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Review Article

Nonalcoholic Fatty Liver Disease (NAFLD) and Extra Hepatic Malignancies

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease, its prevalence reaches 25 % in adults and about 10% in children (1-3). The prevalence of non-obese NAFLD ranged from 25% or less in some countries to higher than 50% in others (4). NAFLD's disease spectrum varies from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH), the most dangerous form with its complications of hepatic fibrosis, cirrhosis, and hepatocellular carcinoma (5,6). The existence of steatohepatitis and severe fibrosis are considered indicators of undesirable outcomes in patients with NAFLD and are associated with an increased risk for morbi-mortality by hepatic and extra hepatic complications (7,8). In decreasing order, mortality in NAFLD patients is due, first, to cardiovascular events and, second, to gastrointestinal (liver, intestine, esophagus, stomach, and pancreas) and extraintestinal (kidney in men and breast in women) malignancies, while end-stage liver disease represents the third cause of death (8,9). The hepatic manifestation of metabolic syndrome (Mets) is generally considered the NAFLD, and a remarkable body of literature shows an enhanced cancer risk in Mets subjects, especially in the gastrointestinal tract. In this environment, NAFLD may either express similar risk factors (i.e., obesity and millets diabetes). The frequency, prevalence, and severity of these complications are related to the histological severity of liver injury, signifying that NAFLD, but especially NASH, may also lead to low-grade inflammatory status by releasing multiple markers of inflammation, oxidative stress, and procoagulant factors (10,11). The aim of this narrative analysis was to synthesize recent evidence of NAFLD extrahepatic malignancies, based on the predominant prevalent incident/risk of such diseases in NAFLD patients. To date, an effective screening approach for extrahepatic malignancies has not yet been established. For patient management, collaborative care with relevant experts seems to be required because extrahepatic cancers can emerge across various organs (12).

Relationship between NAFLD and Colorectal Cancer (CRC)

CCR is the third most widely diagnosed disease and the world's fourth frequent cause of cancer-related deaths, responsible for about 1.4 million new cases, nearly 700,000 deaths in 2012(13). In literature, the relationship between NAFLD and CRC is the largest investigated, hence almost all studies have shown an increased prevalence of CCRs in patients with NAFLD, compared to those without (11). The first data showing the association of NAFLD with an enhanced risk of colorectal adenomatous polyps was reported by Hwang and collaborators. A population of 2917 patients was examined by colonoscopy, abdominal ultrasound, and liver tests in their study. The prevalence of NAFLD in the adenomatous polyp population was 41.5 % against 30.2 % in the control group. NAFLD was associated with a three-fold greater risk of colorectal adenomas (14). This original finding was confirmed in a large retrospective cohort study of 5,517 Korean women, which found a two-fold increase in the incidence of adenomatous polyps and a three-fold increase in CCR risk in patients with NAFLD compared to controls. The existence of NAFLD, nevertheless, did not affect the prognosis of CCR, and especially, on the recurrence of the cancer during follow-up (15). In NAFLD patients, the presence of histological

lesions of NASH is a high-risk factor of for CRC. Patients with NAFLD diagnosed by both proton magnetic resonance spectroscopy and liver biopsy in a cross-sectional study had a substantially higher incidence of colorectal adenomas (34.7% vs. 21.5%) and advanced neoplasms (18.6% vs. 5.5%) than control subjects. CRC has been observed more commonly in NASH patients than in those with simple steatosis (51.0 % vs. 25.6 % and 34.7% vs. 14.0 %). NASH was associated with increased risk for both adenomas (Odds Ratio (OR) 4.89) and advanced neoplasms (OR 5.34) even after risk factors adjustment (16). Blackett et al in a retrospective cross-sectional study of 123 patients with biopsy-proven NAFLD who underwent colonoscopy and controls without liver disease matched by age, sex, and endoscopist, NAFLD had a substantially higher colorectal adenoma prevalence irrespective of hyperlipidemia, diabetes, and obesity (OR, 1.74; 95% CI, 1.05-2.88). Findings from cross-sectional studies were also repeated longitudinally. In a prospective study where, coupled colonoscopies were performed in 1522 participants, Although the colonoscopy index was negative for all of them, the incidence of de novo adenoma occurrence in those with NAFLD increased by 45 % (17). A Danish prospective study assessing the general risk of cancer in hospitalized patient reported an increased risk of CRC in those with hepatic steatosis compared to the general population, but no difference was found between alcoholic and non-alcoholic fatty liver (18). Lastly, an et al in Korean study of 26,540 patients who underwent a first-time colonoscopy and ultrasonography as part of a health check-up program, NAFLD was independently associated with CRC (adjusted OR, 1.10; 95% CI, 1.03-1.17) and advanced colorectal neoplasia (adjusted OR, 1.21; 95% CI, 0.99-1.47) (19). A recent meta-analysis of observational studies revealed that NAFLD was identified to be associated with markedly elevated colorectal adenomas prevalence and cancer incidence (Odds Ratio (OR), 1.28 for prevalent adenomas and 1.56 for prevalent cancer; HR, 1.42 for incident adenomas and 3.08 for cancer) (20).

On the other hand, only two studies have failed to show an increased occurrence of colorectal adenomas in NAFLD patients compared with controls. The first was found to have a higher adenoma incidence in NAFLD patients, but the results did not meet statistical significance. The second revealed a significantly lower prevalence of CRC in NAFLD patients but an increased risk of CRC in the presence of insulin resistance, but it is well known that both increased levels of alanine aminotransferase (ALT) and ultrasound will underestimate the diagnosis of NAFLD (21,22). A well-known risk factor for CCR is the existence of metabolic syndrome, including diabetes mellitus and obesity (23,24). Nevertheless, it is unclear if NAFLD is associated with an increased risk of CCR simply because of shared metabolic disorders or whether NAFLD itself could contribute to CCR growth. As for the current possibility, insulin resistance-induced hyperinsulinemia causes carcinogenesis by activating the process of proliferation via its effect on insulin receptors on tumor cells. Moreover, hyperinsulinemia raises insulin-like growth factor (IGF)-1 expression, which has more effective mitogenic and anti-apoptotic properties than insulin and can serve as a trigger for preneoplastic and neoplastic cell growth (12,23). Following the above possibility, adiponectin, which has anti-carcinogenic effects, has decreased blood levels in NAFLD patients. This process is due to the capacity of adiponectin to interrupt proliferation of colon cancer cells by the Amp-activated protein kinase (AMPK) and to cause a caspase dependent pathway that results in apoptosis of endothelial cells (11).

Table 1: Main Studies on the Association between Non-Alcoholic Liver Fat Disease (Nafld) with Colorectal Neoplasms.

Author, Year of Publication	Study Population	Country	Population Enrolled	Diagnosis of NAFLD	Results
Bhatt BD et al. [23] -2015	Retrospective	USA	591 pts who completed LT evaluation (68 NAFLD vs. 523 non-NAFLD)	Biopsy + clinical criteria	Polyps prevalence: 59% vs. 40%; p < 0.003. OR (Odds Ratio) 2.16; p = 0.003. Adenomatous polyps prevalence: 32% vs. 21%; p = 0.04. OR 1.95, p = 0.02
Lin XF et al. [25] -2014	Retrospective and consecutive cohort study	China	2315 community subjects who underwent a routine colonoscopy (263 NAFLD vs. 2052 non-NAFLD)	Ultrasonography	Total colorectal lesions prevalence: 90.0% vs. 93.3% Adenomatous polyps prevalence: 44.5% vs. 55.7% CRC prevalence: 29.3% vs. 18%; p = 0.001. OR 1.868; 95% CI 1.360-2.567; p < 0.05

Lee YI et al. [16] -2011	Retrospective cohort study	South Korea	5517 women who underwent life insurance company health examinations (831 NAFLD vs. 4686 non-NAFLD)	Ultrasonography	Adenomatous polyps incidence: 628 vs. 185.2/105 person year. RR 1.94; 95% CI 1.11–3.40 CRC incidence: 233.6 vs. 27/105 person year. RR 3.08; 95% CI 1.02–9.34
Touzin NT et al. -2011	Retrospective cohort study	USA	233 patients who underwent screening colonoscopies (94 NAFD vs. 139 non-NAFLD)	US + liver biopsy	Adenomas prevalence: 24.4% vs. 25.1%; p = 1
Huang KW et al. [19] (2012)	Retrospective cohort study	Taiwan	1522 pts with two consecutive colonoscopies (216 with colorectal adenoma vs. 1306 without colorectal adenoma after negative baseline colonoscopy)	US + exclusion of other causes of hepatic disease NAFLD	prevalence: 55.6% vs. 38.8%; p < 0.05. OR = 1.45; 95% CI 1.07–1.98; p = 0.016
Hwang ST et al. [15] (2009)	Cross-sectional	South Korea	2917 pts who underwent routine colonoscopy (556 with polyps vs. 2361 without polyps)	Ultrasonography	NAFLD prevalence: 41.5% vs. 30.2%; p < 0.001. OR, 1.30; 95% CI 1.02–1.66; p = 0.034
Stadlmayr A et al. [18] (2011) 1211	Cross-sectional	Austria	consecutive pts who underwent screening colonoscopy (632 NAFLD vs. 597 non-NAFLD)	US + exclusion of other causes of hepatic disease	Total colorectal lesions prevalence: 34% vs. 21.7%; p < 0.001 Tubular adenoma prevalence in men: 34.6% vs. 23.7%; p = 0.006 Rectum adenoma prevalence in men: 11% vs. 3%; p = 0.004 CRC prevalence in men: 1.6% vs. 0.4%; p < 0.001
Wong VW-S et al. [17] (2012)	Cross-sectional	China	380 community pts + consecutive pts with biopsy proven NAFLD (in total 199 NAFLD vs. 181-non-NAFLD)	Proton-magnetic resonance spectroscopy or liver biopsy	Total polyps prevalence: 52.8% vs. 38.7%; p = 0.057 p = 0.043. OR 1.61; 95% CI 0.9–2.9; p = 0.11 Adenomatous polyps prevalence: 34.7% vs. 21.5%; Villous polyps prevalence: 6% vs. 0.6%; p = 0.042 High grade dysplasia polyps prevalence: 18.1% vs. 5%; p = 0.002 Advance neoplasm prevalence: 18.6% vs. 5.5%; p = 0.005. OR 3.04; 95% CI 1.29–7.2; p = 0.011 CRC 1% vs. 0.6%; p = 0.65
Basyigit S et al. [22] -2015	Prospective observational	Turkey	127 consecutive pts who underwent colonoscopy	Ultrasonography	Adenomas prevalence: 20% vs. 25.8%. OR 1 CRC prevalence: 4.6% vs. 24.2%. OR 1
Ahn et al., 2017 [28]	Retrospective cohort study	Korea	26,540 subjects who underwent a first-time colonoscopy as part of a health check-up program	Ultrasonography	NAFLD was independently associated with colorectal neoplasia (adjusted OR, 1.10; 95% CI, 1.03–1.17) and advanced colorectal neoplasia (adjusted OR, 1.21; 95% CI, 0.99–1.47).
Blackett et al., 2020 [29]	retrospective cross-sectional study	United States	123 patients with biopsy-proven NAFLD and controls without liver disease matched by age, sex, and endoscopist	Histological	Patients with biopsy-proven NAFLD had a significantly higher colorectal adenoma prevalence independently of hyperlipidemia, diabetes, and obesity (OR, 1.74; 95% CI, 1.05–2.88).

Esophageal and Gastric Cancer

Esophageal and gastric cancers are the 7th and 5th most prevalent cancers worldwide, with an estimated 572,000 and 1,000,000 cases in 2018 (25). In males, both cancer forms are more frequent than in females. The pathogenesis of esophageal cancer varies between adenocarcinoma and squamous cell carcinoma, the two major histological subtypes. Smoking and overweight are reported as risk factors for esophageal adenocarcinoma, while smoking and alcoholism are known risk factors for esophageal squamous cell carcinoma (26). Likewise, gastric cancers, known as gastric cardia

and gastric non-cardia, tend to have different anatomical subsite pathologies. Smoking and obesity are recognized risk factors for gastric cardiac cancer, while the risk factors for gastric non-cardiac cancer are Helicobacter Pylori infection and smoking (27,28). The positive correlation between body mass index (BMI) and the risk of esophageal adenocarcinoma and gastric cardiac cancer has been documented in several observational studies. Turabi et al conducted a meta-analysis of 22 studies, including almost 8000 esophageal and gastric cardia adenocarcinoma cases. The overall RR was 1.71 (95% CI 1.50-1.96) for BMI between 25 and 30 and was 2.34 (95% CI 1.95-2.81) for BMI ≥ 30 kg/m^2. The correlation was greater for esophageal adenocarcinoma (RR for BMI ≥ 30 kg/m (2) = 2.73, 95% CI 2.16-3.46) than for gastric cardia adenocarcinoma (RR for BMI ≥ 30 kg/m (2) = 1.93, 95% CI 1.52-2.45) (29). Hoya and al in a meta-analysis of 12 studies (8 North American, 3 European and 1 Australian) comprising 1997 esophageal adenocarcinomas cases, and 11 159 esophagogastric junction adenocarcinomas were assembled. The relationship between theme increased directly with growing BMI (P <0.001). Compared with individual's BMI <25, BMI ≥40 was associated with both cancers (OR 4.76, 95% CI 2.96-7.66) and (OR 3.07, 95% CI 1.89-4.99) (30). Although, prospective cohort studies investigating abdominal obesity by subtype and subsite for esophageal and gastric cancer are marginal, with contrasting results (26). During 8.9 years of follow-up, Steffen et al documented 88 incident cases of esophageal adenocarcinoma EAC and 110 cases of esophageal squamous cell carcinoma ESCC. BMI, waist circumference, and waist-to-hip ratio (WHR) were correlated with EAC risk [relative risk (RR), 2.60; 95% confidence interval (95% CI), 1.23-5.51; P(trend) < 0.01; RR, 3.07; 95% CI, 1.35-6.98; P(trend) < 0.003; and RR, 2.12; 95% CI, 0.98-4.57; P(trend) < 0.004].

Conversely, BMI and waist circumference were negatively correlated to ESCC risk, whereas WHR showed no correlation with ESCC (31,32). In a Netherlands Cohort Study, Merry et al, after 13.3 years of follow-up, from 4552 sub cohort members, 133 esophageal and 163 gastric cardia adenocarcinomas were analysed. The RRs (95% CI) of esophageal adenocarcinoma were 1.40 (0.95 to 2.04) and 3.96 (2.27 to 6.88) for overweight (BMI 25.0-29.9 kg/m (2)) and obese subjects (BMI >or=30.0 kg/m (2)), respectively, related to subjects of average weight (BMI 20.0-24.9 kg/m (2)). For gastric cardia adenocarcinoma, these RRs were 1.32 (0.94 to 1.85) and 2.73 (1.56 to 4.79) (33). Associations between total and abdominal obesity with EAC and gastric adenocarcinoma among 218 854 patients in the prospective NIH-AARP cohort were studied, 253 incident EAC, 191 gastric cardia adenocarcinomas and 125 gastric non-cardia adenocarcinomas reported to the sample. Global obesity (BMI) was positively associated with EAC and gastric cardia adenocarcinoma risk (highest (≥35 kg/m (2)) vs referent (18.5-<25 kg/m (2)); HR 2.11, 95% CI 1.09 to 4.09 and HR 3.67, 95% CI 2.00 to 6.71, respectively). Waist circumference was also positively associated with EAC and gastric cardia adenocarcinoma risk (highest vs referent; HR 2.01, 95% CI 1.35 to 3.00 and HR 2.22, 95% CI 1.43 to 3.47, respectively) (34). In addition, to our findings, only one prospective study examined measurements of body fat composition that differentiate between adipose and non-adipose mass (evaluated using bioelectrical impedance) in relation to esophageal and gastric cancer risk (35). Among 41,295 people followed on average for 11.3 years, 30 cases with cancers in the gastric cardia or lower third of the esophagus and 68 cases with noncardiac gastric adenocarcinomas were ascertained via the population cancer registry. The risk of adenocarcinoma of the lower esophagus and gastric cardia was positively associated with BMI with a hazards ratio (HR) and (95% confidence interval) for people with BMI>or=30 kg/m^2 compared with those<25 kg/m^2, of 3.7 (1.1-12.4), an HR per 10 cm increase in waist circumference of 1.46 (1.05-2.04), and a HR per 10 kg increase on fat-free mass of 2.06 (1.15-3.69). Noncardiac gastric adenocarcinoma showed little relationship with body size. Obesity is related to upper gastrointestinal cancers by many possible biological processes. Obesity may contribute to metabolic disorders, such as higher levels of pro-inflammatory cytokines (such as tumor necrosis factor-alpha and interleukin-6), adipokines (such as glucose, insulin, and leptin), and endogenous sex steroids, which could increase the risk of cancer (26,36,37). There is significant evidence of gender differences in the distribution of body fat. Men appear to produce more visceral fat, while females in the subcutaneous depot hold more fat. In body fat distribution, sex hormones play an important role (38,39). Instead of the visceral adipose depot, estrogen facilitates the accumulation of fat in the subcutaneous depot and the reduction in estrogen levels in menopausal women is accompanied by an increase in visceral fat (39). In addition to controlling the spread of body fat, the occurrence of esophageal and gastric cancers in men relative to women can also be explained by sex hormones. Sex hormones, especially estrogens, have been suspected to protect against the development of esophageal and gastric malignancy (40,41).

Pancreatic Cancer

With more than 50,000 reported new cases in the United States in 2016, the incidence of pancreatic cancer is rising. Pancreatic cancer mortality is high, with a 5-year survival of 8%, considering the fact that most patients are diagnosed in final stages(42)the American Cancer Society estimates the numbers of new cancer cases and deaths that will occur in the United States in the current year and compiles the most recent data on cancer incidence, mortality, and survival. Incidence data were collected by the National Cancer Institute (Surveillance, Epidemiology, and End

Results [SEER] Program. The World Cancer Research Fund Panel's 2007 study notes that obesity is a major modifiable risk factor for pancreatic cancer(11). A meta-analysis recently published found a linear rise in the risk of pancreatic cancer and waist circumference, with a relative risk (RR) of 1.11 for every 10 cm (95% CI 1.05-1.18) and a waist-to-hip ratio of 1.19 (95% CI 1.09-1.31) for every 0.1 unit increase(43). Mets was reported as a neoplastic risk factor in a meta-analysis published in 2012, with an RR of 1.58 (p<0.0001) for female pancreatic cancer, likely influenced by reduced physical activity, high-calorie dense food consumption, high nutritional fat levels, low fiber intake, and oxidative stress(44). In an observational study conducted by Chang et al, NAFLD was an independent risk factor for pancreatic cancer (OR 2.63, 95% CI 1.24-5.58, p = 0.011), and patients without NAFLD had longer survival than patients with NAFLD (p = 0.005, log-rank test). Same with esophageal cancer, NAFLD, although no definitive proof is yet available, may be involved in this relationship.

Renal Cancer

Some of the elements of Mets, have been identified as risk factors in addition to smoking and alimentary habits, whose correlation with renal cancer is well recognized, and mentioned in several recommendations(45-48)treatment and follow-up","title-short":"Renal cell carcinoma","volume":"25 Suppl 3","author":[{"family":"Escudier","given":"B."},{"family":"Porta","given":"C."},{"family":"Schmidinger","given":"M."},{"family":"Algaba","given":"F."},{"family":"Patard","given":"J. J."},{"family":"Khoo","given":"V."},{"family":"Eisen","given":"T."},{"family":"Horwich","given":"A."},{"literal":"ESMO Guidelines Working Group"}],"issued":{"date-parts":[["2014",9]]}},{"id":2952,"uris":["http://zotero.org/users/local/bzZutjSz/items/E9APCJKF"],"uri":["http://zotero.org/users/local/bzZutjSz/items/E9APCJKF"],"itemData":{"id":2952,"type":"article-journal","abstract":"OBJECTIVE: The multimodality approach to treating both localized and metastatic renal cell carcinoma has led to a demand for improved imaging evaluation. We review the information needed from the radiologic studies used to determine treatment strategies.\nCONCLUSION: Adequate preoperative radiologic assessment provides the treating physician with information critical in determining the sequence of treatments, role of nephron-sparing surgery, surgical approach, and timing of systemic therapy for metastatic disease.","container-title":"AJR. American journal of roentgenology","DOI":"10.2214/AJR.10.6249","ISSN":"1546-3141","issue":"6","journalAbbreviation":"AJR Am J Roentgenol","language":"eng","note":"PMID: 21606286","page":"1255-1262","source":"PubMed","title":"Renal cell carcinoma: what the surgeon and treating physician need to know","title-short":"Renal cell carcinoma","volume":"196","author":[{"family":"Chapin","given":"Brian F."},{"family":"Delacroix","given":"Scott E."},{"family":"Wood","given":"Christopher G."}],"issued":{"date-parts":[["2011",6]]}}},{"id":2954,"uris":["http://zotero.org/users/local/bzZutjSz/items/7FJG3WRH"],"uri":["http://zotero.org/users/local/bzZutjSz/items/7FJG3WRH"],"itemData":{"id":2954,"type":"article-journal","container-title":"Annals of Oncology: Official Journal of the European Society for Medical Oncology","DOI":"10.1093/annonc/mdq206","ISSN":"1569-8041","journalAbbreviation":"Ann Oncol","language":"eng","note":"PMID: 20555064","page":"v137-139","source":"PubMed","title":"Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up","title-short":"Renal cell carcinoma","volume":"21 Suppl 5","author":[{"family":"Escudier","given":"B."},{"family":"Kataja","given":"V."},{"literal":"ESMO Guidelines Working Group"}],"issued":{"date-parts":[["2010",5]]}}},{"id":2959,"uris":["http://zotero.org/users/local/bzZutjSz/items/2K5HBN5C"],"uri":["http://zotero.org/users/local/bzZutjSz/items/2K5HBN5C"],"itemData":{"id":2959,"type":"article-journal","container-title":"Annals of Oncology: Official Journal of the European Society for Medical Oncology","DOI":"10.1093/annonc/mdz056","ISSN":"1569-8041","issue":"5","journalAbbreviation":"Ann Oncol","language":"eng","note":"PMID: 30788497","page":"706-720","source":"PubMed","title":"Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†","title-short":"Renal cell carcinoma","volume":"30","author":[{"family":"Escudier","given":"B."},{"family":"Porta","given":"C."},{"family":"Schmidinger","given":"M."},{"family":"Rioux-Leclercq","given":"N."},{"family":"Bex","given":"A."},{"family":"Khoo","given":"V."},{"family":"Grünwald","given":"V."},{"family":"Gillessen","given":"S."},{"family":"Horwich","given":"A."},{"literal":"ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org"}],"issued":{"date-parts":[["2019",5,1]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} . Visceral fat, measured by computed tomography (CT) scan in patients with cT1a renal cell carcinoma, is closely correlated with Fuhrman grade, the most commonly used neoplastic nuclear kidney grading model, and is an independent predictor of high-grade renal cell carcinoma (RCC)(49). Adiponectin levels are inversely related to the magnitude of the disease in a sample of 118 consecutive patients undergoing surgical procedure for RCC, with lower levels in patients with metastatic cancer(50). YH et al in a study included 706 patients with localized renal cell carcinoma who had undergone curative surgery. Visceral total adipose tissue was measured based on preoperative computerized tomography. The distribution of histological subtypes differed significantly among visceral adipose tissue percentage (VAT%) quartiles. The proportion of high-grade tumors increased as VAT% increased (OR 1.023, 95% CI 1.000-1.126, p = 0.037). A U-shaped correlation

between VAT percent quartiles and the risk of disease recurrence was observed for all patients. Disease recurrence was substantially increased in the lowest (HR 3.198, 95% CI 1.765-10.040, p = 0.036) and highest (HR 4.760, 95% CI 2.937-13.210, p = 0.010) VAT% quartiles (51).

Breast Cancer

Breast cancer is the most common cancer in women and is the world's leading cause of cancer-related death in women. Hormonal or reproductive causes are recognized risk factors for breast cancer, including early menarche age, nulliparity, late menopause and pregnancy ages (52,53). Related risk factors are identified between NAFLD and breast cancer, like metabolic disorders and obesity. NAFLD and breast cancer are both related to hyperinsulinemia, suggesting a potential conceptual correlation between the two diseases (54). However, limited studies have tested the relationship between breast cancer and NAFLD. A case-control analysis with a small sample size found that NAFLD was associated with breast cancer (55-57). In a pooled review of two case-control studies of 3869 postmenopausal women with breast cancer and 4082 cases of postmenopausal control, the authors reported a higher risk of neoplasia in women with Mets compared to those without it (OR 1.75; 95% CI 1.37-2.22). The odds ratios (ORs) of postmenopausal breast cancer were 1.33 (95% CI 1.09-1.62) for diabetes, 1.08 (95% CI 0.95-1.22) for hyperlipidemia, 1.19 (95% CI 1.07-1.33) for hypertension, 1.22 (95% CI 1.09-1.36) for waist circumference ≥88 cm and 1.26 (95% CI 1.11-1.44) for body mass index ≥30 kg/m$^{(2)}$. For women with Mets, the risk of postmenopausal breast cancer has been substantially increased. (OR = 1.75, 95% CI 1.37-2.22, for three or more Mets elements, P for trend for increasing number of elements < 0.0001)(58). In a study on 2092 patients treated for stage I-III invasive breast cancer, enrolled in eleven Italian centers 0-5 years after surgical treatment. The adjusted ORs for women with Mets versus women without any Mets traits were 2.17 (CI 1.31-3.60) overall, and 2.45 (CI 1.24-4.82) for distant metastasis. All Mets traits were positively associated with new events, and significantly so for low HDL and high triglycerides. Mets is an important prognostic factor (59). Additionally, one longitudinal study of 25,947 subjects, 8,721 (33.6%) had NAFLD showed that the cancer incidence rate of the NAFLD group was higher than that of the non-NAFLD group (782.9 vs. 592.8 per 100,000 person-years; hazard ratio [HR] 1.32; 95% (CI) 1.17-1.49; p <0.001). When demographic and metabolic factors were adjusted for, NAFLD showed a strong association with the breast cancer in females (HR 1.92; 95% CI 1.15-3.20; p = 0.01)(60). In a case-control study exploring the association between NAFLD and breast cancer, Kim et al reported that NAFLD was significantly associated with breast cancer (P = 0.046), and the subgroup analysis showed that NAFLD was significantly associated with breast cancer in the non-obese subgroup (odds ratio 3.04, 95% CI 1.37-4.32, P = 0.002) but not in the obese group (P = 0.163)(61).

Prostate Cancer

Prostate cancer (PCa) is the second most frequently diagnosed cancer in men worldwide and the sixth leading cause of cancer-related mortality (62). The association between NAFLD and PC a has recently been suggested by increasing PCa and NAFLD incidences, suggesting that NAFLD is an important risk factor for PC a (63), but it remains controversial. In a systematic review and meta-regression analysis, including 31 cohort and 25 case-control studies, authors reported a 1.05 relative risk (95 % CI 1.01-1.08), increased in patients with advanced diseases than localized diseases, for every 5 kg/m^2 increase in BMI (64). The role of NALFD was systematically analyzed by two studies. NAFLD was reported to protect against neoplastic relapse in 293 consecutive patients following radical prostatectomy for prostate cancer (65). Compared to participants without NAFLD in both the training and validation sample, the NAFLD community reported slightly longer time-to-recurrence (hazard ratio: 0.33 and 0.22; 95% CI 0.16-0.69 and 95% CI 0.11-0.43, respectively). In 1600 US-defined NAFLD patients and 1600 matched hepatitis C virus (HCV) infected subjects, the second one analyzed the development of cancers and the location of the illness: prostate cancer occurred in 12.6% of NAFLD compared to 3.5% in HCV patients, and the incidence of prostate malignance in NAFLD was higher than in the general population (11).

The Presumed Role of Insulin Resistance and Gut Microbiota in NAFLD in Extra-Hepatic Cancers Development

Even though data on the pro-inflammatory and pro-carcinogenic implications of insulin resistance (IR) are generally the most substantial evidence of a potential mechanistic between NAFLD and extra-hepatic oncogenesis, gut microbiota has recently been described as a new and fascinating striker in the development of obesity, NAFLD and many types of cancer. Dysbiosis is described in NAFLD patients, and the liver remains at the intersection of a complex relationship between modifications of microbiota, IR, inflammation, and carcinogenesis (66-69). Patients with colon cancer have been shown to have dysbiosis (70). Qualitative and quantitative changes of gut microbiota, through several pathways, contribute to increased intestinal permeability, including the control of tight junctions such as zonulin-1 and the occlusion in the ileum of toll-like receptor 2 (TLR2) (71-73). It is well established that the host diet has a profound effect on the microbial composition of the gut. The myeloid differentiation factor 88 (MyD88)-dependent pathway can mediate diet-induced NAFLD (74). This

factor is a converter molecule that is important for TLR signaling. It is mobilized after interaction between microorganism-associated molecular patterns (MAMPs) and TLRs (particularly TLR4) and stimulates the transcription by activation of NF-B or c-Jun NH2-terminal kinase (JNK) contributing to IR initiation of many pro-inflammatory cytokines. Failure of mutation or knockout mice in TLR4 prevent obesity-induced IRs that underlie the essential role of this receptor in the regulation of the innate immune system (74). The key element of the axis of central obesity contains NAFLD and visceral adipose tissue. Low-grade chronic inflammation and insulin resistance (IR) establish a microenvironment appropriate for the cancer development in this environment by stimulating the insulin growth factor-1 (IGF-1) axis via hyperinsulinemia (75-77). Extra hepatic cancers have been associated with enhanced serum levels of IGF-1. Pertinently, the risk of Barrett's esophagus and esophageal adenocarcinoma may be affected by the insulin/IGF system (78-84), but this is not entirely agreed upon (85). In carcinogenic processes, multiple adipokines, implicated in the control of metabolism, inflammation and fibrogenesis, may also be involved. Adiponectin has anti-carcinogenic effects mediated by its power to stop the growth of colon cancer cells via the protein kinase (AMPK) triggered by AMPc and to induce a caspase-dependent pathway that results in apoptosis of endothelial cells. Tumor necrosis factor (TNF-), implicated in tumor cell proliferation and angiogenesis, may also be directly inhibited by Adiponectin. Given that NAFLD patients have reduced serum adiponectin levels, the pathways mentioned above reflect an important correlation between NAFLD and the development of disease at both the digestive and extra-intestinal sites.

The pro-carcinogenic implications of leptin have been thoroughly explored, particularly in the presence of low rates of adiponectin (86,87). Leptin can promote motility and intrusiveness in human colon cancer cells through mitogen-activated protein kinase (MAPK) process induction. A case-cohort analysis in postmenopausal CRC women found that elevated plasma leptin levels were associated with an increased risk of CRC (88,89). The combination of high leptin and low adiponectin rates can also raise the risk of Barrett's esophagus and esophageal adenocarcinoma in obese patients by increasing cell proliferation and decreasing apoptosis through extracellular signal-regulated kinase (90-93). After that, resisting could also be related to malignancies associated with obesity by triggering the nuclear factor-B (NF-B) pathway and amplifying the procardiogenic actions of interleukin (IL)-1, IL-6 and TNF-ά, respectively. To present, in breast cancer, non-small cell lung cancer and in digestive tumors, a presumed role of resisting has been reported (94-96). IR-associated low-grade chronic inflammation also promotes the activation of macrophages and the large secretion into the systemic circulation of many proinflammatory cytokines, such as IL-6 and TNFά. Animal models have shown a correlation between TNF ά and various malignancies, like CCR (97-99). IL-6 has been related to carcinoma of renal cells, gastric cancer and CCR. By modulating many genes involved in proliferation, survival, and angiogenesis, cancer (100-105).

Conclusion

NAFLD is a complex and multifactorial disorder that is closely linked to obesity and type 2 diabetes and shares a substantially elevated risk of several cancer forms. Further than HCC risk, obviously induced by NASH, there is a clear epidemiological and biological argument, with the strongest support for colorectal tumors, for the correlation between NAFLD and certain extra-hepatic cancers. However, before clear screening guidelines for cancer in NAFLD patients can be given, further studies are required, but we advise health care professionals who care for patients with NAFLD to be cautious about any signs and symptoms of malignancies, especially CCR, and to refer patients for further evaluation and management.

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