Landscape of PIK3CA Mutations in Chinese Patients with Breast Cancer: A Multi-Center Real-World Study

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Abstract

Background: PIK3CA mutations are key therapeutic targets in breast cancer (BC). However, their distribution across clinicopathological strata in Chinese patients remains unclear.

Method: This multicentered, retrospective study analyzed 577 Chinese BC patients with available PIK3CA testing (next-generation sequencing, NGS). Patients were categorized into PIK3CA-mutated (n=226) and wild-type (WT, n=351) groups. Clinicopathological characteristics and survival outcomes were compared.

Result:

- PIK3CA mutation frequency was highest in Luminal A (LA) (56.4%), followed by Luminal B (LB1) (45.8%), HER2-positive (45.5%), and Luminal B2 (LB2) (40.5%), but was lower in triple-negative breast cancer (TNBC) (21.4%).
- The spectrum of PIK3CA mutations revealed H1047R as the most common (42.5%), followed by E545K (17.7%) and E542K (11.5%).
- BRCA mutations were significantly less frequent in PIK3CA-mutated patients than PIK3CA- WT patients(4.0% vs. 16.2%, *P*<0.001).
- With a median follow-up of 38.4 months, no overall survival (OS) difference was found between mutated and WT groups.
- Among patients with LA breast cancer, those harboring PIK3CA mutations exhibited a significantly worse 5-year OS compared with those with WT group(91.8% vs. 100.0%, *P*=0.034).
- Patients with E545K mutations had significantly lower 5-year OS compared to those with other PIK3CA mutations (83.0% vs. 95.3%, *P*=0.028).

Conclusion: This study defines a unique PIK3CA mutational landscape in Chinese pts with BC and its negative clinical impact in LA subtype.

Introduction

- The PIK3CA gene encodes the catalytic subunit of phosphatidylinositol 3-kinase (PI3K), a key enzyme in the PI3K/AKT/mTOR signaling pathway that regulates cell growth, survival, and metabolism[1].
- PIK3CA mutations are detected in 25-40% of breast cancer cases, with hotspot mutations primarily located in exons 9 and 20[2-4]. Common PIK3CA mutations (e.g., E545K, H1047R) contribute to malignant cell transformation and tumor cell survival by suppressing apoptosis[3-6].
- The high frequency of PIK3CA mutations makes them a promising biomarker to guide targeted therapy and personalized treatment in breast cancer[7,8].
- The distribution across key clinicopathological strata in Chinese patients remains to be elucidated.

Methods and Materials

- This retrospective real-world study enrolled Chinese breast cancer patients with confirmed available PIK3CA testing (NGS) from Sun Yat-sen University Cancer Center and Hainan Provincial People's Hospital, between January 1997 and February 2024.
- Patients with complete clinicopathological data were included. Data on demographics, clinical details, treatment, and outcomes were extracted from electronic medical records.
- Patients were classified into two groups: PIK3CA WT and PIK3CA-mutant. The data cutoff date was April 29, 2025 (Figure 1).
- The study outcomes included the incidences of PIK3CA mutations in breast cancer patients and different PIK3CA hotspot mutations within the PIK3CA-mutant group and OS. The Kaplan-Meier method was used to estimate OS.

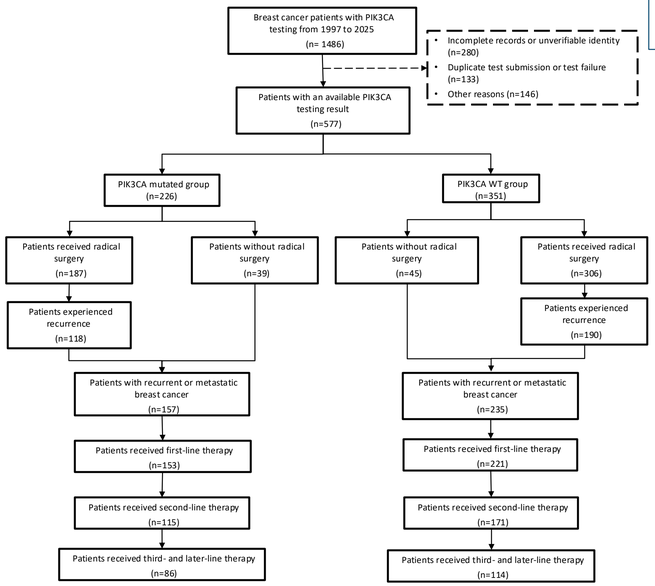


Figure 1. Patient flowchart.

Results

- The study enrolled 577 patients stratified into PIK3CA-mutant (n=226, 39.2%) WT(n=351) groups.
- Baseline clinicopathological characteristics were shown in Table 1.
- No significant differences were found in age, body mass index, menopausal status, family history, or clinical stage between two groups.
- PIK3CA mutation frequency was highest LA (56.4%), followed by LB1 (45.8%), HER2+ (45.5%), and LB2 (40.5%), and was lowest in TNBC (21.4%).
- Among mutated tumors, H1047R was predominant (42.5%), followed by E545K (17.7%) and E542K (11.5%). H1047R mutations showed higher prevalence in HER2+ (22.7% of HER2+ tumors) and LA (21.8%) subtypes compared to TNBC (11.7%). E545K mutations were enriched in LB2 (11.9%) and LA (11.5%) subtypes, while being rare in TNBC (2.8%).
- BRCA mutations were significantly less frequent in PIK3CA-mutated pts (mutated vs. WT: 4.0% vs. 16.2%, *P*<0.001), particularly BRCA1 (0.9% vs. 7.1%) and BRCA2 (3.1% vs. 10.3%).

Table 1. Baseline Clinicopathological Characteristics.

Variables	Total (N=577)	PIK3CA mutated (n=266)	PIK3CA-WT (n=351)	*P*-value
Age, years, median (IQR)	45.0 (37.0, 53.0)	46.0 (38.0, 54.0)	45.00 (37.0, 52.0)	0.149
Clinical stage, n (%)				0.119
I	55 (9.5)	17 (7.5)	38 (10.8)	
II	152 (26.3)	57 (25.2)	95 (27.1)	
III	153 (26.5)	64 (28.3)	89 (25.4)	
IV	68 (11.8)	35 (15.5)	33 (9.4)	
Missing	149 (25.8)	53 (23.5)	96 (27.4)	
Molecular subtype, n (%)				<0.001
HER2-positive	44 (7.6)	20 (8.8)	24 (6.8)	
Luminal A	78 (13.5)	44 (19.5)	34 (9.7)	
Luminal B1	236 (40.9)	108 (47.8)	128 (36.5)	
Luminal B2	42 (7.3)	17 (7.5)	25 (7.1)	
Triple-negative	145 (25.1)	31 (13.7)	114 (32.5)	
Other	30 (5.2)	5 (2.2)	25 (7.1)	
Missing	2 (0.3)	1 (0.4)	1 (0.3)	
BRCA1 mutation, n (%)	27 (4.7)	2 (0.9)	25 (7.1)	0.001
BRCA2 mutation, n (%)	43 (7.5)	7 (3.1)	36 (10.3)	0.001

Results

- After a median follow-up of 38.4 months, no significant OS difference was found between mutant and WT groups (5-yr OS: 92.7% vs. 90.3%) (Figure 2).
- Pts with the LA subtype harboring PIK3CA mutations had a 5-year OS rate of 91.8% (95% CI: 81.6-100.0%). Conversely, PIK3CA WT LA patients achieved a 5-year OS rate of 100.0% (95% CI: 100.0-100.0%) (*P*=0.034) (Figure 3).
- In the subgroup analysis of E545K, the E545K mutation group (n=40) showed significantly lower 5-year OS rate at 83.0% (95% CI: 68.8-100.0%) than PIK3CA-mutant group without E545K mutations (n=186, 5-yr OS: 95.3%, 95% CI: 91.6-99.1%)(*P*=0.028) (Figure 4).

Figure 2. OS in total population by PIK3CA mutation status.

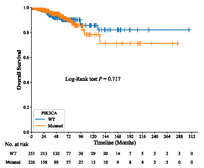


Figure 3. OS in patients with the LA subtype.

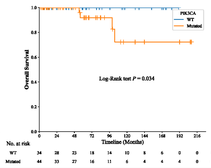
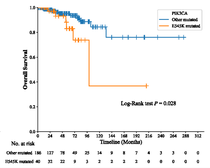


Figure 4. OS in PIK3CA-mutant group by E545K mutation profile.



Discussion

- The distribution of PIK3CA mutations in our cohort aligns with the established oncogenic role of the PI3K pathway, with the highest frequency observed in the LA (56.4%) and LB1 (45.8%) and the predominance of the H1047R mutation (42.5% of all mutations) [1-6].
- This study suggests that patients with the LA subtype harboring PIK3CA mutations present a worse outcome, consistent with previous study[9]. The E545K mutation group was identified as a potential marker of poor prognosis.
- Limitations: (1) Retrospective study design may introduce inherent selection bias and inconsistencies in data collection. (2) The sample size in certain subgroups (e.g., TNBC with PIK3CA mutations) is limited. (3) Heterogeneity in patient management could introduce confounding bias, potentially affecting the validity of the survival outcomes.

Conclusions

- This study delineates a distinct PIK3CA mutational profile in Chinese BC pts, characterized by its highest prevalence in the LA subtype and a mutational spectrum dominated by the H1047R variant.
- This study demonstrates the adverse prognostic impact of PIK3CA mutations in pts with LA breast cancer and identifies the E545K mutation as a potential marker of poor outcome.

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