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ORIGINAL ARTICLE

Association between tamoxifen treatment and the development of different stages of nonalcoholic fatty liver disease among breast cancer patients

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Background/Purpose: For estrogen-receptor positive breast cancer cases, tamoxifen has been the most important adjuvant hormonal therapy for the purpose of reducing recurrence rates and prolonging disease free survival. However, several side effects have been noticed, and fatty liver is one of the most common side effects among them. Since fatty liver is a common problem in the general population, we wanted to examine the effects of tamoxifen under pre-existing fatty liver conditions and evaluate the prevalence of tamoxifen-related impaired liver function.
Methods: We recruited breast cancer cases at ages 20–70 years and divided them into tamoxifen or control groups. Personal information was collected, and fasting blood tests and abdominal ultrasound were performed. The changes of fatty liver degree between the initial and follow-up ultrasound were divided into five categories.
Results: Of the 406 enrolled participants, 266 were in the tamoxifen group and 140 were in the control group. The tamoxifen group had a higher risk of newly developed fatty liver [hazard ratio (HR) = 3.69; 95% confidence interval (CI) 1.67–8.13), lower rate of improved fatty liver (HR = 0.33; 95% CI 0.15–0.75), and higher rate of worsened fatty liver (HR = 2.11; 95% CI 1.02–4.35).
Conclusion: The current study suggests that tamoxifen treatment is associated with the risk of fatty liver either by increasing the risk of newly developed fatty liver conditions or worsening previous fatty liver conditions, and even retarding fatty liver improvement.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.
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Introduction

Breast cancer has emerged as the most common female malignancy in Taiwan since 2003. According to the statistics of the Department of Health in Taiwan, the incidence of breast cancer was 59.9/100,000 women in 2009.[1,2] Tamoxifen was approved by the Food and Drug Administration of the USA in 1977 as an adjuvant hormonal therapy for estrogen-receptor-positive (ER positive) breast cancer patients.[3] As tamoxifen is inexpensive and well-tolerated, it became the first line of adjuvant hormonal therapy. According to meta-analysis, consecutive 5-year tamoxifen treatment can reduce mortality rate by 31%.[4] Even though it is well tolerated, several side effects are inevitable, and fatty liver is one of the most common side effects among these.

Several studies showed that taking tamoxifen may incur a 30–40% risk of developing nonalcoholic fatty liver disease (NAFLD), according to different diagnosis instruments.[5–8] NAFLD is a common benign liver disease, its prevalence is around 20–30% in the West and 11.4–41% in Taiwan.[9,10] In general, fatty liver is most likely to be associated with obesity[11] and unhealthy diet habits[12]; yet, this seems not to be the case in breast cancer patients in Taiwan. We noticed most patients followed a relative healthy lifestyle after being diagnosed with cancer, in order to prevent disease recurrence. From the view point of public health, fatty liver is worth early intervention as this might decrease the risk of all-cause mortality and diabetes.[13–16] Considering that potential adverse effects may reduce compliance when taking tamoxifen, we decided to investigate this issue; although not wishing to raise another medical concern during the 5-year treatment period. Previous studies have focused on the new development of tamoxifen-induced fatty liver and the lack of consideration for real world conditions i.e. the high prevalence of fatty liver in the general population. The more important concern is related to pre-existing liver conditions; hence, we wished to thoroughly explore the drug effect on different pre-existing liver conditions. The aim of this study is to assess the impact of tamoxifen-related fatty liver among breast cancer patients and to evaluate the consequent prevalence of an abnormal liver function test (LFT).

Materials and methods

Patients

This is a hospital-based retrospective cohort study, conducted from April 1, 2013 to March 31, 2014 at the Breast Clinic, Kaohsiung Veterans General Hospital, Southern Taiwan, with the approval of the Kaohsiung Veteran General Hospital institutional review board (IRB). Patient records were de-identified prior to analysis. The IRB reviewed the research proposal, and IRB approval was obtained on March 18, 2013, IRB N0: VGHKS13-CT4-04. Under this permission, the study was conducted from April 1, 2013. Breast cancer cases diagnosed from January 2008 to April 2014 including patients of 20 years to 70 years of age were eligible, and the written informed consent of each participant was obtained for their clinical records to be used in this study. Clinical records include both the first hospitalization (initial data) for breast cancer treatment and laboratory check-up data at follow-up time (later data). The exclusion criteria were the presence of underlying viral hepatitis, alcoholic hepatitis (70 g/wk for women),[17] liver metastasis, and chemotherapy-induced liver disease. Those who were taking antilipid agents or steroids which may influence fatty liver conditions were also excluded. According to the use of tamoxifen (consecutive usage for more than 3 months until the enrolment date) or not, the cases were divided into a tamoxifen group or control group. Those who did not receive tamoxifen or those using aromatase inhibitors were defined as the control group. At enrolment time, personal data were collected from a lifestyle questionnaire and an 8-hour fasting day was arranged to perform the follow-up blood tests and abdominal ultrasound (later ultrasound) to evaluate fatty liver condition.

Lifestyle questionnaire

All demographic data were collected via a lifestyle questionnaire. Measurement of present body height, weight, waist, and body mass index (BMI) was calculated. The questionnaire was used to evaluate the patient's lifestyle after diagnosing breast cancer, including consumption of sweetened soft drinks (yes/no), exercise condition (yes/no), and time given to exercise every week. Regarding exercise time, 150 min/wk was used as a cut-off point, according to the recommendation for adults from the American College of Sports Medicine and the American Heart Association.[18] The personal and family histories of hypertension, diabetes, and hyperlipidemia were also reviewed.

Abdominal ultrasound and blood test at follow-up time

Fasting for 8 hours was required for the blood test and abdominal ultrasound. Serum aspartate aminotransferase (AST, normal range, 0–35 IU/L), alanine transaminase (ALT, normal range, 0–40 IU/L), creatinine, uric acid, triglyceride, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), sugar, hemoglobin A1c (HbA1c), and insulin were measured. Insulin resistance (IR) was calculated using the HOMA-IR formula [HOMA-IR = fasting insulin (mU/L) × fasting glucose (mmol/L)/22.5].

Pathologic diagnosis remains the gold standard for establishing the diagnosis of fatty liver; however, it is invasive and has a relatively high cost. Therefore, multiple radiology modalities such as abdominal ultrasound, computerized tomography, and magnetic resonance imaging are used clinically. In this study, ultrasound was used to diagnose fatty liver. The severity of fatty liver was graded as normal, mild, moderate, and severe, according to the echogenicity of the liver parenchyma.[19] Ultrasound was performed by well-trained radiation technologists and rated by radiology specialists with consensus of grading. The initial body weight, liver function, and abdominal ultrasound of the first hospitalization (initial ultrasound) for breast cancer treatment was obtained and used as a reference for body weight and liver function change.

Definition of other covariates

"Breast cancer disease year" was the duration from the date of first hospitalization for breast cancer treatment to the follow-up blood test date. "Follow-up time", to avoid bias and have an equal base line, we omitted the previous treatment time, including surgery, chemotherapy, and radiotherapy course. Therefore, the follow-up time was calculated from the first tamoxifen prescription date in the tamoxifen group, and the first outpatient clinic follow up in the control group, to the follow-up blood test date.

Outcomes

The primary outcome was fatty liver changes using abdominal ultrasound. To quantify the change of severity, we turned the order scale to a numeric scale for statistical analysis. We rated normal, mild, moderate, and severe fatty liver as 0, 1, 2, and 3, respectively. We compared the scoring change between initial and follow-up ultrasound to assess the development of fatty liver. Accordingly, we obtained the following five categories of fatty liver change: (1) fatty improved; (2) normal and no change; (3) fatty as before; (4) normal to fatty; and (5) worsened fatty (Figure 1). The secondary outcome was the prevalence of abnormal LFT under different fatty liver conditions. The definition of abnormal LFT in this study was AST $\geq$35 IU/L, or ALT $\geq$40 IU/L.

Statistical analysis

The statistical analysis was performed with STATA software v.13.0 (StataCorp LP Texas). All data were expressed as frequency (percentage) or mean standard deviation. We used three models to evaluate the effect of tamoxifen treatment on different developments for NAFLD. The outcomes were: a newly developed fatty liver [compared (4) normal to fatty with (2) normal and no change]; an improved fatty liver [compared (1) fatty improved with (3) fatty as before]; and a worsened fatty liver [compared (5) worsened fatty with (3) fatty as before] in the three models, respectively. The duration for the time observed was the followed-up time from the start of tamoxifen use or the first outpatient clinic follow up in the control group to the examination of NAFLD (at the same time of follow-up blood test date). Patients with censor data were defined as those without the outcomes at the time the NAFLD was examined. Since these assessments were time-dependent, the Cox proportional hazard models were used to evaluate the effect of tamoxifen treatment on different developments for NAFLD adjusted for the possible confounding variables.

Results

Study patients and follow-up

From April 1, 2013 to March 31, 2014, 422 participants were recruited: one participant was older than 70 years, nine participants with incomplete questionnaires, five participants with hepatitis B, and one participant with hepatitis C were all excluded; therefore, 406 participants were enrolled (mean age 53.2 $\pm$ 8.2 years), 306 (75.4%) ER positive, and 100 (24.6%) ER negative. Among the ER positive participants, 266 (86.9%) received tamoxifen treatment and were defined as the tamoxifen group. The control group contained 140 participants, including 100 ER negative participants and 40 ER positive participants who were not taking tamoxifen (32 refused any drugs due to personal reasons, eight were taking aromatase inhibitors). The mean follow-up time was 26.7 months; patient characteristics are summarized in Table 1. The mean weight at the time of
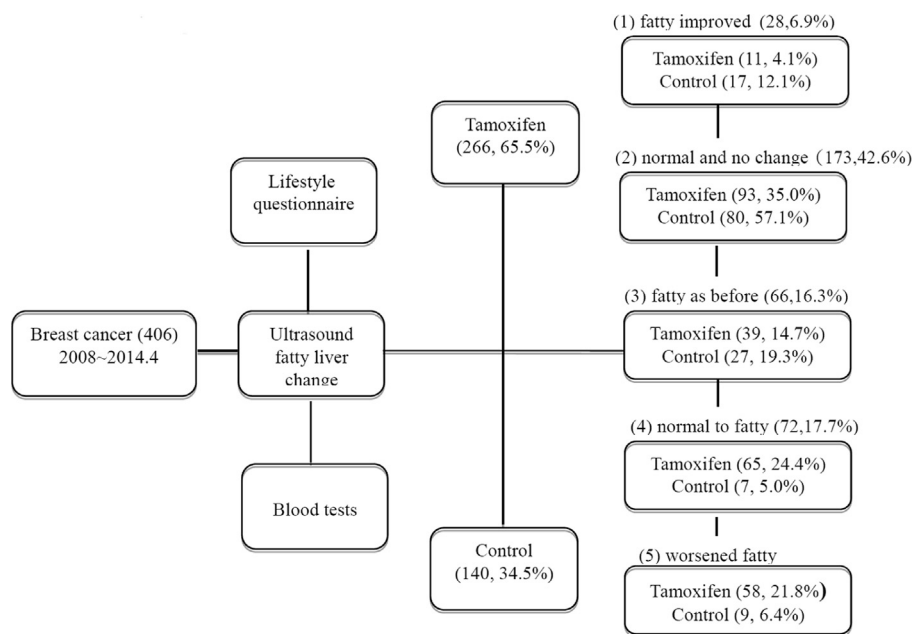

Figure 1 Flow diagram of the patient population and five categories of fatty liver change. This figure indicates that 406 breast cancer cases were eligible in this study, 266 (64%) of the cases were in the tamoxifen group and 140 (36%) were in the control group.

Table 1 Characteristics of 406 participants according to whether they were treated with tamoxifen or not.

	Overall $n = 406$	Control $n = 140$	Tamoxifen $n = 266$	p
Age (y)	53.2 ± 8.2	53.8 ± 8.3	52.9 ± 8.1	0.260
Disease year[a] (y)	2.76 ± 1.39	2.90 ± 1.30	2.69 ± 1.43	0.152
Height (cm)	156.7 ± 5.5	156.6 ± 5.3	156.7 ± 5.6	0.819
Weight, initial[a] (kg)	59.1 ± 9.7	58.9 ± 9.2	59.2 ± 9.9	0.775
BMI, initial[b] (kg/m^2)	24.1 ± 3.9	24.1 ± .6	24.1 ± 4.1	0.799
Weight, later[c] (kg)	59.8 ± 9.9	59.5 ± 9.9	60.0 ± 9.9	0.695
Weight change (kg)	0.75 ± 3.8	0.68 ± 4.2	0.79 ± 3.6	0.770
BMI, later[b] (kg/m^2)	24.4 ± 3.9	24.3 ± 3.7	24.4 ± 4.0	0.691
Waist (cm), later[b]	81.1 ± 9.5	81.1 ± 9.6	81.1 ± 9.4	0.952
Ever pregnant	342 (84.2%)	118 (84.3%)	224 (84.2%)	0.984
First pregnant age (y)	26.4 ± 4.8	25.9 ± 4.9	26.7 ± 4.7	0.162
Menopause	302 (74.4%)	106 (75.7%)	196 (73.7%)	0.656
Biochemistry (initial)[a]				
AST (IU/L)	21.0 ± 6.8	21.2 ± 6.4	20.9 ± 7.0	0.696
ALT (IU/L)	22.6 ± 14.1	23.8 ± 13.7	22.0 ± 14.3	0.226
Sugar, not specific (mg/dL)	111.7 ± 36.4	110.6 ± 39.1	112.3 ± 35.0	0.647
Disease stage				0.068
Carcinoma *in situ*	48 (11.8%)	10 (7.1%)	38 (14.3%)	
I	155 (38.2%)	48 (34.3%)	107 (40.2%)	
II	152 (37.4%)	61 (43.6%)	91 (34.2%)	
III	50 (12.3%)	21 (15.0%)	29 (10.9%)	
IV	1 (0.25%)	0	1 (0.38%)	
Chemotherapy	227 (55.9%)	101 (72.1%)	126 (47.4%)	<0.001*
Family history				
Diabetes	141 (34.7%)	45 (32.1%)	96 (36.1%)	0.427
Hypertension	208 (51.2%)	71 (50.7%)	137 (51.5%)	0.880
Hyperlipidemia	30 (7.4%)	9 (6.4%)	21 (7.9%)	0.591
Breast cancer	76 (18.7%)	32 (22.9%)	44 (16.5%)	0.121
Personal history				
Diabetes	34 (8.4%)	7 (5.0%)	27 (10.2%)	0.075
Hypertension	66 (16.3%)	20 (14.3%)	46 (17.3%)	0.435
Hyperlipidemia	32 (7.9%)	10 (7.1%)	22 (8.3%)	0.689
Regular exercise	270 (66.5%)	98 (70.0%)	172 (64.7%)	0.279
Exercise (min/wk)	166.8 ± 177.1	175.6 ± 167.8	162.1 ± 182.0	0.464
Night sleep (h)	6.5 ± 1.4	6.5 ± 1.3	6.5 ± 1.5	0.723
Sweetened soft drink (yes/no)	52 (12.8%)	22 (15.7%)	30 (11.3%)	0.204
Alcohol (yes/no)	8 (2.0%)	3 (2.1%)	5 (1.9%)	0.856
Follow up period[d] (mo)	26.7 ± 15.5	24.8 ± 13.6	27.7 ± 16.3	0.078

Data are expressed as mean ± SD or n (%).
*Categorical variables using Chi-square test with significant level at $p < 0.05$.
ALT = alanine transaminase; AST = aspartate aminotransferase; BMI = body mass index.
 [a] Disease year was the duration from the date of first hospitalization for breast cancer treatment to the follow-up blood test date.
 [b] Data during the first hospitalization for breast cancer treatment.
 [c] Data at the date of performing follow-up blood test.
 [d] Follow-up period was calculated from the first tamoxifen prescription date in the tamoxifen group and the first outpatient clinic follow-up in the control group to the follow-up blood test date.

breast cancer diagnosis was 59 kg, the mean BMI was 24.1 kg/m^2; at follow-up time, the mean weight and BMI had only slightly increased. Except for a higher chemotherapy rate being found among the control group (72.1% vs. 47.4%), the baseline characteristics of both groups did not significantly differ in terms of age, family, and personal history of diabetes mellitus, hypertension, hyperlipidemia, breast cancer stage, diet habits, and exercise condition.

Regarding the prevalence of fatty liver, as Figure 2 shows, both groups had similar percentages of varying degrees of fatty liver at first; nevertheless, higher moderate and severe degrees and less normal and mild degrees of fatty liver were found in the tamoxifen group at follow-up time. We further discussed the five different categories of fatty liver changes, this revealed that the tamoxifen group tended to exhibit more prominent fatty liver changes; "(4) normal to fatty" 24.4% versus 5.0%, "(5) worsened fatty " 21.8% versus 6.4%. We checked the fasting blood test results at follow-up time, and higher rates of abnormal LFT, triglyceride, and LDL were demonstrated in the tamoxifen group (Table 2). The
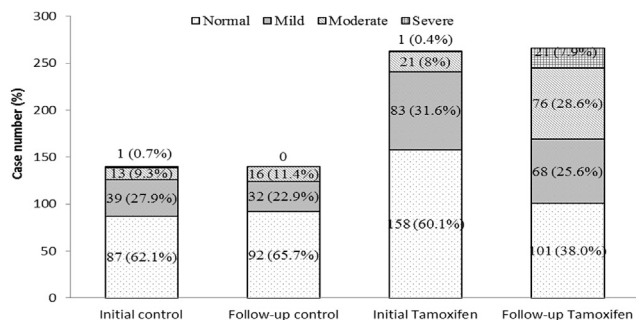
Figure 2 Fatty liver distribution in 406 participants at initial and follow-up time. This figure indicates the changes in various degrees of fatty liver during follow-up time. More prominent fatty liver changes in the tamoxifen treatment group were noticed.

incidence rate of abnormal LFT increased according to the degree of fatty liver, AST $\geq$35 IU/L (normal: 1.0%, mild: 12.0%, moderate: 32.6%, severe: 42.9%) and ALT $\geq$ 40 IU/L (normal: 1.6%, mild: 14.0%, moderate: 35.9%, severe: 52.4%). Of the 406 participants, the tamoxifen group had higher rates of abnormal AST at follow-up time compared with the control group (16.9% vs. 5.7%, $p = 0.001$) and ALT (17.3% vs. 10.7%, $p = 0.078$). Taking into account the different degrees of fatty liver changes (Table 3), elevated liver function was more obvious in the tamoxifen group with "worsened fatty" condition. Table 4 shows the effect of tamoxifen treatment on different condition of fatty liver disease among breast cancer patients with adjusting age, initial BMI, diabetes, chemotherapy, and exercise time over 150 min/wk. In terms of "newly developed fatty liver", the tamoxifen group displayed a higher risk, the adjusted HR was 3.69 (95% CI 1.67–8.13, $p < 0.001$). For the effect of "improved fatty liver", less rate of improvement was found in the tamoxifen group, the adjusted HR was 0.33 (95% CI 0.15–0.75, $p = 0.002$). In contrast to the control group, the tamoxifen group had a higher risk of "worsened fatty" condition, the adjusted HR was 2.11 (95% CI 1.02–4.35, $p < 0.001$).

Discussion

The most anticipated benefit of tamoxifen is improved breast cancer survival rates based on a sufficient treatment time; nevertheless, a 5-year long treatment course may arouse some side effects that may influence drug compliance.[20] In addition, some medical consequences can be avoided if timely intervention takes place. In our study, 40% of participants had different degrees of fatty liver at the initial survey; the prevalence was consistent with previous investigations.[9,10] The severity of the fatty liver was similar in both groups initially; however, different outcomes were noticed later when some showed improved fatty liver, while others either remained at the same condition or worsened. We examine the causes of these differences.

We found higher rates of fatty liver in the tamoxifen group at follow-up time. When considering the possible causes of fatty liver, we evaluated personal lifestyle, body weight, and potential drugs may intervene. In the lifestyle questionnaire, we evaluated sweetened soft drink habits, based on excessive dietary fructose intake playing an important role in the current epidemic of fatty liver,[12] consumption was found not to be as high as in the general population and there was no significant difference in both groups (control 15.7% vs. tamoxifen 11.3%, $p = 0.647$); in addition, 66.5% of the participants had regular exercise, and most of them had made this change to improve their health since being diagnosed with breast cancer. Regarding body weight, the average BMI was 24 kg/m^2, a relatively healthy weight, this finding is similar to a study in Japan, which indicated tamoxifen-related fatty liver was found in about one-third of nonobese breast cancer patients, and BMI = 23.6 kg/m^2 was the cut-off point.[8,21] Therefore, lifestyle or body weight was less likely to be the cause of fatty liver in our study. As we know, the most effective way to improve fatty liver is to control body weight and exercise regularly. Because 40% of the participants had different degrees of fatty liver initially, they should benefit from a healthy lifestyle; however, such kind of lifestyle change seemed not to work in the tamoxifen group. Furthermore, the multivariable Cox proportional hazard

Table 2 Blood test results of 406 participants at follow-up time.

	Overall $n = 406$	Control $n = 140$	Tamoxifen $n = 266$	p
Biochemistry (later)				
AST (IU/L)	27.8 ± 18.0	24.4 ± 12.0	29.5 ± 20.3	0.007*
ALT (IU/L)	26.6 ± 23.3	23.5 ± 12.8	28.2 ± 27.2	0.056
Creatinine (mg/dL)	0.81 ± 0.14	0.82 ± 0.13	0.80 ± 0.14	0.103
UA (mg/dL)	5.5 ± 0.24	5.2 ± 1.2	5.6 ± 2.9	0.175
TG (mg/dL)	135.7 ± 144.6	113.0 ± 71.3	147.6 ± 169.9	0.022*
Cholesterol (mg/dL)	193.8 ± 37.9	205.6 ± 38.9	187.6 ± 35.8	<0 .001*
HDL (mg/dL)	52.0 ± 13.0	52.6 ± 14.0	51.7 ± 12.5	0.479
LDL (mg/dL)	97.4 ± 29.9	107.3 ± 31.3	92.3 ± 27.9	<0.001*
Fasting sugar (mg/dL)	99.5 ± 19.2	100.0 ± 21.4	99.3 ± 18.0	0.753
HBA1C (%)	6.1 ± 5.4	6.5 ± 8.3	5.9 ± 2.9	0.312
Insulin (mU/L)	8.0 ± 8.3	8.3 ± 9.3	7.8 ± 7.8	0.540
HOMAR-IR	2.02 ± 2.21	2.10 ± 2.53	1.97 ± 2.02	0.564

*Continuous variables using two-sample t test with significant level at $p < 0.05$.
ALT = alanine transaminase; AST = aspartate aminotransferase; HBA1C = hemoglobin A1c; HDL = high-density lipoprotein; HOMAR-IR = fasting insulin (mU/L) × fasting glucose (mmol/L)/22.5; LDL = low-density lipoprotein; TG = triglyceride; UA = uric acid.

Table 3   The relationships of five categories of fatty liver change and the percentage of abnormal liver function test (LFT) between two groups of breast cancer patients at follow-up time.

Abnormal LFT	AST $\geq$35		ALT $\geq$40	
Ultrasound	Control $n = 8$ (5.7%)	Tamoxifen $n = 45$ (16.9%)	Control $n = 15$ (10.7%)	Tamoxifen $n = 46$ (17.3%)
(1) Fatty improved $n = 28$	1/17 (5.9%)	0/11 (0)	2/17 (11.8%)	0/11 (0)
(2) Normal no change $n = 173$	1/80 (1.3%)	1/93 (1.1%)	2/80 (2.6%)	1/93 (1.1%)
(3) Fatty no change $n = 66$	5/27 (18.5%)	9/39 (23.1%)	6/27 (22.2%)	8/39 (20.5%)
(4) Normal to fatty $n = 72$	1/7 (14.3%)	11/65 (16.9%)	3/7 (42.9%)	14/65 (21.5%)
(5) Worsened fatty $n = 67$	0/9 (0)	24/58 (41.4%)	2/9 (22.2%)	23/58 (39.7%)
p for χ^2 test		<0.001		<0.001

ALT = alanine transaminase; AST = aspartate aminotransferase.

regression model adjusted for the above factors showed that tamoxifen use had a significant influence, as our study showed that not only "newly developed" fatty liver increased but also "improved" fatty liver was impeded, and it even led to a greater risk of " worsened" fatty liver.

Several drugs can induce variable extents of fatty liver, so to assess drug-related fatty liver we also considered the potential effect of chemotherapy.[22] To discuss the confounding effect of chemotherapy, we noticed the chemotherapy rate was lower in the tamoxifen group than the control group (47.4% vs. 72.1%); this negative association implied that chemotherapy did not influence the development of fatty liver in our study. However, to clarify the influence of chemotherapy, we adjusted it in the multivariate analysis and still found a significant effect of tamoxifen treatment on different conditions of NAFLD among breast cancer patients. The precise mechanisms of drug-induced liver injury are not always known, it is thought that they are mostly related to mitochondrial dysfunction and can lead to hepatic cytolysis and steatosis.[23] The current hypothesis suggests that tamoxifen causes fatty liver via promoting *de novo* fatty acid synthesis and inhibiting fatty acid β-oxidation.[22,24] From laboratory results, relatively higher triglyceride levels were found in the tamoxifen group, and this may explain how the drug exerts its effect through the interference of the triglyceride metabolic pathway. Interestingly, the tamoxifen group had relatively lower total cholesterol (205.6 ± 38.9 mg/dL vs. 187.6 ± 35.8 mg/dL, $p < 0.001$) and LDL (107.3 ± 31.3 mg/dL vs. 92.3 ± 27.9 mg/dL, $p < 0.001$), and some studies have even demonstrated that tamoxifen is beneficial for the cardiovascular system.[25] This topic is beyond the scope of the current

study and additional research is needed to investigate the potential cardiovascular benefits of tamoxifen.

The relationship of NAFLD and LFT

In the general population, NAFLD is recognized as the most common cause of abnormal LFT. In a recent study with 1118 adults in the UK, abnormal LFT was identified in 55% of patients and NAFLD in 26.4% of patients,[26] in contrast, we could not determine what percentage of abnormal LFT would be found in NAFLD. Abdominal ultrasound is aimed at detecting early liver metastasis in routine breast cancer follow-up studies; hence, we wished to have a reference concerning the rate of abnormal LFT under the relevant abdominal ultrasound diagnosed fatty liver. In our study, we determined that the consequent prevalence of abnormal LFT increased in accordance with the severity of fatty liver. For example, if a patient has a moderate fatty liver condition, they might have an approximately 30% possibility of abnormal LFT. The clinical implication is that physicians may have an idea about the possibility of abnormal LFT once the patient develops fatty liver.

Strengths

Many papers have documented the effect of tamoxifen-induced fatty liver; however, few have discussed the impact on the underlying fatty liver condition and lack consideration for personal health conditions. In our study, participants with varying extents of fatty liver were enrolled and three different aspects were used to assess the effect of tamoxifen. We also adjusted for personal lifestyle and initial body weight to clarify the drug effect. The positive relationships between fatty liver and abnormal LFT can offer clinical physicians a reference for evaluation.

Limitations

Firstly, the sensitivity and specificity of abdominal ultrasound are not as accurate as liver biopsy, and interobserver agreement is problematic.[27] Abdominal ultrasound is a simple, noninvasive, and inexpensive instrument to detect fatty liver. It offers a reliable and accurate detection of moderate to severe fatty liver[28] and raters are unaware of the patient's background, hence, it has nondifferential

Table 4   The effect of tamoxifen treatment on different conditions of nonalcoholic fatty liver disease among breast cancer patients.

	HR (95% CI)	p^*
Newly developed fatty liver	3.69 (1.67—8.13)	<0.001
Improved fatty liver	0.33 (0.15—0.75)	0.002
Worsened fatty liver	2.11 (1.02—4.35)	<0.001

Multivariate analysis was adjusted with age, initial BMI, diabetes, chemotherapy, and exercise time >150 min/wk.
*Cox proportional hazard regression analysis. BMI = body mass index; CI = confidence interval.

misclassification and should not influence the result. Secondly, for baseline characteristics, we only had the data of body weight and AST; ALT, and other metabolic results were not available, so we are unable to differentiate such metabolic abnormalities in the tamoxifen group occurring previously or afterwards.

Conclusion

Our study suggests that tamoxifen is associated with the risk of NAFLD development, either by increasing the developed fatty liver or worsening the previous fatty liver condition and even retarding fatty liver improvement. The severity of fatty liver is associated with higher rates of abnormal LFT. During the follow-up period, regular abdominal ultrasound checkup, not just for detecting liver nodules, but also for identifying fatty liver change, is crucial. Further checking of liver function and other metabolic conditions once the fatty liver condition has progressed is essential.

Acknowledgments

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