QUANTITATIVE ASSESSMENT OF FUNCTIONAL ACTIVITY OF MULTIPLE SIGNALING PATHWAYS IN RECURRENT BREAST CANCER WITH LOW-INTERMEDIATE 21 GENE RECURRENCE SCORE

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INTRODUCTION

Molecular characterization of breast cancer has been shown to correlate with prognosis and predict risk of recurrence. The 21-gene recurrence score (RS) is one of the most widely used commercially available tests to predict risk of recurrence in breast cancer based on a molecular approach. Even when classified as low-intermediate risk by RS score (≤ 30), 6.8–14.3% and 4-7.2% of patients will experience distant or locoregional recurrences, respectively. In this study, we investigated the functional activity of key signal pathways in recurrent breast carcinomas with low-intermediate RS score to identify molecular features that may predict recurrence.

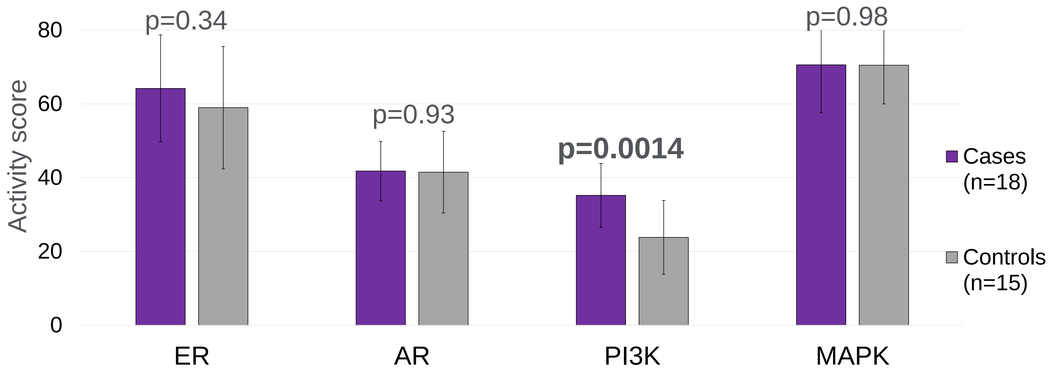
METHODS

This is a case-control study of patients with recurrent breast carcinoma with low-intermediate RS score and a control cohort of patients with non-recurrent breast cancer controlled for age, RS score, and follow-up time. Cases were diagnosed between October 2012 and December 2017 and tested with the 21-gene RS assay. The cases and controls were retrospectively identified from NYU Langone Health Pathology Database. We collected clinicopathologic, treatment, and outcome data. The tissues were macrodissected, and RNA was extracted. mRNA expression of genes involved in ER, AR, PI3K, MAPK signaling pathways was measured by RT-qPCR and translated into quantitative pathway activity scores to characterize the signaling activity of these tumors using the OncoSignal (PhilipsMolecular Pathway Dx) assay. Statistical analysis was performed using student t test and Fisher exact test.

TABLE 1: Clinicopathological characteristics

	Cases (n=18)	Controls (n=15)	p-value
Age (years)	48.1 ± 11.9	48.8 ± 9.19	0.85
Race (%)			0.82
Caucasian	55	40	
Asian	11	20	
Black	17	20	
Other	17	20	
Histologic type (%)			0.31
Ductal	78	66	
Lobular	17	33	
Other	5	0	
Grade (%)			0.13
Grade 3, 4, 5	11	13	
Grade 6, 7	72	87	
Grade 8.9	17	0	
Stage (%)			0.75
I	78	60	
II	22	33	
III	5	7	
Lymphovascular invasion (%)	44	27	0.11
Positive lymph node (%)	33	40	0.73
Positive margins (%)	17	20	0.80
ER expression (%)	96.5 ± 6.4	98.7 ± 1.6	0.20
PR expression (%)	76.9 ± 29.7	74.3 ± 33.5	0.81
Ki67 (%)	17 ± 12	13 ± 10	0.32
RS score	16.5 ± 5.5	16.3 ± 3.2	0.90
Follow-up time (months)	148.1 ± 63.5	165.3 ± 24.4	0.33
Type of surgery (%)			1.00
Conservative surgery	50	46	
Total mastectomy	50	54	
Hormonal therapy (%)	78	100	0.23
Radiotherapy (%)	44	60	1.00
Chemotherapy (%)	22	20	0.50

FIGURE 1: Pathway activity score for ER, AR, PI3K, MAPK



RESULTS

A total of 18 cases with locoregional recurrence or distant metastatic disease and available formalin-fixed paraffin embedded tissue were included. An additional 15 non-recurrent controls matched for age, RS score, and follow-up were retrieved. There were no statistical differences between the groups' characteristics, including age, race, pathologic characteristics (histologic type, grade, staging, lymphovascular invasion, resection margins, lymph node positivity, ER/PR percentage, Ki-67 proliferation index), RS score, follow-up time, and treatment parameters (type of surgery, percentage receiving hormonal treatment, chemotherapy, and radiotherapy) (Table 1). The PI3K pathway showed significantly higher activity score in cases with locoregional recurrence or distant metastatic disease compared to controls (35.2 ± 8.65 vs 23.8 ± 10.03; p=0.0014) (Figure 1). There was no difference in ER, AR, and MAPK pathways between the groups.

CONCLUSION

The PI3K pathway may be involved in recurrence and metastasis of early breast cancer with low-intermediate RS. Further research is warranted to better understand the role of this pathway in the progression of breast cancer and possible preventive therapies.

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