Age-Associated Divergence in Breast Cancer: Clinical, Molecular, and Genomic Insights from a Large Real-World Cohort

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Julia Foldi[1], Sandro Satta[2], Brandie Taylor[2], Punashi Dutta[2], Steffi Oesterreich[1], Adrian V. Lee[1], Ekaterina Kalashnikova[2], Angel A. Rodriguez[2], Minetta C. Liu[2], Marjia Balic[1], Ann Partridge[3]

[1]University of Pittsburgh School of Medicine and UPMC Hillman Cancer Center, UPMC, Pittsburgh, PA; [2]Oncology, Natera, Inc., Austin, TX; [3]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Background

- Breast cancer (BC) in younger individuals is often clinically aggressive and biologically distinct.[1] However, comprehensive real-world evidence comparing the molecular underpinnings in very early-onset BC (age <35 years) vs. BC in older age groups (ages 36-50 years and age >50 years) remains limited.
- Here, we evaluate clinicopathologic features and molecular characteristics between BC diagnosed in younger (≤35 years) and older (>35 years) age groups, with a focus on subtype distribution, circulating tumor DNA (ctDNA) dynamics, relapse patterns, and genomic alterations.

Methods

- This retrospective analysis included patients diagnosed with early-stage BC who underwent personalized tumor-informed ctDNA testing (Signatera™, Natera, Inc.) in a real-world clinical setting (2019–2024).
- Genomic alterations were derived from whole-exome sequencing of tumor tissue as part of personalized ctDNA assay development. Histology, molecular subtype, lymph node (LN) status, recurrence events, ctDNA detection over time, and relapse patterns were compared.

Table 1. Patient and tumor characteristics (N=6,802)

Parameter	# Patients/Mutations* (%)			p values
Age group	**≤35 years (N=322)**	**36-50 years (N=1,923)**	**>50 years (N=4,557)**	
Median age, years (range)	32 (21-35)	44.1 (36-50)	64.6 (51-89)	<0.001
Subtype				
HR+/HER2-	142 (44%)	1,022 (53%)	3,178 (70%)	<0.001
HER2+	61 (19%)	388 (20%)	859 (19%)	
TNBC	119 (37%)	513 (27%)	520 (11%)	
Lymph Node Positive	182 (57%)	978 (51%)	1,975 (43%)	<0.001
TMB status (%mutations)*				
High	27,487 (25.9%)	261,296 (31.9%)	1,093,174 (42%)	<0.001
Low	78,556 (74.1%)	558,802 (68.1%)	1, 511,149 (58%)	

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References

1. Zhu JW, *et al. What Is Known about Breast Cancer in Young Women? Cancers (Basel). 2023 Mar 22;15(6):1917.*

Very early-onset breast cancer (≤35 years) is biologically distinct and clinically aggressive (characterized by higher ctDNA levels, shorter time to relapse, and less favorable ctDNA response), highlighting the importance of age-tailored molecular monitoring and therapeutic strategies.

Figure 1. Mutational landscape overview by age group and subtypes

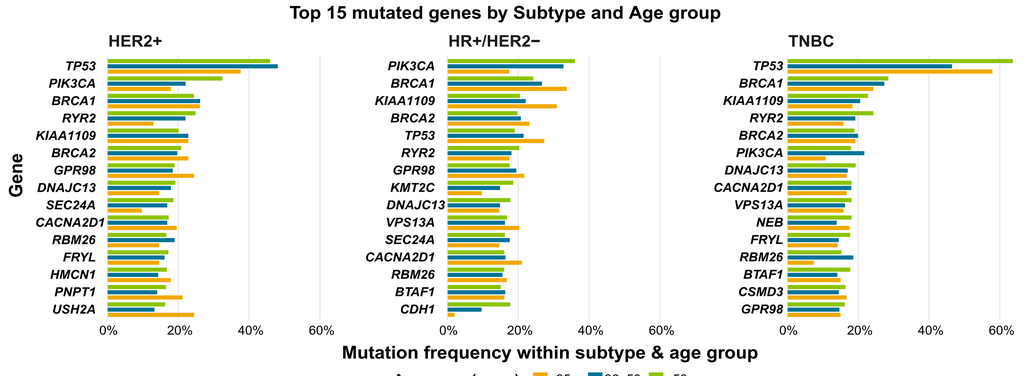


Figure 1. Top 15 mutated genes by subtype and age group. Horizontal bar charts show mutation frequency (%) within each breast cancer subtype—HER2+, HR+/HER2−, and TNBC, stratified by age (≤35, 36–50, >50); genes are ordered by frequency within each panel. In the HR+/HER2− cohort, *CDH1* (p < 0.0001) and *PIK3CA* (p < 0.0001) mutations were significantly more prevalent in patients aged > 50 years, whereas *TP53* mutations (p=0.0171) occurred most frequently in patients aged ≤ 35 years. **Abbreviations:** HR, hormone receptor; TNBC, triple-negative breast cancer.

Figure 2. Association of ctDNA MTM/mL levels and time to relapse with age groups and subtypes

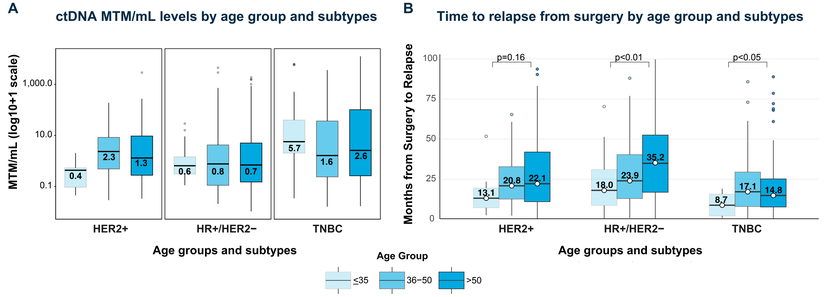


Figure 2: ctDNA MTM/mL and relapse timing by age and subtype. **(A)** Boxplots show ctDNA MTM/mL (log10+1) across age groups (≤35, 36–50, >50) within HER2+, HR+/HER2−, and TNBC; medians are labeled inside boxes. In TNBC, the youngest group (≤35) has the largest median MTM/mL among the age groups. **(B)** Months from surgery to relapse by age group and subtype; the ≤35 group shows shorter median time to relapse, consistent with more aggressive disease (HER2+ p=0.16; HR+/HER2− p<0.01; TNBC p<0.05). **Abbreviations:** HR, hormone receptor; TNBC, triple-negative breast cancer.

Figure 3. Association of age with ctDNA response by subtype and therapy

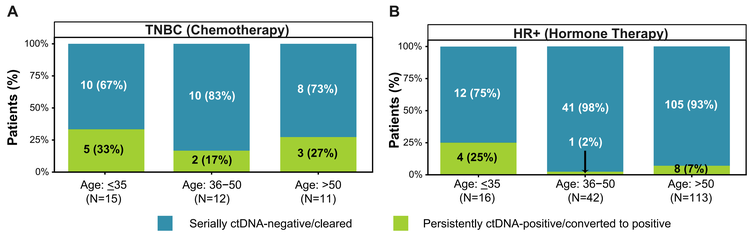


Figure 3: ctDNA response patterns by age group, subtype, and treatment type. **(A)** Among TNBC patients receiving chemotherapy, the ≤35-year age group (previously shown in Figure 2 to have the shortest median time to relapse) demonstrated a disproportionately unfavorable ctDNA response, with 33% remaining persistently ctDNA-positive or converting to positive during treatment. **(B)** Similarly, in HR+ patients on hormone therapy, younger individuals (≤35 years) more frequently exhibited non-clearance or conversion to ctDNA-positivity compared to older cohorts, suggesting an association between early-onset disease and suboptimal ctDNA response across subtypes. **Abbreviations:** HR, hormone receptor; TNBC, triple-negative breast cancer.

Conclusions

- Early-onset breast cancer (≤35 years) exhibits distinct molecular features, including a higher frequency of *TP53* mutations (p=0.0171) and lower *PIK3CA/CDH1* mutation rates compared to older patients, suggesting unique tumor biology.
- ctDNA levels (MTM/mL) were significantly higher in younger TNBC patients (≤35 years) than in older groups, consistent with a higher risk of recurrence.
- Time to relapse was significantly shorter for younger patients (TNBC p<0.05; HR+/HER2– p<0.01), confirming earlier recurrence risk in this cohort.
- Unfavorable ctDNA response (persistent/converted positivity) occurred more often in ≤35-year-old patients, both in TNBC receiving chemotherapy and HR+ patients on hormone therapy, reinforcing the link between early-onset disease and ctDNA-based relapse risk.

Email contact: foldij@upmc.edu