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RESEARCH ARTICLE

Investigation of the Relationship between the AKT1 rs1130233 (G>A) Polymorphism and the Risk of Breast Cancer in Iraqi Women

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Abstract

Background: Genetic changes like as single-nucleotide polymorphisms (SNPs) in the AKT1 gene have been linked to carcinogenesis. The AKT kinases are important regulators of cell survival, proliferation, and apoptosis, and evidence suggests that the rs1130233 (G>A) SNP affects AKT1 expression and leads to breast cancer. The aim of this study was to investigate the association between the AKT1 rs1130233 (G>A) single-nucleotide polymorphism and the susceptibility to breast cancer in Iraqi women, and to evaluate its potential role as a diagnostic biomarker. **Methods:** A case-control study was carried out on 200 people, comprising 100 breast cancer patients and 100 healthy controls. Genomic DNA was isolated from peripheral blood samples and genotyped using the polymerase chain reaction (PCR) technique. **Results:** The wild-type homozygous GG genotype was much more common in healthy women (79%) than in patients (30%), indicating a preventive function against breast cancer. In contrast, the heterozygous GA (30%) and mutant homozygous AA (40%) genotypes were more common among patients, indicating a higher risk of developing breast cancer. Allele frequency analysis revealed that the A allele was linked to a greater incidence of breast cancer ($p < 0.01$). **Conclusion:** The AKT1 rs1130233 (G>A) polymorphism is strongly linked to breast cancer risk in Iraqi women. The G/G genotype may provide protection, while the A allele increases susceptibility. These findings emphasize the potential use of the AKT1 polymorphism as a diagnostic biomarker, while further validation in larger and more diverse populations is suggested.

Keywords: Proto-Oncogene Proteins c-akt- Signal Transduction- Breast Neoplasms- polymorphism

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Introduction

The AKT gene family comprises three isoforms AKT1 (PKBα), AKT2 (PKBβ), and AKT3 (PKBγ) which collectively regulate cell growth, proliferation, and survival. The AKT1gene (is found on chromosome 14) supply order for making a protein that called AKT kinase [1], is a serine/threonine kinase protein that has important role in many cell procedures such as cell proliferation, cell immigration, and direct the intracellular signal transduction [2, 3], also AKT protein helps regulate the cell growth and the proliferation (division), the process by which the mature cells perform specific functions (differentiation), and help it to survival [4]. On the other hand, AKT protein also helps control apoptosis, the process that causes cells to destroy themselves when they are no longer needed or are damaged [5], and angiogenesis in both normal and malignant cells [6]. The AKT kinase is found in many cell types throughout the body [7]. Any disorder of the AKT1 signaling pathway is directly related to many of the most common human diseases, such as cancers [8-11]. The AKT1 gene belongs to a category of featured genes known as oncogenes; the functions of oncogenes are to regulate the growth, cell proliferation, and differentiation, and also regulate apoptosis and the cell cycle [12, 13]. Three isoforms of the AKT1 gene were found in humans, namely AKT1, AKT2, and AKT3, which are coded by different genes [14-17].

The activation of AKT1 can start with several events, mostly when the ligand binds to the receptor of the

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cell membrane [18]. There are many common ligands activating AKT1, like cytokines, mitogens, growth factors, and hormones [19]. Sometimes the oncogene genes are mutated; therefore, normal cells can develop into malignant ones due to oncogenes [20]. The mutation in the AKT1 gene has been found in breast, colorectal, and ovarian cancers [21]. The mutation in the AKT1 gene is somatic, which means it is acquired during a person's lifetime and is found only in tumor cells [22]. The AKT1 gene is aberrantly activated by the mutation, enabling unchecked cell division and growth. This disordered cell proliferation guides the development of malignant tumors [23]. Although the AKT1 rs1130233 G > A mutation has been identified in only a few types of cancer, high expression of the gene AKT1 is found in numerous types of cancer [24-26]. In Iraq breast cancer is consider as high effect between women, many research are show that the breast cancer is cause by genetic mutations such as (eNOS gene SNPs rs1799983/ rs2070744, SNP rs3757318, miR-146) [27-29], and other mutations in genes such as PTEN, TP53, BRCA1, BRCA2 which carry a high risk of breast cancer development [30]. the aim of this study was to investigate the association between the AKT1 rs1130233 (G>A) single-nucleotide polymorphism and the susceptibility to breast cancer in Iraqi women, and to evaluate its potential role as a diagnostic biomarker.

Materials and Methods

Blood samples (200 samples) were collected during the period from January

from April 2024, comprising 100 samples of breast cancer patients and 100 from healthy women as volunteer blood donors (control group). All participants were Iraqi citizens, nonsmokers, and their ages ranged between 30 -70 years. The patients were diagnosed by doctors and a specialist surgeon at Oncology Hospital and Baghdad Teaching Hospital in Baghdad, Iraq. The clinicopathological demographic data for participants were obtained from patients' hospital records, and a questionnaire was prepared for the controls (healthy women). Informed consent was obtained from all participants, and the study was approved by the Ethics Committee of the National Cancer Research Center, University of Baghdad.

Genomic DNA extraction

We collect fresh blood samples from all participants in EDTA K3-containing tubes for molecular studies and store them at -20 °C. DNA is isolated from blood samples from the patients and the healthy women as a control. By using a blood DNA extraction kit (46300-Norgen®, Canada, according to the manufacturer's protocol. DNA was purified. Measurement of DNA Purity and concentration was done by spectrophotometry.

Ethical Approval

Ethical approval and consent to participate

The study protocol entitled "The AKT signaling pathway gene as a diagnostic biomarker in Iraqi women with breast cancer" was reviewed and approved by the Ethical Approval Committee of the Iraqi National Cancer Research Center, University of Baghdad (Approval Ref. 77, dated 03/10/2025). All procedures involving human participants were conducted in accordance with the Declaration of Helsinki and relevant institutional guidelines. Written informed consent was obtained from all participants prior to enrollment, and data were anonymized to protect confidentiality.

Consent for publication

All participants provided consent for publication of de-identified data. All authors reviewed and approved the final manuscript.

Amplification of AKT1 rs1130233 G > A polymorphism

The Polymerase Chain Reaction (PCR) technique was used to identify and amplify the rs1130233 G > A SNP of the gene AKT1. The sequence of AKT1 genomic (NC_000014.8) was obtained from the National Center for Biotechnology Information (NCBI) (http://www.ncbi.nlm.nih.gov). For this experiment, the primer sequences were prepared according to William et al. (2004) [31]. The sequences of these primers are listed in Table 1.

The primers were supplied by Alpha DNA, Canada, as a lyophilized product of different picomole concentrations. The primers were lyophilized, they dissolved in a free DNase/RNase water to give a final concentration of 100 p mol/µl (as a stock solution) and kept as a stock in -20°C to prepare 10 p mol/µl concentration as work primer resuspended 10 µl of the stock solution in 90 µl of free DNase/RNase to reach a final volume 100µl (10 P mol). To perform PCR (Polymerase chain reaction), we used a PCR premix kit from Bioneer, South Korea, according to the manufacturer-recommended protocol. We put 1 µL DNA template,1 µL of primer forward and reverse, 15 µL DNase-free to a 0.2 mL PCR tube that contained the PCR Pre-Mix.The total volume of the PCR reaction was 25µl. After preparing the reaction mixture in a PCR tube, it was vortexed and then placed in the PCR thermal cycler (Pranoto, 2005) [32]. The PCR program used to amplify the G/A (rs1130233) SNP was as follows: at first, five minutes at 95°C, then 30 cycles at 95°C for 30 s, 30 seconds at 58°C, and a final step of 30 seconds at 72°C and again by ten minutes. Afterwards, the PCR product was separated by electrophoresis on 2% agarose gel stained

Table 1. Nucleotide Sequence of Primers SNP rs1130233 G > A

AKT1 gene	Primers	Sequence (5--3)		Product size(bp)
SNP rs1130233 G > A	Forward	5′-TGTTCTTCCACCTGTCCCGGTAG 3′	(G allele)	213 bp
	Reverse	5′-CCGGTCCTCGGAGAACACAAGT-3′	(A allele)	298 bp

Table 2. Effect of Age on CA15.3 in the Patient Group

Age groups (year)	Mean ±SE of CA15.3
<40 yr.	17.70 ±1.52
40-50 yr.	18.87 ±.1.13
>50 yr.	19.61 ±1.83
L.S.D.	2.052 NS
P-value	0.338

NS, Non-Significant.

with 1µl (10mg/ml) ethidium bromide at 75 volts for 1 h in 1X TBE buffer. A total of 6µl aliquot from each sample was loaded onto the gel, and 5µl of a 50 bp DNA ladder was used as a marker.

Statistical Analysis

The Statistical Packages of Social Sciences (2019) [33] program was used to detect the effect of different groups (patients and controls) on study parameters. T-test and Least Significant Difference were used to significantly compare between means. Chi-square test was used to significantly compare percentages (0.05 and 0.01 probability. Estimate of the Odds ratio and Confidence interval of SNP (Hardy-Weinberg law) in this study.

Results and Discussion

The range age of the women participants was 30_70 years in patients with breast cancer and the apparently healthy subjects as a control in a sample of the Iraqi population. There was no significant difference between the groups in CA15-3 levels of patients and age, p-value were 0.338 (Table 2).

The genotype and the allele frequency of the Akt1gene G/A SNP rs1130233 polymorphism are shown in Table 3. Of the 100 patients with breast cancer, the wild-type allele G generated a 213 bp band and the mutant allele A generated a 289 bp band. The frequency of the wild type GG (homozygous) genotype was significantly lower in breast cancer patients (30.00%) compared with healthy women (79.00%) (Chi-Square =22.027 **, P-value =0.0001, O.R. =1). The results show that the GG homozygote could retain a useful effect for the protection against breast cancer risk. The frequency of heterozygous of the GA genotype was significantly lower in apparently healthy women (20.00%)in comparison with breast cancer patients (30.00%) (Chi-Square =2.00 NS, P-value 0.157, O.R=0.671)

The double asterisk (**) in the tables indicates a highly significant difference at $p < 0.01$.

Whereas, the frequency of homozygous mutant AA genotype was significantly higher in patients with breast cancer (40.00%) than in healthy women (1.00%) (Chi-Square =37.09 **, P-value =0.0001, O.R.=1.97). These results indicate that the allele A can be related to an increased risk factor for Iraqi breast cancer patients. The frequency of the G allele was (0.89) and (0.45) in healthy women and patients, respectively, (Chi-Square =28.89 **, P-value =0.0001, O.R. =1.91). In contrast, the frequency of the A allele was (0.11) and (0.55) in the apparently healthy women and breast cancer patients, respectively, (Chi-Square=58.67 **, P-value=0.0001, O.R.=1.86). In the present study, the two types of mutant genotypes frequencies GA, AA, for the AKT1 gene were significantly higher in patients compared with healthy women. A statistically significant difference in gene AKT-1 G > A genotypes was seen between the breast cancer patients and healthy women as controls ** ($P \leq 0.01$).

The results of the relationship between AKT1 rs1130233 G > A polymorphism and CA15.3 levels of the patients group of breast cancer patients are shown in Table 4. There was a highly significant ($P \leq 0.01$) difference. The Mean ±SE of CA15.3 levels of patients with (GG) alleles is 9.51 ±0.47 c, while the Mean ±SE of (GA) 16.08 ±0.37 b, and (AA) alleles are 27.65 ±0.40 a, respectively. The overall CA15-3 levels in all categories (wild type homozygous, heterozygous, and mutant homozygous) of patients were L.S.D.=2.871 **, and P-value=0.0001. The double asterisk (**) in the tables indicates a highly significant difference at $p < 0.01$.

There was a highly significant ($P \leq 0.01$) difference between tumor stage and the rs1130233 G > A SNP is shown in table 5, for the alleles GG, GA, and AA in the tumor stage PT 1, PT2, and PT3, the P-value=0.0001 **,0.0001 **, and 0.0092 **respectively. Also, the effect of tumor stage on the CA15.3 level of the patients group that as shown in Table 5, the results was highly significant ($P \leq 0.01$) between them. The Mean ±SE in CA15.3 on stages PT1,PT2 and PT3 are 12.34 ±0.53 c,24.16 ±0.97 b and 29.00 ±0.79 a, respectively. The double asterisk (**) in the tables indicates a highly significant difference

Table 3. Genotype Distribution and Allele Frequency SNP rs1130233 G > A in Control and Breast Cancer Groups

Genotype/ SNP rs1130233 G > A	Control No. (%)	Breast cancer No. (%)	Chi-Square	P-value	O.R. (C.I)
GG	79 (79.00%)	30 (30.00%)	22.027 **	0.0001	Ref. =1
GA	20 (20.00%)	30 (30.00%)	2.00 NS	0.157	0.671 (0.42-1.15)
AA	1 (1.00%)	40 (40.00%)	37.09 **	0.0001	1.97 (1.22-3.63)
Total	100	100			
Allele	Frequency			---	
G	178 (0.89)	90 (0.45)	28.89 **	0.0001	1.91 (1.27-3.29)
A	22 (0.11)	110 (0.55)	58.67 **	0.0001	1.86 (1.08-2.76)

** ($P \leq 0.01$).

Table 4. Effect of SNP rs1130233 Polymorphism in CA15.3 of Patients Group

SNP rs1130233	Mean ±SE of CA15.3
GG	9.51 ±0.47 c
GA	16.08 ±0.37 b
AA	27.65 ±0.40 a
L.S.D.	2.871 **

Means with the different letters in the same column differed significantly. ** (P≤0.01).

Table 5. Relationship between Tumor Stage and SNP rs1130233 G > A Distribution in Breast Cancer Groups

SNP rs1130233 G > A	Tumors Stage			P-value
	PT1	PT2	PT3	
GG	29 (29.00%)	1 (1.00%)	0 (0.00%)	0.0001 **
GA	21 (21.00%)	9 (9.00%)	0 (0.00%)	0.0001 **
AA	0 (0.00%)	30 (30.00%)	10 (10.00%)	0.0001 **
P-value	0.0001 **	0.0001 **	0.0092 **	---

** (P≤0.01).

Table 6. Effect of Tumor Stage on CA15.3 in the Patient Group.

Tumors Stage	Mean ±SE of CA15.3
PT1	12.34 ±0.53 c
PT2	24.16 ±0.97 b
PT3	29.00 ±0.79 a
L.S.D.	3.557 **
P-value	0.0001

Means with the different letters in the same column differed significantly. ** (P≤0.01).

at $p < 0.01$.

Also, the effect of tumor stage on CA15.3 in the patient group that shown in Table 6.

The Mean ±SE in CA15.3 on stages PT1,PT2 and PT3 are 12.34 ±0.53 c,24.16 ±0.97 b and 29.00 ±0.79 a, respectively.

Table 7 shows the distribution of the sample study according to relative in apparently healthy subjects as a control.

This study aims to see whether the Akt1 SNP G/A (rs1130233) polymorphism, that located on chromosome 14, has any association with breast cancer in Iraqi women. We found there was an association between the AKT1 gene and breast cancer. Both types, the heterozygous G/A and homozygous mutant A/A genotype, seem to be considered to increase susceptibility to breast cancer development in the patients we investigated. AKT plays a key role in the invasion and replication of several microorganisms [34]. The Akt1 gene has several SNP polymorphisms that have been associated with many diseases, such as bipolar disorder, Schizophrenia, and Parkinson's disease [34,35]. In this study, the results are consistent with other studies' results. Such as. Alzahrani, O.R.; et.al (2023) [36], they found that breast cancer patients have the frequencies of gene AKT1 (rs1130233) G > A genotypes GG (50%), GA (40%), and AA (10%), compared to controls that have frequencies of GG (78.43%), GA (19.60%), and AA (1.90%), respectively, and they discovered that the patients in breast cancer had a higher frequency of A allele than controls (0.30 vs. 0.12). [37], have shown that the AKT1 SNP rs1130233 has an effect in increasing brain activation. [36], found that the PI3K-AKT pathway is the intracellular network that plays a big role in breast cancer cells. [37], found that a relationship between genotype type and tumor size (P> 0.05), and suggest that the rs1130233 polymorphism G / A for the AKT1 gene may have to relative risk of developing tumors in the thyroid.

In conclusion, this study demonstrated that the gene AKT1 with SNP rs1130233 G > A has been significantly correlated with breast cancer disease. This finding suggests that SNP rs1130233 G > A polymorphism could be used to detect breast cancer instances, but we need further investigations with large and diverse population samples.

Table 7. The Distribution of the Sample Study According to the Relative in the Control Group

Relative	No	Percentage (%)
Not relative	36	36
Sister	20	20
Aunt	12	12
Nephew	12	12
Daughter	12	12
Mother	8	8
Total	100	100%
P-value	---	0.0001 **

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The raw data required to reproduce these findings are available in the body and illustrations of this manuscript.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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