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ORIGINAL RESEARCH

Characterization of AKT Somatic Mutations in Chinese Breast Cancer Patients

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Purpose: This study aimed to investigate AKT gene mutation status in Chinese breast cancer patients.

Methods: The study included 411 breast cancer patients hospitalized in Guangdong Provincial People's Hospital (GDPH) from June 1, 2017 to September 27, 2018. Mastectomy or breast conserving surgery was performed, and tissue samples were subjected to next-generation sequencing (NGS) to determine AKT gene mutation status. Meanwhile, the expression of human epidermal growth factor receptor 2 (Her2), progesterone receptor (PR), and estrogen receptor (ER) was analyzed by immunohistochemistry staining. The Cancer Genome Atlas (TCGA) database was used for comparative studies.

Results: Patients in the GDPH cohort had an older age ($P < 0.001$), higher postmenopausal rate ($P < 0.001$), larger tumor size ($P < 0.001$), higher histologic type of infiltrating duct cancer ($P < 0.001$), higher metastatic rate ($P < 0.001$), higher expression of ER ($P = 0.015$) and HER2 ($P < 0.001$), and higher percentage of the HR/HER2 subtype ($P < 0.001$) than those in the TCGA cohort. The GDPH cohort displayed lower rates of overall AKT and AKT3 mutation ($P < 0.001$), but a higher AKT1 mutation rate ($P < 0.0001$) compared with the TCGA cohort. Notably, the NGS studies identified missense mutation and copy number amplification as the most common AKT variation type in the GDPH and TCGA cohorts, respectively. Specifically, E17K mutation in AKT1 was predominantly detected in GDPH cohort, while being absent in TCGA cohort. Moreover, in the GDPH cohort, AKT variation was correlated with a number of clinicopathological variables, including age over 50, HER2-, HR+/HER2-, and PR+.

Conclusion: Patients in the GDPH cohort had lower rates of AKT and AKT3 mutation and higher AKT1 mutation rate than those in the TCGA cohort, while harboring missense mutations detected predominantly as E17K mutation in AKT1. In GDPH cohort, there were correlations between AKT mutation and the clinicopathological characteristics of patients.

Keywords: AKT, next-generation sequencing, breast cancer, somatic mutations, population study

Introduction

Breast cancer has become the most prevalent cancer in women worldwide.[1,2] For Chinese women, breast cancer is the most commonly diagnosed cancer (19.2% of all cases) and the fourth cause of cancer-related deaths (9.1% of all cancer deaths) in 2018.[3] As breast cancer patients display diversity in molecular subtypes, pathological features, and therapeutic responses, a comprehensive analysis of new molecular markers and driver gene mutations is crucial for selecting the most appropriate treatment regime for patients.[4]

AKT, also known as protein kinase B, a serine/threonine protein kinase, has been shown to control tumor cell migration, metabolism and proliferation, playing an important role in cell survival and cancer progression. There are three AKT genes known as AKT1, AKT2, and AKT3.[5,6] AKT family proteins are composed of three parts: the pleckstrin homology (PH) domain at the amino terminus, the intermediate catalytic domain and the regulatory domain at the carboxy terminus. AKT is essentially conserved in terms of its carboxy-terminal tail.[7] AKT variations promote cell motility and induce epithelial mesenchymal transition, resulting in tumorigenesis, metastasis, and poor prognosis of breast cancer.[8]

AKT variation in breast cancer patients has been recently investigated. Studies have showed that AKT variation was detected in 4% of breast cancer patients and correlated with poor prognosis in patients receiving adjuvant hormone therapy.[9,10] The Cancer Genome Atlas (TCGA) project is a comprehensive dataset with both cancer genomic and clinical data from cancer patient samples.[11,12] In the TCGA dataset, only 6% of samples are Asian breast cancer patients, whereas 69% are Caucasian cases.[13] Studies of AKT variations in Chinese breast cancer patients are still lacking. AKT may be a reasonable target for cancer treatment, because the AKT signaling pathway is often dysregulated in up to 70% of human breast cancers.[14] AKT is related to and regulated by the metastatic cascade of breast cancer, so it is very important to develop targeted therapy for breast cancer AKT.[15]

Although AKT inhibitors have not yet been used in clinic, a large number of compounds have been demonstrated to inhibit AKT in both *in vitro* and *in vivo* models in preclinical studies. Screening the most effective AKT inhibitors for cancer treatment depends on identification of cancer-related mutations in the AKT gene. Thus, more efforts should be made to explore the efficacy and safety of AKT inhibitors.

In this study, we employed next-generation sequencing (NGS) technology to detect AKT variation status in a total of 411 Chinese breast cancer patients. TCGA data were collected for comparison. This study may contribute to a better understanding of AKT variation in clinical settings and facilitate AKT-targeted treatment selection for Chinese breast cancer patients.

Materials and Methods

Patients and Tumor Specimens

This study included 411 Chinese primary breast cancer patients who underwent mastectomy or breast conserving surgery in Guangdong Provincial People's Hospital (GDPH) from June 1, 2017 to September 27, 2018. This study was performed in accordance with the Declaration of Helsinki and all patients have signed written informed consents approved by the ethics committee of GDPH before surgery. Clinicopathological characteristics and clinical data for each patient were collected. Tumor tissue samples were obtained from the surgical resection specimens. After being quickly frozen in liquid nitrogen, tissue specimens were kept at −80 °C until use. NGS analysis was performed on all tumor specimens.

Both AKT somatic mutation data and clinicopathological features for TCGA groups were obtained from the cBioPortal database (available at: www.cbioportal.org). A total of 1098 breast cancer cases were eligible for this study.

Clinicopathological and Clinical Characteristics

Human epidermal growth factor receptor 2 (HER2), progesterone receptor (PR), and expression of estrogen receptor (ER) for each breast cancer specimen were routinely assessed by immunohistochemistry (IHC) staining conducted at Department of Pathology in GDPH. In the case of ER and PR, specimens were considered positive when at least 10% of tumor cells showed nuclear staining. For HER2, a case was defined as positive expression when total and seriously film recoloring were detected in more than 10% of tumor cells, and/or fluorescence in situ hybridization (FISH) displayed HER2 signals.[16]

Clinical data include gender, age of onset, menstrual status, axillary lymph node status, primary tumor size, distant metastasis status, histological grading, pathological type, and molecular type. The tumors were staged based on TNM classification.

Mutational Analysis of AKT

NGS technology, also known as massively parallel sequencing (MPS), is a parallel sequencing technology capable of sequencing billions of DNA base pairs in a single run, which can be used for analysis of specific cancer samples.[17] For sequence analysis, we employed NGS technology to detect AKT variation status. A commercial panel (OncoScreen Plus) composed of 520 genes was used for target capture, and the indexed samples were sequenced on Nextseq500 (Illumina, Inc., USA), and the average sequencing depth of tissue samples was 1,000×.

DNA isolation and targeted sequencing were performed in Burning Rock Biotech, a College of American Pathologist (CAP)-accredited/Clinical Laboratory Improvement Amendments (CLIA)-certified commercial clinical laboratory, according to optimized protocols as described previously.[18,19] Sequence data analysis was performed according to the study of Xie et al.[20] and the copy number was calculated. Copy number variation is defined as the quantitative and statistically significant difference between the coverage data of the genomic region and the reference control. The limit of detecting copy number variations for copy number deletion and amplified copy number variation were 1.5 and 2.64, respectively.

Data Statistics

Data were summarized by percentage and frequency for categorical variables. Comparisons of those categorical factors between cohorts were performed using Fisher's exact or Chi-square test. All statistical tests were two-sided, and differences were considered statistically significant at $P<0.05$.

Results

Clinicopathological Characteristics of Patients in GDPH and TCGA Cohorts

There were significant differences in the clinicopathological characteristics of breast cancer patients between GDPH and TCGA cohorts, including age of onset ($P < 0.001$), menopausal status ($P < 0.001$), tumor size ($P < 0.001$), histological type ($p < 0.001$), metastasis status ($P < 0.001$), ER status ($P = 0.015$), HER2 status ($P < 0.001$), and HR/HER2 subtype ($P < 0.001$). The above marked disparities prompted us to investigate the differences in AKT variations among different populations of patients with breast cancer. The clinicopathological features of patients in the two cohorts are summarized in Table 1.

Frequency, Type and Location of AKT (Aberration) Mutations of Patients in the Two Cohorts

Among 411 patients in the GDPH cohort, 41 (9.98%) were found to harbor 44 AKT variations, while 17.76% (195/1098) of cases in the TCGA cohort displayed 207 AKT variations (P = 0.0002). As shown in Figure 1, compared with the TCGA cohort, the GDPH cohort had a significantly higher mutation rate in AKT1 (7.06% vs 2.00%, $P < 0.0001$), but a significantly lower mutation rate in AKT3 (2.43% vs 14.2%, $P < 0.0001$).

Next, the NGS studies identified missense mutations and copy number amplification (AMP) as the two most common AKT variation types among patients in the two cohorts, which accounted for approximately two-thirds in all cases with AKT variation. As depicted in Figure 2, the GDPH cohort included 31 cases with missense mutation (70.5%) detected predominantly in AKT1, 10 cases with copy number amplification (22.7%), 1 case with deletion mutation (2.3%), and 2 cases with intron mutation (4.5%). In the meantime, mutation cases in the TCGA cohort comprised 189 cases with AMP (91.3%) identified mainly in AKT3, 8 cases with missense mutation (3.9%), 7 cases with homozygous deletions (HOMDEL) (3.4%), 1 case with same sense mutation (0.5%), and 2 cases with nonsense mutation (1.0%).

We further analyzed AKT variation domains in the two cohorts. As summarized in Figure 3, out of all 31 missense mutations in GDPH cohort, 25 cases were identified as E17K mutation in AKT1. Conversely, E17K-mutation in AKT1 was absent in the TCGA cohort.

Relationship Between AKT Variations and the Clinicopathological Features

Patients in each of the two cohorts were divided into AKT wild-type group and AKT variation group. As summarized in Table 2, relationships between the clinicopathological variables and AKT variation status in the two cohorts were analyzed respectively. In the GDPH cohort, the frequency of AKT variations in patients at age over 50 (10.23%) was significantly higher than that in those at age ≤50 (9.79%) ($P = 0.022$). A significantly higher rate of AKT variation was detected in HER2-negative patients ($P = 0.011$) or HR+/HER2- patients ($P = 0.010$) compared with the corresponding controls. Notably, no significant correlation between AKT variation and ER expression was observed, whereas there was a positive correlation between AKT variation and PR expression ($P = 0.041$). Moreover, no significant correlations were found between AKT variation and other clinicopathological variables, such as menopausal status, tumor sizes, histological type, lymph node involvement, and tumor grade. On the contrary, AKT variation was not significantly correlated with the clinicopathological characteristics in cases of TCGA cohort.

Table 1 Clinicopathological Features of Breast Cancer Patients in GDPH and TCGA Databases

Items	GDPH Cohort		TCGA Cohort		*P* value
	No.	(%)	No.	(%)	
Age					<0.001
≤50	235	(57.2)	331	(30.1)	
>50	176	(42.8)	765	(69.7)	
NA			2	(0.2)	
Menopausal status					<0.001
Yes	181	(44.0)	705	(64.2)	
No	230	(56.0)	268	(24.4)	
NA			125	(11.4)	
Tumor sizes(cm)					<0.001
T1(≤2)	153	(37.2)	183	(16.7)	
T2(2<T≤5)	214	(52.1)	621	(56.6)	
T3 or larger(T>5)	28	(6.8)	249	(22.7)	
T4	16	(3.9)	20	(1.8)	
NA			25	(2.3)	
Histological type					<0.001
IDC	359	(87.3)	819	(74.6)	
ILC	13	(3.2)	211	(19.2)	
Other	39	(9.5)	66	(6.0)	
NA			2	(0.2)	
Lymph node involvement					0.354
Positive	210	(51.1)	576	(52.5)	
Negative	201	(48.9)	495	(45.1)	
NA			27	(2.5)	
Metastasis status					<0.001
Yes	26	(6.3)	24	(2.2)	
No	384	(93.4)	1074	(97.8)	
ER status					0.015
Positive	293	(71.3)	809	(73.7)	
Negative	118	(28.7)	237	(21.6)	
NA			52	(4.7)	
PR status					0.707
Positive	272	(66.2)	701	(63.8)	
Negative	139	(33.8)	342	(31.1)	
NA			55	(5.0)	
Hormone receptor status					0.133
Positive	309	(75.2)	826	(75.2)	
Negative	102	(24.8)	222	(20.2)	
NA			50	(4.6)	
HER2 status					<0.001
Positive	121	(29.4)	196	(17.9)	
Negative	290	(70.6)	760	(69.2)	
NA			142	(12.9)	

(*Continued*)

Table 1 (Continued).

Items	GDPH Cohort		TCGA Cohort		*P* value
	No.	(%)	No.	(%)	
Ki67 index					NA
≥14%	44	(10.7)	NA		
<14%	367	(89.3)			
HR/HER2 status					<0.001
HR-/HER2-	53	(12.9)	160	(14.6)	
HR-/HER2+	49	(11.9)	41	(3.7)	
HR+/HER2-	237	(57.7)	599	(54.6)	
HR+/HER2+	72	(17.5)	155	(14.1)	
NA			143	(13.0)	

Abbreviations: GDPH, Guangdong Provincial People's Hospital; TCGA, The Cancer Genome Atlas; NA, not applicable; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Discussion

In the current public database, the Asian population, especially the Chinese population, accounts for only a small percentage.[13] It is necessary to test the generalizability of the TCGA profiles in the Asian population of breast cancer patients. Here, we performed a comparative study between 411 patients with breast cancer in the GDPH cohort and 1098 cases in the TCGA cohort, and found that AKT variation rates in the two groups were 9.98% and 17.76%, respectively, showing a significant difference between them ($P = 0.0002$).

It has been reported that a subset of human malignancies harbor AKT1 mutations related to overactivation of AKT.[21,22] Gene mutation is less likely to activate

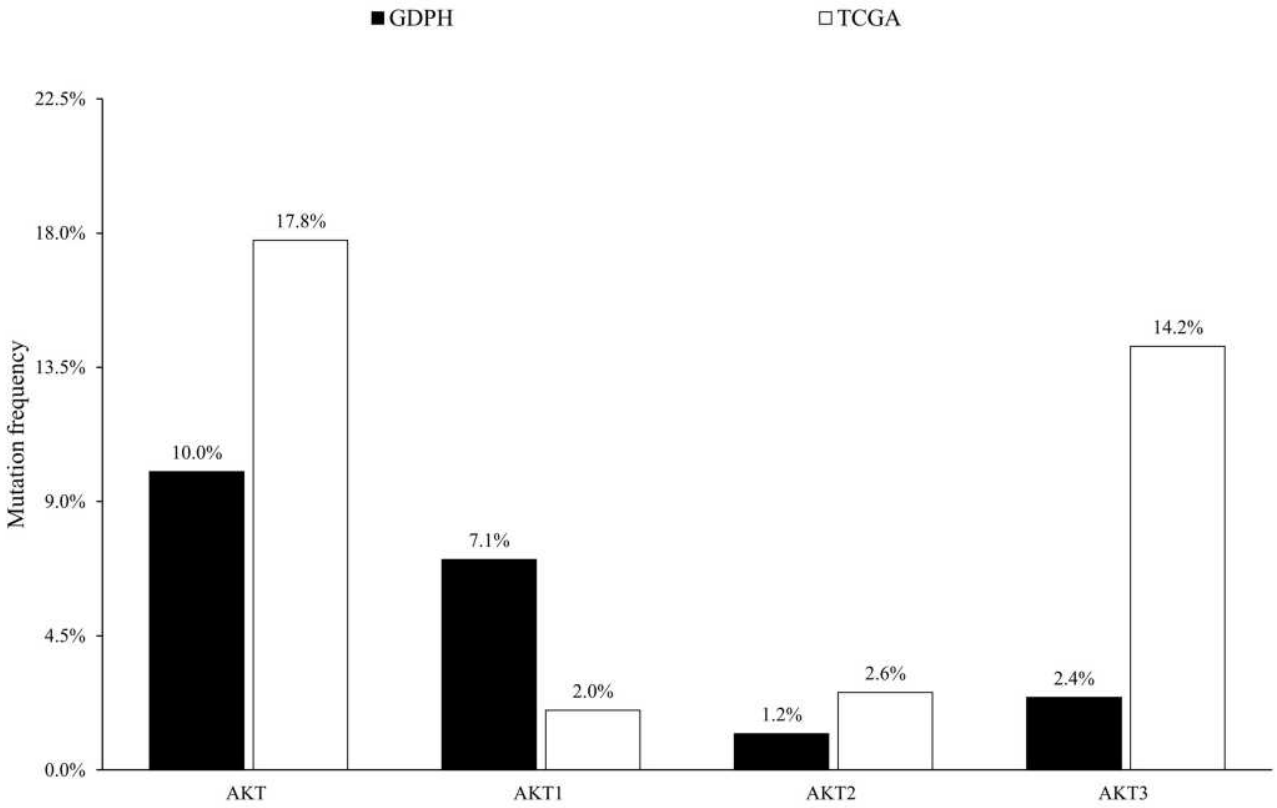

Figure 1 The mutation rates of AKT, AKT1, AKT2, and AKT3 in GDPH and TCGA cohorts of patients with breast cancer.
Abbreviations: GDPH, Guangdong Provincial People's Hospital; TCGA, The Cancer Genome Atlas.

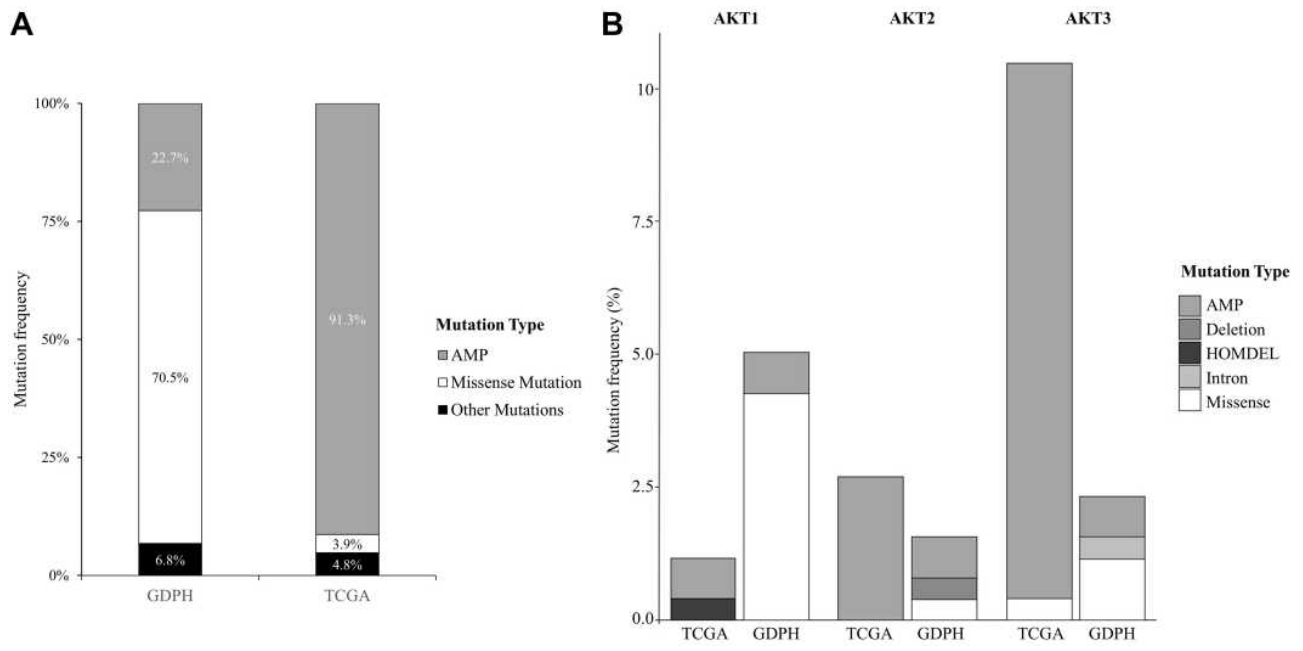

Figure 2 The frequency of different mutation types of (**A**) AKT, (**B**) AKT1, AKT2, and AKT3 in the two cohorts.
Abbreviations: GDPH, Guangdong Provincial People's Hospital; TCGA, The Cancer Genome Atlas; AMP, copy number amplification; HOMDEL, homozygous deletions.

AKT in comparison with other activation modes, such as amplification, overexpression, and phosphorylation. Yet, mutations in upstream/downstream AKT regulators may affect the carcinogenicity of AKT.[23] AKT is considered an attractive target for cancer treatment, and efforts are being made to identify specific inhibitors of AKT with acceptable drug properties. Although AKT inhibitors have been in clinical trials for several years, they have not been specifically evaluated in AKT1-mutant tumors.[24] Identification of the most effective AKT inhibitor for cancer treatment is dependent on cancer-related mutations in the AKT gene. There are a huge number of compounds that can inhibit AKT in both *in vitro* and *in vivo* models on preclinical studies. Based on the inhibition mechanisms and chemical scaffolds, AKT inhibitors are mainly classified as ATP-competitive inhibitors, allosteric inhibitors and Irreversible inhibitors.[25] Commonly used AKT inhibitors in clinical trials are presented in Table 3.[5,25]

Among these AKT inhibitors, AZD5363 is the first-in-human oral evaluation in treating breast cancer. A few phase I clinical trials for AZD5363 alone or in combination with other drugs have been completed. These phase I clinical trials showed well tolerated and accomplished plasma levels as well as vigorous target modulation in breast tumors.[26,27] These phase I data promoted phase II clinical studies of AZD5363.[28,29] Besides, there is an ongoing phase III double-blind randomized study assessing the efficacy and safety of Capivasertib (AZD5363) plus Paclitaxel versus placebo plus Paclitaxel as first-line treatment for patients with histologically confirmed, locally advanced (inoperable) or metastatic triple negative breast cancer (TNBC).

The significance of the E17K mutation in breast cancer is still unclear. According to reports, this mutation has dual effects, such as anti-tumor effects (inhibition of cell proliferation and promotion of apoptosis) and carcinogenic effects (promoting cell migration).[30] Direct or indirect inhibition of E17K function in breast cancer patients is not necessarily an effective treatment strategy.[30] Therefore, further analysis of the role of E17K mutation in tumorigenesis is needed. An oncogenic activating mutation (E17K) within the PH domain of AKT1 has been identified in a few types of solid tumors. This mutation has been reported in 1.4–8% of cases with breast cancer.[31,32] Although this low frequency precludes drawing any authoritative conclusions, a large-scale genotyping study (547 breast tumors and 41 breast cancer cell lines) revealed that AKT1 mutations were solely observed in tumors expressing both ER and PR.[32] Specifically, it has been shown that AKT1-E17K mutation resulted in membrane binding of AKT and decreased sensitivity to allosteric inhibitors.[33] In this study, we found that 70.5% of mutations in the

Figure 3 Diagram of domains of (**A**) AKT1, (**B**) AKT2 and (**C**) AKT3 with mutations identified in the GDPH cohort.
Abbreviation: PH, pleckstrin homology.

Chinese population were missense mutations, among which 80.6% were detected in the major hotspots concentrated in the helical region (E17K). Conversely, AKT1-E17K mutation was absent in patients of the TCGA cohort. This unique high-frequency mutation in the Chinese population suggests that it could serve as a risk factor for breast cancer in the Asian population. The E17K mutation is located near the specific binding site of PI (3,4,5) P_3 in the PH domain of AKT1, and is associated with human breast, colorectal, ovarian, and lung cancer.[34,35] Previous studies have shown that the E17K mutation may cause significant[35] changes in the PH domain of AKT1 and induce resistance to AKT inhibitors.[35] Therefore, more clinical trials are needed to differentiate antineoplastic effects of different AKT inhibitors prior to being used for different patients.

Table 2 Correlation Between Clinicopathological Features and AKT Family Mutation in GDPH and TCGA Databases

	GDPH Group					TCGA Group				
	WT AKT		MT AKT			WT AKT		MT AKT		
	n=370		n=41			n=903		n=195		
	n(%)		n(%)		P	n(%)		n(%)		*P*
Age					0.022					0.117
≤50	212	(90.2)	23	(9.8)		263	(79.5)	68	(20.5)	
>50	158	(89.8)	18	(10.2)		638	(83.4)	127	(16.6)	
NA						2	(100.0)	0	(0.0)	
Menopausal status					0.726					0.384
Yes	164	(90.6)	17	(9.4)		590	(83.7)	115	(16.3)	
No	206	(89.6)	24	(10.4)		218	(81.3)	50	(18.7)	
NA	0	(0.0)	0	(0.0)		95	(76.0)	30	(24.0)	
Tumor sizes (cm)					0.088					0.338
T1 (≤2)	132	(86.3)	21	(13.7)		157	(85.8)	26	(14.2)	
T2 (2<T≤5)	198	(92.5)	16	(7.5)		512	(82.4)	109	(17.6)	
T3 or larger (T>5)	27	(96.4)	1	(3.6)		197	(79.1)	52	(20.9)	
T4	13	(81.3)	3	(18.8)		17	(85.0)	3	(15.0)	
NA	0	(0.0)	0	(0.0)		20	(80.0)	5	(20.0)	
Histological type					0.485					0.255
IDC	325	(88.1)	34	(9.2)		667	(81.4)	152	(18.6)	
ILC	12	(92.3)	1	(7.7)		175	(82.9)	36	(17.1)	
Other	33	(84.6)	6	(15.4)		59	(89.4)	7	(10.6)	
NA	0	(0.0)	0	(0.0)		2	(100.0)	0	(0.0)	
Lymph node involvement					0.315					0.838
Positive	186	(88.6)	24	(11.4)		408	(70.8)	87	(15.1)	
Negative	184	(87.2)	17	(8.1)		472	(95.4)	104	(21.0)	
NA	0	(0.0)	0	(0.0)		23	(85.2)	4	(14.8)	
Metastasis status					0.946					0.495
Yes	24	(92.3)	2	(7.7)		21	(87.5)	3	(12.5)	
No	345	(89.8)	39	(10.2)		882	(82.1)	192	(17.9)	
NA	1	(100.0)	0	(0.0)						
Tumor grade					0.174	NA				
1	15	(100.0)	0	(0.0)						
2	166	(87.4)	24	(12.6)						
3	181	(91.4)	17	(8.6)						
Unknown	8	(100.0)	0	(0.0)						
ER status					0.313					0.448
Positive	261	(89.1)	32	(10.9)		662	(81.8)	147	(18.2)	
Negative	109	(92.4)	9	(7.6)		199	(84.0)	38	(16.0)	
NA						42	(80.8)	10	(19.2)	
PR status					0.041					0.729
Positive	239	(87.9)	33	(12.1)		580	(82.7)	121	(17.3)	
Negative	131	(94.2)	8	(5.8)		280	(81.9)	62	(18.1)	
NA						43	(78.2)	12	(21.8)	

(*Continued*)

Table 2 (Continued).

	GDPH Group					TCGA Group				
	WT AKT		MT AKT			WT AKT		MT AKT		
	n=370		n=41			n=903		n=195		
	n(%)		n(%)		P	n(%)		n(%)		P
Hormone receptor status					0.226					0.635
Positive	275	(89.0)	34	(11.0)		677	(82.0)	149	(18.0)	
Negative	95	(93.1)	7	(6.9)		185	(83.3)	37	(16.7)	
NA						41	(82.0)	9	(18.0)	
HER2 status					0.011					0.444
Positive	116	(95.9)	5	(4.1)		165	(84.2)	31	(15.8)	
Negative	254	(87.6)	36	(12.4)		622	(81.8)	138	(18.2)	
NA						116	(81.7)	26	(18.3)	
Ki67 index					0.836	NA				NA
≥14%	40	(90.9)	4	(9.1)						
<14%	330	(89.9)	37	(10.1)						
HR/HER2 status					0.010					0.890
HR-/HER2-	50	(94.3)	3	(5.7)		132	(82.5)	28	(17.5)	
HR-/HER2+	45	(91.8)	4	(8.2)		35	(85.4)	6	(14.6)	
HR+/HER2-	204	(86.1)	33	(13.9)		490	(81.8)	109	(18.2)	
HR+/HER2+	71	(98.6)	1	(1.4)		130	(83.9)	25	(16.1)	
NA						116	(81.1)	27	(18.9)	

Abbreviations: GDPH, Guangdong Provincial People's Hospital; TCGA, The Cancer Genome Atlas; NA, not applicable; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Clinical trial NCT01226316 showed that AZD5363 treatment led to a longer PFS in AKT1 E17K–mutant patients compared with patients without AKT1 E17K mutation.[36] The effect of AKT inhibitors on the GDPH patients needs further investigation.

HER2 is a receptor tyrosine kinase that is gene-amplified in about 20–25% of patients with breast cancer. Overexpression of HER2 is associated with tumor aggressiveness, while causing recurrent disease progression or shorter overall survival as well as resistance of patients to therapies.[37,38] Previous studies have shown that HER2 and PR expression is correlated with AKT variation status.[39] In the present study, we observed a strong inverse correlation between AKT variation and HER2 expression ($P = 0.011$), and a positive correlation between AKT variation and PR expression, while there was no significant correlation between AKT variation and ER expression. These results are inconsistent with the current data. This inconsistency could be attributed to the differences in AKT variation between the Chinese and European populations. As a result, more studies need to be conducted for understanding HER2 expression and AKT activity in different populations.

In this study, we identified significant differences in AKT variation between the Chinese and TCGA populations. For instances, breast cancer patients in the GDPH cohort had a higher rate of AKT1 mutation, but a lower rate of AKT3 mutation in comparison with those in the TCGA cohort; AKT variation was inversely correlated with HER2 expression, while being positively correlated with PR expression. Despite these observations, the limited sample size in the study may decrease the statistical ability to make accurate comparisons between the two cohorts. In addition, this study did not explore the correlation between AKT variations and the prognosis of breast cancer patients, which is the limitation of this project. Previous studies have shown that the AKT1-E17K

Table 3 AKT Inhibitors in Clinical Development

Drug	Phase	Clinical Trials
Perifosine	II/III	NCT01051557 NCT01049841 NCT01097018 NCT01224730 NCT02238496
MK-2206	II	NCT01802320 NCT01776008 NCT01859182 NCT01783171 NCT01705340
Uprosertib (GSK2141795)	II	NCT01941927 NCT01907815 NCT01935973
Afuresertib (GSK2110183)	I/II	NCT02380313 NCT02235740 NCT02240212 NCT02177682 NCT02040480
Ipatasertib (GDC-0068, RG7440)	I/II	NCT01896530 NCT01485861 NCT01362374 NCT01090960
AZD5363	II	NCT02576444 NCT02664935 NCT02449655 NCT02451956 NCT02525068
ARQ0092	I	NCT02476955 NCT01473095 NCT02594215
AT13148	I	NCT01585701
GSK690963	Failed	
XL148	Failed	

mutation does not seem to have obvious prognostic significance in breast cancer patients, but it has clinical utility in the selection of therapeutic drugs. Given that plenty of studies suggest AKT to be a well-approved target for medicines development, further investigation of mechanisms underlying AKT and its inhibitors in breast cancer could provide a theoretical basis for clinical application of AKT as an effective therapeutic target.

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Disclosure

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