**BACKGROUND**

- Invasive lobular carcinomas (ILC) were first described by Fosse and Stewart in 1947.1
- ILC comprises approximately 10% of all breast carcinomas.2
- Histologically, classic ILC tumor cells are small, form invasive columns, show low nuclear grade and variable mitotic activity, express estrogen and progesterone receptors (ER, PR).3
- Classic ILC is characterized by an absence of lymphoid stromal response, a finding that may be important in the differential diagnosis of ILC/DC,4
- ILC variants (solid, alveolar, and pleomorphic) differ in histologic patterns and potential differences in outcome have been described.4-6
- Although there are no reliable numbers of ILC variants, efforts to define and compare them are ongoing.7
- Recently, using reverse transcriptase polymerase chain reaction (RT-PCR) technology, a wide range of quantitative gene expression has been described in ductal carcinoma, lobular carcinoma, and the special histologic subtypes.8-14

**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 analyze and compare the Oncotype DX3 (Gynecologic Oncology Group) and quantitative expression of ER, PR, HER2, proliferation genes and invasion genes across the ILC variants.
- 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.8
- 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 rate under any complete or partial null hypothesis.
- Analyses performed on de-identified data with IRB approval.

**RESULTS**

- There is a wide range of Recurrence Score biology within the lobular histologic subtypes.
- The classic lobular and pleomorphic lobular subtypes have fewer patients in the high RS group than solid/lobular alveolar and ductal carcinoma, NOS.
- To provide a means to compare the Oncotype DX3 (Gynecologic Oncology Group) and quantitative expression of ER, PR, HER2, proliferation genes and invasion genes across the ILC variants.
- To potentially identify gene expression levels or patterns characteristic of the variant forms of lobular carcinoma.

**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
- Controversy E-cadherin immunohistochemistry not performed
- As expected for clinical Recurrence Score testing, studies included mostly ER-positive tumors
- Only one case per slide 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 subtype compared to ductal, NOS and variant lobular subtypes.
- Lobular carcinoma variants tend to have a greater percentage of high RS disease than classic in this large observational cohort.
- With respect to clinical outcome, differential gene expression may help explain the observed similarities of ILC and ductal, NOS and the reported differences with other lobular carcinoma subtypes; these findings merit further study with associated long term clinical outcomes.

**REFERENCES**