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ORIGINAL ARTICLE

Comparative analysis of clinicopathologic characteristics and molecular subtypes of invasive papillary carcinoma of the breast and invasive ductal carcinoma: results from SEER database

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Summary

Purpose: *To investigate the difference of clinicopathologic characteristics and prognosis between invasive papillary carcinoma (IPC) and invasive ductal carcinoma (IDC) in breast cancer patients, and to further confirm the influence of molecular subtype on prognosis of IPC.*

Methods: *A total of 158,132 eligible patients from 2010 to 2015 were identified from the Surveillance, Epidemiology, and End Results (SEER) database, of which 348 patients were IPC and 157,784 patients were IDC. We assessed the clinicopathologic characteristics, molecular subtypes and prognostic value of IPC and compared them with those of IDC.*

Results: *IPC was more frequently presented with older age at diagnosis, less proportion of married and white race, lower grade, smaller tumor size, higher rates of negative nodal status, more AJCC stage I disease and HR+/Her2- breast cancer, and was less likely to be treated with mastectomy, chemotherapy, and radiation therapy than IDC ($p<0.05$). IPC had a better 5-year breast cancer-specific survival (BCSS) and overall survival (OS) rates than IDC. After adjusting confounding and matching the confounding factors, IPC patients were still associated with better BCSS. Regarding patients with specific subtypes, patients with IPC had more HR+/Her2- subtypes. In addition, HR+/Her2--IPC patients had a better BCSS than HR+/Her2--IDC patients, but OS was similar between the two groups. However, BCSS and OS did not differ in the two groups after matching the confounding factors. Subgroup analysis indicated that molecular subtype may be the main confounding factor in IPC prognosis.*

Conclusions: *IPC showed more favorable behavior than IDC, but prognosis was not as favorable as people once thought. The determination of the appropriate therapeutic regimen for IPC still needs to be made according to risk factors such as histological grade, pathological stage and molecular subtype.*

Key words: *breast cancer, invasive papillary carcinoma, invasive ductal carcinoma, clinicopathologic characteristic, prognosis, molecular subtype*

Introduction

Invasive papillary carcinoma (IPC) is a distinct rare type of invasive breast tumor. The incidence rate of IPC is reported to account for less than 0.5-1.7% of all breast cancers [1-5]. The actual situation may be much lower than that reported in the literature. Most physicians might have not a good knowledge of IPC due to the scarcity of cases. Most of the current studies are based on the data from a single center with small samples [6-8]. There is no enough information to learn whether this special morphologic entity of breast cancer represents its own biological features. Especially after 2010,

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breast cancer was classified into new categories by gene testing and immunohistochemistry. The rare large sample retrospective studies did not include data on molecular subtype and its influence on IPC prognosis [9,10].

As we all know, endocrine therapy and chemotherapy have made monumental achievements in the treatment of breast cancer till now, but previous studies did not include such an information. Our hope was to discover the clinical characteristics, molecular subtypes and prognosis information of IPC treated by these current comprehensive treatments through big data.

Methods

Data resource and patient selection

Data was collected from the US Surveillance, Epidemiology, and End Results (SEER) 18 registries database (November 2018 submission, 1975-2016) from the National Cancer Institute (http://www.seer.cancer.gov/seerstat), which currently covers 27.8% of the United States population. SEER*Stat version 8.3.8 was utilized to identify eligible patients according to the following inclusion criteria: (1) female; (2) patients diagnosed between 2010-2015; (3) age of diagnosis between 18 and 79 years; (4) pathologically confirmed invasive papillary carcinoma (IPC, ICD-O-3 8050/3) or infiltrating ductal carcinoma, not otherwise specified (IDC-NOS, ICD-O-3 8500/3); (4) American Joint Committee on Cancer (AJCC) stages I-III; (5) known tumor and nodal stage; (6) known laterality (left, right or only one side); (7) known breast subtype; (8) surgical treatment with either mastectomy or breast conserving surgery; (9) have record of radiation therapy and chemotherapy; (10) breast cancer as the first and only cancer diagnosis; (11) patients with complete survival data. Patients diagnosed with breast cancer before 2010 were not included because HER2 status were available only after 2010. In addition, in order to ensure adequate follow-up time, patients diagnosed with breast cancer after 2015 were not included. Therefore, a total of 158,132 patients were included, of which 348 were diagnosed with IPC, and the remaining 157,784 were diagnosed with IDC. Figure 1 shows the selection process and the final number of cases included in our present analysis.

Data collection and outcomes

The following factors were extracted: demographic factors (age at diagnosis, marital status and race), clinicopathological factors (laterality, histologic grade [11], tumor size, lymph node status, AJCC stage (AJCC Staging Manual 6th edition) [12], breast subtype, therapeutic factors (surgery of primary site, radiotherapy, chemotherapy), and survival factors (death events and survival months).

Overall survival (OS) was calculated from the date of diagnosis to the date of death from any cause or last follow-up. Breast cancer-specific survival (BCSS) was calculated from the date of diagnosis to the date of death due to breast cancer.

Statistics

The statistical analyses were done by the SPSS version 26.0 software (IBM SPSS Statistics). In descriptive statistics, the continuous variables were described as median and range. The categorical variables were described as frequencies and percentages. Chi square was used to compare categorical variables. The Kaplan-Meier method was used to generate survival curves, and the log-rank test was performed to assess the differences in BCSS and OS. Multivariate Cox proportional hazard regression analysis was used to analyze the independent factors associated with prognosis. Results were expressed in HRs and 95% CIs. A two-side $p<0.05$ was thought to be statistically significant.

In addition, we used propensity matching in SPSS which was designed for the propensity score matching methods and tested the matching quality for the balance after the match. We matched each IPC patient to 1 IDC patient by using the following predetermined factors: age, race, marital status, laterality, tumor grade, tumor size, nodal status, AJCC stage, breast subtype, surgery type, receipt of radiation therapy and chemotherapy. In consideration of the fact that the majority of IPC cases were HR+/Her2- breast cancer, a planned secondary survival comparison within HR+/Her2- patients was also conducted.

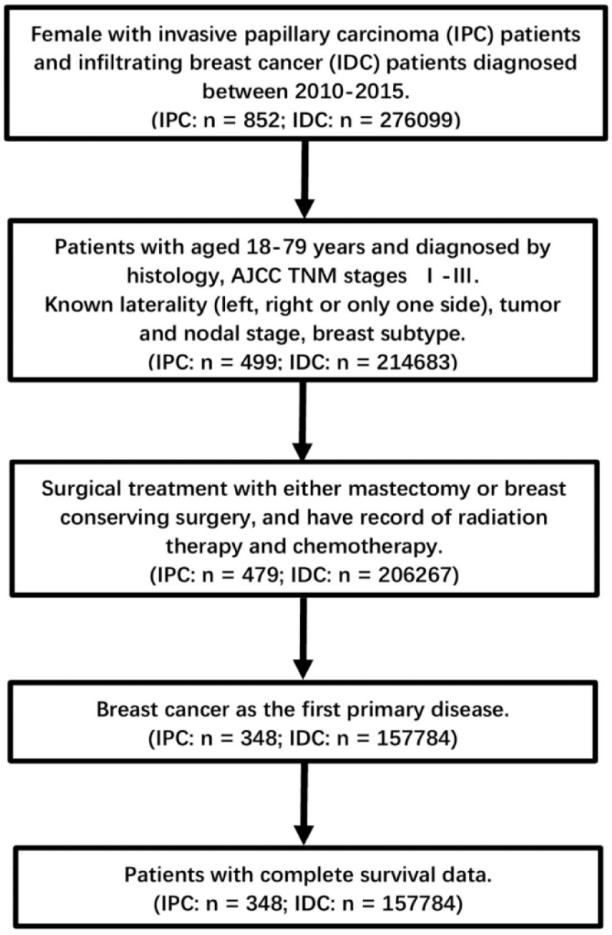

Figure 1. Selection process of our defined population.

Table 1. Characteristics of patients with invasive papillary carcinoma and infiltrating ductal carcinoma

Characteristics	*IPC (n=348)*		*IDC (n=157784)*		*Total (n=158132)*		*p*[c]
	No.	*%*	*No.*	*%*	*No.*	*%*	
Median follow-up (months)	41 (1-83)		41 (0-83)		41 (0-83)		
Age (years)							
18-49	49	14.1	41934	26.6	41983	26.5	<0.001
50-79	299	85.9	115850	73.4	116149	73.5	
Marital status							
Married	172	49.4	93473	59.2	93645	59.2	<0.001
Not married[a]	153	44.0	56832	36.0	56985	36.0	
Unknown	23	6.6	7479	4.7	7502	4.7	
Race							
White	233	67.0	122346	77.5	122579	77.5	<0.001
Black	53	15.2	17969	11.4	18022	11.4	
Other[b]	54	15.5	16453	10.4	16507	10.4	
Unknown	8	2.3	1016	0.6	1024	0.6	
Laterality							
Left	177	50.9	79824	50.6	80001	50.6	0.958
Right	171	49.1	77947	49.4	78118	49.4	
Only one side NOS	0	0.0	13	0.0	13	0.0	
Grade							
1	134	38.5	32803	20.8	32937	20.8	<0.001
2	124	35.6	63603	40.3	63727	40.3	
3 and 4	42	12.1	57563	36.5	57605	36.4	
Unknown	48	13.8	3815	2.4	3863	2.4	
Tumor size (cm)							
≤2	239	68.7	99928	63.3	100167	63.3	0.012
>2 and ≤5	80	23.0	47434	30.1	47514	30.0	
>5	29	8.3	10422	6.6	10451	6.6	
Nodal status							
Negative	306	87.9	108219	68.6	108525	68.6	<0.001
Positive	42	12.1	49565	31.4	49607	31.4	
AJCC stage							
I	223	64.1	81407	51.6	81630	51.6	<0.001
II	107	30.7	59321	37.6	59428	37.6	
III	18	5.2	17056	10.8	17074	10.8	
Breast subtype							
HR+/Her2-	307	88.2	109906	69.7	110213	69.7	<0.001
HR+/Her2+	13	3.7	19280	12.2	19293	12.2	
HR-/Her2+	4	1.1	8411	5.3	8415	5.3	
HR-/Her2-	24	6.9	20187	12.8	20211	12.8	
Type of surgery							
BCS	247	71.0	95249	60.4	95496	60.4	<0.001
Mastectomy	101	29.0	62535	39.6	62636	39.6	
Radiation							
No	176	50.6	65340	41.4	65516	41.4	0.001
Yes	172	49.4	92444	58.6	92616	58.6	
Chemotherapy							
No	289	83.0	82683	52.4	82972	52.5	<0.001
Yes	59	17.0	75101	47.6	75160	47.5	

IPC: invasive papillary carcinoma; IDC: invasive ductal carcinoma; AJCC: American Joint Committee on Cancer; HR: hormone receptor; Her2: human epidermal growth factor receptor 2; BCS: breast conserving surgery; NOS: no otherwise specificied.
[a]Not married includes divorced, separated, single (never married), unmarried or domestic partner and widowed.
[b]Other includes American Indian/Alaskan native, and Asian/Pacific Islander.
[c]p value was calculated among all groups by the x^2, and a bold type indicates significance.

Results

Clinicopathologic characteristics of IPCs and IDCs

A total of 158,132 breast cancer patients who met the eligibility criteria were selected, of which 348 patients were IPC and 157,784 patients were IDC. The process of patient selection is shown in Figure 1. The median follow-up time of IPC was 41 (1-83) months, and that of IDC was 41 (0-83) months. Table 1 summarizes all of the clinical characteristics and treatment patterns according to the histological subtype. There were considerable differences in age, marital status, race, histological grade, tumor size, nodal status, AJCC stage and breast subtype between the two populations. IPC group had more older patients than IDC group (age ≥ 50 years: 85.9% vs. 73.5%, p<0.001). Compared with IPC group, there were more married (59.2% vs. 49.4%, p<0.001) and white race (77.5% vs. 67.0%, p<0.001) patients in IDC group. IPC patients were more frequently present with grade 1 disease (38.5% vs. 20.8%, p<0.001), smaller tumor size (≤ 2cm: 68.7% vs. 63.3%, p=0.012), negative nodal status (87.9% vs. 68.6%, p<0.001), and AJCC stage I disease (64.1% vs. 51.6%, p<0.001) than IDC patients. In terms of breast subtype, the proportion of HR+/Her2- breast cancer was significantly higher in IPC than in IDC (88.2% vs. 69.7%, p<0.001). The treatment patterns of the two groups were also significantly different. IPC patients underwent BCS more frequently than IDC patients (71.0% vs. 60.4%, p<0.001). However, IDC patients were more likely to receive radiation therapy (58.6% vs. 49.4%, p=0.001) and chemotherapy (47.6% vs. 17.0%, p<0.001) than IPC patients.

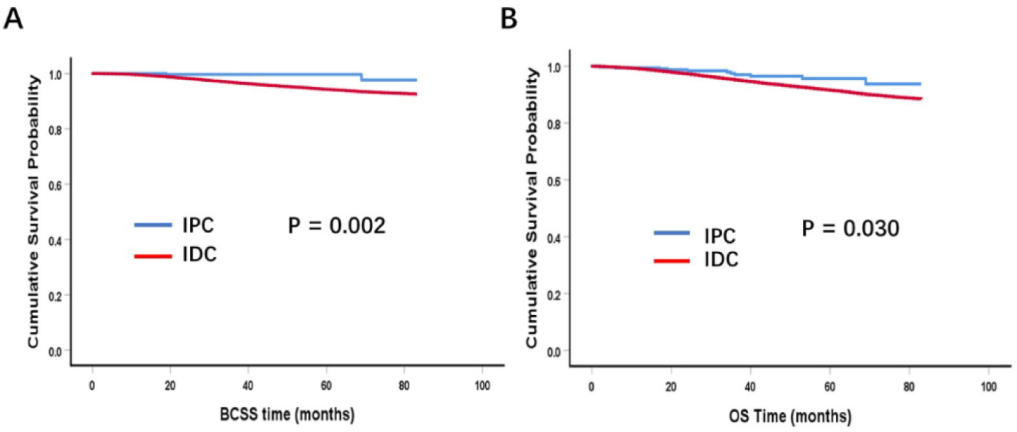

Figure 2. Kaplan-Meier plot and log-rank test compared breast cancer-specific survival (BCSS, **A**) and overall survival (OS, **B**) by histology for all patients, invasive papillary carcinoma (IPC) vs. infiltrating ductal carcinoma (IDC). The 5-year BCSS rates in IPC and IDC were 99.7% and 94.2% respectively, and 5-year OS rates in IPC and IDC were 95.7% and 91.5% respectively. Kaplan-Meier analysis showed that IPC patients had a better prognosis (BCCS: p=0.002; OS: p=0.030) than IDC patients.

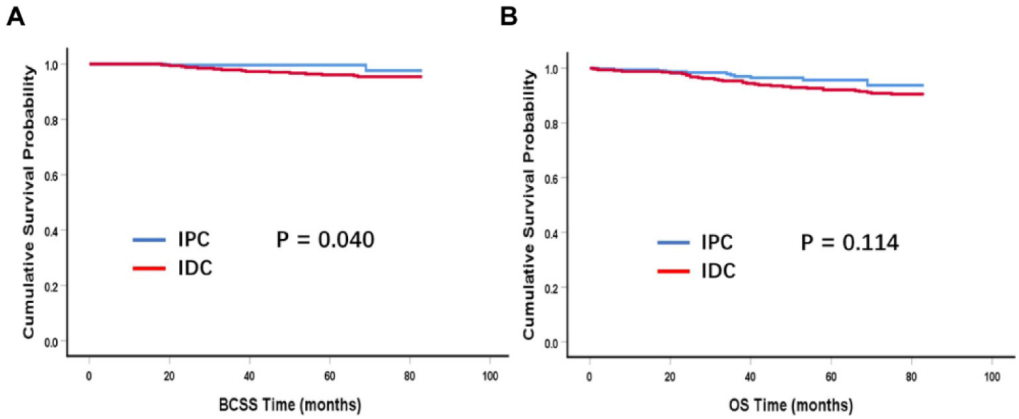

Figure 3. Kaplan-Meier plot and log-rank test compared breast cancer-specific survival (BCSS, **A**) and overall survival (OS, **B**) by histology for 1:1 matched group, invasive papillary carcinoma (IPC) vs. infiltrating ductal carcinoma (IDC). We performed a 1:1 (IPC:IDC) matched case control analysis utilizing the propensity score matching method. After matching, we found that IPC patients still had better BCSS than IDC patients (Figure 3, 5-year BCSS rates: 99.7% vs. 96.1%, p=0.040), but this result was not shown for OS (Figure 3, 5-year OS rates: 95.7% vs. 92.1%, p=0.114).

Survival outcomes of IPCs and IDCs

The median follow-up time was 41 months (range: 0-83). The 5-year BCSS rates in IPC and IDC were 99.7% and 94.2% respectively, and 5-year OS rates in IPC and IDC were 95.7% and 91.5%, respectively. Kaplan-Meier analysis showed that IPC patients had a better prognosis (BCCS: p=0.002; OS: p=0.030) than IDC patients (Figure 2). We further analyzed the predictive factors for outcomes of IPC and IDC patients (Table 2). Adjusting for the significant prognostic variables (age, marital status, race, grade, AJCC stage, breast subtype, type

Table 2. Multivariate Cox proportional hazard model of breast cancer-specific survival (BCSS) and overall survival (OS)

Variables	*BCSS*		*OS*	
	HRs (95%CI)	*p*[c]	*HRs (95%CI)*	*p*[c]
Age (years)				
18-49	Reference	-	Reference	-
50-79	1.166 (1.104-1.232)	<0.001	1.477 (1.407-1.551)	<0.001
Marital status				
Married	Reference	-	Reference	-
Not married [a]	1.216 (1.153-1.281)	<0.001	1.435 (1.375-1.497)	<0.001
Unknown	1.028 (0.909-1.162)	0.661	1.156 (1.049-1.274)	0.004
Race				
White	Reference	-	Reference	-
Black	1.357 (1.274-1.446)	<0.001	1.297 (1.230-1.367)	<0.001
Other [b]	0.738 (0.668-0.815)	<0.001	0.713 (0.657-0.774)	<0.001
Unknown	0.279 (0.139-0.558)	<0.001	0.251 (0.142-0.441)	<0.001
Grade				
1	Reference	-	Reference	-
2	2.532 (2.154-2.976)	<0.001	1.320 (1.217-1.431)	<0.001
3 and 4	3.884 (3.122-4.832)	<0.001	1.705 (1.473-1.975)	<0.001
Unknown	5.382 (4.583-6.322)	<0.001	2.260 (2.080-2.456)	<0.001
Histologic type				
IPC	Reference	-	Reference	-
IDC	4.444 (1.110-17.783)	0.035	1.686 (0.932-3.048)	0.084
AJCC stage				
I	Reference	-	Reference	-
II	3.115 (2.869-3.383)	<0.001	2.131 (2.016-2.253)	<0.001
III	10.924 (9.999-11.934)	<0.001	6.691 (6.278-7.132)	<0.001
Breast subtype				
HR+/Her2-	Reference	-	Reference	-
HR+/Her2+	0.740 (0.676-0.810)	<0.001	0.826 (0.769-0.889)	<0.001
HR-/Her2+	1.048 (0.948-1.158)	0.363	1.046 (0.959-1.140)	0.313
HR-/Her2-	2.490 (2.341-2.648)	<0.001	2.248 (2.132-2.370)	<0.001
Type of surgery				
BCS	Reference	-	Reference	-
Mastectomy	1.338 (1.261-1.418)	<0.001	1.206 (1.150-1.265)	<0.001
Radiation				
No	Reference	-	Reference	-
Yes	0.789 (0.747-0.834)	<0.001	0.716 (0.684-0.749)	<0.001
Chemotherapy				
No	Reference	-	Reference	-
Yes	0.876 (0.815-0.935)	<0.001	0.642 (0.610-0.676)	<0.001

For abbreviations see footnote of Table 1.
[b] Other includes American Indian/Alaskan native, and Asian/Pacific Islander.
[c] p value was adjusted by multivariate Cox proportional hazard regression model including all factors, as categorized in Table 2.

Table 3. Characteristics of patients with invasive papillary carcinoma and infiltrating ductal carcinoma in 1:1 matched group

Characteristics	*IPC (n=348)*		*IDC (n=348)*		*Total (n=696)*		*p*[c]
	No.	*%*	*No.*	*%*	*No.*	*%*	
Median follow-up (months)	41 (1-83)		79 (0-83)		69 (0-83)		
Age (years)							
18-49	49	14.1	68	19.5	117	16.8	0.054
50-79	299	85.9	280	80.5	579	83.2	
Marital status							
Married	172	49.4	180	51.7	352	50.6	0.226
Not married[a]	153	44.0	155	44.5	308	44.3	
Unknown	23	6.6	13	3.7	36	5.2	
Race							
White	233	67.0	205	58.9	438	62.9	<0.001
Black	53	15.2	31	8.9	84	12.1	
Otherb	54	15.5	99	28.4	153	22.0	
Unknown	8	2.3	13	3.7	21	3.0	
Laterality							
Left	177	50.9	195	56.0	372	53.4	0.171
Right	171	49.1	153	44.0	324	46.6	
Grade							
1	134	38.5	105	30.2	239	34.3	<0.001
2	124	35.6	164	47.1	288	41.4	
3 and 4	42	12.1	70	20.1	112	16.1	
Unknown	48	13.8	9	2.6	57	8.2	
Tumor size (cm)							
≤2	239	68.7	216	62.1	455	65.4	0.116
>2 and ≤5	80	23.0	104	29.9	184	26.4	
>5	29	8.3	28	8.0	57	8.2	
Nodal status							
Negative	306	87.9	290	83.3	596	85.6	0.084
Positive	42	12.1	58	16.7	100	14.4	
AJCC stage							
I	223	64.1	195	56.0	418	60.1	0.095
II	107	30.7	130	37.4	237	34.1	
III	18	5.2	23	6.6	41	5.9	
Breast subtype							
HR+/Her2-	307	88.2	284	81.6	591	84.9	0.008
HR+/Her2+	13	3.7	34	9.8	47	6.8	
HR-/Her2+	4	1.1	8	2.3	12	1.7	
HR-/Her2-	24	6.9	22	6.3	46	6.6	
Type of surgery							
BCS	247	71.0	257	73.9	504	72.4	0.396
Mastectomy	101	29.0	91	26.1	192	27.6	
Radiation							
No	176	50.6	151	43.4	327	47.0	0.058
Yes	172	49.4	197	56.6	369	53.0	
Chemotherapy							
No	289	83.0	260	74.7	549	78.9	0.007
Yes	59	17.0	88	25.3	147	21.1	

For abbreviations see footnote of Table 1.

of surgery, radiation therapy and chemotherapy) in univariate analysis, multivariate analysis indicated that the IDC patients showed significantly worse BCSS than IPC patients (HRs=4.444, 95%, CI: 1.110-17.783, p=0.035) and this result was no longer shown for OS (HRs=1.686, 95%, CI: 0.932-3.048, p=0.084).

Survival analysis in matched groups of IPCs and IDCs

Considering that there were many confounding factors that would affect the prognosis of IDC and IPC, we performed a 1:1 (IPC:IDC) matched case control analysis utilizing the propensity score matching method. A total of 696 patients were obtained, including 348 patients in each group. For matched groups, no significant difference in characteristics except race (p<0.001), grade (p<0.001), breast subtype (p=0.008) and receipt of chemotherapy (p=0.007) was observed between IPC and IDC group (Table 3). After matching, we found that IPC patients still had better BCSS than IDC patients (Figure 3, 5-year BCSS rates: 99.7% vs. 96.1%, p=0.040), but this result was not shown for OS (Figure 3, 5-year OS rates: 95.7% vs. 92.1%, p=0.114).

Clinical characteristics and survival outcomes in HR+/Her2- subgroup

Since the majority of IPC patients were HR+/Her2- breast cancer according to molecular subtype (p<0.001), then we analyzed characteristics

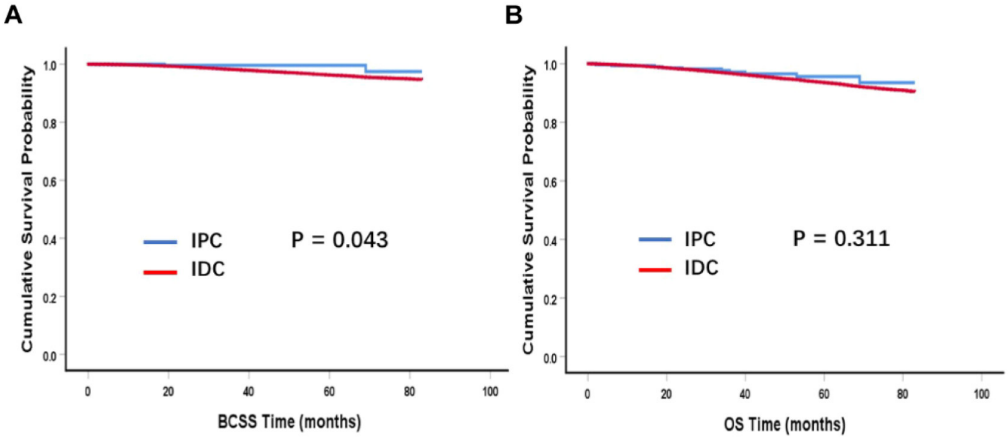

Figure 4. Kaplan-Meier plot and log-rank test compared breast cancer-specific survival (BCSS, **A**) and overall survival (OS, **B**) by histology for HR+/Her2- breast cancer patients, invasive papillary carcinoma (IPC) vs. infiltrating ductal carcinoma (IDC). Kaplan-Meier analysis showed that HR+/Her2--IPC patients had a better BCSS (5-year BCCS: 99.6% vs. 96.2%, p=0.043) than HR+/Her2--IDC patients, but OS was no longer significantly different between the two groups (5-year OS: 95.6% vs. 93.5%, p=0.311).

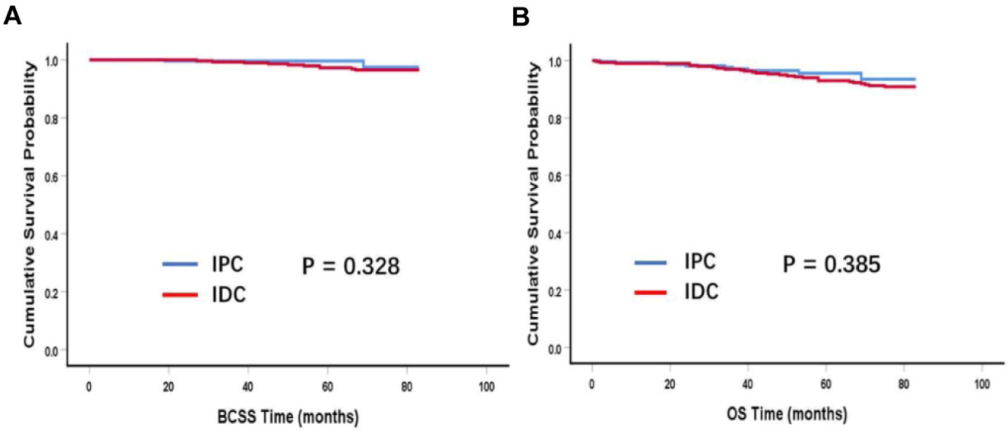

Figure 5. Kaplan-Meier plot and log-rank test compared breast cancer-specific survival (BCSS, **A**) and overall survival (OS, **B**) by histology for 1:1 matched HR+/Her2- breast cancer patients, invasive papillary carcinoma (IPC) vs. infiltrating ductal carcinoma (IDC). We also used propensity score matching method to match 307 HR+/Her2--IPC patients to 307 HR+/Her2--IDC patients. And then we found that both BCSS and OS had no difference between the two groups (BCSS: p=0.328; OS: p=0.385).

Table 4. Characteristics of patients with HR+/Her2- invasive papillary carcinoma and HR+/Her2- infiltrating ductal carcinoma

Characteristics	*IPC (n=307)*		*IDC (n=109906)*		*Total (n=110213)*		*p* [c]
	No.	*%*	*No.*	*%*	*No.*	*%*	
Median follow-up (months)	41 (1-83)		42 (0-83)		42 (0-83)		
Age (years)							
18-49	36	11.7	26336	24.0	26372	23.9	<0.001
50-79	271	88.3	83570	76.0	83841	76.1	
Marital status							
Married	156	50.8	65283	59.4	65439	59.4	0.007
Not married [a]	131	42.7	39419	35.9	39550	35.9	
Unknown	20	6.5	5204	4.7	5204	4.7	
Race							
White	211	68.7	87518	79.6	87729		<0.001
Black	40	13.0	10245	9.3	10285	9.3	
Otherb	49	16.0	11414	10.4	11463	10.4	
Unknown	7	2.3	729	0.7	736	0.7	
Laterality							
Left	159	51.8	55266	50.3	55425	50.3	0.862
Right	148	48.2	54633	49.7	54781	49.7	
Only one side NOS	0	0.0	7	0.0	7	0.0	
Grade							
1	132	43.0	31368	28.5	31500	28.6	<0.001
2	111	36.2	51506	46.9	51617	46.8	
3 and 4	20	6.5	24906	22.7	24926	22.6	
Unknown	44	14.3	2126	1.9	2170	2.0	
Tumor size (cm)							
≤2	219	71.3	76414	69.5	76633	69.5	0.020
>2 and ≤5	65	21.2	28336	25.8	28401	25.8	
>5	23	7.5	5156	4.7	5179	4.7	
Nodal status							
Negative	271	88.3	78091	71.1	78362	71.1	<0.001
Positive	36	11.7	31815	28.9	31851	28.9	
AJCC stage							
I	204	66.4	62814	57.2	63018	57.2	0.002
II	88	28.7	37612	34.2	37700	34.2	
III	15	4.9	9480	8.6	9495	8.6	
Type of surgery							
BCS	221	72.0	71060	64.7	71281	64.7	0.007
Mastectomy	86	28.0	38846	35.3	38932	35.3	
Radiation							
No	156	50.8	42715	38.9	42871	38.9	<0.001
Yes	151	49.2	67191	61.1	67342	61.1	
Chemotherapy							
No	277	90.2	73006	66.4	73283	66.5	<0.001
Yes	30	9.8	36900	33.6	36930	33.5	

For abbreviations see footnote of Table 1.

and survival outcomes of the patients with HR+/Her2- subgroup. The cohort contained 307 IPC patients and 109,906 IDC patients (Table 4), and we got the same results as the whole population. HR+/Her2--IPC patients had younger age at diagnosis, less proportion of married status, white race and higher grade, higher proportion of smaller tumor size, negative nodal status and AJCC stage I disease than HR+/Her2--IDC patients (p<0.001), and the treatment patterns of the two groups were also the same as the whole population. Kaplan-Meier analysis showed that HR+/Her2--IPC patients had a better BCSS (5-year BCCS: 99.6% vs. 96.2%, p=0.043) than HR+/Her2--IDC patients, but OS was no longer significantly different between the two groups (5-year OS: 95.6% vs. 93.5%, p=0.311) (Figure 4). In addition, we also used propensity score matching method to match 307 HR+/Her2--IPC patients to 307 HR+/Her2--IDC patients (Supplementary Table S1), and then we found that both BCSS and OS had no difference between the two groups (BCSS: p=0.328; OS: p=0.385) (Figure 5).

Subgroup analysis with molecular subtype

In order to further analyze the effect of molecular subtype on the prognosis of breast cancer in IPC and IDC patients, multivariate Cox proportional hazard regression analysis was carried out and stratified by molecular subtype (Table 5). There was no difference between BCSS and OS in the two histological groups, suggesting that molecular subtype may be the main confounding factor in IPC prognosis.

Discussion

Due to the low incidence of IPC in breast cancer, previous studies have produced limited data regarding IPC characteristics, and only few studies have reported the outcome. We used SEER population-based data to try to make a detailed comparison in characteristics and outcomes between IPC and IDC, and revealed the influence of molecular subtype on IPC prognosis. The results of this study showed that IPC patients had different clinical characteristics from IDC patients, and had lower proportion of receiving mastectomy, chemotherapy and radiation therapy than IDC patients. IPC patients had more favorable prognosis than IDC patients both in BCSS and OS. After adjusting and matching the confounding factors, IPC patients still showed better outcomes in BCSS, but not in OS than IDC patients. In addition, our findings indicated that HR+/Her2--IPC patients had the same characteristics and treatment patterns as the whole IPC population, and had a better BCSS than HR+/Her2--IDC patients, but OS was similar between the two groups. However, BCSS and OS did not differ in the two groups after matching the confounding factors. Subgroup analysis indicated that molecular subtype may be the main confounding factor in IPC prognosis.

Our study indicated that compared with IDC, IPC usually has favorable behavior. Several reports have shown that IPC usually occurs in elderly women [13-16] and may be more frequently present with low or intermediate grade disease

Table 5. Comparison of breast cancer-specific survival (BCSS) and overall survival (OS) between invasive papillary carcinoma (IPC) and infiltrating ductal carcinoma (IDC) after subgroup analyses by multivariate Cox proportional hazard model

Subtype	*BCSS*			*OS*		
	Events No.	*HRs (95%CI)*	*p*	*Events No.*	*HRs (95%CI)*	*p*
HR+/Her2-			0.165			0.242
IPC (n=307)	2	Reference		10	Reference	
IDC (n=109906)	2720	2.676 (0.667-10.736)		4944	1.451 (0.778-2.703)	
HR+/Her2+			0.921			0.884
IPC (n=13)	0	Reference		0	Reference	
IDC (n=19280)	595	-		924	-	
HR-/Her2+			0.979			0.974
IPC (n=4)	0	Reference		0	Reference	
IDC (n=8411)	478	-		631	-	
HR-/Her2-			0.813			0.218
IPC (n=24)	0	Reference		1	Reference	
IDC (n=20187)	2368	-		2893	3.427 (0.482-24.348)	

For abbreviations see footnote of Table 1

[7], smaller tumor size, negative nodal status [7,9], and early stage [9] than IDC patients. Due to the favorable behavior, IPC patients underwent BCS more frequently than IDC patients, and had lower proportion of receiving chemotherapy and radiation therapy than IDC patients. In addition, this study is currently the largest analysis of molecular subtype in IPC. We found that IPC patients are more likely to be HR+/Her2- breast cancer, and the proportion of HR+/Her2- breast cancer is 88.2% in our study. Hashmi et al [6] have reported the same results, that is to say, the frequency of hormonal receptor expression (ER and PR) was higher, and the frequency of human epidermal growth factor receptor 2 (HER2/neu) expression was lower compared with IDC. However, these results are inconsistent with that of Liu et al [7], who have reported that there is no significant difference in molecular subtype between IPC and IDC, but there were only 284 IPC cases and 300 IDC cases in that report, and the study was a retrospective analysis from a single institution. Our study is a large patient cohort analysis from a multi-center institution, which can better represent the whole situation.

Our study found that IPC has a more favorable prognosis than IDC in BCSS and OS. Liu et al [7] have reported the same results that IPC was associated with a better 5-year OS (92.77% vs. 87.95%) and disease-free survival rate (87.95% vs. 80.72%) than IDC. Hashmi et al [6] have reported that the OS of SPC cases was over 90% with a low frequency of recurrence. This result may be explained by the fact that IPC has better prognostic features than IDC. We also found that after multivariate analysis and matching the confounding factors, IPC still showed a better BCSS than IDC. These results imply that the IPC-specific histological type is an independent prognostic factor for BCSS. However, IPC showed nearly the same outcomes as IDC in OS after adjusting and matching the potential confounders in our study. These results differed from a published study [9]. The authors have reported that survival (disease-specific survival and OS) was significantly better in IPC than in IDC in a univariate analysis, but both the survival advantage in IPC disappeared after multivariate Cox regression analysis. One possible explanation for this inconsistency might be that the data of those cases in the Zheng study were incomplete due to the long-time span (year of diagnosis between 2003-2012), especially for HER2 status. The proportion of unknown HER2 status was 66.3% in their study because HER2 status was available only after 2010. Information about chemotherapy also was not included in their analysis. A possible explanation for the lack of difference of OS between IPC and IDC was that the majority of patients with IPC were older than IDC and may die of other concomitant diseases.

As we all know, the molecular subtype is an important prognostic factor of breast cancer. The Luminal A subtype has shown a better outcome than the other subtypes [17-21]. As previously mentioned, we found that about 88.2% of IPC patients are HR+/Her2- breast cancer. The difference in clinical characteristic features and prognosis between HR+/Her2- IPC and HR+/Her2- IDC breast cancer is not clear. Our study is the first large report to reveal the differences between the two groups. HR+/Her2--IPC patients had the same characteristic features as the whole population. One interesting finding was that there was significant difference of BCSS between the two groups by Kaplan-Meier analysis. However, after matching the confounding factors, both BCSS and OS had nearly the same outcomes between IPC and IDC. It can therefore be assumed that breast cancer molecular subtype may be a confounding factor for IPC outcomes. Then, we further conducted the subgroup analysis with molecular subtype, and got the same results.

The results of this study may be helpful for the choice of treatment. We found that histologic type was an independent prognostic factor for BCSS after multivariate analysis and matching the confounding factors, but not for OS. And in most studies, the main factors that predict prognosis in early breast cancer are nodal status, tumor size and molecular subtype. Therefore, the choice of treatment should not be based solely on whether the pathological type is IDC or IPC which have similar clinical characteristic features, and other risk factors need to be considered as well. Furthermore, we found that better BCSS and OS were relevant to older age, grade 1, AJCC stage I, the subtype of HR+ breast cancer, and this result again proved the above point.

Our study has several limitations. First, the main limitation is its retrospective nature and internal bias. But the rare incidence rate of IPC makes it unlikely to conduct a randomized prospective study. Second, in order to reveal the influence of molecular subtype on prognosis of IPC, we eliminated the cases which were diagnosed before 2010 in SEER database. Apart from that, the SEER database lacks the information of Ki-67, the regimen of endocrine therapy and chemotherapy. These variables are likely to have some impact for the current diagnosis and treatment guidelines.

In conclusion, our investigations revealed that IPC has unique clinicopathologic characteristics and better prognosis than IDC. However, better

outcome in OS was diminished after adjusting and matching the demographic and clinicopathologic factors. It is worth noting that its biological characteristics are not as favorable as people once thought. Determination of the appropriate therapeutic regimen still needs to be made according to histologic grade, pathologic stage and molecular subtype. Prospective studies and large population follow-up can further help understand the biological behavior of IPC.

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Conflict of interests

The authors declare no conflict of interests.

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Supplementary Table S1. Characteristics of patients with HR+/Her2- invasive papillary carcinoma and HR+/Her2- infiltrating ductal carcinoma in 1:1 matched group

Characteristics	*IPC (n=307)*		*IDC (n=307)*		*Total (n=614)*		*p*
	No.	*%*	*No.*	*%*	*No.*	*%*	
Median follow-up (months)	41 (1-83)		79 (0-83)		70 (0-83)		
Age (years)							
18-49	36	11.7	47	15.3	83	13.5	0.194
50-79	271	88.3	260	84.7	531	86.5	
Marital status							
Married	156	50.8	150	48.9	306	49.8	0.243
Not married	131	42.7	145	47.2	276	45.0	
Unknown	20	6.5	12	3.9	32	5.2	
Race							
White	211	68.7	188	61.2	399	65.0	0.001
Black	40	13.0	23	7.5	63	10.3	
Other	49	16.0	86	28.0	135	22.0	
Unknown	7	2.3	10	3.3	17	2.8	
Laterality							
Left	159	51.8	165	53.7	324	52.8	0.628
Right	148	48.2	142	46.3	290	47.2	
Grade							
1	132	43.0	106	34.5	238	38.8	<0.001
2	111	36.2	155	50.5	266	43.3	
3 and 4	20	6.5	40	13.0	60	9.8	
Unknown	44	14.3	6	2.0	50	8.1	
Tumor size (cm)							
≤2	219	71.3	199	64.8	418	68.1	0.183
>2 and ≤5	65	21.2	84	27.4	149	24.3	
>5	23	7.5	24	7.8	47	7.7	
Nodal status							
Negative	271	88.3	263	85.7	534	87.0	0.338
Positive	36	11.7	44	14.3	80	13.0	
AJCC stage							
I	204	66.4	182	59.3	386	62.9	0.185
II	88	28.7	107	34.9	195	31.8	
III	15	4.9	18	5.9	33	5.4	
Type of surgery							
BCS	221	72.0	233	75.9	454	73.9	0.27
Mastectomy	86	28.0	74	24.1	160	26.1	
Radiation							
No	156	50.8	127	41.4	283	46.1	0.019
Yes	151	49.2	180	58.6	331	53.9	
Chemotherapy							
No	277	90.2	262	85.3	539	87.8	0.065
Yes	30	9.8	45	14.7	75	12.2	

For abbreviations see footnote of Table 1