# MORTALITY AMONG BRITISH COLUMBIANS TESTING FOR HEPATITIS C ANTIBODY, 1992-2004

by

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# ABSTRACT

**Background**: Hepatitis C virus (HCV) infection is a major preventable and treatable cause of morbidity and mortality. The ability to link records between population-based centralized laboratory HCV testing data and administrative databases has provided a unique opportunity to compare mortality and morbidity between HCV seronegative and seropositive individuals. Through the use of laboratory testing patterns and results, this study attempts to differentiate the viral effects of mortality due to HCV infection from risk behaviours/activities that are associated with acquisition of HCV infection.

**Methods**: Serological testing data at the British Columbia (BC) Centre for Disease Control from 1992-2004 were linked to the death registry at the BC Vital Statistics Agency. Four groups of HCV testers were defined by their HCV antibody (anti-HCV) testing patterns: single non-reactive (SNR); serial multiple tested non-reactive (MNR); reactive at initial testing (REAC); and seroconverter (previously seronegative followed by reactive, a marker for incident infection) (SERO). Standardized mortality ratios were generated to compare all-cause and disease specific mortality with the BC population. Time-dependent Cox proportional hazard regression was used to compare hazard ratios among HCV serological groups.

**Results**: Anti-HCV testers were found to have higher mortality than the BC population. Referent to the SNR group, the REAC group had higher risks for liver-related mortality (hazard ratio (HR): 9.71, 95% confidence interval (CI): 8.62-10.87) and drug-related mortality (HR: 13.51, 95% CI: 11.63-15.63). When compared to the REAC group, the SERO group had a lower risk for liver-related mortality (HR: 0.53, 95% CI: 0.24-0.92), but a higher risk for drug-related mortality (HR: 1.60, 95% CI: 1.20-2.08).

**Conclusions**: These findings confirm that anti-HCV positive testers have increased mortality due to chronic infection related to progressive liver disease, and that a substantial proportion of the mortality is attributable to drug use and risk behaviours/activities associated with HCV acquisition. Mortality reduction in HCV infected individuals will require comprehensive prevention programming to reduce the impact of mental health and problematic substance use behaviours/activities which relate to HCV acquisition, as well as HCV treatment to prevent progression of chronic liver disease.

# PREFACE

The HCV mortality study is a secondary analysis of existing data which was previously linked for project Krajden 04-017 (UBC REB H04-70266: Mathematical modeling for hepatitis C virus infection public policy development). The HCV mortality study has been approved by the principle investigator of the Krajden 04-017 study, Dr. Mel Krajden; the data steward for the British Columbia Centre for Disease Control, Dr. Robert Brunham; and the academic supervisor, Dr. John Spinelli. All researchers have signed the required schedule B - pledge of confidentiality for the Krajden 04-017 project. The HCV mortality study was approved by the clinical ethical review board at the University of British Columbia/British Columbia Cancer Agency in December, 2008 and renewed in November, 2010 (UBC REB: H08-03034: HCV mortality and cancer incidence). There is no publication arising from work presented in the dissertation. All work presented in this thesis was conceived, instrumented, written and disseminated by the Master's student.

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# LIST OF ABBREVIATIONS

anti-HCV: Hepatitis C antibody
BC: British Columbia
BCCDC: British Columbia Centre for Disease Control
BCLHD: BC Linked Health Database
CHSPR: Centre for Health Services and Policy Research
CI: Confidence interval
CIHI: Canadian Institute for Health Information
DAD: Discharge Abstract Database
EIA: Enzyme immunoassay
EPHN: Encrypted personal health number
HCC: Hepatocellular carcinoma
HBV: Hepatitis B virus
HCV: Hepatitis C virus
HIV: Human immunodeficiency virus
HR: Hazard ratio
ICD: International Classification of Diseases
IDU: Injection drug use
IM/IT: Information Management/Information Technology
MNR: Serial multiple tested anti-HCV non-reactive
MoH: BC Ministry of Health Services
MSP: Medical Services Plan
NHL: Non-Hodgkin lymphoma
PCR: Polymerase chain reaction
PDBC: Population Data BC
PHN: Personal health number
PHSA: Provincial Health Services Authority
PY: Person-years
REAC: anti-HCV Reactive at initial testing
RIBA: Recombinant immunoblot assay
RNA: Ribonucleic acid
SERO: Seroconverter
SMR: Standardized mortality ratio
SNR: Single anti-HCV non-reactive
UBC: University of British Columbia
UBI: United Biomedical Inc
UCOD: Underlying cause of death

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## DEDICATION

*To my parents, with love*

# 1 Introduction

## 1.1 Purpose

Hepatitis C virus (HCV) infection is an important public health issue as it is associated with significant morbidity and mortality world wide.[1-3] Approximately 3% of the global population, or 170 million people, are HCV infected.[1, 3, 4] It is estimated that 243,000 to 300,000 Canadians are infected with HCV, of whom, 60,000 are British Columbians.[5-7] Within the first 6 months after HCV infection, a person is considered as acutely infected. Persistence of HCV for greater than 6 months indicates progression to chronic HCV infection. About 25% (range from 15% to 45%) of infected individuals will spontaneously clear the virus within 6 months (typically within 12 to 14 weeks), the remaining 75% (range from 55% to 85%) will become chronically infected.[8, 9]

HCV is a leading cause of end stage liver disease and liver cancer.[10-13] If left untreated, chronic HCV infected individuals may develop progressive liver disease such as cirrhosis (late stage of hepatic fibrosis), end stage liver disease, hepatocellular carcinoma or require liver transplantation.[1, 14-16] Approximately 10% to 15% of HCV infected individuals will develop cirrhosis during the first 20 years after infection.[11] The probability of cirrhosis by 30 years after infection is much higher, at 41%.[17] About 1% to 5% HCV infected individuals will develop hepatocellular carcinoma within 20-30 years of infection.[10] End stage liver disease caused by HCV infection represents the primary reason for liver transplantation in Western Europe and North America,[1, 14-16] with the five-year survival rate at 69% to 72% after transplantation.[18] The goal of this study was to estimate the HCV-attributable disease burden by examining the all-cause and disease

specific mortality among individuals who underwent serological testing for HCV in the Province of British Columbia (BC), Canada.

While it is generally known that HCV infection is a major preventable and treatable cause of morbidity, mortality, and economic burden, to accurately describe the burden of HCV infection on the BC population has been challenging. Acute HCV infection itself is not associated with significant morbidity or mortality; only one third of acutely infected individuals develop symptoms or jaundice, and deaths due to acute infection are extremely rare.[19] Chronic HCV infection results in progressive liver disease and extrahepatic related morbidity and mortality, but this typically requires decades to manifest.[20-24] Most new HCV infections occur in people who inject drugs whose risk behaviours/activities may result in mortality unrelated to HCV viral infection.[20-23] For this population, the risk of dying from drug-related causes is significantly greater than from liver-related causes.[20-23]

Through the use of laboratory testing patterns and results, this study attempts to differentiate the mortality due to the viral effects of HCV infection from risk behaviour/activity related mortality. Understanding and being able to differentiate the factors that affect HCV mortality due to HCV viral factors versus risk behaviours/activities that lead to acquisition of HCV (e.g., injection drug use (IDU), high-risk sexual activity which can also lead to HIV infection, drug overdose and other drug-related mortality) can provide important information to inform prevention, care and treatment programs for at-risk populations.

There are a few large cohort mortality studies in persons with HCV in the published literature,[20, 21, 23] but none have assessed the relationship to serological status at

the time of diagnosis. This is largely due to the lack of comprehensive serological information. In BC, we are fortunate to have provincial population-based centralized laboratory testing data which has enabled us to longitudinally track testing patterns and results of individuals who undergo HCV testing in BC.

When an individual is infected with HCV, antibody to HCV (anti-HCV) typically develops within 5 to 10 weeks after infection and anti-HCV will remain detectable for decades.[25-28] Anti-HCV testing is typically limited to individuals who might have some risk factors for HCV acquisition or signs and symptoms consistent with liver disease.[29] Thus, individuals who might be tested for anti-HCV only once and are anti-HCV negative, may have some a priori risks such as a history of a blood product transfusion prior to 1990, but such individuals are unlikely to have ongoing risks of HCV infection. In contrast, individuals who undergo serial testing likely have ongoing risks for infection, signs and/or symptoms compatible with liver disease, and/or see various providers who ordered duplicate tests. Examples of symptoms compatible with liver disease include fatty liver disease, autoimmune hepatitis, alcoholic liver disease where HCV infection is in the differential diagnosis of clinical or hepatic abnormalities. Therefore, individuals who are tested for anti-HCV on numerous occasions represent a heterogeneous group of persons who might either be at ongoing risk of HCV infection or of liver disease from any cause. Individuals who are anti-HCV reactive on their first test have been infected but we are unable to determine the timing of their infection. They may be tested due to symptoms or signs of liver disease or because of risk factors. A seroconverter is defined as an individual who demonstrates an anti-HCV non-reactive test result(s) in the past and on the follow up testing is shown to be anti-HCV reactive. This confirms an incident

infection, but the precise time of infection is unknown. The infection likely occurred sometime between the prior non-reactive test result and the current reactive test result.

Longitudinal HCV testing data are contained in the BC Centre for Disease Control (BCCDC) Public Health Microbiology and Reference Laboratory dataset.[30] This HCV laboratory dataset was linked to the BC Ministry of Health Services (MoH) Registration and Premium Billing files[31, 32] for age and gender information, and the BC Vital Statistics Agency[33, 34] to obtain the underlying cause of death information. The longitudinal testing data contained within the linked dataset provides a unique opportunity to compare mortality between HCV seronegative versus seropositive individuals as well as in individuals who seroconverted in BC. Findings from this work will help contribute to our understanding of the population burden of HCV as well as provide estimates of the HCV-attributable disease burden related to risk behaviours versus HCV viral-related sequelae. This information can assist decision-makers to develop rational prevention, care, and treatment strategies and prioritize interventions to help reduce the burden of HCV infection.

## 1.2 Research objectives

**The primary study objectives are:**

1. To compare all-cause and disease specific mortality among HCV serological groups (single non-reactive, serial multiple tested non-reactive, reactive at initial testing, and seroconverters. See section 3.7.2).
2. To compare the mortality of HCV seronegative individuals to that of the general BC population.

**Key research questions:**

1. Do individuals who are anti-HCV reactive at initial test have a higher risk of death from liver-related causes than seroconverters?
2. Is death from drug-related causes more likely to occur in seroconverters than in individuals whose anti-HCV is reactive at initial testing?
3. Do HCV seronegative individuals have an increased risk of mortality compared to the general population of BC?

## 1.3 Following sections

This thesis is comprised of five chapters. The first chapter introduces the research objectives of the study. Background information about HCV is discussed in detail in Chapter 2; this includes a description of liver function, symptoms and signs of liver disease, background on HCV infection, the epidemiology and risk factors for HCV infection, and how HCV infection is diagnosed. Chapter 2 ends with a synthesis of the published literature on the association of HCV infection and mortality. Chapter 3 provides the study methodology, including the study design, data sources, data linkage methodology, definitions of a priori mortality end points, eligibility criteria, and data quality issues due to the use of administrative data for secondary analysis. Statistical methods for determining the standardized mortality ratios and the use of time dependent Cox proportional hazards model are described in Chapter 3. In addition, sample size and ethical considerations are presented in Chapter 3. Two sets of results are presented in Chapter 4, standardized mortality ratios and hazard ratios. The final chapter contains the discussion and conclusions and compares our study results relative to the existing

literature. This chapter also provides an overview of the study strengths, limitations and highlights gaps in current knowledge which is relevant for future research.

# 2 Background

## 2.1 The liver

The liver is the largest and one of the more complex solid organs in the body. It is located below the diaphragm and behind the ribs, in the upper right side of the abdominal cavity. It is about the size of a football and weights about 1.5 to 2 kilograms.[35, 36] The liver has vascular, secretory/excretory and metabolic functions.[35, 36] First, the liver serves as a blood reservoir, storing extra blood which can be quickly released when required. It also filters harmful biochemical products such as bilirubin, a yellow product formed from the breakdown of red blood cells. Second, the liver makes bile which is stored in the gall bladder and drains into the small intestine to help break down fats. Third, the liver metabolizes proteins, fats and carbohydrates in order to provide energy and nutrients to the body. Other functions include storage of vitamins and iron, synthesis of blood clotting proteins, and detoxifying harmful substances such as toxins, drugs and alcohol.[35, 36] A functional liver is required for survival.

## 2.2 Symptoms of liver disease

Symptoms of liver disease can sometimes be mild and nonspecific; for example, acute HCV infection can present with flu-like symptoms such as headache, fatigue, nausea, depression, loss of appetite and muscle aches and pains.[35, 36] Signs and symptoms of liver disease include: cirrhosis, edema, ascites, jaundice, bleeding or easy bruising, dilated vessels, spider angioma, red palms, encephalopathy and muscle wasting.[35, 36] Cirrhosis refers to fibrosis (scarring) of the liver which might be due to alcoholic liver

disease, non-alcoholic liver diseases or chronic viral hepatitis infection. Albumin, the main protein of blood plasma, is made in the liver. When the liver is unable to produce sufficient albumin or when the serum albumin gets too low, edema and ascites can occur. Edema is a medical term for the accumulation of fluid in the extravascular compartments of the legs or other dependent tissues. Ascites is a medical term for the accumulation of fluid in the abdominal cavity. When the liver is unable to properly metabolize or secrete bilirubin in bile, jaundice (yellow pigmentation), can be found in the whites of the eyes and in the skin. Bleeding or easy bruising can occur when the liver is unable to make enough blood clotting proteins. Dilated vessels can occur from obstructed blood flow through the portal vein. Dilated vessels occur when the blood is diverted to the smaller blood vessels surrounding the liver. Both spider angioma and red palms (palmar erythema) result from compromised detoxification of estrogen, resulting in higher estrogen levels. Encephalopathy (confusion and loses of consciousness) results from a build up of toxic substances that are usually filtered or metabolized by the liver, which compromises brain function. Muscle wasting occurs as a result of liver's inability to metabolize proteins.

## 2.3 Background on HCV infection

Hepatitis refers to inflammation of the liver, with the word derived from "hepat-" and "-itis" referring to the liver and inflammation respectively. Viral hepatitis is the clinical term referring to forms of hepatitis which are caused by viruses that preferentially replicate in liver tissue. There are five common types of viral hepatitis, hepatitis A, B, C, D and E.[36] Both hepatitis A and hepatitis E are enterically transmitted. Hepatitis D requires prior or simultaneous infection with hepatitis B virus (HBV). HBV infection is

mostly transmitted through unprotected sexual contact or from mother to neonate. With the successful implementation of universal hepatitis B immunization programs recommended by the World Health Organization since 1992, the incidence of HBV infection has dramatically decreased.[37, 38] Consequently, the future global burden of HBV infection will decrease significantly over the coming decades.

The illness due to HCV infection was initially referred to as non-A and non-B hepatitis. The agent was first characterized in 1989.[39, 40] HCV belongs to the Flaviviridae family and it is a blood borne RNA virus primarily infecting liver hepatocytes that results in an inflammatory liver disease.[8, 39-41] The incubation period, from the time of HCV infection until the onset of symptoms, usually takes about 3 to 20 weeks. Only one third of the infected individuals are symptomatic during the acute infection period.[19] After infection, HCV RNA in serum will be detectable within 1 to 2 weeks of exposure; anti-HCV typically develops within 5 to 10 weeks after infection and generally remains detectable for decades.[8, 29] Within the first 6 months after HCV infection, a person is considered as acutely infected. Persistence of HCV infection is based on the presence of detectable HCV RNA in plasma or serum for greater than 6 months, and this confirms chronic HCV infection. About 25% (range from 15% to 45%) of infected individuals will spontaneously clear the virus within 6 months (typically within 12 to 14 weeks), the remaining 75% (range from 55% to 85%) will remain chronically infected.[8, 9]

HCV infection is potentially treatable, and numerous new therapies are under development.[42] The standard of care is to use combination antiviral therapy, pegylated interferon and ribavirin, which has been approved for use in British Columbia since June, 2003.[43] After completion of HCV antiviral therapy, if patients have achieved sustained

virological response (i.e., HCV RNA is not detectable by using the polymerase chain reaction (PCR) test 6 months after treatment is completed), this implies that the HCV has been cleared, and the patient is considered to be virologically cured of their HCV infection. The cure rate is genotype dependent (genotypes represent viral sequence variants). For patients with genotype 1, they are less likely to respond to the treatment and require a longer treatment duration; the cure rate is about 42% to 46% after 48 weeks of treatment. For genotypes 2 and 3 patients, they are more likely to respond to the treatment and require shorter duration of treatment; the cure rates are 72% to 80% after 24 weeks of treatment.[39, 43-47] Although overall approximately 50% of patients achieve sustained virological response after antiviral therapy of HCV,[45] the rate of treatment is low relative to the HCV prevalence.[43] No vaccine against HCV is currently available. Given the high rate of HCV envelope protein mutations, vaccines have proven challenging to design.[3, 48, 49]

HCV infection is a leading cause of end stage liver disease and liver cancer.[10-13] If left untreated, HCV infected individuals may develop progressive liver disease such as cirrhosis (late stage of hepatic fibrosis), end stage liver disease, hepatocellular carcinoma or require liver transplantation. Approximately 10% to 15% HCV infected individuals will develop cirrhosis during the first 20 years after infection.[11] The probability of cirrhosis by 30 years after infection is much higher, at 41%.[17] About 1% to 5% will develop hepatocellular carcinoma within 20-30 years of infection.[10] End stage liver disease caused by HCV infection is the major cause for liver transplantation in Western Europe and North America,[1, 14-16] with the five-year survival rate at 69% to 72% after transplantation.[18] Overall mortality related to HCV infection is estimated to be

approximately 5% to 7%.[20, 50] The associated health care costs attributable to HCV infection in Canada have been estimated at $500 million per annum, and was projected to reach one billion in 2010.[51]

## 2.4 Epidemiology of HCV infection

Hepatitis C is a global health problem affecting approximately 170 million people worldwide.[1, 3, 4] The HCV prevalence varies widely in different geographic regions. Countries in Africa and Asia have higher HCV prevalence, and industrialized regions like Oceania, North America, and Northern and Western Europe have lower prevalence.[3] Some low HCV prevalence countries include Germany (0.6%), Canada (0.8%), India (0.9%), France and Australia (1.1%); slightly higher HCV prevalence are found in the United States (1.8%), Indonesia (2.1%), Japan (1.5%-2.3%) and Italy (2.3%). Pakistan has a high HCV seroprevalence at 2.4% to 6.5% and China has reported a high HCV seroprevalence of 3.2%.[3] The highest prevalence of anti-HCV infection is in Egypt at 15% to 20%.[52] An estimated 500,000 or more individuals are newly infected with HCV per year in Egypt.[53] This is due to contamination of blood supply and historic use of unsafe needle practices.[52] Iatrogenic transmission is the primary underlining exposure to the ongoing transmission in Egypt.[53]

In Canada, an estimated 243,000 to 300,000 individuals are infected with HCV, and about 3,200 to 5,000 newly infected cases each year.[6] An estimated 65,000 British Columbians are chronically infected with HCV with about 2500 newly reported cases each year.[5] The national rate is about 40 per 100,000 population and the BC provincial reported rate in 2009 was 54.9 per 100,000 population.[5] Both the national and BC provincial reported rate of HCV infection have been declining. However, HCV

prevalence and incidence in BC are among the highest in Canada. This is linked to the high prevalence of IDU in BC.[7, 51, 54] Current surveillance data confirm that most newly acquired infections occur in IDUs and ongoing transmission in this population will account for much of the future burden of HCV infection in BC.[2, 27, 55] Despite a declining incidence of new infections, the burden of disease, both in terms of mortality and in terms of cost, is expected to increase over the next decade as individuals who are already infected age and go on to develop progressive liver disease.[1]

## 2.5 Risk factors for HCV infection

HCV is a blood borne virus that has been transmitted via blood products prior to wide-spread implementations of blood donor screening for anti-HCV. Other sources of transmission are IDU, blood transfusion if donors are not screened for anti-HCV, sexual exposure, occupational, perinatal, body piercing and tattooing.[1, 3, 7, 13-15, 56, 57]

IDU is the primary route of transmission in the United States, which accounts for 60% of HCV transmission and nearly 90% of new HCV infections.[48, 58] Transmission due to IDU is also the primary route of transmission from shared usage of contaminated needles and syringes in Canada.[7, 59, 60] Incarceration is considered as a high risk for HCV infection. When IDU occurs in the correctional facilities, it is at much higher risk because clean needles and syringes are not available. Thus, among IDUs, sharing contaminated needles and syringes is very common in the correctional facilities.

Prior to 1990, there was no routine screening of blood donors for HCV, thus, recipients of blood products or organs were at high risk of acquiring HCV infection. Since then, blood donor testing for HCV has virtually eliminated transfusion related HCV infections.[14] Depending on the level of HCV viral load, some intermediate risks of

acquiring HCV infection include maternal-infant transmission which estimated to be approximately 5% to 6%,[61] and about 2% for occupational needle stick injuries[62, 63]. Other risks include unprotected sex, receiving acupuncture and electrolysis with unsterilized needles, receiving body piercing and tattooing with contaminated instruments, sharing crack pipes to smoke crack, and sharing straws to snort cocaine or other drugs.[1, 48, 56, 58]

## 2.6 Association of HCV infection and cancer

Chronic HCV infection is also known to be associated with the risk of liver cancer (hepatocellular carcinoma, HCC) and non-Hodgkin lymphoma (NHL).[57, 64-66] HCV increases HCC risk by promoting fibrosis. In a meta-analysis of 21 case-control studies, HCC risk was increased 17-fold in HCV-infected patients compared with HCV-negative controls.[67] Sufficient evidence is available to conclude that chronic infection with HCV is associated with the development of NHL, especially B-cell lymphoma.[66, 68, 69] A recent population-based case-control study in BC has found that the risk of NHL is approximately three times greater in HCV seropositive individuals compared to seronegative individuals.[70] HCV has been considered as carcinogenic to humans for NHL in the International Agency for Research on Cancer monograph published on Lancet oncology in April, 2009.[64]

## 2.7 Association of HCV infection and type II diabetes mellitus

Chronic HCV infection is also known to be associated with type II diabetes mellitus. An increased prevalence of diabetes mellitus among HCV infected individuals has been reported in cross-sectional, case-cohort, case-control and community-based

longitudinal studies.[71-75] Shintani et al. has confirmed HCV core protein induces insulin resistance in HCV transgenic mice.[76] Since the liver plays a central role in carbohydrate metabolism, blood glucose homeostasis, and hormone (e.g., insulin) regulation, hepatocyte dysfunction can result in an inability of insulin to stimulate glucose uptake and utilization, and thereby inhibit hepatic glucose production (i.e., insulin resistance).[74, 77] As a result, diabetes may occur more often in HCV infected individuals due to glucose intolerance and insulin resistance.[74, 77] Another factor is that obesity is associated with insulin resistance. Obesity is also associated with non alcoholic fatty liver disease and leads to elevated liver function tests.[78, 79] This can result in testing for viral hepatitis agents, such as HCV infection, which are known to cause elevated liver function tests.

## 2.8 HCV antibody testing

Diagnostic testing has changed over time in BC and this might affect HCV diagnosis over the study period. Testing methods used in BC during the study period are described as follows. Anti-HCV reactivity was determined using the following primary commercial antibody assays: May, 1992 to September, 1993: Organon Teknika (United Biomedical Inc, UBI) v2.0; October, 1993 to July, 1994: Organon Teknika (UBI) v 2.1; August 1994 to March 1997: Organon Teknika (UBI) v4.0; April, 1997 to February, 2005: Abbott AxSYM HCV 3.0; March, 2005 to December, 2005: ADVIA Centaur aHCV (Bayer, Canada). From May, 1992 to April, 1997 reactive specimens were confirmed with supplemental testing by the second or third generation recombinant immunoblot assay (RIBA). As of April, 1997, in lieu of supplemental immunoblot testing for confirmation, all anti-HCV screen reactive specimens underwent secondary enzyme immunoassay (EIA) testing using another manufacturer's EIA: from April, 1997

to July, 1999 specimens reactive by Abbott AxSYM HCV 3.0 were retested by Organon Teknika (UBI) v4.0; from August, 1999 to February, 2004, specimens reactive by Abbott AxSYM HCV 3.0 were retested by Ortho EcI (Ortho, Canada); from March, 2005 to December, 2005, specimens reactive by ADVIA Centaur aHCV (Bayer, Canada) were retested by Architect anti-HCV (Abbott, Canada). Specimens confirmed by immunoblot or reactive by two manufacturers' EIAs were considered to be anti-HCV reactive. An anti-HCV equivocal categorization was assigned when immunoblot test results were indeterminate or when only one EIA was reactive.

Anti-HCV testing patterns and results have been used to classify subject risk groups.[29, 47] Anti-HCV testing is typically limited to individuals who might have some risk factors for HCV acquisition or signs and symptoms consistent with liver disease.[29] Thus, individuals who might be tested for anti-HCV only once and are anti-HCV negative, may have some a priori risks such as a history of a blood product transfusion prior to 1990, but such individuals are unlikely to have ongoing risks of HCV infection. In contrast, individuals who undergo serial testing likely have ongoing risks for infection, signs and/or symptoms compatible with liver disease, and/or see various providers who ordered duplicate tests. Examples of symptoms compatible with liver disease include fatty liver disease, autoimmune hepatitis, alcoholic liver disease where HCV infection is in the differential diagnosis of clinical or hepatic abnormalities. Therefore, individuals who are tested for anti-HCV on numerous occasions represent a heterogeneous group of persons who might be at ongoing risk of HCV infection or of liver disease from any cause. Individuals who are anti-HCV reactive on their first test have been infected but we are unable to determine the timing of their infection. They may have been tested due to

symptoms or signs of liver disease or because of risk factors. A seroconverter is defined as an individual who demonstrates an anti-HCV non-reactive test result(s) in the past and on the follow up testing is shown to be anti-HCV reactive. This confirms an incident infection, but the precise time of infection is unknown. The infection likely occurred sometime between the prior non-reactive test result and the current reactive test result.

## 2.9 Literature review: Association of HCV infection and mortality

Medline was used to search for articles published between 1 January 1989 (when HCV was first identified) to 25 October 2010, by means of the MeSH and non-MeSH terms: 'hepatitis C chronic, hepatitis C, hepatitis C virus, or HCV' and 'mortality' in combination with the keywords 'cohort studies', 'community-based', 'population-based', or 'linkage'. Additional relevant studies were identified in the reference lists of selected articles and authors. Only articles published in English were included. Study designs included in the review were population-based, community-based, and cohort studies. Standardized mortality ratios (SMRs) calculated by comparing the HCV positive/reactive category to the general population, or hazard ratios (HRs) calculated by comparing the HCV positive/reactive category to the HCV negative/non-reactive category must have been reported in order to be included in the review.

The association between HCV infection and mortality has been examined mostly in HCV and HIV co-infected individuals, or in HIV sub-populations.[80-83] However, the association between HCV infection and mortality has not been explored in great detail in large population-based cohort studies. Eleven population-based and community based cohort studies were identified. These 11 studies were conducted from all over the world, including Osella et al. (2000) from Southern Italy,[50] Harris et al. (2006) from UK,[84] Amin

et al. (2006) from Australia,[20] Neal et al. (2007) from England,[85] Duberg et al. (2008) from Sweden,[21] McDonald et al. (2008) from Scotland,[23] Uto et al. (2009) from Japan,[86] Prasad et al. (2009) from Switzerland,[87] Grebely et al. (2009) from Canada,[88] Kirstiansen et al. (2010) from Norway,[22] and Omland et al. (2010) from Denmark[89]. A summary of the study population, type of study, length of study follow-up, methodology used to obtain mortality information, as well as findings and implications are described below for each study.

The first prospective population-based cohort study was conducted in Southern Italy to determine the effect of HCV infection on overall and liver-related mortality by Osella et al. (2000).[50] The cohort consists of 2,472 individuals randomly drawn from the electoral register of 1981 Census in Castellana Grotte, a town of 17,334 residents. The follow up period was from 1985 to 1996. HCV infection was reported in 511/2,472 (21%) individuals. The cause of death information was obtained from reviewing hospital records, death certificates, and interviewing general practitioners. For HCV infected individuals, the crude all-cause mortality rate was 7.7 per 1,000 person years (95% Confidence Interval (CI): 6.7-8.8) and the crude liver-related mortality rate was 0.9 per 1000 person years (95% CI: 0.3-2.2). After adjusting for age, sex and daily alcohol intake, the incidence rate ratios of HCV positive versus HCV negative individuals for all-cause and liver-related mortality were 2.4 (95% CI: 1.8-3.3) and 43.9 (95% CI: 10.5-183.9), respectively. Osella et al. suggested that in order to implement effective prevention strategies for those at high risk of HCV infection, different causal pathways should be assessed for the underlying causes of acquiring HCV infection.

Harris et al. (2006) examined the excess mortality attributable to HCV infection in a cohort of transfusion recipients.[84] The study period was 16 years. One thousand three hundred ninety nine (1,399) individuals were eligible for the study, of whom, 924 were HCV infected transfusion recipients (anti-HCV positive) and 475 were anti-HCV negative transfusion recipients. The cause of death information was obtained from death certificates. The Cox proportional hazard model adjusting for age and sex was used to calculate hazard ratios to compare the excess risk in morality among anti-HCV positive individuals to anti-HCV negative individuals. For all-cause mortality, no excess mortality was found in the anti-HCV positive individuals when compared to the anti-HCV negative individuals (HR=1.2, 95% CI: 0.9-1.5). However, the hazard ratio for liver-related mortality was about three times higher in the anti-HCV positive individuals when compared to the anti-HCV negative individuals (HR=2.7, 95% CI: 1.1-6.8).

Amin et al. (2006) assessed the excess risk of mortality in individuals diagnosed with hepatitis B and/or hepatitis C infection in New South Wales, Australia, from 1990 to 2002.[20] It was the first data linkage study to examine mortality in a large community based setting. In this study, all newly laboratory diagnosed hepatitis B and hepatitis C cases from the New South Wales Health Department Notifiable Disease Database were probabilistically linked to the registered death records from the Australian National Death Index. SMRs were calculated to compare the excess risk of all-cause and disease specific mortality in individuals diagnosed with hepatitis B and/or hepatitis C infection with the general population of New South Wales. 75,834 individuals were reported to be mono-infected with HCV. The risk of all-cause mortality was elevated in the HCV mono-infected individuals when compared to the general population (SMR=3.1, 95% CI: 3.0-

3.2). The SMRs for liver-related and drug-related mortality were 16.8 (95% CI: 15.4-18.3) and 19.3 (95% CI: 18.1-20.5), respectively. Other important findings for this study were 1) young people with hepatitis C infection have a higher mortality risk from ongoing drug use rather than from the viral infection, and 2) older patients with chronic HCV infection had a high risk of death from liver-related mortality or liver cancer.

Tacke et al. (2006) discussed how the findings from Amin et al. could be applied in clinical practice and made some recommendations.[90] Given young individuals with HCV infection died disproportionately from drug-related causes, and older individuals with chronic HCV infection mostly died from liver-related mortality, Tacke et al. suggested that different intervention and prevention programs should be targeted differently in people with different risk behaviours/activities of acquiring HCV. For example, it would be beneficial medically and economically to primarily focus on harm reduction programming in young people. However, anti-viral treatment should be targeted for older HCV infected individuals who have been shown to have a high risk of death from end stage liver diseases and liver cancer.

In 2007, a mortality study was published by Neal et al. in England to explore predictors of all-cause and liver-related mortality in the Trent hepatitis C cohort.[85] The study design was a prospective cohort where 2,285 hepatitis C infected individuals were enrolled in the study from 1992 to 2005, and followed for 1 year or longer. Death information was obtained from the participating clinics and from the National Health Service Central Register which contains deaths, cancer registrations, and emigrations for all residents of England and Wales. SMRs were calculated to compare the mortality rate in the HCV infected individuals with the general population of England. Cox regression

was used to identify predictive factors for all-cause and liver-related mortality. The SMR for all-cause mortality in males and females were 3.0 (95% CI: 2.3-4.2) and 3.0 (95% CI: 2.0-6.3), respectively. Among individuals infected with HCV, statistically significant predictors for all-cause mortality were age, sex, HCV treatment and fibrosis. However, age, HCV treatment, fibrosis and alcohol consumption were found to be predictive factors for liver-related mortality. The findings from this study were similar to the findings from Amin et al. (2006). This study also demonstrated that older individuals were dying from liver-related causes and younger individuals were at increased risk of dying from their risk activities associated with the acquisition of HCV.

Two population-based mortality studies were published in 2008 among HCV infected individuals, a Swedish study by Duberg et al.,[21] and a Scottish study by McDonald et al.[23] Similar to the large Australian community based record linkage study described previously, both studies involved nationwide record linkage. In both studies, laboratory diagnosed hepatitis C cases were linked to the underlying cause of death information from the national cause of death register. The difference between the two studies was the record linkage methodology. In the Swedish study, deterministic linkage was performed because a Swedish national unique personal identifier exists for every resident and this was used to link across difference databases. For the Scottish study, there was no unique identifier available for each person. Therefore, probabilistic record linkage was used to link the laboratory testing records with cause of death information based on a probabilistically weighted combination of last name soundex, first name initial, date of birth, gender and postal code.

Duberg et al. (2008) conducted a nationwide community cohort study to examine all-cause and disease specific mortality in individuals infected with hepatitis B virus (HBV) and/or HCV in Sweden, from 1990 to 2003.[21] In Sweden, communicable cases of hepatitis B (since 1969) and hepatitis C (since 1990) diagnosed by clinicians and laboratories are obliged to report to the Swedish Institute for Infectious Disease Control notification database by law. This notification database was linked to the Cause of Death Register at the National Board of Health and Welfare to obtain the underlying cause of death information. There were 34,235 eligible HCV mono-infected individuals in the study. The mean observation time was 6.3 years. Referent to the Swedish population, the SMRs in HCV mono-infected individuals for all-cause mortality, liver-related mortality, mortality related to mental illness due to alcohol and drugs, and external causes mortality were 5.8 (95% CI: 5.6-6.0), 35.5 (95% CI: 32.9-38.3), 20.7 (95% CI: 18.9-22.7) and 12.4 (95% CI: 11.7-13.1), respectively. The SMR for viral hepatitis mortality was 133 times higher in individuals mono-infected with HCV than the general Swedish population (95% CI: 114.3-153.9). Referent to the general Swedish population, the SMR in HCV mono-infect individuals for deaths due to HIV infection was also found to be very high (SMR=41.2, 95% CI: 31.4-53.2). Findings from this study highlighted the need of having intervention strategies to reduce the risk of IDU related HCV acquisition.

McDonald et al. (2008) examined all-cause, liver-related and drug-related mortality among HCV mono-infected and HCV/HIV co-infected individuals in Scotland.[23] Reported HCV and HIV infected cases from Health Protection Scotland were probabilistically linked to the mortality data from the General Register Office for Scotland. Of 20,163 individuals diagnosed with HCV from 1991 to 2005, a total of

17,954 HCV infected individuals were eligible for the analysis. Four percent of individuals were co-infected with HIV and 62% of individuals were identified as having an IDU risk. Mortality related to liver cancer had the highest SMR in mono-infected HCV individuals when compared to the general Scottish population (SMR=51.0, 95% CI: 39.4-64.8). Referent to the general Scottish population, the SMRs for all-cause, liver-related and drug-related moralities were 4.9 (95% CI: 4.6-5.1), 20.0 (95% CI: 17.9-22.2), 23.5 (95% CI: 21.3-25.7), respectively in mono-infected HCV individuals. The SMR for all-cause mortality in HCV/HIV co-infected individuals was substantially higher when compared to the Scottish general population (SMR=32.9, 95% CI: 29.2-37.0). Referent to the general Scottish population, the SMRs for liver-related and drug-related morality were 34.8 (95% CI: 23.3-50.0), 36.6 (95% CI: 25.2-51.4), respectively in HCV/HIV co-infected individuals. Their research demonstrated a need for considering HIV co-infection status and IDU history when developing interventions for individuals infected with HCV.

In 2009, three cohort studies were published to examine the association between mortality and HCV infection. The three published studies in 2009 were either not population-based or were based on small numbers. All three studies examined mortality among HCV infected individuals in a sub-population. In the first study, an hyperendemic region for HCV infection in Japan was examined by Uto et al.[86] The second study by Prasad et al. looked at a hospital-based cohort in Switzerland.[87] In the third study, Grebely et al. focused on a community-based study of inner city residents in British Columbia, Canada.[88]

Uto et al. conducted a community-based, prospective cohort study in a small town known to be hyperendemic for HCV infection in the mid-western Miyazaki Prefecture in Japan.[86] A total of 1,125 HCV seropositive individuals were followed up from 1995 to 2005. HCV seropositive individuals were categorized into two groups: 1) individuals who were persistently infected with HCV (HCV carriers) and 2) individuals who have had a prior HCV infection (HCV noncarriers). HCV carriers were defined as individuals had a detectable HCV core antigen and/or a detectable HCV RNA. HCV noncarriers were defined as individuals whose HCV core antigen and HCV RNA were both non-detectable. There were 758 (67%) HCV carriers in the study. Cause of death was obtained from the death certificates. The Cox proportional hazard model adjusting for age and sex was used to calculate the hazard ratios to compare HCV carriers to HCV non-carriers. The hazard ratios for both all-cause mortality (HR=1.5, 95% CI: 1.1-2.1) and liver-related mortality (HR=5.9, 95% CI: 2.6-13.7) were found to be statistically significant higher in the HCV carriers when compared to the HCV non-carriers. This Japanese study reconfirms that the chronic HCV infection increases the risk of liver-related death.

The second study published in 2009 by Prasad et al. was based on a cohort of Swiss HCV infected individuals who were recruited from eight secondary and tertiary care centres during 2000 to 2007.[87] An annual follow-up was performed and information on deaths and losses to follow-up were collected. There were 1,645 patients in the cohort and the SMR was calculated to compare all-cause mortality with the general Swiss population. An increased all-cause SMR was observed (SMR=4.49, 95% CI: 3.5-5.8). The SMR was 20 times higher among HCV and HIV co-infected patients when compared

to the general Swiss population (95% CI: 11.1-36.1). Little evidence of excess mortality was found among HCV infected individuals who were not cirrhotic and reported alcohol use ≤ 40g per day. Prasad et al. concluded that preventive advice could be focused on counseling and education in order to avoid excess alcohol intake for those infected HCV infected.

The third study published in 2009 was a Canadian study conducted by Grebely et al. who examined all-cause and disease specific mortality among 2,913 individuals who enrolled in the Community Health and Safety Evaluation cohort in the Downtown Eastside of Vancouver.[88] The enrollment period was from January 2003 to June 2004. HCV status was determined by an anti-HCV serology result. Individuals enrolled in the inner city cohort were linked to the provincial HCV laboratory testing database from 1991 to 2007. There were a total of 2,332 individuals linked who had at least one anti-HCV test during 1991 to 2007. The underlying causes of death were obtained from the BC Vital Statistics Agency database from 2003 to 2007. The Cox proportional hazard model was used to calculate the hazard ratios. Variables examined in the model included age, sex, ethnicity, housing status, use of methadone therapy, illicit drug use, injection drug use, alcohol consumption, health service access, having a regular doctor, and HIV and HCV status. Among HCV seropositive individuals, the crude mortality rates per 10,000 person years for all-cause, liver-related and drug-related mortality were 224 (95% CI: 187-265), 18 (95% CI: 9-33) and 48 (95% CI: 32-69), respectively. They showed no excess mortality in the HCV seropositive individuals when compared to the HCV seronegative individuals (HR=1.2, 0.8-1.7). Findings from this study were consistent with results observed from Neal et al.[85]

In 2010, two population-based data linkage studies on mortality among HCV infected individuals were published - a Norwegian study by Kristiansen et al.,[22] and a Danish study by Omland et al.[89] In these two studies, different HCV diagnosis methodologies were examined. The Norwegian study used RIBA testing to determine HCV status. The Danish study used the PCR testing to determine the presence of HCV viraemia.

Kristiansen et al. conducted a prospective cohort study to examine overall and cause specific mortality among HCV infected individuals in North Norway.[22] The study was conducted at the University Hospital of North Norway from 1990 to 2000. The Department of Microbiology at the University Hospital of North Norway is the only laboratory that performs RIBA testing in North Norway. Positive HCV cases were linked to the Norwegian Causes of Death Register to obtain cause of death information. SMRs were calculated to compare all-cause and disease specific mortality with the Norwegian population. There were 1,010 eligible HCV positive individuals confirmed by the RIBA test. The SMRs for all-cause, liver-related and drug-related mortality were 6.7 (95% CI: 5.5-8.0), 41.1 (95% CI: 22.5-68.9) and 30.2(95% CI: 21.7-40.9) respectively. Findings from this study were consistent with the reported population-based linkage studies from Australia[20], Sweden[21] and Scotland[23].

The most recent published population-based mortality study among HCV infected individuals was conducted by Omland et al. [89] PCR testing was used to determine the presence of HCV viraemia. This is the first nationwide cohort study to examine the associations between the presence of HCV viraemia (HCV RNA +ve versus HCV RNA -ve) and mortality among individuals who tested anti-HCV positive in Denmark. Cause of

death information was obtained by linking the Danish HCV cohort with death certificate information from the Danish Registry of Causes of Death. The 10-digit civil registration number assigned to all residents in Denmark was used for linkage. The Cox proportional hazard model was used to calculate the hazard ratios between chronic HCV infection (HCV RNA positive, viraemia present) and those who cleared the virus (HCV RNA negative, no viraemia) after adjusting for age, sex, comorbidity, calendar period, alcohol abuse, IDU and income. There were 6,292 individuals eligible for inclusion into the study, 63% had chronic HCV infection and 37% had cleared the virus. The chronic HCV infected individuals had elevated HRs for all-cause mortality (HR=16, 95% CI: 1.3-1.9) and liver-related (HR=2.4, 95% CI: 1.5-3.9). A greatly increased risk for death from primary liver cancer (HR=16.5, 95% CI: 2.2-121.0) was also found in the chronic HCV infected individuals when compared to those who cleared the virus.

For all of the reviewed studies, unmeasured confounding factors, selection bias and loss to follow-up may have biased the reported results. Among the large population-based mortality studies, consistent results were observed[20, 21, 23] and the conclusions were that all-cause, liver-related and drug-related mortality were all substantially elevated when compared to the general population. The studies that differed greatly had smaller sample sizes[84, 88] which compromises statistical power and the ability to detect the true differences between the groups. The implications from most mortality studies suggest that chronic HCV infected individuals are more likely to die from liver-related causes. However, mortality in IDUs tends to be associated to risk behaviours/activities that are associated with the acquisition of HCV infection.[20-23] For this population, the risk of dying from drug-related causes is significantly greater than from liver-related causes.[20-23]

Due to the lack of comprehensive serological information, the aforementioned studies have not assessed the relationship of serological status at the time of diagnosis. Furthermore, none of the above studies have longitudinally tracked testing patterns and results of individual who undergo HCV testing, and looked at the difference between individuals with chronic HCV versus multiple serial tested negative individuals, and compared chronic HCV related mortality with individuals who seroconverted (previously seronegative followed by reactive, a marker for incident infection). In BC, we are fortunate to have provincial population-based centralized laboratory testing data which has enabled us to longitudinally track testing patterns and results of individuals who undergo HCV testing in BC. Access to these unique data form the basis for my study.

# 3 Methods

## 3.1 Study design

The study design is a retrospective cohort study that involves secondary data analysis based on the linked administrative databases. Neither primary data collection nor direct contact of study individuals was conducted. A cohort of individuals who underwent serological testing for anti-HCV from April, 1992 to July, 2004 at the BCCDC Public Health Microbiology and Reference Laboratory[30] were linked to the BC Vital Statistics Agency and the BC MoH Registration & Premium Billing files.[31-34] The exposure variable, HCV serological group, was defined based on anti-HCV testing patterns and results.[30] The outcome variables, survival time and underlying cause of death, were taken from the linked BC Vital Statistics Agency data.[33, 34]

## 3.2 Data sources

### BC Centre for Disease Control (BCCDC) Public Health Microbiology and Reference Laboratory anti-HCV testing data, 1992-2004[30]

The BCCDC Public Health Microbiology and Reference Laboratory has performed about 95% of all anti-HCV testing in the province of British Columbia since 1992 and all HCV ribonucleic acid (RNA) testing and HCV genotyping since 2003.[30] The presence of anti-HCV confirms either resolved or active HCV infection, whereas the detection of HCV RNA in the blood by PCR testing is indicative of an active infection. The BCCDC Public Health Microbiology and Reference Laboratory anti-HCV testing data from April 1, 1992 to July 16, 2004 was used for cohort identification and HCV

serological group classification. Anti-HCV tests after the first positive (reactive) test result were removed and not analyzed.

**BC Linked Health Database (BCLHD), 1992-2004**[31, 32, 91]

The BCLHD included longitudinal, person-specific, health data on BC's four million residents from 1985. The health care and health services data were held at the University of British Columbia (UBC) Centre for Health Services and Policy Research (CHSPR) formerly and transitioned to the Population Data BC (PDBC) in 2009.[92] BCLHD contained health services files such as: medical services plan (MSP) payment information (claims submitted by physicians), hospital separations from Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD), home and community care (continuing care), mental health data warehouse from the MoH, BC Cancer Registry incidence files from the BC Cancer Agency and death registry from the BC Vital Statistics Agency.[91] The MoH Registration and Premium Billing files, currently known as the consolidation file, contains the central demographics file.[31, 32] Data from January 1, 1992 to December 31, 2004 was used to determine age, sex and date of last follow-up.[31, 32]

**British Columbia Vital Statistics Agency, 1992-2004**[33, 34]

All deaths from BC residents registered in the province of BC are captured and maintained by the BC Vital Statistics Agency.[33, 34] Date of death was used to determine survival time for time to event analysis. Underlying Cause of Deaths (UCOD) were coded by the standard international coding rules from the tenth edition of International Classification of Diseases (ICD-10). UCOD refers to either the cause or injury that initiated the train of morbid events leading directly to death, or the nature of the accident

or violence that produced the fatal injury. The BC Vital Statistics Agency UCOD data from January 1, 1992 to December 31, 2004 was used to identify the cause of death.[33, 34]

## 3.3 Data linkage and de-identification

Data linkage was done in multiple steps:

1) Staff at the BCCDC Hepatitis Services cleaned the HCV testing data and assigned a unique, temporary study identification number (temp study ID) to each tester in the study cohort. Cleaning steps involved removal of duplicates and manual reviewing records that had the same personal health number (PHN) but different name and date of birth combinations. A password-protected file was sent to the Data Access Services at BC MoH containing the following data elements: temp study ID, last name, first name, date of birth, sex, and PHN, also known as BC Care Card number. All HCV laboratory testing information was retained at BCCDC.

2) The MoH linked the PHNs in the BCCDC file with encrypted PHNs (EPHN) held by the MoH Client Registry System (CRS).[31, 32] A unique final study ID for each unique temp study ID was assigned. The MoH and CHSPR (currently PDBC) work with EPHNs to further protect confidential health information of British Columbians. A record was considered a match between the BCCDC file and the CRS if PHN matched and/or last and first name, sex, and year and month of birth date matched. PHN was used first for simple comparison; if both PHN and demographics (full name, date of birth and gender) matched, then the record was considered a match. If there was a discrepancy, the PHN was dropped and an attempt was made to match on the demographics. Therefore, there were instances in which there was an exact match on name, DOB, and sex but the PHNs were different. This was attributed to previously merged or invalid PHN provided

by BCCDC. After records had been matched, MoH removed the personal identifiers and temp study ID, then forwarded EPHN and final study ID to CHSPR. MoH also provided the BCCDC data steward with a crosswalk file that contained temporary study IDs with their corresponding final study IDs.

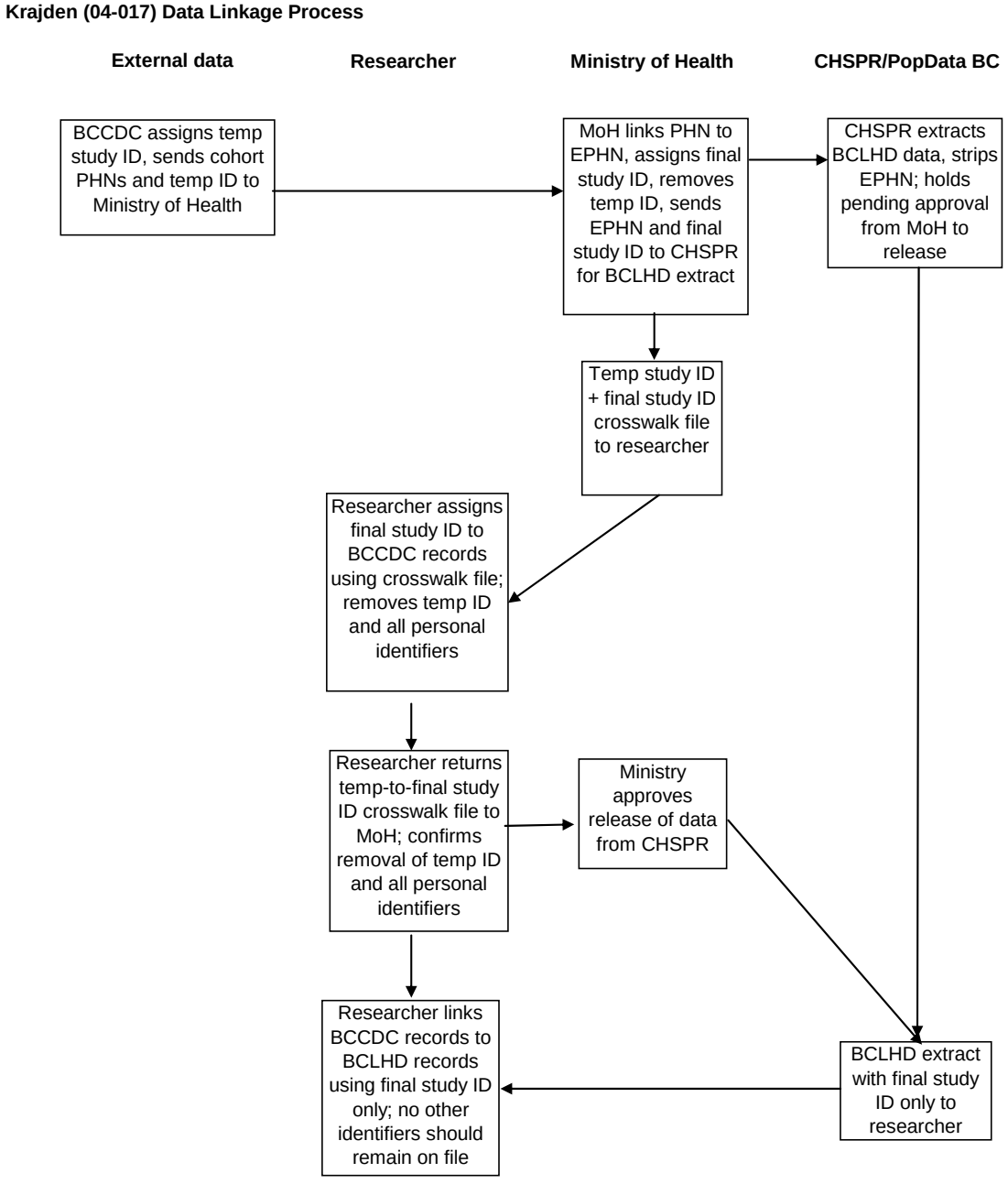
3) CHSPR used the EPHN provided by MoH to extract the health services data from BCLHD and appended the corresponding unique final study IDs. CHSPR then stripped EPHN and sent the health services data with final study ID to BCCDC.

4) A programmer (external to the study team) replaced the temporary study ID in the BCCDC HCV laboratory testing dataset with final study ID from the crosswalk file. This programmer was responsible for ensuring that the file returned to the study team had neither temp study IDs nor other identifying information such as name, date of birth, PHNs, place of residence, specimen IDs, etc. that could be used to directly identify an individual in the original laboratory database. The final file returned to the study team was therefore de-identified. It contained only the final study ID with HCV testing dates and results. After the linkage was completed, the crosswalk file was returned to MoH. (Figure 3.1)

5) From the original BCLHD data export in 2006, only date of death was provided and UCOD information was not available from the death dataset. An additional request was made to obtain UCOD from the BC Vital Statistics Agency.[33] The BC Vital Statistics Agency used the crosswalk file provided by Data Access Services at MoH and re-extracted death information with UCOD in 2008. The new data extraction with UCOD provided by the BC Vital Statistics Agency in 2008 was used for the mortality analysis.

**Figure 3.1 Data linkage process flow chart**

Adapted from original flow-chart created by Leanne Warren from MoH.




Crosswalk files:
1) PHN + temp study ID at BCCDC (original)
2) PHN + temp study ID + EPHN + final study ID at Ministry of Health
a) EPHN + final study ID at CHSPR
b) temp study ID + final study ID at BCCDC ---> returned to MoH

*Data sources: BCCDC Public Health Microbiology and Reference Laboratory,*[30] *Ministry of Health Services,*[31, 32] *and BC Vital Statistics Agency.*[33, 34]

## 3.4 A priori mortality end points

A priori mortality endpoints of interest were: all-cause, liver-related, drug-related, HIV, diabetes mellitus, renal failure, malignant neoplasms, hepatocellular carcinoma, non-Hodgkin lymphoma, and cholangiocarcinoma (Table 3.1). All underlying causes of death from the BC Vital Statistics Agency[33, 34] were ICD-10 coded.[93]

**Table 3.1 A priori mortality endpoints**

| Cause of death | ICD-10 |
|---|---|
| All-cause | A00-R99, V01-Y98 |
| Liver-related | B15-B19, B942, C22, K70-K76 |
| Viral hepatitis | B15-B19, B942 |
| Liver and intrahepatic bile duct cancer | C22 |
| Liver disease | K70-K76 |
| Alcoholic | K70 |
| Non-alcoholic | K71-K76 |
| Drug-related | F11-F16, F19, X40-X44, X60-X64, X85, Y10-Y14 |
| HIV | B20-B24 |
| Diabetes mellitus | E10-E14 |
| Renal failure | N17-N19, I12-I13, N00-N08 |
| Malignant neoplasms | C00-C97 |
| Hepatocellular carcinoma | C22.0, C22.2-C22.9 |
| Non-Hodgkin lymphoma | C82-C85 |
| Cholangiocarcinoma | C22.1, C24.0 |

### 3.4.1 All-cause

A complete list of ICD-10 codes was used to comprehensively capture all causes of mortality: A00-R99 and V01-Y98. A00-R99 includes A00-B99 for certain infectious and parasitic diseases, C00-D48 for neoplasms, D50-D89 for diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism, E00-E90 for endocrine, nutritional and metabolic diseases, F00-F99 for mental and behavioural disorders, G00-G99 for diseases of the nervous system, H00-H59 for diseases of the eye and adnexa, H60-H95 for diseases of the ear and mastoid process, I00-I99 for diseases of

the circulatory system, J00-J99 for diseases of the respiratory system, K00-K93 for diseases of the digestive system, L00-L99 for diseases of the skin and subcutaneous tissue, M00-M99 for diseases of the musculoskeletal system and connective tissue, N00-N99 for diseases of the genitourinary system, O00-O99 for pregnancy, childbirth and the puerperium, P00-P96 for certain conditions originating in the perinatal period, Q00-Q99 for congenital malformations, deformations and chromosomal abnormalities, R00-R99 for symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified. V01-Y98 includes external causes of morbidity and mortality.

### 3.4.2 Liver-related

The liver-related cause of death category was adapted from Amin et al. (2006) and includes three sub-categories:

a) Viral hepatitis (B15-B19, B942) includes acute hepatitis A (B15), acute hepatitis B (B16), other acute viral hepatitis such as acute delta infection of hepatitis B carrier, acute hepatitis C and E, and other specified acute viral hepatitis (B17), chronic viral hepatitis such as chronic viral hepatitis B with and without delta-agent, chronic viral hepatitis C, and other chronic viral hepatitis (B18), unspecified viral hepatitis (B19), and sequelae of viral hepatitis (B942).

b) Liver and intrahepatic bile duct cancer (C22) includes hepatocellular carcinoma (C22.0, C22.2-C22.9) and intrahepatic bile duct cancer (C22.1). Hepatocellular carcinoma includes malignant neoplasms of liver cell carcinoma (C22.0), hepatoblastoma (C22.2), angioscarcoma of liver (C22.3), other sarcomas of liver (C22.4), other specified carcinomas of liver (C22.7), and other unspecified carcinomas of liver (C22.9).

c) Liver diseases (K70-K76) including alcoholic liver disease (K70) and non-alcoholic liver disease (K71-K76). Non-alcoholic liver disease includes toxic liver disease (K71), hepatic failure not elsewhere classified (K72), chronic hepatitis not elsewhere classified (K73), fibrosis and cirrhosis of liver (K74), other inflammatory liver diseases (K75), and other diseases of liver (K76).

### 3.4.3 Drug-related

The drug-related category was also adapted from Amin et al. (2006) which includes deaths from the following five subcategories:

a) Mental and behavioural disorders due to psychoactive substance which includes mental and behavioural disorders due to use of opioids (F11), cannabinoids (F12), sedatives or hypnotics (F13), and cocaine (F14); and mental and behavioural disorders due to multiple drug use and use of other psychoactive substances (F19).

b) Accidental poisoning by and exposure to noxious substances which includes accidental poisoning by and exposure to nonopioid analgesics, antipyretics and antiheumatics (X40); accidental poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not else where classified (X41); accidental poisoning by and exposure to narcotics and psychodysleptics (hallucinogens), not elsewhere classified (X42); accidental poisoning by and exposure to other drugs acting on the autonomic nervous system (X43); accidental poisoning by and exposure to other and unspecified drugs, medicaments and biological substances (X44).

c) Intentional self-harm which includes intentional self-poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics (X60); intentional self-poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and

psychotropic drugs, not elsewhere classified (X61); intentional self-poisoning by and exposure to narcotics and psychodysleptics (hallucinogens), not elsewhere classified (X62); intentional self-poisoning by and exposure to other drugs acting on the autonomic nervous system (X63); and intentional self-poisoning by and exposure to other and unspecified drugs, medicaments and biological substances (X64).

d) Homicidal poisoning by drugs, medicaments and biological substances (X85), and

e) Events of undetermined intent which includes poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics, undetermined intent (Y10); poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified, undetermined intent (Y11); poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified, undetermined intent (Y12); poisoning by and exposure to other drugs acting on the autonomic nervous system, undetermined intent (Y13); and poisoning by and exposure to other and unspecified drugs, medicaments and biological substances, undetermined intent (Y14).

### 3.4.4 HIV

The human immunodeficiency virus (HIV, B20-B24) category includes HIV disease resulting in infectious and parasitic diseases (B20), HIV disease resulting in malignant neoplasms (B21), HIV disease resulting in other specified diseases (B22), HIV diseases resulting in other conditions (B23) and unspecified HIV disease (B24).

### 3.4.5 Diabetes mellitus

The diabetes mellitus (E10-E14) category includes insulin-dependent diabetes mellitus (E10), non-insulin-dependent diabetes mellitus (E11), malnutrition-related diabetes mellitus (E12), and other specified (E13) and unspecified (E14) diabetes mellitus.

### 3.4.6 Renal failure

The renal failure (N17-N19, I12-I13, and N00-N08) category includes three subcategories:

a) Renal failure, including acute renal failure (N17), chronic renal failure (N18), and unspecified renal failure (N19).

b) Hypertensive diseases, including hypertensive renal disease (I12), and hypertensive heart and renal disease (I13).

c) Glomerular diseases, including acute nephritic syndrome (N00), rapidly progressive nephritic syndrome (N01), recurrent and persistent haematuria (N02), chronic nephritic syndrome (N03), nephritic syndrome (N04), unspecified nephritic syndrome (N05), isolated proteinuria with specified morphological lesion (N06), hereditary nephropathy not elsewhere classified (N07) and glomerular disorders in diseases classified elsewhere (N08).

### 3.4.7 Malignant neoplasms

The category of malignant neoplasms (C00-C97) includes malignancies of the lip, oral cavity and pharynx (C00-C14), digestive organs (C15-C26), respiratory and intrathoracic organs (C30-C39), bone and articular cartilage (C40-C41), skin (C43-C44),

mesothelial and soft tissue (C45-C49), breast (C50), female genital organs (C51-C58), male genital organs (C60-C63), urinary tract (C64-C68), eye, brain and other parts of central nervous system (C69-C72), thyroid and other endocrine glands (C73-C75), ill-defined, secondary and unspecified sites (C76-C80), lymphoid, haematopoietic and related tissue (C81-C96) and independent primary multiple sites (C97).

#### 3.4.7.1 Hepatocellular carcinoma

The hepatocellular carcinoma (C22.0, C22.2-C22.9) category includes liver cell carcinoma (C22.0), hepatoblastoma (C22.2), angiosarcoma of liver (C22.3), other sarcomas of liver (C22.4), other specified carcinomas of liver (C22.7) and unspecified liver neoplasm (C22.9).

#### 3.4.7.2 Non-Hodgkin lymphoma

The non-Hodgkin lymphoma (NHL) (C82-C85) category includes follicular (nodular) NHL (C82), diffuse NHL (C83), peripheral and cutaneous T-cell lymphomas (C84) and other and unspecified types of NHL (C85).

#### 3.4.7.3 Cholangiocarcinoma

Cholangiocarcinoma is cancer of the bile duct. Since some of bile duct is located within the liver and some outside the liver, we explored both types of bile duct cancer: intrahepatic (within the liver) cholangiocarcinoma (C22.1) and extrahepatic (outside the liver) cholangiocarcinoma (C24.0).

## 3.5 Study sample

Any individuals without a BC PHN or who were not matched by BC MoH were not eligible for the study (n=113,483). Since individuals with comorbid illness may get tested more often, there was a potential bias towards higher rates of HCV testing prior to death. Thus, to remove this notification bias, all individuals who were not in the study for six months (26 weeks) or who died within six months after first anti-HCV test were excluded. All HCV serological groups were lagged for six months meaning that the start date for that group was delayed for six months.

Of 409,355 individuals linked, 8,914 individuals were excluded due to the 6-month lagging and 1,080 individuals were excluded due to data quality issues. This includes unknown gender (n=3), age less than 1 or over 100 (n=341), the first available lab date was after the date of death (n=430), the first available test date was before the date of birth (n=11), death occurred before the first date of enrollment (n=5), and/or death occurred after the last date of enrollment (n=293). An individual could be excluded as a result of having multiple exclusion criteria. Therefore, 399,361 individuals who had at least one anti-HCV test from 1992 to 2004, and remained alive for six months (26 weeks) after the first anti-HCV test were eligible the for analysis.

## 3.6 Data quality

Since the data were not collected specifically for research purposes, there were data quality issues that required further investigation. In addition to those excluded due to eligibility criteria, two data quality concerns were explored in detail: 1) comparison of

death information from the BCLHD and the BC Vital Statistics Agency, and 2) comparison of cancer related deaths and BC Cancer Registry incidence files.

1) There were data discrepancies found in the death information from the BCLHD and the BC Vital Statistics Agency. We received two data extractions for death information: one in 2006 from BCLHD with date of death only, and one in 2008 directly from the BC Vital Statistics Agency[33, 34] with date of death and underlying cause of death. Both files had deaths from January 1, 1992 to December 31, 2004. In the 2006 data extraction, six individuals had duplicate death information. Among these, five individuals were exact duplicates and one individual had different date of death. When crosschecking between the 2006 and the 2008 data extractions, there were six individuals in the 2006 data extraction but not in the 2008 data extraction; and there were 449 individuals in the 2008 data extraction but not in the 2006 data extraction. Among individuals with death information in both the 2006 and the 2008 data extraction, 16 individuals had different dates of death.

After consulting with the BC Vital Statistics Agency,[94] we were informed that post processing steps were taken at the BC Vital Statistics Agency to review those doubly linked and poor quality matches to ensure that the linked data are as accurate and complete as possible. There were no duplicate death records found in the 2008 extraction. Six individuals in 2006 but not in 2008 extraction would have been dropped if the basic demographics such as birth year and gender did not match between decedent and registered clients. Since more complete death records were available in 2008, an additional 449 individuals previously were not matched were matched. Deaths from these 449 individuals were randomly distributed across all years from 1992 to 2004. Post

processing checking done in the 2008 data extraction but not in the 2006 data extraction would account for the corrections made for inconsistent date of death information. There were only 22 corrections and 449 additions out of about 27,000 death records, and due to the improved accuracy, the 2008 extraction were used for this study.

2) There were data discrepancies found between cancer related deaths from the BC Vital Statistics Agency and the BC Cancer Registry incidence files. Although not relevant for the mortality study, these discrepancies might cause potential problems when we examine HCV related cancer incidence in the future. Among about 7,200 cancer deaths identified in the BC Vital Statistics Agency, there were about 500 deaths (7%) without corresponding cancer diagnoses. Since the time period of the BC Cancer Registry incidence files was from 1992 to 2004, it is hypothesized that these subjects could have been diagnosed with cancer prior to 1992.

## 3.7 Statistical methods

Standardized mortality ratios and the time-dependent Cox proportional hazard regression model were used to examine HCV mortality. Standardized mortality ratios (SMRs) were calculated to compare the relative risk of all-cause and disease specific mortality to that of the BC population. Time-dependent Cox proportional hazard regression was used to compare the risk among the four HCV serological groups (see section 3.7.2), adjusted for age and gender. The numbers and percent of the top 12 underlying cause of deaths were listed for each of the four HCV serological groups. All analyses were performed by the SAS system Version 9.2 (Cary, NC, USA).

### 3.7.1 Survival time

Survival time was defined as the time from group entry until the date of death or last follow-up. A censored observation is defined as an observation with incomplete or partial information at the last follow-up. In the study, right censoring was applied. Right censoring means that the failure times occur after the last follow-up.

For those who were alive at the end of the study, there were two options for assigning the censor date. One was to assume that everyone was alive on 2004-12-31 and censoring those individuals on that date. Another option was to use the MoH Registration and Premium Billing files[31, 32] and censor on the last available enrollment date. Both methods were examined and no major differences were found. Therefore, for those who were still alive at the end of the study, the MoH Registration and Premium Billing files [31, 32] were used for right censoring as the last available enrollment date. Survival time was calculated by using (last available enrollment date - the date of group entry) + 1. For the SMR analysis, person-days were first calculated from group entry until the date of death or censored at the last available enrollment date on the MoH Registration and Premium Billing files[31, 32], then divided by 365.25 to obtain person-years on study.

For those who died, (date of death - date of group entry) + 1 was used to determine survival time. Date of death was obtained from the BC Vital Statistics Agency. [33, 34] However, imputation was required in order to calculate survival time as the date of death was provided in YYYYMM format. If the year and month of the date of death was not the same as year and month of the last anti-HCV test, then date of death was imputed to the 15th of the month. If year and month of date of death was the same as year and month of the last anti-HCV test, then the average from the last HCV date to end of the

month was calculated. For example, if the last anti-HCV test was on 2000-11-20 and the date of death was provided as 2000-11, then the date of death was calculated as follows: (2000-11-30 – 2000-11-20)/2 + 2000-11-20 = 2000-11-25. This rule is not relevant if there is only one available test.

### 3.7.2 Time dependent HCV serological groups

When an individual is infected with HCV, anti-HCV develops within 5 to 10 weeks after infection and the antibody usually remains detectable for decades or more. In the BCCDC laboratory HCV testing database from 1992 to 2004, one individual could have one anti-HCV test, or multiple anti-HCV tests during the period; and the result could be either positive (reactive) or negative (non-reactive, or equivocal) for each test. To best represent the changing of HCV serological status over time, time-dependent HCV groups were created.

Assignment to one of four time-dependent HCV serological groups was made according to the individuals' anti-HCV serology testing patterns and results (Table 3.2). Testing patterns and results were used as an indicator for risk. As discussed in section 2.8, time-dependent serological groups were defined based on perceived risks. Individuals who might be tested for anti-HCV only once and are anti-HCV negative, may have some a priori risks such as a history of a blood product transfusion prior to 1990, but such individuals are unlikely to have ongoing risks of HCV infection. In contrast, individuals who undergo serial testing likely represent a heterogeneous group of persons who might either be at ongoing risk of HCV infection or of liver disease from any cause. Individuals who are anti-HCV reactive on their first test have been infected but we are unable to determine the timing of their infection. They may have been tested due to

symptoms or signs of liver disease or because of risk factors. A seroconverter is defined as an individual who demonstrates an anti-HCV non-reactive test result(s) in the past and on the follow up testing is shown to be anti-HCV reactive. This confirms an incident infection, but the precise time of infection is unknown.

**Table 3.2 Time-dependent HCV serological groups**

| HCV serological groups | Definition | Risk |
|---|---|---|
| SNR: Single non-reactive | SNR group begins at the initial non-reactive (negative) test until a second test was identified. | This group may have some risk(s) such as testing for medical and insurance purposes; prior transfusion; presented with clinical illness correlated with liver disease but they are unlikely to have an ongoing risk of HCV infection. |
| MNR: Serial multiple tested non-reactive | MNR group begins at the time of second non-reactive (negative) test and continued until a positive test result was identified. | This group likely has ongoing risks for HCV infection. (e.g., IDU-high risk, kidney dialysis-low risk, signs or symptoms of liver disease.) |
| REAC: Reactive at initial testing | REAC group begins when the first and only anti-HCV test was reactive (positive). | This group may be tested due to symptoms of liver disease or other remote risk factors. This identifies most of chronic HCV cases. |
| SERO: Seroconverter. A seroconverter is identified by an anti-HCV positive test result with one or more prior anti-HCV non-reactive test result(s). This confirms an incident infection. | SERO group begins at the anti-HCV reactive (positive) test result. | This group may be tested due to ongoing exposure to risk (e.g., IDU). This group represents mostly injection drug users. |

Since classification of the HCV serological groups was time-dependent based on an individual's testing history from 1992 to 2004, individuals might be categorized to one or more categories. For example, all individuals who had serial and multiple non-reactive test results would be in the SNR group during their first test and in the MNR group

during their subsequent tests until a positive test result was identified. A seroconverter who had one single non-reactive test result followed by a reactive test result would be in the SNR group while non-reactive and change to the SERO group at the time of anti-HCV reactive test result. However, if a seroconverter had two non-reactive test results followed by a reactive test result, this individual would be assigned to the SNR group - during first non-reactive test result, MNR group - during second non-reactive test result and the SERO group - at the time of anti-HCV reactive test result.

### 3.7.3 Standardized mortality ratios

Standardized mortality ratios (SMR) with 95% confidence intervals were calculated to compare the risk of all-cause and disease specific mortality with the BC general population. The SMRs were calculated in order to compare with other studies that have been published in the literature.[20, 21, 23] In addition, the SNR group was compared with the general population to determine whether it was representative of the general population.

For each cause of death category, mortality among anti-HCV testers was compared to an age, sex and calendar-year standardized expected mortality rate derived from the general population of BC. A mortality equivalent to the BC population yields a SMR equal to 1.

Standardized Mortality Ratio (SMR)

$$= \frac{Observed\ Deaths}{Expected\ Deaths}$$

The observed deaths were obtained by summarizing number of deaths in the study cohort for each 5-year age group from 1992 to 2004, separately by gender and year. To

obtain the expected deaths, the calculated person-years from the study population were multiplied by the death rate of the BC general population from the BC Vital Statistics Agency.[33, 34] The death rate for the BC general population was calculated by using the total numbers of deaths divided by the annual population of BC. The expected deaths were calculated for each 5-year age group from 1992 to 2004, separately by gender and year. Then, SMR was the sum of all the observed deaths divided by the sum of all the expected deaths. The same calculation was applied for each disease-specific UCOD when calculating a disease-specific SMR.

The 95% confidence limits for the SMR were calculated based on the assumption that the observed number of deaths, D, is Poisson distributed with mean $\mu=E(D)$. For $D \leq 30$, exact Poisson limits were used. For $D > 30$, three different approximations of confidence limits were explored: Byar's approximation, the square root transformation, and confidence limits derived from the standard chi-square test.[95] Results from all three different approximations were found to be similar for $D > 30$. Confidence limits from Byar's approximation were close to the exact limits even with small numbers of deaths, thus, we used Byar's approximation when giving 95% confidence limits for $D > 30$.

Byar's approximation does not require the iterative calculations needed for the exact results. The lower ($\mu_L$) and upper ($\mu_U$) confidence limits from Byar's approximation are shown below:

$$\mu_L = D\left(1-\frac{1}{9D}-\frac{Z_{\alpha/2}}{3D^{1/2}}\right)^3$$

$$\mu_U = (D+1)\left(1-\frac{1}{9(D+1)}-\frac{Z_{\alpha/2}}{3(D+1)^{1/2}}\right)^3$$

where $Z_{\alpha/2}$ denotes the $100(1-\alpha/2)$ percentile of the normal distribution.

The two most common methods of comparing risks between groups are ratios of the individual SMRs and the hazard ratios obtained from the Cox proportional hazard model. For example, when comparing SMR in the REAC group with the SNR group, we can calculate the SMR ratio by using SMR from the REAC group divided by SMR from the SNR group. However, given the age and gender distributions are different between the different HCV serological groups, the estimated relative risk when using the SMR ratios to compare between different HCV serological groups can be biased.[95] Therefore, the second method of using hazard ratio obtained from the Cox proportional hazard model for time to event data, is a better method for comparing the risks among the four HCV serological groups.

### 3.7.4 Cox proportional hazards model

There are two ways to express a survival time: the survival function [ $S(t)$ ] and hazard function [ $\lambda(t)$ ]. Let T represent a continuous random variable called survival time. T has the probability density function $f(t)$ and cumulative distribution function $F(t)$. A survival function is defined as the probability that an individual survives beyond time t, that is,

$$S(t) = \Pr\{T > t\} = 1 - F(t) = 1 - \Pr\{T \le t\} = \int_t^{\infty} f(x)dx$$

The hazard function $\lambda(t)$ is the instantaneous risk of failure at time t, or the instantaneous rate of occurrence of the event, conditional on survival to that time. [96-98] Given $S'(t) = -f(t)$,

$$\lambda(t) = \lim_{dt \to 0} \frac{\Pr\{t < T \le t + dt \mid T > t\}}{dt} = \frac{f(t)}{S(t)} = -\frac{d}{d(t)} \log S(t)$$

When t = 0, $S(0)=1$. Hence, the probability of surviving to time t as a function of the hazard is

$$S(t) = \exp\left[-\int_0^t \lambda(x)dx\right]$$

The Cox proportional hazards model is a regression model which handles time to event data with censored observations. The Cox proportional hazard model assumes the hazard at time *t* for an individual *i* with covariates $x_i$ is

$$\lambda_i(t \mid x_i) = \lambda_0(t)\exp\left\{x_i'\beta\right\}$$

where $\lambda_0(t)$ is the baseline hazard function, $\lambda_0(t, x_i = 0)$. $x_i'$ is the vector of covariates for the i[th] individuals and $\beta$ is a vector of parameters.[96-98] The relative risk associated with a set of covariates $x_i$ is $\exp\left\{x_i'\beta\right\}$. The proportional hazard assumes that the relative risk is proportional, that is, the increase or reduction in the risk is the same for all duration *t*.

For example, for a dummy variable *x*, the hazard function at time *t* is

$$\lambda_i(t \mid x_i) = \begin{cases} \lambda_0(t) & for\ x = 0 \\ \lambda_0(t)\, e^{\beta} & for\ x = 1 \end{cases}$$

$e^{\beta}$ represents the ratio of the risk in group *x*=1 compared to the reference group when *x* = 0 for all duration *t*. (e.g., if *x* is a dummy variable for treatment group where *x* = 1 = treatment, and *x* = 0 = placebo, then $e^{\beta}$ represents the risk ratio or relative risk for the treatment group relative to the placebo group at any time *t*.) $e^{\beta}$ is also known as the hazard ratio. If $e^{\beta} = 1$, that means the relative risk is equal to 1, the risk in group x is the same as its referent group. (e.g., the risk for an individual in both the treatment and the placebo groups are the same.) However, if $e^{\beta} > 1$ (i.e., the relative risk is > 1), the risk for

an individual in group *x* is higher than its referent group (e.g., the risk for an individual in the treatment group is higher than the risk of an individual in the placebo group).

After taking logs on both sides of the equation, we have the Cox proportional hazards model as a simple additive model for the log hazard:

$$\log \lambda_i(t \mid x_i) = \log\left(\lambda_0(t)\right) + \log\left(\exp\left\{x_i'\beta\right\}\right)$$

$$= \alpha_0(t) + x_i'\beta$$

where $\alpha_0(t)$ is the log of baseline hazard, and the effect of the covariate is the same at all time *t*. Please note that the log of the baseline hazard does not depend on the covariates, it depends only on time. The second term $x_i'\beta$ explains how the log of hazard varies with different explanatory covariates. This term depends on the value of the regression coefficients and covariates but not on time.

Up to now, we have assumed that all covariates are fixed. However, in real life, predictors can change over time and these are referred to as time-dependent covariates, that is, covariates that vary with time. Some examples of covariates that may vary with time are: education, blood pressure, or in the HCV mortality study, the time-dependent HCV serological group. In the next section, Cox proportional hazards model with time-dependent covariates will be discussed in detail.

### 3.7.5 Time dependent Cox proportional hazards model

Since the HCV serological groups may change over time, an analysis which can handle censored time-to-event data with time-dependent covariates is essential. Thus, the time-dependent Cox proportional hazard model was used to estimate the unadjusted and

adjusted hazard ratios for mortality between different HCV serological groups. Individuals were censored at death or at the last follow-up.

Similar to the Cox proportional hazards model with fixed covariates, the Cox proportional hazards model with time-dependent covariates assumes that the hazard at time t for an individual i with covariates $x_i$ is

$$\lambda_i(t \mid x_i(t)) = \lambda_0(t)\exp\{x_i(t)'\beta\}$$

where here the covariate values can depend on time.[96-98]

After taking logs on both sides of the equation, we have the Cox proportional hazards model with time-dependent covariates as a simple additive model for the log of the hazard with covariates as a function of *t*:

$$\log \lambda_i(t \mid x_i(t)) = \log(\lambda_0(t)) + \log(\exp\{x_i(t)'\beta\})$$

$$= \alpha_0(t) + x_i(t)'\beta$$

where $\alpha_0(t)$ is the log of baseline hazard, $\beta$ is a vector of parameters, and the $x_i(t)'$ is a vector of the covariates that varies as a function of time *t*.

The Cox proportional hazards model with time-varying covariates has two components: the baseline log hazard function $\alpha_0(t)$ and the effect of parameters with a function of time $x_i(t)'\beta$. The difference between the Cox proportional hazard model with fixed versus time-dependent covariates is that the covariates in the time-dependent model are allowed to change over time. For example, if education is a time-dependent covariate and an individual changes education status from a bachelor degree to a master degree in the middle of study period, then the hazard for the first half of the time period will be assigned to the bachelor degree with *x(t)* = 0, and the hazard for the second half of the time period will be assigned to the master degree with *x(t)* = 1.

The time-dependent Cox regression inference and modeling should be interpreted with extreme caution because it has great potential for biased estimates and may lead to incorrect inference.[99] With fixed covariates, the effect of time and the effect of the covariates can be separated clearly. However, with time-dependent covariates, the separation of time and covariate effects is not as clear and there might be collinearity between the effects of the covariates and time.[96-98]

For 95% confidence limits, both profile likelihood and Wald confidence limits were computed but only profile likelihood was displayed in the results section. Profile likelihood confidence limits are preferable to the Wald confidence limits because the profile likelihood test does not depend on asymptotic of normality assumption of parameter estimates where Wald confidence limits are based on normal approximation of parameter estimates. Thus, profile likelihood confidence limits provide more reliable estimates. The disadvantage of using profile likelihood confidence limits is that they demand more computational power.[100]

Hazard ratios were calculated for the following four comparisons: 1) The multiple non-reactive group versus the single non-reactive group (MNR vs SNR). This was to compare the ongoing risk group (MNR) with the lowest risk group (SNR). 2) The anti-HCV reactive at initial test group versus the single anti-HCV non-reactive group (REAC vs SNR). This was to compare the first time tested anti-HCV reactive group (REAC) with a control group (SNR) for whom the first anti-HCV test result was non-reactive. 3) The seroconverter group versus the multiple non-reactive group (SERO vs MNR). Since a seroconverter is defined as an individual who tested anti-HCV negative and subsequently tested positive, and individuals in the MNR group were tested due to ongoing risk and the

test results were serial multiple non-reactive, the MNR group seems like a good comparative group for the SERO group. 4) The seroconverter group versus the anti-HCV reactive at initial test group (SERO vs REAC). Seroconverter group represents mostly injection drug users and it is a surrogate for acute HCV, and the anti-HCV reactive at initial test group identifies most of chronic HCV infected individuals. Thus, although there might be some misclassification of seroconverters in the REAC group because we might not get the previous non-reactive anti-HCV result, the SERO vs REAC comparison is a good alternative comparison for comparing acute HCV with chronic HCV cases.

Due to small observed deaths in the SERO group, the REAC group and the SERO group were combined to form a new group called the HCV positive group. Time dependent Cox proportional hazards models were not fit for causes of death with less than or equal to five observed deaths in the HCV positive group.

### 3.7.6 Covariates of interests

The reason for adding confounders in the model is that we want to obtain an unbiased estimate of the association between the exposure and the outcome of interest. Confounding occurs when the relationship between the exposure and the outcome is obscured by a hidden factor, also known as a confounder, or sometimes called a covariate. In practice, if the confounder has an effect on the outcome and the confounder is associated with an exposure, then the estimate will be biased if the confounder is not included in the model. Confounders examined in this study were age and gender. Age was defined as age at entry for each of the four time-dependent HCV serological groups. Age was calculated by (entry date – date of birth)/365.25. Since the date of birth was

provided in YYYYMM format, the first day of the month was imputed for age calculation.

Four formulations of age were explored in the model: 1) age as a continuous variable, 2) age categorized into 10-year age groups (i.e., < 20, 20-29, 30-39, 40-49, 50-59, 60-69 and ≥ 70), 3) age categorized into quartiles, and 4) age below and above 40. Five-year age groups were not examined in the model due to high computational requirements and extensive processing time required to fit the models.

The change-in-estimate criterion with a 10% relative change in the hazard ratio was used to select which age formulation to be included in the final model.[101] Among the five formulations of age, the full model is the model with the 10-year age groups included as a covariate variable, and the reduced model refers to each of four other formulations of age. A 10% relative change in hazard ratios was calculated by the following three steps:

1) The absolute value of the relative changes in the hazard ratios from the full model and reduced model for all three HCV serological groups (one HCV serological group was used as a referent group) were calculated.

$$\left| \frac{\left(HR_{\text{full model}} - HR_{\text{reduced model}}\right)}{HR_{\text{full model}}} \right|$$

2) For every age formulation in the reduced model, summed up all three relative changes in the hazard ratios obtained from the step 1.
3) Compared the number obtained from the second step with 10%. If the sum was greater than 10%, then keep the full model, otherwise, use the reduced model.

When compared with the full model (i.e., 10-year age groups), the sum of relative change in the hazard ratios for treating age as a continuous variable was 15.5%, age below and above 40 cut-off was 126.1% and age quartiles was 63.1%. Since the sum of

relative changes in hazard ratios for all formulations all exceed 10%, the full model with age categorized as 10-year age groups was used in the analysis.

Other covariates of interest included hypertension, diabetes, obesity, renal failure, AIDS/HIV, alcohol abuse, drug abuse, and psychoses. These co-morbid conditions were taken from Elixhauser comorbidity index.[102, 103] However, based on the diagnosis coded in the Ninth Edition of International Classification of Diseases (ICD-9) from MSP and DAD data sources, a comparison was conducted among covariates classified using different data sources (MSP, DAD and UCOD from BC Vital Statistics Agency[33, 34]). Inconsistencies of comorbidity were found and the quality of the data was questionable, thus these covariates were not used in the analysis.

### 3.7.7 Interaction analysis

When the association between the exposure and the outcome is different across different strata of a variable, there is a statistical interaction. Interactions between HCV serological groups with age and gender were explored. For the assessment of interactions, individuals were categorized as young (age $< 40$) and old (age $\geq 40$). The score test was used to examine if the age and gender interaction effects were statistically significant ($p < 0.01$). If age and/or gender interaction term was/were statistically significant, we rejected the hypothesis that the association (HR) did not differ between strata. Thus, a separate hazard ratio was calculated for each age group ($< 40$ and $\geq 40$) or gender, or both, where the interaction was statistically significant.

## 3.8 Sample size and power calculation

Minimum detectable relative risks (SMR) were calculated prior to start of the study in order to know what size of relative risk that is required in order to confidently detect with the given person-years for each time-dependent HCV serological group. The cohort consists of 405,441 individuals who were registered with the BC MSP and have at least one anti-HCV test from 1992 to 2004. There were 1,270,668; 255,299; 153,851; 9,383 person-years of exposure in the SNR, MNR, REAC and SERO groups, respectively. Based on average age-specific mortality rates over the period 1992-2004, and using the observed median ages of 41, 40, 43 and 34 for the SNR, MNR, REAC and SERO groups respectively, Table 3.3 gives the minimum detectable relative risks of SMR compared to the BC population (assuming $\alpha$=0.025, 1 sided, and 80% power). Minimum detectable odds ratios were calculated by STPLAN Version 4.5, Houston, TX, USA.

**Table 3.3 Minimum detectable relative risks (SMR)**

| Cause of death | SNR | MNR | REAC | SERO |
|---|---|---|---|---|
| All-cause | 1.05 | 1.12 | 1.15 | 1.83 |
| Liver-related | 1.21 | 1.49 | 1.64 | 6.76 |
| Viral hepatitis | 1.51 | 2.35 | 2.70 | 18.17 |
| Liver and intrahepatic bile duct cancer | 1.53 | 2.30 | 3.00 | 22.96 |
| Liver disease | 1.26 | 1.63 | 1.82 | 8.09 |
| Alcoholic | 1.37 | 1.87 | 2.22 | 13.18 |
| Non-alcoholic | 1.43 | 2.11 | 2.41 | 14.67 |
| Drug-related | 1.20 | 1.47 | 1.61 | 4.25 |
| HIV | 1.27 | 1.67 | 1.89 | 5.16 |
| Diabetes mellitus | 1.45 | 2.16 | 2.47 | 17.46 |
| Renal Failure | 1.97 | 3.44 | 4.23 | 32.81 |
| Malignant neoplasms | 1.09 | 1.20 | 1.27 | 2.97 |
| Non-Hodgkin lymphoma | 1.48 | 2.19 | 2.74 | 15.63 |
| Intrahepatic cholangiocarcinoma | 2.52 | 5.71 | 7.77 | 128.61 |
| Extrahepatic cholangiocarcinoma | 8.68 | 23.45 | 38.92 | 274.37 |
| Leukemia | 1.61 | 2.62 | 3.01 | 24.15 |
| Multiple myeloma | 1.94 | 3.71 | 4.56 | 96.23 |
| Pancreatic cancer | 1.48 | 2.24 | 2.64 | 21.42 |

*Data sources: BCCDC Public Health Microbiology and Reference Laboratory,[30] Ministry of Health Services,[31, 32] and BC Vital Statistics Agency.[33, 34]*

For all-cause mortality, in order to detect an effect with 80% of power requires minimum relative risks of 1.05, 1.12, 1.15 and 1.83 for SNR, MNR, REAC, and SERO groups respectively. Even though we have a fairly large numbers of person-years in the study, for a rare mortality outcome such as extrahepatic cholangiocarcinoma, a very large minimum relative risk is still required. For example, as shown in Table 3.3, in order to be able to detect an effect with 80% of power, we need a true relative risk of at least 8.68, 23.45, 38.92 and 274.37 in the SNR, MNR, REAC and SERO groups, respectively. Due to relatively small person-years in the SERO group, the minimum relative risks required for detecting an effect with 80% of power for most mortality outcomes except for some major mortality outcomes such as all-cause, liver-related, drug-related, HIV, and malignant neoplasms, are quite large.

## 3.9 Ethical considerations

The study is a secondary analysis of existing data which was previously linked for project Krajden 04-017 (UBC REB H04-70266: Mathematical Modeling for Hepatitis C Virus Infection Public Policy Development). The HCV mortality study has been approved by the principle investigator of the Krajden 04-017 study, Dr. Mel Krajden; the data steward for the BCCDC, Dr. Robert Brunham; and the academic supervisor, Dr. John Spinelli. All researchers have signed the required schedule B - pledge of confidentiality for the Krajden 04-017 project. This project opportunity is supported in part by a Western Regional Training Centre studentship funded by Canadian Health Services Research Foundation, Alberta Heritage Foundation for Medical Research, and Canadian Institutes of Health Research. There are no conflicts of interest with funding agencies.

The study was approved by the clinical ethical review board at UBC/ British Columbia Cancer Agency in December, 2008 and renewed in November, 2010 (UBC REB: H08-03034: HCV mortality and cancer incidence). All analysis was performed in a locked office in BCCDC and data were kept on a password protected secure network drive behind a firewall set by Provincial Health Services Authority (PHSA) Information Management/Information Technology (IM/IT). PHSA IM/IT provided all technical support including file storage and backup and complied with privacy and confidentiality agreements.

# 4 Results

## 4.1 Demographics

There were 375,752 testers in the SNR group, 90,136 testers in the MNR group, 29,689 testers in the REAC group, and 2,834 testers in the SERO group. After 6 months lagging was applied to reduce bias due to diagnosis prior to death, there were 367,634 testers in the SNR group (1,270,668 person-years (PY)), 82,126 testers in the MNR group (255,299 PY), 29,086 testers in the REAC group (153,851 PY), and 2,641 testers in the SERO group (9,383 PY) eligible for the analysis. In total, 8,721 testers were excluded due to 6 months lagging, that is, 8,118, 8,010, 603, 193 testers were removed from the SNR, MNR, REAC and SERO group, respectively. (Table 4.1)

Among eligible testers, the highest proportion of males was found in the REAC group (n=18,671, 64%), followed by the SERO group (n=1,457, 55%), the SNR group (n=162,147, 44%), and the MNR group (n=35,244, 43%). The REAC group (mean ± standard deviation, 43.0 ± 11.54) had the oldest mean age, and the SERO group had the youngest mean age (33.8 ± 9.74). Thus, individuals who tested anti-HCV positive at their first test, the REAC group, tended to be older and male. The proportion of deaths were the highest in the REAC group (n=2,963, 10.2%) followed by the SERO group (n=137, 5.2%), the MNR group (n=3,261, 4.0%) and the SNR group (n=14,496, 3.9%). (Table 4.1)

**Table 4.1 Baseline demographics**

| | SNR | MNR | REAC | SERO |
|---|---|---|---|---|
| N (All) | 375,752 | 90,136 | 29,689 | 2,834 |
| N (6M lagging) | 367,634 | 82,126 | 29,086 | 2,641 |
| Person-Years (PY) | 1,270,668 | 255,299 | 153,851 | 9,383 |
| Mean Age at entry (standard deviation) | 41.2 (17.13) | 40.2 (15.16) | 43.0 (11.54) | 33.8 (9.75) |
| Male (%) | 162,174 (44%) | 35,244 (43%) | 18,671 (64%) | 1,457 (55%) |
| N deaths (%) | 14,496 (3.9%) | 3,261 (4.0%) | 2,963 (10.2%) | 137 (5.2%) |

*Data sources: BCCDC Public Health Microbiology and Reference Laboratory,[30] Ministry of Health Services,[31, 32] and BC Vital Statistics Agency.[33, 34]*

## 4.2 Leading causes of deaths

In the SNR group, the top 5 leading causes of death were unspecified acute myocardial infarction (ICD-10 code: I21.9, n=1,177, 8.12%), unspecified malignant neoplasm of bronchus or lung (ICD-10 code: C34.9, n=840, 5.79%), atherosclerotic heart disease (ICD-10 code: I25.1, n=753, 5.19%), stroke/cerebrovascular accident (ICD-10 code: I64, n=551, 3.80%), and unspecified chronic obstructive pulmonary disease (ICD-10 code: J44.9, n=457, 3.15%). Table 4.2 lists the top 12 leading causes of death for the SNR group.

**Table 4.2 Top 12 leading causes of death for the SNR group**

| # | ICD-10 Code | Cause of death | N | % |
|---|---|---|---|---|
| 1 | I21.9 | Acute myocardial infarction, unspecified | 1,177 | 8.12% |
| 2 | C34.9 | Malignant neoplasm of bronchus or lung, unspecified | 840 | 5.79% |
| 3 | I25.1 | Atherosclerotic heart disease | 753 | 5.19% |
| 4 | I64 | Cerebrovascular accident, not elsewhere classified | 551 | 3.80% |
| 5 | J44.9 | Chronic obstructive pulmonary disease, unspecified | 457 | 3.15% |
| 6 | J18.9 | Pneumonia, unspecified | 407 | 2.81% |
| 7 | I25.9 | Chronic ischemic heart disease, unspecified | 404 | 2.79% |
| 8 | C25.9 | Malignant neoplasm of pancreas, unspecified | 366 | 2.52% |
| 9 | C85.9 | Non-Hodgkin's lymphoma, unspecified type | 286 | 1.97% |
| 10 | I50.0 | Congestive heart failure | 273 | 1.88% |
| 11 | C18.9 | Malignant neoplasm of colon, unspecified | 267 | 1.84% |
| 12 | C50.9 | Malignant neoplasm of female breast, unspecified | 252 | 1.74% |

*Data sources: BCCDC Public Health Microbiology and Reference Laboratory,[30] Ministry of Health Services,[31, 32] and BC Vital Statistics Agency.[33, 34]*

In the MNR group, the top 5 leading causes of death were unspecified acute myocardial infarction (ICD-10 code: I21.9, n=175, 5.37%), atherosclerotic heart disease (ICD-10 code: I25.1, n=122, 3.74%), unspecified malignant neoplasm of bronchus or lung (ICD-10 code: C34.9, n=113, 3.47%), other and unspecified cirrhosis of liver (ICD-10 code: K74.6, n=100, 3.07%), and diabetes mellitus with renal complications (ICD-10 code: E14.2, n=93, 2.85%). Table 4.3 lists the top 12 leading causes of death for the MNR group.

**Table 4.3 Top 12 leading causes of death for the MNR group**

| # | ICD-10 Code | Cause of death | N | % |
|---|---|---|---|---|
| 1 | I21.9 | Acute myocardial infarction, unspecified | 175 | 5.37% |
| 2 | I25.1 | Atherosclerotic heart disease | 122 | 3.74% |
| 3 | C34.9 | Malignant neoplasm of bronchus or lung, unspecified | 113 | 3.47% |
| 4 | K74.6 | Other and unspecified cirrhosis of liver | 100 | 3.07% |
| 5 | E14.2 | Diabetes mellitus not elsewhere classified, with renal complications | 93 | 2.85% |
| 6 | N19 | Unspecified renal failure | 91 | 2.79% |
| 7 | N18.9 | Chronic renal failure, unspecified | 84 | 2.58% |
| 8 | X42 | Accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified | 82 | 2.51% |
| 9 | I64 | Cerebrovascular accident, not elsewhere classified | 79 | 2.42% |
| 10 | C85.9 | Non-Hodgkin's lymphoma, unspecified type | 68 | 2.09% |
| 11 | J44.9 | Chronic obstructive pulmonary disease, unspecified | 61 | 1.87% |
| 12 | K70.3 | Alcoholic cirrhosis of liver | 60 | 1.84% |

*Data sources: BCCDC Public Health Microbiology and Reference Laboratory,[30] Ministry of Health Services,[31, 32] and BC Vital Statistics Agency.[33, 34]*

In the anti-HCV non-reactive group (Table 4.2 and Table 4.3), both the SNR and the MNR groups had the same top 3 leading causes of death: unspecified acute myocardial infarction, atherosclerotic heart disease, and unspecified malignant neoplasm of bronchus or lung. However, stroke and pulmonary diseases were ranked as the 4th and the 5th leading cause of death, respectively, in the SNR group. However, liver cirrhosis and diabetes mellitus were ranked as the 4th and the 5th leading cause of death,

respectively, in the MNR group. This likely reflects the fact that individuals who have liver disease or cirrhosis would undergo tests on a number of occasions to rule out HCV as a potential causal agent.

In the REAC group, the top 5 leading causes of death were accidental poisoning by and exposure to narcotics and psychodysleptics such as cannabis, cocaine, codeine, heroin, lysergide, mescaline, methadone, morphine and opium, not elsewhere classified (ICD-10 code: X42, N=349, 11.78%), chronic viral hepatitis C (ICD-10 code: B18.2, N=316, 10.66%), HIV resulting in other infectious and parasitic diseases (ICD-10 code: B20.8, N=136, 4.59%), accidental poisoning by and exposure to other and unspecified drugs, medicaments and biological subs (ICD-10 code: X44, N=123, 4.15%), unspecified malignant neoplasm of bronchus or lung (ICD-10 code: C34.9, N=111, 3.75%). Table 4.4 lists the top 12 leading causes of death for the REAC group.

**Table 4.4 Top 12 leading causes of death for the REAC group**

| # | ICD-10 Code | Cause of death | N | % |
|---|---|---|---|---|
| 1 | X42 | Accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified | 349 | 11.78% |
| 2 | B18.2 | Chronic viral hepatitis C | 316 | 10.66% |
| 3 | B20.8 | HIV resulting in other infectious and parasitic diseases | 136 | 4.59% |
| 4 | X44 | Accidental poisoning by and exposure to other and unspecified drugs, medicaments and biological substances | 123 | 4.15% |
| 5 | C34.9 | Malignant neoplasm of bronchus or lung, unspecified | 111 | 3.75% |
| 6 | I21.9 | Acute MI, unspecified | 90 | 3.04% |
| 7 | C22.0 | Malignant neoplasm of liver cell carcinoma | 75 | 2.53% |
| 8 | B24 | Unspecified HIV disease | 68 | 2.29% |
| 9 | I25.1 | Atherosclerotic heart disease | 66 | 2.23% |
| 10 | B23.8 | HIV resulting in other specified conditions | 53 | 1.79% |
| 11 | K70.3 | Alcoholic cirrhosis of liver | 53 | 1.79% |
| 12 | J44.9 | Chronic obstructive pulmonary disease, unspecified | 45 | 1.52% |

*Data sources: BCCDC Public Health Microbiology and Reference Laboratory,[30] Ministry of Health Services,[31, 32] and BC Vital Statistics Agency.[33, 34]*

In the SERO group, the top 5 leading causes of death were accidental poisoning by and exposure to narcotics and psychodysleptics such as cannabis, cocaine, codeine, heroin, lysergide, mescaline, methadone, morphine and opium, not elsewhere classified (ICD-10 code: X42, N=33, 24.09%), accidental poisoning by and exposure to other and unspecified drugs, medicaments and biological substance (ICD-10 code: X44, N=14, 10.22%), HIV resulting in other infectious and parasitic diseases (ICD-10 code: B20.8, N=10, 7.30%), HIV resulting in other specified conditions (ICD-10 code: B23.8, N=5, 3.65%), and other ill-defined and unspecified causes of mortality (ICD-10 code: R99, N=5, 3.65%). Table 4.5 lists the top 12 leading causes of death for the SERO group.

**Table 4.5 Top 12 leading causes of death for the SERO group**

| # | ICD-10 Code | Cause of death | N | % |
|---|---|---|---|---|
| 1 | X42 | Accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified | 33 | 24.09% |
| 2 | X44 | Accidental poisoning by and exposure to other and unspecified drugs, medicaments and biological substances | 14 | 10.22% |
| 3 | B20.8 | HIV resulting in other infectious and parasitic diseases | 10 | 7.30% |
| 4 | B23.8 | HIV resulting in other specified conditions | 5 | 3.65% |
| 5 | R99 | Other ill-defined and unspecified causes of mortality | 5 | 3.65% |
| 6 | X64 | Suicide by other and unspecified drugs, medicaments and biological substances | <5 | <3.65% |
| 7 | B18.2 | Chronic viral hepatitis C | <5 | <3.65% |
| 8 | C34.9 | Malignant neoplasm of bronchus or lung, unspecified | <5 | <3.65% |
| 9 | X61 | Suicide by antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified | <5 | <3.65% |
| 10 | X70 | Suicide by hanging, strangulation and suffocation | <5 | <3.65% |
| 11 | X41 | Accidental poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified | <5 | <3.65% |
| 12 | X45 | Accidental poisoning by and exposure to alcohol | <5 | <3.65% |

*Data sources: BCCDC Public Health Microbiology and Reference Laboratory,[30] Ministry of Health Services,[31, 32] and BC Vital Statistics Agency.[33, 34]*

In the anti-HCV reactive (positive) group (Table 4.4 and Table 4.5), both the REAC group (12%) and the SERO group (24%) had the same leading cause of death - accidental poisoning by and exposure to narcotics and psychodysleptics hallucinogens such as cannabis, cocaine, codeine, heroin, lysergide, mescaline, methadone, morphine and opium. The second highest cause of death was chronic viral hepatitis and accounted for 11% of deaths in the REAC group. Liver-related deaths were much higher in the REAC group (22%, 646/2,963) compared to the SERO group (6%, 8/137). Drug and HIV related causes of death were remarkably high in the anti-HCV reactive (positive) group; about 29% (861/2,963) of deaths in the REAC group and over 54% (74/137) of deaths were in the SERO group.

## 4.3 Standardized mortality ratios

The SMRs for all-cause and disease specific mortality compared to the general population of BC are given in Table 4.6 to Table 4.11. There are SMR tables for each sex, as well as for all individuals. Each set has an SMR table for a priori mortality end points and an SMR table for disease specific mortality by ICD-10 classification code for underlying cause of death. In total, there are six summary tables for the SMRs. The SMRs for all individuals are shown in Table 4.6 for a priori mortality end points and Table 4.7 for disease specific mortality by ICD-10 classification code for underlying cause of death. The SMRs for males are shown in Table 4.8 and Table 4.9; the SMRs for females are shown in Table 4.10 and Table 4.11.

## Table 4.6 A priori mortality end points SMRs with 95% CIs for males and females

| | SNR (N=367,634) | | MNR (N=82,126) | | REAC (N=29,086) | | SERO (N=2,641) | |
|---|---|---|---|---|---|---|---|---|
| Description | N | SMR (95% CI) | N | SMR (95% CI) | N | SMR (95% CI) | N | SMR (95% CI) |
| All-cause | 14496 | 1.48 ( 1.46- 1.51) | 3261 | 2.74 ( 2.65- 2.84) | 2963 | 4.67 ( 4.51- 4.84) | 137 | 10.18 ( 8.54- 12.03) |
| Liver-related | 717 | 3.09 ( 2.87- 3.32) | 349 | 9.36 ( 8.40- 10.40) | 646 | 24.25 ( 22.42- 26.20) | 8 | 13.07 ( 5.63- 25.74) |
| Viral hepatitis | 37 | 1.17 ( 0.82- 1.61) | 15 | 2.52 ( 1.41- 4.16) | 358 | 64.80 ( 58.26- 71.88) | 5 | 35.92 ( 11.64- 83.70) |
| Liver cancer (C22) | 208 | 2.93 ( 2.55- 3.36) | 60 | 5.94 ( 4.53- 7.64) | 113 | 17.78 ( 14.65- 21.38) | <5 | 7.94 ( 0.20- 44.24) |
| Liver disease | 472 | 3.64 ( 3.32- 3.98) | 274 | 12.90 ( 11.42- 14.52) | 175 | 11.86 ( 10.16- 13.75) | <5 | 5.76 ( 0.70- 20.80) |
| Alcoholic liver disease | 220 | 3.75 ( 3.27- 4.28) | 94 | 8.85 ( 7.15- 10.84) | 94 | 11.43 ( 9.23- 13.98) | <5 | 4.83 ( 0.12- 26.89) |
| Non-alcoholic liver disease | 252 | 3.55 ( 3.12- 4.01) | 180 | 16.92 ( 14.54- 19.58) | 81 | 12.36 ( 9.81- 15.36) | <5 | 7.10 ( 0.18- 39.55) |
| Drug-related | 283 | 1.72 ( 1.53- 1.94) | 154 | 4.42 ( 3.75- 5.18) | 594 | 19.45 ( 17.92- 21.08) | 59 | 38.08 ( 28.98- 49.12) |
| HIV | 83 | 1.90 ( 1.51- 2.35) | 44 | 4.63 ( 3.36- 6.21) | 267 | 25.14 ( 22.21- 28.34) | 15 | 35.45 ( 19.85- 58.49) |
| Diabetes | 547 | 1.97 ( 1.81- 2.15) | 212 | 6.17 ( 5.37- 7.06) | 35 | 2.16 ( 1.51- 3.01) | <5 | 3.97 ( 0.10- 22.13) |
| Renal failure | 350 | 2.37 ( 2.13- 2.64) | 219 | 14.08 ( 12.28- 16.07) | 30 | 4.35 ( 2.94- 6.22) | <5 | 13.15 ( 0.33- 73.23) |
| Malignant neoplasms | 4080 | 1.46 ( 1.41- 1.50) | 735 | 1.95 ( 1.81- 2.10) | 464 | 2.43 ( 2.21- 2.66) | 7 | 2.09 ( 0.84- 4.30) |
| Hepatocellular carcinoma | 151 | 5.62 ( 4.76- 6.59) | 50 | 11.90 ( 8.83- 15.69) | 112 | 37.98 ( 31.27- 45.70) | <5 | 15.06 ( 0.38- 83.88) |
| Non-Hodgkin lymphoma | 287 | 2.50 ( 2.22- 2.81) | 70 | 4.52 ( 3.52- 5.71) | 32 | 3.75 ( 2.56- 5.29) | 0 | 0.00 ( 0.00- 18.25) |
| Intrahepatic cholangiocarcinoma | 57 | 3.65 ( 2.77- 4.73) | 10 | 4.63 ( 2.22- 8.53) | <5 | 1.00 ( 0.03- 5.56) | 0 | 0.00 ( 0.00-164.96) |
| Extrahepatic cholangiocarcinoma | 16 | 3.21 ( 1.84- 5.20) | <5 | 3.41 ( 0.41- 12.31) | 0 | 0.00 ( 0.00- 10.08) | 0 | 0.00 ( 0.00-810.54) |
| Leukemia | 240 | 2.55 ( 2.24- 2.89) | 79 | 6.43 ( 5.09- 8.01) | 15 | 2.41 ( 1.35- 3.98) | <5 | 7.71 ( 0.20- 42.94) |
| Multiple myeloma | 111 | 2.21 ( 1.82- 2.66) | 55 | 8.42 ( 6.34- 10.96) | 8 | 2.53 ( 1.09- 4.98) | 0 | 0.00 ( 0.00- 67.17) |
| Pancreatic cancer | 380 | 2.45 ( 2.21- 2.71) | 57 | 2.76 ( 2.09- 3.58) | 29 | 2.82 ( 1.89- 4.06) | 0 | 0.00 ( 0.00- 19.33) |
| Malignant neoplasms except liver, bile duct, NHL, leukemia, multiple myeloma, pancreas | 3077 | 1.33 ( 1.29- 1.38) | 491 | 1.58 ( 1.44- 1.73) | 282 | 1.80 ( 1.60- 2.03) | 6 | 2.20 ( 0.81- 4.79) |
| Endocrine nutritional and metabolic disease except diabetes | 127 | 1.71 ( 1.43- 2.04) | 38 | 4.15 ( 2.94- 5.70) | 8 | 1.68 ( 0.72- 3.30) | 0 | 0.00 ( 0.00- 29.39) |
| Diseases of the digestive system except liver disease | 404 | 1.63 ( 1.47- 1.80) | 113 | 4.16 ( 3.43- 5.00) | 60 | 4.50 ( 3.43- 5.79) | <5 | 14.69 ( 3.03- 42.90) |
| Certain infectious and parasitic diseases except viral hepatitis and HIV | 145 | 1.57 ( 1.33- 1.85) | 67 | 5.91 ( 4.58- 7.51) | 37 | 6.52 ( 4.59- 8.99) | <5 | 8.50 ( 0.22- 47.35) |

*Data sources: BCCDC Public Health Microbiology and Reference Laboratory,[30] Ministry of Health Services,[31, 32] and BC Vital Statistics Agency.[33, 34] 95% CIs were calculated by Byar's approximation.[95]*

## Table 4.7 Disease specific SMRs with 95% CIs for males and females

| | SNR (N=367,634) | | MNR (N=82,126) | | REAC (N=29,086) | | SERO (N=2,641) | |
|---|---|---|---|---|---|---|---|---|
| Description | N | SMR (95% CI) | N | SMR (95% CI) | N | SMR (95% CI) | N | SMR (95% CI) |
| Certain infectious and parasitic diseases | 265 | 1.58 ( 1.40- 1.79) | 126 | 4.71 ( 3.92- 5.61) | 662 | 30.37 ( 28.10- 32.77) | 21 | 30.91 ( 19.13- 47.29) |
| Neoplasms | 4206 | 1.47 ( 1.42- 1.51) | 760 | 1.98 ( 1.84- 2.12) | 475 | 2.43 ( 2.22- 2.66) | 8 | 2.33 ( 1.00- 4.58) |
| Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism | 49 | 1.75 ( 1.30- 2.32) | 18 | 5.76 ( 3.42- 9.10) | 12 | 7.19 ( 3.72- 12.58) | <5 | 31.56 ( 0.80-175.81) |
| Endocrine, nutritional and metabolic diseases | 674 | 1.92 ( 1.78- 2.07) | 250 | 5.75 ( 5.06- 6.51) | 43 | 2.05 ( 1.49- 2.77) | <5 | 2.83 ( 0.07- 15.75) |
| Mental and behavioural disorders | 271 | 1.15 ( 1.02- 1.30) | 68 | 2.63 ( 2.04- 3.34) | 98 | 7.00 ( 5.68- 8.53) | <5 | 14.08 ( 3.83- 36.04) |
| Diseases of the nervous system | 388 | 1.07 ( 0.97- 1.19) | 62 | 1.52 ( 1.16- 1.95) | 34 | 1.80 ( 1.25- 2.52) | <5 | 6.11 ( 0.74- 22.04) |
| Diseases of the eye and adnexa | <5 | 5.44 ( 0.14- 30.30) | 0 | 0.00 ( 0.00- 88.27) | 0 | 0.00 ( 0.00-233.01) | 0 | 0.00 ( 0.00-4405.1) |
| Diseases of the ear and mastoid process | <5 | 3.22 ( 0.08- 17.95) | 0 | 0.00 ( 0.00- 87.82) | 0 | 0.00 ( 0.00-192.83) | 0 | 0.00 ( 0.00- 22861) |
| Diseases of the circulatory system | 4842 | 1.44 ( 1.40- 1.48) | 788 | 2.23 ( 2.08- 2.39) | 378 | 2.17 ( 1.96- 2.40) | 12 | 5.80 ( 3.00- 10.15) |
| Diseases of the respiratory system | 1326 | 1.31 ( 1.24- 1.38) | 187 | 1.83 ( 1.57- 2.11) | 133 | 2.95 ( 2.47- 3.49) | <5 | 4.71 ( 0.57- 17.02) |
| Diseases of the digestive system | 876 | 2.32 ( 2.17- 2.48) | 387 | 8.00 ( 7.22- 8.84) | 235 | 8.37 ( 7.33- 9.51) | 5 | 9.07 ( 2.94- 21.13) |
| Diseases of the skin and subcutaneous tissue | 35 | 2.34 ( 1.63- 3.26) | <5 | 2.62 ( 0.71- 6.72) | <5 | 4.22 ( 0.87- 12.33) | 0 | 0.00 ( 0.00-341.07) |
| Diseases of the musculoskeletal system and connective tissue | 143 | 2.33 ( 1.97- 2.75) | 37 | 5.01 ( 3.52- 6.90) | 9 | 2.71 ( 1.24- 5.14) | 0 | 0.00 ( 0.00- 45.20) |
| Diseases of the genitourinary system | 346 | 1.94 ( 1.74- 2.16) | 208 | 11.13 ( 9.67- 12.75) | 35 | 4.29 ( 2.99- 5.97) | <5 | 10.81 ( 0.27- 60.23) |
| Pregnancy, childbirth and the puerperium | <5 | 1.11 ( 0.03- 6.19) | <5 | 4.77 ( 0.12- 26.55) | 0 | 0.00 ( 0.00- 40.39) | 0 | 0.00 ( 0.00-348.29) |
| Certain conditions originating in the perinatal period | 7 | 347.22 (139.23-715.27) | <5 | 1253.6 (258.25-3660.6) | <5 | 4995.3 (126.38- 27824) | 0 | - |
| Congenital malformations, deformations and chromosomal abnormalities | 48 | 2.61 ( 1.93- 3.46) | 19 | 5.85 ( 3.52- 9.13) | 5 | 2.50 ( 0.81- 5.82) | 0 | 0.00 ( 0.00- 30.38) |
| Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified | 51 | 0.87 ( 0.65- 1.15) | 28 | 3.38 ( 2.25- 4.90) | 35 | 7.03 ( 4.90- 9.78) | 5 | 23.73 ( 7.69- 55.29) |
| External causes of morbidity and mortality | 966 | 1.45 ( 1.36- 1.54) | 315 | 2.61 ( 2.33- 2.91) | 804 | 8.49 ( 7.92- 9.10) | 75 | 15.60 ( 12.27- 19.56) |

***Data sources: BCCDC Public Health Microbiology and Reference Laboratory,[30] Ministry of Health Services,[31, 32] and BC Vital Statistics Agency.[33, 34] 95% CIs were calculated by Byar's approximation.[95]***

## Table 4.8 A priori mortality end points SMRs with 95% CIs for males

| | SNR (N=162,174) | | MNR (N=35,244) | | REAC (N=18,671) | | SERO (N=1,457) | |
|---|---|---|---|---|---|---|---|---|
| Description | N | SMR (95% CI) | N | SMR (95% CI) | N | SMR (95% CI) | N | SMR (95% CI) |
| All-cause | 8063 | 1.50 ( 1.47- 1.54) | 1869 | 2.79 ( 2.66- 2.92) | 2104 | 4.77 ( 4.56- 4.97) | 92 | 9.59 ( 7.73- 11.76) |
| Liver-related | 444 | 3.08 ( 2.80- 3.39) | 189 | 8.08 ( 6.97- 9.32) | 454 | 21.73 ( 19.78- 23.83) | <8 | 15.08 ( 6.05- 31.06) |
| Viral hepatitis | 21 | 1.02 ( 0.63- 1.56) | 9 | 2.26 ( 1.04- 4.30) | 249 | 53.55 ( 47.11- 60.64) | 5 | 43.83 ( 14.20-102.13) |
| Liver cancer (C22) | 144 | 3.09 ( 2.60- 3.64) | 40 | 5.80 ( 4.14- 7.89) | 89 | 17.08 ( 13.72- 21.02) | <5 | 9.27 ( 0.23- 51.66) |
| Liver disease | 279 | 3.64 ( 3.22- 4.09) | 140 | 11.20 ( 9.42- 13.21) | 116 | 10.51 ( 8.69- 12.61) | <5 | 4.13 ( 0.10- 22.98) |
| Alcoholic liver disease | 149 | 3.92 ( 3.32- 4.60) | 59 | 8.81 ( 6.71- 11.37) | 63 | 9.76 ( 7.50- 12.49) | 0 | 0.00 ( 0.00- 20.26) |
| Non-alcoholic liver disease | 130 | 3.35 ( 2.80- 3.98) | 81 | 13.89 ( 11.03- 17.27) | 53 | 11.53 ( 8.63- 15.08) | <5 | 10.51 ( 0.27- 58.52) |
| Drug-related | 173 | 1.71 ( 1.47- 1.99) | 95 | 4.42 ( 3.57- 5.40) | 435 | 17.67 ( 16.05- 19.41) | 44 | 38.43 ( 27.92- 51.59) |
| HIV | 74 | 2.17 ( 1.70- 2.72) | 39 | 5.32 ( 3.78- 7.28) | 205 | 21.29 ( 18.47- 24.41) | 11 | 31.14 ( 15.54- 55.74) |
| Diabetes | 309 | 1.96 ( 1.75- 2.20) | 107 | 5.30 ( 4.34- 6.40) | 24 | 2.10 ( 1.35- 3.11) | <5 | 5.30 ( 0.13- 29.54) |
| Renal failure | 178 | 2.19 ( 1.88- 2.54) | 131 | 15.05 ( 12.58- 17.85) | 21 | 4.62 ( 2.86- 7.07) | <5 | 19.35 ( 0.49-107.80) |
| Malignant neoplasms | 2238 | 1.49 ( 1.43- 1.55) | 394 | 2.02 ( 1.82- 2.23) | 332 | 2.72 ( 2.43- 3.02) | <5 | 2.01 ( 0.55- 5.16) |
| Hepatocellular carcinoma | 114 | 5.49 ( 4.53- 6.60) | 37 | 11.14 ( 7.85- 15.36) | 88 | 33.39 ( 26.78- 41.14) | <5 | 16.32 ( 0.41- 90.90) |
| Non-Hodgkin lymphoma | 174 | 2.63 ( 2.25- 3.05) | 43 | 4.78 ( 3.46- 6.43) | 22 | 3.61 ( 2.26- 5.45) | 0 | 0.00 ( 0.00- 25.64) |
| Intrahepatic cholangiocarcinoma | 30 | 3.85 ( 2.60- 5.51) | <5 | 2.82 ( 0.58- 8.22) | <5 | 1.54 ( 0.04- 8.60) | 0 | 0.00 ( 0.00-253.82) |
| Extrahepatic cholangiocarcinoma | 9 | 3.23 ( 1.48- 6.14) | <5 | 3.04 ( 0.08- 16.93) | 0 | 0.00 ( 0.00- 15.12) | 0 | 0.00 ( 0.00-1269.1) |
| Leukemia | 135 | 2.36 ( 1.98- 2.79) | 43 | 5.81 ( 4.20- 7.82) | 9 | 2.04 ( 0.94- 3.88) | 0 | 0.00 ( 0.00- 35.86) |
| Multiple myeloma | 60 | 2.11 ( 1.61- 2.72) | 31 | 8.55 ( 5.81- 12.14) | 6 | 2.77 ( 1.02- 6.04) | 0 | 0.00 ( 0.00-103.73) |
| Pancreatic cancer | 196 | 2.52 ( 2.18- 2.90) | 32 | 3.07 ( 2.10- 4.33) | 18 | 2.69 ( 1.59- 4.25) | 0 | 0.00 ( 0.00- 29.38) |
| Malignant neoplasms except liver, bile duct, NHL, leukemia, multiple myeloma, pancreas | 1655 | 1.35 ( 1.29- 1.42) | 247 | 1.57 ( 1.38- 1.78) | 197 | 2.02 ( 1.75- 2.32) | <5 | 1.94 ( 0.40- 5.67) |
| Endocrine nutritional and metabolic disease except diabetes | 62 | 1.75 ( 1.34- 2.24) | 20 | 4.25 ( 2.60- 6.54) | 5 | 1.57 ( 0.51- 3.66) | 0 | 0.00 ( 0.00- 42.61) |
| Diseases of the digestive system except liver disease | 169 | 1.42 ( 1.21- 1.65) | 63 | 4.58 ( 3.52- 5.86) | 44 | 5.14 ( 3.74- 6.91) | <5 | 7.16 ( 0.18- 39.86) |
| Certain infectious and parasitic diseases except viral hepatitis and HIV | 64 | 1.37 ( 1.05- 1.75) | 38 | 6.45 ( 4.56- 8.85) | 20 | 5.40 ( 3.30- 8.31) | <5 | 12.68 ( 0.32- 70.62) |

***Data sources: BCCDC Public Health Microbiology and Reference Laboratory,[30] Ministry of Health Services,[31, 32] and BC Vital Statistics Agency.[33, 34] 95% CIs were calculated by Byar's approximation.[95]***

## Table 4.9 Disease specific SMRs with 95% CIs for males

| | SNR (N=162,174) | | MNR (N=35,244) | | REAC (N=18,671) | | SERO (N=1,457) | |
|---|---|---|---|---|---|---|---|---|
| Description | N | SMR (95% CI) | N | SMR (95% CI) | N | SMR (95% CI) | N | SMR (95% CI) |
| Certain infectious and parasitic diseases | 159 | 1.57 ( 1.33- 1.83) | 86 | 5.00 ( 4.00- 6.18) | 474 | 26.38 ( 24.06- 28.87) | 17 | 31.14 ( 18.15- 49.82) |
| Neoplasms | 2309 | 1.50 ( 1.44- 1.56) | 408 | 2.04 ( 1.85- 2.25) | 338 | 2.70 ( 2.42- 3.01) | 5 | 2.44 ( 0.79- 5.70) |
| Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism | 27 | 2.00 ( 1.32- 2.92) | 11 | 7.14 ( 3.56- 12.78) | 10 | 9.31 ( 4.47- 17.13) | <5 | 47.00 ( 1.19-261.81) |
| Endocrine, nutritional and metabolic diseases | 371 | 1.92 ( 1.73- 2.13) | 127 | 5.10 ( 4.25- 6.07) | 29 | 1.99 ( 1.33- 2.86) | <5 | 3.87 ( 0.10- 21.53) |
| Mental and behavioural disorders | 148 | 1.39 ( 1.18- 1.64) | 42 | 3.23 ( 2.33- 4.37) | 74 | 7.87 ( 6.18- 9.88) | <5 | 9.97 ( 1.21- 35.98) |
| Diseases of the nervous system | 187 | 1.07 ( 0.92- 1.24) | 35 | 1.73 ( 1.20- 2.40) | 14 | 1.21 ( 0.66- 2.03) | <5 | 5.00 ( 0.13- 27.87) |
| Diseases of the eye and adnexa | 0 | 0.00 ( 0.00-624.34) | 0 | 0.00 ( 0.00-5993.9) | 0 | 0.00 ( 0.00-5897.0) | 0 | - |
| Diseases of the ear and mastoid process | <5 | 5.13 ( 0.13- 28.59) | 0 | 0.00 ( 0.00-114.78) | 0 | 0.00 ( 0.00-255.81) | 0 | 0.00 ( 0.00- 22861) |
| Diseases of the circulatory system | 2779 | 1.49 ( 1.43- 1.55) | 466 | 2.25 ( 2.05- 2.46) | 245 | 2.02 ( 1.78- 2.29) | <5 | 2.62 ( 0.71- 6.71) |
| Diseases of the respiratory system | 767 | 1.35 ( 1.25- 1.45) | 111 | 1.90 ( 1.57- 2.29) | 89 | 3.00 ( 2.41- 3.69) | 0 | 0.00 ( 0.00- 10.81) |
| Diseases of the digestive system | 448 | 2.28 ( 2.08- 2.51) | 203 | 7.73 ( 6.71- 8.87) | 160 | 8.17 ( 6.95- 9.54) | <5 | 5.23 ( 0.63- 18.90) |
| Diseases of the skin and subcutaneous tissue | 10 | 1.52 ( 0.73- 2.80) | <5 | 2.71 ( 0.33- 9.78) | <5 | 7.04 ( 1.45- 20.56) | 0 | 0.00 ( 0.00-504.44) |
| Diseases of the musculoskeletal system and connective tissue | 42 | 2.06 ( 1.48- 2.78) | 16 | 6.54 ( 3.74- 10.60) | <5 | 2.59 ( 0.70- 6.62) | 0 | 0.00 ( 0.00-110.36) |
| Diseases of the genitourinary system | 166 | 1.76 ( 1.50- 2.04) | 123 | 12.29 ( 10.21- 14.66) | 25 | 4.82 ( 3.12- 7.14) | <5 | 17.60 ( 0.45- 98.06) |
| Certain conditions originating in the perinatal period | <5 | 164.68 ( 19.93-594.50) | 0 | 0.00 ( 0.00-1795.1) | 0 | 0.00 ( 0.00- 24906) | 0 | - |
| Congenital malformations, deformations and chromosomal abnormalities | 17 | 2.28 ( 1.33- 3.65) | 6 | 4.81 ( 1.77- 10.49) | <5 | 0.83 ( 0.02- 4.64) | 0 | 0.00 ( 0.00- 59.93) |
| Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified | 22 | 0.77 ( 0.48- 1.16) | 17 | 3.71 ( 2.16- 5.94) | 21 | 5.94 ( 3.68- 9.09) | <5 | 13.26 ( 1.60- 47.86) |
| External causes of morbidity and mortality | 608 | 1.37 ( 1.27- 1.49) | 216 | 2.61 ( 2.27- 2.98) | 617 | 7.80 ( 7.19- 8.44) | 56 | 14.60 ( 11.03- 18.97) |

*Data sources: BCCDC Public Health Microbiology and Reference Laboratory,[30] Ministry of Health Services,[31, 32] and BC Vital Statistics Agency.[33, 34] 95% CIs were calculated by Byar's approximation.[95]*

## Table 4.10 A priori mortality end points SMRs with 95% CIs for females

| | SNR (N=205,460) | | MNR (N=46,882) | | REAC (N=10,415) | | SERO (N=1,184) | |
|---|---|---|---|---|---|---|---|---|
| Description | N | SMR (95% CI) | N | SMR (95% CI) | N | SMR (95% CI) | N | SMR (95% CI) |
| All-cause | 6433 | 1.46 ( 1.42- 1.49) | 1392 | 2.68 ( 2.54- 2.83) | 859 | 4.46 ( 4.16- 4.77) | 45 | 11.62 ( 8.48- 15.55) |
| Liver-related | 273 | 3.09 ( 2.74- 3.48) | 160 | 11.51 ( 9.79- 13.44) | 192 | 33.39 ( 28.84- 38.47) | <5 | 6.76 ( 0.17- 37.65) |
| Viral hepatitis | 16 | 1.45 ( 0.83- 2.34) | 6 | 3.05 ( 1.12- 6.65) | 109 | 124.60 (102.30-150.30) | 0 | 0.00 ( 0.00-119.46) |
| Liver cancer (C22) | 64 | 2.64 ( 2.03- 3.37) | 20 | 6.24 ( 3.81- 9.61) | 24 | 20.95 ( 13.43- 31.00) | 0 | 0.00 ( 0.00-165.88) |
| Liver disease | 193 | 3.64 ( 3.15- 4.20) | 134 | 15.34 ( 12.86- 18.17) | 59 | 15.82 ( 12.04- 20.41) | <5 | 9.55 ( 0.24- 53.17) |
| Alcoholic liver disease | 71 | 3.43 ( 2.68- 4.32) | 35 | 8.92 ( 6.21- 12.41) | 31 | 17.50 ( 11.89- 24.85) | <5 | 16.92 ( 0.43- 94.26) |
| Non-alcoholic liver disease | 122 | 3.78 ( 3.14- 4.52) | 99 | 20.58 ( 16.73- 25.06) | 28 | 14.30 ( 9.51- 20.74) | 0 | 0.00 ( 0.00- 65.70) |
| Drug-related | 110 | 1.74 ( 1.43- 2.10) | 59 | 4.43 ( 3.37- 5.72) | 159 | 26.85 ( 22.84- 31.36) | 15 | 37.08 ( 20.76- 61.18) |
| HIV | 9 | 0.94 ( 0.43- 1.78) | 5 | 2.29 ( 0.74- 5.33) | 62 | 62.46 ( 47.89- 80.07) | <5 | 57.21 ( 15.56-146.47) |
| Diabetes | 238 | 1.99 ( 1.74- 2.25) | 105 | 7.42 ( 6.07- 8.98) | 11 | 2.30 ( 1.15- 4.13) | 0 | 0.00 ( 0.00- 47.48) |
| Renal failure | 172 | 2.60 ( 2.23- 3.02) | 88 | 12.85 ( 10.31- 15.83) | 9 | 3.83 ( 1.75- 7.28) | 0 | 0.00 ( 0.00-123.01) |
| Malignant neoplasms | 1842 | 1.42 ( 1.36- 1.49) | 341 | 1.88 ( 1.69- 2.09) | 132 | 1.92 ( 1.60- 2.27) | <5 | 2.19 ( 0.45- 6.39) |
| Hepatocellular carcinoma | 37 | 6.04 ( 4.25- 8.33) | 13 | 14.73 ( 7.84- 25.20) | 24 | 76.46 ( 49.01-113.16) | 0 | 0.00 ( 0.00-585.57) |
| Non-Hodgkin lymphoma | 113 | 2.33 ( 1.92- 2.80) | 27 | 4.16 ( 2.74- 6.08) | 10 | 4.10 ( 1.97- 7.54) | 0 | 0.00 ( 0.00- 63.31) |
| Intrahepatic cholangiocarcinoma | 27 | 3.46 ( 2.28- 5.05) | 7 | 6.41 ( 2.57- 13.20) | 0 | 0.00 ( 0.00- 8.46) | 0 | 0.00 ( 0.00-471.17) |
| Extrahepatic cholangiocarcinoma | 7 | 3.19 ( 1.28- 6.56) | <5 | 3.88 ( 0.10- 21.61) | 0 | 0.00 ( 0.00- 30.24) | 0 | 0.00 ( 0.00-2243.4) |
| Leukemia | 105 | 2.84 ( 2.32- 3.44) | 36 | 7.36 ( 5.16- 10.20) | 6 | 3.30 ( 1.21- 7.20) | <5 | 21.71 ( 0.55-120.93) |
| Multiple myeloma | 51 | 2.33 ( 1.73- 3.06) | 24 | 8.25 ( 5.29- 12.22) | <5 | 2.00 ( 0.24- 7.22) | 0 | 0.00 ( 0.00-190.61) |
| Pancreatic cancer | 184 | 2.38 ( 2.05- 2.75) | 25 | 2.45 ( 1.59- 3.63) | 11 | 3.06 ( 1.53- 5.47) | 0 | 0.00 ( 0.00- 56.51) |
| Malignant neoplasms except liver, bile duct, NHL, leukemia, multiple myeloma, pancreas | 1422 | 1.31 ( 1.24- 1.38) | 244 | 1.59 ( 1.40- 1.80) | 85 | 1.45 ( 1.16- 1.79) | <5 | 2.52 ( 0.52- 7.37) |
| Endocrine nutritional and metabolic disease except diabetes | 65 | 1.68 ( 1.30- 2.14) | 18 | 4.05 ( 2.40- 6.40) | <5 | 1.89 ( 0.39- 5.52) | 0 | 0.00 ( 0.00- 94.73) |
| Diseases of the digestive system except liver disease | 235 | 1.83 ( 1.60- 2.08) | 50 | 3.73 ( 2.77- 4.92) | 16 | 3.35 ( 1.92- 5.42) | <5 | 31.01 ( 3.75-111.96) |
| Certain infectious and parasitic diseases except viral hepatitis and HIV | 81 | 1.78 ( 1.42- 2.22) | 29 | 5.33 ( 3.57- 7.68) | 17 | 8.62 ( 5.03- 13.80) | 0 | 0.00 ( 0.00- 77.39) |

*Data sources: BCCDC Public Health Microbiology and Reference Laboratory,[30] Ministry of Health Services,[31, 32] and BC Vital Statistics Agency.[33, 34] 95% CIs were calculated by Byar's approximation.[95]*

## Table 4.11 Disease specific SMRs with 95% CIs for females

| | SNR (N=205,460) | | MNR (N=46,882) | | REAC (N=10,415) | | SERO (N=1,184) | |
|---|---|---|---|---|---|---|---|---|
| Description | N | SMR (95% CI) | N | SMR (95% CI) | N | SMR (95% CI) | N | SMR (95% CI) |
| Certain infectious and parasitic diseases | 106 | 1.61 ( 1.32- 1.94) | 40 | 4.18 ( 2.98- 5.69) | 188 | 49.06 ( 42.29- 56.59) | <5 | 29.99 ( 8.16- 76.77) |
| Neoplasms | 1897 | 1.43 ( 1.37- 1.50) | 352 | 1.91 ( 1.71- 2.12) | 137 | 1.96 ( 1.64- 2.31) | <5 | 2.15 ( 0.44- 6.29) |
| Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism | 22 | 1.52 ( 0.95- 2.29) | 7 | 4.42 ( 1.77- 9.11) | <5 | 3.36 ( 0.41- 12.13) | 0 | 0.00 ( 0.00-288.26) |
| Endocrine, nutritional and metabolic diseases | 303 | 1.91 ( 1.70- 2.14) | 123 | 6.62 ( 5.50- 7.89) | 14 | 2.20 ( 1.20- 3.70) | 0 | 0.00 ( 0.00- 31.63) |
| Mental and behavioural disorders | 123 | 0.95 ( 0.79- 1.14) | 26 | 2.03 ( 1.32- 2.98) | 24 | 5.21 ( 3.34- 7.72) | <5 | 23.95 ( 2.90- 86.45) |
| Diseases of the nervous system | 201 | 1.08 ( 0.93- 1.23) | 27 | 1.31 ( 0.86- 1.92) | 20 | 2.74 ( 1.67- 4.22) | <5 | 7.83 ( 0.20- 43.60) |
| Diseases of the eye and adnexa | <5 | 5.59 ( 0.14- 31.11) | 0 | 0.00 ( 0.00- 89.59) | 0 | 0.00 ( 0.00-242.59) | 0 | 0.00 ( 0.00-4405.1) |
| Diseases of the ear and mastoid process | 0 | 0.00 ( 0.00- 25.98) | 0 | 0.00 ( 0.00-373.91) | 0 | 0.00 ( 0.00-783.27) | 0 | - |
| Diseases of the circulatory system | 2063 | 1.37 ( 1.31- 1.43) | 322 | 2.20 ( 1.97- 2.45) | 133 | 2.51 ( 2.10- 2.97) | 8 | 14.74 ( 6.35- 29.03) |
| Diseases of the respiratory system | 559 | 1.25 ( 1.15- 1.36) | 76 | 1.73 ( 1.36- 2.16) | 44 | 2.85 ( 2.07- 3.83) | <5 | 13.61 ( 1.65- 49.15) |
| Diseases of the digestive system | 428 | 2.36 ( 2.14- 2.59) | 184 | 8.32 ( 7.16- 9.61) | 75 | 8.82 ( 6.94- 11.06) | <5 | 17.73 ( 3.65- 51.77) |
| Diseases of the skin and subcutaneous tissue | 25 | 2.98 ( 1.93- 4.41) | <5 | 2.54 ( 0.31- 9.18) | 0 | 0.00 ( 0.00- 10.56) | 0 | 0.00 ( 0.00-1053.1) |
| Diseases of the musculoskeletal system and connective tissue | 101 | 2.47 ( 2.01- 3.00) | 21 | 4.25 ( 2.63- 6.50) | 5 | 2.81 ( 0.91- 6.55) | 0 | 0.00 ( 0.00- 76.56) |
| Diseases of the genitourinary system | 180 | 2.15 ( 1.85- 2.49) | 85 | 9.80 ( 7.83- 12.12) | 10 | 3.36 ( 1.61- 6.19) | 0 | 0.00 ( 0.00- 84.10) |
| Pregnancy, childbirth and the puerperium | <5 | 1.11 ( 0.03- 6.19) | <5 | 4.77 ( 0.12- 26.55) | 0 | 0.00 ( 0.00- 40.39) | 0 | 0.00 ( 0.00-348.29) |
| Certain conditions originating in the perinatal period | 5 | 623.78 (202.10-1453.4) | <5 | 4156.3 (856.19- 12136) | <5 | 12542 (317.30- 69856) | 0 | - |
| Congenital malformations, deformations and chromosomal abnormalities | 31 | 2.84 ( 1.93- 4.03) | 13 | 6.50 ( 3.46- 11.11) | <5 | 4.99 ( 1.36- 12.79) | 0 | 0.00 ( 0.00- 61.62) |
| Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified | 29 | 0.98 ( 0.65- 1.41) | 11 | 2.96 ( 1.48- 5.31) | 14 | 9.70 ( 5.30- 16.30) | <5 | 50.14 ( 10.33-146.40) |
| External causes of morbidity and mortality | 358 | 1.59 ( 1.43- 1.77) | 99 | 2.60 ( 2.12- 3.17) | 187 | 12.03 ( 10.37- 13.89) | 19 | 19.54 ( 11.77- 30.49) |

*Data sources: BCCDC Public Health Microbiology and Reference Laboratory,[30] Ministry of Health Services,[31, 32] and BC Vital Statistics Agency.[33, 34] 95% CIs were calculated by Byar's approximation.[95]*

### 4.3.1 All-cause

All four HCV serological groups had elevated all-cause SMR compared to the general BC population. The SMR was the highest in the SERO group (SMR=10.18, 95% confidence interval (CI): 8.54-12.03), followed by the REAC group (SMR=4.67, 95% CI: 4.51-4.84), the MNR group (SMR=2.74, 95% CI: 2.65-2.84) and the SNR group (SMR=1.48, 95% CI: 1.46-1.51). (Table 4.6) Similar results were observed for males and females separately. (Table 4.8, Table 4.10)

### 4.3.2 Liver-related

Both the SNR and the MNR groups had elevated liver-related SMR compared to the BC population. The SNR group had about 3 times the risk of dying from liver-related causes compared to the general BC population (SMR=3.09, 95% CI: 2.87-3.32), where as the MNR group had about 9 times the risk of dying from liver-related causes compared to the BC population (SMR=9.36, 95% CI: 8.40-10.40). The MNR group had the highest SMR for mortality related to liver diseases (SMR=12.90, 95% CI: 11.42-14.52). The risk of dying from non-alcoholic liver diseases was 16 times higher in the MNR group compared to the general BC population (SMR=16.92, 95% CI: 14.54-19.58). (Table 4.6) Similar patterns were found in both males and females. (Table 4.8, Table 4.10)

The SMR for liver-related deaths was substantial higher (SMR=24.25, 95% CI: 22.42-26.20) in the REAC group. The SMR for liver-related mortality was higher in females (SMR=33.39, 95% CI: 28.84-38.47) than in males (SMR=21.73, 95% CI: 19.78-23.83). The SMRs for mortality related to viral hepatitis (SMR=64.80, 95% CI: 58.26-71.88), liver cancer (SMR=17.78, 95% CI: 14.65-21.38), and alcoholic liver disease

(SMR=11.43, 95% CI: 9.23-13.98) were the highest in the REAC group. Similar patterns were also found in both males and females. (Table 4.6, Table 4.8, Table 4.10)

### 4.3.3 Drug-related

The SMR for the drug-related mortality (SMR=38.08, 95% CI: 28.98-49.12) was the highest in the SERO group, followed by the REAC group (SMR=19.45, 95% CI: 17.92-21.08), the MNR group (SMR=4.42, 95% CI: 3.75-5.18) and the SNR group (SMR=1.72, 95% CI: 1.53-1.94). (Table 4.6)

A similar pattern was found in both males and females. In males, the SMR for drug-related mortality was the highest in the SERO group (SMR=38.43, 95% CI: 27.92-51.59), followed by the REAC group (SMR=17.67, 95% CI: 16.05-19.41), the MNR group (SMR=4.42, 95% CI: 3.57-5.40) and the SNR group (SMR=1.71, 95% CI: 1.47-1.99). (Table 4.8)

In females, the drug-related mortality was the highest in the SERO group (SMR=37.08, 95% CI: 20.76-61.18), followed by the REAC group (SMR=26.85, 95% CI: 22.84-31.36), the MNR group (SMR=4.43, 95% CI: 3.37-5.72) and the SNR group (SMR=1.74, 95% CI: 1.43-2.10). (Table 4.10)

### 4.3.4 HIV

The REAC and SERO groups had significantly elevated SMRs for dying from HIV infection compared to the general BC population. The SERO group had the highest SMR for dying from HIV infection (SMR=35.45, 95% CI: 19.85-58.49). The REAC group had about 25 times the risk of dying from HIV infection compared to the general BC population (SMR=25.14, 95% CI: 22.21-28.34). In the REAC group, the SMR for

dying from HIV infection was higher in females (SMR=62.46, 95% CI: 47.89-80.07) compared to males (SMR=21.29, 95% CI: 18.47-24.41). (Table 4.6, Table 4.8, Table 4.10)

Referent to the general BC population, the SMR for dying from HIV infection were about 2 times higher in the SNR group (SMR=1.90, 95% CI: 1.51-2.35), and 5 times higher in the MNR group (SMR=4.63, 95% CI: 3.36-6.21). (Table 4.6)

### 4.3.5 Diabetes mellitus

The MNR group had the highest SMR for mortality due to diabetes mellitus. The MNR group had 6 times the risk of dying from diabetes mellitus compared to the general BC population (SMR=6.17, 95% CI: 5.37-7.06). Referent to the general BC population, the SNR group and the REAC group had an SMR of 1.97 (95% CI: 1.81-2.15) and 2.16 (95% CI: 1.51-3.01) respectively for mortality due to diabetes mellitus. (Table 4.6) A similar pattern was found in both males and females. (Table 4.8, Table 4.10)

### 4.3.6 Renal failure

The MNR group had the highest SMR for mortality due to renal failure. The MNR group had 14 times elevated risk of dying from renal failure compared to the general BC population (SMR=14.08, 95% CI: 12.28-16.07). The SNR group had about 2 times higher risks of dying from renal failure (SMR=2.37, 95% CI: 2.13-2.64) and the REAC group had about 4 times higher risks of dying from renal failure compared to the general BC population (SMR=4.35, 95% CI: 2.94-6.22). (Table 4.6) A similar pattern was found in both males and females. (Table 4.8, Table 4.10) This is consistent with the

fact that individuals with renal failure undergo routine testing for communicable disease markers including viral hepatitis.

### 4.3.7 Malignant neoplasms

The REAC group had 2 times higher risks of dying from malignant neoplasms compared to the general BC population (SMR=2.43, 95% CI: 2.21-2.66). The highest SMR for dying from malignant neoplasms was found in the REAC group, followed by the MNR group (SMR=1.95, 95% CI: 1.81-2.10) and the SNR group (SMR=1.46, 95%=1.41-1.50). In males, the REAC group had a higher SMR for mortality due to malignant neoplasms (SMR=2.72, 95% CI: 2.43-3.02) compared to females (SMR=1.92, 95% CI: 1.60-2.27). (Table 4.6, Table 4.8, Table 4.10)

#### 4.3.7.1 Hepatocellular carcinoma

The SMR for mortality due to hepatocellular carcinoma (SMR=37.98, 95% CI: 31.27-45.70) was the highest in the REAC group, followed by the MNR group (SMR=11.90, 95% CI: 8.83-15.69) and the SNR group (SMR=5.62, 95% CI: 4.76-6.59). Females in the REAC group had a higher elevated SMR for mortality due to hepatocellular carcinoma (SMR=76.46, 95% CI: 49.01-113.16) compared to males (SMR=33.39, 95% CI: 26.78-41.14). (Table 4.6, Table 4.8, Table 4.10)

#### 4.3.7.2 Non-Hodgkin lymphoma

The risk of dying from non-Hodgkin lymphoma was about 5 times higher in the MNR group compared to the general BC population (SMR=4.52, 95% CI: 3.52-5.71). The risk of dying from non-Hodgkin lymphoma was about 4 times and 3 times higher

compared to the general BC population in the REAC (SMR=3.75, 95% CI: 2.56-5.29) and the SNR (SMR=2.50, 95% CI: 2.22-2.81) groups, respectively. (Table 4.6) The pattern is similar in both males and females. (Table 4.8, Table 4.10)

#### 4.3.7.3 Cholangiocarcinoma

The risk of dying from intrahepatic cholangiocarcinoma was about 4 times and 5 times higher compared to the general BC population in the SNR (SMR=3.65, 95% CI: 2.77-4.73) and the MNR (SMR=4.63, 95% CI: 2.22-8.53) groups, respectively. The risk of dying from extrahepatic cholangiocarcinoma was 3 times higher in the SNR group (SMR=3.21, 95% CI: 1.84-5.20) compared to the general BC population. For extrahepatic cholangiocarcinoma, we did not observe any cases in the REAC and SERO groups. (Table 4.6)

### 4.3.8 Other

For all individuals, the SMR for mortality due to certain infectious and parasitic diseases was highly elevated in the REAC group (SMR=30.37, 95% CI: 28.10-32.77) and the SERO group (SMR=30.91, 95% CI: 19.13-47.29). All four HCV serological groups had about 2 times the risk of dying from malignant neoplasms compared to the general BC population. The SMR for mortality due to mental and behavioural disorders was the highest in the SERO group (SMR=14.08, 95% CI: 3.83-36.04), followed by the REAC group (SMR=7.00, 95% CI: 5.68-8.53), the MNR group (SMR=2.63, 95% CI: 2.04-3.34), and the SNR group (SMR=1.15, 95% CI: 1.02-1.30). In the SNR group, the SMR for mortality due to diseases of nervous system was not statistically significantly different from the general BC population (SMR=1.07, 95% CI: 0.97-1.19). The SMR for mortality

due to diseases of circulatory system was elevated in all four serological groups compared to the general BC population, 1.44 (95% CI: 1.40-1.48), 2.23 (95% CI: 2.08-2.39), 2.17 (95% CI: 1.96-2.40), 5.80 (95% CI: 3.00-10.15) times in the SNR, MNR, REAC, and the SERO groups, respectively. All four HCV serological groups had elevated SMR for mortality due to diseases of digestive system compared to the general BC population. The SMR for mortality due to diseases of digestive system was similar in the MNR (SMR=8.00, 95% CI: 7.22-8.84) and REAC (SMR=8.37, 95% CI: 7.33-9.51) groups, but lower in the SNR group (SMR=2.32, 95% CI: 2.17-2.48). The SMR for external causes of morbidity and mortality were the highest in the SERO group (SMR=15.60, 95% CI: 12.27-19.56), followed by the REAC group (SMR=8.49, 95% CI: 7.92-9.10), the MNR group (SMR=2.61, 95% CI: 2.33-2.91), and the SNR group (SMR=1.45, 95% CI: 1.36-1.54). (Table 4.7)

For all disease specific mortality by ICD-10 classification code for underlying cause of death, both males and females had similar patterns of SMRs as all individuals listed in Table 4.7. For both males and females, the SMR for mortality related to certain infectious and parasitic diseases was highly elevated in the REAC group (SMR=26.38, 95% CI: 24.06-28.87 for males; and higher in females, SMR=49.06, 95% CI: 42.29-56.59). For SNR group, the risk of dying from mental and behavioural disorders was not statistically significantly different compared to the general BC population (SMR=0.95, 95% CI: 0.79-1.14) in females, but the risk was higher in males (SMR=1.39, 95% CI: 1.18-1.64). In both males and females, the SMR for external causes of morbidity and mortality were highly elevated in both the SERO group (SMR=14.60, 95% CI: 11.03-18.97 for males; SMR=19.54, 95% CI: 11.77-30.49 for females) and the REAC group

(SMR=7.80, 95% CI: 7.19-8.44 for males; and higher in females, SMR=12.03, 95% CI: 10.37-13.89). (Table 4.8, Table 4.10)

## 4.4 Hazard ratios

Section 4.3 lists the SMR tables for which the risk of dying in the HCV serological groups were compared to the general population of BC. To compare the risks of dying between the HCV serological groups, the hazard ratios from the time-dependent Cox proportional hazard regression model were examined and shown in Table 4.12 to Table 4.15.

As mentioned in the methods section, the hazard ratio is an estimate of the ratio of the hazard rate between two strata, with one group as a referent group. For all causes of death, differences in hazard ratios by age and sex were examined. If a statistically significant interaction terms for sex or age were found, separate hazard ratios were calculated for each sex and age group. Young age was defined as age $< 40$ and old age is defined as age $\geq 40$. The REAC group and the SERO group were combined to form the HCV positive group due to the small number of observed deaths in the SERO group.

Table 4.12 shows the hazard ratios from the time-dependent Cox proportional hazard regression model for a prior mortality endpoints within the four HCV serological groups. For the comparisons of the HCV positive group with the SNR and the MNR groups, the hazard ratios for a priori mortality endpoints, cancer related mortality endpoints, and disease specific mortality endpoints are shown in Table 4.13, Table 4.14 and Table 4.15, respectively.

## Table 4.12 Hazard ratios with 95% CIs for a priori mortality endpoints

| | SNR | MNR | REAC | SERO | MNR vs SNR | | REAC vs SNR | | SERO vs MNR | | SERO vs REAC | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cause of Death | N | N | N | N | HR | 95% CI | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| All | 14496 | 3261 | 2963 | 137 | | | | | | | | |
| Age <40 | 847 | 423 | 791 | 85 | 2.29 | (2.04-2.58) | 6.99 | (6.33-7.75) | 3.68 | (2.89-4.61) | 1.20 | (0.96-1.50) |
| Age ≥40 | 13649 | 2838 | 2172 | 52 | 1.52 | (1.46-1.58) | 2.31 | (2.20-2.42) | 2.29 | (1.72-2.99) | 1.51 | (1.13-1.96) |
| Liver-related | 717 | 349 | 646 | 8 | 3.05 | (2.67-3.46) | 9.71 | (8.62-10.87) | 1.68 | (0.76-3.17) | 0.53 | (0.24-0.92) |
| Drug-related | 283 | 154 | 594 | 59 | 2.49 | (2.04-3.03) | 13.5 | (11.63-15.63) | 8.62 | (6.33-11.63) | 1.60 | (1.20-2.08) |
| HIV | 83 | 544 | 267 | 15 | | | | | | | | |
| Female | 9 | 5 | 62 | <5 | 2.65 | (0.81-7.69) | 66.7 | (35.71-142.86) | 25.6 | (6.37-100.00) | 1.00 | (0.30-2.42) |
| Male | 74 | 39 | 205 | 11 | 2.48 | (1.67-3.64) | 12.1 | (9.17-15.87) | 5.43 | (2.64-10.20) | 1.12 | (0.57-1.97) |

*Data sources: BCCDC Public Health Microbiology and Reference Laboratory,[30] Ministry of Health Services,[31, 32] and BC Vital Statistics Agency.[33, 34] Profile likelihood was used to calculate 95% CI.[100]*

**Table 4.13 Hazard ratios with 95% CIs for a priori mortality endpoints (with HCV positive group)**

| | SNR | MNR | HCV +ve | MNR vs SNR | | HCV +ve vs SNR | | HCV +ve vs MNR | |
|---|---|---|---|---|---|---|---|---|---|
| Cause of Death | N | N | N | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| All | 14496 | 3261 | 3100 | | | | | | |
| Age < 40 | 847 | 423 | 876 | 2.29 | (2.04-2.58) | 7.14 | (6.45-7.87) | 3.11 | (2.77-3.50) |
| Age ≥ 40 | 13649 | 2838 | 2224 | 1.52 | (1.46-1.58) | 2.33 | (2.22-2.43) | 1.53 | (1.45-1.62) |
| Liver-related | 717 | 349 | 654 | | | | | | |
| Female | 273 | 160 | 193 | 3.68 | (3.02-4.46) | 11.63 | (9.62-14.08) | 3.16 | (2.56-3.91) |
| Male | 444 | 189 | 461 | 2.66 | (2.24-3.14) | 8.62 | (7.52-9.90) | 3.24 | (2.73-3.86) |
| Viral hepatitis | 37 | 15 | 363 | 2.59 | (1.38-4.63) | 100 | (71.43-142.86) | 38.46 | (23.26-66.67) |
| Liver cancer | 208 | 60 | 114 | 1.91 | (1.42-2.54) | 7.25 | (5.68-9.17) | 3.79 | (2.76-5.24) |
| Liver disease | 472 | 274 | 177 | | | | | | |
| Age < 40 | 13 | 15 | 27 | 4.95 | (2.35-10.53) | 10.99 | (5.78-22.22) | 2.24 | (1.20-4.33) |
| Age ≥ 40 | 459 | 259 | 150 | 3.47 | (2.98-4.05) | 3.38 | (2.77-4.08) | 0.97 | (0.79-1.19) |
| Alcoholic | 220 | 94 | 95 | | | | | | |
| Female | 71 | 35 | 32 | 2.75 | (1.81-4.10) | 6.13 | (3.97-9.26) | 2.22 | (1.37-3.61) |
| Male | 149 | 59 | 63 | 2.2 | (1.61-2.96) | 2.59 | (1.90-3.50) | 1.18 | (0.82-1.69) |
| Non-alcoholic | 252 | 180 | 82 | | | | | | |
| Age < 40 | <5 | 5 | 12 | 5.38 | (1.42-21.74) | 17.24 | (5.95-62.50) | 3.23 | (1.18-10.20) |
| Age ≥ 40 | 248 | 175 | 70 | 4.61 | (3.79-5.62) | 3.53 | (2.66-4.63) | 0.77 | (0.57-1.01) |
| Drug-related | 283 | 154 | 653 | 2.49 | (2.04-3.03) | 14.08 | (12.20-16.39) | 5.62 | (4.72-6.76) |
| HIV | 83 | 44 | 282 | | | | | | |
| Female | 9 | 5 | 66 | 2.65 | (0.81-7.63) | 66.67 | (35.71-142.86) | 25.64 | (11.49-76.92) |
| Male | 74 | 39 | 216 | 2.48 | (1.67-3.64) | 12.05 | (9.26-15.87) | 4.88 | (3.48-6.99) |
| Renal Failure | 350 | 219 | 31 | 4.78 | (4.03-5.68) | 1.63 | (1.10-2.33) | 0.34 | (0.23-0.49) |
| Diabetes | 547 | 212 | 36 | 2.75 | (2.34-3.23) | 0.99 | (0.69-1.38) | 0.36 | (0.25-0.51) |

***Data sources: BCCDC Public Health Microbiology and Reference Laboratory,[30] Ministry of Health Services,[31, 32] and BC Vital Statistics Agency.[33, 34] Profile likelihood was used to calculate 95% CI.[100]***

## Table 4.14 Hazard ratios with 95% CIs for cancer mortality (with HCV positive group)

| | SNR | MNR | HCV +ve | MNR vs SNR | | HCV +ve vs SNR | | HCV +ve vs MNR | |
|---|---|---|---|---|---|---|---|---|---|
| Cause of Death | N | N | N | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| All Cancers | 4080 | 735 | 471 | | | | | | |
| Age < 40 | 164 | 80 | 34 | 2.3 | (1.75-2.99) | 1.59 | (1.08-2.29) | 0.69 | (0.46-1.03) |
| Age ≥ 40 | 3916 | 655 | 437 | 1.14 | (1.04-1.23) | 1.54 | (1.39-1.70) | 1.36 | (1.20-1.53) |
| Hepatocellular carcinoma | 151 | 50 | 113 | 2.23 | (1.60-3.05) | 9.62 | (7.41-12.50) | 4.33 | (3.09-6.13) |
| Non-Hodgkin lymphoma | 287 | 70 | 32 | 1.48 | (1.13-1.92) | 1.35 | (0.91-1.93) | 0.91 | (0.59-1.38) |
| Leukemia | 240 | 79 | 16 | 2.01 | (1.55-2.58) | 0.85 | (0.49-1.38) | 0.42 | (0.24-0.71) |
| Multiple myeloma | 111 | 55 | 8 | 3.23 | (2.31-4.44) | 0.99 | (0.44-1.92) | 0.31 | (0.13-0.61) |
| Pancreatic cancer | 380 | 57 | 29 | 0.95 | (0.71-1.25) | 1.16 | (0.77-1.67) | 1.22 | (0.77-1.89) |

*Data sources: BCCDC Public Health Microbiology and Reference Laboratory,[30] Ministry of Health Services,[31, 32] and BC Vital Statistics Agency.[33, 34] Profile likelihood was used to calculate 95% CI.[100]*

## Table 4.15 Hazard ratios with 95% CIs for disease specific mortality endpoints (with HCV positive group)

| | SNR | MNR | HCV +ve | MNR vs SNR | | HCV +ve vs SNR | | HCV +ve vs MNR | |
|---|---|---|---|---|---|---|---|---|---|
| Cause of Death | N | N | N | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| Certain infectious and parasitic diseases | 265 | 126 | 683 | 2.89 | (2.33-3.57) | 21.74 | (18.87-25.64) | 7.52 | (6.21-9.17) |
| Neoplasms | 4206 | 760 | 483 | | | | | | |
| Age < 40 | 171 | 83 | 34 | 2.29 | (1.75-2.97) | 1.53 | (1.04-2.19) | 0.67 | (0.44-0.99) |
| Age ≥ 40 | 4035 | 677 | 449 | 1.14 | (1.05-1.24) | 1.54 | (1.39-1.70) | 1.35 | (1.19-1.52) |
| Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism | 49 | 18 | 13 | 2.52 | (1.42-4.27) | 3.32 | (1.67-6.17) | 1.32 | (0.62-2.74) |
| Endocrine, nutritional and metabolic diseases | 674 | 250 | 44 | 2.65 | (2.28-3.06) | 0.98 | (0.71-1.33) | 0.37 | (0.27-0.51) |
| Mental and behavioural disorders | 271 | 68 | 102 | | | | | | |
| Age < 40 | 11 | 11 | 39 | 4.44 | (1.90-10.42) | 20.41 | (10.75-43.48) | 4.63 | (2.43-9.52) |
| Age ≥ 40 | 260 | 57 | 63 | 1.59 | (1.18-2.10) | 2.92 | (2.16-3.89) | 1.84 | (1.28-2.67) |
| Diseases of the nervous system | 388 | 62 | 36 | 1.23 | (0.93-1.60) | 1.35 | (0.93-1.90) | 1.10 | (0.72-1.66) |
| Diseases of the circulatory system | 4842 | 788 | 390 | | | | | | |
| Age < 40 | 52 | 42 | 44 | 3.69 | (2.44-5.52) | 5.05 | (3.33-7.58) | 1.37 | (0.89-2.10) |
| Age ≥ 40 | 4790 | 746 | 346 | 1.26 | (1.17-1.37) | 1.34 | (1.19-1.49) | 1.06 | (0.93-1.20) |
| Diseases of the respiratory system | 1326 | 187 | 135 | | | | | | |
| Age < 40 | 18 | 7 | 16 | 1.76 | (0.68-4.05) | 5.71 | (2.83-11.36) | 3.24 | (1.37-8.47) |
| Age ≥ 40 | 1308 | 180 | 119 | 1.12 | (0.96-1.31) | 1.64 | (1.34-1.98) | 1.46 | (1.15-1.84) |
| Diseases of the digestive system | 876 | 387 | 240 | | | | | | |
| Age < 40 | 29 | 25 | 35 | 3.79 | (2.20-6.45) | 6.80 | (4.13-11.24) | 1.79 | (1.07-3.04) |
| Age ≥ 40 | 847 | 362 | 205 | 2.89 | (2.55-3.27) | 3.03 | (2.58-3.55) | 1.05 | (0.88-1.25) |
| Diseases of the musculoskeletal system and connective tissue | 143 | 37 | 9 | 1.86 | (1.27-2.65) | 0.95 | (0.45-1.79) | 0.51 | (0.23-1.02) |
| Diseases of the genitourinary system | 346 | 208 | 36 | 4.65 | (3.91-5.52) | 1.94 | (1.35-2.71) | 0.42 | (0.29-0.59) |
| Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified | 51 | 28 | 40 | 3.19 | (1.98-5.05) | 7.30 | (4.65-11.36) | 2.29 | (1.39-3.82) |
| External causes of morbidity and mortality | 966 | 315 | 879 | | | | | | |
| Age < 40 | 403 | 164 | 453 | 1.83 | (1.52-2.19) | 7.81 | (6.80-9.01) | 4.29 | (3.58-5.15) |
| Age ≥ 40 | 563 | 151 | 426 | 1.52 | (1.26-1.81) | 5.13 | (4.46-5.85) | 3.38 | (2.80-4.10) |

*Data sources: BCCDC Public Health Microbiology and Reference Laboratory,[30] Ministry of Health Services,[31, 32] and BC Vital Statistics Agency.[33, 34] Profile likelihood was used to calculate 95% CI.[100]*

### 4.4.1 All-cause

Since a statistically significant interaction term for age was found, separate hazard ratios were calculated for each age stratum. Younger individuals (age < 40) in the REAC group were at 7 times the risk of all-cause mortality compared to the SNR group (HR=6.99, 95% CI: 6.33-7.75). All-cause mortality in the SERO group was about 4 times higher than mortality in the MNR group (HR=3.68, 95% CI: 2.89-4.61). The instantaneous rate of dying from all-cause mortality in the MNR group was about 2 times higher than the instantaneous rate of dying from all-cause mortality in the SNR group (HR=2.29, 95% CI: 2.04-2.58). The hazard ratio in the SERO group versus the REAC group was not statistically significant (HR=1.20, 95% CI: 0.96-1.50) for all-cause mortality.

For any given point in time, older individuals (age ≥ 40) had about 2 times the risk of dying from all-cause mortality in the REAC group relative to the SNR group (HR=2.31, 95% CI: 2.20-2.42). For the other three comparisons, MNR vs SNR (HR=1.52, 95% CI: 1.46-1.58), SERO vs MNR (HR=2.29, 95% CI: 1.72-2.99) and SERO vs REAC (HR=1.51, 95% CI: 1.13-1.96), the estimated relative risk in the comparison group were between 1.5 to 2 times higher than their referent group. (Table 4.12)

For younger individuals, the risk of all-cause mortality was significantly higher in the HCV positive group compared to both the SNR (HR=7.14, 95% CI: 6.45-7.87) and the MNR (HR=3.11, 95% CI: 2.77-3.50) groups. For older individuals, the HCV positive group had an increased risk of death by 2 times higher than in the SNR group (HR=2.33, 95% CI: 2.22-2.43) and the MNR group (HR=1.53, 95% CI: 1.45-1.62). (Table 4.13)

### 4.4.2 Liver-related

The REAC group had a substantially higher risk of dying from liver-related deaths than the SNR group (HR=9.71, 95% CI: 8.62-10.87). The risk of dying from liver-related deaths for the SERO group was not statistically significantly different from the MNR group (HR=1.68, 95% CI: 0.76-3.17). However, a lower risk in the liver-related mortality was observed in the SERO group compared to the REAC group. The SERO group had a decreased risk of dying from livered related deaths by 2 times compared to the REAC group (HR=0.53, 95% CI: 0.24-0.92). The MNR group had a higher risk for liver-related mortality referent to the SNR group (HR=3.05, 95% CI: 2.67-3.46). (Table 4.12)

For the combined the REAC and the SERO groups, for liver-related mortality and mortality related to alcoholic liver diseases, a statistically significant interaction term for sex was found; thus, separate hazard ratios were calculated for each sex. In addition, for mortality related to liver diseases and non-alcoholic liver diseases, a statistically significant interaction term for age was found; thus, separate hazard ratios were calculated for each age stratum. The HCV positive group had 100 times (95% CI: 71.43-142.86) greater risk of dying from viral hepatitis compared to the SNR group, and about 38 times increased risk of dying from viral hepatitis in the HCV positive group compared to the MNR group (HR=38.46, 95% CI: 23.26-66.67). Referent to the SNR group, HCV positive group had substantial higher risks of dying from liver cancer (HR=7.25, 95% CI: 5.68-9.17), alcoholic liver disease (HR=6.13, 95% CI: 3.97-9.26 for females, HR=2.59, 95% CI: 1.90-3.50 for males), and non-alcoholic liver disease (HR=17.24, 95% CI: 5.95-62.50 for age $< 40$, HR=3.53, 95% CI: 2.66-4.63 for age $\geq 40$). Referent to the MNR

group, the HCV positive group had about 4 times increased risk for dying from liver cancer (HR=3.79, 95% CI: 2.76-5.24), but the risk for dying from alcoholic liver disease in males (HR=1.18, 95% CI: 0.82-1.69) and non-alcoholic liver disease in age ≥ 40 (HR=0.77, 95% CI: 0.57-1.01) were not statistically different in the HCV positive group versus the MNR group. (Table 4.13)

### 4.4.3 Drug related

For drug related mortality, both the REAC and the SERO groups had substantially higher risks of dying from drug related mortality compared to their reference groups. The REAC group had a considerably higher risk for drug related mortality by about 14 times higher than the SNR group (HR=13.51, 95% CI: 11.63-15.63). The risk for drug related mortality in the SERO group was about 9 times higher compared to the MNR group (HR=8.62, 95% CI: 6.33-11.63) and about 2 times higher compared to the REAC group (HR=1.60, 95% CI: 1.20-2.08). The MNR group had a higher risk for drug related mortality compared to the SNR group as well (HR=2.49, 95% CI: 2.04-3.03). (Table 4.12) In the HCV positive group, the risks were substantially higher for dying from drug related mortality compared to the SNR group (HR=14.08, 95% CI: 12.20-16.39) and the MNR group (HR=5.62, 95% CI: 4.72-6.76). (Table 4.13)

### 4.4.4 HIV

Since a statistically significant interaction term for sex was found, separate hazard ratios were calculated for each sex. Referent to the SNR group, females in the REAC group had 67 times (HR=66.67, 95% CI: 35.71-142.86) greater risk of dying from HIV infection, and males in the REAC group had 12 times (HR=12.05, 95% CI: 9.17-15.87)

greater risk of dying from HIV. Referent to the MNR group, females in the REAC group had 26 times (HR=25.64, 95% CI: 36.37-100.00) greater risk of dying from HIV infection, and males in the REAC group had five times (HR=5.43, 95% CI: 2.64-10.20) greater risk of dying from HIV infection. However, in both males and females, the hazard ratios were similar and not statistically significantly different for the SERO group versus the REAC group (HR=1.00, 95% CI: 0.30-2.42 in females, and HR=1.12, 95% CI: 0.57-1.97 in males). In the MNR group, males had about 2 times increased risk of dying from HIV infection compared to the SNR group (HR=2.48, 95% CI: 1.67-3.64) (Table 4.12)

In females, the risks for dying from HIV infection in the HCV positive group were substantially higher when compared to the SNR group (HR=66.67, 95% CI: 35.71-142.86) and the MNR group (HR=25.64, 95% CI: 11.49-76.92). The risks for dying from HIV infection in the HCV positive group were also higher in males compared to the SNR group (HR=12.05, 95% CI: 9.26-15.87) and the MNR group (HR=4.88, 95% CI: 3.48-6.99). (Table 4.13)

### 4.4.5 Diabetes mellitus

The MNR group had 2 times increased risk for mortality due to diabetes mellitus compared to the SNR group (HR=2.75, 95% CI: 2.34-3.23). However, no excess risk was found in the HCV positive group compared to the SNR group (HR=0.99, 95% CI: 0.69-1.38), and a statistically significantly lower risk was found when compared to the MNR group (HR=0.36, 95% CI: 0.25-0.51). (Table 4.13)

### 4.4.6 Renal failure

The MNR group had 5 times increased risk for mortality due to renal failure compared to the SNR group (HR=4.78, 95% CI: 4.03-5.68). The HCV positive group had 2 times increased risk for mortality due to renal failure compared to both the SNR group (HR=1.63, 95% CI: 1.10-2.33), and a statistically significantly lower risk was found when compared to the MNR group (HR=0.34, 95% CI: 0.23-0.49). (Table 4.13)

### 4.4.7 Malignant neoplasms

Since a statistically significant interaction term for age was found for all malignant neoplasms, separate hazard ratios were calculated for each age stratum. Referent to the SNR group, younger individuals in the HCV positive group had about 2 times (HR=1.59, 95% CI: 1.08-2.29) greater risk for cancer mortality, and older individuals in the HCV positive group also had 2 times (HR=1.54, 95% CI: 1.39-1.70) greater risk for mortality due to cancer. Among younger individuals, no excess risk for cancer mortality was found in the HCV positive group compared to the MNR group (HR=0.69, 95% CI: 0.46-1.03), but increased risk was found for older individuals (HR=1.36, 95% CI: 1.20-1.53). Referent to the SNR group, younger individuals in the MNR group had about 2 times (HR=2.30, 95% CI: 1.75-2.99) greater risk of dying from cancer. Older individuals in the MNR group are only 14 percent more likely to die from cancer (HR=1.14, 95% CI: 1.04-1.23) compared to the SNR group. (Table 4.14)

#### 4.4.7.1 Hepatocellular carcinoma

The HCV positive group had an increased risk for mortality due to hepatocellular carcinoma compared to the SNR group (HR=9.62, 95% CI: 7.41-12.50) and the MNR

group (HR=4.33, 95% CI: 3.09-6.13). The MNR group also had an increased risk for mortality due to hepatocellular carcinoma compared to the SNR group (HR=2.23, 95% CI: 1.60-3.05). (Table 4.14)

#### 4.4.7.2 Non-Hodgkin lymphoma

No excess risk was found in the HCV positive group for mortality due to non-Hodgkin lymphoma (NHL) compared to the SNR group (HR=1.35, 95% CI: 0.91-1.93) and the MNR group (HR=0.91, 95% CI: 0.59-1.38). However the MNR group are 48 percent more likely to die from non-Hodgkin lymphoma compared to the SNR group (HR=1.48, 95% CI: 1.13-1.92). (Table 4.14)

### 4.4.8 Other

No excess risk was found in the MNR and HCV positive groups for mortality due to pancreatic cancer when compared to the SNR group (HR=0.95, 95% CI: 0.71-1.25 in the MNR group, and HR=1.16, 95% CI: 0.77-1.67 in the HCV positive group), and no excess risk was found in the HCV positive group for pancreatic cancer mortality when compared to the MNR group (HR=1.22, 95% CI: 0.77-1.89). Mortality from leukemia and multiple myeloma in the HCV positive group had no excess risk when compared to both the SNR and the MNR groups. The MNR group had 2 times increased risks for mortality due to leukemia (HR=2.01, 95% CI: 1.55-2.58) and 3 times increased risks for mortality due to multiple myeloma when compared to the SNR group (HR=3.23, 95% CI: 2.31-4.44). (Table 4.14)

A statistically significant interaction term for age was found for all malignant neoplasms, mental and behavioural disorders, diseases of circulatory system, disease of

the respiratory system, disease of the digestive system and external causes of morbidity and mortality; thus, for these outcomes, separate hazard ratios were calculated for each age stratum. Referent to the SNR group, the HCV positive group had higher risks of dying from certain infectious and parasitic diseases (HR=21.74, 95% CI: 18.87-25.64), neoplasms (HR=1.53, 95% CI: 1.04-2.19 for younger individuals, and HR=1.54, 95% CI: 1.39-1.70 for older individuals), blood related diseases (HR=3.32, 95% CI: 1.67-6.17), mental and behavioural disorders (HR=20.41, 95% CI: 10.75-43.48 for younger individuals, and HR=2.92, 95% CI: 2.16-3.89 for older individuals), circulatory system (HR=5.05, 95% CI: 3.33-7.58 for younger individuals, and HR=1.34, 95% CI: 1.19-1.49 for older individuals), respiratory system (HR=5.71, 95% CI: 2.83-11.36 for younger individuals, and HR=1.64, 95% CI: 1.34-1.98 for older individuals), digestive system (HR=6.80, 95% CI: 4.13-11.24 for younger individuals, and HR=3.03, 95% CI: 2.58-3.55 for older individuals), genitourinary system (HR=1.94, 95% CI: 1.35-2.71), and external causes of morbidity and mortality (HR=6.80, 95% CI: 4.13-11.24 for younger individuals, and HR=3.03, 95% CI: 2.58-3.55 for older individuals). (Table 4.15)

Referent to the MNR group, the HCV positive group had lower risks of dying from diseases of the genitourinary system (HR=0.42, 95% CI: 0.29-0.59) and malignant neoplasms for younger individuals (HR=0.67, 95% CI: 0.44-0.99). No excess risk was found in the HCV positive group for blood related diseases (HR=0.32, 95% CI: 0.62-2.74), diseases of the circulatory system for both age strata (HR=1.37, 95% CI: 0.89-2.10 for younger individuals, and HR=1.06, 95% CI: 0.93-1.20 for older individuals), diseases of the digestive system for older individuals (HR=1.05, 95% CI: 0.88-1.25) when compared to the MNR group. (Table 4.15)

Similar to the HCV positive group, the MNR group had higher risks of dying from certain infectious and parasitic diseases, neoplasms, blood related diseases, mental and behavioural disorders, circulatory system, digestive system, genitourinary system, and external causes of morbidity and mortality referent to the SNR group. However, in the HCV positive group, the risk of dying from diseases of respiratory system was not statistically significantly different from the SNR group (HR=1.76, 95% CI: 0.68-4.05 for younger individuals, and HR=1.12, 95% CI: 0.96-1.31 for older individuals). In the MNR group, the risks of dying from endocrine, nutritional and metabolic diseases were about 3 times higher (HR=2.65, 95% CI: 2.28-3.06) referent to the SNR group, and about 2 times higher for diseases of musculoskeletal system and connective tissue (HR=1.86, 95% CI: 1.27-2.65) referent to the SNR group. The risks of dying from diseases of nervous system in both the MNR and the HCV positive groups were not statistically significantly different compared to their reference groups (HR=1.23, 95% CI: 0.93-1.60 for MNR vs SNR, and HR=1.35, 95% CI: 0.93-1.90 for HCV positive vs SNR). (Table 4.15)

# 5 Discussion and Conclusions

## 5.1 Discussion

In this study, all-cause and disease specific mortality in individuals who underwent serological testing for HCV at the BC Centre for Disease Control from 1992-2004 were examined. Our study is unique in how it uses serological testing data to identify a large group of HCV tested individuals with different levels of risk for HCV infection and then tracking the longitudinal relationship between test results and outcomes. Given that the provincial population-based centralized laboratory testing database contains both HCV seropositive and seronegative test results, this has enabled the identification of confirmed incident HCV cases (i.e., seroconverters). To our knowledge, this is the first study to: 1) use single and multiple anti-HCV tested non-reactive groups as controls, 2) identify time-dependent HCV serological groups based on different levels of risk behaviours/activities, and 3) identify incident HCV cases, seroconverters, to help evaluate how individuals with incident HCV infection compare with other serological testing groups.

The ability to distinguish anti-HCV testers based on their testing patterns and results is helpful to differentiate viral-related mortality due to progressive liver disease which takes decades to manifest from risk behaviours/activities that are associated with acquisition of HCV infection (e.g., IDU, high-risk sexual activity which can also lead to HIV infection, drug overdose and other drug-related mortality). For example, acute or incident infection (i.e., seroconverters) is typically asymptomatic and rarely associated with acute viral related mortality. Our study demonstrated that mortality in seroconverters

(i.e., incident cases) were more likely to be related to drug-related causes. In contrast, individuals who were anti-HCV reactive at their initial test are more likely to have had chronic HCV, and they had a higher risk of dying from liver-related causes than seroconverters.

We also demonstrated that mortality risks in all anti-HCV testers were significantly elevated when compared to the general BC population. This likely reflects higher morbidity and mortality risks in anti-HCV testers than the BC general population. This confirms that anti-HCV testing is typically limited to individuals who might have some risk factors for HCV acquisition or signs and symptoms consistent with liver disease.

The demographic characteristics of our HCV seropositive testers are comparable to HCV infected individuals from other large population-based record linkage studies by Amin et al. in Australia, Duberg et al. in Sweden and McDonald et al. in Scotland.[20, 21, 23] In their studies, two thirds of HCV infected individuals were reported to be males with median age ranged from 35 to 40 years. In our study, two thirds of individuals who tested anti-HCV reactive at their first test were males, but a slightly lower proportion of males were found in seroconverters at 55%. In general, females are more likely to be tested and they are usually tested more frequently than males (e.g., of 562,541 anti-HCV tests performed, 54% of anti-HCV tests were females versus 46% were males). We hypothesize that this might explain the greater proportion of females found in seroconverters, i.e. this result is due to testing bias. The median age in seroconverters was significantly lower than in individuals who tested anti-HCV reactive at their first test, likely reflecting the large proportion of young IDUs in the seroconverter group.

The standardized mortality ratios identified in our study are consistent with other published large population-based record linkage studies.[20, 21, 23] A summary is given below.

**Table 5.1 Comparison of SMRs with other studies**

| Author | Country | SMR (95% CI) | All-cause | Liver-related | Drug-related |
|---|---|---|---|---|---|
| Amin[20] (2006) | Australia | HCV mono-infected | 3.1 (3.0-3.2) | 16.8 (15.4-18.3) | 19.3 (18.1-20.5) |
| | | HCV/HBV co-infected | 5.6 (4.8-6.6) | 32.9 (23.1-46.7) | 24.7 (18.2-33.5) |
| Duberg[21] (2008) | Sweden | HCV mono-infected | 5.8 (5.6-6.0) | 35.5 (32.9-38.3) | 20.7 (18.9-22.7) |
| | | HCV/HBV co-infected | 8.5 (7.3-9.8) | 46.2 (31.5-62.3) | 27.6 (19.6-39.6) |
| McDonald[23] (2008) | Scotland | HCV mono-infected | 4.9 (4.6-5.1) | 20.0 (17.9-22.2) | 23.5 (21.3-25.7) |
| | | HCV/HIV co-infected | 32.9 (29.2-37.0) | 34.8 (23.3-50.0) | 36.6 (25.2-51.4) |
| Yu (2010) | Canada | All HCV infected | 4.8 (4.6-5.0) | 24.0 (22.2-25.9) | 20.4 (18.8-22.0) |
| | | REAC | 4.7 (4.5-4.8) | 24.3 (22.4-26.2) | 19.5 (17.9-21.1) |
| | | SERO | 10.2 (8.5-12.0) | 13.1 (5.6-25.7) | 38.1 (29.0-49.1) |

*Data sources for Yu(2010): BCCDC Public Health Microbiology and Reference Laboratory,[30] Ministry of Health Services,[31, 32] and BC Vital Statistics Agency.[33, 34] 95% CIs were calculated by Byar's approximation.[95]*

We found strong associations between HCV infection and all-cause, liver-related and drug-related mortality. As illustrated in Table 5.1, the SMRs reported in the Australian and Swedish studies were classified into HCV mono-infected and HCV/HBV co-infected individuals. Individuals in the Scottish study were classified into HCV mono-infected and HCV/HIV co-infected. Since the HCV infected groups were classified differently in different studies, in order to better compare our data with the reported studies, we re-calculated SMRs for all HCV infected individuals by combining the REAC and SERO groups (see Appendix A and B). The combined REAC and SERO groups from our study would include individuals who were either mono-infected with HCV, or co-infected with HBV/HIV. As a result, we would expect that our reported SMRs for all HCV infected individuals should be somewhere in between the reported SMRs of HCV mono-infected individuals and HCV/HBV or HCV/HIV co-infected individuals.

Findings from our study confirm previously reported associations between HCV infection and all-cause, liver-related and drug-related mortality reported by Amin et al. in Australia.[20] The SMRs for all-cause, liver-related and drug-related mortality in our study were similar to those reported in the Australian study and our SMR results ranged between HCV mono-infected and HCV/HBV co-infected individuals in Australia.

In contrast, the Swedish study had higher SMRs for all-cause, liver-related and drug-related mortality when compared to both the Australian and our study, particularly in regard to their reported liver-related mortality which was much higher. We hypothesize that this may be the result of using different data linkage methodologies. The ability to use national personal identifiers in Sweden provides a more robust linkage between the HCV data and mortality data than the probabilistic linkage that was used in both the Australian and Scottish studies. In our study, we used deterministic record linkage based on the subset of individuals who had personal health numbers. Individuals from whom we did not have a personal health number at the time of testing were excluded from the analysis. These excluded individuals are more likely to represent vulnerable populations with no fixed address who may well have had higher risks of all cause morbidity and mortality. For this reason, we suggest that the reported SMRs in our study are likely to be conservative. This is because exclusion of highly vulnerable individuals who are typically at a higher risk of HCV acquisition serves to underestimate the overall risk estimates.

The SERO group is best compared with the HCV/HIV coinfected group in the Scottish study by McDonald et al. As discussed earlier, a larger proportion of the REAC group are more likely to represent chronic HCV infected individuals whereas individuals

within the SERO group are more likely to represent incident infections in IDUs. Given that HCV co-infection in HIV positive population in British Columbia has been reported at 53%[104], we hypothesize the SERO group represents mostly IDUs who are more likely to be HIV/HCV co-infected.

Findings from our study differ from the results reported by the Scottish study. The Scottish study reported significantly higher SMRs for all-cause and liver-related mortality in the HCV/HIV co-infected group when compared to our SERO group. We hypothesize that the significantly lower SMR for all-cause mortality might be attributable to a lower HIV co-infection prevalence in the SERO group. The Scottish study focuses exclusively on HCV/HIV co-infection which has been associated with higher all cause and liver-related mortality. In BC, at least 83% of seroconverters reported a history of IDU[60] and a 17% HIV prevalence has been reported among IDUs.[105] Another possibility is that there maybe a higher proportion of individuals treated with antiretroviral drugs in BC which are publicly funded.[106] Antiretroviral treatment has been shown to reduce the risk of HIV related deaths and thus all-cause mortality would be expected to be decreased. The significantly higher liver-related SMR reported in the Scottish study is also consistent with a previously reported association between HIV and the risk of liver-related death.[107] However, given the small number of liver-related deaths in our SERO group and the lack of information on HIV infection status in our study population, we have a limited ability to compare the Scottish study with our study population.

By using population-based serological data to identify time-dependent HCV serological groups based on different levels of risk, we can attribute the higher risk of death in the MNR group versus the SNR group to be likely due to a number of

confounding factors. These include: potential increased risk behaviours/activities (e.g., ongoing IDU or high-risk sexual activity); the presence of illnesses which are associated with liver disease (e.g., fatty liver disease, autoimmune liver disease, alcoholic liver disease, diabetes) which might result in more frequent anti-HCV testing to rule out co-factors for their underlying clinical condition; or, persons who are systematically tested for HCV because of an increased risk of HCV acquisition (e.g., renal dialysis patients).

In the REAC group, the higher risk for liver-related disease compared to the SNR group likely reflects the consequences of chronic HCV infection. However, drug use and HIV infection were also important co-contributors to increased mortality in the REAC group. In contrast, in the SERO group, risk behaviours/activities were stronger drivers for mortality than the liver related sequelae of chronic HCV infection.

The fact that the SERO group had a significantly decreased risk for liver-related mortality and a significantly higher risk for drug-related mortality compared to the REAC group has important policy implications. This implies that seroconverters would likely benefit more from comprehensive prevention and harm reduction programming which could reduce their risk of acquiring HCV infection, whereas in individuals who are confirmed to have chronic infection more likely to benefit from antiviral treatment which has been shown to reduce the risk of progressive liver disease.

## 5.2 Strengths and limitations

The strengths of this study include the large sample size, cohort design, and longitudinal population-based serological data. Over the 12 years of the study, the number of anti-HCV testers was over 400,000 individuals. The large sample size allowed us to more precisely measure the effect of mortality attributable to HCV infection with

tighter confidence intervals than smaller studies. Given the fact that the BCCDC Public Health Microbiology and Reference Laboratory performs about 95% of all anti-HCV testing in BC, this provided a nearly complete capture of anti-HCV testers in BC. The longitudinal serological data with HCV seropositive and seronegative results enabled the identification of incident HCV cases and multiple non-reactive testers. This information was crucial to help differentiate viral-related mortality due to progressive liver disease itself from risk behaviours/activities that are associated HCV acquisition.

There are several limitations that need to be acknowledged. The 5% of tests that are not performed at the BCCDC Public Health Microbiology and Reference Laboratory are performed in two other hospital labs in Vancouver and Victoria. Given the limited amount of testing that was not captured, and the baseline cohort demographics for anti-HCV testers in the two hospital labs are likely similar to the anti-HCV testers from the provincial BCCDC Public Health Microbiology and Reference Laboratory,[108] this data limitation would be expected to have a limited effect on the overall risk estimates and should not effect the overall conclusions.

The second limitation is that probabilistic data linkage to administrative dataset was not used (i.e., only individuals with a valid personal health number were linked). We were therefore unable to link approximately 20% of individuals who did not have a valid personal health number. The requirement of a personal health number for linkage may have excluded particularly vulnerable individuals from this study. Temporary residents, immigrants, and individuals with no fixed address would be more likely to have been excluded. Such individuals have been shown to have a higher prevalence of HCV infection and display higher morbidity and mortality risks relative to the general

population.[109] The omission of these individuals from the linked dataset would tend to underestimate the risk for all-cause mortality and therefore this exclusion tends to make our risk data more conservative.

The third limitation relates to notification bias. Seriously ill individuals or recipients of blood products prior to implementation of universal anti-HCV screening are more likely to be tested for HCV and have an increased likelihood of all cause morbidity and mortality. We have attempted to compensate for this notification bias by applying a 6-month lag in the study.

The fourth limitation is that individuals who spontaneously clear the virus were categorized as being infected based on their HCV seropositive status. It is known that, overall, approximately 25% of individuals infected with HCV will spontaneously clear their infection within about 12 to 14 weeks, that is, HCV RNA is not detected in their blood or liver. Individuals who have undergone spontaneous clearance (not treatment related) are not known to be at risk of progressive liver disease. Therefore, our reported risk estimates for mortality due to chronic HCV infection, especially in the context of liver related mortality, are likely underestimated because about 25% of the identified SERO and REAC individuals do not have active HCV infection.

Another limitation is that the mortality data from the BC Vital Statistics Agency only contained deaths that were registered in BC.[110] Out of province deaths reported to BC Vital Statistics Agency are only used to crosscheck the MoH Registration and Premium Billing files[31, 32] in order to ensure that deceased people do not keep getting health benefits. However, only a small number of out of province deaths were not captured in the dataset.[110] Such cases primarily reflect individuals who lived on the

eastern part of BC, close to the Alberta border, who occasionally attend hospitals in Alberta in lieu of traveling to tertiary centres in the lower mainland or the interior of BC. Since the proportion of death certificates from BC residents who die out of province was small and all serological testers (i.e., the numerator) as well as the general population (i.e., the denominator) would be affected, it is likely that out of province mortality would have little impact on our overall risk estimates.

As with all administrative data linkages, the ability to control for confounders is limited. Administrative databases are not able to identify HCV risk behaviours/activities (e.g., injection practices, etc), comorbidities (e.g., Hepatitis B, HIV, etc) or social determinants of health (e.g., income, education, etc) that may impact testing behaviours (access), HCV transmission risks (exposure) and morbidity and mortality (outcomes). We examined both the hospitalization and medical health billing records in order to help identify confounding factors, but inconsistent and unreliable data were found. The limited ability to control for confounding factors makes results interpretation challenging. For example, HBV and HIV co-infection are known to potentiate HCV mortality, and therefore the lack of systematic data on potential confounders would tend to overestimate risks.

Another potential limitation relates to data entry errors or data linkage errors. As mentioned previously, data cleaning of both the laboratory and administrative datasets was necessary. Examples of problems included: 1) multiple deaths were found for the same person with different dates of death; 2) individuals whose first available test date was before the date of birth; and 3) individuals whose first enrollment date occurred prior

to their date of birth. It is likely that such errors were random and therefore the impact of such errors was likely negligible with regard to risk estimation.

Another issue is that different HCV diagnostic tests were utilized in BC during the study period and this might have affected the diagnostic accuracy over time. The BCCDC Public Health Microbiology and Reference Laboratory[30] used the second generation EIA for screening tests since 1992 and then switched to the third generation EIA in April, 1997. The third generation screening EIA was known to be more sensitive and specific than the older first and second generation assays.[29, 111] For the first generation EIA screening test, the sensitivity was about 70% to 80%, and the positive predictive value was about 70% to 85% in a high prevalence setting.[29, 111] A large improvement was made with the second generation EIA test with sensitivities of 92% to 95%, and positive predictive values of 88% to 95% in a high prevalence setting.[29, 111] The third generation screening EIA test has reported sensitivities of 97% to 99% and specificities of 95% to 98% in a high prevalence setting.[29, 111] Of note, only about 12% of tests were performed prior to April, 1997 by the second generation screening EIA test, and the differences of sensitivity and specificity between second and third generation screening EIA for identifying chronic HCV infections is relatively small. Therefore, the effect of using different anti-HCV EIA tests for HCV diagnosis on our risk estimates was likely minimal.

Although data on HCV genotypes and HCV RNA test results were available since 1998 this information was not used in our analysis. HCV genotypes reflect viral sequence variants that are not known to be correlated with the rate of disease progression or liver related mortality but are correlated with antiviral treatment response.[112] HCV

genotyping and HCV RNA results were only available for a limited number of individuals between 1998 and 2004 and these tests were not performed consistently on all individuals. Therefore, the case definition for HCV positive individuals was only based on their anti-HCV status. Given the fact that HCV genotyping and HCV RNA tests were not consistently performed on all individuals, it would be difficult to analyze for the impact of these variables on the overall conclusions.

Another possible limitation is potential misclassification of the exposure variable (i.e., time-dependent HCV serology). Misclassification is known to occur between the REAC and the SERO groups. While the SERO group contains individuals who had one or more anti-HCV non-reactive test result(s) followed by a reactive test result, a seroconverter (SERO) would be classified as a first time HCV positive individual (REAC) in the following circumstances: 1) the previous non-reactive test was done in another laboratory; 2) when the data linkage between individuals could not be matched perfectly by personal identifiers; and 3) the person has never been tested. The same issues apply to the SNR and MNR groups. Assignment to the MNR group is dependent on the length of study follow-up. An individual is more likely to be tested more than once when they are followed for a longer period of time. Also, if they are engaged in ongoing risk behaviour/activity they are more likely to become infected. We also noticed that the MNR group contains a mixture of individuals who are at both high and low risk of HCV infection (e.g., IDU-high risk versus kidney dialysis-low risk). This demonstrates the bias of using individuals who test HCV negative as controls. This is an example of non-differential misclassification bias, which is expected to lead to an underestimation of risk.

Finally, misclassification can also occur in the outcome variable, the underlying cause of death (UCOD). Discordances between causes of death reported on the death certificate and other clinical data have been observed in the literature.[113, 114] As deaths attributable to viral hepatitis primarily result from chronic liver disease and liver failure, viral hepatitis may not consistently be listed as the UCOD. It is likely that deaths classified as viral hepatitis underestimate the true number of deaths related to viral hepatitis. In addition, the UCOD was coded by the following coding rules for mortality and morbidity from the WHO ICD-10 guidelines.[115] On page 67 of the document, it stated that "except for HIV disease, no infectious or parasitic disease will be accepted as causing a malignant neoplasms." For example, if the immediate cause was hepatocellular carcinoma and antecedent causes were liver cirrhosis and hepatitis C; the UCOD in this case will be coded as hepatocellular carcinoma. However, if the immediate cause was hepatocellular carcinoma, and antecedent causes were end stage liver disease and HIV; then, UCOD in this case will be coded as HIV. By using this coding algorithm, we likely underestimated deaths due to HCV infection. In addition, when the cause of cancer could have been due to HIV, deaths due to malignant neoplasms may also be underestimated.

## 5.3 Conclusions

Our study found an excess mortality due to chronic HCV infection related to progressive liver disease as well as risk behaviours/activities that relate to the risk of HCV acquisition among HCV positive testers. A substantial proportion of the mortality in HCV positive individuals is attributable to drug use and the risk behaviours/activities associated with HCV acquisition. This attributable mortality will not be reduced by improvements in HCV treatment alone. Mortality reduction in HCV positive individuals

will require comprehensive prevention/harm reduction programming to reduce the impact of mental health and problematic substance use on the behaviours/activities which relate to HCV acquisition, as well as HCV treatment to prevent progression of chronic liver disease in those chronically infected. Findings from this work will assist in estimating the HCV-attributable disease burden for the purpose of assisting decision-makers in allocating resources and strategizing prevention and treatment intervention policies.

## 5.4 Further research

The presence of anti-HCV confirms past or current HCV infection, but does not indicate if HCV RNA or viraemia persists or has resolved. As discussed, approximately 25% of individuals infected with HCV will spontaneously clear the virus, that is, HCV RNA is not detectable and such individuals are not known to be at risk of progressive liver disease. In order to detect active or ongoing HCV infection, baseline HCV RNA data are required to classify individuals into those who have spontaneously cleared (e.g., HCV RNA not detectable, which confirms viral clearance or no HCV in the body) or whose infection is persistent (e.g., HCV RNA detectable, which confirms active infection). We are in the process of updating the linked datasets. As the BCCDC Public Health Microbiology and Reference Laboratory[30] has performed all HCV RNA testing and HCV genotyping since 2003 (and the bulk of HCV RNA and genotype tests since 1998), we expect that the addition of substantial HCV RNA and genotyping results will allow us to better assess the impact of these variables on mortality outcomes. Findings obtained from this future study can then be compared to the recent published nationwide cohort study in Denmark by Omland et al which used HCV RNA data to assess its relationsip to mortality.[89]

In a letter to the editor, Völzke et al. highlighted the fact that the reported association between HCV infection and carotid atherosclerosis is controversial due to inconsistent results. [116] For example, Ishizaka et al. reported an increased risk of carotid artery plaque accumulation in individuals infected with HCV. In contrast, Völzke et al. did not find an excess risk, and Bilora et al. reported a decreased risk.[116] Due to these discrepancies, it was suggested to re-classify deaths from circulatory diseases into: 1) those caused by disease predicted by carotid atherosclerosis such as myocardial infarction or stroke, and 2) those that were not related to atherosclerosis.[116] Amin et al. then re-classified deaths related to carotid atherosclerosis and re-examined circulatory diseases mortality related to atherosclerotic circulatory disorders (ICD 10 codes: I20-I23, I25, I63, I67.2 and I70) as suggested. An increased risk of mortality related to atherosclerotic circulatory disorders in individuals infected with HCV was observed when compared to the general Australian population (SMR=1.9, 95% CI: 1.7-2.1).[117] A similar analysis could be performed on our data to compare atherosclerotic circulatory disorders in the general BC population. We will be approaching the BC Vital Statistics Agency to ask for the data files. Findings from this study could then be compared to those of Amin's et al.[117]

Several studies have shown that chronic HCV infection is associated with an increased risk for non-Hodgkin lymphoma.[60, 62, 63] In BC, Spinelli et al. reported a three fold increased risk of NHL in HCV seropositive individuals when compared to seronegative individuals in a population-based case-control study.[70] In this case-control study, individuals who were infected with HIV were excluded. In our study, HIV cases were included. In order to separate the effect of HIV infection, diagnostic codes from

MSP billing records and hospitalization data could be used to identify HIV cases. We propose to use HIV diagnosis codes from the Elixhauser comorbidity index to identify HIV cases.[102, 103] We would separate the cohort into subgroups of HCV mono-infected, HIV mono-infected, and HCV/HIV co-infected individuals. The association between chronic HCV infection and the risk of NHL mortality will be re-examined after removing HIV cases and comparison will be made with other cohort and case-control studies.[118, 119]

Lastly, we have only focused on mortality data. Another important step in this research will be to analyze cancer incidence among the four HCV serological groups. The limitation of looking only on mortality is that people diagnosed with a disease might not necessary die from the same disease. For example, people diagnosed with diabetes die from many other causes. As mentioned earlier, we did not find an increased risk of dying from NHL among individuals tested positive for anti-HCV, which might be a reflection of the high survival rate for NHL. Fortunately in BC, we have a comprehensive population-based provincial cancer registry which will allow us to examine the association between HCV infection and the risk of incident cancer in the future.

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# APPENDICES

## Appendix A: A priori mortality end points SMRs with 95% CIs for all individuals (HCV positive group)

| | SNR (N=367,634) | MNR (N=82,126) | HCV +ve (N=31,727) |
|---|---|---|---|
| Description | SMR (95% CI) | SMR (95% CI) | SMR (95% CI) |
| All-cause | 1.48 ( 1.46- 1.51) | 2.74 ( 2.65- 2.84) | 4.79 ( 4.62- 4.96) |
| Liver-related | 3.09 ( 2.87- 3.32) | 9.36 ( 8.40- 10.40) | 24.00 ( 22.20- 25.91) |
| Viral hepatitis | 1.17 ( 0.82- 1.61) | 2.52 ( 1.41- 4.16) | 64.09 ( 57.67- 71.04) |
| Liver cancer (C22) | 2.93 ( 2.55- 3.36) | 5.94 ( 4.53- 7.64) | 17.59 ( 14.51- 21.13) |
| Liver disease | 3.64 ( 3.32- 3.98) | 12.90 ( 11.42- 14.52) | 11.72 ( 10.05- 13.57) |
| Alcoholic liver disease | 3.75 ( 3.27- 4.28) | 8.85 ( 7.15- 10.84) | 11.26 ( 9.11- 13.77) |
| Non-alcoholic liver disease | 3.55 ( 3.12- 4.01) | 16.92 ( 14.54- 19.58) | 12.25 ( 9.74- 15.20) |
| Drug-related | 1.72 ( 1.53- 1.94) | 4.42 ( 3.75- 5.18) | 20.35 ( 18.82- 21.97) |
| HIV | 1.90 ( 1.51- 2.35) | 4.63 ( 3.36- 6.21) | 25.53 ( 22.64- 28.69) |
| Diabetes | 1.97 ( 1.81- 2.15) | 6.17 ( 5.37- 7.06) | 2.19 ( 1.53- 3.03) |
| Renal failure | 2.37 ( 2.13- 2.64) | 14.08 ( 12.28- 16.07) | 4.45 ( 3.02- 6.31) |
| Malignant neoplasms | 1.46 ( 1.41- 1.50) | 1.95 ( 1.81- 2.10) | 2.42 ( 2.21- 2.65) |
| Hepatocellular carcinoma | 5.62 ( 4.76- 6.59) | 11.90 ( 8.83- 15.69) | 37.47 ( 30.88- 45.05) |
| Non-Hodgkin lymphoma | 2.50 ( 2.22- 2.81) | 4.52 ( 3.52- 5.71) | 3.68 ( 2.51- 5.19) |
| Intrahepatic cholangiocarcinoma | 3.65 ( 2.77- 4.73) | 4.63 ( 2.22- 8.53) | 0.98 ( 0.02- 5.46) |
| Extrahepatic cholangiocarcinoma | 3.21 ( 1.84- 5.20) | 3.41 ( 0.41- 12.31) | 0.00 ( 0.00- 9.95) |
| Leukemia | 2.55 ( 2.24- 2.89) | 6.43 ( 5.09- 8.01) | 2.52 ( 1.44- 4.08) |
| Multiple myeloma | 2.21 ( 1.82- 2.66) | 8.42 ( 6.34- 10.96) | 2.49 ( 1.07- 4.91) |
| Pancreatic cancer | 2.45 ( 2.21- 2.71) | 2.76 ( 2.09- 3.58) | 2.78 ( 1.86- 4.00) |
| Malignant neoplasms except liver, bile duct, NHL, leukemia, multiple myeloma, pancreas | 1.33 ( 1.29- 1.38) | 1.58 ( 1.44- 1.73) | 1.81 ( 1.61- 2.03) |
| Endocrine nutritional and metabolic disease except diabetes | 1.71 ( 1.43- 2.04) | 4.15 ( 2.94- 5.70) | 1.64 ( 0.71- 3.24) |
| Diseases of the digestive system except liver disease | 1.63 ( 1.47- 1.80) | 4.16 ( 3.43- 5.00) | 4.65 ( 3.58- 5.96) |
| Certain infectious and parasitic diseases except viral hepatitis and HIV | 1.57 ( 1.33- 1.85) | 5.91 ( 4.58- 7.51) | 6.56 ( 4.64- 9.00) |

*Data sources: BCCDC Public Health Microbiology and Reference Laboratory,[30] Ministry of Health Services,[31, 32] and BC Vital Statistics Agency.[33, 34] 95% CIs were calculated by Byar's approximation.[95]*

# Appendix B: Disease specific SMRs with 95% CIs for all individuals (HCV positive group)

| | SNR (N=367,634) | MNR (N=82,126) | HCV +ve (N=31,727) |
|---|---|---|---|
| Description | SMR (95% CI) | SMR (95% CI) | SMR (95% CI) |
| Certain infectious and parasitic diseases | 1.58 ( 1.40- 1.79) | 4.71 ( 3.92- 5.61) | 30.38 ( 28.15- 32.75) |
| Neoplasms | 1.47 ( 1.42- 1.51) | 1.98 ( 1.84- 2.12) | 2.43 ( 2.22- 2.66) |
| Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism | 1.75 ( 1.30- 2.32) | 5.76 ( 3.42- 9.10) | 7.64 ( 4.07- 13.07) |
| Endocrine, nutritional and metabolic diseases | 1.92 ( 1.78- 2.07) | 5.75 ( 5.06- 6.51) | 2.07 ( 1.50- 2.77) |
| Mental and behavioural disorders | 1.15 ( 1.02- 1.30) | 2.63 ( 2.04- 3.34) | 7.14 ( 5.82- 8.66) |
| Diseases of the nervous system | 1.07 ( 0.97- 1.19) | 1.52 ( 1.16- 1.95) | 1.87 ( 1.31- 2.59) |
| Diseases of the eye and adnexa | 5.44 ( 0.14- 30.30) | 0.00 ( 0.00- 88.27) | 0.00 ( 0.00-221.30) |
| Diseases of the ear and mastoid process | 3.22 ( 0.08- 17.95) | 0.00 ( 0.00- 87.82) | 0.00 ( 0.00-191.22) |
| Diseases of the circulatory system | 1.44 ( 1.40- 1.48) | 2.23 ( 2.08- 2.39) | 2.21 ( 2.00- 2.44) |
| Diseases of the respiratory system | 1.31 ( 1.24- 1.38) | 1.83 ( 1.57- 2.11) | 2.96 ( 2.48- 3.51) |
| Diseases of the digestive system | 2.32 ( 2.17- 2.48) | 8.00 ( 7.22- 8.84) | 8.38 ( 7.35- 9.51) |
| Diseases of the skin and subcutaneous tissue | 2.34 ( 1.63- 3.26) | 2.62 ( 0.71- 6.72) | 4.17 ( 0.86- 12.18) |
| Diseases of the musculoskeletal system and connective tissue | 2.33 ( 1.97- 2.75) | 5.01 ( 3.52- 6.90) | 2.65 ( 1.22- 5.04) |
| Diseases of the genitourinary system | 1.94 ( 1.74- 2.16) | 11.13 ( 9.67- 12.75) | 4.36 ( 3.06- 6.04) |
| Pregnancy, childbirth and the puerperium | 1.11 ( 0.03- 6.19) | 4.77 ( 0.12- 26.55) | 0.00 ( 0.00- 36.20) |
| Certain conditions originating in the perinatal period | 347.22 (139.23-715.27) | 1253.6 (258.25-3660.6) | 4995.3 (126.38- 27824) |
| Congenital malformations, deformations and chromosomal abnormalities | 2.61 ( 1.93- 3.46) | 5.85 ( 3.52- 9.13) | 2.38 ( 0.77- 5.55) |
| Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified | 0.87 ( 0.65- 1.15) | 3.38 ( 2.25- 4.90) | 7.71 ( 5.51- 10.50) |
| External causes of morbidity and mortality | 1.45 ( 1.36- 1.54) | 2.61 ( 2.33- 2.91) | 8.84 ( 8.26- 9.44) |

*Data sources: BCCDC Public Health Microbiology and Reference Laboratory,[30] Ministry of Health Services,[31, 32] and BC Vital Statistics Agency.[33, 34] 95% CIs were calculated by Byar's approximation.[95]*