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Long-Term Survival Differences Between T1-2 Invasive Lobular Breast Cancer and Corresponding Ductal Carcinoma After Breast-Conserving Surgery: A Propensity-Scored Matched Longitudinal Cohort Study

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Abstract

The Surveillance, Epidemiology, and End Results (SEER) Program was used to compare survival and local recurrence risk (LR) in patients with 2 histologic types of disease—invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC)—receiving breast-conserving surgery (BCS). Patients with T1-2 ILC were less likely to undergo BCS and had better overall survival compared to patients with IDC, but they had worse second primary cancer-free survival and higher LR than those of patients with IDC in the nuclear grade III subgroup. Continuing efforts to identify a subset of subjects with T1-2 ILC of nuclear grade III is contra-indicated for BCS in further clinical trials.

Background: The role of histology subtype on the prognosis of T1-2 breast cancer patients receiving breast-conserving surgery (BCS) is not clear. **Methods:** The Surveillance, Epidemiology, and End Results (SEER) Program was used to compare overall survival, second primary cancer-free survival (CFS), and local recurrence risk (LR) for patients with invasive lobular carcinoma (ILC) and invasive ductal carcinoma (IDC), both receiving BCS. **Results:** The study enrolled 196,688 patients with T1-2 disease receiving BCS, including 12,906 with ILC and 183,782 with IDC. Patients with IDC showed higher unadjusted annual rates of BCS than ILC. Five- and 10-year estimated survival rates were, respectively, 92.06% and 86.14% in ILC, compared to 90.50% and 85.26% in IDC ($P = .12$). In multivariable Cox regression, ILC patients showed advantage over IDC in overall survival (hazard ratio [HR] = 0.93, $P = .001$), whereas no significant differences in CFS (HR = 1.03, $P = .33$) and LR (HR = 1.17, $P = .06$) were found, which were consistent with results from matched cohort. In subgroup analyses, patients with grade III ILC had poorer CFS (HR = 1.23, $P = .009$) and higher LR (HR = 1.59, $P = .01$) than IDC. **Conclusion:** Histologic type is of prognostic importance in T1-2 patients receiving BCS, and surgeons should be cautious in performing BCS for individuals with grade III ILC.

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Introduction

Breast cancer (BC) is the most frequent malignancy among women, accounting for 30% of new cases and 14% of deaths among cancers of all sites.[1] Invasive lobular carcinoma (ILC) of BC, first described by Stewart and Foote in the 1940s, is the most common special BC subtype, which is a lesion consisting of acinar or scirrhous spheroidal cells.[2-4] ILC is often characterized by higher T stage as well as a higher percentage of multifocal, multicentral, and bilateral cases compared to invasive ductal carcinoma (IDC), but it can also be identified as lower histologic grade, higher rate of hormone receptor positivity, and lower rate of human epidermal growth factor receptor 2 (HER2) positivity, all associated with favorable prognosis.[5] Thus, inconsistent prognostic results of the 2 histologic types, ILC and IDC, has been widely reported.[6-12] Breast-conserving surgery (BCS) followed by radiotherapy for the local management of T1-2 stage BC has been well established as a standard surgical strategy, but postoperatively, prognostic distinctions between the histologic types have not yet been clearly described.

Given the evidence of a lower chance of undergoing BCS compared to IDC,[13] patients with ILC often undergo mastectomy.[14] Although improved imaging techniques such as magnetic resonance tomograph resulted in more conservative surgeries being performed for early BC, prior studies found that ILC patients still experienced higher probability of repeat excision or mastectomy after BCS.[10,14,15] Accordingly, some studies found that patients with ILC were spontaneously associated with both poorer overall survival (OS) and disease-free survival compared to patients with IDC.[8,12] Paradoxically, survival advantage of IDC was not consistently identified; a stage-matched study found better survival for patients with ILC than those with IDC.[11] Moreover, another study suggested that ILC patients treated with BCS had a low local recurrence rate (3.5%).[16]

Regardless of the fact that radiotherapy after BCS has been shown to reduce the risk of recurrence in early BC,[17] Poleszczuk et al[18] suggested that people with early BC who received radiotherapy after surgery had a higher incidence of second primary tumors than people with advanced BC. The disparity of the second primary tumor incidence between ILC and IDC patients who underwent BCS has never been reported before. In addition, some prognostic variables potentially exerted considerable influences on this survival comparison, including stage, nuclear grade, estrogen receptor (ER)/progesterone receptor (PR) status, and chemotherapy.[19-23] Previous series with inadequate sample sizes or balance of groups had difficulty comparing survival differences between BC patients with ILC and IDC after BCS.

In this study, we examined the differences in BCS rate, OS, second primary cancer-free survival (CFS), and local recurrence risk (LR) differences between patients with ILC and IDC after BCS.

Methods

Study Design

The Surveillance, Epidemiology, and End Results (SEER) database (http://seer.cancer.gov/), sponsored by the US National Cancer Institute, covers 18 population-based registries, the cancer data of which represent a large proportion of Americans (30%). The SEER 18 registry including cases followed from 1973 to 2013 was used to perform this retrospective longitudinal cohort study.

To derive a data set of patients with first primary invasive BC, SEER*Stat software and ASCII files were used to access the SEER database. Likewise, another data set of subsequent cancer patients who were derived from prior BC patients was constructed by implementing the MP-SIR session of the SEER*Stat software. The primary end point was OS, and the secondary outcome measures were CFS and LR. OS was defined as the interval from the time of diagnosis to either the death of the patient or the date of last contact (December 2013), and the survival status was considered as censored if the patient was alive until the date of last contact. CFS was estimated as time between the first primary BC and subsequently diagnosis dates of primary tumor at any location. In addition, LR was defined as later cancer identified by sequence records located in the ipsilateral breast (including invasive or in-situ histology), ipsilateral lymph nodes of axilla or arm, and skin of ipsilateral upper limb and shoulder without evidence of metastatic disease, which was calculated to be the difference between the dates of first primary BC diagnosis and the dates of local recurrence incidence. Records were merged by patient identification number to identify dates of a subsequent cancer diagnosis. CFS and LR were censored and set to OS for patients without any record of a subsequent tumor diagnosis.

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Figure 1 provides a flowchart showing SEER data screening.

Identification of Key Variables

SEER*Stat 8.3.4 software was used to extract relevant information released most recently through May 2017, including patient identification, sequence records, year and month of diagnosis, age, race/ethnicity, marital status, primary site, laterality, histology type, nuclear grade, ER, PR, HER2, adjusted American Joint Committee on Cancer (AJCC) tumor, node, metastasis classification system (TNM) (6th edition), surgery type, chemotherapy, radiotherapy, and survival month. International Classification of Diseases for Oncology (ICD-O-3)[24] was used to identify the first primary or subsequent cancer site and histology type. BC was selected using the ICD-O-3 codes C500 to C506, 508 or 509; codes C773 and C446, combined with laterality records, were identified as local recurrence site of lymph nodes of axilla or arm and skin of upper limb and shoulder, respectively. Invasive ductal (8500) and lobular (8520) carcinomas were identified, respectively. BCS was defined following SEER codes for BCS (10, 20-24).

Participants

We identified in the SEER database 238,389 women aged over 18 years who received BCS after being diagnosed with a first case of ILC and IDC with pathologic stage T1 to T2 disease between January 1, 1988, and December 31, 2012. We excluded patients only initially identified by autopsy and death certificate, and patients without baseline and prognostic information, such as race, marital status, histologic grade, and systematic therapy data (ie, chemotherapy and radiotherapy). Additionally, patients with a

Figure 1   Flowchart for SEER Data Screening
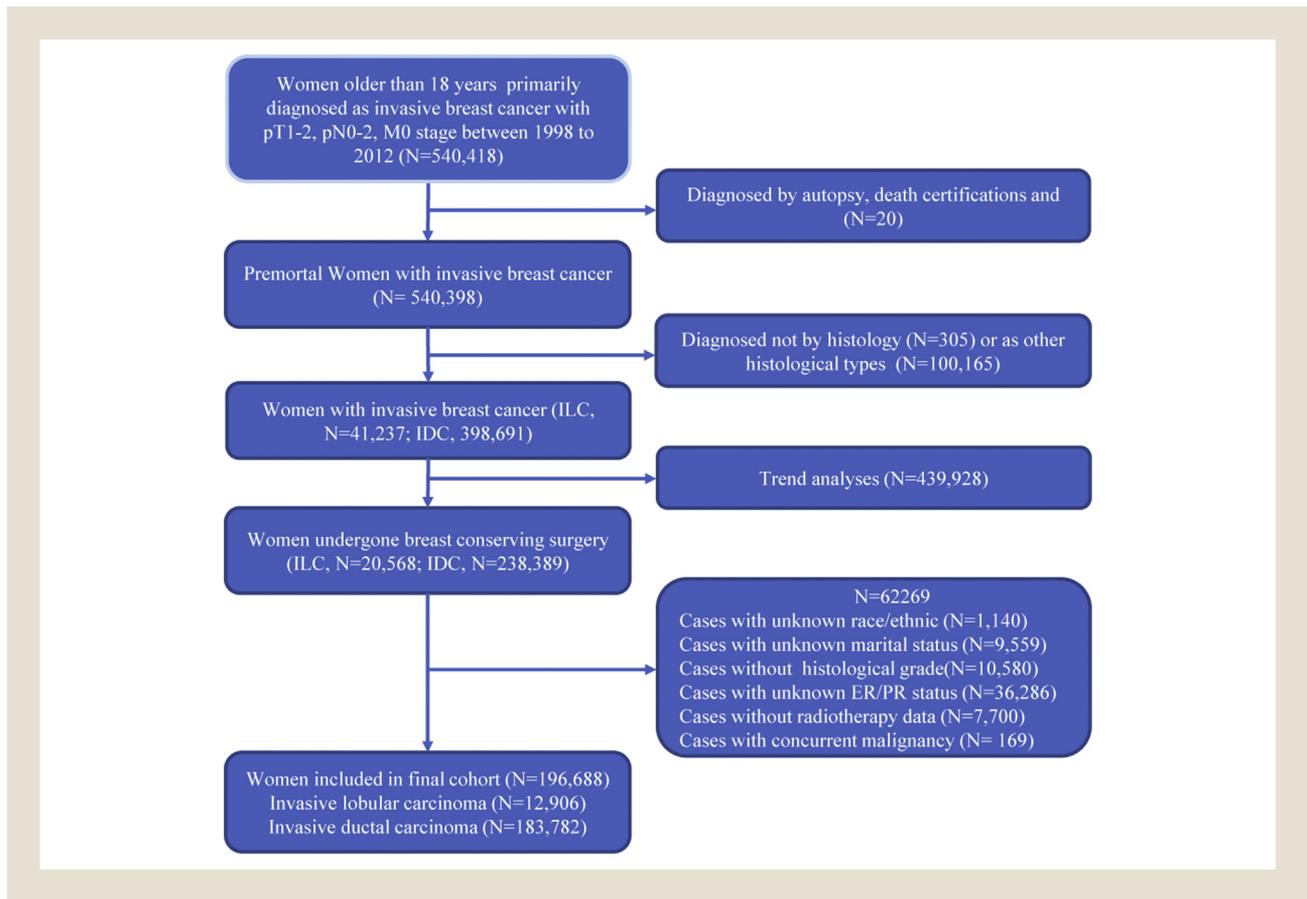
Abbreviation: SEER = Surveillance, Epidemiology, and End Results.

history of any type of in-situ or invasive cancer or patients with concurrent malignancy (defined as in-situ or invasive cancer diagnosed within 6 months of first primary BC diagnosis) were excluded from the study in the process of data merging.

Statistical Analysis

Demographic information, and tumor and treatment characteristics were compared between ILC and IDC by the Pearson chi-square test for categorical variables, which were reported as counts and percentages. To illustrate temporal trends in BCS procedure among IDC and ILC patients, unadjusted annual rates of BCS, calculated as the proportions of all the surgeries performed on patients with T1-2 BC between 1998 to 2012, were reported.

The potential risk factors for survival and relapse included age, race, marital status, TNM stage, histologic grade, ER, PR, and HER2 status, chemotherapy, and radiotherapy. Kaplan-Meier curves were used to visualize the survival distributions, and log-rank tests were conducted to assess the differences between groups. The multivariable Cox proportional hazards models adjusting the aforementioned variables were fitted to evaluate the differences between ILC and IDC in OS and CFS, respectively, where hazard ratio (HR) with 95% confidence interval (CI) for each

variable was calculated. A nonparametric method, the Gray *K*-sample test, was used to assess whether the difference in cumulative incidences between the ILC and IDC groups was significant,[25] where local recurrence was considered as event. Moreover, interaction tests were performed to explore whether any survival benefit after BCS procedure conferred by histologic type varied across subgroups. To minimize the effects of potential modifiers, a 1-to-1 propensity score matching method without replacement was performed for the comparisons using the nearest-neighbor method with a stringent caliper of 0.05 based on the R package MatchIt[26] (Supplemental Figure 1 in the online version). Considering the status of HER2 is available after 2010 in SEER database, we also fitted an additional multivariable Cox proportional hazards model with HER2 status as one variable.

All *P* values were calculated from 2-sided tests with .05 used as the significance level, and all statistical analyses were performed by R 3.3.3 software (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/).

Results

Patient Characteristics and BCS Rate

A total of 196,688 eligible patients with T1-2 BC who underwent BCS were enrolled onto this study, where 12,906 had ILC and

Table 1	Demographics of Patients Who Underwent Breast-Conserving Surgery (N = 196,688)					
	Unmatched Cohort			**Matched Cohort**		
Characteristic	**ILC (N = 12,906)**	**IDC (N = 183,782)**	**P**	**ILC (N = 12,856)[a]**	**IDC (N = 12,856)**	**P**
Year of Diagnosis						
1998-2000	1396 (10.8)	24,454 (13.3)	< .001	1382 (10.7)	1384 (10.8)	.99
2001-2003	2349 (18.2)	37,321 (20.3)		2341 (18.2)	2361 (18.4)	
2004-2006	2931 (22.7)	42,862 (23.3)		2920 (22.7)	2936 (22.8)	
2007-2009	3581 (27.7)	47,304 (25.7)		3576 (27.8)	3556 (27.7)	
2010-2012	2649 (20.5)	31,841 (17.3)		2637 (20.5)	2619 (20.4)	
Age						
< 40 years	143 (1.1)	8301 (4.5)	< .001	137 (1.1)	155 (1.2)	< .001
40-49 years	1619 (12.5)	33,981 (18.5)		1613 (12.5)	1767 (13.7)	
50-59 years	2998 (23.2)	49,523 (26.9)		2985 (23.2)	2841 (22.1)	
60-69 years	3627 (28.1)	45,905 (25.0)		3622 (28.2)	3854 (30.0)	
70-79 years	2963 (23.0)	31,548 (17.2)		2953 (23.0)	2815 (21.9)	
80 + years	1556 (12.1)	14,524 (7.9)		1546 (12.0)	1424 (11.1)	
Race/Ethnicity						
White	11,443 (88.7)	153,368 (83.5)	< .001	11,421 (88.8)	11,459 (89.1)	.75
Black	857 (6.6)	16,360 (8.9)		840 (6.5)	815 (6.3)	
Other[b]	606 (4.7)	14,054 (7.6)		595 (4.6)	582 (4.5)	
Marital Status						
Single	5279 (40.9)	71,812 (39.1)	< .001	5250 (40.8)	5349 (41.6)	.21
Married	7.627 (59.1)	111,970 (60.9)		7606 (59.2)	7507 (58.4)	
AJCC Stage						
I	8185 (63.4)	116,695 (63.5)	< .001	8174 (63.6)	8016 (62.4)	.001
IIa	3447 (26.7)	47,382 (25.8)		3418 (26.6)	3456 (26.9)	
IIb	874 (6.8)	13,549 (7.4)		869 (6.8)	1026 (8.0)	
III	400 (3.1)	6156 (3.3)		395 (3.1)	358 (2.8)	
AJCC T Stage						
pT1mi/T1a/T1b	3540 (27.4)	60,247 (32.8)	< .001	3532 (27.5)	3519 (27.4)	.89
pT1c	5994 (46.4)	80,910 (44.0)		5986 (46.6)	5965 (46.4)	
pT2	3372 (26.1)	42,625 (23.2)		3338 (26.0)	3372 (26.2)	
AJCC N Stage						
pN0	10,458 (81.0)	142,381 (77.5)	< .001	10,422 (81.1)	10,136 (78.8)	< .001
pN1	2048 (15.9)	35,245 (19.2)		2039 (15.9)	2362 (18.4)	
pN2	400 (3.1)	6156 (3.3)		395 (3.1)	358 (2.8)	
Grade						
I	4140 (32.1)	43,078 (23.4)	< .001	4103 (31.9)	4082 (31.8)	.79
II	7392 (57.3)	78,554 (42.7)		7383 (57.4)	7370 (57.3)	
II	1374 (10.6)	62,150 (33.8)		1370 (10.7)	1404 (10.9)	
ER						
Negative	407 (3.2)	36,552 (19.9)	< .001	395 (3.1)	394 (3.1)	.97
Positive	12,499 (96.8)	147,230 (80.1)		12,461 (96.9)	12,462 (96.9)	
PR						
Negative	2409 (18.7)	54,995 (29.9)	< .001	2378 (18.5)	2420 (18.8)	.50
Positive	10,497 (81.3)	128,787 (70.1)		10,478 (81.5)	10,436 (81.2)	
Chemotherapy						
No	9655 (74.8)	112,348 (61.1)	< .001	9624 (74.9)	9627 (74.9)	.97
Yes	3251 (25.2)	71,434 (38.9)		3232 (25.1)	3229 (25.1)	

Table 1	Continued					
	Unmatched Cohort			**Matched Cohort**		
Characteristic	**ILC (N = 12,906)**	**IDC (N = 183,782)**	**P**	**ILC (N = 12,856)[a]**	**IDC (N = 12,856)**	**P**
Radiotherapy						
No	2861 (22.2)	39,401 (21.4)	.05	2828 (22.0)	2834 (22.0)	.93
Yes	10,045 (77.8)	144,381 (78.6)		10,028 (78.0)	10,022 (78.0)	

Data are presented as n (%).
Abbreviations: AJCC = American Joint Committee on Cancer; ER = estrogen receptor; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; PR = progesterone receptor.
[a]Fifty patients were excluded in propensity score matching procedure.
[b]Others included American Indian/Alaskan Native, Asian/Pacific Islander.

183,782 IDC. Demographic and clinical characteristics of ILC and IDC patients are shown in Table 1. The mean age of the ILC group was higher than that of IDC group (64.2 ± 12.3 vs. 60.1 ± 13.0 years; $P < .001$). Except that radiotherapy data were distributed similarly between the 2 groups ($P = .05$), there were significant differences in other baseline variables between ILC and IDC groups, including year of diagnosis, race, marital status, AJCC stage, grade, ER and PR status, and chemotherapy. Specifically, the ILC group contained higher proportions of variables: higher AJCC TNM stage, lower differential grade, more ER and PR positivity (all $P < .05$).

Unadjusted annual rates of BCS from 1998 to 2012 for patients with T1-2 BC are presented in Figure 2. A higher proportion of BCS in IDC compared to ILC was observed in the last 15 consecutive years.

Balance in patients' characteristics was achieved after propensity score matching, except for age and AJCC N stage, and residual factors were similarly distributed between 2 groups (all $P > .05$) (Table 1).

Survival Analysis

Among the 196,688 BC patients with T1-2 disease who underwent BCS, 32,837 died for all causes. The 5- and 10-year estimated survival rates were 92.06% and 86.14% in the ILC group, respectively, compared to 90.50% and 85.26% in IDC group (log-rank $P = .12$; HR = 1.04; 95% CI, 0.99-1.08; Figure 3A). A total of 18,270 patients developed secondary cancer, where 1213 cases were ILC and 17,057 cases were IDC (log-rank $P = .013$; HR = 1.08; 95% CI, 1.02-1.14; Figure 3B). In addition, 2459 local recurrence incidences were observed among all the patients, with only 157 cases in the ILC group and 2302 cases in the IDC group (15-year cumulative rates of ILC vs. IDC: 1.22% vs. 1.24%, $P = .51$, HR = 1.06; 95% CI, 0.90-1.24; Figure 3C).

To adjust potential modifier effects, both the original and the propensity score–matched multivariable Cox proportional hazards models were fitted for different outcomes (ie, OS, CFS, and LR; Table 2). In the original Cox models, patients with ILC showed a survival advantage in the OS after BCS compared to patients with

Figure 2	Proportion Receiving Breast-Conserving Surgery According to Histologic Type, 1998-2012
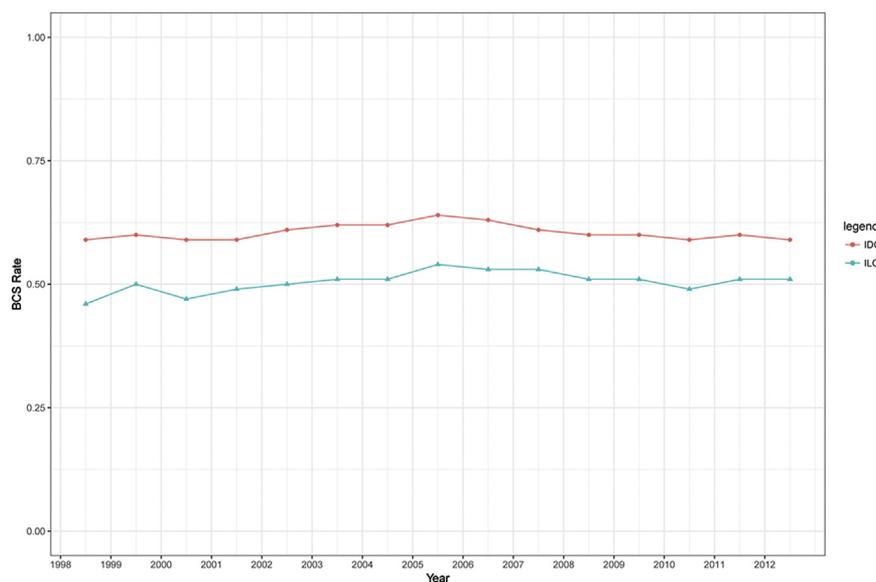
Abbreviations: IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma.

Figure 3 Survival Comparisons Between ILC and IDC. Overall Survival Comparisons Between Patients With ILC and IDC in Whole Cohort (A), Matched Cohort (D), and Grade III Subgroup (G). Second Primary Cancer-Free Survival Comparisons Between Patients With ILC and IDC in Whole Cohort (B), Matched Cohort (E), and Grade III Subgroup (H). RISK of Local Recurrence Comparisons Between Patients With ILC and IDC in Whole Cohort (C), Matched Cohort (F), and Grade III Subgroup (I)
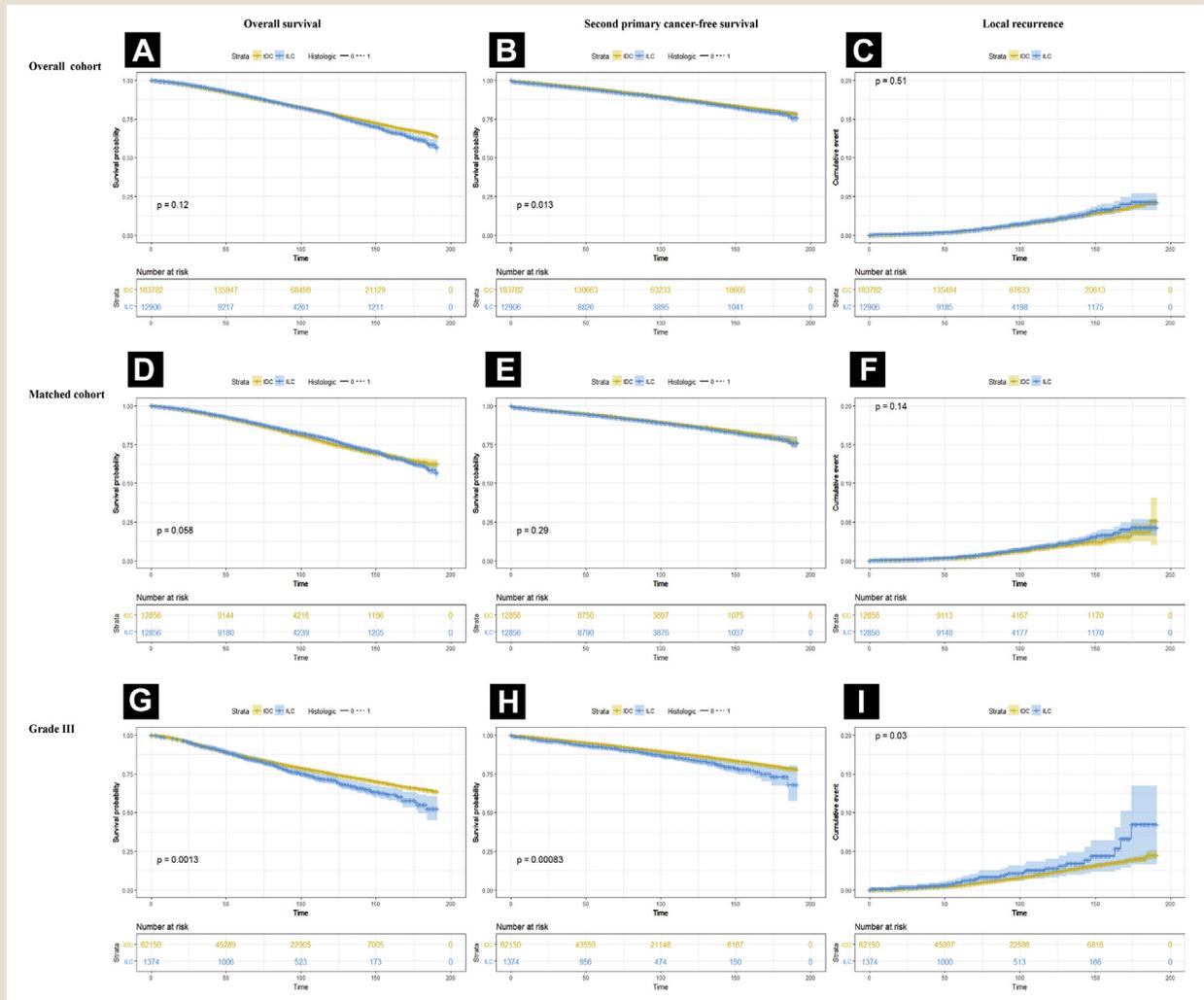
Abbreviations: IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma.

IDC (HR = 0.93; 95% CI, 0.89-0.97; P = .001, Table 2), but no significant differences were observed in CFS (HR = 1.03; 95% CI, 0.97-1.09; P = .33, Table 2) and LR risk (HR = 1.17; 95% CI, 0.99-1.38; P = .06, Table 2). In the propensity score−matched Cox regression model, similar results were observed, where BC patients with ILC had better OS than those with IDC when receiving BCS (HR = 0.94; 95% CI, 0.88-0.99; P = .04, Table 2), whereas no difference was found in other outcomes, including CFS (HR = 1.04; 95% CI, 0.96-1.13; P = .35, Table 2) and LR risk (HR = 1.20; 95% CI, 0.95-1.51; P = .13, Table 2).

When examining the benefit of BCS between patients with ILC and IDC stratified by age, AJCC T and N stage, nuclear grade, ER status, and radiotherapy, which were also adjusted in the multivariable Cox regression model using residual covariates, we found that the OS for the ILC group after BCS was significantly better than that observed in the corresponding IDC group for patients with larger tumor size and fewer positive lymph nodes (Figure 4). Furthermore, higher LR risk for smaller ILC tumors and ER-positive ILC tumors were respectively observed compared to their IDC counterparts (Figure 4). Interestingly, interaction analyses indicated that magnitude of inferior CFS (15-year cumulative incidence: 26.9% vs. 20.6%; P < .001) and higher LR risk (15-year cumulative incidence: 8.5% vs. 4.0%; P = .03) among patients with ILC undergoing BCS compared to IDC were observed in the nuclear grade III subgroup, but no difference in OS between the 2 histologic types was found (Figure 3F-H, Figure 4).

We also conducted a sensitivity analysis in which the variable for HER2 status was added to the aforementioned Cox models. The results were shown in Tables 3 and 4, suggesting that the prior results were robust.

| Table 2 | Prognostic Factors for Survival and Local Recurrence Risk by Multivariate Cox Regression |

	Unmatched Cohort (N = 196,688)						Matched Cohort (N = 25,712)					
	OS		CFS		LR		OS		CFS		LR	
Group	**HR**	**P**	**HR**	**P**	**HR**	**P**	**HR**	**P**	**HR**	**P**	**HR**	**P**
Histologic Type												
IDC	Reference		Reference		Reference		Reference		Reference		Reference	
ILC	0.93*	.001*	1.03	.33	1.17	.06	0.94*	.04*	1.04	.35	1.20	.13
Year of Diagnosis												
1998-2000	Reference		Reference		Reference		Reference		Reference		Reference	
2001-2003	0.97*	.02*	1.00	.93	1.06	.27	1.04	.34	1.09	.19	1.09	.63
2004-2006	0.89*	< .001*	0.96*	.046*	1.10	.11	1.05	.31	0.94	.39	1.20	.33
2007-2009	0.80*	< .001*	0.95	.34	0.89	.14	0.89*	.04*	0.96	.54	0.88	.59
2010-2012	0.74*	< .001*	0.95	.14	0.73*	.03*	0.80*	.01*	0.97	.71	0.91	.80
Age												
< 40 years	Reference		Reference		Reference		Reference		Reference		Reference	
40-60 years	0.88*	< .001*	1.00	.93	0.53*	< .001*	0.73	.09	0.81	.28	0.31*	< .001*
> 60 years	2.70*	< .001*	1.64*	< .001*	0.45*	< .001*	2.74*	< .001*	1.34	.12	0.32*	< .001*
Race/Ethnicity												
White	Reference		Reference		Reference		Reference		Reference		Reference	
Black	1.18*	< .001*	1.09*	.001*	1.51*	< .001*	1.17*	.01*	1.08	.40	1.32	.24
Other	0.77*	< .001*	0.89*	< .001*	0.90	.18	0.67*	< .001*	0.89	.28	0.51	.08
Marital Status												
Single	Reference		Reference		Reference		Reference		Reference		Reference	
Married	0.63*	< .001*	0.91*	< .001*	1.09*	.044*	0.58*	< .001*	0.92*	.045*	0.97	.79
AJCC T Stage												
T1mi/T1a/T1b	Reference		Reference		Reference		Reference		Reference		Reference	
T1c	1.33*	< .001*	1.02	.27	0.89*	.02*	1.30*	< .001*	1.03	.63	0.78	.08
T2	2.02*	< .001*	1.06*	.006*	0.89	.06	1.83*	< .001*	1.07	.28	0.80	.20
AJCC N Stage												
N0	Reference		Reference		Reference		Reference		Reference		Reference	
N1	1.23*	< .001*	1.00	.85	1.00	.97	1.28*	< .001*	0.95	.36	1.01	.65
N2	2.08*	< .001*	1.04	.39	0.94	.61	2.06*	< .001*	0.84	.20	0.83	.64

Table 2 Continued

Group	Unmatched Cohort (N = 196,688)						Matched Cohort (N = 25,712)					
	OS		CFS		LR		OS		CFS		LR	
	HR	P	HR	P	HR	P	HR	P	HR	P	HR	P
Grade												
I	Reference		Reference		Reference		Reference		Reference		Reference	
II	1.13*	< .001*	1.02	.23	1.16*	.006*	1.13*	.001*	1.01	.84	1.21	.17
III	1.40*	< .001*	1.05*	.03*	1.21*	.004*	1.49*	< .001*	1.17*	.03*	1.46*	.048*
ER												
Negative	Reference		Reference		Reference		Reference		Reference		Reference	
Positive	0.82*	< .001*	0.84*	< .001*	0.95	.47	0.86*	.04*	0.74*	.005*	1.32	.41
PR												
Negative	Reference		Reference		Reference		Reference		Reference		Reference	
Positive	0.85*	< .001*	0.98	.27	0.87*	.02*	0.83*	< .001*	1.07	.21	0.90	.47
Chemotherapy												
No	Reference		Reference		Reference		Reference		Reference		Reference	
Yes	0.63*	< .001*	0.87*	< .001*	0.86*	.003*	0.62*	< .001*	0.98	.73	0.91	.54
Radiotherapy												
No	Reference		Reference		Reference		Reference		Reference		Reference	
Yes	0.58*	< .001*	0.89*	< .001*	0.62*	< .001*	0.53*	< .001*	0.82*	< .001*	0.56*	< .001*

Multivariable Cox regression adjusted for year of diagnosis, age of patients, race, marital status, AJCC T stage, AJCC N stage, status of ER and PR, nuclear grade, chemotherapy, and radiotherapy.

Abbreviations: AJCC = American Joint Committee on Cancer; CFS = second primary cancer-free survival; ER = estrogen receptor; HR = hazard ratio; IDC = invasive ductal carcinoma; ILC = infiltrating lobular carcinoma; LR = local recurrence risk; OS = overall survival; PR = progesterone receptor.

*Statistically significant, P < .05.

Figure 4 Hazard Ratios Comparing Survival and Local Recurrence Risk in IDC and ILC. OS, CFS, and LR Risk Shown Between ILC and IDC Groups according to T Stage, N Stage, Nuclear Grade, ER Status, and Radiotherapy. *Multivariate Analysis Adjusted by Year of Diagnosis, Age of patients, Race, Marital Status, AJCC T Stage, AJCC N Stage, Status of ER and PR, Nuclear Grade, Chemotherapy, and Radiotherapy. [a]Square Represents HR for Each Category; Horizontal Line Across Each Square, 95% Confidence Interval, and Dotted Line in Middle, Invalid Line

Group	No. of ILC	No. of IDC	Multivariable* HR (95% CI)[a] of OS	P	Multivariable* HR (95% CI)[a] of DFS	P	Multivariable* HR (95% CI)[a] of LR	P
AJCC pT stage								
T1mic/T1a/T1b	3,540	60,247	0.99	0.85	1.06	0.34	**1.42**	**0.01**
T1c	5,994	80,910	0.96	0.23	1.07	0.14	1.07	0.61
T2	3,372	42,625	**0.92**	**0.046**	0.95	0.38	1.04	0.82
AJCC pN stage								
N0	10,458	142,381	**0.89**	**<0.001**	1.04	0.25	**1.23**	**0.03**
N1	2,048	35,245	1.05	0.35	1.03	0.73	1.05	0.81
N2	400	6,156	1.14	0.18	0.79	0.22	0.62	0.42
Grade								
I	4,140	43,078	1.00	0.91	1.04	0.52	1.11	0.55
II	7,392	78,554	**0.91**	**0.001**	0.99	0.78	1.11	0.34
III	1,374	62,150	1.02	0.78	**1.23**	**0.009**	**1.59**	**0.01**
ER								
Negative	407	36,552	0.88	0.22	0.96	0.8	0.63	0.32
Positive	12,499	147,230	**0.93**	**0.003**	1.03	0.29	**1.22**	**0.02**
Radiotherapy								
No	2,861	39,401	**0.92**	**0.02**	1.05	0.44	1.13	0.42
Yes	10,045	144,381	**0.94**	**0.03**	1.03	0.47	**1.19**	**0.07**

Abbreviations: AJCC = American Joint Committee on Cancer; CFS = second primary cancer-free survival; CI = confidence interval; ER = estrogen receptor; HR = hazard risk; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; LR = local recurrence risk; OS = overall survival; PR = progesterone receptor.

Discussion

In this large population-based cohort study, we observed that BCS rates among patients with T1-2 ILC was lower than those of IDC in the last 15 years. Interestingly, multivariate Cox proportional hazards model and propensity score—matching multivariable Cox proportional hazards models consistently suggested that patients with ILC who underwent BCS had a survival advantage in terms of OS compared to corresponding patients with IDC, whereas CFS and LR risk did not show statistically significant differences. Those results are comparable with previous studies.[6-9,11] In addition, interaction analyses indicated worse CFS and higher LR risk among patients with ILC who underwent BCS compared to IDC were observed in the nuclear grade III subgroup. We suggest that further studies should be conducted to explore the mechanisms of survival difference between early ILC and IDC from the perspective of oncology and pathology, and modify the provision of BCS for patients with grade III ILC.

Previous studies have documented that ILC tends to present characteristics with multicentricity or bilateral disease,[27] occult lesions,[28] and metastases to distinct sites,[29] resulting in losing the chance to undergo BCS. A corresponding result was found in a Dutch study,[13] which also observed that patients with ILC were less likely to undergo BCS compared to IDC. Although up to 31% BCS rate difference between ILC and IDC was indeed identified in this study, the gap was likely overestimated because more patients with IDC than ILC underwent BCS after patients with satisfactory response to neoadjuvant treatments were excluded.[18,30,31] Of note, another reason for the observed BCS rate difference was likely that performing breast magnetic resonance imaging was associated with a reduced number of mastectomies in ILC but an increased number in IDC.[32] Actually, the reason why patients with ILC were less likely to experience BCS was perhaps that candidates with ILC were often eliminated for reasons due to its biological characteristics, such as multicentricity or bilateral disease, which are contraindicated for BCS.[27,33]

A stage-matched study also suggested that prognosis for patients with ILC is better than for those with IDC.[11] Nevertheless, another study investigating the differences in prognoses between the 2 different histologic types consisted of a cohort of 164,958 women based on the SEER database suggested that the survival rates of 50- to 79-year-old women with ILC were higher than those of women with IDC.[7] Although the sample size was large enough in that study, confounding factors such as stage, ER status, chemotherapy, and lifestyle factors have not been well identified or controlled for. Furthermore, in a 1:1 matched cohort of 590 patients after 5 years of follow-up, no differences in disease-free survival or OS were detected between ILC and IDC.[6] Additionally, another age- and stage-matched study observed comparable results.[19] More interestingly, an international BC study group trial indicated that there was a significant early advantage in disease-free survival and OS for the

Table 3 Demographics of Patients Who Underwent Breast-Conserving Surgery Including Variable for HER2 Status (N = 33,091)

Characteristic	Unmatched Cohort			Matched Cohort		
	ILC (N = 2536)	IDC (N = 30,483)	P	ILC[a] (N = 2516)	IDC (N = 2516)	P
Age						
< 40 years	14 (0.6)	909 (3.0)	< .001	11 (0.4)	11 (0.4)	.02
40-49 years	271 (10.7)	4771 (15.7)		268 (10.7)	303 (12.0)	
50-59 years	560 (22.1)	7790 (25.6)		555 (22.1)	519 (20.6)	
60-69 years	802 (31.6)	9070 (29.8)		799 (31.8)	889 (35.3)	
70-79 years	578 (22.8)	5413 (17.8)		577 (22.9)	527 (20.9)	
80+ years	311 (12.3)	2530 (8.3)		306 (12.2)	267 (10.6)	
Race/Ethnicity						
White	2196 (86.6)	24,863 (81.6)	< .001	2185 (86.8)	2186 (86.9)	.998
Black	203 (8.0)	2997 (9.8)		198 (7.9)	198 (7.9)	
Other[b]	137 (5.4)	2623 (8.6)		133 (5.3)	132 (5.2)	
Marital Status						
Single	1079 (42.5)	12,181 (40.0)	.01	1070 (42.5)	1043 (41.5)	.44
Married	1457 (57.5)	18,302 (60.0)		1446 (57.5)	1473 (58.5)	
AJCC Stage						
I	1611 (63.5)	19,738 (64.8)	.06	1606 (63.8)	1600 (63.6)	
IIA	699 (27.6)	7755 (25.4)		687 (27.3)	665 (26.4)	
IIb	160 (6.3)	2205 (7.2)		158 (6.3)	201 (8.0)	
III	66 (2.6)	785 (2.6)		65 (2.6)	50 (2.0)	
AJCC T Stage						
pT1mi/T1a/T1b	699 (27.6)	10,353 (34.0)	< .001	695 (27.6)	696 (27.7)	.999
pT1c	1145 (45.1)	12,842 (42.1)		1142 (45.4)	1142 (45.4)	
pT2	692 (27.3)	7288 (23.9)		679 (27.0)	678 (26.9)	
AJCC N Stage						
pN0	2100 (82.8)	24,358 (79.9)	.001	2085 (82.9)	2044 (81.2)	.04
pN1	370 (14.6)	5340 (17.5)		366 (14.5)	422 (16.8)	
pN2	66 (2.6)	785 (2.6)		65 (2.6)	50 (2.0)	
Grade						
I	839 (33.1)	8104 (26.6)	< .001	823 (32.7)	823 (32.7)	.999
II	1502 (59.2)	13,019 (42.7)		1499 (59.6)	1500 (59.6)	
II	195 (7.7)	9360 (30.7)		194 (7.7)	193 (7.7)	
ER						
Negative	39 (1.5)	4838 (15.9)	< .001	39 (1.6)	39 (1.6)	1.00
Positive	2497 (98.5)	25,645 (84.1)		2477 (98.4)	2477 (98.4)	
PR						
Negative	384 (15.1)	7756 (25.4)	< .001	371 (14.7)	372 (14.8)	.97
Positive	2152 (84.9)	22,727 (74.6)		2145 (85.3)	2144 (85.2)	
HER2[c]						
Negative	2424 (95.6)	26,803 (87.9)	< .001	2409 (95.7)	2409 (95.7)	1.00
Positive	112 (4.4)	3680 (12.1)		107 (4.3)	107 (4.3)	
Chemotherapy						
No	2048 (80.8)	19,844 (65.1)	< .001	2.035 (80.9)	2034 (80.8)	.97
Yes	488 (19.2)	10,639 (34.9)		481 (19.1)	482 (19.2)	
Radiotherapy						
No	542 (21.4)	6646 (21.8)	.61	528 (21.0)	527 (20.9)	.97
Yes	1994 (78.6)	23,837 (78.2)		1988 (79.0)	1989 (79.1)	

Abbreviations: AJCC = American Joint Committee on Cancer; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; PR = progesterone receptor.
[a]Twenty patients were excluded in propensity score matching procedure.
[b]Others included American Indian/Alaskan Native, Asian/Pacific Islander.
[c]Patients were diagnosed after 2010 with known HER2 status.

Table 4	Prognostic Factors for Survival and Local Recurrence Risk by Adjusted Multivariate Cox Regression Including Variable for HER2 Status											
	Unmatched Cohort (N = 33,019)						Matched Cohort (N = 5032)					
	OS		CFS		LR		OS		CFS		LR	
Group	HR	P	HR	P	HR	P	HR	P	HR	P	HR	P
Histologic Type												
IDC	Reference		Reference		Reference		Reference		Reference		Reference	
ILC	0.90	.33	1.19	.09	2.12	.07	0.92	.57	1.18	.25	3.67	.11
Age												
< 40 years	Reference		Reference		Reference		Reference		Reference		Reference	
40-60 years	0.74	.07	1.70	.05	0.53	.30	0.13*	.007*	588.77	.85	1392.17	.96
> 60 years	1.83*	< .001*	2.77*	< .001*	0.35	.09	0.41	.22	1014.34	.84	497.68	.97
Race/Ethnicity												
White	Reference		Reference		Reference		Reference		Reference		Reference	
Black	1.10	.22	1.00	.99	0.81	.66	1.83*	.002*	1.17	.51	1.04	.97
Other	0.70*	.004*	0.70*	.006*	0.60	.39	0.78	.59	0.73	.41	0.001	.88
Marital Status												
Single	Reference		Reference		Reference		Reference		Reference		Reference	
Married	0.60*	< .001*	0.94	.32	1.19	.54	0.53*	< .001*	0.72*	.02*	0.20	.05
AJCC T Stage												
T1mi/T1a/T1b	Reference		Reference		Reference		Reference		Reference		Reference	
T1c	1.53*	< .001*	1.14	.06	0.67	.21	1.10	.69	0.90	.56	0.67	.62
T2	2.48*	< .001*	1.18	.06	0.86	.69	2.71*	< .001*	1.13	.54	1.13	.89
AJCC N Stage												
N0	Reference		Reference		Reference		Reference		Reference		Reference	
N1	1.38*	< .001*	1.09	.29	1.16	.71	1.02	.92	1.07	.76	0.82	.86
N2	2.42*	< .001*	1.26	.21	0.86	.88	1.53	.27	1.94	.11	0.001	.93
Histologic Grade												
I	Reference		Reference		Reference		Reference		Reference		Reference	
II	1.09	.26	0.89	.13	0.43*	.02*	1.01	.94	0.59*	.001*	0.56	.42
III	1.50*	< .001*	1.12	.23	0.86	.72	1.63	.06	1.31	.26	1.26	.85
ER												
Negative	Reference		Reference		Reference		Reference		Reference		Reference	
Positive	0.58*	< .001*	0.99	.92	0.84	.72	0.55	.13	0.37*	.02*	965.42	.94
PR												
Negative	Reference		Reference		Reference		Reference		Reference		Reference	
Positive	0.73*	< .001*	0.93	.40	0.56	.13	0.83	.34	1.42	.12	1.34	.79

Table 4 Continued

Group	Unmatched Cohort (N = 33,019)						Matched Cohort (N = 5032)					
	OS		CFS		LR		OS		CFS		LR	
	HR	P	HR	P	HR	P	HR	P	HR	P	HR	P
HER2[a]												
Negative	Reference		Reference		Reference		Reference		Reference		Reference	
Positive	0.86	.08	1.04	.67	1.14	.76	1.32	.40	2.63*	<.001*	3.36	.29
Chemotherapy												
No	Reference		Reference		Reference		Reference		Reference		Reference	
Yes	0.56*	<.001*	0.73*	<.001*	0.52	.08	0.63	.05	0.53*	.009*	0.32	.34
Radiotherapy												
No	Reference		Reference		Reference		Reference		Reference		Reference	
Yes	0.39*	<.001*	0.70*	<.001*	0.57	.05	0.29*	<.001*	0.63*	.003*	0.22*	.03*

Multivariable Cox regression adjusted for year of diagnosis, age of patients, race, marital status, AJCC T stage, AJCC N stage, status of ER and PR, nuclear grade, chemotherapy, and radiotherapy.

Abbreviations: AJCC = American Joint Committee on Cancer; CFS = second primary cancer-free survival; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; IDC = invasive ductal carcinoma; ILC = infiltrating lobular carcinoma; LR = local recurrence risk; OS = overall survival; PR = progesterone receptor.

[a]Patients were diagnosed after 2010 with known HER2 status.

*Statistically significant, P < .05.

ILC cohort, followed by a significant late advantage for the IDC cohort after 6 and 10 years, respectively.[8] The same pattern was observed in our study, where the OS curves for ILC and IDC crossed, reflecting the tendency for longer latency to distant recurrence in ILC (Figure 3).

Considering that patients treated with BCS would routinely accept radiotherapy (neoadjuvant or adjuvant), CFS and LR are associated with radiotherapy. Prior studies have documented that radiotherapy can enhance antitumor immune responses,[34-37] which can cause immunogenic tumor cell death. In this process, hidden tumor-associated antigens, stress proteins, and danger-associated molecular patterns will be exposed,[38] but a different microenvironment will change these effects. The patients had better survival outcomes (ie, OS, CFS, and LR risk) than those in IDC, and a similar outcome for LR was also found in the radiotherapy-treated subgroup. Our results suggest that different survival outcomes probably depend on the different microenvironments caused by histologic types and nuclear grades.

The National Comprehensive Cancer Network clinical guidelines[33] do not distinguish between the surgical strategies to use between ILC and IDC, and lumpectomy with radiotherapy was considered as the standard approach for patients with stage I, IIA, IIB or T3, N1, M0 BC. Moreover, recent research has sought to determine whether more extensive surgical margins were required for ILC compared to IDC; however, this study found that the rate of local recurrence among patients with ILC is similar to those with IDC in the context of modern BCS.[39] On the one hand, ILC often has a higher T stage,[23] which not only has effects on survival outcomes but likely also has effects on the likelihood of reexcision rates after BCS. Sharma et al[40] found that BCS with ILC was statistically more likely to have successful surgery compared to IDC as tumor size increased; however, they did not do further research or exploration on the survival differences between ILC and IDC.

On the other hand, considering that the true pathologic sizes of ILC are often underestimated as a result of multifocality,[41] those patients with ILC with higher T stage were less likely to present with solitary lesions with favorable prognosis. Accordingly, among T1-2 grade III early BC, we observed obvious survival inferiority among patients with ILC compared to those with IDC. As supporting evidence, an immunohistochemical study by Rakha et al[42] evaluating the prognostic significance of pleomorphic lobular carcinoma suggested that histologic grade in ILC was of prognostic importance, whereas pleomorphic type did not provide useful additional prognostic information. Better-designed studies urgently need to be conducted to compare surgical strategies among patients with nuclear grade III ILC.

Discussions regarding differences in the biological characteristics between ILC and IDC such as tumor stage, ER status, and response to adjuvant chemotherapy are ongoing. Because the early diagnosis rate of ILC is low, ILC patients tends to have disease of a more advanced stage than patients with IDC,[3,8,9] which is a key factor leading to the poor survival of ILC that has been observed in prior studies. Mhuircheartaigh et al[19] suggested that the differences in survival outcomes between ILC and IDC may be determined by ER status, which is in agreement with our interaction analyses that recognized higher LR risk among patients with ILC conferred by ER-positive subsets. Recent studies have proposed that ER status

possibly modified the sensitivity of neoadjuvant/adjuvant chemotherapy, leading to a greater likelihood of resisting chemotherapy among patients with ER-positive ILC compared to ER-positive IDC.[31,43,44] Likewise, our study found comparable results, and no statistically significant difference in survival between patients with ILC and IDC who received adjuvant chemotherapy was detected when ER and PR status between ILC and IDC were comparable. In our unmatched cohort, patients with ILC had less HER2-positive disease than those with IDC; previous series have also identified this.[5,45] Although the sensitivity results are limited by the short follow-up period, consistent outcomes indicated the robustness of the study, regardless of whether or not HER2 status were included.

Some limitations of our study should be acknowledged, and our results ought to be interpreted with caution. Some important confounding factors, such as surgical margin status and receipt of endocrine therapy, are not available in SEER database, which may have influenced our results. Positive surgical margin status was reported to have adverse effects on survival among patients who underwent BCS,[40,46-48] and the question remains whether BCS should be changed to mastectomy for patients with ILC when positive margins are found. Evaluation of the response of ILC patients to endocrine therapy is an emerging direction of clinical BC research,[30,49] and it was reported that the magnitude of benefit of adjuvant letrozole is greater for patients diagnosed with lobular carcinoma compared to those with ductal carcinoma,[50] the effectiveness of which should be discussed for ER-positive ILC after BCS. Finally, we cannot control the quality of the primary data, and pathologic diagnosis from multiple hospitals will lead to inevitable bias.

Nonetheless, to our knowledge, ours is the first study to investigate the survival differences between patients with ILC and IDC after BCS. Optimal matched groups were acquired after conducting the propensity score—matching procedure, which increased between-group comparability compared to the unmatched studies[6-10,12] or partial matched studies[11,19,51] conducted previously.

Conclusion

We found that T1-2 ILC BC patients were less likely to undergo BCS compared to those with IDC. Patients with T1-2 ILC BC receiving BCS have favorable OS, not only in the spontaneous SEER cohort but also in the matched cohort, compared to their counterparts with IDC. However, ILC patients have worse CFS and higher LR risk compared to IDC patients in nuclear grade III subgroup. We suggest that patients with T1-2 ILC of nuclear grade III should be studied, with further efforts made to develop more feasible surgical strategies for them and to identify potential mechanisms of their survival inferiority.

Clinical Practice Points

- ILC is commonly characterized with higher T stage and with higher percentage of multifocal, multicentral, and bilateral disease compared to IDC, but it is also associated with lower histologic grade, higher rate of hormone receptor positivity, and lower rate of HER2 positivity, which are associated with favorable prognosis.
- Inconsistent prognostic results according to the 2 histologic disease types have been widely reported.
- ILC resulted in a higher probability of repeat excision or mastectomy after BCS.
- We found that T1-2 ILC BC patients are likely to undergo BCS compared to IDC.
- Patients with T1-2 ILC BC receiving BCS are associated with having a favorable OS, not only in the spontaneous SEER cohort but also in the matched cohort, compared to IDC. ILC patients have poorer CFS and higher LR risk than that of IDC in the nuclear grade III subgroup.
- Patients with T1-2 ILC of nuclear grade III should be studied to develop more feasible surgical strategies for them and to identify potential mechanisms of survival inferiority.

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Disclosure

The authors have stated that they have no conflict of interest.

Supplemental Data

A supplemental figure accompanying this article can be found in the online version at https://doi.org/10.1016/j.clbc.2018.10.010.

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Supplemental Data

Supplemental Figure 1	Distribution of Propensity Score Before and After Propensity Score Analysis. Distribution of Propensity Score for Patients With (A) ILC and (C) IDC Breast Cancer before Matching Procedure. (B) and (D) show Distribution of Propensity Score After Full Propensity Score Matching
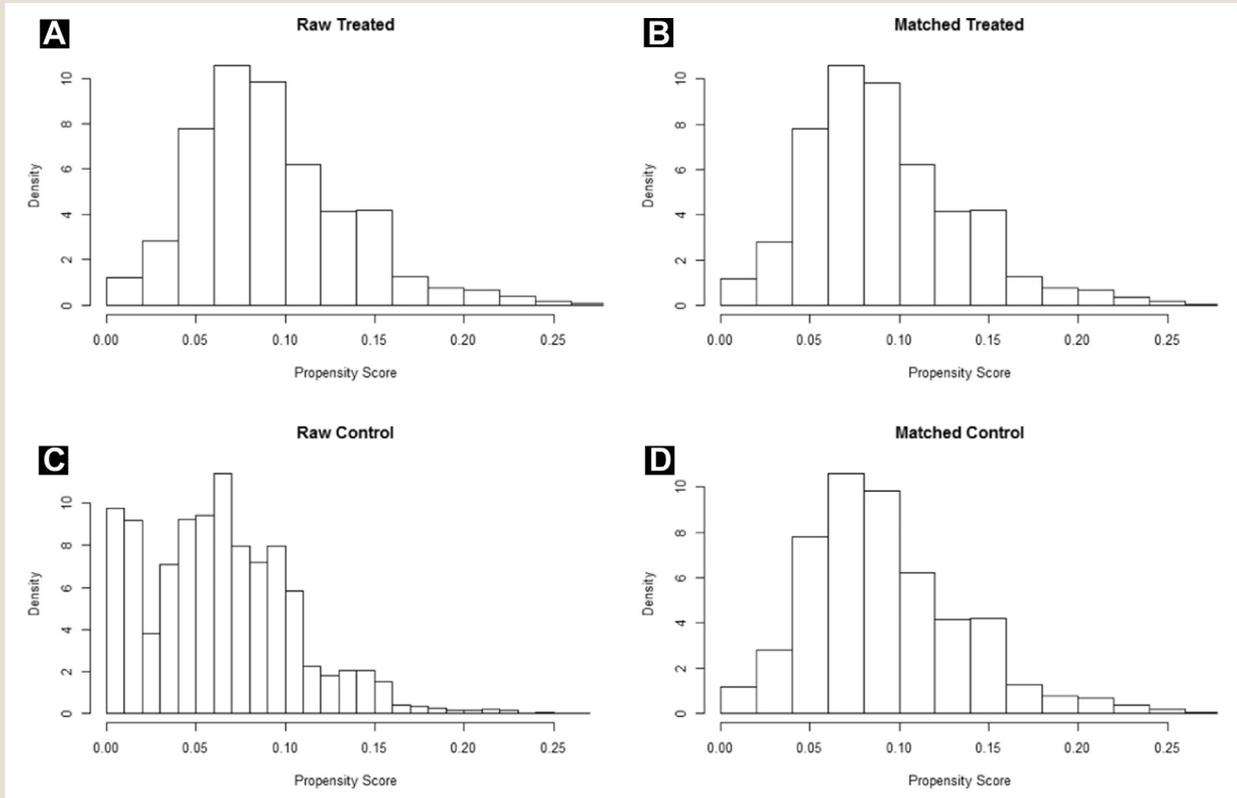
Abbreviations: ILC = invasive lobular carcinoma; IDC = invasive ductal carcinoma.