Non-alcoholic Fatty Liver Disease and Increased Risk of Incident Extra-hepatic Cancers: A Meta-Analysis of Observational Cohort Studies

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ABSTRACT

Objective: We performed a meta-analysis of observational studies to quantify the magnitude of the association between non-alcoholic fatty liver disease (NAFLD) and risk of extra-hepatic cancers.

Design: We systematically searched PubMed, Scopus and Web of Science databases from the inception date to December 2020 using predefined keywords to identify observational cohort studies conducted in individuals, in which NAFLD was diagnosed by imaging techniques or International Classification of Diseases codes. No studies with biopsy-proven NAFLD were available for the analysis. Meta-analysis was performed using random-effects modelling.

Results: We included 10 cohort studies with 182,202 middle-aged individuals (24.8% with NAFLD) and 8,485 incident cases of extra-hepatic cancers at different sites over a median follow-up of 5.8 years. NAFLD was significantly associated with a nearly 1.5 to 2-fold increased risk of developing gastro-intestinal cancers (esophagus, stomach, pancreas or colorectal cancers). Furthermore, NAFLD was associated with an approximately 1.2 to 1.5-fold increased risk of developing lung, breast, gynecological, or urinary system cancers. All risks were independent of age, sex, smoking, obesity, diabetes or other potential confounders. The overall heterogeneity for most of the primary pooled analyses was relatively low. Sensitivity analyses did not alter these findings. Funnel plots did not reveal any significant publication bias.

Conclusion: This large meta-analysis suggests that NAFLD is associated with a moderately increased long-term risk of developing extra-hepatic cancers over a median of nearly 6 years (especially gastro-intestinal cancers, breast cancer and gynecological cancers). Further research is required to decipher the complex link between NAFLD and cancer development.

Keywords: NAFLD; fatty liver; cancer risk; extra-hepatic cancer; meta-analysis

SUMMARY BOX

What is already known about this subject: Non-alcoholic fatty liver disease (NAFLD) is associated with an increased risk of developing certain extra-hepatic cancers. It is currently uncertain which is the magnitude of this cancer risk amongst individuals with NAFLD.

What are the new findings: NAFLD is associated with a nearly 1.5 to 2-fold increased long-term risk of developing several gastro-intestinal cancers, as well as breast and gynecological cancers. These risks are independent of age, sex, smoking, obesity, diabetes and other potential confounders.

How might it impact on clinical practice in the foreseeable future: Health care professionals should be aware that the risk of developing extra-hepatic cancers is increased in people with NAFLD. Further research is required to decipher the complex link between NAFLD and cancer development.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has reached epidemic proportions, affecting up to ~30% of the world population (1,2). Convincing evidence now supports the notion that NAFLD is a "multi-system" disease (3), and that the clinical burden of NAFLD is not only restricted to severe liver-related complications (cirrhosis, liver failure or hepatocellular carcinoma [HCC]), but also includes major extra-hepatic diseases that have considerable effects on health-care expenditure (4,5). Indeed, large cohort studies of individuals with biopsy-proven NAFLD have shown that cardiovascular disease is the predominant cause of mortality in this patient population, followed by extra-hepatic cancers and liver-related complications (5-9).

Owing to the increasing global prevalence of NAFLD, there is mounting evidence that NAFLD has rapidly become a leading cause for many cases of HCC (10). The association between NAFLD and risk of developing some extra-hepatic cancers (especially colorectal cancer) has also gained considerable scientific interest (5). Recent cohort studies and meta-analyses showed that NAFLD is associated with an increased prevalence and incidence of colorectal cancer and adenomas in asymptomatic individuals undergoing screening colonoscopy (11-14), and these associations are independent of age, sex, smoking, obesity, and diabetes. To our knowledge, there is only one previous meta-analysis of observational studies (published between 1996 and 2019) that examined the association between NAFLD and risk of extra-hepatic cancers at different sites (15). However, we consider that the results of this meta-analysis should be interpreted cautiously, because the investigators included a large number of studies which had a cross-sectional design and where, in some cases, the diagnosis of NAFLD was only based on surrogate diagnostic markers. Furthermore, as will be discussed in detail later, longitudinal cohort studies have been published in 2020 after the publication of the aforementioned meta-analysis.

We therefore carried out an updated systematic review and meta-analysis of observational cohort studies to gauge precisely the nature and magnitude of the association between NAFLD and the risk of developing certain extra-hepatic cancers. We believe that clarification of the magnitude of risk of developing some extra-hepatic cancers amongst individuals with NAFLD will help refine assessment of the true clinical and economic burden attributable to NAFLD. These data will also help inform clinicians caring for patients with NAFLD, and increase clinician awareness of the need for prevention and early diagnosis of certain types of extra-hepatic cancers related to NAFLD.

MATERIALS AND METHODS

Registration of protocol

The protocol of this systematic review and meta-analysis was registered in advance in Open Science Framework database (#osf.io/h526w).

Data sources and searches

We performed a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (http://www.prisma-statement.org). Because the included studies were observational in design, we also followed the reporting items proposed by Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines for the meta-analysis of these studies (16).

We conducted a systematic literature search from the inception date to December 30, 2020 (date last searched) of PubMed, Scopus and Web of Science for all observational cohort studies examining the risk of incident extra-hepatic cancers amongst individuals with and without NAFLD. Search free text terms were "nonalcoholic fatty liver disease" (OR "fatty liver" OR "NAFLD" OR "nonalcoholic steatohepatitis" OR "NASH") AND "esophagus cancer" OR "stomach cancer" OR "pancreas cancer" OR "colorectal cancer" OR "colorectal adenomas" OR "gastrointestinal cancer" OR "lung cancer" OR "thyroid cancer" OR "breast cancer" OR "female genital organ cancer" OR "gynecological cancer" OR "prostate cancer" OR "urinary system cancers" OR "kidney cancer" OR "bladder cancer" OR "haematological cancers". Searches were restricted to human studies. No language restrictions were imposed. Additionally, we reviewed references from relevant original papers and review articles to identify further eligible studies not covered by the original database searches.

Study selection

Studies were included if they meet the following criteria: 1) observational cohort studies examining the association between NAFLD and risk of incident extra-hepatic tumours at different sites; 2) all studies should reported hazard ratios (HRs) or incidence rate ratios with 95% confidence intervals (95% CIs) values for the outcome measure of interest; 3) the diagnosis of NAFLD was based on liver

biopsy, imaging techniques or International Classification of Diseases, 9th revision (ICD-9) or ICD-10 codes, in the absence of significant alcohol consumption and chronic viral hepatitis; and 4) the diagnosis of the outcomes of interest was based on imaging techniques or ICD-9/ICD-10 codes. Study participants included in the meta-analysis were of either sex without any restriction in terms of race, ethnicity or comorbidities.

Criteria for exclusion of the selected studies from this meta-analysis were as follows: 1) congress abstracts, theses, case reports, reviews, commentaries, editorials, practice guidelines, and cross-sectional studies; 2) studies where NAFLD diagnosis was based exclusively on serum liver enzyme levels or other surrogate markers of NAFLD (e.g., fatty liver index); 3) studies which did not specifically report any HR and 95% CIs for the outcome measure of interest; 4) studies without an appropriate control group, and 5) studies conducted in pediatric population (<18 years old).

Data extraction and quality assessment

Two investigators (AM and GT) independently examined all titles and abstracts and obtained full texts of potentially relevant papers. Working independently and in duplicate, we read the papers and determined whether they met inclusion criteria. Discrepancies were resolved by consensus, in consultation with a third author. For all studies, we extracted information on study design, sample size, study country, population characteristics, modality of NAFLD diagnosis, follow-up duration, ascertainment of the outcomes of interest, matching and confounding factors included in multivariable regression analyses. In the case of multiple publications, we included the most up-to-date or comprehensive information. We did not contact any corresponding author of the eligible studies in order to obtain additional information for the meta-analysis.

Two authors independently assessed the risk of bias. Any discrepancies were addressed by a re-evaluation of the original article by a third author. Since all the included studies were non-randomized and had a cohort design, the Newcastle-Ottawa Scale (NOS) was used to judge study quality, as recommended by the Cochrane Collaboration (17). The NOS uses a star system (with a maximum of nine stars) in order to evaluate a study in three specific domains: selection of participants, comparability of study groups, and the ascertainment of outcomes of interest. We

judged studies that received a score of eight or nine stars to be at low risk of bias, studies that scored six or seven stars to be at medium risk, and those that scored five or less to be at high risk of bias.

Data synthesis and analysis

The primary outcome measure of this meta-analysis was the development of incident extra-hepatic cancers at different sites in individuals with NAFLD compared to those without NAFLD. The HRs (or incidence rate ratios) with their 95% CIs were considered as the effect size for all eligible studies. When studies had several adjustment models, we extracted those that reflected the maximum extent of adjustment for potentially confounding risk factors. The adjusted HRs (or incidence rate ratios when available) of all eligible cohort studies were then pooled, and an overall estimate of effect size was calculated using the DerSimonian-Laird random-effects model, as this methodology considers any differences between studies even if there is no statistically significant heterogeneity.

Visual inspection of the forest plots was used to investigate the possibility of statistical heterogeneity. Statistical heterogeneity was assessed by the I^2-statistics, which provides an estimate of the percentage of variability across studies that is due to heterogeneity rather than chance alone. According to Higgins and Thompson (18), I^2-values of approximately 25% represent low heterogeneity; approximately 50% represent medium heterogeneity; and approximately 75% represent high heterogeneity. Publication bias was evaluated using the funnel plot and the Begg's rank test (19).

To explore the possible sources of the (expected) heterogeneity among the eligible studies and to test the robustness of the observed associations, we conducted subgroup analyses by study country, study setting, follow-up duration, methodology used for the diagnosis of NAFLD, or whether they had full adjustment for common cancer risk factors (i.e., arbitrarily defined as those studies adjusting at least for age, sex, smoking, diabetes and obesity [or body mass index, BMI]). Additionally, we performed univariable meta-regression analyses to examine the impact of specific moderator variables (age, sex, smoking, BMI or diabetes at baseline) on the effect size for the incidence of extra-hepatic cancers. These subgroup analyses and meta-regressions were performed

only when there were at least four or more eligible cohort studies examining the NAFLD-related risk for each specific extra-hepatic cancer. We also tested for possibly excessive influence of individual studies using a meta-analysis influence test that eliminated each of the included studies at a time. All statistical tests were two sided and used a significance level of $p<0.05$. We used STATA® 16.1 (StataCorp, College Station, Texas, USA) and its meta-analysis package for all statistical analyses.

RESULTS

Characteristics of included studies

Based on the titles and abstracts of 548 selected citations (after excluding the duplicates), we have initially identified 18 potentially relevant studies from the three large electronic databases prior to December 30, 2020 (date last searched) (20-37). After examining the full text of these 18 publications, we excluded 8 studies (30-37), because of unsatisfactory inclusion criteria or unsatisfactory outcome measures (**Supplementary Figure S1**). As a consequence of this exclusion, 10 unique, observational cohort studies (20-29) were eligible for inclusion in the meta-analysis and were assessed for quality (**Supplementary Table S1**). Studies excluded at the eligibility stage of the PRISMA diagram are listed in **supplementary Table S2**. **Supplementary Table S3** shows the syntax used and the records identified through database searching.

The main characteristics of the 10 cohort studies included in the meta-analysis are shown in **supplementary Table S1**. All studies had a retrospective design (20-29, 31). Most of them recruited Asian individuals from large health examination check-ups, in which NAFLD was diagnosed either by imaging techniques (mostly ultrasonography) (n=8) or by ICD-9/10 codes (n=2). No studies using liver biopsy to diagnose NAFLD were available for the meta-analysis. Information on the association between severity of NAFLD (by non-invasive fibrosis scores) and risk of extra-hepatic cancers was available only for one study (24). Nine eligible studies were carried out in Asia (South Korea, China, Taiwan or Japan); one study was carried out in the United States. Diagnosis of extra-hepatic cancers was made by using self-reported data, radiological examinations or, in most cases, by ICD-9/10 codes (**Supplementary Table S1**).

Overall, in the 10 cohort studies included in the meta-analysis there were 182,202 middle-aged individuals (mean [±SD] age 51±6 years; mean BMI 25±3 kg/m^2, 59% men; 19% smokers; 13.3%

pre-existing diabetes), who were followed for a median of 5.8 years (p25-p75: 4-8 years). Of these 182,202 individuals, 45,218 (24.8%) had NAFLD at baseline, as detected by imaging techniques or ICD-9/10 codes.

As summarized in **Supplementary Table S4**, only one cohort study received eight stars on the NOS (indicating an overall low risk of bias), eight cohort studies received six or seven stars (indicating an overall medium risk of bias), and one study received five stars (indicating an overall high risk of bias), thereby suggesting an overall medium risk of bias.

Risk of esophagus cancer

The distribution of eligible studies by estimate of the association between NAFLD and risk of esophagus cancer is plotted in **Figure 1** (panel A). Five studies provided data suitable for the pooled primary analysis, involving a total of 140,014 individuals (26.7% with NAFLD) with 125 incident cases of esophagus cancer over a median of 8 years. NAFLD was associated with a nearly 1.9-fold increased risk of esophagus cancer (pooled random-effects HR 1.93, 95% CI 1.19-3.12, I^2=45.1%). Notably, since we always used the fully adjusted HR estimates for each study (as detailed in **supplementary Table S1**), this pooled random-effects HR (as well as those reported in statistical analyses below for other cancer sites) was independent of age, sex, smoking, obesity and diabetes.

Risk of stomach cancer

The distribution of eligible studies by estimate of the association between NAFLD and risk of stomach cancer is plotted in **Figure 1** (panel B). Six studies provided data suitable for the pooled primary analysis, involving a total of 155,944 individuals (26.1% with NAFLD) with 597 cases of stomach cancer over a median of 8 years. NAFLD was associated with a nearly 80% higher risk of incident stomach cancer (pooled random-effects HR 1.81, 95% CI 1.19-2.75, I^2=80.8%).

Risk of pancreas cancer

The distribution of eligible studies by estimate of the association between NAFLD and risk of pancreatic cancer is plotted in **Figure 1** (panel C). Three studies provided data suitable for the pooled primary analysis, involving a total of 55,655 individuals (27.9% with NAFLD) with 115 incident cases of pancreas cancer over a median of 7 years. NAFLD was associated with a nearly

85% increased risk of pancreas cancer (pooled random-effects HR 1.84, 95% CI 1.23-2.74, I^2=0%). Given the low number of studies included, neither subgroup analyses nor univariable meta-regressions were performed (see below).

Risk of colorectal adenomas and cancer

The distribution of eligible studies by estimate of the association between NAFLD and risk of incident colorectal adenomas and cancer is plotted in **Figure 2** (panels A and B). Four studies provided data suitable for the pooled primary analysis, involving a total of 14,244 individuals (31.8% with NAFLD) with 2,578 incident cases of colorectal adenomas over a median of 3.3 years. NAFLD was associated with a 40% increased risk of colorectal adenomas (pooled random-effects HR 1.40, 95% CI 1.20-1.63, I^2=30.04%).

Eight eligible studies provided data suitable for the pooled primary analysis, involving a total of 167,643 individuals (26.5% with NAFLD) with 776 incident cases of colorectal cancer over a median of 7 years. NAFLD was associated with a nearly 60% higher risk of colorectal cancer (pooled random-effects HR 1.64, 95% CI 1.24-2.19, I^2=57.9%) (**Figure 2**; panel B).

Risk of thyroid cancer

The distribution of eligible studies by estimate of the association between NAFLD and risk of thyroid cancer is plotted in **Figure 3** (panel A). Only two studies were available for this pooled primary analysis (involving a total 64,732 individuals with 38 incident cases of thyroid cancer). NAFLD was associated with a ~2.5-fold increased risk of thyroid cancer (pooled random-effects HR 2.63, 95% CI 1.27-5.45, I^2=0%). Given the low number of studies included in this analysis, neither subgroup analyses nor meta-regressions were performed (see below).

Risk of lung cancer

The distribution of eligible studies by estimate of the association between NAFLD and risk of lung cancer is plotted in **Figure 3** (panel B). Five studies provided data suitable for the pooled primary analysis, involving a total of 140,014 individuals (26.8% with NAFLD) with 837 incident cases of lung cancer over median of 8.5 years. NAFLD was associated with a 30% increased risk of lung cancer (pooled random-effects HR 1.30, 95% CI 1.14-1.48, I^2=0%).

Risk of urinary system cancers

The distribution of eligible studies by estimate of the association between NAFLD and risk of urinary system cancers is plotted in **Figure 3** (panel C). Four studies provided data suitable for the pooled primary analysis, involving a total of 120,851 individuals (27.1% with NAFLD) with 414 incident cases of urinary system cancers (kidney or bladder cancers) over median of 8.7 years. NAFLD was associated with a nearly 30% increased risk of urinary system cancers (pooled random-effects HR 1.33, 95% CI 1.04-1.70, I^2=10.4%).

Risk of breast cancer

The distribution of eligible studies by estimate of the association between NAFLD and risk of breast cancer is plotted in **Figure 4** (panel A). Four studies provided data suitable for the pooled primary analysis, involving a total of 85,827 individuals (23.4% with NAFLD) with 1,347 cases of incident breast cancer over a median of 7.7 years. NAFLD was associated with a nearly 40% higher risk of breast cancer (pooled random-effects HR 1.39, 95% CI 1.13-1.71, I^2=0%).

Risk of female genital organ cancers

The distribution of eligible studies by estimate of the association between NAFLD and risk of gynecological (uterine and ovary) cancers is plotted in **Figure 4** (panel B). Four studies provided data suitable for the pooled primary analysis, involving a total of 85,827 individuals (23% with NAFLD) with 558 cases of incident gynecological cancers over a median of 8 years. NAFLD was associated with a ~60% higher risk of gynecological cancers (pooled random-effects HR 1.62, 95% CI 1.13-2.32, I^2=40.8%).

Risk of prostate cancer

The distribution of eligible studies by estimate of the association between NAFLD and risk of prostate cancer is plotted in **Figure 4** (panel C). Five studies provided data suitable for the pooled primary analysis, involving a total of 140,014 individuals (26.8% with NAFLD) and 1,002 cases of incident prostate cancer over a median of 8 years. NAFLD was not significantly associated with increased risk of prostate cancer (pooled random-effects HR 1.16, 95% CI 0.82-1.64, I^2=62.5%).

Risk of haematological cancers

The distribution of eligible studies by estimate of the association between NAFLD and risk of haematological cancers (lymphomas or leukemias) is plotted in **Supplementary Figure S2**. Only two studies provided data suitable for the pooled primary analysis. NAFLD was not significantly associated with increased risk of haematological cancers (pooled random-effects HR 1.47, 95% CI 0.69-3.12, I^2=62.3%).

Sensitivity-subgroup analyses and meta-regressions

The associations between NAFLD and risk of developing gastro-intestinal cancers, lung cancer, urinary system cancers, breast cancer, gynecological cancers and prostate cancer were consistent after stratifying the eligible studies by study country, follow-up duration, modality of NAFLD diagnosis, degree of covariate adjustment or study setting (**Figure 5, panels A to F**).

We also tested for the possibility of excessive influence of individual studies using an influence test that eliminated each of the included cohort studies one at a time. Removing each of the eligible studies from the analysis had no significant effect on the overall risk of each specific cancer (data not shown).

As shown in **Supplementary Figures S3-S10**, the results of univariable meta-regression analyses did not show any significant effect of age, sex, BMI, smoking, or proportion of pre-existing diabetes on the association between NAFLD and risk of incident esophagus, stomach, lung, and breast cancers (panels A to E). Conversely, the meta-regression analyses showed a significant effect of smoking on the association between NAFLD and risk of colorectal cancer; a significant effect of BMI on the association between NAFLD and risk of urinary system cancers, as well as significant effects of age, BMI or pre-existing diabetes on the association between NAFLD and risk of gynecological and prostate cancers.

Risk of publication bias

As shown in **Supplementary Figure S11**, the Begg's rank correlation tests did not reveal any statistically significant asymmetry of the funnel plots for the eligible studies examining the association between NAFLD and risks of esophagus cancer (panel A), stomach cancer (panel B), colorectal cancer and adenomas (panels C and D), as well as lung cancer (panel E), breast cancer (panel F), gynecological cancers (panel G), prostate cancer (panel H), and urinary system cancers

(panel I), indicating that publication bias was unlikely. Almost identical results were found using the Egger's regression test (**Supplementary Table S5**).

DISCUSSION

Our meta-analysis of 10 observational cohort studies (involving a total of 182,202 individuals with 8,485 incident cases of extra-hepatic cancers over a median of 5.8 years) that examined the association between NAFLD and risk of developing extra-hepatic cancers is the largest and most comprehensive assessment to date. We found that NAFLD, as assessed by either imaging techniques or ICD-9/10 codes, was associated with a nearly 1.5 to 2-fold increased long-term risk of developing several gastro-intestinal cancers. Furthermore, NAFLD was also associated with an approximately 1.2 to 1.5-fold increased risk of incident lung cancer, urinary system cancers, breast and gynecological cancers, as well as with a ~2.5-fold increased risk of thyroid cancer (but only 2 cohort studies with 38 incident cases were available for this analysis). The magnitude of these NAFLD-related cancer risks remained unchanged after stratifying the eligible studies by study country, study setting, length of follow-up or modality of NAFLD diagnosis and, more importantly, these risks remained significant in those studies where statistical analysis was adjusted for age, sex, smoking, adiposity measures, diabetes or other potential confounders.

Previous meta-analyses supported a link between the severity of NAFLD (especially the severity of liver fibrosis) and the risk of developing liver-related complications (including HCC) and some extra-hepatic complications, such as adverse cardiovascular outcomes, type 2 diabetes and chronic kidney disease (38-41). It is reasonable to assume that this may also be true for the risk of extra-hepatic cancers, but, unfortunately, most of the studies included in this meta-analysis did not provide any data on NAFLD severity. Therefore, the question of whether the increased risk for certain extra-hepatic cancers is restricted to patients with more advanced forms of NAFLD or applies to all patients with NAFLD remains largely unsolved so far, and further large prospective studies are needed to definitely prove whether the severity of NAFLD adversely affects the risk of developing certain extra-hepatic cancers. That said, it should be noted that in a nationwide, matched cohort study involving 10,568 individuals with biopsy-proven NAFLD and 49,925 matched control subjects, the investigators found that all histological stages of NAFLD were associated with

increased all-cause mortality, and this risk increased progressively with worsening NAFLD histology. Notably, the excess mortality associated with NAFLD was primarily from extra-hepatic cancers, followed by cardiovascular disease and HCC (9).

Our meta-analysis has some important limitations that are strictly inherent to the design of the included studies. First, the retrospective design of the cohort studies does not allow establishing a causal association between NAFLD and risk of extra-hepatic cancers. Furthermore, the retrospective cohort studies are also susceptible to selection bias and differential losses to follow-up that can also bias the ascertainment of the outcomes of interest. Second, although the large majority of the eligible studies adjusted their results at least for age, sex, smoking, obesity, and diabetes, the possibility of residual confounding by some unmeasured (or unknown) factors cannot be ruled out. For example, the majority of the eligible studies reported incomplete adjustments for some important risk factors, such as family history of cancer, dietary factors, physical activity, waist circumference or drug use (for example, estrogens or progestogens). For these reasons, although the overall heterogeneity for most of our primary pooled analyses was relatively low (except for the risk of stomach cancer, I^2=80.8%), the NOS quality scale of the eligible studies suggested an overall medium risk of bias. Third, no detailed information was available on the different cancer histology. Fourth, another limitation of the meta-analysis is that the eligible studies used imaging techniques or ICD-9/10 codes for diagnosing NAFLD, but none of them used liver biopsy, which is the reference standard for diagnosing and staging this liver disease (42,43). We found that the pooled cancer incidence rates were only marginally (but not significantly) higher in NAFLD cases diagnosed with the ICD-9/10 codes compared to NAFLD cases diagnosed with ultrasonography, with the exception of stomach cancer. Finally, most of the eligible studies, except one conducted in USA (26), originate from various Asian countries, where large populations undergo regular health check-up programs. As Asian and non-Asian populations have different body fat distribution, cultural/genetic backgrounds and lifestyle habits that might have significant effects on cancer development, further larger prospective cohort studies should be conducted in European and United States populations.

Despite these limitations, our meta-analysis has also important strengths. As previously discussed, this meta-analysis provides the most comprehensive and updated assessment to date on the association between NAFLD and the long-term risk of developing extra-hepatic cancers at different

sites. This meta-analysis incorporates data from large cohort studies from Asia and United States that are likely to be an accurate reflection of individuals with NAFLD commonly seen in clinical practice. Moreover, we employed standardized risk estimates from all eligible studies to allow a consistent combination of estimates across studies. Finally, although a selective reporting bias of eligible studies could be not definitely excluded, we made every effort to rule out very low-quality studies by using stringent inclusion criteria. We think our comprehensive search has made it unlikely that any published reports were missed and visual inspection of funnel plots and formal statistical tests did not show any publication bias.

It is beyond the scope of this meta-analysis to discuss in depth the putative underlying mechanisms by which NAFLD may contribute to the development of some extra-hepatic cancers. From a pathophysiological perspective, it is currently uncertain whether NAFLD is associated with an increased risk of some extra-hepatic cancers as a simple consequence of the shared metabolic risk factors, or whether NAFLD *itself* may contribute to the development of extra-hepatic cancers, irrespective of shared metabolic risk factors. Recent research has characterized important pathways that might link metabolism, low-grade inflammation and cancer development (44, 45). It is also becoming increasingly clear that the liver and gut (i.e., intestinal dysbiosis) share a number of pathophysiological pathways that are intrinsically linked to each other and may contribute to increased cancer development (46,47). However, whereas there is now evidence that NAFLD is associated with certain extra-hepatic cancers and many different mechanisms have been explored, the precise mechanisms linking low-grade inflammation and cancer development with NAFLD remain uncertain.

In conclusion, the results of this large and updated meta-analysis suggest that NAFLD is associated with a moderately increased risk of developing some extra-hepatic cancers over a median period of nearly 6 years (especially gastro-intestinal, breast and gynecological cancers). In most studies these risks appear to be independent of age, sex, smoking, adiposity measures and pre-existing diabetes. However, it should be noted that the observational design of the eligible studies does not allow for proving causality. Further prospective and mechanistic studies are needed to decipher the existing but complex link between NAFLD and increased carcinogenesis. In particular, further research is needed to test the effects of NAFLD/obesity/diabetes, as it is possible that

there could be interaction/additive effects or even synergism of NAFLD, obesity and diabetes to influence risk of certain extra-hepatic cancers.

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FIGURE LEGENDS

Figure 1. Forest plots and pooled estimates of the effects of NAFLD on the risk of incident esophagus cancer (n=5 studies included; panel A), stomach cancer (n=6 studies; panel B) or pancreas cancer (n=3 studies; panel C), stratified by methods used for the diagnosis of NAFLD (i.e., imaging techniques or ICD-9/10 codes).

Figure 2. Forest plots and pooled estimates of the effects of NAFLD on the risk of incident colorectal adenomas (n=4 studies; panel A) and colorectal cancer (n=8 studies; panel B), stratified by methods used for the diagnosis of NAFLD.

Figure 3. Forest plots and pooled estimates of the effects of NAFLD on the risk of incident thyroid cancer (n=2 studies; panel A), lung cancer (n=5 studies; panel B), urinary system cancer (n=4; panel C), stratified by methods used for the diagnosis of NAFLD.

Figure 4. Forest plots and pooled estimates of the effects of NAFLD on the risk of incident breast cancer (n=4 studies; panel A), female genital organ cancer (n=4 studies; panel B) and prostate cancer (n=5 studies; panel C), stratified by methods used for the diagnosis of NAFLD.

Figure 5. Subgroup analyses by study country, length of study follow-up, modality of NAFLD diagnosis, degree of covariate adjustment (i.e., minimal vs. maximum adjustment) or study setting. Maximum adjustment was defined as those studies adjusting at least for age, sex, smoking, obesity, and diabetes.

Supplementary Figure S1. The PRISMA flow diagram for search and selection processes of the meta-analysis.

Supplementary Figure S2. Forest plots and pooled estimates of the effects of NAFLD on the risk of incident haematological cancers (n=2 studies), stratified by methods used for the diagnosis of NAFLD.

Supplementary Figure S3. Univariable meta-regression analyses of effect of age (panel A), body mass index (panel B), smoking history (panel C), proportion of pre-existing diabetes (panel D), and

male sex (panel E) on the association between NAFLD with risk of incident esophagus cancer. Note: in these univariable meta-regression models we examined the effect of age (included as mean age of each cohort), male sex (included as proportion of men in each cohort), BMI (included as mean BMI of each cohort), smoking status (included as proportion of current smokers in each cohort), or diabetes (included as proportion of pre-existing diabetes in each cohort) on the association between NAFLD and incidence of esophagus cancer (or other cancer types as also reported in Figure S4 to Figure S10).

Supplementary Figure S4. Univariable meta-regression analyses of effect of age (panel A), body mass index (panel B), smoking history (panel C), proportion of pre-existing diabetes (panel D), and male sex (panel E) on the association between NAFLD with risk of incident stomach cancer.

Supplementary Figure S5. Univariable meta-regression analyses of effect of age (panel A), body mass index (panel B), smoking history (panel C), proportion of pre-existing diabetes (panel D), and male sex (panel E) on the association between NAFLD with risk of incident colorectal cancer.

Supplementary Figure S6. Univariable meta-regression analyses of effect of age (panel A), body mass index (panel B), smoking history (panel C), proportion of pre-existing diabetes (panel D), and male sex (panel E) on the association between NAFLD with risk of incident lung cancer.

Supplementary Figure S7. Univariable meta-regression analyses of effect of age (panel A), body mass index (panel B), smoking history (panel C), and proportion of pre-existing diabetes (panel D) on the association between NAFLD with risk of incident breast cancer.

Supplementary Figure S8. Univariable meta-regression analyses of effect of age (panel A), body mass index (panel B), smoking history (panel C), and proportion of pre-existing diabetes (panel D), and male sex (panel E) on the association between NAFLD with risk of incident female genital organ cancers.

Supplementary Figure S9. Univariable meta-regression analyses of effect of age (panel A), body mass index (panel B), smoking history (panel C), and proportion of pre-existing diabetes (panel D) on the association between NAFLD with risk of incident prostate cancer.

Supplementary Figure S10. Univariable meta-regression analyses of effect of age (panel A), body mass index (panel B), smoking history (panel C), and proportion of pre-existing diabetes (panel D), and male sex (panel E) on the association between NAFLD with risk of incident urinary system cancers.

Supplementary Figure S11. Funnel plots of standard errors by log-hazard ratios for the risk of incident esophagus cancer (panel A), stomach cancer (panel B), colorectal cancer (panel C), colorectal adenomas (panel D), lung cancer (panel E), as well as breast cancer (panel F), female genital organ cancers (panel G), prostate cancer (panel H), and urinary system cancers (panel I). *P*-values were obtained by using the Begg's rank test.

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