

Prevalence of Hepatitis C Virus Infection and Risk for Hepatocellular Carcinoma and Non-Hodgkin Lymphoma in AIDS

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Abstract: Hepatitis C virus (HCV) infection is highly prevalent in some subpopulations with AIDS. HCV is linked to hepatocellular carcinoma (HCC) and possibly non-Hodgkin lymphoma (NHL), but the impact of AIDS on these associations is uncertain. We used U.S. registry data to study HCC and NHL risk in 304,411 adults with AIDS, comparing cohort subgroups with high prevalence (hemophiliacs and injection drug users) or low prevalence (homosexual men, heterosexuals, and others) of HCV infection. The ratio of observed to expected cancer cases (standardized incidence ratio [SIR]) measured risk relative to the general population. Sixty-one HCC cases were observed (SIR, 7.5; 95% confidence interval, 5.7–9.6). Risk for HCC was higher in subgroups with high prevalence of HCV infection than in subgroups with low prevalence of HCV infection (SIR: 11.4 versus 5.5, respectively; $p = .004$). Subjects developed the following NHL grades: low, 35 cases; intermediate, 1035 cases; high, 784 cases; and unspecified, 1395 cases. For each NHL grade, SIRs were highest in subgroups with low prevalence of HCV infection. These data suggest an effect of HCV infection on HCC risk among adults with AIDS. On the other hand, NHL risk was not higher for groups in whom HCV infection was prevalent. **Key Words:** Cancer—Hepatocellular carcinoma—Non-Hodgkin lymphoma—Hepatitis C virus—Epidemiology—HIV—AIDS.

Hepatitis C virus (HCV) is efficiently transmitted through parenteral exposures. HCV infection is therefore highly prevalent in groups with parenterally acquired HIV infection, notably hemophilia patients and injection drug users (1–6). In other HIV-infected persons, such as those who acquired HIV infection vertically or through sexual exposures, HCV coinfection is much less common (3–6).

HCV is an important cause of chronic liver disease and hepatocellular carcinoma (HCC) (7–15). Nonetheless, HCC is rare in the general population and in HIV-infected persons (16). Notably, no previous study has addressed the association between HCV infection and HCC in HIV-infected persons, for whom impaired immunity or other factors could modify cancer risk.

In HIV-uninfected people, HCV infection may also be associated with non-Hodgkin lymphoma (NHL). Several studies have reported five- to 13-fold excess risk for NHL, predominantly low- or intermediate-grade, with HCV infection (17–19). For HIV-infected persons, the relationship between HCV infection and NHL is of considerable interest, given the high frequency

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of coinfection with HIV and HCV and the markedly elevated risk for NHL with HIV infection. However, high-grade NHLs are the most common subtypes in AIDS (20,21), and two case-control studies of AIDS patients found no relationship between HCV infection and risk for intermediate- or high-grade NHL (22,23).

To examine the association between HCV infection and risk for HCC and NHL in HIV-infected persons, we used data from the AIDS-Cancer Match Registry study (24,25). Specifically, we compared risk for these malignancies in various HIV risk groups among whom the prevalence of HCV infection varies widely. An advantage of our investigation was the large number of subjects (>300,000), which allowed us to study rare cancer outcomes.

MATERIALS AND METHODS

Study Subjects

The AIDS-Cancer Match Registry study obtained data on cancer incidence among persons with AIDS through linkage of AIDS and cancer registries from 11 U.S. areas (states of Connecticut, Florida, Illinois, Massachusetts, New Jersey, and New York and metropolitan areas of Atlanta, Los Angeles, San Diego, San Francisco, and Seattle). Included subjects were individuals diagnosed with AIDS during the period of registration of the relevant cancer registry. The period of cancer registration varied by registry, but all periods included January 1983 through December 1994, except in San Diego where registration began January 1988. No data were available after 1996. The present analysis included all adults (age of at least 15 years at AIDS diagnosis).

We used the cancer registries to identify cases of HCC and NHL in cohort subjects. NHLs were categorized using the second edition of the *International Classification of Diseases for Oncology* (26) and grouped according to the Working Formulation (27) as low-, intermediate-, or high-grade. NHLs with unspecified histologic findings were considered separately. Because NHL is itself an AIDS-defining illness, we moved the AIDS diagnosis date for subjects with NHL back to the date documented in the cancer registry, when this date preceded the AIDS date by <5 years. Similarly, the diagnosis date for NHL, as recorded in the cancer registry, was reset to the AIDS registry date when the AIDS registry recorded NHL first.

Calculation of Relative Risks

The timing of HCC cases was noted relative to AIDS onset in accord with previous studies of this cohort (24,25). The overall time interval for registration of cancer cases spanned from -60 to +27 months relative to AIDS onset, which was divided into the following subintervals: -60 to -25 months (distant pre-AIDS period); -24 to -7 months (recent pre-AIDS period); -6 to +3 months (AIDS period); and +4 to +27 months (post-AIDS period). Observed cancer cases in the post-AIDS period were compared directly with the number expected, based on sex-, age-, race-, and year-specific incidence for the general population (24,25). Observed cancer cases in the other three periods were ascertained retrospectively for persons identified at the time of AIDS diagnosis. Therefore, expected cancer cases in these periods were survival-

adjusted to take account that some persons with cancer would have died before developing AIDS (25). The standardized incidence ratio (SIR; calculated as observed count divided by expected counts) measured relative risk compared with the general population and was calculated for the overall time interval. Similarly, SIRs for various NHL grades were calculated based on rates among the general population. SIRs for NHL were calculated only for the post-AIDS period, because by definition no NHLs occurred before AIDS and because NHL incidence in the AIDS period is difficult to interpret (NHL is the initial AIDS-defining diagnosis for some persons). Exact confidence intervals (CIs) for SIRs were derived (28).

Effect of HCV Infection on Cancer Risk

The effect of HCV infection on HCC and NHL risk was examined by classifying subjects into six subgroups with varying prevalence of HCV infection, based on HIV risk category and previously reported data on the prevalence of HCV infection (1-6). Hemophiliacs and two groups of injection drug users (homosexual male drug users and other injection drug users) were identified as having very high prevalence (80%-95%) of HCV infection. Remaining subjects were in three groups with relatively low prevalence (3%-15%) of HCV infection: non-injection-drug-using homosexual males, heterosexuals, and others (many of whom had unknown HIV risk factors). To determine whether HCV infection was associated with risk for HCC or NHL, we compared SIRs for the combined high- and low-prevalence groups using Poisson regression.

RESULTS

The study included 304,411 adults with AIDS. Most subjects (255,054, [84%]) were male, and the median age at AIDS diagnosis was 37 years (interquartile range, 31-43 years). The cohort included 132,820 white subjects (44%), 109,035 black subjects (36%), 59,434 Hispanic subjects (20%), and 3,122 subjects of other or unknown race (1%).

By HIV risk category, 108,622 subjects (36%) were in groups with high prevalence of HCV infection (1,480 hemophiliacs, 15,685 homosexual male injection drug users, and 91,457 other injection drug users). The remaining 195,789 subjects (64%) were in groups with low prevalence of HCV infection (144,018 non-injection-drug-using homosexual males, 25,174 heterosexuals, and 26,597 other subjects).

In the period of observation, 61 persons developed HCC. Fifty-five cases (90%) occurred in male subjects, and the median age at diagnosis was 47 years (interquartile range, 41-55 years). Persons with AIDS had significantly higher HCC risk than did the general population (SIR, 7.5; 95% CI, 5.7-9.6). Risk appeared to be higher in females (SIR, 13.0; 95% CI, 4.8-28.3) than in males (SIR, 7.2; 95% CI, 5.4-9.3), although this finding was not significant ($p = .20$).

Risk for HCC was elevated in the three groups with high prevalence of HCV infection (overall SIR, 11.4;

TABLE 1. Hepatocellular carcinoma (–60 to 27 months relative to AIDS)

Subgroup of subjects	Subjects with AIDS	–60 to +27 mo, relative to AIDS	
		n	SIR (95% CI)
High prevalence groups	108,622	32	11.4 (7.8–16.0)
Hemophiliacs	1480	2	52.9 (6.4–190)
IDUs (homosexual male)	15,685	3	8.9 (1.8–26.0)
IDUs (other)	91,457	27	11.1 (7.3–16.1)
Low prevalence groups	195,789	29	5.5 (3.7–7.8)
Homosexual males (non-IDU)	144,018	20	5.5 (3.4–8.5)
Heterosexuals	25,174	2	3.2 (0.4–11.4)
Others	26,597	7	6.5 (2.6–13.3)

The standardized incidence ratio is calculated as observed cases divided by expected cases and serves as a measure of relative risk (see Methods).

SIR, standardized incidence ratio; CI, confidence interval; IDU, injection drug user.

Table 1). Within the high-prevalence groups, risk was especially high for hemophiliacs (SIR, 52.9 [based on two cases]). For the low-prevalence groups (Table 1), the overall SIR was 5.5 and ranged from 3.2 (heterosexuals) to 6.5 (other subjects). The SIR was significantly higher for the high-prevalence groups than for the low-prevalence groups (relative risk, 2.1; 95% CI, 1.3–3.4; $p = .004$).

In the post-AIDS period, in which cases were ascertained prospectively, HCC incidence was 4.9 cases per 100,000 person-years (based on 15 cases). Some of the 43 cases in the AIDS period may have been diagnosed early as a result of evaluations at the onset of AIDS. Including these cases in the post-AIDS period provides an upper bound for incidence of 18.8 cases per 100,000 person-years.

There were 3,249 NHLs in the post-AIDS period (Table 2), of which 1% were low-grade, 32% were intermediate-grade, 24% were high-grade, and 43% were unspecified-grade. Overall, SIRs were very high for intermediate-, high-, and unspecified-grade NHLs. However, for each NHL grade, SIRs were significantly higher for the groups with low prevalence of HCV infection than for the groups with high prevalence of HCV infection (Table 2). Specifically, SIRs for high- and low-prevalence groups, respectively, were 1.2 and 4.7 for low-grade NHLs ($p = .005$ comparing SIRs), 34.5 and 69.1 for intermediate-grade NHLs ($p < .001$), 51.8 and 126 for high-grade NHLs ($p < .001$), and 68.0 and 140 for unspecified-grade NHLs ($p < .001$).

Table 2 presents SIRs for the six separate groups with high or low prevalence of HCV infection. For low-grade NHL, SIRs were <1 for two high-prevalence groups (hemophiliacs and other injection drug users). For intermediate-grade and high-grade NHLs, SIRs were highest for

non-injection-drug-using homosexual males, a group with low prevalence of HCV infection. For unspecified-grade NHLs, the SIR was highest for hemophiliacs, but it was also high for non-injection-drug-using homosexual males.

DISCUSSION

Our study is the first to examine the effect of HCV infection on risk for HCC specifically in people with HIV infection. We found that HCC risk was twice as high among hemophiliacs and injection drug users, groups with very high prevalence of HCV infection, than among others with AIDS, suggesting that HCV plays a role in development of this cancer in persons with AIDS. Furthermore, the ratio of SIRs for high- and low-prevalence groups (relative risk, 2.1) can be used to estimate the effect of HCV infection. Specifically, using estimates of the prevalence of HCV infection of 90% for the high-prevalence groups and 5% for the low-prevalence groups, the effect of HCV (RR_{HCV}) can be calculated from the following equation (29): $(0.90 \times RR_{HCV} + 0.1) / (0.05 \times RR_{HCV} + 0.95) = 2.1$.

Solving for RR_{HCV} gives 2.4 as an estimate of the relative risk associated with HCV infection. In comparison, prior case-control studies of HCC in Mediterranean Europe and Asia, where HIV infection was presumably rare, found HCV-associated relative risks ranging widely from 4 to 42 (7–13). In the United States, studies of HIV-uninfected persons found relative risks of 7–12 (14,15).

The comparatively small effect of HCV infection in our study could be explained by the younger age of our subjects: the median age at HCC diagnosis was 47 years versus 55–65 years in other studies (7,9,11–13). Because our subjects were younger, the duration of their HCV infection was possibly shorter. HCC typically develops after decades of HCV-related hepatitis (30). For many injection drug users, who acquired HCV infection in adolescence or young adulthood, our follow-up might have been too short to observe their eventual cancer risk. Consistent with this explanation is the relative risk of 52.9 observed for hemophiliacs (Table 1). Many hemophiliacs were probably infected with HCV as children, when they were given plasma products in the 1950s to 1970s. Accumulated hepatic damage might have been greatest in this group, given their longstanding HCV infection. Because there were relatively few HCC cases, we could not estimate the effect of HCV infection separately for other subgroups of interest (e.g., females).

Alternatively, HIV may somehow mitigate HCV-associated damage and risk for HCC. This seems un-

TABLE 2. Non-Hodgkin lymphomas (+4 to +27 months relative to AIDS)

Lymphoma subtype, subgroup of subjects	Subjects with AIDS	+4 to +27 mo, relative to AIDS (post-AIDS period)	
		<i>n</i>	SIR (95% CI)
Low-grade lymphomas			
High prevalence groups	108,622	3	1.2 (0.2–3.4)
Hemophiliacs	1480	0	0 (0–57.9) ^a
IDUs (homosexual male)	15,685	2	5.1 (0.6–18.5)
IDUs (other)	91,457	1	0.5 (0.0–2.6)
Low prevalence groups	195,789	32	4.7 (3.2–6.7)
Homosexual males (non-IDU)	144,018	24	4.6 (3.0–6.9)
Heterosexuals	25,174	2	3.1 (0.4–11.3)
Others	26,597	6	6.2 (2.3–13.5)
Intermediate-grade lymphomas			
High prevalence groups	108,622	200	34.5 (29.9–39.6)
Hemophiliacs	1480	3	35.7 (7.36–104)
IDUs (homosexual male)	15,685	43	45.2 (32.7–60.8)
IDUs (other)	91,457	154	32.3 (27.4–37.8)
Low prevalence groups	195,789	835	69.1 (64.5–73.9)
Homosexual males (non-IDU)	144,018	705	73.9 (68.5–79.5)
Heterosexuals	25,174	76	71.8 (56.6–89.8)
Others	26,597	54	36.4 (27.3–47.4)
High-grade lymphomas			
High prevalence groups	108,622	130	51.8 (43.3–61.5)
Hemophiliacs	1480	1	27.8 (0.7–155)
IDUs (homosexual male)	15,685	44	95.6 (69.5–128)
IDUs (other)	91,457	85	42.4 (33.8–52.4)
Low prevalence groups	195,789	654	126 (117–137)
Homosexual males (non-IDU)	144,018	582	135 (124–146)
Heterosexuals	25,174	31	90.3 (61.3–128)
Others	26,597	41	81.4 (58.4–110)
Unspecified-grade lymphomas			
High prevalence groups	108,622	289	68.0 (60.4–76.3)
Hemophiliacs	1480	12	236 (122–413)
IDUs (homosexual male)	15,685	70	99.2 (77.3–125)
IDUs (other)	91,457	207	59.2 (51.4–67.9)
Low prevalence groups	195,789	1106	140 (132–149)
Homosexual males (non-IDU)	144,018	966	155 (145–165)
Heterosexuals	25,174	79	118 (93.7–148)
Others	26,597	61	63.5 (48.6–81.6)

The standardized incidence ratio is calculated as observed cases divided by expected cases and serves as a measure of relative risk (see Methods).

SIR, standardized incidence ratio; CI, confidence interval; IDU, injection drug user.

^a One-sided 95% confidence interval.

likely, because persons coinfecting with HIV and HCV have higher HCV loads and progress to liver failure more rapidly than do persons infected with HCV alone (31,32). Paradoxically, though, this heightened mortality due to hepatic failure could have reduced the number of observed cancers.

Even in groups with low prevalence of HCV infection, HCC risk was higher than in the general population (SIR, 5.5; Table 1). This finding is almost certainly due to other common exposures. For instance, chronic hepatitis B virus infection markedly increases HCC risk (7–10,13,14,33). Hepatitis B virus is acquired via sexual or parenteral exposures, and infection with this virus is common in all HIV risk categories (34). Similarly, alcohol abuse increases risk for HCC (35) and might be especially prevalent in HIV-infected persons. In previous

studies of cancer in this cohort (24,25), we examined whether HIV-associated immunosuppression was related to cancer risk by testing whether the occurrence of cancer increased with time relative to AIDS onset. We could not do this analysis for HCC, because 43 of the 61 cases arose in the AIDS period itself, suggesting that ascertainment bias affected the timing of HCC diagnosis.

An obvious study limitation is that we lacked individual data on HCV infection and other possible risk factors for HCC and NHL. Nevertheless, by dividing subjects into groups in which HCV infection is known to be extremely common or uncommon, we approximated an analysis in which the HCV status of individual subjects was actually measured. We could not formally analyze the effects of other known cancer risk factors, such as hepatitis B and alcohol use, because there are few

available data on prevalence for people with HIV infection. The prevalence of hepatitis B virus infection appears to be fairly constant across HIV risk groups (34) and so would not contribute to the variation in HCC risk seen in Table 1. Alcohol use might vary across groups, but high levels of consumption are relatively uncommon among hemophiliacs, who had the highest risk for HCC.

NHL risk was lower in groups with high prevalence of HCV infection than in those with lower prevalence (Table 2). This finding contrasts with the positive association between HCV infection and NHL reported for HIV-uninfected persons (17–19), and it is distinct from the null association in two previous studies of AIDS patients (22,23). Indeed, for low-grade NHLs, which have often been associated with HCV infection in HIV-uninfected persons (17,18), groups with high prevalence of HCV infection had the same risk as the general population (SIR, 1.2; Table 2). Since we found a positive association between prevalence of HCV infection and HCC, it is unlikely that our assignment of HCV status was so inaccurate as to reverse the direction of association between HCV infection and NHL.

Instead, we believe that these inverse associations between prevalence of HCV infection and NHL risk were due to confounding. This confounding was not due to differences in sex, race, or age across groups, because the SIRs include an implicit adjustment for these factors. NHL risk differed by registry, but the inverse associations with HCV infection persisted after adjustment for registry (data not shown). We suggest that the negative associations with prevalence of HCV infection can be explained in part by an especially high risk for NHL seen in homosexual males. HCV infection is somewhat uncommon in this group; therefore, their high NHL risk must be caused by other factors. Differences in socioeconomic status may be important, since higher socioeconomic status is more common among homosexual males than injection drug users and higher socioeconomic status has been associated with NHL (36). Taken together, our results and those of prior studies (22,23) suggest that HCV is not a major cause of NHL in persons with AIDS.

In closing, we note that HCC, with an incidence of <19 cases per 100,000 person-years, is much less common in adults with AIDS than is NHL or Kaposi sarcoma. However, HCC risk increases with duration of HCV infection. Highly effective therapies for HIV infection, available beginning in 1996, greatly prolong survival (37,38). With diminished mortality due to other causes, persons coinfecting with HIV and HCV may now live long enough to develop HCC, which will increase

the public health importance of this cancer in persons with AIDS.

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