Prevalence of hepatic steatosis and metabolic associated fatty liver disease among female breast cancer survivors

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To the Editor: Non-alcoholic fatty liver disease (NAFLD) comes to prevail in Asia and the prevalence in China is reported to be 24% to 36%.[1] The prevalence of NAFLD and its associated medical burden might be underestimated. The diagnosis of NAFLD led to the exclusion of other chronic liver diseases including "excess" alcohols, thus the population with alcoholic consumptions or other liver diseases might be neglected. In March 2020, the international expert consensus proposed a new concept, "metabolic associated fatty liver disease (MAFLD)," and replaced the earlier term of "NAFLD."[2] As the most prevalent female malignancy, breast cancer (BC) shares similar risk factors to MAFLD. Higher levels of obesity and physical inactivity are closely correlated to BC and are significant drive for the increasing trends in the prevalence of BC. Some BC survivors may receive chemotherapy and endocrine therapy, both of which are reported to increase the risk of hepatic steatosis (HS), which is the fundamental criteria of the diagnosis of MAFLD.[2] The prevalence of HS among breast cancer survivors (BCS) is routinely ignored by oncologists and HS is usually diagnosed by conventional liver ultrasonography (US), while liver ultrasound elastography (USE) is increasingly used due to its higher sensitivity and specificity compared to US.[3] Therefore, USE was used in our study to investigate the accurate prevalence of HS and MAFLD among BCS.

In this matched cohort study, we enrolled the primary BCS and healthy population representing the cancer cohort and non-cancer controls, respectively. BC diagnosis was confirmed through biopsy by experienced pathologists in the Medical Quality Control Center of Clinical Pathology, Chongqing. The BCS then underwent systemic treatment in the Breast Cancer Center of Chongqing and were then followed up in the outpatient clinic from October 2019 to June 2020. Those BCS with results of liver US and/or USE were included in the research. USE is a newly developed device of controlled attenuation parameter measurement by Vibration Controlled Transient Elastography, which is implemented as a more sensitive tool to diagnose HS than US. Other inclusion criteria included ≥18 years age, detailed anthropological information, and laboratory test results. Exclusion criteria included terminal illness, past medical history of other malignancies. Data of 135,436 physical examinees representing the normal healthy cohort were collected from the database of the Quality Control Center of Health Examination in Chongqing. Finally, we enrolled a total of 370 BCS and 3700 age- and sex-matched normal healthy subjects in the proportion of 1:10.

The median follow-up duration of BCS after surgery was 24 months (interquartile range [IQR] 12–36). The anthropological information, laboratory test results, and other baseline characteristics of BCS and non-cancer controls are presented in Supplementary Table 1 [http://links.lww.com/CM9/B22]. The median age of both BCS and non-cancer controls was 52 years (IQR, 46–57) with no significant difference. Waist circumference and body mass index (BMI) differed significantly between the case and control groups (81.9 *vs.* 77.0 cm and 23.4 *vs.* 22.7 kg/m^2, respectively, <0.05). Fasting blood glucose level in the BC cohort (5.6 mmol/L [IQR, 5.3–6.1]) was significantly higher compared to non-cancer subjects (5.2 mmol/L, [IQR, 4.9–5.7]). Meanwhile, a significant difference was observed in lipid levels among the two groups (all P values < 0.05). BCS had a

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higher triglyceride level of 1.38 mmol/L (IQR 0.99–2.02) compared to the non-cancer controls (1.22 mmol/L [IQR 0.88–1.70]). The high-density lipoprotein (HDL)–cholesterol was significantly lower in the cancer group (1.49 mmol/L) compared to 1.56 mmol/L in the non-cancer controls (1.56 mmol/L); the level of HDL-cholesterol was obviously lower in the cancer group (1.49 mmol/L). The total cholesterol and low-density lipoprotein-cholesterol level among BCS were significantly lower (5.00 mmol/L [IQR 4.37–5.63]) and (2.77 mmol/L [IQR 2.16–3.43]) compared to the controls ((5.01 mmol/L [IQR 4.39–5.66]) and (3.07 mmol/L [IQR 2.52–3.66]), respectively. Furthermore, the clinical characteristics of older participants with age ≥60 years in the case and control groups were compared [Supplementary Table 2, http://links.lww.com/CM9/B22].

The prevalence of US diagnosed HS among BCS was significantly higher than among normal healthy subjects (37.4% [138/369] *vs.* 22.7% [840/3700], $P < 0.05$), and the prevalence further increased to 68.3% (250/366) when HS among BCS were screened with USE. The prevalence of MAFLD based on the US among BCS was significantly higher than normal healthy subjects (35.9%[130/362] vs. 21.6% [788/3648], $P < 0.05$), and the prevalence of MAFLD further increased to 63.2% when screened with USE. Meanwhile, the prevalence of HS and MAFLD based on the US among the elderly BCS (≥60 years) was significantly higher than the normal healthy population (51.9% [41/79] and 50.6% [39/77] vs. 34.2% [270/790] and 33.3% [260/780], $P < 0.05$), respectively. The prevalence of HS and MAFLD based on USE in the elderly BCS (≥60 years) was 78.5% [62/79] and 77.3% [58/75], respectively [Table 1].

In our study, the median age of BCS and non-cancer controls were 53 years without significant difference. While the metabolic index differed significantly among the two groups. Similarly, the BMI and waist circumferences of BCS were significantly higher compared to non-cancer controls [Supplementary Table 2, http://links.lww.com/CM9/B22]. Previous studies have established the evidence of greater weight associated with the increased risk of BC and a similar association is observed in BCS as well. Waist circumference, a more precise reflection of body fat distribution, is dose-independent associated with BC. Among BCS, the mean waist circumference was 82.3 cm, which met the criteria of central obesity defined as excess waist circumference over 80 cm among Asian females. In addition to the above-mentioned risks, the elevated fasting glucose level and triglycerides in BCS pointed to the metabolism disorder as well. The metabolism disorder among BCS may explain the significant disparity of HS and moreover, MAFLD prevalence BCS and non-cancer controls.

Our study found that 22.7% (840/3700) of normal healthy females were diagnosed with HS, consistent with another Chinese research showing that 20.59% females in Shanghai were diagnosed with HS. Among BCS, the prevalence of HS (37.4% [138/369]) according to the liver US was significantly higher compared to normal healthy population and probably even higher. The shared risk factors among BC and HS, synergistically coupled with the existence of metabolism disorder in BCS might be associated with the higher prevalence of HS. Additionally, 43% of BC patients treated with tamoxifen were reported to develop steatosis as well. Studies have reported that the 20-year absolute excess risk of mortality of BC patients increased by 10.7% with HS.[4] The General and BC population should be made aware of the occurrence of HS and be informed of the importance of reversing HS. The public health efforts focused on the prevention and control measures for HS require further knowledge on its prevalence. In order to

Table 1: The prevalence of MAFLD and HS in female BCS and healthy subjects based on conventional liver US and liver elastography USE.

Items	Female BCS		Normal population		*P* values
	Total population	Age ≥ 60 years	Total population	Age ≥ 60 years	
HS					
US					
Normal	231/369 (62.6)	38/79 (48.1)	2860/3700 (77.3)	520/790 (65.8)	<0.05
Positive	138/369 (37.4)	41/79 (51.9)	840/3700 (22.7)	270/790 (34.2)	-
USE					
Normal	116/366 (31.7)	17/79 (21.5)	-	-	-
Positive	250/366 (68.3)	62/79 (78.5)	-	-	-
MALFD					
US					
Normal	232/362 (64.1)	38/77 (49.4)	2860/3648 (78.4)	520/780 (66.7)	<0.05
Positive	130/362 (35.9)	39/77 (50.6)	788/3648 (21.6)	260/780 (33.3)	-
USE					
Normal	129/351 (36.8)	17/75 (22.7)	-	-	-
Positive	222/351 (63.2)	58/75 (77.3)	-	-	-

Categorical variables were expressed as *n*/*N* (%) and compared by chi-squared test. -: indicators were not collected, data are unavailable. BCS: Breast cancer survivors; HS: Hepatic steatosis; MAFLD: Metabolic associated fatty liver disease; US: Ultrasonography; USE: Ultrasound elastography. The diagnosis criteria of MAFLD contain multiple requirements, and therefore whether a few cases were MAFLD is unknown. Those were not included in prevalence calculation. The number of health population enrolled in calculation were accordingly reduced.

explore the specific and accurate prevalence of HS in BCS, we implemented liver USE. Liver USE is regarded as the more sensitive tool for HS diagnosis than conventional liver US. FibroTouch (Wuxi Hisky Medical Technologies, Jiangsu, China) was implemented and we detected more HS (68.3% [250/366]) among the BCS population. In our study, MAFLD was presented 35.9% (130/362) of BCS undertaking liver US, while a previous Korean study reported 30.0% of NAFLD occurrence among BC patients.[5] And using FibroTouch, we found an even higher prevalence of MAFLD (63.2% [222/351]) among BCS, and the prevalence of HS and MAFLD based on USE rose to 78.5% and 77.3%, respectively, which to some extent reflects a more accurate situation involving MAFLD prevalence in the cancer population. As a rapidly growing disease worldwide combined with higher prevalence among BC patients, MAFLD has not drawn oncologists' attention, and despite the high frequency in BC patients, the recognition that MAFLD diagnosis is often delayed or even neglected in breast specialists. HS usually present with no symptoms, therefore, screening of BCS with HS by liver US is neglected leading to the failure of early HS prevention and increased risk of progression to MAFLD. MAFLD is closely associated with the risk of cardiovascular disease (CVD), similarly, BCS also has a higher risk of CVD-related mortality. Therefore, ignoring HS and MAFLD seriously might affect the prognosis of BCS. Considering the high prevalence of HS and MAFLD among BCS, liver US, or liver USE in particular, should be promoted and included in the routine screening protocol. More importantly, HS and MAFLD in BCS should be payed more attention.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal.

The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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