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**Summary on the Seroprevalence of Hepatitis C Among Patients with Hodgkin's Lymphoma, an Implication for Risk by Metanalysis.**

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**Abstract:**

Hepatitis C virus (HCV) infection is an increasing problem, with millions people all over the world being infected. It is accepted as a significant public health problem with several life altering complications, especially hepatocellular carcinoma. The correlation between HCV infection and non – Hodgkin's lymphoma is no doubt at present. However, the reports on the correlation between HCV infection and Hodgkin's lymphoma are still controversy. The correlation between this virus infection and development of Hodgkin's lymphoma is of interest. Here, the author performs an appraisal on the seroprevalence of HCV among patients with Hodgkin's lymphoma comparing with healthy control subjects. Risk analysis was performed. According to the literature review, 3 reports were recruited. According to the metanalysis, 184 cases and 904 healthy subjects were investigated for HCV seroprevalence. The overall Anti HCV seropositive rate in the patients (3/184) and healthy subjects (6/904) are 1.6 % and 0.7 %, respectively. The odds ratio is 2.5. According to this study, it could be seen that having Anti HCV seropositive is a weak risk for Hodgkin's lymphoma.

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**Key Words: Hodgkin's lymphoma, Hepatitis C, Metanalysis.**

## **Introduction:**

Hepatitis C virus (HCV) infection is an increasing problem, with millions of people all over the world being infected. It is accepted as a significant public health problem with several life-altering complications, especially hepatocellular carcinoma.<sup>(1)</sup> The persistence of inflammation following HCV infection is reportedly related to carcinogenesis, and the mechanism of chronic inflammation has been approached by taking viral, immunologic, cytokine and apoptotic responses into consideration.<sup>(1)</sup> Concerning the mode of transmission, most new cases are acquired through the receiving of blood and blood products, the use of illegal injection drugs or sexual transmission.<sup>(2)</sup> Prevention for HCV transmission becomes an important issue in public health (3). From a public health perspective, new interventions to decrease the spread of HCV infection, ongoing surveillance, increased clinician awareness of disease reporting systems and the epidemiology and management of hepatitis C, availability of diagnosis and treatment facilities, and recognition of the need for local resources will be of paramount importance to cope with HCV infection. Unlike hepatitis B virus infection, no vaccination is presently available for prevention of

HCV infection.

Fiorilli et al said that epidemiologic and molecular observations had suggested that HCV might be the causative agent of some B-cell non-Hodgkin lymphomas.<sup>(4)</sup> They noted that about 5% of B-NHL was caused by HCV.<sup>(4)</sup> Hausfater et al noted that the putative role of hepatitis C virus (HCV) infection in the pathophysiology of lymphoproliferative diseases (LPD) is supported by north-American and south-European studies reporting high HCV seroprevalence in patients with B-cell-non-Hodgkin lymphoma<sup>(5)</sup>. They also mentioned that the finding of HCV binding on CD81, a surface-expressed protein present on lymphocyte membrane, enhanced the putative role of HCV in lymphomagenesis.<sup>(5)</sup>

The correlation between HCV infection and non-Hodgkin's lymphoma is no doubt at present. However, the reports on the epidemiological correlation between HCV infection and Hodgkin's lymphoma are still controversial.<sup>(6-9)</sup> The correlation between this virus infection and development of Hodgkin's lymphoma is interesting. Here, the author performs this meta-analysis to make an appraisal on the seroprevalence of HCV among patients with Hodgkin's lymphoma comparing with healthy control subjects. Risk analysis was

performed. The author hypothesized that the Anti HCV seropositive might be an important risk for Hodgkin's lymphoma.

### **Materials and Methods:**

This study was designed as a metanalysis study. A literature review to find the previous reports about seroprevalence of HCV among patients with Hodgkin's lymphoma was performed. The author used the electronic search engine PubMed ([www.pubmed.com](http://www.pubmed.com)) in searching for the literatures (March 2006). The key words for searching are "hepatitis C" and "Hodgkin's lymphoma". Only the reports that involved the seroprevalence of HCV among patients with Hodgkin's lymphoma were recruited for further study.

The available reports were collected and extracted for the data about the seroprevalence of HCV. Those primary data were used for further metanalysis study. Any report that did not present the prevalence in both patients with Hodgkin's lymphoma and healthy control subjects were excluded for further

risk analysis. Concerning the metanalysis study, the overall Anti HCV seropositive rate in the patients and healthy subjects as well as odds ratio were calculated. The correlation between the ethnic of the subjects in each setting and the prevalence of Anti HCV seropositive was also assessed by Chi square test. The SPSS 11.0 for Windows was used for statistical analysis in this study. P value less than 0.05 is accepted as statistical significant level.

### **Results:**

According to the literature review, 3 reports<sup>(6-8)</sup> were recruited (Table 1). According to the metanalysis, 184 cases and 904 health subjects were investigated for HCV seroprevalence. There is no significant correlation between the ethnic of the subjects and the prevalence of Anti HCV seropositive ( $P > 0.05$ ). The overall Anti HCV seropositive rate in the patients with Hodgkin's lymphoma (3/184) and healthy subjects (6/904) are 1.6 % and 0.7 %, respectively (Table 2). The odds ratio is 2.5 (confidence interval = 0.1 – 0.6).

Table 1. Reports on HCV seroprevalence in patients with Hodgkin's lymphoma and healthy subjects.

Reports	Setting	Patients with lymphoma		Healthy subjects	
		Total (N)	Anti HCV +ve (N, %)	Total (N)	Anti HCV +ve (N, %)
Yenice et al, 2002 <sup>(6)</sup>	Turkey	50	1, 2 %	100	1, 1 %
De Renzo et al, 2002 <sup>(7)</sup>	Italy	100	2, 2 %	110	2, 1.8 %
Hausfater et al, 2001 <sup>(8)</sup>	France	34	0, 0 %	694	3, 0.4 %

Table 2. Case-control analysis for the correlation between HCV seroprevalence and lymphoma

Anti HCV	Patients with lymphoma	Healthy subjects
Positive	3	6
Negative	181	898

### Discussion:

Hepatitis virus infections are an increasing problem, with millions people all over the world being infected. It is accepted as a significant public health problem with several life altering complications. HCV, an RNA hepatotropic virus, is the leading cause of viral hepatitis worldwide. The mechanisms of HCV persistence are currently unknown, although it is known that HCV chronicity develops despite humoral and cellular responses to HCV proteins (10). HCV-RNA also shows significant genetic variability.<sup>(10)</sup> Infection with this virus causes a repertoire of liver diseases that include acute hepatitis, chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC), in addition to a number of extra-hepatic

manifestations such as lichen planus and oral cancer.<sup>(11)</sup>

There are many studies on the carcinogenesis of HCV. Major topics of the study are the biological functions of HCV proteins and the interaction between HCV proteins and cellular proteins.<sup>(12)</sup> HCV infection has shown to be strongly linked to the development of hepatocellular carcinoma in epidemiological studies.<sup>(13)</sup> Unlike other human oncogenic viruses, HCV is a typical RNA virus, and thus there is no integration of the viral genome or a piece of the genome into host chromosomes.<sup>(13)</sup> Moreover, trans-acting transcriptional factors, which are coded by other human oncogenic viruses and required primarily for virus replication and often involved in cell immortalization, may not be coded by HCV.<sup>(13)</sup> Observations made

with isolated HCV antigens and/or with HCV subgenomic replicon systems demonstrated that the products encoded in the HCV genome interfere with and disturb intracellular signal transduction, often by phosphorylation of cellular proteins<sup>(14)</sup>. Moreover, some of the HCV-encoded proteins seem to serve as substrates for host cell protein kinases.<sup>(14)</sup> The identification of these small polypeptide elements and the subsequent development of strategies to inhibit protein-protein interactions involving them may be the first step towards reducing the chronicity and/or of the carcinogenicity of the virus.<sup>(14)</sup>

Considering the lymphomagenesis due to HCV infection, molecular data also indicate a close relationship between HCV infection and B cell non – Hodgkin's lymphoma (NHL).<sup>(1)</sup> Quinn et al proposed that that some HCV-associated lymphomas originate from B cells that were initially activated by the HCV-E2 protein and might explain the association between HCV infection and some B-cell lymphoproliferative disorders<sup>(15)</sup> Indeed, Montella et al said that HCV was a RNA virus that cannot be integrated with the host genome, however, exerted its oncogenetic potential indirectly by contributing to the modulator effects of the host immune system, probably through a capacity to elude the immune

system.<sup>(16)</sup> Fiorilli et al said that molecular data indicated a close relationship between HCV-associated B-NHL and type II mixed cryoglobulinemia.<sup>(17)</sup> They noted that the latter disorder appeared to reflect the benign monoclonal proliferation of B cells expressing a specific cross-reactive idiotype that might recognize an antigen of HCV, perhaps the E2 protein then genetic abnormalities occurring during this phase of antigen-induced clonal expansion might drive the neoplastic transformation into low- or high-grade lymphoma.<sup>(17)</sup> They also mentioned that the recent demonstration that splenic B cell lymphomas associated with HCV-infection might regress after successful antiviral therapy confirmed a role for this virus in B-cell lymphomagenesis.<sup>(17)</sup>

Concerning the relationship between HCV infection and Hodgkin lymphoma, there are only a few reports. Keresztes et al proposed that HCV positivity in patients with Hodgkin's disease differs significantly (about 1.5 times) from that in blood donors.<sup>(9)</sup> They also noted that there was no significant difference between hepatitis positive and negative patients concerning mean age at the time of diagnosis, sex, disease stage, histology type, treatment, risk factors in the history of the infection and liver enzymes.<sup>(9)</sup> According to

their report, 9 % of the patients with Hodgkin's lymphoma were Anti HCV seropositive.<sup>(9)</sup> Recently, Yenice et al noted that HCV might play a role in the development of B-cell non-Hodgkin lymphoma, but not in Hodgkin lymphoma.<sup>(6)</sup> Here, the author tried to summarize the previous reported on the seroprevalence of HCV among patients with Hodgkin's lymphoma comparing with healthy control subjects. According to this study, it could be seen that having Anti HCV seropositive is a weak risk for Hodgkin's lymphoma.

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