Original Article Open Access

Archives Of Breast Cancer

DOI: 10.32768/abc.8063149720-581

Association of Obesity with Premenopausal Breast Cancer: Analyzing Molecular Subtypes

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ARTICLE INFO

Received:
19 May 2025
Revised:
2 August 2025
Accepted:
7 August 2025

Keywords:
breast neoplasms, premenopause, body mass index, obesity, interleukin-6, insulin, CA15-3 Antigen

ABSTRACT

Background: Breast cancer (BC) is a common disease among women. Research on obesity and premenopausal breast cancer shows mixed results. In this study, we examined the associations between premenopausal BC and obesity by analyzing molecular subtypes.

Methods: We interviewed 74 women diagnosed with early and advanced stages of BC. Interleukin-6 (IL-6), cancer antigen 15-3 (CA15-3), and insulin levels were determined by immunoassay. Biochemical analyses were used to measure serum levels of glucose and lipid profiles. Descriptive statistics, χ^2 test, *t* test, and analysis of variance were used for statistical analysis.

Results: Our results suggested that obesity was associated with tumor proliferation, size, and status of progesterone hormone receptors. Differences in lipid profiles were observed between patients with and without obesity, as well as between molecular subtypes. An increase in the levels of IL-6, glucose, and the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index was observed in luminal B and HER2-enriched subtypes in patients with obesity. In patients with triple-negative breast cancer (TNBC), only the glucose level was significantly associated with obesity. A moderate inverse correlation was found between the CA15-3 level and body mass index ($r = -0.40$, $P = 0.008$.

Conclusion: Our findings support the putative role of obesity BC development and the formation of its molecular subtypes in premenopausal women. Metabolic monitoring, especially of glucose and lipid profiles, proved to be useful for premenopausal patients with BC and obesity to evaluate potential risks for specific molecular subtypes.

INTRODUCTION

Breast cancer (BC) is the most common type of cancer among women worldwide. The International Agency for Research on Cancer reported that in 2022, 2.31 million women were diagnosed with BC. According to World Health Organization (WHO) data, more than 1 billion adults were living with obesity in 2022. Obesity is a main risk factor for different types of cancer. Studies suggest that for every 5-kg/m² increase in body mass index (BMI), the probability of developing BC increases by 2%.[1] The association between metabolic syndrome or obesity

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and postmenopausal BC has been confirmed in several studies. However, views on the link between premenopausal BC and obesity are controversial. Several studies have suggested that overweight and obesity confer a preventive benefit against BC in premenopausal women, except for those with a familial history of the disease.[1,2] A few studies have found that obesity increases the risk of BC in premenopausal women.[3,4] A meta-analysis of cohort studies indicated that for Asian women, a 5-kg/m² increase in BMI was associated with a 16% increased risk of premenopausal breast cancer. In contrast, the same BMI increase was associated with a 9% lower risk in North American women.[3] The development of BC in individuals with obesity is often explained by a high level of active estrogen in the blood. Adipocytes exhibit endocrine activity by synthesizing various substances, including estrogen. These substances can promote cancer cell growth by stimulating cell proliferation.[5]

Obesity is often accompanied by hyperinsulinemia and insulin resistance (IR), which have a multifaceted effect on cancer development.[2,3] Several studies have also confirmed that IR and hyperinsulinemia are risk factors for BC.[6,7] Insulin may have a crucial mitogenic role in BC formation. In vitro studies suggest that insulin stimulates breast and colon cancer proliferation and migration.[7,8] Research has shown that insulin could promote cell proliferation in normal and cancerous breast tissue. For instance, the MDA-MB-157 BC cell line was stimulated by exogenous insulin, and strong mitogenic responses were observed.[2] On the other hand, in women with obesity, hypercholesterolemia affects increased estrogen synthesis in the ovaries.[3]

In addition to stimulating androgen production, insulin ensures the long-term biological viability of androgens and estrogens by decreasing the production of sex hormone–binding globulin.[9] However, the link between insulin and cancer development has been refuted in some clinical studies of both pre- and postmenopausal patients.[2] IR leads to an increase in blood glucose levels, which may result in an increased nutrient supply to tumor cells.[10] This is significant because studies have shown that tumor cells can use glucose as nourishment and for energy. A hyperglycemic environment can simultaneously foster both immune evasion and the development of drug resistance in cancer cells.[11] The formation of IR is also regulated by the production of proinflammatory cytokines—adipokine and interleukin-6 (IL-6), secreted by adipocytes.[12] IL-6 affects glucose metabolism and insulin signaling pathways in β-cells and leads to a chronic inflammatory process, which plays a key role in cancer development.[9,12,13]

Preclinical studies concluded that IL-6 stimulates carcinogenesis, angiogenesis, and metastasis[14], while clinical studies confirmed the correlation of serum IL-6 levels with tumor invasion, metastasis to lymph nodes and distant organs, and advanced TNM stage.[15,16] Chronic inflammation and IR, in turn, also affect lipid metabolism regulation, leading to dyslipidemia. There is evidence that cholesterol and its metabolites accelerate the proliferation of estrogen receptor (ER)–positive BC cells. A correlation was also found between an increase in 27-hydroxycholesterol (27HC) and disease recurrence in luminal A cancer. It has also been reported that the concentration of 27HC is higher in BC tissue than in healthy breast cells. This indicates the necessary role of serum and tumor tissue cholesterol in tumor development.[17] All the above-mentioned metabolic disorders interact with each other. Each of these changes can lead to cancer development both independently and together. This is clearly illustrated in BC, where studies indicate that obesity mainly affects the development of the postmenopausal subtype.[1,18]

Although often associated with postmenopausal breast cancer, obesity is also linked to premenopausal BC, which has a high mortality incidence in women aged 20 to 50 years.[18,19] The metabolic disorders in obesity drive this poor outcome by promoting tumor progression, metastasis, drug resistance, and an aggressive phenotype through effects on the tumor microenvironment. This hypothesis of a correlation between obesity and premenopausal BC led us to assess alterations in serum metabolic biomarkers and evaluate their association with disease progression across molecular subtypes, comparing patients with and without obesity.

BC is divided into molecular subtypes depending on the presence or absence of ER, PR, and HER2 and the expression of the Ki-67 protein. Table 1 presents the molecular subtypes of BC.20

Table 1. Summary of the BC main molecular subtypes

Molecular subtypes	IHC parameters				Outcome	Prevalence
	ER	PR	HER2/neu	Ki-67		
Luminal A	+	+	-	-	Good	23.7%
Luminal B[a]	+	+	-/+	+	Intermediate/poor	38.8/14%
HER2/neu enriched	-	-	+	+	Poor	11.2%
TNBC	-	-	-	+	Poor	12.3%

BC, breast cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemical; PR, progesterone receptor; TNBC, triple-negative breast cancer. [a]Luminal B has 2 subgroups based on HER2 status.

METHODS

Study design and patient selection

We performed a cross-sectional study to compare clinical and metabolic parameters between premenopausal patients with BC with and without obesity. A total of 74 premenopausal patients with histologically confirmed early- and advanced-stage BC were included in the study at the National Cancer Center of Uzbekistan between 2023 and 2024. This study was approved by the Ethics Committee of the Ministry of Health of Uzbekistan (report No. 4/6-1876). Informed consent was obtained from all patients.

Exclusion criteria

Patients were excluded based on the presence of classic breast cancer risk factors, including a family history of cancer, current use of oral contraceptives, or nulliparity. We also excluded patients taking drugs affecting blood lipid profile and glucose levels, such as those with diabetes mellitus.

Data collection

Clinicopathological data (age, menopausal status, histological type of cancer, lesion size, histological grade, lymph node status, and immunohistochemical [IHC] parameters) were obtained from medical and pathologic records.

Classification of BC molecular subtypes

Immunohistochemical parameters—ER, progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 protein—were used to classify BC subtypes.

Based on medical and pathomorphological records, patients were studied in 4 molecular subgroups: luminal A (n = 10), luminal B (n = 31), HER2/neu (n = 16), and triple-negative breast cancer (TNBC) (n = 17).

Anthropometric measurements

In the patient reception department, height (in centimeters) was measured using a height gauge (Magnum Med-Servis, Uzbekistan) and body weight was measured with electronic medical scales (Massa-K). Obesity was defined by a BMI of 30 or greater. BMI was calculated according to the formula: BMI = weight (kg) / height $(m)^2$

According to the WHO classification, a BMI of 30 kg/m^2 or greater is considered obesity.[22,23] Overall, 31 patients did not have obesity, and 41 patients had obesity.

Blood collection and laboratory examination

All blood samples were collected from the cubital vein before chemotherapy and after 8 hours of fasting early in the morning. The serum was separated from the blood sample by centrifugation for 8–10 minutes at 3000 rpm. Biochemical methods were used to evaluate dyslipidemia and blood sugar level. Dyslipidemia is a condition caused by increased total cholesterol (TC), triglyceride (TG), and low-density lipoprotein (LDL) levels and decreased high-density lipoprotein (HDL) levels. Total cholesterol, TG, HDL-C, and LDL-C concentrations were determined by diagnostic kits (Spinreact, Spain). Glucose liquidator (Human, Germany) was used to detect serum glucose levels. Serum IL-6, insulin, and the CA15-3 tumor marker were determined by the immunoassay method. All assays and biochemical tests were performed according to the manufacturer's instructions. The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index was calculated by the following formula: fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5 [22]

Statistical analyses

Statistical analyses were performed using GraphPad Prism. Descriptive statistics were used to determine the mean (SD). Baseline characteristics of populations with and without obesity were compared by the χ^2 test and Fisher exact test to evaluate categorical variables. For group comparisons, the Kruskal-Wallis test and Mann-Whitney test were used for nonparametrically distributed data, and the *t* test was applied for normally distributed data. Pearson correlation was used to detect the association between *CA15-3* and BMI. A P-value of less than 0.05 was considered significant.

RESULTS

Patient characteristics

A total of 74 patients were assigned to 2 groups according to BMI. The mean (SD) age of patients without and with obesity were 38.2 (3.9) and 43.8 (4.6) years, respectively. Tumor characteristics are given in Table 2.

By comparing BC groups, we found no significant difference in tumor histological types ($P = 0.30$). However, it should be noted that infiltrative and rare histological types (tubular, medullary, etc.) were more common in patients with obesity. No significant difference was found in histologic grade, lymph node status, ER status, or HER2 expression. There was no difference in the observation of tumors 5 cm or smaller in both groups, but the incidence of tumors larger than 5 cm was significantly higher in patients with obesity ($P = 0.001$).

Table 2. Comparison of Baseline Characteristics of Premenopausal Patients With Breast Cancer by Obesity Status

Tumor characteristic	Total patients, No. (%) (N = 74)	Without obesity, No. (%) (N = 31)	With obesity, No. (%) (N = 41)	*P* value
Histologic type				
Ductal invasive	62 (83.8)	30 (96.8)	32 (78.0)	0.03
Ductal infiltrative	6 (8.1)	1 (3.2)	5 (12.2)	
Adenocarcinoma	2 (2.7)	0 (0)	2 (4.9)	
Other (tubular, mucinous, medullary)	4 (5.4)	0 (0)	4 (9.8)	
Histologic grade				
I	26 (35.1)	11 (35.5)	15 (36.6)	0.91
II	39 (52.7)	17 (54.8)	22 (53.7)	
III	9 (12.2)	3 (9.7)	6 (14.6)	
Tumor size, cm				
<2	10 (13.5)	6 (19.4)	4 (9.8)	0.001
2-5	44 (59.5)	22 (71.0)	22 (53.7)	
>5	20 (27.0)	3 (9.7)	17 (41.5)	
Lymph node status				
Positive	64 (86.5)	27 (87.1)	37 (90.2)	0.83
Negative	10 (13.5)	4 (12.9)	6 (14.6)	
Estrogen receptor status				
Positive	41 (55.4)	22 (71.0)	19 (46.3)	0.08
Negative	33 (44.6)	9 (29.0)	24 (58.5)	
Progesterone receptor status				
Positive	42 (56.8)	24 (77.4)	18 (43.9)	0.01
Negative	32 (43.2)	7 (22.6)	25 (61.0)	
HER2 Status				
Not overexpressed	50 (67.6)	21 (67.7)	29 (70.7)	0.81
Overexpressed	24 (32.4)	10 (32.3)	14 (34.1)	
Ki-67 expression				
High	51 (68.9)	18 (58.1)	33 (80.5)	0.001
Low	23 (31.1)	13 (41.9)	10 (24.4)	

[a] Data are presented as number (percentage). Percentages were calculated based on column totals and may not sum to 100 because of rounding. The χ^2 test was used to calculate P values, which represent the statistical significance of the difference between the groups with and without obesity. Abbreviations: HER2, human epidermal growth factor receptor 2.

Assessment of metabolic biomarkers in molecular subtypes in patients with and without obesity

We assessed lipid profile, glucose, insulin, IL-6, CA15-3, and HOMA-IR across molecular subtypes and between patients with and without obesity.

Figure 1 shows the occurrence of dyslipidemia in all molecular subtypes. A clear difference was recorded in serum levels of TC between luminal A and luminal B ($P = 0.03$) and between luminal B and HER2-enriched ($P = 0.01$). No significant difference was observed in serum levels of TG, HDL, and LDL among molecular subtypes. However, a significant difference was found between patients with and without obesity in lipid profile (Figure 2).

Figure 2 indicates that, despite similar mean values of lipid profiles among various groups, the prevalence of dyslipidemia differed in patients with and without obesity across all molecular subtypes.

While no clear differences were observed in the luminal B, HER2-enriched, and TNBC subtypes for some parameters, HDL levels were consistently higher in individuals without obesity compared with individuals with obesity. Significant differences in HDL levels between patients with and without obesity were found within each subtype ($P = 0.05$ for luminal A, $P < 0.001$ for luminal B, $P = 0.04$ for HER2-enriched, and $P < 0.001$ for TNBC). In the luminal B and TNBC subtypes, a significant difference was observed in lipid profile indicators, except for TC ($P = 0.08$ and $P = 0.15$, respectively), in patients with and without obesity ($P < 0.001$). In the HER2-enriched subtype, all the lipid profile indicators were significantly different between patients with and without obesity ($P = 0.02$ for HDL, $P = 0.04$ for LDL, $P = 0.04$ for TC, and $P = 0.006$ for TG).

The frequent observation of statistically significant differences in the following 3 subtypes with poorer prognoses (luminal B, HER2-enriched, TNBC) suggests a potential link between dyslipidemia and disease aggressiveness. It should also be noted that there is no significant difference in the level of TC in patients with and without obesity in all 4 molecular subtypes, implying a potential role for TC in the development of BC, regardless of obesity.

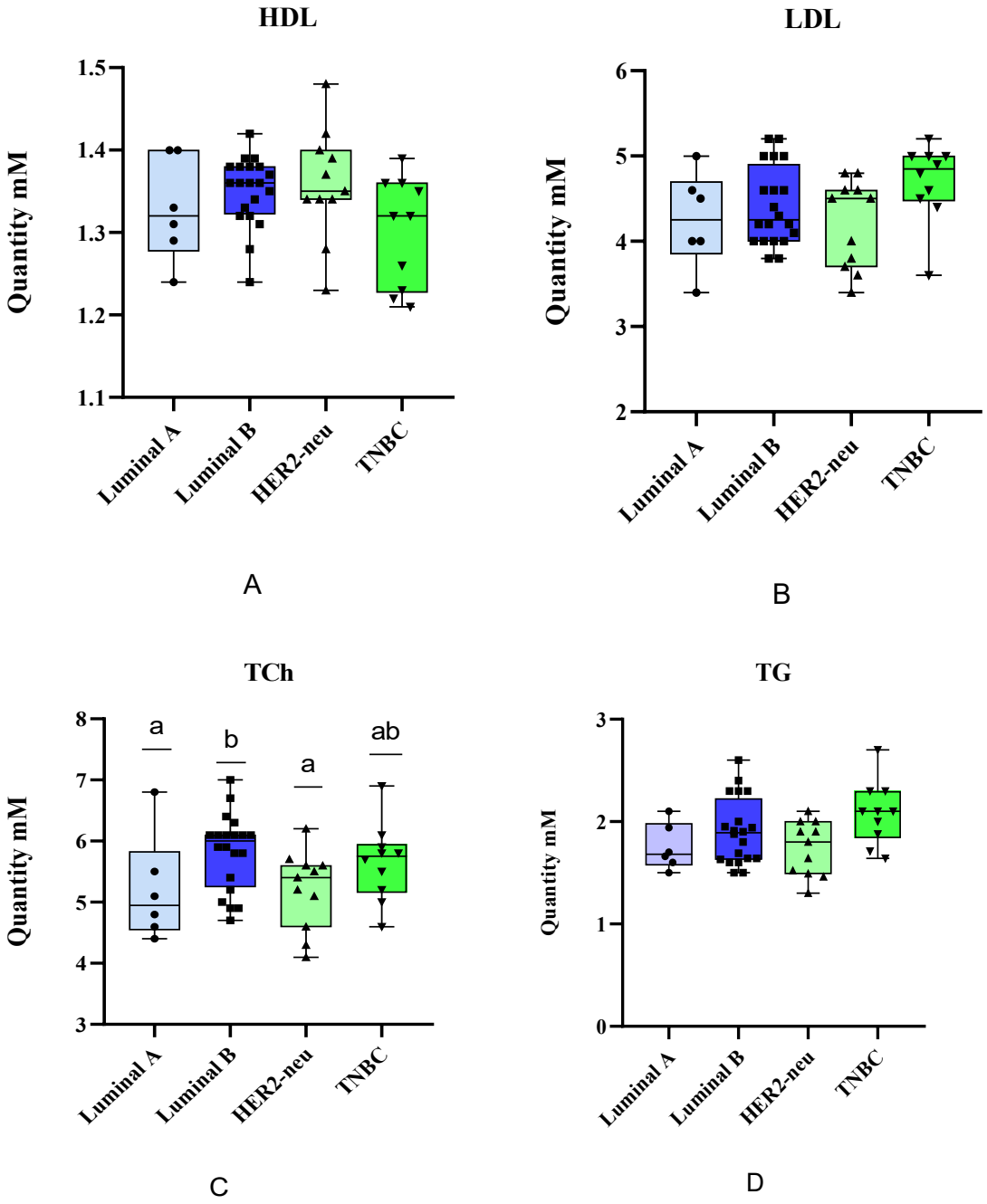

Figure 1. Comparison of Lipid Profile Parameters Among BC Molecular Subtypes. A, High-density lipoprotein (HDL); B, low-density lipoprotein (LDL); C, total cholesterol (TC); and D, triglycerides (TG) in patients classified into luminal A, luminal B, HER2-enriched, and triple-negative breast cancer (TNBC) subtypes. mmol/L indicates millimoles per liter. [a]Significant difference ($P < 0.05$).

Figure 3 represents the distribution of glucose, insulin, HOMA-IR, IL-6, and CA15-3 levels among 4 subtypes of premenopausal BC patients. In terms of glucose levels, no significant difference was observed among the subtypes, with higher values noted in the luminal B and TNBC groups. Although insulin and HOMA-IR indicators were higher in the luminal B and HER2-enriched subtypes, these differences were not statistically significant ($P = 0.66$ and $P = 0.98$, respectively).

Glucose is one of the energy sources of cancer cells. According to the Warburg effect, cancer cells consume more glucose than normal cells.[2525] However, blood glucose does not directly reflect glucose uptake by tumor cells. It should be noted that blood glucose levels can remain elevated due to insulin resistance. This can lead to more glucose reaching tumor cells through the bloodstream and stimulating their progression. In our work, significant differences were not found between all the molecular

subtypes in terms of glucose, insulin, and HOMA-IR index ($P > 0.05$). Nearly all patients had hyperinsulinemia and IR. Our findings are consistent with previous studies on the role of hyperinsulinemia and IR in cancer development[24,26].[24,26]

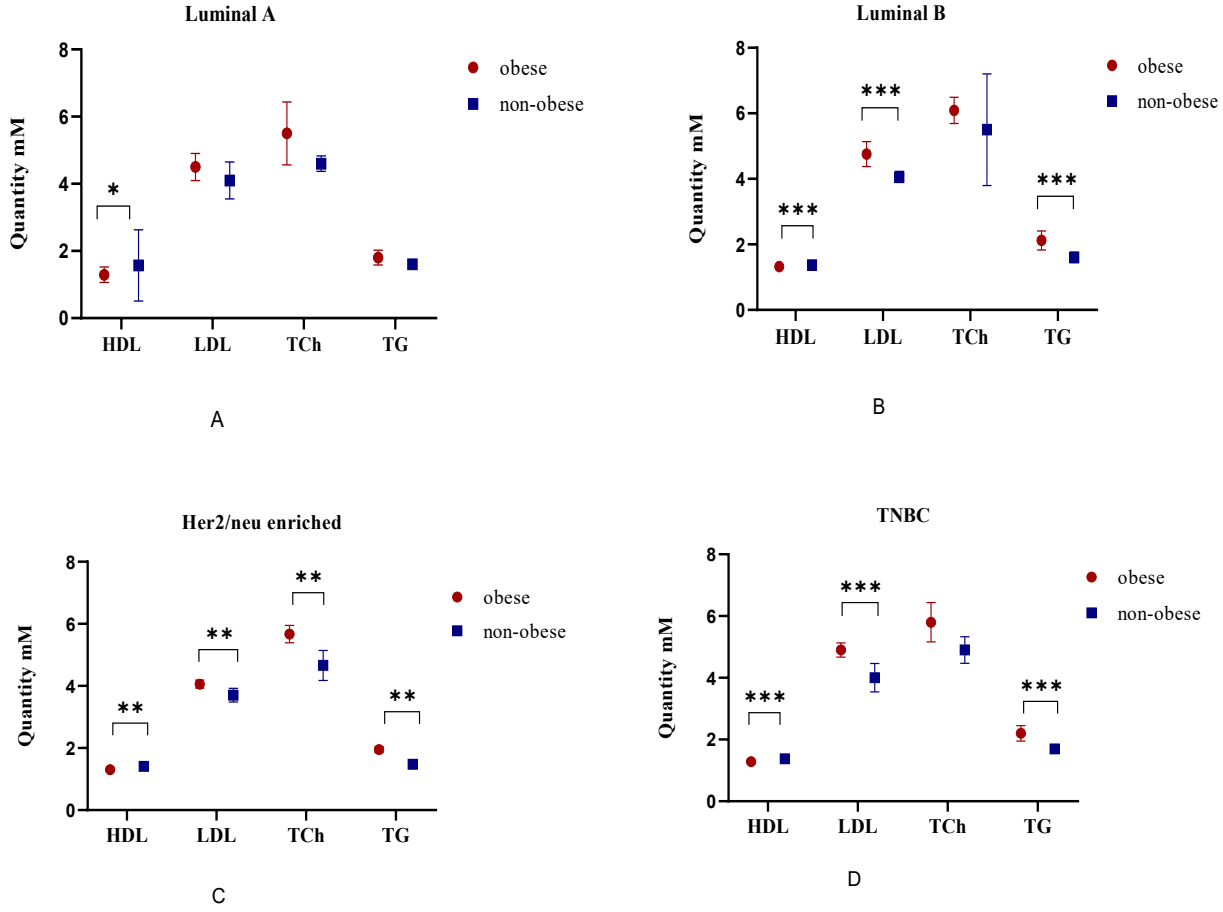

Figure 2. Comparison of serum lipid profiles between obese and non-obese patients within molecular subtypes. Box and whisker plots depict the concentrations of high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TC), and triglycerides (TG) in (A) Luminal A, (B) Luminal B, (C) HER2-enriched, and (D) triple-negative breast cancer (TNBC) subtypes. Data are presented as mean ± SEM. Statistical significance is indicated as $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

CA15-3 is a more specific tumor marker used for prognosis in BC. An increase in the value of this marker has been associated with disease recurrence in patients. This association was also observed in all molecular subtypes.[27,27] Our results showed no significant difference in the serum CA15-3 level among the subtypes ($P > 0.05$), regardless of the tumor's aggressiveness. Very high values of CA15-3 were mainly observed in the luminal B and TNBC subtypes.

No significant differences were found among the molecular subtypes for IL-6 ($P > 0.05$). However, the serum levels of IL-6 in HER2-enriched and TNBC, which are highly aggressive, were elevated. Figure 4 shows the association between obesity and quantitative changes in all metabolic markers.

We observed no significant difference in any metabolic biomarkers between patients with and without obesity in the luminal A subtype ($P > 0.05$). However, in the luminal B and HER2-enriched subtypes, significant differences were observed between patients with and without obesity for IL-6 ($P = 0.03$ and $P = 0.04$, respectively), glucose ($P = 0.004$ and $P < 0.001$, respectively), and HOMA-IR ($P = 0.02$ and $P = 0.05$, respectively). In TNBC, there was only an intergroup difference in glucose levels ($P = 0.04$). A similar result was observed in the level of CA15-3 in patients without obesity in the TNBC ($P = 0.84$) and luminal B ($P = 0.30$) subtypes. There was a negative correlation between serum levels of *CA15-3* and BMI ($r = -0.40$, $P = 0.008$).

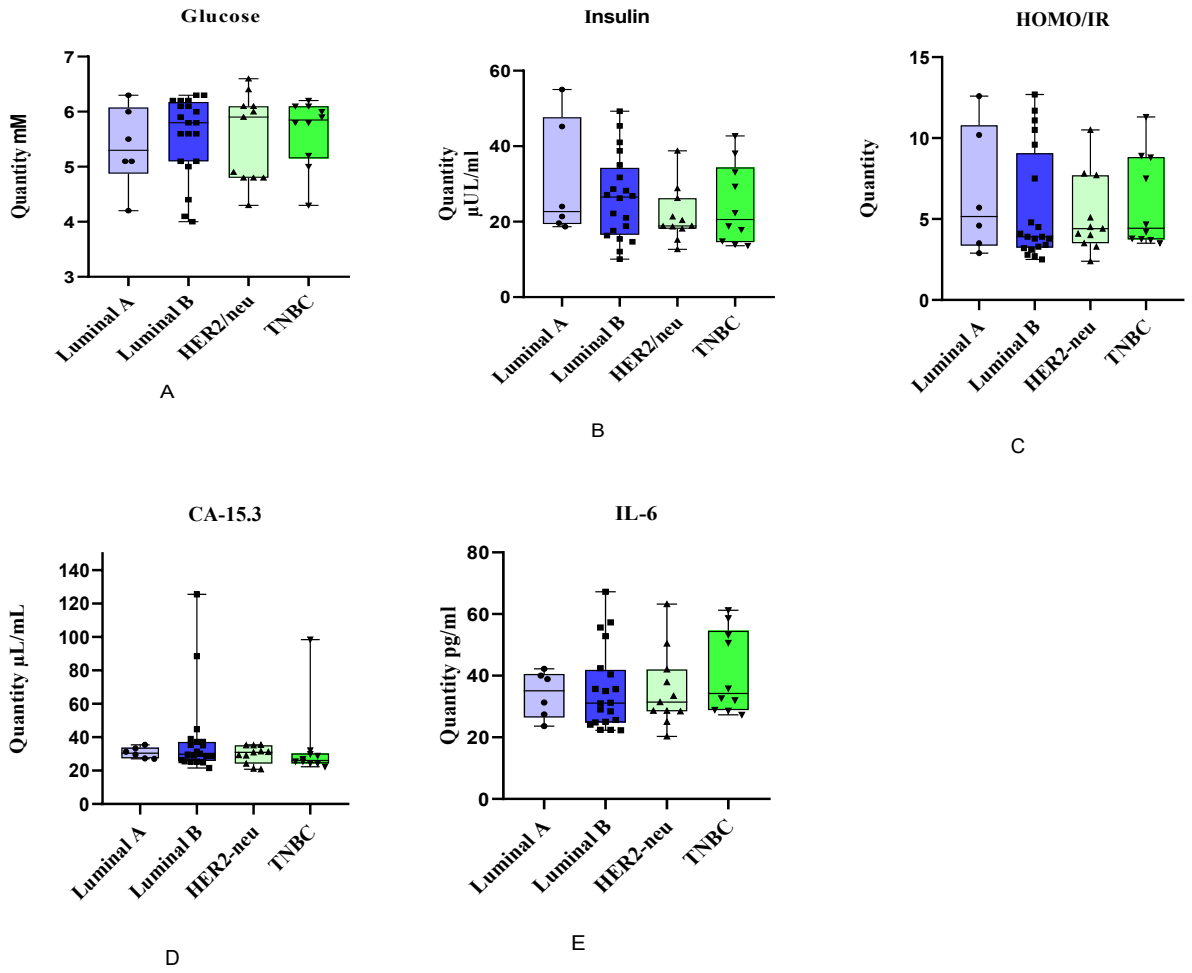

Figure 3. Comparison of Metabolic and Tumor-Related Markers Across Breast Cancer Molecular Subtypes in Premenopausal Women. A, Glucose; B, insulin; C, HOMA-IR index; D, CA15-3; and E, interleukin-6. Boxes indicate median and interquartile range. HOMA-IR indicates Homeostatic Model Assessment for Insulin Resistance; TNBC, triple-negative breast cancer.

DISCUSSION

Several studies have reported that obesity (high BMI) is not a risk factor for premenopausal breast cancer and may instead be associated with a reduced risk.[9,18,21,28] Korean researchers conducted a large-scale study to assess the association between obesity and BC occurrence in approximately 6.5 million women[18] and observed that high BMI affected the development of postmenopausal BC and decreased the occurrence of premenopausal BC. A key limitation is that this study only included women aged 40 years and older. Because the median age of menopause is 51 years,[29] this age threshold fails to capture the entire premenopausal population, which is significant given the high rate of breast cancer mortality among women aged 20–49 years.[30]

Recent studies confirm the positive association between obesity and BC in premenopausal women,[31–3331-33] which is consistent with our findings. Our findings are also consistent with research reporting a significant association between obesity and the histological phenotype of tumors.[34,35]

Large tumor sizes and infiltrative, rare tumor forms were more common in patients with obesity. It is important to note that our results refute the evidence that ER-positive status is less common in premenopausal BC with obesity.[28,36] No significant difference was found between the ER-positive status in patients with and without obesity.

Also, PR-negative status was more common in individuals with a high BMI ($P = 0.01$). The proportion of patients with high Ki-67 expression was significantly greater in patients with obesity than in those without obesity ($P = 0.001$). This higher prevalence of invasive forms in patients with obesity may be related to chronic inflammatory processes. The observed higher proliferative activity could be mediated by the influence of factors such as insulin in the obese state. Our results are consistent with findings from other studies,[2,22,24] including *in vitro* studies confirming that exogenous insulin can increase cancer cell division rates.[2]

Progesterone receptor–negative (PR-negative) status was significantly more common ($P = 0.01$).

This aligns with research by Harris *et al.*, which found that obesity decreases ER-positive and increases ER-negative breast cancer in premenopausal women.[2828] However, US researchers have observed that since 2016, the incidence of ER-positive BC has been increasing, while ER-negative BC has been decreasing among young women in the premenopausal period.[30]

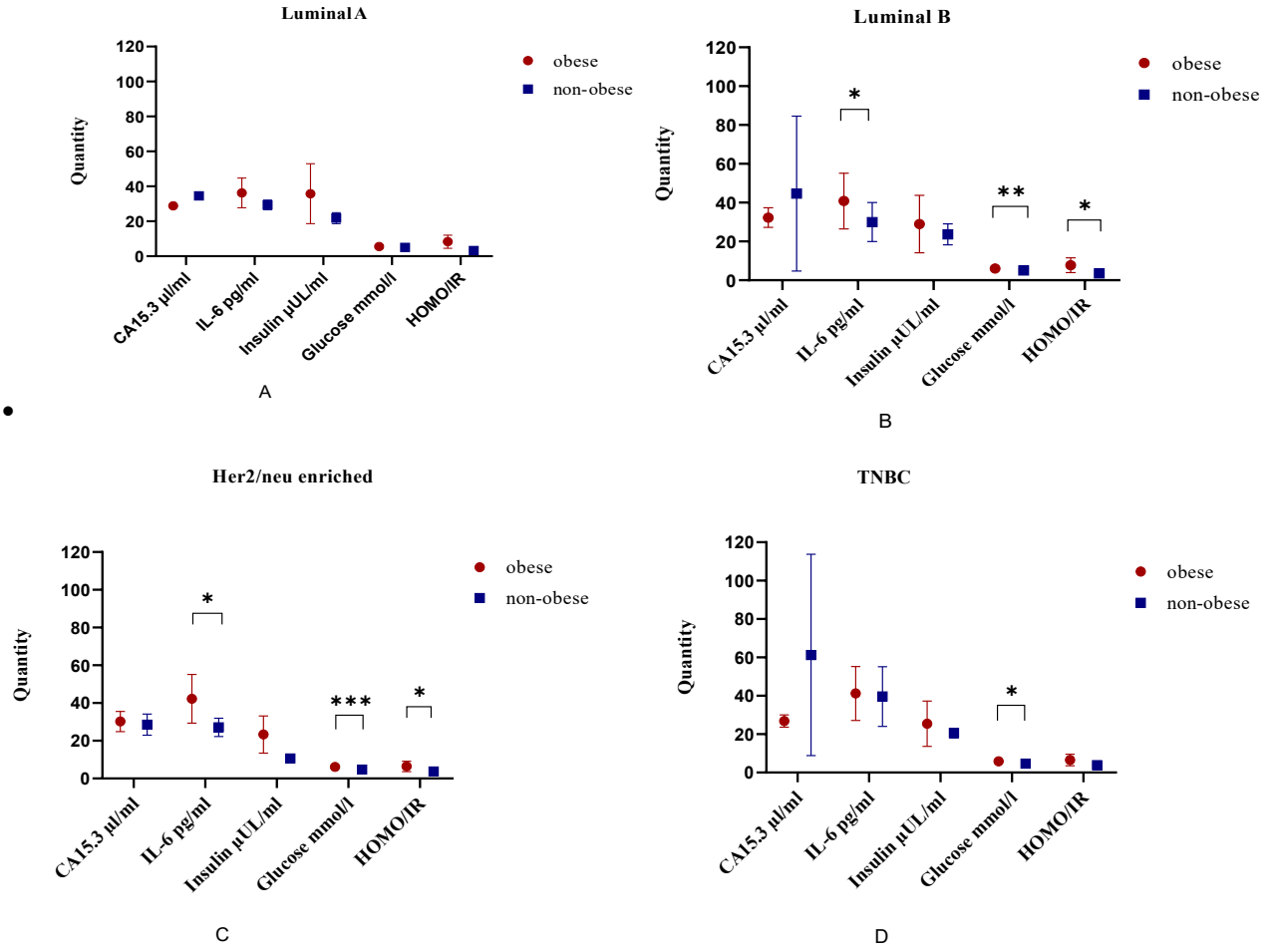

Figure 4. Variations in Metabolic Serum Markers Across Molecular Subtypes of BC. Statistically significant differences ($P < 0.05$) were observed in glucose, IL-6, and HOMA-IR levels between patients with and without obesity in the luminal B and HER2-enriched subtypes. An inverse correlation was found between CA15-3 and BMI ($r = -0.40$, $P = 0.008$). BC indicates breast cancer; BMI, body mass index; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; IL-6, interleukin-6; TNBC, triple-negative breast cancer.

Proliferation of tumor cells was more often observed in premenopausal BC with obesity ($P = 0.001$). All this confirms the link between obesity and the formation of the aggressive tumor phenotype and tumor histopathology. However, the data on the prevalence of aggressive subtypes in premenopausal patients were not confirmed.[31,3231,32] In our study, although aggressive subtypes (TNBC, HER2-enriched) were numerically predominant in patients with obesity, the intergroup difference was not statistically significant ($P = 0.44$), which may be related to a small sample size. However, some recent studies have reported that BMI in premenopausal patients with BC is not always associated with the prevalence of TNBC and HER2-enriched subtypes.[32]

Research on the positive link between dyslipidemia and the development of BC has found contradictory results. A recent meta-analysis revealed a positive correlation between low serum HDL and the development of BC.[37] Large case-control studies have confirmed an association between dyslipidemia (low HDL and high LDL) and the risk of TNBC and luminal B breast cancers.[38] This lipid profile may be particularly significant due to the fundamental biochemical differences between these cholesterol carriers. Unlike HDL, which has a balanced 50:50 mass ratio of lipid to protein, LDL has a lipid-rich 75:25 ratio.[39] This structure allows LDL to carry at least twice the amount of free cholesterol and cholesterol esters, potentially contributing to the tumor-promoting microenvironment observed in these aggressive cancer subtypes.[40] These results deserve deeper analysis of lipid composition and its effects in clinical studies. Our study confirmed the

influence of dyslipidemia on the formation of aggressive molecular subtypes (TNBC, HER2-enriched, and luminal B). However, we found that the high levels of lipid markers in these subtypes are dependent on the presence of obesity (Figure 2). This aligns with large-scale studies concluding that dyslipidemia is linked to poorer disease outcomes. Specifically, elevated TG levels have been identified as a marker of poor prognosis in early-stage breast cancer.[41] A large retrospective cohort study conducted by researchers in China showed that dyslipidemia was less frequent in patients with cancer than in healthy individuals.[42] Significantly, they assessed changes in lipid profile indicators under the influence of chemotherapy. The results showed that chemotherapy leads to an increase in TC and a decrease in HDL. One study reports that changes in the lipid profile under the influence of adjuvant chemotherapy were accompanied by an increase in BMI in premenopausal patients with BC. In contrast, in postmenopausal patients with BC, such changes were not recorded.[43] These results suggest that chemotherapy may have influenced changes in the lipid profile in our study as well. However, our patients received neoadjuvant chemotherapy, and the blood sample was collected before receiving the treatment.

Consistent with the work of Japanese researchers, our study observed no significant differences in insulin levels or obesity among molecular subtypes. This supports their conclusion that, regardless of menopausal status, insulin has no significant etiological role and is not a predictive biomarker for breast cancer. Furthermore, their findings confirm the absence of a significant association between insulin and the status of key hormone receptors (ER, PR, HER2).[22] A meta-analysis conducted in China also showed that serum levels of insulin have no effect on the development of BC in both premenopausal and postmenopausal women.[19] The role of hyperinsulinemia in the development of postmenopausal BC was also assessed in a case-control study of women in Mexico. The study evaluated the association between serum insulin level and BC depending on the C-peptide level. C-peptide is an element of insulin metabolism and a marker of hyperinsulinemia. Although the registration of new cases of diabetes mellitus in patients was monitored, information about exogenous insulin use was not provided.[44] Another study involving 20 years of observation suggested the probability of developing BC in women with high IR in postmenopausal periods.[45] Another study reported that fasting insulin is a marker predicting a poor disease outcome for early BC.[46] This prospective cohort study in patients without diabetes showed that high levels of insulin are associated with metastasis to distant organs and increased mortality. It should also be noted that in several *in vitro* experiments, BC cell lines increased their ability to divide under the influence of exogenous insulin.[47] According to the mitogenic effect of insulin, its serum levels can predict the outcome of the disease. However, research on insulin's influence on cancer development has yielded conflicting results, highlighting a critical need for further investigation.

Preclinical and epidemiological studies have found an association between glucose and cancer development. Glucose affects cancer development and progression independently of obesity.[4848] There is evidence that the development of several cancers, including BC, is also linked to sugar consumption.[49,50] Some studies found that diabetes mellitus and high sugar levels contribute to BC development depending on BMI without the influence of insulin.[51] On the other hand, recent analyses show that high levels of glucose can lead to cancer development depending on the Warburg effect, chronic inflammation, and IR.[1111] Among women aged 40 years or older, a moderate correlation between BC and sugar consumption has been suggested, which is associated with an insulin-related mechanism.[50] Recent studies have also confirmed the positive influence of increased sugar consumption on the risk of developing BC in women in the premenopausal period.[49] This study substantiates that increased fructose consumption is associated with a higher frequency of the TNBC subtype.[52] Furthermore, our findings on glucose revealed a significant difference between patients with and without obesity across all groups except luminal A. This indicates that obesity-associated hyperglycemia may drive breast cancer development and influence the formation of its more aggressive molecular subtypes.

Serum IL-6 has been confirmed in many studies as a predictor for the survival[53,54] of patients with BC.[53,54,55] In particular, a high level of IL-6 predicts a poor prognosis for the overall survival of patients with metastatic BC.[56] While several studies investigate the correlation between serum IL-6 and tumor histology, some suggest it serves as a favorable prognostic marker in both early and advanced breast cancer.[57] Milovanović *et al.* claimed that in premenopausal patients with positive hormone receptors, IL-6 is associated with a good prognosis, irrespective of HER2 status.[14,58]

While literature links elevated serum IL-6 to advanced tumor stage, lymph node metastasis, and distant spread, our data reveal no significant difference in IL-6 levels across molecular subtypes. Instead, high IL-6 was significantly associated with obesity specifically in luminal B and HER2-enriched

patients. This suggests that in premenopausal women, the role of IL-6 in these aggressive subtypes is potentially mediated by obesity.

Conversely, CA15-3 is a highly sensitive biomarker for monitoring chemotherapy response and predicting survival in metastatic breast cancer,[59,60] although it is ineffective for detecting early-stage disease. Recent scientific studies have also noted a prognostic value for early-stage BC,[25] showing a correlation between disease recurrence and the level of CA15-3 in all molecular subtypes. In follow-up monitoring of patients with early BC with CA15-3, its serum levels have been found to significantly increase in 37% of patients with metastasis.[61] While previous research has established that high serum CA15-3 levels correlate with larger tumor size, lymph node metastasis, advanced disease stage, HER2 overexpression, and hormone receptor–negative status,[62] our results did not show a significant difference in CA15-3 levels across molecular subtypes. Instead, we identified a significant negative correlation between CA15-3 levels and obesity, suggesting that CA15-3 may not be an independent prognostic marker in patients with a high BMI. This finding aligns with the recognized low specificity of CA15-3 and is supported by the work of Santillán-Benítez *et al.*, who also found no direct link between obesity and CA15-3 in their cohort of 88 patients (40 with breast cancer) investigating combined biomarkers.[6363] Another study found that CA15-3 levels were associated with tumor characteristics and serum resistin levels, although they did not directly assess the CA15-3 level in relation to obesity or BMI. This suggests that metabolic alterations and adipokine profiles, rather than BMI itself, may influence CA15-3 expression.[6464]

Also, although there are no specific studies related to CA15-3, scientific studies have shown an inverse association between prostate-specific antigen (PSA) and BMI. Research has linked this association with hemodilution in individuals with obesity.[6565] The observed inverse correlation between obesity and CA15-3 may be unique to our cohort of premenopausal women with early-stage disease and distinct metabolic profiles, a hypothesis requiring validation in future studies.

The obtained results show that metabolic monitoring, especially glucose and lipid metabolism control, can be useful for patients with obesity and premenopausal BC in terms of reducing the risks specific to molecular types of tumors.

A key limitation is the small luminal A subgroup, potentially due to random selection or the higher prevalence of subtypes associated with obesity in our cohort.[66–68] Furthermore, the absence of a healthy control group prevents comparison of biomarker levels to a baseline population, limiting a full assessment of their clinical significance.

CONCLUSION

The results of this study confirmed the presence of an association between obesity and BC in premenopausal women. There were also positive associations between luminal A, HER2-enriched, and luminal B subtypes and total cholesterol. In premenopausal patients with BC and obesity, the formation of the luminal B and HER2-enriched subtypes was influenced by chronic inflammation, high glucose levels, and IR. High glucose levels played a significant role in the development of TNBC. Our findings indicate that BMI is a significant confounding variable in the interpretation of the CA15-3 tumor marker. To ensure accurate clinical assessment, CA15-3 values in patients with a high BMI should be interpreted with caution due to the potential for reduced diagnostic sensitivity.

FUNDING

This work was supported by the Innovation Agency of the Ministry of Higher Education, Science and Innovation of Uzbekistan, within the framework of the Future Scientist competitions. We also acknowledge the financial support of CAS PIFI project (2026PVB0055).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICAL CONSIDERATIONS

The study was approved by the Ethics Committee of the Ministry of Health of the Republic of Uzbekistan (report No. 4/6-1876) and performed according to the Declaration of Helsinki.

DATA AVAILABILITY

The original contributions presented in the study are included in the article/supplementary material; further inquiries can be directed to the corresponding author(s).

AI DISCLOSURE

We didn't use AI-based tools in writing the article.

AUTHOR CONTRIBUTIONS

MM: Conceptualization, Writing – Original Draft, Writing – Review & Editing, Methodology, Data Curation; BI: Conceptualization, Visualization; AA: Writing – Original Draft, Writing – Review & Editing; AM: Methodology, Data Curation; IH: Methodology, Data Curation; MN: Methodology, Data Curation; RT: Methodology, Data Curation.

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Mirzaeva M, Iriskulov B, Asrorov AM, Hudoynazarov I, Norbekova M, Tadjibayeva R, et al. Association of Obesity with Premenopausal Breast Cancer: Analyzing Molecular Subtypes. Arch Breast Cancer. 2025; 12(4):481-93.
Available from: https://www.archbreastcancer.com/index.php/abc/article/view/1134