Association between nonalcoholic fatty liver disease and extrahepatic cancers: a systematic review and meta-analysis

Shou-Sheng Liu
Qingdao Municipal Hospital Group
Xue-Feng Ma
Qingdao Municipal Hospital Group
Jie Zhao
Zibo Central Hospital
Shui-Xian Du
Qingdao Municipal Hospital Group
Jie Zhang
Qingdao Municipal Hospital Group
Meng-Zhen Dong
Qingdao Municipal Hospital Group
Yong-Ning Xin (xinyongning@163.com)
Qingdao Municipal Hospital https://orcid.org/0000-0002-3692-7655

Research

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Abstract

Background NAFLD was tightly associated with various diseases such as diabetes, cardiovascular disease, kidney disease and cancer. Previous studies had investigated the association between NAFLD and various extrahepatic cancers, but the conclusions were remains to be improved. The aim of this study was to investigate the association between NAFLD and various extrahepatic cancer comprehensively.

Methods Electronic databases PubMed, EMBASE, Medline, and the Cochrane Library were searched for observational studies published from 1996 to January 2020. Observational studies that reflected the association between NAFLD and extrahepatic cancers were included in this study. The pooled OR/HR/IRR of the association between NAFLD and various extrahepatic cancers were analyzed.

Results A total of 26 studies were included for investigating the association between NAFLD and various extrahepatic cancers. As the result shown, the pooled OR values of the risk of colorectal cancer and adenomas in patients with NAFLD were 1.72 (95%CI: 1.40-2.11) and 1.38 (95%CI: 1.22-1.56), respectively. The pooled OR values of the risk of intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma in patients with NAFLD were 2.40 (95%CI: 1.75-3.31) and 2.24 (95%CI: 1.58-3.17), respectively. The pooled OR value of the risk of breast cancer in patients with NAFLD was 1.68 (95%CI: 1.44-1.97). In addition, NAFLD was also tightly associatied with the risk of gastric cancer, pancreas cancer, prostate cancer, and esophagus cancer.

Conclusions NAFLD could significantly increase the development risk of colorectal adenomas and cancer, intrahepatic and extrahepatic cholangiocarcinoma, breast cancer, gastric cancer, pancreas cancer, prostate cancer, and esophagus cancer.

Introduction

Nonalcoholic fatty liver disease (NAFLD) has become one of the most prevalentchronic liver diseases globally with an estimated overall prevalence of 25.2% in the world and 29.62% in the Asia [1–4]. The diasease spectrum of NAFLD ranges from nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis, and eventual to the hepatocellular carcinoma (HCC) [5]. In view of the key physical functions of liver, the NAFLD is a complex multifactorial disease which involving sedentariness, obesity, poor dietary habit, sarcopenia, insulin resistance, genetic susceptibility, intestinal flora and other factors [6–9]. In addition, NAFLD is closely related to many diseases such as diabetes, cardiovascular disease and kidney disease, which demonstrating that NAFLD is a multisystem disease with extrahepatic complications [10–15].

Accumulated evidences have shown that the cardiovascular disease was the leading cause of deaths in patients with NAFLD, and malignancies at both gastrointestinal (liver, colon, esophagus, stomach, and pancreas) and extra-intestinal site (kidney in men, and breast in women) were also significant contribute to the mainly death of patients with NAFLD [16, 17]. Wongiarupong et al. conducted an meta-analysis to investigate the assoicaiton of NAFLD with the risk of cholangiocarcinoma, they found that NAFLD might potential contribute to the risk of development of cholangiocarcinoma [18]. Lee et al. reported the association between NAFLD and esophageal, stomach, or colorectal cancer in Korea recently, they found that the mortality in patients with esophageal, stomach, or colorectal cancer were markedly increased in the patients with NAFLD, which implied the significant association of NAFLD with the risk of esophageal, stomach, or colorectal cancer [19]. Lots of attention has been paid to the association between NAFLD and extrahepatic cancers. Recently, Allemet al. investigated the effect of NAFLD on the occurance rate of extrahepatic cancers in the US population. They found that NAFLD was associated with 90% higher risk of cancers, which included the uterine, stomach, pancreas, and colon cancer [20]. In consideration of the diverse kinds of cancers, and the difference of risk of cancers in different countries and district, the present studies still can not summary the authentic status of the association of NAFLD with the extrahepatic cancers.

The aim of this study was to identify the association between NAFLD and extrahepatic cancers comprehensively, and updata the previous results of the overall association between NAFLD andextrahepatic cancers.

Methods

Search Strategy

We performed multiple systematic reviews and meta-analysis of the available studiesrelying on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for the conduct of meta-analyse of observational studies [21]. The following cancers were included in our study: 1) Colon neoplasm; 2) Cholangiocarcinoma; 3) Breast cancer; 4) Gastric cancer; 5) Pancreas cancers; 6) Prostate cancer; 7) Esophageal cancer. For colon neoplasm, cholangiocarcinoma, and breast cancer, the separate meta-analysis for each cancer was performed. Relevant studies were identified by searching PUBMED, EMBASE, MEDLINE, and the Cochrane Systematic Review Database from 1996 through January 2020. The following search terms were used: Colon neoplasm, colon cancer, colorectal cancer, gastric neoplasm, stomach neoplasm, stomach cancers, gastric cancer, pancreatic neoplasm, pancreas cancers, PDAC, PaC, esophageal neoplasm, esophageal cancer, breast carcinoma, breast cancer, breast neoplasm, breast tumor, breast malignant neoplasm, prostate neoplasms, prostate cancer. Only the observational studies (i.e., case-control studies and cohort studies) and written in English language were considered eligible for inclusion in our meta-analysis. Studies were excluded if they were only published as abstracts.

Inclusion And Exclusion Criteria

The initially retrieved publications were reviewed by two investigators (Shou-Sheng Liu and Xue-Feng Ma) independently. The discrepancy was resolved by discussion with all investigators. Studies were included if they meet the criteria as follows: 1) studies explored the correlation between NAFLD and related cancers; 2) NAFLD or NASH was defined by either histopathological examination, imaging study or International Classification of Diseases, Ninth Revision

(ICD-9) or ICD-10 codes, Hepatic steatosis index; 3) extrahepatic cancers were also defined by either histopathological examination, imaging study or ICD-9 or ICD-10 codes; 4) risk estimates (odds ratios [ORs], hazard ratios [HRs] or incidence rate ratios [IRRs]) with their corresponding 95% confidence intervals (CIs) were reported or could be calculated from the data provided; 5) studies were published full-text report in English language. The following studies were excluded: abstracts, reviews, case reports, and letters. Studies that did not provide sufficient data to calculate the risk estimates were also excluded.

Quality Assessment

The quality of the included studieswere assessed independently by two authors (Shousheng Liu and Xuefeng Ma) using the Newcastle-Ottawa Scale (NOS) [22].The NOS comprises three sections: selection (up to 4 points), comparability (up to 2points) and outcome (up to 3 points), with a maximum of 9 points. The study quality was classified as poor (score 0–3), fair (score 4–6), or good (score 7–9).The discrepancy was resolved by discussion with all investigators.

Data Extraction

The following information was extracted from each study: first author, publication time, country, number of subjects, diagnosis method of NAFLD, patientssource, dates, study design, diagnosis method of each cancer, adjusted confounding factors and Study quality. The data were collected independently by two investigators (Shou-Sheng Liu and Xue-Feng Ma).

Data Synthesis And Analyses

The correlation between NAFLD and related cancers were calculated by OR with the corresponding 95% CI. In the forest plots, OR > 1 represented a risk effect and OR < 1 represented a protective effect. Because the overall risk of extra-hepatic cancers is low, the HR and IRR in the cohort studies were similar to the OR in the case-control studies mathematically, which approving to the combination of case-control and cohort studies. Statistical heterogeneity among studies was assessed by Q and I^2statistics. For the Q statistic, heterogeneity was considered to be present when $P < 0.1$ or $I^2 > 50\%$. The fixed-effect model was used when literature heterogeneity did not exist; otherwise, the random-effect model was used. Publication bias was evaluated visually by funnel plots and the publication bias was considered significant when P value was less than 0.05 in Begg's test. The subgroup was carried out according to the design of the study. The pooled OR was calculated by STATA 13.0 software (Stata Corporation, College Station, TX, USA).

Results

Literature search and study characteristics

A total of 3221 potentially relevant published studies were identified from the database. After removed the animal studies, reviews, nontopic studies, case reports, comments, non-English written articles, duplicates and irrelevant resources, 131 potentially relevant studies were left for detailed evaluation. After the full-text evaluation, 26 studies were included in this systematic review and meta-analysis [20, 23–47] (Fig. 1). Among these studies, 15 studies for colon cancer, 7 studies for cholangiocarcinoma, 4 studies for breast cancer, 3 studies for gastric cancer, 3 studies for pancreas cancer, 3 studies for prostate cancer, 2 studies for esophagus cancer.

Association Between Nafld And Colorectal Adenomas Or Cancer

We systematic investigated the relationship bentween NAFLD with the colorectal adenomas of colorectal cancer. As shown in the Table 1, 15 studies were included to evaluate the relationship between NAFLD and colorectal adenomas or colorectal cancer. Among these studies, 7 studies were from South Korea, 5 studies were from China, 1 study was from Austria, 1 study was from Japan and 1 study was from the USA. All of these studies wereobservational studies, which contain 6 cohort studies and 9 cross-sectional studies. Quality assessment of all these studies suggested that 11 studies were high quality, and 4 studies were fair quality based on the NOS scores (Table 2).

Table 1
Summarization of the relationship between NAFLD and all kinds of extrahepatic cancers.

Types of Cancer	Number of studies	OR/HR/IRR	(95%CI)	I^2	P value
Gastrointestinal cancers					
Colorectal cancer	10	1.72	1.40–2.11	83.50%	< 0.01
Colorectal adenomas	9	1.38	1.22–1.56	49.40%	0.045
Cholangiocarcinoma					
Intrahepatic cholangiocarcinoma	7	2.40	1.75–3.31	68.40%	0.004
Extrahepatic cholangiocarcinoma	4	2.24	1.58–3.17	68.04%	0.023
Breast cancer	4	1.68	1.44–1.97	0.00%	0.727
Gastric cancer	3	1.89	1.31–2.71	49.60%	0.094
Pancreas cancer	3	2.12	1.58–2.83	0.00%	0.476
Prostate cancer	3	1.36	1.03–1.79	81.90%	0.001
Esophagus cancer	2	1.77	1.19–2.62	0.00%	0.983
Abbreviation: OR, odds ratio; HR, hazard ratio; IRR, incidence rate ratio. CI: confidence interval.					

Table 2

The association between NAFLD and colorectal adenomas or colorectal cancer.

Study	Country	Sample size	NAFLD diagnosis	Patients source	Date	Study design	Colorectal cancer diagnosis	Adjusted confounding factors	Study quality
Chen et al. 2018 [25]	China	764	Ultrasonography	Community	2014–2016	Cross-sectional	Colonoscopy	Age, sex, smoking, alcohol intake, metabolic syndrome	Good
Ahn et al. 2017 [24]	South Korea	26540	Ultrasonography	Community	2003–2012	Cross-sectional	Histology	Age, sex, BMI, smoking, alcohol intake, first degree family history of colorectal cancer, aspirin use, fasting plasma glucose, total cholesterol, triglycerides, systolic blood pressure, use of any hypoglycemic, anti-hypertensive drugs or use of statin	Good
Chen et al. 2017 [46]	China	3686	Ultrasonography	Hospital	2007–2014	Cross-sectional	Endoscopy	Age, CEA, stage, tumor location, and tumor differentiation	Good
Pan et al. 2017 [30]	China	1793	Ultrasonography	Community	2011–2015	Cross-sectional	Colonoscopy	Age, sex, ALT, uric acid, metabolic syndrome	Good
Lee et al. 2016 [27]	South Korea	44221	Ultrasonography	Community	2010–2011	Cross-sectional	Colonoscopy	Age, sex, BMI, smoking, family history of colorectal cancer, aspirin use, hypertension, diabetes mellitus	Good
Lin et al. 2014 [29]	China	2314	Ultrasonography	Hospital	2007–2011	Cross-sectional	Colonoscopy	Age, sex, BMI, hypertension, plasma triglycerides, uric acid, ALT, albumin, hemoglobin, platelet count	Fair
Wong et al. 2011 [35]	China	380	^{1}H-MRS/Liver biopsy	Community/Hospital	2008–2010	Cross-sectional	Colonoscopy	Age, sex, BMI, smoking, family history of colorectal cancer, hypertension, diabetes mellitus	Good
Stadlmayr et al. 2011 [34]	Austria	1211	Ultrasonography	Hospital	2007–2009	Cross-sectional	Colonoscopy	Age, sex, BMI, glucose intolerance status (impaired fasting glycaemia or diabetes mellitus)	Good
Hwang et al. 2010 [33]	South Korea	2917	Ultrasonography	Hospital	2007	Cross-sectional	Colonoscopy	Age, sex, smoking, hypertension, diabetes mellitus, metabolic syndrome	Good
Allen et al. 2019 [20]	USA	276	HCIDA/ICD-9	Community	1997–2016	Cohort	ICD-9	NA	Good

Abbreviation: HICDA, Hospital International Classification of Diseases Adapted; ICD, International Classification of Diseases.

Study	Country	Sample size	NAFLD diagnosis	Patients source	Date	Study design	Colorectal cancer diagnosis	Adjusted confounding factors	Study quality
Hamaguchi et al. 2019 [26]	Japan	15926	Ultrasonography.	Community	2004–2016	Cohort	Endoscopy	Sex, age and lifestyle factors including smoking habits, alcoholic consumption and physical activities and diabetes	Good
Kim et al. 2018 [23]	South Korea	NA	Ultrasonography	Community	2004–2005	Cohort	Pathology	Demographic and metabolic factors	Good
Yang et al. 2017 [31]	South Korea	882	Ultrasonography/ computed tomography	Hospital	2009–2013	Cohort	Colonoscopy	Age, sex, smoking, hypertension, diabetes mellitus, use of aspirin or lipid-lowering agents; imaging for diagnosis of NAFLD	Fair
Huang et al. 2013 [32]	South Korea	1522	Ultrasonography	Hospital	2003–2010	Cohort	Colonoscopy	Age, sex, BMI, smoking, hypertension, diabetes mellitus, metabolic syndrome	Fair
Lee et al. 2012 [28]	South Korea	5517	Ultrasonography	Hospital	2002–2006	Cohort	Colonoscopy	Age, BMI, smoking, hypertension, dyslipidemia, fasting glucose level	Fair

Abbreviation: HICDA, Hospital International Classification of Diseases Adapted; ICD, International Classification of Diseases.

For the pooled OR of colorectal cancer in patients with NAFLD, 10 studies were analyzed [20, 23–31]. The meta-analysis was conducted with the random-effect ($P < 0.01$, $I^2 = 83.5\%$) and the results shown that there was a significant development risk of colorectal cancer in patients with NAFLD (OR = 1.72, 95%CI: 1.40–2.11) (Fig. 2A). Publication bias was tested by the Begg's test and the results suggested that there was an obvious publication bias among these studies ($P < 0.01$) (Fig. 4A). Furthermore, the results of subgroup anslysis shown that the pooled OR ofcolorectal cancer in cross-sectional studies [24, 25, 27, 29, 30] were 1.93 (95%CI: 1.48–2.53) and the pooled OR of colorectal cancer in cohort studies [20, 23, 26, 28, 31] were 1.52 (95%CI: 1.18–1.95) (Table 1) (Fig. 2A). For the pooled OR of colorectal adenomas in patients with NAFLD, 9 studies were analyzed [27–30, 32–35, 46]. The meta-analysis was conducted with the random-effect ($P = 0.045$, $I^2 = 49.4\%$) and the results shown that there was a significant development risk of colorectal adenomasin patients with NAFLD (OR = 1.38, 95%CI: 1.22–1.56) (Fig. 2B).Publication bias was tested by the Begg's test and no obvious publication bias was observed ($P = 0.754$) (Fig. 4B). Furthermore, the results of subgroup anslysis shown that the pooled OR of colorectal adenomas in cross-sectional studies[27, 29, 30, 33–35, 46] were 1.35(95%CI: 1.17–1.55)and the pooled OR of colorectal adenomas in cohort studies [28, 32] were 1.55 (95%CI: 1.18–2.03) (Table 1) (Fig. 2B)

Association Between Nafld And Cholangiocarcinoma

In this systematic review and meta-analysis, seven studieswere included to evaluate the relationship between NAFLD and the risk of cholangiocarcinoma [36–42]. In these studies, 3 studies were from the United States, 1 studywas from Europe,1 studywas from China,1 study was from Japan, and 1study wasfrom South Korea. All of these studies were cross-sectional studies, and patients in 4 studies were from community and 3 studies were from hospital. Quality assessment of all these studies suggested that 4 studies were high quality, and 3 studies were fair quality based on the NOS scores (Table 3).

Table 3
The association between NAFLD with cholangiocarcinoma and breast cancer.

	Study	Country	Sample size	NAFLD diagnosis	Patients source	Date	Study design	Cancer diagnosis	Adjusted confounding factors	S q
Cholangiocarcinoma	Petrick et al. 2017 [40]	US	328688	ICD-9	Community	2000–2011	Case-control	ICD-9	Age, race/ethnicity, geographic region, and state buy-in status	G
	Choi et al. 2016 [37]	US	7164	Histology/Imaging	Hospital	2000–2014	Case-control	ICD-9	The differences in frequencies of aspirin current users	G
	Kinoshita et al. 2016 [38]	Japan	103	Histology	Hospital	1995–2014	Case-control	Pathology	NA	Fa
	Stepien et al. 2016 [41]	Europe	495	Hepatic steatosis index	Community	1992–2000	Case-control	ICD-9	Smoking status, baseline, lifetime alcohol intake pattern, body mass index, physical activity, hepatitis B, C infection, diabetes status, CRP	G
	Lee et al. 2015 [39]	South Korea	243	Histology/Imaging	Hospital	2007–2013	Case-control	Pathology	NA	G
	Chang et al. 2013 [36]	China	25785	ICD-9	Community	2004–2008	Case-control	ICD-9	Possible intermediate factors	Fa
	Welzel et al. 2007 [42]	US	103866	ICD-9	Community	1999–2009	Case-control	ICD-9	NA	Fa
Breast cancer	Allen et al. 2019 [20]	USA	676	ICD-9	Community	1997–2016	Cohort	ICD-9	NA	G
	Kim et al. 2018 [23]	Korea	NA	Ultrasonography	Community	2004–2005	Cohort	Pathology radiology	Demographic and metabolic factors	G
	Nseir et al. 2017 [44]	Israel	146	Ultrasonography	Community	2008–2011	Cohort	Ultrasonography	NA	G
	Kwak et al. 2019 [43]	USA	540	Ultrasonography.	Community	2008–2017	Case-control	Ultrasonography	NA	G

Abbreviation: ICD, International Classification of Diseases.

For the pooled OR of intrahepatic cholangiocarcinoma (ICC) in patients with NAFLD, seven studies were analyzed [36–42]. The meta-analysis was conducted with the random-effects($P = 0.004$, $I^2 = 68.4\%$) and the results shown that there was a significant development risk of ICC in patients with NAFLD (OR = 2.40, 95%CI: 1.75–3.31) (Fig. 3A). Publication bias was tested by the Begg's test and no obvious publication bias was observed ($P = 0.501$) among these studies (Table 1) (Fig. 4C). Four studies were analyzed for the pooled OR of extrahepatic cholangiocarcinoma (ECC) in patients with NAFLD [36, 39, 40, 42]. The meta-analysis was conducted with the random-effect ($P = 0.024$, $I^2 = 68.04\%$) and the results shown that the development risk of ECC was significant high in patients with NAFLD (OR = 2.24, 95%CI: 1.58–3.17) (Table 1) (Fig. 3B).

Association Between Nafld And Breast Cancer

In this systematic review and meta-analysis, 4 studies were included to evaluate the relationship between NAFLD and the development risk of breast cancer [20, 23, 43, 44]. Among these studies, 2 were from the United States, 1 was from Korea, and 1 study was from Israel. Three studies of them were cohort studies

and onestudy was case-control study. Quality assessment of these studies suggested that all of them were high quality based on the NOS scores (Table 3). As shown in Table 1 and Supplementary Fig. 1, the pooled OR of breast cancer in patients with NAFLD was 1.68 (95%CI: 1.44–1.97), which suggested that patients with NAFLD was more susceptabilitable to the breast cancer.

Association Between Nafld And Other Cancers

As shown in the Supplementary Table 1, three studies were included to evaluate the association between NAFLD and the development risk of gastric cancer [20, 23, 26]. All of them were cohort study and the quality of them were high based on the NOS scores. The pooled OR of gastric cancer was 1.89 (95%CI: 1.31–2.71) (Table 1), which suggested that patients with NAFLD possess the high risk of gastric cancer. In order to investigate the association of NAFLD and the development risk of pancreas cancer, three studies were included [20, 23, 45] (Supplementary Table 1). Both of the three studies were cohort study, and the quality of them were high based on the NOS scores. The pooled OR of pancreas cancer was 2.12 (95%CI: 1.58–2.83) (Table 1), which suggested that patients with NAFLD possess the high risk of pancreas cancer. In addition, three studies also found that the patients with NAFLD also possess the high risk of prostate cancer (OR = 1.36, 95%CI: 1.03–1.79) (Tables 1 and 5). Furthermore, two studies reported the association between NAFLD and the development risk of esophagus cancer [20, 23], they found that the OR value of esophagus cancer was 1.77 (95%CI: 1.19–2.62) (Tables 1 and 5).

Discussion

NAFLD is widely epidemic chronic liver diseaeall over the world, and it is the manifestation metabolic syndrome in liver [3]. Accumulated evidences had suggested that NAFLD was tightly associated with various diseases such as diabetes, cardiovascular disease, kidney disease and cancers[11–13, 48]. In recent years, more attention were paid to the association of NAFLD and the risk of cancers, and accumulated clincal observational studies were conducted to investigate the relationship of the risk of cancers, especially the extrahepatic cancers, such as colon, stomach, and pancreas and so on. Kim et al. and Allen et al. also conducted the reviews to demonstrate this issue [20, 23], but the resutls could not reflect the newest conclusion of the association of NAFLD and cancer absolutely. With the publication of new studies, a lastestsummary is needed to expound the new research progresses in ths issue. In this study, we conducted a systematic review and meta-analysis to investigate the association of NAFLD with the risk of various extrahepatic cancers comprehensively.

In this systematic review and meta-analysis, we investigated the relationship of NAFLD with the gastrointerstinal cancers (colorectal cancer and colorectal adenomas), the cholangiocarcinoma (intrahepatic and extrahepatic cholangiocarcinoma), and other cancers include breast cancer, gastric cancer, pancreas cancer, prostate cancer, and esophagus cancer. Interestingly, we found that NAFLD was tightly associated with all of these extrahepatic cancers. The detailed mechanism of how the NAFLD promotes the tumorigenesis was remains unclear. NAFLD is caused by the excess accumulation of triglyceride, which could be regarded as a kind of visceral adiposity [49]. Previous reports suggested that visceral adipose tissue could affect the function of other organs by relasingthe cytokines such as adipocytokines, growth factors and some pro-inflammatory factors [50]. This opinion could provide the light to illuminate the detailed mechanism of NAFLD in the tumorigenesis. Previous meta-analysis investigated the association of incident and recurrence of colorectal adenoma and cancer with NAFLD, they found that the presence and severity of NAFLD were associated with the increased risk of incident colorectal cancar or adenomas [51]. Mantovani et al. summarized the association between NAFLD and colorectal tumors in asymptomatic adults who undergoing seceening colonoscopy, they found that the presence of NAFLD was moderately increased the risk of colorectal adenomas and cancer [52]. In this study, we complied with the inclusion and exclusion criteria and included all the suitable studies to investigated the association of NAFLD with the development risk of colorectal cancer and colorectal adenomas. Our results shown that the NAFLD significant increased the risk of colorectal cancer (OR = 1.72, 95%CI: 1.40–2.11) and colorectal adenomas (OR = 1.38, 95%CI: 1.22–1.56) compared to the health controls, which was consistent with the previous studies. More attentions should be paid in the detailed mechanism that NAFLD promotes the riks of colorectal cancer in the further studies.

Besides the colorectal adenomas or cancer, the association of NAFLD with othr extrahepatic cancers is less proven [53]. Wongjarupong et al. conducted a meta-analysis to investigate the relationship between NAFLD and cholangiocarcinoma, they found that NAFLD was associated with both the ICC (OR = 2.22, 95%CI: 1.52–3.24) and the ECC (OR = 1.55, 95%CI: 1.03–2.33) [18]. In this study, we added the newest publication and conducted the meta-analysis. We found that NAFLD significant increases the development risk of both the ICC (OR = 2.40, 95%CI: 1.75–3.31) and the ECC (OR = 2.24, 95%CI: 1.58–3.17), which was consistent with the previous study. What's more, we also reviewed the link between NAFLD and breast cancer, gastric cancer, pancreas cancer, prostate cancer, esophagus cancer. However, the association between NAFLD and extrahepatic cancers has not been fully illustrated, and the necessary clinical studies still need to be performed in the futher studies. A recent study demonstrated that patients with NAFLD are more likely to have chronic inflammation with insulin resistance, which may generate a microenvironment for developing cancers [54, 55]. Emerging translational and epidemiologic data supportedthat local ectopic fat may exert the functional factors by the paracrine pathway to inducethe cancer development in the liver, pancreasand breast [56, 57]. Therefore, we study reached a biological agreement with other previous studies that NAFLD is a risk factor for cancers, not only for the liver but also for the extrahepatic cancers.

There were several limitations in this study. First, the tightly assocaiton between NAFLD and extrahepatic cancers were investigaged, but we did not classified the degrees of NAFLD, so the association of severity of NAFLD with the extrahepatic cancers was not demonstrated in this study. Second, a small number of studies were available to analyze the association between the NAFLD and the risk of gastric cancer, pancreas cancer, prostate cancer, and esophagus cancer, further studies should be focus on the risk of these extrahepatic cancer in patients with NAFLD.

Conclusion

In summary, we conducted a systematic review and meta-anaylsis to comprehensive investigate the association between NAFLD and the development risk of extrahepatic cancers. We found that NAFLD could significant increase the development risk of colorectal adenomas and cancer, intrahepatic and extrahepatic

cholangiocarcinoma, breast cancer, gastric cancer, pancreas cancer, prostate cancer, and esophagus cancer. Besides the colorectal adenomas and cancer, the evidences for the association of NAFLD with various extrahepatic cancers are insufficient, and the detailed mechanism of NAFLD promote the tumorgenesis was also unclear, which were the key research areas in the further studies.

Abbreviations

CI, confidence intervals; ECC, extrahepatic cholangiocarcinoma; HCC, hepatocellular carcinoma; HR, hazard ratio; ICC, intrahepatic cholangiocarcinoma; ICD-9, International Classification of Diseases, Ninth Revision; IRR, incidence rate ratio; NAFL, nonalcoholic fatty liver; NAFLD, Nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NOS, Newcastle-Ottawa Scale; OR, odds ratio; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

Study concept and design: LSS and XYN. Acquisition and analysis of data: LSS, MXF, ZJ, DSX, ZJ, and DMZ. The drafting and writing of the manuscript: LSS and MXF. The revision of the manuscript: XYN. All authors approved the final manuscript.

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References

1. European Association for the Study of the L, European Association for the Study of D, European Association for the Study of O: EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 2016, 64:1388-1402.
2. Lonardo A, Nascimbeni F, Maurantonio M, Marrazzo A, Rinaldi L, Adinolfi LE: Nonalcoholic fatty liver disease: Evolving paradigms. *World J Gastroenterol* 2017, 23:6571-6592.
3. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M: Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016, 64:73-84.
4. Li J, Zou B, Yeo YH, Feng Y, Xie X, Lee DH, Fujii H, Wu Y, Kam LY, Ji F, et al: Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999-2019: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2019, 4:389-398.
5. Diehl AM, Day C: Cause, Pathogenesis, and Treatment of Nonalcoholic Steatohepatitis. *N Engl J Med* 2017, 377:2063-2072.
6. Fan JG, Kim SU, Wong VW: New trends on obesity and NAFLD in Asia. *J Hepatol* 2017, 67:862-873.
7. Chang Y, Jung HS, Cho J, Zhang Y, Yun KE, Lazo M, Pastor-Barriuso R, Ahn J, Kim CW, Rampal S, et al: Metabolically Healthy Obesity and the Development of Nonalcoholic Fatty Liver Disease. *Am J Gastroenterol* 2016, 111:1133-1140.
8. Koo BK, Kim D, Joo SK, Kim JH, Chang MS, Kim BG, Lee KL, Kim W: Sarcopenia is an independent risk factor for non-alcoholic steatohepatitis and significant fibrosis. *J Hepatol* 2017, 66:123-131.
9. Wong VW, Wong GL, Tse CH, Chan HL: Prevalence of the TM6SF2 variant and non-alcoholic fatty liver disease in Chinese. *J Hepatol* 2014, 61:708-709.
10. Li Y, Xu C, Yu C, Xu L, Miao M: Association of serum uric acid level with non-alcoholic fatty liver disease: a cross-sectional study. *J Hepatol* 2009, 50:1029-1034.
11. Cusi K, Sanyal AJ, Zhang S, Hartman ML, Bue-Valleskey JM, Hoogwerf BJ, Haupt A: Non-alcoholic fatty liver disease (NAFLD) prevalence and its metabolic associations in patients with type 1 diabetes and type 2 diabetes. *Diabetes Obes Metab* 2017, 19:1630-1634.

12. Targher G, Byrne CD, Lonardo A, Zoppini G, Barbui C: Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: A meta-analysis. *J Hepatol* 2016, 65:589-600.
13. Armstrong MJ, Adams LA, Canbay A, Syn WK: Extrahepatic complications of nonalcoholic fatty liver disease. *Hepatology* 2014, 59:1174-1197.
14. Byrne CD, Targher G: NAFLD: a multisystem disease. *J Hepatol* 2015, 62:S47-64.
15. Chacko KR, Reinus J: Extrahepatic Complications of Nonalcoholic Fatty Liver Disease. *Clin Liver Dis* 2016, 20:387-401.
16. Angulo P: Long-term mortality in nonalcoholic fatty liver disease: is liver histology of any prognostic significance? *Hepatology* 2010, 51:373-375.
17. Tilg H, Moschen AR: Mechanisms behind the link between obesity and gastrointestinal cancers. *Best Pract Res Clin Gastroenterol* 2014, 28:599-610.
18. Wongjarupong N, Assavapongpaiboon B, Susantitaphong P, Cheungpasitporn W, Treeprasertsuk S, Rerknimitr R, Chaiteerakij R: Non-alcoholic fatty liver disease as a risk factor for cholangiocarcinoma: a systematic review and meta-analysis. *BMC Gastroenterol* 2017, 17:149.
19. Lee JM, Park YM, Yun JS, Ahn YB, Lee KM, Kim DB, Lee JM, Han K, Ko SH: The association between nonalcoholic fatty liver disease and esophageal, stomach, or colorectal cancer: National population-based cohort study. *PLoS One* 2020, 15:e0226351.
20. Allen AM, Hicks SB, Mara KC, Larson JJ, Therneau TM: The risk of incident extrahepatic cancers is higher in non-alcoholic fatty liver disease than obesity - A longitudinal cohort study. *J Hepatol* 2019, 71:1229-1236.
21. Shamseer L MD, Clarke M, et al. BMJ. 2015;349(1):g7647.: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ 2015;349(1):g7647*.
22. G . A . W e l l s BShea DOConnelletal: The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-analyses. . 2012.
23. Kim GA, Lee HC, Choe J, Kim MJ, Lee MJ, Chang HS, Bae IY, Kim HK, An J, Shim JH, et al: Association between non-alcoholic fatty liver disease and cancer incidence rate. *J Hepatol* 2017.
24. Ahn JS, Sinn DH, Min YW, Hong SN, Kim HS, Jung SH, Gu S, Rhee PL, Paik SW, Son HJ, Gwak GY: Non-alcoholic fatty liver diseases and risk of colorectal neoplasia. *Aliment Pharmacol Ther* 2017, 45:345-353.
25. Chen ZF, Dong XL, Huang QK, Hong WD, Wu WZ, Wu JS, Pan S: The combined effect of non-alcoholic fatty liver disease and metabolic syndrome on colorectal carcinoma mortality: a retrospective in Chinese females. *World J Surg Oncol* 2018, 16:163.
26. 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.
27. Lee T, Yun KE, Chang Y, Ryu S, Park DI, Choi K, Jung YS: Risk of Colorectal Neoplasia According to Fatty Liver Severity and Presence of Gall Bladder Polyps. *Dig Dis Sci* 2016, 61:317-324.
28. Lee YI, Lim YS, Park HS: Colorectal neoplasms in relation to non-alcoholic fatty liver disease in Korean women: a retrospective cohort study. *J Gastroenterol Hepatol* 2012, 27:91-95.
29. Lin XF, Shi KQ, You J, Liu WY, Luo YW, Wu FL, Chen YP, Wong DK, Yuen MF, Zheng MH: Increased risk of colorectal malignant neoplasm in patients with nonalcoholic fatty liver disease: a large study. *Mol Biol Rep* 2014, 41:2989-2997.
30. Pan S, Hong W, Wu W, Chen Q, Zhao Q, Wu J, Jin Y: The relationship of nonalcoholic fatty liver disease and metabolic syndrome for colonoscopy colorectal neoplasm. *Medicine (Baltimore)* 2017, 96:e5809.
31. Yang YJ, Bang CS, Shin SP, Baik GH: Clinical impact of non-alcoholic fatty liver disease on the occurrence of colorectal neoplasm: Propensity score matching analysis. *PLoS One* 2017, 12:e0182014.
32. Huang KW, Leu HB, Wang YJ, Luo JC, Lin HC, Lee FY, Chan WL, Lin JK, Chang FY: Patients with nonalcoholic fatty liver disease have higher risk of colorectal adenoma after negative baseline colonoscopy. *Colorectal Dis* 2013, 15:830-835.
33. Hwang ST, Cho YK, Park JH, Kim HJ, Park DI, Sohn CI, Jeon WK, Kim BI, Won KH, Jin W: Relationship of non-alcoholic fatty liver disease to colorectal adenomatous polyps. *J Gastroenterol Hepatol* 2010, 25:562-567.
34. Stadlmayr A, Aigner E, Steger B, Scharinger L, Lederer D, Mayr A, Strasser M, Brunner E, Heuberger A, Hohla F, et al: Nonalcoholic fatty liver disease: an independent risk factor for colorectal neoplasia. *J Intern Med* 2011, 270:41-49.
35. Wong VW, Wong GL, Tsang SW, Fan T, Chu WC, Woo J, Chan AW, Choi PC, Chim AM, Lau JY, et al: High prevalence of colorectal neoplasm in patients with non-alcoholic steatohepatitis. *Gut* 2011, 60:829-836.
36. Chang JS, Tsai CR, Chen LT: Medical risk factors associated with cholangiocarcinoma in Taiwan: a population-based case-control study. *PLoS One* 2013, 8:e69981.
37. Choi J, Ghoz HM, Peeraphatdit T, Baichoo E, Addissie BD, Harmsen WS, Therneau TM, Olson JE, Chaiteerakij R, Roberts LR: Aspirin use and the risk of cholangiocarcinoma. *Hepatology* 2016, 64:785-796.
38. Kinoshita M, Kubo S, Tanaka S, Takemura S, Nishioka T, Hamano G, Ito T, Tanaka S, Ohsawa M, Shibata T: The association between non-alcoholic steatohepatitis and intrahepatic cholangiocarcinoma: A hospital based case-control study. *J Surg Oncol* 2016, 113:779-783.
39. Lee BS, Cha BH, Park EC, Roh J: Risk factors for perihilar cholangiocarcinoma: a hospital-based case-control study. *Liver Int* 2015, 35:1048-1053.
40. Petrick JL, Yang B, Altekruse SF, Van Dyke AL, Koshiol J, Graubard BI, McGlynn KA: Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: A population-based study in SEER-Medicare. *PLoS One* 2017, 12:e0186643.
41. Stepien M, Fedirko V, Duarte-Salles T, Ferrari P, Freisling H, Trepo E, Trichopoulou A, Bamia C, Weiderpass E, Olsen A, et al: Prospective association of liver function biomarkers with development of hepatobiliary cancers. *Cancer Epidemiol* 2016, 40:179-187.
42. Welzel TM, Graubard BI, El-Serag HB, Shaib YH, Hsing AW, Davila JA, McGlynn KA: Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: a population-based case-control study. *Clin Gastroenterol Hepatol* 2007, 5:1221-1228.

43. Kwak MS, Yim JY, Yi A, Chung GE, Yang JI, Kim D, Kim JS, Noh DY: Nonalcoholic fatty liver disease is associated with breast cancer in nonobese women. *Dig Liver Dis* 2019, 51:1030-1035.
44. 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, 19:242-245.
45. 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, 13:191-197.
46. Chen QF, Zhou XD, Sun YJ, Fang DH, Zhao Q, Huang JH, Jin Y, Wu JS: Sex-influenced association of non-alcoholic fatty liver disease with colorectal adenomatous and hyperplastic polyps. *World J Gastroenterol* 2017, 23:5206-5215.
47. Cho Y, Lim SK, Joo SK, Jeong DH, Kim JH, Bae JM, Park JH, Chang MS, Lee DH, Jung YJ, et al: Nonalcoholic steatohepatitis is associated with a higher risk of advanced colorectal neoplasm. *Liver Int* 2019, 39:1722-1731.
48. Vongsuvanh R, George J, Qiao L, van der Poorten D: Visceral adiposity in gastrointestinal and hepatic carcinogenesis. *Cancer Lett* 2013, 330:1-10.
49. van der Poorten D, Milner KL, Hui J, Hodge A, Trenell MI, Kench JG, London R, Peduto T, Chisholm DJ, George J: Visceral fat: a key mediator of steatohepatitis in metabolic liver disease. *Hepatology* 2008, 48:449-457.
50. Despres JP, Lemieux I: Abdominal obesity and metabolic syndrome. *Nature* 2006, 444:881-887.
51. Chen J, Bian D, Zang S, Yang Z, Tian G, Luo Y, Yang J, Xu B, Shi J: The association between nonalcoholic fatty liver disease and risk of colorectal adenoma and cancer incident and recurrence: a meta-analysis of observational studies. *Expert Rev Gastroenterol Hepatol* 2019, 13:385-395.
52. Mantovani A, Dauriz M, Byrne CD, Lonardo A, Zoppini G, Bonora E, Targher G: Association between nonalcoholic fatty liver disease and colorectal tumours in asymptomatic adults undergoing screening colonoscopy: a systematic review and meta-analysis. *Metabolism* 2018, 87:1-12.
53. Sanna C, Rosso C, Marietti M, Bugianesi E: Non-Alcoholic Fatty Liver Disease and Extra-Hepatic Cancers. *Int J Mol Sci* 2016, 17.
54. Gilbert CA, Slingerland JM: Cytokines, obesity, and cancer: new insights on mechanisms linking obesity to cancer risk and progression. *Annu Rev Med* 2013, 64:45-57.
55. Hui JM, Hodge A, Farrell GC, Kench JG, Kriketos A, George J: Beyond insulin resistance in NASH: TNF-alpha or adiponectin? *Hepatology* 2004, 40:46-54.
56. Hori M, Takahashi M, Hiraoka N, Yamaji T, Mutoh M, Ishigamori R, Furuta K, Okusaka T, Shimada K, Kosuge T, et al: Association of pancreatic Fatty infiltration with pancreatic ductal adenocarcinoma. *Clin Transl Gastroenterol* 2014, 5:e53.
57. Lashinger LM, Malone LM, McArthur MJ, Goldberg JA, Daniels EA, Pavone A, Colby JK, Smith NC, Perkins SN, Fischer SM, Hursting SD: Genetic reduction of insulin-like growth factor-1 mimics the anticancer effects of calorie restriction on cyclooxygenase-2-driven pancreatic neoplasia. *Cancer Prev Res (Phila)* 2011, 4:1030-1040.

Figures

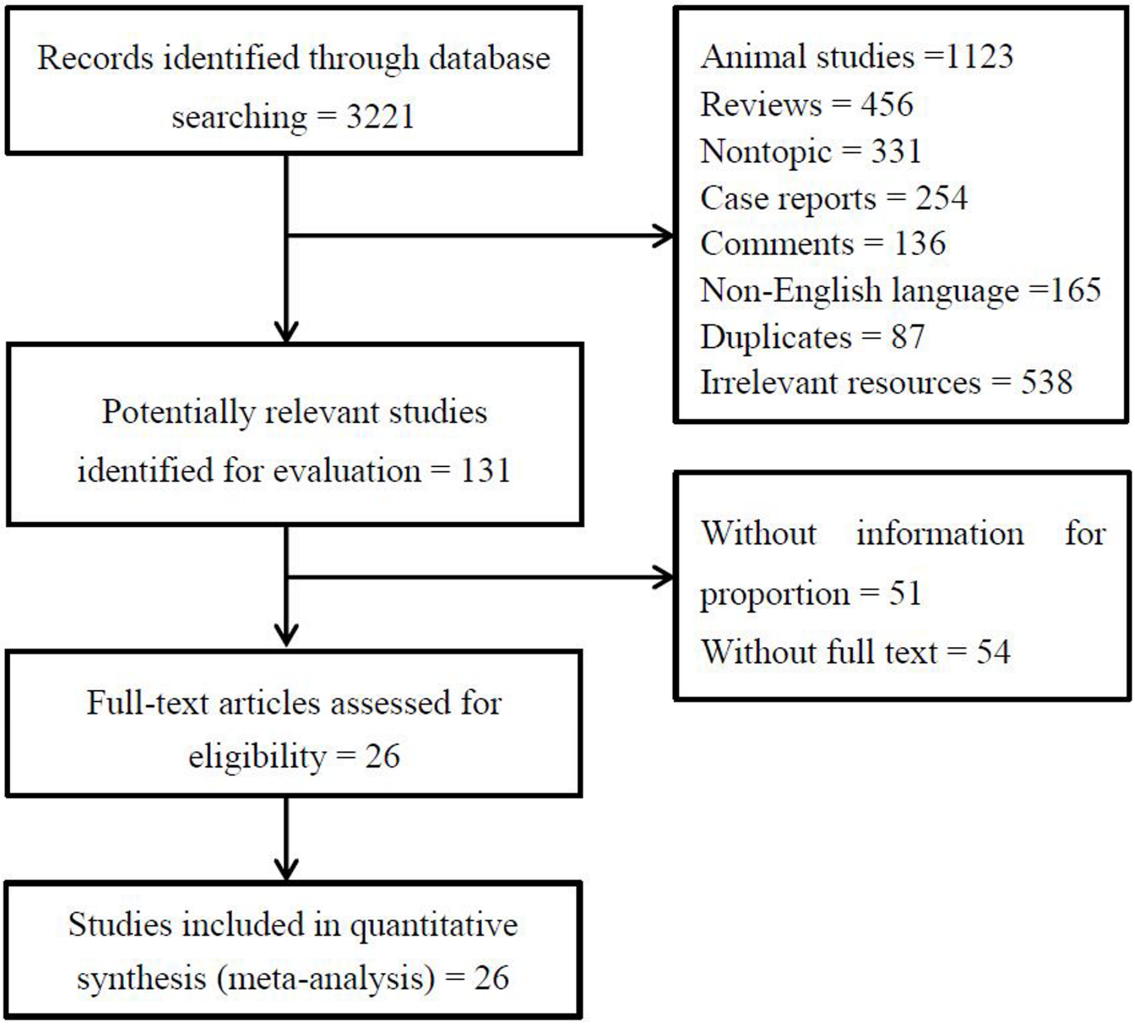

Figure 1

Flow chart of the literature search process.

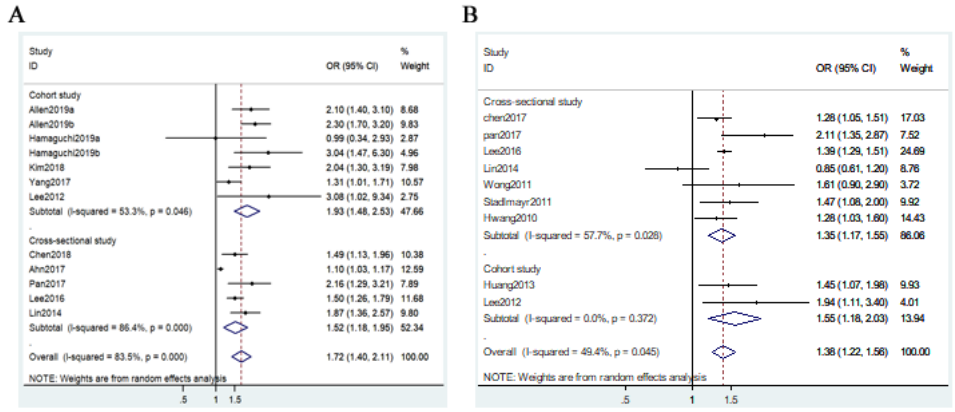

Figure 2

Meta-analysis of the association between NAFLD and colorectal cancer or colorectal adenomas. (A) Forest plots for colorectal cancer; (B) Forest plots for colorectal adenomas.

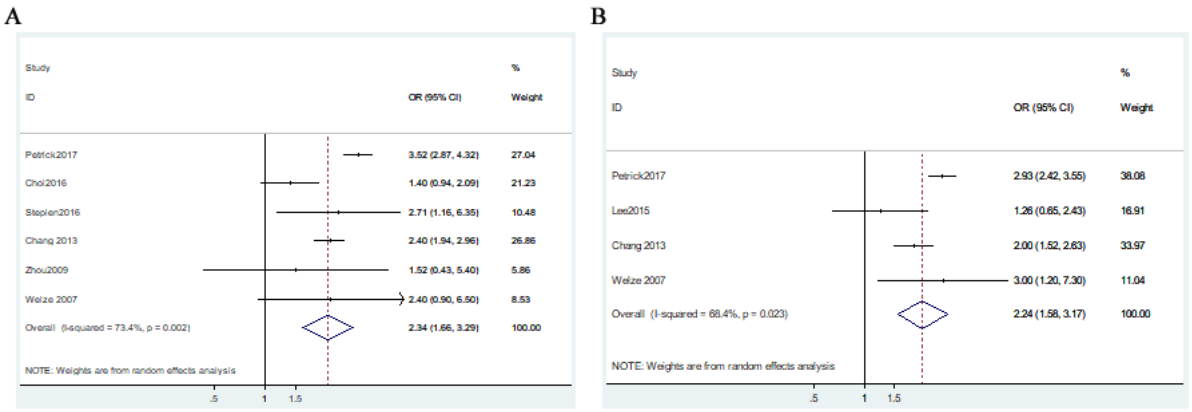

Figure 3

Meta-analysis of the association between NAFLD and cholangioarcinoma. (A) Forest plots for the intrahepatic cholangiocarcinoma; (B) Forest plots for the extrahepatic cholangiocarcinoma.

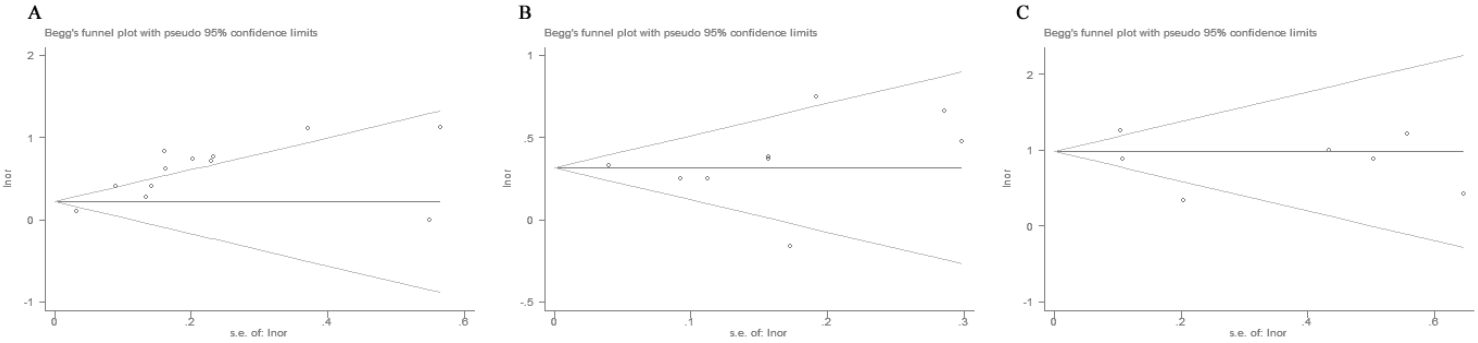

Figure 4

Identified the publication bias by Begger's funnel plot for (A) colorectal cancer; (B) colorectal adenomas; (C) intrahepatic cholangiocarcinoma.

Supplementary Files

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