

BACKGROUND

- Invasive lobular carcinoma (ILC) was first described by Foote and Stewart in 1941.¹
- ILC comprises approximately 10% of all breast carcinomas.²
- Histologically, classic ILC tumor cells are small, form invasive columns, show low nuclear grade and infrequent mitoses, and more frequently express estrogen and progesterone receptors (ER, PR).³
- Clinically, ILC has an older age of onset, is less likely to present clinically as a discrete mass, has an increased propensity for multifocality/multicentricity, and has a higher risk of presenting as bilateral breast cancer.⁴
- Molecularly, ILC is characterized by a loss of the adhesion molecule E-cadherin as a result of a deletion of the CDH1 gene on chromosome 16 (del 16q).²
- Classic ILC may be associated with differences in clinical outcomes compared to IDC.⁴⁻⁶
- ILC variants (solid, alveolar, and pleomorphic) with distinct morphologies and potential differences in outcome have been described.^{2,7-9}
- Relatively small numbers of variant lobular forms have hindered attempts to molecularly define and compare them.³
- Recently, using reverse transcriptase polymerase chain reaction (RT-PCR) technology, a wide range of quantitative gene expression has been described in ductal carcinoma, NOS and the special histologic subtypes.¹⁰⁻¹¹

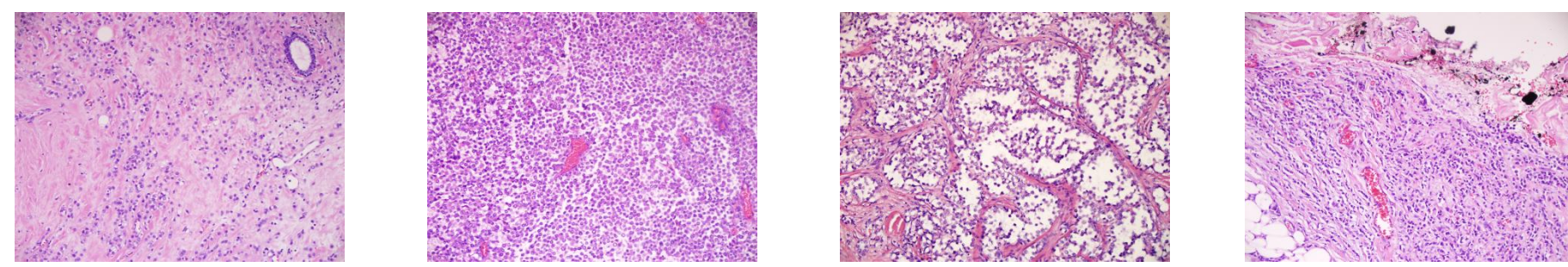


Figure 1. Lobular Carcinoma (CA): Classic and Variant Forms

STUDY OBJECTIVE

- To explore gene expression and patterns of gene expression in classic and variant forms of estrogen receptor-positive lobular carcinoma as measured by the 21 gene RT-PCR assay as compared to ductal carcinoma, NOS
 - To examine and compare the Oncotype DX[®] Recurrence Score[®] (RS) and quantitative expression of ER, PR, HER2, proliferation genes and invasion genes across the variant forms
 - To potentially identify gene expression levels or patterns characteristic of the variant forms of lobular carcinoma

STUDY DESIGN AND METHODS

- 133,234 tumor specimens examined in the central reference laboratory from June 2004 through March 2010 were included in these analyses.
- Board-certified surgical pathologists reviewed a single H&E slide from all specimens for invasive carcinoma and categorized them by histologic subtype using World Health Organization criteria.²
- Ductal carcinoma, NOS and classic and variant lobular carcinoma were included in the exploratory analyses.
- Descriptive statistics were calculated for the RS, individual genes (ER, PR, HER2), and gene groups (invasion and proliferation) for the different subtypes.
- Due to multiple comparisons of means (for all possible pairs of subtypes), significance levels were adjusted to control the overall false positive error rate under any complete or partial null hypothesis.
- Analyses performed on de-identified data with IRB approval.

RESULTS

Histologic Subtype	n	Percentage
Ductal carcinoma, NOS	120,449	90.4%
Classic lobular carcinoma	10,891	8.2%
Pleomorphic lobular carcinoma	1,019	0.8%
Solid/alveolar lobular carcinoma	875	0.7%

Table 1. Distribution of ILC and Variants in This Study

- As reported in the literature, the observed frequency of ILC and the variants was approximately 10%.
- As reported in the literature, classic ILC is the most frequent type of lobular carcinoma.

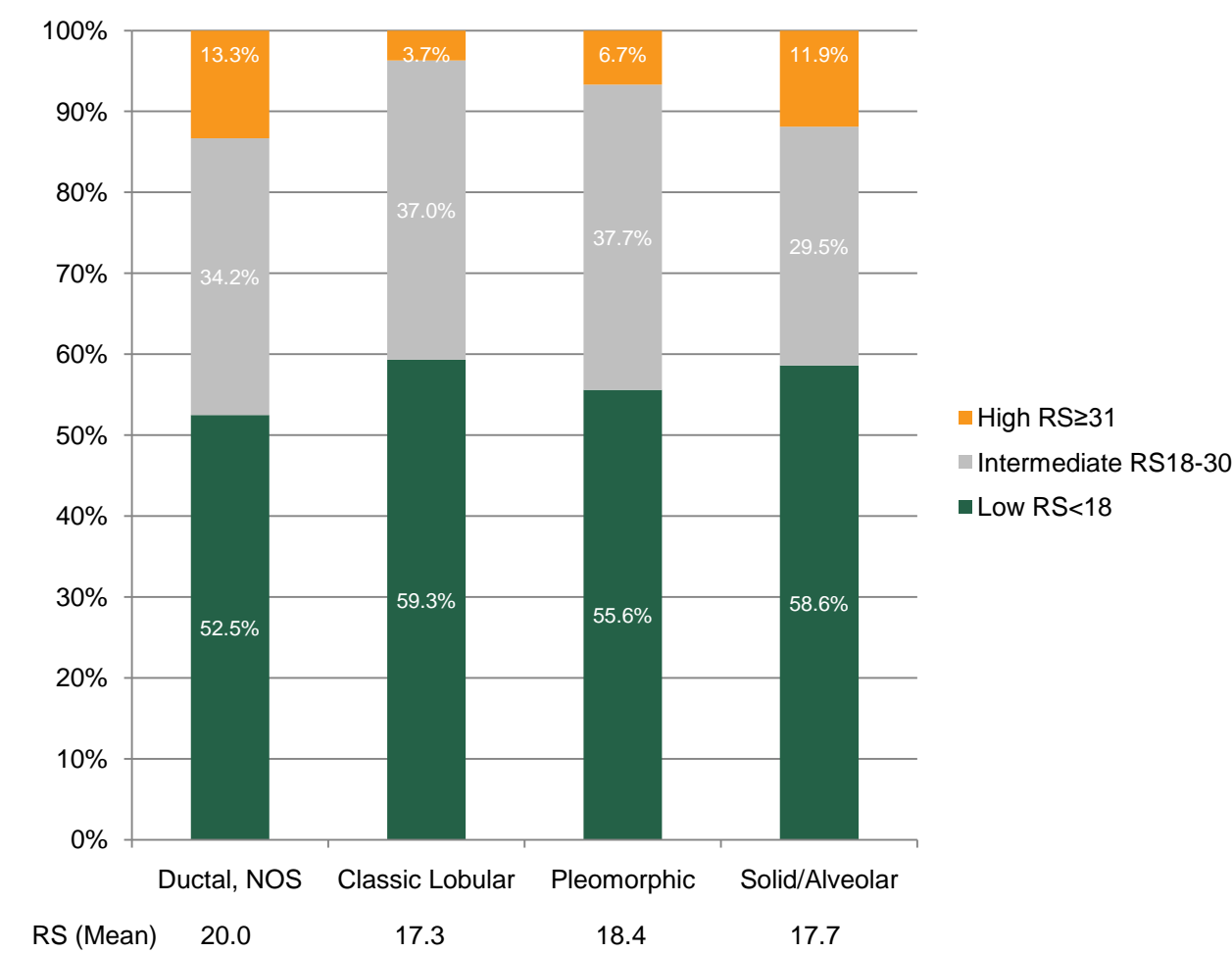


Figure 2. Distribution of RS Risk Groups by Histologic Subtype

- There is a wide range of Recurrence Score biology in all the lobular histologic subtypes.
- The classic lobular and pleomorphic lobular subtypes have fewer patients in the high RS group than solid/alveolar lobular and ductal carcinoma, NOS.

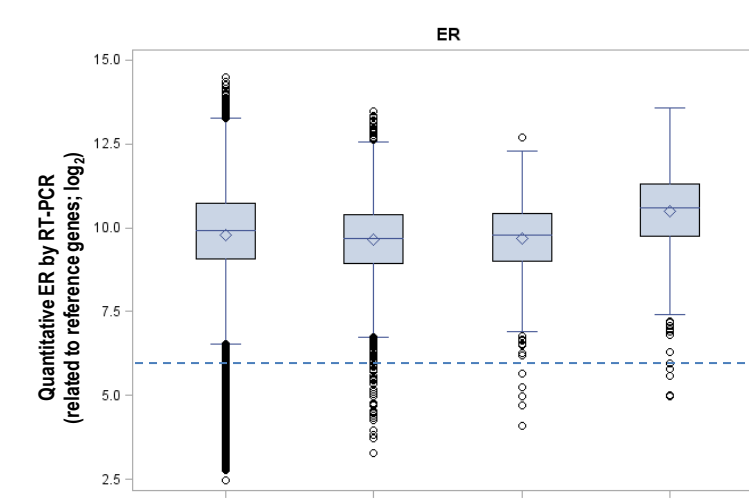


Figure 3. Comparison of ER Means Among ILC and Lobular Carcinoma Variants

- The mean ER for solid/alveolar lobular carcinoma was significantly higher than the means for other lobular subtypes and for ductal CA.
- The mean ER for ductal CA was significantly greater than the mean for classic lobular CA, but not significantly different from the mean for pleomorphic lobular CA.

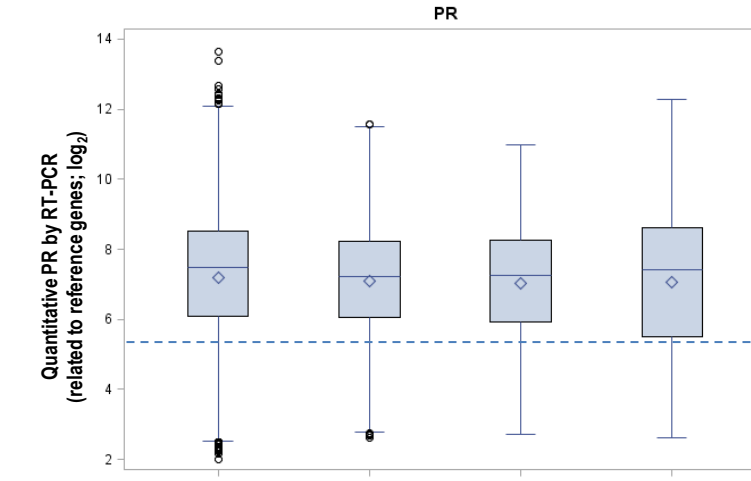


Figure 4. Comparison of PR Means Among ILC and Lobular Carcinoma Variants

- The mean PR for ductal carcinoma was significantly higher than the means for the three lobular subtypes.
- There was no significant difference among the means of the three lobular subtypes.

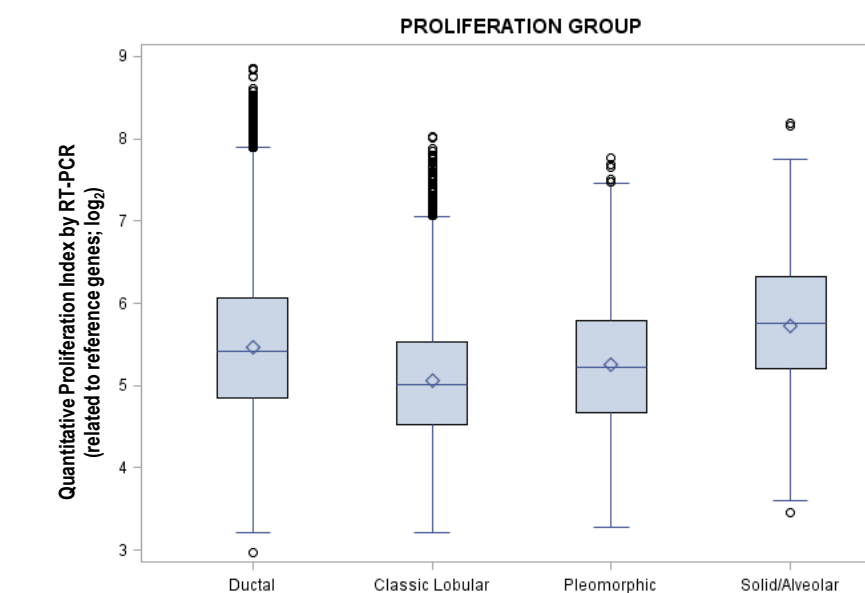


Figure 5. Comparison of Proliferation Gene Group Means Among ILC and Lobular Carcinoma Variants

- The mean proliferation gene group was greatest in solid/alveolar lobular CA, followed in decreasing order by ductal CA, pleomorphic lobular CA, and classic lobular CA.
- All means were significantly different from each other.

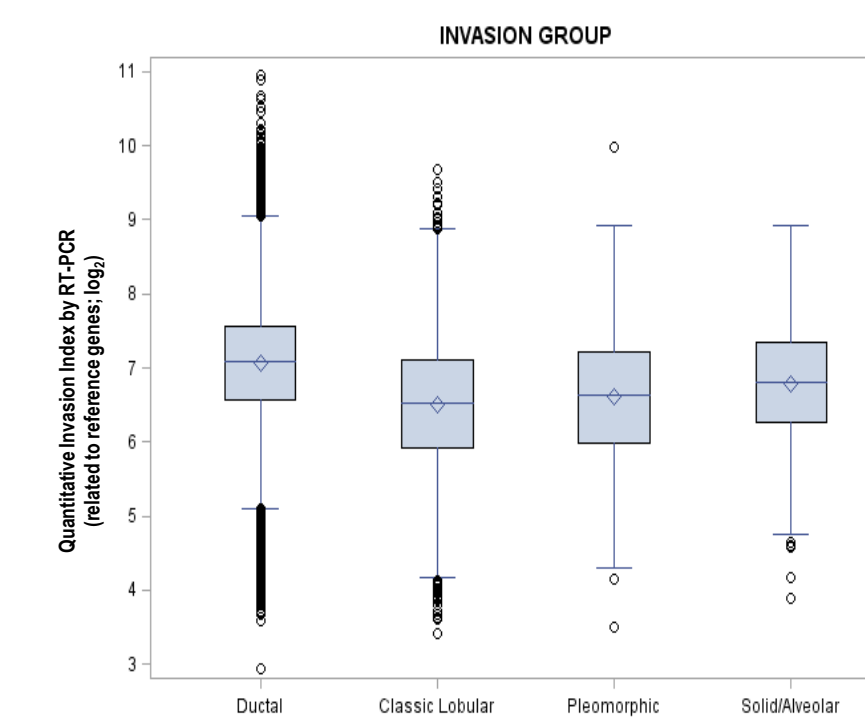


Figure 6. Comparison of Invasion Gene Group Means Among ILC and Lobular Carcinoma Variants

- The mean invasion group was greatest in ductal CA, followed in decreasing order by solid/alveolar CA, pleomorphic lobular CA, and classic lobular CA.
- All means were significantly different from each other.

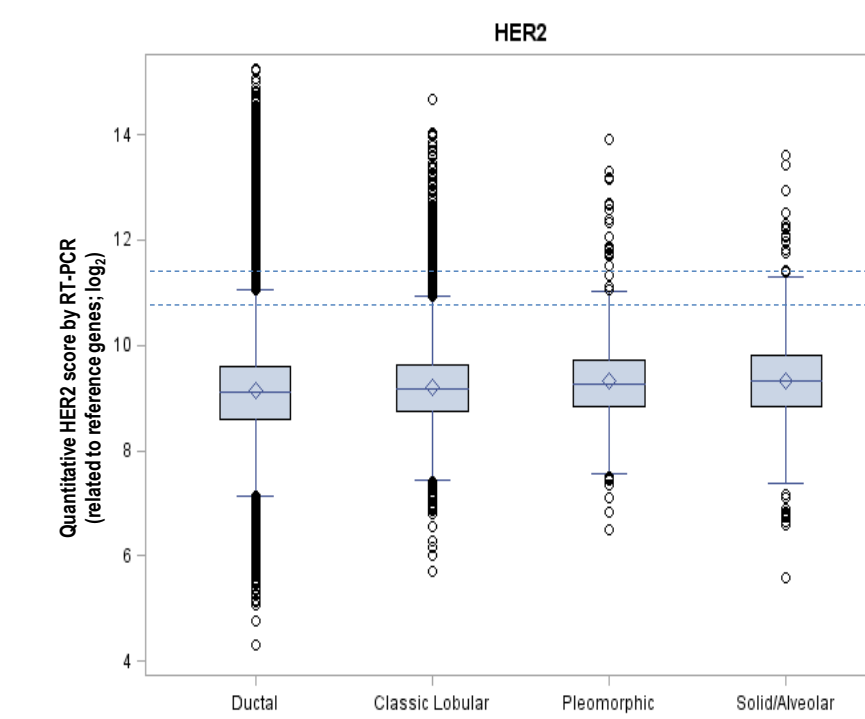


Figure 7. Comparison of HER2 Means Among ILC and Lobular Carcinoma Variants

- The mean HER2 for ductal CA was significantly lower than the mean HER2 values for classic lobular CA, which was significantly lower than the means for pleomorphic lobular or solid/alveolar lobular CA.
- There was no significant difference between pleomorphic lobular or solid/alveolar lobular CA.

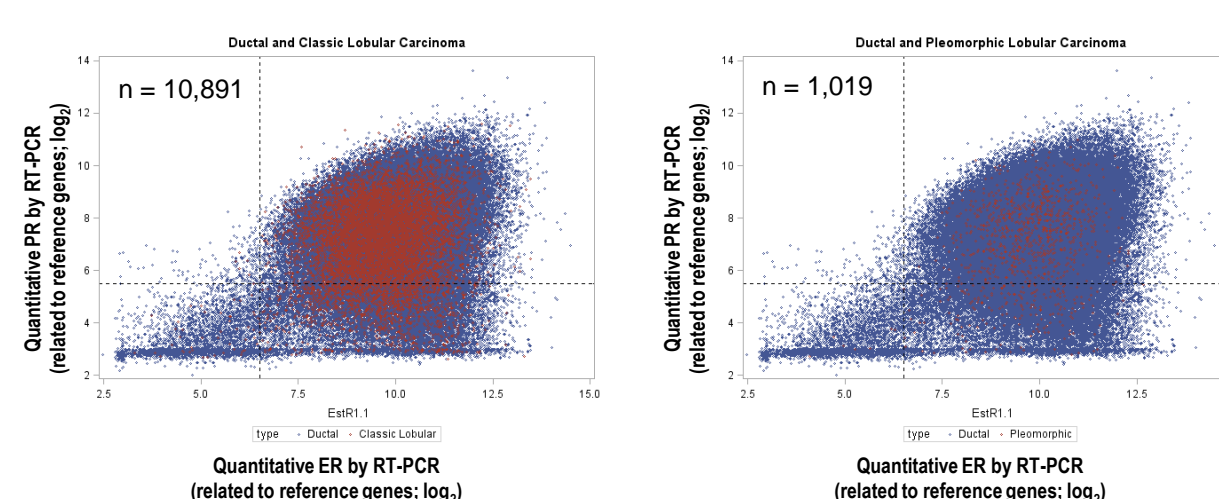


Figure 8. Comparison of Quantitative ER and PR Expression in Ductal Carcinoma, NOS and Classic ILC

- Cases of ductal carcinoma, NOS in blue dots; cases of classic ILC in red dots

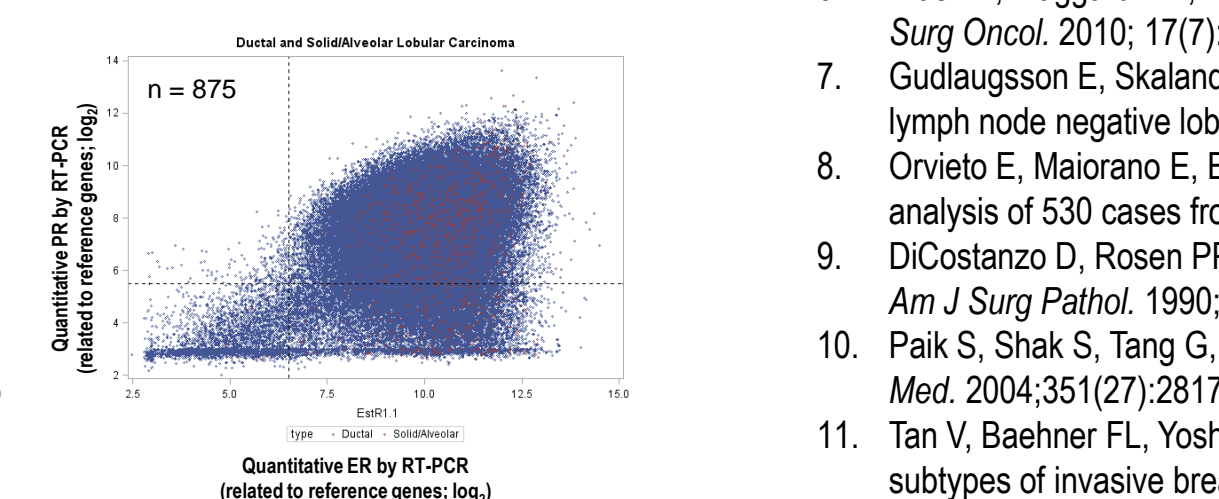


Figure 9. Comparison of Quantitative ER and PR Expression in Ductal Carcinoma, NOS and Pleomorphic Lobular Carcinoma

- Cases of ductal carcinoma, NOS in blue dots; cases of pleomorphic LC in red dots

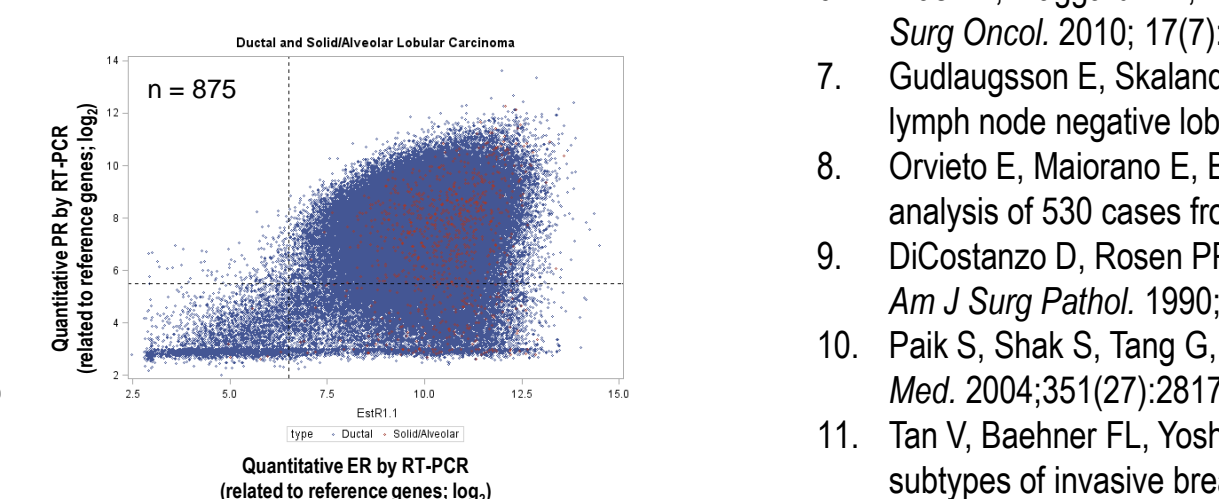


Figure 10. Comparison of Quantitative ER and PR Expression in Ductal Carcinoma, NOS and Solid/Alveolar Lobular Carcinoma

- Cases of ductal carcinoma, NOS in blue dots; cases of solid/alveolar LC in red dots

STRENGTHS AND LIMITATIONS

Strengths

- More than 100,000 breast carcinomas analyzed
- Precision, dynamic range, and reproducibility of RT-PCR
- Central pathology review

Limitations

- No long term follow-up for patient outcomes
- Confirmatory E-cadherin immunohistochemistry not performed
- As expected for clinical Recurrence Score testing, study included mostly ER-positive tumors
- Only one slide per case was reviewed

SUMMARY AND CONCLUSIONS

- Quantitative RT-PCR reveals a wide range of gene expression within each lobular carcinoma subtype, consistent with a wide and continuous range of tumor biology.
- The Recurrence Score, on average, was slightly lower for the classic lobular subtype compared to ductal, NOS and variant lobular subtypes.
- Lobular carcinoma variants tend to have a greater percentage of high RS disease than classic lobular in this large observational cohort.
- With respect to clinical outcome, differential gene expression may help explain the reported similarities between ILC and ductal, NOS and the reported differences within lobular carcinoma subtypes; these findings merit further study with associated long term clinical outcomes.

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