

Association between nonalcoholic fatty liver disease and colorectal adenoma: a systemic review and meta-analysis

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Background: Nonalcoholic fatty liver disease (NAFLD) is considered to be a hepatic manifestation of metabolic syndrome (MetS) and the most common chronic liver disease worldwide. The association between NAFLD and colorectal adenoma has been investigated in multiples studies but the results have been conflicting. We performed a systematic review and meta-analysis to evaluate this in asymptomatic patients who underwent screening colonoscopy.

Methods: We searched the literatures of all languages from PubMed, EMBASE and the Cochrane library from January 1, 1980 through July 15, 2014. Combined and subgroup analyses stratified by study designs, study locations, characteristics of adenoma (location, size, number, and advanced adenoma) were performed.

Results: Four cross-sectional and one cohort studies with a total of 6,263 subjects were included in the meta-analysis. NAFLD was significantly associated with colorectal adenoma [pooled odds ratio (OR) 1.74, 95% confidence interval (CI): 1.53-1.97]. The association was more significant in Asian population (pooled OR =1.77, 95% CI: 1.52-2.05, n=3 studies), compared to European/North American population (pooled OR =1.42, 95% CI: 0.75-2.67, n=2 studies). NAFLD was significantly associated with the number of colorectal adenoma (pooled OR =1.78, 95% CI: 1.10-2.86, n=2 studies), but not the location, size, or presence of advanced adenoma.

Conclusions: Our results suggest NAFLD is significantly associated with the presence of colorectal adenoma in asymptomatic patients undergoing screening colonoscopy. This finding provides additional risk stratifications for applying colorectal cancer (CRC) screening strategies. However, more studies of western population are needed to further investigate the ethnic disparity.

Keywords: Nonalcoholic fatty liver disease (NAFLD); colorectal adenoma; colorectal cancer (CRC)

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Introduction

Colorectal cancer (CRC) is the third most common cancer and the third leading cause of cancer death in the United States (1). For the past two decades, the incidence and mortality rate of CRC has been reduced due to the early detection and removal of precancerous polyps/adenomas by screening colonoscopy (2-4). However, the risk stratification of the target screening population needs to be further addressed in order to improve

the CRC screening strategies (5,6).

In many epidemiological studies, metabolic syndrome (MetS) and its individual components, including obesity, impaired glucose tolerance, dyslipidemia, and hypertension, have been associated with an increased risk of colorectal adenoma and/or cancer (7-13). Nonalcoholic fatty liver disease (NAFLD) is considered to be a hepatic manifestation of MetS and the most common chronic liver disease worldwide (14,15). The independent relationship between

NAFLD and colorectal adenoma has been investigated in multiple studies but the results have been conflicting. Some studies indicated that NAFLD was associated with a high prevalence of colorectal adenoma and/or cancer, whereas one study from USA showed no significant association (16-22). Hence we performed a systematic review and meta-analysis to evaluate the association of NAFLD with colorectal adenoma in asymptomatic patients who underwent screening colonoscopy.

Methods

Literature search and inclusion criteria

We searched the literatures of all languages from PubMed, EMBASE and the Cochrane library from January 1, 1980 through July 15, 2014, using the search terms (“nonalcoholic fatty liver disease” or “NAFLD” or “nonalcoholic steatohepatitis” or “NASH” or “fatty liver”) AND (“colorectal neoplasm” or “colorectal cancer” or “colon cancer” or “colorectal adenoma” or “colonic adenoma” or “adenomatous polyps”). The publications that meet the following criteria were included for meta-analysis: (I) they were case-control or cohort studies; (II) the study subjects were over age 18 years; (III) they reported estimates of the unadjusted and/or multivariable adjusted odds ratio (OR)/risk ratio (RR) with corresponding 95% confidence interval (CI); (IV) NAFLD patients were diagnosed at least by abdominal ultrasound or computed tomography (CT); (V) the participants were asymptomatic and undergoing screening colonoscopy.

Data extraction and quality assessment

The data was extracted independently by two reviewers and included first author, year of publication, country of study population, type of study design, sample size, number of exposed and unexposed, assessment of NAFLD, outcome measures, controlled confounders, unadjusted and/or adjusted effects estimates. We searched the reference lists of retrieved articles for additional studies. Two reviewers assessed the quality of the included studies independently by using the Newcastle-Ottawa Scale (NOS) for cohort and cross-sectional studies. The NOS judge the quality by assigning stars, with maximum of 9, based on selection of study groups, comparability of study groups, and ascertainment of either the exposure or outcome of interest. Any discrepancies regarding inclusion/exclusion and quality

assessment were addressed by consensus.

Statistical analysis

For dichotomous data results from individual studies were summarized as OR and 95% CI and pooled under a random effects model. Mantel-Haenszel chi-square tests were carried out to assess the significant level of difference. Statistical heterogeneity was measured using the chi-square test and the inconsistency index (I^2) statistics. The P value <0.05 or $I^2 >50\%$ indicated substantial heterogeneity. The random effects model was selected if there was obvious heterogeneity; otherwise, the fixed effects model was used. The potential publication bias was assessed by visual inspection of funnel. The P value <0.05 was considered statistically significant. All analyses were performed using Review Manager 5.2. The work has been conducted and reported according to MOOSE guidelines (23).

Results

Characteristics of the studies

We initially identified a total of 403 relevant publications. After excluding 396 articles by title and abstract review, seven studies were included for further full-text review. Two studies were further excluded as they did not meet the specific inclusion criteria. Finally, five studies were included in our meta-analysis (*Figure 1*) (16-20).

Table 1 showed the main characteristics of the included studies. Among them, four were cross-sectional and one was retrospective cohort. Three studies were conducted in Asia, one in Europe and one in North America, with a total of 6,263 participants. All five studies had medium to high quality according to the NOS score.

Outcome results

There was no significant heterogeneity across the five studies ($P=0.24$, $I^2=27\%$), the fixed-effect model was considered to estimate the pooled OR (1.74, 95% CI: 1.53-1.97) for association between NAFLD and colorectal adenoma (*Figure 2*). Subgroup analyses stratified by study designs, study locations, characteristics of adenoma (location, size, number, and advanced adenoma), were also performed (*Table 2*). The relationship between NAFLD and colorectal adenoma was more significant in the Asian population (pooled OR =1.77, 95% CI: 1.52-2.05, $n=3$

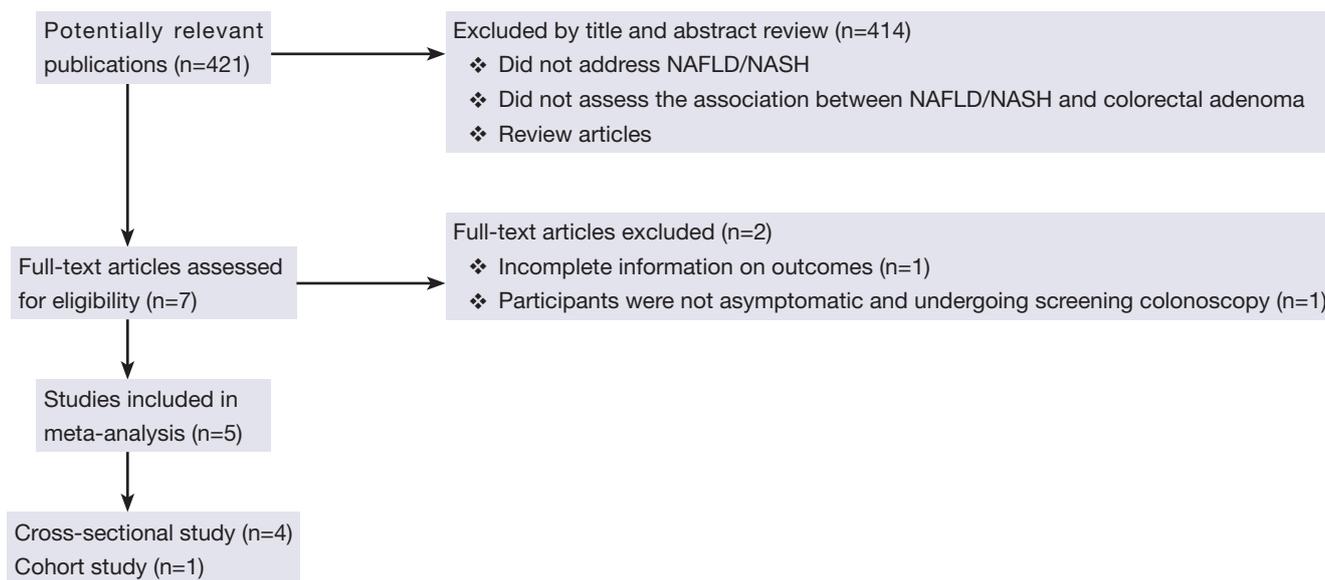


Figure 1 Study flow diagram. NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

studies), compared to the European/North American population (pooled OR =1.42, 95% CI: 0.75-2.67, n=2 studies). NAFLD was significantly associated with the number of colorectal adenoma (pooled OR =1.78, 95% CI: 1.10-2.86, n=2 studies), but not the location, size, or presence of advanced adenoma. *Table 3* showed different comparisons regarding the type of neoplasm (adenoma or cancer) or type of exposure (NAFLD or NASH). The association between NASH and colorectal adenoma was statistically significant (pooled OR =2.54, 95% CI: 1.07-6.03, n=2 studies). Visual inspection of funnel plot did not show major asymmetrical appearance.

Discussion

Previous studies have shown that NAFLD is independently associated with the presence of colorectal adenoma and cancer (16-21,24). To our best knowledge, this is the first meta-analysis to investigate this relationship in asymptomatic patients undergoing screening colonoscopy.

The exact mechanisms linking NAFLD and colorectal adenoma remain unclear. NAFLD is regarded as a condition of profound insulin resistance and systemic low-grade inflammatory state (25-27). Insulin and Insulin growth factor-1 (IGF-1) have been shown to increase the risk of CRC by inhibiting apoptosis and promoting proliferation (27,28). Multiple studies have reported that tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6),

and other pro-inflammatory cytokines play a crucial role in development of colorectal adenoma and cancer (29-31). Decreased adiponectin level and increased leptin level in NAFLD patients are also suggested to be associated with an increased risk of colorectal adenoma (25,32-34).

In our meta-analysis, we found NAFLD was significantly associated with colorectal adenoma in asymptomatic patients undergoing screening colonoscopy. However, this association was less prominent in the European/North American populations, compared to the Asian population. It may be due to the small sample size of the two studies conducted in Europe and North America. Prospective studies with larger sample size of western populations to further investigate the ethnic disparity are needed in the future. Our subgroup analyses indicated NAFLD was related to more colorectal adenomas detection in screening colonoscopy. We found no association between NAFLD and CRC. Because the CRC yield rate was small in the asymptomatic patients who underwent screening colonoscopy, there was a small statistical power to detect such association. NASH which was confirmed by liver biopsy was also found to be significantly associated with colorectal adenoma.

This meta-analysis has several limitations. Firstly, the diagnosis of NAFLD in most of our studies was based on ultrasonography but not confirmed by liver biopsy. Secondly, other potential confounders, such as diet, physical activity, genetic or socioeconomic factors, etc.,

Table 1 Characteristics of studies include in meta-analysis

Study (first author, year) (Reference)	Study design	Study location	NAFLD cases/ subjects	Diagnosis of NAFLD/NASH	Outcome measures	Confounders controlled	Crude/adjusted OR	NOS ^y
Wong, 2011 (17)	Cross-sectional study	Hong Kong, China	199 ^a /380	Liver biopsy or H-MRS ^c with exclusion of other liver disease and excess alcohol consumption (men >30 g/day, women >20 g/day)	Presence of colorectal adenoma, advanced neoplasm, colorectal cancer	Age, gender, smoking status, colorectal cancer in first degree relatives, BMI, diabetes, hypertension	Crude: 1.93 (1.22-3.06); adjusted: 1.61 (0.90-2.90)	6
Stadlmayr, 2011 (18)	Cross-sectional study	Austria	632/1,211	US ^b with exclusion of other liver disease and excess alcohol consumption (>20 g/day)	Presence of colorectal adenoma, advanced adenoma, colorectal carcinoma, location and number of colorectal lesions	Age, gender, BMI, glucose intolerance	Crude: 1.85 (1.43-2.40); adjusted: 1.47 (1.08-2.00)	7
Hwang, 2010 (16)	Cross-sectional study	South Korea	945/2,917	US with exclusion of other liver disease and excess alcohol consumption (>20 g/day)	Presence of colorectal adenoma, advanced adenoma, location, size, and number of adenoma	Age, gender, smoking, hypertension, diabetes, metabolic syndrome	Crude: 1.64 (1.36-1.98); adjusted: 1.28 (1.03-1.60)	7
Huang, 2013 (20)	Retrospective cohort study	Taiwan	620/1,522	US with exclusion of other liver disease and excess alcohol consumption (>20 g/day)	Presence of colorectal adenoma, advanced adenoma, location, size, and number of adenoma	Age, gender, BMI, smoking, hypertension, diabetes, metabolic syndrome	Crude: 2.02 (1.51-2.69); adjusted: 1.45 (1.07-1.98)	8
Touzin, 2011 (19)	Cross-sectional study	USA	94/233	US and liver biopsy with exclusion of other liver disease and excess alcohol consumption (>20 g/day)	Presence of colorectal adenomas, size, location and attachment of adenoma	Age, race, BMI, and family history	Crude: 0.96 (0.52-1.77); adjusted: not calculated	7

* , 135 biopsy-proven + 64 by H-MRS; ^c H-MRS, proton-magnetic resonance spectroscopy; ^b US, Liver ultrasound; , NOS score, Newcastle-Ottawa scale, NOS scores of 1-3, 4-6, and 7-9 for low, intermediate, and high-quality studies, respectively; OR, odds ratio; CI, confidence interval; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

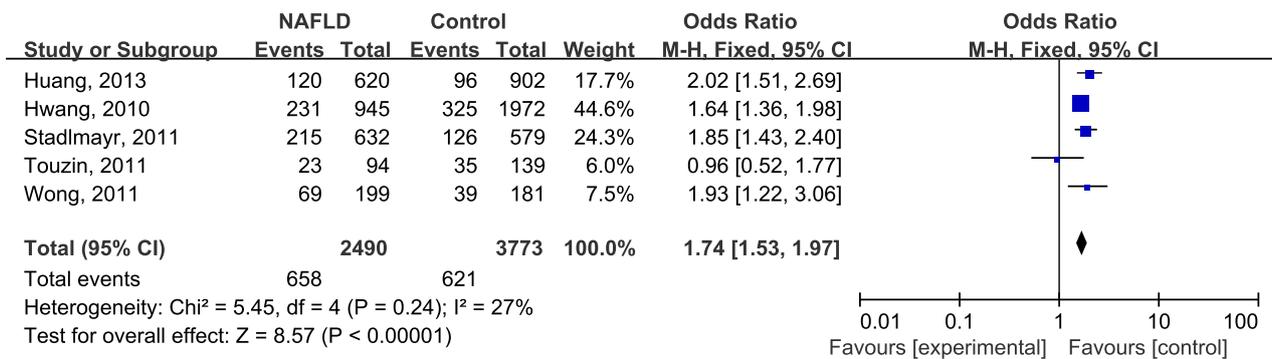


Figure 2 Forest plot: association between NAFLD and colorectal adenoma. NAFLD, nonalcoholic fatty liver disease; CI, confidence interval.

Table 2 Subgroup analyses stratified by study designs, study locations, characteristics of adenoma

Subgroup	Number of studies	Pooled OR (95% CI)	Heterogeneity (P; I ²)
All studies	5 (16-20)	1.74 (1.53-1.97)	0.24; 27%
Study design			
Cross-sectional	4 (16-19)	1.68 (1.46-1.93)	0.24; 29%
Cohort	1 (20)	2.02 (1.51-2.69)	–
Study location			
Asia	3 (16,17,20)	1.77 (1.52-2.05)	0.47; 0%
Europe/North America	2 (18,19)	1.42 (0.75-2.67)	0.05; 74%
Characteristics of adenoma			
Location (proximal vs. distal)	2 (16,20)	1.31 (0.98-1.74)	0.63; 0%
Size (≥10 vs. <10 mm)	2 (16,20)	0.99 (0.55-1.81)	0.22; 33%
Number (≥3 vs. <3)	2 (16,20)	1.78 (1.10-2.86)	0.39; 0%
Advanced adenoma*	4 (16-18,20)	1.18 (0.59-2.39)	0.02; 69%

*, adenomatous polyp with villous or tubulovillous architecture or high-grade dysplasia; OR, odds ratio; CI, confidence interval; I², inconsistency index.

Table 3 Summary estimates by different comparisons

Comparisons	Number of studies	Pooled OR (95% CI)	Heterogeneity (P; I ²)
NAFLD and neoplasm			
Adenoma	5 (16-20)	1.74 (1.53-1.97)	0.24; 27%
Cancer	2 (17,18)	2.45 (0.65-9.28)	0.78; 0%
NAFLD/NASH and adenoma			
NAFLD	5 (16-20)	1.74 (1.53-1.97)	0.24; 27%
NASH	2 (17,19)	2.54 (1.07-6.03)	0.11; 61%

OR, odds ratio; CI, confidence interval; I², inconsistency index; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

were not considered in the analysis. Thirdly, the majority of the participants were from Asian countries which made it difficult to assess the ethnic disparity. Lastly, only five studies were included in this meta-analysis, which made it difficult to assess the potential publication bias.

Despite these limitations, our meta-analysis has several important strengths. Firstly, we included relatively homogeneous populations who were asymptomatic and undergoing screening colonoscopy. Secondly, the definitions of exposure and outcome were also homogeneous. Lastly, the heterogeneity between studies was not significant, which increased the statistical power compared to a single study.

In conclusion, our results suggest NAFLD is significantly associated with the presence of colorectal adenoma in asymptomatic patients undergoing screening colonoscopy. More studies of western populations are needed to further investigate the ethnic disparity. Given the rising prevalence of NAFLD, we should take it into consideration when applying CRC screening strategies.

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