2025-A-2246-SABCS– Exceptionally High Frequency of ESR1 Mutations in Pakistani Women with Endocrine Resistant Hormone Receptor positive Her2 neu negative Metastatic Breast Cancer

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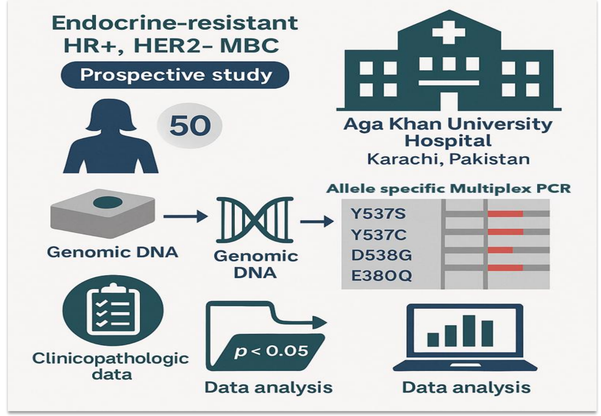
Introduction

Aromatase inhibitor (AI)–based therapy combined with CDK4/6 inhibitors is the standard of care for HR+, HER2– metastatic breast cancer (MBC). Ligand-binding domain mutations in the ESR1 gene are a well-recognized mechanism of resistance, with reported frequencies of 15–50% in AI-treated patients. However, data from South Asia are scarce, and no study has reported ESR1 mutation frequencies in a Pakistani cohort, highlighting a major regional evidence gap in resistance biology.

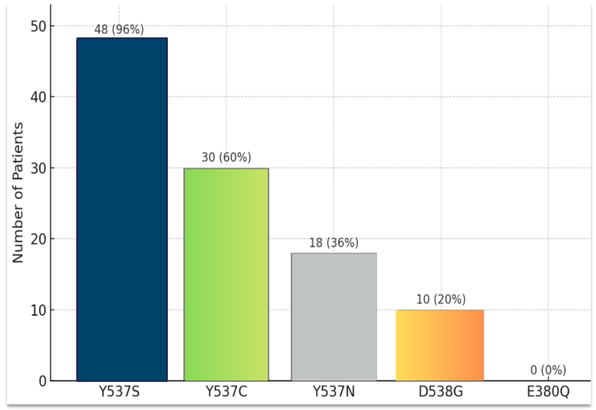
Materials and Methods

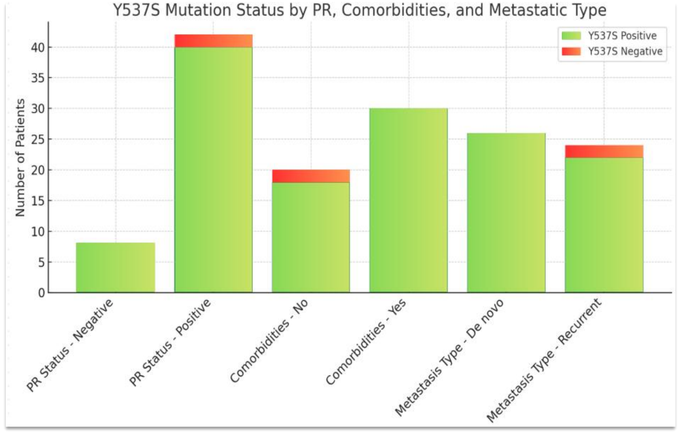
We prospectively enrolled 50 Pakistani women with endocrine-resistant HR+, HER2– metastatic breast cancer at Aga Khan University Hospital. Genomic DNA from FFPE biopsies was analyzed using allele-specific multiplex PCR for ESR1 mutations (Y537S, Y537C,Y537N,D538G,E380Q).

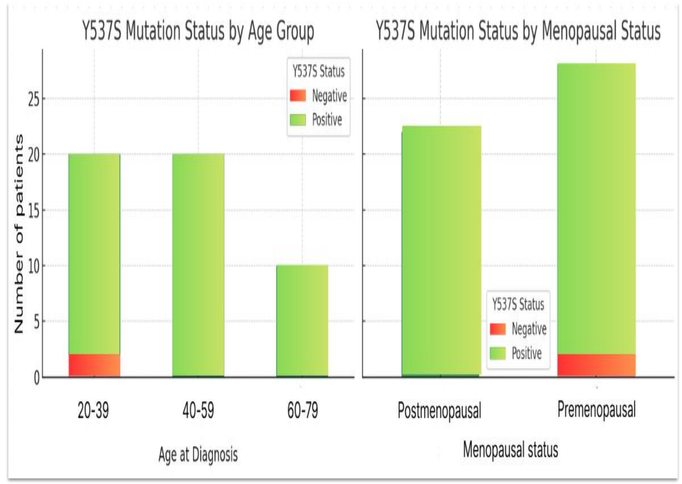
Clinicopathologic variables including age, metastatic presentation, ER/PR, HER2 status, comorbidities, and prior chemotherapy—were recorded. Statistical analyses (t test, Fisher's exact, Chi-square, Kolmogorov–Smirnov, Mann-Whitney) were conducted using SPSS v25 and GraphPad Prism 4, with $p < 0.05$ considered significant.



Results







Discussion

Our cohort revealed near-universal Y537S mutations even in de novo metastatic cases, a finding that diverges from global reports where ESR1 mutations typically arise after endocrine exposure. This suggests that resistance biology in Pakistani HR+/HER2– MBC may be embedded at presentation rather than solely therapy-induced. The coexistence of multiple ESR1 mutations highlights polyclonal evolution and aggressive tumor behavior. These insights underscore the need for early molecular surveillance and evaluation of next-generation SERDs or rational combinations to overcome multi-clonal resistance.

Conclusions

We observed a markedly high prevalence of the ESR1 Y537S mutation in endocrine-resistant HR+/HER2– metastatic breast cancer in Pakistani women, highlighting distinct tumor biology, supported by:

-Its association with high ER/PR expression and younger age.

-A strong rationale for routine ESR1 testing.

-The need for locally informed therapeutic strategies aligned with regional genomic patterns.

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