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Hepatosteatosis may predict late recurrence of breast cancer: A single-center observational study

Tulay Kus[a,*], Havva Yesil Cinkir[b], Gokmen Aktas[c], Huseyin Abali[d]

[a] Adıyaman University, Training and Research Hospital, Clinics of Medical Oncology, Adıyaman, Turkey
[b] Gaziantep University, School of Medicine, Department of Medical Oncology, Gaziantep, Turkey
[c] Kahramanmaras Sütçü İmam University, School of Medicine, Department of Medical Oncology, Kahramanmaraş, Turkey
[d] King Hamad Hematology-Oncology Center, Department of Medical Oncology, Bahrain

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ABSTRACT

Aim: The positive energy balance and insulin resistance caused by weight gain, physical inactivity, poor dietary quality are linked to a decreased breast cancer (BC)-specific survival. The aim of the present study was to assess whether or not hepatosteatosis, which reflect underlying insulin resistance, has a predictive value on recurrence in patients with nonmetastatic BC.

Material method: All diagnosed nonmetastatic BC patients between 2005 and 2016 were included in this retrospective analysis. Patients' medical characteristics included for analysis were age, menopausal status, presence of obesity, diabetes, dyslipidemia, and tumor features. Liver parenchyma was evaluated by ultrasonography, and then patients divided into 2 groups according to final follow-up findings; group 1: without hepatosteatosis or presence of grade 1 steatosis; group 2: presence of grades 2 and 3 hepatosteatosis. Survival distributions were estimated with the Kaplan-Meier method and compared between groups with the log-rank statistic.

Results: Four hundred twenty-four patients included in this study. The median follow-up period of all patients was 6.7

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* Correspondence to: Tulay Kus, Adıyaman University, Training and Research Hospital, Department of Medical Oncology, 1164. Sreet, Adıyaman, TR-02040 Adıyaman, Turkey.
E-mail address: drtulaykus83@hotmail.com (T. Kus).

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years (range, 0.6-13 years). The mean age was 48.2 ± 0.5 years. Of total, 154 (36.3%) patients experienced recurrence. In total, 171 (40.6%) patients had grades 2 and 3 hepatosteatosis, and the remaining had no, or grade 1 hepatosteatosis during last follow-up or at recurrence. The clinicopathologic characteristics of the participants were well balanced between the 2 groups. Younger age (odds ratio [OR]: 2.19; 95% confidence interval [CI]: 1.3-3.8, $P = 0.005$), and higher tumor stage (OR: 7.52; 95% CI: 1.2-48.5, $P = 0.035$ for stage Ia vs stage IIIC) were associated with recurrence of BC during the entire follow-up in multivariate analysis. Hepatosteatosis predicted late recurrence after 5 years in nonmetastatic BC after adjusted for age, diabetes, tumor stage, grade, and luminal type (OR: 2.45; 95% CI: 1.1-5.6, $P = 0.034$) and the hazard ratio was 0.40 (95% CI: 0.18-0.88, $P = 0.023$ adjusted value) for relapse-free survival after 5 years.
Conclusion: Higher degree of hepatosteatosis may predict recurrence after 5 years in BC survivors.

Introduction

Hepatosteatosis (fatty liver) is a very common disease worldwide, which is easily diagnosed with ultrasonography. Obesity and insulin resistance are 2 major risk factors for fatty liver except for the patients with heavy alcohol consumption and hepatitis C. Although the underlying mechanism of hepatosteatosis is not fully clarified, the chronic low-grade inflammatory state accompanying obesity, and the increased levels of leptin, which is a proinflammatory and proangiogenic cytokine, can lead to accumulation of fat in the liver.[1] Cholesterol overload in the liver leads to oxidative distress and mitochondrial changes, which may render damaged hepatocytes proliferative and resistant to cell death named as apopitosis.[2] In addition to obesity, hyperinsulinemia and insulin-like growth factor (IGF) may promote the development of cancer by activating inflammation, oxidative stress, and various oncogenic pathways.[3] Weight loss, increasing physical activity, and choosing a healthy diet are among the recommendations to reverse hepatosteatosis and insulin resistance. Thus, existence of fatty liver may reflect the unhealthy lifestyle or insulin resistance and can allow the clinician to be alert to question the etiologic causes of fatty liver during follow-up of cancer survivors.

For patients with newly diagnosed, nonmetastatic breast cancer, the following clinicopathologic features have been classically used to determine prognosis in routine practice; age, tumor size, nodal involvement, tumor morphology, histologic grade, peritumoral lymphovascular invasion (LVI), tissue markers, including estrogen receptor and progesterone receptor status, human epidermal growth factor receptor-2 (HER2) status, and luminal subtypes.[4,5] Additionally, a growing body of evidence suggests that energy balance is also strongly associated with increasing risk of developing breast cancer. A positive energy balance caused by weight gain, physical inactivity, poor dietary quality, and the metabolic syndrome, also known as insulin resistance syndrome, is linked to decreased overall and cancer-specific survival in patients with breast cancer at diagnosis.[6-10] On the other hand, it is a big question whether making lifestyle changes after diagnosis improves breast cancer outcomes or no. Although some evidence suggests that dietary modifications, weight loss, and increased physical activity can improve breast cancer outcomes, there have been inconsistent results, and no strong evidence is available.[11,12] We think that assessment of lifestyle changes items as a whole is hard for a long term and evaluation parameter is lacking about this matter. Hepatosteatosis can be a tool that warns the physician by reflecting the unhealthy lifestyle or pathologies underlying insulin resistance. Effect of traditional prog-

nostic parameters on recurrence of BC is generally excepted to be predominantly in early period while lifestyle changes may have effect on late recurrence. In this regard, we hypothesize that the presence of hepatosteatosis, which can be a tool for indicating the unhealthy lifestyle status, may predict the late recurrence of breast cancer.

Materials and methods

Study design

This was a single-center retrospective study at Gaziantep University Hospital in Turkey. It was approved by the Institutional Ethics Committee and conducted in compliance with the ethical principles according to the Declaration of Helsinki.

Primary aim of the study was to identify the predictive impact of hepatosteatosis on the recurrence-free survival and disease recurrence rate in nonmetastatic breast cancer.

Its secondary end-point was to evaluate effect of the parameters on recurrence-free survival and disease recurrence rate after 5 years in nonmetastatic breast cancer.

Patients and treatments

All newly diagnosed nonmetastatic and operated breast cancer patients between December 2005 and December 2016 at the Gaziantep University were included in this retrospective analysis. We excluded patients with metastatic disease or any other malignancy. We included patients who were treated with neoadjuvant or adjuvant chemotherapy, but all patients underwent surgery. Patient's clinicopathologic data were recorded. The study involved the patients in pathologic stages Ia to IIIc according to the eighth edition of American Joint Committee on Cancer Tumor-Node-Metastasis classification. The clinical features analyzed were age, menopausal status, presence of obesity, diabetes and hyperlipidemia, tumor features, including histologic type; nuclear grade, estrogen and progesterone receptors, HER2 overexpression, stage, luminal types, LVI, and perineural invasion. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2) at diagnosis, and patients were classified into 2 categories: BMI $<$30.0 kg/m^2 and BMI $\geq$30.0 kg/m^2, which was categorized as obese. As there are many causes for hepatic steatosis other than lifestyle, the most common etiologic causes such as diabetes, dyslipidemia, and hepatitis C were also clarified and analyzed during follow-up. Four cycles of anthracyclines followed by taxanes with or without 5-fluorouracil/carboplatin were the chemotherapy regimen administered in most of the patients according to their stage and pathologic subtypes. Anti-HER2 and endocrine therapies were added to chemotherapy if indicated. All patients were in remission when they completed their adjuvant chemotherapy. Forty-three of patients (10.1%) were treated only endocrine therapy. Patients were followed up every 3 months for first 2 years, then every 6 months up to 5 years, then annually with ultrasonography. Liver parenchyma was evaluated by ultrasonography. Patients were divided into 2 groups according to final follow-up findings; group 1: without hepatosteatosis, or presence of grade 1 steatosis; group 2: presence of grade 2 or 3 hepatic steatosis. Because ultrasonography is operator dependent and degree of steatosis may be changeable, we evaluated the average of last 3 ultrasonography finding to assess degree of hepatosteatosis and assessed under 2 categories (0-1 vs 2-3).

Statistics

Clinical characteristics were compared between grades 2 and 3 hepatosteatosis group and grade 1 hepatosteatosis and without hepatosteatosis groups with the chi-square test. Quantitative variables were described as means with standard deviation), while qualitative variables were summarized as frequencies with proportions. Median follow-up was calculated as the median observation time among all patients. Recurrence-free survival was calculated from the start

of treatment to the date of disease recurrence or last follow-up. Survival distributions were estimated with the Kaplan-Meier method and compared between groups with the log-rank statistic for group of hepatosteatosis.

All parameters were assessed by binary logistic regression analysis to predict the patients who have experienced recurrence for any time and after 5 years recurrence. Then, all potential predictive factors with a probability value of <0.10 on univariate analyses were included in the multivariate binary logistic regression analysis.

P values of less than or equal to 0.05 were considered statistically significant and statistical analyses were carried out using the statistical software package SPSS 22.0.

Results

Four hundred twenty-four patients included in this study. Median follow-up among all patients was 6.7 years (range, 0.6-13 years). The mean age was 48.2 ± 0.5 years. Among all patients, 154 patients (36%) were in stage III, 149 patients (35.1%) had obesity, 19 patients (4.7%) had diabetes, and 28 patients (6.6%) had hyperlipidemia. Of total, 154 (36.3%) patients have experienced recurrence. Of the 424 patients included in this analysis, 171 (40.6%) patients had grades 2 and 3 hepatosteatosis and remaining had no, or grade 1 hepatosteatosis at the last follow-up or at recurrence time. The clinical and pathologic characteristics of the participants were well balanced between the 2 groups (Table 1). Previous breast cancer therapies were comparable in 2 groups. As chemotherapy and endocrine therapies may have a role on hepatosteatosis, these therapies were well balanced between 2 groups. As expected, incidence of obesity at diagnosis and diabetes at last follow-up were higher in patients with high-grade hepatosteatosis.

Estimates of the cumulative and beyond 5 years rates of recurrence by clinical and pathologic parameters of patients according to hepatosteatosis grade are shown in Table 2. The cumulative incidence and incidence of recurrence after 5 years curves are shown in Figures 1 and 2, respectively. While younger age (<40 vs ≥ 40), higher tumor grade, and stage, presence of LVI, presence of diabetes, and higher hepatosteatosis grades affected the cumulative recurrence rate in univariate analysis, younger age (odds ratio [OR]: 2.19; 95% confidence interval [CI]: 1.3-3.8, $P = 0.005$) and higher tumor stage (when we evaluated that stage 1a disease was as reference, OR was 1.21, 1.57, 2.37, 2.98, 6.05, and 7.52 for stage 1b, 2a, 2b, 3a, 3b, and 3c, respectively, and OR was 7.52; 95% CI: 1.2-48.5 for stage 1a vs stage 3c, $P = 0.034$) were independent predictive parameters in multivariate logistic regression model. When the recurrence rate after 5 years was analyzed; among all clinicopathologic parameters, only hepatosteatosis was found to be associated with higher recurrence rate in univariate analysis (OR: 2.18; 95% CI: 1.0-4.7, $P = 0.049$) and after adjusted for diabetes, age, tumor grade, stage, and luminal types (OR: 2.45; 95% CI: 1.1-5.6, $P = 0.034$).

For relapse-free survival—the primary endpoint—the hazard ratio of an event in without hepatosteatosis and grade 1 hepatosteatosis group compared with grades 2 and 3 hepatosteatosis group was 0.85 (95% CI: 0.60-1.19; Fig 1, $P = 0.85$ for adjusted Cox model analysis). The influence of hepatosteatosis was examined based on age, tumor grade, stage, luminal types, and diabetes by using adjusted Cox model.

For relapse-free survival after 5 years—the secondary endpoint—the hazard ratio of an event in without hepatosteatosis and grade 1 hepatosteatosis group compared with the grades 2 and 3 hepatosteatosis group was 0.40 (95% CI: 0.18-0.88; Fig 2, $P = 0.023$ for adjusted Cox model analysis). The influence of hepatosteatosis was analyzed based on age, tumor grade, stage, luminal types, and diabetes by using adjusted Cox model.

Discussion

The aim of the present study was to assess whether the hepatosteatosis have a predictive value on recurrence in patients with nonmetastatic breast cancer. We revealed that while

Table 1
Patients' demographic and clinicopathologic features.

Parameters	Grades 2 and 3 hepatosteatosis*N* (%)	Without hepatosteatosis or grade 1*N* (%)	*P*
Age			
<40	38 (22.1)	70 (28.2)	0.16
≥40	134 (77.9)	178 (71.8)	
Menopausal status			
Premenopausal	87 (50.6)	135 (54.9)	0.38
Postmenopausal	85 (49.4)	111 (45.1)	
ER			
Positive	132 (76.7)	180 (72.6)	0.33
Negative	40 (23.3)	68 (27.4)	
PR			
Positive	126 (73.3)	171 (69.0)	0.34
Negative	46 (26.7)	77 (31.0)	
HER2			
Positive	46 (26.7)	71 (28.6)	0.67
Negative	126 (73.3)	177 (71.4)	
Histologic grade			
1	12 (7.0)	22 (8.9)	0.71
2	87 (50.6)	128 (51.6)	
3	73 (42.4)	98 (39.5)	
Genotype			
Luminal A	51 (29.7)	67 (27.0)	0.80
Luminal B	64 (37.2)	86 (34.7)	
Luminal B HER2+	33 (19.2)	57 (23.0)	
HER2+	12 (7.0)	16 (6.5)	
Triple negative	12 (7.0)	22 (8.9)	
Pathologic subtype			
IDC	157 (91.3)	229 (92.3)	0.58
ILC	7 (4.1)	12 (4.8)	
Other	8 (4.7)	7 (2.8)	
LVI			
Presence	36 (45.6)	57 (48.7)	0.67
Absence	43 (54.4)	60 (51.3)	
PNI			
Presence	7 (9.0)	17 (14.9)	0.22
Absence	71 (91.0)	97 (85.1)	
Stage*			
1a	7 (4.1)	13 (5.2)	0.44
1b	25 (14.5)	47 (19.0)	
2a	54 (31.4)	56 (22.6)	
2b	24 (14.0)	40 (16.1)	
3a	15 (8.7)	29 (11.7)	
3b	38 (22.1)	52 (21.0)	
3c	9 (5.2)	11 (4.4)	
Chemotherapy			
Received	157 (91.8)	218 (88.3)	0.24
None	14 (8.2)	29 (11.7)	
Endocrine therapy			
Tamoxifen	32 (18.6)	52 (21.0)	0.25
Tamoxifen + LHRH	29 (16.9)	55 (22.2)	
Tamoxifen then AI	40 (23.3)	45 (18.1)	
AI	56 (32.6)	66 (26.6)	
Triple negative	15 (8.7)	30 (11.1)	
Diabetes			
Present	18 (10.5)	1 (0.4)	*<0.001*
Absent	154 (89.5)	247 (99.6)	
Obesity (BMI)			
<30	62 (44.0)	129 (64.2)	*<0.001*
≥30	79 (56.0)	72 (35.8)	
Hyperlipidemia			
Present	14 (10.7)	14 (8.1)	0.45
Absent	117 (89.3)	158 (91.9)	

AI, aromatase inhibitör; BMI, body mass index; CI, confidence interval; ER, estrogen receptor, HR, hazard ratio; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LHRH, luteinizing hormone-releasing hormone receptor agonist; LVI, lymphovascular invasion; PNI, perineural invasion; PR, progesterone receptor.

* According to eighth version American Joint Committee on Cancer (AJCC) TNM staging system.

Table 2
Relationship of patients' clinicopathologic features and recurrence rate.

	Total recurrence rates Univariate analysis		Multivariate analysis		Recurrence rate after 5 years Univariate analysis	*P*
Parameters	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	
Age						
<40	*1.92 (1.2-3.0)*	*0.004*	*2.19 (1.3-3.8)*	*0.005*	1.61 (0.7-3.7)	0.27
≥40	*1 (ref)*		*1 (ref)*		1 (ref)	
Menopausal status						
Premenopausal	1.24 (0.8-1.9)	0.30			1.56 (0.7-3.4)	0.26
Postmenopausal	1 (ref)				1 (ref)	
ER						
Positive	1 (ref)	0.51			1 (ref)	0.29
Negative	1.16 (0.7-1.8)				1.57 (0.7-3.6)	
PR						
Positive	1 (ref)	0.96			1.06 (0.5-2.4)	0.89
Negative	1.01 (0.7-1.6)				1 (ref)	
HER2						
Positive	1 (ref)	0.95			1 (ref)	0.48
Negative	1.01 (0.7-1.6)				1.38 (0.57-3.4)	
Histologic grade						
1	*1 (ref)*	*0.37*	1 (ref)	0.08	1 (ref)	0.65
2	*2.67 (1.1-6.7)*	*0.03*	0.69 (0.2-2.1)		1.8 (0.4-8.3)	
3	*2.81 (1.1-7.2)*		1.66 (0.9-2.9)		1.3 (0.3-6.5)	
Genotype						
Luminal A	1 (ref)	0.72			1 (ref)	0.92
Luminal B	0.91 (0.6-1.5)	0.82			0.93 (0.4-2.4)	
Luminal B HER2+	1.07 (0.6-1.9)	0.71			0.7 (0.2-2.1)	
HER2+	0.85 (0.6-2.0)	0.79			0.96 (0.2-4.9)	
Triple negative	1.11 (0.5-2.4)				1.44 (0.3-5.9)	
Pathologic subtype	1.64 (0.4-6.6)	0.49				
IDC	1 (ref)					
ILC						
Other						
LVI						
Absent	1 (ref)	0.02[†]			1 (ref)	0.92
Present	2.00 (1.11-3.61)				1.06 (0.3-3.3)	
PNI						
Absent	1 (ref)	0.46			1 (ref)	0.52
Present	0.70 (0.27-1.79)				0.50 (0.1-4.1)	
Stage[*]						
1a	1 (ref)	0.23	*1 (ref)*	*088*	1 (ref)	0.77
1b	2.57 (0.5-12.3)	0.11	*1.21 (0.2-6.4)*	*0.58*	1.6 (0.2-14.4)	
2a	3.44 (0.7-15.7)	0.09	*1.57 (0.3-7.9)*	*0.31*	1.6 (0.2-14.1)	
2b	3.80 (0.8-18.0)	*0.019*	*2.37 (0.5-12.6)*	*0.21*	2.2 (0.2-20.0)	
3a	*6.58 (1.4-31.8)*	*0.002*	*2.98 (0.5-16.7)*	*0.028*	3.8 (0.4-37.3)	
3b	*11.3 (2.5-51.4)*	*0.002*	*6.05 (1.2-30.1)*	*0.034*	3.02 (0.3-26.6)	
3c	*14.6 (2.7-80.5)*		*7.52 (1.2-48.5)*		2.7 (0.1-49.7)	
Hepatosteatosis						
Without or grade 1	*1 (ref)*	*0.048*	1 (ref)	0.12	1 (ref)	*0.049*
Grade 2 or 3	*1.50 (1.0-2.3)*		1.49 (0.9-2,5)		2.18 (1.0-4.7)	*0.034*
Hepatosteatosis[*]					1 (ref)	
Without or grade 1 grade 2 or 3					2.45 (1.1-5.6)	
Diabetes						
Absent	*1 (ref)*	*0.012*	1 (ref)	0.098	1 (ref)	0.92
Present	*3.38 (1.3-8.8)*		2.68 (0.8-8.6)		1.1 (0.1-9.4)	
Obesity (BMI)						
<30	1 (ref)	0.51			1 (ref)	0.27
≥30	0.86 (0.6-1.4)				1.65 (0.7-4.1)	

BMI, body mass index; CI, confidence interval; ER, estrogen receptor, IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LVI, lymphovascular invasion; OR, odds ratio; PNI, perineural invasion; PR, progesterone receptor.

[*] adjusted for diabetes, age, tumor grade, and stage.

[†] PNI was not included in multivariate analysis due to lack of information of almost half of patients.

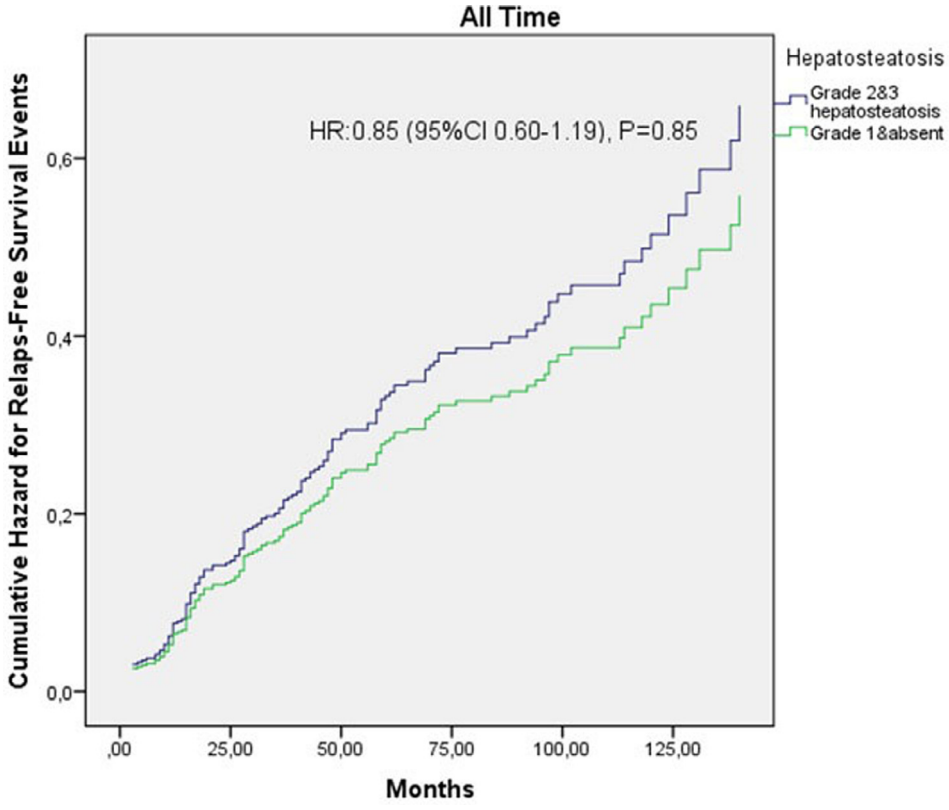

Fig. 1. Kaplan-Meier estimates of relapse-free survival for all time. Hazard ratio (HR) and 95% confidence interval (CI) were calculated from adjusted Cox proportional hazard model comparisons of grades 2 and 3 hepatosteatosis to absent and grade1 hepatosteatosis adjusted for age, stage, tumor grade, luminal types, and diabetes.

younger age, and higher tumor stage were associated with recurrence of breast cancer for whole follow-up period in multivariate analysis, only hepatosteatosis predicted the recurrence after 5 years in nonmetastatic breast cancer. Hepatosteatosis mostly reflects the pathologies underlying the insulin resistance after excluding diseases specific to liver. Insulin resistance, a signature characteristic of metabolic syndrome, has been associated with a poorer survival in cancer.[13] Elevated insulin can cause decreased levels of IGF-binding proteins and increased IGF-I synthesis, which regulates cellular growth. Thus the phosphatidylinositol 3′-kinase and mitogen activated protein kinase pathways are induced and eventually result in inhibition of apoptosis.[14] Goodwin et al indicated that the recurrence risk of breast cancer in patients with higher fasting insulin levels was increased when compared to the lowest.[15] Additionally, other metabolic hormones, such as adipokines leptin and adiponectin, and presence of diabetes have been found to be associated with poor outcomes in patients with early-stage breast cancer.[15,16] A growing evidence suggested that obesity and positive energy balance which are the most significant causes of insulin resistance have been linked to outcomes in several cancers, including breast, endometrial, prostate, and colorectal cancer at diagnosis.[17] Although most research focused on the impact of lifestyle modification at the time of cancer diagnosis, only a few studies evaluated this effect in the follow-up period. We hypothesized that degree of hepatosteatosis in the final follow-up of patients can reflect the lifestyle of survivors, since hepatosteatosis is related to many parameters, including dietary content (heavy fat and carbohydrate diet), physical inactivity, obesity, and diabetes. The present study, severity of hepatosteatosis in the final

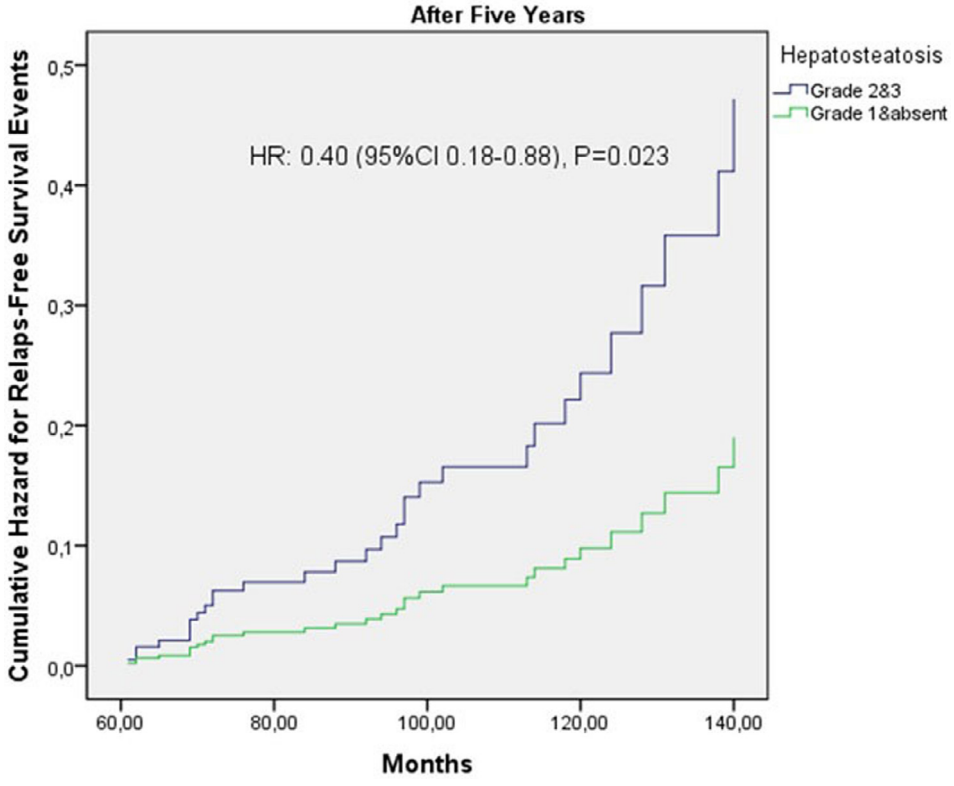

Fig. 2. Kaplan-Meier estimates of relapse-free survival for after 5 years follow-up period. Hazard ratio (HR) and 95% confidence interval (CI) were calculated from adjusted Cox proportional hazard model comparisons of grades 2 and 3 hepatosteatosis to absent and grade1 hepatosteatosis adjusted for age, stage, tumor grade, luminal types, and diabetes.

follow-up was found to be related to the recurrence after 5 years in early-breast cancer after adjusted for age, diabetes, tumor stage, and grade. (OR: 2.45; 95% CI: 1.1-5.6, $P = 0.034$). It can be speculated that lifestyle changes may be more effective for late period recurrence of breast cancer.

There have been some studies separately assessing relationship between lifestyle changes, including weight loss, calorie or fat restriction, physical activity, and cancer-specific survival. Restriction of calories has been shown to decrease the cell proliferation and increase the apoptosis by antiangiogenic processes.[17] WINS is the first large-scale randomized trial to evaluating whether a dietary intervention can improve the clinical outcome of patients with breast cancer. The WINS results indicated that a lifestyle intervention designed to reduce dietary fat intake improved the recurrence-free survival in early stage breast cancer for the first 5 years (hazard ratio: 0.76; 95% CI: 0.60-0.98, $P=0.034$ for adjusted Cox model analysis).[18] On the other hand, the adoption of a diet with a high percentage of vegetables, fruits, fiber, and low fat in the WHEL study did not improve cancer-specific survival in patients with early breast cancer during a 7.3-year follow-up period.[19] When we evaluated these 2 large-scale studies, it can be concluded that the independent effect of energy intake on cancer-specific survival may be difficult to evaluate because obesity, diabetes and other metabolic syndrome parameters and physical activity may an impact on breast cancer outcome.

Obesity at diagnosis has been found to be a risk factor for the development of new cases of breast cancer, worse outcome, and a higher risk of recurrence.[20] According to a meta-

analysis, relative risk of total mortality was 1.75 (95% CI: 1.26-2.41) for premenopausal and 1.34 (95% CI: 1.18-1.53) for postmenopausal breast cancer.[21] There are few studies showing the relationship between weight loss after breast cancer diagnosis and disease outcomes. However, the effect of weight gain following diagnosis or weight loss on outcomes have not been defined very well and there is no evidence that weight loss after diagnosis improves survival.[22]

Physical activity, one of the other lifestyle changes, provides a decrease in fat stores, free radical generation, insulin and IGF-I levels and inflammation, and has effects on immune function positively and provides recovery on hepatosteatosis.[17] A large prospective cohort study found that women who engaged in physical activity after the diagnosis of breast cancer may reduce the risk of death from cancer with the greatest benefit in patients with hormone positive tumor (hazard ratio: 0.50; 95% CI: 0.34-0.74).[23] The another prospective cohort study assessed the influence of physical activity on survival in both early and late postdiagnostic periods. It was shown that physical activity has a significant benefit on survival regardless of the interval since breast cancer diagnosis.[24] A recently published meta-analysis showed that physical activity after cancer diagnosis was associated with a 24% reduced risk of total mortality among breast cancer survivors independent from BMI, menopausal status, and hormone receptor positive and negative tumors.[25] This effect has been attributed to the impact of physical activity on decreasing insulin resistance. On the other hand, possible benefit improved dietary intake and weight loss on breast cancer outcome were not explored in these analysis.

When we evaluated all the studies assessing the effect of lifestyle changes after diagnosis on breast cancer-specific survival, they could not reflect to lifestyle changes as a whole. Actually, all efforts to change all lifestyle parameters aim to break insulin resistance that also affecting hepatosteatosis. An ongoing study called BWEL (Alliance A011401) study was designed to evaluate the combined effect of weight loss, calorie intake, and physical activity on breast cancer survival and is expected to be finalized forthcoming few years.[26] Perhaps, this study may answer the question of whether the integration of combining of lifestyle changes has an impact on breast cancer outcome.

The question of whether combination of all lifestyle interventions, including weight loss, diet interventions, and physical activity, should be adapted to the adjuvant treatment recommendations of breast cancer is the unanswered. These interventions have been studied separately before, however, there are no study evaluating combination of all lifestyle changes due to the difficulty of evaluation. Thus, we need a tool such as biomarkers of insulin resistance or hepatosteatosis probably reflecting to wrong lifestyle of patients. Most of the studies about lifestyle changes included the patients with early breast cancer and follow-up duration was mostly limited up to 5 years. In the present study, one-third of the patients were stage III, and median follow-up was 6.7 years. We indicated that while age and stage were important parameters for higher recurrence rate any all time as expected, grades 2 and 3 hepatosteatosis predicted the higher recurrence of breast cancer and longer recurrence-free survival after 5 years even after adjusted for diabetes, age, stage, grade, luminal types. We found a 60% reduction risk of relapse in patients without hepatosteatosis or grade 1 hepatosteatosis compared with the grades 2 and 3 hepatosteatosis after adjusted for other parameters for after 5 years follow-up (hazard ratio: 0.40; 95% CI: 0.18-0.88). Considering that favorable lifestyle changes have been recommended to downgrade degree of hepatosteatosis to lower grade, assessment of hepatosteatosis can be used as a biomarker of lifestyle as a whole. As it is known, patients with invasive lobular carcinoma and hormone positive tumor present with late recurrence, lifestyle changes may have an impact on late period of breast cancer recurrence according to the results of this study.

Limitations of our study are to be designed as retrospective and to have relatively low number of patients. However, we included in study the patients with all stage and pathologic features of nonmetastatic breast cancer and attracted attention to significance of existing hepatosteatosis, as a tool, on late recurrence of breast cancer. Hepatosteatosis may be a predictor for the late recurrence of breast cancer and the present study may pave the way of designing new prospective studies with validated scanning method.

Conclusion

Our study showed that patients with nonmetastatic breast cancer who have higher degree of hepatosteatosis presented with increased risk of recurrence after 5 years. We believe that hepatosteatosis reflecting underlying insulin resistance or unfavorable lifestyle can represent a future biomarker, which may help to select patients in need of lifestyle modifications.

References

1. Piscaglia F, Svegliati-Baroni G, Barchetti A, et al. Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: a multicenter prospective study. *Hepatology*. 2016;63:827–838. doi:10.1002/hep.28368. Epub 2016 Jan 14.
2. Domínguez-Pérez M, Simoni-Nieves A, Rosales P, et al. Cholesterol burden in the liver induces mitochondrial dynamic changes and resistance to apoptosis. *J Cell Physiol*. 2018. doi:10.1002/jcp.27474.
3. Chettouh H, Lequoy M, Fartoux L, Vigouroux C, Desbois-Mouthon C. Hyperinsulinaemia and insulin signalling in the pathogenesis and the clinical course of hepatocellular carcinoma. *Liver Int*. 2015;35:2203–2217. doi:10.1111/liv.12903. Epub 2015 Jul 23.
4. Voduc KD, Cheang MC, Tyldesley S, Gelmon K, Nielsen TO, Kennecke H. Breast cancer subtypes and the risk of local and regional relapse. *J Clin Oncol*. 2010;28:1684–1691. doi:10.1200/JCO.2009.24.9284. Epub 2010 Mar 1.
5. Anders CK, Hsu DS, Broadwater G, et al. Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with shared patterns of gene expression. *J Clin Oncol*. 2008;26:3324. doi:10.1200/JCO.2007.14.2471.
6. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. *JAMA*. 2005;293:2479–2486. doi:10.1001/jama.293.20.2479.
7. Chlebowski RT, Aiello E, McTiernan A. Weight loss in breast cancer patient management. *J Clin Oncol*. 2002;20:1128–1143. doi:10.1200/JCO.2002.20.4.1128.
8. Holick CN, Newcomb PA, Trentham-Dietz A, et al. Physical activity and survival after diagnosis of invasive breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2008;17:379–386. doi:10.1158/1055-9965.EPI-07-0771. Epub 2008 Feb 4.
9. Cespedes Feliciano EM, Kroenke CH, Meyerhardt JA, et al. Metabolic dysfunction, obesity, and survival among patients with early-stage colorectal cancer. *J Clin Oncol*. 2016;34:3664–3671. doi:10.1200/JCO.2016.67.4473.
10. Chlebowski RT, Blackburn GL, Thomson CA, et al. Dietary fat reduction and breast cancer outcome: interim efficacy results from the Women's Intervention Nutrition Study. *J Natl Cancer Inst*. 2006;98:1767–1776. doi: 10.1093/jnci/djj494.
11. Schwedhelm C, Boeing H, Hoffmann G, Aleksandrova K, Schwingshackl L. Effect of diet on mortality and cancer recurrence among cancer survivors: a systematic review and meta-analysis of cohort studies. *Nutr Rev*. 2016;74:737–748. doi:10.1093/nutrit/nuw045.
12. Pierce JP, Natarajan L, Caan BJ, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. *JAMA*. 2007;298:289–298. doi:10.1001/jama.298.3.289.
13. Perseghin G, Calori G, Lattuada G, et al. Insulin resistance/hyperinsulinemia and cancer mortality: the Cremona study at the 15th year of follow-up. *Acta Diabetol*. 2012;49:421–428. doi:10.1007/s00592-011-0361-2. Epub 2012 Jan 4.
14. Gallagher EJ, LeRoith D. The proliferating role of insulin and insulin-like growth factors in cancer. *Trends Endocrinol Metab*. 2010;21:610–618. doi:10.1016/j.tem.2010.06.007. Epub 2010 Jul 19.
15. Goodwin PJ, Ennis M, Pritchard KI, et al. Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. *J Clin Oncol*. 2002;20:42–51. doi:10.1200/JCO.2002.20.1.42.
16. Chen DC, Chung YF, Yeh YT, et al. Serum adiponectin and leptin levels in Taiwanese breast cancer patients. *Cancer Lett*. 2006;237:109–114. doi:10.1016/j.canlet.2005.05.047.
17. Fair AM, Montgomery K. Energy balance, physical activity, and cancer risk. *Methods Mol Biol*. 2009;472:57–88. doi:10.1007/978-1-60327-492-0_3.
18. Chlebowski RT, Blackburn GL, Thomson CA, et al. Dietary fat reduction and breast cancer outcome: interim efficacy results from the Women's Intervention Nutrition Study. *J Natl Cancer Inst*. 2006;98:1767–1776. doi: 10.1093/jnci/djj494.
19. Pierce JP, Natarajan L, Caan BJ, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. *JAMA*. 2007;298:289–298.
20. 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;123:627–635. doi:10.1007/s10549-010-0990-0.
21. Chan DS, Vieira AR, Aune D, et al. Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. *Ann Oncol*. 2014;25:1901–1914. doi:10.1093/annonc/mdu042.
22. Caan BJ, Emond JA, Natarajan L, et al. Post-diagnosis weight gain and breast cancer recurrence in women with early stage breast cancer. *Breast Cancer Res Treat*. 2006;99:47–57. doi:10.1007/s10549-006-9179-y.
23. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. *JAMA*. 2005;293:2479–2486. doi:10.1001/jama.293.20.2479.
24. Holick CN, Newcomb PA, Trentham-Dietz A, et al. Physical activity and survival after diagnosis of invasive breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2008;17:379–386. doi:10.1158/1055-9965.EPI-07-0771.
25. Schmid D, Leitzmann MF. Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis. *Ann Oncol*. 2014;25:1293–1311. doi: 10.1093/annonc/mdu012.
26. Ligibel JA, Barry WT, Alfano C, et al. Randomized phase III trial evaluating the role of weight loss in adjuvant treatment of overweight and obese women with early breast cancer (Alliance A011401): study design. *NPJ Breast Cancer*. 2017;3:37. doi:10.1038/s41523-017-0040-8. eCollection 2017.