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Locoregional Recurrence Patterns in Patients With Different Molecular Subtypes of Breast Cancer

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IMPORTANCE While numerous studies have consistently reported that the molecular subtypes of breast cancer (BC) are associated with different patterns of distant metastasis, few studies have investigated the association of tumor subtypes with locoregional recurrence.

OBJECTIVE To investigate the patterns of ipsilateral breast tumor recurrence (IBTR), regional recurrence (RR), and contralateral BC (CBC) according to tumor subtypes.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study used the clinical records of patients who underwent BC surgery at a single institution in South Korea between January 2000 and December 2018. Data were analyzed from May 1, 2019, to February 20, 2023.

EXPOSURES Ipsilateral breast tumor recurrence, RR, and CBC events.

MAIN OUTCOMES AND MEASURES The primary outcome was differences in annual incidence patterns of IBTR, RR, and CBC according to tumor subtypes. Hormone receptor (HR) status was assessed by immunohistochemical staining assay, and *ERBB2* status was evaluated according to American Society of Clinical Oncology and College of American Pathologists guidelines.

RESULTS A total of 16 462 female patients were included in the analysis (median age at time of operation, 49.0 years [IQR, 43.0-57.0 years]). The 10-year IBTR-, RR-, and CBC-free survival rates were 95.9%, 96.1%, and 96.5%, respectively. On univariate analysis, HR−/*ERBB2*+ tumors had the worst IBTR-free survival (vs HR+/*ERBB2*− subtype: adjusted hazard ratio, 2.95; 95% CI, 2.15-4.06), while the HR−/*ERBB2*− subtype had the worst RR- and CBC-free survival among all subtypes (vs HR+/*ERBB2*− subtype, RR: adjusted hazard ratio, 2.95; 95% CI, 2.37-3.67; CBC: adjusted hazard ratio, 2.12; 95% CI, 1.64-2.75). Subtype remained significantly associated with recurrence events in Cox proportional hazards regression analysis. Regarding the annual recurrence pattern, the IBTR patterns of HR−/*ERBB2*+ and HR−/*ERBB2*− subtypes showed double peaks, while HR+/*ERBB2*− tumors showed a steadily increasing pattern without distinguishable peaks. Additionally, the HR+/*ERBB2*− subtype seemed to have a steady RR pattern, but other subtypes showed the highest RR incidence at 1 year following surgery, which then gradually decreased. The annual recurrence incidence of CBC gradually increased among all subtypes, and patients with the HR−/*ERBB2*− subtype had a higher incidence than patients with other subtypes over 10 years. Younger patients (age ≤40 years) had greater differences in IBTR, RR, and CBC patterns between subtypes than did older patients.

CONCLUSIONS AND RELEVANCE In this study, locoregional recurrence occurred with different patterns according to BC subtypes, with younger patients having greater differences in patterns among subtypes than older patients. The findings suggest that tailoring surveillance should be recommended regarding differences in locoregional recurrence patterns according to tumor subtypes, particularly for younger patients.

Invited Commentary

Supplemental content

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Breast cancer (BC) is the leading cause of newly diagnosed malignant tumors and cancer-related death in women worldwide.[1] Locoregional recurrence after initial treatment is associated with higher BC mortality.[2,3] Accordingly, BC surveillance, including mammography, focuses on early detection of recurrence before clinical symptoms develop.[4,5] Moreover, early treatment of locoregional recurrence is also well known to be associated with improved prognosis.[6-8] Major guidelines recommend annual breast mammography for BC surveillance.[9-11]

Identifying tumor subtypes is essential for decision-making about treatments and prognosis; thus, most institutions routinely conduct immunohistochemical (IHC) tests.[12] Interestingly, BC subtypes are correlated with recurrence in that the cumulative recurrence rates of the luminal subtype are more favorable than those of other subtypes.[3,13,14] Additionally, the annual hazard ratio of recurrence, including distant metastasis, varies over time after initial treatment according to subtype.[15,16] Patients with the *ERBB2*-enriched subtype and basal-like BC had higher recurrence rates than did those with the luminal subtype at 12 months after surgery, but rates declined dramatically after that.[17] In contrast, the recurrence incidence of the luminal subtype showed a steadily increasing pattern exceeding that of other subtypes after 3 years of treatment.[17]

Nevertheless, current major guidelines do not include tailored postoperative surveillance for tumor subtypes.[9-11] Furthermore, few studies have reported the annual pattern of locoregional recurrence according to tumor subtypes. We retrospectively investigated the patterns of ipsilateral breast tumor recurrence (IBTR), regional recurrence (RR), and contralateral breast cancer (CBC) with a large number of patients with BC and long-term follow-up at a single institution.

Key Points

Question What are the patterns of locoregional recurrence in patients with breast cancer stratified by molecular subtype?

Findings In this cohort study of 16 462 Korean patients, locoregional recurrence occurred with different patterns according to breast cancer subtypes. Patients aged 40 years or younger had greater differences in ipsilateral breast tumor recurrence, regional recurrence, and contralateral breast cancer patterns among subtypes than did patients older than 40 years.

Meaning The findings suggest that tailoring breast cancer surveillance should be recommended regarding differences in locoregional recurrence patterns according to tumor subtypes, particularly for younger patients.

Methods

Patients

This cohort study was approved by the institutional review board of Seoul National University Hospital in South Korea. All procedures were performed following the Declaration of Helsinki,[18] and the requirement for informed consent was waived because this was a retrospective study that had no potential harm to the included patients. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[19] We retrospectively reviewed the clinicopathological records associated with BC survival of all patients who underwent surgery for BC between January 2000 and December 2018.[20] We used the database of our institution, which collects comprehensive data from a single institution.[21] Patients with phyllodes tumors, synchronous or metachronous malignant tumors, and secondary BC were excluded. In addition, we excluded patients with bilateral breast cancer to minimize potential bias, as it is difficult to distinguish in-breast recurrence as either IBTR or CBC and axillary lymph node metastasis as either RR or distant metastasis. Lastly, patients with indistinguishable subtypes were excluded (eFigure 1 in Supplement 1). Age was categorized with a cutoff of 40 years due to the small number of patients younger than 35 years, which is a generally accepted cutoff for categorizing women as younger.[22,23]

Pathologic Assessment

Positive hormone receptor (HR) was defined as 1% or more of stained cells with estrogen or progesterone receptor on IHC staining assay. The *ERBB2* status was evaluated according to the American Society of Clinical Oncology and College of American Pathologists guidelines.[24] In the case of equivocal results on IHC assay, the specimen was reevaluated with fluorescence in situ hybridization (FISH). Patients with 2+ on IHC assay for *ERBB2* but who did not undergo FISH or silver in situ hybridization (SISH) testing were excluded. A Ki-67-labeling index of less than 10% was regarded as low according to a previous study conducted in our institution.[25]

Definition of Recurrence

We classified the recurrence events into IBTR, RR, and CBC. Ipsilateral breast tumor recurrence was confined to the first recurrence in the ipsilateral breast. Accordingly, only patients who underwent breast-conserving surgery were analyzed for IBTR. Regional recurrence events included any recurrence at the ipsilateral chest wall, mastectomy scar, skin of the breast, or regional lymph nodes including ipsilateral axillary, supraclavicular, infraclavicular, or internal mammary lymph nodes. Recurrence-free survival was defined as the interval between the date of surgery and the date of pathologic or radiologic confirmation of recurrence. Considering the competing risk, distant metastasis without prior IBTR, RR, or CBC was treated as censored at the time of occurrence. The maximum observation period was set at up to 10 years following surgery since no further surveillance was performed for most patients who were disease free for 10 years after surgery in our institution.

Statistical Analysis

The continuous variables were compared using the Kruskal-Wallis test and post hoc Mann-Whitney *U* test. The Pearson χ^2 test was used for categorical variables. The Cox

Table 1. Demographic and Clinicopathological Characteristics of Patients

Characteristic	Patients, by breast cancer subtype[a]				
	All (N = 16 462)	HR+/*ERBB2*− (n = 10 075)	HR+/*ERBB2*+ (n = 1846)	HR−/*ERBB2*+ (n = 1908)	HR−/*ERBB2*− (n = 2633)
Age at operation, median (IQR), y	49.0 (43.0-57.0)	48.0 (43.0-57.0)	48.0 (42.0-56.0)	52.0 (46.0-58.0)	50.0 (42.0-57.0)
BMI, median (IQR)	23.1 (21.2-25.4)	23.1 (21.1-25.5)	22.9 (21.1-25.2)	23.4 (21.5-25.4)	23.3 (21.5-25.6)
Surgeon					
A	7780 (47.3)	4500 (44.7)	890 (48.2)	952 (49.9)	1439 (54.6)
B	6443 (39.1)	4121 (40.9)	724 (39.2)	682 (35.7)	916 (37.8)
C	1303 (7.9)	853 (8.5)	144 (7.8)	144 (7.5)	162 (6.2)
Other	936 (5.7)	601 (6.0)	88 (4.8)	130 (6.8)	117 (4.4)
Year of operation					
2000-2009	5478 (33.3)	2989 (29.7)	607 (32.9)	741 (38.8)	1141 (43.3)
2010-2018	10 984 (66.7)	7086 (70.3)	1239 (67.1)	1167 (61.2)	1492 (56.7)
Breast operation					
Breast conserving	10 313 (62.6)	6618 (65.7)	996 (54.0)	918 (48.1)	1781 (67.6)
Mastectomy	6149 (37.4)	3457 (34.3)	850 (46.0)	990 (51.9)	852 (32.4)
Axillary operation					
Sentinel lymph node biopsy	8419 (51.1)	5441 (54.0)	873 (47.3)	868 (45.5)	1237 (47.0)
Axillary lymph node dissection	6543 (39.7)	3604 (35.8)	825 (44.7)	896 (47.0)	1218 (46.3)
Not done	413 (2.5)	326 (3.2)	38 (2.1)	33 (1.7)	16 (0.6)
Unknown	1087 (6.6)	704 (7.0)	110 (6.0)	111 (5.8)	162 (6.2)
T stage[b]					
Tis	1549 (9.4)	936 (9.3)	239 (12.9)	289 (15.1)	85 (3.2)
T1	8597 (52.2)	5354 (53.1)	947 (51.3)	968 (50.7)	1328 (50.4)
T2	5531 (33.6)	3329 (33.0)	566 (30.7)	558 (29.2)	1078 (40.9)
T3-4	733 (4.5)	432 (4.3)	86 (4.7)	85 (4.5)	130 (4.9)
Unknown	52 (0.3)	24 (0.2)	8 (0.4)	8 (0.4)	12 (0.5)
N stage[b]					
N0	10 809 (65.7)	6459 (64.1)	1143 (61.9)	1330 (69.7)	1877 (71.3)
N1	3579 (21.7)	2329 (23.1)	413 (22.4)	350 (18.3)	487 (18.5)
N2	1031 (6.3)	622 (6.2)	149 (8.1)	113 (5.9)	147 (5.6)
N3	507 (3.1)	268 (2.7)	83 (4.5)	66 (3.5)	90 (3.4)
Unknown	536 (3.3)	397 (3.9)	58 (3.1)	49 (2.6)	32 (1.2)

(continued)

proportional hazards regression model was used for multivariate analysis and to estimate the adjusted hazard ratios. Variables with a 2-sided *P* value <.05 in the univariate analysis were included in multivariate analysis, and those that violated the proportional hazards assumption or showed multicollinearity were excluded. The proportional hazards assumption was assessed by the Schoenfeld residual test, and a variance inflation factor greater than 4.0 was considered to indicate the presence of multicollinearity. Missing data were addressed by applying a complete case analysis approach. The goodness of fit of the model was assessed using the Hosmer-Lemeshow test, with 2-sided *P* > .05 indicating a good fit. All analyses were performed using SPSS, version 26.0 (IBM), and the Kaplan-Meier curves were drawn using GraphPad Prism, version 8.0 (GraphPad Software). Patterns of annual recurrence incidence were smoothed with the kernel smoothing method using the ksmooth function in R, version 3.6.3 (R Project for Statistical Computing).[26] Statistical significance was set at 2-sided *P* < .05. Data were analyzed from May 1, 2019, to February 20, 2023.

Results

Patients

We identified 16 462 female patients who met the inclusion criteria. The median age at the time of operation was 49.0 years (IQR, 43.0-57.0 years) (**Table 1**). Patients underwent mammography and breast sonography with a median interval of 12.0 months (IQR, 10.7-13.3 months) and 10.1 months (IQR, 7.5-12.1 months), respectively. Approximately 73.8% and 50.4% of

Table 1. Demographic and Clinicopathological Characteristics of Patients (continued)

Characteristic	Patients, by breast cancer subtype[a]				
	All (N = 16 462)	HR+/*ERBB2*− (n = 10 075)	HR+/*ERBB2*+ (n = 1846)	HR−/*ERBB2*+ (n = 1908)	HR−/*ERBB2*− (n = 2633)
Lymphovascular invasion					
Present	4397 (26.7)	2687 (26.7)	580 (31.4)	477 (25.0)	653 (24.8)
Absent	10 052 (61.1)	6373 (63.3)	985 (53.4)	1059 (55.5)	1635 (62.1)
Unknown	2013 (12.2)	1015 (10.1)	281 (15.2)	372 (19.5)	345 (13.1)
Ki-67 index, %					
≥10	4212 (25.6)	1222 (12.1)	639 (34.6)	819 (42.9)	1532 (58.2)
<10	12 022 (73.0)	8719 (86.5)	1181 (64.0)	1058 (55.5)	1064 (40.4)
Unknown	228 (1.4)	137 (1.3)	26 (1.4)	31 (1.6)	37 (1.4)
Histologic grade, No./total No. (%)[c]					
I-II	8252/14 861 (55.5)	6582/9115 (72.2)	733/1599 (45.8)	435/1611 (27.0)	502/2536 (19.8)
III	5648/14 861 (38.0)	1981/9115 (21.7)	780/1599 (48.8)	1038/1611 (64.4)	1849/2536 (72.9)
Unknown	961/14 861 (6.5)	552/9115 (6.1)	86/1599 (5.4)	138/1611 (8.6)	185/2536 (7.3)
Resection margin, No./total No. (%)[d]					
Clear	8412/10 313 (81.6)	5279/6618 (79.8)	812/996 (81.5)	757/918 (82.5)	1564/1781 (87.8)
Close or involved	1834/10 313 (17.8)	1301/6618 (19.7)	175/996 (17.6)	149/918 (16.2)	209/1781 (11.7)
Unknown	67/10 313 (0.6)	38/6618 (0.6)	9/996 (0.9)	12/918 (1.3)	8/1781 (0.4)
Neoadjuvant chemotherapy					
Administered	2674 (16.2)	1119 (11.1)	494 (26.8)	439 (23.0)	622 (23.6)
Not administered	13 788 (83.8)	8956 (88.9)	1352 (73.2)	1469 (77.0)	2011 (76.4)
Adjuvant chemotherapy					
Administered	6955 (42.2)	3615 (35.9)	851 (46.1)	916 (48.0)	1573 (59.7)
Not administered	8244 (50.1)	5613 (55.7)	866 (46.9)	876 (45.9)	889 (33.8)
Unknown	1263 (7.7)	847 (8.4)	129 (7.0)	116 (6.1)	171 (6.5)
Adjuvant radiotherapy					
Administered	11 093 (67.4)	6894 (68.4)	1225 (66.4)	1058 (55.5)	1916 (72.8)
Not administered	4634 (28.1)	2689 (26.7)	560 (30.3)	771 (40.4)	614 (23.3)
Unknown	735 (4.5)	492 (4.9)	61 (3.3)	79 (4.1)	103 (3.9)
Adjuvant hormonal treatment					
Administered	11 368 (69.1)	9620 (95.5)	1677 (90.8)	29 (1.5)	42 (1.6)
Not administered	5008 (30.4)	388 (3.9)	151 (8.2)	1879 (98.5)	2590 (98.4)
Unknown	86 (0.5)	67 (0.7)	18 (1.0)	0	1 (0.0)
ERBB2-targeted treatment					
Administered	1894 (11.5)	0	1001 (54.2)	893 (46.8)	0
Not administered	14 568 (88.5)	10 075 (100)	845 (45.8)	1015 (53.2)	2633 (100)
Interval of mammography, median (IQR), mo	12.0 (10.7-13.3)	12.0 (10.6-13.3)	12.1 (10.9-13.5)	12.1 (10.8-13.5)	12.0 (10.8-13.5)
Interval of clinic visits, median (IQR), mo					
≤5 y After surgery	6.0 (4.2-8.5)	5.8 (4.1-8.2)	6.2 (4.4-8.6)	6.5 (4.5-9.1)	6.3 (4.3-9.1)
>5 y After surgery	35.6 (24.0-61.2)	36.1 (24.0-61.6)	34.3 (24.0-60.0)	36.8 (24.0-61.8)	32.4 (24.0-60.0)
IBTR, No./total No. (%)[d]	286/10 313 (2.8)	137/6618 (2.1)	33/996 (3.3)	53/918 (5.8)	63/1781 (3.5)
RR	466 (2.8)	187 (1.9)	54 (2.9)	82 (4.3)	143 (5.4)
CBC	325 (2.0)	167 (1.7)	33 (1.8)	35 (1.8)	90 (3.4)
Follow-up period, median (IQR), mo	73.7 (46.3-116.2)	74.4 (48.4-114.8)	69.8 (43.3-110.1)	72.0 (43.2-116.0)	76.0 (41.1-120.0)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CBC, contralateral breast cancer; IBTR, ipsilateral breast tumor recurrence; RR, regional recurrence; Tis, tumor in situ.

[a] Data are presented as the number (percentage) of patients unless otherwise indicated.

[b] Stratified according to the *AJCC Cancer Staging Manual, Eighth Edition* TNM stage. Patients who received neoadjuvant chemotherapy were evaluated clinically.

[c] Among patients with invasive cancer.

[d] Among patients who underwent breast-conserving surgery.

patients underwent mammography and breast sonography more than once a year, respectively. During the median follow-up period of 73.7 months (IQR, 46.3-116.2 months), RR occurred in 466 (2.8%) and CBC in 325 (2.5%) of all patients, and IBTR occurred in 286 of 10 313 patients (2.8%) who underwent breast-conserving surgery.

When examining tumor subtypes, the HR+/*ERBB2*−, HR+/*ERBB2*+, HR−/*ERBB2*+, and HR−/*ERBB2*− constituted 61.2%,

11.2%, 11.6%, and 16.0% of the sample, respectively. Patients with the HR+/*ERBB2*− subtype had less aggressive pathologic features, such as lower T/N stage, histologic grade, and Ki-67 level, and less lymphovascular invasion (eTable 1 in Supplement 1). They also received significantly less adjuvant and neoadjuvant chemotherapy compared with patients who had other subtypes. Patients with the HR−/*ERBB2*− subtype required more adjuvant chemotherapy (vs HR+/*ERBB2*−: odds ratio [OR], 2.75 [95% CI, 2.51-3.01]; vs HR+/*ERBB2*+: OR, 1.80 [95% CI, 1.59-2.04]; vs HR−/*ERBB2*+: OR: 1.69 [95% CI, 1.49-1.92]) and radiotherapy (vs HR+/*ERBB2*−: OR, 1.22 [95% CI, 1.10-1.35]; vs HR+/*ERBB2*+: OR, 1.43 [95% CI, 1.25-1.63]; vs HR−/*ERBB2*+: OR, 2.27 [95% CI, 2.00-2.59]). Adjuvant hormonal treatment was administered to 95.5% and 90.8% of the groups with HR+/*ERBB2*− and HR+/*ERBB2*+ subtypes, respectively. While none of the patients with the *ERBB2*− subtype received *ERBB2*-targeted treatment, it was administered to 54.2% and 46.8% of the groups with HR+/*ERBB2*+ and HR−/*ERBB2*+ subtypes, respectively.

Survival Outcomes According to Tumor Subtypes

The 10-year IBTR-, RR-, and CBC-free survival rates were 95.9%, 96.1%, and 96.5%, respectively. The IBTR-free survival rate was significantly better for patients with the HR+/*ERBB2*− subtype than for patients with other subtypes, while those with the HR−/*ERBB2*+ subtype had the worst survival (vs HR+/*ERBB2*−: adjusted hazard ratio, 2.95; 95% CI, 2.15-4.06) (**Figure 1**A). In contrast, patients with the HR−/*ERBB2*− subtype had the worst RR-free survival among all subtypes (vs HR+/*ERBB2*−: adjusted hazard ratio, 2.95; 95% CI, 2.37-3.67) (Figure 1B). Similarly, CBC-free survival among patients with the HR−/*ERBB2*− subtype was significantly poorer than among patients with other subtypes (vs HR+/*ERBB2*−: adjusted hazard ratio, 2.12; 95% CI, 1.64-2.75), but there were no significant differences among the other subtypes (Figure 1C).

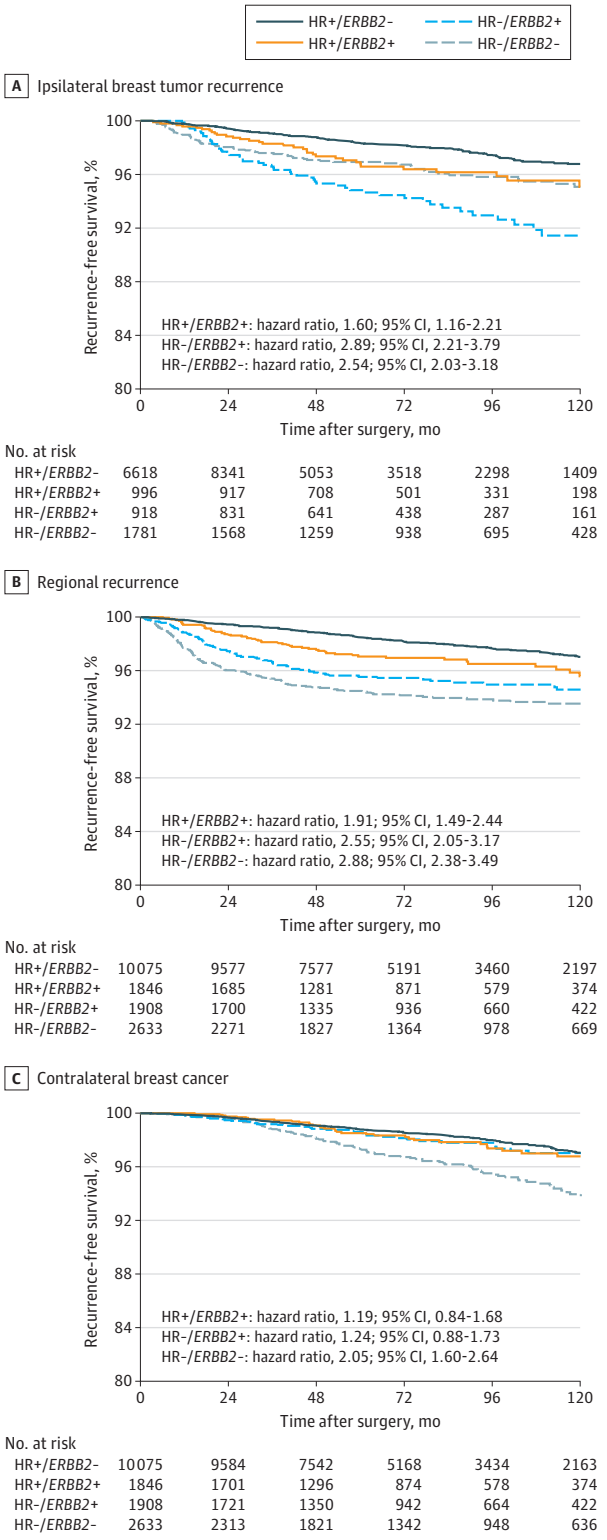
After adjusting for clinicopathological variables affecting recurrence, older age at operation was an independent factor associated with lower IBTR and CBC (**Table 2**). In addition, both IBTR and RR were significantly associated with lymphovascular invasion and administration of radiotherapy. There was a significant association between the HR−/*ERBB2*+ subtype and worse IBTR-free survival, and patients with the HR−/*ERBB2*− subtype had the worst RR- and CBC-free survival among tumor subtypes.

Annual Recurrence Pattern According to Tumor Subtypes

The rate of IBTR showed a double-peak pattern, with the first peak at year 2 and the second peak between years 8 and 9 after surgery (**Figure 2**A). The HR−/*ERBB2*+ subtype was associated with a higher annual IBTR incidence than other subtypes and had a double-peak pattern. The HR−/*ERBB2*− subtype showed a similar annual pattern but was associated with lower recurrence incidence compared with the HR−/*ERBB2*+ subtype. On the contrary, HR+/*ERBB2*− tumors showed a steadily increasing pattern with indistinguishable peaks.

In the case of RR, the HR−/*ERBB2*− subtype showed the highest incidence, with a peak at 1 year after surgery, followed by the HR−/*ERBB2*+, HR+/*ERBB2*+, and HR+/*ERBB2*− subtypes (Figure 2B). The difference in the incidence of recurrence among tumor subtypes was evident until 2 years

Figure 1. Kaplan-Meier Curves for Recurrence-Free Survival



Hazard ratios and 95% CIs were adjusted for surgeon and year of surgery. Reference is the HR+/*ERBB2*− subtype. HR indicates hormone receptor.

Table 2. Univariate and Multivariate Analyses for Ipsilateral Breast Tumor Recurrence–, Regional Recurrence–, and Contralateral Breast Cancer–Free Survival[a]

Characteristic	Univariate analysis		Multivariate analysis[b]	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Ipsilateral breast tumor recurrence				
Initial age, y[c]	0.96 (0.94-0.97)	<.001	0.97 (0.95-0.98)	<.001
BMI[c]	0.94 (0.90-0.98)	.002	0.97 (0.93-1.02)	.21
T stage[d]				
Tis	1 [Reference]	.009	1 [Reference]	.02
T1	0.64 (0.45-0.90)		0.54 (0.29-0.98)	
T2-4	0.87 (0.60-1.24)		0.77 (0.41-1.46)	
N stage[d]				
N0	1 [Reference]	.55	NA	NA
N1-3	1.09 (0.83-1.43)		NA	
Lymphovascular invasion				
Absent	1 [Reference]	<.001	1 [Reference]	.001
Present	1.90 (1.44-2.50)		1.70 (1.25-2.30)	
Ki-67 index, %				
<10	1 [Reference]	<.001	1 [Reference]	.17
≥10	1.86 (1.44-2.40)		1.26 (0.91-1.74)	
Resection margin				
Clear	1 [Reference]	<.001	1 [Reference]	<.001
Close or involved	2.02 (1.54-2.65)		1.77 (1.29-2.44)	
Tumor subtype				
HR+/*ERBB2*−	1 [Reference]	<.001	1 [Reference]	<.001
HR+/*ERBB2*+	1.68 (1.15-2.46)		1.49 (0.93-2.40)	
HR−/*ERBB2*+	2.95 (2.15-4.06)		3.08 (2.01-4.63)	
HR−/*ERBB2*-	1.75 (1.29-2.36)		1.84 (1.24-2.71)	
Neoadjuvant chemotherapy				
Administered	1 [Reference]	.02	1 [Reference]	.10
Not administered	0.70 (0.51-0.95)		0.74 (0.51-1.07)	
Adjuvant chemotherapy				
Administered	1 [Reference]	.78	NA	NA
Not administered	0.97 (0.76-1.23)		NA	
Adjuvant radiotherapy				
Administered	1 [Reference]	<.001	1 [Reference]	<.001
Not administered	2.70 (1.95-3.73)		2.52 (1.68-3.77)	
Adjuvant hormonal treatment[e]				
Administered	1 [Reference]	<.001	NA	NA
Not administered	2.16 (1.71-2.73)		NA	
ERBB-targeted treatment				
Administered	1 [Reference]	.18	NA	NA
Not administered	0.78 (0.54-1.13)		NA	
Regional recurrence				
Initial age, y	0.98 (0.97-0.99)	<.001	0.99 (0.97-1.00)	.004
BMI	1.01 (0.99-1.04)	.34	NA	NA
T stage[d]				
Tis	1 [Reference]	<.001	1 [Reference]	<.001
T1	1.91 (1.12-3.24)		2.37 (0.58-9.76)	
T2-4	4.64 (2.76-7.81)		4.92 (1.19-20.35)	
N stage[d]				
N0	1 [Reference]	<.001	1 [Reference]	<.001
N1-3	2.67 (2.21-3.21)		1.64 (1.27-2.10)	

(continued)

Table 2. Univariate and Multivariate Analyses for Ipsilateral Breast Tumor Recurrence–, Regional Recurrence–, and Contralateral Breast Cancer–Free Survival[a] (continued)

Characteristic	Univariate analysis		Multivariate analysis[b]	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Lymphovascular invasion				
Absent	1 [Reference]	<.001	1 [Reference]	<.001
Present	3.40 (2.77-4.17)		2.41 (1.88-3.08)	
Ki-67 index, %				
<10	1 [Reference]	<.001	1 [Reference]	.004
≥10	2.49 (2.07-3.01)		1.40 (1.11-1.77)	
Resection margin				
Clear	1 [Reference]	.17	NA	NA
Close or involved	0.79 (0.57-1.10)		NA	
Tumor subtype				
HR+/*ERBB2*−	1 [Reference]	<.001	1 [Reference]	<.001
HR+/*ERBB2*+	1.64 (1.21-2.22)		1.18 (0.82-1.69)	
HR−/*ERBB2*+	2.37 (1.83-3.08)		1.98 (1.43-2.73)	
HR−/*ERBB2*−	2.95 (2.37-3.67)		3.03 (2.31-3.98)	
Neoadjuvant chemotherapy				
Administered	1 [Reference]	<.001	1 [Reference]	<.001
Not administered	0.31 (0.26-0.38)		0.31 (0.24-0.40)	
Adjuvant chemotherapy				
Administered	1 [Reference]	<.001	1 [Reference]	.37
Not administered	0.49 (0.40-0.60)		1.13 (0.87-1.48)	
Adjuvant radiotherapy				
Administered	1 [Reference]	<.001	1 [Reference]	<.001
Not administered	1.88 (1.55-2.26)		2.93 (2.33-3.68)	
Adjuvant hormonal treatment[e]				
Administered	1 [Reference]	<.001	NA	NA
Not administered	2.55 (2.12-3.06)		NA	
ERBB2-targeted treatment				
Administered	1 [Reference]	.08	NA	NA
Not administered	0.78 (0.59-1.03)		NA	
Contralateral breast cancer				
Initial age, y	0.98 (0.97-1.00)	.005	0.99 (0.97-1.00)	.02
BMI	0.97 (0.93-1.00)	.050	0.97 (0.94-1.01)	.13
T stage[d]				
Tis	1 [Reference]	.87	NA	NA
T1	0.91 (0.63-1.33)		NA	
T2-4	0.95 (0.64-1.39)		NA	
N stage[d]				
N0	1 [Reference]	.37	NA	NA
N1-3	0.90 (0.70-1.14)		NA	
Lymphovascular invasion				
Absent	1 [Reference]	.69	NA	NA
Present	1.06 (0.81-1.37)		NA	
Ki-67 index, %				
<10	1 [Reference]	.06	NA	NA
≥10	1.26 (0.99-1.62)		NA	
Resection margin				
Clear	1 [Reference]	.66	NA	NA
Close or involved	1.08 (0.77-1.53)		NA	

(continued)

Table 2. Univariate and Multivariate Analyses for Ipsilateral Breast Tumor Recurrence–, Regional Recurrence–, and Contralateral Breast Cancer–Free Survival[a] (continued)

Characteristic	Univariate analysis		Multivariate analysis[b]	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Tumor subtype				
HR+/*ERBB2*−	1 [Reference]	<.001	1 [Reference]	<.001
HR+/*ERBB2*+	1.14 (0.79-1.66)		1.10 (0.75-1.62)	
HR−/*ERBB2*+	1.14 (0.79-1.64)		1.25 (0.87-1.81)	
HR−/*ERBB2*−	2.12 (1.64-2.75)		2.13 (1.63-2.79)	
Neoadjuvant chemotherapy				
Administered	1 [Reference]	.04	1 [Reference]	.22
Not administered	0.73 (0.54-0.99)		0.82 (0.60-1.12)	
Adjuvant chemotherapy				
Administered	1 [Reference]	.80	NA	NA
Not administered	1.03 (0.82-1.30)		NA	
Adjuvant radiotherapy				
Administered	1 [Reference]	.56	NA	NA
Not administered	1.07 (0.85-1.37)		NA	
Adjuvant hormonal treatment[e]				
Administered	1 [Reference]	<.001	NA	NA
Not administered	1.83 (1.47-2.29)		NA	
ERBB2-targeted treatment				
Administered	1 [Reference]	.26	NA	NA
Not administered	1.26 (0.85-1.87)		NA	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, not applicable; Tis, tumor in situ.

[a] Hosmer-Lemeshow goodness-of-fit test results: ipsilateral breast tumor recurrence: χ^2_8, 7.55; *P* = .48; regional recurrence: χ^2_8, 5.79; *P* = .67; contralateral breast cancer: χ^2_8, 12.04; *P* = .49. All variables were adjusted for the surgeon and the year of surgery.

[b] Variables with a *P* value <.05 in the univariate analysis were included in the multivariate analysis.

[c] Analyzed as a continuous variable. The hazard ratio represents the value when the age or BMI increased by 1.

[d] Stratified according to the *AJCC Cancer Staging Manual, Eighth Edition* TNM stage. Patients after neoadjuvant chemotherapy were evaluated with clinical stage.

[e] Adjuvant hormonal treatment showed multicollinearity for ipsilateral breast tumor recurrence, so it was excluded from multivariate analysis.

after surgery. After that, the incidence of all subtypes except the HR+/*ERBB2*− subtype gradually decreased, showing a similar annual recurrence pattern after 5 years postsurgery. The HR+/*ERBB2*− subtype showed a stable and increasing pattern of annual RR incidence. Conversely, the annual recurrence rate of CBC gradually increased for all subtypes, and the HR−/*ERBB2*− subtype showed the highest rate over 10 years (Figure 2C).

Annual Recurrence Pattern According to Age and Tumor Subtypes

In total, 13 556 patients (82.3%) were older than 40 years, and we compared the recurrence patterns between younger (age ≤40 years) and older (age >40 years) patients. The difference in the early recurrence patterns between HR+ and HR− subtypes was larger in the younger age group. In the younger age group, the double peaks of annual IBTR incidence were more prominent for younger patients than for older patients, especially for the HR−/*ERBB2*+ subtype (**Figure 3**A and D). Additionally, the incidence of RR decreased during the first 5 years, and all subtypes except the HR−/*ERBB2*− subtype showed a rebounded increasing pattern thereafter (Figure 3B and E). The annual CBC incidence among younger patients was higher with more diverse patterns than that among older patients (Figure 3C and F). On the contrary, older patients showed a steady annual IBTR and RR incidence after 5 years postsurgery, and the pattern was nearly identical among subtypes.

Annual Recurrence Pattern According to Adjuvant Treatment

Patients who received *ERBB2*-targeted treatment had better locoregional recurrence-free survival (hazard ratio, 1.42; 95% CI, 1.08-1.87) but comparable CBC-free survival (hazard ratio, 1.40; 95% CI, 0.86-2.28) compared with those who did not receive this treatment (eFigure 2 in Supplement 1). The annual recurrence pattern indicated that patients treated with *ERBB2*-targeted treatment had a lower risk of locoregional recurrence until 8 years after surgery (eFigure 3 in Supplement 1). The peaks of the 2 curves were consistent at 2 to 3 years after surgery.

Similarly, compared with patients who were administered hormonal treatment, both locoregional recurrence-free survival (hazard ratio, 2.27; 95% CI, 1.32-3.90) and CBC-free survival (hazard ratio, 2.75; 95% CI, 1.95-3.87) were poorer for those who omitted hormonal treatment (eFigure 2 in Supplement 1). The annual incidence of locoregional recurrence was consistently higher in the hormonal treatment–omission group for 10 years, peaking between 1 and 4 years after surgery (eFigure 3 in Supplement 1).

Recurrence Outcomes Without Treating Distant Metastasis as a Competing Risk

Treating distant metastasis as a competing event could lead to underestimation of events and overestimation in survival analysis. Therefore, we performed post hoc analyses without considering distant metastasis as a competing event and including all events that occurred after competing events. Multivariate analysis showed that IBTR-free survival was still significantly associated with the HR−/*ERBB2*+ subtype, whereas CBC-free survival was worst for the HR−/*ERBB2*− subtype (eTable 2 in Supplement 1). The HR−/*ERBB2*+ subtype showed poorer RR-free survival than did the other subtypes. The annual incidence pattern showed a more pronounced increase in incidence rates in the late period, but the overall trend of the pattern was not significantly different (eFigure 4 in Supplement 1).

Discussion

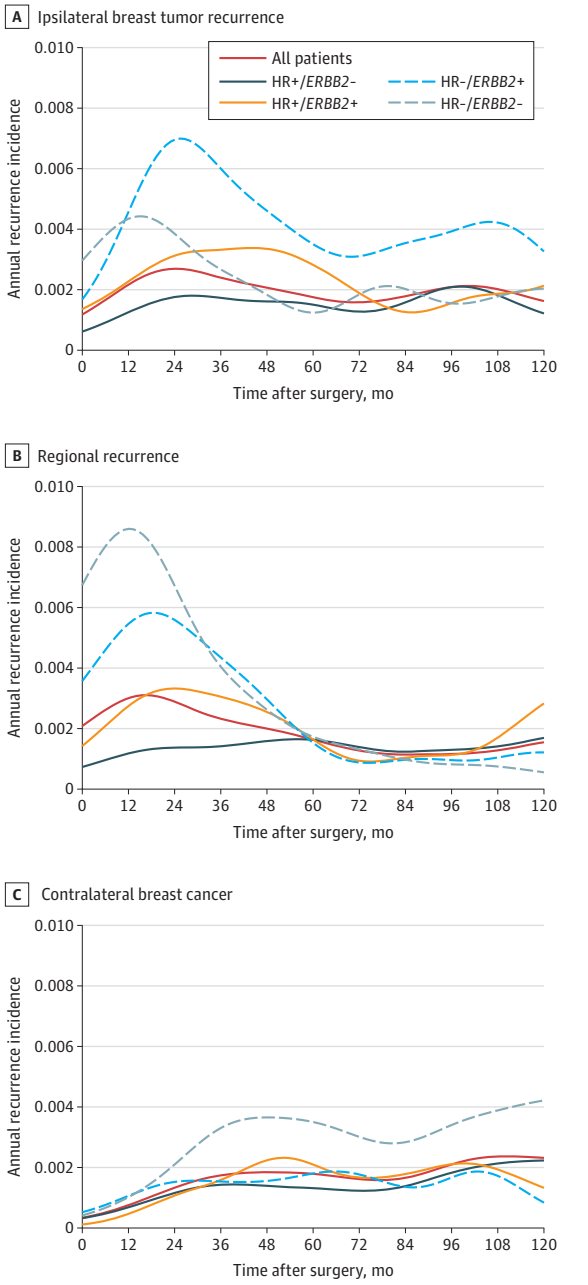
Locoregional recurrence after initial treatment of BC is associated with higher mortality.[2,3] In the current study, we found differences in annual patterns of recurrence incidence according to tumor subtypes in a large cohort with long-term follow-up. Knowledge of the recurrence pattern may help identify the periods of prevalent BC recurrence and optimize the surveillance strategy. For example, physicians may consider surveillance every 6 months for patients with HR− subtypes until 5 years after surgery, while surveillance for patients with HR+ tumors may continue to follow the current guideline of 1-year intervals. For younger individuals, more frequent surveillance may be recommended.

Several studies have reported different locoregional recurrence survival rates among patients with different BC subtypes.[27-29] Ignatov et al[27] analyzed 12 053 patients and showed that patients with *ERBB2*-enriched and triple-negative BC had significantly poorer locoregional recurrence-free survival than did those with the luminal subtype. Lee et al[28] reported significantly higher local, CBC, and nodal recurrence for *ERBB2*-enriched and triple-negative BC subtypes, and another study[29] analyzing 514 patients without lymph node involvement observed similar results. Our study has strengths in that we included a larger cohort than did previous studies and provided the results of recurrence patterns according to a 10-year time frame.

Regarding the recurrence pattern, Kimura et al[30] analyzed 2209 patients with 10 years of follow-up and reported that the recurrence pattern peaked at the second year and then gradually decreased. Additionally, patients with HR− subtypes showed double peaks at the second and between the sixth and seventh years after surgery, while patients with HR+ subtypes had a constant recurrence pattern. Demicheli et al[31] also found double-peak recurrence patterns for all subtypes. They assumed that the unstable status of micrometastatic foci affected the first peak, while the second peak reflected the effect of adjuvant treatments that delay or suppress recurrence. In the current study, a second peak was present at 8 or 9 years after surgery, while the second peak in previous studies was at 5 or 7 years.[30,31] This difference may be due to the considerable development in treatments compared with studies published more than 10 years ago.[30,31] Notably, a large-scale study in the Netherlands used registry data to analyze BC recurrence patterns and found that subtype was an important factor associated with recurrence.[32] Despite similar results to ours, that study used registry data, included nearly half the number of patients in the cohort in our study, and analyzed patients diagnosed more than a decade ago. Moreover, as both IBTR and RR events were relatively small compared with distant metastasis, a diverse change in patterns of locoregional recurrence was difficult to distinguish.

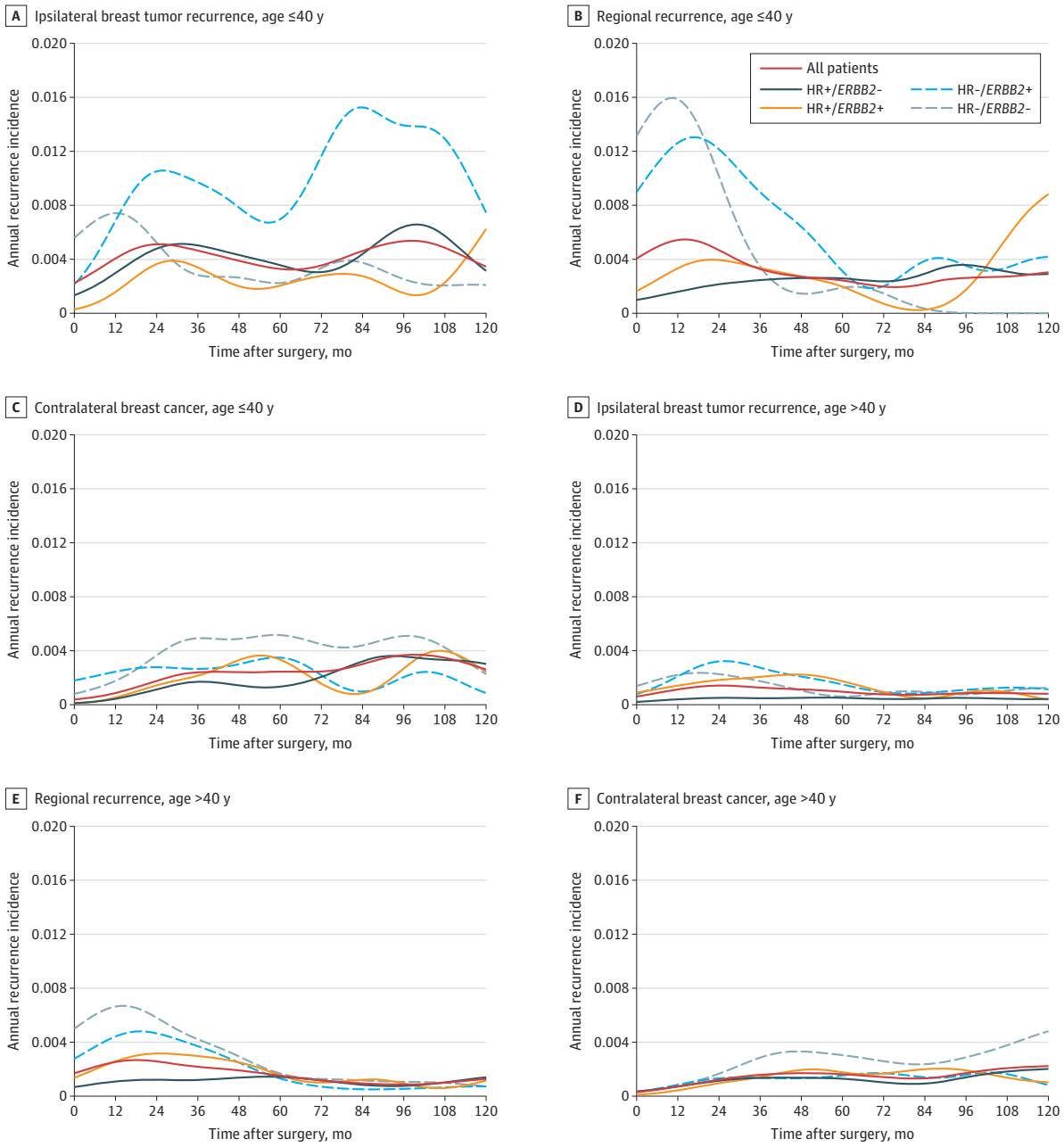
Patients with the HR−/*ERBB2*+ subtype had higher IBTR incidence than those with other subtypes in the current study, especially during the first postoperative year. We assumed that the delayed peak at 1 year would have been associated with 1 year of *ERBB2*-targeted treatment.[33] Recurrence patterns after stratifying patients with *ERBB2*+ subtypes according to the administration of *ERBB2*-targeted treatment indicated that the significantly increased risk of early recurrence in patients with *ERBB2*+ subtypes may be associated with the biological properties of tumor subtypes rather than the suppression effect of recurrence during the adjuvant treatments. The crossover between the group that received *ERBB2*-targeted treatment and the group that did not at 8 years after surgery may be due to the decreased number of patients in the group that omitted

Figure 2. Patterns of Annual Recurrence Incidence by Tumor Subtype



Ipsilateral breast tumor recurrence was analyzed for patients who underwent breast-conserving surgery. HR indicates hormone receptor.

Figure 3. Patterns of Annual Recurrence Incidence Among Patients Aged 40 Years or Younger or Older Than 40 Years



Ipsilateral breast tumor recurrence was analyzed for patients who underwent breast-conserving surgery. HR indicates hormone receptor.

ERBB2-targeted treatment, as those patients are at a higher risk of distant metastasis or death.[17] Similarly, hormonal therapy was assumed to have been associated with the steady and late recurrence pattern for the HR+ subtype. Although the number of patients was too small to provide strong statistical evidence, these results suggest that administering appropriate adjuvant treatment is critical in reducing recurrences.

Our results showed an increasing and diverse pattern beyond 5 years following surgery for younger patients (age ≤40 years). As younger patients, especially those with HR+ subtypes, are known to develop more distant metastasis than older patients,[34] the late recurrence incidence among younger patients was expected to be higher than in the current study. Additionally, our findings showed that IBTR incidence was more prominent in younger patients than in older patients with the HR−/*ERBB2*+ subtype. The results are consistent with a previous study[35] that included 25 284 patients and found that among young patients, those with the HR−/*ERBB2*+ subtype had significantly more IBTR events than did those with other subtypes. These findings support the need for intensive surveillance for younger patients with the HR− subtype.

To assess the need for different surveillance according to subtypes, we conducted a post hoc analysis to investigate the association between intensive surveillance and early detection of recurrence. To reduce the selection bias raised by the high chance of frequent surveillance in the high-risk group, we analyzed only the patients who experienced recurrence. Survival curves showed that conducting mammography and breast sonography at least twice a year detected IBTR, RR, and CBC events significantly earlier than conducting these imaging examinations less frequently. The result remained consistent for each subtype (eFigures 5 and 6 in Supplement 1). Despite the small number of patients in the subgroups, this finding supports the need for intensive surveillance during high-risk periods after BC treatment.

Limitations

This study has several limitations. First, as IBTR can be classified as either true recurrence or secondary BC, the number of true IBTR events in our study may have been overestimated.[36,37] However, since several IBTR events were diagnosed without histologic confirmation and the purpose of this study was to identify the pattern of recurrence for appropriate treatment, we did not differentiate IBTR as a true recurrence or a new tumor. Second, the relatively small number of subgroups may limit the statistical power of the subgroup analysis and the generalizability of our findings. Third, the HR−/*ERBB2*− subtype distribution at our institution was higher than previously reported in Asian patients.[38] This may be due to the role of our institution as a leading national hospital in Korea that treats patients with aggressive BC, and this distribution was similar to that reported in a previous study conducted at a branch institution of Seoul National University Hospital.[28] Fourth, excluding patients with 2+ on IHC for *ERBB2* but not tested with FISH or SISH may have led to selection bias. Fifth, we included a period of over 20 years, and the results could not reflect the change in modalities of treatments over the years. To address this issue, we conducted a post hoc subgroup analysis for the patients who underwent surgery after 2010. The second peak of the recurrence pattern for several subtypes was more prominent in the late period compared with that of all subtypes, but the overall features were similar to that of overall subtypes (eFigure 7 in Supplement 1). Finally, we conducted a sensitivity analysis excluding distant metastasis as a competing event but could not further adjust for competing risk due to events that may have occurred if patients had not died.

Conclusions

In this cohort study, locoregional recurrence occurred in different patterns according to BC subtypes, with younger patients having greater differences in patterns among subtypes than older patients. Patients with HR− subtypes had high recurrence rates in the early period of treatment, while those with HR+ subtypes had a steady pattern beyond 5 years after surgery. These findings suggest that tailoring surveillance should be recommended regarding differences in locoregional recurrence patterns according to subtypes, particularly for young patients. Validating our study at a multi-institutional level with a large number of patients, taking into account the recent advancement in BC treatments, would be necessary to generalize our findings.

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