Digestive and Liver Disease 44 (2012) 160–165

Contents lists available at SciVerse ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

# Chronic viral hepatitis and risk of lymphoid malignancies: A retrospective twelve-year population-based cohort study in Côte d'Or, France

Claire Proby[a,*], Anne Minello[b], Catherine Quantin[c], Valérie Jooste[d], Christine Binquet[c], Mathieu Hägi[c], Morgane Mounier[a], Eric Benzenine[c], Patrick Hillon[b], Marc Maynadié[a]

[a] Registre des hémopathies malignes de Côte d'Or, EA 4184, Faculté de médecine, Dijon, France
[b] Registre des hépatites virales de Côte d'Or, Inserm U866, Faculté de médecine de Dijon, France
[c] Service de biostatistique et informatique médicale, Centre Hospitalier Universitaire (CHU) de Dijon, France
[d] Registre bouguignon des cancers digestifs, Inserm U866, Faculté de médecine de Dijon, France

ARTICLE INFO

*Article history:*
Received 1 March 2011
Accepted 28 August 2011
Available online 4 October 2011

*Keywords:*
Cirrhosis
Lymphoproliferative disorders
Standardized incidence ratio
Viral hepatitis B
Viral hepatitis C

ABSTRACT

*Background:* The association between hepatitis C infection and lymphoid malignancies is still a matter of debate. The hypothesis of a relationship between hepatitis B and lymphoid neoplasms is more recent and has been far less thoroughly explored.
*Aim:* The aim of this study was to evaluate the association between hepatitis C and B infections and B cell non-Hodgkin and Hodgkin lymphomas.
*Methods:* We took advantage of the co-existence in the French administrative area of Côte d'Or of two specialized registries – one for viral hepatitis and one for haematological diseases – to conduct a population-based, cohort study covering a 12-year period. The databases were anonymized and then linked using a probabilistic model.
*Results:* There were 8234 person-years at risk in the hepatitis C cohort and 2784 in the hepatitis B cohort. We found 6 cases of non-Hodgkin lymphoma in the hepatitis C cohort, resulting in an overall adjusted standardized incidence ratio of 3.42 (CI: 1.25–7.45). Three of these 6 cases were diffuse-large-B-cell-lymphoma. Cirrhosis was associated with a higher risk of non-Hodgkin lymphoma in the hepatitis C cohort (relative risk = 8.4, $p < 0.01$, using a Poisson regression). We found one case of chronic lymphocytic leukaemia amongst the hepatitis B carriers.
*Conclusion:* Hepatitis C carriers are at a higher risk of developing non-Hodgkin lymphoma than the general population. The role of cirrhosis and the association between hepatitis B and lymphoid malignancies deserve to be further assessed.


## 1. Introduction

Viral hepatitis B and C infections are major public health issues. Their incidence and prevalence are high and chronic forms are responsible for considerable morbi-mortality. The World Health Organization (WHO) estimates that around the world, 170 million people (approximately 3% of the world's population) are infected with hepatitis C, and twice as many are infected with hepatitis B (350 million, 6% of the world's population) [1]. A cross-sectional survey conducted in 2004 amongst residents of metropolitan France (aged 18–80 years old) estimated the prevalence of hepatitis C virus (HCV) infection at 0.84% (95%CI: 0.65–1.10), with 57% of patients knowing their sero-status; and that of hepatitis B virus (HBV) infection at 0.65% (95%CI: 0.45–0.93), with 45% of these chronic carriers knowing they were HBs Ag seropositive [2].

Hepatitis B and C viruses are the leading causes of cirrhosis in the world and people with chronic hepatitis infection are at an increased risk of developing hepatocellular carcinoma. These viruses are both hepatotropic and lymphotropic, and besides the well-known hepatic complications, they could be etiologic factors for some lymphoproliferative malignancies.

Lymphoproliferative malignancies as a whole are the 5th most frequent cancer in France, accounting for about 7% of incident cancer cases and 7% of cancer deaths in 2005 [3]. In developed countries, the incidence has been rising steadily for the past 30 years but has levelled off more recently. The incidence of non-Hodgkin lymphoma (NHL) in particular has evolved in this way. Demographic factors, population ageing in particular, do not totally explain this progression. Various risk factors for lymphoproliferative diseases have already been put forward: environmental and professional exposure, heredity [4], immunodepression and infectious agents. Amongst the latter, HBV and HCV are lymphotropic viruses and

* Corresponding author at: Laboratoire d'Hématologie, CHU de Dijon, Plateau Technique de Biologie, 2 rue Angélique Ducoudray, 21000 Dijon, France.
*E-mail address:* claire.proby@gmail.com (C. Proby).

1590-8658/$36.00 
doi:10.1016/j.dld.2011.08.025

potential risk factors, HCV being a more likely candidate in the light of recent studies [5–7].

However, the role of HCV and HBV as etiological factors in the pathogenesis of lymphoproliferative disorders is still controversial. Some studies have disclosed a strict correlation between HCV and B cell NHL whilst other studies did not found it. The great majority of studies were case–control design and often found increased prevalence of both HCV [6–10] and HBV [11–13] amongst persons with NHL. To our knowledge, there has been only one cohort study that assessed the risk of NHL in a population of HBV-infected patients; this was conducted in Detroit and Oakland, and found a relative risk of about 3 [14].

The hypothesis of an increased risk of lymphoproliferative malignancies, apart from NHL, in patients with viral hepatitis is quite controversial, and the results of the few studies are contradictory [15,16].

We took advantage of the coexistence, in the French area of Côte d'Or, of two specialized registries – a haematologic registry and a viral hepatitis registry – to conduct a population-based, cohort study covering a period of 12 years. The aim of this study was to investigate the association between hepatitis C and B virus infections and NHL, Hodgkin lymphoma (HL) and chronic lymphocytic leukaemia (CLL).

## 2. Design and methods

### 2.1. Study population

This study is a retrospective population-based, cohort study that included all new cases of HCV and HBV diagnosed between the 1st of January 1994 and the 31st of December 2005 in the French area of Côte d'Or (Burgundy). These cases were recorded in a specialized viral hepatitis registry, created in 1994, that collects and follows up all new patients with HCV antibody and/or HBV antigen seropositivity. The exhaustiveness of the registry is ensured by the use of several sources of information, which are regularly contacted to notify new cases: medical laboratories, pathology laboratories and specialist doctors (hepato-gastroenterologists, internists and infectiologists). The quality and comprehensiveness of registration has been certified by an audit of the National Institute of Health and Medical Research (INSERM) and the French Institute for Public Health Surveillance (InVS).

Patients with human immunodeficiency virus (HIV) co-infection (69 cases in the HCV cohort, i.e. 5.2% and 28 cases in the HBV cohort, i.e. 5.7%) were excluded. Indeed, HIV infection is associated with viral hepatitis and is a well-known risk factor for NHL. It is thus a potential confounding factor.

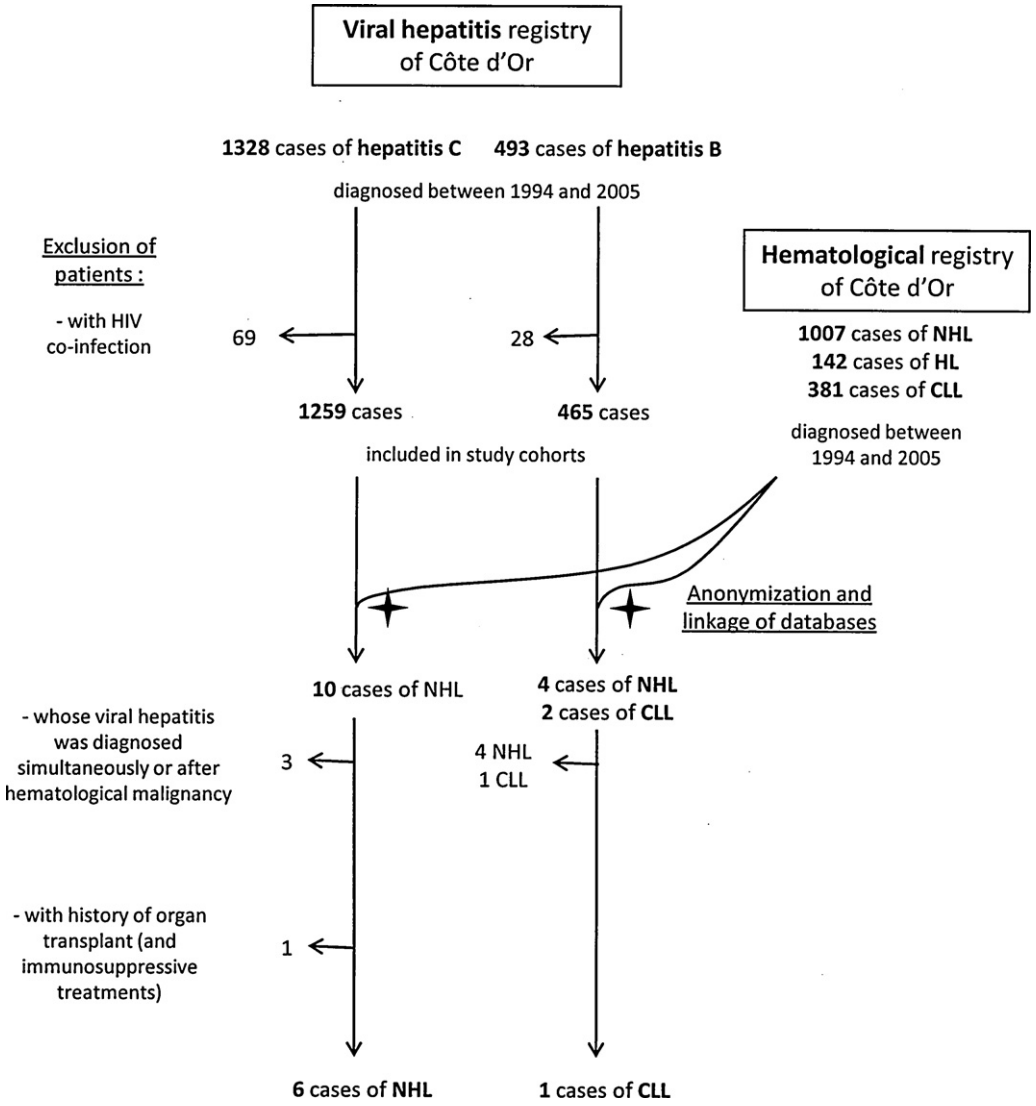


**Fig. 1.** Patients' selection process and database linkage. NHL: Non-Hodgkin lymphoma; HL: Hodgkin lymphoma; CLL: chronic lymphocytic lymphoma.

After exclusion of HIV co-infected patients, a total of 1259 patients with HCV infection and 465 patients with HBV infection were included (Fig. 1).

### 2.2. Endpoints

The primary endpoint was the occurrence of NHL except for CLL in the study population (ICD-O-3 codes 9590/3 to 9596/3, 9670/3 to 9719/3, 9727/3 to 9729/3 and 9832/3 to 9834/3, that is to say mainly follicular lymphoma 9690/3, mantel cell lymphoma 9673/3, diffuse large B-cell lymphoma 9680/3 and splenic B-cell marginal zone lymphoma 9689/3). Secondary endpoints were related to other lymphoproliferative malignancies: HL (ICD-O-3 codes 9650/3 to 9667/3) and CLL (code 9823/3), that we studied separately from other NHL.

### 2.3. Haematological registry of Côte d'Or

The incidence rates of these malignancies in the study population and in the reference population were computed, using data from the haematological registry of Côte d'Or. This specialized registry has collected every case of haematological malignancy in residents of Côte d'Or since 1980. It was the first of its type in the world at the time of its creation and it has proved to be quite comprehensive and exhaustive (certification delivered every four years by INSERM and InVS). Diseases are registered according to the International statistical classification of diseases for oncology, 3rd edition (ICD-O-3), published by the WHO [17].

#### 2.3.1. Endpoints in the cohorts

All diagnosis criteria and dates were manually verified in patients' medical files.

Events had to occur after the diagnosis of viral hepatitis. Patients whose lymphoid malignancy was diagnosed before or at the same time as the viral hepatitis were excluded. This precaution was essential since up to now, in the general population in France, screening for viral hepatitis is neither systematic nor recommended. Retaining such patients would have induced a differential misclassification bias, and an overestimation of the standardized incidence ratio (SIR). For this reason, seven cases of NHL (four in the hepatitis C cohort and three in the hepatitis B cohort) and one case of CLL (in the hepatitis B cohort) were not taken into account, even though the hepatitis infection obviously predated the onset of the malignancy. Another case of high-grade lymphoma, immunoblastic lymphoma, discovered several months after the diagnosis of hepatitis C, was not included since the patient's medical records showed that he had had a heart transplant a decade earlier. Immunosuppressive drugs as well as hepatitis C may thus have been responsible for the NHL.

#### 2.3.2. Endpoints in the reference population

Côte d'Or, Burgundy, is a French administrative area, with a total of 531,286 inhabitants (35% rural, 65% urban) according to last census in 2006. Information about this population is provided by the French cancer incidence and mortality (FRANCIM) network, which utilizes census data from the National Institute of Statistics and Economic Studies (INSEE). It gives the total person-years at risk by year, sex and age group, calculated from census data. We could not exclude from this population HIV infected patients and chronic hepatitis carriers who were diagnosed before 1994, because this information is not available.

The raw incidence rates of NHL, HL and CLL in our reference population over the twelve-year study period were respectively 17.98, 2.51 and 6.78 per 100,000 person-years for men and 15.14, 2.16 and 5.75 per 100,000 person-years for women. These results are quite consistent with those published by the French Institute for Public Health Surveillance (InVS) [3].

The main NHL subtypes and their proportions were as follows: diffuse large B-cell lymphoma (30%), follicular lymphoma (17.58%), small lymphocytic lymphoma (8.54%), marginal zone B-cell lymphoma (5.36%), splenic marginal zone lymphoma (4.77), mantel cell lymphoma (4.37%), lymphoplasmocytic lymphoma (3.28%), Burkitt lymphoma (1.79%), immunoblastic lymphoma (1.69%) and T-cell lymphoma (12.02%). The remaining 10% corresponded to non-labelled lymphomas.

### 2.4. Linkage procedure between registries

A computerized record hash coding and linkage procedure was used to allow data linkage between the viral hepatitis database and the haematologic registry. Before the files were extracted, they were anonymized using a one-way hash coding algorithm based on the standard hash coding algorithm (SHA) function [18,19]. Once the database had been made anonymous, the linkage of patients' information was accomplished by means of a probabilistic model that takes into account several identification variables: last-name, first-name, date of birth and INSEE place of birth [20]. In previous studies, this anonymous record linkage procedure has shown specificity of 100% and sensitivity of 95% [19].

The study was approved by the French data protection authority CNIL (authorization no. 1311636).

### 2.5. Statistical analysis and handling of lost to follow-up patients

The incidence rates of NHL in our cohorts and the SIR were calculated using Stata 10® (Stata Corporation, College Station, TX, USA) and SAS 9® (SAS Institute Inc., Cary, NC, USA). Person-time at risk was calculated between the diagnosis of hepatitis, that is to say the first sample that was seropositive for HCV antibody or HBV antigen, and either the outcome occurrence or the end of follow-up or the date when the patient died. As there was a significant number of patients for whom the date at last contact was earlier than the study end point (31/12/2005), we calculated person-years at risk and SIR under the hypothesis of maximum bias. We assumed that patients lost to follow-up were all still alive and had not developed any lymphoid malignancies at the end point.

SIR was adjusted for gender and age group affected. The significance of SIR was tested using the Breslow and Day formula [21] and its resulting approximate confidence limits.

We performed Poisson regression analysis to model the data and study the risk factors for NHL amongst chronic hepatitis C carriers. Candidate factors were the gender, the age group, and the existence of cirrhosis.

## 3. Results

### 3.1. Cohort descriptions

#### 3.1.1. Hepatitis C cohort (Table 1)

Individual follow-up ranged from 0 to 12 years (median: 6.93 years), resulting in a total of 8234 person-years under the maximum-bias hypothesis of no subjects lost to follow-up. Mean age at hepatitis diagnosis was 47 (standard deviation: 19.5 years), and sex ratio 1.35. Hepatitis C was diagnosed because of clinical or biological symptoms in 28.8% and the presence of identified risk factors such as transfusion in 24%.

The mean alanine aminotransferase (ALAT) value at diagnosis was 2.86 times as high as the norm (missing values: 35%). The viral genotype was known in 37% of patients: it was genotype 1 in 55.7% (mainly 1b), genotype 2 in 15.3%, 3 in 22.7%, 4 in 4.1%, 5 in 1.6% and 6 in 0.4%.

**Table 1**
Description of the study cohorts, which included all new HCV and HBV positive cases diagnosed between 1994 and 2005 in Côte d'Or and recorded by our specialized viral hepatitis C registry: demographic characteristics, length of follow-up, and prevalence of cirrhosis.

| | HCV | HBV |
|---|---|---|
| Number of patients | 1259 | 465 |
| Median follow-up (years) | 6.93 | 6.15 |
| Person-years at risk | 8233.72 | 2783.90 |
| Sex ratio (men/women) | 1.35 | 1.29 |
| Mean age at diagnosis of infection (standard deviation) | 47.07 (19.46) | 38.01 (18.25) |
| Cirrhosis: number of cases (percentage) | 161 (12.8) | 41 (8.8) |
| ALAT value at diagnosis of infection (ULN) | 2.86 | 6 |
| Missing values (percentage) | 35 | 27 |

ULN: upper limit of normal; HCV: hepatitis C virus; HBV: hepatitis B virus.

The results of at least one liver biopsy were available for 30% of the patients. Distribution of the fibrosis stages according to the METAVIR five-point scale was as follows: no fibrosis (F0) in 11.4% cases, minor fibrosis (F1) in 30.7%, mild fibrosis (F2) in 36.1%, severe fibrosis (F3) in 14.7% and cirrhosis (F4) in 7.1%. Cirrhosis was confirmed in 12.7% of patients on the basis of either liver biopsy or a FibroTest or clinical evidence.

#### 3.1.2. Hepatitis B cohort (Table 1)

The median follow-up was about 6.15 years, corresponding to 2,784 person-years at risk in the whole cohort. The mean age at diagnosis was nine years younger than in the hepatitis C cohort: 38 years old (standard deviation: 18.3), and the sex ratio was 1.29.

The mean ALAT value at diagnosis was about 6 times as high as norm (missing values: 27%).

The results of at least one liver biopsy were available for only 12% of the patients. Distribution of the fibrosis stages in these patients was as follows: F0 in 8.9% cases, F1 in 28.6%, F2 in 39.2%, F3 in 14.2% and cirrhosis in 8.9%

### 3.2. Case descriptions

#### 3.2.1. Hepatitis C cohort (Table 2)

Six cases of NHL were observed, five cases amongst men and one amongst women. Five of the six were B-cell lymphomas: three diffuse large B-cell lymphomas (9680/3), one mantel cell lymphoma (9673/3) and one small lymphocytic lymphoma (9670/3). The last one was mature T-cell neoplasm mycosis fungoides (9700/3).

Four of the six cases presented advanced fibrosis: severe fibrosis (F3 METAVIR stage) in one case and cirrhosis in three cases.

#### 3.2.2. Hepatitis B cohort

There was only one case of lymphoid malignancy that fulfilled the inclusion and exclusion criteria. It was a man who was diagnosed with hepatitis B at age 58 in a context of cirrhosis symptoms. Cirrhosis was confirmed afterwards by liver biopsy (Child A). Four years later, during follow up, this man was diagnosed with CLL.

### 3.3. Standardised Incidence Ratio (SIR)

In the hepatitis C cohort, the expected numbers of NHL, HL and CLL over the twelve-year period were 1.01, 0.13 and 0.37 in men and 0.75, 0.08 and 0.29 in women, respectively (under the maximum bias hypothesis). We observed 6 cases of NHL, but neither HL nor CLL. Hence, the SIR for NHL was significantly greater than 1, with an age group and gender adjusted ratio of 3.42 (CI: 1.25–7.45). This ratio was equal to 4.97 (CI: 2.07–11.95) in men and 1.34 (CI: 0.18–9.49) in women.

We tested cirrhosis as a risk factor for LNH occurrence amongst hepatitis C carriers, using a Poisson regression. Cirrhosis proved to be a significant risk factor (relative risk = 8.42, $p < 0.01$) for NHL in our cohort, and this result remained statistically significant after adjustment for age (adjusted relative risk = 5.43, $p < 0.05$).

In the hepatitis B cohort, the expected numbers of NHL, HL and CLL were 0.23, 0.037 and 0.08 in men and 0.11, 0.041 and 0.02 in women. We found only one case of CLL, which resulted in a statistically significant SIR for CLL in men (12.1, 95%CI: 1.7–86.5). This result was no longer significant after adjustment for gender (SIR = 9.09, 95%CI: 0.12–50.59).

## 4. Discussion

This study offers strong evidence that hepatitis C infection is associated with a higher risk of NHL, especially in the presence of cirrhosis. It also suggests a potential association between hepatitis B infection and CLL.

However, we were not able to show any association between HBV infection and NHL, or between HCV and HBV infection and other lymphoid malignancies. With regard to the latter, the negative findings may only result from a lack of power as our HBV cohort was rather small.

The SIR we calculated is most probably underestimated for several reasons. First, we could not exclude HIV infected patients from our reference population since HIV sero-status in the general population is not known, but HIV-positive patients were excluded from the study population to avoid this confounding factor. In the same way, authentic hepatitis carriers whose disease was diagnosed before the creation of the registry were taken into account in the reference population, but they were excluded from the study population. In addition, new cases of lymphoproliferative malignancies will probably be diagnosed during the next decades in the study population, increasing the number of observed cases in the cohort. Since over 40% of hepatitis C carriers do not know their sero-status, we can assume that a certain number of undiagnosed viral hepatitis may have been included in the reference population

**Table 2**
Description of the six cases of NHL in the HCV cohort: demographic characteristics, ages at HCV infection and NHL diagnosis, HCV genotype and transmission mode when known, hepatic fibrosis and types of NHL.

| | Cases | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| Sex | Female | Male | Male | Male | Male | Male |
| Age at diagnosis of HCV infection (years) | 70 | 70.8 | 64.1 | 25.5 | 68.1 | 74.5 |
| Genotype | 2 | – | 1a | – | 1b | – |
| HCV transmission mode | Blood transfusion | Blood transfusion | Blood transfusion | Injection drug use | – | – |
| Hepatic fibrosis | Severe fibrosis | Cirrhosis | Cirrhosis | Mild fibrosis | Cirrhosis | – |
| Age at diagnosis of NHL (years) | 75.4 | 75.3 | 64.2 | 30.7 | 71.7 | 74.6 |
| Type of NHL | Mycosis fungoides | DLBCL | Small lymphocytic l. | DLBCL | DLBCL | Mantel cell l. |

NHL: non-Hodgkin lymphoma; HCV: hepatitis C virus; DLBCL: diffuse large B-cell lymphoma.

and not in the study population. Finally, we excluded one patient with NHL following hepatitis C infection because of his history of heart transplantation. However, a recent study has brought to light the role of hepatitis C infection in the multifactorial pathogenesis of post-transplant lymphoproliferative disorders [22].

Despite these reservations, these results are in line with those of previous epidemiological studies in particular the study of Duberg et al. [5], the first cohort study, which was conducted in Sweden, another country with a low prevalence of HCV. This study included 27,150 HCV-infected persons between 1990 and 2000, resulting in an observation time of 122,272 person-years. In this study, the authors constructed a model to approximate the date of HCV infection according to the date of birth, the route of transmission and the date of notification. The risk of non-Hodgkin's lymphoma was significantly increased in patients with an assumed duration of previous HCV infection of more than 15 years (SIR 1.89 [95%CI: 1.10–3.03]), but not in patients with 0–14 years of infection. The association was not significant in chronic lymphatic leukaemia in either of the strata. In our study, we did not model the date of infection, and person-time at risk was calculated from the diagnosis of hepatitis even if the onset of infection may have occurred months or years earlier. That is the reason why we could not reliably compare patients according to the duration of their hepatitis. However, our finding of a significant association between severe fibrosis and the occurrence of NHL in the hepatitis C cohort is in agreement with a higher risk in cases with longer exposure to the virus.

A nation-wide case–control study was also conducted from 1999 to 2002 in the populations of Denmark and Sweden, during which 2819 lymphoma patients and 1856 controls were screened for HCV infection [23]. Anti-HCV antibody positivity was associated with a non-significant increased risk of NHL (OR = 2.2 [95%CI 0.9–5.3], $n = 20$ cases). All of the cases were B-cell lymphomas. When the definition was further restricted to require HCV RNA positivity, the OR was 1.7 [95%CI 0.2–16.2] ($n = 3$ cases). Even if not statistically significant, such an association also reinforce our findings.

Moreover, our results are strengthened by observations from small clinical studies, which report that some HCV-associated NHL appears to be highly responsive to antiviral therapy [24,25]. Half of the cases we observed were diffuse large B cell lymphomas, which is in agreement with the observations of the European multicenter case–control study EPILYMPH [6].

The most likely pathophysiological mechanism for hepatitis C-induced B-cell clonal disorders is as follows: chronic antigenic stimulation may play a significant role in the development of initial polyclonal B-cell expansion which may progress to autonomous B-cell proliferation, immune dysregulation and eventually B cell malignancy [26]. HCV-E2 envelope glycoprotein was identified by Quinn et al. as one of the viral antigens that could drive B-cell expansion [27]. Indeed, the B-cell receptor (BCR) from HCV-associated lymphoma binds the E2 protein of many HCV genotypes, which supports the hypothesis of receptor-mediated lymphomagenesis leading to HCV-associated NHL. Levy suggested two possible mechanisms by which the immune response of normal B cells to HCV infection could go awry [28]. First, B-cells that bind E2 via their specific BCR could receive a chronic activating signal through two signalling complexes simultaneously – the BCR and the CD19/CD21/CD81 complex – thus putting them at risk for malignant transformation. Apart from this *dual stimulation* hypothesis, she puts forward a *facilitated viral entry* hypothesis, whereby B cells that bind the virus through both receptors efficiently internalize the virus, which could cause genomic instability.

All types together, cirrhosis develops in about 20% of patients with chronic hepatitis C infection. This evolution to severe fibrosis is much more frequent in genotype 1 (in particular 1b) patients than in genotype 2 patients, and the former have a lower rate of response to interferon therapy than the latter [29]. Our study reinforces the hypothesis that HCV infection is also a risk factor for lymphoproliferative disorders. Amongst HCV carriers, those with severe fibrosis or cirrhosis seemed to be at a higher risk for developing a lymphoma than those with no or minor fibrosis; this is an original observation. This could result from a direct implication of fibrosis in lymphomagenesis or more likely, lymphoma may be more frequent in patients with severe fibrosis and cirrhosis because such patients were exposed to viral infection for a longer time. The former hypothesis has not been clearly demonstrated by clinical studies contrary to the latter. Pellicelli et al. found a longer duration of HCV infection in patients with diffuse large B cell lymphomas than in patients with lower grade lymphomas [30]. Regrettably, in our study, genotype was only available for 37% of the hepatitis C cohort and three out of the six cases of NHL. It would be most interesting to assess the association between HCV genotype and the risk of lymphoma in future studies. Despite the statistical significance, the results must be interpreted with caution given the small number of cases.

This study is thus worth continuing. A longer follow-up may enable us to bring evidence of a significant association between HBV infection and lymphoid malignancies. It would also be very useful to further assess the role of severe fibrosis and cirrhosis in the development of NHL in hepatitis C carriers.

## Conflict of interest

None declared.

## Acknowledgments

The authors want to thank Philip Bastable for having reviewed the English.

## References

[1] http://www.who.int/topics/hepatitis/en/.
[2] Prevalence of hepatitis B and hepatitis C in France. InVS; 2004, http://apheis.net/publications/2006/prevalence_b_c/vhb_france_2004.pdf.
[3] http://www.invs.sante.fr/surveillance/cancers/estimations_cancers/default.htm.
[4] Casey R, Brennan P, Becker N, et al. Incidence of familiar cancer history on lymphoid neoplasms risk validated in the large European case–control study epilymph. Eur J Cancer 2006;42:2570–6.
[5] Duberg AS, Noldström M, Törner A, et al. Non-Hodgkin's lymphoma and other non-hepatic malignancies in Swedish Patients with hepatitis C virus infection. Hepatology 2005;41:652–9.
[6] Nieters A, Kallinowski B, Brennan P, et al. Hepatitis C and risk of lymphoma: results of the European multicenter case–control study Epilymph. Gastroenterology 2006;13:1879–86.
[7] Engels EA, Chatterjee N, Cerhan JR, et al. Hepatitis C virus and risk of lymphoma: results of the NCI-SEER multi-center case-control study. Int J Cancer 2004;111:76–80.
[8] Spinelli JJ, Lai AS, Kradjen M, et al. Hepatitis C virus and risk of non-Hodgkin lymphoma in British Colombia, Canada. Int J Cancer 2008;122:630–3.
[9] Cowgill KD, Loffredo CA, Abdel-Latif S, et al. Case control study of non-Hodgkin's lymphoma and hepatitis C virus infection in Egypt. Int J Epidemiol 2004;33:1034–9.
[10] Guida M, D'Elia G, Benvestito S, et al. Hepatitis C virus infection in patients with B-cell lymphoproliferative disorders. Leukemia 2002;16:2162–3.
[11] Lim ST, Fei G, Quek R, et al. The relationship of hepatitis B virus infection and non-Hodgkin's lymphoma and its impact on clinical characteristics and prognosis. Eur J Haematol 2007;79:132–7.
[12] Wang F, Xu RH, Han B, et al. High incidence of hepatitis B virus infection in B-cell subtype non-Hodgkin lymphoma compared with other cancers. Cancer 2007;109:1360–4.
[13] Marcucci F, Mele A, Spada E, et al. High prevalence of hepatitis B virus infection in B-cell non-Hodgkin's lymphoma. Haematologica 2006;91:554–7.
[14] Ulcikas Yood M, Quesenberry CP, Guo D, et al. Incidence of non-Hodgkin's lymphoma among individuals with chronic hepatitis B virus infection. Hepatology 2007;46:107–12.
[15] Dal Maso L, Franceschi S. Hepatitis C virus and risk of lymphoma and other lymphoma and other lymphoid neoplasms: a meta-analysis of epidemiologic studies. Cancer Epidemiol Biomarkers Prev 2006;15:2078–95.
[16] Lakatos PL, Fekete S, Horanyi M, et al. Development of multiple myeloma in a patient with chronic hepatitis C: a case report and review of the literature. World J Gastroenterol 2006;12:2297–300.

[17] Percy C, Fritz A, Jack A, et al. International classification of diseases for oncology (ICD-O). 3rd ed. WHO; 2000.
[18] Quantin C, Bouzelat H, Allaert AA, et al. How to ensure data security of an epidemiologic follow-up: quality assessment of an anonymous record linkage procedure. Int J Med Inf 1998;49:117–22.
[19] Jaro MA. Probabilistic linkage of large public health data files. Stat Med 1995;14:491–8.
[20] Quantin C, Binquet C, Allaert FA, et al. Decision analysis for the assessment of a record linkage procedure: application to a perinatal network. Methods Inf Med 2005;44:72–9.
[21] Breslow NE, Day NE. Statistical methods in cancer research, vol. II. The design and analysis of cohort studies (IARC Scientific Publication No. 82). Lyon, France: International agency for research on cancer; 1987.
[22] Burra P, Buda A, Livi U, et al. Occurrences of post transplant lymphoproliferative disorders among over thousand adult recipients: any role for hepatitis C infection? Eur J Gastroenterol Hepatol 2006;18:1065–70.
[23] Schöllkopf C, Ekström Smedby K, Hjalgrim H, et al. Hepatitis C infection and risk of malignant lymphoma. Int J Cancer 2008;122:1885–90.
[24] La Mura V, De Renzo A, Perna F, et al. Antiviral therapy after complete response to chemotherapy could be efficacious in HCV-positive non-Hodgkin's lymphoma. J Hepatol 2008;49:557–663.
[25] Hermine O, Lefrere F, Bronowicki JP, et al. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. N Engl J Med 2002;347:89–94.
[26] Viswanatha DS, Dogan A. Hepatitis C virus and lymphoma. J Clin Pathol 2007;60:1378–83.
[27] Quinn ER, Chan CH, Hadlock KG, et al. The B-cell receptor of a hepatitis C virus (HCV)-associated non-Hodgkin lymphoma binds the viral E2 envelope protein, implicating HCV in lymphomagenesis. Blood 2001;98:3745–9.
[28] Levy S. Alteration of B cell function by hepatitis C virus. Haematol Rep 2005;1:55–8.
[29] Zein NN, Rakela J, Krawitt EL, et al. Hepatitis C virus genotypes in the United States: epidemiology, pathogenicity and response to interferon therapy. Ann Intern Med 1996;125:634–9.
[30] Pellicelli M, Zoli V, Remtti D, et al. Hepatology 2009;50:929A.