Hepatitis B or C virus infection and risk of non-Hodgkin lymphoma among solid organ transplant recipients

Hepatitis B and C viruses (HBV/HCV) substantially increase risk for hepatocellular carcinoma, likely through both direct oncogenic effects (e.g. interaction of HCV proteins with host proteins that regulate cell proliferation, integration of HBV DNA into the host genome) and indirect effects (e.g. chronic inflammation, fibrosis).[1] Epidemiological studies also have demonstrated increased non-Hodgkin lymphoma (NHL) risk with chronic HBV or HCV infection, with potential specificity for particular NHL subtypes.[2-5] However, the mechanisms by which chronic viral hepatitis may contribute to lymphomagenesis are unclear. The ability of HCV to replicate within lymphocytes and thereby exert a direct oncogenic effect is uncertain,[6] and an indirect effect through chronic antigenic stimulation is plausible.[5] Nonetheless, a causal relation between HCV and NHL is strongly supported by regression of lymphomas in HCV-infected individuals following antiviral treatment.[7] Although there are no comparable data for

Table 1. Selected characteristics of 178,265 solid organ transplants,* United States, 1994-2009.

Characteristic	Total population N	(%)†	HCV status at transplantation % Infected‡	% Unknown‡	HBV status at transplantation % Active Infection‡	% Resolved Infection‡	% Unknown‡
Total	178,265	(100.0)	11.1	12.6	2.6	7.5	26.5
Sex							
Male	109,188	(61.3)	13.0	12.6	2.9	8.3	26.3
Female	69,077	(38.7)	8.2	12.6	2.1	6.1	26.8
Age at transplantation (years)							
0-19	15,016	(8.4)	1.6	17.9	2.1	4.1	31.6
20-34	25,264	(14.2)	3.1	12.2	2.2	4.2	27.3
35-49	54,650	(30.7)	13.5	12.4	2.8	7.7	27.1
50-64	66,891	(37.5)	15.0	12.1	2.7	9.3	25.2
65+	16,444	(9.2)	8.4	11.2	2.4	7.6	24.0
Race/ethnicity							
White, non-Hispanic	108,606	(60.9)	11.3	12.7	2.0	6.1	27.0
Black, non-Hispanic	30,991	(17.4)	10.3	11.8	2.3	9.0	27.3
Hispanic	28,584	(16.0)	12.6	12.8	1.8	7.8	24.7
Asian/Pacific Islander	10,084	(5.7)	7.7	13.7	11.9	16.8	23.5
Transplanted organ							
Kidney	103,108	(57.8)	4.6	11.7	1.7	6.1	28.3
Liver	39,542	(22.2)	35.0	15.7	5.9	14.2	21.1
Heart and/or lung	24,591	(13.8)	1.7	12.0	1.3	2.9	28.5
Other/multiple organs	11,024	(6.2)	8.0	11.4	2.1	6.0	24.5
Calendar year of transplantation							
1994-1999	61,273	(34.4)	10.2	13.9	2.3	6.0	31.9
2000-2004	64,715	(36.3)	11.6	12.4	2.6	8.1	26.0
2005-2009	52,277	(29.3)	11.6	11.3	2.9	8.4	20.8
Epstein-Barr virus serology status§							
Positive	65,154	(36.6)	12.9	4.7	2.9	8.3	17.5
Negative	13,795	(7.7)	9.0	10.6	2.5	6.9	14.8
Unknown	99,316	(55.7)	10.5	22.6	2.4	7.0	34.0
Incident NHL during follow up							
Total	1427	(100.0)	9.0	14.1	2.4	5.8	28.9
DLBCL	843	(59.1)	9.4	15.2	2.6	4.4	28.1
MZL	36	(2.5)	16.7	16.7	2.8	22.2	27.8
BL	81	(5.7)	8.6	8.6	3.7	4.9	29.6
CLL/SLL	33	(2.3)	6.1	15.2	3.0	9.1	33.3
FL	35	(2.5)	5.7	20.0	0.0	11.4	14.3
PTCL	37	(2.6)	2.7	21.6	2.7	2.7	37.8
Rare NHL subtypes	90	(6.3)	5.6	7.8	3.3	13.3	22.2
NOS	272	(19.1)	7.7	14.0	1.1	5.1	33.5
Median follow up (years)	3.59		2.86	3.43	3.26	2.97	3.46

*BL: Burkitt lymphoma/leukemia; CLL/SLL: chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HBV: hepatitis B virus; HCV: hepatitis C virus; MZL: marginal zone lymphoma; NHL: non-Hodgkin lymphoma; NOS: not otherwise specified; PTCL: peripheral T-cell lymphoma. *Includes 178,265 solid organ transplants (n=161,403 first, n=15,389 second, n=1473 third or higher transplants) occurring among 167,781 individuals. Follow-up time was contributed separately for successive transplants. †Represents percent of total number of transplants (i.e. column percent), except for NHL subtypes for which (%) represents percent of total NHL diagnoses. ‡Represents percent of transplants within that category (i.e. row percent). §Restricted to the 116,992 transplants performed in 2000 or later, when EBV serostatus was routinely recorded by the SRTR.*

HBV, peripheral blood mononuclear cells are an established extra-hepatic HBV reservoir.[8]

Chronic viral hepatitis-induced liver disease is a major indication for liver transplantation, and thus infection with HBV and HCV is more common among solid organ transplant recipients than in the general population. A null association for HCV and HBV with post-transplantation lymphoproliferative disorder (PTLD) has been reported,[9,10] supporting the hypothesis that immunocompetence is required for HBV- or HCV-induced lymphoproliferation. However, those previous reports were limited by potential underascertainment of PTLD diagnoses and inability to conduct analyses specifically for NHL or individual NHL subtypes. Additionally, a recent small case series of PTLD suggested HCV may act as a co-factor for Epstein-Barr virus,[11] supporting the need for further research.

Investigation of chronic viral hepatitis and NHL in immunosuppressed populations may provide a unique insight into lymphomagenesis as well as further our understanding of NHL etiology following solid organ transplantation. We therefore investigated HBV, HCV, and NHL risk in the Transplant Cancer Match Study (*www.transplantmatch.cancer.gov*),[12] linking the US Scientific Registry of Transplant Recipients (SRTR) with state/regional population-based cancer registries to provide comprehensive, systematic cancer ascertainment for solid organ transplant recipients. The SRTR collects detailed data on all US solid organ transplants since 1987. During 2008-2012, serial record linkages were completed between SRTR and 15 population-based cancer registries to identify NHL cases, with NHL subtypes (n. >30 cases) defined by World Health Organization guidelines. The study population was restricted to transplants performed in 1994 or later, when viral hepatitis testing of recipients became routine, and excluded individuals with unknown race/ethnicity (0.7%) or history of human immunodeficiency virus (HIV) infection (0.1%). Recipients with a positive enzyme immunoassay screening test for serum HCV antibodies and/or positive for HCV RNA were considered HCV-infected. Recipients positive for hepatitis B surface antigen (HBsAg) were considered to have active HBV infection, whereas those positive for hepatitis B core antibody and negative for HBsAg were considered to have resolved HBV infection.

For each transplant, follow up began on the date of transplantation or start of cancer registry coverage (whichever came later) and ended at NHL diagnosis, graft failure, retransplantation, death, or loss to follow up (whichever came first). Patients contributed follow-up time separately for successive transplants. Relative risk (RR) of NHL and corresponding 95% confidence intervals (CI) according to HBV- or HCV-infection status were derived from multivariate Poisson regression models.

Our study population included 178,265 solid organ transplants, with a median age at transplantation of 48 years (Table 1). A total of 19,828 transplants (11%) occurred in HCV-infected recipients, 4596 (2.6%) in those

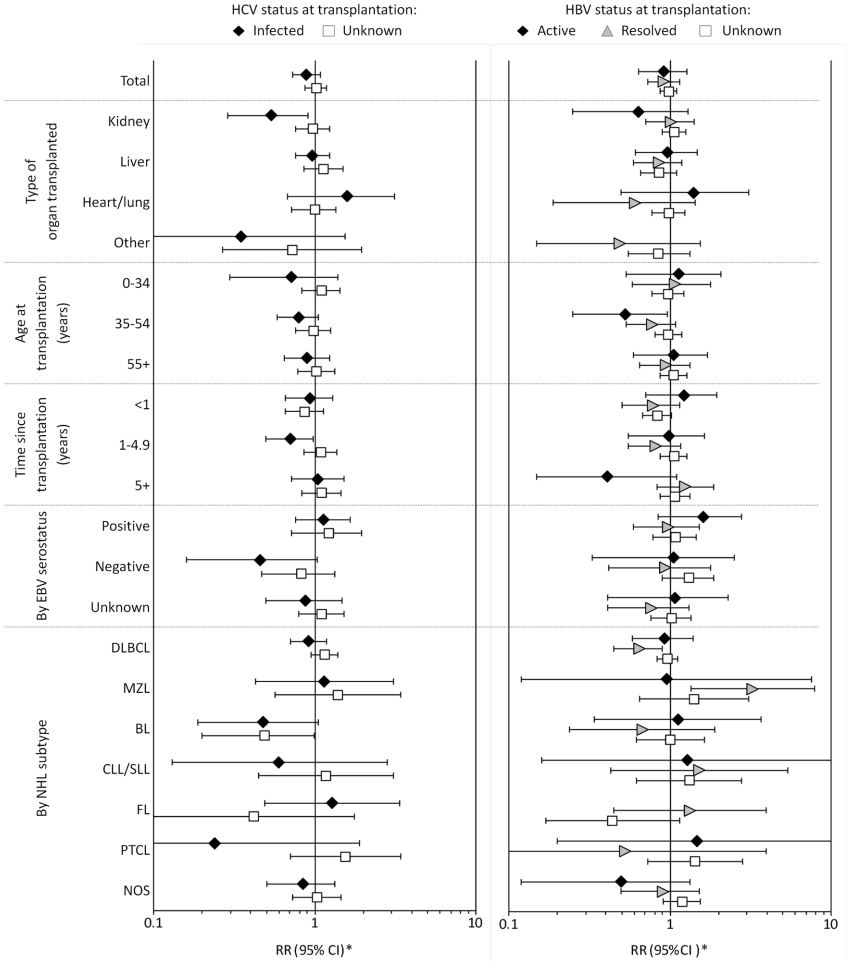

Figure 1. HBV and HCV infection and risk of NHL following solid organ transplantation, by patient and transplant characteristics and NHL subtype. BL: Burkitt lymphoma/leukemia; CLL/SLL: chronic lymphocytic leukemia/small lymphocytic lymphoma; CI: confidence interval; DLBCL: diffuse large B-cell lymphoma; EBV: Epstein-Barr virus; FL: follicular lymphoma; HBV: hepatitis B virus; HCV: hepatitis C virus; MZL: marginal zone lymphoma; NHL: non-Hodgkin lymphoma; NOS: not otherwise specified; PTCL: peripheral T-cell lymphoma; RR: relative risk. *RR (95%CI) derived from Poisson regression model adjusted for sex, race/ethnicity, age and calendar year at transplantation, and type of organ transplanted (see categories in Table 1), with an offset of the expected number of cases occurring in the general population to provide indirect adjustment for cancer registry and attained age. The referent group was comprised of HBV- or HCV-uninfected recipients.

with active HBV infection, and 13,320 (7.5%) in those with resolved HBV infection. HCV and HBV prevalence were highest among males, the middle-aged (35-64 years), and liver recipients.

We identified 1427 incident cases of NHL, of whom 9% were HCV-infected, 2.4% had active HBV infection, and 5.8% had resolved HBV infection. Hepatitis viral infection status at the time of transplantation was not significantly related to overall NHL risk, with an RR of 0.89 (95%CI: 0.73-1.09) for HCV-infected compared with HCV-uninfected recipients, and RRs of 0.92 (0.64-1.29) for active HBV infection and 0.92 (0.73-1.15) for resolved HBV infection compared with HBV-uninfected recipients (Figure 1). The lack of a positive association between HBV, HCV, and NHL was consistent across recipients regardless of transplanted organ, age and EBV serostatus at transplantation, and time since transplantation, despite differences in NHL incidence by these characteristics.[12]

Although previous studies in immunocompetent populations have reported differences in associations according to NHL subtype,[2,4,5] we observed no association for any NHL subtype among solid organ transplant recipients, with the exception of elevated risk for marginal zone lymphoma among individuals with resolved HBV infection. This finding could represent risk associated with HBV reactivation, as suggested in a recent study of 4 PTLD cases,[13] but we could not address this hypothesis because we lacked data on HBV reactivation. Alternatively, our observation may have been due to chance. We note that reactive 'early' lesions and polymorphic PTLDs not considered invasive were thereby not reportable to the cancer registries and thus could not be included in this analysis.

The general lack of association that we observed between chronic viral hepatitis and NHL risk among solid organ transplant recipients in this large, population-based study lends support to the notions that an intact immune system is required for HBV and HCV to cause NHL, and that these viruses contribute indirectly to lymphomagenesis through chronic antigenic stimulation. Additional data on immunosuppressive medications might help address this hypothesis, but all transplant recipients are substantially more immunosuppressed than people in the general population. Our study results are consistent with 2 small studies reporting no association between HCV infection and NHL risk among immunosuppressed individuals with HIV/AIDS.[14,15] In both transplant recipients and HIV-infected individuals, the majority of NHLs are diffuse large B-cell lymphoma, and Epstein-Barr virus plays an important etiological role. Our results suggest that neither HBV nor HCV contribute to this distinct pathway in immunocompromised individuals.

In the light of the substantial global burden of chronic infection with HBV and HCV, further research is needed in the general population to advance understanding of the indirect oncogenic effects of HBV and HCV on lymphocytes and to confirm optimal management of NHL in patients with a history of chronic viral hepatitis.

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doi:10.3324/haematol.2013.101600

Key words: HCV, HBV, NHL after solid organ transplantation.

Funding: this research was supported in part by the Intramural Program of the National Cancer Institute, National Institutes of Health. During the initial period when registry linkages were performed, the SRTR was managed by Arbor Research Collaborative for Health in Ann Arbor, MI (contract HHSH234200537009C); beginning in September 2010, the SRTR was managed by Minneapolis Medical Research Foundation in Minneapolis, MN (HHSH250201000018C). The following cancer registries were supported by the National Program of Cancer Registries of the Centers for Disease Control and Prevention: California (agreement 1U58 DP000807-01), Colorado (U58 DP000848-04), Georgia (5U58DP000817-05), Illinois (5658DP000805-04), Michigan (5U58DP000812-03), New Jersey (5U58/DP000808-05), New York (U58DP0038789), North Carolina (U58DP000832), and Texas (5U58DP000824-04). The following cancer registries were supported by the SEER Program of the National Cancer Institute: California (contracts HHSN261201000036C, HHSN261201000035C, and HHSN261201000034C), Connecticut (HHSN261201000024C), Hawaii (HHSN261201000037C, N01-PC-35137, and N01-PC-35139), Iowa (HSN261201000032C and N01-PC-35143), New Jersey (HHSN261201000027C and N01-PC-54405), Seattle-Puget Sound (N01-PC-35142), and Utah (HHSN261201000026C). Additional support was provided by the states of California, Colorado, Connecticut, Illinois, Iowa, New Jersey, New York (Cancer Surveillance Improvement Initiative 14-2491), Texas, and Washington, as well as the Fred Hutchinson Cancer Research Center in Seattle, WA.

Acknowledgments: the authors gratefully acknowledge the support and assistance provided by individuals at the Health Resources and Services Administration (Monica Lin), the SRTR (Ajay Israni, Bertram Kasiske, Paul Newkirk, Jon Snyder), and the following cancer registries: the states of California (Tina Clarke), Colorado (Jack Finch), Connecticut (Lou Gonsalves), Georgia (Rana Bayakly), Hawaii (Marc Goodman), Iowa (Charles Lynch), Illinois (Lori Koch), Michigan (Glenn Copeland), New Jersey (Xiaoling Niu), New York (Amy Kahn), North Carolina (Chandrika Rao), Texas (Melanie Williams), and Utah (Janna Harrell), and the Seattle-Puget Sound area of Washington (Margaret Madeleine). We also thank analysts at Information Management Services for programming support (David Castenson, Matthew Chaloux, Michael Curry, Ruth Parsons).

The views expressed in this paper are those of the authors and should not be interpreted to reflect the views or policies of the National Cancer Institute, Health Resources and Services Administration, SRTR, cancer registries, or their contractors.

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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