Incidence and Determinants of Hepatocellular Carcinoma in Autoimmune Hepatitis: A Systematic Review and Meta-Analysis

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Abstract

Background—The risk of hepatocellular carcinoma (HCC) in patients with autoimmune hepatitis (AIH) is unclear. We conducted a systematic review and meta-analysis of the incidence of HCC and associated risk factors among patients with AIH.

Methods—We searched PubMed, Embase, and reference lists from relevant articles through June 2016 to identify cohort studies that examined the incidence of HCC in patients with AIH. We used

random effects models to estimate pooled incidence rates overall and in subgroup of patients with cirrhosis. The between-study heterogeneity was assessed using I^2 statistic.

Results—A total of 25 studies (20 papers and 5 abstracts) including 6,528 patients met the eligibility criteria. The median cohort size was 170 AIH patients (range 25–1721 patients) followed for a median of 8.0 years (range 3.3–16.0 years). The pooled incidence rate for HCC in patients with AIH was 3.06 per 1,000 patient-years (95% CI 2.22–4.23, I^2 51.5%, p 0.002). The pooled incidence of HCC in patients with cirrhosis at AIH diagnosis was 10.07 per 1,000 patient-years (95% CI 6.89–14.70, I^2 48.8%, p 0.015). In addition, 92 of 93 patients that had HCC had evidence of cirrhosis prior to or at time of HCC diagnosis. The risk of HCC appears to be lower in patients with AIH cirrhosis compared to that reported in patients with hepatitis B cirrhosis, hepatitis C cirrhosis, and primary biliary cholangitis.

Conclusions—Based on elevated HCC risk shown in this meta-analysis, there may be a role for HCC surveillance in patients with AIH cirrhosis.

Keywords

hepatocellular carcinoma; autoimmune hepatitis; systematic review; meta-analysis

Introduction

Autoimmune hepatitis (AIH) occurs globally and is characterized by interface hepatitis, hypergammaglobulinemia, and autoantibodies. [1–7] Clinical manifestations of AIH range from no symptoms to severe acute hepatitis, and rarely fulminant hepatic failure. [5,8] Approximately one third of patients with AIH have evidence of cirrhosis at the time of initial diagnosis. [3,4] Additionally, patients with AIH progress to cirrhosis at variable rates (ranging from 0.1 to 8.1% annually) despite treatment with immunosuppressive therapies. [9–12]

In the United States, the combination of rising incidence of hepatocellular carcinoma (HCC) in both men and women and a low 5-year survival rate has made HCC the fastest growing cause of cancer-related death. [13,14,15] The American Association for the Study of Liver Diseases (AASLD) guidelines recommends HCC surveillance of high-risk patient groups (defined as those with an annual HCC risk of 1.5% or higher).[16] Cirrhosis is a known precursor for HCC in over 80–90% of cases.[13] AIH with cirrhosis has been associated with an increase in HCC risk; however, estimates of HCC risk among patients with AIH in cohort studies have varied widely.[17–20] The European Association for the Study of Liver Diseases guidelines for autoimmune hepatitis recommend HCC screening in patients with underlying cirrhosis.[21] However, AASLD guidelines while acknowledging HCC risk may be present make no recommendation for surveillance for patients with AIH cirrhosis per AASLD guidelines.[16]

There has not been a systematic effort to consolidate and critically evaluate the evidence regarding the risk of HCC in AIH patients. Furthermore, studies have reported different and inconsistent findings of determinants other than cirrhosis in increasing the risk for HCC. [19] We performed a systematic review and meta-analysis to estimate the incidence of HCC in

patients with AIH, and to examine demographic, clinical, biochemical, and treatment-related factors associated with HCC risk in AIH.

Methods

We performed the study in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) guidelines and MOOSE guidelines with an *a priori* study protocol. [22,23]

Search strategy

We searched PubMed and Embase databases from inception up to June 2016 for original research studies regardless of language or design using a combination of MESH and free text terms for AIH and liver cancer (search strategy in Appendix Table 1). Additionally, we manually searched reference lists of relevant articles for further studies.

Study selection

Two investigators (AT and LK) independently determined study eligibility and any disagreements were resolved after discussion with a senior investigator (FK). Studies were eligible for inclusion if they fulfilled the following criteria: (1) cohort study design (prospective or retrospective), (2) study population included at least 20 patients with AIH, (3) provided incidence rate of HCC or sufficient raw data to calculate incidence rates, and (4) AIH patients did not have additional etiologies for liver disease (e.g., hepatitis B, hepatitis C). If multiple articles were published using the same cohort, we used the study with the most complete data on the largest number of patients.

Data extraction and study quality assessment

Two independent reviewers (AT and LK) used standardized data collection forms to extract the following from each study: publication date, authors, country where the study was performed, follow-up years, number of participants, study design, sample size, mean age, sex, methods and intervals for HCC screening if performed, methods used for diagnosing AIH and HCC, liver disease severity or cirrhosis at AIH diagnosis and at the time of HCC diagnosis (if available), and risk factors associated with HCC. We classified patients as subjects with cirrhosis based on authors' definition (of cirrhosis) or histology with stage 3 or 4 fibrosis. Further classification of decompensated cirrhosis (ascites, variceal bleeding, or hepatic encephalopathy) was recorded when available. Any data discrepancy was resolved by referring back to the original studies. Authors of studies were contacted for further clarification when necessary.

Two investigators (AT and LK) independently determined study eligibility and assessed quality with a modified version of the Newcastle-Ottawa quality assessment scale in three main areas: (1) selection process of cohorts, (2) similarity and comparability between cohorts, and (3) ascertainment of the outcome of interest. Disagreements were resolved with a third investigator (FK).

Statistical methods

For each study, we recorded or calculated incidence rates of HCC per 1,000 person-years with 95% confidence intervals (CI) based on the event rates in relation to the duration of follow up. We calculated pooled incidence rates and 95% CI using a Poisson distribution. Meta-analysis models were conducted using the log incidence rates of HCC and corresponding CIs with a random effects model. We assessed the between-study heterogeneity using I^2 statistic, and used I^2 values of 25%, 50% and 75% as evidence of low, moderate, or high levels of heterogeneity, respectively. We used a correction factor of 0.5 for both the number of HCC cases and total person-years of follow-up in instances when HCC counts were zero.[24] We assessed for publication bias with the funnel plot, Begg's test, and Egger's test.

We conducted subgroup analyses based on presence of cirrhosis, sex, continent, and source population (i.e., single center, multiple centers, general population). We conducted sensitivity analyses by excluding low quality studies and abstracts, studies with zero HCC cases, and retrospective studies.

We conducted statistical analyses with Stata, version 13.1 (StataCorp, College Station, Texas, US). Tests were two tailed and p values <0.05 were considered significant.

Results

Our search strategy identified 811 articles. Of these, 59 were retrieved for detailed evaluation.

We identified 15 articles that used data from 5 cohorts (1 abstract and 2 papers from a cohort in Sweden;[11,25,26] 1 abstract and 2 papers from a cohort in Japan;[27,28] 2 papers from a cohort in the UK;[19,29] 1 abstract and 1 paper from a different cohort in the UK;[30,31] and 4 papers from a cohort in the US).[17,32–34] In each instance, we used the most recent paper that met criteria for inclusion in our analysis; these studies reported the most complete data on the largest number of patients from each cohort.[9,15,17,11,28]

A total of 25 studies, involving 6,425 patients with AIH, met our selection criteria and were included in the meta-analysis (between reviewer kappa=0.92). A total of 20 studies were published as full papers and 5 were reported only as abstracts (Figure 1). Of the 25 studies, five were performed in North America, twelve in Europe, seven in Asia, and one in Australia. We did not find any studies from South America or Africa. Four studies were prospective, four were both retrospective and prospective and the remaining 17 were retrospective cohort in design (Table 1). Most studies used liver biopsy and the International Autoimmune Hepatitis guidelines to establish the diagnosis of AIH, and radiology or pathology for HCC diagnosis. The method of AIH diagnosis was not mentioned in five out of six studies published only as abstracts. None of the included studies reported external funding sources.

Eight of the 25 studies were comparative (comparative groups included national population, local population, and patients with PBC).[11,18,35–40] We assessed study quality with a

modified Newcastle Ottawa scale. Scores ranged from 3 to 7 (with a maximum score of 9). The median scores were 6 and 5 for comparative and non-comparative studies, respectively (Appendix Table 2).

Baseline characteristics

The median cohort size was 170 patients (range 25–1721). Patients were followed for a median of 8.0 years (range 3.3–16.0). The majority of AIH patients were women (80.4%, range 61.6–91.7%). The mean age of patients at the time of study enrollment was 46.1 years (range 36.0–62.0 years). In 22 studies that reported cirrhosis status, 32.4% (median, range 6.3–100%) of patients had cirrhosis at the time of AIH diagnosis. Based on six studies that reported concurrent autoimmune disease, 29.1% patients with AIH had concurrent autoimmune disease at AIH diagnosis.[12,41–45]

HCC incidence rate in AIH

Of the 6,528 patients included in the analysis, 118 patients developed HCC during a median follow up of 8.0 years (53,026 total person-years). A total of nine patients from three studies had HCC at the time of initial AIH diagnosis or cohort entry and were excluded from HCC incidence calculations.[18,41,39] The pooled HCC incidence rate was 3.06 (95% CI 2.22–4.23) per 1,000 person-years, with moderate heterogeneity between the studies ($I^2 = 49.5\%$, Figure 2). The range of HCC incidence in individual studies was from 0 to 11.34 per 1,000 person-years.

HCC incidence rate in patients with AIH cirrhosis

A total of 16 studies examined HCC incidence in patients with evidence of cirrhosis at the time of AIH diagnosis. The pooled HCC incidence rate in patients with AIH cirrhosis was 10.07 per 1,000 person-years with low between-study heterogeneity (95% CI 6.90–14.70, $I^2 = 29.3\%$, Figure 3A). The range of HCC incidence for this subgroup was from 0.80 to 29.76 per 1,000 person-years.

A total of 13 studies reported HCC incidence among patients without cirrhosis at AIH diagnosis. The pooled HCC incidence rate was 1.14 per 1,000 person-years (95% CI 0.60–2.17, $I^2 = 15.6\%$, Figure 3B).

A total of 16 studies reported cirrhosis status at the time of HCC diagnosis. Of 93 patients with HCC, 92 had evidence of cirrhosis. Of these, 22 patients (23.7%) did not have cirrhosis at the time of initial AIH diagnosis but developed cirrhosis during follow up.

HCC incidence rate in AIH by sex

In the eleven studies examining the incidence of HCC by sex, the pooled HCC incidence rate was 3.13 per 1,000 person-years (95% CI 1.88–5.18) in women and 4.65 per 1,000 person-years (95% CI 2.69–8.03) in men, with low to moderate between-study heterogeneity ($I^2 = 64.8\%$ women, $I^2 = 23.3\%$ men, Figure 4A).

HCC incidence rate in AIH by continent

The pooled annual incidence rate of AIH was higher in studies performed in Asia (5.06 per 1,000 person-years, 95% CI 3.54–7.23, I^2= 0.0%, 7 studies) compared with Europe (1.97 per 1,000 person-years, 95% CI 1.15–3.40, I^2= 64.5%, 12 studies), Australia (2.60 per 1,000 person-years, 95% CI 0.69–9.77, one study) and North America (3.63 per 1,000 person-years, 95% CI 2.20–6.00, I^2= 0.0%, 5 studies) (Figure 4B). Patients included in the studies from Asia were older (mean age of 54.7 years) at the time of AIH diagnosis compared to patients in studies from other continents (mean age: Europe 46.1 years, North America 49.4 years, and Australia 50.0 years).

HCC incidence rate in AIH by source population

The pooled annual incidence rate of HCC was higher in single specialized tertiary center studies (4.58 per 1,000 person-years, 95% CI 3.42–6.13, I^2= 0.0%, 14 studies) than multicenter studies (2.75 per 1,000 person-years, 95% CI 1.77–4.26, I^2= 46.7%, 8 studies) or studies including AIH patients identified from general populations (1.41 per 1,000 person-years, 95% CI 0.50–3.97, I^2= 53.8%, 4 studies, Figure 4C).

Sensitivity analysis

After excluding six studies published only as abstracts, the pooled annual HCC incidence rate decreased to 2.60 per 1,000 person-years (95% CI 1.84–3.66, I^2=34.16) in the remaining 19 studies (Appendix Figure 1). The results did not change when we removed three studies with zero HCC counts (3.12 per 1,000 person years, 95% CI 2.24–4.34, I^2=48.0%, Appendix Figure 2). The pooled HCC incidence rate was 2.98 per 1,000 person-years (95% CI 1.86–4.78) in retrospective, and 3.07 per 1,000 person-years (95% CI 2.05–4.60) in prospective or retrospective/prospective studies. There was low to moderate between-study heterogeneity among the studies (I^2= 59.3% retrospective, I^2= 30.6 % prospective, Appendix Figure 3).

Other determinants of HCC

A total of five studies used multivariable regression analyses to identify factors associated with the development of HCC in AIH.[31,40,46–48] These studies identified older age, male gender, cirrhosis status at baseline, number of AIH relapses and alcohol use as independent factors associated with risk of HCC in patients with AIH (Appendix Table 3).

Two studies reported the risk of HCC in AIH patients with overlap syndrome with primary biliary cholangitis (PBC); the pooled HCC rate was 14.4 per 1,000 person years (95% CI 1.7–51.0).[36,49] None of the 5 patients with AIH and primary sclerosing cholangitis overlap, reported in one study developed HCC.[36] A total of six studies reported HCC surveillance but it was not possible to compare the incidence of HCC according to screening status because this information was not provided in most studies. [15,17,40,40,49,50]

Publication bias

Egger's plot and Begg's plot did not demonstrate significant bias (p values 0.35 and 0.12, respectively). The funnel plot did not show significant asymmetry (Figure 5).

Discussion

In this systematic review and meta-analysis, we found that HCC developed at an overall incidence rate of 3.06 per 1,000 patient-years (95% CI 2.22–4.23) among patients with AIH. Cirrhosis was a predominant risk factor for HCC. The incidence of HCC in patients with cirrhosis at time of AIH diagnosis was 10.07 per 1,000 patient-years (95% CI 6.90–14.70). Although HCC was reported to occur in patients who did not have cirrhosis at time of AIH diagnosis, it was a relatively rare and not statistically significant scenario (1.14 per 1,000 patient-years, 95% CI 0.60–2.17).

AASLD guidelines suggest that HCC surveillance is cost-effective if the expected risk of HCC exceeds 1.5% per year.[51–53] In this meta-analysis, the overall pooled incidence of patients with AIH cirrhosis was 1.007% per year (10.07 per 1,000 patient-years). However, the 95% CI nearly encompasses the recommended cut-off value of 1.5% and in five of the 16 studies, the annual incidence rate (that reported HCC incidence in patients with AIH cirrhosis) exceeded 1.5%.[44,46–49] We also found that almost all patients (92 of 93) who developed HCC had progressed to cirrhosis during their follow up. Collectively, these data support the importance of regular monitoring of disease severity in AIH with initiation of HCC screening in patients who progress to cirrhosis despite medical management.

Based on published literature, in patients with hepatitis B, HCC incidence varies between 0–7 per 1,000 person-years in carriers, 1–10 per 1,000 person-years in chronic hepatitis and 9–54 per 1,000 person-years in patients with hepatitis B cirrhosis.[54,55] The HCC incidence among patients with hepatitis C has been reported to be 1–8 per 1,000 person-years in patients with chronic hepatitis and 37–71 per 1,000 person-years in patients with cirrhosis.[54] The incidence of HCC among patients with PBC has been reported to be 0–11 per 1,000 person-years and in patients with PBC cirrhosis has been reported to be 7–24 per 1,000 person-years.[55–60] The incidence of HCC among patients with PSC is not known but likely very low.[61] Based on our study findings, the risk of HCC in patients with AIH cirrhosis is lower than patients with cirrhosis related to hepatitis B, hepatitis C, or PBC.

Besides cirrhosis, we found several demographic and clinical factors associated with HCC risk. Older age at AIH diagnosis was associated with risk of HCC. Men with AIH had a slightly higher risk of developing HCC than women, but the difference was not statistically significant, likely due to sample size limitations (only 1138 men were included in this analysis and of these 26 developed HCC) and relatively younger age of men at time of AIH diagnosis compared to women. While the effect of AIH treatment was difficult to assess given the heterogeneity of disease severity in this population, two studies suggested that increased frequency of AIH relapses portend increased risk of HCC. Macaron et al. found that AIH patients with concomitant alcohol abuse had 6-fold higher risk of HCC than patients without alcohol use.[40] These data support careful monitoring of patients with AIH, particularly older men, patients with multiple AIH relapses, and those with ongoing alcohol abuse. On the other hand, the concomitant presence of primary sclerosing cholangitis was associated with low HCC risk; similar findings were reported in studies of patients with primary sclerosing cholangitis alone.[61] Asian populations have the highest incidence of HCC; in this study we also found a higher HCC risk in Asian patients with AIH than

patients in other continents.[14] This increased risk may be related to the older mean age of patients or from other factors such as aflatoxin exposure. [62,63] Additionally, we found the incidence rates varied by source population. Studies using single tertiary center data found higher rates of HCC than studies using multicenter or country data. This may reflect increased risk of HCC in patients with more complicated or severe disease that were referred to those tertiary centers.

Our study has several limitations related to the available primary studies. All studies had small numbers of patients who developed HCC (n=0–15), and therefore the incidence rate estimates are likely not precise, particularly in the subgroup analyses. Most studies lacked a comparison cohort and followed patients for relatively short durations. Inconsistent reporting limited our ability to assess the influence of various risk factors. We were also unable to measure the effects of HCC surveillance in this population because this information was not included in most studies.

We used a comprehensive systematic search strategy that included hand searches and searches for unpublished reports. We did not find any evidence of publication bias, providing support to the decision to incorporate gray literature in our study. Additionally, we conducted several subgroup and sensitivity analyses to evaluate HCC incidence rates in various subgroups. The between study heterogeneity was reduced in the subgroups including prospective and single tertiary centers studies, suggesting that some of the heterogeneity in the HCC incidence rates resulted from differences in study design and source population.

In conclusion, patients with AIH related cirrhosis are at an increased risk for HCC. HCC surveillance might be cost effective in this population. On the other hand, AIH patients without cirrhosis at index diagnosis, particularly those identified from general populations, are at an extremely low risk of HCC.

Acknowledgments

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APPENDIX

Appendix Table 1

Search strategy for PubMed and Embase.

PubMed

1	"hepatitis, autoimmune"[mesh: noexp]
2	"autoimmune hepatitis" [TIAB] OR "lupoid hepatitis"[tiab]
3	#1 OR #2
4	(liver[TIAB] OR hepatocellular[TIAB])
5	(carcinoma[TIAB] OR cancer*[TIAB] OR neoplasm*[TIAB] OR malignanc*[tiab])
6	#4 AND #5
7	liver neoplasms [mesh: noexp]
8	#6 OR #7
9	#3 AND #8

Embase
autoimmune AND hepatitis AND 'hepatocellular carcinoma'

Appendix Table 2

Modified New Castle Ottawa.

Comparative studies

Study	Selection	Comparability	Outcome	Total
Danielsson Borssen (2015)	4	1	2	7
Umemura (2014)	4	1	2	7
Grønbæk (2014)	3	1	2	6
Van Gerven (2014)	4	0	2	6
Ngu (2012)	3	1	2	6
Macaron (2010)	1	1	2	4
Poulson (2002)	3	1	2	6
Kanzler (2001)	3	1	2	6

Non-comparative studies				
Study	**Selection**	**Outcome**		**Total**
Sonavane (2016)	1	2		3
Martens (2013)	2	2		4
Zachou (2013)	2	2		4
Yoshizowa (2012)	3	3		6
Migita (2012)	3	2		5
Hino-Arinaga (2012)	4	3		7
Wong (2011)	2	2		4
Hoeroldt (2009)	3	2		5
Ng (2009)	2	2		4
Teufel (2009)	3	2		5
Muratori (2009)	3	2		5
Montano-Loza (2008)	3	3		6
Seo (2008)	3	2		5
Yeoman (2008)	3	3		6
Miyake (2006)	3	2		5
Floreani (2006)	3	3		6
Seela (2005)	3	2		5

Appendix Table 3

Risk factors for hepatocellular cancer in autoimmune hepatitis. Table displays risk factors identified as significant based on multivariable regression models. HR=hazard ratio; OR; OR=odds ratio

Risk factors	Study	Statistics
Demographics		
Older age	Macaron[40]	HR 1.1, $p < 0.001$
	Hoeroldt[64]	HR not reported, $p = 0.034$
Clinical factors		
Two or more relapses	Yoshizawa[46]	HR 9.1, $p = 0.007$
High relapse rate	Hoeroldt[64]	HR not reported, $p = 0.034$
Cirrhosis	Migita[47]	HR 11.47, $p = 0.005$
	Hino-Arinago[48]	OR 4.08, $p = 0.01$
Alcohol consumption	Macaron[40]	HR 5.9, $p < 0.001$

Incidence HCC in AIH per 1,000 person years (without abstracts)

Study	ES (95% CI)	% Weight
Danielsssson Borssen, 2015	1.24 (0.59, 2.27)	8.80
Grønbæk, 2014	0.68 (0.29, 1.33)	8.05
Umemura, 2014	3.91 (1.44, 8.51)	7.01
Van Gerven, 2014	1.37 (0.59, 2.70)	8.05
Yoshizowa, 2012	3.16 (1.27, 6.51)	7.57
Ngu, 2012	2.60 (0.54, 7.58)	4.44
Migita, 2012	4.53 (1.82, 9.34)	7.57
Hino-Arinaga, 2012	4.99 (1.83, 10.86)	7.01
Wong, 2011	2.98 (1.09, 6.49)	7.01
Teufel, 2009	0.26 (0.00, 2.40)	0.54
Muratori, 2009	0.92 (0.02, 5.13)	1.44
Montano-Loza, 2008	3.55 (1.62, 6.74)	8.45
Seo, 2008	3.40 (0.41, 12.29)	3.11
Yeoman, 2008	4.95 (2.77, 8.17)	10.00
Miyake, 2006	5.43 (1.12, 15.88)	4.44
Floreani, 2006	1.81 (0.05, 10.06)	1.44
Seela, 2005	0.74 (0.00, 6.95)	0.54
Poulsen, 2002	2.78 (0.34, 10.03)	3.11
Kanzler, 2001	1.19 (0.03, 6.62)	1.44
Overall (I-squared = 47.3%, p = 0.012)	2.60 (1.84, 3.66)	100.00

NOTE: Weights are from random effects analysis

.001   .01   .1   1   10   100

Appendix Figure 1.
Sensitivity analysis: Forest plot of incidence of hepatocellular cancer (HCC) in autoimmune hepatitis (AIH) patients after excluding abstracts and low-quality studies.

Incidence HCC in AIH per 1,000 person years (without zero)

Study	ES (95% CI)	% Weight
Sonavane, 2016	10.02 (4.32, 19.73)	6.28
Danielssson Borssen, 2015	1.24 (0.59, 2.27)	6.77
Grønbæk, 2014	0.68 (0.29, 1.33)	6.28
Umemura, 2014	3.91 (1.44, 8.51)	5.59
Van Gerven, 2014	1.37 (0.59, 2.70)	6.28
Martens, 2013	1.10 (0.03, 6.15)	1.30
Zachou, 2013	6.16 (1.68, 15.77)	4.52
Yoshizowa, 2012	3.16 (1.27, 6.51)	5.97
Ngu, 2012	2.60 (0.54, 7.58)	3.75
Migita, 2012	4.53 (1.82, 9.34)	5.97
Hino-Arinaga, 2012	4.99 (1.83, 10.86)	5.59
Wong, 2011	2.98 (1.09, 6.49)	5.59
Macaron, 2010	11.34 (1.37, 40.96)	2.71
Hoeroldt, 2009	3.31 (1.43, 6.52)	6.28
Muratori, 2009	0.92 (0.02, 5.13)	1.30
Montano-Loza, 2008	3.55 (1.62, 6.74)	6.55
Seo, 2008	3.40 (0.41, 12.29)	2.71
Yeoman, 2008	4.95 (2.77, 8.17)	7.51
Miyake, 2006	5.43 (1.12, 15.88)	3.75
Floreani, 2006	1.81 (0.05, 10.06)	1.30
Poulsen, 2002	2.78 (0.34, 10.03)	2.71
Kanzler, 2001	1.19 (0.03, 6.62)	1.30
Overall (I-squared = 56.2%, p = 0.001)	3.12 (2.24, 4.34)	100.00

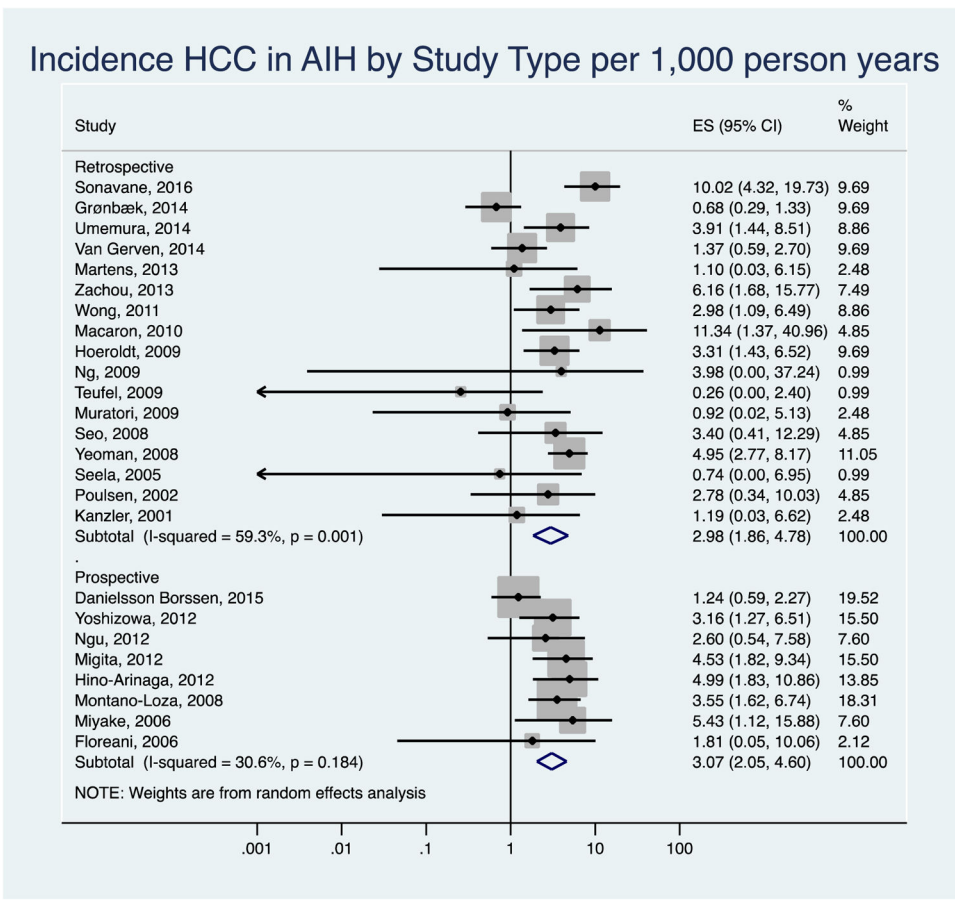NOTE: Weights are from random effects analysis

Appendix Figure 2.
Sensitivity analysis: Incidence of hepatocellular cancer (HCC) in autoimmune hepatitis (AIH) patients after excluding studies with zero HCC cases.

Incidence HCC in AIH by Study Type per 1,000 person years

Study	ES (95% CI)	% Weight
Retrospective		
Sonavane, 2016	10.02 (4.32, 19.73)	9.69
Grønbæk, 2014	0.68 (0.29, 1.33)	9.69
Umemura, 2014	3.91 (1.44, 8.51)	8.86
Van Gerven, 2014	1.37 (0.59, 2.70)	9.69
Martens, 2013	1.10 (0.03, 6.15)	2.48
Zachou, 2013	6.16 (1.68, 15.77)	7.49
Wong, 2011	2.98 (1.09, 6.49)	8.86
Macaron, 2010	11.34 (1.37, 40.96)	4.85
Hoeroldt, 2009	3.31 (1.43, 6.52)	9.69
Ng, 2009	3.98 (0.00, 37.24)	0.99
Teufel, 2009	0.26 (0.00, 2.40)	0.99
Muratori, 2009	0.92 (0.02, 5.13)	2.48
Seo, 2008	3.40 (0.41, 12.29)	4.85
Yeoman, 2008	4.95 (2.77, 8.17)	11.05
Seela, 2005	0.74 (0.00, 6.95)	0.99
Poulsen, 2002	2.78 (0.34, 10.03)	4.85
Kanzler, 2001	1.19 (0.03, 6.62)	2.48
Subtotal (I-squared = 59.3%, p = 0.001)	2.98 (1.86, 4.78)	100.00
.		
Prospective		
Danielsson Borssen, 2015	1.24 (0.59, 2.27)	19.52
Yoshizowa, 2012	3.16 (1.27, 6.51)	15.50
Ngu, 2012	2.60 (0.54, 7.58)	7.60
Migita, 2012	4.53 (1.82, 9.34)	15.50
Hino-Arinaga, 2012	4.99 (1.83, 10.86)	13.85
Montano-Loza, 2008	3.55 (1.62, 6.74)	18.31
Miyake, 2006	5.43 (1.12, 15.88)	7.60
Floreani, 2006	1.81 (0.05, 10.06)	2.12
Subtotal (I-squared = 30.6%, p = 0.184)	3.07 (2.05, 4.60)	100.00

NOTE: Weights are from random effects analysis

.001 .01 .1 1 10 100

Appendix Figure 3.
Sensitivity Analysis: Forest plot of incidence of hepatocellular cancer in autoimmune hepatitis patients by study design. Incidence rate reported per 1,000 person-years.
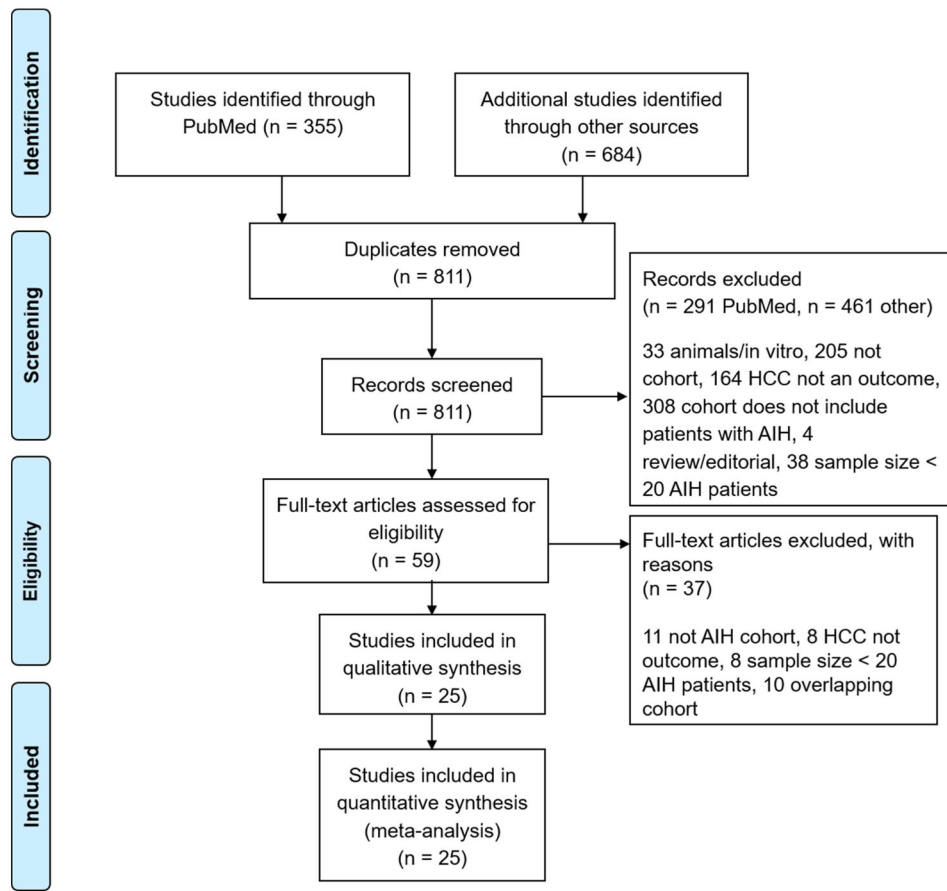
Figure 1.
PRISMA Flow Diagram. AIH – autoimmune hepatitis. HCC-hepatocellular cancer
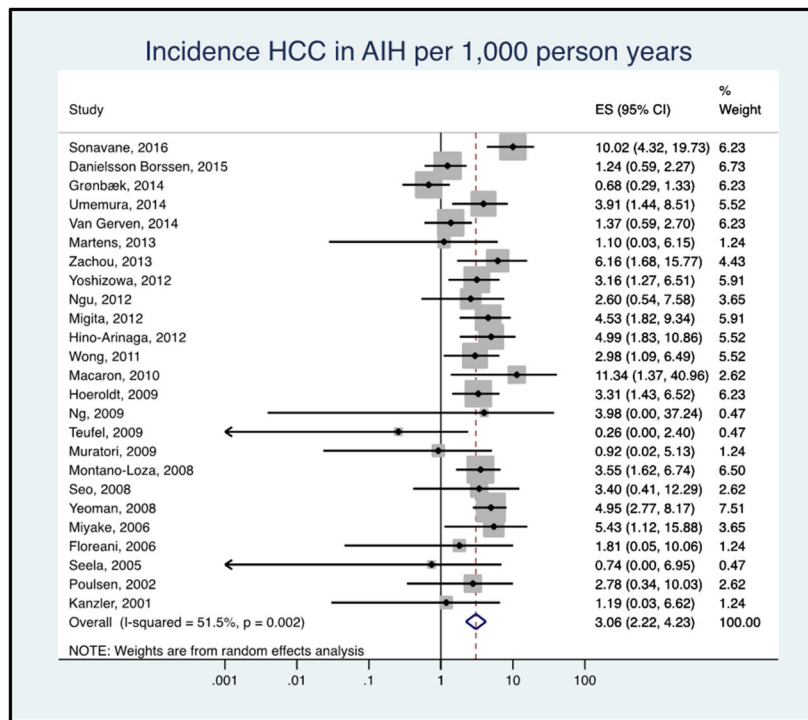
Figure 2.

Forest plot of incidence of hepatocellular cancer in patients with autoimmune hepatitis.

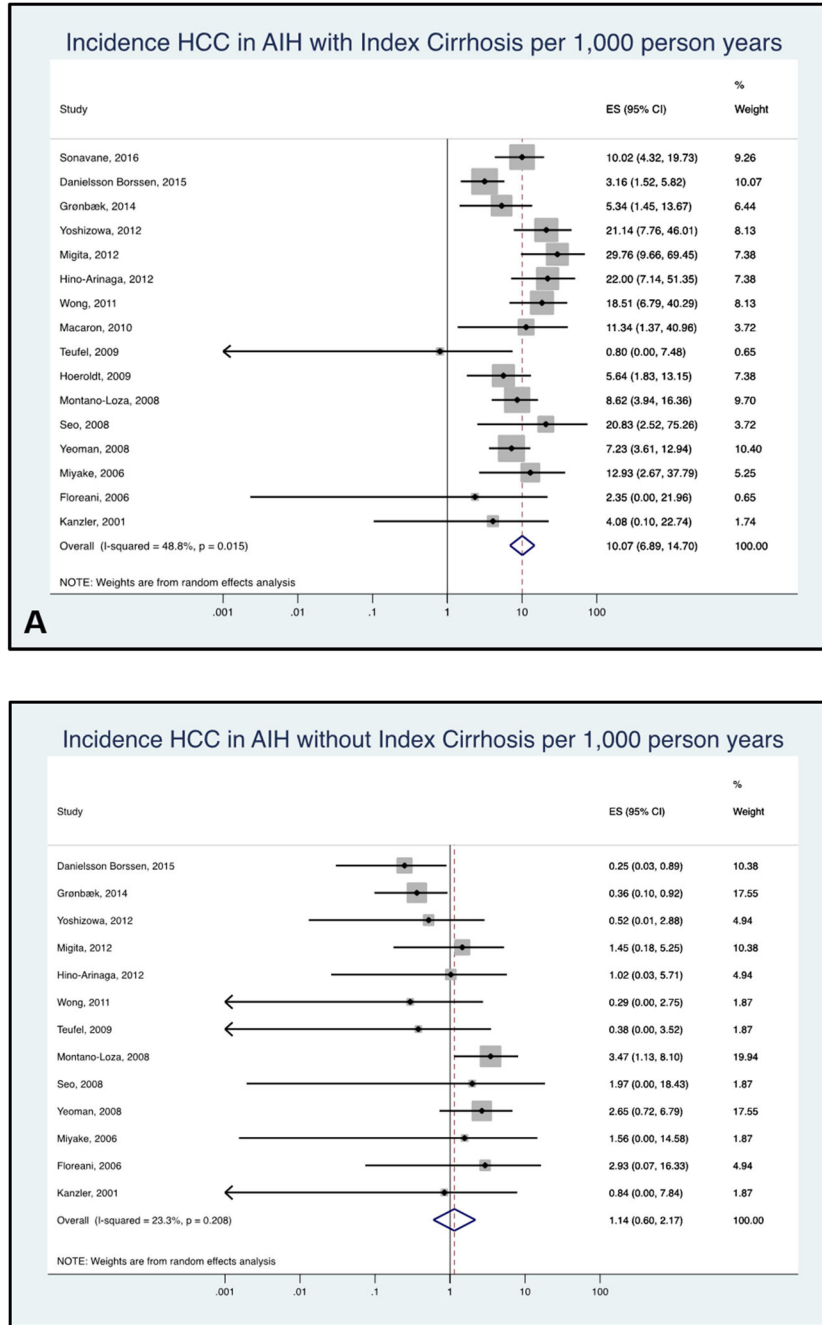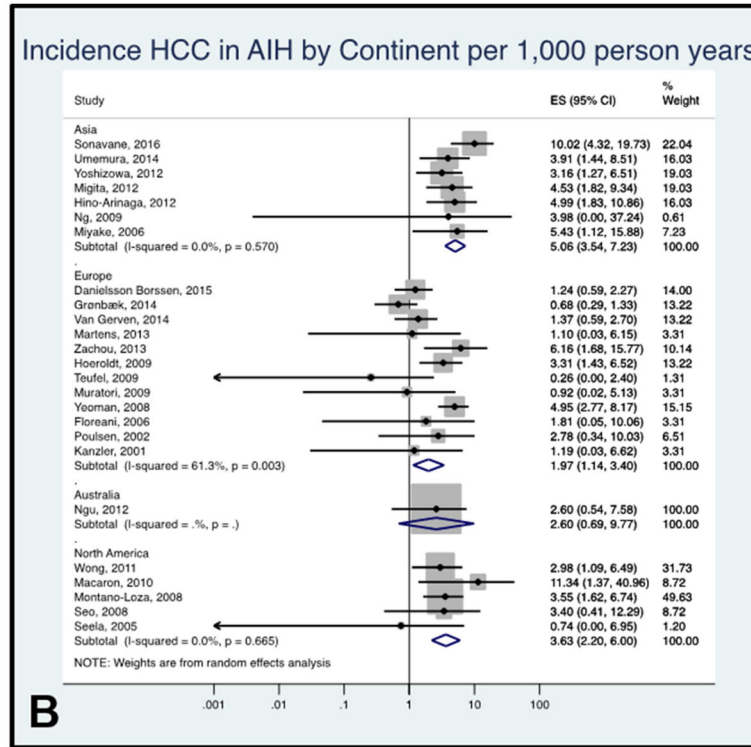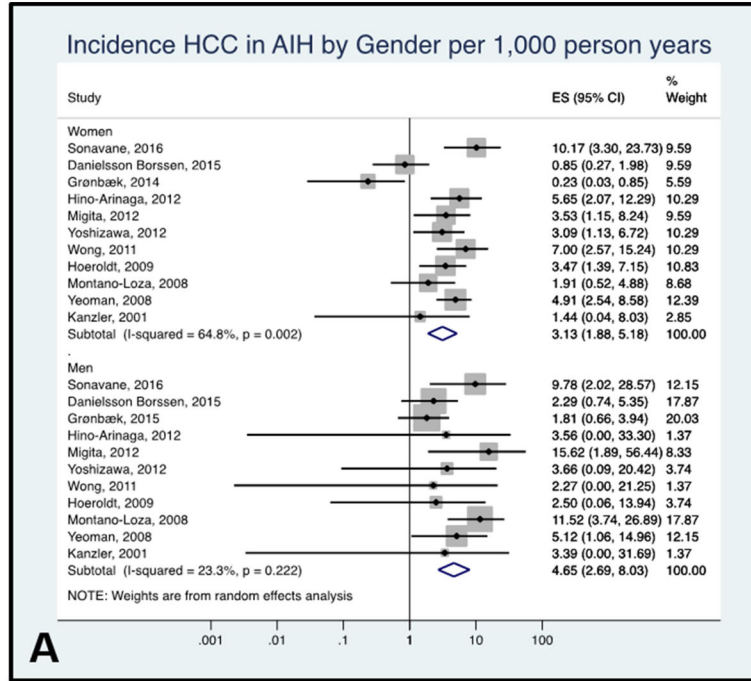Incidence rate reported per 1,000 person-years.

Figure 3.

Figure 3A: Forest plot of incidence of hepatocellular cancer in autoimmune hepatitis patients with cirrhosis at baseline. Incidence rate reported per 1,000 person-years.

Figure 3B: Forest plot of incidence of hepatocellular cancer in autoimmune hepatitis patients without cirrhosis at baseline. Incidence rate reported per 1,000 person-years.
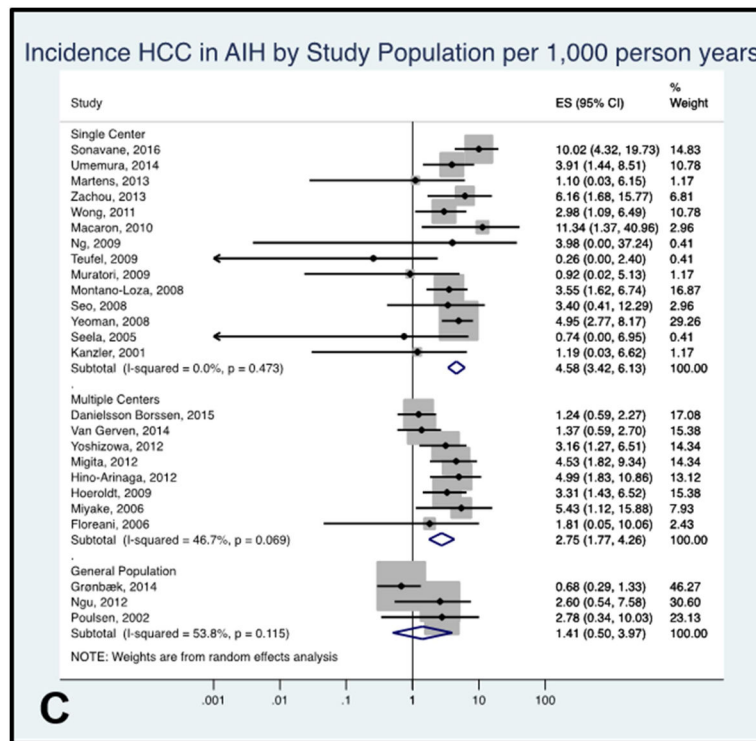
Incidence HCC in AIH by Gender per 1,000 person years

Incidence HCC in AIH by Continent per 1,000 person years

Figure 4.

Figure 4A: Forest plot of incidence of hepatocellular cancer in autoimmune hepatitis patients by sex. Incidence rate reported per 1,000 person-years.

Figure 4B: Forest plot of incidence of hepatocellular cancer in autoimmune hepatitis patients by continent. Incidence rate reported per 1,000 person-years.

Figure 4C: Forest plot of incidence of hepatocellular cancer in autoimmune hepatitis patients by study population. Incidence rate reported per 1,000 person-years.
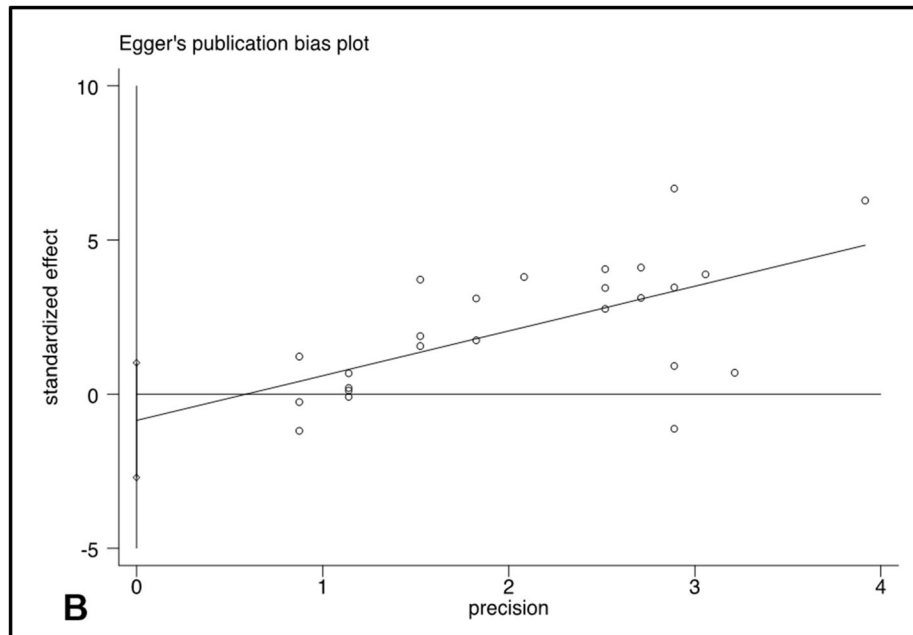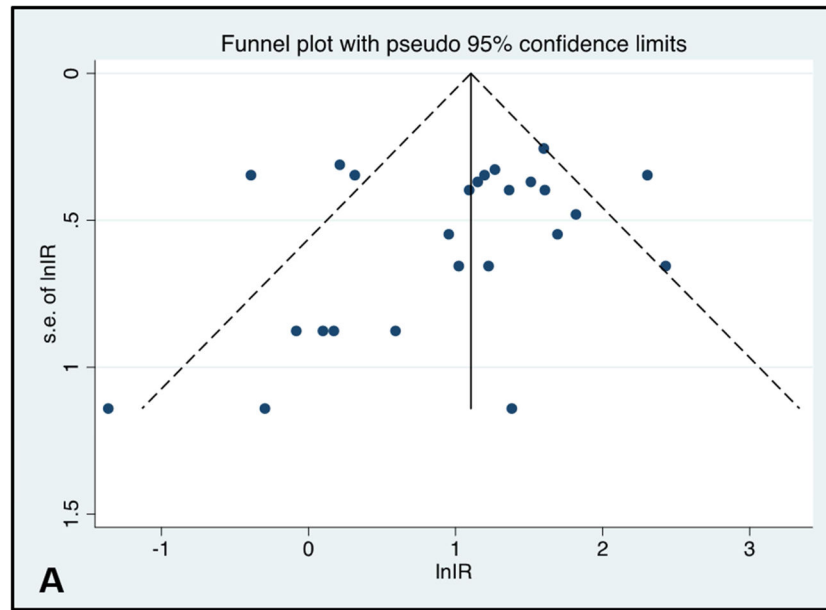
Figure 5.
Funnel Plot and Egger's publication bias plot

Table 1

Characteristics of included studies

Authors (Year)	Country	Years of study	Study type	Source of study population	Study N	Mean age at AIH	% Women	% Cirrhosis at Index AIH diagnosis	Mean follow up in months	Incidence HCC per 1,000 person-years
Sonavane (2016) **[64]	West India	Not provided	R	Single	242	44.7	61.6	71.9	39.6	10.02
Danielsson Borssen (2015)[11]	Sweden	Not provided	R	Multiple	634	46*	73.0	28.0	152.8	1.24
Grønbæk (2014)[18]	Denmark	1994–2012	R	General Population	1721	-	72.0	6.3	82.5	0.68
Umemura (2014)[35]	Japan	1999–2013	R	Single	156	62	89.0	-	118.0*	3.91
Van Gerven (2014)[36]	Netherlands	1967–2011	R	Multiple	730	48	78.0	12.0	96.0*	1.37
Martens (2013) **[65]	Germany	1980–2010	R	Single	170	-	-	8.2	64.0	1.10
Zachou (2013) **[12]	Greece	2000–2012	P	Single	159	47	69.8	32.7	49.0	6.16
Yoshizowa (2012)[46]	Japan	1974–2010	R/P	Multiple	203	55.5	87.2	12.3	131.0	3.16
Ngu (2012)[66]	New Zealand	1980–2006	R/P	General Population	130	50	70.8	-	106.7	2.60
Migita (2012)[47]	Japan	1995–2008	P	Multiple	193	56.6	91.7	10.9	96.0	4.53
Hino-Arinaga (2012)[27]	Japan	11/1978–4/2008	R/P	Multiple	180	59.9	88.3	18.9	80.2	5.00
Wong (2011)[49]	USA	1999–2009	R	Single	322	51.8	79.6	1.6	75.0	0.00
Macaron (2010) **[40]	USA	2001–2007	R	Single	49	-	-	100.0	43.2	11.34
Hoeroldt (2009)[30]	UK	1971–2007	R	Single***	248	57	83.5	36.7	117.0	3.31
Ng (2009) **[41]	Hong Kong	1/1996–5/2008	R	Single	25	56	-	32.0	60*	0.00
Teufel (2009)[50]	Germany	1970–2008	R	Single	278	-	-	11.0	84.2	0.26
Muratori (2009)[67]	Italy	1992–2007	R	Single	163	36	82.2	55.0	80	0.92
Montano-Loza (2008)[17]	USA	Not provided	P	Single	227	46	81.5	43.2	134.0	3.55
Seo (2008)[44]	USA	4/1979–7/2007	R	Single	72	50.5	84.0	56.9	98.0*	3.40
Yeoman (2008)[19]	UK	1971–2007	R	Single	243	42	80.7	50.2	149.6	4.95
Miyake (2006)[43]	Japan	11/1988–06/2005	P	Multiple	69	54	89.9	42.0	96.0*	5.44
Floreani (2006)[68]	Italy	1981–2004	R/P	Multiple	73	47.7	86.3	38.4	91	1.81

Authors (Year)	Country	Years of study	Study type	Source of study population	Study N	Mean age at AIH	% Women	% Cirrhosis at Index AIH diagnosis	Mean follow up in months	Incidence HCC per 1,000 person-years
Seela (2005)[42]	USA	Not provided	R	Single	42	47	76.2	42.6	192.0	0.74
Poulsen (2002)[38]	Denmark	1977–1993	R	General Population	96	-	-	-	90.0	2.78
Kanzler (2001)[39]	Germany	Not provided	R	Single	103	45.8	83.0	29.1	98	1.19

**
abstract, R=retrospective, P=prospective, R/P=retrospective and prospective,

*
represents median,

***
represents nontransplant center