Relationship between Non-Alcoholic Fatty Liver Disease and Breast Cancer

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ABSTRACT:
Background: Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease which refers to the presence of hepatic steatosis. Breast cancer is now the most common cancer in women and is the leading cause of death from cancer among women.
Objectives: To assess the relationship between NAFLD and newly diagnosed cases of breast cancer.
Methods: The results of mammography screening examinations in women referred to the Breast Center, Holy Family Hospital, Nazareth during a 4 year period were collected. We identified cases of women who were newly diagnosed with breast cancer and who underwent abdominal computed tomography (CT) within 1 month of the diagnosis. The control group comprised women with normal mammography and breast ultrasonography who underwent abdominal CT within 3 months from the date of the breast cancer screening during the same study period. The control cases were matched by age and body mass index (BMI). We compared the cases with the controls in terms of the presence of diffuse hepatic fatty liver and other known risk factors for breast cancer.
Results: Of the 133 women with new diagnosis of cancer, 73 were eligible for the study. NAFLD was found in 33 of the women with breast cancer and in 12 in the control group (45.2% vs.16.4%, respectively, $P = 0.002$). Multivariate analysis showed NAFLD (odds ratio 2.82, 95% confidence interval 1.2–5.5, $P = 0.016$) to be associated with breast cancer.
Conclusions: NAFLD is associated with breast cancer.

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KEY WORDS: non-alcoholic fatty liver disease (NAFLD), breast cancer, screening mammography.

Worldwide, breast cancer is now the most common cancer diagnosed in women and the leading cause of death from cancer among women, with approximately 1.3 million new cases and an estimated 458,000 deaths reported in 2008 [1]. The search for risk factors for breast cancer continues. Many risk factors have been thoroughly studied, such as genetics, diet, lifestyle, hormonal replacement therapy, alcohol consumption,

obesity, and breastfeeding [2-5]. Non-alcoholic liver disease (NAFLD) has been described in case reports of patients with breast cancer due to tamoxifen [6]. Fatty liver was reported in 30–38% of breast cancer patients receiving tamoxifen. Bilici et al. [7] reported a high prevalence of NAFLD (63%) among patients with newly diagnosed breast cancer.

NAFLD is a common clinical condition and is considered a significant health problem in our generation. NAFLD can progress to non-alcoholic steatohepatitis (NASH), a fatty liver with hepatitis. This form of liver injury carries a risk for progressive fibrosis (20–40%), cirrhosis (30%), end-stage liver disease and hepatocellular carcinoma [8]. The definitive diagnosis of NAFLD is based on liver biopsy, which is used sparingly in clinical practice. Unenhanced computed tomography (CT) is an accurate imaging modality used to help detect and characterize hepatic steatosis. A combination of dietary modifications and increased physical activity remain the mainstay of NAFLD management [9]. NAFLD may develop due to either disease or treatment such as chemotherapy and endocrine therapy in cancer patients. In addition, NAFLD bears several extrahepatic consequences including cardiovascular disease, malignancy, and infection [10-12]. Moreover, obesity is a major risk factor for NAFLD and is well associated with breast cancer [4]. Against this background, the rationale of this study was to explore any correlation between fatty liver and breast cancer.

PATIENTS AND METHODS

From January 2008 through December 2011, we retrospectively analyzed data of women who were referred for a mammography screening examination at the Breast Center, Holy Family Hospital, Nazareth, Israel. The study was approved by the local medical ethics committee. The annual number of mammograms performed at this hospital is about 4000–5000, and 800–1000 breast ultrasonographic examinations are conducted. Data obtained from the charts and questionnaires from the Breast Center were reviewed (A.Z. and W.N.) and the abdominal CT examinations were assessed for the presence of fatty steatosis by two experienced radiologists. We evaluated demographic features as well as major risk factors for breast

cancer, such as age at first menstrual cycle, age at first delivery, number of pregnancies, number of children, age at menopause, estrogen use of all known types, family history of malignant breast cancer, body mass index (BMI), history of smoking, and major risk factors for NAFLD (obesity and diabetes).

We excluded subjects who were younger than 18 years, were diagnosed as having benign breast tumors, had a past history of malignant breast cancer, exhibited secondary causes for NAFLD (positive serology for hepatitis B, hepatitis C, antinuclear antibody, alcohol consumption > 20 g per day, hypothyroidism and past or current tamoxifen use), and did not have an abdominal CT examination within 1 month of the histological results of breast cancer.

The control group included 73 women with normal screening mammography and breast ultrasonography and who underwent abdominal CT within a period of 3 months from the date of the breast cancer screening during the same study period. The control cases were matched by age and BMI. Demographic information, anthropometric measurements (height, weight, BMI), clinical evaluations, imaging data of the liver (fatty steatosis or not), and laboratory data were collected.

The diagnosis of NAFLD was based on the presence of hepatic steatosis on abdominal CT examination and an attenuation of -5–10 Hounsfield units (HU) (calculated as liver attenuation minus spleen attenuation), no alcohol consumption (< 20 g/day), negative serology for hepatitis B or C virus, negative to antibodies for autoimmune hepatitis, or the absence of history of another known liver disease. Cases for which there was no information regarding the criteria for the NAFLD diagnosis were excluded. Moreover, if any variant of the causes of secondary fatty liver was missed, the case was excluded. The diagnosis of breast cancer was based on the histological examination. We included cases of ductal carcinoma in situ (DCIS), invasive (or infiltrating) ductal carcinoma (IDC), invasive (or infiltrating) lobular carcinoma (ILC), and mixed types.

STATISTICAL ANALYSIS

All variables were presented in appropriate summary tables for descriptive statistics by study groups (breast cancer vs. control group). Continuous variables were presented in tables providing sample size (n), arithmetic mean, and standard deviation. Categorical variables were presented in tables providing sample size, absolute and relative frequency by study group. The two-sample t-test was applied for testing the statistical significance of the difference in the continuous variables between the study groups. Chi-square test was applied for testing the statistical significance of the difference in categorical variables between the study groups. Multivariate analysis was applied for analyzing the effect of fatty liver on breast cancer. All tests applied were two-tailed, and a P value of 5% or less was considered statistically significant. The data were analyzed using SAS® version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Over a 4 year period, 18,500 mammographic examinations and 3200 breast ultrasonographic examinations for suspected masses were performed. A total of 133 new cases of breast cancer were identified. For this study, 73 eligible cases of malignant breast cancer with imaging data (abdominal CT) obtained within one month from the date of the diagnosis of breast malignancy were included in the study. The 73 cases of breast cancer were compared randomly with 73 healthy women matched for age and BMI. The control group included those with normal mammography and breast ultrasonography who underwent abdominal CT within 3 months from the date of breast cancer screening. NAFLD was found in 33 of the 73 women with breast cancer and in 12 of the 73 controls (45.2% vs.16.4%, respectively, P = 0.002).

Demographic and clinical characteristics of the 73 women with breast cancer and the 73 control subjects are shown in Table 1. There was a significant difference between the study group and the control group in the number of cases of fatty liver, age at first delivery, and estrogen use. No significant differences were found between the breast cancer cases and controls regarding age at first menstrual cycle, number of pregnancies, number of children, age at menopause, smoking history, or family history of breast cancer.

Multivariate analysis showed that NAFLD [odds ratio (OR) = 2.82, 95% confidence interval (95%CI) 1.2–5.5, P = 0.016], age over 25 years at first delivery (OR = 1.11, 95%CI 1.008–1.238, P = 0.034) and estrogen use (OR = 3.6, 95%CI 1.30–12.8, P = 0.043) were associated with breast cancer [Table 2].

Table 1. Demographic and clinical characteristics of patients with breast cancer and control subjects

	Breast cancer (n=73)	Control group (n=73)	P value
Age, years (mean)	54.8 ± 12	57.5 ± 9.6	NS
BMI, kg/m² (mean)	29.7 ± 4.4	28.8 ± 5.6	NS
Age at first cycle, years (mean)	13.8 ± 1.5	13.7 ± 1.4	NS
Age at first delivery, years (mean)	22.6 ± 4.8	20.9 ± 3.5	0.023
No. of pregnancies (mean)	6.2 ± 3.6	6.9 ± 2.9	NS
No. of children (mean)	5 ± 2.7	5.4 ± 2.6	NS
Age at menopause, years (mean)	47.9 ± 5.6	48.6 ± 5.1	NS
Smoking	5 (7%)	10 (13.7%)	NS
Estrogen use	13 (17.8%)	5 (7%)	0.05
Family history of breast cancer	14 (19%)	8 (10.9%)	NS
Diabetes mellitus	17 (23%)	18 (25%)	NS
Metabolic syndrome	16 (22%)	12 (16.4%)	NS
Fatty liver	33 (45.2%)	12 (16.4%)	0.002

NS = not significant

Table 2. Results of multivariate analysis

	OR (95%CI)	P value
Fatty liver	2.82 (1.20–5.50)	0.016
Age › 25 years at first delivery	1.11 (1.01–1.24)	0.034
Estrogen use	3.6 (1.30–12.8)	0.043

OR = odds ratio, CI = confidence interval

DISCUSSION

Our findings indicate that NAFLD is associated with breast cancer, independent of known risk factors for breast cancer. In addition, we found that first delivery at age > 25 years and estrogen use were significant risk factors for breast cancer.

NAFLD has an increased overall mortality rate deriving from liver-related and cardiovascular disease. Recently, emerging data have reported an association between NAFLD and the risk of extrahepatic malignancies [13]. In a cross-sectional study, 199 patients with NAFLD defined histologically and by proton magnetic resonance spectroscopy were compared to 181 healthy controls. NAFLD patients had a higher prevalence of colorectal adenomas (34.7% vs. 21.5%, $P = 0.043$) and advanced neoplasms (18.6% vs. 5.5%, $P = 0.002$) than healthy controls [10]. Hwang et al. [14] presented the first evidence for an association of NAFLD with increased rate of colorectal adenomatous polyps. In contrast, Touzin and colleagues [15] failed to demonstrate an increase in incidence of colorectal adenomas in patients with NAFLD.

The proposed mechanism(s) implicating extrahepatic carcinogenesis of fatty liver is not completely understood. Muhidin et al. [16] proposed three major factors that may explain the mechanistic link. The first linkage is via high levels of inflammatory cytokines, especially tumor necrosis factor-alpha. These inflammatory cytokines promote insulin resistance, increase circulating triglycerides, influence growth, and increase apoptosis and tumor cell proliferation in many cancers [17]. The second factor is hyperinsulinemia and high levels of leptin which induce the carcinogenesis effect [18]. Elevated insulin levels lead to increased secretion of estrogen by binding to the circulating sex hormone-binding globulin. The increased estrogen-mediated downstream signaling favors breast carcinogenesis [19]. The third factor is the decreased levels of adiponectin, which leads to marked insulin resistance and subsequent increased levels of insulin growth factor-1 (IGF-1). Insulin binds to IGF-1 receptors and plays an important role in cell proliferation, apoptosis, and increased production of vascular endothelial growth factor. Previous studies in humans have shown an association between hypoadiponectinemia and increased risk of colorectal adenomas [20]. Further studies are needed to assess this association and explore the mechanistic link between fatty liver infiltration and breast cancer.

In our study, we found that women with early age at first delivery (< 25 years old) had a low risk for breast cancer. One study showed that pregnancy is the most significant modifiable factor affecting the risk of breast cancer in women [21]. Although a transient increase in breast cancer risk is observed immediately after parturition in women over 25 years old, the long-term consequences of pregnancy include a strong and life-long breast cancer protective effect.

Several studies have shown that elevations in blood levels of estrogen are associated with a risk of breast cancer. Speroff and co-authors [22] demonstrated in the Million Women Study that the use of hormone or estrogen replacement therapy led to a significant increase in risk of breast cancer. Breast tissue is particularly susceptible to exposure between menarche and first pregnancy, and a longer interval between these reproductive events is associated with increased risk of cancer [23]. Furthermore, some studies have shown that pregnancy could be associated with breast cancer [24]. Therefore, estrogen's response and time of exposure alter the breast cancer risk. Estrogen can exert its action through an extranuclear estrogen receptor pathway that is involved in cell proliferation, migration, secretion, and apoptosis especially in breast carcinogenesis; however, its function and mechanisms are not fully understood [25]. Our finding indicates that there is a significant risk between estrogen use and malignant breast cancer.

LIMITATIONS

Our study has several limitations: it was retrospective, had a small pool of patients, the type and duration of estrogen use and its hormone composition were unknown, and nutritional and genetic data were lacking.

CONCLUSIONS

NAFLD is associated with breast cancer independent of known risk factors of breast cancer. In addition, a significant association was found linking breast cancer, age at first delivery (> 25 years old), and estrogen use. Further studies are needed to explore the relationship between NAFLD and breast cancer.

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"Well done is better than well said "

Benjamin Franklin (1705–1790), one of the Founding Fathers of the United States. A polymath and leading author, politician, scientist, inventor, civic activist, statesman, and diplomat, Franklin is known for his discoveries and theories regarding electricity,

as well as lightning rod, bifocals, and the Franklin stove, among other inventions