The prevalence of hepatic steatosis and metabolic associated fatty liver disease among breast cancer survivors

Shen Tian
The First Affiliated Hospital of Chongqing Medical University
Hao Li
The First Affiliated Hospital of Chongqing Medical University
Ren-hua Li
The First Affiliated Hospital of Chongqing Medical University
Liang Ran
The First Affiliated Hospital of Chongqing Medical University
Shu Li
The First Affiliated Hospital of Chongqing Medical University
Juan Wu
The First Affiliated Hospital of Chongqing Medical University
Zhou Xu
The First Affiliated Hospital of Chongqing Medical University
Xin-yu Liang
The First Affiliated Hospital of Chongqing Medical University
Yu-ling Chen
The First Affiliated Hospital of Chongqing Medical University
Jun Xiao
The First Affiliated Hospital of Chongqing Medical University
Jia-ying Wei
The First Affiliated Hospital of Chongqing Medical University
Chen-yu Ma
The First Affiliated Hospital of Chongqing Medical University Department of Neurology
Jing-yu Song
The First Affiliated Hospital of Chongqing Medical University
Rui-ling She
The First Affiliated Hospital of Chongqing Medical University
Kai-nan Wu
The First Affiliated Hospital of Chongqing Medical University
Ling-guan Kong (huihuikp@163.com)

Chongqing Medical University First Affiliated Hospital https://orcid.org/0000-0001-5705-9001

Research Article

Keywords: Metabolic Associated Fatty Liver Disease (MAFLD), Hepatic Steatosis (HS), Breast Cancer (BC), Liver ultrasonography, Liver ultrasound elastography

Posted Date: March 18th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-325344/v1

Abstract

Background and aims

An international expert consensus statement was released on 2020 that non-alcoholic fatty liver disease (NAFLD) should be replaced by metabolic associated fatty liver disease (MAFLD) and hepatic steatosis (HS) is fundamental for the diagnosis of MAFLD in the new set of criteria. While female breast cancer has surpassed lung cancer as the most commonly diagnosed malignant tumor and shares the same risk factors with HS and MAFLD, but their prevalence in breast cancer survivors (BCS) is unknown. Herein, we employed the liver ultrasound elastography (USE), a more sensitive detector for HS diagnosis, to explore the more accurate prevalence of HS and MAFLD among BCS.

Method

A total of 263 BCS with conventional liver ultrasonography (US) and USE tests, followed up in the clinic of the Breast Cancer Center of Chongqing, as well as age and sex matching controls (1:10) with US test, from 135,436 healthcare population in the Quality Control Center of Health Examination of Chongqing of the First Affiliated Hospital of Chongqing Medical University, were enrolled. Both US and USE were implemented to diagnose HS. Afterwards the anthropology information and relative laboratory test results were collected to estimate the prevalence of MAFLD based on USE and US according to the 2020 international consensus.

Results

The prevalence of HS detected by US in BCS was significantly higher than that in healthcare population (41.8% vs. 22.4%, P<0.001), and it rose to 69.6% when the BCS were screened by USE. Accordingly, the prevalence of MAFLD based on US in BCS was also significantly higher than that in healthcare population (39.5% vs. 21.2%, P<0.001) and it rose to 63.5% when the BCS were screened by USE. The prevalence of HS and MAFLD based on US in elderly BCS (≥60 yr) were obviously higher than those in healthcare population (56.7% & 56.7 % vs. 31.3% & 30.7%, P<0.001), respectively, and they rose to 80.0% and 73.3%, respectively when the BCS were screened by USE.

Conclusion

HS and MAFLD prevail in breast cancer survivors, especially in most of the elderly breast cancer survivors (≥60 yr). Their prevalence are much higher than in the general population. Early prevention, diagnosis and treatment of HS and MAFLD in breast cancer survivors should be implemented.

Introduction

Non-alcoholic fatty liver (NAFLD) has become the most common type of chronic liver disease. It is estimated that more than 25% of adults have NAFLD in the USA. [1] Moreover, as a result of inactive foods, its prevalence is rising worldwide.[1, 2]

NAFLD comes to prevail in countries of the Asian subcontinent and the Far East, and the prevalence in China is reported to be 24%-36% [3]. The condition has become the center of attention as a result of its high prevalence and growing contribution to the burden of end-stage liver disease in the general population. Significant excess mortality risk was observed even with simple hepatic steatosis.[4] While the prevalence and medical burden caused by NAFLD might be underestimated, considering that the diagnosis of NAFLD necessitated the exclusion of other chronic liver disease including “excess” alcohols and thus the population with alcoholic consumptions or other liver diseases might be neglected. The knowledge gained from the past decades has demonstrated that NAFLD is a purely metabolic disorder and could be concomitant with other metabolic diseases[5]. In this context of the urgent unmet needs for a clear nomenclature and defined clinical criteria, on March 2020 the international expert consensus proposed a new concept, “metabolic associated fatty liver disease (MAFLD)”, to replace the old “NAFLD” and the “positive criteria” to diagnose the disease.[6] The criteria are based on the evidence of hepatic steatosis (HS), either determined by imaging techniques, blood biomarkers/scores or by liver histology, as well as one of the following criteria, namely overweight/obesity, presence of type 2 diabetes mellitus, or evidence of metabolic dysregulation. [6] HS is fundamental for the diagnosis of MAFLD, which also emerges in breast cancer patients, leading to adverse outcomes.[7, 8] Female breast cancer has surpassed lung cancer as the most commonly diagnosed malignant tumor [9]. Great levels of obesity and physical inactivity, are closely correlated to BC and become a significant drive for the trends of growing BC prevalence. A cluster of metabolic disorders, closely correlating with HS, are defined as metabolic syndrome, which is reported to be 15.1–26.1% among breast cancer patients in developed countries and the percentage escalates to 32.1–43.9% in developing countries.[10] Some BC survivors may receive chemotherapy and endocrinology therapy, both of which are reported to increase the risk of HS.[11, 12] HS is usually concomitant with BC occurrence, and in previous studies, HS in breast cancer was usually diagnosed by conventional liver ultrasonography (US), while liver ultrasound elastography (USE) is increasingly implemented due to its higher sensitivity and specificity than US. [13] Therefore, we implemented USE to investigate the accurate prevalence of HS and MAFLD in breast cancer survivors (BCS).

Patients And Methods

Study design and population

This was a matched cohort study enrolling the primary breast cancer survivors and healthcare population respectively as the cancer cohort and non-cancer controls. Breast cancer diagnosis was confirmed through biopsy by experienced pathologist in the Clinical Pathological Diagnosis Center of Chongqing Medical University and the Medical Quality Control Center of Clinical Pathology, Chongqing. Chongqing is a megacity in southwest China with 82,402.95 square kilometer, where approximately 31.4 million people live and a municipality directly under the administration of central government of China.

These BCS underwent systemic treatment in the Department of Endocrine and Breast Surgery of The First [redacted] is also the breast cancer center of Chongqing,

and were then followed up from October 2019 to June 2020 in the clinic.
Those breast cancer survivors with results of liver ultrasonography and/or liver ultrasound elastography, a newly developed device of controlled attenuation parameter (CAP) measurement by Vibration Controlled Transient Elastography (VCTE) in order for a more sensitive tool to diagnose hepatic steatosis than ultrasonography [14, 15], were included in the research. Other inclusion criteria included age of ≥ 18, detailed anthropology information and laboratory test results. Exclusion criteria included terminal illness and past medical history of other malignancy. The healthcare population information was from the database of 135,436 physical examinees from the Quality Control Center of Health Examination in Chongqing, which is also the Health Management Center of the First Affiliated Hospital of Chongqing Medical University. [16] Finally, a total of 263 BCS as well as age and sex matching physical examinees as non-cancer controls (1:10) were enrolled.
This study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University and conducted in accordance with the Principles of the Helsinki Declaration.
Requirement for informed consent was waived because all information was anonymous and retrospective.

Clinical assessments

Anthropometric parameters, namely height, weight, hip as well as waist circumferences were measured. Waist circumference was measured at a level of the umbilicus or navel with the tape all around the body in the horizontal position. Hip circumference measurement was taken around the widest portion of the buttocks. BMI was calculated as body weight (kg) divided by height (m) squared. Venous blood samples were taken after at least 8 hours of fasting for liver biochemistry, plasma glucose and lipids detecting in the laboratory of the First Affiliated Hospital of Chongqing Medical University, which has been certified by the College of American Pathologists (CAP No.: 7215494). After at least 8 hours of fasting, hepatic steatosis diagnosis was performed by the experienced imaging physicians through liver US and / or USE (FibroTouch, Wuxi Hisky Medical Technologies Co., Ltd., China). Ten successful reads were required and the median was recorded. The ratio of the IQR divided by median (IQR/median) of all measurements less than 30% with a success rate (successful tests/total tests) ≥ 60% was regarded as a valid measurement and controlled attenuation parameter (CAP) ≥ 240 was defined as hepatic steatosis. [14]

MAFLD diagnosis standard is conformed to the 2020 international consensus. [6] All data collection was completed and registered in the electronic medical record system of the Health Management Center of the First Affiliated Hospital of Chongqing Medical University.

Statistical analysis

We conducted statistical analyses using IBM SPSS version 23.0. Continuous variables were tested normality and accordingly expressed as mean ± standard deviation or medians (interquartile range), while categorical variables were expressed as number (%). We conducted *t* test of two independent-samples to explore the difference of anthropology information and laboratory test results between cancer cohort and

non-cancer controls. The chi-square was employed to compare the prevalence of HS and MAFLD in the two groups. P values < 0.05 were considered to be statistically significant.

Results

Cohort and controls characteristics

A total of 263 breast cancer survivors with complete data were enrolled in the study. The median of follow-up duration were 24 months (IQR 12 to 36) after surgery. A 1:10 match in terms of age and sex was conducted, and 2630 physical examinees as non-cancer controls were finally enrolled in the study. The anthropology information, laboratory test results and other baseline characteristics of BCS and non-cancer controls are presented in Table 1. The median age of both breast cancer survivors and non-cancer controls were 53 (IQR, 46 to 57) without significant difference between each other. Waist circumference and BMI were significantly different between the case and control groups (82.3 vs. 77.0 and 23.6 vs. 22.8 respectively, P□0.001). Fasting glucose level in breast cancer cohort (5.7 mmol/L, (IQR, 5.3 to 6.2)) was significantly higher than that in non-cancer population (5.3 mmol/L, (IQR, 5.0 to 5.7)). Significant difference was seen in lipids level of the two groups as well (all p values□0.001). BCS had a higher triglycerides level of 1.43 mmol/L (IQR 1.05 to 2.06) than that of the non-cancer controls (1.21 mmol/L (IQR 0.88 to 1.68)). Compared with 1.58±0.46 mmol/L in the non-cancer population, the level of HDL–cholesterol was obviously lower in the cancer group (1.47 mmol/L (IQR 1.24 to 1.70)). The total cholesterol and LDL-Cholesterol levels in the breast cancer survivors (4.16 mmol/L (IQR 4.00 to 5.21) & 2.77 mmol/L (IQR 1.05 to 2.06)) were significantly lower than those in the controls ((5.01 mmol/L (IQR 4.39 to 5.66) & 3.07 mmol/L (IQR 2.52 to 3.66)), respectively).

Prevalence of hepatic steatosis and MAFLD in the breast cancer survivors and healthcare population

The prevalence of HS detected by US in BCS was obviously higher than that in healthcare population (41.8% vs. 22.4%, P<0.001), and the prevalence rose to 69.6% when BCS were screened by USE. The prevalence of MAFLD based on US in breast cancer survivors was significantly higher than that in healthcare population (39.5% vs. 21.2%, P<0.001), and the prevalence of MAFLD in rose to 63.5% when USE was implemented. In the meantime, the prevalence of HS and MAFLD based on US in elderly BCS (≥60 yr) were obviously higher than those in healthcare population (56.7% & 56.7 % vs. 31.3% & 30.7%, P<0.001), respectively; the prevalence of HS and MAFLD based on USE in the elderly breast cancer survivors (≥60 yr) were 80.0% and 73.3%, respectively (Table 2.).

Table 1. Baseline characteristics of breast cancer survivors and healthcare population.

Characteristics	Breast cancer survivors (N=263)	Healthcare population (N=2630)	*P* values
Follow-up duration(month)	24(12,36)	/	
Treatment (n=258)			
endocrinology therapy	31(12.0%)	/	
Chemotherapy	93(36.0%)	/	
Chemotherapy plus endocrinology therapy	132(51.2%)	/	
None*	2(0.8%)	/	
Age(years)	53(46,57)	53(46,57)	1.00
Height(cm)	157(153,160)	156(152,160)	0.01
Body weight(kg)	57.5(53.0,63.0)	56.0(51.0,60.3)	0.001
Waist circumference(cm)	82.3±8.3	77.0±7.8	0.001
Body mass index (kg/m^2)	23.6(21.6,25.4)	22.8(21.1, 24.9)	0.001
Hip circumference(cm)	92(88.0,97.0)	/	/
Fasting glucose (mmol/L)	5.7(5.3,6.2)	5.3(5.0,5.7)	0.001
Alanine aminotransferase (U/L)	18.0(14.0,25.0)	18.0(13.0,24.0)	0.467
Aspartate aminotransferase (U/L)	21.0(17.0,25.0)	21.0(18.0,25.0)	0.943
Alkaline phosphatase (U/L)	72.0(58.0,98.5)	72.0(59.0,89.0)	0.787
Gamma-Glutamyl Transferase(U/L)	21.0(15.0,34.0)	17.0(13.0,25.0)	0.001
Uric acid (umol/L)	4.5(3.8,5.6)	4.9(4.1,5.8)	0.001
Creatinine (umol/L)	57.0(51.5,65.0)	56.0(50,62.5)	0.073
Urea (mmol/L)	291.0(255.5,358.5)	276.0(238.0,321.0)	0.001
Total cholesterol (mmol/L)	4.61(4.0,5.21)	5.01(4.39,5.66)	0.001
HDL−cholesterol (mmol/L)	1.47(1.24,1.70)	1.58±0.46	0.001
LDL−cholesterol (mmol/L)	2.77(2.2,3.41)	3. 07(2.52,3.66)	0.001
Triglycerides (mmol/L)	1.43(1.05,2.06)	1.21(0.88,1.68)	0.001
High Sensitivity	0.60(0.30, 1.28)	0.60(0.31,1.27)	0.052

C-Reactive Protein(mg/L)

Continuous variables were expressed as mean ± standard deviation or median (interquartile range), and compared by unpaired t test or Mann-Whitney U test as appropriate.

Abbreviation: HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index.

*Patients didn't receive neither chemotherapy nor endocrinology therapy.

Table 2. The prevalence of metabolic associated fatty liver disease and hepatic steatosis in female breast cancer survivors and healthcare population based on conventional liver ultrasonography (US) and liver elastography (USE).

	Detection methods		Female breast cancer survivors		Healthcare population		*P* values
			Total population	Age≥60	Total population	Age≥60	
HS	US	Normal	153(58.2%)	26(43.3%)	2042(77.6%)	412(68.7%)	□0.001
		Positive	110(41.8%)	34(56.7%)	588(22.4%)	188(31.3%)	
	USE	Normal	80(30.4%)	12(20.0%)	/	/	
		Positive	183(69.6%)	48(80.0%)	/	/	
MALFD	US	Normal	159(60.5%)	27(45.0%)	2072(78.8%)	416(69.3%)	□0.001
		Positive	104(39.5%)	33(55.0%)	558(21.2%)	184(30.7%)	
	USE	Normal	96(36.6%)	16(36.7%)	/	/	
		Positive	167(63.5%)	44(73.3%)	/	/	
		Total	263	60	2630	600	

Categorical variables were expressed as number (%) and compared by chi-square test.

Abbreviation: HS, Hepatic steatosis; MALFD, Metabolic associated fatty liver; US, conventional liver ultrasonography; USE, liver ultrasound elastography

Discussion

In our study, the median age of breast cancer survivors and non-cancer controls were 53 years without existence of significance. While there were significant difference of the metabolism index between the two groups. Both the BMI and waist circumferences of BCS were significantly higher than those of non-cancer controls (Table 1). Previous studies have established the evidence that greater weight relates to [illegible] well [10, 17], and waist circumferences, a more

precise reflection of body fatty distribution, is dose-independent associated with breast cancer [18]. 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 in Asian female. In addition to the risks mentioned, the elevated fasting glucose level and triglycerides in BCS indicated the metabolism disorder as well. The existence of metabolism disorder in BCS may explain the obvious disparity of hepatic steatosis and further MAFLD prevalence between breast cancer survivors and non-cancer controls.

Jeffrey Browning et.al, using proton magnetic resonance spectroscopy (proton-MRS), found the hepatic steatosis was presented in 31% of 2,287 urban participants in the United States. [19] While our study found 22.4% of female general population was diagnosed with HS, consistent with another Chinese research that 20.59% female in Shanghai were diagnosed with HS [20]. The disparity might be attributable to the different ethnic groups and detection methods. In breast cancer survivors, the prevalence of HS (41.8%) according to liver ultrasonography was significantly higher than that of healthcare population and even higher than Browning's results. The shared risk factors between breast cancer and HS, synergistically coupled with the existence of metabolism disorder in BCS might be associated with the higher prevalence of HS. In addition, 43% of breast cancer patients treated with tamoxifen are reported to develop steatosis as well. [21] Researches have revealed that 20-year absolute excess risk of mortality was 10.7% higher with steatosis, [4] and thus general and breast cancer population in particular should be alerted the occurrence of hepatic steatosis and informed the importance of the reversing hepatic steatosis. The public health efforts focused on the prevention and control measures of HS require knowledge on its prevalence and in order to explore the specific and accurate prevalence rate of HS in BCS, we implemented liver ultrasound elastography. Liver ultrasound elastography was regarded as the more sensitive tool for HS diagnosis than conventional liver ultrasonography [15, 22]. We used FibroTouch, a new generation of transient elastography, and more HS in the same BCS was detected (69.5%). The diagnosis of MAFLD requires pre-diagnosis of HS according to the 2020 international consensus, and the high prevalence of HS directly reflected the current epidemiology of MAFLD. In our study, MAFLD was presented in 39.5% in BCS via liver ultrasonography detection, while a previous Korean reported 30.0% rate of NAFLD occurrence in breast cancer patients [23]. Since NAFLD diagnosis necessitates the exclusion of "excess" alcoholic consumption, which is not necessary for the diagnosis of MAFLD, MAFLD prevalence is not equal to NAFLD prevalence and ought to be higher despite of the same detection modality. And using Fibrotouch, we found an even higher prevalence of MAFLD (63.5%) among BCS, and the prevalence of HS and MAFLD based on USE rose to 80.0% and 73.3%, respectively, which to some extent reflected more accurate situation involving MAFLD prevalence in cancer population. As a rapid increase disease worldwide, MAFLD does not draw surgeon's attention, and despite of the high frequency in breast cancer patients, the recognition that MAFLD has occurred is often delayed or even neglected in breast specialists. According to the guidelines, liver ultrasonography is not recommended for routine follow-up in a asymptomatic patient with no specific findings on clinical examination[24, 25]. While HS usually present with no symptoms, therefore liver ultrasonography ultrasound for screening of BCS with HS might be absent, which leads to the failure of early prevention of HS and increases the risk of progress to MAFLD. MAFLD is highly linked to a rise in

the risk of cardiovascular disease (CVD), and BCS are at a greater risk for CVD-related mortality. The ignorance of HS and MAFLD seriously affected the prognosis of BCS.Considering the frequency of HS and MAFLD in breast cancer survivors, liver ultrasonography screening for HS should be enhanced and further, the liver ultrasound elastography detection should be promoted and constituted into the routine screening items.

Our study has the strengths of an initial use of liver ultrasound elastography to detect the HS prevalence among breast cancer survivors. However, it also has a few limitations. First, all subjects were Chinese. Further studies are required to shed light on the epidemiology of MAFLD. Second, in light of the relatively small sample size, we obtained the HS prevalence among breast cancer survivors without the stratification of therapy methods and molecular types of breast cancer, otherwise we could obtain a more specific prevention strategies accordingly. While one aim of this study has achieved that breast oncologist were alerted to the high prevalence of hepatic steatosis.

It is to our knowledge the first study reporting estimates on the prevalence of MAFLD in breast cancer survivors by means of liver ultrasound elastography. We found that BCS are predisposed to HS and MAFLD than healthcare population and most of the elderly breast cancer survivors (≥60 yr) suffered HS and MAFLD, which alerts the importance of early prevention, diagnosis and treatment of HS and MAFLD in breast cancer survivors. Considering the frequency of HS and MAFLD in breast cancer survivors, liver ultrasonography screening for HS should be enhanced and further, the liver ultrasound elastography detection should be promoted and constituted into the routine screening items. Further well-designed, prospective cohort studies are required to validate our findings, and an intervention study of MAFLD development is needed to be conducted in the future.

Declarations

Financial support

The authors received no financial support to produce this manuscript.

Conflicts of interests

The authors declare no conflicts of interest that pertain to this work.

Author’s contributions

Study design: Ling-quan Kong, Shen Tian, Kai-nan Wu. Data collection: Shen Tian, Hao Li, Ren-hua Li, Liang Ran, Shu Li, Juan Wu, Zhou Xu, Xin-yu Liang, Yu-ling Chen, Jun Xiao, Jia-ying Wei, Chen-yu Ma, Jing-yui Song, Rui-ling She. Data analysis: Shen Tian, Hao Li, Shu Li, Juan Wu, Zhou Xu, Xin-yu Liang, Yu-

ling Chen, support: Ling-quan Kong, Kai-nan Wu, Ren-hua Li, Liang Ran. Manuscript drafting: Shen Tian, Hao Li, Shu Li, Juan Wu. All authors read, and approved the final version of the manuscript.

References

1. Sanyal AJ. Past, present and future perspectives in nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol. 2019;16:377–86. doi:10.1038/s41575-019-0144-8.
2. Farrell GC, Wong VW-S, Chitturi S. NAFLD in Asia—as common and important as in the West. Nat Rev Gastroenterol Hepatol. 2013;10:307–18. doi:10.1038/nrgastro.2013.34.
3. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64:73–84. doi:10.1002/hep.28431.
4. Simon TG, Roelstraete B, Khalili H, Hagström H, Ludvigsson JF. Mortality in biopsy-confirmed nonalcoholic fatty liver disease: Results from a nationwide cohort. Gut 2020. doi:10.1136/gutjnl-2020-322786.
5. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. From NAFLD to MAFLD: when pathophysiology succeeds: An international expert consensus statement. J Hepatol 2020. doi:10.1016/j.jhep.2020.03.039.
6. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol 2020. doi:10.1016/j.jhep.2020.03.039.
7. Buono G, Crispo A, Giuliano M, Angelis C de, Schettini F, Forestieri V, et al. Metabolic syndrome and early stage breast cancer outcome: Results from a prospective observational study. Breast Cancer Res Treat. 2020;14:2. doi:10.1007/s10549-020-05701-7.
8. Iyengar NM, Gucalp A, Dannenberg AJ, Hudis CA. Obesity and Cancer Mechanisms: Tumor Microenvironment and Inflammation. J Clin Oncol. 2016;34:4270–6. doi:10.1200/JCO.2016.67.4283.
9. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA: A Cancer Journal for Clinicians. 2020;70:7–30. doi:10.3322/caac.21590.
10. Shahril MR, Amirfaiz S, Lua PL, Nurnazahiah A, Zakarai NS, Kow VL, et al. Prevalence of Metabolic Syndrome among Breast Cancer Survivors in East Coast of Peninsular Malaysia 2020. doi:10.21203/rs.3.rs-22221/v3.
11. Duman BB, Gunaldi M, Tasdogan BE, Usul Afsar C, Paydas S, Gumurdulu Y. Nonalcoholic fatty liver disease after adjuvant therapy in nonmetastatic breast cancer. Journal of Clinical Oncology. 2013;31:9587. doi:10.1200/jco.2013.31.15_suppl.9587.
12. Palmisano BT, Zhu L, Eckel RH, Stafford JM. Sex differences in lipid and lipoprotein metabolism. Mol Metab. 2018;15:45–55. doi:10.1016/j.molmet.2018.05.008.
13. Li Q, Dhyani M, Grajo JR, Sirlin C, Samir AE. Current status of imaging in nonalcoholic fatty liver disease. World J Hepatol. 2018;10:530–42. doi:10.4254/wjh.v10.i8.530.

14. Zhu S-H, Zheng KI, Hu D-S, Gao F, Rios RS, Li G, et al. Optimal thresholds for ultrasound attenuation parameter in the evaluation of hepatic steatosis severity: Evidence from a cohort of patients with biopsy-proven fatty liver disease. Eur J Gastroenterol Hepatol 2020. doi:10.1097/MEG.0000000000001746.
15. Eslam M, Sarin SK, Wong VW-S, Fan J-G, Kawaguchi T, Ahn SH, et al. The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. Hepatol Int 2020. doi:10.1007/s12072-020-10094-2.
16. Li H, Wang Z, Liu J-S, Zou B-S, Chen H-R, Xu Z, et al. Association Between Breast and Thyroid Lesions: A Cross-Sectional Study Based on Ultrasonography Screening in China. Thyroid. 2020;30:1150–8. doi:10.1089/thy.2019.0184.
17. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018;68:394–424. doi:10.3322/caac.21492.
18. Lee KR, Seo MH, Do Han K, Jung J, Hwang IC. Waist circumference and risk of 23 site-specific cancers: A population-based cohort study of Korean adults. Br J Cancer. 2018;119:1018–27. doi:10.1038/s41416-018-0214-7.
19. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, et al. Prevalence of hepatic steatosis in an urban population in the United States: Impact of ethnicity. Hepatology. 2004;40:1387–95. doi:10.1002/hep.20466.
20. Fan J-G, Zhu J, Li X-J, Chen L, Li L, Dai F, et al. Prevalence of and risk factors for fatty liver in a general population of Shanghai, China. J Hepatol. 2005;43:508–14. doi:10.1016/j.jhep.2005.02.042.
21. Yan M, Wang J, Xuan Q, Dong T, He J, Zhang Q. The Relationship Between Tamoxifen-associated Nonalcoholic Fatty Liver Disease and the Prognosis of Patients With Early-stage Breast Cancer. Clin Breast Cancer. 2017;17:195–203. doi:10.1016/j.clbc.2016.12.004.
22. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67:328–57. doi:10.1002/hep.29367.
23. Kwak M-S, Yim JY, Yi A, Chung G-E, Yang JI, Kim D, et al. Nonalcoholic fatty liver disease is associated with breast cancer in nonobese women. Dig Liver Dis. 2019;51:1030–5. doi:10.1016/j.dld.2018.12.024.
24. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol. 2019;30:1194–220. doi:10.1093/annonc/mdz173.
25. Khatcheressian JL, Hurley P, Bantug E, Esserman LJ, Grunfeld E, Halberg F, et al. Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013;31:961–5. doi:10.1200/JCO.2012.45.9859.