Deciphering the inferior prognosis of young women with estrogen receptor-positive early-stage breast cancer through full transcriptome analysis: a FLEX database sub-study

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INTRODUCTION

- Young women with estrogen receptor (ER)-positive early-stage breast cancer (EBC) frequently present with larger, higher-grade, more aggressive tumors, with lower ER expression than older women.
- Post-hoc analyses within the MINDACT and TAILORx cohorts reported that women aged 40-50 with ER+ EBC exhibited a chemotherapy benefit independent of genomic risk compared to women aged >50, possibly that distinguish tumors in younger women from older women.
- To understand the biological basis underlying why younger women have poorer outcomes than older women, this study aimed to identify genes that distinguish tumors in younger women from older women.

 METHODS

FLEX Study: EBC patients enrolled in the FLEX study (NCT03053193) underwent standard care of MammaPrint (MP) and BluePrint (BP) tests, and consent to clinically annotated whole transcriptome data collection. MP categorizes tumors as High Risk (HR) or Low Risk (LR) of recurrence. Together, MP and BP classify the molecular subtype of tumors as Luminal A-Type, Luminal B-Type, HER2- Type, or Basal- Type.

Gene Expression and Statistical Analysis: Whole transcriptome gene expression differences were compared among ER+ tumor specimens from three age groups: <40 years old, 40-54 years old, and ≥55 years old.

RESULTS

Tables 2-4

Figure 1. Distribution MP risk classification results per age group

Figure 2. Distribution of tumor subtype by BP per age group

Table 1. Patient numbers by MammaPrint and BluePrint

Table 2. DEGs in Luminal A-Type tumors

Table 3. DEGs in Luminal B-Type tumors

Table 4. DEGs in Basal- Type tumors

Overall, 76.0% of women <40 years, 53.6% of women aged 40-54, and 48.5% of women ≥55 years had MP HR tumors (Figure 1).

Women <40 years had higher frequencies of BP Basal-Type and HER2-Type tumors (20.5% and 9.2%, respectively) compared with women ≥55 years (8.0% and 2.4%, respectively; p<0.0001; Figure 1).

In line with unsupervised hierarchical clustering and previous studies1, tumors from patients aged 40-54 exhibited limited DEGs in comparison to women ≥55 years (3 DEGs; data not shown). In contrast, most gene expression differences, albeit small, were observed between women <40 and ≥55 years (30 DEGs; data not shown).

We identified fewer DEGs within BP Luminal A-Type (n=27; Figure 3A), Luminal B-Type (n=14; Figure 3B), and Basal-Type (n=8; Figure 3C) tumors from women aged <40 relative to women ≥55 years.

Significant DEGs in tumors of women <40 years compared with women ≥55 years and their functions per BP subtype are listed in (Tables 2-4).

No DEGs were found in HER2-Type tumors. In addition, no DEGs with a fold change >2 were observed between pre- and post-menopausal women (data not shown).

CONCLUSIONS

Overall, there were relatively few gene expression changes identified by age.

Few transcriptional differences were observed between tumors from women aged 40-54 and ≥55, had, suggesting observed chemotheray benefit represents differences in host biology rather than intrinsic tumor biology.

The most DEGs were found in tumors from women <40 versus ≥55 and were associated with proliferation and metabolism.

Fewer DEGs were observed by menopausal status than age, indicating age is a more relevant cutoff.

The authors wish to thank our patients who inspire us everyday. Navigating a cancer diagnosis is never easy, doing so during a pandemic requires heroic personal strength.