Hepatitis C Virus (HCV) and non-Hodgkin lymphoma (NHL)
Outline

• Background
  – NHL
  – HCV
  – NHL and HCV
• Current Study
• Results
• Conclusions/Discussion
Lymphoma

• A cancer of the lymphatic system, specifically of lymphocytes.

• The lymphatic system, which is composed of the tissues and organs that produce and store cells that fight infection and disease, includes the bone marrow, spleen, thymus, lymph nodes, and a network of vessels that carry fluid and infection-fighting cells (lymphocytes).
Lymphoma

- Lymphomas fall into two categories: Hodgkin lymphoma (formerly referred to as Hodgkin’s Disease) and non-Hodgkin lymphoma (NHL).
- 90% of lymphomas are NHL
- NHL fall into 2 main categories: B-cell, T-cell
- In B.C., 85%-90% of NHL are B-cell
- There are many subtypes of NHL (29?).
Epidemiology of NHL

- In Canada (2001) estimated 6200 new cases
- In British Columbia (2001) 773 new cases
- Fifth most common cancer (after Lung, Prostate, Breast, Colorectal)
- More common in males (60%)
- Median age - 66
Non-Hodgkin's Lymphoma

Males

- **Incidence**
  - Relative rate (% log scale)
  - Year of diagnosis

- **Mortality**
  - Relative rate (% log scale)
  - Year of death

Females

- **Incidence**
  - Relative rate (% log scale)
  - Year of diagnosis

- **Mortality**
  - Relative rate (% log scale)
  - Year of death

Legend:
- All Ages with 95% CI
- Age 0-44
- Age 45-64
- Age 65+

Additional information:
- Age 0-44
- Age 45-64
- Age 65+

Cases with >10 cases per year

All Ages with 95% CI
Known Causes of NHL

- Immunosuppression
  - Congenital
  - Acquired (HIV/AIDS)
  - Therapeutic - transplant patients
- Familial/Genetic (RR=2-3)
Known Causes of NHL

- Microorganisms
  - Epstein-Barr Virus (Burkitt’s Lymphoma)
  - HTLV-1 (T-cell NHL)
  - Heliobactor Pylori Infection (Gastric Lymphoma)

- Vaccination and Medication
  - Bacillus Calmette-Guerin (BCG) Vaccination
  - Chemotherapy
  - Blood Transfusion
Other Possible Causes of NHL

- Occupation
  - Farmers/Pesticide
  - Organochlorines, Phenoxy Herbicides
- Animal Exposure
  - Meat workers
- Hair Dyes
- Radiation
Hepatitis C virus (HCV)

- Hepatitis C virus was first identified in 1989
- HCV is a major cause of chronic liver diseases including liver cirrhosis and liver cancer.
- 170 million people worldwide are infected & 3 to 4 million people are newly infected each year.
- Higher prevalence among developing countries (14% in Egypt), lower prevalence in Northern European countries (< 1%)
- Prevalence is higher in persons of low socioeconomic status and in those engaged in illicit drug use and high-risk sexual practices.
HCV and NHL

- HCV infection is strongly associated with various autoimmune phenomenon, including vasculitis and other skin changes, kidney, endocrine, and hematological disorders.
- HCV is a lymphotropic virus.
- HCV-antigens have been found in peripheral B- and T-lymphocytes, lymph nodes and lymphocytes infiltrating the liver.
- HCV is strongly associated with mixed cryoglobulinemia, a lymphoproliferative disorder that sometimes evolves into B-cell non-Hodgkin lymphoma.
Epidemiology of HCV and NHL

- First study showing association in 1994, recently several publications showing association.
- Studies in Southern Europe and Japan (high prevalence) have suggested an association.
- North American and Northern European studies have been primarily negative.
Epidemiology of HCV and NHL

• Ontario study (Collier, 1999)
  – 100 b-cell NHL cases – 100 other cancer controls
  – No cases and no controls were HCV+

• BC study (Shariff, 1999)
  – 88 b-cell NHL cases - 1085 health care workers
  – 2.3% cases and 1% of controls HCV+ (p>.05)
Current Study

• Main Hypotheses
  – Ultraviolet exposure
  – Organochlorine exposure
  – Immunological disease
  – Viral exposure
  – Genetic susceptibility
  – Gene-environment interactions
Current Study

• Study Design
  – Case-control study
  – 829 cases/848 controls
  – March 2000 – February 2004
  – GVRD & CRD
  – Age 20-70
  – HIV-

• For HCV analysis
  – 796 cases/697 controls
Current Study

• Postal Questionnaire
  – Family history
  – Residence and Vacation History
  – Host Factors - skin, hair, eye colour, moles
  – Usual Occupation
Current Study

- Computer Aided Telephone Interview
  - Demographic Information (ethnic origin, SES)
  - Medical History
    - Immunological diseases
    - Immunosuppressive medication
    - Allergies
    - Viruses
  - Exercise
  - Sun Exposure
  - Other (Hair Dye, Pets, Farming)
• Biological Sample (Blood or Mouthwash/Saliva)
  – Organochlorine and PCB levels
  – Virology (HCV, EBV?, SV-40?)
  – DNA
Current Study

• HCV testing recommended for all NHL patients in British Columbia
• Information not reliably recorded in BCCA databases
• Linkage with BCCDC HCV database
• HCV determination for 459 cases and 93 controls
Current Study

• Examine HCV antibodies in remaining subjects
  – April 2003 – 470 blood samples assessed
    National Microbiology Lab (NML) in Winnipeg
  – Nov 2005 – 565 blood samples assessed by BCCDC
# Replicated Test Results (NML & BCCDC)

<table>
<thead>
<tr>
<th></th>
<th>Non-Reactive (NML)</th>
<th>Reactive (NML)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non Reactive (BCCDC)</td>
<td>99</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Reactive (BCCDC)</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>99</td>
<td>5</td>
<td>104</td>
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</tbody>
</table>
# Overall Results

<table>
<thead>
<tr>
<th>HCV</th>
<th>Cases</th>
<th>Controls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>777</td>
<td>692</td>
<td>1469</td>
</tr>
<tr>
<td>Positive</td>
<td>19</td>
<td>5</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>(2.39%)</td>
<td>(0.72%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>796</td>
<td>697</td>
<td>1493</td>
</tr>
</tbody>
</table>

Odds Ratio = 3.29 (95% CI = 1.20, 9.02) p = 0.011
## Major NHL Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse large B-cell</td>
<td>194</td>
<td>24.4%</td>
</tr>
<tr>
<td>Follicular</td>
<td>212</td>
<td>26.6%</td>
</tr>
<tr>
<td>Other B-cell</td>
<td>312</td>
<td>39.2%</td>
</tr>
<tr>
<td>T-cell</td>
<td>78</td>
<td>9.8%</td>
</tr>
</tbody>
</table>
## B-cell lymphoma

<table>
<thead>
<tr>
<th>HCV</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>700</td>
<td>692</td>
</tr>
<tr>
<td>Positive</td>
<td>18 (2.51%)</td>
<td>5 (0.72%)</td>
</tr>
</tbody>
</table>

Odds Ratio = 3.42 (95%CI=1.24, 9.43) p=0.009
**Diffuse Large B Cell**

<table>
<thead>
<tr>
<th>HCV</th>
<th>Case</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>185</td>
<td>692</td>
</tr>
<tr>
<td>Positive</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>(6.09%)</td>
<td>(0.72%)</td>
</tr>
</tbody>
</table>

Odds Ratio = 9.32 (95%CI=3.13, 27.8) p<0.001
## B-cell Lymphoma by Ethnicity

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>HCV+/Total</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>17/630</td>
<td>3/570</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0/74</td>
<td>0/55</td>
<td></td>
</tr>
<tr>
<td>South Asian</td>
<td>0/27</td>
<td>1/27</td>
<td></td>
</tr>
<tr>
<td>Other/mixed</td>
<td>1/37</td>
<td>1/26</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1/28</td>
<td>0/19</td>
<td></td>
</tr>
</tbody>
</table>
Discussion

• First population based case-control study in Canada to confirm an association between HCV infection and NHL, particularly DLBC.

• Prevalence of HCV infection in the study controls in British Columbia was 0.7%; true HCV prevalence in BC may be as high as 1.5%.

• These results suggest that approximately 1.6%-3.3% of NHL and 5.6%-11.1% of DLBC in BC are related to HCV infection.
Discussion

- Mechanisms responsible for association remain unclear.
- Chronic stimulation of B-cells by HCV-antigens causes nonmalignant B-cell polyclonal expansion that may evolve into B-cell NHL.
- Association may depend on co-infection with other infectious agents (Epstein-Barr virus)
- Regression of B-NHL after anti-viral treatment points to cause-effect relationship.
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  – Pat Ostrow
  – Lynne Tse

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Limitations

- Case-control studies are unable to establish causation, nor can they determine if the exposure of interest (HCV infection) occurred before or after onset of disease (NHL).
- Approximately 25% of HCV infected people clear their infection spontaneously.
- The estimated median time of HCV infection the cases and controls in unknown, as are the percent of active infections.
- It is unknown if the duration of infection affects the risk of NHL.
Current Study

• HCV testing recommended for all NHL patients in British Columbia
  – Information not reliably recorded in CAIS
• Self report
• BCCDC clinical database (2003-2005)
  – June 2003 - approached BCCDC to obtain HCV results
    • June 2004 - HCV determination for 436 cases
    • May 2005 - HCV determination for 1690 cases
Current Study

• Examine HCV antibodies (2003-2005)
  – Using Enzyme Immunoassay, 2\textsuperscript{nd} & 3\textsuperscript{rd} ELISA
    • Sensitivity: 98.9\%, Specificity: 97.2\%
  – HCV infection positive (reactive): Bayer (signal >2)
  – Weakly reactive cases are confirmed by Abbott Architect
  – April 2003 – 468 blood samples sent to National Microbiology Lab (NML) in Winnipeg (EIA 3.0)
  – Nov 2005 – 579 blood samples sent to BCCDC for HCV determination (EIA 3.0)