The Impact of Breast Cancer Histology and Tumor Molecular Subtype on Nodal Positivity

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Introduction

- Previous studies have demonstrated higher rates of nodal metastasis in invasive lobular carcinoma (ILC) compared to invasive ductal carcinoma (IDC) of the breast.
- Although nodal burden also varies by tumor molecular subtype, how this relationship differs by histology is incompletely understood.
- ILC tumors are generally ER+ HER2 non-amplified with poor response to neoadjuvant chemotherapy.
- Recent data highlighting efficacy of targeted therapy in HER2 low disease provide the opportunity to identify additional patients for whom a neoadjuvant approach might confer a benefit.
- This study characterizes pathological nodal disease (pN+) among patients with clinically node negative (cN0) IDC and ILC hypothesizing that pN+ disease occurs more frequently in ER+ HER2 low ILC.

Methods and Materials

- The NCDB was queried for patients with cN0 invasive breast cancer from 2018-2021 who underwent surgery with axillary staging.
- HER2 IHC 1/2+ with FISH non-amplified was considered as HER2 low.
- Multivariable logistic regression was used to identify factors associated with pN+ in the entire cohort and for the cohort with ER+ disease adjusting for age, race, ethnicity, grade and subtype as well as the interaction between histology type and tumor size.

Table 1. Cohort Characteristics by Histologic Subtype

	Ductal (n=348,730)	Lobular (n=55,402)	P-value
Age, years			<.0001
Median (IQR)	63.0 (54.0,71.0)	65.0 (57.0,72.0)	
Race, n (%)			<.0001
White	290550 (84.1)	47727 (86.8)	
African American / Black	33492 (9.7)	4911 (8.9)	
Asian / Pacific Islander	16003 (4.6)	1573 (2.9)	
Other	5578 (1.6)	770 (12.1)	
Hispanic, n (%)			<.0001
Hispanic	20879 (6.1)	2881 (5.3)	
Non-Hispanic	321570 (93.9)	51521 (94.7)	
Tumor Size, n (%)			<.0001
≤ 1 mm	3806 (1.1)	330 (0.6)	
2-20 mm	261561 (75.5)	32886 (59.6)	
21-50 mm	75311 (21.7)	16807 (30.5)	
> 51 mm	5817 (1.7)	5128 (9.3)	
Pathological Nodal Positivity, n (%)			<.0001
Positive	54142 (15.5)	11344 (20.5)	
Negative	294588 (84.5)	44058 (79.5)	
Tumor Subtype, n (%)			<.0001
ER+/PR+/HER2+	17487 (5.0)	1340 (2.4)	
ER+/PR+/HER2-	256877 (73.7)	45003 (81.2)	
ER-/PR-/HER2+	6678 (1.9)	84 (0.2)	
ER-/PR-/HER2-	25300 (7.3)	461 (0.8)	
Unknown	42388 (12.2)	8514 (15.4)	

Results

- Of the 404,132 patients identified, 86.3% had IDC and 13.7% had ILC.
- Most patients had a tumor size of 2-20mm, well/moderately differentiated tumor grade and ER/PR+ and HER2- tumors (Table 1).
- Lobular histology was associated with greater pN+ (20.5% ILC vs 15.5% IDC; p<0.001).
- ER+ HER2 low lobular carcinomas had higher pN+ than IDC with similar molecular subtype (21.4% ILC vs 17% IDC; p<0.001).
- On multivariable analysis main effect of histology type was no longer significantly associated with nodal positivity for the entire cohort or for the cohort with ER+ tumors with no missing data on tumor molecular subtype (n=118,533) (Table 2).
- Increasing tumor size, age < 51 years, and African American race were associated with increased likelihood of pN+ disease.
- On assessing the interaction between tumor size and histology it was noted that ILC tumors sized 21-50mm had 7% lower odds of pN+ disease compared to IDC (aOR 0.93, 95% CI 0.87-1.00, p=0.039). However, ILC tumors sized ≥51 mm had 53% higher odds of pN+ disease compared to IDC patients (aOR 1.53, 95% CI 1.33-1.77).

Table 2. Factors Associated with pN+ Disease

Variables	Adjusted OR (95% CI)	P-value
Age (binary)		<0.001
<51	1.55 (1.49-1.61)	
51+	Ref	
Race		0.002
White	Ref	
African American/Black	1.07 (1.01-1.13)	
Asian/Pacific Islander	0.93 (0.87-1.00)	
Other	1.16 (1.02-1.32)	
Subtype		0.005
ER+ HER2 Negative	Ref	
ER+ HER2 Low	1.03 (0.99-1.07)	
ER+ HER2 Positive	0.93 (0.86-1.00)	
Interaction: Histology x Tumor Size		<0.001
Patients with tumor size≤1 mm		
Invasive Ductal Carcinoma	Ref	
Invasive Lobular Carcinoma	0.84 (0.11-6.81)	
Patients with tumor size 2-20 mm		
Invasive Ductal Carcinoma	Ref	
Invasive Lobular Carcinoma	1.01 (0.94-1.09)	
Patients with tumor size 21-50 mm		
Invasive Ductal Carcinoma	Ref	
Invasive Lobular Carcinoma	0.93 (0.87-1.00)	
Patients with tumor size ≥51 mm		
Invasive Ductal Carcinoma	Ref	
Invasive Lobular Carcinoma	1.53 (1.33-1.77)	

Conclusions

In this study, exploring the relationship of nodal positivity by tumor molecular subtype and breast cancer histology, tumor size was the dominant contributor to pN+ status. As such further investigation is needed to delineate which tumors, particularly as it relates to ILC, may benefit from novel upfront systemic therapy.

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