Hepatitis b and c viruses and hodgkin lymphoma: A case-control study from northern and southernItaly

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Dear Sir,

In a recent issue of this journal, Bianco *et al.*[1] evaluated the association between hepatitis C virus (HCV) infection and Hodgkin lymphoma (HL). So far, the only virus established to be causally related to a subset of HL is the Epstein-Barr virus (EBV).[2,3]

To explore further this topic, we have used data from another Italian case-control study conducted on lymphomas and hepatocellular carcinomas in the province of Pordenone, North-East of Italy, and the town of Naples, in the South.[4] Information on hepatitis B virus (HBV) was also available.

The study design was described elsewhere.[4] Briefly, the present report includes 62 incident histologically confirmed HL cases aged 18 or more, median age = 30 years (Table). Controls were the same 504 individuals used in the case-control study on non-Hodgkin lymphoma and hepatocellular carcinomas and, therefore, they had a different age distribution than HL cases. This imbalance was, however, compensated by careful age adjustment (see below). Controls were admitted as in-patients for a wide spectrum of acute conditions to the same hospitals as HL. Specifically excluded from the control group were patients whose hospital admission was caused by malignant diseases, conditions related to alcohol and tobacco consumption or hepatitis viruses. Haematological, allergic, and autoimmune diseases were also excluded. Comorbidity for the diseases listed above was not, however, an exclusion criterion.

All sera were screened for antibodies against HCV using a third generation microparticle enzyme immunoassay (MEIA) (AxSYM HCV, version 3.0; Abbott, Wiesbaden, Germany), positive samples were confirmed using a third generation line immunoassay (LIA) (Innogenetics, Ghent, Belgium). Serum HCV RNA was assessed using Amplicor version 2.0 (Roche, Pleasanton, CA). Samples were considered HCV-positive when HCV antibodies or HCV RNA were detected.

Testing for anti-HBsAg was performed using MEIA (AxSYM AUSAB, Abbott). Samples were considered HBsAg-positive when positive at the neutralization test. HBsAg was tested using MEIA (AxSYM HBsAg, version 2; Abbott) and confirmed using a neutralization test (AxSYM, Abbott). Samples were classifed as HbsAg-positive when positive at the neutralization test. Nine HL cases and 20 controls, reporting vaccination against HBV, were not included in the analyses of HBV markers.

Adjusted ORs and corresponding 95% confidence intervals (CI) were calculated by means of unconditional multiple logistic regression including age (groups shown in Table plus a term for age as continuous variable), sex, center, and years of education.

Education was negatively associated with HL (OR=0.4, in the highest tertile compared to the lowest, 95%CI: 0.1-1.0) while place of birth (North versus South of Italy, where HCV infection is most prevalent)[4] and occupation were unrelated to HL risk (*data not shown in Table*).

Table 1. Distribution of 62 cases of Hodgkin lymphoma (HL) and 504 controls and corresponding odds ratio (OR) and 95% confidence intervals (CI)1 for selected socio-demographic factors and hepatitis B (HBV) and C virus (HCV) markers. Italy, 1999-2002.

	HL Cases		*Controls*		*OR (95% CI)*	
	N.	*(%)*	*N.*	*(%)*		
Gender						
Males	33	(53.2)	341	(67.7)		
Females	29	(46.8)	163	(32.3)		
Age (years)						
<25	14	(22.6)	13	(2.6)		
25-29	16	(25.8)	20	(4.0)		
30-39	16	(25.8)	40	(7.9)		
40-59	14	(22.6)	138	(27.4)		
≥60	2	(3.2)	293	(58.1)		
Center						
Aviano/Pordenone	37	(59.7)	280	(55.6)		
Naples	25	(40.3)	224	(44.4)		
HCV status						
Negative	61	(98.4)	459	(91.1)		1[3]
Positive	1	(1.6)	45	(8.9)		0.9
(0.1-7.2)						
HBV markers[2]						
Anti-HbsAg Negative	39	(73.6)	341	(73.7)		1[3]
Anti-HbsAg Positive	13	(24.5)	118	(25.5)	1.1	(0.5-2.5)
HBsAg Positive	1	(1.9)	4	(0.9)	1.8	(0.1-21.5)

[1]Estimated from unconditional logistic regression adjusted for sex, age (periods in table plus a continuous term), center, and education. [2]The sum does not add up to the total because of some missing values. [3]Reference category.

Only one (1.7%) HL was HCV-positive (genotype 1b). After adjustment for sex, age, center, and education, no difference was found between HL cases and controls (OR = 0.9; 95% CI: 0.1-7.2). Moreover, markers of HBV infection (Table) and self-reported history of different types of hepatitis (A, B or C) were not associated with HL (*data not shown*).

Hospital-based case-control studies are prone to selection bias, but it is unlikely that a lack or an excess of HCV-positivity among control subjects distorted our OR for HCV. Indeed, the prevalence of HCV-positivity in our control group was consistent with the findings of previous HCV surveys conducted in Italy.[5,6] HL cases were an unselected group as shown by the distribution of histological subtypes in our study (72% nodular sclerosis, 20% mixed cellularity, and 8% nodular lymphocyte predominance), which was similar to that expected in the general population.[2,3] The different age distribution of cases and controls is another possible weakness of our study, but a fine age-adjustment should have remedied to it; furthermore, the results were virtually the same when restricting the analyses to subjects younger than 60 years.

The current pathogenetic hypotheses on HCV lymphomatogenesis might have supported the involvement of a broad spectrum lymphomas, whose B-cells of origin were chronically stimulated by HCV-related antigens in germinal center-like structures.[3,7,8] Although most epidemiological studies, including the present one, were too small to allow conclusions,[1,7,8] taken together they do not suggest a role of HCV in the etiology of HL.

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