Current Hepatology Reports (2019) 18:455–472
https://doi.org/10.1007/s11901-019-00499-5

FATTY LIVER DISEASE (V AJMERA, SECTION EDITOR)

Extrahepatic Malignancies in Nonalcoholic Fatty Liver Disease

Omar T. Ahmed[1] · Alina M. Allen[1]

Published online: 15 November 2019

Abstract

Purpose of Review Malignancy is the second most common cause of death in individuals with nonalcoholic fatty liver disease (NAFLD). Understanding unique characteristics of malignancy risk beyond hepatocellular carcinoma in NAFLD has significant implications in counseling and personalized preventative measures in this high-risk population. Herein, we systematically review the literature reporting extra-hepatic malignancies in NAFLD and discuss the key biological mechanisms underpinning the association between excess adiposity and cancer risk.

Recent Findings Several studies have shown significant associations between NAFLD and extrahepatic malignancies. The strongest association was found with cancers of the gastrointestinal tract and hormone-sensitive cancers. Recent data support sex-specific differences in cancer risk increase in NAFLD: colorectal cancer in men and uterine cancer in women. The risk of cancer development is higher in NAFLD than obesity alone.

Summary A growing body of observational evidence over the last decade supports the association between NAFLD and extrahepatic malignancies. This association requires further studies, ideally designed to include more detailed measures of body fat deposition beyond BMI in well-characterized, large cohorts of NAFLD patients, to determine if screening policies should be individualized in this group.

Keywords Cancer · Malignancy · NAFLD · Epidemiology · Obesity

Abbreviations

aHR	Adjusted hazard ratio
aOR	Adjusted odds ratio
aRR	Adjusted relative risk
BMI	Body mass index
CI	Confidence interval
CRC	Colorectal cancer
CRP	C-reactive protein
CT	Computed tomography
FIB-4	Fibrosis-4 index
FLI	Fatty liver index
GI	Gastrointestinal
HIS	Hepatic steatosis index
HR	Hazard ratio
ICD	International Classification of Diseases
IL	Interleukin
IR	Insulin resistance
IRR	Incidence rate ratio
LT	Liver transplant
MetS	Metabolic syndrome
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
OR	Odds ratio
SIR	Standardized incidence ratio
TNF	Tumor necrosis factor
US	Ultrasound

✉ Alina M. Allen
Allen.alina@mayo.edu

[1] Department of Internal Medicine, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First Street SW, Rochester, MN, USA

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide, with an estimated global prevalence of 25% in adults [1–3]. NAFLD is more predominant in those with obesity and metabolic syndrome (MetS) [4]. In North America, the prevalence of NAFLD in the severely obese ranges from 75 to 92%, while the prevalence in patients with type 2 diabetes is estimated to be between 60 and 70% [5–11]. Obesity has become one of the largest public health

threats. Strong evidence supports an association between obesity and 11 cancers (esophageal adenocarcinoma, multiple myeloma, gastric cardia, colon, rectum, biliary tract, pancreas, breast, endometrium, ovary, and kidney) [12–14]. NAFLD is an established risk factor for hepatocellular carcinoma [15], but emerging evidence supports its association with several extrahepatic cancers. Indeed, malignancy is the second most common cause of death in NAFLD individuals [13, 16].

In this manuscript, we systematically review the literature relating extra-hepatic malignancy in NAFLD and discuss the key biological mechanisms underpinning the association between excess adiposity and cancer risk.

Methodology

We searched the PubMed with the help of a professional librarian using the following two search criteria: *Search 1*: (extrahepatic or extra-hepatic) AND (NAFLD or steatohepatitis or "fatty liver"[ti] or "Fatty Liver"[Mesh] OR "Non-alcoholic Fatty Liver Disease"[Mesh]) AND (malignan* or neoplasm* or cancer* or carcino* or tumor* or tumour* or adenoma* or adenocarcinoma*). *Search 2*: (colorectal[Title] OR rectal[Title] OR intestin*[Title] OR breast[Title] OR gastrointestinal[Title] OR pancreas*[Title] OR hematologic[Title] OR mammary[Title] OR skin[Title] OR spleen*[Title] OR urogen*[Title]) AND (NAFLD or steatohepatitis or "fatty liver"[ti] or "Fatty Liver"[Mesh] OR "Non-alcoholic Fatty Liver Disease"[Mesh]) AND (malignan* or neoplasm* or cancer* or carcino* or tumor* or tumour* or adenoma* or adenocarcinoma*). The filters used were language (English) and species (humans). The total articles found from search 1 (97) and search 2 (349) were 446. We reviewed the abstracts and included all studies that described the prevalence or incidence of extrahepatic malignancies in NAFLD patients. We excluded studies focusing on intrahepatic malignancies (i.e., hepatocellular carcinoma and cholangiocarcinoma), studies discussing the reverse relationship (i.e., incidence of NAFLD in cancer patients), review articles, systematic reviews, and meta-analysis.

Extrahepatic Cancers Associated with NAFLD

Significant association was found between NAFLD and several extrahepatic malignancies. The strongest association was found with GI (colorectal, gastric/esophageal, and pancreatic) cancers, in part due to the substantial number of supporting studies. Additional associations were found with hormone-sensitive cancers, such as breast, uterine, and prostate, as well as renal and hematologic malignancies. All the studies are summarized in Table 1 (arranged in chronological order).

Gastrointestinal Cancers

Colorectal Neoplasia

NAFLD Is Associated with Increased Incidence and Prevalence of Colorectal Polyps and Cancer The association between NAFLD and the incidence and prevalence of colorectal lesions (polyps or cancer) has been investigated in 23 observational studies, the vast majority showing a significant association. The relationship was first established in 2003 by Sørensen et al., who investigated the incidence of cancers in a Danish cohort (n = 7326; 25% with NAFLD) and presented the first evidence of higher incidence of colon cancer in NAFLD patients, despite the results being statistically nonsignificant in their study [17]. Next, in 2009, Hwang et al. investigated the incidence of colorectal adenomas in a South Korean population that underwent a routine health checkup and presented evidence for significant increase in risk of colorectal adenomatous polyps in NAFLD patients [18]. Subsequently, several studies, mostly conducted on Asian populations, confirmed the increased risk of colorectal lesions in NAFLD patients [19–24] (Table 1).

In contrast, only two small studies suggested an inverse or nonsignificant association between NAFLD and colorectal lesions. In a study that included 233 patients (94 were NAFLD) who underwent screening colonoscopy and abdominal ultrasonography (US) and liver biopsy, the prevalence of colonic adenomas in NAFLD vs. non-NALFD group was not significantly different (24.4% vs 25.1%; p = 1). However, the authors found a higher burden of adenomas in the NAFLD vs. non-NAFLD group [28]. Another study included 127 NAFLD patients who underwent screening colonoscopy and abdominal US, to investigate the risk for colorectal cancer (CRC) in NAFLD patients, considering insulin resistance (IR) effects. The study found that the prevalence of CRC was significantly lower in subjects with NAFLD (P = 0.001), and the risk for CRC was significantly higher in non-NAFLD patients (OR 7.4, 95% CI 3.07–7.96, P = 0.010), while the prevalence and risk of CRC and adenoma were significantly higher in patients with IR [29]. The obvious common factor between these two studies is the smaller number of study sample compared to the large-sampled studies providing evidence for increased colorectal lesions in NAFLD patients.

NAFLD Severity Correlates with Risk of Colorectal Neoplasia The risk of colorectal lesions appears to correlate with disease severity in NAFLD, as assessed by liver biopsy, abdominal US, or noninvasive biomarkers of steatosis or fibrosis. Wong et al. first demonstrated higher prevalence of adenomas and advanced neoplasms in nonalcoholic steatohepatitis (NASH) vs. simple steatosis, among patients with biopsy-proven NAFLD [30]. Lee et al. concluded that colorectal neoplasm risk increased with worsening fatty liver severity on abdominal ultrasonography [31•]. Similarly, Ahn et al. proved that the risk of any colorectal

Table 1 Extrahepatic malignancies associated with NAFLD. All cancers that had at least one positive association with NAFLD were included

Cancer Associated with NAFLD	Study	Country	Type of Study	Population Enrolled	Findings
COLORECTAL					
Colon	Allen AM, *et al.* (2019)[36••]	USA	Retrospective cohort	**19,163** individuals (24.6% NAFLD) were identified using a medical record linkage system. NAFLD and colorectal cancer were identified using ICD codes. Each NAFLD patient was matched with 3 non-NAFLD subjects. Median follow-up: 8 years	NAFLD patients had higher incidence of colon cancer IRR=1.76 (95%CI 1.08-2.8).
	Cho Y, *et al.* (2019)[34]	South Korea	Cross-sectional	**476** individuals (79.6% NAFLD) underwent screening colonoscopy and liver biopsy	NASH was an independent risk factor for both colorectal polyps (OR 2.08; 95% CI 1.12–3.86) and advanced colorectal neoplasm (OR 2.81; 95% CI 1.01–7.87).
	Kim MC *et al.*, (2019)[33]	South Korea	Cross-sectional	**6332** individuals (37.8% NAFLD) underwent screening colonoscopy and abdominal US	NAFLD was an independent risk factor for colorectal adenoma (aOR 1.15; 95% CI 1.02-1.30), advanced adenoma (aOR 1.50; 95% CI 1.12–2.01), and multiple adenomas (aOR 1.32; 95% CI 1.01–1.73).
	Ze EY *et al.*, (2018)[19]	South Korea	Cross-sectional	**2976** individuals (50.8% fatty liver)	Fatty liver index ≥30 was associated with an increased risk of colorectal adenoma

Table 1 (continued)

				underwent screening colonoscopy and abdominal US	(OR 1.27; 95% CI 1.06–1.49).
	Kim GA, *et al.* (2017)[35••]	South Korea	Retrospective cohort	**25,947** individuals (33.6% NAFLD) underwent screening colonoscopy and abdominal US. Median follow-up: 7.5 years	NAFLD patients had higher incidence of colorectal cancer (69.4 vs. 34.1 per 100,000 person-years; IRR 2.04; 95% CI 1.30–3.19).
Colon	Ahn JS *et al.*, (2017)[32]	South Korea	Cross-sectional	**26,540** individuals (36.8% NAFLD) underwent screening colonoscopy and abdominal US	NAFLD patients had a higher prevalence of any colorectal neoplasia (38.0% vs. 28.9%) and advanced colorectal neoplasia (2.8% vs. 1.9%). The aOR in NAFLD patients was 1.10 (95% CI: 1.03–1.17) for any colorectal neoplasia and 1.21 (95% CI: 0.99–1.47) for advanced colorectal neoplasia.
	Chen QF *et al.*, (2017)[37]	China	Cross-sectional	**3686** individuals (65.9% males, 13.3% NAFLD) underwent screening colonoscopy and abdominal US	NAFLD was significantly associated with adenomatous polyps (OR = 1.53, 95%CI: 1.18-2.00) and hyperplastic polyps (OR = 1.42, 95%CI: 1.04-1.95) in men, but not in females.
	Pan S *et al.*, (2017)[57]	China	Cross-sectional	**1793** individuals (32% NAFLD) underwent screening colonoscopy and abdominal US	NAFLD was independently associated with increased risk of prevalent colorectal cancer (aOR 2.16, 95% CI 1.29–3.22).

Table 1 (continued)

	Yang YJ *et al*., (2017)[20]	South Korea	Retrospective cohort	**1023** individuals (43.1% NAFLD) underwent screening colonoscopy and abdominal US or CT. Followed up to 5 years	Cumulative incidence rates of colorectal neoplasm at 3 and 5 years in the NAFLD group were 9.1% and 35.2% vs. 5.0% and 25.3% in non-NAFLD group. NAFLD was associated with increased risk of overall colorectal tumors (aHR 1.31, 95% CI 1.01–1.71), and the development of ≥3 adenomas at the time of surveillance colonoscopy (aHR: 2.49, 95% CI: 1.20-5.20).
	Mahamid M *et al*., (2017)[48]	Israel	Retrospective cohort	**223** individuals (55.2% NASH) underwent screening colonoscopy and liver biopsy	NASH group had higher prevalence of hyperplastic polyps (22.7% vs. 8%). NASH was associated with increased risk for hyperplastic polyps (OR 1.69, 95%CI 1.36–1.98).
	Lee T *et al*., (2016)[31•]	South Korea	Cross-sectional	**44,220** individuals (33.1% NAFLD) underwent screening colonoscopy and abdominal US	aOR for colorectal cancer with varying severity o NAFLD was: 1.13 for mild, 1.12 for moderate, and 1.56 for severe (P for the trend = 0.007).
	Bhatt BD *et al*., (2015)[56]	USA	Retrospective cohort	**591** individuals (12% NAFLD) completed LT evaluation (liver biopsy and colonoscopy)	NAFLD group had higher prevalence of polyps (59% vs. 40%) and adenomas (32% vs. 21%). NAFLD was predictive of finding a polyp on colonoscopy (OR 2.42, P=0.001) and was associated with adenoma (OR 1.95, P=0.02).

Table 1 (continued)

Colon	Sun LM et al., (2015)[41]	Taiwan	Retrospective cohort	**2109** individuals identified as NAFLD with cirrhosis using ICD codes from the Taiwan National Health Insurance program. Each NAFLD patient was matched to 4 non-cirrhotic individuals. Mean follow-up: 3.62 years	NAFLD with cirrhosis group had higher incidence of colorectal cancer (aHR 2.58, 95% CI 1.59–4.18)
	Aktas E *et al.*, (2014)[21]	Turkey	Case-control	**105** patients with CRC were matched with **94** patients without CRC. Abdomnopelvic CT images were compared.	The CT score (liver density) of the CRC group (68.70±18.7) was lower (more fat density) than that of the control group (96.87±11.9) p<0.001.
	Lin XF *et al.*, (2014)[22]	China	Cross-sectional	**2315** individuals (11.4% NAFLD) underwent screening colonoscopy and abdominal US	NAFLD group had higher prevalence of colorectal cancer (29.3 % vs. 18.0%). NAFLD was independently associated with increased risk of colorectal cancer (aOR 1.87, 95% CI 1.36–2.57).
	Huang KW *et al.*, (2013)[23]	Taiwan	Retrospective cohort	**1522** individuals (40.7% NAFLD) underwent two consecutive colonoscopies (first was negative baseline) and abdominal US. Follow-up: 2.6 years	NAFLD prevalence was 55.6% in the adenoma group and 38.8% in the nonadenoma group. NAFLD was an independent risk factor for colorectal adenoma development (OR = 1.45; 95% CI: 1.07–1.98) after adjusting.

Table 1 (continued)

	Lee YI *et al.*, (2012)[38]	South Korea	Retrospective cohort	**5517** women (15.1% NAFLD) underwent screening colonoscopy and abdominal US. Mean follow-up: 4.5 years	NAFLD was associated with aRR 1.94 (95% CI 1.11–3.40) for adenomatous polyps, and aRR 3.08 (95% CI 1.02–9.34) for colorectal cancer.
	Wong VW *et al.*, (2011)[30]	China	Cross-sectional	**380** individuals (52.4% NAFLD) were recruited for screening colonoscopy from a community-based cohort (had MRS) and a hospital-based cohort (had liver biopsy)	NAFLD group had higher prevalence of colorectal adenomas (34.7% vs 21.5%) and advanced neoplasms (18.6% vs 5.5%) than healthy controls. Among the biopsy group: NASH had higher prevalence of adenomas (51.0% vs 25.6%) and advanced neoplasms (34.7% vs 14.0%) than those with simple steatosis. NASH was also associated with adenomas (aOR 4.89, 95% CI 2.04-11.70) and advanced neoplasms (OR 5.34, 95% CI 1.92-14.84).
Colon	Stadlmayr A *et al.*, (2011)[24]	Austria	Cross-sectional	**1211** individuals (45.7% NAFLD) underwent screening colonoscopy and abdominal US	NAFLD was independently associated with increased risk of colorectal adenomas (aOR 1.47, 95% CI 1.08–2.00).
	Hwang ST *et al.*, (2009)[18]	South Korea	Cross-sectional	**2917** individuals (32.3% NAFLD) underwent screening colonoscopy and abdominal US	Prevalence of NAFLD was 41.5% in the adenoma group and 30.2% in the nonadenoma group. NAFLD was associated with increased risk of colorectal adenomas (OR 1.28, 95% CI:

Table 1 (continued)

					1.03–1.60).
	Nonsignificant Association				
	Touzin NT *et al.*, (2011)[28]	USA	Retrospective cohort	**233** individuals (40.3% NAFLD) underwent screening colonoscopy and abdominal US and liver biopsy	Prevalence of polyps between NAFLD and non-NALFD groups was not significantly different (24.4% vs 25.1%; p=1)
	Sørensen HT *et al.*, (2003)[17]	Denmark	Retrospective cohort	**7326** individuals (25% NAFLD) were filtered using the ICD codes for fatty liver disease and colon and rectal cancers	The standardized incidence ratio of colon and rectal cancers in the NAFLD group were: SIR 1.6, 95% CI 0.9-2.9 and SIR 0.5, 95% CI 0.1-1.7, respectively
	Negative Association				
	Basyigit S *et al.*, (2015)[29]	Turkey	Cross-sectional	**127** individuals (100% NAFLD) underwent screening colonoscopy and abdominal US	The risk for CRC was associated with the absence of NAFLD (OR: 7.38, 95% CI 3.07-7.96).
	GASTRIC AND ESOPHAGEAL				
Gastric/Esophageal	Allen MA, *et al.* (2019)[36••]	USA	Retrospective cohort	**Described above**	NAFLD patients had higher incidence of gastric cancer (IRR=2.3, 95%CI 1.3-4.1)
	Sun LM *et al.,* (2015)[41]	Taiwan	Retrospective cohort	**Described above**	NAFLD with cirrhosis group had significantly higher incidence of esophageal cancer (aHR 7.25; 95% CI

Table 1 (continued)

					2.44–21.6) and gastric cancer (aHR 5.50; 95% CI 2.78–10.9).
	Uzel M *et al.*, (2015)[42]	Turkey	Retrospective cohort	**14** individuals diagnosed with distal gastric cancer on EGD, 5 of which were NAFLD (35.7%)	The prevalence of NAFLD was higher in gastric cancer patients compared to that in the Turkish general population.
	Sørensen HT *et al.*, (2003)[17]	Denmark	Retrospective cohort	**Described above**	The standardized incidence ratio of esophageal cancer in the NAFLD group was: SIR 2.9; 95% CI 0.4-10.3.
PANCREAS					
Pancreas	Allen MA, *et al.* (2019)[36••]	USA	Retrospective cohort	**Described above**	NAFLD patients had higher incidence of pancreatic cancer (IRR=2.1, 95%CI 1.2-3.3)
	Chang CF *et al.*, (2017)[43]	Taiwan	Case-control	**143** (11.9% NAFLD) with and **414** (5.1% NAFLD) without pancreatic cancer underwent abdominal CT	NAFLD prevalence was higher in cancer group (11.9% vs. 5.1%). NAFLD was an independent risk factor for pancreatic cancer (OR 2.63, 95% CI 1.24–5.58).
	Kim GA, *et al.* (2017)[35••]	South Korea	Retrospective cohort	**25,947** individuals (33.6% NAFLD) underwent screening abdominal US. Median follow-up: 7.5 years	NAFLD patients had higher incidence of pancreatic cancer (16.0 vs. 13.8 per 100,000 person-years) but was statistically insignificant (IRR 1.16; 95% CI 0.51-2.65).
	Sun LM *et al.,* (2015)[41]	Taiwan	Retrospective cohort	**Described above**	NAFLD with cirrhosis group had higher crude and adjusted incidence risk of pancreatic cancer (HR

Table 1 (continued)

					4.18; 95% CI 1.67–10.4 and aHR 2.72; 95% CI 0.93–7.95, respectively), however the adjusted incidence risk was statically insignificant.
	Sørensen HT *et al*., (2003)[17]	Denmark	Retrospective cohort	**Described above**	The standardized incidence ratio of pancreatic cancer in the NAFLD group was: SIR 3.0, 95% CI 1.3-5.8.
BREAST					
	Allen MA, *et al.* (2019)[36••]	USA	Retrospective cohort	**Described above**	Breast cancer incidence was higher in NAFLD vs. controls, SIR 1.68 (95% CI 1.05-2.76)
Breast	Kwak M-S, *et al.* (2018)[25]	South Korea	Case-control	**270** women diagnosed with breast cancer by screening mammography and breast US (30.0% NAFLD) were matched with **270** with no breast cancer on imaging (20.0% NAFLD). All underwent hepatic US.	NAFLD was independently associated with breast cancer (OR 1.63 95% CI 1.01–2.62; p 0.046), and was significantly associated with breast cancer in the non-obese (OR 3.04, 95% CI 1.37–4.32; p 0.002) but not in the obese group (p 0.163)
	Kim GA, *et al.* (2017)[35••]	South Korea	Retrospective cohort	**11,981** female pts (21% NAFLD) underwent screening abdominal US	NAFLD group had higher incidence of breast cancer (181.6 vs. 102.5 per 100,000 person-years) than non-NAFLD group, with IRR 1.77, 95% CI 1.15–2.74
	Nseir W, *et al.* (2017)[26]	Israel	Case-control	**73** newly diagnosed breast cancer patients (by mammography	45.2% of cancer pts vs. 16.4% of controls had NAFLD, OR 4.19; 95% CI 1.9-9.1, P = 0.0003

Table 1 (continued)

				or US), matched with **73** patients without breast cancer on imaging. Both groups underwent CT abdomen within 1 month (cancer pts) or 3 months (controls) of breast cancer screening	
	Bilici A, *et al.* (2007)[27]	Turkey	Case-control	**40** *new untreated* breast cancer pts (group 1), **45** breast cancer pts treated with systemic therapy (group 2), **40** ovarian cancer pts (group 3), and **40** healthy women (group 4). All evaluated with hepatic US.	Hepatic steatosis in 63%, 72%, 77%, and 48% of pts in groups 1, 2, 3, and 4, respectively. Grade-2 and 3 hepatic steatosis were more prevalent in all breast cancer pts (P = 0.03).
	Chu CH, *et al.* (2003)[46]	China	Case-control	**217** newly diagnosed breast cancer individuals matched with **182** individuals with no breast cancer. All underwent hepatic US	45.2% of cancer patients vs. 20.3% of the controls had NAFLD (OR 3.23; 95% CI 2.1-5.1, P<0.0001).
	Nonsignificant Association				
	Lee S, *et al.* (2017)[47]	South Korea	Cross-sectional	**104** pts who underwent surgical treatment for breast cancer	18.3% of the breast cancer patients were diagnosed with NAFLD, which is insignificantly different

Table 1 (continued)

				also underwent liver MRIs	from the prevalence of NAFLD in the South Korean general population.
	Sun LM *et al.,* (2015)[41]	Taiwan	Retrospective cohort	**Described above**	NAFLD with cirrhosis group had higher adjusted incidence risk (aHR 1.23; 95% CI 0.28–5.38) compared to the control group, however this difference was statistically insignificant.
	Sørensen HT *et al*., (2003)[17]	Denmark	Retrospective cohort	**Described above**	The standardized incidence ratio of breast cancer in the NAFLD group was: SIR 0.9, 95% CI 0.4-1.7
UTERINE					
Uterine	Allen MA, *et al.* (2019)[36••]	USA	Retrospective cohort	**Described above**	NAFLD patients had higher incidence of uterine cancer IRR=2.3 (95%CI 1.4-4.1).
	Kim GA, *et al.* (2017)[35••]	South Korea	Retrospective cohort	**11,981** female pts (21% NAFLD) underwent screening abdominal US. Median follow-up: 7.5 years	NAFLD patients had higher incidence of uterine/cervical/ovarian cancers (48.4 vs. 23.5 per 100,000 person-years) but was statistically insignificant (IRR 2.06; 95% CI 0.86-4.91).
	Sun LM *et al.,* (2015)[41]	Taiwan	Retrospective cohort	**Described above**	NAFLD with cirrhosis group had higher crude and adjusted hazard ratios of uterine cancer (HR 2.11; 95% CI 0.67–6.63; and aHR 2.03; 95% CI 0.60–6.80), however both were statistically insignificant.

Table 1 (continued)

PROSTATE					
Prostate	Choi YJ *et al.*, (2018)[49•]	South Korea	Cross-sectional	**10,516,985** males were filtered from a national database registry. NAFLD was identified using the fatty liver index (FLI, ≥60) or hepatic steatosis index (HIS), and prostate cancer was identified by ICD codes	Prevalence of NAFLD was: 19% FLI and 25% HIS. Each FLI ≥60 and HSI ≥36 was independently associated with the development of prostate cancer (HR 1.09, 95% CI 1.06-1.12 and HR 1.19, 95% CI 1.16-1.23).
	Kim GA, *et al.* (2017)[35••]	South Korea	Retrospective cohort	**13,966** males (44.4% NAFLD) underwent screening abdominal US	NAFLD patients had **lower** incidence of prostate cancer (126.0 vs. 138.9 per 100,000 person-years) but was statistically insignificant (IRR 0.91; 95% CI 0.63-1.31).
	Sørensen HT *et al.*, (2003)[17]	Denmark	Retrospective cohort	**Described above**	The standardized incidence ratio of prostate cancer in the NAFLD group was: SIR 1.3, 95% CI 0.5-2.8.
KIDNEY					
Kidney	Kim GA, *et al.* (2017)[35••]	South Korea	Retrospective cohort	**25,947** individuals (33.6% NAFLD) underwent screening abdominal US. Median follow-up: 7.5 years	NAFLD patients had higher incidence of renal cancer (35.6 vs. 20.3 per 100,000 person-years) but was statistically insignificant (IRR 1.76; 95% CI 0.96-3.22).

neoplasia or advanced colorectal neoplasia was higher for those with severe liver diseases than those with mild liver diseases, according to the non-invasive parameters of liver disease severity [32]. Moreover, Kim et al. proved that NAFLD subjects with

Table 1 (continued)

	Sun LM *et al.*, (2015)[41]	Taiwan	Retrospective cohort	**Described above**	NAFLD with cirrhosis group had higher crude and adjusted hazard ratios of urinary system cancer (HR 1.19; 95% CI 0.53–2.66; and aHR 1.60; 95% CI 0.69–3.72), however both were statistically insignificant.
	Sørensen HT *et al.*, (2003)[17]	Denmark	Retrospective cohort	**Described above**	The standardized incidence ratio of renal cancer in the NAFLD group was: SIR 2.7, 95% CI 1.1-5.6.
HEMATOLOGIC					
Hematologic	Sun LM *et al.*, (2015)[41]	Taiwan	Retrospective cohort	**Described above**	NAFLD with cirrhosis group had significantly higher adjusted incidence of hematologic cancer (aHR 3.12; 95% CI 1.34–7.25).

advanced fibrosis had a significantly higher risk for colorectal adenomas than those without advanced fibrosis, using various noninvasive score models [33]. Additionally, Cho et al. found that patients with advanced colorectal neoplasm had higher grade of steatosis and higher stage of hepatic fibrosis than those with normal colonoscopic findings or low-grade adenomatous polyp [34]. While Kim et al.'s results showed no significant association between the severity of hepatic *steatosis* detected on US and any cancer development, they demonstrated evidence for a higher risk of development of all cancers in patients with high NAFLD Fibrosis Score (≥ − 1.455) or a high FIB-4 score (≥ 1.45) among the NAFLD subjects, but this increase in fibrosis severity was not associated with increased colorectal cancer risk in their study [35••].

The Colorectal Neoplasia Risk Is High in Men but Not in Women One unique characteristic of the association between NAFLD and colorectal neoplasia is the sex-related difference in risk. Several studies showed a significant association in men, but not in women. This difference was noted in two large studies of colorectal cancer.

In one study, among the male subjects (n = 13,966), those with NAFLD had significantly higher incidence rates of colorectal cancer (IRR 2.21; 95% CI 1.26–3.87; p = 0.006), while among female subjects (n = 11,981), the incidence rate of colorectal cancer did not differ between the NAFLD and control groups (IRR 1.00; 95% CI 0.37–2.70; p = 0.99) [35••]. Similarly, in a population-based study of over 19,000 subjects, NAFLD was associated with higher incidence of colorectal cancer in men (IRR 2.4; 95% CI 1.6–3.9), but not in women (IRR 1.3; 95% CI 0.8–2.1) when compared to age- and sex-matched controls [36••]. The prevalence of colorectal polyps follows a similar sex-specific pattern; OR = 1.40, 95% CI 1.14–1.71 in men and OR = 0.78, 95% CI 0.47–1.28 in women [37]. Only one smaller retrospective cohort study conducted exclusively on South Korean women (n = 5517, 15.1% NAFLD) suggested that the risk of colorectal neoplasia is high in women with NAFLD [38].

The reason for the sex-related predisposition to colon cancer in NAFLD remains elusive. Nevertheless, this observational evidence, coupled with similar disparities described in obesity-related colorectal cancer [39], serves as an important framework for future studies that examine whether counseling and screening should be individualized by sex.

Esophageal and Gastric Cancer

Central adiposity has been linked to esophageal inflammation promoting metaplasia and neoplasia via reflux-dependent and reflux-independent mechanisms. A recent meta-analysis of 6 studies demonstrated that central adiposity, independent of BMI, was associated with increased risk of esophageal adenocarcinoma (aOR, 2.51; 95% CI, 1.54–4.06) in reference to normal body habitus [40]. The association of NAFLD with esophageal or gastric cancer is less clear. In the three large retrospective studies designed to explore the incidence of gastroesophageal cancers in individuals with NAFLD, there were trends in increased risk of both cancer types. However, the results are inconsistent and limited due to small number of cancer outcomes and without sufficient statistical power [17, 36••, 41]. A very small retrospective cohort (n = 14) found higher prevalence of NAFLD in gastric cancer patients than the Turkish general population [42].

Pancreatic Cancer

Pancreatic cancer was found to be highly associated with NAFLD. In 4 studies that found higher incidence of pancreatic cancer in NAFLD patients, 3 large retrospective cohort studies were statistically significant [17, 35••, 36••], and one study found significantly higher crude incidence risk but nonsignificant adjusted risk [41]. Further, a smaller case-control study (143 pancreatic cancer patients vs. 414 controls) showed higher prevalence of NAFLD in pancreatic cancer patients [43].

Hormone-Sensitive Cancers

Breast Cancer

Several studies have described an association between obesity and breast cancer risk, especially in postmenopausal women who have never used hormone-replacement therapy [44]. The risk of developing breast cancer increases by 11% with each 5 kg of weight gain [45]. A similar association between NAFLD and breast cancer has been found in most retrospective studies [35, 36, 46, 57, 19, 20], the largest of which estimated a 60–70% increase in incidence [35••, 36••] and 3-fold higher prevalence [46]. A few smaller-size studies failed to show significant association between NAFLD and the incidence [17, 41] or prevalence [47] of breast cancer.

Uterine Cancer

Few studies showed evidence of an association between NAFLD and uterine cancer. Three large retrospective cohort studies demonstrated higher incidence of uterine cancer in NAFLD patients [35••, 36••, 41], but only one of them was statistically significant [36••].

Prostate Cancer

Large-scale studies have examined the incidence of prostate cancer in NAFLD and showed inconsistent results. There were trends of direct or inverse association, but not statistically significant [42] [48]. The largest study of a South Korean population that included over 10 million males filtered from a national database registry showed marginally significant higher incidence of prostate cancer in NAFLD patients with fatty liver index $\geq$ 60 or hepatic steatosis index $\geq$ 36 [49•]. Overall, the evidence does not appear to support prostate cancer as a significant threat in men with NAFLD.

Other Cancers

Renal Cancer

NAFLD was associated with increased incidence of renal cell carcinoma in 3 large retrospective cohort studies [17, 35••, 41], but this risk was statistically significant in only one of them [17].

Hematologic

A single retrospective cohort study that investigated the incidence of cancers in over 2000 NAFLD patients found statistically significant higher incidence of hematologic cancer [41].

Mechanistic Hypotheses in Obesity-Associated Cancers

Several mechanisms by which obesity induces tumorigenesis have been proposed. Chronic *hyperinsulinemia* may contribute to cancer development through a direct mechanism of growth-promoting signaling and indirectly through insulin-like growth factor 1 which triggers tumorigenic intracellular signaling cascades [42]. *Adipokine pathophysiology* has been proposed as an additional hormonal pathway to cancer risk. Leptin, which is secreted in excess in obesity, has anti-apoptotic, proliferative, and immunity suppression effects [50, 51]. In contrast, adiponectin, which is decreased in obesity, has opposite effects through pathways that inhibit cell proliferation and inflammation [52]. Excess adipose tissue is accompanied by increased release of inflammatory mediators like C-reactive protein (CRP), tumor necrosis factor (TNF), interleukin-1β (IL-1β), IL-6, and IL-18

[53–55]. This chronic *inflammatory state* has been linked to increased cancer risk. *Hyper-estrogenism* may explain the link between obesity and breast, endometrial, and ovarian cancers. Excess peripheral adipose tissue accelerates aromatase activity which converts androgen precursors to estrogen (aromatization), which has proliferative effects.

Malignancy Risk in NAFLD Versus Obesity

New paradigms related to systemic versus local effects of excess adiposity on the tumor microenvironments are emerging. Renehan et al. review preclinical and epidemiological research that suggests an effect of local fat in the development of breast cancer, hepatocellular carcinoma, and pancreatic cancer via paracrine inflammatory effects [42]. These findings support the hypothesis that assessment of body fat distribution and organ-specific ectopic fat may be more relevant than BMI, which is a crude measure of excess adiposity. In the specific case of NAFLD, the question whether the increased malignancy risk is related to ectopic fat or to obesity in general (as measured by BMI) is highly relevant.

A few observational studies aimed to tease out the association between cancer and obesity, with and without NAFLD. In a large population-based study, Allen et al. found that in reference to non-obese controls, obesity (defined by BMI > 30 kg/m^2, irrespective of NAFLD status) was associated with a trend towards increased malignancy risk: IRR = 1.2 (95% CI 0.9, 1.6). However, when analyzed by the presence or absence of NAFLD, in reference to non-obese controls, NAFLD was associated with a higher risk of incident cancers (overall malignancy IRR = 2.0, 95% CI 1.5, 2.9, with the largest increase noted among hepatic and gastrointestinal cancers), while obesity alone was not (IRR = 1.0, 95% CI 0.8, 1.4) [36••]. Another study by Bhatt et al. concluded that colon polyps had a stronger association with NAFLD than MetS or diabetes [56]. Pan et al. studied the effect of NAFLD vs. MetS on CRC development by comparing 4 groups with and without NAFLD (N) and MetS (M) (M+N+ vs. M-N+ vs. M+N- vs. M-N-) and found the additive risk effect of NAFLD and MetS to be significantly higher than the other combinations [57].

These studies suggest that NAFLD may be a more important intermediary biomarker of cancer risk than BMI or metabolic syndrome. Whether NAFLD is a predictor of cancer risk or a mediator on the causal pathway remains to be elucidated. Nevertheless, the fact that the largest increase in incident extrahepatic cancers in NAFLD relate to gastrointestinal sites may serve as epidemiological evidence to support the biological plausibility of local tumorigenic effects of ectopic hepatic or visceral fat.

Conclusion

A large body of observational evidence supports an increase in the overall risk of extrahepatic cancers in patients with NAFLD. Noteworthy characteristics of the NAFLD-associated cancers include organ-specificity (gastrointestinal tract) and sex-related differences (increased risk of colorectal cancer in men). Emerging data suggest that the association between NAFLD and malignancy is not explained solely by increased body mass index. This association requires further studies, ideally designed to include more detailed measures of body fat deposition beyond BMI in well-characterized, large cohorts of NAFLD patients, to determine if screening policies should be individualized in this group.

Funding Information Alina M. Allen: National Institute of Diabetes and Digestive and Kidney Diseases (K23DK115594); American College of Gastroenterology Junior Faculty Development Grant.

Compliance with Ethical Standards

Conflict of Interest Omar T. Ahmed and Alina M. Allen each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Armstrong MJ, et al. *Presence and severity of non-alcoholic fatty liver disease in a large prospective primary care cohort*. J Hepatol. 2012;**56**(1):234–40.
2. El-Kader SMA, El-Den Ashmawy EMS. *Non-alcoholic fatty liver disease: the diagnosis and management*. World J Hepatol. 2015;**7**(6):846.
3. Younossi ZM, et al. *Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes*. Hepatology. 2016;**64**(1):73–84.
4. Fabbrini E, Sullivan S, Klein S. *Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications*. Hepatology. 2010;**51**(2):679–89.
5. Williams CD, et al. *Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study*. Gastroenterology. 2011;**140**(1):124–31.
6. Wanless IR, Lentz JS. *Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors*. Hepatology. 1990;**12**(5):1106–10.
7. Lazo, M. and J.M. Clark. *The epidemiology of nonalcoholic fatty liver disease: a global perspective*. in *Seminars in liver disease*. 2008. © Thieme Medical Publishers.

8. Silverman, J.F., et al., *Liver pathology in morbidly obese patients with and without diabetes.* Am J Gastroenterol, 1990. **85**(10).
9. Younossi ZM, et al. *Nonalcoholic fatty liver disease in lean individuals in the United States*. Medicine. 2012;**91**(6):319–27.
10. Angulo P, et al. *Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis*. Hepatology. 1999;**30**(6):1356–62.
11. Machado M, Marques-Vidal P, Cortez-Pinto H. *Hepatic histology in obese patients undergoing bariatric surgery*. J Hepatol. 2006;**45**(4):600–6.
12. Ligibel JA, et al. *American Society of Clinical Oncology position statement on obesity and cancer*. J Clin Oncol. 2014;**32**(31):3568.
13. Demark-Wahnefried W, et al. *The role of obesity in cancer survival and recurrence*. Cancer Epidemiology and Prevention Biomarkers. 2012;**21**(8):1244–59.
14. Sanna C, et al. *Non-alcoholic fatty liver disease and extra-hepatic cancers*. Int J Mol Sci. 2016;**17**(5):717.
15. Margini C, Dufour JF. *The story of HCC in NAFLD: from epidemiology, across pathogenesis, to prevention and treatment*. Liver Int. 2016;**36**(3):317–24.
16. Tilg H, Moschen AR. *Mechanisms behind the link between obesity and gastrointestinal cancers*. Best practice & research. Clin Gastroenterol. 2014;**28**(4):599–610.
17. Sørensen HT, et al. *Risk of cancer in patients hospitalized with fatty liver: a Danish cohort study*. J Clin Gastroenterol. 2003;**36**(4):356–9.
18. Hwang ST, et al. *Relationship of non-alcoholic fatty liver disease to colorectal adenomatous polyps*. J Gastroenterol Hepatol. 2010;**25**(3):562–7.
19. Ze EY, et al. *The fatty liver index: a simple and accurate predictor of colorectal adenoma in an average-risk population*. Dis Colon Rectum. 2018;**61**(1):36–42.
20. Yang YJ, et al. *Clinical impact of non-alcoholic fatty liver disease on the occurrence of colorectal neoplasm: propensity score matching analysis*. PLoS One. 2017;**12**(8):e0182014.
21. Aktas E, et al. *Assessment of hepatic steatosis on contrast enhanced computed tomography in patients with colorectal cancer*. Int J Clin Exp Med. 2014;**7**(11):4342–6.
22. Lin XF, et al. *Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study*. Mol Biol Rep. 2014;**41**(5):2989–97.
23. Huang KW, et al. *Patients with nonalcoholic fatty liver disease have higher risk of colorectal adenoma after negative baseline colonoscopy*. Color Dis. 2013;**15**(7):830–5.
24. Stadlmayr A, et al. *Nonalcoholic fatty liver disease: an independent risk factor for colorectal neoplasia*. J Intern Med. 2011;**270**(1):41–9.
25. Kwak MS, et al. *Nonalcoholic fatty liver disease is associated with breast cancer in nonobese women*. Dig Liver Dis. 2019.
26. Nseir W, et al. *Relationship between non-alcoholic fatty liver disease and breast cancer*. Isr Med Assoc J. 2017;**19**(4):242–5.
27. Bilici A, et al. *A case–control study of non-alcoholic fatty liver disease in breast cancer*. Med Oncol. 2007;**24**(4):367–71.
28. Touzin NT, et al. *Prevalence of colonic adenomas in patients with nonalcoholic fatty liver disease*. Ther Adv Gastroenterol. 2011;**4**(3):169–76.
29. Basyigit S, et al. *Absence of non-alcoholic fatty liver disease in the presence of insulin resistance is a strong predictor for colorectal carcinoma*. Int J Clin Exp Med. 2015;**8**(10):18601–10.
30. Wong VW, et al. *High prevalence of colorectal neoplasm in patients with non-alcoholic steatohepatitis*. Gut. 2011;**60**(6):829–36.
31.• Lee T, et al. *Risk of colorectal neoplasia according to fatty liver severity and presence of gall bladder polyps*. Dig Dis Sci. 2016;**61**(1):317–24 **Important cross-sectional study on 44,220 individuals evaluated the risk of colorectal cancer in relation to the severity of liver steatosis**.
32. Ahn JS, et al. *Non-alcoholic fatty liver diseases and risk of colorectal neoplasia*. Aliment Pharmacol Ther. 2017;**45**(2):345–53.
33. Kim MC, et al. *Liver fibrosis is associated with risk for colorectal adenoma in patients with nonalcoholic fatty liver disease*. Medicine (Baltimore). 2019;**98**(6):e14139.
34. Cho, Y., et al., *Nonalcoholic steatohepatitis is associated with a higher risk of advanced colorectal neoplasm.* Liver International. **0**(0).
35.•• Kim GA, et al. *Association between non-alcoholic fatty liver disease and cancer incidence rate*. J Hepatol. 2017; **Very important retrospective study on 25,947 individuals studied the incidence rates of cancers in NAFLD patients, and the sex-specific difference in risk**.
36.•• Allen AM, et al. *The risk of incident extrahepatic cancers is higher in nonalcoholic fatty liver disease than obesity - a longitudinal cohort study*. J Hepatol. 2019; **Very important retrospective study on 19,163 individuals investigated the effect of NAFLD versus obesity on cancer incidence rates.**
37. Chen QF, et al. *Sex-influenced association of non-alcoholic fatty liver disease with colorectal adenomatous and hyperplastic polyps*. World J Gastroenterol. 2017;**23**(28):5206–15.
38. Lee YI, Lim YS, Park HS. *Colorectal neoplasms in relation to nonalcoholic fatty liver disease in Korean women: a retrospective cohort study*. J Gastroenterol Hepatol. 2012;**27**(1):91–5.
39. Renehan AG, Zwahlen M, Egger M. *Adiposity and cancer risk: new mechanistic insights from epidemiology*. Nat Rev Cancer. 2015;**15**(8):484–98.
40. Singh S, et al. *Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis*. Clin Gastroenterol Hepatol. 2013;**11**(11):1399–1412.e7.
41. Sun LM, et al. *Nonalcoholic cirrhosis increased risk of digestive tract malignancies: a population-based cohort study*. Medicine (Baltimore). 2015;**94**(49):e2080.
42. Uzel M, Sahiner Z, Filik L. *Non-alcoholic fatty liver disease, metabolic syndrome and gastric cancer: Single center experience*. J Buon. 2015;**20**(2):662.
43. Chang CF, et al. *Exploring the relationship between nonalcoholic fatty liver disease and pancreatic cancer by computed tomographic survey*. Intern Emerg Med. 2018;**13**(2):191–7.
44. Calle EE, Kaaks R. *Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms*. Nat Rev Cancer. 2004;**4**(8):579–91.
45. Kyrgiou M, et al. *Adiposity and cancer at major anatomical sites: umbrella review of the literature*. BMJ. 2017;**356**:j477.
46. Chu CH, et al. *Fatty metamorphosis of the liver in patients with breast cancer: possible associated factors*. World J Gastroenterol. 2003;**9**(7):1618–20.
47. Lee S, et al. *Prevalence and risk factors of nonalcoholic fatty liver disease in breast cancer patients*. Tumori. 2017;**103**(2):187–92.
48. Mahamid M, et al. *Association between fatty liver disease and hyperplastic colonic polyp*. Isr Med Assoc J. 2017;**19**(2):105–8.
49.• Choi YJ, et al. *Is nonalcoholic fatty liver disease associated with the development of prostate cancer? A nationwide study with 10,516, 985 Korean men*. PLoS One. 2018;**13**(9):e0201308 **Important cross-sectional study on over 10 millions Korean men investigated the risk of prostate cancer with NAFLD, and the only study that showed an increased risk in NAFLD individuals.**
50. Bray GA. *The underlying basis for obesity: relationship to cancer*. J Nutr. 2002;**132**(11 Suppl):3451s–5s.
51. Rose DP, Komninou D, Stephenson GD. *Obesity, adipocytokines, and insulin resistance in breast cancer*. Obes Rev. 2004;**5**(3):153–65.
52. Dalamaga M, Diakopoulos KN, Mantzoros CS. *The role of adiponectin in cancer: a review of current evidence*. Endocr Rev. 2012;**33**(4):547–94.

53. Hotamisligil GS, Erbay E. *Nutrient sensing and inflammation in metabolic diseases*. Nat Rev Immunol. 2008;**8**(12):923–34.
54. Osborn O, Olefsky JM. *The cellular and signaling networks linking the immune system and metabolism in disease*. Nat Med. 2012;**18**(3):363–74.
55. Weisberg SP, et al. *Obesity is associated with macrophage accumulation in adipose tissue*. J Clin Invest. 2003;**112**(12):1796–808.
56. Bhatt BD, et al. *Increased risk of colorectal polyps in patients with non-alcoholic fatty liver disease undergoing liver transplant evaluation*. J Gastrointest Oncol. 2015;**6**(5):459–68.
57. Pan S, et al. *The relationship of nonalcoholic fatty liver disease and metabolic syndrome for colonoscopy colorectal neoplasm*. Medicine (Baltimore). 2017;**96**(2):e5809.