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• BRIEF REPORTS •

Fatty metamorphosis of the liver in patients with breast cancer: Possible associated factors

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Abstract

AIM: To investigate the relationship between breast cancer and fatty liver in Chinese patients.

METHODS: The study group consisted of 217 patients with newly diagnosed breast cancers and the control group of 182 subjects undergoing routine health examination in the same hospital. All subjects were female and the groups were matched for date of study. Ultrasound scanning was performed by the same operator using a 3.5 mHz transducer. Steatosis of the liver was diagnosed based on the criteria of Saverymuttu *et al*. Clinical variables were statistically analyzed.

RESULTS: Fatty liver was diagnosed in 98 patients of the study group and 37 patients of the control group, a significant difference was found in incidence (98/217, 45.2 % and 37/182, 20.3 %; $P<0.0001$). On univariate analysis, fatty liver in breast cancer patients was associated with overweight, hyperlipidemia, and hepatitis. On multivariate analysis in the same patients, obesity and hyperlipidemia were significantly associated with fatty liver.

CONCLUSION: The cause of fatty liver in women with breast cancer may be multifactorial. The present study confirms its link with overweight and hyperlipidemia.

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INTRODUCTION

Breast cancer is a common cancer in the developed countries such as Western Europe and North America where women tend to be well-nourished. In 1973, the reported crude annual incidence rate of new breast cancer was 71.5 per 100 000 in Canada[1]. This contrasts with the incidence in Taiwanese women of 6.11 per 100 000 published in 1971[2]. However, more recent epidemiological studies revealed an increasing incidence of breast cancer with 12.46 per 100 000 in Taiwan[3]. The development of breast cancer is multifactorial. Genetic, dietary, environmental, menstrual, endocrine and ethnic factors all influence it[4]. In the course of using ultrasonography to assess liver metastases from breast cancer, we have noted a fair number of women with breast cancer who also have fatty liver. The aim of this study was to investigate the incidence and clinicopathological factors associated with fatty liver in patients with breast carcinoma.

MATERIALS AND METHODS

A hospital-based prospective study was conducted to investigate the relationship between fatty liver and breast cancer. From May 1994 to August 1997, 217 consecutive, newly diagnosed women with breast cancer were enrolled as the study group. 182 subjects presenting to the same hospital for routine health examination was served as the control group of the same period. All subjects underwent abdominal ultrasonography performed by the same operator using a 3.5 mHz transducer (Toshiba SSA-340A). Fatty liver was diagnosed in the presence of at least two of the following sonographic features: (1) increase in liver echoes, (2) loss of echoes from the wall of the portal veins, (3) exaggeration of liver and kidney echo discrepancy, and (4) ultrasonic attenuation of the liver parenchyma. Overweight was defined as a BMI >25 [body mass index = weight (kg)/height (m^2)]. Subjects were excluded if they were pregnant, on a weight reduction diet in the 6 months preceding the study, or taking cholesterol-lowering therapy or steroids. Data collected included age, the presence of hepatitis C virus antibodies with elevation of alanine aminotransferase (GPT) and aspartate aminotransferase (GOT), BMI, a history of diabetes or hyperlipidemia, drug use (contraceptives, steroids, tamoxifen, alcohol), and chemotherapy.

Statistical analysis

The chi-square test was used for univariate analysis of these factors. Statistically significant variables on univariate analysis were subsequently subjected to multivariate analysis with logistic regression. A P value less than 0.05 was considered to be statistically significant.

RESULTS

The mean age of the breast cancer patients was slightly higher than that of the controls (48.6±10.5 *vs* 46.8±12.0; $P=0.029$). None of the subjects in either group drank alcohol. Fatty liver was found in 98/217 (45.2 %) of the study group and in 37/182 (20.3 %) of the control group, with a statistically significant difference ($P<0.0001$). The breast cancer subjects were also significantly more likely to be obese than controls (124/217, 57.1 % *vs*. 45/182, 24.7 %, $P<0.0001$). There were no significant differences in the presence of hyperlipidemia or hepatitis C (Table 1).

On univariate analysis, fatty liver in subjects with breast cancer was significantly associated with overweight, hyperlipidemia, and hepatitis C but not with diabetes mellitus, tamoxifen, contraceptives, or chemotherapy (Table 2). Using logistic regression, the odds of fatty liver were increased in the breast cancer subjects in the presence of overweight (OR 1.406, $P<0.0001$) and hyperlipidemia (OR 1.206, $P=0.0473$) (Table 3).

Table 1 Clinical variables in patients with breast cancer and controls

Variables	Cases (*n*=217) Number (%)	Controls (***n***=182) Number (%)	*P*
Fatty liver			
No	119 (54.8)	145 (79.7)	
Yes	98 (45.2)	37 (20.3)	<0.0001
Overweight			
No	93 (42.9)	137 (75.3)	
Yes	124 (57.1)	45 (24.7)	<0.0001
Hyperlipidemia			
No	177 (81.6)	154 (84.6)	
Yes	40 (18.4)	28 (15.4)	0.432
Hepatitis C			
No	204 (94.0)	165 (90.6)	
Yes	13 (6.0)	17 (9.4)	0.144
Age			
Mean ± SD	48.6±10.5	46.8±12.0	0.029

Table 2 Clinical factors associated with fatty liver in patients with breast cancer (*n*=217)

Variables	Number of cases		*P*
	Fatty Liver (-)	Fatty Liver (+)	
Contraceptives			
No	117	94	
Yes	2	4	0.28
Tamoxifen			
No	25	13	
Yes	94	85	0.14
Chemotherapy			
No	52	49	
Yes	58	47	0.59
Hepatitis C			
No	116	88	
Yes	10	3	0.031
Diabetes			
No	113	92	
Yes	6	6	0.73
Overweight			
No	71	21	
Yes	48	77	<0.0001
Hyperlipidemia			
No	106	71	
Yes	13	27	0.017

Table 3 Significant variables on multivariate analysis for patients with breast cancer

Variables	Coefficient estimates and significant test			
	Coefficient	SD	*P*	Odds ratio
Overweight	0.3410	0.0474	0.0000	1.4064
Hyperlipidemia	0.0263	0.0132	0.0473	1.2066

DISCUSSION

Fatty liver is associated with alcohol abuse, obesity, malnutrition, diabetes mellitus, toxic agents, corticosteroids and endocrine imbalance. However, there had been little investigation of this disorder in relation to malignancy until Lanza reported in 1968 that a fair number of patients with known cancer had steatosis on percutaneous liver biopsy[5]. The diagnostic criteria and high accuracy of ultrasound in the detection of fatty liver were documented by Foster and Saverymuttu *et al*[6,7]. In a similar manner, an unusually high proportion of fatty liver in patients with carcinoma of breast was observed in the present study (Table 1). In this study, fatty liver was observed in 37 out of 182 (20.3 %) asymptomatic control subjects, significantly less than the 45.2 % of breast cancer subjects. Fatty liver was related to BMI, dietary fat intake, and ethnic differences. The actual incidence in the general population was varied.

The results of numerous epidemiological studies have demonstrated that the risk for breast cancer is related to a variety of factors, including age at menarche and at first childbirth, parity, level of education, previous benign breast tumor, family history of breast cancer, young age at menopause, environmental factors, ethnicity, BMI, dietary fat intake, and high central adiposity[2,8-10]. A significantly higher proportion of the breast cancer subjects were obese compared with controls (57.1 % *vs.* 15.4 %). With increasing weight, long chain fatty acid synthesis also increases, which in turn leads to lipid accumulation in the liver. It is likely that the higher incidence of fatty liver in our breast cancer subjects is related at least in part to their higher BMI.

The excess estrogen and insulin-like growth factor (IGF-1) produced by obese women have been suggested to be the key factor in promoting proliferation of mammary epithelial cells[11-14]. Furthermore, obesity may lead to delay in diagnosis, and it appears to be a poor prognostic factor[15,16].

Tamoxifen is an anti-estrogenic drug utilized in adjuvant therapy for breast cancer. Ogawa and colleagues suggested in 1998 that tamoxifen induced fatty liver in patients with breast cancer[17]. Nguyen published a study in 2001 demonstrating an increase in fatty liver and accumulation of visceral adipose tissue in breast cancer patients receiving tamoxifen[18]. Fatty liver can occur because of increased delivery of free fatty acids to the liver, increased synthesis of fatty acids in the liver, decreased β-oxidation of free fatty acids, and decreased synthesis or secretion of very low density lipoprotein[19]. Tamoxifen must therefore disarrange some of the steps in lipid metabolism[20].

There are a few reports of tamoxifen-associated steatohepatitis and multi-focal fatty infiltration of the liver[21,22]. Generally speaking, patients with fatty liver are usually symptom-free, but severe steatohepatitis may lead to liver cirrhosis in some cases. Therefore, careful attention should be paid to functional and morphological changes of the liver during tamoxifen treatment[21]. We have not yet found a significant relationship between tamoxifen and fatty liver in our subjects. This may be resulted from the insufficient length of tamoxifen treatment. Our subjects who took tamoxifen did for a mean of 12 months (range: 2-38 months), compared with a mean of 30 months (range: 4-84 months) in Nguyen' s series[18].

The clinical appearance of hepatic fatty changes may be diffuse, focal, multi-focal, the latter findings possibly mimic or harbor either primary or metastatic cancer[17,22]. Because of the possibility of liver metastases as well as the possibility of fatty liver (including the chance of progression to steatohepatitis or cirrhosis) with or without tamoxifen, it would be wise to monitor liver function and imaging in patients with breast cancer.

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