Original Article

Eur J Breast Health 2025; 21(1): 57-62
DOI: 10.4274/ejbh.galenos.2024.2024-6-1

Carbonic Anhydrase IX Enzyme in Triple Negative Breast Carcinoma: Relationship With Prognostic Factors and Response to Neoadjuvant Chemotherapy

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ABSTRACT

Objective: Triple negative breast carcinoma (TNBC) is characterized by the absence of estrogen receptor, progesterone receptor and human epidermal growth factor receptor-2 receptor expression. Carbonic anhydrase IX (CA IX) is a tumor-associated cell surface glycoprotein that is involved in adaptation to hypoxia-induced acidosis and plays a role in cancer progression. The aim of this study was to investigate CA IX expression in TNBC and its relationship with treatment effect.

Materials and Methods: Immunohistochemical staining was performed on tru-cut biopsy materials with CA IX antibody. Positive staining was graded as low (<10%) and high (>10%). In addition, the relationship between tumor diameter, histological grade and the treatment effect on mastectomy materials performed after neoadjuvant treatment was evaluated.

Results: TNBCs with positive staining for CA IX exhibited higher histological grade, and higher Ki-67 index compared to TNBCs with negative staining ($p < 0.05$). The response to treatment decreased as the degree of CA IX staining increased. There was no significant difference between the high staining group and low staining group in terms of patient age, tumor diameter and breast localisation.

Conclusion: CA IX enzyme is a poor prognostic marker in TNBC cases. However, overexpression of CA IX was associated with reduced response to treatment.

Keywords: Triple negative breast carcinoma; carbonic anhydrase IX; treatment effect; Ki-67 proliferation index

Cite this article as: Arslan Solmaz Ö, Kutluer N, Bozan MB. Carbonic anhydrase IX enzyme in triple negative breast carcinoma: relationship with prognostic factors and response to neoadjuvant chemotherapy. Eur J Breast Health. 2025; 21(1): 57-62

Key Points

- Understanding carbonic anhydrase-9 levels' affect on triple-negative breast cancer.
- Additionally it affects on the prognosis of the triple negative breast cancer cases.

Introduction

Breast cancer is the most common tumor in women and the second most common cause of cancer-related deaths. According to cancer data published in 2021, approximately 2,260,000 women were diagnosed with breast cancer, and 684,996 women died due to breast cancer (1, 2). Over the past 20 years, breast cancer has been recognized as a family of diseases with distinct pathological, molecular, and clinical characteristics. Various classification systems have been proposed, affecting prognosis and treatment. Breast cancer has been categorized into estrogen/progesterone receptor-positive (luminal), human epidermal growth factor receptor-2 (HER2) receptor-positive, and triple-negative breast carcinoma (TNBC), where all three receptors are negative (3). TNBCs account for approximately 15% of all breast cancer cases. They are more common in women under 40 years of age and have poorer survival rates compared to other types of breast cancer. Approximately 40% of women with TNBC die within the first five years after diagnosis. Distant metastasis is observed in around 46% of TNBC patients with a mean survival time of 13.3 months after metastasis (1, 3).

Since Warburg's (4) study in 1927 described the so-called Warburg effect, which is characterized by irregular glucose uptake and disruption of glycolytic metabolism in cancer cells, irregular energy metabolism has become known as an important part of the pathogenesis behind uncontrolled growth in cancer cells. Moreover, hypoxic areas are commonly found in more than half of breast tumors due to high metabolic proliferative rates and abnormal vascularization. In healthy breast tissue, the average oxygen pressure (pO_2) is 65 mmHg, whereas

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Received: 15.06.2024
Accepted: 15.10.2024
Available Online Date: 01.01.2025

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in breast tumors, it has been reported to be reduced to 10 mmHg. Tumor areas exhibit acidic pH (<6.5) (5). Hypoxia poses a life-threatening condition for all aerobic organisms, and they develop various adaptative mechanisms to survive in such conditions (6). The rapid proliferation of cancer cells increases the demand for oxygen, but the vessels supplying oxygen-carrying blood cannot keep up with this demand. Consequently, hypoxia occurs in rapidly growing tumor tissues, and tumor cells develop adaptive responses to cope with this stress (7).

Carbonic anhydrase IX (CA IX) is a tumor-associated cell surface glycoprotein enzyme that aids in adaptation to acidosis induced by hypoxia and plays a role in cancer progression. The active site of the CA IX enzyme in the catalytic domain is positioned towards the extracellular space, contributing to pH regulation across the plasma membrane by facilitating CO_2 hydration. This, in turn, enhances CO_2 diffusion and proton mobility in the tumor tissue. Simultaneously, CA IX exacerbates extracellular acidosis, which can activate proteases to degrade the extracellular matrix, promote epithelial-mesenchymal transition and invasion, reprogram metabolism, affect cell adhesion, and stimulate inflammation and angiogenesis. CA IX is more abundant in tumor tissues compared to normal tissues (8, 9).

Many tumor studies have reported CA IX overexpression as a poor prognostic marker. Previous clinical trials on invasive breast cancer have also demonstrated that CA IX is associated with poor outcomes, suggesting its relationship with an aggressive phenotype. CA IX overexpression has also been associated with shorter disease-free survival time in invasive breast cancer. However, there is little information regarding its role in TNBC (10).

TNBCs have poor prognoses and are resistant to chemo-radiotherapy, making them a focal point of cancer research. In this study, we investigated the relationship between CA IX expression and prognostic factors of TNBC, as well as its contribution to treatment. The aim was to identify the causes of poor prognosis and make recommendations for exploring new treatments.

Materials and Methods

This retrospective study was initiated after obtaining approval from the Ethics Committee of Fırat University (approval no: 2023/04-34, date:13.07.2023). One thousand seven hundred and fifty-three cut biopsy samples sent to our hospital laboratory between August 2018 and May 2023 were examined. These cases were compared, first by classifying according to their diagnosis with 541 cases diagnosed with carcinoma. Among these, 397 patients were diagnosed with invasive carcinoma NST were included in the study and those diagnosed with other carcinomas were excluded from the study. The 397 invasive carcinoma cases were evaluated according to estrogen, progesterone and HER 2 receptors. Triple negative tumor cases were thus identified. Among these cases, 40 cases who underwent breast resection in our hospital by receiving neoadjuvant chemotherapy (adriamycin, cyclophosphamide, and then paclitaxel for four cycles) were included in the study (Figure 1). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or ethical standards.

Hematoxylin-eosin stained preparations of tru cut biopsies and immunohistochemical staining preparations for estrogen, progesterone and HER2 receptors were re-examined using a Leica DM 2000 light microscope (Leica Biosystems 21440 W. Lake Cook Road Floor 5 Deer Park, IL 60010 United States). Patients with a score of +2 for HER2 antibody staining were excluded from the study, due to the unavailability of fluorescent *in situ* hybridization in our clinic. A total of 40 patients were included in the study, and histopathological evaluation was conducted on parameters which included histological type and histological grade. Histological grading was performed using the Nottingham score (Elston Ellis modification of Scarff-Bloom-Richardson grading system) (11). Tumor diameter evaluation was based on the measurements determined during radiological examinations.

Paraffin blocks of these cases were cut into 3 µm thick sections and placed on slides. The tissue samples were deparaffinized and treated with 3% H_2O_2 for 5 minutes, blocked with 10% serum in blocking solution for 1 hour, and incubated overnight at 4 °C with anti-CA IX antibodies (Leica Biosystems 21440 W. Lake Cook Road Floor 5 Deer Park, IL 60010 United States) at a 1/400 dilution in an antibody diluent. As CA IX is a transmembrane protein, it exhibits cytoplasmic membrane staining. Immunohistochemically positive cells were graded as "low staining" if they constituted <10% of the total or "high staining" if they constituted ≥10%, as previously described (12). Due to the small number of patients, in order to facilitate statistical comparison, the classification made by Zhu et al. (12), based on a previous meta-analysis of neck and head tumors, was chosen. Ogston et al. (13) grading was used to evaluate treatment effect after neoadjuvant chemotherapy in breast excision materials (Table 1).

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences version 20 (IBM Corp., Armonk, NY, USA). All analyses were conducted based on the normality assumption and according to the low case count all the parametric values were accepted as non-normal distribution. Descriptive data are expressed as median (25–75

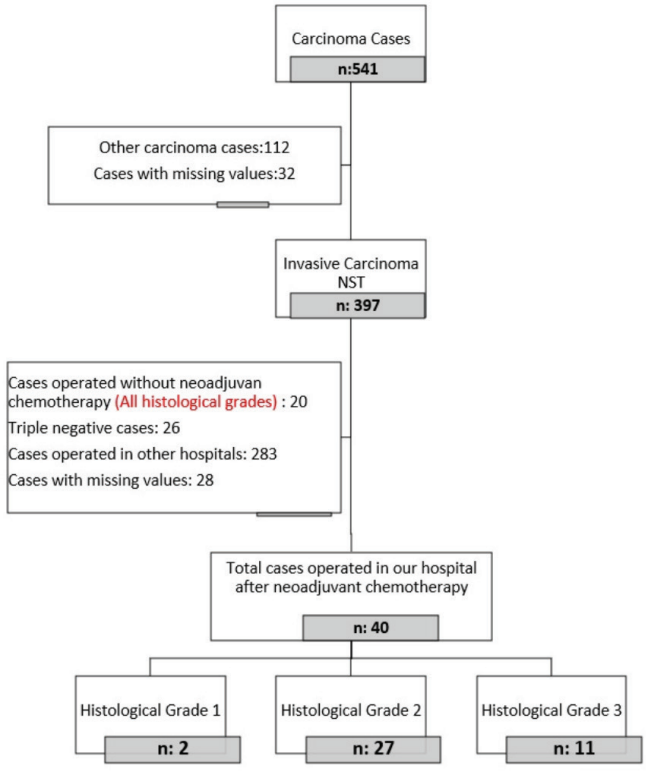

Figure 1. Flowchart of the study design

percentiles). The association between clinicopathological parameters, treatment effect and CA IX staining was tested using the chi-square test, Fisher's exact test or likelyhood ratio. Statistical significance was set at $p < 0.05$.

Results

All patients included in the study were female, with a mean age of 48.43±11.92, ranging from 33 to 84 years. The tumor was located in the right breast in 23 patients (57.5%) and in the left breast in 17 patients (42.5%). The median tumor diameter of all patients was 22.31 mm (5.5–100 mm). Based on histopathological grading, 2 patients (5%) were classified as Grade 1, 27 patients (67%) as Grade 2, and 11 patients (28%) as Grade 3. The median Ki-67 proliferation index was 40.62% (5–90%).

Immunohistochemical staining of CA IX in tumor tissues showed that 77.5% (n=31) had high staining (Figure 2) and 22.5% of patients (n=9) had low staining (Figure 3, Table 2). The tumor diameter of the low staining group was 17 mm (13–22 mm) and high staining group was 21 mm (17.5–25 mm) ($p = 0.337$).

Statistical analysis revealed a significant difference between CA IX staining level and histological grade of the tumor and Ki-67 proliferation index ($p = 0.003$, and $p = 0.008$, respectively) (Table 3). In other words, as the tumor histological grade and Ki-67 proliferation index increased, the CA IX staining level also increased. However, CA IX staining level showed no significant relationship with patient age, tumor diameter and tumor localization ($p = 0.975$, $p = 0.337$ and $p = 0.456$, respectively) (Table 4).

In the evaluation made using Miller Payne scoring (MPS), nine of the cases had a grade 2, 13 of them had a grade 3, 12 of them had a grade 4 and six of them had a grade 5 treatment effect. A significant difference was detected between MPS and CA IX expression ($p = 0.005$ (Table 3).

Discussion and Conclusion

Breast cancer is a complex disease with various histological types, natural courses, clinical behaviors, and treatment responses. In addition to classification based on histopathological characteristics, several molecular subtypes have been defined based on different expressions of cell surface receptors. TNBCs are breast carcinomas that test negative for estrogen, progesterone, and HER2 receptor and have worse prognoses compared to other breast carcinoma subtypes (14, 15). Conventional treatment methods remain valid for TNBCs, with systemic treatment being the primary protocol for both first-line and advanced treatments. However, patients often develop treatment resistance over time (16). Resistance to treatment leads to recurrence and distant metastasis in 40–80% of cases, resulting in death. The tumor microenvironment has been identified as one of the parameters influencing treatment response, emphasizing its importance in tumor development, growth, metastasis, recurrence, and treatment response (17). Recent studies have demonstrated that the hypoxic tumor microenvironment, influenced by CA IX, affects tumor growth, invasion, and treatment resistance (10). The hypoxia promotes an invasive phenotype characterized by decreased tumor

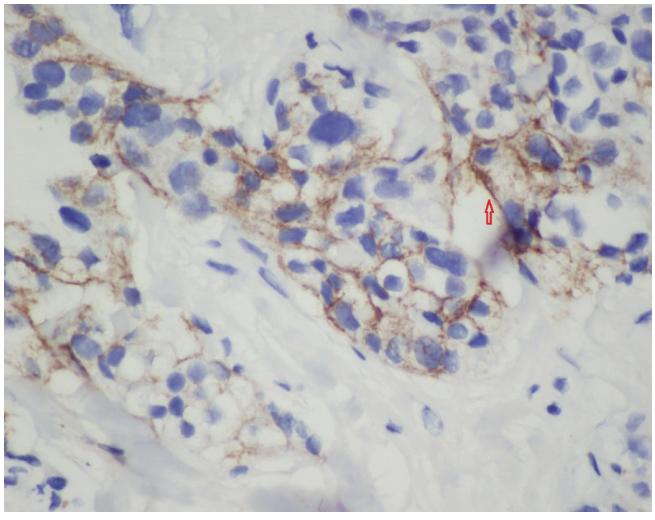

Figure 2. Membranous CA IX high staining x 400

CA IX: Carbonic anhydrase 9

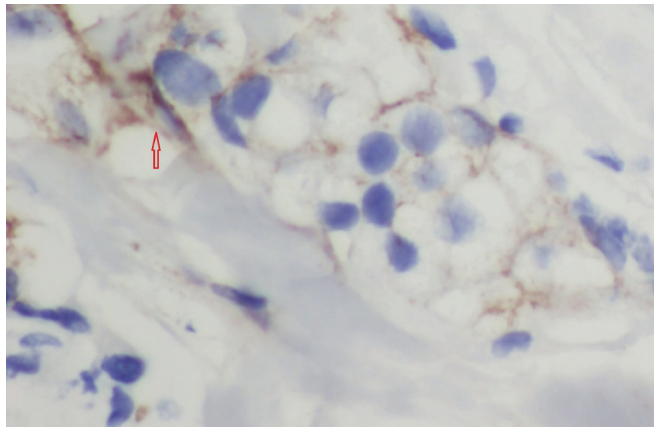

Figure 3. Membranous CA IX low staining x 400

CA IX: Carbonic anhydrase 9

Table 1. Miller and Payne histological grading system

Grade	Miller and Payne histological grading system
Grade 1	No change or some alteration to individual malignant cells but no reduction in overall cellularity.
Grade 2	A minor loss of tumour cells but overall cellularity still high; up to 30% loss.
Grade 3	Between an estimated 30% and 90% reduction in tumour cells.
Grade 4	A marked disappearance of tumour cells such that only small clusters or widely dispersed individual cells remain; more than 90% loss of tumour cells.
Grade 5	No malignant cells identifiable in sections from the site of the tumour; only vascular fibroelastotic stroma remains often containing macrophages. However, ductal carcinoma *in situ* (DCIS) may be present.

adhesion, increased invasion, mobility, migration, and stimulation of angiogenesis (18). This study investigated the relationship between CA IX expression and prognostic factors in TNBC. TNBCs with high CA IX staining exhibited higher histological grade, and higher Ki-67 index compared to TNBCs with negative staining.

Studies examining the relationship between breast carcinomas and CA IX overexpression have reported varying results (18). Few studies have specifically investigated the relationship between CA IX and TNBC, reporting that poor prognostic factors were common in TNBC patients with CA IX overexpression (19, 20). In the study conducted by Jin et al. (21) involving 270 TNBC cases, they observed that CA IX expression increased with higher histological grades. However, they found a negative correlation with lymphovascular invasion and disease-free survival (21). Ong et al. (22) found that positive CAIX membrane staining was associated with larger tumor size, higher histological grade, and worse survival rates. BRCA1 mutation was found to be present, especially in patients expressing CA IX in their TNBCs, which

Table 2. CA-IX expression according to histological grades

Histologic Grade	CA-IX		Total	*p*-value
	Low staining group	High staining group		
Grade 1, n (%)	1 (2.5)	1 (2.5)	2 (5.0)	0.029*
Grade 2, n (%)	8 (20.0)	19 (47.5)	27 (67.5)	
Grade 3, n (%)	0 (0.0)	11 (27.5)	11 (27.5)	
Total, n (%)	9 (22.5)	31 (77.5)	40 (100)	

*: According to likelyhood ratio
CA IX: Carbonic anhydrase 9

Table 3. Relationship of MPS and CA-IX expression degree

MPS	CA-IX		Total	*p*-value
	Low staining group	High staining group		
Grade 2, n (%)	0 (0.0)	9 (22.5)	9 (22.5)	0.005*
Grade 3, n (%)	1 (2.5)	12 (30.0)	13 (32.5)	
Grade 4, (n)	4 (10.0)	8 (20.0)	12 (30.0)	
Grade 5, n (%)	4 (10.0)	2 (5.0)	6 (15.0)	
Total, n (%)	9 (22.5)	31 (77.5)	40 (100)	

*: According to likelyhood ratio
CA IX: Carbonic anhydrase 9; MPS: Miller and Payne histological grading system

Table 4. Relationship of tumor localisation, Ki-67 proliferation index, age and tumor diameter with CA-IX

	CA-IX		*p*-value
	Low staining group	High staining group	
Tumor side			
Left	5 (12.5%)	12 (30.0%)	0.301*
Right	4 (10.0%)	19 (47.5%)	
Total	9 (22.5%)	31 (77.5%)	
Median (IQR) Ki-67 index (%)	20 (15-35)	40 (30-50)	0.008**
Median (IQR) age, (years)	45 (38-61)	46 (41-54)	0.975**
Median (IQR) diameter, (mm)	17 (12.5-24)	21 (17-26)	0.337**

*: According to Fischer's Exact Test
**: According to Mann Whitney U Test
CA IX: Carbonic anhydrase 9; IQR: interquartile range (25th to 75th percentiles)

hindered DNA repair (23). However, a study conducted by Ozretic et al. (24) found no significant relationship between CA IX expression and poor prognosis. In additionally, a small number of studies have reported that carbonic anhydrase inhibitors are a viable anticancer treatment, especially for TNBC (25).

In previous studies, pathological complete response (PCR) in TNBC was found to be between 15–30%. In this study, it was 15%, consistent with the literature. It is known that PCR after treatment increases the disease-free survival time in TNBCs. In previous studies investigating the relationship between CA IX expression and PCR, Aomatsu et al. (26) observed that high CA IX expression was associated with a low PCR rate and evaluated this protein as a marker of chemoresistance. However, Betof et al. (27) reported that PCR was higher in tumors showing high CA IX expression in tumor tissues before neoadjuvant chemotherapy. As a result of this study, it was shown that as CA IX expression increased, the pathological response decreased.

The most important limitation of the current study is the small number of cases. Since not all diagnosed patients were treated in our hospital, it was not possible to access the data. In addition, survival time and disease-free survival time could not be evaluated for this reason.

Significant advances have been made in understanding the biology of TNBCs in recent years. These tumors are now known to have more than one biological subtype, implying that there will be no single optimal treatment method. Considering the importance of the tumor microenvironment in treatment resistance, targeting the microenvironment that facilitates tumor growth, proliferation, and spread is likely to be a crucial factor in combating the tumor. Inhibiting the CA IX enzyme, which contributes to acidosis which benefits tumor survival and growth, may be a fundamental step in treatment. Our study showed that poor prognostic factors were more common and response to treatment was less in patients with TNBC and CA IX positive features. We believe that CA IX enzyme inhibition may be an important treatment approach. Studies involving larger patient groups with multicentric studies will provide more reliable results and help determine optimum treatment protocols.

Ethics

Ethics Committee Approval: This study was initiated after obtaining approval from the Ethics Committee of Fırat University (approval no. 2023/04-34, date:13.07.2023).

Informed Consent: This retrospective study.

Footnotes

Authorship Contributions: Surgical and Medical Practices: M.B.B., N.K., Ö.A.S.; Concept: M.B.B., N.K., Ö.A.S.; Design: M.B.B., N.K., Ö.A.S.; Data Collection and/or Processing: M.B.B., N.K., Ö.A.S.; Analysis and/or Interpretation: M.B.B., N.K., Ö.A.S.; Literature Search: M.B.B., N.K., Ö.A.S.; Writing: M.B.B., N.K., Ö.A.S.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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