



Correlation Between dyslipidemia, CA15-3 and Ki67 in diabetic Women with Breast Cancer

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Abstract: Aim: To investigate the effect of dyslipidemia and the level of hyperglycemia on expression of tumor markers in diabetic women. Method: A total of 100 women patients, 66 of them had breast cancer divided in to two groups 32 diabetic women with breast cancer (G1) and 34 breast cancer women (G2) and 34 women with diabetes (G3) women in Al-Amal Tumors Center in Baghdad (3 Aug to 3 Oct) were, the level of tumor markers (Ki67, CA15-3), Age, body mass index BMI, glycosylated hemoglobin HbA1c, Cholesterol, triglyceride TG, HDL, LDL and VLDL in the two groups were determined . Results: The level of Ki67 and CA15-3 were significantly higher in G1 and G2 compared to G3 while HbA1c were significantly higher in (G1) than (G2) at ($p > 0.0001$) The current study also show a positive correlation between Ki67 and CA15-3 and lipid profile in G2 ,G3 groups and no correlation between tumor markers and lipid profile in (G1). Conclusion: dyslipidemia had positive correlation with tumor markers Ki67 and CA15-3 in G1 and G2 that may contribute to high risk of breast cancer and had the main role effecting on the progression of tumor.

Keywords: Lipid profile, CA15-3, Ki67, Breast cancer, Diabetes mellites

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Introduction

Two of the most common diseases in today's society are breast cancer and type 2 diabetes (T2D). The World Health Organization (WHO) has recognized breast cancer as the most prevalent malignancy among women globally (1). T2D, a chronic metabolic disease characterized by elevated blood glucose levels, stems from a combination of two primary factors: defective insulin secretion by pancreatic cells and the inability of insulin-sensitive tissues to respond appropriately to insulin (2). Both breast

cancer and type 2 diabetes share common risk factors, such as obesity, poor diet, physical inactivity, and genetic predispositions. These factors also contribute to dyslipidemia, creating a complex relationship between the conditions (3)(4).

Dyslipidemia, characterized by abnormal levels of serum lipids, has been consistently associated with an increased risk of breast cancer development and progression. In diabetic women, this association appears to be even more pronounced, potentially due to the synergistic effects

of insulin resistance and altered lipid metabolism (5,6). Due to its role in membrane synthesis and as a precursor for sex hormones like progesterone, estrogens, and androgens, elevated cholesterol may contribute to the growth of breast cancer. Cancer cells may also utilize elevated exogenous cholesterol for cell proliferation (7). In type 2 diabetes, they are especially at risk. The combination may be a consequence of obesity, poor control of diabetes, or both, which may increase circulating free fatty acids (FFAs), leading to increased hepatic (VLDL) production. TG-rich VLDL then transfers TG and cholesterol to LDL and HDL, promoting the formation of TG-rich LDL. Diabetic dyslipidemia is often exacerbated by the increased caloric intake and physical inactivity that characterize the lifestyle of some patients with type 2 diabetes (8,9).

CA15-3, a widely used serum tumor marker for breast cancer, has shown promise in monitoring disease progression and treatment response. Interestingly, recent research has uncovered a potential link between CA15-3 levels and lipid profiles in breast cancer patients (10). Ki67, a nuclear protein associated with cellular proliferation, serves as an important prognostic marker in breast cancer. Recent investigations have explored the relationship between Ki67 expression, lipid profiles, and CA15-3 levels in breast cancer patients, with a focus on diabetic women (11).

Clinical data of subjects

A total of one hundred of sera and whole blood samples were collected from Iraqi women divided into three groups (32) patients with BC and T2D (G1), (34) patients with BC (G2) and (34) patients with T2D (G3) are matched in age. Pregnant women, patients with pancreatitis, or obstruction

in bile ducts, or acute and chronic inflammatory period and patients suffered from autoimmune diseases were excluded. All procedures involving human participants in this study were conducted in accordance with the Declaration of Helsinki (2013 revision). The study received approval from the hospital's ethics committee, and informed consent was obtained from all participants.

Observation indexes

In the morning, five milliliters of blood were collected from all subjects; divided in to two parts: two milliliters placed in an EDTA tube for measuring HbA1c and three milliliters was transferred into gel tubes to get the serum by centrifugation at a force of 3000 R/ for ten minutes, and stored in a deep freeze at a temperature of -20 °C until used to measure CA15-3 and Ki67 level and lipid profile (HDL, TG and Cholesterol). The height and weight of subjects were recorded, and BMI was calculated based on the measurement results.

Research methods

The three groups of subjects were observed and compared in terms of the levels of tumor markers CA153 and Ki67 and the parameters BMI HbA1c, HDL, TG, VLDL, LDL and cholesterol. The correlation between these two types of indexes was analyzed. Univariate analysis was performed to analyze the general clinical data of patients and the influencing factors leading to complications.

Statistical analysis

The data were statistically analyzed using SPSS 25.0 software and the individual correlation test has been utilized to highlight the difference between CA15-3 and Ki67 and other parameters within the patient groups. A significant level of 0.05 or less was considered statistically significant.

Results

Comparison of age, BMI between the two groups

There was no significant difference in age, BMI, stage of cancer and duration of disease between the three groups (table 1).

Table (1): Comparisons of Age, BMI, Stage of cancer, Duration of Cancer, and Duration of Diabetes in all studied groups

Parameters		G1	G2	G3
Age Year	Mean± Std. Error	57.6± 1.5	54.3± 1.3	57.2±1.8
	Lower 95% CI of mean	54.5	51.5	53.5
	Upper 95% CI of mean	60.7	57.1	60.9
	P Value	P= 0.001		
BMI	Mean± Std. Error	29.8 ±0.95	31.8 ±1.1	31.6±0.9
	Lower 95% CI of mean	27.9	29.4	29.6
	Upper 95% CI of mean	31.7	34.4	33.6
	P Value	P=0.17		
Stage of cancer	Mean± Std. Error	2.3 ±0.1	2.1 ±0.12	-
	Lower 95% CI of mean	1.9	1.9	-
	Upper 95% CI of mean	2.64	2.39	-
Duration of Cancer	Mean± Std. Error	-	-	-
	Lower 95% CI of mean	-	-	-
	Upper 95% CI of mean	2.8	4.4	-
Duration of Diabetes	Mean± Std. Error	6.9 ±1.3	-	8.6 ±1.0
	Lower 95% CI of mean	4.1	-	6.6
	Upper 95% CI of mean	9.4	-	10.6

One- way ANOVA with Tukey's multiple comparisons test at the level of 0.05

Comparison of tumor markers between the three groups

The levels of serum Ki67 and CA15-3 were significantly higher in G1

diabetic women with breast cancer than G2 non-diabetic women with breast cancer, in comparison with (G3) at ($P>0.0001$) (Table 2).

Table(2): Comparisons of Ki67and Ca15-3 in all studied groups.

Parameters		G1	G2	G3
Ki67	Mean± Std. Error	8.7 ±0.3 ^a	4.5 ± 0.33 ^a	3.3 ±0.09
	Lower 95% CI of mean	7.4	3.8	3.1
	Upper 95% CI of mean	8.8	5.2	3.5
	P Value	0.0001		
Ca15-3	Mean± Std. Error	37 ±1.9 ^a	23.9±2.0 ^a	13.2±0.44
	Lower 95% CI of mean	32.9	19.7	12.3
	Upper 95% CI of mean	41	28.1	14.1
	P Value	0.0001		

One- way ANOVA with Tukey's multiple comparisons test at the level of 0.05

a: represented significant analysis between G1 and G2 and G3

Comparison of HbA1c, Cholesterol, HDL, TG, LDL and VLDL between the three groups

The level of glycated hemoglobin HbA1c was highly significant in G1

diabetic women with breast cancer comparing to G2 breast cancer women, but there's no different between the two groups in the levels of lipid profile. As shown in Table 3

Table (3): Comparisons of HbA1C, TG, Cholesterol, HDL, LDL and VLDL in all studied groups.

Parameters		G1	G2	G3
HbA1c	Mean± Std. Error	7.38±0.25 ^a	5.65±0.1 ^a	8.29 ± 0.36
	Lower 95% CI of mean	6.89	5.43	7.55
	Upper 95% CI of mean	7.88	5.86	9.03
	P Value	0.0001		
TG mg/l	Mean± Std. Error	168 ±0.5	170±1.5	210± 7.0
	Lower 95% CI of mean	167	166	195
	Upper 95% CI of mean	169	173	224
	P Value	0.0001		
Cholesterol mg/l	Mean± Std. Error	180±0.8	179±1.7	213±6.2
	Lower 95% CI of mean	178	175	201
	Upper 95% CI of mean	181	182	226
	P Value	0.0001		
HDL mg/l	Mean± Std. Error	34.2± 0.98	36.1 ± 0.80	41.2 ± 1.7
	Lower 95% CI of mean	32.2	34.5	37.7
	Upper 95% CI of mean	36.2	37.8	44.7
	P Value	0.003		
LDL mg/l	Mean± Std. Error	112± 1.0	109 ± 1.1	130 ± 4.9
	Lower 95% CI of mean	110	106	120
	Upper 95% CI of mean	114	111	140
	P Value	0.0001		
VLDL mg/l	Mean± Std. Error	33.7 ± 0.11	33.9 ± 0.31	41.9 ± 1.4
	Lower 95% CI of mean	33.4	33.3	39.0
	Upper 95% CI of mean	33.9	34.6	44.8
	P Value	0.0001		

One- way ANOVA with Tukey's multiple comparisons test at the level of 0.05

a: represented significant analysis between G1 and G2 and G3

Correlation between tumor markers (Ki67 and CA15-3) and lipid profile level (Cholesterol, HDL, LDL, VLDL and TG)

There was a positive correlation between Ki67 and Ca15-3 with lipid profile (cholesterol, TG, LDL, and

VLDL) in G2 and G3 ,while a weak positive correlations were noticed in group G1 between Ki67 and CA15-3 with TG, LDL and VLDL as shown in table 4 and 5 and Figures. A, B, C, D, E, F, G, H, I, J

Table (4): Correlation Analysis for Ki67 with lipid profile in all studied groups

	Ki67 (ng/mL)			
		Breast cancer & Diabetes patients Group No. (32) (G1)	Breast cancer patients Group No. (34) (G2)	Diabetes patients Group No. (34) (G3)
Cholesterol (mg/dL)	R	.113	.785**	.433*
	P	.538	.000	.01
Triglyceride(mg/dL)	R	.048	.895**	.523**
	P	.793	.000	.002
HDL-C (mg/dL)	R	.068	.531**	.124
	P	.711	.001	.484
LDL-C (mg/dL)	R	.022	.565**	.351*
	P	.903	.001	.042
VLDL-C (mg/dL)	R	.048	.895**	.523**
	P	.793	.000	.002
**Correlation is significant at the 0.01 level.				

Table (5): Correlation analysis for Ca15-3 with lipid profile all patients Groups

	Breast cancer with Diabetes Patients Group No. (32) (G1)		Breast cancer patients Group No. (34) (G2)	Diabetes patients Group No. (34) (G3)
	R	P		
Cholesterol (mg/dL)	.092	.618	.761**	.397*
			.000	.02
Triglyceride(mg/dL)	.050	.785	.864**	.448**
			.000	.008
HDL-C (mg/dL)	-.012	.948	.596**	.051
			.000	.775
LDL-C (mg/dL)	.083	.653	.491**	.352*
			.003	.041
VLDL-C (mg/dL)	.050	.785	.864**	.448**
			.000	.008
**Correlation is significant at the 0.01 level.				

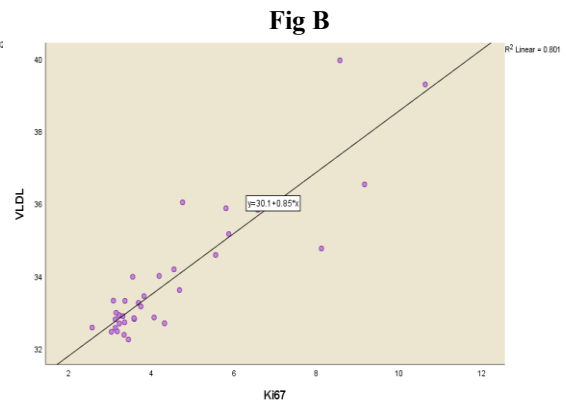
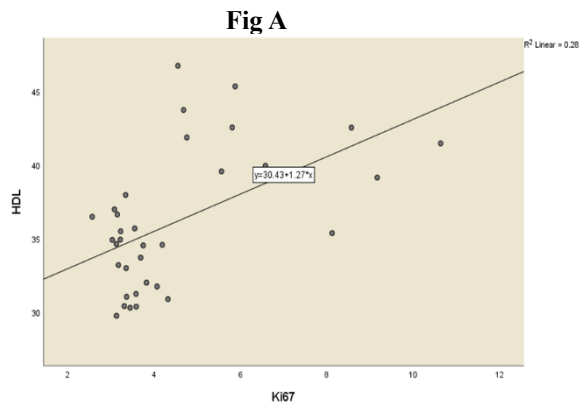
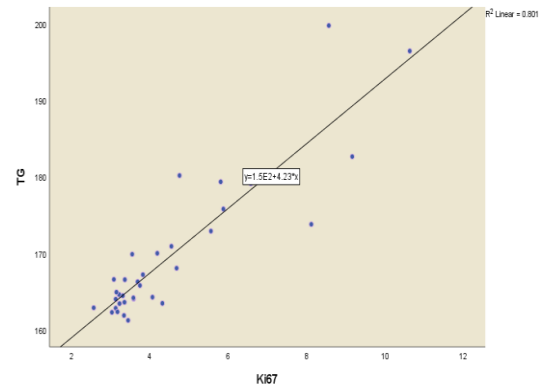
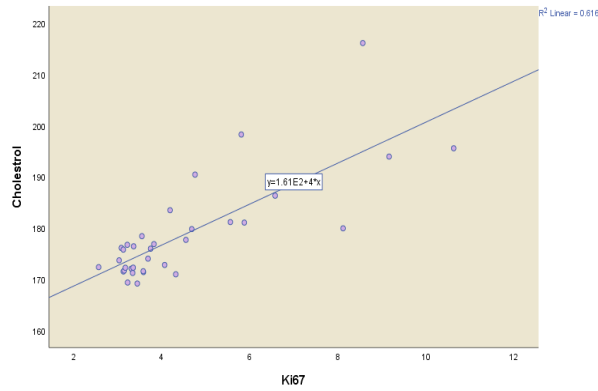


Fig C

Fig D

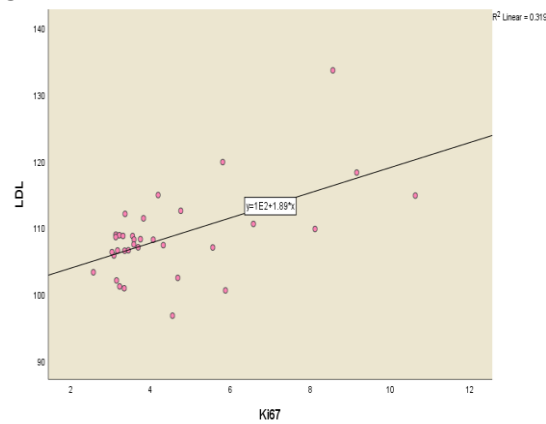


Fig E

Figure (1.A): A,B,C,D,E are correlation regression between lipid profile and tumor marker CA15-3 in breast cancer group

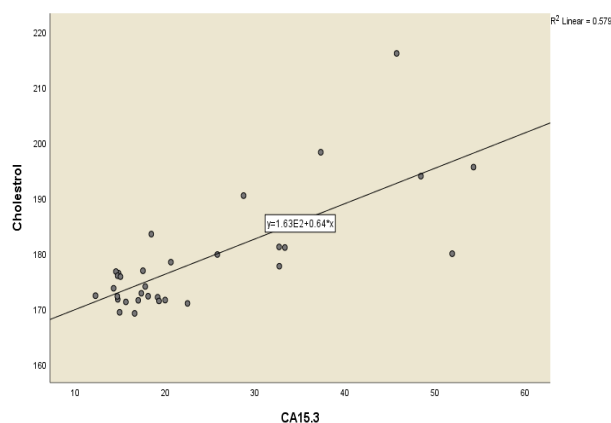


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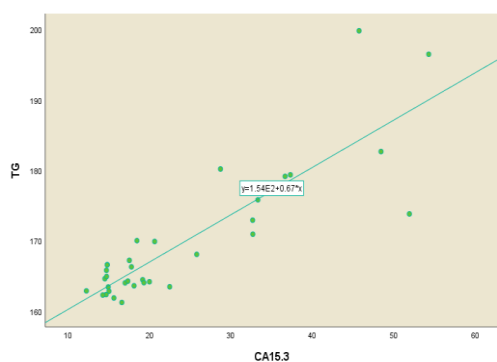


Fig G

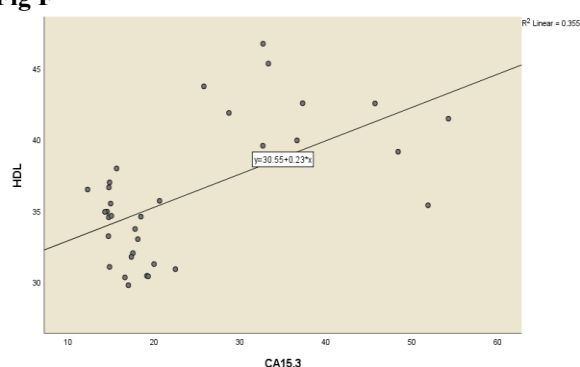


Fig H

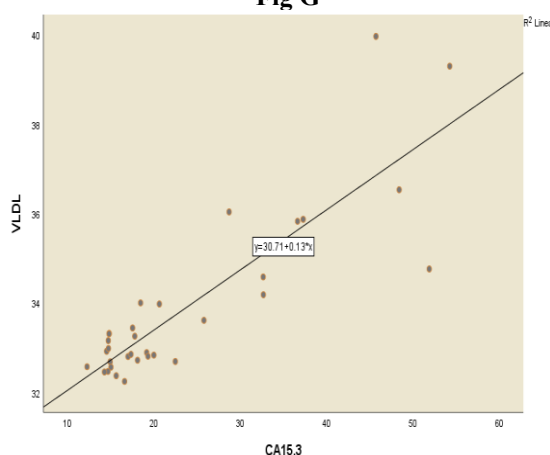


Fig I

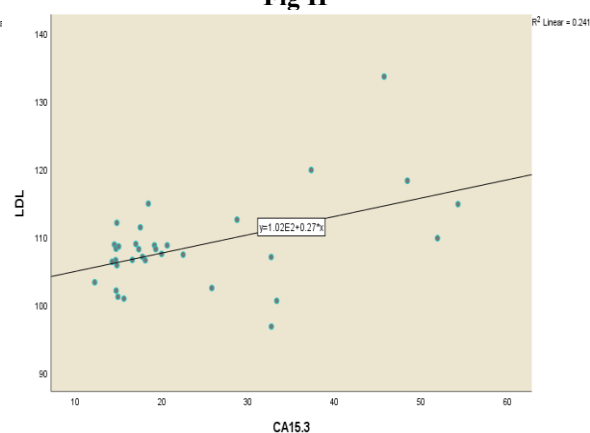


Fig J

Figure (1.B): F, G, H, I, J are correlation regression between lipid profile and tumor marker CA15-3 in breast cancer group

Discussion

The fact of the incidence of dyslipidemia in breast cancer women and diabetic women is higher than that in healthy people that lead to development and progression of tumor cells which is consistent with the current study, this study was based on the relation of tumor markers with lipid

profile levels and hyperglycemia and how tumor development depends on the amount of circulation fats in the body (12,13).

Hyperglycemia could provide nutrients for the rapid proliferation of malignant tumor cells, thereby accelerating the process of tumor cells. Li et al. reported that high-concentration

glucose significantly increased the proliferation of breast cancer cells (such as MDAMB231) compared to low-concentration glucose (14). Guanosine triphosphatases (GTPases) may activate the epidermal growth factor receptor (EGFR) to accelerate cell cycle progression and promote breast cancer cell proliferation (15). The glucose metabolism in tumor cells is characterized by the "Warburg" effect. Under aerobic or anaerobic conditions, the cells initiate glycolysis pathway of glucose, a process in which energy is produced. Because of the deficiency of adenosine triphosphate (ATP) produced by glycolysis, the tumor cells increase the intake of glucose to boost energy-providing glycolysis. Hyperglycemia helps tumors grow in a number of ways, such as by encouraging tumor cell growth, invasion, and migration and by making cells resistant to apoptosis and chemotherapy (16,17). All these facts supported our study, which demonstrated that the tumor markers CA15-3 and Ki67 in diabetic women were significantly correlated with HbA1c, more so than in breast cancer alone.

Recent research on diabetic women with breast cancer highlights the intricate relationship between dyslipidemia, tumor markers, and proliferation indices, particularly in those with comorbid diabetes mellitus. Dyslipidemia, characterized by abnormal levels of serum lipids, has been consistently associated with an increased risk of breast cancer development and progression. The study by Aseel et al (2018) in Iraq show the correlation between CA15-3 and the mean values of serum levels of TC, TG and LDL-C in breast cancer women were found to be significantly higher (18). Another study included 312 breast cancer patients had a retrospective

analysis conducted at the Henan Cancer Hospital in China. The study concluded that serum lipids should be closely monitored throughout breast cancer treatment, and patients with dyslipidemia should be treated promptly to potentially improve prognosis (19). Several studies have reported significantly elevated levels of total cholesterol, triglycerides, and LDL-C in breast cancer patients compared to healthy controls, with a particularly strong correlation observed in diabetic individuals. This study confirms the association between dyslipidemia, insulin resistance and increased BC risk(11).

Studies have demonstrated that women with breast cancer exhibit significantly higher CA15-3 levels compared to those with benign breast tumors, and these elevated levels correlate positively with serum total cholesterol, triglycerides, and LDL-C15. The association is notably more pronounced in diabetic women, indicating a potential interaction among glucose metabolism, lipid profiles, and tumor marker expression(10). Another study by Yixin Z. at (2018) found that dyslipidemia correlates with an elevated risk of breast cancer. Serum lipid levels varied among patients according on lymph node status and tumor stages. The CA153 level has a positive correlation with the TG level to a certain degree with more aggressive clinicopathological features (20).

Ki67, a nuclear protein linked to cellular proliferation, functions as a significant prognostic indicator in breast cancer. Recent studies have examined the correlation of Ki67 expression, lipid profiles, and CA15-3 levels in breast cancer patients, particularly in diabetic women (10). Studies have reported a positive correlation between high Ki67 expression and elevated serum lipid

levels, particularly in patients with comorbid diabetes. Furthermore, a significant association has been observed between high Ki67 indices and increased CA15-3 levels, suggesting a potential link between tumor proliferation, lipid metabolism, and tumor marker expression (19). A study involving 170 patients with invasive breast cancer revealed a significant correlation between serum dyslipidemia and Ki67 expression levels. The study reveals that high cholesterol and LDL-C levels, and low HDL-C and apolipoprotein A1 levels are linked to increased Ki67 expression. This suggests a poor prognosis for breast cancer patients, including those with diabetes. The research emphasizes the importance of monitoring serum lipid profiles and the complex relationship between dyslipidemia, tumor proliferation, and patient outcomes, emphasizing the need for comprehensive management strategies(21).

One of the few recent studies that discussed this connection is a study of Xi-Bo Sun, *et al.* (2022) in China was conducted that the circulating Cholesterol and LDL-C levels were positively correlated with Ki-67 expression levels, while HDL-C levels were negatively correlated with Ki-67 expression levels (22). Faur and others (2024) in Romania approved that lipid levels (especially LDL and triglycerides) were associated with increased Ki-67 expression, indicating more rapid tumor growth and higher proliferation rates (23). The complex interplay between dyslipidemia, tumor markers, and proliferation indices in diabetic women with breast cancer presents a compelling area of research with significant clinical implications. Recent studies have shed light on the intricate relationships between serum

lipid profiles, cancer antigen 15-3 (CA15-3), and Ki67 expression in breast cancer patients, particularly those with comorbid diabetes mellitus.

Conclusion

The association between dyslipidemia, CA15-3, and Ki67 in diabetic women with breast cancer suggests that lipid profile monitoring could serve as a valuable tool in risk assessment and prognosis. The emerging evidence points out a significant correlation between dyslipidemia, CA15-3 levels, and Ki67 expression in diabetic women with breast cancer. This intricate relationship underscores the importance of a comprehensive approach to breast cancer management, particularly in patients with comorbid diabetes.

List of abbreviations:

BC: Breast Cancer, T2D: Type 2 Diabetes, CA15-3: Cancer Antigen 15-3, HbA1c: Glycated Hemoglobin, HDL: High density lipoprotein, LDL: Low density lipoprotein, TG: Triglyceride, VLDL: Very Low-density lipoprotein.

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