Increased Risk for Lymphoma Following Hemorrhagic Fever With Renal Syndrome

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Hemorrhagic fever with renal syndrome (HFRS) is a severe acute disease. Although long-term consequences to public health have been reported, no association with cancer is known. We examined the risk of cancer development after HFRS in the Swedish population between 1997 and 2011 (n = 6582) and report a 73% increased risk for lymphoma.

Keyhords. lymphoma; HFRS; hantavirus; Puumala virus.

Several viruses are linked with increased risks for various forms of cancer. For example, infections with Epstein-Barr virus (EBV), hepatitis C virus (HCV), human immunodeficiency virus type 1 (HIV-1), and human T-lymphotrophic virus type 1 (HTLV-1) have been associated with increased risk of developing lymphoma [1].

Viral hemorrhagic fevers (VHFs) are a cluster of zoonotic emerging infectious diseases caused by viruses of the Arenaviridae, Bunyaviridae, Filoviridae, and Flaviviridae families. Although the pathogenic mechanisms behind different VHF are diverse, a common feature is that these viruses cause systemic infection and often interfere with normal immune cell functions in manners that lead to impaired or aberrant immune responses [2]. Rodent-borne hantaviruses (family Bunyaviridae, genus Hantavirus) are the causative agent of hemorrhagic fever with renal syndrome (HFRS) in Eurasia. In the Americas, hantaviruses cause hantavirus pulmonary syndrome (HPS; also called hantavirus cardiopulmonary syndrome). HFRS and HPS are, like most VHFs, severe acute diseases with case-fatality rates of up to 15% for HFRS and approximately 40% for HPS [3, 4]. Currently, no specific treatment is available and no US Food and Drug Administration–approved vaccine exists. In Europe, including Sweden, Puumala virus (PUUV) is the predominant causative agent of HFRS. Infection results in a relatively mild variant of the disease with case-fatality rates normally <1% [4]. Following the specific diseases HFRS and HPS, several long-term consequences of human hantavirus infection have been reported, including effects on the cardiovascular, renal, and endocrine systems [3, 4]. Here, we investigated the possibility of an association between HFRS and cancer.

METHODS

HFRS is a notifiable disease in Sweden. Diagnosis is based on seroconversion, that is, detection of PUUV-specific antibodies in patient samples by either enzyme-linked immunosorbent assay or an indirect immunofluorescence method [5]. All diagnosed cases are, with their National Registration Number (NRN), reported to the Public Health Agency of Sweden (formerly Swedish Institute for Communicable Disease Control). Using NRNs, individuals diagnosed with HFRS between 1997 and 2011 were followed up by linkage to the Swedish Cancer Registry through 31 December 2011. Age- and sex-standardized incidence ratios (SIRs) and associated 95% confidence intervals (CIs) were calculated against corresponding incidence rates for the entire Swedish population. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

RESULTS

Of the 6603 individuals diagnosed with PUUV-associated HFRS in Sweden from 1997 to 2011, 21 were excluded from the present analyses because of death before the diagnostic report (n = 11), emigration (n = 5), or missing citation of age in the report (n = 5). The majority of the patients were male (59.7%), and the median age at HFRS diagnosis was 52.0 years (range, 2–94 years). Of the 6582 individuals included in the study, with an accumulated 42 136 person-years (mean person-years of follow-up, 6.4 [range, 0–15 years]), 353 were diagnosed with cancer. The overall risk for development of cancer among the HFRS-diagnosed individuals did not differ significantly compared with the general population (SIR, 0.95...
of cancer, suggests the possibility that a causal link exists between HFRS and lymphoma development, possibly mediated by the hantavirus infection.

Of the viruses that earlier have been associated with lymphoma [1], EBV is of particular interest because it can cause infectious mononucleosis that, like HFRS, has an acute onset [6]. Here, we observed a high risk for lymphoma early after HFRS diagnosis (Table 1), resembling the pattern of infectious mononucleosis–associated Hodgkin lymphoma [7].

An interesting feature of human hantavirus infection is the strong lymphocyte responses observed; long-lasting elevated levels of lymphocytes are frequently found in patients with HFRS [3, 4, 8]. Moreover, lymphocytes are potential target cells for hantaviruses [9], and hantaviruses have potent antiapoptotic capacities in infected cells [10]. Hantaviruses inhibit apoptosis in general and protect infected cells from cytotoxic granule-dependent induction of apoptosis. These effects can, at least partly, be attributed to the capacity of hantavirus nucleocapsid protein to inhibit the enzymatic activities of both caspase 3 and granzyme B [10], enzymes required for execution of apoptosis (caspase 3) and for cytotoxic granule–dependent induction of apoptosis (granzyme B). Furthermore, it was recently reported that the hantavirus nucleocapsid protein stimulates Mdm2-dependent degradation of p53 [11]. Resisting cell death is an important hallmark of cancer, and loss of p53 function has been shown to promote lymphoma development [12]. Taken together, these observations suggest that hantaviruses are equipped with mechanisms that, at least theoretically, might be involved in carcinogenesis, an issue that remains to be further investigated.

All known carcinogenic viruses establish chronic infection, but they differ in how they induce cancer. The International Agency for Research on Cancer classifies the lymphoma-associated viruses EBV and HTLV-1 as direct carcinogens, whereas HCV and HIV-1 are indirectly carcinogenic—HCV infection causes chronic inflammation and HIV-1 infection mediates immune suppression in infected individuals [1]. Whether hantaviruses have any direct carcinogenic effect remains to be elucidated. Hantaviruses are zoonotic viruses that establish chronic infection in the natural hosts, rodents [3]. Chronic hantavirus infections in humans have never been described; however, the possibility has not been extensively investigated.

In summary, the present study demonstrates an increased risk for lymphoma following PUUV-associated HFRS. Future investigations of other HFRS- and HPS-causing hantaviruses should address if the association between HFRS and lymphoma is PUUV-specific or a general feature of disease-causing hantaviruses in humans. Furthermore, the possibility that other viruses within the Bunyaviridae family, and perhaps also other viruses causing hemorrhagic fever, are associated with lymphoma remains to be investigated. The possibility that hantaviruses have carcinogenic properties needs to be carefully considered.

### DISCUSSION

The finding that individuals diagnosed with PUUV-associated HFRS exhibit an increased risk of lymphoma is new. After being diagnosed with HFRS, in total 32 individuals were diagnosed with lymphatic/hematopoietic malignancies (International Classification of Diseases, Seventh Revision codes 200–205) whereas 26 were diagnosed with lymphoma (Table 1). Although there are indications that hantavirus-infected individuals can experience long-term negative health effects [3, 4], no association with cancer has previously been reported. Moreover, to the best of our knowledge, this is the first time that a virus of the Bunyaviridae family, and a virus causing hemorrhagic fever, has been associated with any form of cancer. The observed finding of an increased risk for lymphoma, and not for other forms of cancer, suggests the possibility that a causal link exists

### Table 1. Cancer Risk Following Diagnosis of Hemorrhagic Fever With Renal Syndrome

<table>
<thead>
<tr>
<th>Cancer Site (ICD-7 Code)</th>
<th>No. of Cases</th>
<th>Observed</th>
<th>Expected</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>359</td>
<td>377.8</td>
<td>0.95</td>
<td>0.85–1.05</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>58</td>
<td>53.2</td>
<td>1.09</td>
<td>0.83–1.41</td>
<td></td>
</tr>
<tr>
<td>Lung (162)</td>
<td>24</td>
<td>28.1</td>
<td>0.85</td>
<td>0.55–1.27</td>
<td></td>
</tr>
<tr>
<td>Breast (170)</td>
<td>39</td>
<td>42.4</td>
<td>0.92</td>
<td>0.65–1.26</td>
<td></td>
</tr>
<tr>
<td>Prostate (177)</td>
<td>95</td>
<td>87.4</td>
<td>1.09</td>
<td>0.88–1.33</td>
<td></td>
</tr>
<tr>
<td>Urinary system</td>
<td>26</td>
<td>27.4</td>
<td>0.95</td>
<td>0.62–1.39</td>
<td></td>
</tr>
<tr>
<td>Nonmelanoma skin cancer</td>
<td>10</td>
<td>25.7</td>
<td>0.39</td>
<td>0.19–0.72</td>
<td></td>
</tr>
<tr>
<td>Lymphoma (200–204.1)</td>
<td>26</td>
<td>15.0</td>
<td>1.73</td>
<td>1.13–2.54</td>
<td></td>
</tr>
<tr>
<td>Lymphoma, follow-up time, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>4</td>
<td>1.95</td>
<td>2.05</td>
<td>0.56–5.25</td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>13</td>
<td>7.22</td>
<td>1.80</td>
<td>0.96–3.08</td>
<td></td>
</tr>
<tr>
<td>5–9</td>
<td>7</td>
<td>4.25</td>
<td>1.65</td>
<td>0.66–3.39</td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td>2</td>
<td>1.58</td>
<td>1.27</td>
<td>0.15–4.57</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ICD-7, International Classification of Diseases, Seventh Revision; SIR, standardized incidence ratio.

[95% CI, .85–1.05]); however, and strikingly, the risk of developing lymphoma was significantly increased (SIR, 1.73 [95% CI, 1.13–2.54]). Except for a decreased risk of nonmelanoma skin cancer (SIR, 0.39 [95% CI, .19–.72]), the risk for other forms of cancer did not differ significantly between HFRS-diagnosed individuals and the general population (Table 1).

The highest risk for lymphoma occurred early after HFRS diagnosis (Table 1). The risk for lymphoma remained higher than expected during the entire time of follow-up, but decreased with time after HFRS diagnosis (Table 1).
Notes

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