

## ORIGINAL ARTICLE

# Non-alcoholic fatty liver disease and extra-hepatic malignancies

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## Summary

*Non-alcoholic fatty liver disease (NAFLD) is now one of the leading causes of chronic liver disease, with high rates of morbidity and mortality worldwide, as well as a possible risk factor for non liver-related complications. NAFLD is considered a multisystemic disease and is associated with many extrahepatic malignancies such as colorectal, oesophageal, gastric, pancreatic, kidney and breast cancer, and consequently, more rigorous surveillance and early treatment*

*interventions are required to decrease all-cause mortality. The aim of this review is to summarize the reported NAFLD – associated extrahepatic malignancies, which include colorectal, gastric, breast and pancreatic cancer.*

**Key words:** extra-hepatic, malignancies, non-alcoholic fatty liver disease

## Introduction

Seen as a multisystemic disease with extrahepatic complications, non-alcoholic fatty liver disease (NAFLD) has been associated with a risk for extrahepatic malignancies [1,2] which can be classified into liver-related (hepatocellular carcinoma) and extrahepatic, such as colorectal cancer (CRC), oesophageal, gastric, pancreatic and kidney in men and breast cancer in women [1,2]. The physiopathological mechanism underlying NAFLD tumorigenesis is still not fully understood. It is presumed that due to triglyceride accumulation in the liver, patients with NAFLD associate also visceral adiposity. This condition may cause dysfunction in many organs due to the release of proinflammatory and growth factors, as well as cytokines, these processes being responsible for tumorigenesis in different extrahepatic organs [3,4]. The causal relationships between NAFLD and different extrahe-

patic malignancies need to be supported by further large prospective studies. Of all malignancies linked to NAFLD, CRC has been strongly associated with this condition [5].

## NAFLD and colorectal cancer

According to the GLOBOCAN 2018 data, CRC is the third leading cause of death and the fourth most diagnosed form of cancer in the world. Along with modifiable risk factors such as diet, alcohol consumption and smoking, obesity and lack of physical inactivity are also a major contributor to CRC development [6]. In this respect, several large studies have researched the link between NAFLD and CRC development in patients. Lin et al analyzed in a large cohort study (n= 2315) the link between CRC found at screening colonoscopy and the preva-

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lence of NAFLD in the group. CRC prevalence was reported to be significantly higher in the NAFLD group compared with those without NAFLD (29.3% vs 18 %,  $p < 0.005$ ). Sigmoid carcinoma and highly differentiated colorectal adenocarcinoma were more commonly found in the NAFLD group [7].

NAFLD also associates a risk of adenomas. Touzin et al found that, out of 233 patients who underwent colonoscopy, 58 (24.8%) had adenomatous polyps, 23 of whom were in the NAFLD group [8]. A similar study carried out by Wong et al assessed the incidence of adenomas and advanced CRC in two groups of patients, the results showing a higher prevalence of colorectal adenomas (34.7% vs 21.5%,  $p = 0.005$ ) and advanced colon cancer (18.6% vs 5.5%,  $p < 0.005$ ) in the NAFLD group than in the healthy controls [9]. Lee et al found in a large cohort of Korean women a high prevalence of adenomatous polyps and CRC associated with the presence of NAFLD in the patients included in the study. Thus, 15% of patients in the study group ( $n = 5517$ ) have been diagnosed with NAFLD, 65 of whom had adenomatous polyps and 15 had CRC [10]. In agreement with this study several other studies have shown that metabolic syndrome and NAFLD are associated with an increased risk for CRC [11-14].

There are several studies investigating the association between NAFLD and colorectal adenoma or cancer which have reported conflicting results. Thus, in a recent meta-analysis including five studies with 6,263 subjects, NAFLD was significantly associated with colorectal adenoma pooled (odds ratio (OR) 1.74, 95% confidence interval (CI): 1.53-1.97). Such association was more significant in Asian populations compared to North American or European populations [15,16].

### **NAFLD and breast cancer**

A general concern was raised linking NAFLD to other extrahepatic malignancies. There is an association between breast cancer risk in women and components of the metabolic syndrome [17]. Therefore, several large studies have evaluated the relation between postmenopausal women with breast cancer and NAFLD [17-19]. Two combined case control studies which analyzed a large number of women in the postmenopausal period, 3869 with breast cancer and 4082 controls, showed a higher breast malignancy risk in those with metabolic syndrome as opposed to those without (OR, 1.75; 95% CI 1.37-2.22) [17,18]. Three other studies regarding the relationship between NAFLD and breast cancer, showed that NAFLD is an independent risk factor for breast cancer [19-21].

### **NAFLD and gastric cancer**

Gastric cancer is the fifth most common and the third deadliest cancer worldwide, especially in elderly people [22]. Possible association between NAFLD and gastric cancer has been suggested in a recent study conducted on Turkish population. In 1840 patients who underwent upper gastrointestinal endoscopy, regardless of the limited cases of gastric carcinoma discovered, the prevalence of NAFLD in subjects with this malignancy was higher than in the Turkish general population [23]. Another three high quality cohort studies found that NAFLD patients have an additional risk for gastric cancer (OR ,1.74) [19,24,25].

### **NAFLD and pancreatic cancer**

Pancreatic cancer is the seventh leading cause of global cancer mortality in industrialized countries and GLOBOCAN 2018 estimated it to be the 11<sup>th</sup> most common cancer in the world with 458,918 new cases, leading to 432,242 deaths [26]. The causes of pancreatic cancer are multifactorial such as age over 50 years, male gender, ethnicity, family history, diabetes mellitus, genetic and smoking [26].

More than a decade ago the World Cancer Research Fund / American Institute for Cancer Research established the association between pancreatic cancer and obesity, while a meta-analysis showed a linear increase between waist circumference and pancreatic cancer risk [27,28]. Another retrospective study made by Chang et al included 557 patients (143 with and 414 without pancreatic cancer). Out of 143 patients, 17 (11.9%) had been diagnosed with NAFLD and out of 414 only 21 (5.1%) had NAFLD. The authors found that NAFLD was an independent factor associated with a higher risk of pancreatic cancer (adjusted OR, 2.63), following multivariate logistic regression analysis [29]. However, to confirm this relationship between NAFLD and pancreatic cancer further prospective studies are required.

### **Conclusions**

In the light of the latest evidence, it is clear that the clinical burden of NAFLD extends beyond liver-related mortality and is associated with a significantly increased risk of several types of cancer. Besides the risk of hepatocellular carcinoma, substantial evidence is reported in the literature for NAFLD as an independent risk factor for extrahepatic cancer. Further studies are required to better define the high-risk patients with NAFLD, to raise

awareness for extrahepatic cancers, especially CRC, gastric, breast and pancreatic, and aid clinicians in the early detection and screening.

### Author contributions

All authors made substantial contributions to acquisition of data, or analysis, conception and design, and interpretation of data; took part in drafting the article or revising it critically for

important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

### Conflict of interests

The authors declare no conflict of interests.

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