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Breast-conserving Surgery Rates in Breast Cancer Patients With Different Molecular Subtypes

An Observational Study Based on Surveillance, Epidemiology, and End Results (SEER) Database

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Abstract: This study used the Surveillance, Epidemiology, and End Results database to compare breast-conserving surgery (BCS) rates across patients with different molecular subtypes.

We identified female breast cancer patients who were diagnosed between 2010 and 2012 using the Surveillance, Epidemiology, and End Results database. Patients without available critical clinicopathological information were excluded. The chi-square test and logistic regression analysis were used to investigate factors associated with BCS.

This study identified 85,415 T1–2N0–3M0 breast cancer patients. Among the patients with HR+/HER2−, HR+/HER2+, HR−/HER2+, and HR−/HER2− diseases, 63.5% (38,823/61,142), 51.2% (4850/9473), 43.2% (1740/4030), and 55.7% (6000/10,770), respectively, received BCS ($P < 0.01$). Patients with HR−/HER2+ (odds ratio 0.58; 95% confidence interval, 0.54–0.62) disease were significantly less likely to receive BCS than patients with HR+/HER2− disease after adjustment for T-stage, N-stage, age, tumor grade, county type, and race. Differences in BCS rates between the HR+/HER2− and HR−/HER2+ subgroups were 29.1%, 14.0%, 10.1%, 8.5%, and 0.2% in patients with tumor sizes <10 mm, 10 to 20 mm, 20 to 30 mm, 30 to 40 mm, and 40 to 50 mm, respectively. Differences in BCS rates between the HR+/HER2− and HR−/HER2+ subgroups were 20.3% and 5.7% in node-negative and node-positive patients, respectively. BCS rates in patients with grades I, II, and III tumors in the HR+/HER2− and HR−/HER2+ subgroups were 72.2% and 34.6%, 62.7% and 42.3%, and 54.7% and 43.4%, respectively.

Our study demonstrated that BCS rates varied significantly across molecular subtypes, especially in patients with lower tumor burden. HR+/HER2− and HR−/HER2+ patients exhibited the highest and lowest BCS rates, respectively.

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Abbreviations: AIC = Akaike Information Criterion, AJCC = American Joint Committee on Cancer, BCS = breast-conserving surgery, CI = confidence interval, HER2 = human epithelial growth factor receptor 2, HR = hormone receptor, IRB = institutional review board, OR = odds ratio, PR = progesterone receptor, SEER = Surveillance, Epidemiology, and End Results, TN = triple-negative, VIF = variance inflation factor.

INTRODUCTION

Breast-conserving surgery (BCS) is the standard surgical treatment for early-stage breast cancer patients. BCS provides equivalent long-term survival and much better cosmetic outcomes than mastectomy. Tumor size, margin status, and the presence of multifocal lesions are the major clinical factors to consider before performing BCS.[1–3] Biological factors, such as tumor histology, tumor grade, and receptor status, are rarely considered selection factors during surgical decision-making. The recognition that breast cancer is a heterogeneous group of diseases has dramatically changed the management of this cancer.[4] Molecular subtype approximations defined by estrogen receptor (ER), progesterone receptor (PR), and human epithelial growth factor receptor 2 (HER2) statuses are the primary determinants of adjuvant systemic therapy, and these factors strongly predict patient long-term survival. However, less attention has been paid to the impact of molecular subtype approximations on local therapy.

Retrospective studies demonstrated that HER2+ cancers are prone to exhibit multifocal/multicentric disease, extensive intraductal components, lymph node involvement, and positive cavity margins.[2,5] These findings indicate that the likelihood of successful breast conservation in the HER2+ subtype may be lower than the other subtypes. Furthermore, an increasing body of evidence also demonstrates that the risk of local recurrence after surgery varied by subtypes.[6,7] HER2+ and triple-negative (TN) subtypes generally exhibit higher risks of local recurrence than luminal subtypes. The time course of local recurrence also differs between subtypes. The majority of local failures in HER2+ and TN subtypes occur within 5 years after surgery, but local recurrences continue to occur 5 years after surgery.[8] Therefore, knowledge of the varied risk of local recurrences across subtypes may impact the surgical decision and lead to different BCS rates between subtypes. However, this hypothesis was never confirmed in population-based studies. The

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Surveillance, Epidemiology, and End Results (SEER) database covers an estimated 28% of the US population. Information of HER2 status has been collected, and data are available for access since 2010.[9,10] This study aimed to compare BCS rates across different molecular subtypes. We hypothesized that BCS rates would be relatively lower in patients with HER2+ or TN diseases than in patients with ER+ diseases.

METHOD

We identified female breast cancer (Code 8500: Infiltrating duct carcinoma) patients who were diagnosed between 2010 and 2012 from the SEER database (18 registries, Nov 2014 submission). Patients with T1−2, N0−3, and M0 diseases were included. Patients with insufficient information on T and N-stages were excluded. The detailed selection code used in SEER∗Stat Software were attached (Supplementary File 1, http://links.lww.com/MD/A657). This study used a national dataset of deidentified patient information, which did not meet the Sun Yat-sen Memorial Hospital's criteria for institutional review board (IRB) approval. Therefore, this study waived the need for IRB approval. This is a retrospective study and the patient consent was not required.

Tumor grade, adjusted American Joint Committee on Cancer (AJCC) 7th stage, AJCC 7th T and N-stages, surgery of the primary site, radiation treatment, race, marital status at diagnosis, laterality (left or right breast), ER status, PR status, HER2 status, molecular subtype, number of positive nodes, number of nodes examined, primary site, and county type (metropolitan/nonmetropolitan) were extracted. The breast surgery code as reviewed was based on the SEER Program Coding and Staging Manual, 2012. Codes 20 to 24 were classified as BCS. Codes 40 to 59, 63, and 75 were classified as simple/modified radical mastectomy. Codes 43 to 49, 53 to 59, 63, and 75 were classified as reconstruction surgery after a mastectomy. Patients with a borderline ER and PR status were classified as ER and PR-positive, respectively.

All data were collected using SEER∗Stat Software. We performed a descriptive analysis of patient characteristics. We used chi-square tests to screen for potential factors that are associated with BCS. Significant factors revealed by chi-square tests were incorporated into the logistic regression model for multivariate analysis. We used the variance inflation factor (VIF) to prevent multicolinearity in the regression model. We used Akaike information criterion (AIC) to select the best regression model. Interactions between molecular subtypes and critical factors, such as T-stage, N-stage, and age, were assessed. All P values were 2-sided, and P values <0.001 were considered statistically significant. Statistical analyses were performed using Stata/MP, version 13.0 (StataCorp LP, College Station, TX).

RESULTS

Clinicopathological Features

A total of 85,415 patients were included in this study. There were 61,142, 9473, 4030, and 10,770 patients who were classified as HR+/HER2−, HR+/HER2+, HR−HER2+, and TN, respectively. The median age of this population was 60 years, and most patients (79%) were white. Table 1 summarizes the clinicopathological features of the included patients. HR−/HER2+ patients were more likely to have grade III (71.4% vs 21.7%), T2 (45.6% vs 28.2%), node-positive (37.9% vs 26.8%), or stage II−III (56.7% vs 37.9%) diseases than HR+/HER2− patients (Supplementary Table 1, http://links.lww.com/MD/A657).

TABLE 1. Clinical Features of Included Patients (n = 85,415)

Features	n	%
Age group		
<40 y	4723	5.5
40−59 y	37,638	44.1
≥60 y	43,054	50.4
Race		
White	67,411	78.9
African American	9047	10.6
Others	8333	9.8
Unknown	624	0.7
County type		
Metropolitan	76,809	89.9
Nonmetropolitan	8478	9.9
Unknown	128	0.1
Marital status		
Married	48,414	56.7
Single[†]	37,001	43.3
Laterality		
Left	43,146	50.5
Right	42,258	49.5
Others	11	0.0
Grade[*]		
I	18,374	21.5
II	35,051	41.0
III	29,539	34.6
IV	281	0.3
Unknown	2170	2.5
Primary site		
Nipple/central portion	3906	4.6
UIQ	11,322	13.3
LIQ	5232	6.1
UOQ	30,647	35.9
LOQ	6629	7.8
Overlapping/unknown	27,679	32.4
T-stage		
T1	57,119	66.9
T2	28,296	33.1
N-stage		
N0	60,983	71.4
N1	19,035	22.3
N2	3809	4.5
N3	1588	1.9
AJCC-stage		
I	48,829	57.2
II	31,189	36.5
III	5397	6.3
Breast surgery		
Breast-conserving surgery	51,413	60.19
Mastectomy	30,641	35.87
Others/no surgery	3361	3.93
Radiation therapy		
No	37,528	43.94
Yes	44,287	51.85
Unknown	3600	4.21
Molecular subtype		
HR+/HER2−	61,142	71.58
HR+/HER2+	9473	11.09
HR−/HER2+	4030	4.72
TN	10,770	12.61

HER2 = human epithelial growth factor 2, HR = Hormone receptor, LIQ = lower-inner quadrant, LOQ = lower-outer quadrant, TN = triple-negative, UIQ = upper-inner quadrant, UOQ = upper-outer quadrant.

[*] In the SEER database, histological grades were categorized into I (well differentiated), II (moderately differentiated), III (poorly differentiated), and IV (undifferentiated/anaplastic).

[†] Divorced/separated/single/widowed were included.

Univariate and Multivariate Analyses

Among patients with HR+/HER2−, HR+/HER2+, HR−/HER2+, and HR−/HER2− diseases, 63.5% (38,823/61,142), 51.2% (4850/9473), 43.2% (1740/4030), and 55.7% (6000/10,770) received BCS (chi-square test, $P < 0.001$), respectively. We also noticed that age, race, county type, grade, primary site, T-stage, N-stage, and AJCC stage were significantly associated with BCS in univariate analyses (Supplementary Table 2, http://links.lww.com/MD/A657). These factors and the molecular subtype were incorporated into the multivariate logistic model. We observed that patients with HR+/HER2+ (odds ratio [OR] 0.77; 95% confidence interval [CI], 0.74–0.81) or HR−/HER2+ (OR 0.58; 95% CI, 0.54–0.62) disease were significantly less likely to receive BCS than patients with HR+/HER2− disease after adjustment (Table 2).

The Impact of Tumor Burden

Stratification analyses revealed that the variations in BCS rates across subtypes were more significant in patients with lower tumor burden. The differences in BCS rates between HR+/HER2− and HR−/HER2+ subgroups were 29.1%, 14.0%, 10.1%, 8.5%, and 0.2% in patients with tumor sizes <10 mm, 10 to 20 mm, 20 to 30 mm, 30 to 40 mm, and 40 to 50 mm, respectively (Figure 1A and B). Figure 1(C–F) shows that HR−/HER2+ patients consistently received less BCS than patients with the other subtypes when controlling for N-stage, grade, age, or county type. BCS rates in HR+/HER2− and HR−/HER2+ subgroups were 69.5% and 49.2% in node-negative patients, and 47.1% and 41.4% in node-positive patients, respectively. BCS rates in patients with tumor grades I, II, and III in HR+/HER2− and HR−/HER2+ subgroups were 72.2% and 34.6%, 62.7% and 42.3%, and 54.7% and 43.4%, respectively.

DISCUSSION

HR−/HER2+ Subtype Correlated With the Lowest BCS Rate

The BCS rate may be influenced by a variety of factors, including tumor burden, surgeons' recommendations,[2] patients' preferences, and the accessibility of radiation centers.[1,11] Anatomical factors in terms of tumor burden, such as tumor size, margin status, and multifocal/multicentric lesions, are major determinants for successful BCS. Surgeons may not prefer BCS in patients who are at a high risk of local failure. Biological factors, such as molecular subtype, are also becoming more and more important as risk factors of local failure. A meta-analysis [12] of 12,592 breast cancer patients revealed that patients with HER2/neu-overexpressing diseases exhibited the highest risk of local recurrences. A randomized clinical trial[13] also demonstrated that the addition of trastuzumab to traditional chemotherapy regimen reduced the risk of local recurrence by 40%. Therefore, BCS may be less successful in HER2+ patients. Our study observed that the BCS rate was generally lower in patients with HR−/HER2+ diseases, after adjustments for tumor size, nodal status, tumor grade, county type, and age. However, several important factors, such as margin status or multifocal diseases, were unavailable, and these factors were not controlled in this study. Wiechmann et al reported a retrospective study of 6072 patients in Memorial Sloan-Kettering Cancer Center and demonstrated that patients with the HR−/HER2+ subtype were more likely to exhibit multifocal/multicentric disease (HR−/HER2+ vs HR+/HER2−: 37.2% vs 27.3%), nodal involvement (HR−/HER2+ vs HR+/HER2−: 57.0% vs 43.0%), and extensive intraductal components (HR−/HER2+ vs HR+/HER2−: 26.8% vs 27.3%).[2] Our previous study also suggested that HER2+ patients demonstrated a significantly higher positivity rate of the cavity margins during BCS.[5] Taken together, the lower BCS rate in HR−/HER2+ patients may be due to the higher probability of multifocal/multicentric diseases in this subgroup.

The Impact of Tumor Burden of HR−/HER2+ Subtype

Several studies[14–16] demonstrated no association between T-stage/tumor size and the presence of multifocal diseases. Therefore, we speculated that the HR−/HER2+ patients, who are more likely to exhibit multifocal diseases, may have had consistently lower BCS rates in patients with varied tumor sizes. However, our study demonstrated that the variations in BCS rates across subtypes were inversely correlated with tumor size (Figure 1B). The differences in BCS rates between HR+/HER2− and HR−/HER2+ subgroups were 29.1% and 0.2% in patients with tumor sizes <10 mm and 40 to 50 mm, respectively. There was a trend that the variation of BCS rate across subtypes was higher in patients with lower tumor burden (Figure 1C and D). This result is interesting, and the underlying reasons are not known. The chances of successful BCS were generally lower in patients with a larger tumor, and smaller variations in BCS rates across subtypes are reasonable. Mastectomies with or without reconstructions are the major surgical options in this scenario. In contrast, there are relatively more surgical options for patients with smaller tumors. BCS or mastectomy with reconstruction may be appropriate approaches. Therefore, a significant variation of BCS rate across subtypes was possible. Surgeons or patients may be more likely to recommend a mastectomy than BCS for HR−/HER2+ diseases because of its high risk of local recurrence. Fisher et al[17] reported that the fear of recurrence and perceived survival benefit are primary motivators for choosing mastectomy over BCS. A survey of more than 3000 breast cancer patients[18] revealed that patients tended to choose mastectomy over BCS in the absence of surgeon recommendations. Therefore, it is possible that molecular subtype per se may impact surgical decisions, especially when pathology review of ER, PR, and HER2 determinations before surgery is available in most hospitals in the United States.[19] HR−/HER2+ patients only constituted a small proportion (less than 5% in SEER database[9]) of the entire population. Therefore, previous randomized controlled trials[20–22] with long-term follow-ups, which support the safety of BCS, may not be applicable to HR−/HER2+ patients. Further investigations are needed in this patient subgroup.

BCS Rate in TN Subtype

The lack of targeted therapy and the aggressive biological behavior of TN diseases have raised controversy about the safety of BCS in this subtype. However, observational data from cancer registries or prospective collected databases suggested that BCS and mastectomy are equivalent in long-term overall survival in TN patients.[23–25] Therefore, it would be interesting to know the BCS rate in TN in real-world scenarios. Our study found that the BCS rate in the TN subtype is similar to and higher than in HR+/HER2− and HR−/HER2+ patients, respectively. This result is an interesting finding with unknown reasons. TN was associated with higher pathological complete

TABLE 2. Factors Associated With BCS

		Univariate Analysis					Multivariate Analysis	
		BCS (n = 15,321)		Mastectomy/ Others/No Surgery† (n = 9877)				
	Total	n	%	n	%	P‡	ORs (95% CI)	P§
Age group								
<40 y	4723	1552	3.0	3171	9.3	<0.001	1	
40–59 y	37,638	21,416	41.7	16,222	47.7		2.26 (2.12–2.42)	<0.001
≥60 y	43,054	28,445	55.3	14,609	43.0		2.98 (2.79–3.19)	<0.001
Race								
White	67,411	41,340	80.4	26,071	76.7	<0.001	1	
African American	9047	5251	10.2	3796	11.2		1.05 (1.00–1.10)	0.046
Others	8333	4450	8.7	3883	11.4		0.78 (0.74–0.82)	<0.001
Unknown	624	372	0.7	252	0.7		1.01 (0.85–1.19)	0.95
County type								
Metropolitan	76,809	46,574	90.6	30,235	88.9	<0.001	1	
Nonmetropolitan	8478	4778	9.3	3700	10.9		0.78 (0.75–0.82)	<0.001
Unknown	128	61	0.1	67	0.2		0.73 (0.51–1.06)	0.102
Marital status								
Married	48,414	29,243	56.9	19,171	56.4	NS	N/A‖	
Single*	37,001	22,170	43.1	14,831	43.6			
Laterality								
Left	43,146	25,930	50.4	17,216	50.6	0.033	N/A‖	
Right	42,258	25,477	49.6	16,781	49.4			
Others	11	6	0.0	5	0.0			
Grade								
I	18,374	13,183	25.6	5191	15.3	<0.001	1	
II	35,051	21,355	41.5	13,696	40.3		0.80 (0.77–0.83)	<0.001
III	29,539	15,582	30.3	13,957	41.0		0.79 (0.76–0.83)	<0.001
IV	281	148	0.3	133	0.4		0.75 (0.58–0.96)	0.024
Unknown	2170	1145	2.2	1025	3.0		0.63 (0.57–0.69)	<0.001
Primary site								
Nipple/central portion	3906	1795	3.5	2111	6.2	<0.001	1	
UIQ	11,322	7480	14.5	3842	11.3		2.08 (1.93–2.25)	<0.001
LIQ	5232	3296	6.4	1936	5.7		1.85 (1.69–2.02)	<0.001
UOQ	30,647	19,745	38.4	10,902	32.1		2.19 (2.04–2.35)	<0.001
LOQ	6629	3956	7.7	2673	7.9		1.77 (1.63–1.93)	<0.001
Overlapping/unknown	27,679	15,141	29.4	12,538	36.9		1.40 (1.31–1.50)	<0.001
T-stage								
T1	57,119	38,760	75.4	18,359	54.0	<0.001	1	
T2	28,296	12,653	24.6	15,643	46.0		0.52 (0.51–0.54)	<0.001
N-stage								
N0	60,983	40,625	79.0	20,358	59.9	<0.001	1	
N1	19,035	9072	17.6	9963	29.3		0.59 (0.57–0.61)	<0.001
N2	3809	1302	2.5	2507	7.4		0.38 (0.35–0.41)	<0.001
N3	1588	414	0.8	1174	3.5		0.27 (0.24–0.31)	<0.001
AJCC-stage								
I	48,829	34,422	67.0	14,407	42.4	<0.001	N/A‖	
II	31,189	15,275	29.7	15,914	46.8			
III	5397	1716	3.3	3681	10.8			
Molecular subtype								
HER2−/HR+	61,142	38,823	75.5	22,319	65.6	<0.001	1	
HER2+/HR+	9473	4850	9.4	4623	13.6		0.77 (0.74–0.81)	<0.001
HER2+/HR−	4030	1740	3.4	2290	6.7		0.58 (0.54–0.62)	<0.001
TN	10,770	6000	11.7	4770	14.0		0.91 (0.87–0.96)	<0.001

BCS = breast-conserving surgery, CI = confidence interval, HER2 = human epithelial growth factor 2, HR = hormone receptor, LIQ = lower-inner quadrant, LOQ = lower-outer quadrant, OR = odds ratio, TN = triple-negative, UIQ = upper-inner quadrant, UOQ = upper-outer quadrant.

* Divorced/separated/single/widowed were included.

† Subcutaneous mastectomy, radical mastectomy, and reconstruction surgery were included in this category.

‡ Chi-square test.

§ Logistic regression.

‖ In the multivariate analysis, only significant factors revealed by univariate analysis were included. We did not include the AJCC-stage due to the concerns of co-linearity between AJCC-stage, N-stage, and T-stage.

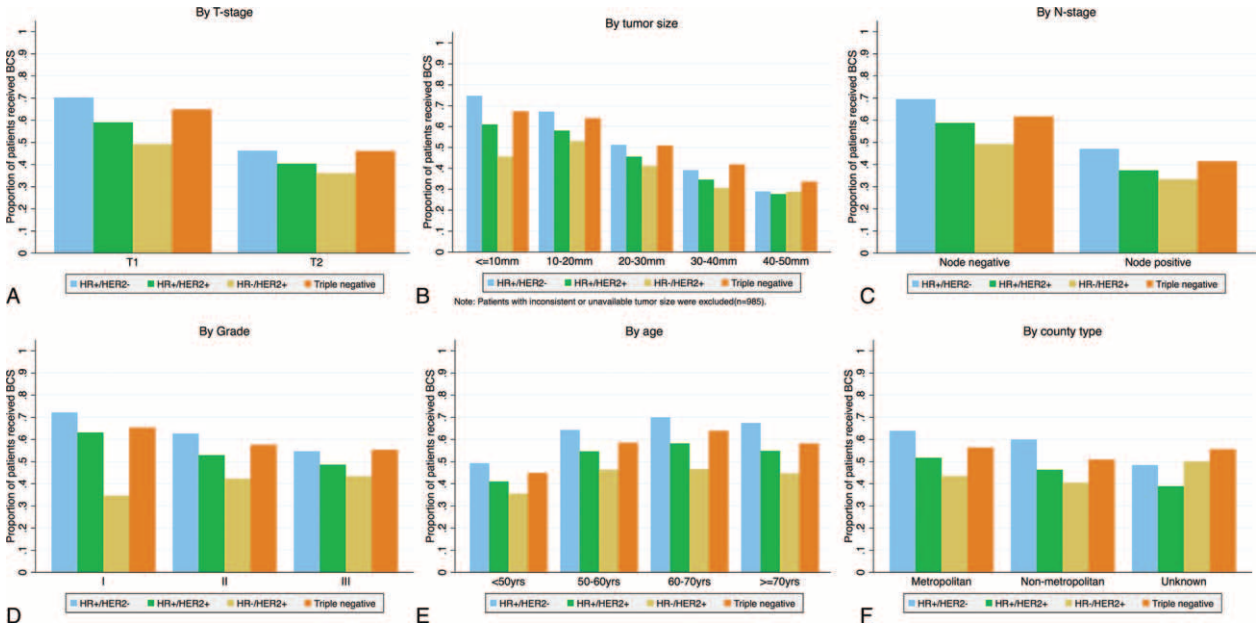

FIGURE 1. BCS rates across molecular subtype stratified by T-stage (A), tumor size (B), N-stage (C), grade (D), age (E), and county type (F). BCS = breast-conserving surgery.

response (pCR) rates and higher BCS rates for patients receiving neoadjuvant chemotherapy.[26] We did not obtain information on neoadjuvant chemotherapy in this study.

LIMITATION

The major limitation of this study is the lack of critical information. Unavailable margin status or multifocal diseases, as discussed above, rendered it difficult to explore the underlying mechanism of the relatively lower BCS rate in HR−/HER2+ patients. Socioeconomic factors, such as insurance, income, or education, may also influence the choice of BCS and the use of trastuzumab. Income or education was only available as county attribute data in the SEER database. For example, median income and educational attainment in each county were not suitable for analysis. Neoadjuvant chemotherapy data were unavailable in our study, but their influence on our results is not clear. A study level meta-analysis[6] involving 8095 patients from 20 studies revealed that pooled pCR rates were 8.3%, 18.7%, 38.9%, and 31.1% in HR+/HER2−, HR+/HER2+, HR−/HER2+, and TN patients, respectively. The higher pCR rate in the HR−/HER2+ subgroup should have led to a higher BCS rate. However, our results revealed the opposite result.

CONCLUSIONS

In summary, our study revealed that BCS rates varied across molecular subtypes. Patients with the HR−/HER2+ subtype exhibited the lowest BCS rate of all subtypes. The variations in BCS rates across subtypes seemed to be associated with tumor burden. The difference in BCS rate between HR+/HER2− and HR−/HER2+ subtypes reached up to 30% in patients with a tumor <10 mm, but the BCS rates were similar across all subtypes in patients with a tumor 40 to 50 mm in size. This population-based study is the first to investigate BCS rates across molecular subtypes and provide useful epidemiological information for patient consulting. Further study is needed to explore the underlying mechanisms of the lowest BCS rate in the HR−/HER2+ subtype, especially in patients with small tumors.

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