Original Article ISSN (O):2395-2822; ISSN (P):2395-2814



# Role of Angiotensin Converting Enzyme (ACE) Gene Polymorphism in Breast Cancer among North Indian Population

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Received: September 2019
Accepted: September 2019



## ABSTRACT

**Background:** The most common cause of cancer related death among women in the world is Breast cancer (BCa). Almost Every year, approximately 1,300,000 cases and 450,000 deaths are related with Carcinoma of Breast are reported worldwide. The incidence of invasive Carcinoma of Breast and mortality in American women in 2017 was 252,710 and 40,610 respectively as quoted by a study. According to latest survey conducted by the Indian Council of Medical Research (ICMR) in India, there were an estimated 150,000 new cases of Carcinoma of Breast in the year 2016. The rise in both Carcinoma of Breast incidence and mortality, therefore, necessitates an examination of risk factors associated with this disease. Molecular subtypes-based classification system characterized by the presence or absence of immunohistochemical expressions like Progesterone receptor (PR), Estrogen receptor (ER), and Human epidermal growth factor receptor 2 (HER2) may show certain limitations. The gene encoding ACE (Angiotensin Converting Enzyme,) in humans is located in the chromosome 17 (17q23), consisting of 26 exons and 25 introns and spanning 21 kb. ACE is a zinc dependent dipeptidyl carboxypeptidase which catalyzes conversion of inactive decapeptide Angiotensin I (Ang I) to active octapeptide Ang II . Ang II mediates physiological effects by binding to two subtypes of the receptors, AGTR1 and Angiotensin II receptor type II (AGTR2), which belongs to superfamily of G-protein-coupled receptors (GPCRs).So, keeping all these physiological effects in mind, this study was conducted to see the role of ACE gene in carcinoma of breast. **Methods:** From confirm and control cases 3.0 ml of venous blood from each study subject was collected in an EDTA vial. Genomic DNA was extracted by phenol-chloroform method. The genotyping was performed by using PCR (Polymerase Chain reaction), using gene-specific primers. The resulting PCR products were separated on 2% agarose gels using ethidium bromide stain and visualized under UV light. The clinicopathologic parameters of breast cancer patients were obtained from medical records. **Results:** Of the 10 patients, 3 (30%) had Deletion/deletion genotype DD, 6 (60%) had ID, and 1 (10%) had II genotypes. In control subjects, 2 (20%) had DD, 6 (60%) had ID, and 2 (20%) had II genotypes. **Conclusion:** The results showed no significant association of ACE gene polymorphism with breast cancer (p>0.05). There is a necessity to conduct large-scale studies with adequate methodological quality and larger sample size in order to come to a definitive conclusion.

***Keywords:*** Breast cancer, ACE gene, polymorphism, Genomic DNA, PCR.

## INTRODUCTION

One of the most common malignant tumors among women around the world is breast cancer.[1] Breast cancer develops due to complex interactions between genetic and factors. Single nucleotide polymorphism (SNP) is a common genetic variation that affects biological function.[2-4] In these genes, ACE gene polymorphism was considered as risk factor for breast cancer and it has been reported in several published papers.[5-10] In the past decade there is increasing scientific interest in understanding the complex relationship between Carcinoma Breast and renin–angiotensin system (RAS).[11-13] The RAS plays a very important role in blood pressure and cardiovascular homeostasis.[14] In, recently published data indicated that angiotensin II, the main biologically active peptide of RAS, contributed to breast cancer development and its progression.[15] The production of angiotensin II is regulated by Angiotensin Converting Enzyme (ACE), its serum levels is governed by genetic variation at the ACE locus.

Chromosome 17 contains the ACE gene and contains a restriction fragment length polymorphism consisting of the presence insertion [I] or absence deletion [D] of a 278 base pair Alu repeat sequence in intron 16. The physiologic role of this enzyme is

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to convert angiotensin I (Ang I) to angiotensin II (Ang II) and to inactivate bradykinin. It has been recently shown that Ang II has promitotic proliferative, and angiogenic effects and therefore has a role in the proliferation and growth of the tumor cells via the Ang II type 1 receptor.[16,17] It has been suggested that long-term use of ACE inhibitors may protect against the risk of cancer,[18] and in experimental studies, inhibitors of ACE, such as captopril and perindopril, have been shown to inhibit the proliferation of cells and to reduce growth owing to the antiangiogenic effect, including human breast cancer.[19]

Homozygotes for the deletion (DD) can exhibit about a two-fold higher plasma and tissue ACE level than homozygotes for the insertion (II), whereas ID heterozygotes can exhibit an intermediate level.

Breast cancer is a cancer that develops from breast tissue and is the leading cause of cancer related death among women worldwide.[20] Several risk factors are considered for the development of breast cancer which includes being female, obesity, lack of physical exercise, drinking alcohol, hormone replacement therapy during menopause, ionizing radiation, early age at first menstruation, having children late or not at all, older age, prior history of breast cancer and family history.[21] [Figure 1] About 5–10% of cases are due to genes inherited from a person's parents, including BRCA1 and BRCA2 among others.[21] Most commonly, breast cancer develops in cells from the lining of milk ducts and the lobules that supply the ducts with milk.[21]

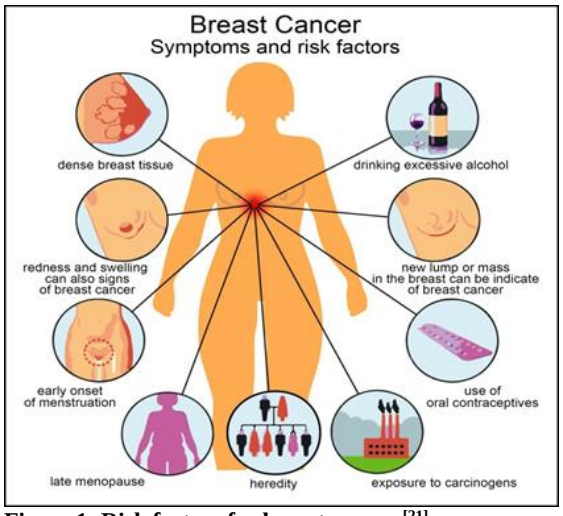


**Figure 1: Risk factors for breast cancer [21]**

## Incidence:

The incidence of breast cancer varies large around the world: it is lowest in less-developed countries and greatest in the more-developed countries. In the twelve world regions, The annual age-standardized incidence rates per 100,000, women, in the 12 regions of the world are as follows: in Eastern Asia, 18; South Central Asia, 22; sub-Saharan Africa, 22; South-Eastern Asia, 26; North Africa and Western Asia, 28; South and Central America, 42; Eastern Europe, 49; Southern Europe, 56; Northern Europe, 73; Oceania, 74; Western Europe, 78; and in North America, 90.[22]

Every year, More than 1,300,000 cases and 450,000 deaths related to breast cancer are reported worldwide.[23] In 2017, the incidence of invasive breast cancer and mortality in American women was projected to be 252,710 and 40,610 respectively.[24] A latest survey conducted by Indian Council of Medical Research (ICMR) of India stated that 150,000 new cases of breast cancer were estimated in the year 2016 from India.[25] Therefore, there is rise in both breast cancer incidence and mortality triggers urgent need to examine risk factors associated with this disease.

## Breast Cancer Classification:

Breast cancers are classified by different grading systems which influence the prognosis and can affect treatment response. Description of a breast cancer optimally includes all of these factors.

- **Histopathology:** Histological appearance is usually used to classify breast cancer. Most breast cancers are derived from the lobules or epithelium lining the ducts and these cancers are
  Classified as ductal or lobular carcinoma. Carcinoma in situ is growth of low-grade cancerous or precancerous cells within a particular tissue compartment such as the mammary duct without invasion of the surrounding tissue. In contrast, invasive carcinoma does not confine itself to the initial tissue compartment.[26]
- **Grade:** Grading compares the appearance of the breast cancer cells to the appearance of normal breast tissue. The normal cells in an organ like the breast become differentiated, meaning that they take on specific shapes and forms that reflect their function as part of that organ. Cancerous cells lose that differentiation. The cells that would normally line up in an orderly way to make up the milk ducts become disorganized in the case of cancer and the cell division becomes uncontrolled. Cell nuclei become less uniform. Cells are described as well differentiated (low grade), moderately differentiated (intermediate grade), and poorly differentiated (high grade) as the cells progressively lose the features seen in normal breast cells. Poorly differentiated cancers (the ones whose tissue is least like normal breast tissue) have a worse prognosis.
- **Stage:** Breast cancer staging using the TNM system is based on the tumor size (T), whether or not the tumor has spread to the lymph nodes (N) in the armpits, and whether the tumor has metastasized (M) (i.e. spread to a more distant part of the body). Larger size, nodal spread, and metastasis have a larger stage number and a worse prognosis.

**The main stages are [Figure 2]:**

- Stage 0 is a pre-cancerous or marker condition, either ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS).

- Stages 1–3 are within the breast or regional lymph nodes.
- Stage 4 is 'metastatic' cancer that has a less favorable prognosis since it has spread beyond the breast and regional lymph nodes.

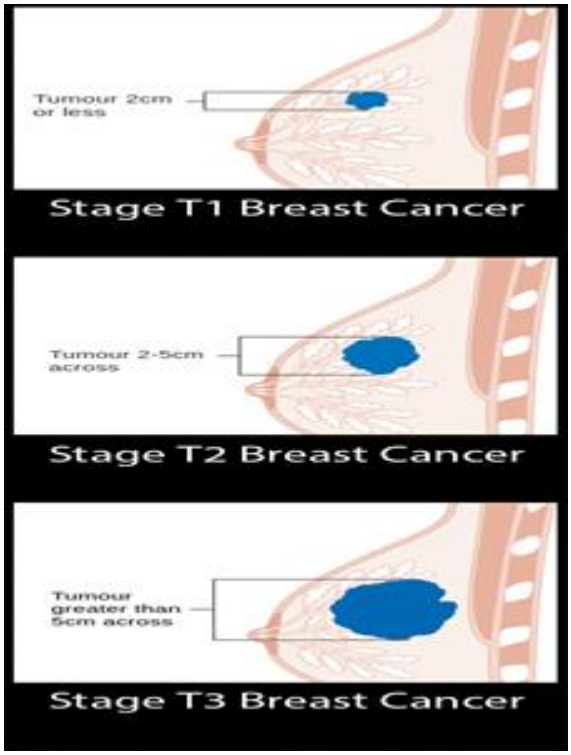


**Figure 2: Different Stages of Breast cancer (26)**

**TNM staging scheme for breast carcinoma**

**Pathologic**

**Tumor (pT)**

p:- Primary tumor cannot be assessed

pT0:- No evidence of primary tumor

pT1:- Tumor ≤ 20 mm in greatest dimension

T2:- Tumor > 20 mm but ≤ 50 mm in greatest dimension

T3:- Tumor > 50 mm in greatest dimension

T4:- Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules

**Pathologic (pN)***

**pNX**

Regional lymph nodes cannot be assessed (for example, previously removed, or not removed for pathologic study)

**pN0**

Histologically, no regional lymph node metastasis is identified. Note: Isolated tumor cell clusters (ITCs) are defined as small clusters of cells ≤ 0.2 mm, or single tumor cells, or a cluster of < 200 cells in a single histologic cross-section; ITCs may be detected by routine histology or by immunohistochemical (IHC) methods; nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated

**pN1**

Micrometastases; or metastases in 1-3 axillary lymph nodes and/or in internal mammary nodes, with metastases detected by sentinel lymph node biopsy but not clinically detected*

**pN2**

Metastases in 4-9 axillary lymph nodes or in clinically detected* internal mammary lymph nodes in the absence of axillary lymph node metastases

**Metastasis**

M0: - No clinical or radiographic evidence of distant metastasis

M1: - Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven > .02 mm

**AJCC staging groupings: (7th Edition)**

| Stage 0 | Tis | N0 | M0 |
|---|---|---|---|
| Stage IA | T1 | N0 | M0 |
| Stage IB | T0 | N1 mi | M0 |
| | T1 | N1 mi | M0 |
| Stage IIA | T0 | N1 | M0 |
| | T1 | N1 | M0 |
| | T2 | N0 | M0 |
| Stage IIB | T2 | N1 | M0 |
| | T3 | N0 | M0 |
| Stage IIIA | T0 | N2 | M0 |
| | T1 | N2 | M0 |
| | T2 | N2 | M0 |
| | T3 | N2 | M0 |
| | T3 | N2 | M0 |
| Stage IIIB | T4 | N0 | M0 |
| | T4 | N1 | M0 |
| | T4 | N1 | M0 |
| Stage IIIC | Any T | N3 | M0 |
| Stage IV | Any T | Any N | M1 |

**Genetics of breast cancer:**

A minor role may be played by some genetic susceptibility in most breast cancer cases.[27] Genetics, however, is believed to be the primary cause of 5–10% of all cases.[28] Women whose mother was diagnosed before 50 have an increased risk of 1.7 and those whose mother was diagnosed at age 50 or after has an increased risk of 1.4.[29] in Those with zero, one or two affected relatives, the risk probability before the age of 80 is 7.8%, 13.3%, and 21.1% with a subsequent mortality from the disease of 2.3%, 4.2%, and 7.6% respectively.[30] The risk of breast cancer in those with a first degree relative with the disease between the age of 40 and 50 is double that of the general population.[31]

Genetics plays a more significant role in less than 5% of cases by causing a hereditary breast–ovarian cancer syndrome.[27] This includes those who carry the BRCA1 and BRCA2 gene mutation.[27] These mutations account for up to 90% of the total genetic influence with a risk of breast cancer of 60–80% in those affected.[28] p53 (Li–Fraumeni syndrome), PTEN (Cowden syndrome), and STK11 (Peutz–Jeghers syndrome), CHEK2, ATM, BRIP1, and

PALB2 are the other significant mutations.[28] ACE is another gene that plays a major role and genetic polymorphism leads to causation of breast cancers.

**Genetics of ACE gene in Breast Cancer:**

Renin–angiotensin system (RAS) is mainly involved with systemic regulation of cardiovascular system and homeostasis and is also known to be expressed in multiple cancer types including Carcinoma Breast.[32,33] Overexpression of AGTR1 and ACE gene often reported in most of the neoplastic stages.[34] In humans, the gene encoding ACE is located on chromosome 17 (17q23), spanning 21 kb and comprising of 26 exons and 25 introns.[32] ACE is a zinc dependent dipeptidyl carboxypeptidase that catalyzes conversion of inactive decapeptide Angiotensin I (Ang I) to active octapeptide Ang II.[32] Ang II mediates its physiological effects by binding to two subtypes of receptors, AGTR1 and Angiotensin II receptor type II (AGTR2), which belong to a superfamily of G-protein-coupled receptors (GPCRs). Both receptors have approximately 32% structural homology, different tissue distribution and distinct intracellular signaling pathways.[35] Notably, the variable expression of ACE is associated with the polymorphisms in ACE gene, in which most studied is ACE (I/D) polymorphism (NCBI reference ID: rs 1,799,752). The presence of a 287 bp Alu sequence of DNA in the intron 16 of ACE gene is represented as "Insertion"or "I", and absence of the same denotes "Deletion" or "D". Enzymatic activity of ACE was found to be almost twice in the DD carriers as compared to II carriers and intermediate in ID carriers, indicating codominance among these alleles.[36-38] It has been proposed that ACE (I/D) polymorphism might play a role in altered transcriptional regulation and/or in the splicing of ACE pre-mRNA.[36,38] However, the mechanism on how this polymorphism affects ACE activity levels is still debated and under research.

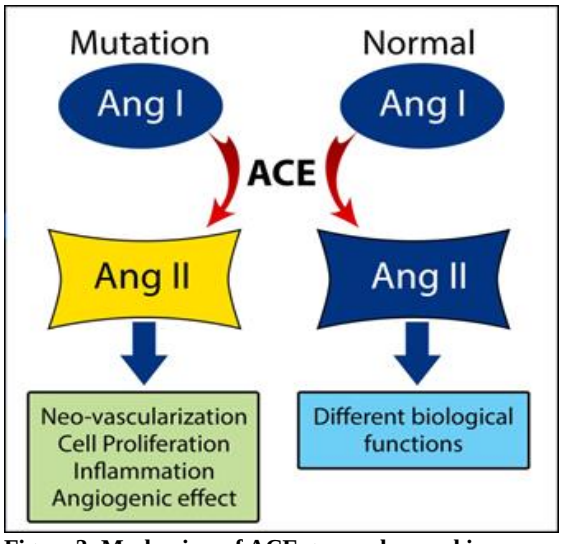


**Figure 3: Mechanism of ACE gene polymorphism**

There are several studies on different population showing protective and susceptible effect of ACE gene polymorphism. A study on Chinese women of ACE gene in Singapore demonstrated that individuals carrying AA (A240T) and II (ACE I/D) genotypes predispose these individual to lower plasma concentrations of ACE.

**Aims and Objectives:**

To investigate the distribution of the insertion/deletion (I/D) polymorphism of the Angiotensin-Converting Enzyme (ACE) gene in North Indian Breast Cancer patients.

## MATERIALS AND METHODS

**Subjects**

A total of 10 breast cancer patients were included in the present study from the Department of Pathology, a super specialty center in Era's Lucknow Medical College & Hospital, Lucknow, UP, India. All the cases in the study population had histologically confirmed invasive ductal carcinoma, and the prognostic factors, including Lymph Node involvement, Tumor size and Staging, Histologic grade, Hormone receptors, c erb B2 status, and Type of treatment, such as Surgery, Chemotherapy, or Radiotherapy, were obtained from the department of medical records.

A control group consisted of 10 healthy age-matched women without a history of neoplasia at any site, including a benign breast lesion, a history of cardiovascular disease, and use of any drug affecting the ACE system. Patients who were using ACE inhibitors or any other drug affecting the ACE enzyme system were excluded from the study.

The ethical guidelines of the Declaration of Helsinki have been conformed to in the study protocol as reflected in a prior approval by the institution's human research committee. The study got approved by the Ethics Committee of Era's Lucknow Medical College & Hospital, Lucknow, Era University and written informed consent were obtained from each of the participant.

**Blood collection and genotyping**

To analyse the I/D polymorphism in intron 16 of the ACE gene, 3.0 ml of venous blood from each study subject was collected in an EDTA vial. Genomic DNA was extracted by phenol-chloroform method [20]. The genotyping was performed by using PCR, using gene-specific primers. Amplification was carried out in a total volume of 25 µL that contained 15 nM of each primer (F: 5'-CTGGAGACCACTCCCATCCTTTCT-3', R: 5'-GATGTGGCCATCACATTCGTCAGAT-3'), 67 mM Tris-HCl (pH 8.8), 16.6 mM of ammonium sulfate, 6.7 mM MgCl2, 6.7 µM EDTA, 10 mM mercaptoethanol, 170 mg BSA, 1.0 mM of each dNTP and one unit of Taq-polymerase ('Bion',

Moscow, Russia). The PCR was performed under the following conditions: denaturation at 94°C for 5 min., followed by 34 cycles of amplification at 94°C for 1 min; 58.5°C for 1.5 min; 65°C for 40 sec; and 72°C for 2 min. The resulting PCR products were separated on 2% agarose gels using ethidium bromide stain and visualized under UV light. The ACE I/D genotype were characterized by the length of the PCR product, 190 bp in the case of homozygous for the deletion (DD) and 490 bp in the presence of the insertion (II). Heterozygotes were reported as ID with both the base pairs 490bp and 190bp.

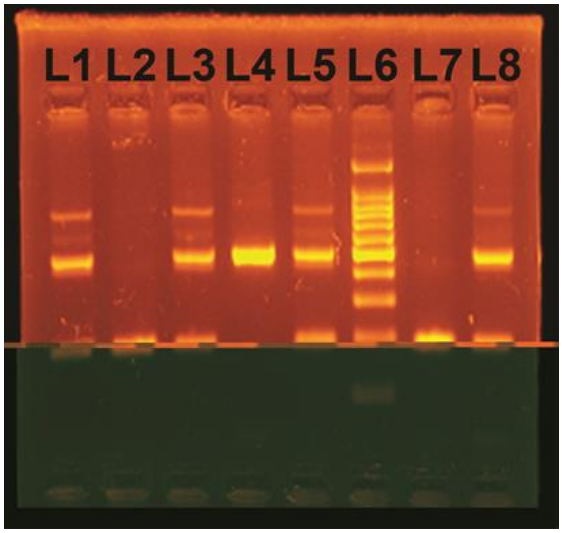


**Figure 4: Agarose gel Picture showing PCR products for ACE gene polymorphism. Lane 6 shows DD genotype, lane 1, 2 & 5 shows II genotype lane 3 show 100 bp ladder, lane 7 is blank**

**Statistical analysis**

All analyses was performed with SPSS for Windows, version 21 software (SPSS Inc, Chicago, IL). The frequency of ACE genotypes in breast carcinoma patients and control subjects and the detecting of the association between the gene polymorphism and clinicopathologic parameters was assessed using the chi-square test and Fisher's exact test. The odds ratios (ORs) for ACE genotypes or alleles were calculated by using the chi-square test, the corresponding 95% confidence interval (CI). All p-values are two tailed and p-values <0.05 were considered statistically significant.

## RESULTS

Distribution of Angiotensin converting enzyme (ACE) gene among Breast cancer cases and control women

The angiotensin converting enzyme converts angiotensin I to angiotensin II, which has vasoconstrictor properties and consequently participates in vascular tone regulation. ACE influences tumor cell proliferation, tumor cell migration, angiogenesis, and metastatic behavior. Keeping this background information in mind we carried out the genotype and allelic distribution of ACE in both the groups i;e cases and controls [Table 1].

**Table 1: Distribution of genotype and allele frequency of ACE I/D gene in Breast cancer cases and control**

| Genotype | Control (N=10) | Patients (N=10) | p-value | OR (95 % CI) |
|---|---|---|---|---|
| **Genotype frequency of ACE SNP ID rs1799752** | | | | |
| II | 2 (20%) | 1 (10%) | 0.5312 | 2.25(0.17-29.78) |
| ID | 6 (60%) | 6 (60%) | 1.0 | 1.00 (0.16-5.98) |
| DD | 2 (20%) | 3 (30%) | 0.6056 | 0.58 (0.07-4.56) |
| **Allele Frequency** | | | | |
| I | 10 (50%) | 8 (40%) | 0.7506 | 1.50 (0.42-5.25) |
| D | 10 (50%) | 12 (60%) | 0.7506 | 0.66(0.19-2.33) |

**Abbreviations:** CI, confidence interval; OR, odds ratio.

For ACE I/D polymorphism, 10% of Breast cancer patients showed II, 60 % had ID and 30% harbor DD genotype (Figure 5). While the genotype frequencies of II, ID, DD among healthy women were 20%, 60%, and 20% respectively. Both groups were in Hardy-Weinberg equilibrium. No significant association was observed in genotype frequencies of ID, DD and II genotypes. When we looked at the allele frequency distribution we did not observed any significant differences at the allelic level (OR=0.66; 95 % CI=0.19–2.33 p=0.7506).

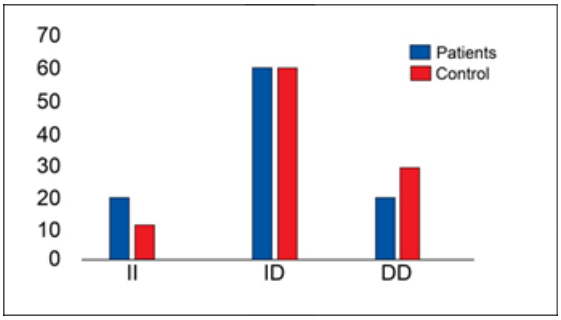


**Figure 5: Genotypic distribution of ACE gene polymorphism among patients and control**

## DISCUSSION

In present study, we studied the frequency of the ACE genotypes and alleles and the association between these ACE genotypes or alleles in breast cancer patients. However, we did not find any significant association between the distribution of the ACE genotypes and alleles in Carcinoma Breast patients and even in healthy controls.

The association of ACE (I/D) polyorphism with breast cancer in various cohorts was explored in

several studies; however, the risk lines up with different alleles. No association between ACE (I/D) polymorphism and Carcinoma of Breast risk was observed in the present study. In another study the association of D allele with breast cancer risk in Mexican and Ukranian women (age 34–45 years) was observed.[38,39] Also, in a multi-ethnic cohort study a marginal increase in breast cancer risk for women with II genotype was observed and noted.[40]

On the other hand, a study on Kashmiri women reported II genotype to be significantly associated with breast cancer and showed protective role of ID genotype against breast cancer.[41] Another study conducted in North India showed significant association of DD genotype of ACE gene polymorphism with risk of developing breast cancer.[42]

A study show no association of the polymorphism with breast cancer was noticed among post-menopausal Egyptian females which was in accordance to our results.[32] Furthermore, a meta analysis conducted by pie et al also showed lack of association of ACE gene polymorphism with breast cancer.[43]

It has been reported in several other cancers types that ACE gene polymorphism was associated with some prognostic parameters. In gastric carcinoma patients, the number of the lymph node metastases correlated with DD genotype but there were no correlation between tumor type, tumor location, local tumor growth, distant metastasis and even I/D gene polymorphism.[44] The patients with prostate cancer who had DD genotype had increasingly presented with advanced disease.[45]

In our study, there was no significant association between the ACE gene polymorphism in Breast Cancer and has got poor prognostic value. The role of ACE in the development of breast cancer may be a possible explanation for the findings, because this gene is associated with other important genes involved in the process of oncogenesis.

In epidemiological studies, ACE gene polymorphisms, including I/D polymorphism were found to be associated with increased Carcinoma Breast risk except the Multiethnic Cohort Study.[9,33,35] The Multiethnic Cohort Study showed that in contrary to the expectations, women with II genotype had increased risk of Carcinoma Breast.[9] Taken together, genetic polymorphisms may affect the development of breast cancer and may be helpful for a better understanding the molecular epidemiology of Carcinoma Breast.

The study's main limitation was that it was retrospective which limited access to patient data and sample size. As there is high genetic heterogeneity in the Indian population, we restricted our study to Northern India; however, a multicentric association study of polymorphism across India is highly recommended.

## CONCLUSION

In conclusion, our study shows no association between ACE I/D polymorphism and breast cancer risk. As few studies are available in this field and current evidence remains limited, it should be emphasized that.

***Acknowledgement***

Indian Council for Medical Research (ICMR) for granting and funding this STS Project.

## REFERENCES

1. Mituś JW, Blecharz P, Reinfuss M, et al. Changes in the clinical characteristics, treatment options, and therapy outcomes in patients with phyllodes tumor of the breast during 55 years of experience. Med Sci Monit 2013; 19: 1183–1187.
2. Tang W, Qiu H, Ding H, et al. Association between the STK15 F31I polymorphism and cancer susceptibility: A meta-analysis involving 43,626 subjects. PLoS One 2013; 8: e82790.
3. Jahan P, Ramachander VR, Maruthi G, et al. Foxp3 promoter polymorphism (rs3761548) in breast cancer progression: A study from India. Tumour Biol. Epub ahead of print 2013 Dec; 35(4): 3785-3791.
4. Merriman JD, Aouizerat BE, Cataldo JK, et al. Association between an interleukin 1 receptor, type I promoter polymorphism and self-reported attentional function in women with breast cancer. Cytokine 2013: 65:192–201.
5. Alves Corrêa SA, Ribeiro de Noronha SM, Nogueira-de-Souza NC, et al. Association between the angiotensin-converting enzyme (insertion/deletion) and angiotensin II type 1 receptor (A1166C) polymorphisms and breast cancer among Brazilian women. J Renin Angiotensin Aldosterone Syst 2009; 10: 51–58.
6. Van der Knaap R, Siemes C, Coebergh JW, et al. Reninangiotensin system inhibitors, angiotensin I-converting enzyme gene insertion/deletion polymorphism, and cancer: The Rotterdam Study. Cancer 2008; 112: 748–757.
7. Yaren A, Turgut S, Kursunluoglu R, et al. Insertion/deletion polymorphism of the angiotensin I-converting enzyme gene in patients with breast cancer and effects on prognostic factors. J Investig Med 2007; 55: 255–261.
8. González-Zuloeta Ladd AM, Arias Vásquez A, Sayed-Tabatabaei FA, et al. Angiotensin-converting enzyme gene insertion/deletion polymorphism and breast cancer risk. Cancer Epidemiol Biomarkers Prev 2005; 14: 2143–2146.
9. Haiman CA, Henderson SO, Bretsky P, et al. Genetic variation in angiotensin I converting enzyme (ACE) and breast cancer risk: The multiethnic cohort. Cancer Res 2003; 63: 6984–6987.
10. Koh WP, Yuan JM, Sun CL, et al. Angiotensin I-converting enzyme (ACE) gene polymorphism and breast cancer risk among Chinese women in Singapore. Cancer Res. 2003; 63: 573–578.
11. Salata C, Ferreira-Machado SC, Mencalha AL, et al. Chemotherapy and radiation regimens to breast cancer treatment induce changes in mRNA levels of renin-angiotensin system related genes in cardiac tissue.J Renin Angiotensin Aldosterone Syst. 2013; 14: 330–336.
12. Du N, Feng J, Hu LJ, et al. Angiotensin II receptor type 1 blockers suppress the cell proliferation effects of angiotensin II in breast cancer cells by inhibiting AT1R signaling. Oncol Rep. 2012; 27: 1893–1903.
13. Ramírez-Expósito MJ, Carrera-González Mdel P, Mayas MD, et al. Neoadjuvant chemotherapy modifies serum

angiotensinase activities in women with breast cancer. Maturitas. 2012; 72: 79–83.
14. Xiao X, Du HJ, Hu WJ, et al. The influence of long term hydrochlorothiazide administration on the relationship between renin-angiotensin-aldosterone system activity and plasma glucose in patients with hypertension. Oxid Med Cell Longev. 2013; 2013: 434618.
15. Napoleone E, Cutrone A, Cugino D, et al. Inhibition of the renin-angiotensin system downregulates tissue factor and vascular endothelial growth factor in human breast carcinoma cells. Thromb Res. 2012; 129: 736–742.
16. Egami K, Murohara T, Shimada T, et al. Role of host angiotensin II type 1 receptor in angiogenesis and growth. J Clin Invest 2003; 112: 67–75.
17. Lyall F, Dornan ES, McQueen J, Kelly M. Angiotensin II increases protooncogene expression and phosphoinositide turnover in vascular smooth muscle cells via the angiotensin II AT1 receptor. J Hypertens. (1992);10(12):1463–1469.
18. Lever AF, Hole DJ, Gillis CR, et al. Do inhibitors of angiotensin I-converting enzyme protect against risk of cancer? Lancet. (1998); 352: 179–84.
19. Volpert OV, Ward WF, Lingen MW, et al. Captopril inhibits angiogenesis and slows the growth of experimental tumors in rats. J Clin Invest. (1996);98(3): 671–679.
20. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM,Forman D, and Bray F. Cancer incidence and mortality world wide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 Mar; 136 (5): 359-386.
21. World Cancer Report 2014. World Health Organization; 2014.
22. Stewart B. W. and Kleihues P. (Eds): World Cancer Report. IARCPress. Lyon Archived 20 October 2008 at the Wayback Machine; 2003.
23. Comprehensive molecular portraits of human breast tumours Nature.2012; 490(7418):61–70.
24. American Cancer Society (2017). Cancer Facts and figures 2017. Atlanta: American Cancer Society; 2017 .
25. Singh R and Turuk A A study to assess the knowledge regarding breast cancer and practices of breast self-examination among women in urban area.Int J Commun Med Public Health; (2017).
26. Merck Manual, Professional Edition Archived 10 November 2011 at the Wayback Machine., Ch. 253, Breast Cancer; 2011.
27. Boris Pasche. Cancer Genetics (Cancer Treatment and Research). Berlin: Springer; (2010).
28. Gage M, Wattendorf D, Henry LR (1 April 2012). "Translational advances regarding hereditary breast cancer syndromes". Journal of surgical oncology. 2012 Mar; 105 (5): 444–51.
29. Colditz, Graham A.; Kaphingst, Kimberly A.; Hankinson, Susan E.; Rosner, Bernard. Family history and risk of breast cancer: nurses' health study. Breast Cancer Research and Treatment. 2012 Feb; 133 (3): 1097–1104.
30. Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease". Lancet. 2001 Oct; 358 (9291): 1389–99.
31. Nelson HD, Zakher B, Cantor A, Fu R, Griffin J, O'Meara ES, Buist DS, Kerlikowske K, van Ravesteyn NT, Trentham-Dietz A, Mandelblatt JS, Miglioretti DL."Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis. Annals of Internal Medicine. 2012; 156 (9): 635–48.
32. El Sharkawy RM, Zaki AM, Kamel AAEF, Bedair RN, and Ahmed AS. Association between the polymorphisms of angiotensin converting enzyme (Peptidyl-Dipeptidase A) INDEL mutation (I/D) and Angiotensin II type I receptor (A1166C) and breast cancer among post menopausal Egyptian females.Alex J Med. 2014; 50: 267–274.
33. Koh WP, Yuan JM, Sun CL, van den Berg D, Seow A, Lee HP, and Yu MC. Angiotensin I-converting enzyme (ACE) gene polymorphism and breast cancer risk among Chinese women in Singapore.enzyme genes and breast cancer risk among Chinese women in Singapore. Cancer Res 63, 573 – 578. Carcinogenesis; 2003: 2, 459 –464.
34. Louis SN, Wang L, Chow L, Rezmann LA, Imamura K, MacGregor DP, Casely D, Catt KJ, Frauman AG, and Louis W. Appearance of angiotensin II expression in non-basal epithelial cells is an early feature of malignant change in human prostate. Cancer Detect Prev. 2007; 31: 391–395.
35. Koh WP, Yuan JM, Van Den Berg D, Lee HP, and Yu MC. Polymorphisms in angiotensin II type 1 receptor and angiotensin I-converting enzyme genes and breast cancer risk among Chinese women in Singapore. Carcinogenesis. 2005; 26: 459 – 464.
36. Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, and Soubrier F. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. J Clin Investig. 1990; 86: 1343.
37. Alves Corrêa SA, Ribeiro de Noronha SM, Nogueira-de-Souza NC, Valleta de Carvalho C, Massad Costa AM, Juvenal Linhares J, Vieira Gomes MT, and Guerreiro da Silva IDC. Association between the angiotensin-converting enzyme (insertion/deletion) and angiotensin II type 1 receptor (A1166C) polymorphisms and breast cancer among Brazilian women. J Renin Angiotensin Aldosterone Syst. 2009; 10: 51–58.
38. Fishchuk LE and Gorovenko NG. Genetic polymorphisms of the renin-angiotensin system in breast cancer patients. Exp Oncol 35, 101–104.
39. Mendizábal-Ruiz AP, Morales J, Castro Martinez X, Gutierrez Rubio SA, Valdez L, Vásquez-Camacho JG, Sanchez Corona J, and Moran Moguel MC (2011). RAS polymorphisms in cancerous and benign breast tissue. J Renin Angiotensin Aldosterone Syst. 2013; 12: 85 –92.
40. Haiman CA, Henderson SO, Bretsky P, Kolonel LN, and Henderson BE. Genetic variation in angiotensin I-converting enzyme (ACE) and breast cancer risk: the multiethnic cohort. Cancer Res. 2003; 63: 6984 –6987.
41. Syeed N, Abdullah S, Sameer A, Husain S, Nisar S, Rasool A, and Siddiqi M. ACE gene polymorphism in breast cancer patients of ethnic Kashmiri population. Chron Young Sci. 2010; 1:40 –45.
42. Singh A, Srivastava N, Amit S, Prasad SN, Misra MP, Ateeq B. Association of AGTR1 (A1166C) and ACE (I/D) Polymorphisms with Breast Cancer Risk in North Indian Population. Transl Oncol. 2018; 11(2): 233-242.
43. Pei XH, Li HX. Insertion/deletion (I/D) in the angiotensin-converting enzyme gene and breast cancer risk: lack of association in a meta- analysis. Asian Pac J Cancer Prev. 2012; 13(11):5633-5636.
44. Röcken, C., Lendelkel, U., Dierkes, J., Westphal, S., McGrath, S.C., Peters, B., Kruger, S., Malfertheiner, P., Roessner, A. & Ebert, M.P. The number of the lymph node metastasis in gastric cancer correlates with the Angiotensin I-converting enzyme gene Insertion/Deletion polymorphism. Clin. Cancer Res. 2005; 11: 2526-2530.
45. Medeiros, R., Vasconcelos, A., Costa, S., Pinto, D., Lobo, F., Morais, A., Oliveira, J. & Lopes, C. Linkage of angiotensin I-converting enzyme gene insertion/deletion polymorphism to the progression of human prostate cancer. J. Pathol. 2004; 202: 330-335.

**How to cite this article:** Khan S, Ahmad S. Role of Angiotensin Converting Enzyme (ACE) Gene Polymorphism in Breast Cancer among North Indian Population. Ann. Int. Med. Den. Res. 2019; 5(6):PT17-PT23.

**Source of Support:** Nil, **Conflict of Interest:** None declared