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The Importance of RTK Signaling Genes and their Inhibitors in Breast Cancer

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ABSTRACT

Receptor tyrosine kinase (RTK) signaling is a crucial pathway in the development of many cancers. *KIT*, *PI3K*, and *AKT* are the major genes in this pathway. *KIT* RTK functions in cell signal transduction in various cell types, such as cancer cells. A central element of RTK signaling is phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit A (PIK3CA), involved in cell proliferation, survival, and growth. *AKT* is a serine/threonine-specific protein kinase that has an important role in several processes, such as apoptosis and cell proliferation.

The importance of mutations and overexpression of *KIT*, *PI3K*, and *AKT* genes in breast cancer has been previously demonstrated.

This review investigated the relationship between gene mutations and overexpression and clinicopathological variable of *KIT*, *PI3K*, and *AKT* in breast cancer. Finally, the use of inhibitor drugs of these genes in breast cancer treatment. These data were collected from PubMed and Google Scholar databases from 2000 to 2021.

The expression of *KIT*, *PI3K*, and *AKT* genes in normal breast tissues has been observed. However, mutations and overexpression of these genes are associated with malignancies.

The mutations in *KIT*, *PI3K*, and *AKT* genes are different from those found in other malignancies.

Also, most of the drugs that inhibit the RTK signaling are being tested in clinical trials for the treatment of breast cancer. Monitoring and timely management of adverse effects are critical to minimize toxicities and optimize the efficacy of this targeted therapy. Therefore, further development of predictive biomarkers can better select patients who will benefit from RTK inhibitors.

Keywords: *AKT* gene, Breast cancer, *KIT* gene, *PI3K* gene, *RTK* signaling

Introduction

Breast Cancer

The origin of breast cancer is breast tissue. This cancer is very a common cancer and the second cause of women's death. Despite notable development in timely diagnosis and treatment over the past decades, breast cancer is still the leading cause of cancer death in women in several countries, especially in less developed countries **(1)**.

Breast cancer usually starts from lobules and milk duct cells. It leads to lobular and ductal carcinomas. This cancer has about 18 subtypes **(2)**.

Breast cancer risk factors are female gender, lack of physical exercise, obesity, hormone replacement therapy during menopause, drinking alcohol, first menstruation at an early age, ionizing radiation, family history, having children late in life or not having any, and older age **(2, 3)**.

Recognizing clinical, biological, and pathological factors in Breast cancer can have mainly prognostic costs and factors that can use as a warning risk classification, treatment selection, and development of novel treatments **(4)**.

In recent years, the importance of personalized medicine and other biomarkers has been emphasized, which may help explain the residual risk posed by traditional factors **(4)**.

Most genes mutated in human cancers play a crucial role in the cell cycle, but most of them are involved in signal transduction. These signal transduction pathways are essential pathways through which cells communicate with their environment and play a pivotal role in regulating cell proliferation and death **(5)**.

By inhibiting the genes of these pathways, the suppression of malignant tumors, such as breast cancer,

could be possible. Better cancer treatments will hopefully be found by research and development in this field **(6)**.

In about 5% of breast cancer, genetic factors have a more prominent role in developing hereditary breast-ovarian cancer syndromes, such as people with *BRCA1* and *BRCA2* gene mutations **(7)**. These mutations cause 90% of the total genetic impact with a 60%-80% risk of breast cancer in people. Other cancers such as Li–Fraumeni syndrome (*p53* gene mutation), Cowden syndrome (*PTEN* gene mutation), and Peutz–Jeghers syndrome (*STK11* gene mutation) are also some other examples **(8)**.

In 2012, it was found that, genetically, there were four types of breast cancer. In each type, specific genetic changes led to different types of cancer **(9)**.

Normal cells will no longer need cell apoptosis; until then, they are protected by many clusters of proteins and pathways, such as receptor tyrosine kinase (RTK)/mTOR and RAS/MEK/ERK pathways. Sometimes, genes in these conservative pathways mutate constantly and prevent cell apoptosis if it is no longer needed. This is one of the stages that cause cancer, along with other mutations. Generally, in the apoptosis process, the PTEN protein inhibits mTOR and RTK signaling. The gene in the PTEN protein is mutated in several breast cancers; thus, in the "on" position, the RTK/mTOR pathway is unchanged, and the cancer cell does not destroy itself **(10)**.

RTK Signaling

In cancer development, RTK signaling is one of the critical signal transduction pathways. This pathway is vital in the cell processes, such as cell division, growth, survival, and angiogenesis **(11, 12)**. *KIT*, *PI3K*, and *AKT* genes play critical roles in this pathway **(11)**.

As a receptor, *KIT* functions in cell signal transduction in various cell types, such as cancer cells. Usually, *KIT* is activated by binding to the stem cell factor. This pathway activation is followed by activating several transcription factors regulating cell differentiation, apoptosis, proliferation, and angiogenesis **(13, 14)**.

In humans, the *KIT* gene is located on chromosome 4q12, adjacent to the highly homologous *PDGFRA* gene **(15, 16)**. Recent studies have shown that mutations and overexpression of its gene can lead to developing malignancies, such as gastrointestinal stromal tumors (GISTs), leukemia, and melanomas **(17-22)**.

The *PI3K* gene is located on chromosome 3q26. It is a heterodimeric enzyme, and p110a is a catalytic subunit encoded by *PI3K* **(23)**.

Important mutations in this gene generally involve activating a central element of this signaling pathway and phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit A (PIK3CA) involved in cell proliferation, survival, and growth **(23)**. *PI3K* mutation has been reported in breast cancer subtypes **(24)**.

Several studies have been conducted on the association between mutation and expression of the *PI3K* gene and malignancies, such as breast cancer **(25)**.

AKT is a serine/threonine-specific protein kinase that has an important role in several processes, such as apoptosis and cell proliferation. This gene is present downstream of *KIT* and *PI3K* genes.

It is associated with tumor cell survival, proliferation, and invasiveness. Also, activation of this gene is crucial in human cancers and tumor cells. Understanding the role of *AKT* and its pathways is crucial to find an appropriate method for cancer treatment **(26, 27)**.

AKT has three isoforms, namely *AKT1*, *AKT2*, and *AKT3*. *AKT1* is located on 14q32, *AKT2* on 19q13, and *AKT3* on 1q44.

AKT1 plays a crucial role in tumor development and angiogenesis. Although disruption of *AKT1* in mice suppressed physiological angiogenesis, it increased angiogenesis and tumor growth related to matrix abnormalities in skin and blood vessels **(28, 29)**.

AKT1 is involved in the KIT/PI3K/AKT pathway and other signaling pathways. *AKT2* regulates other *AKT* isoforms under hypoxic conditions; therefore, it operates as a significant regulator of *AKT* activity. Hypoxia induces the expression of *AKT2*. The importance of *AKT3* in proliferation, apoptosis, and tumor growth was examined next **(30, 31)**.

KIT Gene Mutations and Expression in Breast Cancer

The *KIT* gene is approximately 89 kb and has 21 exons **(32, 33)**.

Exons 1-9 of *KIT* encode an extracellular domain with five immunoglobulin-like loops, exon 10 encodes transmembrane domain, exon 11 encodes a juxtamembrane domain, and exons 13-21 encode a tyrosine kinase domain (Figure 1) **(34)**.

Several *KIT* mutations have specific clinicopathologic values and differ in their sensitivity to the inhibitor. In GISTs, exon 11 (KIT JM) and exon 17 (KIT TK2) have the highest frequency. Less frequently, mutations are reported in KIT exons 2, 8, and 9 (extracellular domain) or exons 13 and 14 (KIT TK1) **(35, 36)**.

Mutation of *KIT* sequences in the subtype of breast cancer has been reported. In general, *KIT* is positive in the normal ductal epithelial of the breast. However, breast carcinomas have been found with increased expression.

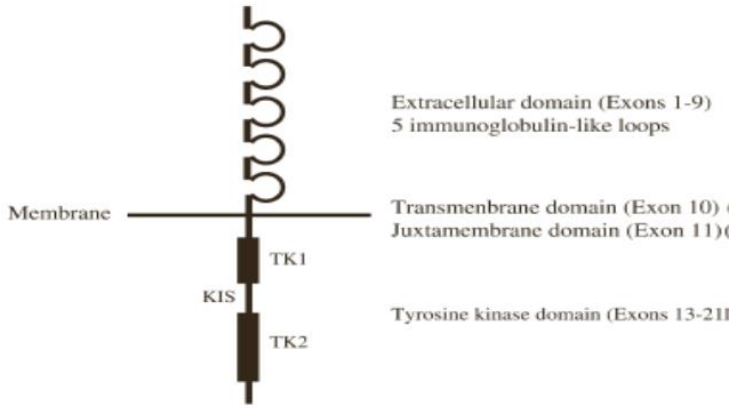

Figure 1. The KIT protein and its different domains (13)

This finding has been observed in *KIT* messenger RNA (mRNA) expressions in benign breast tumors (such as cystic fibrosis) that may retain *KIT* expression by the high differentiation status of epithelial and other cell sources **(37-39)**.

In a recent study, 27 out of 48 patients' tissues (56%) increased *KIT* gene expression compared to normal tissues **(40)**.

Another subset of tumors with myoepithelial-like components is adenoid cystic carcinoma of the breast, found as *KIT* positive **(41)**.

KIT positivity is almost prevalent in ductal carcinomas, HER2-positive, ER/PR, high-grade, keratin-positive, and prognostically unfavorable tumors.

KIT expression was observed in several typical cell types, including melanocytes, gastrointestinal Cajal cells, germ cells, mast cells, hematopoietic stem cells, and epithelial cells, especially ductal epithelia of the breast subsets neurons **(42-47)**. For study and diagnostic purposes, these tissues can be used as a positive control in immunohistochemistry (IHC) for *KIT*.

Accordingly, several studies have been conducted on the relationship between mutation types and overexpression in the *KIT* gene, but less frequent of these results have been significant.

A study on 348 cases revealed a relationship between enhancing copy numbers in exons 15 and 18 and overexpression in phyllodes tumors; 46% and 12% of the patients respectively showed an increase in expression and copy number of this gene **(48)**.

In another research, one mutation in exon 11 was found in triple-negative breast cancer (TNBC) tumors, and its overexpression was found in them **(49)**.

In another study on phyllodes tumors, 2 of 13 cases of *KIT* had exon 17 alterations and overexpression **(50)**.

In another study, 9 of 29 cases with TNBC and 9 of 18 cases with non-TNBC enhanced copy numbers and overexpression **(51)**. A recent study showed that 27% of patients enhanced copy numbers **(52)**. Another study indicated that patients with increased exon 7 CNV were in stage 3. Also, 60% of cases in exon 17, 60% in exon 18, and nearly 67% in exon 19 with enhanced CNVs had a tumor size of 2-5 cm; these findings are significant **(53)**.

In a research study, *KIT* gene mutations were determined as 3.44%, 5.17%, 5.17%, 3.44%, 3.44%, and 5.17%, respectively, in exons 8, 9, 11, 13, 15, and 17 in breast cancer. The frequency of all *KIT* mutations in these exons was 25.86% **(54)**.

These mutations can be distinguished from the activating mutations reported in GISTs. Genetically, they can indicate variations in cancer tumors. Also, an increased *KIT* copy number has almost been seen in breast cancer, unlike other cancers **(17, 18, 48, 55-61)**. Table 1 shows the classification of studies performed.

Table 1. *KIT* variations and expression in various breast cancer types

Type	Overexpression	CNV	Exon mutation	References
TNBC	31-85%	22-42%	Exon: 11	**(49,51,58,59)**
Non-TNBC	7-50%	18-50%		
Malignant	12-100%	46%	Exons: 1,2,7,8,9,11,13,15,17,18,19,21	**(40,52,53,54,56)**
Ductal carcinoma	24-60%	28-50%	Exons: 11,13,17	**(58,59,60,61)**
Phyllodes tumor	46%	12%	Exons: 15,17,18	**(48,50)**

We believe that the pattern of expression, mutation, and copy number genes in breast cancer is different from other cancers. This phenomenon is due to different mechanisms by which cancers develop. However, the type of mutations and expression are useful in categorizing different cancer types and subtypes. This matter can be helpful in breast cancer treatment, especially TNBCs.

Kit Inhibitors

Several monoclonal and polyclonal antibodies against the kit have been produced and are available. In several cancers, such as leukemia and GISTs, tyrosine kinase inhibitors are crucial drugs **(62, 63)**.

The novel kit tyrosine kinase inhibitor, named imatinib mesylate (Gleevec formerly known as STI571), has shown to be effective in the treatment of metastatic cancers and GISTs; this encourages researchers to investigate other possible *KIT*-induced tumors. Imatinib drug is an adenosine triphosphate (ATP) analog for inhibiting kit. This drug is used against chronic myeloid leukemia and GISTs **(64)**.

Tumors with exon 11 mutations have a good response. Those with exon 9 mutations are associated with moderate response and inadequate response with wild-type sequences. Those with exon 17 mutations have an inadequate response because of primary resistance **(65)**.

Reciprocally, overexpression of the *KIT* gene leads to tumors of *KIT*-dependent cell types, such as mast cells, Cajal cells (GISTs), and germ cells **(66)**.

Secondary resistance, such as the development of *KIT* gene amplification and *KIT* mutations, was also reported **(67)**.

Another tyrosine kinase inhibitor is sunitinib, a small-molecule tyrosine kinase inhibitor for imatinib-resistant patients **(68)**.

Sorafenib is another drug investigated in combination with other drugs in breast cancer. The clinical efficacy and safety of these drugs are still being investigated in clinical trials and studies. For instance, sorafenib has limited efficacy as a single agent in breast cancer; thus, studies are ongoing to evaluate its use combined with other drugs. Dose decreasing is the critical problem when sorafenib is used with other drugs or endocrine therapy. Further research can help discover a suitable dose **(69)**.

Ponatinib is a multi-kinase inhibitor, such as *KIT*, *FGFR*, and *BCR-ABL*, to treat leukemia **(70, 71)**. Nevertheless, no studies have been conducted on the effect of this drug on the inhibition of the *KIT* gene in breast cancer.

Regorafenib is a multi-kinase inhibitor that suppresses the activity of several tyrosine kinases involved in angiogenesis and oncogenesis, such as VEGFR, PDGFR, FGFR, BRAF, RET, and *KIT* **(72)**. Table 2 shows the drugs of kit inhibitors.

Currently, almost all tumors are tested for *KIT* positivity as potential targets for treatment with kit inhibitors. However, mutations in *KIT* activation are rarely found, leading to less successful treatment, with the possible exception of some myeloid leukemias. Insufficient variation and reproduction of kit staining have been common problems, especially with polyclonal antiserums. This matter has led to significant heterogeneity in the data, which is currently challenging to adapt to tumors (Figure 2) **(13, 73)**.

Table 2. Drugs of kit inhibitors

Drug name	Product name	Groups	References
Imatinib	Gleevec	Approved	**(64)**
Sunitinib	Sutent	Approved	**(68)**
Sorafenib	Nexavar	Approved	**(69)**
Ponatinib	Iclusig	Approved	**(70,71)**
Regorafenib	Stivarga	Approved	**(72)**

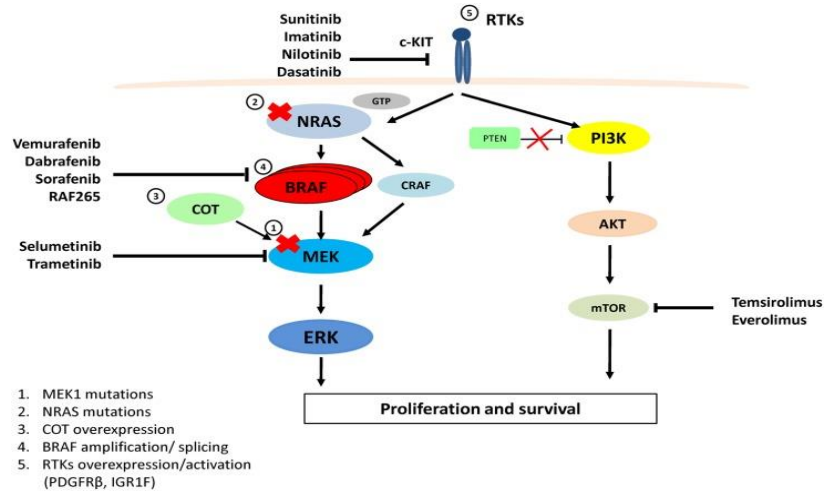

Figure 2. RTK signaling genes and drug inhibitors (73)

PI3K Gene Mutations and Expression in Breast Cancer

Overexpression of the *PI3K* gene can cause cell proliferation and develop cancer cells, and it can be used as a biomarker for breast cancer treatment **(74)**. To date, several intracellular pathways have been identified, and *PI3K* has a crucial role in breast cancer development **(75, 76)**. Mutation and overexpression of the *PI3K* gene can be discussed as a crucial target in breast cancer treatment **(77)**.

Oncogenic mutation in *PI3K* is estimated in two various functions: activating mutation in the *PI3K* gene and downregulation of the expression of *PTEN*. Mutation in *PI3K* can be considered a key targeted therapy in breast cancer. *PI3K* opens a new window for clinicians to treat breast cancer. Several studies have indicated that the prevalence of *PI3K* mutations in breast cancer is from 8% to 40% **(75, 78)**.

One study showed that *PI3K* overexpression occurred in 24% of all tumor samples in breast carcinomas **(79)**.

However, some studies have shown different results. For example, in a study, 54.5% of patients showed overexpression of the *PI3K* gene. It was shown that 20% and 17.5% of patients had mutations and CNV in the *PI3K* gene, respectively **(52, 80)**. In contrast, another study showed a significant positive relationship between mutations and *PI3K* expression in breast cancer **(81).**

Other studies have reported that activating mutations in *PI3K* account for approximately 30% of breast cancers and more in ER-positive. In particular, in exons 9 and 20, 80% of *PI3K* mutations are found. These two exons encode the helical and kinase domains, and they are considered hot spots for mutations **(82-84)**.

Also, in TNBC, *PI3K* interacted directly or indirectly with ER and ER phosphorylation **(85, 86)**. Estrogen deprivation has been shown to reduce *PI3K* activity. *PI3K* is generally mutated positively in ER. Another study showed that *PI3K* mutation occurred in at least 41.3% of ER-positive tumors **(87, 88)**.

It has been indicated that about 40% of *PI3K* mutations are ER-positive and HER2-negative in both metastatic and primary breast malignancies. *PI3K/AKT* activation can occur by attached HER signaling as a ligand **(89)**.

Also, in TNBC, even though the mutation is at a low rate, the PI3K pathway activity by gene expression or protein array signatures is at a high level **(90)**.

Another investigation showed that the proportion of *PI3K* mutations in HR-positive/HER2-negative is 42%, in HER2-positive is 31%, and in TNBC is 16% **(91)**.

PI3K mutation was found in 28% of HR-positive/HER2-negative tumors and 10% of TNBCs **(92)**.

PI3K mutation was 12.5% in the TNBC subgroup to 41.1% in the HR-positive/HER2-negative subgroup **(93)**.

Another review study showed that the rate of *PI3K* mutation is 23%-33% in HER2-positive tumors and 8% in TNBC or basal-like TNBC (94).

Activating *PI3K* mutation has been seen in 30%-50% of advanced ER-positive/HER2-negative breast cancers, but *PI3K* is low in ER-negative breast cancers **(95)**.

In another study on exons 9 and 20, on the contrary, regarding the relationship between *PI3K* mutations and some clinical features, such as age, lymph node metastases, tumor size, ER status, and PR, p53 expression, and mutations in breast cancer, no significant results were reported **(81)**.

We believe that differences between the present study and other studies are due to variations in samples. Table 3 shows the classification of studies performed.

Table 3. *PI3K* variations and expression in various breast cancer types

Type	Overexpression	CNV	Exon mutation	References
All types	24-54%	17%	8-80%	**(52,75,77-81)**
TNBC	-	-	8-16%	**(75,77-79,90-94)**
ER-positive	86-100%	-	30-50%	**(82-84,87-89,95)**
HER2- positive	-	-	23-33%	**(91,92,94)**
HER2- negative	-	-	28-70%	**(89,91-93,95)**

PI3K Inhibitors

PI3K mutations can be considered as biomarkers and have been the main focus of developing cancer drugs. The first clinical trials of RTK pathway inhibitors are underway. *PI3K* mutation screening can be helpful in genetic tests for diagnosis and targeted therapeutics.

PI3K inhibitors have received a great deal of attention in the development of breast cancer drugs **(96)**.

There are several PI3K inhibitors, such as sonolisib (PX-866; for solid tumors), perifosine (for colorectal cancers), idelalisib (for CML), copanlisib (BAY 80-

6946), serabelisib (for hematologic cancers), duvelisib, alpelisib, umbralisib, taselisib, buparlisib, and endocrine therapies **(96-104)**. Table 4 shows the drugs of PI3K inhibitors.

Table 4. Drugs of PI3K inhibitors

Drug name	Product name	Groups	References
Idelalisib	Zydelig	Approved	**(96-104)**
Perifosine	KRX-0401	Phase III clinical trials	**(96-104)**
Sonolisib	PX-866	Phase III clinical trials	**(96-104)**
Copanlisib	BAY 80-6946	Approved	**(96-104)**
Duvelisib	Copiktra	Approved	**(96-104)**
Serabelisib	INK1117	Phase I	**(96-104)**
Alpelisib	BYL719	Approved	**(96-104)**
Umbralisib	Ukoniq	Approved	**(96-104)**
Taselisib	GDC-0032	Phase III clinical trials	**(96-104)**
Buparlisib	BKM120	Phase III clinical trials	**(96-104)**

On the other hand, despite many kit inhibitors, such as imatinib, resistance is frequently observed **(105)**; as a result, PI3K inhibitors can be helpful in RTK inhibiting.

An investigation showed that p110α isoform-selective inhibitors were highly potental for inhibiting *PI3K* mutant inhibitors and promising **(106)**. *PI3K* mutations can lead to resistance to kinase inhibitors. Therefore, there are various molecular features for breast tumors that should be considered when making treatment decisions. If there is no *PI3K* mutation, we can estimate the clinical/preclinical effect for the treatment **(107)**.

A drug that acts by inhibiting one or more PI3K enzymes, the PI3K inhibitor, is part of the RTK pathway leading to metabolism, growth control, and translation initiation. The inhibition of many components in this pathway may lead to tumor suppression. These drugs are examples of targeted cancer therapy **(107)**. Further investigation may demonstrate the efficacy of these medicines in the treatment of breast cancer.

AKT Gene Mutations and Expression in Breast Cancer

Several studies have investigated the relationship between *AKT* overexpression and breast cancer, with inconsistent results **(108)**.

Many studies have reported the relationship between *AKT* and prognosis of breast cancer, onset, metastasis, and hormone therapy resistance. Evaluation of the expression and activation of *AKT* isoform in breast cancer and *AKT1* and *AKT2* expression in all breast cancer cell lineages has been done; however, the luminal breast cancer subtype has a high frequency. Also, *AKT3* expression is associated with the TNBC subtype **(109)**.

AKT1 has a crucial role in the onset of breast cancer and tumor development. In contrast, *AKT2*, through the formation of metastases, has an essential role in breast cancer progression. *AKT3* has a crucial role in TNBC and ER-negative breast cancer. *AKT3* is a pro-proliferative, anti-metastatic, and pro-oncogenic factor **(109)**.

Generally, *AKT* overexpression in cancer is related to a poor prognosis **(110)**.

Another study showed that 33% to 40% of breast tumors have *AKT* mutation **(111)**.

In 2016, it was demonstrated that 4% of tumors had a mutation in *AKT*, and 14% had overexpression of this gene **(112)**.

One study showed that 2.6% to 3.8 % of mutations in *AKT* were HR-positive/luminal, and 0% were HER2-positive and TNBC or basal-like. Also, 2.8% of HR-positive/luminal tumors showed *AKT* amplification **(92)**.

Increasing evidence suggests that in early-stage breast cancer, *AKT* is associated with a good prognosis in ER-positive and a poor prognosis in ER-negative. In node-positive breast cancer, *AKT* is identified as a predicted benefit of paclitaxel chemotherapy **(113)**.

A study showed that 1.4% of all tumors, 2.6% of HR-positive tumors, 3.2% of ER-positive/PR-positive tumors, and 0% of TNBCs have *AKT* mutation **(114)**.

In a study, 33% of cases showed overexpression of *AKT*, 33% had DCIS, and 38% had invasive cancer **(115)**.

Overexpression of *AKT* was observed in 44% of HER2-positive tumors compared to 22% of HER2-negative tumors **(116)**.

One study showed that the frequency of *AKT1* expression was about 24% **(116)**.

A microarray study on invasive breast cancer showed a positive correlation between *AKT1* expression and ER and HER2 status, as well as an inverse relationship between *AKT1* expression and metastatic, tumor stages, and nodal status **(117, 118)**.

Immunohistochemical staining showed that 24% of tumors were associated with *AKT1* and 4% with *AKT2* **(117)**.

In other breast cancer tissues, HER2 expression was associated with overexpression of *AKT2*, but not *AKT1*; also, *AKT2* protein overexpression was found in a breast cancer cell line by ectopic expression HER2 **(116)**.

Gene amplification of *AKT2* was found in 3% of tumors in a breast cancer study **(119)**.

Based on a study, an increase in the copy number gene of *AKT2* was observed in 2.8% to 4% of breast cancer tumors. **(117, 119)**.

In metastatic HER2-positive breast cancer, AKT1 and AKT2 overexpression levels were 12.2% and 35.1% **(120)**.

In breast cancer tissue, *AKT3* is overexpressed compared to the adjacent normal breast tissue **(121)**. The findings of this study did not show a significant relationship between its expression and hormone status, but *AKT3* was expressed in TNBCs **(122, 123)**.

AKT3 is amplified in 28% of breast cancers, according to The Cancer Genome Atlas (TCGA) **(124)**.

Based on TCGA, the importance of *AKT3* in TNBC was the amplification of this gene in 14% of TNBCs and 3% of luminal breast cancers, and overexpression of mRNA was found in 21% of TNBCs and 2% of luminal breast cancers **(125)**.

Also, the increased copy number of the *AKT3* gene was seen in TNBC **(126)**.

Table 5 shows a classification of studies performed.

Table 5. *AKT* variations and expression in various breast cancer types

Type	Overexpression	CNV	Exon mutation	References
All types	4-38%	2.8-28%	1.4-40%	**(110-112,114-117,119,121,124)**
TNBC	21%	14%	0	**(92,109,114,122,123,125,126)**
ER-positive	76%	-	3.2%	**(114)**
HER2-positive	12.2-44%	-	0%	**(92,116-118,120)**
HER2-negative	22%	-	-	**(116-118)**

Akt Inhibitors

Akt inhibitors can be helpful to treat cancers due to the Akt functions mentioned earlier. Several Akt inhibitors are currently in the clinical trial stage **(127)**.

The findings obtained from the Akt inhibitor process were associated with adenosine triphosphate (ATP)-competitive factors with different approaches using allosteric sites to suppress a very structural similarity between Akt isoforms in the catalytic domain and regardable structural analogy to the cytoplasmic serine/threonine kinase family. This process resulted in finding inhibitors with higher specificity, decreased toxicity, and fewer side effects. The second-generation Akt inhibitors are chemically reactive using a Michael acceptance pattern to target the nucleophilic cysteines in the catalytic activation loop **(128)**.

All of the major components of the RTK pathway, including Akt, are being studied in depth in order to develop targeted therapies **(129)**.

In 2011, phase 1 of the MK-2206 study on advanced solid tumors was reported **(130)**. Several phase II studies have also been conducted on numerous cancer types **(131)**.

In 2013, the results of the AZD5363 phase I study in solid tumors were reported **(132)**. Also, a study of AZD5363 with olaparib was reported in 2016 **(133)**.

In another study, ipatasertib is in phase II trials for TNBC **(134)**.

Triciribine (TCN) or triciribine phosphate (TCN-P) monotherapy is used for solid tumors, such as breast cancer. However, clinical efficacy is limited due to toxicity **(135)**.

GSK2110183 (afuresertib) is an orally available ATP-competitive and pan-AKT kinase inhibitor. It attenuated the phosphorylation levels of various Akt substrates (FOXO and caspase-9) in breast cancer **(136)**. Table 6 shows the drugs of Akt inhibitors.

However, Akt inhibitors alone almost demonstrate limited clinical activity. Then, combinatorial treatments are helpful for Akt inhibitors.

Table 6. Drugs of Akt inhibitors

Drug name	Product name	Groups	References
MK-2206	-	Phase II clinical trials	**(130-131)**
Capivasertib	AZD5363	Phase I	**(132-133)**
Ipatasertib	PX-866	Phase II clinical trials	**(134)**
Afuresertib	GSK2110183	Phase I	**(136)**

Conclusion

The findings revealed that *KIT*, *PI3K*, and *AKT* genes might have a role in cancer progression, especially in the development of sporadic breast cancer. These genes affect clinicopathological variables, such as angiogenesis (CD34), stage, grade, HER2, and ER. On the other hand, these genes alone can directly lead to the development of breast cancer because they start many critical pathways.

Studies have been conducted in some populations, such as Europe, Asia, America, etc., and the subtypes of different breast cancers.

Several tyrosine kinase inhibitors are currently used as drugs in other cancers to suppress these genes; accordingly, they can be used to treat and suppress the subtypes of different breast cancers, especially TNBC, with no common tissue markers in the future. Also, administering the inhibitors of these genes can suppress sporadic breast cancer.

Also, this matter is crucial that mutations in these pathway genes can cause resistance to tyrosine kinase drugs.

In this regard, more detailed studies are needed to confirm these findings and better understand and manage breast cancer patients.

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Conflict of Interest

The authors declared no conflict of interest.

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