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Clinicopathological Characteristics and Survival Outcomes of Invasive Cribriform Carcinoma of Breast

A SEER Population-Based Study

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Abstract: Invasive cribriform carcinoma (ICC) is a rare histologic subtype of breast cancer. We aimed to investigate the clinicopathological characteristics and survival outcomes of ICC.

Using the Surveillance, Epidemiology, and End Results (SEER) database, we identified 233,337 female patients diagnosed with ICC (n = 618) or infiltrating ductal carcinoma (IDC) (n = 232,719). Univariate and multivariate survival analyses were utilized to calculate and compare disease-specific survival (DSS) and overall survival (OS). A 1:1 paired match was carried out on age, tumor stage, tumor grade, estrogen receptor (ER) status, and progesterone receptor (PR) status. Baseline characteristics and survival outcomes were also analyzed in ER-positive tumors. Subgroup analyses summarized the hazard ratio (HR) of IDC versus ICC using a forest plot.

ICCs presented smaller size, lower grade, higher ER and PR positive rate, less nodal metastasis, and were less likely to be treated with mastectomy compared to IDCs. Five-year DSS rates were significantly better for patients with ICC than for patients with IDC (98.8% vs. 93%, $P < 0.001$). Five-year OS rates were 95.3% versus 90.1% ($P < 0.001$). After adjustment for common clinicopathological factors in the multivariate analysis, patients with ICC showed limited DSS advantage over the IDC group (HR = 0.75, 95% CI: 0.38–1.51, $P = 0.421$). No significant difference in DSS nor OS was observed in matched groups between ICC and IDC. Analysis among ER-positive patients revealed similar prognostic factors as among all patients. Survival analysis in different tumor grade subgroups showed no significant difference between ICC and IDC.

ICCs have unique clinicopathological characteristics, higher rates of breast-conserving surgery, and more favorable prognosis compared to the overall IDC population. Difference in tumor grade between the 2 groups may partially explain the different outcome. Improved clinical and biological understanding of ICC might lead to more individualized and tailored therapy for breast cancer patients.

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Abbreviations: AJCC = American Joint Committee on Cancer, CI = confidence interval, CMH = Cochran-Mantel Haenszel, EIO = European Institute of Oncology, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio, ICC = invasive cribriform carcinoma, ICD-O-3 = International Classification of Diseases for Oncology Version 3, IDC = infiltrating ductal carcinoma, IQR = interquartile range, LN = lymph node, NOS = no other specific, OS = overall survival, PR = progesterone receptor, SEER = Surveillance, Epidemiology, and End Results, UD = undifferentiated, WHO = World Health Organization.

INTRODUCTION

Invasive cribriform carcinoma (ICC) of breast grows in a cribriform pattern similar to that seen in intraductal cribriform carcinoma, which was first described by Page et al in 1983.[1] This unique subtype of breast cancer accounts for 0.3% to 0.8% of overall breast cancer cases, while some studies report an occurrence rate of up to 4%.[1–3] Generally, ICCs are divided into pure and mixed ICCs. Previous studies have done some work in uncovering the (unique) characteristic properties of ICC. It has been reported that pure ICC has a 10-year overall survival (OS) of 90% to 100%, and while the prognosis of mixed ICC is less favorable, it is still better than that of invasive ductal carcinoma.[1,2,4–7] The majority of ICCs exhibit positive estrogen receptor (ER) and progesterone receptor (PR) statuses, while human epidermal growth factor receptor 2 (HER2) amplification is rarely observed, thus ICCs could be classified as luminal breast cancer.[5,7,8] For these reasons, there are some recommendations that this favorable histological subtype of tumor may be suitable for no adjuvant therapy or just endocrine therapy alone.[9]

However, the prognostic value of demographic and clinicopathological characteristics in ICC is relatively unclear. Of the limited number of studies reported, most are case reports, or small retrospective studies due to the low disease incidence. Page et al first identified 51 ICCs from 1003 patients in

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Edinburgh, reporting an adjusted 10-year survival rate of 75%.[1] Louwman et al reported a 100% survival rate in ICC based on the Netherlands Cancer Registry, in which 503 patients with cribriform were enrolled from 1989 to 2003. However, this may have brought in misclassification bias since ICC may not have been clearly classified before 2003.[6] Colleoni et al[7] analyzed 250 pure ICCs from the European Institute of Oncology (EIO) and divided them into luminal A (n = 191) and luminal B (n = 59) subtypes, which subsequently drew researchers' attention to ICC when studying luminal tumors. Available data on comprehensive summarization of clinicopathological characteristics and prognostic factors of ICC are limited. Previous studies have often lacked adequate follow-up, detailed description of clinical characteristics, adjustment of confounding factors and were of small sample size. Currently, treatment of ICC is based on evidences from IDC, which might lead to inappropriate therapy. Identifying effective prognostic factors of ICC could help physicians acquire a better understanding of the disease and make better informed treatment decisions. Thus it is of great importance to clarify the clinicopathological characteristics and prognostic factors of ICC based on a large population and treat ICC patients accordingly.

By utilizing the Surveillance, Epidemiology, and End Results (SEER) database, we aimed to compare survival outcomes of ICC patients with infiltrating duct carcinoma (IDC) patients. We sought to identify prognostic factors that may account for survival differences between these histologic subtypes of breast cancer.

METHODS

Ethics Statement

Our study was approved by an independent ethical committee/institutional review board at Fudan University Shanghai Cancer Center (Shanghai Cancer Center Ethical Committee). The data released by the SEER database do not require informed patient consent because cancer is a reportable disease in every state in the United States.

Data Acquisition and Patient Selection

We used SEER data released in April 2015, which includes data from 18 population-based registries (1973–2012) and covers approximately 28% of U.S. cancer patients. Data of tumor location, grade, and histology were recorded according to the International Classification of Diseases for Oncology Version 3 (ICD-O-3). The inclusion criteria we used to identify eligible patients were as follows: female aged between 18 and 79, unilateral breast cancer, breast cancer (ICD-O-3 site code C50) as the first and only cancer diagnosis, diagnosis not obtained from a death certificate or autopsy, only one primary site, pathologic confirmation of infiltrating ductal carcinoma, not otherwise specified (IDC-NOS) (ICD-O-3 8500/3) and invasive cribriform carcinoma (ICD-O-3 8201/3), surgical treatment with either mastectomy or breast conserving surgery, known ER and PR statuses, American Joint Committee on Cancer (AJCC) stages I–III, and known time of diagnosis from January 1, 2003 to December 31, 2012. Patients diagnosed with breast cancer before 2003 were excluded because the World Health Organization (WHO) did not recognize ICC as a distinct pathologic entity until 2003. Additionally, patients diagnosed with breast cancer after 2012 were not included because the database was only updated up to December 31, 2012, and also because we wanted to ensure adequate follow-up time. Finally, 233,337 patients were included. Of these patients, 618 were diagnosed with ICC and 232,719 with IDC.

Demographic statistics included age at diagnosis, year of diagnosis, race, and marital status. We treated age at diagnosis as a binary variable classified into the following age groups: 18 to 49 years and 50 to 79 years. Tumor characteristics included laterality, histologic grade, tumor size, regional lymph node (LN) status, AJCC stage, ER status, PR status, and HER2 status. Among those variables, tumor size was treated as a categorical variable: <20 mm, 20 to 50 mm, and >50 mm. For HER2 status, data were only available after 2010 for both subtypes due to the limitation of the SEER dataset.

Outcome Measurement

In the present study, disease-specific survival (DSS), which we used as the primary study outcome, was calculated from the date of diagnosis to the date of death caused by breast cancer. Patients who died from other causes unrelated to breast cancer diagnosis or were alive were censored on the date of death or the date of last contact. OS, as secondary outcome, was defined from the date of diagnosis to the date of death from any cause, and patients who were alive on the last follow-up were censored.

Study cut-off date is a predetermined date for the submission, the SEER November 2014 submission databases will contain complete death data through 2012. Therefore, December 31, 2012 will be the study cut-off date. The following algorithm is used in SEER databases: Date of last contact = min (date of last contact, study cut-off date). Survival months = floor ((date last contact − date dx)/days in a month).

Statistical Analysis

Clinicopathological characteristics were compared across groups by the Pearson Chi-square test or Fisher exact test for categorical nominal data and the Cochran–Mantel Haenszel (CMH) Chi-square test for categorical ordinal data. Kaplan–Meier curves were used to calculate 5-year DSS and OS rates, with the log-rank test used to determine differences across groups. Univariate and multivariate Cox proportional hazard models were applied to identify factors associated with survival, with hazard ratios (HRs) and 95% confidence intervals (CIs) reported.

To account for differences in baseline characteristics across groups, we matched each ICC patient to 1 IDC patient on the following predetermined factors: age, tumor stage, tumor grade, ER status, and PR status, utilizing psmatch2 in Stata designed for the propensity score matching methods and test the matching quality for the balance after the match. Because the majority of ICC cases show ER-positive (ER+) status, a planned secondary survival comparison within ER+ patients was also conducted. Subgroup analyses using univariate Cox proportional hazard modeling summarized the HRs of ICC versus IDC, and a forest plot was calculated to better clarify each prognostic factor's effect on survival.

All the statistical analysis was performed using Stata statistical software, version 12.0 (StataCorp, College Station, TX). Two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Clinicopathological Characteristics of ICC

According to the inclusion criteria mentioned above, we finally enrolled 233,337 patients, including 618 ICC patients

TABLE 1. Characteristics of Patients From the SEER Database by Histologic Subtype, ICC Versus IDC[a]

	ICC, n = 618 (%)	IDC, n = 232,719 (%)	Total, n = 233,337 (%)	*P*-Value[b]
Median follow-up (months) (IQR)	59 (27–88)	46 (21–76)	46 (21–76)	
Year of diagnosis				
2003–2007	333 (53.9)	102,597 (44.1)	102,930 (44.1)	<0.001
2008–2012	285 (46.1)	130,122 (55.9)	130,407 (55.9)	
Age at diagnosis (years)				
18–49	165 (26.7)	68,453 (29.4)	68,618 (29.4)	0.139
50–79	453 (73.3)	164,266 (70.6)	164,719 (70.6)	
Race				
White	492 (79.6)	184,695 (79.4)	185,187 (79.4)	0.410
Black	58 (9.4)	25,119 (10.8)	25,177 (10.8)	
Others[c]	66 (10.7)	21,666 (9.3)	21,732 (9.3)	
Unknown	2 (0.3)	1239 (0.5)	1241 (0.5)	
Marital status				
Married	339 (54.9)	140,749 (60.5)	141,088 (60.5)	<0.001
Not married[d]	249 (40.3)	83,318 (35.8)	83,567 (35.9)	
Unknown	30 (4.9)	8652 (3.7)	8682 (3.7)	
Laterality				
Left	323 (52.3)	117,870 (50.7)	118,193 (50.7)	0.48
Right	295 (47.7)	114,824 (49.3)	115,119 (49.3)	
Only one side, NOS	0 (0.0)	25 (0.0)	25 (0.0)	
Grade				
1	330 (53.4)	43,263 (18.6)	43,593 (18.7)	<0.001
2	199 (32.2)	91,506 (39.3)	91,705 (39.3)	
3 and UD[e]	52 (8.4)	91,926 (39.5)	91,978 (39.4)	
Unknown	37 (6.0)	6024 (2.6)	6061 (2.6)	
Tumor size (cm)				
<2	466 (75.4)	137,751 (59.2)	138,217 (59.2)	<0.001
2–5	136 (22.0)	82,197 (35.3)	82,333 (35.3)	
>5	15 (2.4)	11,659 (5.0)	11,674 (5.0)	
Unknown	1 (0.2)	1112 (0.5)	1113 (0.5)	
LN status				
Negative	490 (79.3)	151,131 (64.9)	151,621 (65.0)	<0.001
Positive	98 (15.9)	75,707 (32.5)	75,805 (32.5)	
Unknown	30 (4.9)	5881 (2.5)	5911 (2.5)	
AJCC stage				
I	442 (71.5)	119,336 (51.3)	119,778 (51.3)	<0.001
II	154 (24.9)	84,860 (36.5)	85,014 (36.4)	
III	22 (3.6)	28,523 (12.3)	28,545 (12.2)	
ER status				
Negative	34 (5.5)	54,219 (23.3)	54,253 (23.3)	<0.001
Positive	584 (94.5)	178,500 (76.7)	179,084 (76.8)	
PR status				
Negative	69 (11.2)	77,808 (33.4)	77,877 (33.4)	<0.001
Positive	549 (88.8)	154,911 (66.6)	155,460 (66.6)	
HER2 status				
Positive	11 (5.8)	12,882 (16.1)	12,893 (16.0)	0.002
Negative	171 (90.0)	63,592 (79.3)	63,763 (79.3)	
Borderline	4 (2.1)	1858 (2.3)	1862 (2.3)	
Unknown	4 (2.1)	1864 (2.3)	1868 (2.3)	
Total	190 (100.0)	80,196 (100.0)	80,386 (100.0)	
Surgery type				
Mastectomy	200 (32.4)	92,243 (39.6)	92,443 (39.6)	<0.001
Lumpectomy	418 (67.6)	140,476 (60.4)	140,894 (60.4)	
Radiation				
No	254 (41.1)	93,299 (40.1)	93,553 (40.1)	0.051

	ICC, n = 618 (%)	IDC, n = 232,719 (%)	Total, n = 233,337 (%)	*P*-Value[b]
Yes	354 (57.3)	131,798 (56.6)	132,152 (56.6)	
Unknown	10 (1.6)	7622 (3.3)	7632 (3.3)	

AJCC = American Joint Committee on Cancer, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, ICC = invasive cribriform carcinoma, IDC = infiltrating ductal carcinoma, IQR = interquartile range, LN = lymph node, NOS = no other specific, PR = progesterone receptor, SEER = Surveillance, Epidemiology and End Results, UD = undifferentiated.
[a] Data are presented as No.(percentage) of patients unless otherwise indicated.
[b] *P*-value of the Chi-square test comparing the ICC and IDC groups.
[c] Including American Indian/Alaskan native, and Asian/Pacific Islander, and others-unspecified.
[d] Including divorced, separated, single (never married), and widowed.
[e] Including grade 3 and undifferentiated.

and 232,719 IDC patients. The demographics, tumor, and treatment characteristics by histologic subtype are summarized in Table 1. There were significant differences in tumor characteristics including grade, tumor size, lymph node status, AJCC stage, ER status, and PR status between the 2 populations. ICC patients presented smaller tumors (for tumor size < 20 mm: 75.4% vs. 59.2%, $P < 0.001$) and more grade 1 disease, namely well-differentiated disease (53.4% vs. 18.6%, $P < 0.001$). Furthermore, the LN-negative rate of ICC tumors was higher compared to IDC tumors (79.3% vs. 64.9%, $P < 0.001$). Collectively, it is not incomprehensible that ICC patients had more AJCC stage I than IDC patients (71.5% vs. 51.3%, $P < 0.001$). ER positivity was detected in 94.5% of ICC compared to 76.7% of the IDC ($P < 0.001$). Likewise, PR were expressed in 88.8% of ICC compared to 66.6% of IDC ($P < 0.001$). Table 1 and Supplementary Table 1, http://links.lww.com/MD/A358 summarized HER2 amplification status as well. Patients with ICC showed less HER2 positive status than IDC (Table 1: 5.8 vs. 16.1%, $P = 0.002$; Supplementary Table 1, http://links.lww.com/MD/A358: 5.0% vs. 13.4%, $P = 0.01$). Treatment was also different between groups. Lumpectomy rates were higher in patients with ICC compared to IDC (67.9% vs. 60.4%, $P < 0.001$). Adjuvant radiation, however, was used with similar frequency in patients with ICC or IDC.

Comparison of Survival Between ICCs and IDCs

Kaplan–Meier plots were used to evaluate DSS and OS in these 2 histologic subtypes (Figure 1). Patients with ICC had better survival than the overall IDC population in both DSS and OS ($P < 0.001$, respectively). Five-year DSS rate of ICC is 98.8% (95% CI: 97.0–99.5%), while 5-year DSS rate of IDC is 93.0% (95% CI: 92.9–93.1%). Five-year OS rate of ICC is 95.3% (95% CI: 92.8–97.0%), while 5-year OS rate of IDC is 90.1% (95% CI: 89.9–90.2%).

The Cox proportional hazards model was utilized to further investigate the effect of baseline characteristics on DSS and OS (Table 2 and Supplementary Table 2, http://links.lww.com/MD/A358). In univariate analysis, factors were proved to be significantly associated with DSS including age, year of diagnosis, race, marital status, tumor grade, tumor size, lymph nodes status, ER status, PR status, and surgery type (Supplementary Table 2, http://links.lww.com/MD/A358). Patients with ICC histology were found to be a protective factor (HR = 0.27, 95% CI 0.13–0.54, $P < 0.001$). All these variables mentioned above were therefore included in the multivariate analysis. Multivariate analyses confirmed the prognostic factors identified on univariate analysis (Table 2). However, after adjusting other prognostic factors, the histology type were no longer an independent prognostic factor in multivariate analysis (HR = 0.75, 95% CI 0.38–1.51, $P = 0.421$).

Survival Analysis in Matched Group

To make sure that baseline differences in demographic and clinical characteristics across histologic subtypes were not responsible for outcome differences, we carried out a 1:1 (ICC/IDC) matched case–control analysis using the propensity score matching method. We obtained a group of 1236 patients, including 618 patients for each histology type (Table 3). For matched groups, we found no statistically significant difference in characteristics between ICC and IDC. Furthermore, we found that ICC histology no longer presented better prognosis for

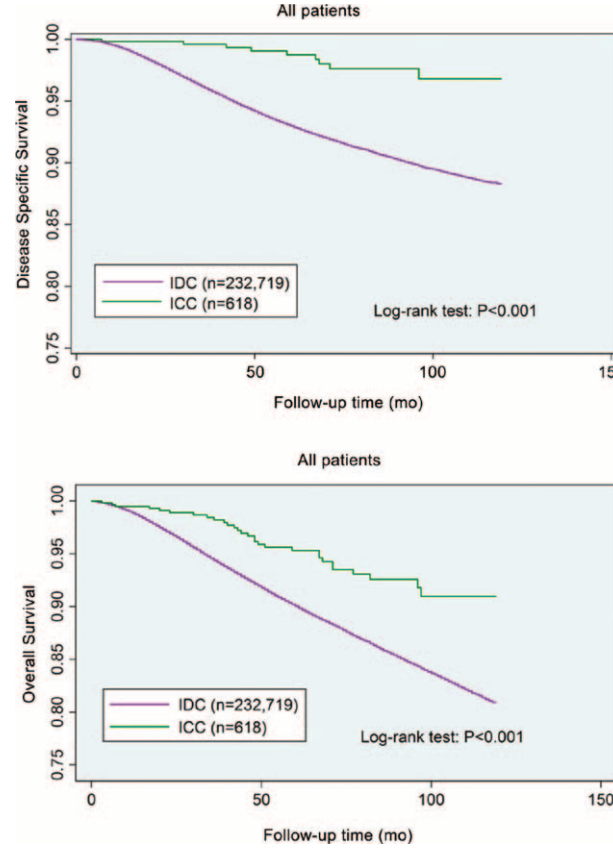

FIGURE 1. Kaplan–Meier curves by histologic subtypes of breast cancer, ICC versus IDC. Abbreviations: ICC, invasive cribriform carcinoma; IDC, infiltrating ductal carcinoma.

TABLE 2. Multivariate Analysis of Disease-Specific Survival (DSS) and Overall Survival (OS) Predictors Using Cox Proportional Hazards Modeling

	DSS		OS	
Variables	**HR (95% CI)**	***P*-Value**	**HR (95% CI)**	***P*-Value**
Year of diagnosis				
2003–2007	1.17 (1.11–1.22)	<0.001	1.17 (1.12–1.21)	<0.001
2008–2012	Reference	–	Reference	–
Patient age at diagnosis (years)				
18–49	0.83 (0.80–0.87)	<0.001	0.61 (0.59–0.63)	<0.001
50–79	Reference	–	Reference	–
Race				
White	Reference	–	Reference	–
Black	1.24 (1.18–1.31)	<0.001	1.26 (1.21–1.31)	<0.001
Others[a]	0.78 (0.72–0.84)	<0.001	0.77 (0.73–0.82)	<0.001
Marital status				
Married	Reference	–	Reference	–
Not married	1.25 (1.20–1.30)	<0.001	1.47 (1.42–1.51)	<0.001
Grade				
1	0.44 (0.39–0.49)	<0.001	0.81 (0.76–0.86)	<0.001
2	Reference	–	Reference	–
3 and UD	1.66 (1.58–1.74)	<0.001	1.34 (1.29–1.39)	<0.001
Histology type				
IDC	Reference	–	Reference	–
ICC	0.75 (0.38–1.51)	0.421	0.68 (0.43–1.06)	0.088
Tumor size (cm)				
<2	Reference	–	Reference	–
2–5	2.32 (2.21–2.43)	<0.001	1.83 (1.76–1.89)	<0.001
>5	4.32 (4.05–4.61)	<0.001	3.29 (3.12–3.48)	<0.001
LN status				
Negative	Reference	–	Reference	–
Positive	2.68 (2.57–2.80)	<0.001	1.98 (1.92–2.05)	<0.001
ER status				
Positive	Reference	–	Reference	–
Negative	1.49 (1.41–1.57)	<0.001	1.40 (1.33–1.46)	<0.001
PR status				
Positive	Reference	–	Reference	–
Negative	1.63 (1.54–1.72)	<0.001	1.33 (1.27–1.39)	<0.001
Surgery type				
Mastectomy	1.28 (1.23–1.34)	<0.001	1.23 (1.19–1.28)	<0.001
Lumpectomy	Reference	–	Reference	–
Radiation				
Yes	Reference	–	Reference	–
No	1.13 (1.09–1.18)	<0.001	1.26 (1.22–1.30)	<0.001

CI = confidence interval, ER = estrogen receptor, HR = hazard ratio, ICC = invasive cribriform carcinoma, IDC = infiltrating ductal carcinoma, LN = lymph node, PR = progesterone receptor, UD = undifferentiated. Multivariate analysis includes year of diagnosis, age at diagnosis, race, marital status, grade, tumor size, lymph nodes status, ER status, PR status, and surgery type.

[a] Including American Indian, Alaska Native, Asian, Pacific Islander, and others-unspecified.

either DSS or OS (Figure 2, $P = 0.480$ and 0.117 for OS and DSS, respectively).

Baseline Characteristics and Survival Outcomes in ER-Positive Subgroup

The majority of ICCs are ER-positive tumors. In analysis limited to ER-positive ICC and IDC patients, which including 179,084 patients (584 ICCs and 178,500 IDCs), similar results were observed (Supplementary Table 1, http://links.lww.com/MD/A358). Specifically, compared to ER-positive IDC patients, ER-positive ICC patients had lower grade, smaller tumor size, lower AJCC stage, lower lymph node positive rate, and higher PR positive rate. Mastectomy or lumpectomy rates between subtypes, however, were no longer statistically different. The comparison of ER-positive subset had relatively the same curves as analysis above for all patients (Supplementary Figure 1, http://links.lww.com/MD/A358). In ER-positive subset, patient with ICC had a better DSS and OS than patient with IDC ($P < 0.001$ and $P = 0.005$ for DSS and OS, respectively).

Subgroup Analyses

A forest plot of HRs summarizing exploratory subgroup analyses suggested that in some subgroups, ICC subtype was no

TABLE 3. Characteristics of Patients by Histology Subtype in 1:1 Matched, ICC Versus IDC

	ICC, n = 618 (%)	IDC, n = 618 (%)	Total, n = 1236 (%)	*P*-Value[b]
Median follow-up (months) (IQR)	59 (27–88)	47 (23–76)	52 (25–82)	
Year of diagnosis				
2003–2007	333 (53.9)	263 (42.6)	596 (48.2)	<0.001
2008–2012	285 (46.1)	355 (57.4)	640 (51.8)	
Age at diagnosis (years)				
18–49	165 (26.7)	165 (26.7)	330 (26.7)	0.526
50–79	453 (73.3)	453 (73.3)	906 (73.3)	
Race				
White	492 (79.6)	521 (84.3)	1013 (82.0)	0.042
Black	58 (9.4)	46 (7.4)	104 (8.4)	
Others[c]	66 (10.7)	45 (7.3)	111 (9.0)	
Unknown	2 (0.3)	6 (1.0)	8 (0.7)	
Marital status				
Married	339 (54.9)	384 (62.1)	723 (58.5)	0.024
Not married[d]	249 (40.3)	214 (34.6)	463 (37.5)	
Unknown	30 (4.9)	20 (3.2)	50 (4.1)	
Laterality				
Left	323 (52.3)	319 (51.6)	642 (51.9)	0.864
Right	295 (47.7)	299 (48.4)	594 (48.1)	
Grade				
1	330 (53.4)	330 (53.4)	660 (53.4)	0.887
2	199 (32.2)	199 (32.2)	398 (32.2)	
3 and UD[e]	52 (8.4)	52 (8.4)	104 (8.4)	
Unknown	37 (6.0)	37 (6.0)	74 (6.0)	
Tumor size (cm)				
<2	466 (75.4)	490 (79.3)	959 (77.4)	0.133
2–5	136 (22.0)	119 (19.3)	255 (20.6)	
>5	15 (2.4)	6 (1.0)	21 (1.7)	
Unknown	1 (0.2)	3 (0.5)	4 (0.3)	
LN status				
Negative	490 (79.3)	460 (74.4)	950 (76.9)	0.065
Positive	98 (15.9)	130 (21.0)	228 (18.5)	
Unknown	30 (4.9)	28 (4.5)	58 (4.7)	
AJCC stage				
I	442 (71.5)	442 (71.5)	884 (71.5)	1.000
II	154 (24.9)	154 (24.9)	308 (24.9)	
III	22 (3.6)	22 (3.6)	44 (3.6)	
ER status				
Negative	34 (5.5)	34 (5.5)	68 (5.5)	1.000
Positive	584 (94.5)	584 (94.5)	1168 (94.5)	
PR status				
Negative	69 (11.2)	69 (11.2)	138 (11.2)	1.000
Positive	549 (88.8)	549 (88.8)	1098 (88.8)	
Surgery type				
Mastectomy	200 (32.4)	186 (30.1)	386 (31.2)	0.425
Lumpectomy	418 (67.6)	432 (69.9)	850 (68.8)	
Radiation				
No	254 (41.1)	217 (35.1)	471 (38.1)	0.095
Yes	354 (57.3)	391 (63.3)	745 (60.3)	
Unknown	10 (1.6)	10 (1.6)	20 (1.6)	

AJCC = American Joint Committee on Cancer, ER = estrogen receptor, ICC = invasive cribriform carcinoma, IDC = infiltrating ductal carcinoma, IQR = interquartile range, LN = lymph node, NOS = no other specific, PR = progesterone receptor, SEER = Surveillance, Epidemiology and End Results, UD = undifferentiated.

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

[b] *P*-value of the Chi-square test comparing the ICC and IDC groups.

[c] Including American Indian/Alaskan native, and Asian/Pacific Islander, and others-unspecified.

[d] Including divorced, separated, single (never married), and widowed.

[e] Including grade 3 and undifferentiated.

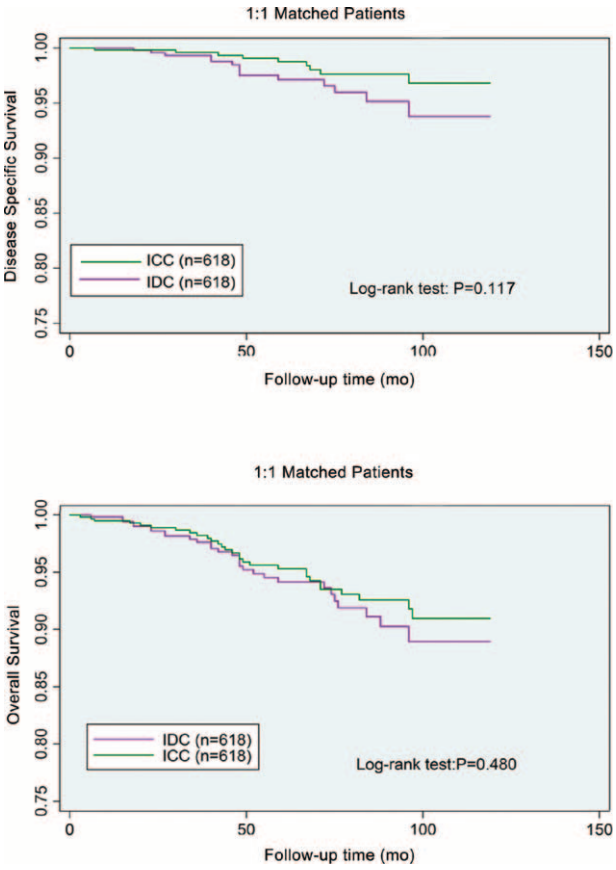

FIGURE 2. Kaplan–Meier curves for 1:1 matched groups by histology, ICC (matched) versus IDC (matched). Abbreviations: ICC, invasive cribriform carcinoma; IDC, infiltrating ductal carcinoma.

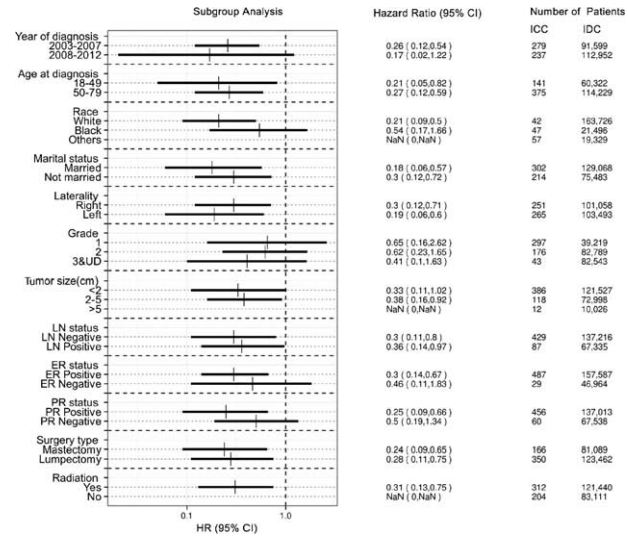

FIGURE 3. Forest plot of hazard ratios for ICC versus IDC in subgroup analysis. The *X*-axis shows the hazard ratio and 95% CI of each subgroup, ticks are arranged at 0.1, 1.0, and 10. Abbreviations: ICC, invasive cribriform carcinoma; IDC, infiltrating ductal carcinoma.

longer a protective factor for DSS (Figure 3). HRs in different tumor grade subgroups showed no significant difference between ICC and IDC (grade 1: HR = 0.65, 95% CI 0.12–2.62, $P = 0.547$; grade 2: HR = 0.62, 95% CI 0.23–1.65, $P = 0.337$; grade 3: HR = 0.41, 95% CI 0.11–1.63, $P = 0.204$). These results suggested that tumor grade may be a principal confounder for ICC prognosis.

DISCUSSION

In this study, we retrospectively investigated the clinicopathological characteristics and survival outcomes of ICC based on a large population. Our findings indicate that ICCs have unique pathological characteristics, more likely to receive breast-conserving surgery and are associated with more favorable prognosis over IDCs both in DSS and OS. However, survival of ICCs did not show significant advantage over IDC after adjusting confounding factors. Further subgroup analyses revealed that the different distribution of tumor grade could account for the better survival of ICC over IDC.

As the largest analysis of ICC to date, we summarized the clinicopathological characteristics of ICC. This special histologic type exhibits lower grade, smaller tumor size, lesser lymph nodes involvement, earlier stage, higher positivity rate of hormone expression, and lower HER2 amplification rate than IDC, some of which were concordant with previous studies.[5,6,8] The survival of ICC was significantly better than IDC in univariate analysis, which was in line with previous studies.[1,5] However, after multivariate Cox regression analysis adjusting for potential confounders, we found no survival advantage in ICC compared with IDC. Furthermore, after 1:1 matching of ICC with IDC by age, tumor stage, tumor grade, ER status, and PR status, ICC showed nearly the same outcomes as IDC in DSS and OS. Collectively, these results imply that the ICC histological type is not an independent prognostic factor. To find underlying factors contributing to this phenomenon, we conducted subgroup analyses. Results from subgroup analyses showed that the prognostic superiority of ICC was not exhibited in tumor grade subgroups, indicating that different survival outcomes between ICC and IDC primarily resulted from the distribution of tumor grade in the 2 tumor types.

Limited information about tumor grade has been reported in previous studies. Page et al and Venable et al only reported the nuclear grade information.[1,5] In Louwman's study, the percentage of grade 1 was only 19%, while 50% of the tumor lacked of grade information.[6] Colleoni et al[7] presented a much higher rate of grade 1 (89.6%) for the pure ICCs in their study. Analyses were sporadically reported on the value of tumor grade in ICC. Dawson et al conducted a multivariate analysis of tumor type, tumor grade, and blood vessel invasion, and found these factors to be of prognostic value.[4] Louwman et al observed better age-, stage- and grade-adjusted prognosis for patients with lobular, mucinous, medullary, and tubular but not papillary or cribriform.[6] Colleoni et al[7] conducted a multivariate analysis in a subgroup of grade 1 breast cancer and showed that there were no significant differences between ICCs and IDCs both in disease-free survival and OS. However, none of these studies systematically and convincingly proved the dominating prognostic value of tumor grade in ICCs. Our study support the hypothesis that tumor grade is a predominant prognostic factor in the subtype of ICC, as the results showed in subgroup analysis and matched comparison. The underlying mechanisms for the prognostic value of tumor grade may be

explained by the followings. Subjectively, tumor grading system judged by pathologists combined the cell morphology (nuclear pleomorphism), differentiation (tubule formation) and proliferation conditions (mitotic counts) by the criteria of grading judging. Lower grade describes a cancer with tubular structure, less nuclear pleomorphism and less mitosis, and points to a carcinoma with less invasive biologic behaviors. Objectively, there is an association between tumor grade and molecular markers of tumor proliferation and differentiation. Poorer tumor grade presented higher Ki-67 index,[10] more DNA aneuploidy,[11] increased expression of epidermal growth factor receptor[12] and HER2 expressions,[13] as well as a more rapid replication in cell kinetic studies.[14]

Inevitably, our study had several limitations. First, records of Ki-67 expression, adjuvant chemotherapy and endocrine therapy are not available in the current SEER database, which concealed important prognostic factors for researchers. Second, ICC consists of 2 subtypes, pure and mixed, which shared disparity in immunohistochemical characteristics and survival. SEER database, however, does not distinguish between these 2 types of ICC. Furthermore, we used the propensity score method to complete our matching. In the procedure, 618 IDCs matched with ICCs were selected randomly from the patient population, and may be a cause for sampling bias and decrease the external validity of our study.

Our investigations revealed that ICCs have unique clinicopathological characteristics, higher rates of breast-conserving surgery and favorable prognosis compared to the overall IDC population. However, this advantage diminishes after adjusting for tumor grade and other clinicopathological factors. Further validation in large population may help clarify this problem. Improved clinical and biological understanding of ICC might lead to more individualized and tailored therapy for breast cancer patients.

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