INTRODUCTION

Approximately 75% of breast cancer patients have tumors that express the predictive biomarker estrogen receptor α (ER) and are consequently offered endocrine therapy. Around one third eventually relapse in their disease with the majority still expressing ER. However, the mechanism behind endocrine resistance is elusive and tumor cell expression of ER is the only clinically utilized biomarker for endocrine therapeutic response. Studies imply interesting findings of gene mutations and differential gene expression, where investigations of the phosphoinositide 3-kinase (PI3K) signaling pathway and more specifically the gene coding for PI3Kα’s catalytic subunit PIK3CA are ongoing. This calls for a broader understanding of the transcriptional and genetic involvement in the resistance mechanism in order to develop novel tools for therapy prediction.

AIM

This study aims to assess predictive and prognostic tools in a unique paired cohort of patients with verified endocrine-resistant disease. Assessing transcriptomics and genomics for prediction of endocrine therapy response with specific insight into PIK3-related patterns.

MATERIALS & METHODS

- Retrospective cohort collection of endocrine-resistant patients diagnosed in 2009-2014 at Karolinska University Hospital, Sweden, full process described in Figure 1.
- Inclusion criteria: ER+ human epidemic growth factor 2 receptor (HER2) negative primary breast cancer with ER-HER2 double loss during ongoing endocrine therapy (n=54).
- Control inclusion criteria: ER-HER2 breast cancer diagnosed in 2005, without relapse or disease progression at 10 years follow-up (n=64). Matched by age and stage to cases.
- Formalin-fixed paraffin-embedded (FFPE) tumor material RNA/DNA extraction.
- RNA samples analyzed by Affymetrix DNA Microarray, assessed through Transcriptome Array Console and R.
- DNA analyzed through gene panel sequencing with following assessments in R. Demonstrated in Figure 2.

RESULTS

The preliminary transcriptomic analysis generated sets of differentially expressed genes in the comparison of primary tumors of cases eventually relapse compared to controls, visualized in the heatmap in Figure 3. Gene expression of PI3Kα associated genes PIK3CA, phosphatase and tensin homolog (PTEN), cyclin dependent kinase 4 and 6 (CDK4 and CDK6), estrogen receptor 1 (ESR1) and insulin-like growth factor receptor 1 (IGF1R) in the cohort was evaluated on signal level in the three tumor groups, available in boxplots, Figure 4.

Gene analysis of PIK3CA revealed mutations in 53.7% of the cases, with mutations in 47.9% of primary tumors and 65.2% in relapse tumors. 40.7% of the patients had mutations in the 11 known hotspots of PIK3CA with hotspot mutations in 37.5% primary tumors and 63.5% in relapse tumors, all visualized in Figure 5.

SUMMARY AND CONCLUSION

On the transcriptional level, the differential patterns shown in the heatmap of the primary tumors compared to controls suggest gene profiles that are associated with a later recurrence in ER+ disease. Further, the individual gene expression assessment of the PI3Kα associated genes show a downregulation in IGF1R in relapse tumors compared to primary tumors and a suggested upregulation in primary versus control. In primary tumors there is an indicated upregulation of CDK6 compared to controls. For PTEN and ESR1, a downregulation is implied in relapses, whilst CDK4 tends to be upregulated.

In PIK3CA, there is no tendency to differential expression, however, in the gene level analysis several mutations are identified in cases. Over half of the patients exhibit a PIK3CA mutation with the highest abundance in relapse tumors, 65.2% compared to 47.9% in primary tumors. Regarding the 11 known hotspot mutations, a similar pattern is seen, where 40.7% of patients have one or several hotspot mutations, with highest abundance in relapse tumors, 43.5% and 37.5% in primary tumors. The increase in relapse tumors thus seems to be gained outside hotspot regions.

The discrepancy in the abundance compared to previous studies might be due to a smaller selected sample size and distinct endocrine resistant cohort. In addition, this could reflect intratumoral heterogeneity in primary tumors and/or a true gain in occurrences. Further investigations to decipher eventual truncation, nonsense alterations and clonal expansions will be performed.

This study of a unique cohort with verified endocrine-resistant patients, comparing paired samples of primary and relapse tumors as well as relapse-free controls, show PIK3 associated gene expression differentiation between the tumor groups. Additionally, the results illustrate a high abundance of PIK3CA mutations in cases, especially in relapse tumors.

Our findings suggest that endocrine-resistant tumors are associated with genomic and transcriptional profiles that potentially could be utilized as predictive and prognostic markers for endocrine-resistant breast cancer. These preliminary results will further be investigated to continue deciphering the mechanisms of endocrine resistance in breast cancer.

REFERENCES

- This is a non-interventional study set up as a research collaboration between Karolinska Institutet and Novo Nordisk AB.
- This study was supported by grants from the Swedish Cancer Society MedTech-lab, Region Stockholm, the Cancer Society in Stockholm, the Swedish Breast Cancer Association and the Swedish Society for Medical Research.

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