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SYSTEMATIC REVIEWS

Possible association between hepatitis C virus and malignancies different from hepatocellular carcinoma: A systematic review

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Author contributions: Fiorino S conceived the study and coordinated the search activity of colleagues; Visani M and Acquaviva G contributed to the design of the review and coordinated the preparation of the first draft of manuscript; Masetti M and Lombardi R independently and in a parallel manner, performed the literature search, identified and screened the articles; Bacchi-Reggiani L and Fornelli A supervised the literature search analysis; Grizzi F and di Tommaso L contributed to write the first draft of manuscript; Tura A and Pontoriero L checked the accuracy of data collection; Zanello M and Mastrangelo L independently extracted and tabulated all relevant data from included studies by means of a standardized flow path and contributed to writing the manuscript; Fabbri C and Cuppini A commented on drafts of the manuscript; Bondi A and Pession A supervised and critically reviewed the manuscript; Sabbatani S and Jovine E were responsible for the final approval of manuscript; de Biase D contributed to the design of the study and commented on drafts of the manuscript; all authors approved the final version of the manuscript.

Conflict-of-interest statement: All authors declare that they have no competing interest.

Data sharing statement: The dataset is available from the corresponding author at sirio.fiorino@ausl.bologna.it.

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Abstract

AIM: To summarize the current knowledge about the potential relationship between hepatitis C virus (HCV) infection and the risk of several extra-liver cancers.

METHODS: We performed a systematic review of the literature, according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) Statement. We extracted the pertinent articles, published in MEDLINE and the Cochrane Library, using the following search terms: neoplasm/cancer/malignancy/tumor/carcinoma/adeno-carcinoma and non-Hodgkin lymphomas, kidney/renal-, cholangio-, pancreatic-, thyroid-, breast-,oral-, skin-, prostate-, lung-, colon-, stomach-, haematologic. Case series, case-series with control-group, case-control, cohort-studies as well as meta-analyses, written in English were collected. Some of the main characteristics of retrieved trials, which were designed to investigate the prevalence of HCV infection in each type of the above-mentioned human malignancies were summarised. A main table was defined and included a short description in the text for each of these tumours, whether at least five studies about a specific neoplasm, meeting inclusion criteria, were available in literature. According to these criteria, we created the following sections and the corresponding tables and we indicated the number of included or excluded articles, as well as of meta-analyses and reviews: (1) HCV and haematopoietic malignancies; (2) HCV and cholangiocarcinoma; (3) HCV and pancreatic cancer; (4) HCV and breast cancer; (5) HCV and kidney cancer; (6) HCV and skin or oral cancer; and (7) HCV and thyroid cancer.

RESULTS: According to available data, a clear correlation between regions of HCV prevalence and risk of extra-liver cancers has emerged only for a very small group of types and histological subtypes of malignancies. In particular, HCV infection has been associated with: (1) a higher incidence of some B-cell Non-Hodgkin-Lymphoma types, in countries, where an elevated prevalence of this pathogen is detectable, accounting to a percentage of about 10%; (2) an increased risk of intra-hepatic cholangiocarcinoma; and (3) a correlation between HCV prevalence and pancreatic cancer (PAC) incidence.

CONCLUSION: To date no definitive conclusions may be obtained from the analysis of relationship between HCV and extra-hepatic cancers. Further studies, recruiting an adequate number of patients are required to confirm or deny this association.

Key words: Neoplasm; Cancer; Hepatitis C virus; Risk factors; Extra-hepatic malignancies; Hepatocellular carcinoma; Pancreatic cancer; Cholangiocarcinoma

Core tip: Hepatitis C virus (HCV) is an oncogenic virus and a well-known risk factor for hepatocellular carcinoma. Some reports suggested that its infection is associated with development of cholangiocarcinoma and some types of lymphomas, but a comprehensive assessment of the possible role of HCV in extrahepatic carcinogenesis has not been yet performed. Aim of this review is to focus on HCV infection association with extra-liver neoplasms, as lymphomas, pancreatic cancer and breast-, renal-, oral- and thyroid-cancers. Our results strongly support the need of additional studies to ensure a precise estimate of the effect of HCV on these different types of extra-hepatic cancers.

Fiorino S, Bacchi-Reggiani L, de Biase D, Fornelli A, Masetti M, Tura A, Grizzi F, Zanello M, Mastrangelo L, Lombardi R, Acquaviva G, di Tommaso L, Bondi A, Visani M, Sabbatani S, Pontoriero L, Fabbri C, Cuppini A, Pession A, Jovine E. Possible association between hepatitis C virus and malignancies different from hepatocellular carcinoma: A systematic review. *World J Gastroenterol* 2015; 21(45): 12896-12953 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i45/12896.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i45.12896

INTRODUCTION

Hepatitis C virus (HCV) is a major global health problem, because it represents a very important cause of mortality, morbidity and resource utilization. Although remarkable differences are detectable in the world, depending on geographical areas and ethnicity, it is estimated that the prevalence of HCV infection is about 2% worldwide (Figure 1)[1]. Approximately 180 million people carriers this pathogen persistently[2]. HCV chronic infection can lead to a necro-inflammatory liver disease, with different pattern of severity and course. This condition is associated with an increased risk of cirrhosis, liver failure and hepatocellular carcinoma[3]. Although liver is the main target for HCV, it is now well-known that this pathogen may induce extra-hepatic pathological conditions, including mixed cryoglobulinemia, porphyria cutanea tarda, membranoproliferative glomerulonephritis, Sjögren's syndrome, thyroiditis, a high prevalence of autoantibodies[4] as well as Central and Peripheral Nervous System demyelinating disorders[5]. Several of these manifestations are thought to be caused by the host immune response to this micro-organism

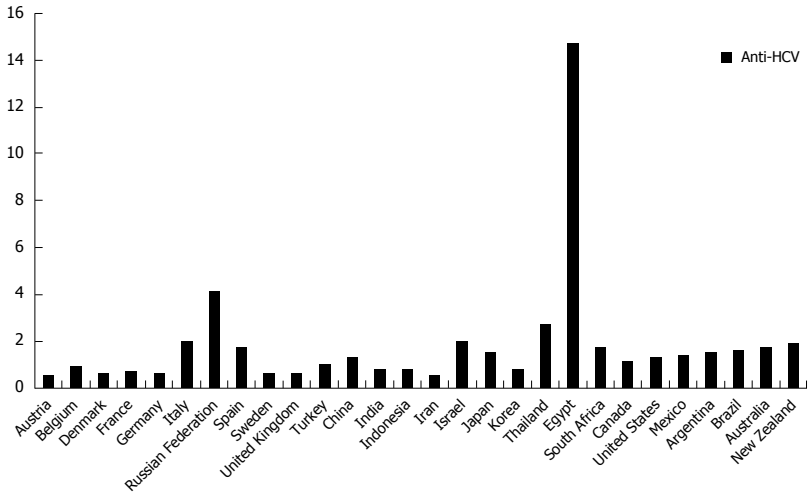


Figure 1 Prevalence of chronic hepatitis C virus status in different coutries worldwide. HCV: Hepatitis C virus.

and not by a direct viral cytopathic effect. In particular, chronic antigenic stimulation by HCV promotes B-lymphocyte clonal expansion, with the production and release of monoclonal and polyclonal antibodies and generation of immune complexes[6]. Their deposition in small vessels and glomerular capillary walls induces complement activation and, as consequence, tissue injury[7]. In addition, several studies have shown that HCV may infect organs and tissues other than the liver. In particular, presence of antigens, genome and/or replicative sequences of HCV have been detected in several extra-hepatic localizations, such as peripheral blood cells (*i.e.,* neutrophils, T- and B-lymphocytes)[8,9] or kidney[10], skin[11,12], oral mucosa[13], salivary glands[14] and pancreas tissues as well as, in a small number of cases, from heart, gallbladder, intestine and adrenal glands tissues[15,16].

Although HCV antigens and replicative forms have been detected in various extra-hepatic sites, the possible role on the onset of malignancies in these organs is still under investigation. Some evidences have recently suggested the possibility that this pathogen may be associated with the development of a wide spectrum of hematologic or solid cancers, such as non-Hodgkin lymphomas, biliary duct-, bladder-, renal-, pancreatic-, thyroid-, breast- and prostate-carcinomas. Here we summarize the current knowledge about the potential link between HCV infection and risk of these malignancies and we performed a systematic review of the literature that reports the prevalence of HCV infection in patients, suffering from above mentioned malignancies.

MATERIALS AND METHODS

Search strategy and selection of studies

See supplementary Material and Methods for further information.

A systematic computer-based search of published articles, according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) Statement, issued in 2009, was conducted through Ovid interface, in order to identify relevant studies on the potential association between HCV infection and malignancies other than hepatocellular carcinoma (HCC). The literature review was performed in February 2015. The following electronic databases were used: MEDLINE (1950 to February, 2015) and the Cochrane Library (until the fourth quarter of 2014) for all relevant articles. The search strategy and the search terms were developed with the support of a professional research librarian. The search text words were identified by means of controlled vocabulary, such as the National Library of Medicine's MESH (Medical Subject Headings) and Keywords. In our review, assessing the possible association between HCV infection and risk of malignancies other than HCC, we focused on the following malignancies: (1) lymphomas and, in particular, non-Hodgkin lymphomas; (2) biliary ducts-/gallbladder-; (3) renal-/kidney-; (4) pancreatic-; (5) thyroid-; (6) breast-; (7) lung-; (8) stomach-; (9) colon-; (10) skin-/oral-; (11) bladder-; and (12) prostate-carcinomas. The inclusion criteria for our analysis were: (1) study designs by considering data from all published case series, case-control-, hospital-based case-control-, population-based case-control- as well as cohort-studies; (2) articles which were reported in English, as peer-reviewed, full-text publications, whereas papers that were not published as full reports, such as conference abstracts, case reports, and editorials were excluded; (3) clinical series or studies evaluating histological specimens, that included at least 15 patients, therefore reports with fewer than 15 subjects were not considered; and (4) papers describing the type of tests used to assess HCV presence; in particular, in all studies virus search was performed by means of second- or third-generation enzyme-linked immunosorbent assay

(ELISA) or recombinant immunoblot assay (RIBA) for confirmation as well as in a large part of available trials HCV-RNA presence was also tested.

Study selection

Data extraction: Two authors (Masetti M and Bacchi-Reggiani L), independently and in a parallel manner, performed the literature search, identified and screened relevant articles, based on title or title and abstract. If a study was considered potentially eligible by either of the 2 reviewers, the full article of this research was collected for further assessment. Other two authors (Zanello M and Mastrangelo L) independently extracted and tabulated all relevant data from included studies by means of a standardized flow path, according to the Cochrane handbook section 7.3a checklist of domains. The following information was obtained from each study, by means of a predefined data extraction form, including: first author's name, study design, inclusion and exclusion criteria, year of publication, country of origin, ethnicity, matching criteria, number of cases and controls, diagnostic methods to detect each malignancy, HCV detection assays. The accuracy of data collection was checked by Tura A and any disagreements concerning the results were settled by consensus between all authors. With the purpose to prevent multiple inclusions of the same data, we searched the presence of possible duplicates, examining the first author's name as well as the place and the period of subjects' enrolment. When different versions of the same study were detected, only the most recent one was considered.

RESULTS

The search of MEDLINE and Cochrane Library produced the following citations: (1) haematopoietic malignancies: 1424; (2) biliary ducts-/cholangio-: 616; (3) renal-/kidney-: 891; (4) pancreatic-: 244; (5) thyroid-: 126; (6) breast-: 180; (7) lung-: 247; (8) stomach-: 141; (9) colon-: 115; (10) skin-/oral-: 598; (11) bladder-: 150; and (12) prostate-carcinomas: 43.

After a preliminary review of the titles and/or abstracts with the exclusion of non-pertinent articles, we obtained these results: (1) haematopoietic malignancies, including lymphomas/non-Hodgkin lymphomas: 126; (2) biliary ducts-/cholangio-: 48; (3) renal-/kidney-: 10; (4) pancreatic-: 15; (5) thyroid-: 11; (6) breast-: 8; (7) lung-: 3; (8) stomach-: 2; (9) colon-: 5; (10) skin-/oral-: 11; (11) bladder-: 3; and (12) prostate-carcinomas: 5.

We screened the potentially relevant studies and, in accordance with predefined criteria, we identified and considered in our systematic review the following number of studies: (1) haematopoietic malignancies: 108 articles considered, 6 reviews/meta-analyses, 12 papers excluded[17-146]; (2) biliary ducts/cholangiocarcinoma: 36 articles considered, 3 reviews/meta-analyses, 9 papers excluded[147-195]; (3) renal/kidney: 8 articles considered, 2 papers excluded[118,146,196-203]; (4) pancreatic: 9 articles considered, 3 reviews/meta-analyses, 3 papers excluded[118,146,170,197,204-214]; (5) thyroid: 7 articles considered, 4 papers excluded[52,73,118,146,196,197,215-217]; (6) breast: 6 articles considered, 2 papers excluded[117,118,146,196,197,202,218,219]; (7) lung: 2 articles meeting inclusion criteria, 1 not[146,196,197]; (8) stomach: 2 articles meeting inclusion criteria[146,220]; (9) colon: 3 articles meeting inclusion criteria, 2 not[118,146,196,197,202]; (10) skin/oral: 10 articles considered, 1 paper excluded[118,146,197,221-228]; (11) bladder: 3 articles meeting inclusion criteria[118,146,197]; and (12) prostate-carcinomas: 4 articles meeting inclusion criteria, 1 not[118,146,196,197,202] (Tables 1-7). A limited number of identified studies were formally designed as "cohort-" or "case-control" trials, adequately reporting inclusion criteria for the control group, such as "odds ratios" after adjustment for the most important confounding factors, or showing that cases and controls were matched by sex and age. Whether these data were not indicated, but an acceptable series of healthy subjects or patients with different diseases were recruited for comparison and were described, we defined the considered study, as: "case series with control group".

On the basis of our results, we summarised some of the main characteristics of retrieved trials, which were designed to investigate the prevalence of HCV infection in each type of the above- mentioned malignancies. In particular, we created a main table and included a short description in the text for each of these tumours, whether at least five studies, evaluating this parameter and meeting inclusion criteria, were available in literature. In each of these tables, we reported the following data of studies considered: first author's name, study design, year of publication, country of origin, matching criteria, number of cases and controls, diagnostic methods to detect each malignancy, percentage of HCV-positive cases with 95% confidence intervals (CIs) and main conclusions. CIs for each proportion were calculated according to normal distribution or binomial distribution as appropriate. Accordingly to these pre-definite criteria, we created the following sections and the corresponding Tables: (1) HCV and haematopoietic malignancies (Table 1); (2) HCV and cholangiocarcinoma (Table 2); (3) HCV and pancreatic cancer (Table 3); (4) HCV and breast cancer (Table 4); (5) HCV and kidney cancer (Table 5); (6) HCV and skin or oral cancer (Table 6); and (7) HCV and thyroid cancer (Table 7). Furthermore, we created additional tables, reporting both the studies not considered in our systematic review and the meta-analyses, assessing the association between HCV infection and risk of each human malignancy (see Tables 1-7). A summary of number of studies and meta-analyses is shown in Figure 2. Age-standardized incidence rates of each malignancy per 100000 person-years are reported for sex and for different countries in

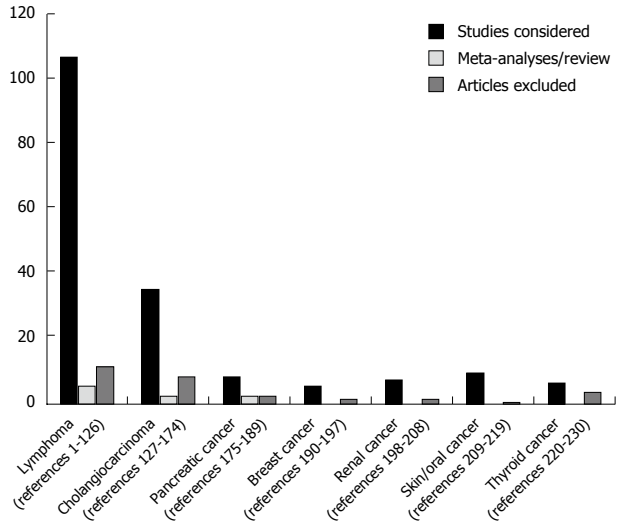


Figure 2 Number of studies and meta-analyses, assessing the association between hepatitis C virus infection and different types of malignancies, included in the present systematic review. References are reported in the supplementary section.

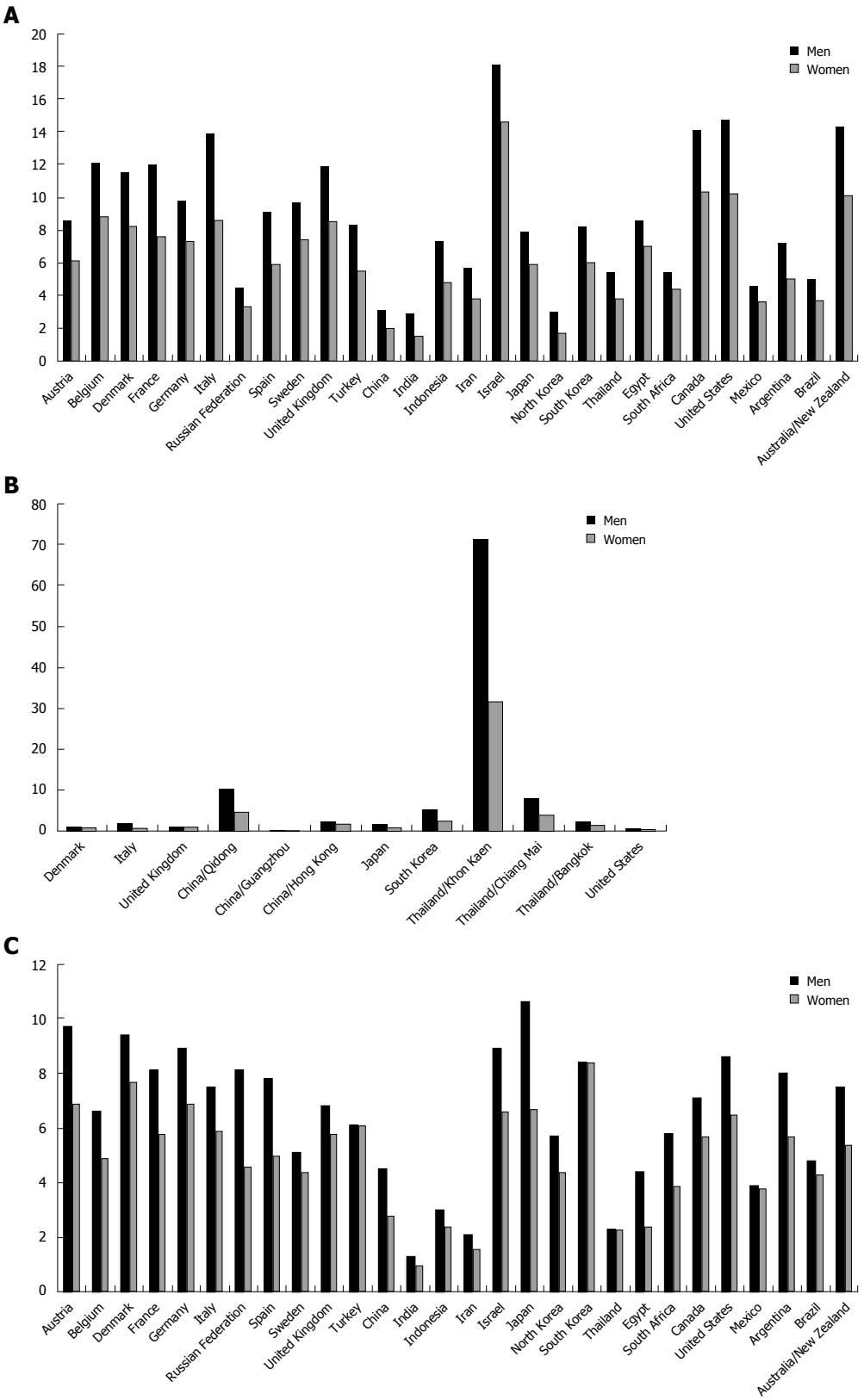
Figure 3[229].

HCV and haematopoietic malignancies risk

The analysis revealed that most of available studies assessed the prevalence of this pathogen in patients with non-hodgkin-lymphomas (NHLs) and, in particular, in subjects with B-lymphocyte NHLs. However, the aim, design, inclusion criteria and definition of controls widely varied among the identified trials. In particular, available studies assessed the prevalence of HCV infection either in B-, T-, NK-, subtypes of NHLs or in B-cell NHLs alone or in NHLs together with different lymphoprolipherative disorders or in lymphoprolipherative malignancies other than NHLs.

When we examined the large series of these trials, evaluating NHLs, it was necessary to take into account some problems of comparability, such as: type of NHL classification; ASSAYS used to detect HCV infection; and aim of selected studies.

Depending on year of publication, different classifications for NHLs have been used, including: Working Formulation, REAL or WHO classifications. In addition, only in some articles a detailed description of nodal or extra-nodal NHLs has been performed as well as a few studies were identifiable as formal case-control, reporting an adequate description of control groups characteristics, such as matching factors (*i.e.,* age, gender, birthplace and performance status), odds ratios adjusted for potential confounding factors. Furthermore, the sensitivity and specificity of diagnostic tests, used to detect antibodies anti-HCV or viral genome, largely differed among the trials considered in our systematic review (Table 1). In some studies the presence of anti-HCV antibodies was assayed by second-generation-, in others by third-generation-immune-enzymatic screening tests or by confirmatory tests, such as second-/third-generation-RIBA assays or by search of viral genome by means of different polymerase chain reaction (PCR)-based techniques. Furthermore, some hematologic malignancies, such as chronic lymphocytic leukemia have been classified into the category of NHLs in several trials, whereas they have been considered as entities distinct from NHLs in other reports. However, to date even if a large methodological heterogeneity exists among all these studies, the number of trials performed worldwide to assess the potential effect of HCV infection on the risk of NHLs is wide. Therefore, the available data, collected in peoples of various ethnicities as well as in populations of different geographical areas may provide a valid representation of the real situation in a large number of distinct countries. In particular, according to the results of available studies and meta-analyses, an association between HCV infection and B-lymphocyte NHLs development has emerged, with an assessed moderate risk for lymphoma development and odds ratios ranging between 2 and 3 on average. Nevertheless, this estimation differs largely, not only depending on the histological types considered but also on the geographical location and race of populations included in the different trials. An increased risk of NHLs has been described in studies performed in countries, where an elevated HCV prevalence is detectable, including Italy and Spain in Southern Europe, Japan and Taiwan in Asia as well as in Egypt and in southern United States areas. In these regions the percentage of HCV-associated NHLs can also reach a value equal to 10%. On the other hand, the association between HCV and NHLs development has not been confirmed in countries with low viral prevalence, such as countries of Northern Europe (United Kingdom, German, France, Denmark) or North America (Canada, Northern and United States regions). According to the results of a large European multicenter case-control-study as well as of available meta-analyses some subtypes of B-lymphocyte NHLs have resulted to be more frequently associated with diffuse large B-cell lymphoma (DLBCL) with an OR equal to 2.24, marginal zone lymphoma (MZL) with an OR equal to 2.47, and lymphoplasmocytic lymphoma (LPL) with an OR equal to 2.57[129]. In an additional large population-based trial in United States, an enhanced risk for follicular lymphoma (OR = 1.88), Burkitt's lymphoma (OR = 5.21), DLBCL (OR = 1.52) and MZL (OR = 2.20) was reported[119]. However, other than above mentioned lymphoprolipherative diseases, no clear relationship has emerged, concerning HCV infection and haematological malignancies. In particular, even if some trials reported a higher prevalence of HCV in patients with Multiple Myeloma[36,76,133], this observation has not been confirmed in further reports[24,119,126]. In addition, no statistically significant association has been found between anti-HCV sero-positivity and Hodgkin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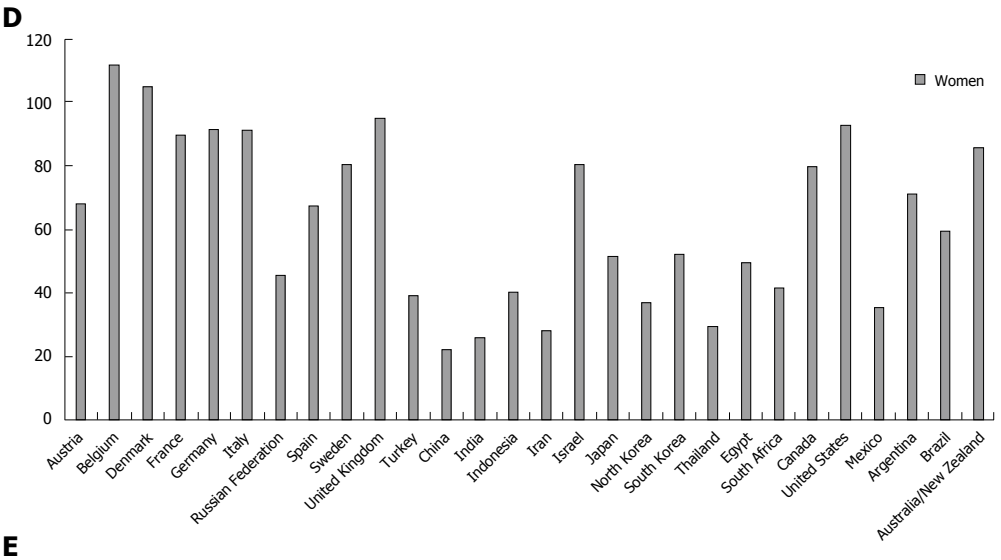
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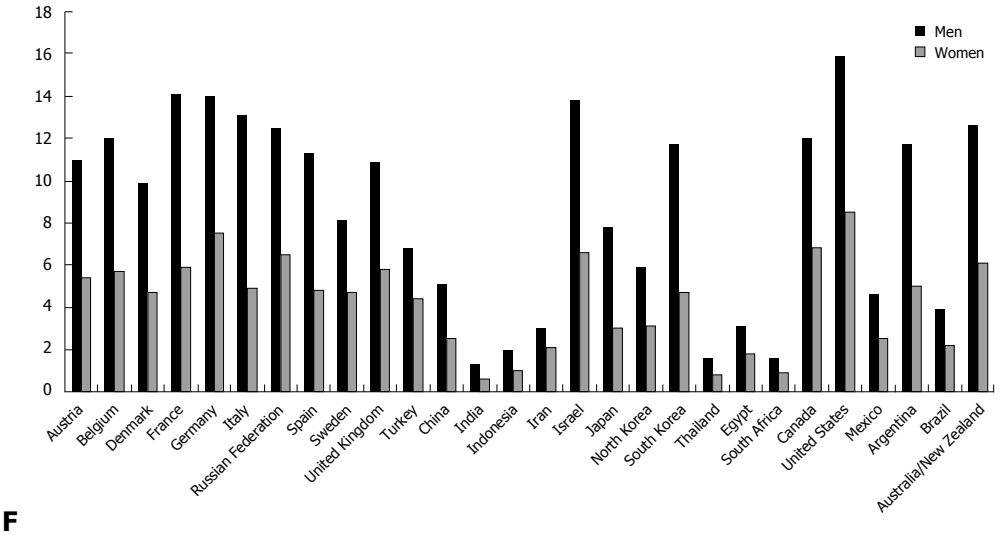
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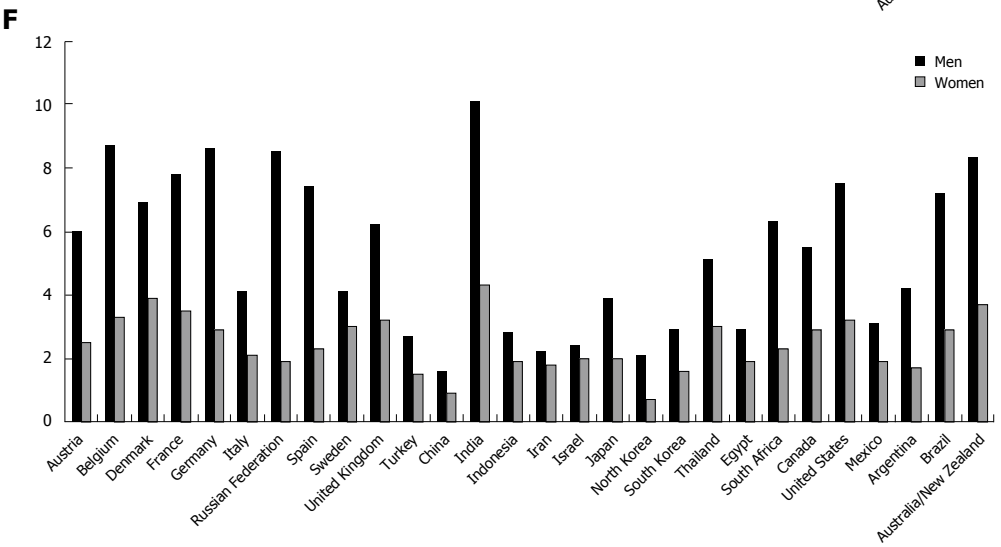
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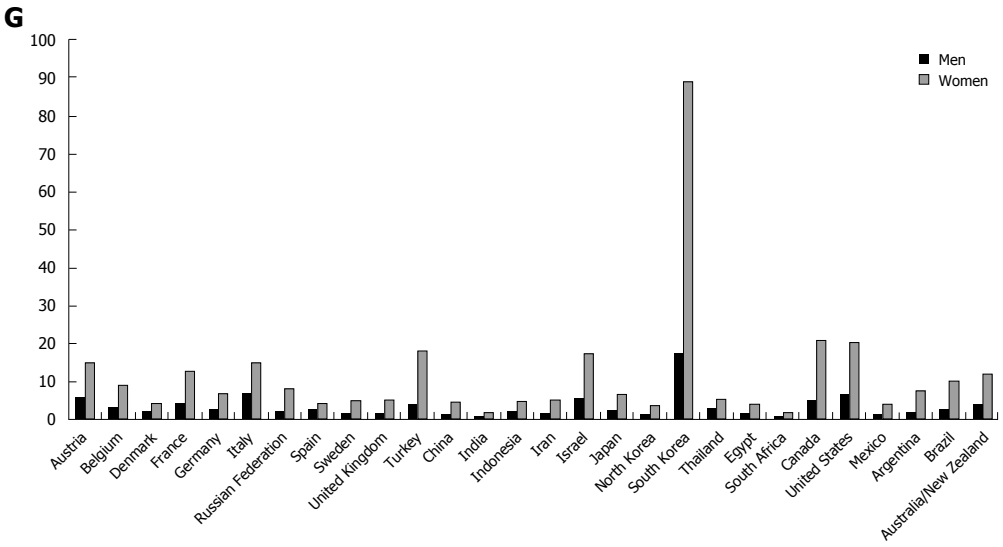

Figure 3 Age-standardized incidence rates of each malignancy per 100000 person-years are reported for sex and for different countries. A: Incidence rates of non-hodgkin-lymphomas (GLOBOCAN 2012); B: Incidence rates of cholangiocarcinoma (by Shin HR, *Asian Pacific Journal of Cancer Prevention* 2010; 11); C: Incidence rates of pancreatic cancer (GLOBOCAN 2012); D: Incidence rates of breast cancer (GLOBOCAN 2012); E: incidence rates of kidney cancer (GLOBOCAN 2012); F: Incidence rates of oral/skin cancers (GLOBOCAN 2012); G: Incidence rates of thyroid cancer (GLOBOCAN 2012).

Lymphoma risk. To date, no studies have evaluated whether some risk factors, such as smoking habit, alcohol use or diabetes may act in cooperation with this virus and increase the risk of lymphoprolipherative disorders. The results of our research, concerning the possible association between HCV infection and hematopoietic malignancies, studies not considered, as well as meta-analyses are summarised in Tables 1, 8 and 9. Figure 3A shows the age-standardized incidence rates of main haematopoietic malignancies per 100000 person-years.

HCV and cholangiocarcinoma risk

Colangiocarcinoma (CCAs) arises from the biliary tract and can be classified into two major types with respect to location: intrahepatic cholangiocarcinoma (ICCA) and extrahepatic cholangiocarcinoma (ECCA). The latter form of malignancy may be further divided into ductal or peri-hilar cancers. The second-order bile ducts and the cystic duct represent the point of distinction between ICCAs and peri-hilar CCAs as well as respectively. The importance of this distinct classification reflects differences in clinical presentation, natural history and treatment of intra- and extra-hepatic cholangiocarcinomas.

Overall, a large series of trials, have been performed in different populations and geographical areas. Some of these studies have been carried out both in areas with an elevated prevalence of cholangiocarcinoma, including China, Korea, Japan and Egypt, and in regions with low prevalence of this cancer, including Italy, United States and Denmark. Therefore, these reports may be considered as a rather representative estimation of the real epidemiological burden of this tumour worldwide. In our systematic review we identified 36 studies. The aim, design, inclusion criteria and definition of controls widely varied among the identified trials and some of these have not distinguished among ICCs from ECCs. In particular, 6 have been carried out in United States, 3 in China, 2 in Korea, 9 in Japan, 4 in Thailand, 3 in Italy, 1 in Egypt, 1 in Iran, 1 in Greece, although a low number of studies Northern Europe. However, from the identified studies HCV infection has emerged as risk for ICC, but not for ECC, in a large number of distinct countries worldwide, even if, in some regions in Southern-East Asia, other factors are potentially involved in CCAs development. In these areas, further infectious agents, such as Opisthorchis viverrini and Clonorchis sinensis, represent risk factors for CCAs. In available meta-analyses, the presence of HCV was associated with a statistically significant increased risk of ICC incidence, with an OR ranging from 3.42 (95%CI: 1.96-5.99) to 4.84 (95%CI: 2.41-9.71)[168,190]. The results of our review, concerning the possible association between HCV infection and CCA risk, studies not considered, as well as meta-analyses are summarised in Tables 2, 10 and 11. Age-standardized incidence rates of ICC malignancies per 100000 person-years is reported in Figure 3B.

HCV and pancreatic cancer risk

Until few years ago, although it was well-known that several viruses, including HCV, may infect pancreas and cause the acute inflammation of this organ[230], no studies had been specifically designed to investigate the possible role of HCV in the PDAC development. Different viral and host factors have contributed to make the study of the pancreas extremely hard, including the localization of this organ in retro-peritoneum, the small size of precursor malignant lesions, the difficulty to identify HCV antigens and/or

Table 1 Characteristics of available studies, reported in English, designed to assess the association between hepatitis C virus infection and haematopoietic malignancies

Author/Journal/ Publication year	Study design	Diagnosis	HCV positive HM/total HM	Control source	HCV positive controls/total controls	Percentage of HCV-positive cases with 95%CI	Main conclusions
Akdogan M *Turk J Gastroenterol* 1998	Case series study with control group Period: NR	All lymphomas: NHLs: 30 HL: 18 NHLs NHL classification: Working Formulation	(1) NHL: 4/30 (13.3%) (2) Patients with Hodgkin Lymphoma	(2) Healthy blood donors	(1) 17/9488 (0.8%)	13.3 (3.8-30.7)	Increased prevalence of HCV persistent infection in patients with NHL, but not in patients with HL, in comparison with general population
Amin J *J Hepatol* 2006	Community-based cohort-study Period: 1990-2002	NHLs Cohort of HCV positive patients: 75834, Cohort of HBV/ HCV positive patients: 2604 Incidence of LNHs observed in the study cohort was compared to expected incidence derived from New South Wales population cancer rates by calculating standardised incidence ratios	Individuals with HCV infection: 75834 LNH cases detected: 33	Incidence observed in the study cohort was compared to expected incidence derived from NSW population cancer rates by calculating standardised incidence ratios (SIR)	SIR: 0.9 (0.6-1.2)	0.04 (0.03-0.05)	In HCV infection group no increased overall risk of NHL-cell lymphoma, but, a number of B-cell NHLs (diffuse NHL, immunoproliferative malignancies and chronic lymphocytic leukaemias) had SIRs greater than one
Anderson LA *Epidemiol Biomarkers Prev* 2008	Population-based nested case-control study of hematopoietic malignancies Period: 1993 and 2002	Subjects with hematopoietic malignancies identified, using SEER-Medicare data. SEER program: a cancer surveillance program supported by the National Cancer Institute and covering about 25% of United States population NHL classification: World Health Organization classification Myeloproliferative malignancies classification: acute- and chronic myeloid leukaemia, myelodysplastic syndrome, chronic myeloproliferative disease	195/61464 (0.3%) cases with Hemato-poietic malignancies identified NHLs: 103/33940 (0.3%) DLBCL: 34/10144 (0.3%) BL: 2/197 (1.5%) MZL: 12/1908 (0.6%) FL: 19/4491 (0.4%) CLL: 23/10170 (0.2%) LL: 2/1148 HL: 3/1155 (0.3%) PCM: 31/9995 (0.3%) Myeloid neoplasm: 47/11945 (0.4%) AML: 23/6068 (0.4%) CML: 1/1528 (0.1%) MS: 18/3084 (0.6%) CMD: 1/1346 (0.1%)	Controls were identified by means of Medicare, a federally funded program administered by the Centres for Medicare and Medicaid Services, For each included case, two controls were selected at random from the 5% random sample of Medicare beneficiaries	264/122531 (0.2%) population-based controls identified	0.3 (0.2-0.4)	Association between HCV and elevated risk of NHLs and acute myeloid leukemia. HCV may induce lymphoproliferative malignancies through chronic immune stimulation
Arcaini L *Clinical Lymphoma, Myeloma & Leukemia* 2011	Case series study with control group Period: NR	Splenic MZLs NHL classification: World Health Organization classification	25/92 Splenic MZL patients (27.2%)	Patients (122) with WMc 66/122 subjects with HCV markers	6/66 WMc patients (9%)	27.2 (18.1-36.2)	Despite similar outcomes among SMZL and WM, SMZL appears as a disease with distinct clinical and histologic characteristics, and a peculiar association with HCV infection

Arican A *Med Oncol* 2000	Case series Period: February-October 1997	NHLs Low-grade: 12 (27%) Intermediate grade: 24 (55%) High-grade: 8 (18%) NHL classification: Working Formulation	2/44 (4.5%)	NR	NR	4.5 (0-10.7)	No association between HCV chronic infection and NHL development in this study. The prevalence of HCV infection reported to be 0.3%-1.5% in healthy Turkish-blood donors in previous studies be 1.5% in healthy Turkish-blood donors in previous
Aviles A *Med Oncol* 2003	Case-control study Period: January 1997-December 1999	B-cell NHLs: 416 Diffuse large cell: 236 Follicular: 97 Marginal B-cell zone: 83 NHL classification: World Health Organization classification	B-cell NHLs 2/416 (0.5%)	Group 1: 682 first-degree relatives (spouses, children, fathers, and brothers of the patient) living in the neighboring area of the patient. Group 2: 832 healthy blood donors, donating during the same period of time at the central blood bank. Group 3: Neoplastic disease group, with 408 patients with solid tumors, breast cancer:127 colon cancer: 94 gastric cancer; 79 lung cancer: 98 Group 4: 353 patients with HCV-positive related chronic liver disease	Prevalence of HCV equal to: (1) 0 among first-degree relatives of patients (2) 0.12 (0.02-0.88) among healthy blood donors (3) 0.56, (0.28-0.75). among patients with solid tumors (4) No patients with HCV chronic liver disease developed malignant lymphoma in a median follow-up of 7.9 yr	0.5 (0-1.1)	Association between HCV infection and development of malignant lymphoma represents an hazardous observation, the close association reported in areas with a higher prevalence of HCV infection has to be considered with caution, because other epidemiological factors have not been considered, such as a high prevalence of HCV infection compared to other areas
Bauduer F *Hematol Cell Ther* 1999	Case series Period: January 1995-June 1998	NHLs: 136 subjects B-cell-NHLs: 110 patients NHL classification: Revised European American Lymphoma (REAL) histological scheme	2/136 (1.5%)	NR	NR	1.5 (0-3.4)	No evidence of relationship between HCV and NHLs
Besson C *J Clin Oncol* 2006	Case control Period: March 1993-June 2002	B-NHL (DLBCL) NHL classification: Working Formulation	26/5586 (0.5%)	(1) HCV negative patients with DLCL enrolled in the present study (2) individuals with DLCL randomly chosen among HCV-negative patients included in the GELA program	(1) 5586 (2) 35	0.5 (0.29-0.64)	HCV-positive patients with DLBCL differ from other patients both at presentation and during chemotherapy. Specific protocols evaluating antiviral therapy should be designed for these patients
Bianco E *Haematologica* 2004	Italian multi-center case-control study Period: January 1998 -February 2001	All lymphomas: 637 HD: 157 CLL: 100 ALL: 54 MM: 107 AML: 140 CML: 49 T-NHL: 30 NHL classification for T-NHLs: REAL/WHO classification	44/637 (6.9%) HD: 5/157 (3.2%) CLL: 9/100 (9%) ALL: 4/54 (7.6%) MM: 5/107 (4.7%) AML: 11/140 (7.9%) CML: 6/49 (12.2%) T-NHL 4/30 (13.8%)	Patients from other departments of the same hospitals: the departments of dentistry, dermatology, general surgery, gynecology, internal medicine, ophthalmology, orthopedics, otorhinolaryngology, and traumatology	22/396 (5.6%)	6.9 (4.9-8.8)	Possible association of HCV infection not only with B-NHL but also with some other lymphoid and myeloid malignancies, however no definitive significant results, due to the absence of large groups of patients to confirm this assumption

Bronowicki JP *Hepatology* 2003	Case records Data obtained from the hepatology gastroenterology, hematology, internal medicine and pathology departments of 64 French hospitals Period: 1992-1999	All PLL: 31 cases, 27/31 patients with a B-cell lymphoma: -DLBCL: 22, -BL: 1, -EMZBL of mucosa-associated lymphoid tissue type: 3, unclassified, small B-cell lymphoma:1, T-cell lymphomas: 4 NHL classification: World Health Organization classification	HCV-test available for 28 subjects, HCV test available in 23 patients with B-cell PLL 1 HCV positive patient with peripheral T-cell lymphoma 5/23 (21.7%)	NR	NR	21.7 (7.5- 43.7)	This study confirms the rarity of PLL and demonstrates an increased prevalence of HCV infection
Cavanna L *Haematologica* 1995	Case- control study Period: 1985-1990	All LPDs: 300 patients Anti-HCV positive patients 57/300 (19.7%) NHLs: 150; HL: 20 CLL: 40 Plasma cell discrasias: 90	NHL: 38/150 (25.3%) HL: 2/20 (10%) CLL: 2/40 (5%) Plasma cell discrasias: 15/90(16%)	Blood donors	53/3108 (1.7%)	25.3 (18.3-32.3)	High prevalence of anti-HCV antibodies among patients with lymphoprolipherative disorders as compared with the control group of healthy blood donors
Caviglia GP J *Gastroenterol Hepatol* 2014	Cohort study Period: January 2006 -December 2013	1313 patients with chronic HCV hepatitis 121 patients with extra-hepatic manifestations: B-NHL: 41/1323 (3.1%) MCS: 25/1323 (1.9%) MGUS: 55/1323 (4.2%) NHL classification: World Health Organization classification	B-cell NHL: 41 MZL: 15 (36.6%), had DLBCL: 10 (24.4%), FL: 4 (9.8%) LPL; 1 (2.4%), MM: 1 (2.4%), CLL: 1 (2.4%) and B-NHL not otherwise specified: 9 (22%)	Controls selected on the basis of the absence of extra-hepatic manifestation of HCV infection	130 HCV positive subjects without extrahepatic manifestation	3.1 (2.2-4)	Cirrhosis is an additional risk factor for the development of lymphoproliferative disorders in patients with chronic HCV infection
Chindamo MC *Oncol Rep* 2002	Case series with control group Period: May 1995 -September 1998	All lymphomas: 207 -HL: 67 -B-NHL: 87 -T-NHL: 22 -CLL: 31 NHL classification: Revised European American Lymphoma (REAL) histological scheme	B-cell NHL: 8/87 (9.2%)	(1) Blood donors (2) Other haematological malignancies (Hodgkin's disease and chronic lymphocytic leukaemia)	(1) 472/39371 (1.2%) (2) 2/98 (2%)	9.2 (3.1-15.2)	Association between HCV infection and NHLs
Chuang SS *J Clin Pathol* 2010	Case-control study Period: January 2004 -December 2008	All malignancies: 346 -HL: 25 (3HCV+) -B-NHL: 321 (DLBCL, FC CLL, MZL, BL, others) -T- or NK/T-cell NHL: 55 NHL classification: World Health Organization classification	All NHL: 35/321 (11%) B-cell NHL: 34/266 (12.8%) (3/38 with HBV coinfection)	Healthy Taiwanese subjects	15/824 (1.8%)	12.8 (8.7-16.8)	The incidence of HCV infection among lymphoma patients in Taiwan was significantly higher than that for healthy controls Non-MALT (nodal and splenic) MZL was the only group significantly associated with HCV
Cocco P *Int J Hematol* 2008	Case-control study Period: -February 1999 - October 2002 - January 2002 - July 2003	All malignancies (277): -HL: 13 -NHL: 264 (DLBCL, FC CLL, MZL, MM, T-cell NHL, others) NHL classification: World Health Organization classification	(1) All B cell- NHL: 20/237 (8.4%) (2) NHLs (excluding CLL and MM): 15/177 (8.5%)	Randomly selected controls from population registrars	9/217 (4.1%)	(1) 8.4 (4.9-11.9) (2) 8.5 (4.3-12.5)	Acute or chronic hepatitis C is associated with a consistent risk increase in all lymphoma subtypes, but follicular lymphoma

Collier JD *Hepatology* 1999	Case series with control group Period: February 1997 and May 1997	B-cell NHLs: 100 NHL classification: Working Formulation	1/100 (1%)	In-Hospital patients with nonhematologic malignancies, treated at the Princess Margaret Hospital	1/100 (1%)	1 (0-3)	No association between hepatitis C and B-cell lymphoma
Cowgill KD *Int J Epidemiol* 2004	Case-control study Period: October 1999- and January 2003	B-cell NHL: 220 NHL classification: NR	Total: 106/220 (48.1%) (1) anti-HCV+/RNA- 12/220 (5.4%) (2) anti-HCV+/RNA+ 94/220 (42.7%)	In-Hospital patients with fractures, treated at the Kasr El-Aini Orthopaedic Hospital,	Total: 80/222 (36%) (1) anti-HCV+/ RNA-28/222 (12.6%) (2) anti-HCV+/RNA+ 52/222 (23.4%)	48.2 (41.5-54.7)	Strong association between chronic HCV infection and risk of developing NHL, persisting after adjustment in multivariate models and after several sensitivity analyses
Cucuianu A *Br J Haematol* 1999	Case series with control group Period: December 1997 and March 1999	All B-cell NHL: 68 NHL classification: Working Formulation	20/68 (29.5%)	Non-hospitalized Romanian individuals	46/943 (4.9%)	9.1 (5.3-12.9)	Detection of high prevalence (29.5%) of anti-HCV in patients with NHL, especially in low-grade types
De Renzo A *Haematologica* 2002	Case-control Period: NR	All LPDs: 227 -B-cell LPds: 127 -HL 100 NHL classification: Revised European American Lymphoma (REAL) histological scheme	B-cell LPds: 22/127 (17.3%) B-NHL 12/61(19.7%) MM 4/48 (8.3%) WM 4/9 44.4%) CLL 2/9 (22.2%)	A group of occasional blood donors from the same geographical area, studied as healthy controls	-HL 2/100 (2%) -Controls: 2/110 (1.8%)	19.7 (9.7-29.6)	Detection, in Southern Italy, of a higher prevalence of HCV infection in patients suffering from B-LPD in comparison with healthy subjects, particularly in patients with B-cell-NHL, CLL and WMc
De Renzo A *Euro J Haematology* 2008	Case series Period: 1990-2005	All NHLs patients observed: 550 Primary hepatic lymphomas (PHL): 6 Primary splenic Lymphomas (PSL): 19 NHL classification: World Health Organization classification	PHL: 4/6 PSL: 13/19	NR	NR	PHL 66.7 (22.3-95.7) PSL 68.4 (43.5-87.4)	High prevalence of HCV infection among patients with rare haematologic malignancies (PHL and PSL), favourable outcome of these subjects
De Rosa G *Am J Hematol* 1997	Case series with control group Period: November 1994 -November 1995	All Lympho-prolipherative Disorders (315): (1) No-B LPD: 52 HD: 43 (1 HCV+) T-NHL: 9 (2) B LPD: 272, including; NHL-B-cell lymphoma, CLL, HCL, MGUS, WMc, MM, (59 HCV+) NHL classification: Working Formulation	B-cell NHL: 21/91 (23.1%)	(1) Patients with Hodgkin Lymphoma (2) Healthy blood donors	(1) 1/43 (2.3%) 0/9 (2) 30/1568 (1.9%)	23.1 (14.4-33.7)	Detection of a higher prevalence of anti-HCV antibodies patients with B-Lymphoprolipherative disorders, as compared to the normal population and to patients with a non-B-lymphoprolipherative disorders
De Vita S *Br J Cancer* 1998	Case-control study Period: January 1994-June 1997	All malignancies 84 NHLs NHL classification: Working Formulation	20/84 (23.8%)	Controls recruited at Aviano, with cancers in: ovary: 13 uterus:14, colon-rectum:13, pancreas:10, lung: 8, stomach: 6, oesophagus: 4 other sites: 5 HCC: 27	Controls: 3/73 (4.1%) HCC: 11/27 (40.7%)	23.8 (15.2-34.3)	Detection of a higher than expected prevalence of HCV infection in B-cell NHL patients

Duberg AS *Hepatology* 2005	Nationwide cohort of HCV-infected persons Cancer Registry used to identify all incident cancers diagnosed in the cohort malignant NHL Period: 1990-2000	All malignancies: Patients with B-Cell NHLs, after exclusion of patients with HIV coinfection: 16 CLL: 4 MM:7 ALL: 1 HL: 1 NHL classification: NR	B-Cell NHLs: 16 in 27150 HCV positive patients included in the cohort, HCV infection diagnosis made to the Swedish Institute for Infectious Disease Control (SMI)	NR	NR	0.06 (0.04-0.1)	A significantly increased risk of NHL and MM observed in this study, although an underestimation of the risk may have been caused by the delayed diagnosis of HCV
Ellenrieder VJ *Hepatol* 1998	Case series Period: 1991- 1995	B-cell NHLs: Low-grade B-cell NHL: 55 High- low-grade B-cell: 14 NHL classification: Kiel Classification	3/69 (4.3%) CLL: 1/14 CC: 0/4 CB: 1/14 CCBC: 1/19 IC = 0/18	NR	NR	4.3 (0.9-12.2)	No aetiological role of HCV in the development of NHL in German
El-Serag HB *Hepatology* 2002	Cohort study Period: 1992- 1999	Identification of LNHs cases by means of ICD-9-CM diagnosis codes NHL classification: NR	421/34204 (1.23%)	34204 HCV positive patients and 136816 randomly selected patients without HCV (controls)	1669/136816 (1.22%)	1.23 (1.1-1.3)	Significant high association between HCV infection and NHL, after adjustment for age
Engels EA *Int J Cancer* 2004	Case-control study Period: July 1998-June 2000	All NHL subtypes: (1) 32/813 (3.9%) (2) Low-grade B-cell NHL 18/411 (4.4%) (3) Intermediate-and high-grade B-cell NHL 8/275 (2.9%) (4) T-cell NHL 2/50 (4.0%) (5) other/unknown 4/77 (5.2%) NHL classification: Revised European American Lymphoma (REAL) histological scheme	26/686 (3.8%)	Eligible cases and controls sampled from individuals 20-74 yr old, prospectively identified by using Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute (NCI)	14/684 (2.1%)	3.8 (2.3-5.2)	Detection of an association between HCV infection and NHL in the United States. HCV infection may be a cause of NHL
Ferri C *Br J Haematol* 1994	Case series with control group Period: NR	B-cell NHL: 50 NHL classification: Working Formulation	B-cell NHL: 17/50 (34%)	(1) Patients with Hodgkin Lymphoma (2) Healthy subjects (3) anti-HCV negative patients with type B or delta chronic active hepatitis	1/30 (3%) 30 15 HCV prevalence in in the healthy Italian population: 1.3%	34 (20.8-47.1)	Presence of HCV infection in a substantial number of unselected NHL patients, particularly in comparison with HCV prevalence in control groups and in healthy Italian population
Franceschi S *Cancer Epidemiol Biomarkers Prev* 2011	Nested case-control study Period: standardized lifestyle and personal history questionnaires collected between 1991 and 2000. Vital status followed up to 2004 and 2006	All lymphomas: 1023 cases NHL: 739 MM: 238 HL: 46 HCV positive: 12/1023 (1.17%) NHL classification: World Health Organization classification	B-cell NHLs: 628/1023 (61.4%) Number of HCV positive patients in B-NHLs not reported 9/730 HCV positive patients in all NHLs 14/1454 HCV positive in controls HL: 2/46 (4.3%) MM: 1/238 (0.4%)	Lymphoid tissue Malignancies classified according to the second revision of the International Classification of Diseases for Oncology (ICD-O-2) and to the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Third Edition	18/2028 controls (0.9%)	61.4 (58.4-64.3)	The present study neither weakened nor strengthened the evidence of an association between HCV and NHL or other lymphoid tissue malignancies

Gentile G *Cancer Epidemiol Biomarkers Prev* 1996	Hospital-based case-control study of risk factors for acute leukemias Period: 1 November 1986 - 31 March 1990	All acute leukemias: 430 Diagnosis performed by means of: French-American-British classification of bone marrow aspirates for acute leukemias and RAEB, whereas diagnosis for CML was based on typical dinical and cytogenetic laboratory features	All acute leukemias: 27/430 (6.3%): AML: 15/172 (8.7%) ALL: 5/67 (7.5%) CML: 2/125 (1.6%) RAEB: 5/66 (7.6%)	Controls recruited in the region of the three hospitals (Rome, Bologna, Pavia) during the study period among outpatients without hematobogical malignancies who were seen in the same hospitals at which cases had been identified	44/857 (5.1%)	6.3 (3.9-8.5)	Association between acute leukemias, RAEB, and CML Possible association between hepatitis B virus, AML, RAEB, and CML, but further confirmation required
Genvresse I *Ann Hematol* 2000	Case series Period: 1995-2000	All lymphomas: 119 (1) B-NHLs: 105 (2) T-NHLs: 14 NHL classification: REAL histological scheme	(1) 2/105 (1.9%) (2) 0/14	NR	NR	1.9 (0-4.5)	Possible HCV involvement in NHLs development *via* a continuous antigenic stimulation, leading to a B-cell clonal expansion
Germanidis G *Blood* 1999	Case series with control group Period: January 1994 -July 1997	B-NHL: 201 HD: 94 NHL classification: Revised European American Lymphoma (REAL) histological scheme	B-NHL: 4/201 (2%)	Hematologic malignancies different from B-cell NHL (HD)	1/94 (1.1%)	2 (0-3.9)	No existence of a significant relationship between HCV infection and B-NHL in France
Giordano TP *JAMA* 2007	Cohort study Period: 1997-2004	Identification of LNH cases by means of ICD-9-CM diagnosis codes NHL classification: NHL (200, 202.0-202.2, 202.8), WMc (273.0, 273.3), HL (201), MM (203.0-203.1, 238.6), ALL (204.0), CLL (204.1) AnLLs 205.0, 206.0), CML (205.1), other leukemia (204.2, 204.8-204.9, 205.2, 205.8-205.9, 206.1-206.2, 206.8-206.9, 207.8, 208.0-208.2, 208.88.9), MGUS (273.1, 273.2)	HCV- positive cohort: 146394 patients During follow-up, 813 patients in HCV-infected cohort (0.5%) had a HIV diagnosis NHL: 319 HL: 65 MM: 95 CCL:69 ALL: 27 WMc: 67 CML: 30	Inpatients records from more than 150 United States Veterans Affairs (VA) hospitals in the Patients' treatment file and outpatients records from any VA facility in the Output Clinic File	HCV- negative cohort: 572293 patients. During follow-up, 35696 uninfected HCV patients (6.2%) had a recorded HCV diagnosis and 1539 patients (0.3%) a HIV diagnosis NHL: 1040 HL: 295 MM: 431 CCL:343 ALL; 184 WMc: 98 CML: 163	0.2 (0.19-0.25)	An increased risk of: (1) non-Hodgkin lymphoma overall (20%-30%), (2) Waldenström macroglobulinemia, a low-grade lymphoma (3-fold higher risk), (3) cryoglobulinemia, in subjects with HCV infection. An etiological role for HCV, in causing lymphoproliferation and non-Hodgkin lymphoma, supported by these results
Goldman L *Cancer Causes Control* 2009	Case-control study Period: October 1999 -March 2004	All lymphomas: 139/296 (47%) -T-NHL: 8/24 (34.8%) -DLBCL:79/146 (54.9%) -MZL: 14/24 (58.3%) -CLL: 24/58 (41.4%) -FC: 9/23 (40.9%) -MCL: 5/16 (31.3%) NHL classification: World Health Organization classification	B-NHL: 131/272 (48.2%)	Cancer-free subjects, sampled from the Kasr El Aini Faculty of Medicine Orthopaedic Hospital in Cairo	283/786 (37.4%)	48.2 (42.2-54.1)	HCV is a risk factor for diffuse large B cell, marginal zone, and follicular lymphomas in Egypt

Guida M *Leukemia* 2002	Case-control study Period: September 1999-October 2001	All Lymphomas: 12/60 (20%) MM: 5/60 B-NHL: 55/60 NHL classification: Working Formulation	B-NHL: 12/55 (21.8%)	Control patients with non-hematological malignancies recruited from the Surgery Department the Oncology Institute of Bari (Italy)	9/63 (14.2%)	21.8 (10.9-32.7)	Moderate increase of prevalence of HCV infection among patients with B cell lymphoproliferative disorders in a very homogeneous population of southern Italy
Hanley J *Lancet* 1996	Case series Period: NR	All LPDs: 72. B-cell NHLs: 38 MM: 24 MGUS: 10 NHL classification: Working Formulation	0/72	NR	NR	0 (0-4.9)	No association between chronic HCV infection and risk of NHLs development
Harakati MS *Saudi Med J* 2000	Case series with control group Period	B-cell NHLs: 56 patients NHL classification	B-NHL: 12/56 (21.4%)	(1) Blood donors and general medical patients) (2) Other hematologic malignancies other than B-cell NHL	(1) 3/104 (3%), (2) 2/41 (5%)	21.4 (10.6-32.7)	Higher prevalence of Hepatitis C virus infection in Saudi Arab patients with B-cell non-Hodgkin's lymphoma than in the control groups
Hausfater P *Am J Hematol* 2001	Prospective controlled study Period: June to September 1998	All LPD: 394 B-NHL: 164 HD: 34 CLL: 107 MM: 54 WMc:12 NHL classification: NR	B-NHL: 3/164 (1.8%)	(1) In-Hospital patients without cancers (2) Nonmalignant hematological diseases (3) Hematological malignancies other than B-cell NHL	(1) 3/694 (0.43%) (2) 8/224 (3.6%) (3) 9/425 (2.1%)	1.8 (0-3.8)	No increased prevalence of HCV infection in patients admitted to the Hematology department for B-NHL. No major pathophysiologic role of HCV in lymphoproliferative disorders in Paris
Hwang JP *J Oncol Pract* 2014	Cohort-study Period: January 2004 -April 2011	Patients'data, obtained from four institutional sources: Tumor registry: to assess patients' demographic characteristics Pharmacy informatics: to evaluate chemotherapy drugs and dates administered. Patient accounts: to identify study patients' International Classification of Diseases (ninth edition; ICD-9) codes Laboratory informatics: to determine HCV antibody (anti-HCV) and ALT test dates and results	141877 patients with cancer, who were newly registered at MD Anderson Cancer during the study period. Patients considered in the study: 16, 773. HCV screened subjects: 1628/16773 (9.7%) with NHLs, 1400 patients with anti-HCV test 42 NHLs antiHCV-positive (3%)	NR	NR	3 (2.1-3.9)	HCV screening rates were low, even among patients with risk factors, and the groups with the highest rates of screening did not match the groups with the highest rates of a positive test result
Imai Y *Hepatology* 2002	Cohort study Period: February 1992 -July 1992	NHLs: 187 B-cell NHLs: 156 T-cell NHL:31 NHL classification: World Health Organization classification	21/156 (13.5%)	Use of screening data of 197600 first-time voluntary blood donors to the Osaka Red Cross Blood Center	Expected numbers of anti-HCV-positive patients with NHL categorized by gender and phenotype in general population: 4.64 117	13.5 (8.1-18.8)	A significantly higher frequency of HCV infection in B cell NHL in comparison with that in birth cohort- and sex-matched blood donors; chronic HCV infection may be associated with B-cell NHL in Japan
Isikdogan A *Leuk Lymphoma* 2003	Case series with control group Period: December 1997-September 2001	NHLs: 119 High-grade NHLs: 10 Intermediate-grade: 64 Low-grade: 45 NHL classification: Working formulation	0/119	Subjects admitted as outpatients at Internal Medicine of Dicle Univeristy, Diyarbakir, without history of haematological disordres, during the same period		0 (0-3)	No relationship between HCV and NHLs in the Southeastern Anatolia of Turkey

Iwata H *Haematologica* 2004	Hospital-based case control Study Period: 1995-2001	All NHLs: 145, 140 with anti-HCV test NHL classification: World Health Organization classification	16/140 (11.4%)	Randomly selected controls from patients admitted to the (1) orthopedics (290 patients, 286 with anti-HCV markers) or (2) ear, nose and throat (284 patients, 282 with anti-HCV markers) departments of the hospital	(1) 9//286 (3.1%) (2) 20/282 (7%)	11.4 (6.1-16.7)	Significant association between HCV infection, and malignant lymphoma by multivariate analysis
Izumi T *Blood* 1996	Case series Period: 1992-1997	All lymphomas: 83 patients, B-cell NHLs: 54 Non-B-cell NHLs: 20 HLs: 9 NHL classification: NR	B-cell NHLs: 12/54 (22.2%) Non-B-cell NHLs: 0/20 HLs: 0/9	NR	NR	22.2 (11.2-33.3)	Direct causal relationship between the occurrence of PHSL and chronic HCV infection
Izumi T *Leukemia* 1997	Case series Period: NR	B-cell LPDs: 50 patients B-cell NHLs: 25 MM: 21 WMc: 4 NHL classification: NR	4/25 (16%)	NR	NR	16 (4.5-36.1)	Association between HCv infection and B-cell NHLs
Karavattathayyil SJ *Am J Clin Pathol* 2000	Case series Period: January 1993-December 1996	Patients with B-cell NHLs: 31 NHL classification: World Health Organization classification	Positive HCV-RNA strands: 8/31 (25.8%) Negative HCV-RNA strands: 6/31 (19.4%)	(1) T-cell NHLs: 2 cases (2) HL: 2 cases (3) Patients with lymph nodes removed for reasons other than lymphoma: 28	0/32	Positive HCV-RNA strands: 25.8 (10.4-41.2) Negative HCV-RNA strands 19.4 (5.4-33.2)	Presence of HCV infection in a significant percentage of paraffin-embedded tissue from B-cell NHLs patients, compared with control subjects; detection of negative-strand RNA suggests HCV replication in these tissues, excluding the possibility of contamination with viral RNA or blood
Kashyap A *Ann Intern Med* 1998	Case series with control group Period: February 1992-December 1995	All NHLs: 312 36 HCV positive patients NHL classification: NR	NHLs: 36/312 (11.5%)	(1) Healthy United States blood donors (2) Black and Hispanic patient population at City of Hope National Medical Center	(1) (0.4%) (2) approximately 25%	11.5 (8-15.1)	Prevalence of HCV positivity is still much higher than expected, even after adjustment for differences in patient demographic characteristics
Kaya H *Clin Lab Haematol* 2002	Case-control study Period: NR	All NHLs: 70 patients Low-grade NHLs: 22, Intermediate- grade NHLs: 17 high-grade NHLs: 31 NHL classification: Working Formulation	1/70 (1.4%)	Healthy-subjects admitted at Departments of Haematology, Ataturk University, Erzurum	1/70 (1.4%)	1.4 (0-4.2)	No aetiologic role of HCV in NHL development
Kim JH *Jpn J Cancer Res* 2002	Case-control study Period: January 1997 -December 1998	NHLs: 233 patients 214 patients with anti-HCV positivity NHL classification: Working Formulation	7/214 (3.3%)	Control groups comprised patients with (1) non-hematological malignancy (control group 1) and subjects with (2) non-malignant conditions (control group 2) diagnosed at Seoul National University Hospital during the same period. For each case, four controls selected	(1) 7/426 (1.6%) (2) 12/439 (2.7%)	3.3 (0.8-5.6)	No association between NHL and HCV infection
King PD *Clin Lab Haematol* 1998	Case series series with control group Period: June 1995-May 1997	All lymphomas: 93 patients. NHLs: 73 patients HL: 20 patients 438 HCV positive patients NHL classification: Working Formulation	1/73 (1.4%)	Patients with HL admitted at Department of Gastroenterology, University of Missouri Hospital	0/20 1/438 (0.22%) patients developed NHL	1.4 (0-4)	No association between NHL and HCV infection

Kocabaş E *Eur J Epidemiol* 1997	Case series with control group Period: October 1993-March1994	137 Children with malignancies: Acute leukemia: 48 Lymphoma: 51 Solid tumours: 38 NHL classification:	8/137 children were anti HCV positive, 129 patients were anti- HCV negative, but 7/129 were HCV-RNA positive	Children admitted, at Balcah Hospital, Adana, during the same period with diseases other than malignancies	1/45	5.8 (1.9-9.7)	HCV infection is common among Turkish children with different types of cancer
Kuniyoshi M *J Gastroenterol Hepatol* 2001	Case-control Study Period:January 1990-March 1998	NHLs 348 patients 20/348 (8.1%) HCV positive patients with NHLs NHL classification: Working Formulation	B-cell NHLs: 15/348 (4.3%)	1658234 blood donors, representing general population in the area (Fukuoka, Japan)	11922/1658234 (0.72%)	4.3 (2.1-6.4)	Involvement of HCV infection in the development of a subgroup of NHL, in males
Luppi M *Ann Oncol* 1998	Case series Period: January 1989-August 1993	B-cell NHLs: 157 patients NHL classification: Revised European American Lymphoma (REAL) histological scheme	35/157 (22.3%) HCV positive B-cell NHLs: LDBCL 8/35 (23%) FC: 14/35 (40%) LPL: 2/35 (6%) 122/157 (67.7%) HCV negative B-cell NHLs	NR	NR	22.3 (15.8-28.8)	Association of HCV infection with the malignant proliferation of defined B-cell subsets other than the immunoglobulin Mk B-cell subset involved in the pathogenesis of mixed cryoglobulinemia type II and associated lymphoplasmacytoid lymphoma type
Markovic *Hepato-Gastroenterology* 1999	Case-series Period: January 1991-April 1996	All lymphomas: 305 patients NHLs: 300 patients HL: 5 patients 181 patients with anti-HCV test NHL classification: NR	3/181 (1.6%)	NR	NR	1.7 (0-3.5)	No association between HCV infection and non-Hodgkin's lymphomas, because of low HCV prevalence in Slovenia
Mazzaro C *Br J Haematol* 1996	Case-series with control group Period: NR	All lymphomas: 199 patients Low-grade NHLs: 105 (52.7%) Intermediate grade NHLs: 48 (24.1%) High-grade: 39 (19.6%) MALT: 5 (2.5%) T-cell NHLs: 2 (1%) NHL classification: Working Formulation	57/199 (28.6%) Low-grade NHLs: 40/110 (36.47%) Intermediate grade NHLs: 6/48 (12.5%) High-grade: 9/39 (23.1%)	(1) Patients with other haematological malignancies, including HL (21 patients), CLL (41), myelodysplastic syndrome (72), plasma cell myeloma (19); (2) general population of two towns in the same geographical area (Cormons and Campogalliano) in the cohort study called Dyonisos project	(1) 5/153 (3.1%) (2) 199/6917 (2.9%)	28.6 (22.4-34.9)	Important role of HCV in the development of low-grade non-Hodgkin's lymphomas
McColl MD *Leuk Lymphoma* 1997	Case series Period: NR	B-Cell NHL: 72 patients Low-grade: 41 Intermediate-grade: 23 High grade: 8 NHL classification: Working Formulation	0/72	Patients with CLL, recruited at two Hospital in the West of Scotland	0/38	0 (0-9.2)	Possible role of HCV infection in the aetiology of certain subgroups of NHLs, although this effect may be regional
Mele A *Blood* 2003	Multicenter case-study with control group Period: 1998-2001	B-Cell NHL: 400 patients NHL classification: REAL/ World Health Organization classifications	70/400 (17.5%) Aggressive B-NHL: 43/230 (18.7%) Indolent NHL:27/170 (15.9%)	Patients recruited n other departments of the same Hospitals: the departments of dentistry, dermatology, general surgery, gynecology, internal medicine, ophthalmology, orthopedics, otorhinolaryngology and traumatology	22/396 (5.6%)	17.5 (13.8-21.2)	Detection of an association between HCV and B-NHL

Mizorogi F *Intern Med* 2000	Case series with control group Period: January 1993-December 1998	Patients with LPDs: 161, subdivided into 2 groups: (1) patients with B-cell LPDs, including B-cell-NHLs: 100 MM: 17 CLL: 4 (2) patients with non B-cell LPDs: 38 NHL classification: Working Formulation	B-cell NHLs: 17/100 (17%)	Subjects with miscellaneous diseases other than liver diseases or LPDs, used as controls	nonB-cell LPDs: 0/25 34/516 (6.6%)	17 (9.6-24.3)	Higher prevalence of HCV infection in patients with B-cell NHL than in those with non-B-cell NHL and the control group, frequent primary liver involvement and liver-related causes of death in HCV-positive patients with B-cell NHL
Montella M *Leuk Res* 2001	Case-control study Period: January 1997 and December 1999	-B-cell-NHLs: 101 -HL: 63 -T-cell NHLs: 10 -MM: 41 NHL classification: Working Formulation/REAL	25/101 (24.8%)	Controls: patients with no history of malignant tumor, admitted to the National Cancer Institute and Cardarelli Hospital of Naples, in the same period	-Controls: 17/226 (8%) -HL: 6/63 (10%) -T-cell NHLs: 3/10 (30%) -MM: 13/41 (32%)	24.8 (16.3-33.1)	Detection of a significant association between HCV infection and B-cell NHLs in the extranodal localization, and also indicate an association for the nodal seat
Morton LM *Cancer Epidemiol Biomarkers Prev* 2004	Population-based case-control study of women in Connecticut The Yale Comprehensive Cancer Center's Rapid Case Ascertainment Shared Resource (RCA), a part of the Connecticut Tumor Registry (CTR), a population-based tumor registry Period: 1995-2001	All lymphomas: B cell 362 T cell 34 Others: 60 NHL classification: World Health Organization classification Incident cases of NHL identified by means of (ICD)-O: M-9590-9595, 9670-9687, 9690-9698, 9700-9723	B cell 7/362 (1.9%) T cell 0/4 Others 1/60 (1.6%) Total: 8/464 (2%)	A population-based control group of female residents of Connecticut, aged 21-84, assembled using two methods:- Random digit dialing used to contact women less than 65 yr of age,-random selection from the files of the Centers for Medicare and Medicaid Services for women aged 65 yr and older	5/534 (1%)	1.9 (0.5-3.3)	Indirect HCV involvement in the development of B-NHL, this risk varying by B-NHL subtype among women
Musolino C *Haematologica* 1996	Case series Period: NR	All-NHLs:24 HCV positive: 2 patients HCV-RNA positive: 5 patients NHL classification: Working Formulation	5/24 HCV-RNA positive/ NHLs	NR	NR	20.8 (7.1-42.2)	Possible HCV involvement in NHL development
Musto P *Blood* 1996	Case series with control group Period: NR	B-LPDs B-NHL: 150 HCL: 9 CLL: 41 MM: 90 WMc:13 MGUS: 47 NHL classification: NR	B-NHLs: 40/150 (26.7%) HCL:1/9 (11.1%) CLL: 8/41 (19.5%) MM: 10/90 (11.1%) WMc: 3/13 (23%) MGUS: 6/47 (12.8%)	Patients hospitalized for acute trauma	25/466 (5.4%)	26.7 (19.6-33.7)	A significantly higher prevalence of anti-HCV in patients with B-NHLs than in controls and independent of age
Nicolosi *Guidicelli S Hematol Oncol* 2012	Case-control study Period: July 2001 to March 2002	All lymphomas: 137 NHL classification: World Health Organization's classification	6/137 (4.4%)	Patients observed in Hospital Clinic, Barcelona and San Giovanni Hospital, Bellinzona, (ideally in traumatology and orthopaedic divisions	7/125 (5.6%)	4.4 (0.9-7.8)	Existence of marked geographic differences in the prevalence of HCV in NHL but no significant evidence for an association between HCV and B-cell NHLs

Nieters A *Gastroenterology* 2006	European Multicenter Case-Control Study Period: 1998-2004	Total Lymphomas: 1807 NHL classification: World Health Organization's classification	53/1807 (2.9%)	Controls drawn randomly from population registers of the study regions in Germany and Italy. In the remaining countries, controls recruited from the same hospital as cases	41/1788 (2.3%)	2.9 (2.1-3.7)	Positive association between HCV infection and B-cell lymphoma and a role of viral replication in lymphomagenesis
Ogino H *Hepatol Res* 1999	Case-control sudy Period: 1991-1997	All LPDs: 43 patients NHLs: 33 ALL: 10 NHL classification: Working Formulation	4/33 (12.1%)	(1) 45 patients, undergoing colonscopy from July 1995 to June 1996 (2) 10599 healthy subjects, receiving a general medical check-up in Toyama prefecture from April 1996 to March 1997	2/45 (4.4%)	12.1 (3.4-28.2)	High prevalence of HCV infection in patients with NHL in Toyama prefecture in Japan
Ohsawa M *Int J Cancer* 1999	Cohort-study Period: 1957-1997	Patients with HCV chronic infection, included in the present study: 2162 NHL classification: World Health Organization's classification	Patients developing B-cell NHLs: 4/2162 During follow-up	Expected number of cases of NHLs in the sex-, age- and calendar year-matched general population: 1.90	NR	0.2 (0-0.3)	Chronic HCV infection moderately associated with increased risk of NHL
Okan V *Int J Hematol* 2008	Case series with control group Period: NR	All Lymphomas: 334 NHL classification: World Health Organization's classification	9/334 (2.7%) MM: 1/67 (3.1%) CLL: 2/78 (2.5%) DLBCL: 4/67(6%) Follicular 0/9 Mantle: 1/11 (9%) Other: 0/26 T-cell lymphoid tumors: 1/16 (6.2%) HL: 0/60	Controls recruited, using records from the University blood center in Gaziantep	9/802 (1.1%)	2.7 (0.9-4.4) 6 (0.3-11.6)	Higher HCV- seropositivity rate in patients with DLBCL in comparison with controls. No significant differences in the prevalence of HCV seroposity between patients with lymphoproliferative disorders and controls
Omland LH *Int J Cancer* 2012	Cohort-study Period:1991-2006 Patients and subjects with HCV infection identified by means of: -Danish HCV cohort (DANVIR). -Civil registration system (CRS)-Danish cancer registry (DCR). -Danish national patient registry (DNPR)	10 digit civil registration number assigned to all individuals in Denmark Analysis of the association between HCV and risk of NHL (ICD-10 codes: C82.0-85.9 and C96) NHL classification: Cancers classified according to the "International Classification of Diseases" 7th revision (ICD-7) for the period 1943-1977 and the 10th revision (ICD-10) for the period 1978-2006	-11975 anti- HCV-positive patients LNH cases detected: 12 12/11975: 0.1%	Comparison cohort, which consisted of 6 age- and gender-matched individuals (without a HCV diagnosis) from the general population randomly selected from the CRS, on the day HCV-infection was diagnosed in the corresponding DANVIR cohort member	-71850 anti- HCV-positive patients LNH cases detected: 24	0.1 (0.04-0.15)	Possible increased risk of NHLs in patients with chronic HCV infection
Panovska I *Br J Haematol* 2000	Case-series with control group Period: NR	B-cell-NHLs: 112 NHL classification: REAL histological scheme	1/112 (0.9%)	Patients with other B-cell malignancies HL: 38 CLL: 43, ALL: 9 MM: 26 WMc: 1 Prevalence of HCV carriers in Republic of Macedonia within the general population is equal to 2.0%	1/137 (0.72%)	0.9 (0-2.6)	Low prevalence of HCV infection in patients with B-cell NHL from Macedonia and a lack of association between the two disorders

Park SC *J Med Virol* 2008	Case-control study Period: January 1998-December 2001	235 patients with NHLs, B-cell subtypes: 168 T-cell subtypes: 57 not identified subtypes: 10 NHL classification: NR	5/235 (2.1%) No information about number of patients with HCV infection and B-NHL cases	Patients with advanced gastric cancer diagnosed at the Korea Cancer Center Hospital	7/235 (3%)	2.1 (0.3-3.9)	No association between HCV infection and non-Hodgkin's lymphoma
Paydas S *Br J Cancer* 1999	Case series Period: NR	LPDs: 228 patients NHL: 98 CLL: 38 MM: 47 HD: 36 ALL: 9 NHL classification: NR	NHL: 9/98 (9.2%) CLL: 4/38 (10.5%) MM: 5/47 (10.6%) HD: 7/36 (19.4%) ALL: 1/9 (11.1%)	NR	NR	9.2 (3.4-14.9)	HCV infection as a causative and/or contributing factor in lymphoproliferation in this study
Pellicelli *World J Gastroenterology* 2011	Case-series Period: January 2008 -January 2009	125 patients with B-cell NHLs NHL classification: World Health Organization's classification	24/125 (19.2%)	NR	NR	19.2 (12.3-26.1)	HCV genotypes and duration of HCV infection differed between B-NHL subtypes. Indolent lymphomas can be managed with antiviral treatment, while DLBCL is not affected by the HCV infection
Pioltelli P *Lancet* 1996	Case-series with control groups Period: January-June 1995	All Lymphomas: 204 NHLs: 126 HL: 78 28HCV positive lymphomas NHL classification: Working Formulation	26/126 (20.6%)	(1) HL (2) candidated blood donors (3) elderly people	(1) 2/78 (2) 9/832 (3) 9/94	20.6 (13.5-27.7)	High prevalence of HCV infection in NHLs, in the absence of an increased risk for HCV infection and of a clinical history of MC
Pioltelli P *Am J Hematol* 2000	Case-control study Period: 01/01/96-30/06/97	Patients with B-cell NHLs: 300 NHL classification: Working Formulation (WF) and REAL histological scheme	48/300 (16%)	Individuals consecutively recruited during routine visits at medicine, surgery, or traumatology departments during the recruitment period of the study population (1) Patients with internal and surgical diseases (2) Patients with solid neoplasm (3) Patients with autoimmune disorders	(1) 51/600 (2) 15/247 (3) 6/122	16 (11.8-20.1)	The prevalence of HCV infection is higher in patients with NHLs than in non-neoplastic people and in patients with non-lymphoproliferative malignancies or receiving immunosuppressive treatment, but the small difference among these groups, the identical genotype pattern between NHL and controls do not support the hypothesis that HCV plays a role in lymphomagenesis
Pivetti S *Br J Haematol* 1996	Case-series with control group Period: NR	Patients with LPDs: 167 patients (30 HCV positive) HL: 30 NHLs: 47 CLL: 29 MM: 18 MGUS: 31 WMc: 12 NHL classification: NR	7/47 (14.9%)	(1) Patients with connective tissue diseases (2) Patients with idiopathic thrombocytopenic purpura	(1) 26/100 (26%) (2) 12/33 (36.4%)	14.9 (4.7-25)	HCV may link lymphoid malignancies and autoimmune diseases by skewing the activity of the immune system toward the production of autoAbs
Pozzato G *Blood* 1994	Case series Period: NR	31 patients with MC. 12 patients/31 with low-grade NHLs 26/31 HCV positive NHL classification: Working Formulation	10/12 patients with low-grade NHLs were anti-HCV positive	NR	NR	83.3 (51.6-97.9)	HCV associated with a high prevalence of low-grade non-Hodgkin's lymphomas
Prati D *Br J Haematol* 1999	Case series Period: January 1989 -August 1998	Primary cutaneous B-cell NHL. NHL classification: European Organisation for Research and Therapy of Cancer (EORTC)	1/34 (2.9%)	NR	NR	2.9 (0-8.6)	Primary cutaneous B-cell NHL might represent a distinctive group among B-cell NHLs

Rabkin CS *Blood* 2002	Cohort study Period: June 1959 and September 1966	All LPDs: 95 B-cell NHL: 57 MM: 24 HL: 14. NHL classification: Tumors classified according to the International Classification of Diseases for Oncology, second edition, as NHL (histologic classifications 9590 through 9642 and 9670 through 9698), multiple myeloma (9730 through 9732), or Hodgkin disease (9650 through 9667)	4/95 (4.2%) 0/95 at RIBA 0/95 at HCV-RNA	Study subjects (48 420 individuals) recruited from the Child Health and Development Study (CHDS) cohort established in 1959 at the Kaiser Foundation Health Plan, Oakland, CA	1/48.420 at ELISA 0/48420 at RIBA	4.2 (0.1-8.2)	Not substantial role of chronic HCV infection in the etiology of B-cell neoplasia
Ramos-Casals M *J Rheumatol* 2004	Case series Period: 1994-2000	NHL classification: World Health Organization's classification	6/98	NR	NR	6.1 (1.3-10.8)	Description concerning a triple association of HCV infection, autoimmune diseases and NHLs
Salem AK *Gulf J Oncol* 2009	Case series with control-group Period: January 2005-January 2007	All NHLs: 192 patients NHL classification: NR	29/192 (15.1%)	Patients checked for HCV infection with several acute medical conditions and coming from different parts of the country	814/20329 (4%)	15.1 (10-20.1)	Higher prevalence of HCV infection among Yemeni patients with NHL than among persons in the control group
Salem Z *Eur J Epidemiol* 2003	Case-series with control group Period: NR	B-cell NHL: 35 patients. NHL classification: NR	0/35	(1) Patients with different malignancies (malignant myeloproliferative disorders: 12, malignant lymphoproliferative disorders: 28, non haematological cancers: 23 patients) (2) Healthy blood donors and patients without malignant conditions, attending General Medicine of American university, Beirut	(1) 0/63 (2) 0/220	0 (0 -10)	No association between HCV infection and B-cell NHLs development in Lebanese patients
Sansonno D *Blood* 1996	Case series Period: January 1991 to December 1995	12 HCV-positive patients with MC and 2 HCV-positive patients with reactive lympho-adenopaties NHL classification: Working Formulation	3/12 (25%)	NR	NR	25 (0.5-49.5)	These data emphasize that lymphoid organs may be a site of HCV infection. The demonstration of HCV-related proteins in a nonmalignant condition, namely HRL, indicates that HCV infection precedes the neoplastic transformation and possibly plays a major role in lymphomagenesis in MC

Schöllkopf C *Int J Cancer* 2008	Nation-wide Danish-Swedish case-control study (Scandinavian Lymphoma Etiology study, SCALE) Period: The SCALE study population includes the entire Danish population between June 1, 2000 - August 30, 2002, and the Swedish population between October 1, 1999-April 15, 2002	All lymphomas: 2819 NHLs: 2353 HL: 466 NHL classification: World Health Organization's classification	HCV positive NHLs: 57 (2.4%) HL: 6 (1%) at III G ELISA test,only NHLs: 7/2353 (0.7%) HL: 0 positive at ELISA test and positive or intermediate at RIBA test for anti-HCV antibodies	Controls randomly sampled from the entire Danish and Swedish populations using continuously updated, computerized population registers	21/1856 (1%)	2.4 (1.8-3)	Positive association between HCV and risk of NHL, in particular of B-cell origin
Seve P *Eur J Gastroenterol Hepatol* 2004	Cross-sectional study Period: January 1997-December 1998	B-NHL:212 patients BL 6 DLBCL 109 FC 31 LL 7 LPL 5 MALT 17 MCL 21 MZL16 NHL classification: Revised European American Lymphoma (REAL) classification	(1) 6/212 (2.8%) (2) MALT 3/17	Transfusion patients from surgical emergency, internal medicine pneumology, endocrinology, gastroeterology, nephrology, oncology, general surgery, orthopaedics, rheumatology, obstetrics and gynaecology, and intensive care wards	20/974 (2.05%)	(1) 2.8 (0.6-5) (2) 17.6 (3.8-43.4)	Possible association between HCV and MALT lymphoma
Shariff S *Ann Oncol* 1999	Case series with control group Period: 1996 and part of 1997	patients with B-cell NHL NHL classification: Working Formulation/Revised European American Lymphoma (REAL) classification	2/88 (2.3)	(1) patients with a T-cell NHL (2) second control group, including health-care workers, recruited between 1995 and 1997	0/37 11/1085 (1%)	2.3 (0-5.3)	Chronic HCV infection as a risk factor for B-cell NHL in certain populations or with certain genotypes of the virus, no significant association in British Columbia
Shirin H *Isr Med Assoc J* 2002	Case control group Period: May 1997 -September 1999	B-NHL (DLCL FC CLL) NHL classification: Revised European American Lymphoma (REAL) classification	Total: 212 patients Lymphoproliferative disorders: 10/128 (7.8%)	(1) Patients with Myeloprolipherative and myelodisplastic disorders: (2) Israeli blood donors	(1) 1/84 (1.1%) (2) HCV prevalence equal to 0.64%	7.8 (3.1-12.4)	Significant association between HCV infection and diffuse large B cell lymphoma
Silvestri F *Bood* 1996	Case series with control group Period: NR	537 unsekected patients with LPDs B-cell NHLs: 311 T-cell NHLs: 57 MM: 78 HL:88 ALL: 23 NHL classification: Kiel classification/Revised European American Lymphoma (REAL) classification	29/311 (9%)	NR	T-cell NHLs: 2/57 (4%) MM: 3/78 (4%) HL:0/88 ALL: 1/23 (4%)	9 (6-12.5)	High prevalence of HCV infection in patients with B-cell NHL

Silvestri F *Haematologica* 1997	Case series Period: NR	B-cell NHLs NHL classification: Revised European American Lymphoma (REAL) classification	42/470 (8.9%) 21/22 (95.4%) B cell-NHLs patients with cryo-globulinemia 21/448 (4.6%) B cell-NHLs patients without cryo-globulinemia	NR	NR	8.9 (6.3-11.5)	Close association between HCV infection and B-cell NHLs
Singer IO *Leuk Lymphoma* 1997	Case-series with control group Period: NR	All Lymphomas: 50 unselected patients B-cell NHLs: 31 T-cell NHLs: 6 HL: 13 NHL classification: Working Formulation	0/31	No information about control groups	0/19	0 (0-11.2)	No evidence supporting an association between HCV infection and LNH development
Sonmez M *Tumori* 2007	Case-control study Period: 2002-2005	B-cell NHLs: 109 DLBCL: 71 Small-cell LL: 38 NHL classification: World Health Organization's classification	3/109 (2.8%) Low grade: 1/38 (2.6%) High grade: 2/71 (2.9%)	Patients selected from orthopedics, general surgery, urology, ophthalmology, otorhino-laryngology clinics with irrelevant diseases	28/551 (5.1%)	2.8 (0-5)	No difference in the incidence of HCV infection between NHL- and control-group
Spinelli JJ *Int J Cancer* 2008	Population-based case-control study Period: March 2000 and February 2004	All-NHL cases:795, from the Greater Vancouver Regional District (GVRD) and the Capital Regional District (CRD), including the city of Victoria, enrolled from the BC Cancer Registry NHL classification: World Health Organizations classification	NHLs: 19/795 (2.4%) B-cell NHLs:18/717 (2.5%) T-cell NHLs: 1/78	Controls selected from the Client Registry of the BC Ministry of Health	5/697 (0.7%)	2.4 (1.3-3.4)	HCV infection contributes to increase NHL risk
Swart A *BMJ Open* 2012	Cohort-study Period: 1 January 1993-31 December 2007	Individuals registered on the Pharmaceutical Drugs of Addiction System, a record of all NSW Health Department authorities that administer methadone or buprenorphine to opioid-dependent people as opioid substitution therapy. Solid cancers classified according to the International Classification of Diseases (ICD), 10th revision, haematopoietic neoplasms and Kaposi sarcomas classified according to the ICD for Oncology, 3rd edition	Patients considered in the study: 29613 Subjects with HCV infection alone: 14892 Observed number of LNH in HCV-positive cohort: 75	Calculation of expected number of incident LNHs	Expected number of LNH: 49.6	0.5 (0.4-0.6)	Association between HCV infection and LNHs

Takai S *Eur J Haematol* 2005	Case series Period: January 1996 to September 200	All haematological malignancies: 601 NHL: 218 DLBCL: 110 FCL: 100 MCL: 3 PTCL: 5 Acute Leukemia: 246 AML: 193 ALL: 53 Adult T-cell Leukaemia: 13 MM:124	37/601 patients were anti-HCV positive NHL: 22/218 (10.1%) DLBCL: 13/110 (11.8%) FCL: 8/100 (8%) MCL: 1/3 (33%) PTCL:1/5 (20%) AML: 5/193 (2.6%) ALL: 2/53 (1.8%) adult T-cell Leukaemia: 0/13 MM: 8/124	NR	NR	NHLs: 10.1 (6.1-14.1) DLBCL: 11.8 (5.8-17.8) FCL: 8 (2.7-13.3) MCL: 33 (0-86.2) PTCL:20 (0-63) AML: 2.6 (0.4-4.8) ALL: 1.8 (0-8.9) MM: 6.5 (2.2-10.8)	High prevalence of HCV infection in NHL Possible role of HCV in the pathogenesis of NHs
Takeshita M *Histopathology* 2006	Case series with control group Period: NR	All-Lymphomas: 537 (1) HL: 18 -B-NHL: 400 (DLBCL, FC CLL, MALT, PCM, MCL, MZL, BL, others) -T-cell NHL: 96 -NK/T-cell NHL: 23 NHL classification: World Health Organization's classification	B-cell NHL 45/400 (11.3%) Primary Effusion Lymph: 3/6 (50%) BL: 1/7 (14.3%) DLCL:28/161 (17.4%) FL: 3/47 (6.4%) MALTOMA: 5/52 (9.6%) MM: 4/81 (4.9%) CLL, SMZL, Mantle cell Lymp: 0	(1) Other haematological malignancies (2) Blood donors	(1) HL: 1/18 (5.6%) T-cell NHL: 5/96 (5.2%) NK-Tcell Lymphomas: 2/23 (8.7%) (2) 396/15567 (2.5%)	11.3 (8.1-14.3)	HCV infection may play a role in lymphomagenesis of splenic and gastric DLBCL
Talamini R *Int J Cancer* 2004	Case-control study Period: January 1999 -July 2002	Total NHL: 225 cases 44/225 HCV positive patients NHL classification: International Classification of Diseases for Oncology, updated to include categories in the Revised European-American Lymphoma (REAL)/ World Heath Organization classification	44/225 HCV positive patients 40/225 (17.8%) patients with B-cell NHLs (1) Low-grade B-cell: 24 (2) Intermediate- and high-grade B-cell: 16 (3) T-cell: 2 (4) Unknown:2	Patients with a wide spectrum of acute conditions admitted at National Cancer Institute, Aviano; the "Santa Maria degli Angeli" General Hospital, Pordenone; the "Pascale" National Cancer Institute, Naples and 4 general hospitals, Naples	45/504 (8.9%)	17.8 (12.8-22.8)	HCV infection associated with an increased NHL risk
Teng CJ *Clinics* 2011	Case series Period: 2003-2008	MM: 155 patients 30 patients with chronic hepatitis MM diagnosis: International Myeloma Working Group	14/155 (9%) 1/155 with HBV/HCV co-infection	NR	NR	9 (4.5-13.5)	High prevalence of cytogenetic abnormalities in patients with HCV chronic hepatitis
Thalen DJ *Br J Haematol* 1997	Case series Period: NR	NHLs: 115 patients B-cell NHLs: 99/115 (86%) T-cell NHLs: 15 (13%) Unclassified: 1 (1%) NHL classification: Working Formulation	B-cell-NHLs: 0/99 T cell NHLs: 0/15	NR	NR	0 (0-3.7)	No association between HCV infection and B-cell NHLs in the study
Timuragaoğlu A *Haematologia* 1999	Case series with control group Period: NR	NHLs: 48 patients NHL classification: Working Formulation	Anti HCV positive: 0/48 HCV-RNA positive: 3/35 (8.6%)	Patients with various haematological disorders (MM, HL, acute myeloblastic leukaemia, acute lymphoblastic leukaemia, chronic myelogenous leucemia, idiopathic thrombocytopenic purpura, myelodysplastic syndrome)	0/28	8.6 (1.8-23.1)	Association between HCV infection and B-cell NHLs in the study

Tkoub EM *Blood* 1998	Case series with control group Period: NR	46 patients with gastric MALT: High grade: 21 Low-grade 25 37/46 patients with *Helicobacter Pylori* NHL classification: NR	1/46 (2.2%)	Patients with gastroduodenal disease: 84 with duodenal ulcer 43 with gastric ulcer 38 with dispepsia	4/165 (2.4%)	2.2 (0-6.3)	No link between HCV infection and gastric MALT in France
Tursi A *Am J Gastroenterol* 2002	Case series Period: NR	25 HCV positive patients with gastric MALT. -20/25 (80%) with grade 2-5/25 (20%) with grade 3. 18/25 patients with *Helicobacter Pylori* NHL classification: World Health Organization's classification	NR	NR	NR	MALT grade 2: 80 (59.3-93.2) MALT grade 3: 20 (6.8-40.7)	HCV may colonize gastric MALT, allowing the development of a grade of acquired MALT, this represents the first step toward a MALT lymphoma
Udomsakdi-Auewarakul C *Blood* 2000	Case series Period: NR	All malignancies: 130 Intermediate- to high-grade NHL: 98 Low-grade NHL 32 patients NHL classification: Working Formulation	2/98 (2%) 1/32 (3.1%)	NR	NR	2.(0-4.8)	No association between HCV infection and NHLs in this study from Thailand, where HCV infection is highly prevalent
Vajdic CM *Cancer Epidemiol Biomarkers Prev* 2006	Population-based case-control study Period: January 2000 and August 2001	Total Lymphomas:694 -B-cell NHLs: 659 (95%) -T-cell NHLs: 28 (4%) -Undetermined: 7 (1%) NHL classification: World Health Organization's classification	NHLs: 3/694 (0.4%)	Potential participants (both cases and controls) received a letter to inviting their participation in research about the development of NHL	2/694 (0.3%)	0.4 (0-0.9)	No strong evidence for an association between any infection and non-Hodgkin lymphoma risk in immunocompetent people, but increased risk between HCV infection and non-Hodgkin lymphoma in subjects with injecting drug use
Vallisa D *Am J Med* 1999	Case-control study Period: 1990-1996	B-cell-NHLs: 175 patients NHL classification: Working Formulation/Revised European American Lymphoma clasification	65/175 (37.1%)	Subjects without lymphoma selected from: (1) inpatients (175) (2) outpatients (175) cared at Civil Hospital, Piacenza, subdivided into 2 groups	(1) 17/175 (10%) (2) 15/175 (9%)	37.1 (30-44.3)	Possible HCV role as an etiologic agent in non-Hodgkin's B-cell lymphoma
Varma S *Hepatol Int* 2011	Case-control study Period: NR	B-NHLs: 57 patients High-grade disease (DLBCL): 44 (77.2%) Intermediate-disease (FC): 6 (10.5%) Low grade disease: (small lymphocytic): 7 (12.3%) NHL classification: World Health Organizations classification	1/57 (1.7%)	Patients with non-hematological conditions admitted to Departments of Ophthalmology, Otorhinolaryngology, Dermatology, and Internal Medicine in the Hematology Clinic, Institute of Medical Education and Research, Chandigarh	2/171 (1.2%)	1.7 (0-5.1)	No significant association between HCV infection and NHL in Northern India
Veneri D *Am J Hematol* 2007	Case series Period: January 1995 -December 2006	947 patients with lymphoproliferative disorders: DLBCL: 361 MM: 139 B-cell MZL: 62 HL: 103 B-CLL: 186 FL. 96 NHL classification: World Health Organization's classification	55/947 patients were HCV positive DLBCL: 27/361 (7.5%) MM: 1/139 (0.7%) B-cell MZL: 15/62 (24.2%) HL: 4/103 (3.9%) B-CLL: 4/186 (2.1%) FL: 4/96 (4.2%)	NR	NR	DLBCL: 7.5 (4.7-10.2) B-cell MZL: 24.2 (13.5-34.8)	Confirmed association between a subset of B-cell lymphomas and HCV infection

Yamac K *Eur J Epidemiol* 2000	Case series Period: August 1996-June 1998,	All Lymphomas: 92 NHLs: 73 HL 19 NHL classification: Revised European American Lymphoma clasification	1/92 (1.1%)	NR	NR	1.1 (0-3.2)	No significant association between HCV and NHL in the study
Yenice N *Turk J Gastroenterol* 2003	Case series with control group	All Lymphomas: 134 B cell NHLs: 84 HLs: 50	B-cell NHLs: 6/84 (7.1%) HLs: 1/50 (2%)	Healthy blood donors	1/100 (1%)	7.1 (1.6-12.6)	HCV may play a role in the development of B-cell non-Hodgkin lymphoma, but not in Hodgkin lymphoma
Yoshikawa M *J Clin Gastroenterol* 1997	Case series with control group Periood: NR	All Lymphomas: 100 B-NHLs: 55 T-NHLs: 10 HL: 5 MM: 25 B-CLL: 2 MGUS: 3 NHL classification: Working Formulation	B-NHLs: 9/55 (16.4%) MM:5/25 (20%) MGUS: 1/3 (33.3%)	Patients with any cancer in digestive organs except liver enrolled at Nara Medical University	1/25 (4%)	16.4 (6.5-26.1)	High rates of HCV infection detected in B-NHL and MM
Yu SC *Kaohsiung J Med Sci* 2013	Case series Period: 1988-2011	All lymphomas: 74 patients: -B-cell lymphomas: 69 -T-cell lymphomas: 3 -Lymphoblastic Lymphoma: 1 -Unspecified high-grade lymphoma: 1 41/74 patients with serology for HCV infection NHL classification: World Health Organization's classification	Patients with B-cell-NHL and with serology for HCV infection: 39 Patients with B-cell-NHL and HCV positive 10/39 (25.6%)	NR	NR	25.6 (11.9-39.3)	High HCV sero-prevalence in patients with early-stage DLBCL suggests a role of HCV in the pathogenesis of primary DLBCL
Zucca E *Haematologica* 2000	Case series Period: 1990 and 1995	B-cell NHLs: 180 Anti-Helicobacter antibodies detected in 81/180 (45%) patients. NHL classification: REAL histological scheme	17/180 (9.4%) Gastric lymphoma: 2 Non gastric lymphoma: 15	A survey of 5424 subjects new blood donors from the same area tested between 1992 and 1997 (Swiss Red Cross Transfusional Medicine Service for Canton Ticino)	49/5424 (0.9%)	9.4 (5.1-13.7)	High prevalence of HCV infection detected in NHL lymphoma patients and associated with a shorter time to lymphoma progression. HCV infection not correlated with primary gastric presentation or with MALT-type histology
Zuckerman E *Ann Intern Med* 1997	Controlled, cross-sectional study. Period: October 1994 and May 1996	B-cell NHLs: 120 patients NHL classification: Working Formulation	B-cell NHLs 26/120 (22%)	(1) Patients with hematologic malignancies other than B-cell NHLs; (2) Patients without hematologic malignancies, attending the general medicine clinic at LAC-USC and with: systemic hypertension or ischemic heart disease: 69 diabetes mellitus: 35 primary hypothyroidism: 10	268 patients 7/154 (4.5%) (2) 6/114 (5%)	21.7 (14.3-29)	Increased prevalence of HCV infection among patients from the United States with B-cell lymphoma, but uncertain generalizability to other populations, because of high number of patients, belonging to Hispanic ethnicity

ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; AnLLs: Acute non-lymphocitic leukemia; B-LPD: B-cell lymphoproliferative disorders; BL: Burkitt lymphoma; CC: Centrocitic; CB: Centroblastic; CBCC: Centroblastic/centrocitic; CLL: Chronic lymphocytic leukemia; CML: Chronic myeloid leukemia; CMD: Chronic myeloprolipherative disease; DLBCL: Diffuse large B-Cell lymphoma; CLISA: Chemiluminescence immunoassay; ELISA: Enzyme-linked immunosorbent assay; EIA: Enzyme–immunoassay; EMZBL: Extranodal marginal zone B-cell lymphoma; FC: Follicular lymphoma; FCL: Follicle center lymphoma; HCL: Hairy cell leukemia; HL: Hodgkin lymphoma; IC: Immunocytoma; LAC-USC: Los Angeles County-University of Southern California; LL: Lymphocitic lymphoma; LPds: Lymphoproliferative diseases; LPD: Lymphoproliferative disorders; LPL: Lymphoplasmocitoid lymphoma; MCL: Mantle Cell Lymphoma; MGUS: Monoclonal Gammopathy of uncertain significance; MEIA: Microparticle enzyme immunoassy; MCS: Mixed cryoglobulinemia syndrome; MGUS: Monoclonal gammopathy of undetermined significance; MM: Multiple myeloma; MS: Myelodisplastic syndrome; MZL: Marginal zone lymphoma; PCM: Plasma cell myeloma; PHL: Primary hepatic non-Hodgkin's lymphoma; PLL: Primary Liver Lymphoma; PSL: Primary splenic non-Hodgkin's lymphoma; PTCL: Peripheral T-cell lymphoma; RAEB: Refractory anemia with excess of blasts; SIR: Standardised incidence ratio; WMc: Waldenström's microglobulinemia; Y: Determined; N: Not determined; NR: Not reported.

Table 2 Characteristics of available studies, reported in English, assessing the association between hepatitis C virus infection and cholangiocarcinomas (A) or bile duct dysplasia (B)

Author/Journal/ Publication year	Study design study period	CCA diagnosis	HCV positive colangiocarcinoma (*n*)/ total colangiocarcinoma cases (*n*)	Total patients enrolled and control source	HCV positive controls (*n*)/controls (*n*)	Percentage of HCV-positive cases with 95%CI	Main conclusion
(A)							
Abdel Wahab M 2007	Case series Period: Januiary 1995-October 2004	Histologic confirmation/CT/MRI/ ERCP/PTD	440 patients with hilar cholangiocarcinoma 238 anti-HCV positive patients 238/440 (54%)	NR	NR	54.1 (49.4-58.7)	Liver cirrhosis and HCV may be risk factors For hilar cholangiocarcinoma in Egypt
Barusrux S *Asian Pacific J Cancer Prev* 2012	Case series with control group Period: NR	Histologic confirmation	8/295 (2.7%)	Total patients: 6120 Controls randomly selected from people in 4 provinces in Thailand, representing 4 geographically distinct areas and thus, populations in the North, North-east, South and Center of the country, respectively	125/5825 (2.15%) HCV-Ab prevalence in Thailand ranging from 1.5% to 2.15%. Sunanchaikarn S, Theamboonlers A, Chongsrisawat V *et al* (2007). Seroepidemiology and genotypes of hepatitis C virus in Thailand. *Asian Pac J Allergy*, 25, 175-182	2.7 (0.8-4.5)	No significant association between CAA and HCV in northeast Thailand, with prevalence of HCV infection comparable among CCA and general population
Chantajitr S *J Hepatobiliary Pancreat Surg* 2006	Case series with control group Period: 2000-2004	Histologic confirmation	HCC-CCA = 25 15 patients with test for anti- HCV 2/15 (13.3%)	Total patients: 75. 50 individuals, diagnosed with HCC at Ramathibodi Hospital	HCC = 50 32 patients with test for anti- HCV 1/32 (3.1%)	13.3 (1.6-40.5)	No significant differences in presence of hepatitis C virus (HCV) antibody (13% *vs* 3%) as etiologic risk factor between HCC-CC and HCC patients
Donato F *Cancer Causes and control* 2001	Hospital-based case-control study Period: January 1, 1995-July 31, 2000	Histologic confirmation	6/24 (25%)	Total individuals: 848. Subjects unaffected by liver diseases or malignant neoplasms, admitted to the Department of Ophtalmology, Dermatology, Urology, Surgery, Cardiology, Internal Medicine in the two main Hospitals in Brescia, enrolled as controls	50/824 (6%)	25 (7.7-42.3)	HCV as possible risk factor for ICC in Western countries
El-Serag H *Hepatology* 2009	Cohort study Period: October 1, 1988, and September 30, 2004	Identification of PAC cases by means of ICD-9-CM diagnosis codes (157.0, 157.1, 157.2, 157.3, 157.8, 157.9) Identification of HCV infected subjects by means of ICD-9-CM diagnosis codes (070.41, 070.44, 070.51, 070.54 and V02.62)	HCV-infected cohort: 146394 patients ICC = 14 ECC = 15	718687 patients (146394 HCV-infected cohort, 572293 HCV-uninfected cohort) , ICC: 37 and ECC: 75 (14 ICC and 15 ECC in HCV infected patients, 23 ICC and 60 ECC in HCV uninfected subjects)	HCV-uninfected cohort: 572293 patients ICC = 23 ECC = 60	ICC: 0.01 (0-0.15) ECC: 0.01 (0-0.15)	A more than twofold elevated risk of ICC in patients with HCV infection, absence of an association with ECC

Hai S *Dig Surg* 2005	Case series with control group Period: January 1997 - December 2002	Histologic confirmation	19/50 (38%)	Total patients: 50 Subjects admitted to the Osaka City University Hospital or the Osaka City General Hospital	31/50 (62%)	38 (24.5-51.4)	Possibility to detect a small ICC or a hepatocellular carcinoma by means of a follow-up for patients with chronic HCV by imaging series at regular intervals
Hsing AW *Int J Cancer* 2008	Population-based case-control study Period: June 1997 - May 2001,	Histologic confirmation or by means of ERCP	3/234 (2%) with gallbladder cancers 2/134 (1.5%) with extrahepatic bile duct cancers 1/49 (2%) with Ampulla of Vater carcinomas	Total patients: 1696 Controls represented by biliary stone case patients and by healthy subjects without a history of cancer, randomly selected from all permanent residents listed in the Shanghai Resident Registry	2/301 (0.7%) patients with gallbladder stones, 5/216 (2.3%) with bile duct stones and 15/762 (2%) healthy individuals	1.5 (0-3.5)	Low prevalence of HCV infection in this population (2%), therefore limited ability to detect an association with biliary diseases
Kobayashi M *Cancer* 2000	Case series with control group Period: 1980-1997	Cirrhosis confirmation by means of liver biopsy, peritoneoscopy, or both	14/600 (2.3%) developed CCA 11/14 patients with CCA 3/14 patients with CCA-HCC	600 HCV positive patients in follow-up between 1980 to 1997	206/600 (34.3%) patients developed HCC in the same period	2.3 (1.1-3.5)	HCV-related cirrhosis as a major risk factor for primary CCA in Japanese patients
Kuper H *Soz Praventivmed* 2001	Case-control study Period: January 1995-December 1998	Histologic confirmation	0/6 with CCA	Total subjects: 699 Controls represented by patients with injuries or eye, ear, nose and throat conditions admitted to three teaching Hospitals in Athens	52/333 (16%) with HCC 1/360 (0.3%) controls	0 (0-45.9)	No HCV positivity in CCA patients
Lee CH *Br J Cancer* 2009	Case-control study Period: 1991-2005	Histologic confirmation	21/160 (13.1%)	Individuals generally surveyed for any disease Chang Gung Memorial Hospital at the Lin-Ko Medical Center	10/160 (6.3%)	13.1 (7.9-18.3)	HCV-associated ICC and HCC shared common disease process for carcinogenesis and, possibly, both arose from the hepatic progenitor cells
Lee TY *Am J Gastroenterol* 2008	Hospital-based case-control study Period: 2000-2004	Histologic confirmation	12/622 (1.9%)	Total subjects:3110 2488 healthy controls selected from 192655 individuals undergoing routine health examinations at the health promotion center at Asan Medical Center, Seoul	47/2488 (1.9%)	1.9 (0.8-3)	No significant association between ICC and HCV
Lee WS *Surg Today* 2006	Case series with control group Period: November 1994-December 2003	Histologic confirmation	ICC = 3/79 (3.8%) HCC-CCA = 4/33 (12.1%)	Total patients: 952, subjects, undergoing surgical resection at Samsung Medical Center, because of: HCC-CCA = 33 ICC = 79 HCC = 832	HCC = 61/832 (6.5%)	3.8 (0-8)	Significantly poorer survival rates of patients with transitional type HCC-CCA in comparison with HCC after hepatic resection

Matsumoto K *Intern Med* 2014	Case series with control group Period: NR	Histologic confirmation	145 patients undergoing surgical resection because of ICC: 50 ECC: 95 (1) ECC: 7/95 (7.4%) (2) ICC: 10/50 (20%)	General Japanese population (individuals ⩾ 20 yr of age)	HCV-Ab prevalence equal to 1.2% in the Japanese individuals ⩾ 20 yr of age	(1) 7.4 (2.1-12.6) (2) 20 (8.9-31)	HCV infection as a possible risk factor for the development of CCA. Surveillance of ICC and ECC required in HCV carriers
Mohammad-Alizadeh AH *Asian Pac J Cancer Prev* 2012	Case series with control group Period: 2004-2011	Histologic confirmation ERCP MRCP	CCA: 43/283 (15.2%) No distinction between HCV and number of ICC and ECC cases	Total subjects: 566 Patients with the primary or final diagnosis of CAA, admitted to gastroenterology ward of a tertiary academic center in Tehran-Iran	Gallstones 72/283 (25.4%), diabetes 70/283 (24.6%), HBV infection 52/283 (18.3%), primary sclerosing cholangitis 16/283 (5.6%) smoking 120/283 (42.3%)	15.2 (11-19.3)	In current study smoking, opiate and alcohol use as the most common risk factors in CCA patients, chronic hepatitis C infection and cirrhosis represent further risk factors
Nuzzo G *Updates Surg* 2010	Case series with control group Period: 1997-2008	Histologic confirmation	8/55 (14.5%) (2 patients with HBV coinfection), undergoing surgical resection at Policlinico Gemelli, Rome	Total subjects: 55	47/55 (76.5%)	14.5 (5.2-23.8)	ICC associated with chronic HCV infection in 14.5% of patients
Perumal V *Human Pathology* 2006	Case series with control group Period: NR	Histologic confirmation	2/11 (18.2%)	10 liver specimens from anti-HCV negative individuals and 13 liver specimens from individuals who were negative for HBV surface antigen by serologic testing, used as negative controls HCV RNA-positive liver tissues from HCV positive cases used as positive controls for HCV RNA detection, at Johns Hopkins Hospital, Baltimore	Total subjects: 21	18.2 (2.2-51.8)	Possible etiologic role of HCV in some cases of ICC
Portolani N *Annals of Surgical Oncology* 2008	Case series with control group Period: 1990-2006	Histologic confirmation or typical findings on ultrasound, CT-, MRI-examination	ICC = 33 patients undergoing resection and 16 not resected 6/33 (18.1%)	Total subjects: 51 Patients diagnosed with ICC-HCC at the Surgical Clinic of Brescia University, Italy	ICC-HCC = 18 patients undergoing resection 11/18 (61.1%)	18.1 (5-31.3)	HCV infection and cirrhosis as a risk condition for ICC and combined HCC-ICC
Qu Z *Asia-Pacific Journal of Clinical Oncology* 2012	Case series with control group Period: January 1990 - June 2001	Histologic confirmation of ECC	ECC: 305, 139 with test for anti- HCV ECC: 6/139 (4.3%)	Total subjects: 353 Patients with BBD with cholelithiasis or acute cholangitis, undergoing surgical intervention selected as controls at Tianjin Nankai Hospital, Tianjin Third Central Hospital, Tianjin Medical University General Hospital and The Second Hospital of Tianjin Medical University hospitals in the corresponding time period	BBD:480, 214 with test for anti-HCV BBD:12/214 (5.6%)	4.3 (0.9-7.6)	No association between chronic HCV infection and ECC

Shaib YH *Gastroenterology* 2005	Hospital-Based Case-Control Study Period: 1993-1999	Histologic confirmation HCV defined by using ICD-9 codes for HCV (ICD-9 codes 070.41, 070.44, 070.51, 070.54, and V02.62) or for unspecified hepatitis (ICD-9 codes 070.9, 571.4, 571.8, and 571.9)	Data obtained from the National Cancer Institute (NCI)'s Surveillance, Epidemiology and End Results program SEER-Medicare database, linking SEER registry information with Medicare claims data, it is a program of the NCI to collect population-based cancer incidence and survival data, including population-based cancer registries in 5 states and 6 metropolitan areas (about 14% of the United States population). ICC cases: 625 (3) HCV-specific codes: 5/625 (0.8%) (1) HCV (including unspecified hepatitis):35/625 (5.6%)	Controls included in the study derived from the 5% random sample of Medicare-enrolled beneficiaries with no cancer of any type residing in the geographic regions of SEER registries	90834 controls (1) HCV (including unspecified hepatitis): 940 (1%) (3) HCV-specific codes: 161 (0.2%)	0.8 (0.1-1.4)	Chronic HCV infection as possible risk factors for ICC
Shaib YH *Am J Gastroenterol* 2007	Hospital-Based Case-control Study Period: 1992-2002	Histologic confirmation	246 patients undergoing surgical resection because of ICC: 5/83 (6%) ECC: 6/163 (3.7%)	Total patients: 482 Controls randomly selected from an existing database of healthy individuals at M.D. Anderson	2/236 (0.8%)	ICC: 6 (0.9-11.1) ECC: 3.7 (0.8-6.5)	Chronic HCV infection as possible risk factors for ICC but not ECC
Shin RH *Int J Epidemiol* 1996	Case-control study Period: August 1990-August 1993	Histologic confirmation or typical findings on ultrasound, CT-, MRI-examination	41 patients with CCAs 203 patients with HCC (1) 29/41 patients with tests for antiHCV/HBV status. 4/29 (13.8%) HCV positive (2) 128/203 patients with test for antiHCV/HBV status 17/128 (13.3%) HCV positive	(1) Inpatients without liver disease, systemic disease, and malignant disorders from the Departments of Ophthalmology or Otorhinolaryngology (2) healthy people who had visited the Non-Communicable Disease Control Center All subjects were visited at the Tnje University Pusan Paik Hospital	(3) 203 (4) 203 394/406 subjects with tests for anti-HCV status. 23/394 (6.6%) HCV positive	(1) 13.8 (1.2-26.3) (2) 13.3 (7.4-19.1)	No association between chronic HCV infection and CCA
Songsivilai S *Trans R Soc Trop Med Hyg* 1996	Case series with control group Period: July 1993 - June 1995	Histologic confirmation	0/30	Total subjects: 110 Patients with HCC, undergoing surgical resection at Siriraj Hospital, Mahidol University, Bangkok	9/80 (11.2%)	0 (0-11.6)	No association between chronic HCV infection and CCA
Srivatanakul P *Asian Pacific J Cancer Prev* 2010	Case-control study Period: September 1999 -2001	Histology, or typical findings on ultrasound examination with an elevated titre (⩾ 40 units/mL) of CA 19-9 and normal level of alpha-fetoprotein (AFP < 20 ng/mL)	7/103 (6.8%)	Total subjects: 206 Community hospitals in Nakhon Phanom Province and Nakhon Phanom Provincial Hospital	0/103	6.8 (1.9-11.6)	Possible role of HCV infection in the development of CCA in northeast Thailand
Taguchi J *J Gatroenterol Hepatol* 1996	Case series with control group Period: January 1988-July 1995	Histologic confirmation	14/20 (70%)	Total subjects: 367 HCC-CCA: 23/367, 20 patients with anti-HCV markers	6/20 (30%)	70 (49.9-90)	HCC-CCA associated with chronic HCV infection in 70% of patients
Tanaka M *J Viral Hepat* 2010	Cohort study Period: 1991-1993	ICC cases identified by the ICD-10 code (C22.1). diagnosis of ICC was based on histological examination and/or combined clinical, radiological (echography, CT and endoscopic retrograde cholangio-pancreatography) and laboratory findings	ICC: 11 cases 1/11 (9.1%)	154814 study subjects voluntary blood donors	1927/154814 (1.2%)	9.1 (0.2-41.3)	No association between HCV infection and ICC development

Tomimatsu M *Cancer* 1993	Case series with control group Period: January 1985 - December 1990	Histologic confirmation	(1) CCA: Anti-HCV +: 4/13 (30.8%) $HBsAg^+$: 3/13 (23.1%) Anti-HCV-/ $HBsAg^-$: 6/13 (46.1%) (2) CCA-HCC: Anti-HCV +: 5/7 (71.4%) $HBsAg^+$: 1/7 (14.3%) Anti-HCV- / $HBsAg^-$: 1/7 (14.3%)	Total subjects: 141 Patients with HCC, undergoing surgical resection at the Institute of Gastroenterology of Tokyo Women's Medical College	Anti-HCV +: 85/121 (70.3%), Anti-HCV+ /$HBsAg^+$: 5/121 (4.1%) $HBsAg^+$: 16/121 (13.2%) $HBsAg^-$/anti-HCV -: 15/121 (12.4%)	(1) 30.8 (9-61.4) (2) 71.4 (29-96.3)	The anti-HCV-positive rate was high in combined HCC-CC as well as in HCC
Uenishi T *Journal of Surgical Oncology* 2014	Case series with control group Period: January 2000 - December 2011	Histological confirmation	33/90 (36.7%)	Total subjects: 90 Patients enrolled at Hirakata and Osaka University Hospital	57/90 (63.4%)	36.7 (26.7-46.6)	HCC-related death often occurred in patients undergoing curative resection for HCV-related ICC. HCV as adverse prognostic factor after curative resection for mass-forming ICC
Yamamoto M *Cancer* 1998	Case-series Period: February 1990 - March 1996	Histologic confirmation	50 patients with ICC Anti-HCV positive: 16/50 (32%) $HBsAg^+$/ Anti-HCV positive: 1 (2%)	NR	NR	32 (19-44.9)	Minute nodular ICC appears to be related to hepatitis viral infection and could be detected at an early stage, similar to hepatocellular carcinoma, by following up cases of chronic hepatitis or cirrhosis
Yamamoto S *Cancer Sci* 2004	Hospital case-control based study Period: January 1991 - December 2002	Histologic confirmation	18/50 (36%)	Total subjects: 255 Control patients enrolled at the two major medical centers of Osaka City	7/205 (3%)	36 (22.7-49.3)	HCV infection as a possible etiology of ICC in Japan
Yano Y *Jpn J Clin Oncol* 2003	Case-control study Period: January 1978 - December 1998	Histologic confirmation	HCV alone: (1) HCC-CCA = 10/26 (38.5%) (2) CCA = 5/53 (9.4%) HCV + HBV: 1/53 (2%)	Total subjects: 1172 Patients with HCC, undergoing surgical resection at the Department of Surgery, National Cancer Center Hospital, Tokyo	HCV alone: HCC = 526/1093 (48%) HCV + HBV: 16/1093 (1%)	(1) 38.5 (19.8-57.1) (2) 9.4 (1.5-17.3)	HCC-CCA represents a variant of ordinary HCC with cholangiocellular features, rather than an intermediate disease entity between HCC and CCA
Wahab A *M Hepatogastro-enterology* 2007	Case series Period: January 1995 - October 2004	Histologic confirmation or typical findings on CT, ERCP, MRI and PTD	Total patients: 440238/440 (54.1%)	NR	NR	54.1 (49.4-58.7)	HCV chronic infection as possible risk factor for hilar CCA in Egypt

Welzel TM *Clin Gastroenterol Hepatol* 2007	Population-based case-control study Period: 1993-1999	Identification of CAA cases from the Surveillance, Epidemiology and End Results-Medicare databases by means of ICD-9-CM diagnosis codes: (C22.0, C22.1, C24.0, 8010, 8020, 8041, 8070, 8140, 8144, 8160, 8161, 8260, 8310, 8480, 8490, 8560). Identification of HCV infection by means of ICD-9-CM diagnosis codes 070.41, 070.44, 070.51, 070.54 and 070.7	(1) ICC = 5/535 (0.9%) (2) ECC = 5/549 (0.9%)	102782 cancer-free controls identified using the Surveillance, Epidemiology and End Results-Medicare databases	142/102782	ICC: 0.9 (0.1-1.7) ECC: 0.9 (0.1-1.7)	Association between HCV infection and ICC
Zhou HQ *Hepatobiliary Pancreat Dis Int* 2007	Case-series Period: January 1996 - November 2005	Histologic confirmation	(1) HCC: 132 patients Anti-HCV positive: 26/132 (19.7%) (2) CCA: 44 patients Anti-HCV positive: 4/44 (9.1%) (3) HCC-CCA: 15 anti-HCV positive: 3/15 (20%)	NR	NR	(1) 19.7 (12.9-26.4) (2) 9.1 (0.6-17.5) (3) 20 (4.3-48)	Percentage of cHCC-CC patients with serum anti-HCV antibodies were similar to those of HCC patients but different from CC patients
Zhou YM *World J Gastroenterol* 2008	Hospital-based-case control Study Period: February 2004 - May 2006	Histologic confirmation	9/312 (2.9%)	Total patients: 750 Controls were selected from patients who were unaffected by liver diseases in the Changhai Hospital of the Second Military Medical University	6/438 (1.4%)	2.9 (0.9-4.7)	No significant difference between cases and controls in the prevalence of anti-HCV seropositivity
(B)							
Torbenson M *Am J Surg Pathol* 2007	Review of liver explants with control group from 3 transplant centers Period: 1995 -2005	Histologic confirmation in explanted livers	(1) HCV alone = 10/511 (2%) (2) HCV + alcohol = 4/85 (5%)	1058 total liver explants Control groups included: (1) alcohol cirrhosis, (2) chronic hepatitis B infection, (3) nonviral causes of cirrhosis such as cryptogenic cirrhosis, (4) noncirrhotic livers that were transplanted for fulminant liver failure	(1) Alcohol cirrhosis = 5/112 (4%) (2) HBVchronic hepatitis = 0/67 (0%) (3) Cirrhosis from nonviral and non alcohol causes = 0/149 (0%) (4) Noncirrhotic =/134 (0%)	(1) 2 (0.7-3.1) (2) 4.7 (0.2-9.2)	Dysplasia detectable within the intrahepatic bile ducts in chronic HCV cirrhosis; chronic HCV, alone or in association with alcohol, as major risk factor for ICC
Wu TT *Cancer* 2009	Review of liver explants with control group at Mayo Clinic Rochester, Minnesota Period: 1995 - 2007	Histologic confirmation in explanted livers	(1) Alcohol-related and HCV-related cirrhosis: 24/26 (92%) (2) HCV-related cirrhosis: 27/44 (61%)	244 total liver explants Causes: 94 alcohol-related cirrhosis, 44 HCV-related cirrhosis, 26 alcohol- and HCV-related cirrhosis, 28 massive hepatic necrosis, 24 correction of metabolic conditions, 16 primary or metastatic tumors, 8 nodular regenerative hyperplasia, 2 subacute Budd- Chiari syndrome, 2 liver failure during the first week after transplantation	Noncirrhotic 27/80 (34%) alcohol-related cirrhosis 86/94 (91%)	(1) 92.3 (74.9-99) (2) 61.4 (46.9-75.7)	Epidemiologic role of HCV and alcohol in the development of CCA

BIN: Biliary intraepithelial neoplasia; BBD: Benign biliary disease; CT: Computed tomography; ERCP: Endoscopic retrograde cholangiopancreatography; HBsAg: Hepatitis surface antigen; cHCC-CC patients: Combined HCC and CCA; ICC: Intrahepatic colangiocarcinoma; ECC: Extrahepatic colangiocarcinoma colangiocarcinoma; CCA: Colangiocarcinoma; HCC: Hepatocellular carcinoma; MRI: Magnetic resonance imaging; PTD: Percutaneous transhepatic cholangiography; NR: Not reported; NA: Not available.

Table 3 Characteristics of available studies, reported in English, designed to assess the association between hepatitis C virus infection and pancreatic cancer risk

First author/ Journal/ Publication year	Study design/ study period	PAC diagnosis	HCV positive PAC (*n*)/ total PAC cases (*n*)	Control source	HCV positive controls (*n*)/ controls (*n*)	Percentage of HCV-positive cases with 95%CI	Main conclusions
Amin J *J Hepatol* 2006	Community-based cohort-study Period: 1990-2002	Identification of pancreatic cancer cases by means of ICD-10- diagnosis codes	-Individuals with HCV infection: 75834 PAC detected: 17/75834 (0.02%)	Incidence observed in the study cohort was compared to expected incidence derived from NSW population cancer rates by calculating standardised incidence ratios	SIRs: 1.4 (0.8-2.2)	0.02 (0.01-0.03)	No evidence supporting an association between HCV infection and PAC development
Chang MC *World J Gastroenterol* 2014	Case-control study Period: 2000-2013	Histological or citological	22/585 (3.8%)	Controls were individuals recruited from a free screening program in a community located in Northern Taiwan	45/1716 (2.6%)	3.8 (2.2-5.3)	HCV infection not associated with higher risk of PAC development, after adjustement for age, sex, diabetes and smoking (independent risk factors for PAC)
El Serag *Hepatology* 2009	Cohort study Cohort: 718687 patients PAC detected: 617 Period: 1988-2004	Identification of PAC cases by means of ICD-9-CM diagnosis codes (157.0, 157.1, 157.2, 157.3, 157.8, 157.9) Identification of HCV infected subjects by means of ICD-9-CM diagnosis codes (070.41, 070.44, 070.51, 070.54 and V02.62)	146394 patients in HCV-infected cohort PAC detected:140/146,394 (0.09%)	Sources included inpatients records from more than 150 of USA Veterans Affairs (VA) hospitals in the Patients treatment file and outpatients records from any VA facility in the Output Clinic File	572293 patients in HCV-uninfected cohort PAC detected: 477	0.09 (0.08-0.11)	Higher risk of PAC in patiens of HCV-infected cohort , but this association was attenuated after adjustement for alcohol use, pancreatitis, choledocholitiasis, cholelithiasis or primary sclerosing cholangitis
Hassan MM *J Clin Oncol* 2008	Hospital-based case-control study Period: 2000-2007	Histological confirmation	6/474 (1.5%)	Community-based (healthy genetically unrelated family members of patients with cancer other than pancreatic, GI, lung or head cancers)	9/872 (1%)	0.8 (0.02-1.6)	HCV infection not associated with higher risk of PAC development
Huang J *Br J Cancer* 2013	Retrospective Nationwide cohort study 197208 participants: Period: 1990-2006	Identification of PAC cases from the Swedish Cancer Register (International Classification of Disease ICD-7: 157) and from the Cause of Death Register (ICD-9: 157; ICD-10: C25)	Individuals in HCV reference cohort: 39442 PAC detected: 34/39442 (0.09%)	Control population obtained from the national surveillance database at the Swedish Institute for Infectious Disease Control. The expected numbers of calculated PAC from the observed person-time in each 5-yr age group by sex and the corresponding Swedish population incidence rates.	Expected number of PAC: 16.5	0.09 (0.05-0.11)	Statistically significant increased risk of PAC development
Omland LH *Clinical Epidemiology* 2010	Cohort-study Period: 1994 - 2003	Patients and subjects with HCV infection identified by means of: -The Danish National Hospital Registry (DNHR) -The Danish Cancer Registry People listed in DNHR with at least one diagnosis of acute or chronic HCV infection (ICD-10 B17.1 and 18.2) were included Cancer diagnoses based on the Danish version of the international classification of diseases, 8th revision (ICD-8) until Dec 31, 1993, and 10th version (ICD-10) thereafter	4349 patients with HCV infection in the DNHR 4/4349 PAC detected (0.1%)	The expected number of cases of cancer after a diagnosis of HCV infection using Danish incidence rates of first cancer diagnoses according to sex, age, and year of diagnosis in 1-yr intervals was calculated	Expected number of PAC: 1.01	0.1 (0-0.18)	Association between HCV infection and higher risk of PAC development

Qiwen Ben *Pancreas* 2012	Double-centre ongoing hospital-based case-control study. Period: January 1, 2004-August 31, 2008 January 1, 2003-Octobet 31, 2009	Histological or citological confirmation	14/943 (1.5%)	Patients admitted to the same Hospitals (Ruijin Hospital and Changai Hospital, Shangai for any acute conditions)	12/1128 (1.1%)	1.5 (0.7-2.2)	No higher HCV prevalence in patients with PAC in comparison with controls
Swart A *BMJ Open* 2012	Cohort-study Patients considered in the study: 29613 1 January 1993 - 31 December 2007	Individuals registered on the Pharmaceutical Drugs of Addiction System, a record of all NSW Health Department authorities that administer methadone or buprenorphine to opioid-dependent people as opioid substitution therapy. Solid cancers classified according to the International Classification of Diseases (ICD), 10th revision, haematopoietic neoplasms and Kaposi sarcomas classified according to the ICD for Oncology, 3rd edition	Subjects with HCV infection alone: 14892 Observed number of PAC in HCV-positive cohort: 20/14892 (0.1%)	Calculation of expected number of incident PAC	Expected number of PAC: 7.12	0.13 (0.08-0.21)	Increased risk of PAC in patients with HCV infection
Woo SM *J Korean Med Sci* 2013	Case-control study Period: 2001-2011	Histological or radiological/clinical confirmation	753 patients with PAC 724/753 with available anti-HCV test 21/724 (2.8%)	Individuals subjected to routine health examination in the Cancer Screening Cohort	36/3012 (1.2%)	2.9 (1.7-4.1)	Seropositivity for anti-HCV, infection, may increase the risk of developing PC in Korea

NR: Not reported; SIR: Standardised incidence ratio; HCV: Hepatitis C virus; PAC: Pancreatic cancer.

genome in normal and/or cancerous pancreatic tissue specimens. Nevertheless, since 2008, this topic has gained a progressive interest, and an increasing number of case-control-, cohort-studies and meta-analyses with different design have been carried out with this purpose. To date the number of available studies, concerning the association between HCV and PAC risk, is still limited, but among these trials, some have suggested that HCV infection represents a risk factor for PDAC, whereas others have not confirmed this association[205-207]. Two trials have been carried out in Chinese population, 2 in United States, 2 in Australia and 1 in Sweden and 1 in Korea. Among these studies, the largest-sized one has been performed in United States. On the basis of these reports, up to now, three meta-analyses have been carried out. One of these reported no statistically significant relationship between anti-HCV positivity and PDAC risk because of the small number of studies available, although a borderline value was detected in this comparison (RR = 1.16 with 95%CI ranging from 0.99 to 1.3)[211], but the others found an increased risk of this malignancy in HCV-infected patients, in comparison to controls (RR = 1.21 with 95%CI ranging from 1.02 to 1.44 or RR = 1.26 with 95%CI ranging from 1.03 to 1.5)[204,212]. However, none of these studies, available to date, included the Swedish-, the Korean-, the Australian-reports as well as the last Chinese case-control research. The majority of these trials have been published only recently, in particular, between the end of 2013 and the beginning of 2014, therefore their results were not included in the described meta-analyses. They showed that HCV infection is associated with an increased risk to develop PDAC. The characteristics and number of studies included in the reported meta-analyses vary among the 3 identified meta-analyses, depending on the different selection criteria used by each author. Furthermore, although most studies included as matching factors smoking habit, alcohol use or diabetes, no research has assessed whether these variables may act in cooperation with HCV and increase the risk of PAC. The results of our review, concerning the possible association between HCV infection and PAC risk, studies not considered, as well as meta-analyses are summarised in Tables 3, 12 and 13. Age-standardized incidence rates of pancreatic cancer per 100000 person-years is shown in Figure 3C.

Table 4 Characteristics of available studies, reported in English, designed to assess the association between hepatitis C virus infection and breast cancer risk

Author/Journal/ Publication year	Country	Study design/ study period	Diagnosis	Sample size (HCV positive breast cancer cases)	Control source	HCV positive controls/ controls	Matching factors	Percentage of HCV-positive cases with 95%CI	Main conclusions
Amin J *J Hepatol* 2006	Australia	Community-based cohort-study Period: 1990-2002	Patients'data obtained from: -New South Wales (NSW) Australia Health Department's Notifiable Diseases Database (NDD) for notification of newly diagnosed HCV infection -NSW Central Cancer Registry (CCR) for notification of incident cancer cases -National Death Index (NDI) database, containing records of all deaths in Australia since 1980 Identification of breast cancer cases by means of ICD-10-diagnosis codes	Individuals with HCV infection: 75834 Breast cancers detected: 50 50/75834	Incidence observed in the study cohort was compared to expected incidence derived from NSW population cancer rates by calculating standardised incidence ratios	SIR: 0.3 (0.4-0.5)	NR	(0.05-0.09)	No evidence supporting an association between HCV infection and breast cancer development
Hwang JP *J Oncol Pract* 2014	United States	Cohort-study Period: January 2004 - April 2011	Patients'data, obtained from four institutional sources: Tumor registry: to assess patients' demographic characteristics Pharmacy informatics: to evaluate chemotherapy drugs and dates administered. Patient accounts: to identify study patients' International Classification of Diseases (ninth edition; ICD-9) codes Laboratory informatics: to determine HCV antibody (anti-HCV) and ALT test dates and results	141877 patients with cancer, who were newly registered at MD Anderson Cancer during the study period. Patients considered in the study: 16773. HCV screened subjects: 2330/16773 (13.9%) HCV screened females: 1038 HCV-positive patients with cancers: 35/2330 (1.5%) HCV-positive females with cancers: 12 (1) HCV-positive females with breast cancers: 3/12 (2) HCV-negative females with breast cancer: 102/1026	NR	NR	NR	(1) 25 (5.5-57.2) (2) 9.9 (8.1-11.8)	HCV screening rates were low, even among patients with risk factors, and the groups with the highest rates of screening did not match the groups with the highest rates of a positive test result
Larrey D *World J Gastroenterol* 2010	France	Case serie with control gorup Period: NR	Females with history of HCV-related chronic infection, observed in Liver Unit of Montpellier School of Medicine, France, for chronic liver diseases in several occasions for a period longer than 1 yr. Chronic hepatitis proved by liver biopsy and/or biological markers of inflammation and fibrosis	17/294 (5.8%)	Females sequentially and prospectively seen during the same period with chronic liver disease over 1 yr, with well defined clinical, radiological and histological characteristics [chronic-HBV, alcoholic-liver disease, auto-immune hepatitis, hemochromatosis, non alcoholic fatty liver disease (NAFLD), cholangitis]	5/107 (4.7%)	NR	5.8 (3.1-8.4)	Chronic HCV infection is not a strong promoter of breast carcinoma in adult females of any age

Omland LH *Clinical Epidemiology* 2010	Denmark	Cohort-study Period: 1994-2003	Patients and subjects with HCV infection identified by means of: The Danish National Hospital Registry (DNHR) -The Danish Cancer Registry People listed in DNHR with at least one diagnosis of acute or chronic HCV infection (ICD-10 B17.1 and 18.2) were included Cancer diagnoses based on the Danish version of the international classification of diseases, 8th revision (ICD-8) until Dec 31, 1993, and 10th version (ICD-10) thereafter	4349 patients with HCV infection in the DNHR 2 breast cancer detected 2/4349 (0.05%)	The expected number of cases of cancer after a diagnosis of HCV infection using Danish incidence rates of first cancer diagnoses according to sex, age, and year of diagnosis in 1-yr intervals was calculated	Expected number of breast cancers 8.05	NR	0.05 (0-0.1)	No association between HCV infection and higher risk of breast cancer development
Su FH *BMC Cancer* 2011	Taiwan	Population-based study Period: 2000-2008	Data retrieved from National Health Insurance Research Database (NHIRD), which is maintained by the National Health Research Institute (NHRI), Taiwan. Newly diagnosed breast cancer identified from the registry for Catastrophic Illness Patients Database (ICD-9-CM code 174 and 175). Identification of HCV infected subjects by means of ICD-9-CM diagnosis codes (ICD-9-CM 070.41, 070.44, 070.51, 070.54, and V02.62)	56/1958 (2.9%)	Randomly selected and matched individuals without a history of breast cancer (control to patient ratio was 4:1)	178/7832 (2.3%)	age- and sex	2.9 (2.1-3.5)	HCV infection associated with early onset risk of breast cancer in areas endemic for HCV
Swart A *BMJ Open* 2012	Australia	Cohort-study 1 January 1993 - 31 December 2007	Individuals registered on the Pharmaceutical Drugs of Addiction System, a record of all NSW Health Department authorities that administer methadone or buprenorphine to opioid-dependent people as opioid substitution therapy. Solid cancers classified according to the International Classification of Diseases (ICD), 10th revision, haematopoietic neoplasms and Kaposi sarcomas classified according to the ICD for Oncology, 3rd edition	Patients considered in the study: 29613 Subjects with HCV infection alone: 14892 Observed number of breast cancer in HCV-positive cohort: 48 48/14892 (0.03%)	Calculation of expected number of incident breast cancer	Expected number of breast cancers: 101	NR	0.03 (0.02-0.04)	No evidence supporting an association between HCV infection and breast cancer development

NR: Not reported; SIR: Standardised incidence ratio; HCV: Hepatitis C virus.

HCV and breast cancer risk

On the basis of the observation that the wide geographical differences in the age-standardized incidence of breast cancer[229] cannot be entirely explained by variations in known risk factors among countries, it was hypothesized, since 1997, that a relationship might exist between this malignancy and late exposure to a common virus[231]. It has been reported that some viruses may be involved in the occurrence of this malignancy[232], but, in particular, in 1999 an anecdotal report suggested, for the first time, the HCV might play a role in the development of some solid tumors other than liver, including breast cancer. Since then, some studies investigated the possible involvement of HCV in breast carcinogenesis. Among the 6 trials identified in our review, 5 were cohort- and 1 case-control-studies. Two of them were performed in Australia, 1 in United States, 1 in Denmark, 1 in Taiwan and 1 in France, respectively. Two studies, 1 case-control performed in Taiwan and 1 cohort trials in France were designed with the primary aim to assess the potential relationship between HCV and breast cancer risk, whereas the others were not. Only the research carried out in Taiwan found an association with early onset risk of breast cancer.

Table 5 Characteristics of available studies, reported in English, assessing the association between hepatitis C virus infection and renal cancer

Author/Journal/ Publication year	Country	Study design/ study period	Diagnosis	Sample size (HCV positive RCC cases)	Control source	HCV positive controls/controls	Matching factors	Percentage of HCV-positive cases with 95%CI	Main conclusions
Amin J *J Hepatol* 2006	Australia	Community-based cohort-study Period: 1990-2002	Identification of renal cancer cases by means of ICD-10- diagnosis codes	Individuals with HCV infection: 75834 RCC detected: 19 19/75834	Incidence observed in the study cohort was compared to expected incidence derived from NSW population cancer rates by calculating standardised incidence ratios	SIR: 0.9 (0.6-1.4)	NR	0.02 (0.01-0.03)	No evidence supporting an association between HCV infection and kidney cancer development
Budakoğlu B *Med Oncol* 2012	Turkey	Case series with control group 2005-2010	Histological confirmation	15/903 (1.7%)	Data collected in previous prevalence studies in healthy subjects in three different geographical areas of the Turkey, used as control group	81/5267 (1.5%)	NR	1.7 (0.8-2.4)	No higher frequency of HCV positivity in RCC patients in comparison with healthy people
Gonzalez HC *Dig Dis and Sci* 2015	United States	Case series with control group January 2011 - August 2013	Histological confirmation	Anti-HCV positive: 11/140 (7.9%) (2) HCV-RNA positive: 9/140 (6.4%)	Consecutive individuals newly diagnosed with colon cancer. The control group recruited simultaneously and from the same health care system (Henry Ford Health System in Detroit, Michigan)	Anti-HCV positive: 1/100 (1%) HCV-RNA positive: 0/100	NR	(1) 7.9 (3.4-12.3) (2) 2.3 (10.5)	Increased risk of RCC in subjects with HCV chronic infection
Gordon SC *Cancer Epidemiol Biomarkers Prev* 2010	United States	Cohort study Period: 1997-2006	Use of administrative data from Henry Ford Hospital, an integrated healthcare delivery system serving southeastern Michigan. Cancer diagnosis codes in administrative databases [International Classification of Diseases, 9th ed., Clinical Modification (ICD-9-CM) codes in the range of 140 through 208.9]	72487 patients tested for anti-HCV 3057/72487 anti-HCV positive patients 17/3057 (0.6%) with RCC	Control cohort of patients who tested negative for anti-HCV	64006/72487 anti-HCV negative patients 177/64006 (0.3%) with RCC	NR	0.6 (0.3-0.8)	Chronic infection with HCV confers an increased and independent risk for developing RCC
Hofmann JN *Eur J Cancer Prev* 2011	Sweden	Nationwide register-based cohort- study Period: 1990-2008	HCV diagnosis extracted from the national surveillance database at the Swedish Institute for Infectious Disease Control (SMI). Cancer diagnoses were coded using the seventh revision of the International Classification of Diseases (ICD-7) (ICD-7 codes 180.0 and 180.9)	43000 Lag period after HCV notification (1) None: 38, Expected: 27.1 (2) Three months 33 Expected: 26.5 (3) One year: 29 Expected: 24.9	A non-HCV-infected cohort selected from the general population	215000	Year of birth, sex, and county of residence in Sweden, five subjects never diagnosed with HCV infection were matched to each HCV-infected subject	(1) 0.06 (0.09-0.21) (2) 0.05 (0.08-0.21) (3) 0.05 (0.07-0.21)	In the cohort of HCV-infected subjects, no increased risk of developing kidney cancer but an enhanced risk of non-cancer chronic kidney disease, particularly among women

Malaguarnera M *Eur J Int Medicine* (2006)	Italy	Case-control study Period: NR	All cancer patients: 236 HCV diagnosis performed with II G ELISA test. Cancers diagnosed at Garibaldi Hospital	15 patients with RCC 8/15 (53%) HCV positive patients	Elderly volunteers evaluated at Garibaldi Hospital, Catania	30/300 (10%)	Age, sex and previous blood transfusions	53.3 (26.5-78.7)	High prevalence of anti-HCV antibodies in patients with renal cancer
Omland LH *Clinical Epidemiology* 2010	Denmark	Cohort-study Period: 1994-2003	Patients and subjects with HCV infection identified by means of: -The Danish National Hospital Registry (DNHR) -The Danish Cancer Registry People listed in DNHR with at least one diagnosis of acute or chronic HCV infection (ICD-10 B17.1 and 18.2) were included Cancer diagnoses based on the Danish version of the international classification of diseases, 8th revision (ICD-8) until Dec 31, 1993, and 10th version (ICD-10) thereafter	4349 patients with HCV infection in the DNHR 4 renal cancer detected 4/4349	The expected number of cases of cancer after a diagnosis of HCV infection using Danish incidence rates of first cancer diagnoses according to sex, age, and year of diagnosis in 1-year intervals was calculated	Expected number of kidney cancers: 1.11	NR	0.1 (0-0.2)	Association between HCV infection and higher risk of renal cancer development
Swart A *BMJ Open* 2012	Australia	Cohort-study 1 January 1993 - 31 December 2007	Individuals registered on the Pharmaceutical Drugs of Addiction System, a record of all NSW Health Department authorities that administer methadone or buprenorphine to opioid-dependent people as opioid substitution therapy. Solid cancers classified according to the International Classification of Diseases (ICD), 10th revision, haematopoietic neoplasms and Kaposi sarcomas classified according to the ICD for Oncology, 3rd edition	Patients considered in the study: 29613 Subjects with HCV infection alone: 14892 Observed number of RCCs in HCV-positive cohort: 20 20/14892	Calculation of expected number of incident RCCs	Expected number of RCCs: 18.1	NR	0.1 (0.08-0.20)	No evidence supporting a strong association between HCV infection and RCC development

NR: Not reported; SIR: Standardised incidence ratio; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma.

The results of our review, concerning the possible association between HCV infection and renal cancer risk as well as studies not considered are summarised in Table 4 and 14. To date, no meta-analysis has been published on this topic. Age-standardized incidence rates of breast cancer per 100000 person-years is reported in Figure 3D.

HCV and kidney cancer risk

Although some authors have reported, several years ago, that HCV is associated with an higher probability to develop chronic end-stage renal diseases[233] or that a relationship may exist between this virus and a major risk of kidney cancer, as reported in some case reports[234,235] or in very small series of patients[236], only in the last 5 years, the interest for this topic has progressively increased and adequately powered studies have been carried out in different geographical areas worldwide. To date 4 cohort-, 1 case-control- and 2 case series with control groups studies available in literature, have been considered in our systematic review. Two among cohort-trials were performed in Australia, 1 in United States and 1 in Sweden, whereas the case-control trial in Italy. One case series study was carried out in United States[199] and one in Turkey[198]. The results of these reports are not univocal. In particular, only 1 of these cohort studies as well as 1 case series with control group research and

Table 6 Characteristics of available studies, reported in English, assessing the association between hepatitis C virus infection and oral or skin cancer

Author/Journal/ Publication year	Study design/study period	Diagnosis	Sample size (cases/ controls)	Control source	HCV positive controls/ controls	Percentage of HCV-positive cases with 95%CI	Main conclusions
Amin J *J Hepatol* 2006	Community-based cohort-study Period: 1990-2002	Identification of skin/oral cancer cases by means of ICD-10- diagnosis codes	Individuals with HCV infection: 75834 Skin/oral cancer: 19 including , mouth (7 cases), tongue (6 cases), tonsil (6 cases) no skin cancers described	Incidence observed in the study cohort was compared to expected incidence derived from NSW population cancer rates by calculating standardised incidence ratios	SIR: Mouth: 1.5 (0.7-3.2) Tongue: 1.1 (0.5-2.4) Tonsil: 2.1 (1-4.8)	0.02 (0.01-0.03)	No evidence supporting an association between HCV infection and skin/oral cancer development, low increased risk for tonsil cancer
Eftekharian A *Eur Arch Otorhinolaryngol* 2012	Case-series 107 patients with SCCHN Period: October 2008-June2010	Histological confirmation: SCCHN	1/107 (0.9%)	NR	NR	0.9 (0-2.7)	HCV at least in Iran not a risk factor for SCCHN
Gandolfo S *Oral Oncol* 2004	Case-series 402 patients with OLP Patients with available HCV test: 357 HCV positive patients: 69/357 (19.3%) Period: January 1988 - July 1999	During the follow-up period: 9 patients developed an oral squamous cell carcinoma Histological confirmation: OSCC	HCV positive patients with OSCC: 4/9 (44.5%)	NR	NR	44.5 (11.9-76.9)	Possible increased risk for OSCC in HCV-related infection in patients oral lichen planus (OLP)
Nagao Y *J Oral Pathol Med* 1995	Case-series 100 patients with oral cancer enrolled Period: January 1989-October 1993	Histological confirmation: Different histotypes	24/100 (24%)	Patients with non-malignant disease receiving dental treatment at the Department of Oral Surgery of the Kurume University Patients with gastric cancer	(1) 11/104 (10.6%); (2) 12/113 (10.6%)	24 (15.6-32.3)	HCV causing pathologic changes in the oral cavity, with HCV involved in cancerization
Nagao Y *J Oral Pathol Med* 2000	Biopsies of 36 patients, including: (1) OLP: 19; (2) Oral cancer: 17 Period: NR	Histological confirmation: Well-differentiated SCCHN	(1) 14/19 (73.7%); (2) 7/17 (41. 2%)	Biopsies of 10 patients, including: (3) Non-malignant disease with HCV (4) Non-malignant disease without HCV	(3): 6 (4): 4	(1) 73.7 (53.8-93.4); (2) 41.2 (17.8-64.5)	HCV causing pathologic changes in the oral cavity, with HCV involved in cancerization
Nobles J *Laringoscope* 2004	Case-series 100 patients with SCCHN enrolled. Period: June 1991-December 2002	Histological confirmation: SCCHN	21/100 (21%)	NR	NR	21 (13-28.9)	A large number of patients (21%) with SCCHN, included in this study, coinfected with HCV. This prevalence is significantly increased when compared with the general population (1.4%) or the population at VA hospitals (9.9%)

Omland LH *Clinical Epidemiology* 2010	Cohort-study Period: 1994-2003	Patients and subjects with HCV infection identified by means of: -The Danish National Hospital Registry (DNHR) -The Danish Cancer Registry People listed in DNHR with at least one diagnosis of acute or chronic HCV infection (ICD-10 B17.1 and 18.2) were included Cancer diagnoses based on the Danish version of the international classification of diseases, 8th revision (ICD-8) until Dec 31, 1993, and 10th version (ICD-10) thereafter	4349 patients with HCV infection in the DNHR 4 oropharyngeal cancers detected	The expected number of cases of cancer after a diagnosis of HCV infection using Danish incidence rates of first cancer diagnoses according to sex, age, and year of diagnosis in 1-yr intervals was calculated	Expected number of oropharyngeal cancers: 1.73	0.1 (0-0.2)	No sssociation between HCV infection and higher risk of oropharyngeal cancer development
Su FH *PlosOne* 2012	Nationwide Population-Based Cohort Study HCV positive patients: 5311 HCV and HBV positive patients: 3519 Period: 1996-2008	Data obtained from the Taiwan National Health Insurance Research Database (NHIRD). HCV cases identified by means of ICD-9-CM diagnosis codes (ICD-9-CM: 070.41, 070.44, 070.51, 070.54, V02.62)	(1) 21/5311; (2) 9/3519	Controls identified by means of a systematic random sampling method to select 4 insured people without viral hepatitis for every insured person with viral hepatitis during the same period	147/84796	(1) 0.4 (0.2-0.5); (2) 0.3 (0.09-0.4)	HCV infection is a risk factor for oral cavity cancer. In addition, subjects with HCV infection tend to be at early onset risk for oral cavity malignancy
Swart A *BMJ Open* 2012	Cohort-study 1 January 1993 - 31 December 2007	Individuals registered on the Pharmaceutical Drugs of Addiction System, a record of all NSW Health Department authorities that administer methadone or buprenorphine to opioid-dependent people as opioid substitution therapy. Solid cancers classified according to the International Classification of Diseases (ICD), 10th revision, haematopoietic neoplasms and Kaposi sarcomas classified according to the ICD for Oncology, 3rd edition	Patients considered in the study: 29613 Subjects with HCV infection alone: 14892 Observed number of following cancer in HCV-positive cohort: (1) Tonsil: 10; (2) Mouth:8; (3) Salivary gland: 4; (4) Tongue: 9 Total: 31	Calculation of expected number of incident tonsil/ mouth/salivary gland/ tongue cancers	Expected number of oral cancers: Tonsil: 2.96 Mouth; 3.54 Salivary gland: 2.75 Tongue:5.35	0.2 (0.1-0.3)	Possible association between HCV and tonsil/mouth cancers. No association between HCV infection and tongue/ salivary cancers
Takata Y *Oral Diseases* 2002	Case series Patients with anti-HCV antibodies: 2613 HCV positive patients: 151/2613 (5.8%) Period: January 1989 -December 1998	Histological confirmation Histotype not reported	25/245 (10.2%)	NR	NR	10.2 (6.4-13.9)	High HCV antibody prevalence in patients with oral cancer. Possible no important association between oral cancer and HCV infection, with increased prevalence, depending on higher age of anti-HCV positive patients

NR: Not reported; SIR: Standardised incidence ratio; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma.

Table 7 Characteristics of available studies, reported in English, assessing the association between hepatitis C virus infection and thyroid cancer

Author/Journal/ Publication year	Study design/study period	Diagnosis	Sample size	Control source	Controls	Percentage of HCV-positive cases with 95%CI	Main conclusions
Amin J *J Hepatol* 2006	Community-based cohort-study Period: 1990-2002	Identification of thyroid cancer cases by means of ICD-10- diagnosis codes	Individuals with HCV infection: 75834 Thyroid cancers detected: 9	Incidence observed in the study cohort was compared to expected incidence derived from NSW population cancer rates by calculating standardised incidence ratios	SIR: 0.3 (0.2-0.7)	0.01 (0-0.02)	No evidence supporting an association between HCV infection and thyroid cancer development
Antonelli A *Clin Exp Rheumat* 2002	Case-control study Period: 1999-2001	FNA PTC	94 patients with HCV-associated MC Patients with PTC and HCV-associated MC/patients with HCV-associated MC: 2/94 (2.1%)	Control group obtained from a sample (2401 individuals) of the general population, 5 controls were randomly associated with each MC patient	0/470	2.1 (0-5)	Possible association between HCV-related MC and thyroid cancer, careful monitoring of the thyroid opportune, during the clinical follow-up of HCV-associated MC patients
Antonelli A *Thyroid* 2007	Case-control study Period: January 1995 - December 2001	FNA PTC	308 HCV positive patients PTC and HCV positive cases/all HCV positive cases: 6/308 (1.9%)	(1) subjects from an iodine deficient area; (2) subjects from an iodine-sufficient area	PTC cases/all HCV negative controls: (1) 0/616; (2) 1/616	1.9 (0.4-3.4)	High prevalence of thyroid papillary cancer in HCV+ patients, overall in presence of thyroid autoimmunity; careful thyroid monitoring is indicated during the follow-up of these patients
Giordano TP *JAMA* 2007	Cohort study Period: 1997-2004	Identification of HCV infected subjects by means of ICD-9-CM , diagnosis codes of HCV infection (070.41, 70.44, 070.51, 070.54, V02.62) Identification of thyroid cancer by menas of ICD-9-CM diagnosis codes: 193	HCV-positive cohort: 146394 patients During follow-up, 813 patients in HCV-infected cohort (0.5%) had a HIV diagnosis. 46 patients developed thyroid cancer	Inpatients records from more than 150 United States Veterans Affairs (VA) hospitals in the Patients' treatment file and outpatients records from any VA facility in the Output Clinic File	HCV- negative cohort: 572293 patients. During follow-up, 35696 uninfected HCV patients (6.2%) had a recorded HCV diagnosis and 1539 patients (0.3%) a HIV diagnosis 274 patients developed thyroid cancer	0.03 (0.02-0.04)	No increased, risk for thyroid cancer in HCV-positive cohort
Montella M *Oncol Rep* 2003	Case-control study Period 1997-1999	Histological confirmation PTC	HCV positive PTC cases/all PTC cases: 16/130 (12.3%)	Control group including subjects, operated for benign diseases. Cases and controls selected from the hospital tumor registry	242 controls and 311 surgical procedures. HCV positive controls/ total controls 18/311	12.3 (6.6-17.9)	Association between HCV and thyroid cancer. This malignancy more readily detectable in countries with a high prevalence of HCV

Omland LH *Clinical Epidemiology* 2010	Cohort-study Period: 1994-2003	Patients and subjects with HCV infection identified by means of: -The Danish National Hospital Registry (DNHR) -The Danish Cancer Registry People listed in DNHR with at least one diagnosis of acute or chronic HCV infection (ICD-10 B17.1 and 18.2) were included Cancer diagnoses based on the Danish version of the international classification of diseases, 8th revision (ICD-8) until Dec 31, 1993, and 10th version (ICD-10) thereafter	4349 patients with HCV infection in the DNHR 1 thyroid cancer detected	The expected number of cases of cancer after a diagnosis of HCV infection using Danish incidence rates of first cancer diagnoses according to sex, age, and year of diagnosis in 1-yr intervals was calculated	Expected number of thyroid cancers: 0.46	0.02 (0-0.06)	No association between HCV infection and higher risk of thyroid cancer development
Swart A *BMJ Open* 2012	Cohort-study 1 January 1993 - 31 December 2007	Individuals registered on the Pharmaceutical Drugs of Addiction System, a record of all NSW Health Department authorities that administer methadone or buprenorphine to opioid-dependent people as opioid substitution therapy. Solid cancers classified according to the International Classification of Diseases (ICD), 10th revision, haematopoietic neoplasms and Kaposi sarcomas classified according to the ICD for Oncology, 3rd edition	Patients considered in the study: 29613 Subjects with HCV infection alone: 14892 Observed number of thyroid cancer in HCV-positive cohort: 48	Calculation of expected number of incident thyroid cancer	Expected number of thyroid cancers: 34.4	0.3 (0.2-0.4)	No evidence supporting an association between HCV infection and thyroid cancer development

FNA: Fine needle-aspiration; MC: Mixed cryoglobulinemia; PTC: Papillary thyroid cancer; SIR: Standardised incidence ratio; HCV: Hepatitis C virus.

case-control study have detected an association between HCV infection and risk of kidney malignancy[196,199,200], whereas the remaining articles did not. However, it has to be underlined that 2 of these cohort studies were designed to assess the incidence for all cancer types following HCV infection and not specifically the renal one [118,146]. In addition, a significant relationship between renal carcinoma and viral hepatitis has been described in a further research, but it has not been considered, because no data on the type viral hepatitis infection were reported[203]. The results of our review, concerning the possible association between HCV infection and renal cancer risk as well as studies not considered are summarised in Tables 5 and 15. To date, no meta-analysis has been published on this topic. Age-standardized incidence rates of renal cancer per 100000 person-years is reported in Figure 3E.

HCV and oral/skin cancer risk

A relationship between HCV and oral squamous cell carcinoma (OSCC) was described, for the first time, in 1995[224] and then it was also reported in 1997, when a high prevalence of anti-HCV antibodies and of viral genome was showed in patients with head and neck squamous cell carcinomas[237]. Since then, cases of OSCC and verrucous carcinoma have been described in anti-HCV positive subjects with or without associated oral lichen planus (OLP)[238,239]. The prevalence of this inflammatory mucocutaneous condition varies largely among different geographical areas, with the highest rates observed in countries with HCV hyperendemia[240]. According to one study performed in 1557 patients with OLP, a more elevated HCV prevalence was observed in individuals, suffering from this disease, than that in the control group (1.9%, 0.4% respectively, $P < 0.001$)[241]. The association between HCV infection and OLP has been recently confirmed by three independent meta-analyses and it emerged across throughout the world. However, this relationship was most frequently detected in East- and South-East Asia as well as in South American- and Mediterranean-regions[242-244]. HCV might be involved in this type of process[245]. It has been suggested that OLP is a precancerous lesion, although the degree of risk of this disease for development of oral cancer is controversial[225,239]. Additional studies have shown a significant higher prevalence of HCV infection in patients with squamous cell carcinoma of head and neck (SCCHN) than that described in controls[225], whereas others did not[227]. To date, 10 studies, concerning relationship between HCV infection and oral/skin cancers have been published. Our findings, concerning the possible association between HCV infection and oral/skin cancer risk as well as studies not

Table 8 Main findings of studies, concerning the association between hepatitis C virus infection and lymphomas, not considered in the present systematic review because of not reported in English or as full-text or including incomplete data or assessing lymphoproliferative disorders other than B-cell lymphomas

Studies (First author/Journal/ Year of publication)	Study title	Main findings for exclusion	Study conclusion
Arcaini L *Cancer* 2004	Splenic and nodal marginal zone lymphomas are indolent disorders at high hepatitis C virus seroprevalence with distinct presenting features but similar morphologic and phenotypic profiles	Duplicate	High HCV seroprevalence in patients with MZL
Catassi C *Rec Prog Med* 1998	High prevalence of hepatitis C virus (HCV) infection in patients with non-Hodgkin lymphoma at the onset: preliminary results of a multicentre Italian study	Full-text in Italian	Possible causative role of the HCV in lymphomagenesis
Dal Maso L *Haematologica* 2004	Hepatitis B and C viruses and Hodgkin lymphoma: a case-control study from northern and southern Italy	Evaluation of the association between HCV infection and HL risk	No role of HCV in the etiology of HL
de Sanjose S *Int J Cancer* 2004	Role of hepatitis C virus infection in malignant lymphoma in Spain	Duplicate	HCV infection is associated with an increased risk of lymphoma in Spain
Domingo JM *Med Clin* (Barc) 2001	Hepatitis C virus infection in patients with non Hodgkin's lymphoma	Full-text in Spanish	Possible association between HCV infection and NHLs
Ferri C *JAMA* 1994	Non-Hodgkin's lymphoma: possible role of hepatitis C virus	Duplicate	Possible role of HCV infection in B-cell NHLs development
Ferri C *QJM* 1996	Chronic hepatitis C and B-cell non-Hodgkin's lymphoma	Duplicate	Possible role of HCV infection in B-cell NHLs development
Gasztonyi B *Orv Hetil* 2000	Hepatitis C virus infection and B-cell non-Hodgkin's lymphoma	Full-text in Humgarian	HCV might have an aetiological role in the lymphoproliferation leading to B-cell NHL
Grudeva-Popova J *BUON* 2013	Non-Hodgkin lymphomas and carrier state of viral hepatitis B and C	Incomplete data concerning the association between HCV infection and NHLs	Hepatitis virus carrier state did not alter significantly the clinical course and disease prognosis
Izumi T *Leukemia* 1997	B cell malignancy and hepatitis C virus infection	Duplicate	Association between persistent HCV infection and the occurrence of B- cell malignancy
Montella M *Liver* 2001	HCV and cancer: a case-control study in a high-endemic area	Duplicate	Expected increases not only in liver cancer, but also in tumors associated with the immune system
Sánchez Ruiz AC *Med Clin* (Barc) 2001	Prevalence of hepatitis C virus infection in patients with non-Hodgkin's lymphoma	Full-text in Spanish	Higher prevalence of HCV in our B-NHL patients

MZL: Marginal zone lymphoma.

considered are summarised in Tables 6 and 16. To date, no meta-analysis has been published on this topic. Age-standardized incidence rates of oral-cancer per 100000 person-years is reported in Figure 3F.

HCV and thyroid cancer risk

The first description of an association between HCV and risk of thyroid cancer development dates back to 1999, when Antonelli *et al*[246] reported a high prevalence (2.2%) of thyroid cancer in a series of 139 patients with chronic hepatitis C infection in comparison to no case among 835 control subjects, who were long-term residents of an iodine-deficient area[246]. Since then some case-control studies have been carried out to assess this finding[73,74,215-217,247]. These trials have been performed in Italy and all have confirmed the previous above-mentioned assumption, although, some of these represent duplicates[73,74,215-217,247]. Afterwards, three cohort studies have been published to assess this subject in the last years, but no evidence supporting an association between HCV infection and thyroid cancer development has emerged from these reports. Two of these trials were designed to assess the incidence for all cancer types following HCV infection and not specifically the thyroid one[118,146]. Our findings, concerning the possible association between HCV infection and renal cancer risk as well as studies not considered are summarised in Table 7 and 17. To date, no meta-analysis has been published on this topic. Age-standardized incidence rates of thyroid cancer per 100000 person-years is reported in Figure 3G.

DISCUSSION

To our knowledge, this is the first study aimed to review systematically the prevalence of HCV infection in a wide spectrum of human malignancies, to summarise the retrieved data and to discuss the possible role of this pathogen in the genesis of the discussed tumours. Since several years the possible involvement of different viruses in human carcinogenesis has been reported, with increasing frequency, in a large series of epidemiological studies. Recently, the International Agency for Research on Cancer (IARC) has comprehensively assessed and confirmed the human carcinogenicity of 7 viral

Table 9 Characteristics of available systematic review and/or meta-analyses, reported in English, assessing the association between hepatitis C virus infection and lymphomas

First author/ Country	Title	Number of studies considered	Main conclusion	Matching factors considered
Gisbert JP, 2003	Prevalence of hepatitis C virus infection in B-cell non-Hodgkin's lymphoma: systematic review and meta-analysis	23	HCV prevalence in patients with B-NHL is approximately 15%, higher than that reported not only in general population (1.5%) but also in patients with other hematologic malignancies (2.9%), suggesting a role of HCV in the etiology of B-NHL	Age, sex, smoking, race, when available
Matsuo K, 2004	Effect of hepatitis C virus infection on the risk of non-Hodgkin's lymphoma: a meta-analysis of epidemiological studies	23	Strongly positive association between anti-HCV seropositive test subjects and risk of NHL. Individualists with anti-HCV positive test have approximately five times higher risk of NHL. This association is consistent regardless of the endemic status of HCV, as well as subgroup analysis for B-/T-NHL	Age and sex, when available
Negri E, 2004	B-cell non-Hodgkin's lymphoma and hepatitis C virus infection: a systematic review	15	A high HCV prevalence in B-NHL was found in southern and eastern Europe, Japan and the southern United States, but not in central and northern Europe, Canada, northern United States, or a few Asian countries. The odds ratio of B-NHL for HCV infection was relatively weak, ranging from 2 to 4 in most studies. Thus, even if the observed association were causal, the percentage of cases of B-NHL attributable to HCV infection would be relatively low (10%) also in countries with a high prevalence of HCV infection in the general population, and extremely low in other countries	Age and sex, whether available
Dal Maso L, 2006	Hepatitis C Virus and Risk of Lymphoma and Other Lymphoid Neoplasms: A Meta-analysis of Epidemiologic Studies	18	The pooled relative risks (RR) were consistently increased for all major B-NHL subtypes, T-NHL, and primary sites of NHL presentation. The etiologic fraction of NHL attributable to HCV varies greatly by country, and may be upward of 10% in areas,where HCV prevalence is high .Associations weaker than with NHL were found between HCV infection and Hodgkin's lymphoma	Age and sex, when available
de Sanjose S, 2008	Hepatitis C and non-Hodgkin lymphoma among 4784 cases and 6269 controls from the International Lymphoma Epidemiology Consortium	7	The results of the present study confirm the association between HCV infection and NHL and specific B-NHL subtypes (diffuse large B-cell lymphoma, marginal zone lymphoma and lymphoplasmacytic lymphoma). This research has sufficient statistical power to confirm these associations in populations with low HCV prevalence	Age, sex, county of residence, study site, geographic area, when available
Libra M, 2010	Extrahepatic disorders of HCV infection: A distinct entity of B-cell neoplasia?	18 Review of Italian studies	The results of the study confirm the association between HCV infection and NHL and specific B-NHL subtypes. The higher prevalence of anti-HCV Abs was observed among lymphoplasmacytoid/ lymphoplasmacytic/immunocytoma histotype whereas the lowest was among small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL). Overall, these studies strongly support the notion that HCV-associated lymphomas may be a distinct entity and further characterization of the mechanisms by which HCV infection contributes to B-cell NHL development may improve its diagnosis, classification and treatment	NR

HCV: Hepatitis C virus; NHL: Non-hodgkin-lymphoma.

agents, including HCV. In particular, it has been recognised that HCV acts as an indirect carcinogen, by promoting and maintaining a state of chronic inflammation in infected sites[248]. This event is now a well-known condition that is involved in the process of hepatic carcinogenesis. However, even if liver is the main target of HCV, its tropism for this organ is not exclusive. In particular, viral antigens and genomes have been also detected in extra-hepatic tissues[249]. All these evidences have contributed to consider the possible role of this pathogen as a pro-cancerous agent also in organs other from liver. On the basis of this assumption, as it has been observed for the strong relationship between HCV and hepatocellular carcinoma (HCC) development, it is conceivable to think that a similar ecological correlation might exist between HCV infection and a major risk of some extra-hepatic cancers in regions where the prevalence of this pathogen is high in comparison with geographical areas with a lower one. However, to date, the possibility that this virus may be involved in the carcinogenesis of organs other than liver has been systematically investigated only for a very limited number of malignancies. In particular, available studies have been mainly focused on hematopoietic malignancies and on cholangiocarcinomas, also on the basis of some epidemiological observations, reporting a major risk of mixed cryoglobulinemia and monoclonal gammopathy in HCV positive patients[250] as well as of a higher incidence of cholangiocarcinoma

Table 10 Main findings of studies concerning the association between hepatitis C virus infection and cholangiocarcinomas with no complete data or not reported as full-text

Studies (First author/Journal/ Year of publication)	Study title	Main findings	Study conclusion
Choi D *J Hepatology* 2006	Cholangiocarcinoma and Clonorchis sinesis infection: A case-control study in Korea	Assessment of Clonorchis sinensis role in the risk of developing CCA, including extrahepatic CCA	HCV infection detected in 1/51 (2%) patients in CCA group and 1/51 (2%) in control gorup
Jarnagin WR *Cancer* 2002	Combined hepatocellular and cholangiocarcinoma: demographic, clinical, and prognostic factors	No distinction between HBV/HCV infected patients	The demographic and clinical features of patients with combined tumors were most similar to those of patients with CC. Most important, combined tumors were not found to be associated with chronic liver disease
Liu X *Zhonghua Wai Ke Za Zhi* 2002	Pathogenesis of hilar cholangiocarcinoma and infection of hepatitis virus	Full-text in Chinese	HCV-core protein may play an important role in the pathogenesis of hilar cholangiocarcinoma. HCV-infected patients with hilar cholangiocarcinoma infected may have a high grade malignancy and a poor prognosis
Lu H *Chin Med J* (Engl) 2000	Detection of hepatitis C virus RNA sequences in cholangiocarcinomas in Chinese and American patients	Only 12 patients included	High rate of HCV-RNA detection in CCA cases, mainly in Chinese patients as compared to United States subjects
Shirakawa H *Hokkaido Igaku Zasshi* 1996	Analysis of hepatitis C virus (HCV) genotypes in hepatocellular carcinoma	Full-text in Japanese	2/11 HCV seropositive Japanese patients with cholangiocarcinoma
Tao LY *Liver International* 2009	Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: a case-control study in China	Shortage of information on HCV infection	No possible assessment of significant association between HCV infection and ICC or ECC
Yin F *Chin Med J* (Engl) 1998	Detection of hepatitis C virus RNA sequences in hepatic portal cholangiocarcinoma tissue by reverse transcription polymerase chain reaction	Only 6 patients included	High rate of HCV-RNA detection in CCA cases
Zhang H *Zhonghua Bing Li Xue Za Zhi* 1996	Detection of hepatitis B virus DNA and hepatitis C virus RNA in human hepatocellular carcinoma by polymerase chain reaction	Full-text in Chinese	HCV may play an important role in hepatic carcinogenesis because of its high positive rate
Zou SQ *Zhonghua Wai Ke Za Zhi* 2003	The retrospective analysis of HBV and HCV infection in cholangiocarcinoma	Full-text in Chinese	The HCV infection is associated with hilar cholangiocarcinoma, in particular with the proximal bile duct. The hilar cholangiocarcinoma in HCV-infected patients presents higher malignant degree and a poor prognosis

Table 11 Characteristics of available meta-analyses, reported in English, assessing the association between hepatitis C virus infection and cholangiocarcinoma

First author	Title	Number of studies considered	Main conclusion	Matching factors considered
Shin HR, 2010	Epidemiology of cholangiocarcinoma: An update focusing on risk factors	11	HCV infection is associated with an increased risk for CCA, but its possible role in development of this malignancy requires further investigation	NR
Palmer WC, 2012	Are common factors involved in the pathogenesis of primary liver cancers? A meta-analysis of risk factors for intrahepatic cholangiocarcinoma	8	HCV infection is associated with an increased risk for intrahepatic cholangiocarcinoma	NR
Zhou Yanming, 2012	Hepatitis viruses infection and risk of intrahepatic cholangiocarcinoma: evidence from a meta-analysis	16	HCV infection is associated with an increased risk of ICC	NR

NR: Not reported; HCV: Hepatitis C virus.

and other types of human cancer other than liver in subjects with cirrhosis, irrespective of etiology[251]. In this study, enrolled patients suffered from alcoholic-, primary biliary-, and chronic-hepatitis-related cirrhosis, whereas in a group of patients the causes of this pathological condition were non-specified. Unfortunately, no detailed information was available, concerning the HCV status in the cohort of

Table 12 Main findings of available studies, not reported in English, evaluating hepatitis C virus infection and pancreatic cancer risk (A) and characteristics of studies, reported in English, assessing hepatitis C virus infection and pancreatic cancer risk, with no complete data or not reported as full-text (B)

Studies (First author/Journal/Year of publication)	Study title	Main findings	Study conclusion
(A)			
Hong SG, 2010 *Korean J Hepatol* 2010; 16: 1	The relationship between hepatitis B virus infection and the incidence of pancreatic cancer: a retrospective case-control study	Full-text in Korean	Absence of significant association between anti-HCV positivity and pancreatic cancer
Xu P, 2011 *Cancer* (Chinese J) 2011; 31: 653-657 (52)	Risk factors for pancreatic cancer: a case-control study	Full-text in Chinese	Absence of significant relationship between anti-HCV positivity and pancreatic cancer
(B)			
Fang Zhu Asian Pacific J Cancer Prev 2011	Chronic hepatitis virus infection and pancreatic cancer: a case-control study in southern China	No detailed description of number of patients with HCV-infection in case- and control group	Increased prevalence of anti-HCV antibodies in patients with pancreatic cancer

HCV: Hepatitis C virus.

Table 13 Characteristics of available meta-analyses, reported in English, assessing the association between hepatitis C virus infection and pancreatic cancer risk

First author/ Country	Title	Number of studies considered	Main conclusion	Adjustment for diabetes, alcohol, cigarette
Fiorino S, 2013 Italy	Association between hepatitis B or hepatitis C virus infection and risk of pancreatic adenocarcinoma development: a systematic review and meta-analysis	3 studies available for assessment of HCV infection and PAC risk	No statistically significant relationship between anti-HCV positivity and PAC risk, although a borderline value was detected in this comparison (RR = 1.16 (95%CI: 0.99-1.3)	Y Y Y
Xing S, 2013 China	Chronic hepatitis virus infection increases the risk of pancreatic cancer: a meta-analysis	7 studies included for assessment of HCV infection and PAC risk	Higher PAC risk in anti-HCV positive patients: RR = 1.21 (95%CI: 1.02-1.44)	Y Y Y
Xu JH, 2013 China	Hepatitis B or hepatitis C virus infection and risk of pancreatic cancer: a meta-analysis of observational studies	5 studies available for assessment of HCV infection and PAC risk	Higher risk of pancreatic cancer in subjects with past-exposure to HCV: RR = 1.26 (95%CI: 1.03-1.5)	Y Y Y

HCV: Hepatitis C virus; PAC: Pancreatic cancer; Y: Yes.

Table 14 Characteristics of available studies, assessing the association between hepatitis C virus infection and breast cancer, not considered and causes of exclusion

Studies (First author/ Journal/Year of publication)	Study title	Main findings for exclusion	Study conclusion
Bruno G *Clin Ter* 1999	Hepatitis C virus: a high risk factor for a second primary malignancy besides hepatocellular carcinoma. Fact or fiction?	Very small number of patients considered in the present study	HCV could have played an important role not only in the development of HCC but of the second primary malignancy
Malaguarnera M *Eur J Int Medicine* 2006	Hepatitis C virus in elderly cancer patients	No available information concerning number of HCV positive patients with breast cancer	No higher prevalence of breast cancer in patients with HCV infection

HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma.

subjects with persistent viral hepatitis. Even if this observation was very interesting, it has not stimulated the achievement of studies investigating specifically the possible association between hepatitis viruses (in particular HCV) and human cancers other than HCC. Only in the last years this idea has gained interest an increasing number of trials have been designed and carried out with the purpose. Nevertheless, to date, few data are available yet and no final or univocal conclusions may be drawn. However, putting together the results of published studies on the possible association between HCV and risk of NHLs,

Table 15 Characteristics of available, assessing the association between hepatitis C virus infection and renal cancer, not considered and causes of exclusion

Studies (First author/ Journal/Year of publication)	Study title	Main findings for exclusion	Study conclusion
Macleod LC *J Urol* 2013	Risk Factors for Renal Cell Carcinoma in the VITAL Study	No data on the type of viral hepatitis infection reported in VITAL study	A significant association of RCC with viral hepatitis
Bruno G *Clin Ter* 1999	Hepatitis C virus: a high risk factor for a second primary malignancy besides hepatocellular carcinoma. Fact or fiction?	Very small number of patients considered in the present study	HCV could have played an important role not only in the development of HCC but of the second primary malignancy

RCC: Renal cell carcinoma.

Table 16 Characteristics of available studies, assessing the association between hepatitis C virus infection and oral or skin cancer, not considered and causes of exclusion

Studies (First author/ Journal/Year of publication)	Study title	Main findings for exclusion	Study conclusion
Hunt J *Laringoscope* 2005	Outcome Analysis of Patients with Squamous Cell Carcinoma of the Head and Neck and Hepatitis C Virus	Duplicate	HCV positive with SCCHN patients have not a worse outcome than their HCV negative counterparts

SCCHN: Squamous cell carcinoma of the head and neck.

Table 17 Characteristics of available studies, assessing the association between hepatitis C virus infection and thyroid cancer, not considered and causes of exclusion

Studies (First author/ Journal/Year of publication)	Study title	Main findings for exclusion	Study conclusion
Antonelli A *JAMA* 1999	Thyroid cancer in patients with hepatitis C infection	Duplicate	Higher prevalence of thyroid cancer in a series of patients with chronic hepatitis C infection in comparison to no case in controls
Montella M *Int J Cancer* 2000	Is HCV infection associated with thyroid cancer? A case-control study	Duplicate	Possible oncogenetic role of HCV for thyroid cancer, possible association more detectable in countries with a high prevalence of HCV
Montella M *Liver* 2001	HCV and cancer: a case-control study in a high-endemic area	Duplicate	Expected increases not only in liver cancer, but also in tumors associated with the immune system
Malaguarnera M *Eur J Int Medicine* 2006	HCV in elderly cancer patients	No available information concerning number of HCV positive patients with thyroid cancer	No higher prevalence of thyroid cancer in patients with HCV infection

HCV: Hepatitis C virus.

cholangio-, pancreatic-, breast-, renal-, skin/oral- and thyroid-cancers, the reports concerning the estimates of prevalence of HCV infection worldwide as well as the tables on the age-standardized incidence rates of the mentioned malignancies per 100000 person-years in different geographical areas, some interesting consideration may be made (Figures 2 and 3). Actually, a clear correlation between regions of HCV prevalence and risk of extra-liver cancers has emerged only for a very small group of types and histological subtypes of malignancies. In particular, HCV infection has resulted to be associated with: (1) a higher incidence of some B-cell NHLs types, in countries, where an elevated prevalence of this pathogen is detectable, accounting to a percentage of about 10%. Furthermore, an additional factor potentially confirming the causal role between HCV and lymphomas, in particular B-cell NHLs, is represented by the observation of the regression of a significant percentage of low-grade B-cell NHLs after HCV eradication by means of an efficacious antiviral treatment. Early evidences, concerning this assumption, date back to the end of Twentieth Century with anecdotal reports and the beginning of the following Century, when further studies, enrolling a wider number of patients, were carried out for the first time[252]; and (2) an increased

risk of intra-hepatic cholangiocarcinoma development in subjects with anti-HCV positivity, as reported by a large number of available studies with OR ranging from 3.42 to 4.84. According to an epidemiological view-point, it has to be considered the following evidence: liver flukes are associated with an increased risk both for ICC and ECC, but in endemic-nations (such as Taiwan, Singapore and Korea) and in other Eastern areas with low rates of this type of infection, the incidence of ICC is more elevated in comparison with ECC. On the other hand, in the western areas ECC incidence is higher than that of ICC. Taking into account HCV epidemiology, the prevalence of this virus presents a wide variability worldwide. More elevated percentages are detectable in developing areas, such as in South-Eastern-Asia and Egypt, intermediate ones in Southern Europe and the lowest ones in Northern Europe and America. Therefore, a correlation between HCV prevalence and ICC incidence seems to emerge from these observations.

Concerning the possible association between the infection caused by this hepato-tropic virus, surprisingly, although a higher risk of PADC in HCV-positive patients has been observed in some trials and it has been reported in the available meta-analyses, age-standardized rates of this cancer present interesting geographical variations. In particular, PADC incidence worldwide is 3-4 times higher in more economically developed countries as well as in northern area of the world, where HCV prevalence is lower in comparison with less developed countries. Different reasons may explain these results, including the accuracy of diagnostic methods used to diagnose pancreatic malignancies in distinct geographical regions worldwide and of data to assess the rates of incidence of PDAC. However, it is well-known that on the basis of a morphogenetic viewpoint, pancreas and liver share several characteristics in their embryological development, arising from common multi-potent cells of endoderm origin. Therefore, HCV might replicate also in pancreatic cells as it does in hepatocytes[253,254]. Furthermore, according to epidemiological studies, type 2 diabetes represents a risk factor for PAC[255,256] with chronic hyperglycemia and hyperinsulinemia as proposed pathogenetic mechanisms involved in the promotion of this type of malignancy. Both conditions may induce proliferation, decrease apoptosis and promote invasion ability of pancreatic cancer cells[257-259]. A recent and interesting systematic review and dose-response meta-analysis, assessing blood glucose concentration and risk of pancreatic cancer, has shown that every 0.56 mmol/L (10 mg/dL) increase in fasting blood glucose , a 14% enhancement in the rate of PADC occurs[260]. On the other hand, it is now accepted that HCV infection is associated with an increased risk of type 2 diabetes[261,262]. Therefore, HCV infection, promoting and diabetes might act in cooperation with hyperinsulinemia, hyperglycemia in the promotion of PAC. This consideration may contribute to explain the epidemiological evidence of a more elevated incidence of this cancer in the most economically developed countries, where high rates of obesity, metabolic syndrome and diabetes are observed, in comparison with less developed regions in the world.

On the other hand, up to now no definitive and univocal conclusions may be obtained from the analysis of relationship between HCV and breast-, renal-, skin/oral- and thyroid-cancers. Most of the available studies, in particular a large part of cohort trials, have not confirmed the existence of these associations. However, the lack of similar evidences may be only apparent and some elements potentially limiting the conclusions of these reports have to be taken into account. In particular, most of available data have been obtained from some retrospective cohort-trials. Although the large size and the lengthy follow-up of this type of research provides the statistical power to obtain adequate information on cancer risk in the investigated population, the retrospective nature of these studies has to be considered. The use of routinely collected administrative data, based on population registries may represent a potential limiting factor in these trials. Possible errors in diagnosis, in codes of cancers or infective diseases and in reported data may affect the hospitalization records in some case/control subjects as well as the possibility that in several countries worldwide only a part of general population is included in national cancer registry may influences the obtained results. In addition, some of these trials have evaluated the incidence of a wide spectrum of malignancies and they have been not designed to assess a specific type of human tumors. It has to be also underlined that, according to age-standardized incidence rates of these neoplasms, remarkable temporal changes in human cancer trends have been observed worldwide. The combined analysis of these figures, as performed some years ago for HCV-related liver cancer, has induced some authors to hypothesize a possible role of HCV in the development of these malignancies. For example, in Japan, Tanaka *et al* have examined temporal trends for HCC incidence rates in a period ranging from 1981 and 2003 in Osaka Prefecture. They provided an explanation in the context of HCV infection rates. According to these findings, they noted that in that span of time the incidence peak of HCC was detectable in men during their 50s, 60s and 70s of age in 1986, 1995 and 2000 and then it was progressively decreasing. He postulated that the observed trend was due to the restriction of virus transmission[263]. As previously suggested, it should be taken into account that an enhanced incidence of ICC has been observed in the most developed regions in the years, ranging from 1980 to 2000, has been considered as caused by the parallel increase of HCV infection in these areas. This hypothesis has been definitively shown in United States[264]. In addition, the relationship between HCV and risk

of ICC has been assessed in patients with different degree of hepatic damage. It has been demonstrated that the probability of ICC development increases as the hepatic damage impairs[167]. Furthermore, a previous Italian research had suggested that HCV might have a role in thyroid cancer. This represents a rather rare malignancy, but its standardized incidence ratio has progressively increased between the end of '80s and the beginning of '90s in several well-developed countries, including Italy. In this country, in the same period of time an increasing prevalence of HCV infection was observed[247]. Unfortunately, no additional trials have been performed, with the purpose to assess the possible impact of HCV infection worldwide on the age-standardized incidence rates of the aforementioned malignancies in different geographical areas and to distinguish the potential contribution of this pathogen as pro-carcinogenic agent from other risk factors. Therefore this field of research still remains largely unexplored. In addition, it has to be taken into account that HCV represents a common cause of cirrhosis development and this condition itself is a well-known independent risk factor for the development of a wide spectrum of human malignancies different from liver. Several mechanisms may be responsible for carcinogenetic role of this pathogen. It may act indirectly as well as directly. Both these activities have been proposed for this virus and plausible evidences reported in literature. To date the existence of an indirect action of this microorganism is the most convincing pathogenic mechanism. In particular, as widely reported for liver, HCV might promote in extra-hepatic organs a persistent inflammation and induce the cancerous transformation, as a consequence of a progressive rearrangement of their structure. This event might play a role in the development of all the types of the aforementioned malignancies and not only involved in hepatic carcinogenesis. This process is characterized by the interaction and the cooperation among viral-related proteins, homing-cells (specific-tissue-cells, depending on the considered organ, endothelial cells, and stem cells), not homing cells (lymphomononuclear and polymorfonuclear specific and nonspecific cells), cytokines, costimulatory molecules and additional biological mediators (*i.e.,* PGs and oxidants). This situation promotes a self-maintaining and amplifying loop, in which HCV stimulate, in turn, PGE2, enzymes (such as cyclo-oxygenase-2 or COX-2), growth factors, interleukins production and cellular signaling pathway function. The complex cooperation and interaction among these mediators is one of the main factors responsible for final outcome: viral control with recovery or its persistence in the infected-organs, with progressive development of a tissue necro-inflammatory process, potentially evolving toward malignant transformation. Presence of inflammation favours genetic instability in cells and increases the probability which further genetic and epigenetic alterations arise. Perturbance of homeostasis in adult-cells may re-modulate activity and expression of genes as well as of transcription factors that govern their regeneration and/or differentiation programs as well as the processes involved in energy production. In addition, alteration of function of some intracellular pathways, such as K-RAS, Hedgehog-, Jak-STAT-, Notch-and TGF-β signalling-cascades, may also play a key role in carcinogenesis. In particular, this events may be induced not only by inflammation itself, but also by the direct action of some viral proteins such as: core- and NS5A on the intracellular cascades pathways function. These viral elements may affect the levels of activities of the afore-mentioned signalling-cascades and contribute to deregulation of cell-cycle checkpoint controls. To date a few studies have been performed with the aim to specifically investigate the pathogenetic mechanisms, potentially involved in the development of extra-liver malignancies in anti-HCV positive patients. The majority of reports upon this topic concerns lymphoproliferative malignancies. A study has described an increased expression of genes associated with lymphomagenesis in peripheral blood B cells of chronic HCV positive patients[265].

Furthermore, it has been shown that the telomere deletion of 1p36.3 in B-cell NHLs is significantly more frequent in patients with HCV infection in comparison with anti-HCV negative individuals[266]. Deletion of the 1p36 genomic locus is associated with the loss of p73, a tumour suppressor gene, that may be inactivated both in lymphomas and in other human cancers[267,268]. On the basis of available studies, this topic is progressively acquiring an increasing importance, but to date only some definitive conclusions have been obtained, while a large number of questions still remain unanswered. Further well-designed trials, enrolling an adequate number of patients as well as focusing on populations of different geographical areas and involving larger series of patients are required to confirm or deny this association as well as to identify the pathogenetic mechanisms, potentially involved in HCV-associated human carcinogenesis.

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COMMENTS

Background

Hepatitis C virus (HCV) is an oncogenic virus and a well-known risk factor for hepatocellular carcinoma. In the last years, some studies have shown that its antigens and replicative sequences are detectable also in organs other than

liver. However, the significance of this feature is uncertain. Some reports and meta-analyses suggested that its infection is associated with development of cholangiocarcinoma and some types of lymphomas, but a comprehensive assessment of the possible role of HCV in extrahepatic carcinogenesis has not been yet performed.

Innovations and breakthroughs

Actually, a clear correlation between regions of HCV prevalence and risk of extra-liver cancers has emerged only for a very small group of types and histological subtypes of malignancies. In particular, HCV infection has resulted to be associated with a higher incidence of: (1) some B-cell NHLs types, in countries, where an elevated prevalence of this pathogen is detectable, accounting to a percentage of about 10%; (2) intra-hepatic-, but not extrahepatic-cholangiocarcinoma; and (3) pancreatic cancer development. No definitive and univocal conclusions may be obtained from the analysis of relationship between HCV and breast-, renal-, skin/oral- and thyroid-cancers, although a possible association between renal-, skin/oral- and thyroid-malignancies and HCV infection has been suggested by some studies. These results strongly supports the need of additional studies with large sample size to ensure a precise estimate of the effect of HCV on these different types of cancers to improve our knowledge on carcinogenetic potential of HCV for extra-hepatic organs and on possible pathogenetic mechanisms. Few published studies available on the association of HCV and some types of human malignancies, such as breast, kidney, oral/skin and thyroid cancers and mainly enrolling populations of Asian ethnicity. Substantial variation by different geographical areas in serum prevalence of HCV antibodies and genotypes.

Peer-review

This paper is very interesting because it clarifies a neglected aspect of HCV infection: the role of virus in pathogenesis of extrahepatic neoplasms. The data analysis is very accurate as well as the description of pathophysiological mechanisms of HCV-mediated cancerogenesis.

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