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Association of Lipid Profile Markers with Breast Cancer: An Analysis of the KFSH Study in Dammam, Saudi Arabia

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ABSTRACT

Background: Breast cancer (BC) is a heterogeneous disease characterized by the presence of a lump or mass in the breast tissue. BC has been associated with an abnormal lipid profile; however, this relationship is controversial. This study investigated the relationship of circulating lipid profiles with BC among Saudi women attending King Fahad Specialist Hospital, Dammam (KFSH-D), KSA.

Methods: Three hundred and ninety-nine (399) women between the years 2018 and 2021 were selected for this case control study based on the presence (for cases) or absence (for controls) of BC at the KFSH-D. The lipid levels of women with BC were compared to the lipid levels of healthy women. Data on total cholesterol (TC), triglyceride (TG), high-density lipoproteins (HDL), and low-density lipoproteins (LDL) were collected from 200 BC diagnosed patients and 199 healthy individuals. Statistical analysis was performed using the t-test and regression analysis.

Results: This study showed significant differences between BC patients and healthy controls in terms of total cholesterol, HDL, and TG levels. No significant difference was observed in LDL levels.

Conclusion: This study revealed a significant relationship between the circulating lipid profile and breast cancer in a cohort of Saudi women.

Keywords:

breast neoplasm, lipid profile, cholesterol, HDL, LDL, triglyceride

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INTRODUCTION

Breast cancer (BC) is a heterogeneous disease characterized by the presence of a lump or mass in the breast tissue. It ranges from non-invasive to aggressive and invasive, depending on the degree of cancer spread and the type of lymph nodes affected.¹ Globally, BC is the most commonly diagnosed cancer and the second leading cause of cancer death in

women, with more than 2 million new diagnosed cases and above 626,000 deaths in 2018.² In the US, BC accounts for more than 13% of new invasive cancer diagnoses and 3% cancer deaths.³ In Saudi Arabia, the prevalence of BC accounted for 25.1% of all newly diagnosed female cancers (5,205 cases) in 2009.⁴ The incidence rate for invasive BC has rapidly increased in parallel with the increased obesity.⁵⁻⁷ Despite the early detection of BC using advanced technologies, such as radiography and mammography, more than 50% of BC cases in Saudi Arabia are detected at a late stage.⁸

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Several studies have shown that women with BC are associated with obesity and dyslipidemia.^{6,9,10} Furthermore, BC has been associated with an abnormal lipid profile, including hypercholesterolemia, and altered levels of high-density lipoproteins (HDLs), low-density lipoproteins (LDLs), and triglycerides (TGs).^{5,11-14} Recently, lipid metabolism-associated genes (LMGs) have been identified as a new prognostic indicator for predicting the survival of patients with BC.^{4,15} It has been suggested that metabolic disorders and dyslipidaemia are strongly associated with the occurrence of breast cancer. However, findings from other studies have reported contradictory results, showing no role for HDL^{16,17}, triglyceride^{10,19}, and cholesterol levels in BC.¹⁶⁻²¹

There are several diagnostic techniques for breast examination, such as mammography, breast ultrasound, computed tomography (CT), breast biopsy and breast magnetic resonance imaging (MRI).^{22,23} However, lipid profiles, which are common tests performed in general chemistry laboratories, are not usually requested to diagnose women with breast cancer. Not only is the early detection of BC essential for treating the disease, but it also raises the potential for treatment and reduction of the mortality rate. Thus, it is crucial to investigate the relationship between lipid test abnormalities and the manifestation of breast cancer. The most common cancer among Saudi nationals is BC, which reached 21% in 2016.²⁴ Since 2015, the prevalence of breast cancer in women has risen from 21.1% to over 30%. Although it is still uncommon in males (less than 1%), the incidence of male breast cancer in Saudi Arabia has considerably increased since 2013, which is indicative of the country's fast population expansion, societal and economic transformation, and shifts in the main risk factors for cancer.²⁵

Due to the high number of undiagnosed cases, significant efforts are needed to diagnose, monitor, and manage these patients as their condition progresses. Therefore, early diagnosis is an essential protocol for women at risk for breast cancer.

The relationship between BC and increased levels of serum lipids is controversial, with conflicting reports on the serum lipid profiles of patients with breast cancer compared with healthy controls.^{4,5,12,13,25,26} Moreover, there are no studies that have investigated the link between circulating levels of serum lipids and BC in women in Saudi Arabia.

This study investigated the relationship of the circulating lipid profile with BC among Saudi women. We hypothesized that, compared with healthy individuals, high levels of circulating lipid profile would be associated with a worse prognosis of breast cancer.

METHODS

Study participants

In this case control study, 399 female participants were selected on the basis of the presence (cases) or absence (controls) of BC at KFSH-D, KSA, in the period between 2018 to 2021. This study was approved by the human research ethics committees at KFSH-D (LAB0318).

Data collection and preparation

The data on TC, HDL, LDL, and TGs levels were collected from the records of 200 diagnosed patients with BC and 199 healthy individuals attending KFSH-D, KSA. Dyslipidemia was defined according to the National Cholesterol Education Program–Adult Treatment Panel III (NCEP– ATP III) guidelines as TC > 5.2 mmol/L, LDL > 3.40 mmol/L, HDL < 1.3 mmol/L, or TG > 1.7 mmol/L.

Instrumentation

The Alinity ci (chemistry immunoassay) system was used to analyze the lipid profiles (total cholesterol, TG, LDL, and HDL) from the blood specimens of the participants after an overnight fast (10–12 hours). The Alinity ci system is a fully automated chemistry analyzer designed to generate up to 1350 tests per hour and allows for random and continuous access as well as priority and automated retest processing. In addition, this system uses photometric detection technology to measure the sample absorbance for the quantification of the analyte concentration. A calculated absorbance is generated based on the reaction mode of the assay (rate or endpoint), and this absorbance is measured using a calibration curve to generate a result.

Statistical analysis

The raw data were collected and organized using Microsoft Excel (Microsoft Corp) and then analyzed using SPSS, version 26 (IBM Corp). Descriptive statistics, such as frequencies and percentages, were used to describe the characteristics of the study sample. Comparisons of the total cholesterol, TG, LDL, and HDL levels in the patients with BC and in the healthy control participants were performed using the independent samples *t* test. Associations of lipid profiles of patients with BC and healthy controls were assessed using binary logistic regression, and odds ratios (ORs) with 95% confidence interval (CI), were calculated. A *P* value ≤ 0.05 was considered statistically significant.

RESULTS

Participant characteristics

Table 1 shows the demographic and clinical characteristics of the 399 participants. They were 199



healthy adults, who ranged in age between 26 and 87 years, and 200 BC patients, ranging in age between 25 and 60, with a mean age of 41 and 59, respectively. The age of the majority of participants (49.6%), ranged between 45 and 64 years, and the fewest number of participants (14%) were ≥ 65 . The average

levels of total cholesterol, HDL, LDL, and TG for the patients were 4.88 mmol/L, 1.36 mmol/L, 3.00 mmol/L, and 1.54 mmol/L, respectively. The mean levels of total cholesterol, HDL, LDL, and TG for the healthy controls were 2.50 mmol/L, 1.20 mmol/L, 2.98 mmol/L, and 0.95 mmol/L, respectively.

Table 1. Descriptive Statistics of Lipid Profiles and Age for Patients and Healthy Control Participants

Group	Parameter	n	Minimum	Maximum	Mean (SD)
Patients	Total cholesterol, mmol/L	200	2.60	8.38	4.88 (1.12)
	HDL, mmol/L	200	0.32	2.46	1.36 (0.37)
	LDL, mmol/L	200	0.64	5.99	3.00 (0.97)
	Triglycerides, mmol/L	200	0.33	8.26	1.54 (1.00)
	Age, year	200	26.00	87.00	59.22 (9.54)
	Valid number (listwise)	200			
Controls	Total cholesterol, mmol/L	199	0.34	6.70	2.50 (1.39)
	HDL, mmol/L	199	0.54	4.90	1.20 (0.45)
	LDL, mmol/L	199	2.15	3.99	2.98 (0.27)
	Triglycerides, mmol/L	198	0.34	5.10	0.95 (0.42)
	Age, year	199	25.00	60.00	40.97 (8.09)
	Valid number (listwise)	198			

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Comparison of lipid levels in patients with BC and healthy controls

Table 2 shows the results of the statistical analysis of the total cholesterol, TG, LDL, and HDL levels in patients with BC and the healthy controls. The analysis using independent samples *t* tests

indicated significant differences ($P < 0.001$) between the total cholesterol, TG, and HDL levels of the patients with BC and the healthy controls. However, there was no significant difference ($P = 0.74$) between the LDL cholesterol levels of the 2 groups.

Table 2. Comparison of Serum Lipid Profiles Between Healthy Participants and Patients With Breast Cancer

Parameter	Healthy (n = 199), mean (SD)	Cancer (n = 200), mean (SD)	Independent <i>t</i> test		
			t	df	P value
Total cholesterol, mmol/L	2.48 (1.39)	4.88 (1.12)	-18.84	378.67	<0.001
Triglycerides, mmol/L	0.95 (0.41)	1.53 (1.00)	-7.52	266.37	<0.001
LDL, mmol/L	2.98 (0.27)	3.00 (0.96)	-0.33	230.88	0.74
HDL, mmol/L	1.20 (0.45)	1.35 (0.37)	-3.64	381.14	<0.001

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Lipid profile association between BC patients and normal control subjects

Table 3 below shows regression analysis of the lipid profile parameters and age, which indicates a significant association with BC, and the p-values were as follows: TC (p-value < 0.001); HDL (p-value < 0.001); TGs (p-value < 0.001); and age (p-value < 0.001). Table 3 also shows that TC, TG, HDL, and age increases the risk for breast cancer by 5.10 fold (95% CI = 3.60–7.23), 6.88 fold (95% CI = 3.95–12.00), 3.26 fold (95% CI = 1.66–6.44), and 1.27 fold

(95% CI = 1.22–1.34), respectively. After adjusting for other types of lipids and age the odds of developing breast cancer for TC and HDL were found to be 4.6 fold (95% CI = 3.60–7.23) and 3.2 fold (95% CI = 1.11–4.82), respectively, which remains stable and strongly increases breast cancer risk, independent of TG and age. TG showed a strong crude effect but a weaker after adjustment with odds of 2.3 fold (95% CI = 1.29–8.33). Older age increases breast cancer risk by 1.3 times (95% CI = 1.23–1.44) independently of TC, HDL and TG.

Table 3. Association Between Lipid Profile, Age, and Breast Cancer

Parameter	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Total cholesterol (TC)	5.10 (3.59-7.23)	< 0.001*	4.62 (2.79-7.65)	< 0.001*
High-Density Lipoproteins (HDL)	3.26 (1.65-6.43)	< 0.001*	3.27 (1.29-8.33)	< 0.013*
Triglyceride (TG)	6.88 (3.94-11.99)	< 0.001*	2.30 (1.10-4.82)	< 0.027*
Age	1.27 (1.21-1.34)	< 0.001*	1.32 (1.22-1.43)	< 0.001*

*Significant at 0.05



DISCUSSION

BC continues to be the most commonly diagnosed cancer in women and is the second leading cause of cancer death worldwide. It is the most common cause of cancer among women in both high-resource and low-resource settings.²⁸ The descriptive epidemiology of BC in Saudi Arabia provides an important explanation for this recent trend, confirming the significance of the disease among women. Female breast cancer in Saudi Arabia is increasing annually, especially in the eastern and western regions.^{4,24,29} The importance of this study is to examine risk factors that may increase BC in females and to help reduce the morbidity of this disease. The results of our study showed a significant difference between the mean lipid profile (TC, TG, and HDL) of the breast cancer group and the control group. Additionally, the binary logistic regression model demonstrates a significant association between the incidence of breast cancer and TC, TG, HDL, and age. This finding raises the possibility that lipid metabolism contributes to the development or spread of breast cancer.

Several studies have found that elevated serum total cholesterol levels play a significant role in the development of cancer, while others have found no significant effect. The results of this study indicated that total cholesterol was significantly higher in the patients with BC than in the healthy controls. These findings are in line with several previous studies.^{7,10,14,16,30,31,32} Baek and Nelson *et al.* stated that high cholesterol is strongly linked to obesity and has emerged as a separate risk factor for the onset and recurrence of BC.¹⁰ This suggests that cholesterol has a role in the pathogenicity of obesity in breast cancer. BC severity, recurrence, and outcome may be affected by circulating cholesterol. In a study of 520 Canadian women diagnosed with early-stage breast cancer, women with a greater fasting baseline TC or LDL-C had a higher chance of recurrence.^{4,33}

In contrast to our study, some research has found that hypercholesterolemia is either negatively associated with BC or has no effect.^{19-21,27} The processes through which cholesterol promotes BC progression are less known. However, cholesterol may have direct effects on cancer cells as a limiting factor in membrane production or as a component of lipid raft formation and PI3K/AKT signalling. It could also potentially influence macrophages, enhancing the inflammatory tumor-friendly microenvironment.^{10,14} According to Lauridsen *et al.*, many breast cancers exhibit overexpression of the StAR-related lipid transfer protein 3 (STARD3) gene, which can increase the cholesterol content of the plasma membrane and encourage lipid raft-dependent signaling of lipid-anchored Src kinase. This, in turn,

modulates cell adhesion by inducing focal adhesions via activation of the Focal adhesion kinase (FAK) in HER2-negative breast cancer cells, increasing invasion, metastasis, and poor patient prognosis.³⁰ Studies have also shown that cholesterol serves as a precursor for the biosynthesis of steroid hormones such as estrogens that send signal to estrogen receptors activated by 27-hydroxy cholesterol, which is mainly transported with HDL and LDL; thus, controlling the growth of most breast cancers.¹⁰

Our study also showed a significant difference between the TG levels of BC cases and healthy. Similar results were reported by previous studies.^{9,13,14,16,34,35} In a study conducted by Ali in 2018 involving 30 Iraqi women with stage III BC and 40 age-matched apparently healthy control subjects, a significant increase in the TG levels of cancer patients was observed compared to normal women.³⁵ Franky *et al.*, found that the TG levels were significantly higher in 125 untreated patients with BC and 30 patients with benign breast disease compared with 70 controls.²⁷ In another study, Potischman *et al.*, found that 83 women diagnosed with BC in Buffalo, NY, had significantly higher plasma TG levels than the 113 women who were not diagnosed with BC.⁹ The association between hypertriglyceridaemia and BC could be explained by the fact that higher TG levels are linked to lower levels of sex hormones, which raises the risk of breast cancer. It could also be explained by lower hepatic TG lipase activity. Moreover, through increased growth factor production, insulin resistance, and chronic inflammation, hypertriglyceridemia and poor glycemic control can accelerate the development of cancer.^{18,34}

The results for HDL also showed a significant difference between the HDL levels of BC cases and healthy individuals. Similar results were also obtained in several studies, which reported a significant association between HDL and the risk of breast cancer.^{11,19,20,36-38} These results could suggest that high HDL cholesterol may be a marker of increased BC risk. In contrast to our findings, other studies suggest that a lower serum HDL level could be a biochemical index of the increased risk of having BC.^{19,27,30,39}

The way in which higher HDL levels are associated with BC is unknown; however, it could be due to the fact that higher HDL levels may reflect higher levels of endogenous estrogens or a stronger response to them, both of which are linked to an increased risk of BC.⁴⁰ Moreover, lipoproteins may have a direct impact on breast cancer. According to Rotheneder and Kostner, the *in vitro* exposure to HDL stimulated the proliferation of some cancer cell lines in a dose-dependent manner.⁴¹ These effects



have been linked to cholesterol ester absorption by HDL, as well as the stimulation of signal transduction via the scavenger receptor B1 (SR-B1).^{37,38,42}

In this study, we found no significant differences in the LDL levels between the patients with BC and the healthy controls, which is supported by several studies but refuted by others.^{43,44,45} According to Cedo *et al.*, LDL cholesterol mostly enhances proliferation and migration in estrogen receptor-negative cells but not in estrogen receptor (ER)-positive cell lines. Because of the enhanced activity of acyl-CoA:cholesterol acyltransferase 1, ER-negative cells have a greater ability to take in, store, and utilize exogenous cholesterol than ER-positive cells.³⁷ Lipid biomarkers have potential therapeutic uses as a result of the documented connections between lipid profiles and breast cancer.⁴⁶ Treatments that target the enzymes fatty acid synthase (FASN) and Acetyl CoA carboxylase (ACCA), which are crucial for lipid biosynthesis and have been linked to several cancer types, including breast cancer, have drawn more attention in recent years.⁴⁷

The higher odds ratios obtained by regression analysis indicate that there is a significant association between serum lipid profiles and age and the chance of developing breast cancer. It is important to note that, compared to healthy individuals, people with breast cancer have a greater likelihood of developing hypercholesterolemia, hypertriglyceridemia, and high HDL levels. The results of this research suggest that abnormal lipid metabolism and age are related to the development of breast cancer. This result is consistent with the available data in the literature, which views lipids^{6,9-21,48} and age^{49,50} as breast cancer risk factors.

The findings of this study may encourage further research into the processes through which lipid metabolism may influence the occurrence and progression of breast cancer. These findings may also have implications for risk assessment, the development of early detection methods, and the formulation of treatment strategies that focus on lipid pathways with a view to lowering the risk of breast cancer.

It is of utmost significance to recognize the limitations of the research, which include its retrospective design, possible confounding variables that were not accounted for in the analysis,

menopausal status, and the absence of causal inference owing to the observational character of the study. Further investigations using larger sample sizes and more extensive data gathering have the potential to provide a more thorough understanding of the complicated association between lipid profiles and breast cancer.

CONCLUSION

In summary, our findings confirm that dyslipidemia is linked to the development of BC and that total cholesterol, HDL cholesterol, and TGs are major risk factors for the development of BC. This study highlights the need to reduce the incidence and mortality of breast cancer by altering lifestyle choices, monitoring serum lipid levels, and preventing and treating dyslipidemia. Further clinical studies that focus on lipid metabolism in cancer are necessary because the most prevalent method of lowering serum lipid levels to support cancer treatments is the use of medications that block lipid production.

ETHICAL CONSIDERATIONS

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board at King Fahad Specialist Hospital-Dammam (protocol LAB0318; approved June 9, 2021). Patient consent was waived due to the retrospective nature of the study and the fact that the participants remained anonymous.

DATA AVAILABILITY

The data that support the findings of this study are not publicly available due to privacy and ethical restrictions.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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