ORIGINAL ARTICLE

The role of serum lipid profile, fasting blood sugar, and body mass index on recurrence and metastasis in patients with estrogen receptor-positive breast cancer: A case–control study

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Background: Breast cancer (BC) is the leading cause of cancer death in women. The current study is designed to evaluate the association of lipid profiles, FBS, and body mass index (BMI) with BC recurrence and metastasis. **Materials and Methods:** This is a case–control study on estrogen receptor-positive BC patients in Isfahan Province, Central Iran, between 2008 and 2020. The control group was patients who had no evidence of recurrence or metastasis at least 1 year after the end of chemotherapy and hormone therapy. The case group was patients with evidence of metastasis or recurrence within 1 year after the end of chemotherapy and hormone therapy. Fasting blood sugar (FBS), total cholesterol (Chol), triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were measured before treatment, after chemotherapy, and after hormone therapy as well as BMI in the case and control groups. **Results:** There were 108 patients in the case and 119 patients in the control group with a mean age of 50.72 ± 13.26 and 51.91 ± 11.79, respectively. There were no meaningful differences between the case and control groups regarding serum FBS, Chol, TG, HDL, LDL, and BMI. **Conclusion:** We found no association between serum FBS, lipid profile, and BMI at initial diagnosis and BC recurrence or metastasis.

Key words: Breast cancer, fasting blood sugar, metabolic syndrome, recurrence, serum lipid profile

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INTRODUCTION

Breast cancer (BC) is the most common cancer diagnosed in the world and the leading cause of cancer death in women.[1] In Iran, the most prevalent neoplasm in women is breast neoplasm and is ranked as the fifth cause of death among Iranian women.[2]

BC is classified into five subtypes according to gene expression profiling: luminal A has the highest amount of estrogen receptor (ER) expression and has a good prognosis. The prognosis of luminal B subtype is fairly worse than luminal A. The normal breast-like subtype's prognosis is like luminal B. The human epidermal growth factor receptor 2 (HER2)-amplified subtype previously had a poor prognosis, but with the emergence of the targeted therapies, its prognosis is considerably improving. The triple-negative subtype is ER/progesterone receptor (PR) negative, HER2 negative and has a poor prognosis.[3]

The classic determinants of BC prognosis are the TNM pathological stage, ER, PR, and HER2. Recently, some

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researches have focused on the new prognostic factors which are modifiable.[4] A growing body of research suggests that components of metabolic syndrome (MtS) may contribute to the development of BC and influence the prognosis of the disease.[5,6] Different studies have drawn inconsistent conclusions, and the impact of these new players on BC is a matter of controversy.[4,6]

MtS and obesity cause Insulin elevation and inflammation which have mitogenic, angiogenic, and antiapoptotic effects, which result in tumor progression. Obesity, type 2 diabetes, and MtS increase the level of estrogen and leptin and decrease the level of adiponectin. These changes cause increased BC risk and develop more aggressive tumors.[7,8]

MtS can increase the risk of BC development, recurrence, and mortality.[9,10] Central obesity has been associated with an elevated risk of BC occurrence, metastasis, and recurrence.[1,11] In a 2015 cohort study, the high levels of high-density lipoprotein (HDL) in triple-negative BC (TNBC) patients were correlated to less recurrence and mortality.[5] Meanwhile, FBS higher than 87 mg/dl seems to be associated with more recurrence and distant metastasis in BC.[11]

Although the relationship between components of MtS and the risk of BC has been investigated in most of the studies, fewer ones have focused on the role of MtS or its components in the prognosis and outcome of the disease. Accordingly, in this case–control study, we investigated the relationship between lipid profile, body mass index (BMI), and FBS with recurrence and metastasis of ER-positive BC.

MATERIALS AND METHODS

Ethical aspects

This study was conducted according to the principles of the Declaration of Helsinki. Ethics approval was obtained from the Research Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1398.554).

Cases and controls

This was a case–control study on ER-positive BC patients whose information had already been recorded in Omid Hospital and Iranian Cancer Control Center (MACSA), two referral cancer centers in Isfahan Province, Central Iran, between 2008 and 2020.

At first, we selected patients who were diagnosed with ER-positive BC. We considered a group of patients who showed no evidence of recurrence or metastasis after at least 1 year after the end of chemotherapy and hormone therapy as the control group. Those patients who had presented metastasis or recurrence within 1 year after the end of chemotherapy and hormone therapy were considered the case group. According to patients' clinical symptoms and signs, recurrence or metastasis was ruled out by appropriate imaging tests and biopsy, if needed. Controls were frequently matched with the cases for age and histopathology (luminal A and luminal B). Patients whose medical documents did not have FBS, lipid profile, and BMI were excluded from the study.

Research variables

Demographic and clinical data

Age at diagnosis, menarche age, age of marriage, age of first delivery, age of menopause, history of infertility treatment or hormone therapy, occupation, family history of non-BC or BC, weight, height, and BMI were collected from patients' documents.

According to Gail score model, patients were classified into two major groups: low risk (score <1.7) and high risk (score >1.7) before the initiation of BC.[12]

Histopathologic information

Pathological type, tumor grade, and immunohistochemical markers including PR, HER2, Ki67, and P53 were collected from patients' documents. According to the histopathological criteria, patients were divided into two groups: luminal A and luminal B. The luminal A group included ER- or PR-positive patients whose tumors were HER2 negative with Ki67 levels < 15%, and the luminal B group consisted of ER- or PR-positive patients with HER2-positive tumor or Ki67 levels more than 15%.[13]

Laboratory data

FBS, cholesterol (Chol), triglyceride (TG), HDL, and low-density lipoprotein (LDL) before starting hormone therapy and chemotherapy were recorded.

Data analysis

Quantitative data were reported as mean ± standard deviation. Qualitative data were reported as number and percentage. Kolmogorov–Smirnov test was used to determine whether or not the variables followed a normal distribution. We used nonparametric tests for nonnormal variables. The independent *t*-test, Mann–Whitney *U*-test, and Chi-square tests were used to evaluate differences in selected characteristics. The logistic regression model was used to estimate the odds ratios with a 95% confidence interval for risk of BC metastasis and recurrence associated with serum lipid profile, FBS, and BMI. Age and histopathology (luminal A and luminal B) were considered covariates. All analyses were conducted using SPSS Statistics version 16 software (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Altogether, 227 ER-positive BC patients were included in this study. The number of patients in the control and case groups was 119 and 108, respectively. The mean age of patients at the time of diagnosis was 50.72 ± 13.26 and 51.91 ± 11.79 respectively for the case and control groups, respectively.

Among patients for whom other molecular markers were checked, it was as follows: 185 (85.1%) PR positive, 89 (41.5%) HER2 positive, 10 (6.7%) P53 positive, and 53 (37.9%) had a Ki67 above 15%.

There was no significant difference between the case and control groups regarding demographics, reproductive factors, Gail score, family history of BC, and tumor characteristics [Table 1].

In the case group, the chemotherapy regimen was as follows: 22.7% of patients received anthracycline, 12.4% received taxane, 59.8% received anthracycline plus taxane, and 5.1% received other regimens. In the control group, the chemotherapy regimen was as follows: 14.9% of patients received anthracycline, 2.1% received taxane, 76.6% received anthracycline plus taxane, and 6.4% received other regimens ($P = 0.015$).

In the case group, the hormone therapy regimen was as follows: 19.8% of patients received aromatase inhibitor, 43.7% received tamoxifen, and 36.5% received tamoxifen plus aromatase inhibitor. In the control group, the hormone therapy regimen was as follows: 8.5% of patients received aromatase inhibitor, 35.9% received tamoxifen, and 55.6% received tamoxifen plus aromatase inhibitor ($P = 0.007$).

FBS, lipid profile, and BMI were not significantly different between the case and control groups [Table 2].

The logistic regression analyses showed no association between the serum levels of FBS, Chol, TG, HDL, LDL, BMI, and metastasis or recurrence of BC [Table 3].

Table 1: Comparison of demographics, reproductive factors, Gail score, family history, pathology, and histopathology of breast cancer between case and control groups

Variables	Mean±SD		*P*
	Case (*n*=108)	Control (*n*=119)	
Age at diagnosis	50.72±13.26	51.91±11.79	0.477‖
BMI	27.67±4.79	27.70±4.76	0.954¶
Reproductive factors			
Menarche age	13.62±1.54	13.57±1.40	0.833¶
Age of marriage	20.34±6.34	23.48±17.96	0.198¶
Age of first delivery	22.37±6.37	21.34±5.35	0.458¶
Age of menopause	44.38±10.39	46.63±6.53	0.462¶
Risk of BC (Gail score), *n* (%)			
High risk	7 (7.7)	16 (14.3)	0.140¶
Low risk	84 (92.3)	96 (85.7)	
BC family history, *n* (%)			
Yes	27 (29.3)	39 (35.1)	0.381**
No	65 (70.7)	72 (64.9)	
Tumor characteristic			
Pathology			
IDC	80 (87.0)	90 (78.9)	0.057**
DCIS	3 (3.3)	4 (3.5)	
ILC	5 (5.4)	19 (16.7)	
Others	4 (4.3)	1 (0.9)	
Histopathology			
Luminal A	42 (45.2)	52 (46.4)	0.888**
Luminal B	51 (54.8)	60 (53.6)	

**Resulted from Chi-square test; ‖Resulted from independent *t*-test; ¶Resulted from Mann–Whitney *U*-test. IDC = Invasive ductal carcinoma; DCIS = Ductal carcinoma *in situ*; ILC = Invasive lobular carcinoma; BMI = Body mass index; BC = Breast cancer; SD = Standard deviation

DISCUSSION

Various factors affect the outcome of chemotherapy and hormone therapy for BC patients. MtS and its components are among these factors.[5,10] In this study, among ER-positive BC patients in the two groups, with and without metastasis or recurrence, BMI, lipid profile, and FBS were not significantly different.

Metabolic syndrome

A significant association between MtS and the risk of BC recurrence has been shown in two recent meta-analytic studies by Li *et al*.[10] and Protani *et al*.[14] Another study suggested that MtS could increase the BC recurrence, but none of the components of MtS, when considered alone, had a significant association with the BC recurrence.[15] A recent case–control study performed in Iran showed that the prevalence of MtS in participants with BC was significantly higher than participants without BC.[16]

Since there were no acceptable records regarding the patients' blood pressure, we could not measure the total score of MtS for our patients.

Obesity

Obesity has been introduced as a risk factor for death and distant metastasis in BC.[14] As suggested by a cross-sectional study in our country, obesity exacerbates the inflammatory status in BC patients which has the potential to predispose the BC patients to metastasis.[17] According to an ancient study, those premenopausal BC women who had received chemotherapy and had weight gain more than median represented more relapse and death than those who had

Table 2: Fasting blood sugar and blood lipid profiles before the start of treatment in case and control groups

Variables	Mean±SD		*P*
	Cases (*n*=108)	Control (*n*=119)	
FBS	109.16±35.97	102.58±19.42	0.101‖
Cholesterol	202.38±58.22	203.56±44.97	0.869‖
LDL	117.80±42.92	120.62±35.31	0.605‖
HDL	50.16±16.76	51.43±13.28	0.545‖
TG	167.17±76.68	160.03±104.35	0.582‖

‖Resulted from independent *t*-test. FBS = Fasting blood sugar; LDL = Low-density lipoprotein; HDL = High-density lipoprotein; TG = Triglyceride; SD = Standard deviation

Table 3: Adjusted odds ratios of fasting blood sugar, lipid profile, and body mass index for metastasis and recurrence of breast cancer under logistic regression model

	AOR*	95% CI for AOR		*P*
		Lower	Upper	
FBS	1.00	0.98	1.02	0.870
Cholesterol	1.00	0.99	1.02	0.362
LDL	0.98	0.96	1.00	0.224
HDL	0.98	0.95	1.01	0.447
TG	1.00	0.99	1.00	0.334
BMI	0.99	0.92	1.07	0.893

*Adjusted for age and histopathology (luminal A and luminal B). TG = Triglyceride; FBS = Fasting blood sugar; LDL = Low-density lipoprotein; HDL = High-density lipoprotein; BMI = Body mass index; AOR = Adjusted odds ratio; CI = Confidence interval

weight gain less than the median.[18] In our research, BMI did not associate with BC recurrence or metastasis. The discordance between our results and the above studies may be due to the longer time of follow-up and analyzing the data according to menopausal status in those researches.

Lipid profile

In a study, high levels of LDL, TG, and total cholesterol were related to the higher incidence of BC. This association was not seen for very LDL and HDL.[19] In a cohort study, the lower levels of HDL at initial diagnosis were related to poor overall survival and disease-free survival in TNBC cases. This relation was not observed in non-TNBC patients.[5] In another study, BC patients with high levels of LDL-C at diagnosis had a higher differentiation grade, higher proliferative rate (assessed by Ki67 immunostaining), and more frequency of Her2-neu-positive feature and were more commonly diagnosed in advanced stages.[20] A case–control study in our country showed that Chol levels in BC patients were significantly higher than controls without BC.[21]

In the current study, there was no significant difference between the case and control groups in terms of lipid profile. This may be because our study was restricted to ER-positive ones (which have a better prognosis and less recurrence and metastasis[22]) and that triple-negative patients were excluded from our study. One of the above opposing studies has confined its samples to invasive ductal carcinoma; pathological features influence the outcome, and may be the reason for different results.[19]

FBS

According to one study, a high blood glucose level and BMI were correlated with increased mortality in ER/PR-positive BC patients.[23]

In another retrospective study, the overall survival decreased in advanced stages in BC patients with blood glucose of more than 130 mg/dl who received chemotherapy.[24] A systematic review and meta-analysis showed that BC patients with preexisting diabetes mellitus had less survival and were diagnosed in more advanced stages than their nondiabetic counterparts.[25]

In contrast to the mentioned studies, we found no association between FBS and BC outcomes. The explanation may include these facts: in one of the above opposing studies, only about half of the patients received chemotherapy, but in our study, all of the patients received chemotherapy and this may have led to better outcomes in our study.[23] The other one has limited its samples to metastatic patients (who we know have worse outcomes). Moreover, in that study, the average of FBS before and after chemotherapy was used to compare the study groups and we know that chemotherapy can change the blood glucose level.[24]

Strengths and limitations

The small sample size, retrospective nature of the study, lack of access to all components of MtS, and not recording the comorbidities of the patients were the weaknesses of our study. Gathering a large amount of data of our patients and the fact that demographic, clinical, and pathological variables were not significantly different between the case and control groups, are strengths of our study.

CONCLUSION

We found no association between lipid profile, FBS, and BMI at the initial diagnosis of BC with recurrence or metastasis.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. DeVita VT, Lawrence TS, Rosenberg SA. DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology. 11th ed. Philadelphia: Lippincott Williams & Wilkins (LWW); 2018.
2. Shamshirian A, Heydari K, Shams Z, Aref A, Shamshirian D, Tamtaji O, *et al*. Breast cancer risk factors in Iran: a systematic review & meta-analysis. Hormone Molecular Biology and Clinical Investigation 2020;41:20200021. https://doi.org/10.1515/hmbci-2020-0021.
3. Hayes DF, Lippman ME. Breast cancer. In: Jameson JF, Kasper DL, Hauser SL, Longo DL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. 20th ed. New York: McGraw-Hill; 2018.
4. Jung SM, Kang D, Guallar E, Yu J, Lee JE, Kim SW, *et al.* Impact of serum lipid on breast cancer recurrence. J Clin Med 2020;9:2846.
5. Fan Y, Ding X, Wang J, Ma F, Yuan P, Li Q, *et al.* Decreased serum HDL at initial diagnosis correlates with worse outcomes for triple-negative breast cancer but not non-TNBCs. Int J Biol Markers 2015;30:e200-7.
6. Bahl M, Ennis M, Tannock IF, Hux JE, Pritchard KI, Koo J, *et al.* Serum lipids and outcome of early-stage breast cancer: Results of a prospective cohort study. Breast Cancer Res Treat 2005;94:135-44.
7. Vona-Davis L, Howard-McNatt M, Rose DP. Adiposity, type 2 diabetes and the metabolic syndrome in breast cancer. Obes Rev 2007;8:395-408.
8. Hauner D, Hauner H. Metabolic syndrome and breast cancer: Is there a link? Breast Care (Basel) 2014;9:277-81.
9. Zhao P, Xia N, Zhang H, Deng T. The metabolic syndrome is a risk factor for breast cancer: A systematic review and meta-analysis. Obes Facts 2020;13:384-96.
10. Li P, Wang T, Zeng C, Yang M, Li G, Han J, *et al.* Association between metabolic syndrome and prognosis of breast cancer: A meta-analysis of follow-up studies. Diabetol Metab Syndr 2020;12:10.
11. Contiero P, Berrino F, Tagliabue G, Mastroianni A, Di Mauro MG, Fabiano S, *et al.* Fasting blood glucose and long-term prognosis of non-metastatic breast cancer: A cohort study. Breast Cancer Res Treat 2013;138:951-9.
12. Spiegelman D, Colditz GA, Hunter D, Hertzmark E. Validation of the Gail *et al.* Model for predicting individual breast cancer risk. J Natl Cancer Inst 1994;86:600-7.
13. Soliman NA, Yussif SM. Ki-67 as a prognostic marker according to breast cancer molecular subtype. Cancer Biol Med 2016;13:496-504.
14. Protani M, Coory M, Martin JH. Effect of obesity on survival of women with breast cancer: Systematic review and meta-analysis. Breast Cancer Res Treat 2010;123:627-35.
15. Oh SW, Park CY, Lee ES, Yoon YS, Lee ES, Park SS, *et al.* Adipokines, insulin resistance, metabolic syndrome, and breast cancer recurrence: A cohort study. Breast Cancer Res 2011;13:R34.
16. Tarimoradi M, Darehbagh RR, Babahajiani M, Ghaderi B. The relationship between metabolic syndrome and breast cancer in women referred to radiotherapy and chemotherapy clinics of Tohid hospital in Sanandaj. Iran J Breast Dis Sociol 2022;15:59-70.
17. Babaei Z, Moslemi D, Parsian H, Khafri S, Pouramir M, Mosapour A. Relationship of obesity with serum concentrations of leptin, CRP and IL-6 in breast cancer survivors. J Egypt Natl Canc Inst 2015;27:223-9.
18. Camoriano JK, Loprinzi CL, Ingle JN, Therneau TM, Krook JE, Veeder MH. Weight change in women treated with adjuvant therapy or observed following mastectomy for node-positive breast cancer. J Clin Oncol 1990;8:1327-34.
19. Kumar V, Singh A, Sidhu DS, Panag KM. A comparitive study to evaluate the role of serum lipid levels in aetiology of carcinoma breast. J Clin Diagn Res 2015;9:C01-3.
20. Rodrigues Dos Santos C, Fonseca I, Dias S, Mendes de Almeida JC. Plasma level of LDL-cholesterol at diagnosis is a predictor factor of breast tumor progression. BMC Cancer 2014;14:132.
21. Fadaeipuor S, Babaei Z, Parsian H, Ardekani AM, Nikbakhsh N. Comparison of the serum total bile acids and cholesterol levels in breast cancer patients with control group. J Babol Univ Med Sci 2016;18:48-53.
22. Abeloff MD, Armitage JO, Niederhuber JE, Kastan MB, McKenna WG. Abeloff's Clinical Oncology E-Book. Philadelphia: Elsevier Health Sciences; 2008.
23. Minicozzi P, Berrino F, Sebastiani F, Falcini F, Vattiato R, Cioccoloni F, *et al.* High fasting blood glucose and obesity significantly and independently increase risk of breast cancer death in hormone receptor-positive disease. Eur J Cancer 2013;49:3881-8.
24. Villarreal-Garza C, Shaw-Dulin R, Lara-Medina F, Bacon L, Rivera D, Urzua L, *et al.* Impact of diabetes and hyperglycemia on survival in advanced breast cancer patients. Exp Diabetes Res 2012;2012:732027.
25. Peairs KS, Barone BB, Snyder CF, Yeh HC, Stein KB, Derr RL, *et al.* Diabetes mellitus and breast cancer outcomes: A systematic review and meta-analysis. J Clin Oncol 2011;29:40-6.