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ORIGINAL ARTICLE

Retrospective Study

Association of nonalcoholic fatty liver disease and liver cancer

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Abstract

AIM: To investigate the association between nonalcoholic fatty liver disease (NAFLD) and liver cancer, and NAFLD prevalence in different liver tumors.

METHODS: This is a retrospective study of the clinical, laboratory and histological data of 120 patients diagnosed with primary or secondary hepatic neoplasms and treated at a tertiary center where they underwent hepatic resection and/or liver transplantation, with subsequent evaluation of the explant or liver biopsy. The following criteria were used to exclude patients from the study: a history of alcohol abuse, hepatitis B or C infection, no tumor detected in the liver tissue examined by histological analysis, and the presence of chronic autoimmune hepatitis, hemochromatosis, Wilson's disease, or hepatoblastoma. The occurrence of NAFLD and the association with its known risk factors were studied. The risk factors considered were diabetes mellitus, impaired glucose tolerance, impaired fasting glucose, body mass index, dyslipidemia, and arterial hypertension. Presence of reticulin fibers in the hepatic neoplasms was assessed by histological analysis using slide-mounted specimens stained with either hematoxylin and eosin or Masson's trichrome and silver impregnation. Analysis of tumor-free liver parenchyma was carried out to determine the association between NAFLD and its histological grade.

RESULTS: No difference was found in the association of NAFLD with the general population (34.2% and 30.0% respectively, 95%CI: 25.8-43.4). Evaluation by cancer type showed that NAFLD was more prevalent in patients with liver metastasis of colorectal cancer than in patients with hepatocellular carcinoma and intrahepatic cholangiocarcinoma (OR = 3.99, 95%CI: 1.78-8.94, $P < 0.001$ *vs* OR = 0.60, 95%CI: 0.18-2.01, $P = 0.406$ and OR = 0.70, 95%CI: 0.18-2.80, $P = 0.613$,

respectively). There was a higher prevalence of liver fibrosis in patients with hepatocellular carcinoma (OR = 3.50, 95%CI: 1.06-11.57, *P* = 0.032). Evaluation of the relationship between the presence of NAFLD, nonalcoholic steatohepatitis, and liver fibrosis, and their risk factors, showed no significant statistical association for any of the tumors studied.

CONCLUSION: NAFLD is more common in patients with liver metastases caused by colorectal cancer.

Key words: Hepatocellular carcinoma; Colorectal liver metastases; Intrahepatic cholangiocarcinoma; Liver fibrosis; Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis

Core tip: There has not been a study clearly showing a relation between the nonalcoholic steatohepatitis cirrhosis and hepatocellular carcinoma (HCC). Some studies have suggested that the early stage of hepatic steatosis can be a favorable microenvironment for the development of liver metastases of colorectal cancer (LMCC). Others have suggested that hepatic steatosis has a protective role in the development of LMCC. Our analysis of the association of nonalcoholic fatty liver disease (NAFLD) with liver primary and secondary malignancies found a statistically higher prevalence of NAFLD in patients with LMCC, but not in non-cirrhotic HCC patients.

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INTRODUCTION

With the increasing prevalence of obesity and insulin resistance in the Western world, nonalcoholic fatty liver disease (NAFLD) has become a major cause of chronic liver disease[1]. Based on studies using different diagnostic methods, the current estimates of NAFLD worldwide prevalence vary from 6.3% to 33.0% (average = 20%)[2]. Molecular and pathophysiological changes caused by NAFLD may lead to liver cancer, increasing the incidence rate and modifying the epidemiology of primary and metastatic liver cancer[3-6]. It is predicted that NAFLD will emerge as the main risk factor for the development of hepatocellular carcinoma (HCC), which is the primary and most common liver cancer (70%-85% of cases), as the incidence of hepatitis B and C becomes reduced due to the expected development of better antiviral vaccines and drugs[7,8].

The actual incidence rate of the NAFLD-HCC association is unknown, but it has been reported that 30%-40% of the tumors diagnosed in patients with cryptogenic cirrhosis may be associated with obesity, insulin resistance, metabolic disorders, and NAFLD[9]. Furthermore, an increased incidence rate of intrahepatic cholangiocarcinoma (IHCC), as compared to extrahepatic cholangiocarcinoma in Western countries[6], suggests a possible interference of NAFLD[7,10-12] by the same pathophysiological mechanisms related to HCC and in the genesis of bile duct tumors[7]. NAFLD and colorectal cancer share some of the same risk factors, namely obesity, insulin resistance, and diabetes. One study demonstrated an increased risk of colorectal cancer in patients with NAFLD[13], while other studies have suggested that metabolic syndrome could be a predictor for the development of liver metastases of colorectal neoplasms[14].

To date, no study in the publicly available literature has shown an association between NAFLD and hepatic malignancy, either primary or secondary. The aim of this study was to evaluate the possible association of NAFLD with the most common primary and secondary liver cancers.

MATERIALS AND METHODS

Study design

This retrospective study encompasses clinical, laboratory and histological data of 120 patients diagnosed with either primary or secondary hepatic neoplasms. Patients were treated in the Hospital of Santa Casa Medical School of São Paulo between the dates of January 2007 and December 2011. All of the studies were conducted following approval by the local Ethics in Human Research Committee.

All of the 120 patients underwent hepatic resection and/or liver transplantation followed by subsequent evaluation of the explant or liver biopsy. Patients were excluded from the study due to: history of alcohol abuse, defined as intake of 20 g/d or more[15]; hepatitis B or C infection; absence of tumor-free liver tissue in histological material; presence of chronic autoimmune hepatitis, hemochromatosis, or Wilson's disease; hepatoblastoma cases due to very specific characteristics and histopathological features.

The medical records of the included patients were reviewed for clinical data such as age, sex, and comorbidities. Comorbidities were defined as: previous diagnosis of diabetes mellitus (DM) or impaired glucose tolerance (GI) and/or impaired fasting glucose (defined as $\geqslant$ 100 mg/dL); overweight, using the patient's height and weight to calculate the body mass index (BMI) and with the overweight threshold set as a BMI of $\geqslant$ 25 kg/m^2; history of dyslipidemia or laboratory tests demonstrating low-density lipoprotein > 160 mg/dL or triglyceride levels > 150 mg/dL; previous diagnosis of arterial hypertension, defined as systolic blood pressure $\geqslant$ 140 and/or diastolic blood pressure $\geqslant$ 90 mmHg.

Table 1 Neoplasms of 120 patients with primary and secondary hepatic neoplasm *n* (%)

Neoplasms	Incidence rate	Age, yr	Sex (male)	Steatosis	Fibrosis	NASH
NCLM	48 (40.0)	56.9	19 (39.6)	11 (22.9)	24 (50.0)	2 (4.2)
LMCC	40 (33.3)	57.5	25 (62.5)	22 (55.0)	15 (37.5)	0 (0.0)
HCC	16 (13.3)	57.9	13 (81.3)	4 (25.0)	12 (75.0)	0 (0.0)
IHCC	11 (9.2)	63.3	2 (18.2)	3 (27.3)	7 (63.6)	0 (0.0)
Others	5 (4.2)	64.4	0 (0.0)	1 (20.0)	2 (40.0)	0 (0.0)

HCC: Hepatocellular carcinoma; IHCC: Intrahepatic cholangiocarcinoma; LMCC: Liver metastasis of colorectal cancer; NASH: Nonalcoholic steatohepatitis; NCLM: Non-colorectal liver metastasis; Others: Lymphoproliferative tumors and sarcoma.

Table 2 Association of risk factors for nonalcoholic fatty liver disease with steatosis and liver fibrosis in 120 patients with primary and secondary hepatic neoplasm

NAFLD risk factor (*n*)	Liver steatosis			Liver fibrosis		
	n (%)	*P* value	OR (95%CI)	*n* (%)	*P* value	OR (95%CI)
GI and/or DM (41)	14 (34.1)	0.182	1.70 (0.78 -3.71)	31 (51.7)	0.196	0.62 (0.30-1.28)
Dyslipidemia (17)	9 (52.9)	0.078	2.50 (0.88-7.06)	8 (47.1)	0.793	0.87 (0.31-2.44)
Hypertension (55)	24 (43.6)	< 0.001[1]	3.99 (1.73-9.16)	31 (56.4)	0.200	1.60 (0.78-3.31)
Overweight (53)	26 (49.1)	0.002	3.76 (1.56-9.05)	30 (56.6)	0.165	1.74 (0.79-3.81)

[1]A statistically significant difference. DM: Diabetes mellitus; GI: Glucose intolerance; NAFLD: Nonalcoholic fatty liver disease.

Histopathology

All 120 histopathological examinations were reviewed by a pathologist with over 30 years of experience in liver pathology, who was blinded to the clinical, laboratory and/or patient demographics. The histological diagnosis of hepatic neoplasms was made using slide-mounted specimens stained with hematoxylin and eosin or Masson's trichrome and silver impregnation to assess reticulin fibers. Using the Kleiner *et al*[16] classification scoring system, we assessed the histological grade of lesions in the tumor-free liver parenchyma.

Statistical analysis

Descriptive statistics using the previously defined variables were performed to assess the results. The Statistical Package for Social Sciences version 13.0 was used for statistical calculations. Epi Info version 3.4.3 was used to evaluate confidence intervals (CIs) and odds ratios (ORs). Descriptive analyses were performed on the summary measures for quantitative variables. Qualitative variables were calculated, and absolute and relative frequencies were determined. The Student's *t*-test was used for comparisons of NAFLD with liver malignancy. The Mann-Whitney test was used for nonparametric variables. The χ^2 test and Fisher's exact test were used for statistical analysis. Significance level for all tests was defined at 5% ($P < 0.05$).

RESULTS

The demographic characteristics and histological features of the 120 included patients are listed in Table 1. Milder degrees of steatosis (grade 1; 39 cases) and liver fibrosis (grades 1 and 2, 51 cases) were predominant. When the association of steatosis with fibrosis was evaluated, no statistically significant difference ($P = 0.564$) was observed.

Neither liver fibrosis nor NAFLD showed any statistically significant relationship with their risk factors for any of the tumors studied (Table 2). Although two individuals with steatohepatitis had GI and/or DM, these findings were not statistically significant ($P = 0.507$). An analysis based on the type of liver cancer showed an association of steatosis only in liver metastasis due to colorectal cancer (Table 3) and fibrosis only in HCC.

DISCUSSION

The clinical course of NAFLD may vary according to the initial histological diagnosis and can range from a reversible benign outcome (steatosis) to the development of an inflammatory steatohepatitis (NASH) in 10%-20% of cases. Once established, 3%-5% of NASH cases progress to cirrhosis within 15-20 years, with an increase in risk of developing HCC[2,17]. In the Western population, the cumulative annual incidence rate of HCC in patients with NASH and cirrhosis was reported as 2.6%[18], while in the Asian population this rate was reported as 11.3%[19].

Recently, Hamady *et al*[20] identified hepatic steatosis as an independent risk factor for recurrence following curative resection of liver metastasis from colorectal cancer (LMCC) and was also associated with a worse prognosis. The biological characteristics of these metastases include bilateral distribution, lymph node involvement, and the presence of extrahepatic disease at diagnosis. Changes in inflammatory cytokines and extracellular matrix remodeling proteinases were associated with an increased risk of metastasis in many different organ systems[21].

Table 3 Prevalence of steatosis and hepatic fibrosis according to type of hepatic neoplasm

Histologic type (*n*)	Liver steatosis			Liver fibrosis		
	n (%)	*P* value	OR (95%CI)	*n* (%)	*P* value	OR (95%CI)
LMCC (40)	22 (55.0)	< 0.001[1]	3.99 (1.78-8.94)	15 (37.5)	0.053	0.47 (0.21-1.02)
NCLM (48)	11 (22.9)	0.034	0.42 (0.18-0.95)	24 (50.0)	1.000	1.00 (0.48-2.08)
HCC (16)	4 (25.0)	0.406	0.60 (0.18-2.01)	12 (75.0)	0.032[1]	3.50 (1.06-11.57)
IHCC (11)	3 (27.3)	0.613	0.70 (0.18-2.80)	7 (63.6)	0.343	1.85 (0.51-6.68)

[1]A statistically significant difference. HCC: Hepatocellular carcinoma; IHCC: Intrahepatic cholangiocarcinoma; LMCC: Liver metastasis of colorectal cancer; NCLM: Non-colorectal liver metastasis.

Significant changes that occur in steatosis and NASH cause an increase in certain signaling molecules, such as transforming growth factor-beta (TGF-β) and some cell matrix metalloproteinases, which may be important in tumor formation and angiogenesis stimulation[21-24]. However, other studies indicated that LMCC is less frequent in subjects with NAFLD and suggested that steatosis may be, in fact, an unfavorable factor for the development of LMCC[25-29]. Therefore, it is not clear whether NAFLD influences the development of LMCC, as demonstrated in this study, or has a protective effect (blocking LMCC development).

The incidence rate of malignant liver tumors in patients involved in the current study was similar to that reported in the literature[6,7]. No statistical differences were found in the association of hepatic steatosis neoplasms compared with the general population (34.2% in the study group *vs* 20%-30% in the general population[2]). However, when analysis was performed in our study according to the different cancer types, we found a higher prevalence of hepatic steatosis in patients with LMCC, even in cases with milder liver fibrosis, suggesting that even milder degrees of steatosis may be used as predictors for the development of hepatic neoplasms. Steatosis and liver cancer share several risk factors (including obesity, hyperinsulinemia, GI, and DM), with hepatic steatosis directly changing the liver microcirculation and inflammatory cytokines promoting the development of liver metastases[4,30]. It is also possible, however, that there is no direct relationship of steatosis with the onset of metastasis. Previous exposure to chemotherapy has been shown to result in an increase in both steatosis and steatohepatitis, in up to 92% of cases studied[4,31,32]. Furthermore, steatosis induced by neoadjuvant chemotherapy was shown to lead to greater circulation disorder with increased susceptibility to complications, such as micro-metastases[31]. Yet another possibility is that the association of NAFLD with liver colorectal metastases may occur randomly, as suggested by the high prevalence of hepatic steatosis in the general population, with no real relationship existing between these two diseases.

A discrete prevalence (with no statistically significant association) of steatosis was observed in the presence of GI and/or DM, hypertension, dyslipidemia, and overweight status. GI, DM and obesity are considered risk factors for the development of most of the hepatic neoplasms studied[12-14,33-40]. The presence of these factors, and not that of hepatic steatosis, could contribute to the development of neoplasms. However, cases of primary and secondary hepatic neoplasms associated with the presence of NAFLD even in the absence of these metabolic risk factors have been reported in other studies[41,42], suggesting that hepatic steatosis could be a predictor of these neoplasms, regardless of the presence or absence of obesity, GI and/or DM[42].

The main limitations of the present study were its retrospective design and its use of incomplete patient medical records as the source of information, which in some cases represented an absence of demographic information, anthropometric measurements, laboratory data, and other patient details. A prospective study may have provided more accurate evidence of a causal relationship between NAFLD and hepatic neoplasms. However, such a study design is logistically very difficult to perform due to the low annual incidence rate of different cancers in non-cirrhotic liver[42].

Surveillance screening of hepatic neoplasms in every obese or diabetic non-cirrhotic individual would not be cost-effective, considering that both metabolic disorders are epidemic in Brazil and several other countries around the world[37,43]. Thus, defining risk factors responsible for the development of liver cancer is crucial for increasing response rates of patients diagnosed at an early disease stage and treated with appropriate therapies for malignant tumors, which would consequently lead to a better prognosis.

In conclusion, the present study found no statistically significant association of NAFLD in patients with liver neoplasms in the general population. Only liver metastasis of colorectal cancer showed a significant association with NAFLD.

COMMENTS

Background

Some studies have suggested that early stages of hepatic steatosis can be considered a favorable microenvironment for the development of liver metastases of colorectal cancer (LMCC) as well as for the development of primary liver cancers such as hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Yet, other studies have suggested a protective role of hepatic steatosis in the development of LMCC.

Research frontiers

Nonalcoholic fatty liver disease (NAFLD) includes a spectrum of diseases

starting with simple steatosis, steatohepatitis (NASH), fibrosis, and finally cirrhosis. Associations of NAFLD with cirrhotic stage and primary liver cancer have already been shown. Although primary liver cancer has been extensively studied, there has not been strong scientific evidence reported for non-cirrhotic NAFLD patients. In early stages of steatosis, the associations with liver cancer have ranged from protection to NAFLD as a causal factor in the development of LMCC.

Innovations and breakthroughs

This study found a significant association between NAFLD and liver metastasis of colorectal cancer, but not with any of the other liver neoplasms studied.

Applications

Surveillance screening of hepatic neoplasms in every obese or diabetic non-cirrhotic individual would be cost prohibitive since both metabolic disorders are epidemic. Thus, defining risk factors responsible for the development of liver cancer is crucial for increasing response rates of patients diagnosed at an early disease stage and treated with appropriate therapies for malignant tumors, which would consequently lead to a better prognosis.

Peer review

The authors evaluated the role of hepatic steatosis as a risk factor in patients who underwent liver surgery for either primary liver tumors (hepatocellular carcinoma and colorectal carcinoma) or liver metastases (colorectal or other tumors). Although the study did not include a large number of patients with steatosis/fibrosis and there were no patients with NASH, the study does provide important insights into the influence of NAFLD in the development of liver cancer.

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