Ten-year outcomes of Chinese early breast cancer patients with *PIK3CA/AKT1* mutations: A retrospective cohort study

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Abstract

We evaluated the prevalence and long-term prognostic impact of *PIK3CA/AKT1* mutations in 569 Chinese patients with stage I–III early breast cancer. The overall mutation rate was 50.1%, with the HR+/HER2− subtype having the highest rate. Single mutation showed no significant association with survival over a median 12.4-year follow-up. However, patients harboring ≥2 mutations demonstrated a consistently higher risk of disease progression or death. These findings highlight the potential clinical relevance of mutational burden within the *PI3K/AKT* pathway.

Introduction

The *PI3K/AKT* signaling pathway plays a critical role in regulating tumor cell proliferation, metabolism, and survival. *PIK3CA* and *AKT1* mutations have been implicated in the development of endocrine resistance in hormone receptor–positive breast cancer and are increasingly recognized as clinically actionable biomarkers, particularly with the expanding use of *PI3K* and *AKT* inhibitors. However, the long-term prognostic impact of these mutations remains inconsistent across molecular subtypes, and evidence in Asian populations is limited. This study aimed to evaluate the prevalence and long-term prognostic impact of *PIK3CA/AKT1* mutations among EBC patients in China.

Methods and Materials

The Breast Cancer Information Management System (BCIMS)
Prospective enrollment of pathologically diagnosed breast cancer patients at West China Hospital since 2008

Inclusion criterias:
Underwent radical surgery from 2008 to 2014
Had sufficient fresh frozen tumor tissue samples
Exclusion criterias:
Bilateral and multifocal breast cancer
Received neoadjuvant therapy
Had incomplete clinical and follow-up information

Study Cohort (N=569)

Clinical Information:
Age at diagnosis, menopause at diagnosis, tumor size, lymph node metastasis, ER, PR, HER2, Ki67, histological grade, surg-ery, radiotherapy, chemotherapy, endocrine therapy, and target therapy.
Mutation Information:
Obtain the information of PIK3CA/AKT mutations through gene sequencing (QIAGEN Gene Read panel on MiSeq, KAPA Hyper Prep Ki on NovaSeq X Plus)

Association Tests:
T tests, chi-square tests, or Fisher's exact tests (Mutation and Clinical factors)
Survival Analysis:
Kaplan-Meier estimates with log-rank test (iDFS/DDFS/OS)

Patients with ≥10 years of follow-up or those who experienced an event (N=522)

Multivariate Analysis:
Cox proportional hazards regression (Prognostic impact of mutations)

Figure1. Flowchart of patient inclusion, mutation detection and statistical analysis

Results

1. Prevalence and characteristics of *PIK3CA* and *AKT1* mutations

- Overall *PIK3CA/AKT1* mutation rate was 50.1%.
- Specifically, 47.3% patients harbored *PIK3CA* mutations, while 3.9% carried *AKT1* mutations.

PIK3CA/AKT1	Overall (n=569)	HR+/HER2- (n=319)	HER2+ (n=179)	TNBC (n=71)
WT	284 (49.9%)	129 (40.4%)	105 (58.7%)	50 (70.4%)
1MT	240 (42.2%)	153 (48.0%)	68 (38.0%)	19 (26.8%)
2MTs	45 (7.9%)	37 (11.6%)	6 (3.4%)	2 (2.8%)

Table1. The mutation status of PIK3CA/AKT1 stratified by molecular subtypes

1.1 *AKT1* mutation

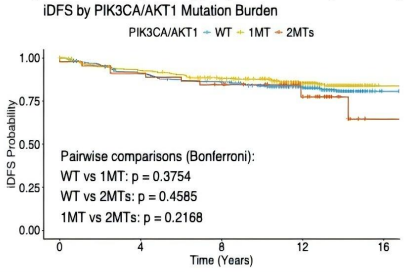
- *AKT1* mutations were significantly associated with ER+, PR+, HER2-, lower tumor grade, and Ki67 high expression.

1.2 *PIK3CA* mutation

- *PIK3CA* mutations were significantly associated with ER+, HER2-.

2. Association of *PIK3CA* and *AKT1* mutations with survival

2.1 There was no statistically significant difference in iDFS, DDFS, and OS between the mutant patients and the wild-type patients in the total patients or by subtype (HR+/HER2-, HER2+, TNBC)



- Median follow-up time: 12.4 years (IQR: 10.7-13.8 years).
- Number of events: iDFS: 95, DDFS: 89, OS: 65.
- 10-year survival rates for *PIK3CA/AKT1* mutation: iDFS 87.1%, DDFS 87.5%, OS 91.1%.
- 10-year survival rates for *PIK3CA/AKT1* wildtype: iDFS 83.8%, DDFS 84.5%, OS 88.4%.

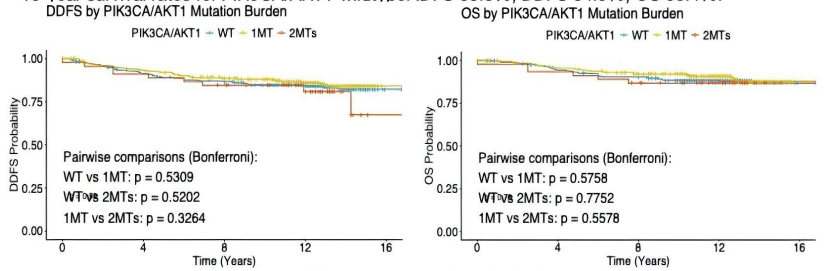


Figure2. Impact of PIK3CA/AKT1 mutations on iDFS, DDFS and OS in the total patients

2.2 Multivariate analysis revealed that patients with ≥2 mutations had a poorer prognosis.

- In the COX univariate analysis, there was no significant prognostic differences among the MT, 1MT, and 2MTs groups of *PIK3CA/AKT1*.
- Furthermore, after adjusting for age, menopausal status, T stage, N stage, molecular typing, and treatment, multivariable Cox regression indicated that patients with ≥2 *PIK3CA/AKT1* mutations conferred a significantly higher risk of progression or death compared to wild-type patients, whereas single *PIK3CA/AKT1* mutation did not show significant impact on prognosis.
- Similar trends persisted within the HR+ subgroup treated with endocrine therapy and within the Ki67 high expression subgroup.

	PIK3CA/AKT1 mutation					
	iDFS		DDFS		OS	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Total (n=522)						
WT	1		1		1	
1MT	1.097 (0.696-1.731)	0.689	1.112 (0.698-1.770)	0.656	1.305 (0.747-2.282)	0.350
2MTs	2.228 (1.063-4.672)	0.034	1.989 (0.919-4.305)	0.081	2.579 (0.989-6.721)	0.053
HR+ receiving endocrine therapy (n=362)						
1MT	1.164 (0.657-2.061)	0.602	1.116 (0.624-1.997)	0.711	1.444 (0.668-3.122)	0.350
2MTs	2.536 (1.121-5.733)	0.025	2.157 (0.924-5.037)	0.076	3.123 (1.018-9.577)	0.046
Ki67 high (n=410)						
1MT	1.124 (0.666-1.896)	0.661	1.147 (0.671-1.961)	0.617	1.053 (0.549-2.020)	0.877
2MTs	2.582(1.102-6.049)	0.029	2.214 (0.901-5.435)	0.083	2.708 (0.902-8.125)	0.076

Table2. Cox multivariate risk model for patients with different mutant burdens

Discussion

In this long-term Chinese EBC cohort, *PIK3CA/AKT1* mutations were common and strongly enriched in HR+/HER2− tumors. Single mutations did not impact long-term outcomes; however, patients harboring ≥2 mutations showed a consistent and independent association with poorer survival, with the strongest effect observed in TNBC. These findings suggest that multi-hit activation of the *PI3K/AKT* pathway may underlie more aggressive disease biology. This mutation-burden–based risk signal may inform clinical stratification and the potential application of PI3K/AKT-targeted therapies in selected high-risk subgroups. Validation in larger prospective studies is warranted.

Conclusions

Half of Chinese EBC patients harbored *PIK3CA/AKT1* mutations, with a notably higher prevalence in the HR+/HER2- subgroup. While the long-term prognosis of patients with *PIK3CA/AKT1* mutations overall was generally comparable to that of wild-type patients, those harboring multiple mutations may exhibit an increased risk of disease progression or mortality.

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