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Non-Alcoholic Fatty Liver Disease and Hepatocellular Cancer: A Systematic Review

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Abstract

Background—Non-alcoholic fatty liver disease (NAFLD) has been implicated as a possible cause of hepatocellular carcinoma (HCC) in several general review articles. We performed the first systematic review of the epidemiologic literature.

Methods—We searched PubMed for original reports published between 1/1992–12/2011 evaluating the association between NAFLD, non-alcoholic steatohepatitis (NASH) and cryptogenic cirrhosis (CC) presumptively NASH-related and the risk of HCC. Studies were categorized as offering potential direct evidence (e.g., cohort studies) or indirect evidence (e.g., case-control or cross-sectional studies or case-series) of an association.

Results—A total of 17 cohort studies [3 population-based, 9 clinic-based (6 limited to cirrhotics), and 5 natural history], 18 case-control and cross-sectional studies, and 26 case-series were study-eligible. NAFLD or NASH cohorts with few or no cirrhosis cases demonstrated a minimal HCC risk (cumulative HCC mortality between 0%–3% for study periods up to two decades). Consistently increased risk was observed in NASH-cirrhosis cohorts (cumulative incidence between 2.4% over 7-years to 12.8% over 3-years). However, HCC risk was substantially lower in NASH-cirrhosis (NASH-C) cohorts than in HCV-related cirrhosis cohorts. The determinants of elevated risk among NASH-C cohorts were unclear as most studies were underpowered to perform multivariate analysis.

Conclusions—This systematic review shows that despite several limitations, the epidemiologic evidence supports an association between NAFLD or NASH and an increased HCC risk that seems to be predominantly limited to individuals with cirrhosis.

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Keywords

epidemiology; hepatology; gastroenterology; endocrinology; obesity; metabolic syndrome

Introduction

Rising hepatocellular carcinoma (HCC) incidence rates have been observed in many Western countries, with HCC a rapidly increasing cause of cancer-related deaths in the United States[1]. Hepatitis C is the most common etiologic risk factor for HCC within western countries, accounting for 30–50% of cases, followed by alcohol-related liver disease (10–20%) and hepatitis B (10–15%). Genetic disorders (e.g., Wilson's disease, alpha-1 antitrypsin deficiency, and hereditary hemochromatosis) account for only a very small proportion of cases. HCC arising in the background of cryptogenic liver disease accounts for another 15–50% of HCC cases in the U.S.[2]

Non-alcoholic fatty liver disease (NAFLD) has been proposed as the underlying cause of most cases of cryptogenic cirrhosis (CC). NAFLD and its more advanced clinical manifestation, non-alcoholic steatohepatitis (NASH), typically occur in patients with key features of the metabolic syndrome including visceral adiposity and insulin resistance. Coincident with large secular increases in both obesity and diabetes, NAFLD is now the leading cause of chronic liver disease in the U.S.[3]

Over the last two decades there has been considerable growth in the literature evaluating the association between NAFLD, NASH or CC and HCC. However, the only systematic reviews and meta-analyses in this area evaluated the association between NAFLD/NASH and overall liver disease-related mortality without distinguishing between cirrhosis and HCC.[4,5] The association between NAFLD and HCC remains unclear; studies have arrived at different findings as to the presence of an association and the magnitude or determinants of such as an association.

We performed a systematic review of the literature on the association between NAFLD/NASH and HCC reported in: (1) longitudinal studies on HCC in adults with NAFLD/NASH or cryptogenic cirrhosis (CC) presumptively NAFLD/NASH-related; (2) cross-sectional and case-control studies that examined the association between diabetes or obesity and HCC ascribed to NAFLD/NASH or CC; and (3) case-reports and case-series which described a HCC case-group with etiology ascribed NASH/NAFLD or CC. Our goals were to critically review and synthesize the collective literature and also to identify potential gaps that may be addressed by future research studies.

Methods

We followed published guidelines for the conduct and reporting of systematic reviews.[6] We performed a structured keyword search in PubMed to identify original research reports published in print or online in peer-reviewed journals reporting results in English between 1/1/1992 and 12/31/2011 that evaluated the association between NAFLD/NASH or CC and HCC either directly (e.g., population- and clinic-based cohort studies) or indirectly (e.g., cross-sectional and case-control studies and case-series/reports). Eligible studies had to have data to calculate an estimate of HCC incidence or mortality for cohort studies, relative risk of HCC or prevalence of diabetes or obesity in HCC cases attributed to NAFLD/NASH or CC and in a comparison group with another type of liver disease for case-control and cross-sectional studies, or prevalence of obesity or diabetes for case-reports/case-series.

Our search included all combinations of individual terms presented in Appendix 1. We also performed ancestry searches by reviewing the bibliography of all retrieved manuscripts as well as of relevant meta-analyses and systematic and narrative reviews on NAFLD/NASH to identify additional studies not identified by our keyword searches.

We excluded publications that: did not report original research findings (e.g., editorials) or were published as abstracts or letters; were performed in pediatric cohorts; had data on participants only post-hepatic transplant, post-bariatric surgery, or after other clinical interventions (e.g., pharmaceutical trials); did not differentiate HCC incidence or mortality from either overall or liver disease-related incidence or mortality; included cryptogenic liver disease cases where viral hepatitis and alcohol-related disease were not specifically excluded; did not report or have data to calculate requisite measures of effect (e.g., cumulative HCC incidence rate in cohort studies or prevalence of diabetes and obesity in case-control studies or case-reports), provided outcome data for only a non-random subset of the baseline cohort, or included data on only secondary or recurrent HCC. We also excluded studies published prior to 1992 because of lack of serological test to specifically exclude the hepatitis C virus as an alternate cause for observed liver disease.

We applied additional study design eligibility criteria to help assure the internal validity of our review. These additional criteria were: 1) case-control and cross-sectional studies had to have a minimum of 5 HCC cases attributed to NAFLD/NASH with at least one control group with HCC attributed to another cause of liver disease to plausibly allow comparisons of at least baseline prevalence or risk between groups as well as data on prevalence of diabetes or obesity in both the case and control groups; 2) cohort studies had to have a NAFLD/NASH or cryptogenic liver disease cohort followed collectively for HCC incidence or mortality and meet sample size requirements (a minimum cohort sample size of 20 and study follow-up period of 3 years if restricted to cirrhosis at baseline or a minimum cohort sample size of 75 with 10 years follow-up if not restricted to cirrhosis at baseline as minimum plausible for HCC to develop); and 3) case-reports or case-series had to have minimum reporting of at least one cardinal feature of the metabolic syndrome in HCC cases attributed to NAFLD/NASH or cryptogenic disease. If a case-control or cohort study did not meet minimum eligibility criteria for those designs, if adequate data was provided on individual HCC cases, they were included as case-series or case-reports instead.

When more than one eligible report was available for the same study population, we included either the most recent or the largest study unless an earlier study contained more detailed data on comorbidities and outcomes. However, if two separate study designs were employed to evaluate the same underlying target population (e.g., case-control and population-based cohort designs), or if two studies utilized the same NAFLD/NASH or cryptogenic cases but had different comparison groups (e.g., HCV-related and alcohol-related), results from each study are reported.

Two independent reviewers (DW and FK) abstracted data from eligible reports using a structured data collection template that interrogated data on patient sociodemographic and clinical characteristics as well as on study design (e.g., source of cases and any comparison groups, study country and performance dates, and a general synopsis of criteria used to define NAFLD/NASH or cryptogenic disease). All results are provided in summary tables stratified according to study design (cohort studies, case-control and cross-sectional studies, and case-report and case-series).

Results

Our combined PubMed keyword and review article ancestry searches identified >14,000 citations (see study flow diagram Figure 1). Among the 265 full citations reviewed, the most common reason for exclusion was report did not contain specific results for HCC or did not adequately distinguish HCC attributed to NAFLD/NASH or CC from HCC attributed to other causes (e.g., alcohol-related HCC) or other health outcomes (e.g., overall liver-related mortality or total mortality). A total of 17 cohort studies, 18 case-control and cross-sectional studies, and 26 case-reports/series were eligible for inclusion in our review.

Cohort studies

Among the 17 eligible cohort studies, 3 were population-based studies with a case and a comparison cohort,[7–9] 9 were clinic-based cohort studies with a comparison cohort (6 of which were limited to patients with cirrhosis),[10–18] and 5 were natural history cohorts without a comparison cohort.[19–23]

Population-based cohort studies with a comparison group—Two population-based cohort studies were from the U.S. and dealt with all comers with presumed NAFLD[8,9], while the third study from Denmark evaluated only those with cryptogenic cirrhosis (CC).[7] (Table 1A) One U.S. population-based study identified NAFLD using data collected in the Nutrition Health and Exercise Study (NHANES).[9] NAFLD was defined as presence of elevated liver enzymes measured at baseline in the absence of other causes of liver disease. In this study, none of the 817 NAFLD cases or the 10,468 study eligible normal controls without liver disease died from HCC during the median 8.7 year follow-up period. (Table 2A) The validity of their NAFLD/NASH definition was not examined.

The second U.S. population-based study used a national health insurance database to identify NAFLD/NASH (via an ICD-code based algorithm) in >729,000 enrolled study-eligible participants.[8] (Table 1A) The cumulative HCC incidence in the 6 years between 2002 and 2008 was 0.3% in NAFLD/NASH cases compared to 0.6% in those with HCV-related liver disease. (Table 2A) The validity of the NAFLD/NASH definition was again not examined.

The third study performed in Denmark utilized nationwide hospitalization data and reported that 1.9% of the 2,430 cirrhosis cases who had a hospital discharge for CC developed HCC during the follow-up period, which ranged between 5.5 years for males and 5.9 years for females.[7] (Table 2A) The standardized incidence rate (SIR) for HCC was lower in those with CC than those with alcohol-related cirrhosis (SIR= 43/100,000 and 71/100,000 person-years for CC-related HCC and alcoholic cirrhosis-related HCC, respectively), but was the same as that observed for HCV-related HCC.

None of these population-based cohort studies reported the proportion of participants with biopsy-confirmed features of NAFLD/NASH. (Table 1A) Sociodemographic and clinical characteristics of the resulting HCC cases attributed to NAFLD/NASH were also generally not reported. Finally, neither of the two studies where HCC cases occurred during the follow-up period included multivariate analyses to identify risk factors for HCC.

Clinic-based cohort studies of cirrhosis potentially NASH-related with comparison cohort—All six studies in this group evaluated HCC risk in a cohort with cirrhosis or advanced fibrosis with clinically-confirmed NASH or cryptogenic cirrhosis (presumptively NASH-related) and in a comparison cohort with HCV-related cirrhosis.[10–15] (Table 1A) Diabetes was more prevalent in all NASH cirrhosis and CC cohorts compared with their comparison HCV-related cirrhosis cohorts except in one study. (Table 2A)

Obesity and dyslipidemia were uniformly higher in NASH cirrhosis and CC cohorts compared to HCV-related cohorts.

Five studies reported cumulative HCC *incidence* for the NASH-cirrhosis or CC cohorts and the comparison HCV cirrhosis cohorts.[10,12–15] (Table 2A) The cumulative HCC incidence in NASH-cirrhosis or CC cohorts varied widely (range: 2.4% – 38%) over generally modest follow-up periods (range: 3.2–10 years). However, cumulative HCC incidence was always lower in NASH cirrhosis or CC than in the HCV-related cirrhosis (i.e., internal control) cohorts except for one sub-group comparison in a single study from France (29.6% vs. 19.5% cumulative HCC incidence in overweight CC and HCV-related cirrhosis subgroups over a 3.4 year follow-up period, respectively).[10] The single study reporting only cumulative HCC *mortality* also found a lower mortality rate with CC than in the HCV cohort (6.7% vs. 17.0% cumulative 25-year HCC mortality among the CC and HCV-related cirrhosis cohorts, respectively).[11]

Information on the sociodemographic and clinical characteristics for the incident HCC cases attributed to NASH-cirrhosis or CC were generally not reported. Three of four studies which performed multivariate analyses found no independent risk factors for HCC in the background of NASH-cirrhosis or CC.[11,13,15] (data not shown) However, a recent study performed in the U.S. found that NASH-cirrhosis cases with any type of alcohol consumption had a significant 3.6-fold excess HCC risk compared to NASH-cirrhosis cases who were never drinkers.[14] (data not shown)

In summary, although the cumulative HCC incidence and mortality rates were variably elevated over observed study periods, the relative HCC risk was almost universally lower in NASH-cirrhosis and CC cohorts relative to their respective cirrhosis comparison cohorts (range overall excess HCC risk with HCV vs. NASH-C or CC: 58%–172%).

Clinic-based cohort study of NAFLD-NASH (not cirrhosis restricted) and a comparison cohort—Three clinic-based cohort studies evaluated HCC risk in a cohort with NAFLD or NASH, two with biopsy-confirmed NAFLD/NASH cases (n=1 Denmark, n=1 Sweden)[16,17] and one with ultrasound-confirmed NAFLD/NASH cases (Japan).[18] (Table 1A)

The cumulative HCC incidence reported in these studies varied widely. In the Danish cohort study, none of the 170 subjects in the NAFLD cohort without significant fibrosis at baseline developed HCC during an average of almost 21 years follow-up compared to 1% in a cohort with alcohol-related fatty liver.[17] The Swedish cohort followed for 21 years found 3%, 6%, 7% and 8% cumulative HCC mortality for the NAFLD, NASH, HCV, and alcohol abuse cohorts, respectively.[16] The Japanese cohort study was performed in adults aged 60 years or older at baseline and reported 6% cumulative HCC incidence in the NAFLD/NASH cohort vs. 63% in the HCV cohort during the average 8.2 year follow-up period.[18] (Table 2A) That study also included multivariate analyses that identified older age, smoking and glucose level as significant independent predictors of malignancies in the NAFLD cohort including HCC. (data not shown)

Diabetes was modestly more prevalent in NAFLD/NASH cohorts compared to their respective comparison cohorts with other causes of liver disease (e.g., 34% in NAFLD vs. 28% HCV in the Japanese cohort study). (Table 2) NAFLD cohort members were also more likely to be obese (e.g., 69% vs. 20% obesity prevalence in the NAFLD vs. HCV comparison cohort in the Danish study).

In summary, the findings of these three studies show between no HCC occurrence in a NAFLD cohort without significant fibrosis (Danish study) to a small elevated absolute risk of HCC in the NAFLD/NASH cohorts in the other two studies (3–6%) over study periods ranging between approximately 1–2 decades, with all three demonstrating HCC was less likely to develop in NAFLD/NASH cohorts compared to their respective alcohol- or HCV-related comparison cohorts.

Clinic based cohorts without control groups (Natural history cohort) studies— Five natural history cohort studies were included (n=2 Japan, n=1 Sweden, and n=2 U.S.).[19–23] (Table 1B) Three reported cumulative HCC mortality rates, which ranged between 0.25% in the Rochester, Minnesota cohort of NAFLD/NASH cases or CC cases with features of metabolic syndrome followed for an average of 7.6 years,[20] 1% in the Cleveland Clinic cohort which was followed an average of 8.3 years and included 26% with ballooning degeneration and fibrosis at baseline,[19] and 2.3% in the Swedish cohort study which included cases with fatty infiltration and persistent abnormal liver tests at baseline (only 3.4% cirrhotic) and followed on average for 13 years.[21] (Table 2B) The Rochester, Minnesota study, while population-based, did not provide a population standardized mortality risk estimate given only 2 HCC cases were recorded (one in a NAFLD case and one in a CC case).[20]

The rates reported in the Japanese studies ranged between a 7.6% 5-year cumulative incidence rate in a cohort of 118 cases with advanced NASH-related fibrosis or cirrhosis at baseline (41% male and 43% diabetic)[22] vs. a 0.25% cumulative incidence rate in a cohort of >6,500 ultrasound confirmed NAFLD/NASH cases (88% male and 8% diabetic) and followed on average of 5.6 years.[23] Only the larger study identified significant predictors NAFLD-related HCC in multivariate analysis (BMI, AST, platelet count and diabetes). (data not shown)

Case-control and cross-sectional studies

The largest number of eligible studies in this review were case-control and cross-sectional studies (n=18),[8,22,24–39] with 8 performed in Asia (n=7 in Japan), 6 in Europe and 4 in the U.S. (Table 1C) All compared a case group with HCC attributed to NASH/NAFLD or to CC presumptively NAFLD-related with at least one control group, typically with HCC attributed to another cause of liver disease (n=16), though two had only NASH-related cirrhosis controls without HCC as their sole comparison or control group. Most (n=15) also utilized case and control groups identified from single medical centers, with 9 studies having biopsy-based confirmation of fatty liver disease in >80% of their NAFLD/NASH-related HCC cases (7 with verification in 100% of cases) either prior to or associated with HCC diagnosis or treatment.

Among studies reporting results for each gender, NAFLD/NASH or cryptogenic HCC cases were generally more likely to be male than HCC controls with other underlying causes of liver disease (8 of 10 studies). (Table 2C) Most studies included NAFLD/NASH or cryptogenic HCC cases either entirely or predominantly comprised of one ethnic/racial group (e.g., 83–100% White or 100% Japanese).

Prevalence of cirrhosis among HCC cases attributed to NAFLD/NASH in studies not restricted to cirrhotics ranged between 36% and 90%, with 9 of 12 studies reporting on cirrhosis prevalence reporting rates ≥70%. (Table 1C) Most studies reported significantly higher diabetes prevalence in the NAFLD/NASH- or CC-related disease related HCC cases than in HCC control groups with other types of liver disease. (Table 2C) Diabetes was also more prevalent in HCC-NASH or CC-related HCC cases than in NASH controls without HCC in two of three studies with that control group (86% vs. 52%, p=0.02; 74% vs. 43%,

p=0.002; and 71% vs. 73%, NS, respectively). Many studies also reported higher obesity prevalence or greater BMI in HCC-NASH or HCC-CC cases than that observed in HCC control groups with other types of liver disease, though fewer comparisons reached statistical significance.

Case-reports and Case-series

We identified 26 case-reports and case-series comprising a total of 257 HCC cases attributed to NAFLD/NASH or metabolic syndrome (presumptive fatty liver disease).[40–65] (Appendix 2) The majority of the reports were from Japan (n=15), while 5 were from Europe, 3 from the U.S., and 3 from Brazil. Most included data on prevalence of two primary features of the metabolic syndrome, diabetes and obesity, with overall estimated sample-size weighted prevalence of 58% and 63% for diabetes and obesity, respectively. Approximately 60% of cases had cirrhosis either prior to or at HCC diagnosis. Only five reports specifically noted that their HCC cases had presence of biopsy-confirmed features of NAFLD/NASH prior to HCC diagnosis. (Appendix 2)

None of the studies included in this review explicitly assessed for potential selection or information biases that may have influenced the validity and reliability of their reported findings, including for potential case misspecification bias that might occur in studies which solely relied on diagnostic code searches to identify NAFLD/NASH cases.

Discussion

This systematic review shows that despite several limitations, the epidemiologic evidence supports an association between NAFLD/NASH and an increased HCC risk that seems to be predominantly limited to those with cirrhosis. The studies that followed NAFLD or NASH cohorts with either few or no cirrhosis cases at baseline were consistent in showing that NAFLD/NASH was associated with a minimal HCC risk; cumulative HCC mortality rates ranged between 0%–3% in NAFLD/NASH cohorts, with 5 of 7 studies reporting 0%–1% cumulative HCC mortality over study periods ranging from 5.6–21 years. In contrast, cirrhosis related to NASH consistently signaled increased HCC risk, with cumulative HCC incidence ranging between 2.4% in a study that combined clinic-based cohorts from 4 countries with median follow-up of 7.2 years[15] and 12.8% in a single clinic-based cohort from the U.S. with 3.2 year median follow-up.[14] HCC risk was universally lower in the NASH-cirrhotic cohorts than in HCV-related cirrhosis comparison cohorts followed over similar timeframes. However, the determinants of this elevated HCC risk among NASH-cirrhosis cases were not clear as most studies were underpowered to perform multivariate analysis. Indirect evidence of a NAFLD–HCC association was provided by numerous case-control and cross-sectional studies showing universally higher prevalence of both diabetes and obesity among patients with HCC attributed to NASH or cryptogenic disease presumptively fatty liver disease-related compared to controls with HCC due to other causes of liver disease (e.g., 2.3–8.3 fold excess diabetes risk and 3.6–5.7 fold excess obesity risk in NAFLD/NASH/CC-related HCC cases vs. their respective HCV-related HCC comparison groups).

Direct comparison of findings from analytic studies that belong to different design categories (e.g., population-based cohort, clinic-based natural history studies, and case-control or cross-sectional studies) is generally not possible. Furthermore, differences in the risk estimates among studies that belonged to the same design category may be attributed to their source population or their inclusion of cases with more advanced disease at baseline. Therefore, it is important that individual study findings be discussed and qualified according to study design.

Cohort studies, particularly those that are population-based, prospective, have *a priori* well-defined exposure and outcome groups, and have sufficient sample size and longitudinal follow-up periods, are considered the strongest direct observational epidemiologic design in support of a potential causal association. However, none of the cohort studies included in this review met all of these design criteria. Low numbers of HCC cases in many of these cohort studies often resulted in imprecise risk estimates and an inability to perform meaningful multivariate analyses. Several of the largest cohort studies relied on diagnostic codes (e.g., ICD-9 571.8, 571.9, 573.4, 573.8, 573.9). However, they may have potentially substantial misclassification rates because none of these codes are specific for NAFLD/NASH, with none of the studies reporting on efforts to validate codes against clinical data. Additionally, all the studies except for NHANES evaluated NASH/NAFLD/CC that was ascertained in the setting of clinical practice. The generalizability of these clinic-based findings to population or community-based NAFLD/NASH screening cohorts is unclear.

Cross-sectional and case-control studies have evaluated the association between NAFLD/NASH and HCC indirectly by concomitantly examining diabetes and obesity, primary features of the metabolic syndrome and also well-established NAFLD risk factors. Diabetes prevalence was uniformly greater in the NASH/NAFLD case-groups compared to their respective control groups with other types of chronic liver disease. Similarly, obesity prevalence was significantly greater in all NASH/NAFLD case groups. However, in addition to their inherent inability to establish temporality necessary to firmly establish causality, cross-sectional and case-control studies are also limited by the difficulty in ascertaining the exposure (histopathological features for confirmed NAFLD/NASH diagnosis) once cirrhosis is established. Moreover, these studies are limited by the possibility of reverse causality in the case of diabetes. Most of the studies that reported on obesity used BMI but provided no information on potentially more relevant parameters of obesity such as waist circumference, % body fat or visceral adiposity. Measurement and reporting on additional aspects of both insulin resistance and adiposity, including disease severity, duration and treatment may be useful in identifying sub-groups at particularly increased risk of progression to HCC in the background of NAFLD/NASH. Although qualified given the limited numbers of women with HCC in most studies, there was also a potentially suggestive finding regarding gender, with NAFLD/NASH-and cryptogenic-related HCC case groups often having an even greater preponderance of males than similar HCC case groups attributed to other causes of liver disease. Given women constitute a substantial proportion of NAFLD/NASH cases seen in the U.S.,[66] especially at older ages, this potentially particularly enhanced excess HCC risk among males with NAFLD/NASH bears further examination.

Additional indirect evidence suggestive of an association comes from multiple case-reports and case-series describing well-documented NAFLD/NASH patients who developed HCC. Although the prevalence of cirrhosis among HCC cases in case-control and cross-sectional studies was >70%, these studies nonetheless also suggest that a substantial minority of NAFLD/NASH-related HCC cases develop in the absence of clinically manifest cirrhosis. However, the interpretation of findings from these reports must be qualified because of the small number of cases.

This systematic review has several limitations. The search for PubMed indexed papers published in peer-reviewed journals in English may have missed some relevant papers in this area. However, we believe our comprehensive search strategy likely captured most published original research, while assuring a minimum standard of comparability and quality of reported data among studies thus enhancing our review's internal validity. We did not use quality scores to rate individual studies included this review as they can introduce bias of unknown dimensions when employed in systematic reviews and meta-analyses of observational studies.[67] Instead, we categorized studies based on meaningful differences in

design and explained the overall strengths and limitations of each design. We included studies that had HCC cases attributed to cryptogenic cirrhosis where other major causes of liver disease had been explicitly excluded as this is widely considered to most usually be associated with fatty liver disease. Many studies were based on results from routine clinical care and thus most did not have confirmatory biopsy data on their entire study sample. Therefore, it is possible that some NAFLD/NASH cohorts may have contained some nearly cirrhotic or well-compensated cirrhosis cases. We were not able to reliably or validly calculate annual or age- or gender-adjusted estimates of HCC incidence in multiple studies because adequate data was rarely provided (e.g., person-years at risk by gender or age-group and losses to follow-up). We were also unable to perform meta-analyses to obtain pooled estimators for incidence or prevalence rate of NAFLD/NASH-associated HCC as there were too few comparably conducted studies that reported similar effect measures. Finally, we did not evaluate survival differences between NAFLD-related HCC and other types of HCC, although some studies suggested that NAFLD-related HCC may be diagnosed later or at a more advanced stage.[24,26,35,37]

The currently available data do not support routine HCC surveillance among general cohorts of NAFLD or NASH patients who do not have cirrhosis. For the latter group, while the risk of HCC may be increased, this is only one aspect of an otherwise complicated progression that bears further examination from an epidemiologic as well as decision analytic perspective.

Our review has also identified several key gaps in current knowledge, including the lack of data on associations in ethnic minority populations including in Hispanics in whom NAFLD is disproportionately common,[68] and in African Americans in whom HCC risk incidence rates are higher and increasing more rapidly than in whites.[69] Additional research performed in substantially larger cohorts with longer follow-up is needed to identify risk factors that may be associated with progression to HCC in particular sub-groups of interest, including in the absence of clinically manifest cirrhosis.

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Abbreviations

HCC	hepatocellular carcinoma
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatosis
CC	cryptogenic cirrhosis
LD	liver disease

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Table 1

Study characteristics analytic epidemiology studies evaluating association between NAFLD, NASH or Cryptogenic cirrhosis presumptively NAFLD-related and HCC by study design.

1A. Cohort studies with a comparison group:

Population-based cohort studies with a comparison group

Reference	Author (Year)	Country	Timing	Population-based	Study Period	Primary data source	NAFLD/NASH/CC cohort definition	Control cohort definition	Matching	Biopsy-confirmation of NAFLD/NASH (timing)	Cirrhosis prevalence NAFLD/NASH cohort	Prevalence NAFLD/NASH in the source cohort	Follow-up period (years)
7	Sorensen H (1998)	Denmark	retro	Yes	1977–1989	Danish National Hospitalizations Registry	ICD code cirrhosis unspecified (C-U), survive at least 1 yr	ALD-C, HCV-C	No	NR	100%	21% of all C-U	5.5 yr M C-U, 5.9 y F C-U
9	Ong J(2008)	USA	pros	Yes	1988–2000	NHANES (cohort study)	NAFLD (elevated serum aminotransferases absent HCV, HBV, ALD, or elevated transferrin serology baseline)	Normal-non-OLD	No	NR	NR	6.4% of study eligible cohort without OLD	Median =8.7 yrs
8	Sanyal A (2010)	USA	retro	Yes	2002–2008	18 million persons in national insurance database	NAFLD (ICD codes)	HCV	No	NR	46% of HCC-NAFLD	prevalence NAFLD overall 4% (including NAFLD co-diagnosis other causes)	NR

Clinic-based cohort studies of cirrhosis possibly NASH-related with a comparison group

Reference	Author (Year)	Country	Timing	Population-based	Study Period	Primary data source	NAFLD-C/NASH-C/CC cohort definition	Control cirrhosis cohort definition	Matching	Biopsy-confirmation of NAFLD/NASH (timing)	Cirrhosis prevalence NAFLD/NASH/CC cohort	Prevalence NAFLD/NASH/CC in source cohort	Follow-up period (years)
10	Ratziu V (2002)	France	retro	No	1988–2000	single hospital (case registry)	CC (clinical exclude OLD)---divided into CC-O (overweight BMI>25 current + last 10 years), CC-L (lean, not overweight)	HCV-C	Yes (gender and age)	NR	100%	NR	3.4 yrs
11	Sanyal A (2006)	USA	pros	No	1992–2004	single medical center	NASH-C (clinical, laboratory suggest no OLD, biopsy-confirmed steatohepatitis)	HCV-C	Yes (age, sex, race)	100% (baseline or explant)	100%	NR	NR
12	Kojima H (2006)	Japan	retro	No	1990-NR	single medical center (inpatient registry)	CC (clinical, laboratory, and histopathology exclude OLD)	HCV-C	Yes (age, gender, Child-Pugh)	NR	100%	4.4% of cirrhosis CC-related	5.7 yrs CC, 6.5 yrs HCV-C, 6.4 HBV-C
13	Yatsuji S (2009)	Japan	retro	No	1990–2006	single medical center (NAFLD registry)	NASH-C (clinical, laboratory suggest no OLD, biopsy-confirmed steatohepatitis)	HCV-C	Yes (age and sex)	100% (NR)	100%	NR	3.4 yrs NASH-C, 6.25 yrs HCV-C
14	Ascha MS (2010)	USA	pros	No	2003–2007	single medical center (liver transplant registry)	NASH-C (histology and clinical or if cryptogenic and metabolic syndrome +, clinical/laboratory no OLD)	HCV-C	No	NR	100%	NR	3.2 yrs
15	Bhala A (2011)	UK, Italy, USA, Australia	pros	No	1984–2006	four medical centers-1 per country	NAFLD-CCA(F3–F4) (clinical, laboratory and/or radiology suggest no OLD, elevated aminotransferase>=6 months, patient & relative interview alcohol <20 g/day)	HCV-C	No	100% (NR)	52% cirrhosis, 48% F3 fibrosis	NR	7.5 yrs/6.3 yrs

Clinic-based cohort studies of NAFLD-NASH with a comparison cohort with other cause liver disease (OLD)

Reference	Author (Year)	Country	Timing	Population-based	Study Period	Primary data source	NAFLD/NASH cohort definition	Control cohort definition	Matching	Biopsy-confirmation of NAFLD/NASH (timing)	Cirrhosis prevalence NAFLD/NASH cohort	Prevalence NAFLD/NASH in source cohort	Follow-up period (years)
16	Soderberg C (2010)	Sweden	retro	No	1980–2008	single hospital (GI/ Hepatology unit)	NAFLD/NASH (liver biopsy, clinical and laboratory exclude OLD)	HCV and ALD	No	100% (NR)	4/67 (6%) among NAFLD, 5/51 (10%) NASH	46% patients persistent ALT elevation were NAFLD/NASH-related	21 yrs overall
17	Dam-Larsen S (2009)	Denmark	retro	No	1976–2004	single center (biopsy registry)	NAFLD (biopsy-proven fatty liver without inflammation or significant fibrosis, clinical and laboratory suggest no OLD)	ALD (biopsy-proven without significant fibrosis)	No	100% (baseline)	0%	NR	20.7 yrs NALFD, 12.8 yrs ALD

Clinic-based cohort studies of NAFLD-NASH with a comparison cohort with other cause liver disease (OLD)

Reference	Author (Year)	Country	Timing	Population-based	Study Period	Primary data source	NAFLD/NASH cohort definition	Control cohort definition	Matching	Biopsy-confirmation of NAFLD/NASH (timing)	Cirrhosis prevalence NAFLD/NASH cohort	Prevalence NAFLD/NASH in source cohort	Follow-up period (years)
18	Arase Y (2011)[^]	Japan	retro	No	1994–2007	single medical center (ultrasound case registry)	NAFLD/NASH (US diagnosis, clinical/ laboratory suggest no OLD, >=60 years old)	HCV(>=60 Yes (age, NR years old) sex, follow-up period)	Yes (age, sex, follow-up period)	NR	NR	NR	8.2 yrs/8.2 yrs

1B. Natural history cohort studies without a comparison erouo:

Reference	Author (Year)	Country	Timing	Population-based	Study Period	Primary data source	NAFLD/NASH cohort definition	Control cohort definition	Matching	Biopsy-confirmation of NAFLD/NASH (timing)	Cirrhosis prevalence NAFLD/NASH cohort	Prevalence NAFLD/NASH in source cohort	Follow-up period (years)
19	Matteoni C (1999)	USA	retro	No	1979–1987	single medical center (fatty liver case registry)	NAFLD (clinical/labs exclude OLD, biopsy-confirmed NAFLD)	NA	NA	100% (baseline)	4% type 1 (FL alone), 0% type 2 (FL+inflammation), 21% type 3 (FL+ballooning degeneration), 26% Type 4(FL+ballooning+Mallory hyaline or fibrosis)	NR	8.3 yrs
20	Adams LA (2005)	USA	pros	Yes	1980–2003	Rochester epidemiology project (cohort study)	NAFLD (diagnosis Mayo clinic, imaging or biopsy findings positive, clinical, laboratory, biopsy/imaging no OLD) or CC (if prior MS features)	NA	NA	NR	5% (2% baseline, 3% follow-up)	NR	7.6 years
21	Ekstedt M (2006)	Sweden	retro	No	1988–1993	single medical center(GI referral registry)	NAFLD/NASH (fatty infiltration in liver after persistent abnormal liver function test, no OLD per clinical criteria)	NA	NA	100% (baseline)	3.4% (baseline)	65% of patients referred abnormal LFTs	13.7 yrs
22	Hashimoto E (2009)	Japan	pros	No	1990–2007	single center (NAFLD registry)	NASH-Advanced Fibrosis(NASH-AdvF)- (biopsy-confirmed, restrict moderate/extensive fibrosis or cirrhosis, clinical/laboratory biopsy suggest no OLD)	NA	NA	100% (baseline)	100% advanced fibrosis or cirrhosis	NR	3.4 yrs
23	Kawamura Y (2011)[^]	Japan	retro	No	1997C2010	single medical center (case registry)	NAFLD/NASH (US diagnosis, clinical/laboratory suggest no OLD)	NA	NA	NR	NA	NR	5.6 yrs

1C. Case-control and cross-sectional studies:

Reference	Author (Year)	Country	Timing	Population-based	Study Period	Primary data source	NAFLD/NASH/CC exposed cohort definition	Compeer cohort definition	Matching	Biopsy-confirmation of NAFLD/NASH (timing)	Cirrhosis prevalence NAFLD/ NASH/CC exposed cohort	Prevalence NAFLD/ NASH/CC in source population
24	Marerro JA (2002)	USA	retro	No	2000–2002	single medical center (liver unit registry)	HCC-CC (clinical, laboratory, and US or biopsy suggest no OLD)	HCC-OLD	NO	20% (pre-HCC)	100% among subset n=6 with pre-HCC NASH+biopsy	29% (2nd most common)
25	Bugianesi E (2002)	Italy	retro	No	1990-NR	single medical center (liver unit registry)	HCC-CC (clinical, laboratory, US suggest no OLD)	HCC-OLD (HCC-ALD, HCC-HCV, HCC-HBV)	Yes (age, gender, dx time)	NR	NA	6.9% (5th most common)
26	Regimbeau JM (2004)	France	retro	No	1990–1999	single medical center (liver resection registry)	HCC-CC (clinical, laboratory, biopsy suggest no OLD; restrict moderate extensive/severe fibrosis or cirrhosis)	HCC-HBV/HCV & HCC-ALD	Yes (age, gender, degree fibrosis)	89% steatosis present (resection), 61% steatosis p>20% (resection)	NA	8.6% prevalence among 210 resected HCCs (5th most common)
27	Abe H (2008)	Japan	retro	No	2000–2006	single medical center(HCC case registry)	HCC-NASH (clinical and laboratory suggest no OLD, and US or biopsy suggest NAFLD and BMI>=25 past or present)	HCC-HBV/HCV & HCC-ALD	No	100% NAFLD per US or biopsy (NR)	90%	3.1% prevalence (4th most common)
38	Hashimoto E (2004)	Japan	retro	No	1989–2003	single medical center (HCC & NAFLD registry)	HCC-NASH (clinical, laboratory, US, biopsy suggest no OLD, biopsy-confirmed NASH with severe fibrosis or cirrhosis)	HCC-ALD	No	100% (NR)	88%	0.7% biopsy-proven from 1202 HCC cases
28	Paradis V (2009)	France	retro	No	1995–2007	single medical center(HCC resection registry)	MS (metabolic syndrome-at least 3 risk factors), clinical and laboratory exclusion OLD)	HCC-OLD, HCC-C	No	81% HCC-MS steatosis 5% + (resection)	36% F3–F4	24% of HCC resections

1C. Case-control and cross-sectional studies:

Reference	Author (Year)	Country	Timing	Population-based	Study Period	Primary data source	NAFLD/NASH/CC exposed cohort definition	Compeer cohort definition	Matching	Biopsy-confirmation of NAFLD/NASH (timing)	Cirrhosis prevalence NAFLD/ NASH/CC exposed cohort	Prevalence NAFLD/ NASH/CC in source population
39	Donadon V (2009)	Italy	retro	No	1994–2006	single medical center(HCC registry)	HCC-CC (criteria not specified other than exclude viral and alcoholism)	HCC-HCV, HCC-ALD, HCC-HBV	No	NR	NR	6% of HCC cases
29	Malik SM (2009)	USA	retro	No	1997–2008	single medical center (transplant case registry)	HCC-NASH-C (histopathology confirmation, OLD excluded clinical/ laboratory data)	NASH-C & HCC-OLD	No	100% (baseline or explant)	100%	0.83% all transplants study period
30	Sorrentino P (2009)	Italy	retro	No	1999–2007	single medical center (GI/ Hepatology case registry)	HCC-NASH-C (histopathology confirmation, OLD excluded clinical/ laboratory data)	NASH-C	Yes (age, gender, disease stage)	100% (baseline)	100%	NR
22	Hashimoto E (2009)	Japan	retro	No	1990–2007	single medical center (NAFLD registry)	HCC-NASH (clinical, laboratory, biopsy suggest no OLD, biopsy-confirmed NASH)	NASH	No	100% (baseline)	88% F3–F4	8.9% NAFLD prospective cohort develop HCC
8	Sanyal A (2010)	USA	retro	Yes	2002–2008	18 million persons in national insurance claims database (2002–2008)	HCC-NAFLD/NASH (ICD codes absent codes alcohol, HBV, HCV, at least 2 claims, 180 day washout period)	HCC-HCV	No	NR	46%	44% of HCC cases NAFLD/NASH either with/without diabetes and no HBV,ALD, HCV
32	Tokushige K (2010)	Japan	retro	No	1990–2007	single medical center (NAFLD & HCC case registry)	HCC-NASH (clinical, laboratory, US or biopsy suggest no OLD, biopsy-confirmed NASH)	HCC-HCV	Yes (age, gender)	100% (32% pre-HCC)	71%	8.2% of all NAFLD cases seen had HCC
31	Ertle J (2010)	Germany	retro	No	2007–2008	single GI/hepatology clinic (HCC registry)	HCC-NASH (clinical suggest no OLD, histology confirmed) or HCC-CC-MS (clinical suggest no OLD and metabolic syndrome)	HCC-HBV, HCC-HCV, HCC-OLD, HCC-ALD	No	100% HCC-NASH (NR) and 0% HCC-C-MS	53% HCC-NASH, 39% HCC-C-MS	24% HCC NASH (2nd most common), 15% HCC-C-MS (4th most common)
33	Cho EJ (2011)	Korea	retro	No	2001˜2010	single medical center (HCC registry)	HCC-NAFLD(US or CT suggest FLD, laboratory, clinical suggest no OLD including HBVcore− as well antibody negative)	HCC-anti-HBVcore+, IgG+ (HCC-HBVprior), HCC-U (unknown, HBVcore-, NAFLD-US or CT)	NO	NR	80% cases and controls combined	3.8% 2001–2005, 12.2% 2006–2010 HCC-NAFLD HBVcore−, 4.5% 2001–2005 11.6% HCC-NAFLD HBVcore+
37	Wakai T (2011)	Japan	retro	No	1990–2007	single medical center (HCC resection registry)	HCC-NAFLD (clinical, laboratory, biopsy suggest no OLD, biopsy confirmed hepatic steatosis)	HCC-HCV and HCC-HBV	No	100% (baseline or explant)	75%	5.5% of HCC resections
34	Tokushige K (2011)	Japan	retro	Yes	2009	nationwide survey of 115 hospitals	HCC-NAFLD (biopsy or imaging suggest steatosis, exclude alcohol >20 g day, exclusion OLD)	HCC-ALD and HCC-U	No	NR	62%/78% HCC-ALD/52% HCC-U	2%
35	Takuma Y (2011)	Japan	retro	No	1992–2009	2 hospitals (HCC registry)	HCC-CC (clinical, laboratory suggest no OLD, eligible curative therapy)	HCC-HCV (interferon naive)	No	NR	NA	7.8% of HCC cases eligible curative therapy and meeting Milan criteria
36	Yang JD (2011)	USA	retro	No	2007–2009	single medical center (digestive disease center--members of HCC BRIDGE study)	HCC-NAFLD (previous clinical dx (clinical, laboratory, US/biopsy suggest FLD age>60)	HCC-OLD, age >60 yrs & HCC-U, age>60	No	NR	NR	5% HCC <60, 19% HCC > age 60 (3rd most common)

LEGEND FOR TABLE 1 (1A–1C):

Abbreviations:, ALD, alcohol-related liver disease; C, cirrhosis; CC, cryptogenic cirrhosis; CLD, chronic liver disease known cause; F, female; FLD, fatty liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; M, male; MS, metabolic syndrome; NA, not applicable; NR, not reported; OLD, other liver disease cause; pros, prospective; retro, retrospective; SIR, standardized incidence rate ratio; U, unknown, US, ultrasound.

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Table 2

Sociodemographic and clinical characteristics and outcomes in analytic epidemiology studies evaluating association between NAFLD, NASH or Cryptogenic cirrhosis presumptively NAFLD-related and HCC by study design.

2A. Cohort studies with a comparison group:

Population-based cohort studies with a comparison group

Ref	Author (year)	# NAFLD/NASH/CC cohort	# compeer cohort	Age NASH/NAFLD cohort/compeer cohort	Race/Ethnicity % NAFLD/NAS H cohort/Compeer cohort	Gender % NASH/ NAFLD cohort/ compeer cohort	Diabetes % NASH/ NAFLD cohort/compeer cohort (p-value)	Obesity % NASH/NAFLD cohort/compeer cohort (p-value)	Hypertension % NASH/ NAFLD cohort/compeer cohort (p-value)	Dyslipidemia % NASH/NAFLD cohort/compeer cohort (p-ualue)	HCC incidence NASH/ NAFLD cohort/compeer cohort	HCC mortality NASH/NAFLD cohort/compeer cohort
7	Sorensen H (1998)	1,210 M C-U, 1,220 F C-U	7,165 ALD-C, 1690 HCV-C	58 M and 62 F C-U/52 M 53 M ALD-C , 43 M and 55 F HCV-C	NR	50% M/42% M HCV-C , 71 % M ALD-C	NR (NA)	NR (NA)	NR (NA)	NR (NA)	1.9% cumulative incidence among C-U, 1.1% HCV-C, 2.0% ALD-C, SIR Danish population ---43 C-U, 43 HCV-C, 71 ALD-C	NR
9	Ong J (2008)	817 NAFLD	10,468 Normal (no OLD)	50.4% <40 NAFLD/ 47.6% <40 Normal-NoOLD	72% W/79% W	45% F/54% F	12%/6% (p<0.0001)	BMI 30+ 40%/ 22% (p<0.0001)	33%/23% (p<0.0001)	NR (NA)	NR	0%/0% cumulative mortality
8	Sanyal A (2010)	729,018 NAFLD	154,386 HCV	HCC cases overall mean 64 years (NR by subgroup)	NR	66% M HCC cases overall (NR by subgroup)	NR (NA)	NR (NA)	NR (NA)	NR (NA)	cumulative incidence 0.3% HCC with NAFLD (with HCV, HBV, ALD excluded) vs. 0.6% incidence HCV during 6 yrs study period (2002–2008); NAFLD/NASH without HCV, HBV, ALD leading risk factor account 39% cases	NR

Clinic-based cohort studies of Cirrhosis possibly NASH-related

Ref	Author (year)	# NAFLD/NASH/CC cohort	# compeer cohort	Age NASH/ NAFLD cohort/ compeer cohort (years)	Race/Ethnicity % NAFLD/NAS H cohort/Compeer cohort	Gender % NASH/NAFLD cohort/compeer cohort	Diabetes % NASH/ NAFLD cohort/compeer cohort (p-value)	Obesity % NASH/NAFLD cohort/compeer cohort (p-value)	Hypertension % NASH/ NAFLD cohort/compeer cohort (p-value)	Dyslipidemia % NASH/NAFLD cohort compeer cohort (p-value)	HCC incidence NASH/NAFLD cohort compeer cohort	HCC mortality NASH/NAFLD cohort / compeer cohort
10	Ratziu V (2002)	27 CC-O, 10 CC-L	117 HCV-C-O,148 HCV-C-L	62 CC-O, 45 CC-L/54 HCV-C-O and 54 HCV-C-O	NR	Ratio M:F: 1.7 CC-O, 0.7 CC-L/ 1.7 HCV-C-O and 1.7 HCV-C-L	88% CC-O, 20% CC-L/ 39% HCV-C-O and 27% HCV-C-L (p<0.001 CC-O vs. HCV-C-O, CC-L VS. HCV-C-L, NS)	BMI: 30.9 CC-O vs. 28.9 HCV-C-O, 22.6 CC-L vs. 22 HCV-C-L	NR (NA)	Hitrigly---56% CC-O, 13% CC-L/26% HCV-C-O 17% HCV-C-L (<0.001 CC-O vs. HCV-C-O, CC-L vs. HCV-C-L, NS)	29.6% cumulative incidence in CC-O over 1.8 yrs, 0% CC-L over 3.8 yrs/ 9.4% HCV-C-O over 2.3 yrs and 19.6% HCV-C-L over 2.5 yrs	NR
11	Sanyal A (2006)	74 Child Class A (CCA), 43 Child Class B (CCB), 35 Child Class C (CCC) NASH-C	75 CCA HCV, 42 CCB HCV, 32 CCC HCV	55/57 CCA, 43/42 yrs CCB B, 60/69 yrs CCC	96% White/95% White	49% M/49% M	53% CCA, 65% CCB, 63% CCC NASH-C/40% CCA HCV-C, 48% CCB HCV-C, 50% CCC HCV-C (p=0.01)	BMI=33.6 CCA, 34.1 CCB, 34.2 CCC NASH-C/28.3 CCA HCV-C, 30.3 CCB, 29.7 CCC HCV-C (p=0.05)	47% CCA, 70% CCB, 23% CCC NASH-C/37% CCA, 36% CCB, 14% CCC HCV-C (0.004)	Trigly---210 CCA, 199 CCB, 172 CCC NASH-C/176 CCA, 145 CCB, 110 CCC HCV-C, Chol---210 CCA, 199 CCB, 172 CCC NASH-C/196 CCA, 165 CCB, 128 CCC HCV-C (p=0.003 Trigly, p=0.03, Chol)	NR	Cumulative 10 yr HCC mortality 10 NASH-C 2 of 29 deaths vs. 8 of 44 deaths HCV-C, 25 yr HCC mortality 10 of 149 deaths vs. 25 of 147 HCV-C, p<0.01
12	Kojima H (2006)	24 CC	48 HCV-C, 24 HBV-C	58 (/59) and 58	NR	52% M/62% M HCV-C and 76% HBV-C	54%/35% and 13% (NS, p=0.01)	17%/2% and 0% (p<0.01 both comparisons)	25%/19% and 13% (NS)	Htrigly-21%/2% and 13% (p<0.01 and NS)	9 of 24 CC (38% cumulative incidence over 5.7 yrs)vs. 74%HCC in HCV-HBV combined	NR

Clinic-based cohort studies of Cirrhosis possibly NASH-related

Ref	Author (year)	# NAFLD/NASH/CC cohort	# compeer cohort	Age NASH/ NAFLD cohort/ compeer cohort (years)	Race/Ethnicity % NAFLD/NAS H cohort/Compeer cohort	Gender % NASH/NAFLD cohort/compeer cohort	Diabetes % NASH/ NAFLD cohort/compeer cohort (p-value)	Obesity % NASH/NAFLD cohort/compeer cohort (p-value)	Hypertension % NASH/ NAFLD cohort/compeer cohort (p-value)	Dyslipidemia % NASH/NAFLD cohort compeer cohort (p-value)	HCC incidence NASH/NAFLD cohort compeer cohort	HCC mortality NASH/NAFLD cohort / compeer cohort
											cumulative incidence over 5.9 yrs	
13	Yatsuji S (2009)	68 NASH-C	69 HCV-C	63/61	NR	57% F/57% F	68%/33% (p>0.001)	OB (BMI >=25) 66%/32% (p>0.001)	47%/43% (NS)	Hyperlip-- 68%/33% (p<0.004)	5-yr HCC cumulative incidence rate 11.3%/30.5%, (p=0.185)^^^	HCC leading cause death both groups (47% all deaths NASH-C vs. 68% deaths HCV-C) ^^^
14	Ascha MS (2010)	195 NASH-C	315 HCV-C	57/48 yrs	96% W/77% W	44% M/77% M	73%/33% (p=0.001)	BMI 34.6/28.3 (p<0.001)	Diastolic 64/71 (p<0.001)	NR (NA)	Cumulative incidence 12.8% NASH-C vs. 20.3% HCV-C p=0.03, yearly incidence 2.6% vs. 4.0%, p=0.09	NR
15	Bhala A (2011)	247 NAFLD-CCA (F3-F4)	264 HCV-F3-F4	55 yrs/48 HCV-F3-F4 fibrosis	92%W/72% W	60% F/35% F	51%/17% (p<0.001)	BMI 32.8/27.3 (p<0.001)	NR (NA)	Trigly (mmol/L) 2.2/1.3 Chol (mmol/L) 5.2/4.2 (p<0.001 both)	6 (2.4%) HCC cumulative incidence over 7.1 yrs/18 (6.8%) HCV-F3-F4 during 6.2 yrs	NR

Clinic-based cohort studies of NAFLD-NASH

Ref	Author (year)	# NAFLD/NASH/CC cohort	# compeer cohort	Age NASH/ NAFLD cohort/ compeer cohort	Race/Ethnicity % NAFLD/NAS H cohort/compeer cohort	Gender % NASH/ NAFLD cohort/compeer cohort	Diabetes % NASH/ NAFLD cohort/ compeer cohort (p-value)	Obesity % NASH/ NAFLD cohort/ compeer cohort (p-value)	Hypertension % NASH/NAFLD cohort/compeer cohort (p-value)	Dyslipidemia % NASH/ NAFLD cohort/compeer cohort (p-value)	HCC incidence NASH/NAFLD cohort/compeer cohort	HCC mortality NASH/NAFLD cohort/compeer cohort
16	Soderberg C (2010)	118 NAFLD/NASH (67 NAFLD, 51 NASH)	30 HCV, 10 ALD	NR	NR	71% M NAFLD, 51% M NASH/ALD, 47% M HCV	NR (NA)	NR (NA)	NR (NA)	NR (NA)	NR	Cumulative HCC mortality 3% NAFLD, 6% NASH/8% ALD and 7% HCV over mean 21 yr follow-up period
17	Dam-Larsen S (2009)	170 NAFLD	247 ALD (biopsy-proven w/o significant fibrosis)	mean baseline: 40 NAFLD, 50 ALD	NR	28% M/74% M/ALD	6%/4% ALD (NR)	69%/20% (NR)	NR (NA)	NR (NA)	NR	0% NAFLD, 1% ALD cumulative HCC mortality during 20.0 and 21.0 yrs follow-up
18	AraseY (2011)^^^^	1,600 NAFLD/NASH	1,600 HCV (age>=60)	62.5/62.6	100% Japanese/100% Japanese	75% M/75% M	34% DM or pre-DM/ 28% DM or pre-DM (p<0.001)	BMI 25.1 (2.6)/21.8 (4.0) (<0.001)	17%/19% (NS)	Trigly--161/99 (p<0.001)	10 (6% cumulative) HCC incidence or 0.78 per 1000 py rate, 0.83/1000 py M, 0.63/1000 py F/267 (67.9% cumulative HCC with HCV) 20.86 per 1000 py rate 23.75/1000 py M, 10.83/1000 py F HCV)	NR

2B. Natural history cohort studies without a comparison eroup:

Ref	Author (year)	# NAFLD/NASH/CC cohort	# compeer cohort	Age NASH/NAFLD cohort	Race/Ethnicity % NAFLD/NASH cohort	Gender % NASH/ NAFLD cohort	Diabetes % NASH/ NAFLD cohort (p-value)	Obesity % NASH/ NAFLD cohort (p-value)	Hypertension % NASH/NAFLD cohort (p-value)	Dyslipidemia % NASH/NAFLD cohort (p-value)	HCC incidence NASH/NAFLD cohort	HCC mortality NASH/ NAFLD cohort
19	Matteoni C (1999)	49 Type 1 (FL alone), 10 Type 2 (FL +inflammation), 19 Type 3 (FL and ballooning degeneration), 54 Type 4 (FL, ballooning, and Mallory hyaline or fibrosis)	NA	53 (15) type 1, 46 (12) type 2, 49 (15) Type 3, 56 (11) Type 4	92% W Type 1, 90% W Type 2, 84% Type 3, 83% Type 4	59% M Type 1, 40% Type 2, 68% Type 3, 33% Type 4	39% Type 1/60% Type 2/50% Type 3/54% Type 4 (NS across subtypes)	BMI 29 Type 1, 32 Type 2, 30 Type 3, 29 Type 4 (NS across subtypes)	NR (NA)	NR (NA)	NR	1 of 45 with cause death (cumulative 8 year HCC mortality 1.0%, account 2.2% all deaths)-follow-up restricted to 98 outcome data
20	Adams LA (2005)	433 NAFLD, 2 CC-MS	NA	49 (15) yrs	92% W	49% M	26% (NA)	71% (NA)	36% (NA)	Hitrigly-68% (NA)	0.47% cumulative HCC incidence	0.25% cumulative HCC mortality (2% of all deaths) over 7.6 yr period
21	Ekstedt M (2006)	81 NAFLD/NASH	NA	51 (13), yrs	NR	70% M	42% (NA)	33% (NA)	94% (NA)	Htrigly-40% (NA)	NR	2 HCC deaths---2.3% cumulative mortality over 13.7 yr period
22	Hashimoto E (2009)	118 NASH-AdvFib (HCC free at baseline)	NA	50 yrs (*population 348 NASH cases from which 118 cases drawn, no specific data 118)	100% Japanese	59% F (*population 348 NASH cases from which 118 cases drawn, no specific data 118)	43% (*population 348 NASH cases from which 118 cases drawn, no specific data 118) (NA)	69% (*population 348 NASH cases from which 118 cases drawn, no specific data 118) (NA)	33% (*population 348 NASH cases from which 118 cases drawn, no specific data 118) (NA)	Hyperlip - 62%^^^ (NA)	5-yr cumulative HCC incidence 7.6%	NR
23	Kawamura Y (2011)^^^^	6,508 NAFLD/NASH	NA	49 (23–86)	NR	88% M	8% (NA)	BMI 24.8 (NA)	13% (NA)	Htrygly--138, Total chol 210 (NA)	16 HCC incidence (0.25%) cumulative rate 0.02% end yr 4, 0.19 end yr 8, 0.51 end year 12, annual incidence 0.043%	NR

2C. Case-control and cross-sectional studies:

Ref	Author (year)	# HCC-NAFLD/NASH/CC cases	# controls	Age cases/controls	Race/Ethnicity % case/controls	Gender % case/controls	Diabetes % case/controls (p-value)	Obesity % case/controls (p-value)	Hypertension % case/ controls (p-value)	Dyslipidemia % case/controls (p-value)
24	Marerro JA (2002)	30 HCC-CC	75 HCC-OLD	57 (16) yrs/62 (13) yrs	90% White/72% White	60% F/28% F	47%/8% (p=0.006)	58%/25% BMI>30 (p=0.02)	NR (NA)	Htrigly---16%/2%; Hchol---13%/ 2% (p=0.001, p=0.7)
25	Bugianesi E (2002)	23 HCC-CC	115 (HCC-OLD)---23 HCC-ALD, 46 HCC-HBV, 46 HCV-HCC	66/63 HCC-OLD---62 (8) HCC-ALD, 58 (9) HCC-HBV, and 67 (8) HCC-HCV	100% White/100% White HCC-OLD	17% F/19% F HCC-OLD	52%/20% HCC-OLD---39% HCC-ALD, 11% HCC-HBV, 20% HCC-HCV (<0.05 HCC-OLD, HCC-HBV, HCC-HCV---NS HCC-ALD)	41%/16% HCC-OLD pre-cirrhosis obesity; 39%/50% pre-cirrhosis overweight (p=0.009 obesity, NS overweight)	22%/15% HCC-OLD--0% HCC-ALD, 7% HCC-HBV, 30% HCC-HCV (NS for all)	Hchol---43%/12% HCC-OLD---17% HCCALD, 11% HCC-HBV, 9% HCCHCV Htrigly---26%/3% HCC-OLD---4% HCVALD, 2% HCC-HBV, 2% HCCHCV (p<0.01 all)
26	Regimbeau JM (2004)	18 HCC-CC	HCC-ALD=36, HCC-HBV/HC V=36	66 yrs/NR HCC-HCV/HB V or HCC-ALD	NR	100% M/100% M	56%/17% HCC-ALD & 11% HCC-HBV/HC V(0.004 HCC-ALD, 0.009 HCC-HBV/HCV)	50%/17% HCC-ALD/14% HCC-HBV/HCV (p=0.01 HCC-ALD, p=0.006 HCC-HBV/HCV)	NR (NA)	Hchol--38%/14% HCC-ALD & 17% HCC-HBV/HCV (p=0.04 HCC-ALD, NS HCC-HBV/ HCV)
27	Hashimoto E (2004)	8 HCC-NASH	50 HCC-ALD	65 yrs/68 yrs	NR	37% M/94% M	63%/43% (NS)	63%/25% BMI>25 (NS)	50%/22% (NR)	Hyplip--25%/10% (NS)
38	Abe H (2008)	10 HCC-NASH	HCC-ALD=45, HCC-HBV/HC V=256, HCC-U=7	median: 71 yrs/69 yrs HCC-ALD/68 HCC-HBV/HC V/65 HCC-U	NR	30% M/93% M HCC-ALD/71% M HCC-HBV/ HCV/71% M HCC-U	80%/44% HCC-ALD & 31% HCC-HBV/HCV & 14% HCC-U (0.08 HCC-ALD, <0.05 HCC-U, <0.01 HCC-HCV/HBV)	60%/13% HCC-ALD/9% HCC-HBV/HCV/0% HCC-U for BMI>25, Asian standard OB <0.01 (both HCC-ALD & HCC-HCV/HBV), p<0.05 HCC-U)	NR (NA)	NR (NA)
28	Sanyal A (2010)	3,562 HCC-NAFLD/NASH	458 HCC-HCV	HCC cases overall mean 64 years (NR by subgroup)	NR	66% M HCC cases overall (NR by subgroup)	37%/20% (NR)	NR (NA)	NR (NA)	NR (NA)
39	Paradis V (2009)	31 HCC-MS(3+ signs)	81 HCC-CLD, 16 HCC-Cryp	67 HC-CMS, 59 HCC-CLD, 53 HCC-Cryp	100% White HCC-MS, NR (HCC-CLD and HCC-Cryp	97% M HCC-MS, 93% HCC-CLD, 81% HCC-Cryp	77%/12 % HCC-CLD and 0% HCC-Cryp (p<0.0001)	48%/12% HCC-CLD and 6% HCC-Cryp (p<0.001)	84%/18% HCC-CLD and 12.5% HCC-Cryp (p<0.001)	Dyslip-84%/18% HCC-CLD and 13% HCC-Cryp (p<0.001)

2C. Case-control and cross-sectional studies:

Ref	Author (year)	# HCC-NAFLD/NASH/CC cases	# controls	Age cases/controls	Race/Ethnicity % case/controls	Gender % case/controls	Diabetes % case/controls (p-value)	Obesity % case/controls (p-value)	Hypertension % case/ controls (p-value)	Dyslipidemia % case/controls (p-value)
29	Donadon V (2009)	27 HCC-CC	HCC-HCV 177, HCC-ALD 141, HCC-HBV 20	69/72 HCC-HCV,63 (HCC-HBV, 67 HCC-ALD	NR	NR	70%/27% HCC-HCV, 37% HCC-ALD, 15% HCC-HBV (p<0.00 1 vs. HCC-HCV, and p<0.002 HCC-ALD)	NR(NA)	NR (NA)	NR (NA)
30	Malik SM (2009)	17 HCC-NASH-C	430 HCC-NonNASH 7 81 NASH-C	59 NASH/63 NASH-HCC/57 HCC-NonNASH	98% White NASH/94% NASH-HCC W/7% Black HCC-NonNASH 0% Black HCC-NASH	71% M/40% M NASH/ 79% M HCC-NonNASH	73% NASH/71% NASH-HCC/ 21 % HCC-NonNASH (NS for NASH-C vs. HCC-NASH, p<0.000 1 HCC-NASH vs. HCC-NonNASH)	61% NASH/71% NASH-HCC BMI>=30/27% HCC-NonNASH (NS vs. NASH-C, p<0.0001 vs. HCC-NonNASH)	51% NASH-C/47% NASH-HCC/20% HCC-NonNASH (NS vs. NASH-C, p=0.01 vs. HCC-NonNASH)	NR (NA)
22	Sorrentino P (2009)	51 HCC-NASH-C	102 NAMSH-C	68/66 NASH-C	100% White	76% M/76% M	86%/52% NASH-C (p=0.02)	BMI 31.8/29.9 NASH-C (NS)	29%/22% NASH-C (NS)	NR (NA)
8	Hashimoto E (2009)	34 HCC-NASH	348 NASH	70/50 yrs	100% Japanese	38% F/59% F	74%/43% (p=0.002)	62%/69% (NS)	47%/33% (NS)	Hyplip 29%/62% (p=0.001)
32	Ertle J (2010)	36 HCC-NASH & 23 HCC-C, MS	35 HCC-HCV, 29 HCC-HBV, 19 HCC-ALD, 8 HCC-OLD	69 HCC-NASH & 68) HCC-C-MS/60 HCC-HBV, 64 HCC-HCV, 66 HCC-ALD, 60 HCC-OLD	97% W HCC-NASH & 100% W HCC-C-MS/ 55% HCC-HBV, 77% HCC-HCV, 89% HCC-ALD, 88% HCC-OLD	89% HCC-NASH and 78% HCC-C-MS Male/ 83% HCC-HBV, 77% HCC-HCV, 89% HCC-ALD, 88% HCC-OLD Male	64% NASH and 22% HCC-C-MS/35%, 29%, 58%, 25% (NR)	BMI 29 HCC-NASH & 24 HCC-C-MS/27, 25, 28, 27 (NR)	NR (NA)	NR (NA)
31	Tokushige K (2010)	34 HCC-NASH	56 HCC-HCV	70/72 yrs	NR	62% M/59% M	74%/23% HCC-HCV (p<0.001)	(BMI>=25) 65%/34% (0.004)	41%/30% (NS)	Hyplip-29%/8% (p=0.008)
33	Cho EJ (2011)	54 HCC-NAFLD (27 HBVcore−, 27 HBVcore+, none HBVsAg+ or IgG+)	252 HCC-HBVprior, 23 HCC-U	67 HCC-NAFLD (HBVc−), 64 HCC-NAFLD (HBVC+, prior), 61 (HCC-HBVc+Ig G +,62 HCC-U	100% Korean	76% M overall (NR case/ control status)	69%/24% HCC-HBVprior, 26% HCC-U (p<0.001, p<0.05)	63%/26% HCC-HBVprior, 27% HCC-U (<0.001, <0.05)	NR (NA)	NR (NA)
37	Tokushige K (2011)	292 HCC-NAFLD	991 HCC-ALD and 614 HCC-U	72/68 HCC-ALD/73 HCC-U	NR	38% F/4% HCC-ALD F/ 37% HCC-U F	70%/49% HCC-ALD/43% HCC-U (p<0.001)	27%/24% HCC-ALD/24% HCC-U BMI>25 (p<0.001)	60%/43%/46% (p<0.001)	Hyplip-35%/14%/15% (p<0.001)
34	Takuma Y (2011)	36 HCC-CC	211 HCC-HCV (interfer on naïve)	74/70	NR	56% M/64% M	53%/30% (p=0.01)	56%/18% OB (p<0.001)	47%/46% (NS)	Hylip-17%/4% (p=0.01)
35	Yang JD (2011)	52 HCC-NAFLD	139 HCC-OLD and 77 HCC-U	100% > 60	83% White overall	NR	80%/37% HCC-OLD/35% HCC-U (p=0.88)	mean BMI (SD)=34 (5.5) vs 28 (5.0) HCC-OLD vs 29 (5.9) HCC-U (0.24)	72%/51% HCC-OLD/ 61% HCC-U (p=0.20)	NR (NA)
36	Wakai T (2011)	17 HCC-NAFLD	147 HCC-HCV and 61 HCC-HBV	>65yrs = 76%/57% HCC-HCV and 23% HCC-HBV	100% Japanese	41% F/27% F HCC-HCV and 30% F HCC-HBV	NR (NA)	BMI>=25 41%/16% HCC-HCV and 20% HCC-HBV (<0.001)	NR (NA)	NR (NA)

LEGEND FOR TABLE 2 (2A-2C):

Abbreviations:, ALD, alcohol-related liver disease; C, cirrhosis; CC, cryptogenic cirrhosis; Chol, cholesterol; CLD, chronic liver disease known cause; Cryp, cryptogenic; DYS, dyslipidemia; F, female; FL, fatty liver; hepatitis B virus, HBV; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; HypChol, hypercholesteremia; HypTrigl, hypertriglycedemia; M, male; MS, metabolic syndrome; NA, not applicable; NR, not reported; NS, not statistically significant; OLD, other liver disease cause; OV, overweight; pros, prospective; retro, retrospective; Trigly, Triglyceride; U, unknown cause.

^ % obesity unless otherwise specified;

^^ 21 concomitantly diagnosed HCC at baseline not included HCC incidence calculations;

^^^ population 348 NASH cases from which 118 cases drawn, no specific data 118;

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