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Anderson, L., & Engels, E. A. (2008). Hepatitis C virus infection and non-Hodgkin lymphoma: Interesting association or causal relationship? International journal of cancer. Journal international du cancer, 122(8)(8), x-xii. DOI: 10.1002/ijc.23462

Published in:
International journal of cancer. Journal international du cancer

Editorial

Hepatitis C virus infection and non-Hodgkin lymphoma: Interesting association or causal relationship?

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Numerous population-based studies have demonstrated an association between hepatitis C virus (HCV) infection and non-Hodgkin lymphoma (NHL),[1,2] pointing to the possibility that HCV plays a role in the development of this malignancy. The Scandinavia Lymphoma Etiology (SCALE) study, reported in this issue of the *International Journal of Cancer*, adds to the accumulating body of epidemiological evidence supporting this association. The large sample size (2,819 NHL cases and 1,856 controls), comprehensive population-based recruitment strategy, rapid case ascertainment, and detailed classification of NHL subtypes make SCALE one of the most comprehensive case–control studies to date. One limitation of the SCALE study was the very low prevalence of HCV infection (0.4% of controls, even when the investigators included individuals with intermediate serologic evidence for infection), which limited the power and precision of some statistical analyses. HCV seropositivity was associated, although not significantly, with overall NHL risk (OR 2.2, 95% CI 0.9–5.3), and was significantly associated with risk of B-cell lymphomas (OR 2.4, 95% CI 1.0–5.8), specifically lymphoplasmacytic lymphoma (OR 5.2, 95% CI 1.0–26.4). The findings of the SCALE study are consistent with the prior literature, which now includes multiple case–control studies and several cohort studies, most of which find a positive association between HCV infection and NHL.[1,2]

Given the repeated demonstration of an association, the question arises whether HCV infection is actually a cause of NHL. Bradford Hill in his landmark paper, ''The Environment and Disease: Association or Causation,'' suggested 9 criteria to consider when assessing causation.[3] In Table I, we use these criteria to review the existing evidence for a causal relationship between HCV and NHL. Although Schollkopf *et al*. discuss some of this evidence in relation to their findings in the accompanying article, the table organized around the Bradford Hill criteria provides a useful framework to evaluate the epidemiological and experimental evidence more formally.

It is useful to begin with a consideration of the biological plausibility of a causal relationship, based on what we know about HCV infection and the etiology of NHL. In most individuals, HCV manifests as chronic liver infection, which can eventually develop into cirrhosis.[4] This chronic infection leads to chronic stimulation of the immune system and has been associated with the development of immune-related disorders, such as essential mixed (Type II) cryoglobulinemia,[4,5] which can itself progress to B-cell NHL.[5] HCV envelope protein E2 binds to CD81 on the cell surface of B lymphocytes, lowering their activation threshold.[6,7] With continued stimulation of the immune system, B lymphocytes may develop DNA mutations, perhaps through the action of activation-induced cytidine deaminase, leading to transformation.[8] Also, HCV-infected individuals have an elevated frequency of circulating lymphocytes with chromosomal translocations involving the *bcl2* oncogene,[9] implicated in essential mixed cryoglobulinemia[10,11] and many B-cell NHLs.[10,12] Causality is also supported here by analogy, in that the proposed process of HCV-induced lymphomagenesis (*i.e*. chronic immune stimulation), is similar to the posited mechanism by which *Helicobacter pylori* infection causes gastric NHL[13] and Sjögren syndrome causes salivary gland NHL.[14] Although HCV can infect B lymphocytes,[15] HCV is less likely to cause lymphomagenesis by a direct oncogenic mechanism, since the RNA virus cannot integrate its viral nucleic acid sequences into the lymphocyte genome.

Strength of association and consistency are two important criteria for assessing causality. Two meta-analyses of 18 and 23 epidemiologic studies examined the association between HCV infection and overall NHL risk.[1,2] The first presented a pooled odds ratio (OR) of 5.7 (95% confidence interval (CI) 4.1–8.0).[1] In contrast, the more recent meta-analysis by Dal Maso *et al*. included only studies with $\geq$100 patients and reported more modest pooled ORs of 2.5 (95% CI 2.1–3.1) and 2.0 (95% CI 1.8–2.2) for case–control and cohort studies, respectively.[2] These associations are moderately strong, but still substantially weaker than other associations between viruses and cancer generally accepted as causal, e.g., human papillomavirus and cervical cancer (OR 29, 95% CI 16–53),[16] or HCV and liver cancer (pooled OR 17, 95% CI 14–22).[17] Importantly, the associations between HCV and NHL have been inconsistent across epidemiologic studies: while most studies report an association,[1,2] the magnitude varies across a very wide range (ORs and relative risks 2–20). In the meta-analyses, this heterogeneity in associations across studies has been attributed to differences in study design, including the type of control group used, differences in the measurement of HCV infection, and differences in HCV prevalence across populations.[1,2] Most recent studies have found ORs typically in the range of 2–3, as seen in Schollkopf *et al*. Cohort studies that have measured HCV infection before development of NHL have also produced rather modest estimates of the effect of HCV on NHL risk (relative risks 1.3–2.0).

Specificity of association is an area where the evidence for causality is not convincing. NHL is now considered a diverse group of separate entities that differ in their pathologic features, molecular lesions, clinical outcomes and perhaps etiology.[18] It has been difficult to determine from epidemiologic studies whether the HCV-NHL association is specific to particular NHL subtypes or instead pertains to a wide range of subtypes. This limitation is at least partly due to the relative rarity of HCV as an exposure and the small numbers of cases for each NHL subtype within individual studies. Pooled studies have suggested that both B-cell[1,2,19] and T-cell lymphomas[1,2] are associated with HCV infection. Among B-cell NHLs, associations with HCV were seen for diffuse large B-cell, follicular, marginal zone and chronic lymphocytic leukemia/small lymphocytic lymphoma in the meta-analyses by Dal Maso *et al*.[2] The absence of a specific association between HCV and one, or a few, well-defined NHL subtypes (e.g., as is seen for human T lymphotropic virus I and adult T cell leukemia/

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Grant sponsor: Ireland-Northern Ireland-USA Consortium (Research and Development Office, Northern Ireland) and the Intramural Research Program of the National Cancer Institute.

DOI 10.1002/ijc.23462

Published online 12 February 2008 in Wiley InterScience (www.interscience.wiley.com).

TABLE I – EVIDENCE ACCORDING TO BRADFORD HILL CRITERIA FOR THE ASSOCIATION BETWEEN HEPATITIS C VIRUS (HCV) INFECTION AND NON-HODGKIN LYMPHOMA (NHL)

Bradford Hill Criteria	Evidence	Strength of evidence
Plausibility	HCV can cause chronic antigenic stimulation of B-cells leading to DNA mutations	++
Analogy	Analogous to the mechanisms proposed for NHL caused by *Helicobacter pylori* and Sjögren syndrome	+
Strength of association	Case–control studies: pooled odds ratio 2.5 (95% confidence interval 2.1–3.1). Cohort studies: pooled odds ratio 2.0 (95% confidence interval 1.8–2.2)	++
Consistency	Substantial heterogeneity among studies	+
Specificity	Associations reported between HCV and several NHL subtypes	0
Temporality	Cohort studies demonstrate that HCV infection precedes development of NHL	++
Experiment	Antiviral treatment causes NHL regression	++
Coherence	The data are mostly coherent with outside considerations. However, HCV is not associated with NHL in immunosuppressed populations	+
Biological gradient	No evidence	0

+++, strong evidence; ++, moderate evidence; +, weak evidence; 0, no evidence.

lymphoma[20] and for human herpesvirus 8 and primary effusion lymphoma[21]) is disconcerting, although given limitations in the data, ambiguous specificity does not argue strongly against a causal role for HCV.

The remaining criteria in Table 1 also deserve comment. Temporality (*i.e*., that exposure precedes the outcome) is likely to be present, since most HCV infections are acquired in early adulthood, decades before development of NHL, and it is improbable that NHL would itself increase risk for infection. Evidence for temporality derives from a recent cohort study which showed that HCV-infected individuals have an increased risk for NHL during at least 6 years of subsequent follow-up.[22] By ''experimental evidence,'' Bradford Hill meant evidence from experimental studies in humans. While it is unethical to deliberately infect persons with HCV, indirect experimental evidence for an HCV effect comes from case reports of HCV treatment in NHL patients.[23,24] In these reports, clearance of HCV appears to result in remission of NHL, and reappearance of infection is associated with NHL relapse. Coherence refers to agreement of the available data with what is known in other settings. The HCV-NHL association is generally coherent with what is known about the development of NHL. However, we note a striking absence of association between HCV and NHL among people infected with human immunodeficiency virus[25–27] and transplant patients,[28] two groups with very high NHL risk. If HCV causes NHL, the absence of an association in these immunosuppressed populations is somewhat surprising. One explanation might be that an intact immune system is required for full activation of B lymphocytes by chronic HCV infection.

Finally, there is no evidence for a biological gradient of increasing NHL risk with increasing severity of HCV infection, although research on this aspect has been hampered by the lack of a clearly relevant measure of HCV severity. One possible surrogate for HCV severity, which to our knowledge has not been investigated in the context of NHL, is HCV viral load, *i.e*., the level of virus in plasma. It may be possible to consider HCV infected subjects in three categories: (*i*) individuals with resolved infection (*i.e*., seropositive but with undetectable viral load, indicating clearance of HCV); (*ii*) individuals with ongoing HCV infection and low viral load; and (*iii*) individuals with ongoing HCV infection and high viral load. Investigating the strength of association with NHL across these categories could be an intriguing approach to take with prospectively collected specimens. Likewise, evidence for causality would be strengthened by data showing that treatment for HCV infection, which clears or reduces viral replication, lowers the subsequent risk of NHL.

On the basis of this analysis, we would argue that, despite an extensive body of population-based and laboratory evidence on HCV infection and NHL, a causal relationship is not fully established. Several avenues might warrant further investigation. Further case–control studies, even well-conducted ones like the one provided by Schollkopf *et al*., are probably not needed unless they can provide a unique perspective. However, conducting larger registry-based studies, or pooling data from existing studies, will increase the power to detect associations between HCV infection and specific NHL subtypes. In addition, more laboratory research is required to understand how chronic immune stimulation may lead to NHL. This research would help inform the interpretation of epidemiologic data on subtype-specific associations and possibly clarify why an association between HCV and NHL is not seen in immunosuppressed populations. Finally, we need additional data from clinicians regarding HCV treatment responses among patients with NHL, to confirm the small case series reported thus far. We hope that further investigation of the association between HCV infection and NHL will provide a better understanding of the etiology of NHL. Ultimately, this work may lead to prevention of NHL, by allowing for the targeting and treatment of high risk HCV-infected individuals, and it could help inform treatment strategies for HCV-associated NHLs.

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