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INSIGHTS INTO LIPID ALTERATIONS FOLLOWING CHEMOTHERAPY IN BREAST CANCER PATIENTS

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Abstract:
Background: Postoperative breast cancer (BC) patients may experience changes in serum lipids as a result of breast cancer chemotherapy; however, the precise changes produced by various chemotherapy regimens are not yet known.
Aim: The aim of this study was to assess the fluctuations in lipid profile parameters among women with breast cancer who have not undergone treatment compared to those undergoing chemotherapy.
Materials and Methods: This case-control study examines 60 women diagnosed with breast cancer alongside 35 control subjects, spanning from June 2023 to February 2024. Patients were recruited from three healthcare facilities and divided into groups based on diagnosis and treatment status. Clinical data were collected via questionnaire, and breast cancer diagnosis was confirmed through histopathological examination. Blood samples were analyzed for lipid profile parameters. Findings from four tables explore age-related prevalence, lipid profiles, treatment dynamics, and disease staging in breast cancer research.
Results: The study showed that the oldest age group has the highest percentage of breast cancer cases, accounting for 41.67% of total cases. The youngest age group has the lowest percentage, comprising 23.33%. The lipid profile of breast cancer women compared to healthy women in a control group showed significantly higher cholesterol levels, elevated triglycerides, and lower levels of high-density lipoprotein (HDL). The breast cancer group also had higher levels of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) compared to the control group. Cholesterol levels were high pre-treatment, declining significantly after treatment and increasing after two doses. High-density lipoprotein levels peaked after one dose, then decreased slightly after two doses. Low-density lipoprotein levels consistently rose with treatment, reaching statistical significance after two doses. The study categorized 60 breast cancer patients into three stages: T1N0M0, T2N1M0, and T3N2M1, with 28.33% under T1N0M0, 46.67% under T2N1M0, and 25.0% under T3N2M1, revealing the distribution of cases according to the TNM classification system.
Conclusion: This study highlights the age-related prevalence of breast cancer, lipid profiles as potential biomarkers for disease detection, dynamic changes in lipid profiles during treatment, and the heterogeneity of disease progression. It emphasizes the importance of accurate staging for treatment planning and contributes to understanding breast cancer pathophysiology.

Keywords: Breast cancer; Chemotherapy; Lipid; Cholesterol; TNM.

Introduction

Globally, 2,100,000 new instances of breast cancer (BC) were reported in 2018, with a mortality rate of about 630,000, making it one of the most common malignancies (1). On the other hand, more people are surviving breast cancer these days than in the past because of improvements in early detection and thorough treatment (2). Some BC patients have recently passed away from causes other than cancer, despite the fact that the survival rate of these patients has been steadily rising. In early BC survivors, the proportion of deaths due to causes other than cancer has progressively grown and now surpasses that of cancer itself, according to the most recent figures (3). Although cancer is the top cause of death overall, cardiovascular disease (CVD) is second only to cancer in terms of mortality in older individuals diagnosed with early-stage BC (4). CVD is responsible for 35% of all fatalities that are not cancer-related. Lipids have a significant role in cellular structure, signaling pathways, and cancer progression; in particular, cancer cells are characterized by an increased need for lipids in order to synthesize new membranes, which are essential for cell proliferation. Thus, lipid investigations have evolved into a crucial instrument for the detection of breast cancer (BC) markers. Here, cancer-related metabolic reprogramming involves the enhancement of specific metabolic processes—such as protein, nucleic acid, and lipid synthesis—to meet the demands of cell growth and proliferation (5). No definitive evidence of a causal link between cholesterol and BC has been found in the existing literature from clinical trials or epidemiological studies. Lipid levels and BC risk have been found to be positively, negatively, or not at all related in observational epidemiological research; however, it is important to note that these studies are susceptible to confounding. Medications that lower cholesterol have been linked to better outcomes in breast cancer patients undergoing hormonal therapy, and a thorough meta-analysis indicated that statin use may lower the risk of BC (6). This suggests that there may be an interaction between circulating cholesterol levels and estrogen-sensitive breast tissues. These contradictory results highlight the importance of conducting a robust causal inference study of lipids on BC. A number of recent studies have attempted to address these inconsistencies by testing the hypothesis that genetically higher lipid levels are associated with BC risk using the Mendelian randomization (MR) paradigm. Using multivariable MR, Orho-Melander and colleagues inferred a link between BC and triglycerides and HDL cholesterol but found no association between LDL cholesterol and the disease in a small sample of 1,187 BC cases (7,8). Second, using genetic association data from big genome-wide association studies (GWASs) for lipids and BC (9-12), Nowak and colleagues [10] conducted an MR analysis. The aim of this study was to assess the fluctuations in lipid profile parameters among women with breast cancer who have not undergone treatment compared to those undergoing chemotherapy.

Materials and Methods

Participating in this case-control study were sixty women with a breast cancer diagnosis and thirty-five healthy controls ranging in age from twenty-five to eighty. The patients were sourced from three primary healthcare facilities in Kirkuk: the Kirkuk Oncology Center, the Breast

Tumor Early Detection Consultation at Azadi Hospital, and Kirkuk General Hospital. The recruitment period lasted from June 2023 to February 2024.

The people who took part in the research were split into six categories:

Twenty patients recently diagnosed with breast cancer who underwent a triple assessment using ultrasonography, fine-needle aspiration cytology, and a physical examination of the breast.

Twenty patients who were administered the initial chemotherapy dose.

Twenty patients who were administered a second round of chemotherapy.

A total of 35 healthy females without a family history of breast cancer volunteered.

A brief questionnaire was used to gather clinical data, such as subjects' ages, weights, heights, marital status, menopausal status, family history of breast cancer, chronic disease status, and details of their treatment courses.

Histopathological analysis of a surgically excised breast mass from each participant woman confirmed the presence of breast cancer. This indicates that the histopathologist's discussion led to the diagnosis of breast cancer.

Approach: Using a sterile disposable syringe, we extracted around 5 ml of venous blood from every subject and placed it into gel tubes. For 20 minutes, the blood samples were left at room temperature to coagulate. After that, for 15 minutes, each sample was spun in a centrifuge at 3000 rpm. Next, 500 µl of serum was distributed to each of three Eppendorf tubes from the collected sera. Until they were needed for biochemical tests, such as lipid profile characteristics, the samples were kept at -30°C.

Results

Table 1 delineates the correlation between age and the prevalence of breast cancer. It categorizes cases into three distinct age groups: 35-44 years, 45-56 years, and 55-76 years. Notably, the highest percentage of breast cancer occurrences is observed in the oldest age bracket, constituting 41.67% of the total cases, followed by the middle age group at 35.00%. Conversely, the youngest age group exhibits the lowest percentage of cases, comprising 23.33% of the total.

Table 1: Correlation between age and the prevalence of breast cancer

Age groups (years)	No.	%
35-44	14	23.33
45-56	21	35.00
55-76	25	41.67
Total	60	100

Table 2 compares the lipid profile levels between breast cancer women and healthy women in a control group. Notably, the breast cancer group exhibits significantly higher levels of cholesterol (197.3 ± 43.9 mg/dL) compared to the control group (170.3 ± 17.1 mg/dL), as well

as elevated triglycerides (TG) (160.9 ± 44.5 mg/dL vs. 94.9 ± 16.1 mg/dL), and lower levels of high-density lipoprotein (HDL) (41.9 ± 21.7 mg/dL vs. 51.33 ± 6.3 mg/dL). Moreover, the breast cancer group demonstrates higher levels of low-density lipoprotein (LDL) (126.9 ± 39.7 mg/dL) and very low-density lipoprotein (VLDL) (32.1 ± 8.8 mg/dL) compared to the control group (LDL: 100.1 ± 25.2 mg/dL, VLDL: 18.9 ± 3.23 mg/dL)., the difference was highly significant at P. value < 0.01,

Table 2: Level of lipid profile in breast cancer women and healthy women

Studied groups	Cholesterol	TG	HDL	LDL	VLDL
Breast Cancer women	197.3±43.9	160.9±44.5	41.9±21.7	126.9 ±39.7	32.1 ±8.8
Control Group (n:35)	170.3±17.1	94.9±16.1	51.33±6.3	100.1±25.2	18.9±3.23
P. value	0.001	0.001	0.001	0.001	0.001

Table 3 presents the lipid profile dynamics among breast cancer women at various disease stages, showcasing changes before treatment and after one and two doses of treatment. Pre-treatment, cholesterol levels were notably high at 233.5 ± 19.5 mg/dL, declining significantly to 213.5 ± 24.3 mg/dL after one dose and further to 189.3 ± 25.4 mg/dL after two doses (p = 0.03). Triglyceride levels experienced a significant decrease from 178.4 ± 15.4 mg/dL before treatment to 156.6 ± 13.6 mg/dL after two doses (p = 0.01). High-density lipoprotein (HDL) levels peaked after one dose, then decreased slightly after two doses, with an overall significant change (p = 0.013). Conversely, low-density lipoprotein (LDL) levels consistently rose with treatment, reaching statistical significance after two doses (p = 0.017). Very low-density lipoprotein (VLDL) levels decreased significantly after one dose and remained stable thereafter (p = 0.019).

Table 3: Relation of lipid profile with stage of disease breast cancer women

Breast cancer women	Cholesterol	TG	HDL	LDL	VLDL
before treatment (n:20)	233.5±19.5	178.4±15.4	38.45±4.56	132.4 ±15.3	35.4 ± 3.67
1 dose treatment (n:20)	213.5±24.3	178.3±21.3	41.45±5.45	138.7±15.4	30.2± 4.31
2 dose treatment (n:20)	189.3±25.4	156.6±13.6	39.46±3.47	143.2±11.4	30.1± 2.52
P. value	0.03	0.01	0.013	0.017	0.019

Table 4 delineates the distribution of breast cancer patients across various stages according to the TNM (Tumor, Nodes, Metastasis) classification system. The stages are categorized as T1N0M0, T2N1M0, and T3N2M1. The data reveals that 17 patients (28.33%) were classified under stage T1N0M0, 28 patients (46.67%) under stage T2N1M0, and 15 patients (25.00%) under stage T3N2M1. Overall, the table encompasses a total of 60 patients, highlighting the distribution of breast cancer cases across different stages as per the TNM classification system.

Table 4: Distribution of breast cancer patients across different stages according to TNM (Tumor, Nodes, Metastasis) classification system

Stage	Number of Patients (n)	Percentage (%)
T1N0M0	17	28.33
T2N1M0	28	46.67
T3N2M1	15	25.00
Total	60	100

Discussion

The relationship between age and the frequency of breast cancer is seen in Table 1. There are three separate age groups into which cases are grouped: 35–44, 45–56, and 55–76. Of particular note is the fact that the oldest age group accounts for 41.67 percent of all breast cancer diagnoses, with the medium age group coming in at 35.0%. Although they make up 23.33% of the total, the youngest age group has the lowest percentage of cases. The majority of beast cancer patients are women over the age of 50, which is in line with our findings (Mishra et al., 13). Women older than 48 years old had the highest illness prevalence, according to Ali et al., (14). Factors related to hormones and family history may explain why the age-standardized incidence of breast cancer among British women in the 50–60 age bracket is so high (1,2). Compared to the control group, the breast cancer group in this study had substantially higher cholesterol levels (197.3 ± 43.9 mg/dL) and elevated triglycerides (160.9 ± 44.5 mg/dL vs. 94.9 ± 16.1 mg/dL). They also had lower levels of high-density lipoprotein (HDL) (41.9 ± 21.7 mg/dL vs. 51.33 ± 6.3 mg/dL). In addition, the control group had lower levels of low-density lipoprotein (LDL) (100.1 ± 25.2 mg/dL) and very low-density lipoprotein (VLDL) (18.9 ± 3.23 mg/dL), while the breast cancer group had higher levels of both (126.9 ± 39.7 mg/dL and 32.1 ± 8.8 mg/dL, respectively). This difference was highly significant with a P-value of less than 0.01. In cancer, lipids play a well-documented role in preserving cell integrity (15). Measuring the plasma lipid profile may help in figuring out the diagnostic and prognostic importance of breast cancer, since any change to the profile raises the risk status of the disease (16). Additionally, there is evidence linking lipids and lipoproteins to an increased risk of cancer (17). Researchers found that compared to a healthy control group, breast cancer patients had significantly higher cholesterol levels. This is because endogenous steroid hormones are directly linked to breast cancer (18), and cholesterol is a building block of steroid hormones.

These findings corroborated those of AL-Hamamy (19), who also discovered that breast cancer patients' cholesterol levels tend to be higher. In a similar vein, Al-Swelmien (20) discovered that breast cancer patients had substantially higher levels of total cholesterol, suggesting a link between the two diseases. A recent study found that, compared to other types of cancer, breast cancer is closely associated with high cholesterol levels (21,22). Patients with breast cancer had higher triglyceride concentrations compared to the control group. Our findings are consistent with those of previous research (34,24). Elevated triglyceride (TG) levels have been linked to an increased risk of breast cancer in previous investigations (25). An increased risk of breast cancer has been linked to elevated free estradiol levels, which in turn are caused by an association between increased TG concentrations and decreased sex hormone binding globulin levels (Panigoro et al., 2021). Due to its important function in oxidation, an increased LDL-C content is thought to increase the likelihood of developing cancer (22). There is no proven causal relationship between hyper- or hypo-cholesterolemia and cancer progression, however there are pathways via which lipoproteins may have an impact. Under oxidative stress, there is an increase in lipid peroxidation because LDL-C is easily oxidized. Depending on the individual's oxidative status, the increased concentration of reactive oxygen species and/or the inadequacy of the cellular or circulating plasma antioxidant to clear free radicals leads to an increase of lipid peroxidation products of LDL-C, as reported by Delimaris et al. (2007). Finding a statistically significant difference between sera LDL-C, this study's results corroborated those of Al-Swelmien (20). This table displays the findings of the VLDL-C concentrations (1). The results showed that the control group and the women with breast cancer were significantly different. Consistent with the findings of Shah et al.(24), who discovered substantially higher plasma levels of VLDL in the work group compared to the control group and patients with benign breast cancers, this investigation also observed a significant rise in VLDL-C levels. Table 3 displays the changes in lipid profiles of breast cancer patients both before and after therapy. The cholesterol levels, which were elevated before therapy, dropped dramatically following the first and second dosages. After one dose, triglyceride levels dropped, and after two doses, HDL levels peaked and then dropped somewhat. Treatment resulted in an increase in low-density lipoprotein levels. Breast cancer patients are categorized into several phases based on the TNM (Tumor, Nodes, Metastasis) method, as shown in Table 4. T1N0M0, T2N1M0, and T3N2M1 are the steps that make up the process. Among the patients categorized according to the data, 17 (or 28.33%) fell into stage T1N0M0, 28 (or 46.67%) into stage T2N1M0, and 15 (or 25.0%) into stage T3N2M1. The table displays the distribution of breast cancer cases across different stages according to the TNM classification method. It covers a total of 60 patients. Findings in the literature suggest that a considerable proportion of breast cancer cases are detected at this more advanced stage owing to reasons such as delayed diagnosis or improved awareness and screening. This is in line with the majority of patients in the T2N1M0 stage. Research by groups like Al-Khafaji et al. (27) has highlighted the need for prompt diagnosis and treatment to decrease the proportion of patients in advanced stages. On the other side, breast cancer in its early stages typically has a better prognosis and can be treated less aggressively, which explains why there are comparatively fewer individuals at the

T1N0M0 stage (29.63%). Extensive field research also supports the use of the TNM classification method in the table. Studies such as Brierley et al. (28), which show that the TNM approach has been used in clinical practice for many years for breast cancer staging, reveal that it is generally recognized. It provides a thorough framework for evaluating the disease's extent by considering the main tumor's size (T), the involvement of regional lymph nodes (N), and the occurrence of distant metastasis (M). Lastly, the presence of T3N2M1 (24.81% of cases) is in line with previous studies by authors like Sakamoto et al. (29), which demonstrate that this stage is marked by large tumors, widespread lymph node involvement, and distant metastasis; consequently, this stage is associated with a worse prognosis and faster disease progression.

Conclusions

This study highlights the age-related prevalence of breast cancer, lipid profiles as potential biomarkers for disease detection, dynamic changes in lipid profiles during treatment, and the heterogeneity of disease progression. It emphasizes the importance of accurate staging for treatment planning and contributes to understanding breast cancer pathophysiology.

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