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ORIGINAL RESEARCH PERIOPERATIVE MEDICINE

# Evaluation of new tumor marker CA 27-29 as a diagnostic biomarker for breast cancer in comparison to the standard CA 15-13

**Samah Fadhil Hadi [1], Shrouk A. Hassan Al.Ibraheem [1*], Hamid Jaddoa Abbas[2]**

**Author affiliations:**

1. Samah Fadhil Hadi, Medical Laboratory Technical Dept., College of Health & Medical Techniques, Southern Technical University, Basrah, Iraq; Email: Samah.f.hadi@fgs.stu.edu.iq
2. Shrouk A. Hassan Al.Ibraheem, Medical Laboratory Technical Dept., College of Health & Medical Techniques, Southern Technical University, Basrah, Iraq; E-mail; shrouk.aibraheem@stu.edu.iq
3. Hamid Jaddoa Abbas, Al-Faiha'a Teaching Hospital, Al- Zehra 'a Medical College, University of Basra, Basra, Iraq; Email: hamedjadoa@yahoo.com

**Correspondence:** Samah Fadhil Hadi**, Email:** Samah.f.hadi@fgs.stu.edu.iq; **Phone:** 0773 984 2522

## ABSTRACT

**Background:** Breast cancer diagnostics often employ tumor markers for disease diagnosis, monitoring, progression, and recurrence. CA 15-3 and CA 27-29 are two such markers used in the clinical management of breast cancer. The aims of this research to evaluate the efficacy of new CA 27-29 as a diagnostic biomarker for breast cancer and risk assessment capability in comparison with well-established CA 15-3.

**Methodology:** A case- control study, that included 70 Iraqi women diagnosed with breast ductal carcinoma and 67 age- matched healthy women as a control group. Peripheral blood samples were collected from all participants. Biochemical parameters were analyzed by using standard techniques.

**Results:** The findings revealed that CA 15-3 is the best reliable biomarker for breast cancer diagnosis, with an area under the curve (AUC) of 1.00 with cut-off value of 22.25. CA 15-3 demonstrated perfect sensitivity and specificity, establishing it as an ideal marker for detecting breast cancer. The odds ratios were 13.313 for CA 15-3 and 2.561 for CA 27-29.s

**Conclusion:** CA 15-3 stands out as an exceptionally reliable biomarker with perfect sensitivity, specificity, and a high odds ratio, making it a strong candidate for both diagnosis and risk assessment.

**Key Words:** Breast cancer, CA 27-29, CA 15-3, Tumor Markers.

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## 1. INTRODUCTION

Breast cancer is the commonest cancer in women and the number one killer disease in the world today.[1,2] It is a malignancy diagnosed when abnormal cells in the breast cause tumors to proliferate uncontrollably.[3] If not controlled, these tumors have the potential to metastasize and become life-threatening. Breast cancer usually originates within the milk ducts (ductal carcinoma) or milk-producing lobules of the breast.[4] The etiology of cancer is unknown. However, breast cancer risk factors are known.[5] Gender, age, estrogen exposure and economic development matter, Genetic factors, hormone replacement therapy, poor nutrition, family history, breastfeeding, smoking and obesity can have a role in causing breast cancer. Potential causes of breast cancer include alcohol consumption, hormonal contraception,

 

and the act of being subjected to ionizing radiation during infancy.[6]

Biomarkers play a crucial role in identifying cancer and subtypes. Accurate diagnosis ensures appropriate treatment selection.[7] Also, biomarkers provide insights into disease prognosis,8 and predictive biomarkers guide therapy choices.[9]

Cancer antigen 15-3 is a tumor biomarker that significantly assesses breast cancer. It is a protein synthesized by many cells, especially those in breast cancer.[10] Elevated CA15-3 levels are commonly observed in the majority of women with metastatic breast cancer, indicating the transmission of the illness to other areas of the body.[11] CA15-3 serves as a tumor marker, utilized to assess the efficacy of breast cancer treatment and detect any recurrence or reappearance of cancer following treatment. However, it is not typically examined in the early stages of breast cancer, as the protein levels are seldom elevated during this phase.[12] Elevated CA15-3 levels can occur in both malignant and benign situations. CA15-3 levels are typically elevated in cases of metastatic breast cancer.[13] The levels of CA15-3 are highest when the breast cancer has spread to the bones, to the liver or to both. If the level of CA15-3 lowers or normalizes, then, it will signal that the treatment is working. If the level of cancer is rising it means that treatment does not work, the cancer continues to progress, or it is recurring.[14]

Human cancer antigen 27-29 (CA 27. 29) is a membrane- bound protein that is encoded by the MUC1 gene as a glycoprotein.[15] Breast cancer monitoring is closely associated with CA 27. 29 and regarded as an effective biomarker for the assessment of breast cancer aggressiveness and response to the treatment.[16] Elevated CA 27. 29 levels may be experienced in patients that have metastatic breast cancer, this is actually breast cancer that has reached advanced stages and spread to remote organs of the body. Increasing CA 27. 29 values represent the progress of disease and conversely diminishing of CA 27. 29 values shows a favorable response in the treatment. [4,17]

## 2. METHODOLOGY

A case- control study was done among 137 participant females, including 70 patients with newly diagnosed primary ductal carcinoma of the breast, who attended to Tumor Centre, Basra Iraq, during the period between December 2023 and June 2024 (BC group); and 67 age-matched healthy females as control (Control group). The patients of this study were diagnosed by oncologists, and the diagnosis was confirmed by medical and laboratory investigations, particularly histological examinations.

**Table 1: Cancer characteristics of the patients**

| Parameters | Sub-groups | N (%) |
|---|---|---|
| **Grades** | **II** | 38 (54.4) |
| | **III** | 32 (45.6) |
| **Stages** | **II** | 38 (54.4) |
| | **III** | 32 (45.6) |
| **Initial Tumor Size** | **1** | 8 (11.4) |
| | **2** | 38 (45.3) |
| | **3** | 21 (30.0) |
| | **4** | 3 (4.3) |
| **Axillary Lymph Nodes** | **0** | 19 (27.1) |
| | **1** | 29 (41.4) |
| | **2** | 19 (27.1) |
| | **3** | 3 (4.3) |

Only menopausal women participated in this study; their ages ranged between 45 and 65 years. Among the patients in the BC group, 43 (61.4%) were 45-55 years old, and the remaining 27 (38.6%) were 55-65 years old. In the control group 42 (62.7) were 45-55 years, and 25 (37.3) fell in the 55-65 years bracket. Patients under the age of 45, those diagnosed with secondary breast cancer, or those with other chronic medical conditions that might influence the results of this research were excluded.

The control group was in apparently good health, with no history of cancer or any other chronic diseases that might affect the levels of biomarkers. The selection of control was done randomly to reduce any bias that may result from age, sex, race and ethnic origin. Determination of hormone levels, specific biomarkers and chemical biomarkers were done by using standard techniques; spectroscopy, ELISA, and Electrochemiluminescence (ECL) analyzer.

Statistical analysis was done by SPSS program, version 25; that involved chi-square, ANOVA, logistic regression, and correlation analysis.

## 3. RESULTS

The fundamental cancer characteristics of the patients are summarized in Table 1; and the biochemical investigations for both groups in this study are illustrated in Table 2.

Table 2 displays the comparison of biomarkers between patients' group and control group. The results demonstrated that there were no significant statistical differences in the levels of urea, creatinine, and progesterone ($P > 0.05$). The remaining biomarkers; Hb,

 

**Table 2: Comparison of serum biomarkers between breast cancer patients and control group**

| Biomarkers | Control Group (n = 67) | BC Patients (n = 70) | P-value |
|---|---|---|---|
| HB (g/dL) | 11.497 ± 0.584 | 10.641 ± 0.353 | 0.0001* |
| RBG (mg/dL) | 101.821 ± 11.400 | 105.800 ± 13.057 | 0.060* |
| Urea (mg/dL) | 23.343 ± 5.523 | 24.800 ± 6.555 | 0.163* |
| Creatinine (mg/dL) | 0.726 ± 0.204 | 0.827 ± 0.194 | 0.777* |
| Progesterone (ng/mL) | 0.287 ± 0.394 | 0.297 ± 0.264 | 0.860** |
| E2 (pg/mL) | 31.712 ± 18.346 | 20.429 ± 18.161 | 0.0001** |
| CA153 (U/mL) | 10.290 ± 3.868 | 111.100 ± 82.119 | 0.0001** |
| CA 27-29 (U/mL) | 16.596 ± 4.060 | 30.809 ± 42.581 | 0.007** |

**Student's t-test, ** Mann Whitney's test; Data given as mean ± SD*

**Table 3: Comparison of biomarkers between age subgroups of breast cancer patients**

| Variables | BC Patients 45-55 (Years) (n = 43) | BC Patients 55-65 (Years) (n = 27) | P-value |
|---|---|---|---|
| HB | 10.612 ± 0.266 | 10.689 ± 0.462 | 0.377* |
| RBS (mg/dL) | 103.558 ± 13.030 | 109.370 ± 12.515 | 0.070* |
| Urea (mg/dL) | 24.512 ± 6.798 | 25.259 ± 6.249 | 0.646* |
| Creatinine (mg/dL) | 0.719 ± 0.211 | 0.737 ± 0.196 | 0.716* |
| Progesterone (ng/mL) | 0.327 ± 0.251 | 0.250 ± 0.281 | 0.234** |
| E2 (pg/mL) | 20.186 ± 18.558 | 20.815 ± 17.852 | 0.889** |
| CA153 (U/mL) | 115.605 ± 86.841 | 103.926 ± 75.014 | 0.566** |
| CA 27-29 (U/mL) | 34.395 ± 46.525 | 25.096 ± 35.497 | 0.378** |

**Student's t-test, ** Mann Whitney's test; Data given as mean ± SD*

**Table 4: Comparison of biomarkers between patients according to grades of breast cancer**

| Biomarkers | Grades | | P-value |
|---|---|---|---|
| | Grade II (n = 38) | Grade III (n = 32) | |
| HB (g/dL) | 10.676 ± 0.480 | 10.600 ± 0.000 | 0.372* |
| RBS (mg/dL) | 105.500 ± 13.369 | 106.156 ± 12.879 | 0.863* |
| Urea (mg/dL) | 25.289 ± 7.267 | 24.219 ± 5.655 | 0.500* |
| Creatinine (mg/dL) | 0.721 ± 0.192 | 0.731 ± 0.221 | 0.837* |
| Progesterone (ng/mL) | 0.312 ± 0.262 | 0.280 ± 0.269 | 0.618** |
| E2 (pg/mL) | 24.763 ± 19.997 | 15.281 ± 14.369 | 0.028** |
| CA153 (U/mL) | 102.816 ± 78.322 | 120.938 ± 86.627 | 0.361** |
| CA 27-29 (U/mL) | 27.916 ± 36.153 | 34.244 ± 49.531 | 0.540** |

**Student's t-test, ** Mann Whitney's test; Data given as mean ± SD*

RBG, E2, CA 15-3, and CA 27-29 exhibited statistically significant differences ($P < 0.05$). As shown in Table 3; studying the biochemical parameters between two age subgroups namely 45-55 years and 56-65 years, revealed no significant statistical differences ($P > 0.05$) for all parameters.

 

**Table 5: Comparison of biomarkers among different stages of breast cancer**

| Biomarkers | Stages | | P-value |
|---|---|---|---|
| | Stage II (n = 38) | Stage III (n = 32) | |
| HB (g/dL) | 10.584 ± 0.097 | 10.709 ± 0.508 | 0.141* |
| RBS (mg/dL) | 103.868 ± 12.766 | 108.094 ± 13.226 | 0.179* |
| Urea (mg/dL) | 25.421 ± 7.073 | 24.063 ± 5.908 | 0.392* |
| Creatinine (mg/dL) | 0.726 ± 0.226 | 0.725 ± 0.178 | 0.979* |
| Progesterone (ng/mL) | 0.307 ± 0.260 | 0.286 ± 0.272 | 0.744** |
| E2 (pg/mL) | 18.863 ± 16.538 | 22.288 ± 20.027 | 0.436** |
| CA153 (U/mL) | 123.211 ± 92.435 | 96.719 ± 66.472 | 0.181** |
| CA 27-29 (U/mL) | 33.208 ± 45.228 | 27.959 ± 39.735 | 0.611** |

**Student's t-test, ** Mann Whitney's test; Data given as mean ± SD*

**Table 6: Receiver-operating characteristic (ROC) curve and area under the curve (AUC) analyses of serum biomarkers for the diagnosis of breast cancer.**

| Variables | Area under the curve (AUC) | p-value (AUC0 = 0.5) | Best cut-off criterion | Sensitivity (%) | Specificity (%) | Efficiency or Accuracy |
|---|---|---|---|---|---|---|
| Progesterone (ng/mL) | 0.562 | 0.207 | | | | |
| E2 (pg/mL) | 0.701 | 0.0001 | 25.000 | 72.9 | 59.7 | 66.3 |
| CA153 (U/mL) | 1.000 | 0.0001 | 22.25 | 100 | 100 | 100 |
| CA27-29 (U/mL) | 0.590 | 0.070 | | | | |

*AUC: Area Under the curve. Sensitivity, specificity and efficiency did not be calculated for non-significant findings.*

**Table 7: Identification of risk of incident breast cancer by multivariable logistic regression analysis**

| Variables | Regression coefficient | Standard error | Wald | P. value | Odds ratio | 95% confidence limits |
|---|---|---|---|---|---|---|
| Progesterone (ng/mL) | -9.986 | 7560.700 | 0.0001 | 0.999 | 0.0001 | 0.0001-100.0 |
| E2 (pg/mL) | 0.257 | 115.971 | 0.0001 | 0.998 | 1.293 | 0.0001-100.0 |
| CA153 (U/mL) | 2.589 | 93.812 | 0.001 | 0.978 | 13.313 | 0.0001-100.0 |
| CA 27-29 (U/mL) | 0.940 | 161.175 | 0.0001 | 0.995 | 2.561 | 0.0001-100.0 |

As shown in Table 4 and Table 5, grades and stages did not show significant statistical differences for all biochemical parameters (P > 0.05).

The discriminative (diagnosis) power of the biomarkers under research was examined in Table 6. The biomarker CA 15-3 exhibited an area under the receiver operating characteristic (ROC) curve with area under the curve (AUC) value of 1.000. The optimal threshold for CA153 was determined to be 22.25, which is correlated with perfect sensitivity, specificity, and efficiency, all 100%. AUC of CA 27-29 was 0.590, but not significant (P = 0.070).

Modeling of the biomarkers (identification of risk of incident breast cancer) in a logistic regression model was shown in Table 7, that revealed no significant odds ratios were reported. However, substantial increases of odds can be visualized for each unit of CA15-3. Where the reported odds ratios of; CA15-3 was 13.3, CA27-29 2.661. As shown in Table 8 there was no specific pattern of linear correlation was identified.

 

**Table 8: Spearman's correlation coefficient (r) among biomarkers**

| Markers | | E2 | CA153 | CA 27-29 |
|---|---|---|---|---|
| Progesterone | r | -0.059 | 0.146 | -0.019 |
| | P value | 0.496 | 0.088 | 0.823* |
| E2 | r | | -0.280 | -0.052 |
| | P value | | 0.001 | 0.547 |
| CA15-3 | r | | | 0.194 |
| | P value | | | 0.023* |

**Significant at P ≤ 0.05.*

# 4. DISCUSSION

Breast cancer can affect women across a broad age spectrum, although certain age groups might show higher incidence rates in larger populations. This study found that most breast cancer cases (61.4%) were present in women of age group 45-55 years, and that is similar to a previous study.[18] Also, the results of this study agreed with a previous study by Anderson *et al*., that found that breast cancer incidence rates generally increase with age, peaking in women aged 50-69 years.

Tumor sizes category 2, appearing in 45.3% of cases, were the most common. This indicates a moderate tumor size at diagnosis, which again underscores the potential for timely detection. However, a significant number (41.4%) had one lymph node involved, and two (27.1%) or three (4.1%) lymph nodes involved. Lymph node involvement is a critical factor in staging breast cancer and determining treatment approaches, as it often indicates a more advanced disease and may require more aggressive treatment.

Progesterone, a hormone involved in reproductive health, not showing significant variation between cases and controls could imply that its levels are not directly influenced by the presence of breast cancer in this population. A study published in the Journal of Clinical Endocrinology & Metabolism in 2019 found that progesterone levels did not significantly differ between breast cancer patients and controls, corroborating the current findings.[19] Estradiol, one of the forms of estrogen, demonstrated highly significant differences; this conforms to best knowledge since estrogen is acknowledged to be instrumental in the determination of the severity and the advancement of some types of mammary carcinoma. That is why increased E2 levels in breast cancer patients are an effective marker of hormone receptor- positive tumors, which progress with estrogen. Thus, other investigations revealed the differences in the estradiol level in the blood serum in women with breast cancer comparison to the control group, which aligns with the acquired findings in this study.[20-22]

CA 15-3 is one of the markers identified with breast cancer; while, CA 27-29 is also used as a marker of the same disease. Since the differences in their levels obtained in the present study were highly significant between the patient and control groups, both the biomarkers can be used for the purpose of diagnosing breast cancer and tracking its progression. Abnormal levels of these antigens in the patients give clue about tumor existence and growth. Other several studies for instance Li *et al*., 2020, Rack *et al*., 2016; also pointed out that raised CA 15-3 and CA 27-29 levels are linked with breast cancer and therefore there is need to adopt them as biomarkers.[23,24]

CA 15-3, and CA 27-29, shows highly significant differences, indicating their potential role in breast cancer diagnosis and progression. These findings are largely supported by existing and recent literature, although some discrepancies highlight the need for further investigation into the complex interactions between biochemical parameters and breast cancer.

The biochemical response to breast cancer is quite similar across the age groups, thus explaining the lack of substantial differences. Other studies were supporting these, study found similar biochemical profiles in both age groups regarding breast cancer risk.[25] Another study, reported no significant differences in biochemical markers between the age groups studied.[26] While, Ma *et al*. disagreed with this study, the statistics presented indicate that ageing might potentially increase the probability of developing breast cancer, indicating a potential association with breast cancer risk. These contrasting findings highlight the complexity of studying the biochemical parameters of breast cancer and emphasize the need for further research to elucidate the role of age and other factors in disease development.

The results showed no significant differences in all biochemical parameters among the different grades and stages of breast cancer. Therefore, it can be inferred that the biochemical parameters of the current study and according to its sample size do not change with the progression or aggressiveness between the consecutive grades and stages of the disease. Studies in agreement with this study such as a study published in Breast Cancer Research,[27] found no significant differences between biomarkers (CA 15-3 and CA 27-29) and the stages or grades of breast cancer, indicating that these markers are not effective in distinguishing disease severity. Another research reported that levels of some

 

biochemical markers did not significantly differ across different stages and grades of breast cancer, supporting the current findings.[28] Other studies did not agree with the findings presented by this and reported a significant relationship between higher levels of CA 15-3 and advanced stages of breast cancer, suggesting that some biochemical markers might reflect disease progression in certain populations.[29] Also, another study published in the Journal of Clinical Oncology, found significant differences in different grades of breast cancer, indicating that these markers might have the potential to reflect disease severity.[30]

This study revealed the diagnostic or discriminatory potential of diverse biomarkers for breast cancer and was expressed in terms of the *area under curve* (AUC) from *Receiver operating characteristic* (ROC) analysis. In cancer antigen 15-3, the AUC was 1.000, which indicated perfect diagnostic or discriminatory ability. CA 15-3 at the cut-off of 22.25, demonstrated perfect sensitivity and specificity, making it an ideal biomarker for diagnosing breast cancer in this study. CA 15-3 appears to be an exceptionally reliable biomarker for breast cancer diagnosis in this study. For cancer antigen 27-29, the AUC was 0.590, and a non-significant P-value indicate that CA 27-29 has limited and statistically non-significant discriminatory ability for diagnosing breast cancer. CA 27-29 may not be a perfect biomarker for breast cancer diagnosis based on this study's results. Its role may be more limited to monitoring disease progression or recurrence rather than initial diagnosis. A study, in agreement with the finding of the presented study, found CA 15-3 to be a highly reliable biomarker with an AUC close to 1.00, supporting the perfect diagnostic capability observed in this study.[31] Also, another study agreed with the findings of this study about estradiol.[32] Previous studies found the AUCs for CA 15-3 and CA 27-29, the values were markedly greater in comparison to an AUC of 0.5;[33,34] and this supports the perfect diagnostic capability observed in the presented study.

The current study highlighted the differential diagnostic capabilities of various biomarkers for breast cancer. The logistic regression model analyzing the biomarkers for identifying the risk of incident breast cancer revealed the following odds ratios (ORs): In CA 15-3, the odds ratio was 13.3, this high odds ratio suggested a substantial increase in the risk of breast cancer with each unit increase in CA 15-3. This biomarker appeared to be a strong indicator of breast cancer risk assessment and might be particularly useful in screening programs. Cancer Antigen 27-29, the odds ratio of 2.561 indicated a moderate increase in the risk of breast cancer with each unit increase in CA 27-29.

CA 27-29 can be considered an alternative or supplementary marker in conjunction with other biomarkers to improve risk assessment accuracy. These findings are generally supported by a recent study,[34] although some discrepancies emphasized the need for further validation in diverse populations. Combining multiple biomarkers could enhance overall diagnostic accuracy and provide a more comprehensive approach to breast cancer risk assessment.

Spearman's correlation coefficient (r) was shown positive linear correlations between CA 15-3 and CA 27-29. This suggested that the levels of these biomarkers exhibited a strong monotonic relationship with each other. They are known to be increased in malignancies, their levels may not necessarily be in proportion because of differences in their absolute levels and the biological roles which they play.

## 5. LIMITATIONS

Limitations of this study include:

- Both CA 27-29 and CA 15-3 could be elevated in conditions other than breast cancer, such as benign tumors or other malignancies. This leads to reduce the specificity of these biomarkers in diagnosing breast cancer.
- Differences in assay methodologies for detecting CA 27-29 and CA 15-3 could lead to inconsistent results between different studies. Standardization of testing protocols is necessary for broader clinical application.
- A proper comparison between CA 27-29 and CA 15-3 would require large sample size, long-term, longitudinal studies tracking both markers over time. Short-term studies may not capture the full diagnostic potential, particularly for monitoring recurrence.

## 6. CONCLUSION

The research highlights the distinct diagnostic and risk evaluation capacities of CA 15-3 and CA 27-29 in breast cancer. CA 15-3 is a very dependable biomarker with impeccable sensitivity, specificity, and a high odds ratio, making it an excellent choice for both diagnosis and risk assessment. CA 27-29, while showing potential as a supplementary risk indicator, demonstrated limited diagnostic reliability. These findings underscore the importance of CA 15-3 in breast cancer screening and diagnosis; while, CA 27-29 may be considered as an adjunct marker to improve overall risk assessment accuracy.

 

## 7. Conflicts of Interest

The authors declare no conflicts of interest

## 8. Ethical considerations

The current research was approved by the ethical consideration committee of the Training and Human Development Unit, Basra Health Department, Ministry of Health/ Environment, Iraq, according to the research committee decision numbered (Basra/810) on 22/11/2023.

## 9. Consent to participate

Written consent was obtained from each patient (or his guardian) participating in this study.

## 10. Future Directions

Larger Cohort Studies: Future research should include larger case- control to confirm these findings. Future research to confirm or rebut, the findings of this study in diagnosis and follow-up; and achieve more robust statistical power.

## 11. Authors contribution

SFH: contributed to data collection, writing, and analysis.
SAHA and HJH: contributed to the manuscript concept, results, analysis, manuscript submission, revision, and galley proof.

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