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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 NO: 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.