

Incidence and risk factors for non-alcoholic steatohepatitis in females treated with tamoxifen for breast cancer

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 - Received 13 July 2010. Accepted 19 October 2010. Available online 3 February 2011.
 - <http://dx.doi.org/10.1016/j.ajg.2011.01.003>, [How to Cite or Link Using DOI](#)
 - Cited by in Scopus (0)
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Abstract

Background and study aims

Tamoxifen used in the treatment of breast cancer is reported to cause hepatic steatosis. This study aimed to assess the incidence and risk factors of the development of fatty liver disease, resulting from tamoxifen use, in females with breast cancer.

Patients and methods

Seventy females aged between 28 and 80 years with breast cancer were recruited from Shahid Sadoughi Clinic, Yazd, Iran in 2006–2008. The patients underwent chemotherapy followed by 20 mg tamoxifen daily as postoperative endocrine treatment. Only in patients with normal baseline liver function, negative test for hepatitis C virus (HCV) and hepatitis B surface antigen (HbsAg) and normal liver ultrasonography were included. The development of fatty changes over a 6-months period of treatment was the main outcome measurement assessed by ultrasonography.

Results

Thirty-five of 70 patients developed fatty change during follow-up, in which nine were in grade one, 20 in grade two and six patients in grade three. Risk factors associated with the development of fatty change were elevation of triglycerides (2.4, 1.2–4.8), elevation of fasting blood sugar (FBS) and low high-density lipoprotein (HDL) (3.4, 1.4–7.8). No relation was found between the development of fatty change and age (1.3, 0.87–2.00), menopause (1.13, 0.69–1.9), previous history of diabetes (2.4, 0.7–8.4), previous chemotherapy regimen and receptors type (c-erbB2, P53, progesterone receptor (PR), oestrogen receptor (ER)) and stage of breast cancer. Further, there was no relation between the

development of fatty change and hypercholesterolemia, low-density lipoprotein (LDL), arterial hypertension and body mass index (BMI).

Conclusion

Tamoxifen was associated with a high risk of development of non-alcoholic steatohepatitis in patients with higher triglycerides and FBS and lower HDL. However, no relationship was found with the level of BMI, LDL, hypertension, overweight and obesity.

Keywords

- Tamoxifen;
 - Breast cancer;
 - Fatty liver
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Introduction

Breast cancer is the most common cancer in females, the second most common cause of cancer death and the main cause of death in women aged 45–55 in the USA [1]. It is also the most common malignancy among Iranian women with an incidence rate of 18.2/100,000 [2].

Tamoxifen is a partial oestrogen receptor antagonist; it has a 10-fold greater antitumour activity in breast-cancer patients whose tumours express oestrogen receptors than in those who have low or no levels of expression. Side effects include increased risk of oestrogen-related cardiovascular complications, such as thrombo-embolic phenomena, and development of non-alcoholic fatty liver and non-alcoholic steatohepatitis (NASH) [3] and [4].

A number of case reports have described hepatic steatosis associated with adjuvant tamoxifen therapy. Hepatic steatosis associated with tamoxifen was observed to be transient and occurred with or without hepatic dysfunction, histologically proven NASH or even cirrhosis of the liver [5], [6], [7] and [8].

Tamoxifen has been shown to increase hepatic fat content by blocking the role of oestrogen in maintaining hepatic lipid homeostasis by supporting the expression of genes involved in lipid β -oxidation, albeit the exact mechanism is not known [9].

In this study, our aim was to assess the effect of tamoxifen on the liver and its ability to induce NASH in Iranian females with breast cancer, who were under tamoxifen medication as chemoprevention.

Patients and methods

This is a prospective study on 70 women with breast cancer aged 28–80 years, who underwent chemotherapy and subsequently received tamoxifen (20 mg) as adjuvant chemotherapy in Shahid Sadoughi Clinic, Yazd, Iran in 2006–2008.

The inclusion criteria included normal liver ultrasonography, normal baseline liver function test and negative antihepatitis C virus (HCV) antibodies and hepatitis B surface antigen (HbsAg) tests. Patients were excluded if they had a history of liver diseases, evidence of liver disease on physical examination, history of alcohol abuse or other hepatotoxic drugs, were under steroid treatment or had concomitant other illness and fatty change at the beginning of the study.

Real time ultrasonography (Siemens, Sonoline G, USA) was used to evaluate the hepatic parenchymal fat changes in patients at the beginning of tamoxifen usage and then 6 months later. All ultrasonography procedures were performed by the same operator (N.M), who was unaware of the clinical and laboratory results. The presence of fatty liver was determined in a qualitative manner using conventional criteria, including a bright hepatic echopattern. The diagnosis of fatty liver was established according to the standard criteria of American Gastroenterology Association [10] and [11]: An increase in hepatic echogenicity with respect to renal echogenicity as a reference, the presence of enhancement and lack of differentiation in periportal intensity and the vesicular wall due to great hyperechogenicity of the parenchyma. Measurement was standardised using a semiquantitative scale of the degree of hepatic enhancement.

Laboratory tests including transaminases, blood glucose and lipid profile were done in all the patients.

Statistical analysis

Using Statistical Package for Social Sciences (SPSS) software (version 11.5), the Fisher's exact test, chi square and analysis of variance (ANOVA) tests were selected to assess the differences in the frequency of the outcomes. Further, Cox proportional hazards regression was used to determine the independent effects of multiple factors on the development of fatty change during treatment.

Results

Tamoxifen induced fatty change in 35 out of 70 (50%) patients. These changes were of grade one in nine, grade two in 20 and grade three in six patients (Fig. 1). However, no relationship was found between age and incidence of fatty liver with a relative risk (RR) of 1.3%, $p = 0.339$ confidence limit (CL) (0.87–2) and 95% confidence interval (CI) (Fig. 2). Further, there was no significant relationship between body mass index (BMI) and incidence of fatty change in these patients. The mean BMI in patients without fatty changes was $26.65 \pm 3.6 \text{ kg m}^{-2}$ and in the fatty change group, it was $27.80 \pm 5.05 \text{ kg m}^{-2}$ (ANOVAs $P = 0.278$).

■ grade 1 ■ grade 2 ■ grade3

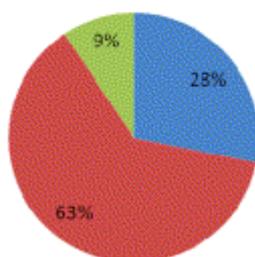


Fig. 1. Grade of fatty changes in 35 patients.

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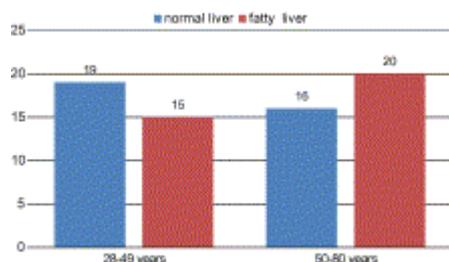


Fig. 2. Age groups in fatty and normal liver patients.

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Elevation of triglycerides was observed to be related to the induction of fatty change with mean triglyceride level of 145.62 mmol l⁻¹ in the normal group and 222.51 mmol l⁻¹ in the fatty liver group (ANOVA $P = 0.003$).

There was no association between cholesterol, low-density lipoprotein (LDL)-cholesterol and fatty liver in patients using tamoxifen (ANOVA $P = 0.948$ and $P = 0.933$, respectively). However, low high-density lipoprotein (HDL) was related to the incidence of fatty change with mean HDL being 48.74 mmol l⁻¹ in the normal group and 43.77 mmol l⁻¹ in the fatty change group ($P.V = 0.020$). Therefore, lower HDL could be a risk factor for the incidence of fatty liver in patients using tamoxifen. The mean of FBS in the normal group was 96 ± 19 mg dl⁻¹ while the mean of FBS in the fatty liver group was 113.41 mg dl⁻¹ (ANOVA $P = 0.026$).

There were no statistically significant differences in the alanine aminotransferase (ALT) mean during pre- and posttreatment, although it was higher in the fatty change group ($P = 0.413$). ALT elevations occurred five times more often in the fatty group than in the normal liver group. ALT and aspartate aminotransferase (AST) means were significantly higher in the group of females with fatty change on ultrasonography than in patients with normal liver who were using tamoxifen ($P = 0.056$), being four times more common in the fatty group compared with the normal group.

In this study, no association was found between menopause status and the development of fatty change in the liver (RR = 1.3, CI (0.69–1.9)).

There was no relationship between fatty change and positive or negative c-erbB2 receptor in breast-cancer patients (chi-square RR = 0.89, CI (0.56–1.4), $P = 0.632$) in the presence of hypertension; p53 receptor, oestrogen receptor and progesterone receptor did not differ significantly in the two groups ([Table 1](#)). Furthermore, there was no association between the stage of cancer and the development of fatty change in the liver in patients who underwent chemotherapy ([Fig. 3](#)).

Table 1. Association between several parameters and the development of fatty changes.

Factor	Hazard ratio	Confidence interval
Triglycerides	2.6	(1.2–4.7)
Diabetes	2.4	(0.7–8.4)
Lower HDL	3.4	(1.4–7.8)
Age	1.3	(0.87–2.00)
Menopause	1.13	(0.69–1.9)
Oestrogen receptor	0.81	(0.46–1.4)

Factor	Hazard ratio	Confidence interval
Progesterone receptor	0.65	(0.38–1.1)
P53	1.2	(0.73–1.9)
CERbB2	0.89	(0.56–1.42)
Arterial hypertension	0.73	(0.39–1.4)

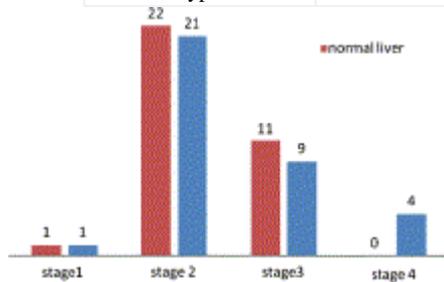


Fig. 3. Frequency of patients in stage of breast cancer and fatty liver.

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Discussion

The present study was conducted on 70 female patients with breast cancer, who used tamoxifen as postoperative endocrine treatment, and demonstrated the development of fatty change in the liver for over 50% of patients. In another similar study in Japan, a lower percentage (38%) of patients developed fatty change [6]. However, they used 40 mg of tamoxifen as a postoperative hormonal therapy; in our study we used daily doses of 20. They also used computed tomography (CT) scan instead of ultrasonography for the evaluation of fatty change in the liver. Their patients showed milder fatty change than our patients, with no significant correlation between age and the development of fatty liver. They also found no correlation between BMI and the incidence of fatty change, while in another study by an Italian group, BMI was strongly associated with the development of non-alcoholic fatty liver disease [12]. Our result is in agreement with the Italian study in which high BMI showed no role in the induction of fatty change, and fatty liver changes were purely due to tamoxifen usage.

Our study is in agreement with other reports in which hypertriglyceridaemia was recognised as a risk factor for inducing NASH in patients using tamoxifen. Tamoxifen may induce hypertriglyceridaemia and, via this mechanism, also may produce fatty change in the liver [13].

We were not able to detect an association between serum levels of cholesterol and LDL-cholesterol with fatty liver in patients using tamoxifen, which is in contradiction with other studies which found high cholesterol to be associated with a higher incidence of fatty change [4] and [5].

However, tamoxifen has been shown to increase serum triglyceride and lower LDL and cholesterol and could possibly reduce the ability of hepatic lipid β -oxidation and ultimately enhance hepatic fat content and hypertriglyceridaemia [6].

Although we found no association between menopause status and the induction of fatty change in the liver, this was not confirmed by the other studies, which showed that the menopause was a determinant factor for hepatic steatosis in women.[14] and [15].

The finding that ALT and AST were significantly higher in the group of women with fatty change than in women with normal liver while using tamoxifen indicates the steatohepatic nature of the lesions,

rather simple fatty changes. This is an important finding because it implies that high rates of ALT and AST may increase the risk of cirrhosis in some patients.

In conclusion, tamoxifen induced hepatic steatosis in over 50% of patients, and, in many of them, these changes correlated with elevation of aminotransferase. These changes might be steatohepatic in nature, which could lead to cirrhosis. It is, therefore, recommended that patients be monitored closely during treatment by measuring transaminases and liver ultrasonography. Based on previous research, it might be appropriate to use the drugs in a lower dosage or even discontinue them [16]. Many cases appear to improve after tamoxifen is discontinued, but whether treatment should always be withdrawn permanently is not still clear, as the effect of tamoxifen on survival from breast cancer appears to be impressive.

Conflicts of interest

The authors declared that there was no conflict of interest.

Acknowledgement

We thank Zohreh Chiti for English language editing.

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