ORIGINAL ARTICLE

HEPATOLOGY

doi.org/10.1590/S0004-2803.24612023-027

Non-alcoholic fatty liver disease and extra-hepatic cancer: a narrative review

Achiles Queiroz Monteiro de **REZENDE** and Everton **CAZZO***

*Universidade Estadual de Campinas, Departamento de Cirurgia, Campinas, SP, Brasil.

HIGHLIGHTS

- There is solid evidence showing associations of NAFLD with extra-hepatic cancer.
- The most reported types of extra-hepatic NAFLD-related cancer are colorectal, gastric, pancreatic, breast, prostate and bladder.
- NAFLD has been demonstrated as an independent risk factor for extra-hepatic cancer.

ABSTRACT – Background – Recently, significant associations between non-alcoholic fatty liver disease (NAFLD) and extra-hepatic cancer have been reported. **Objective –** To carry out a comprehensive review of the current evidence in the literature on the association between NAFLD and extra-hepatic cancer. **Methods –** A narrative literature review was performed through an online search for the MeSH terms "fatty liver" and "cancer" in MEDLINE (via PubMed) and LILACS (via BVS). Original studies that described the impact of NAFLD on different types of extra-hepatic malignancies were included. **Results –** After careful analysis, nine prospective cohort studies, one retrospective cohort study, three case-control studies, and three cross-sectional studies were selected. **Conclusion –** There is consistent evidence on the association between NAFLD and extra-hepatic carcinogenesis, especially in relation to colorectal, gastric, pancreatic, breast, prostate, and bladder cancers.

Keywords – Non-alcoholic fatty liver disease; obesity; cancer; carcinogenesis; fatty liver.

INTRODUCTION

The association between non-alcoholic fatty liver disease (NAFLD) and liver carcinogenesis is well recognized and significant, especially among individuals with non-alcoholic steatohepatitis (NASH) and cirrhosis. Björkström et al. found a 12-fold increased risk of hepatocellular carcinoma in individuals with NAFLD[1]. Bengtssön et al., analyzing individuals with cirrhosis related to already established NAFLD, demonstrated a risk approximately 22 times greater than the control group. Recently, significant associations between NAFLD and extra-hepatic manifestations have been increasingly reported as well, including the role of NAFLD as an independent risk factor for several types of extra-hepatic cancer, particularly colorectal[2].

Received: 15 February 2023
Accepted: 27 July 2023

Declared conflict of interest of all authors: none
Disclosure of funding: none
Declaration of use of artificial intelligence: none
Corresponding author: Everton Cazzo. notrevezzo@yahoo.com.br

The aim of the present study is to carry out a comprehensive narrative review of the current evidence in the literature on the association between NAFLD and extra-hepatic cancer, as well as to gain insight into possible mechanisms underlying this association.

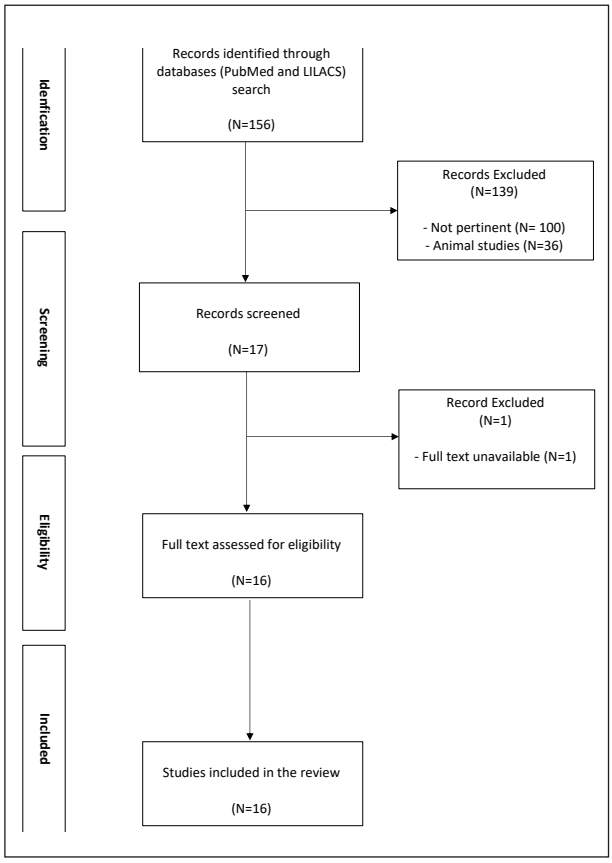

FIGURE 1. Flowchart of the articles' selection.

METHODS

A narrative literature review was performed through an online search for the MeSH terms "fatty liver" and "cancer" in MEDLINE (via PubMed) and LILACS (via BVS) (FIGURE 1).

Original studies that described the impact of NAFLD on different types of extra-hepatic malignancies were included. All articles were checked according to their titles and abstracts (screening). NAFLD could be diagnosed through abdominal ultrasound scan, computed tomography, magnetic resonance, elastography, liver biopsy, or non-invasive markers. The complete articles were obtained from journals available on the website of the Higher Education Personnel Improvement Commission (CAPES, Department of Education, Brazil). Unavailable articles were requested from their authors. Articles that presented potentially relevant studies were read and analyzed to assess their inclusion criteria. Articles that exclusively analyzed liver cancer, in vitro or animal studies, summaries of poster sessions, literature reviews, and other types of publications (studies without adequate follow-up; studies without appropriate diagnostic assessment of NAFLD or that included individuals with other liver diseases, or studies with critical methodological problems) were excluded. Other articles were used for contextualization and discussion.

Ethical approval is not required for this type of study.

Statement of human and animal rights

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

RESULTS

Selection of articles

There was significant overlap between databases. After careful analysis, nine prospective cohort studies, one retrospective cohort study, three case-control studies, and three cross-sectional studies were selected. TABLE 1 summarizes the main articles found and their respective characteristics and reported results.

DISCUSSION

Main evidence in the literature

Studies on the association between NAFLD and extra-hepatic cancer have mostly analyzed various neoplasms of the digestive tract. The most representative are aimed at colorectal cancer, especially because of its higher incidence, but studies showing associations with gastric, esophageal, and pancreatic cancers have also been conducted[3].

Wong et al., in a study that correlated findings of colonoscopies and NAFLD assessed through nuclear magnetic resonance spectroscopy, observed a higher

TABLE 1. Studies included in the review.

Study	Year of publication	Country of origin	N	Type of cancer	Methodology	Mean follow-up (years)	Level of evidence	NAFLD Diagnosis	Main findings
Hamaguchi et al.[5]	2019	Japan	27,944	Gastric and colorectal	Single-center prospective	6.5	2b	Ultrasound scan	NAFLD with obesity was a risk factor for both incident gastric cancer and colorectal cancer
Nseir et al.[14]	2017	Israel	133	Breast	Single-center cross-sectional	NA	3b	Computed tomography	Multivariate analysis showed NAFLD to be associated with breast cancer
Kim et al.[10]	2017	South Korea	25,947	Several	Single-center prospective	7.5	2b	Ultrasound scan	NAFLD was associated with the development of hepatocellular carcinoma, colorectal cancer in males, and breast cancer in females
Chang et al.[36]	2018	Taiwan	557	Pancreatic	Single-center cross-sectional	NA	2c	Computed tomography	NAFLD is positively correlated with pancreatic cancer, a result suggesting that NAFLD may increase the incidence and risk of pancreatic cancer. Patients with pancreatic cancer and NAFLD have poorer overall survival than patients without NAFLD
Hwang et al.[41]	2018	South Korea	318,224	Mortality cause by any cancer	Single-cente-r prospective	5.7	2b	Ultrasound scan	NAFLD was associated with increased overall mortality from cancer
Choi et al.[16]	2018	South Korea	10,516,985	Prostate	Nationwide population-based prospective	5.33	2b	Fatty liver index	NAFLD may help identify high-risk individuals for developing prostate cancer, even in the absence of obesity or metabolic syndrome
Kwak et al.[15]	2019	South Korea	540	Breast	Single-center case-control	NA	3b	Ultrasound scan	NAFLD was significantly associated with breast cancer independent of traditional risk factors in women without obesity
Park et al.[13]	2020	South Korea	7,046,153	Breast	Nationwide population-based prospective cohort	7.0	2b	Fatty liver index	High FLI values significantly associated with increased breast cancer risk in postmenopausal women, but not in premenopausal women
Choi et al.[42]	2020	South Korea	21,592,374	Colorectal	Nationwide population-based prospective	5.3	2b	Fatty liver index	Multivariate logistic regression analysis demonstrated an independent association between NAFLD and colorectal cancer after adjusting for other confounders. In subgroup analyses, fatty liver index ≥60 was associated with CRC regardless of body mass index, but the association was more prominent in lean persons
Chiang et al.[17]	2020	Taiwan	517	Bladder	Single-center case-control	NA	3b	Computed tomography	NAFLD was positively associated with bladder cancer and was a poor prognostic factor of bladder cancer
Lee et al.[43]	2020	South Korea	8,120,674	Esophageal, gastric, and colorectal	Nationwide population-based cross-sectional	NA	2c	Fatty liver index	FLI ≥60 was significantly associated with the development of esophageal, stomach, and colon cancer after multivariable adjustment
Simon et al.[12]	2021	Sweden	8,892	Several	Nationwide population-based prospective cohort	15.5	2b	Liver biopsy	NAFLD was associated with highly increased rates of HCC and modestly increased rates of pancreatic cancer, kidney/bladder cancer, and melanoma, but no other cancers
Yamamoto et al.[44]	2021	Japan	30,172	Several	Single-center retrospective	14.0	2b	Ultrasound scan	NAFLD associated with the development of gastrointestinal malignancies, especially in the stomach and small intestine
Rezende et al.[8]	2021	Brazil	56	Pancreatic	Single-center case-control	NA	3b	Liver Biopsy	Significant associations were identified between histopathological aspects of NAFLD (microvesicular steatosis, hepatocellular ballooning, fibrosis, and steatohepatitis) and pancreatic cancer
Lee et al.[45]	2022	South Korea	8,933,017	Colorectal	Nationwide population-based prospective	10.1	2b	Fatty liver index	NAFLD was associated with a higher risk of CRC development
Park et al.[46]	2022	South Korea	8,120,674	Pancreatic	Nationwide population-based prospective	7.2	2b	Fatty liver index	NAFLD was independently associated with an increased risk of pancreatic cancer, regardless of obesity

N: number of individuals; NA: not applicable; NAFLD: non-alcoholic fatty liver disease; FLI: fatty liver index. Levels of evidence according to the Oxford classification - 1a: systematic reviews (with homogeneity) of randomized controlled trials; 1b: individual randomized controlled trials (with narrow confidence interval); 1c: all or no randomized controlled trials; 2a: systematic reviews (with homogeneity) of cohort studies; 2b: individual cohort study or low-quality randomized controlled trials (e.g. < 80% follow-up); 2c: "outcomes" research; ecological studies; 3a: systematic review (with homogeneity) of case-control studies; 3b: individual case-control study; 4: case series (and poor quality cohort and case-control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles".

incidence of polyps and colorectal cancer in individuals with NAFLD compared with non-affected individuals[4]. Hamaguchi et al. attempted to demonstrate the association of NAFLD with gastric and colorectal adenocarcinomas by evaluating several subgroups (patients without both NAFLD and obesity; without NAFLD and with obesity; with NAFLD without obesity, and patients with both comorbidities). There was clear evidence of increased incidence of gastric and colorectal cancer, respectively, in the NAFLD with obesity group. Individuals with NAFLD without obesity also showed a slightly increased incidence of gastric cancer compared to the group of patients without NAFLD[5].

Allen et al., in a cohort study involving 4,722 individuals with ultrasound-demonstrated NAFLD followed-up for approximately 8 years, demonstrated an incidence of 2,224 cases of cancer, with an approximately 90% increase in the overall risk of any malignancy. Gastrointestinal tract cancers were the most frequent, followed by hormone-related neoplasms. The risk was mostly increased for liver cancer, followed by uterine, gastric, pancreatic, and colorectal malignancies[6].

The association of NAFLD with pancreatic cancer is more difficult to demonstrate because of the overall lower incidence of this type of cancer in the general population. However, there is both direct and indirect evidence pointing towards this outcome. A meta-analysis showed an increase in the incidence of pancreatic cancer in direct correlation with the abdominal waist, with a 10%-increase in risk for each 10 cm[3,7]. Rezende et al., comparing histopathological findings of liver biopsies from individuals operated on because of pancreatic cancer with non-cancer controls matched by BMI, sex, and age, observed significantly higher frequencies of microvesicular steatosis, lobular inflammation, hepatocellular ballooning, and fibrosis among the individuals with cancer, reinforcing the possibility of an association between NAFLD and pancreatic cancer, especially in individuals with NAFLD without obesity[8].

Liu et al., in a meta-analysis that included 26 studies that correlated NAFLD assessed by surrogate non-invasive scores, demonstrated a clear association between NAFLD and extra-hepatic cancers, with a 2.2-odds ratio[9]. Kim et. al., in a prospective study, with a follow-up of 7.5 years, also observed a significant association of NAFLD assessed by ultrasound and/or non-invasive markers with hepatocellular carcinoma, colorectal cancer in men and breast cancer in women. In this study, a significant correlation was observed between the presence of both Fibrosis Index Based on 4 Variables (FIB-4) and NAFLD fibrosis score (NFS) greater than 1.45 and the occurrence of hepatic and extra-hepatic cancers[10]. Peleg et al., in a retrospective study with a mean follow-up of 100 months, also demonstrated that the presence of liver fibrosis detected by biopsy and/or by FIB-4 and NFS were factors independently associated with higher mortality from malignancies[11]. A nationwide study performed by Simon et al., which enrolled 8,892 individuals with histologically proven NAFLD, demonstrated associations with highly increased rates of HCC and modestly increased rates of pancreatic cancer, kidney/bladder cancer, and melanoma, but no other cancers[12].

The association of NAFLD with breast cancer has also been reported in recent years. Park et al.[13], in a study that analyzed a prospectively collected nationwide database of 7,046,153 participants, observed a significantly higher and independent risk of breast cancer among postmenopausal women with NAFLD detected by the fatty liver index (FLI), similarly to the findings observed by both Nseir et al.[14] and Kwak et al.[15] in smaller single-center studies.

There are also isolated studies that have shown correlations between NAFLD and urinary tract cancer. Choi et al., analyzing a prospectively collected nationwide database of 10,516,985 participants, demonstrated that NAFLD was an independent risk factor for the development of prostate cancer[16]. Chiang et al., in a single-center case-control study, demonstrated an association between NAFLD and bladder cancer; moreover, NAFLD also associated with a worse oncological prognostic factor for bladder cancer in this study, with an apparently higher occurrence of more aggressive forms in individuals with NAFLD[17].

A systematic review performed by Mantovani et al., that enrolled 10 prospective observational studies, found that NAFLD assessed by imaging techniques associated with a nearly 1.5-fold to twofold increased long-term risk of developing gastrointestinal cancers. Moreover, NAFLD also associated with an approximately 1.2-fold to 1.5-fold increased risk of incident lung cancer, urinary system cancers, breast,

and gynecological cancers, as well as with an about 2.5-fold increased risk of thyroid cancer[18].

Most appropriately designed studies published to date pointed to some degree of higher overall extra-hepatic cancer risk in individuals with NAFLD. However, a few studies failed to show associations with some specific cancer sites. A systematic review conducted by Thomas et al., analyzing 64 studies that involved 41,027 individuals, observed higher incidences of uterine, breast, prostate, colorectal, and lung cancers, but not gastric, biliary, pancreatic, or bladder cancer[19]. Björkström et al., in a large population study with 8,415 individuals from the Swedish National Registry, observed an increased risk of developing hepatocellular carcinoma among individuals with NAFLD; on the other hand, the absolute risk for other forms of cancer was generally comparable to the control population[1]. Nevertheless, these findings are not consonant with most available evidence to date, emphasizing the necessity of further research.

Mechanisms of NAFLD-related carcinogenesis

NAFLD and visceral adipose tissue are the main components of the central obesity axis that has been previously reported to be relevant in carcinogenesis. In this scenario, chronic low-grade inflammation and insulin resistance create a suitable microenvironment for cancer development through stimulation of the insulin growth factor-1 (IGF-1) axis by hyperinsulinemia. Through its proliferative and anti-apoptotic effects, this pathway can drive mutations that favor carcinogenesis[3].

With an increased accumulation of fatty acids and triglycerides in the liver, gluconeogenesis is activated, leading to the release of a series of inflammatory cytokines. Abnormal levels of cytokines can induce anti-apoptotic effects, proliferation, angiogenesis, and invasiveness of cancer cells. Particularly, adiponectin has anticarcinogenic effects by directly inhibiting tumor necrosis factor-alpha (TNF-α) and interrupting caspase activation of cancer cells. However, in individuals with NAFLD and/or central obesity, there is a decrease in the levels of this cytokine and an increase in leptin, another adipocytokine, but with an antagonistic effect, associated with the maintenance of a pro-inflammatory environment, favorable to tumor development, and related to effects that promote cancer progression, including angiogenesis, cell migration, and mitogenesis[20,21].

Another critically relevant and more specific pathway linking NAFLD with carcinogenesis is the hedgehog signaling pathway, which is present in the tissue regeneration process and is activated in chronic hepatic inflammation and that also has been shown to be active in pancreatic precursor lesions, such as pancreatic intraepithelial neoplasms (panIN), and also in already degenerated ductal adenocarcinomas. Once active, it provides cellular activity, and there are reports that activation of the hedgehog pathway and KRAS mutation together can perform cell initiation in pancreatic cancer[22].

Furthermore, it is also noteworthy that recent advances demonstrate that a potential role of the intestinal microbiota on carcinogenesis is emerging. Intestinal dysbiosis share a number of pathophysiological pathways with NAFLD and NASH, which may be intrinsically linked to each other and may contribute to increased cancer development[23]. The association of NAFLD with gut dysbiosis has been described and the liver seems to be a relevant part of a complex interaction between changes in microbiota composition, insulin resistance, inflammation, and carcinogenesis. Dysbiosis has also been observed in individuals with colorectal cancer and the putative connections have been proposed. A series of specific alterations of gut microbiota leads to increased intestinal permeability through several mechanisms, including the regulation of tight junctions. These abnormalities favor the translocation of bacterial metabolites, such as lypopolysacharides and other endotoxins, and activation of toll-like receptors via the recognition of bacterial-associated molecular pattern. This can promote tumorigenesis through the reduced release of the inflammasome-derived interleukin 18 (IL-18) and the increased IL-6 signaling that, in turn, protects normal and premalignant cells from apoptosis[3,23,24].

Future perspectives

Considering the rapidly emerging epidemiological importance of NAFLD, because of its association with the obesity epidemic, studies that seek to associate this disease with long-term clinical outcomes are of great importance. As with the risk of progression to severe forms of liver disease, including cirrhosis

and hepatocellular carcinoma, the association with extra-hepatic outcomes has been frequently described in recent years. Thus, it is of great importance to study and develop therapeutic modalities that can prevent the occurrence and/or progression of NAFLD, as well as attempt to achieve improvement or even resolution of the disease.

Currently, the treatment of NAFLD is based on several aspects of its pathophysiology, mainly its relationship with excess weight and insulin resistance. Long-term sustained weight loss is the most important therapeutical goal. Lifestyle changes, especially through diet and physical activity, are associated with reductions in liver enzyme levels and hepatic fat content, and improvement in liver histology. However, poor long-term adherence to these conservative measures compromises the durability of their results[25-27].

Drug treatment also focuses on weight loss and/or direct effects on liver disease. Insulin sensitizers such as rosiglitazone and pioglitazone have shown significant impact on hepatic steatosis in clinical trials, but their use is very restricted because of evidence linking these drugs to cardiovascular risk and bladder cancer, respectively[28]. Metformin did not demonstrate benefits or an independent therapeutic role in NAFLD individuals in a meta-analysis study. However, there is level III evidence showing that metformin may have a chemopreventive role in patients with diabetes and chronic liver disease, reducing the incidence of both hepatocellular carcinoma and cholangiocarcinoma[29]. Glucagon-like peptide-1 (GLP-1) analogues (mainly liraglutide and semaglutide) and vitamin E have also shown to promote significant improvement in liver histology after prolonged use in clinical trials; however, longer-term outcomes are yet to be presented[30].

Bariatric surgery is the treatment modality with more consistent and sustained long-term results demonstrated to date. It is associated with high rates of reversal of all main histopathological aspects of NAFLD, especially steatosis and inflammation, with somewhat more modest, albeit significant, degrees of fibrosis reversal[31-34]. Usually, procedures with a greater metabolic impact, such as Roux-en-Y gastric bypass, lead to better results than those more related to mechanical restriction of food intake, such as sleeve gastrectomy and gastric banding[35]. Large population studies have shown a significant reduction in the overall incidence of cancers of any type in populations undergoing bariatric surgery. Adams et al. reported a 60% reduction in mortality from any type of cancer after bariatric surgery, demonstrating the importance of these procedures in controlling obesity-associated carcinogenesis and NAFLD[36].

Based on the findings of the current study, all these therapeutic modalities, which are proven to be effective for treating NAFLD, might also be considered equally effective to mitigate the potential NAFLD-related carcinogenesis.

Limitations

The current study has some limitations that should be taken into consideration. The reliability of diagnostic methods used to detect NAFLD is highly variable, and several studies, especially those which enrolled larger populations, used methods whose accuracy is acceptable, but far from high or nuanced, such as non-invasive markers and ultrasound scans[37-40]. Some included studies were retrospective, which may associate with poor-quality data. Other included data were from cross-sectional studies, which do not permit the establishment of causal links. Moreover, it is difficult, even for well-designed studies, to detect impact of some risk factors on cancers whose overall incidences are very low.

CONCLUSION

There is consistent evidence on the association between NAFLD and extra-hepatic carcinogenesis, especially in relation to colorectal, gastric, pancreatic, breast, prostate, and bladder cancers. More prospective studies, mainly involving large populations, are needed to confirm and emphasize this association.

Authors' contribution

Rezende AQM: Data curation; investigation; methodology; writing – original draft. Cazzo E: Conceptualization; formal analysis; methodology; writing – review & editing.

Orcid

Achiles QM de Rezende: 0000-0002-9696-7616.
Everton Cazzo: 0000-0002-5804-1580.

Rezende AQM, Cazzo E. Doença hepática gordurosa não-alcoólica e neoplasias extra-hepáticas: uma revisão narrativa. Arq Gastroenterol. 2024;61:e23027.

RESUMO – Contexto – Recentemente, associações significativas entre a doença hepática gordurosna não-alcoólica (DHGNA) e neoplasias extra-hepáticas têm sido descritas. **Objetivo –** Realizar uma revisão abrangente acerca das evidências atuais na literatura sobre a associação entre DHGNA e neoplasias extra-hepáticas. **Métodos –** Uma revisão narrativa de literatura foi realizada através da busca on-line pelos descritores "fígado gorduroso" e "câncer" em MEDLINE (através do PubMed) e LILACS (através da BVS). Estudos originais que descreveram o impacto da DHGNA em diferentes tipos de neoplasias malignas extra-hepáticas foram incluídos. **Resultados** – Após análise criteriosa, nove estudos prospectivos de coorte, um coorte histórica, três estudos de caso-controle, e três estudos transversais foram selecionados. **Conclusão** – Existem evidências consistentes a respeito da associação entre DHGNA e a carcinogênese extra-hepática, especialmente em relação aos cânceres de cólon e reto, estômago, pâncreas, mama, próstata e bexiga.

Palavras-Chave – Hepatopatia gordurosa não-alcoólica; obesidade; câncer; carcinogênese; fígado gorduroso.

REFERENCES

1. Björkström K, Widman L, Hagström H. Risk of hepatic and extra-hepatic cancer in NAFLD: a population-based cohort study. Liver Int. 2022;42:820-8.
2. Bengtsson B, Stål P, Wahlin S, Björkström NK, Hagström H. Characteristics and outcome of hepatocellular carcinoma in patients with NAFLD without cirrhosis. Liver Int. 2019;39:1098-1108.
3. Sanna C, Rosso C, Marietti M, Bugianesi E. Non-Alcoholic Fatty Liver Disease and Extra-Hepatic Cancers. Int J Mol Sci. 2016;17:717.
4. Wong VW, Wong GL, Tsang SW, Fan T, Chu WC, Woo J, et al. High prevalence of colorectal neoplasm in patients with non-alcoholic steatohepatitis. Gut. 2011;60:829-36. doi:10.1136/gut.2011.237974
5. Hamaguchi M, Hashimoto Y, Obora A, Kojima T, Fukui M. Non-alcoholic fatty liver disease with obesity as an independent predictor for incident gastric and colorectal cancer: a population-based longitudinal study. BMJ Open Gastroenterol. 2019;6:e000295.
6. Allen AM, Hicks SB, Mara KC, Larson JJ, Therneau TM. The risk of incident extra-hepatic cancers is higher in non-alcoholic fatty liver disease than obesity - A longitudinal cohort study. J Hepatol. 2019;71:1229-36.
7. Aune D, Greenwood DC, Chan DS, Vieira R, Vieira AR, Navarro Rosenblatt DA, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. Ann Oncol. 2012;23:843-52.
8. Rezende AQM, Gestic MA, Utrini MP, Chaim FDM, Saito HPA, Chaim E, et al. Is there a link between non-alcoholic fatty liver disease aspects and pancreatic cancer? Results of a case-matched study. Rev Col Bras Cir. 2021;48:e20202913.
9. Liu SS, Ma XF, Zhao J. Association between nonalcoholic fatty liver disease and extra-hepatic cancers: a systematic review and meta-analysis. Lipids Health Dis. 2020;19:118.
10. Kim GA, Lee HC, Choe J, Kim MJ, Lee MJ, Chang HS, et al. Association between non-alcoholic fatty liver disease and cancer incidence rate. J Hepatol. 2017;S0168-8278:32294-8.
11. Peleg N, Sneh Arbib O, Issachar A, Cohen-Naftaly M, Braun M, Shlomai A. Noninvasive scoring systems predict hepatic and extra-hepatic cancers in patients with nonalcoholic fatty liver disease. PLoS One. 2018;13:e0202393.
12. Simon TG, Roelstraete B, Sharma R, Khalili H, Hagström H, Ludvigsson JF. Cancer Risk in Patients With Biopsy-Confirmed Nonalcoholic Fatty Liver Disease: A Population-Based Cohort Study. Hepatology. 2021;74:2410-23.
13. Park JH, Choi IS, Han KD, Park H, Kim KH, Kim JS. Association Between Fatty Liver Index and Risk of Breast Cancer: A Nationwide Population-Based Study. Clin Breast Cancer. 2020;20:e450-e457.
14. Nseir W, Abu-Rahmeh Z, Tsipis A, Mograbi J, Mahamid M. Relationship between Non-Alcoholic Fatty Liver Disease and Breast Cancer. Isr Med Assoc J. 2017;19:242-5.
15. Kwak MS, Yim JY, Yi A, Chung GE, Yang JI, Kim D, et al. Nonalcoholic fatty liver disease is associated with breast cancer in nonobese women. Dig Liver Dis. 2019;51:1030-5.
16. Choi YJ, Lee DH, Han KD, Yoon H, Shin CM, Park YS, 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. 2019;13:e0201308.
17. Chiang CL, Huang HH, Huang TY, Shih YL, Hsieh TY, Lin HH. Nonalcoholic Fatty Liver Disease Associated With Bladder Cancer. Am J Med Sci. 2020;360:161-5.
18. Mantovani A, Petracca G, Beatrice G, Csermely A, Tilg H, Byrne CD, Targher G. Non-alcoholic fatty liver disease and increased risk of incident extra-hepatic cancers: a meta-analysis of observational cohort studies. Gut. 2022;71:778-88.
19. Thomas JA, Kendall BJ, Dalais C, Macdonald GA, Thrift AP. Hepatocellular and extrahepatic cancers in non-alcoholic fatty liver disease: A systematic review and meta-analysis. Eur J Cancer. 2022;173:250-62.
20. Lauth M, Toftgård R. Hedgehog signaling and pancreatic tumor development. Adv Cancer Res. 2011;110:1-17.
21. Baltieri L, Chaim EA, Chaim FDM, Utrini MP, Gestic MA, Cazzo E. Correlation between nonalcoholic fatty liver disease features and levels of adipokines and inflammatory cytokines among morbidly obese individuals. Arq Gastroenterol. 2018;55:247-51.
22. Karamitopoulou E. Tumour microenvironment of pancreatic cancer: immune landscape is dictated by molecular and histopathological features. Br J Cancer. 2019;121:5-14.
23. Tilg H, Zmora N, Adolph TE, Elinav E. The intestinal microbiota fuelling metabolic inflammation. Nat Rev Immunol. 2020;20:40-54.
24. Ohtani N, Yoshimoto S, Hara E. Obesity and cancer: A gut microbial connection. Cancer Res. 2014;74:1885-9.
25. Wong VW, Chan RS, Wong GL, Cheung BH, Chu WC, Yeung DK, et al. Community-based lifestyle modification programme for non-alcoholic fatty liver disease: a randomized controlled trial. J Hepatol. 2013;59:536-42.
26. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. Gastroenterology. 2015;149:367-78.
27. Thoma C, Day CP, Trenell MI. Lifestyle interventions for the treatment of non-alcoholic fatty liver disease in adults: a systematic review. J Hepatol. 2012;56:255-66.
28. Snyder HS, Sakaan SA, March KL, Siddique O, Cholankeril R, Cummings CD, et al. Non-alcoholic Fatty Liver Disease: A Review of Anti-diabetic Pharmacologic Therapies. J Clin Transl Hepatol. 2018;6:168-74.
29. Cunha Júnior AD, Bragagnoli AC, Costa FO, Carvalheira JBC. Repurposing metformin for the treatment of gastrointestinal cancer. World J Gastroenterol. 2021;27:1883-904.
30. Mantovani A, Petracca G, Beatrice G, Csermely A, Lonardo A, Targher G. Glucagon-Like Peptide-1 Receptor Agonists for Treatment of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis: An Updated Meta-Analysis of Randomized Controlled Trials. Metabolites. 2021;11:73.

31. Amanullah I, Khan YH, Anwar I, Gulzar A, Mallhi TH, Raja AA. Effect of vitamin E in non-alcoholic fatty liver disease: a systematic review and meta-analysis of randomised controlled trials. Postgrad Med J. 2019;95:601-11.
32. Bower G, Toma T, Harling L, Jiao LR, Efthimiou E, Darzi A, et al. Bariatric Surgery and Non-Alcoholic Fatty Liver Disease: a Systematic Review of Liver Biochemistry and Histology. Obes Surg. 2015;25:2280-9.
33. Cazzo E, Pareja JC, Chaim EA. Nonalcoholic fatty liver disease and bariatric surgery: a comprehensive review. Sao Paulo Med J. 2017;135:277-95.
34. Jimenez LS, Mendonça Chaim FH, Mendonça Chaim FD, Utrini MP, Gestic MA, Chaim EA, et al. Impact of Weight Regain on the Evolution of Non-alcoholic Fatty Liver Disease After Roux-en-Y Gastric Bypass: a 3-Year Follow-up. Obes Surg. 2018;28:3131-5.
35. Kreve F, Callejas GH, Jimenez LS, Marques RA, Chaim FDM, Utrini MP, et al. Trajectory of NAFLD characteristics after Roux-en-Y gastric bypass: a five-year historical cohort study. Sao Paulo Med J. 2022;140:739-46.
36. Chang CF, Tseng YC, Huang HH, Shih YL, Hsieh TY, Lin HH. Exploring the relationship between nonalcoholic fatty liver disease and pancreatic cancer by computed tomographic survey. Intern Emerg Med. 2018;13:191-7.
37. Tincopa MA, Loomba R. Non-invasive diagnosis and monitoring of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Lancet Gastroenterol Hepatol. 2023:S2468-1253;00066-3.
38. Jimenez LS, Marques RA, Gestic MA, Utrini MP, Chaim FDM, Ramos AC, et al. Non-Invasive Markers in Non-Alcoholic Fatty Liver Disease: Reliability Is Variable According to BMI Status. Obes Surg. 2021;31:3888-92.
39. Henry L, Eberly KE, Shah D, Kumar A, Younossi ZM. Noninvasive Tests Used in Risk Stratification of Patients with Nonalcoholic Fatty Liver Disease. Clin Liver Dis. 2023;27:373-95.
40. Concon MM, Gestic MA, Utrini MP, Chaim FDM, Chaim EA, Cazzo E. Should routine liver biopsy be considered in bariatric surgical practice? An analysis of the limitations of non-invasive NAFLD markers. Arq Gastroenterol. 2022;59:110-6.
41. Hwang YC, Ahn HY, Park SW, Park CY. Nonalcoholic Fatty Liver Disease Associates With Increased Overall Mortality and Death From Cancer, Cardiovascular Disease, and Liver Disease in Women but Not Men. Clin Gastroenterol Hepatol. 2018;16:1131-7.e5.
42. Choi YJ, Lee DH, Han KD. Association between high fatty liver index and development of colorectal cancer: a nationwide cohort study with 21,592,374 Korean. Korean J Intern Med. 2020;35:1354-63.
43. Lee JM, Park YM, Yun JS, Ahn YB, Lee KM, Kim DB, et al. The association between nonalcoholic fatty liver disease and esophageal, stomach, or colorectal cancer: National population-based cohort study. PLoS One. 2020;15:e0226351.
44. Yamamoto K, Ikeya T, Okuyama S, Fukuda K, Kobayashi D. The association between non-alcoholic fatty liver disease (with or without metabolic syndrome) and extra-hepatic cancer development. J Gastroenterol Hepatol. 2021;36:1971-8.
45. Lee H, Lee HW, Kim SU, Chang Kim H. Metabolic Dysfunction-Associated Fatty Liver Disease Increases Colon Cancer Risk: A Nationwide Cohort Study. Clin Transl Gastroenterol. 2022;13:e00435.
46. Park JH, Hong JY, Han K, Kang W, Park JK. Increased risk of pancreatic cancer in individuals with non-alcoholic fatty liver disease. Sci Rep. 2022;12:10681.