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# Diagnostic Significance of Tumor Markers CA 15-3, CA 125, TBARS, fasting blood sugar (RBS), and hemoglobin A1C (HbA1c) in Women with a Family History of Breast Cancer in Eastern Libya

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**ABSTRACT**

Breast cancer remains one of the most prevalent malignancies among women worldwide, with family history being a major non-modifiable risk factor. Tumor markers such as cancer antigen 15-3 (CA15-3) and cancer antigen 125 (CA125), alongside oxidative stress indicators like thiobarbituric acid reactive substances (TBARS), can provide insights into subclinical molecular changes in at-risk populations. While CA15-3 is more closely associated with breast cancer progression, CA125 is primarily linked to gynecologic malignancies but may have secondary implications in breast pathology. Evaluating these biomarkers in women with a family history of breast cancer could reveal early molecular alterations preceding overt disease. This study was conducted to compare tumor marker levels (CA15-3, CA125), oxidative stress markers (TBARS), and glycemic indicators (fasting blood sugar [RBS] and hemoglobin A1C [HbA1c]) between women with and without a family history of breast cancer, and to assess correlations between these parameters from a molecular oncology perspective. This comparative cross-sectional study included two groups: women with a family history of breast cancer and matched controls without such a history. Serum levels of CA15-3 and CA125 were measured using immunoassay techniques, while TBARS concentrations were determined as a proxy for lipid peroxidation. RBS and HbA1c were quantified using enzymatic and chromatographic methods, respectively. Pearson's correlation coefficients were calculated to examine relationships between tumor markers, glycemic status, and oxidative stress in both groups. CA15-3 levels were marginally higher in the family history group (15.07 ± 8.77 U/mL) compared to controls (12.81 ± 6.12 U/mL), suggesting subtle subclinical variations in mucin-1 antigen expression that may indicate early tumorigenic processes in genetically predisposed women. CA125 levels were notably lower in the family history group (9.56 ± 3.86 U/mL) versus controls (21.44 ± 22.44 U/mL), likely reflecting reproductive or hormonal factors rather than direct breast cancer risk modulation. TBARS levels were similar between groups (controls: 0.093 ± 0.009 µmol/mL; family history: 0.092 ± 0.010 µmol/mL), indicating comparable systemic oxidative stress. A strong positive correlation was observed between RBS and HbA1c ($r = 0.809$, $p = 1.00$), validating HbA1c as a reliable indicator of chronic glycemic exposure. Moderate positive correlations were observed between glycemic markers and CA15-3 (RBS: $r = 0.417$; HbA1c: $r = 0.393$), as well as between HbA1c and CA125 ($r = 0.697$); however, these associations did not reach statistical significance. TBARS showed weak negative correlations with most glycemic and tumor markers, suggesting that other biological or environmental factors may modulate oxidative stress.

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## INTRODUCTION

Breast cancer remains the most common malignancy among women worldwide, accounting for significant morbidity and mortality despite advancements in early detection and targeted therapies [1]. Familial aggregation of breast cancer has been strongly associated with inherited genetic mutations, such as BRCA1 and BRCA2, which significantly increase lifetime risk [2]. Women with a family history of breast cancer not only face a higher genetic predisposition but also may exhibit distinct biochemical and oxidative stress profiles that could contribute to tumorigenesis [3]. Therefore, identifying reliable biomarkers in this high-risk population is essential for improving early diagnosis, prognosis, and personalized surveillance strategies. Tumor markers such as cancer antigen 15-3 (CA 15-3) and cancer antigen 125 (CA 125) have been widely

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investigated for their diagnostic and prognostic potential in breast and ovarian malignancies, respectively. CA 15-3, a circulating epitope of MUC1 mucin, is frequently elevated in breast cancer patients, particularly in advanced disease stages, while CA 125, although primarily associated with ovarian cancer, can also be elevated in certain subtypes of breast cancer [4]. The integration of these markers into risk assessment protocols could enhance screening precision in genetically predisposed populations. In addition to tumor-associated glycoproteins, oxidative stress markers have emerged as crucial indicators in cancer biology. Thiobarbituric acid reactive substances (TBARS) represent a well-established measure of lipid peroxidation, reflecting oxidative damage to cell membranes. Elevated TBARS levels have been reported in breast cancer patients, indicating the role of reactive oxygen species (ROS) in tumor initiation, progression, and metastasis [5]. Emerging evidence also suggests a significant link between altered glucose metabolism and breast cancer risk. Fasting blood sugar (FBS) and random blood sugar (RBS) levels, along with glycated hemoglobin (HbA1c), are established indicators of glucose homeostasis and long-term glycemic control [6]. Hyperglycemia and insulin resistance have been implicated in breast cancer development through mechanisms involving chronic inflammation, oxidative stress, and increased bioavailability of insulin-like growth factors [7]. Elevated HbA1c levels, in particular, have been associated with increased breast cancer incidence and poorer outcomes, underscoring the relevance of metabolic markers in cancer risk assessment [8]. Given the high prevalence of breast cancer in Libya and the paucity of studies integrating tumor markers, oxidative stress indicators, and glycemic parameters in genetically predisposed women, this study aims to evaluate the diagnostic significance of CA 15-3, CA 125, TBARS, FBS/RBS, and HbA1c in women with a family history of breast cancer in Eastern Libya. Understanding these biomarker profiles could provide valuable insights for early detection, risk stratification, and preventive strategies tailored to high-risk populations.

## METHODS

This cross-sectional analytical study was conducted over six months from January 2025 to June 2025, at the IDEA Medical Laboratory located in Al-Bayda City, Eastern Libya. The aim was to assess and compare tumor markers and associated biochemical parameters in women with and without a family history of breast cancer. The study enrolled a total of 50 women aged between 20 and 65 years. Participants were divided into two groups: Group I (Case group): 25 women with a confirmed family history of breast cancer (first-degree relatives). Group II (Control group): 25 healthy women with no personal or familial history of breast cancer. Participants were recruited through structured interviews and medical record verification. Inclusion criteria included Libyan nationality, residence in Al-Bayda, no history of active malignancy, and willingness to provide informed consent. Women undergoing chemotherapy, radiotherapy, or recent surgery were excluded to avoid confounding effects on the studied biomarkers. The study protocol was approved by the Research Ethics Committee of the Faculty of Medical Sciences at the Libyan Academy for Postgraduate Studies, Jabal Al-Akhdar Branch. All participants signed a written informed consent form before enrollment. Data confidentiality and anonymity were maintained throughout the study. Approximately 10 mL of fasting venous blood was collected from each participant using sterile Vacutainer tubes. Blood samples were processed as follows: 3 mL into EDTA tubes for hematological analysis and 7 mL into plain tubes for serum separation by centrifugation at 3000 rpm for 10 minutes at room temperature. Serum was aliquoted and stored at –20°C until further analysis. All blood samples were collected between 8:00 AM and 11:00 AM to minimize circadian variation in biochemical markers. Serum levels of CA 15-3 and CA 125 were measured using commercially available enzyme-linked immunosorbent assay (D10) kits following the manufacturer's instructions. All assays were performed in duplicate to ensure accuracy. The technique described by methods [9] was used to measure the amount of thiobarbituric acid-reactive compounds" (or "TBARS") in plasma. Commercial kits for glucose, insulin, and HbA1c analysis were obtained from D10 and used according to the manufacturer's instructions [10]. All statistical analyses were performed using JASP statistical software (Version 0.19.1.0, University of Amsterdam)**.** The data were initially entered into Microsoft Excel and then imported into JASP for further processing. Descriptive statistics, including mean ± standard deviation (SD), were calculated for all measured parameters. To assess the statistical significance of differences between groups, one-way analysis of variance (ANOVA) was applied, followed by Tukey's Honest Significant Difference (HSD) post-hoc test for multiple comparisons. For non-normally distributed data, the Kruskal-Wallis test was used as a non-parametric alternative, followed by Dunn's test for pairwise comparisons. A *p*-value of less than 0.05 was considered statistically significant. Graphical representations of the data, including bar plots and boxplots, were also generated within JASP to visualize the distribution and differences between groups.

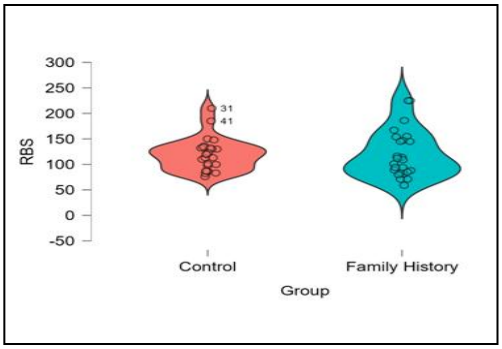
## RESULTS

Regarding tumor markers, CA15-3 levels were marginally elevated in the family history group (15.07 ± 8.77 U/mL) compared to controls (12.81 ± 6.12 U/mL). Although these values are within normal clinical ranges, the upward trend could

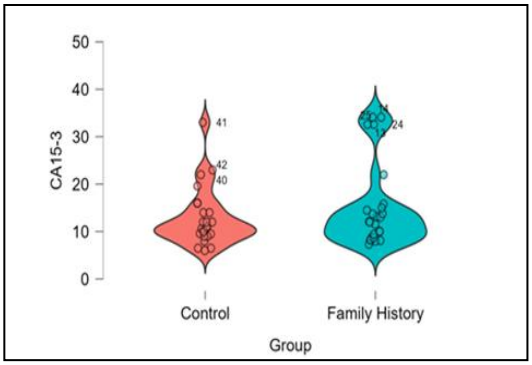
suggest subclinical variations in mucin-1 antigen expression, which has been linked to early tumorigenic processes in high-risk populations (Duffy et al., 2010). In contrast, CA125 levels were notably lower in the family history group (9.56 ± 3.86 U/mL) compared to controls (21.44 ± 22.44 U/mL). Given CA125's association with gynecologic malignancies rather than breast cancer specifically, this reduction may be incidental or linked to population-specific reproductive or hormonal factors rather than breast cancer risk per se. TBARS levels, reflecting lipid peroxidation and oxidative stress, were similar between the two groups (control: 0.093 ± 0.009 µmol/mL; family history: 0.092 ± 0.010 µmol/mL). From a genetic engineering and molecular oncology perspective, these findings hint at subtle biochemical differences in tumor-associated antigen expression in individuals with a family history of breast cancer, despite similar metabolic and oxidative stress markers. This may suggest that tumor marker monitoring could provide earlier indications of risk modulation than standard metabolic profiles in genetically predisposed cohorts.

***Table 3. Descriptive Statistics of fasting blood sugar (RBS), hemoglobin A1C (HbA1c) , CA15-3, CA125, and Thiobarbituric acid reactive substances (TBARS) in control and family history.***

| Descriptive Statistics | Mean & Std. | Minimum | Maximum | Mean & Std. | Minimum | Maximum |
|---|---|---|---|---|---|---|
| | Control | | | Family History | | |
| RBS | 119.44 ± 31.94 | 76 | 210 | 119.84 ±46.16 | 59 | 225 |
| HbA1C | 6.25 ± 1.52 | 4 | 11.8 | 5.72 ± 1.24 | 4 | 8.3 |
| CA15-3 | 12.81 ± 6.12 | 6 | 33 | 15.07 ± 8.77 | 7.3 | 34.1 |
| CA125 | 21.44± 22.44 | 6.2 | 100 | 9.56 ± 3.86 | 5.3 | 17.80 |
| TBARS | 0.093 ± 0.009 | 0.081 | 0.121 | 0.092 ± 0.010 | 0.069 | 0.117 |




***Figuer 1. Plot depicting fasting blood sugar (RBS) distribution among women in the control group and those with a family history of breast cancer.***




***Figuer3. Plot depicting CA15-3 distribution among women in the control group and those with a family history of breast cancer***

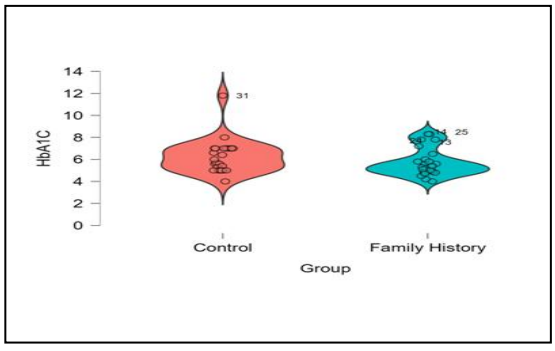



***Figure 2. Plot depicting hemoglobin A1C (HbA1c) distribution among women in the control group and those with a family history of breast cancer.***

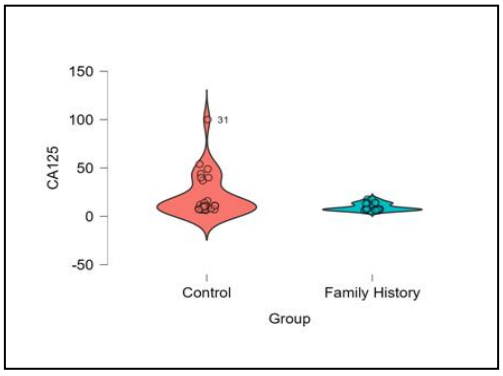



***Figure 4. Plot depicting CA 125distribution among women in the control group and those with a family history of breast cancer.***

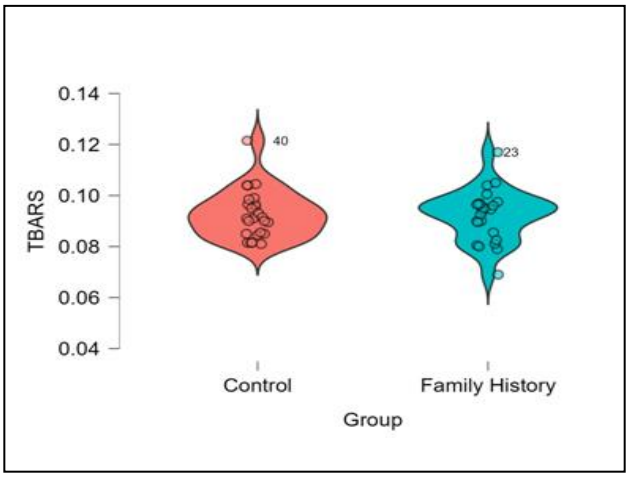



***Figure 5. Plot depicting TBARS distribution among women in the control group and those with a family history of breast cancer***

(Table 2) presents Pearson's correlation coefficients between fasting blood sugar (RBS), hemoglobin A1C (HbA1c), tumor-associated antigens (CA15-3 and CA125), and thiobarbituric acid reactive substances (TBARS) in women without and with a family history of breast cancer. A notably strong positive correlation was observed between RBS and HbA1c (r = 0.809, p = 1.00), consistent with the established biochemical relationship between acute glycemic levels and their long-term average, as reflected in glycated hemoglobin values. This finding reinforces the reliability of HbA1c as a proxy measure for chronic glycemic exposure in both groups. Moderate positive correlations were seen between glycemic markers and CA15-3 (RBS: r = 0.417; HbA1c: r = 0.393) and between HbA1c and CA125 (r = 0.697). While the lack of statistical significance (high p-values) suggests these associations could be due to random variation, the directionality of these relationships is biologically plausible. Interestingly, TBARS—an indicator of lipid peroxidation—showed weak and negative correlations with most glycemic and tumor markers (e.g., RBS: r = -0.126; HbA1c: r = -0.051; CA125: r = -0.071), suggesting that systemic oxidative stress levels, at least as measured by TBARS, may be influenced by factors other than glycemic status or tumor antigen expression in this cohort. Given that TBARS reflects only one dimension of oxidative damage, integrating complementary oxidative stress biomarkers could provide a more robust mechanistic insight. From a genetic engineering perspective, individuals with a family history of breast cancer may possess inherited genomic variants, particularly in DNA repair pathways such as BRCA1/2, that could modulate tumor antigen expression independently of metabolic status. This could explain the modest coupling between glycemic indices and tumor markers, even in the absence of significant oxidative stress variation.

***Table 2. Correlations among fasting blood sugar (RBS), hemoglobin A1C (HbA1c), CA15-3, CA125 and Thiobarbituric acid reactive substances (TBARS) in control and family history.***

| Variable | | RBS | HbA1C | CA15-3 | CA125 | TBARS |
|---|---|---|---|---|---|---|
| RBS | Pearson's r | — | | | | |
| | p-value | — | | | | |
| HbA1C | Pearson's r | 0.809 | — | | | |
| | p-value | 1.00 | ---- | | | |
| CA15-3 | Pearson's r | 0.417 | 0.393 | — | | |
| | p-value | 0.997 | 0.998 | — | | |
| CA125 | Pearson's r | 0.387 | 0.697 | -0.062 | — | |
| | p-value | 0.997 | 1.00 | 0.334 | — | |
| TBARS | Pearson's r | -0.126 | -0.051 | 0.160 | -0.071 | — |
| | p-value | 0.191 | 0.363 | 0.867 | 0.311 | — |

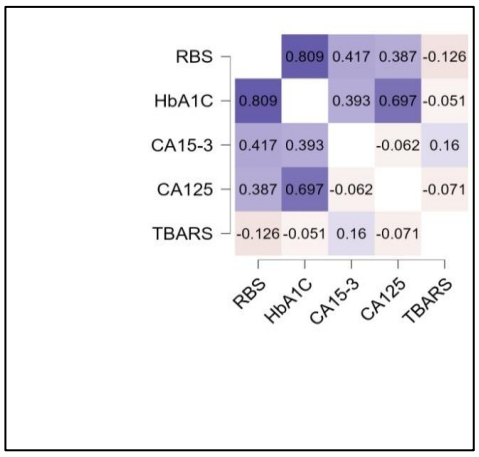



***Figure 6. Heatmap of Pearson's Correlation Coefficients Among the control group and those with a family history of breast cancer.***

## DISCUSSION

Both groups—control and family history—show similar mean levels of random blood sugar and HbA1, well below diabetes thresholds. Epidemiological evidence suggests a modest increase in breast cancer risk associated with elevated fasting glucose, even in non-diabetic individuals, with a relative risk of around 1.11. ResearchGate. Moreover, higher HbA1c levels in women without diagnosed diabetes correlate with elevated risk of future breast cancer events, with adjusted hazard ratios climbing with each quartile [8]. The slightly lower HbA1c in women with a family history may reflect better glycemic control—possibly due to heightened health awareness, though this difference did not reach statistical significance. Mean CA15-3 levels are marginally higher in the family history group, yet both remain well below the standard upper reference limit of 30 U/mL Medscape. CA15-3 is primarily used for monitoring metastatic disease or treatment response, not early detection, due to low sensitivity in early stages [11].

CA125, conversely, is higher in the control group. While CA125 can sometimes assist in the prognosis or monitoring of advanced breast cancer, its role in early-stage detection or familial risk remains uncertain and inconsistent across studies [12]. TBARS levels (a marker of lipid peroxidation and oxidative stress) are nearly identical in both groups, exhibiting negligible variation. This suggests that familial predisposition alone does not alter systemic oxidative stress at baseline. Elevated TBARS levels tend to emerge during active disease or metabolic disturbance, rather than as a preclinical heritable trait [13]. Although none of the measured biomarkers differ significantly between groups, the literature suggests even subtle glucose elevations could portend increased cancer risk, justifying vigilance in glycemic control among high-risk individuals ResearchGateBioMed Central. The absence of disparities in tumor markers (CA15-3, CA125) and TBARS aligns with their generally limited utility in early detection or familial risk stratification. These markers typically show relevance in the context of established disease progression or treatment monitoring [14]. The strong RBS–HbA1c link echoes robust clinical understanding: HbA1c reflects average plasma glucose levels over weeks to months, while RBS captures an instantaneous measure. This relationship is consistently demonstrated in both clinical practice and the literature [15]. The moderate correlations between glycemic markers (RBS/HbA1c) and CA15-3 hint at a potential metabolic influence on tumor marker expression. Hyperglycemia and metabolic dysregulation may subtly influence tumor biology or biomarker clearance. However, the lack of statistical significance and known limitations of CA15-3 as an early diagnostic marker caution against overinterpretation [16]. The notable correlation between HbA1c and CA125 ($r = 0.697$) raises an intriguing possibility of metabolic influences on this tumor-associated antigen. Yet, CA125 is primarily linked to ovarian pathology and lacks specificity for breast cancer risk. Without significant p-values, this relationship remains speculative [17]. TBARS levels, indicative of lipid peroxidation, do not correlate significantly with any markers. This suggests that baseline oxidative stress is not directly linked to glycemic status or tumor marker levels in asymptomatic individuals. Elevated TBARS typically emerge during disease progression or metabolic derangement—not at the genetic predisposition stage. Elevated fasting blood glucose is associated with increased incidence and worse prognosis in breast cancer patients [18]. HbA1c has been identified as a potential predictor of recurrence risk in non-diabetic breast cancer patients, with higher quartiles linked to increased likelihood of new breast cancer events [8]. These findings underscore the broader epidemiological significance of glycemic control in cancer risk and prognosis, despite the absence of significant associations with tumor markers in our correlation analysist [19,20].

## CONCLUSION

Women with a family history of breast cancer exhibited marginally elevated CA15-3 levels, despite normal clinical ranges, potentially indicating early molecular changes in mucin-1 expression. The reduction in CA125 among these women appears unrelated to breast cancer risk and may be population-specific. Oxidative stress, as measured by TBARS, did not differ significantly between groups, underscoring the need for broader oxidative stress profiling. From a genetic engineering perspective, inherited variants in tumor suppressor or DNA repair genes (e.g., BRCA1/2) may influence tumor antigen

expression independently of glycemic status or oxidative damage. These findings highlight the potential of tumor marker monitoring as an early risk stratification tool in genetically predisposed women, warranting further longitudinal and multi-marker investigations.

***Conflict of interest***. Nil

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