874	< 0.001
HRT versus non-HRT	0.804	0.698	0.925	0.002
Model II				
Age at diagnosis	1.040	1.032	1.048	< 0.001
Pathologic stage	2.655	2.456	2.871	< 0.001
BMI (kg/m^2)				
Underweight	1.767	1.211	2.578	0.003
Normal	Reference			
Overweight	0.950	0.818	1.103	0.499
Obesity	0.945	0.826	1.081	0.408
Severe obesity	0.938	0.746	1.179	0.583
HRT versus non-HRT	0.810	0.701	0.936	0.004
Model III				
Age at diagnosis	1.040	1.032	1.048	<0.001
Pathologic stage	2.666	2.472	2.876	<0.001
HRT duration (yr)				
No HRT	Reference			
< 1	0.780	0.610	0.997	0.047
1 to < 5	0.932	0.765	1.137	0.489
5 to < 10	0.736	0.541	1.002	0.052
≥ 10	0.580	0.354	0.950	0.030
Model IV				
Screening				
Yes				
Age at diagnosis	1.033	1.019	1.048	< 0.001
Pathologic stage	3.043	2.677	3.459	< 0.001
HRT versus non-HRT	0.789	0.640	0.973	0.027
No				
Age at diagnosis	1.047	1.036	1.058	< 0.001
Pathologic stage	2.396	2.139	2.683	< 0.001
HRT versus non-HRT	0.921	0.709	1.196	0.536

HR = hazard ratio; CI = confidence interval; HRT = hormone replacement therapy; BMI = body mass index.

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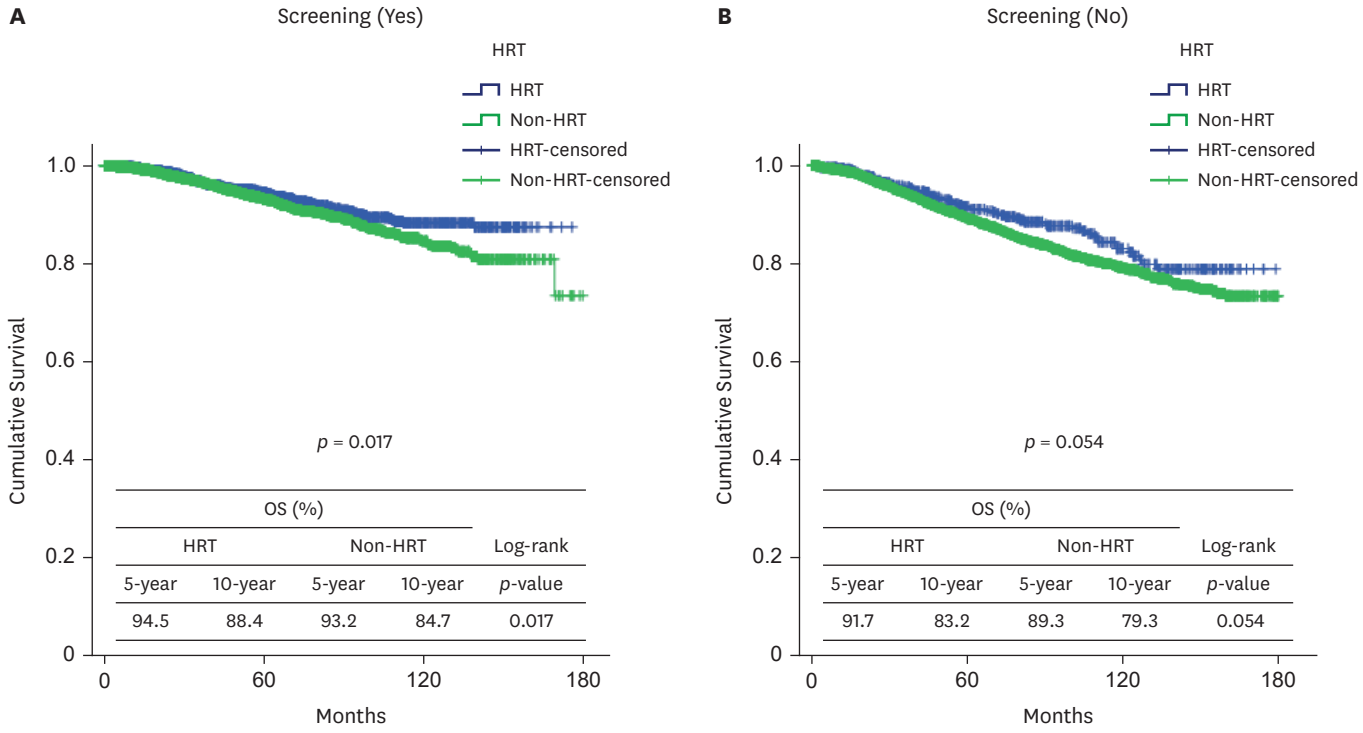

Figure 2. Overall survival of the screening subgroups in the hormone replacement therapy and non-hormone replacement therapy groups.
(A) OS of 8,713 screened patients. (B) OS of 5,017 patients who did not receive screening.
OS = overall survival; HRT = hormone replacement therapy.

The HRT group exhibited a better OS in the Luminal B and TNBC subtypes ($p < 0.001$ and $p = 0.003$, respectively) (**Supplementary Figure 2**). Among the Luminal B patients, a longer HRT duration (> 5 years) was associated with a better prognosis (**Supplementary Figure 3**).

DISCUSSION

Although HRT is a known risk factor for BC, its impact on prognosis remains controversial [16]. Despite this, recent studies have suggested that HRT before BC diagnosis may reduce recurrence and mortality risks [11]. Patients receiving HRT have been found to have a significantly better disease-free survival and a longer time to distant metastasis compared to non-users [7,17].

In this study, the HRT group had more favorable clinicopathological characteristics and better OS outcomes than the non-HRT group, including lower pathologic stages, smaller tumors, lymph node-negative status, and lower histologic and nuclear grades [1,7,17-20]. The impact of HRT on BC incidence increased with duration among the patients included in the Korean National Health Insurance Service database [9]. However, clinical opinions on BC prognosis are subjective and can vary. Some studies found a better OS and lower mortality with HRT, regardless of duration [21,22], while others found no significant difference with HRT duration under 5 years or a better prognosis with long-term HRT [11,23,24].

In the present study, a longer HRT duration was associated with lower pathological stages and histologic and nuclear grades, indicating a “well-differentiated” status. Long HRT

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duration was also found to be correlated with a higher proportion of ER/PR-positive tumors and a greater ratio of Luminal A and B subtypes (**Supplementary Table 1**).

Although the frequency of BC screening was unknown in this study, the HRT group had a higher screening rate than the non-HRT group. Analysis of screening data (**Supplementary Table 2**) showed that both groups had high rates of Tis, T1, N0, and Stage I cancers, with the HRT group having better OS outcomes. However, among those who did not undergo screening, OS did not show significant differences between the two groups. This suggests that early detection through screening contributed to a better prognosis and reduced mortality in the HRT group [25]. Furthermore, in the HRT group, IHC subtypes showed no significant differences between screened and non-screened patients. However, in the non-HRT group, screening was associated with higher rates of Luminal A and HER2 overexpression, while non-screened patients had more Luminal B and TNBC (**Supplementary Table 2**).

Although increased BMI is associated with an increased risk of BC in postmenopausal women [17], HRT and BC risk factors vary across patients with different BMI values. In a previous study, a greater HRT-related BC risk was observed in lean women [9]. In the present study, the HRT group had more patients with normal and overweight BMI compared to the non-HRT group. Subgroup analysis indicated that a higher BMI was correlated with a higher pathologic stage (**Supplementary Table 3**). Patients with a normal or overweight BMI in the HRT group had a better OS than those in the non-HRT group (**Supplementary Table 4**). These results suggest that the impact of HRT on BC prognosis may vary according to BMI.

The ER/PR and Ki-67 levels are known prognostic factors in BC, and hormone receptor-positive BC generally has a better prognosis [17,26]. Previous studies have reported a higher proportion of hormone receptor-positive tumors, especially, ER-positive, in the HRT group [8,12,20,27,28]. HRT users have found reported to have a higher prevalence of the Luminal A-like subtype, while Luminal B-like and HER2 overexpression subtypes tend to be more common in non-HRT patients [28,29]. However, the results in the present study showed no significant differences in the ER and Ki-67 levels between groups, and the HRT group had more PR- and HER2-negative tumors. The HRT group also exhibited a better OS in the Luminal B and TNBC subtypes. These findings emphasize the intricate relationship among IHC subtypes, HRT, and BC prognosis, suggesting the necessity for further research on IHC classification and treatment regimens.

Previous studies have suggested that HRT regimens can affect BC OS [1,14]. However, specific HRT regimen data were unavailable in this study. Because the HRT regimen may differ based on whether a hysterectomy is performed, a subgroup analysis was conducted accordingly. The results showed no differences in OS in patients with hysterectomy ($p = 0.720$), but better prognosis for non-hysterectomy patients on HRT ($p < 0.001$) (**Supplementary Figure 4**). A key limitation of this result is the lack of specific HRT regimen details, indicating a need for further research.

Taken together, these findings suggest that the HRT group had better clinicopathological characteristics and OS compared to the non-HRT group, suggesting potential benefits for BC prognosis. The positive impact of HRT was more significant with a longer duration, early detection, and appropriate BMI management. However, the complexity of the relationship between HRT and BC prognosis highlights the need for further research to clarify the

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optimal use and long-term effects of HRT. Thus, these findings emphasize the importance of personalized BC management and the need for continued investigation into HRT protocols.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
Subgroup analysis according to hormone replacement therapy duration

Supplementary Table 2
Subgroup analysis according to screening

Supplementary Table 3
Subgroup analysis according to body mass index

Supplementary Table 4
Multivariate analysis for overall survival of the hormone replacement therapy and non-hormone replacement therapy groups according to the body mass index subgroup

Supplementary Figure 1
Overall survival of the body mass index subgroup in the hormone replacement therapy and non-hormone replacement therapy groups.

Supplementary Figure 2
Overall survival of immunohistochemistry subtypes in the hormone replacement therapy and non-hormone replacement therapy groups.

Supplementary Figure 3
Overall survival between immunohistochemistry subtypes and hormone replacement therapy duration in the hormone replacement therapy and non-hormone replacement therapy groups.

Supplementary Figure 4
Overall survival with or without hysterectomy in the hormone replacement therapy and non-hormone replacement therapy groups.

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