

# Hepatitis C: Hepatocellular carcinoma, mortality, and the impact of treatment

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# Dedication

I dedicate this dissertation to my husband, Rob, and my parents, Jan and Dennis.

# Abstract

Hepatitis C (HCV) infection is the most common bloodborne illness in the United States and the prevalence is highest in those born between 1945 and 1965. Most of those with HCV infection in this cohort have been infected for decades and some are now experiencing the long-term consequences of HCV infection, including cirrhosis and hepatocellular carcinoma. At the same time, this cohort is just reaching the age of eligibility for Medicare. The introduction of new treatment protocols including direct-acting antivirals for HCV infection has resulted in better outcomes for those undergoing treatment with many achieving a cure of their HCV infection. Despite an awareness of the potential burden of disease from HCV infection in this cohort, there is still a lack of information regarding hepatocellular carcinoma outcomes in persons with HCV and the impact of treatment for HCV outcomes and transmission. Using the Surveillance, Epidemiology, and End Results data linked to Medicare claims, this research describes (1) changes in risk factors for hepatocellular carcinoma, including HCV infection, over time and (2) differences in outcomes of persons with hepatocellular carcinoma by HCV infection status in the Medicare population. In addition, a state transition model with a transmission equation was used to compare the impact of treatment on mortality and HCV transmission using direct-acting antivirals to treat persons born between 1945 and 1965 in two risk populations, persons who inject drugs and persons who don't inject drugs. Overall, this research adds to our understanding of the consequences of HCV-infection-related hepatocellular carcinoma and the impact of treatment in the population with the highest prevalence of HCV infection.

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# Chapter 1

## Introduction and background

### 1.1 Statement of purpose

The purpose of this dissertation is to contribute to the body of knowledge on the outcomes of hepatitis C infection and hepatitis C treatment with a particular focus on HCC. While there are a number of areas where more information is needed, the focus of this research is to address three questions:

1. Among Medicare beneficiaries diagnosed with HCC, are there differences in risk factors over time, and do HCC cases with risk factors have differences in cancer characteristics at diagnosis and different prognosis after HCC diagnosis?
2. Among Medicare beneficiaries diagnosed with HCC, is the prognosis different for those who have hepatitis C infection and those who do not have hepatitis C infection after HCC diagnosis?
3. What is the impact of new treatments for hepatitis C infection on morbidity and mortality from hepatitis C infection in the United States?

### 1.2 Background and significance

#### 1.2.1 Hepatitis C disease

Hepatitis C is a viral infection that primarily affects the liver. Hepatitis C virus (HCV) infection is transmitted through blood-to-blood contact such as blood transfusions before screening of the blood supply in 1990, medical procedures with unsterile equipment, sharing of injection-drug-use equipment, and contaminated supplies for tattooing and body piercing. An estimate based on National

Health and Nutrition Examination Survey (NHANES) data is that there are 2.7 million to 3.9 million (1.0–1.5 %) persons living with chronic HCV infection in the United States, making it the most common bloodborne infection.<sup>1</sup> The Centers for Disease Control and Prevention (CDC) estimates that there were approximately 16 500 new HCV infections in 2011.<sup>2</sup> Chronic HCV infection develops in 75–85 % of those initially infected with HCV.<sup>3</sup> Chronic HCV infection can lead to cirrhosis, hepatocellular carcinoma, and death. A recent review of studies estimating the costs of HCV infection in the United States found that estimates of the direct costs of HCV infection ranged from \$694 million to \$1660 million and indirect costs ranged from \$51 million to \$3370 million, but all of the studies included in the review were based on publications from the 1990s, and estimates of the costs of sequelae of HCV infection may not be correct 20 years later.<sup>4</sup>

Data on chronic HCV infection in the United States come from a number of sources. Prevalence estimates used by CDC are largely based on the results of NHANES. Not all states conduct follow-up on cases of chronic HCV infection. For 2010, the most recent year for which data are available, only 10 states had reported chronic HCV data to CDC and agreed to have it included in the annual data summary.<sup>2</sup> The case definition for HCV includes both current chronic infections and resolved infections, so these data include persons with no evidence of current infection.

A study published in 2008 found that deaths in the United States from HCV infection had increased from 2798 in 1995 to 7426 in 2004.<sup>5</sup> The prevalence of HCV infection varies by birth year in the United States with the highest rates of reported infection occurring in those born in the 1940s, 1950s, and 1960s.<sup>6</sup> In 2012, CDC recommended screening for all persons born between 1945 and 1965.<sup>6</sup> This is the first group for which universal screening for HCV is recommended. Data from NHANES was used to estimate the number of cases of chronic HCV in this cohort at 2.06 million.<sup>6</sup> This represents 54–77 % of the total estimated infections in the United States, while this cohort makes up only 11 % of the U.S. population.<sup>1,6,7</sup> This cohort was exposed to hepatitis C primarily through injection drug use and blood transfusions before the blood supply was screened for HCV. Persons born in 1945–1948 are currently 65 years of age or older and are now eligible for Medicare, and over the next 16 years these HCV-infected persons will continue to age into Medicare. This has created concern about what costs of caring for this group of people will be as they have been living

with HCV for decades, many undiagnosed and not receiving appropriate care.<sup>4</sup> While persons born between 1945 and 1965 represent a large proportion of cases in the United States, HCV is not only a disease of those over 49. Over the last five to ten years, viral hepatitis surveillance systems in a number of states have detected an increase in HCV in younger adults. New York and Massachusetts were the first to detect clusters of cases and overall increases in cases in young adults.<sup>8,9</sup> This increase has resulted in increasing concern about previous assumptions regarding the future costs of HCV infection in the United States.<sup>4</sup>

### **1.2.2 Hepatitis C prevention and treatment**

There is currently no vaccine available for HCV, and prevention consists of encouraging use of safer injection-drug-use practices or discontinuation of injection drug use. Continued use of sterile medical equipment, testing of the blood and organ supply, and universal precautions are also prevention strategies. Treatment is available for chronic HCV infection, and until 2011, the recommendation of the American Association for the Study of Liver Disease (AASLD) was combination treatment with pegylated interferon alfa and ribavirin.<sup>3</sup> This combination takes over 24 to 48 weeks to complete and has serious side effects such as severe fatigue, flu-like symptoms, anxiety, depression, and hair loss. The goal of treatment is to achieve clearance of the virus demonstrated by two undetectable HCV ribonucleic acid tests, one immediately following treatment, and a second six months after the end of treatment. If both are negative, the outcome of treatment is called a sustained virologic response (SVR). In its guidelines, the AASLD recommends that certain patients, primarily those with evidence of liver damage, receive treatment to decrease the likelihood of disease progression and outcomes like severe liver disease, hepatocellular carcinoma, and death.<sup>3,10</sup> The high costs of treatment, both monetary and personal, and moderate success rates lead to caution when recommending treatment universally.

Between 2011 and 2013, the U.S. Food and Drug Administration approved four new direct-acting antivirals (DAAs) for the treatment of HCV infection. In clinical trials, these drugs have shown increased rates of SVR when added to the previously recommended HCV treatments.<sup>11–23</sup> There are six genotypes of HCV infections, designated with the numbers 1 through 6. Genotype 1

is the most common in the United States at an estimated 74–80 % of cases.<sup>24–26</sup> The rate of SVR varies by genotype, with genotype 1 having the lowest rates of SVR with treatment protocols without DAAs.<sup>10</sup> Some new treatment protocols eliminate interferon completely, eliminating some side effects that have kept some from treatment until this point. DAAs are currently recommended for all HCV genotypes.<sup>10</sup>

The goal of treatment guidelines such as those created by the AASLD is to prevent serious long-term consequences of HCV infection. In general, public health agencies such as CDC and state health departments have focused their limited HCV-related resources on determining the burden of disease in the United States from HCV infection and preventing new HCV infections through education and provision of access to clean injection-drug equipment. Public health interventions up to this point have focused on reducing the risk of exposures occurring by educating people to avoid exposure and reducing the likelihood of transmission when exposures occur. Referral to care and financial assistance for treatments for HCV infection have been limited mostly to those who are co-infected with HIV. The goals of HCV treatment are not out of line with the public health goals for reducing the burden of disease from HCV infection and prevention of continued transmission of HCV. By achieving SVR in an individual patient, the provider has assisted in preventing long-term consequences of HCV infection for that person and potentially preventing transmission to others by reducing the reservoir of HCV in the community.

### **1.2.3 Liver cancer and hepatitis C**

Liver cancer incidence is increasing in the United States, with an increase from 5.84 per 100 000 in 1999 to 8.35 per 100 000 in 2011.<sup>27</sup> Hepatocellular carcinoma (HCC), the most common liver cancer, is one of the potential long-term consequences of HCV infection. HCC usually occurs as a result of cirrhosis of the liver, which can be caused by HCV infection as well as hepatitis B (HBV), alcohol abuse, autoimmune disorders, liver inflammation, and high iron levels.<sup>28</sup> Certain persons with HCV infection are more likely to get HCC, including men, older persons, persons who use large amounts of alcohol, persons with hepatitis B infection, persons with HIV, and those with evidence of cirrhosis.<sup>29</sup> Estimates of the prevalence of HCC in those with chronic HCV infection range from 4 to 9 % after

10 to 40 years of infection.<sup>30,31</sup> The 5-year relative survival for HCC is 30 % for localized HCC, 11 % for regional HCC, and 3 % for distant spread.<sup>27</sup>

#### **1.2.4 Literature review**

##### **Hepatitis C and hepatocellular carcinoma**

The literature on HCV-related HCC is well developed in some areas and limited in others. The existing studies tend to focus on two areas: progression to HCC in persons with HCV infection, and outcomes of HCC in persons with HCV infection. The literature on the former is more extensive than the latter. The literature on the progression of HCV infection to HCC can be further divided into two separate areas: (1) determinates of progression from HCV infection to HCC and (2) the effect of treatment on progression from HCV infection to HCC. I will discuss each of these three areas in detail.

##### **Progression of hepatitis C infection to hepatocellular carcinoma**

Reviews by Fattovich, Stroffolini, Zagni, and Donato and Bruno, Savojardo, Almasio, and Mondelli identified a number of risk factors for progression to HCC in persons with HCV.<sup>32,33</sup> Fattovich et al. found 28 longitudinal studies from various geographic areas that looked at HCC in persons with HCV.<sup>32</sup> These studies were grouped into two categories: those looking at persons with chronic HCV and those looking at persons with compensated cirrhosis. The cumulative 5-year risk of HCC in persons with HCV was 17 % in the United States and 30 % in Japan.<sup>32</sup> The difference in risk between geographic areas was not explained by differences in patient characteristics, and the authors recommended further exploration of why the risks were so much higher in Japan. The review identified a number of risk factors for HCC that were deemed important. These included age at infection, age at diagnosis, severity of liver disease at diagnosis, gender, alcohol use, co-infection with hepatitis B, and porphyria cutanea tarda.<sup>32</sup> A number of potential factors affecting progression to HCC were not included as important factors labeled by the authors as controversial, insufficient evidence, or growing evidence. These included diabetes mellitus, occult hepatitis B infection, HIV infection, iron overload and smoking.<sup>32</sup> As recently as 2011, a review by Bruno et al. contained an almost identical

list with no major changes in risk factor classifications.<sup>33</sup>

Ikedo et al. followed a cohort of 183 patients with HCV-related cirrhosis at monthly intervals for blood work and annual imaging.<sup>34</sup> They found that 29 % had HCC five years after diagnosis and 54 % had HCC ten years after diagnosis of cirrhosis.<sup>34</sup> They also identified elevation of alpha-fetoprotein greater than 20 ng/mL, gender, and platelet count less than 100 000/mm<sup>3</sup> as predictors of HCC.<sup>34</sup> A Japanese cohort study examined the relationship between viral load of HCV and HCC incidence and found the hazard ratio for those with detectable viral load compared to those without detectable viral load was 35.8, but, for those with a detectable viral load, there was no viral-load-dependent risk increase.<sup>35</sup> Although a Canadian cohort study looked at the impact of immigrant status on HCC development in HCV-infected persons with advanced fibrosis and found it not to be an independent risk factor, the study did find an association between type 2 diabetes and HCC in the cohort.<sup>36</sup> It found that immigrants in their cohort had a higher prevalence of type 2 diabetes and were older than other cases, which resulted in higher incidence of HCC.<sup>36</sup>

Walter et al. used health department data from an area in Australia to explore risks for HCC in cases of HCV reported to the health department.<sup>29</sup> The cancer diagnoses for cases were gathered from the cancer registry for the same geographic area. The authors found that being male, having hepatitis B, having alcoholic liver disease, having cirrhosis, living in an urban area, and having a higher comorbidity score were all indicators of higher risk of HCC. In addition to the cohort studies that have looked at HCC incidence, a study from India using a case-control design found many of the same risks, but also suggested that poor standards of living, HCV genotype 4, and certain host gene mutations were associated with developing HCC in those with HCV.<sup>37</sup>

Measuring the impact of therapy on progression from HCV infection to HCC is challenging, as there can be a long interval between treatment and onset of HCC. Currently published studies that try to answer this question are largely evaluating older treatment protocols or using other surrogate endpoints to estimate the impact of treatment on HCC in the future. A review by Shen et al. of 22 studies found that antiviral therapy was associated with decreased HCC incidence at three and five years post treatment.<sup>38</sup> The resulting decrease at five years was 7.8 %. A number of different treatment protocols were examined in separate studies and all showed at least some benefit in some



patients.<sup>38-43</sup> Interferon treatment was shown to reduce the risk of HCC in persons who achieved SVR.<sup>39,41,42</sup> The benefits of interferon in non-responders to therapy have been mixed; one of three studies showed a significant decrease in risk among non-reponders.<sup>42</sup>

### **Outcomes of hepatocellular carcinoma**

Only two studies looked at outcomes of persons with HCV and HCC compared to others with HCC only. Reddy et al. compared HCC cases with HCV to those with nonalcoholic hepatitis and found that HCV patients had a shorter overall survival time, but not a significant difference in recurrence-free survival after curative therapy.<sup>44</sup> In contrast, Takuma et al. found that persons with HCV and HCC had lower rates of recurrence and lower mortality than those with HCC and cirrhosis of an unknown cause.<sup>45</sup> One additional study looked only at patients with HCV and HCC to examine the role of viral load in determining outcomes of HCC after resection. Shindoh et al. found that patients with low viral load had better long-term outcomes after resection.<sup>46</sup> Other studies have looked at outcomes for persons with HCC, but not looked at HCV patients specifically. Higher body mass index was also found to be a predictor of poorer outcomes, including increased recurrence and shorter survival times.<sup>47</sup>

### **Models of hepatitis C outcomes/Impact of treatment on outcomes**

The literature on models of the impact of HCV treatment from a public health perspective is limited, but Volk, Tocco, Saini, and Lok attempted to determine the public health impact, measured as deaths prevented, of treatment of HCV infection using current treatment protocols (which, at the time, did not include HCV DAAs).<sup>48</sup> That study found that with treatment 14.5 % of deaths from liver-related causes resulting from HCV infection would be prevented.<sup>48</sup> Zhang, Mehra, and DiBello also looked at the impact of HCV treatment on morbidity and mortality for HCV infection.<sup>49</sup> The goal of their model was to examine the impact of the new HCV protease inhibitors on HCV prevalence and outcomes. Their analysis included outcomes in addition to mortality and included the secondary impact of cases prevented due to treatment of existing cases. Zhang et al. found that there would be a reduction in prevalent cases of HCV infection of 19 % by 2040 if protease inhibitors were added

to the treatment protocol starting in 2011.<sup>49</sup> The model predicted 5 % fewer deaths when using new treatments between 2011 and 2040 compared to the previous treatment protocol.<sup>49</sup>

There are a number of models of the impact of HCV treatment on HCV prevalence specifically in persons who inject drugs.<sup>50-55</sup> While conducted in other countries, primarily Australia, Canada, and the United Kingdom, the results are of interest. Overall treatment of persons who inject drugs was found to reduce the prevalence of HCV infection, but the impact varied by the prevalence of HCV in the population.<sup>50-55</sup> This was found even when potential reinfection in those treated for HCV was taken into account.<sup>53</sup> Treatment of persons who inject drugs was found to be cost-effective when the prevalence of HCV infection in persons who inject drugs was less than 60%.<sup>53</sup> With the introduction of DAAs and expected introduction of DAA regimens without interferon, Martin et al. estimated costs of \$3.2 million to \$5 million to halve the prevalence of HCV infection depending on the prevalence in the geographic area.<sup>50</sup>

After the introduction of DAAs, Liu et al. conducted a cost-effectiveness analysis for the early DAAs in persons with genotype 1 HCV infection with mild or advanced fibrosis and Liu, Schwarzniger, Carrat, and Goldhaber-Fiebert conducted a cost-effectiveness analysis of screening for fibrosis before treatment.<sup>56,57</sup> The findings indicated a decrease in HCC risk and an increase in quality-adjusted life expectancy for both mild and advanced fibrosis. It was also found that protease inhibitors are cost effective for treatment of genotype 1 and that screening for fibrosis is not preferred prior to treatment.

### **Limitations of the literature: Hepatitis C and hepatocellular carcinoma**

There are a number of gaps in the existing literature, some of which will be difficult to address in the near future. Information on the impact of current treatment protocols on the incidence of HCC in persons with HCV is not available, and will likely take a number of years to fully describe. In addition, the outcomes of those with HCC have been described, but the differences in outcomes between those with HCV and HCC compared to others are lacking. To make up for these gaps, results of studies looking at the outcomes of persons with HCC in general have been used in place of specific HCV-infection-related HCC outcomes. This substitution appears to be based on the progression to

HCC in persons with HCV infection where the infected person first develops cirrhosis and then HCC.<sup>30,31,58</sup> Since cirrhosis is also the precursor to HCC in persons without HCV infection, the outcomes of persons with HCV infections are assumed to not differ from the overall outcomes for persons with HCC.<sup>32</sup>

### **Models of hepatitis C outcomes/Impact of treatment on outcomes**

Previous modeling studies begin to answer the question of what the public health impact of HCV treatment might be and what can be done to increase the public health impact of treatment for HCV infection, but only uses reductions in mortality to measure the impact of HCV treatment.<sup>48</sup> Volk did not attempt to quantify the impact of HCV treatment on other outcomes such as hepatocellular carcinoma. There are models that incorporate HCV transmission to predict reductions in HCV infection, morbidity, and mortality, but the authors do not use their model to identify strategies to increase the impact of HCV treatment beyond the addition of protease inhibitors to treatment protocols.<sup>49</sup> Most of the models looking at HCV treatment as prevention were done using older treatment protocols with only one looking at interferon-free treatment.<sup>50</sup> The Liu, Schwarzinger, Carrat, and Goldhaber-Fiebert model focused solely on cases of chronic HCV genotype 1 with fibrosis and did not look at other genotypes or treatment for persons without fibrosis.<sup>57</sup> In general, the results of previous modeling studies indicate that treatment of persons who inject drugs is preferred in some populations with lower prevalence. At this time there is nothing looking at new HCV treatment protocols in a population of great interest in the United States, persons born between 1945 and 1965, and whether treating persons who inject drugs in this population would be preferred.

### **1.2.5 Contribution**

Based on gaps in the current literature and building on the research described above, there are a number of areas where research would contribute a new understanding of HCV outcomes and treatment. I will attempt to improve the understanding of changes in risk factors for HCC over time, the differences in outcomes from HCC related to HCV versus other causes, and the impact of new HCV treatments as they pertain to morbidity and mortality from HCV.

Continuing to build on the available information on the proportion of HCC cases with HCV will allow for better estimates of the impact of HCV in the United States. Describing differences in the populations with and without HCV and other HCC risk factors will contribute to our knowledge of the causes of HCC in the United States and changes in those risks over time. Identifying differences in outcomes of those who have progressed to HCC by HCV status will add to the knowledge of health care providers and those researching new treatments for HCC.

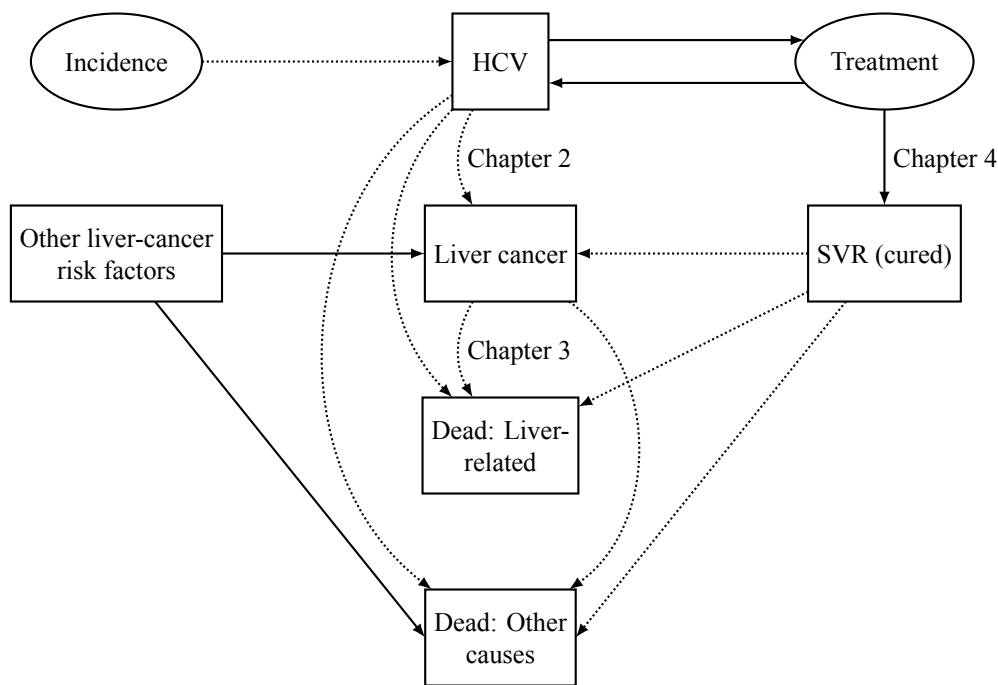
The impact of treatment on HCV outcomes is of interest as persons with HCV are being identified as a result of new screening guidelines and are aging into Medicare. The approval of DAAs has changed the treatment protocols for HCV infection and it appears reasonable to expect that these new drugs will increase the impact of HCV treatment beyond the levels predicted in past models. By adding new treatments, including genotype-specific disease states, and focusing on a population currently targeted for treatment in the United States, my model will provide information on the benefit of treating persons who inject drugs compared to those who are not actively injecting.

### **1.2.6 Theory and conceptual model**

As described in the literature, viral hepatitis is a public health problem currently being faced by the United States. Strategies for addressing HCV through state and local health departments have focused on case counting, describing the disease burden, educating the public, educating providers, and integrating viral hepatitis services into HIV and STD programs. At the same time, research has expanded to include factors affecting HCV transmission, progression to serious sequelae, therapies for treating those infected, vaccines to prevent transmission, and more. To better address the public health problem of HCV infection, steps must be taken to incorporate data from current research into health department programs as well as to further expand on what is known about HCV.

One possible area for public health intervention for HCV is linkage to care. State health departments have started programs to get newly diagnosed persons with HIV into care and to identify persons who are no longer in care. Viral hepatitis programs have been unable to undertake this for a number of reasons including lack of funding for public health programs addressing HCV, no data of populations infected with chronic HCV, a larger population infected with HCV, lack of availabil-

**Figure 1.1:** Conceptual model



ity of funding for HCV-related health care, and difficult treatment regimens with varying success. Most of these barriers still exist, but with the development of new treatments, increased availability of data on the burden of disease, and potential for a higher proportion of cases to have health insurance (through Medicare as they age or through new coverage options from the Affordable Care Act), exploring the best ways to focus linkage to care programs seems to be appropriate.

Figure 1.1 illustrates the conceptual model of the progression of HCV infection. In the model, I have identified the three relationships that I plan to explore in my thesis:

1. Differences in HCV infection and other risk factors for HCC in Medicare beneficiaries over time and differences in populations with and without risk factors identified.
2. Differences between Medicare beneficiaries diagnosed with hepatocellular carcinoma who have HCV infection compared to those who do not have HCV infection.
3. The impact of new treatments for HCV on morbidity and mortality from HCV in the United States in persons born from 1945 to 1965.

The first question deals with differences in persons with HCC by HCV diagnosis and other risk

factors over time, while the second deals with differences in persons with HCC depending on HCV diagnosis. The third question looks at the impact of treatment on outcomes including HCC and mortality. As shown in the conceptual model, the number of persons with HCV depends on the number of new cases and the number of treatment failures. These numbers are influenced by the likelihood of exposure to HCV (prevalence of HCV in the population and the individual risk of exposure through routes such as injection drug use) and the likelihood of treatment success. Treatment has two potential outcomes: SVR and no SVR (detectable viral load remaining at the end of treatment). The outcome of treatment is influenced by patient characteristics including race. Successful treatment results in clearance of the virus and a decrease in risk for long-term consequences of HCV infection. Those with ongoing HCV infection are at risk of a number of consequences of HCV infection including liver cancer and cirrhosis. The model has been simplified to show all persons with chronic HCV infection as “infected” regardless of disease status. Death can occur from HCV-infection-related causes other than liver cancer (shown in the model as progression from chronic HCV infection to death: liver-related) or through progression to liver cancer.

## Chapter 2

# Risk factors for hepatocellular carcinoma in Medicare beneficiaries, 2000–2009

**Context** Liver-cancer incidence and mortality are increasing in the United States and hepatitis C is a likely contributor to that increase. The increasing age and duration of infection of the population with hepatitis C infection has the potential to increase the number of Medicare beneficiaries with hepatocellular carcinoma caused by hepatitis C infection over the next 20 years. Screening recommendations for hepatocellular carcinoma in those with hepatitis C infection and cirrhosis should lead to earlier diagnosis and better hepatocellular carcinoma outcomes over time.

**Objective** To describe changes in the Medicare population with hepatocellular carcinoma, changes in stage at diagnosis, and changes in outcomes over time

**Design** Cohort study

**Setting** SEER-Medicare matched data

**Patients** Cases of hepatocellular carcinoma reported to SEER.

**Main outcome measures** Changes over time in risk factors for hepatocellular carcinoma, stage at diagnosis, and survival duration after hepatocellular carcinoma diagnosis

## 2.1 Introduction

In the United States, liver-cancer incidence has increased from 5.0 per 100 000 in 1999 to 7.1 per 100 000 in 2010.<sup>59</sup> HCC, the most common liver cancer, is one of the potential long-term consequences of HCV infection. HCC usually occurs as a result of cirrhosis of the liver, which can be caused by HCV infection as well as HBV infection, alcohol abuse, autoimmune disorders, liver inflammation, and high iron levels.<sup>28</sup> Estimates of the prevalence of HCC in those with chronic HCV infection range from 4 to 9% after 10 to 40 years of infection.<sup>30,31</sup> The highest prevalence of HCV infection in the United States is in those born in the 1940s, 1950s, and 1960s, and most of these infections occurred decades ago.<sup>6</sup> Two previous studies using the Surveillance, Epidemiology and End Results (SEER) cancer registry and Medicare-linked database found that the proportion of HCC cases with HCV infection had increased over the 1990s from 11% to 17% of HCC cases.<sup>60,61</sup> Although the cohort with the highest rates of HCV infection is not yet present in the linked SEER-Medicare data set, HCV prevalence is higher in those born in the late 1930s and early 1940s compared to earlier cohorts.<sup>6</sup> As the population with the highest prevalence of HCV infection continues to reach the age of eligibility for Medicare, HCV-related HCC will likely continue to increase. Other risk factors for HCC have been increasing over the same period.<sup>60,61</sup> Both previous SEER-Medicare HCC studies looking at risk factors over time found a decrease in the number of cases without an identified risk factor for HCC.<sup>60,61</sup>

Screening for HCC is recommended in some groups at increased risk for HCC. These include certain persons with HBV infection and those with cirrhosis, including those with cirrhosis and HCV infection, HBV infection, alpha 1-antitrypsin deficiency, or genetic hemochromatosis.<sup>62</sup> The AASLD recommends screening persons who fall into one of these categories using ultrasound every six months.<sup>62</sup> Screening for HCC has been shown to increase the number of cases detected at an earlier stage and to improve survival.<sup>63-66</sup> Survival in persons with HCC has been shown to be higher for cancers diagnosed at an earlier stage.<sup>65,67-69</sup> With an increasing number of HCC cases occurring in those with an identified risk for HCC and recommendations for routine screening for HCC on pace in those with high risk, HCC should be diagnosed at an earlier stage leading to better outcomes from HCC for those HCC cases. The goal of this study is to examine whether stage at



diagnosis changes over time for Medicare beneficiaries with HCV or another identified risk factor, whether survival increases over time, and whether survival is associated with diagnosis at an earlier stage of HCC treatment.

## **2.2 Methods**

### **2.2.1 Data**

The data used for this analysis were from the SEER registry linked to Medicare claims data. SEER is a surveillance system made up of a number of population-based tumor registries in states and metropolitan areas. For cases diagnosed in 2000 and later, SEER registries cover 27% of the U.S. population.<sup>70,71</sup> Data are collected on demographic, clinical, and cause-of-death information for persons with cancer in these areas. The data are then linked with Medicare claims and distributed by the National Cancer Institute (Calverton, MD).<sup>72</sup> The cohort for this analysis was persons who were Medicare enrolled and diagnosed with HCC between 2000 and 2009. Medicare claims data were available through 2010. Louisiana SEER registry data from 2005 were excluded due to data-collection issues following hurricane Katrina. Rural Georgia SEER registry data were excluded from the analysis due to the small sample size.

### **2.2.2 Case classification**

HCC cases were defined using International Classification of Disease for Oncology codes 8170–8172 and 8174–8175 identified from SEER sources. All HCC cases diagnosed at age 66 or older with current enrollment based on age were included. We limited cases to those who were likely to have complete claims. That is, they had at least one year of continuous enrollment in Part A and Part B before the HCC. The cohort was limited to those not enrolled in a health maintenance organization due to lack of claims data for those in managed care plans. Cases without a diagnosis date or any Medicare claims prior to diagnosis were excluded. Cases with dates of death or dates of birth varying by more than three months between the SEER death date and Medicare death date were excluded. We limited our cohort to those reported through hospitals, radiation treatment centers or

medical oncology centers, laboratories, physician's offices, and hospital outpatient units or surgery centers. We excluded cases who were diagnosed based on death certificate, autopsy, or nursing home reporting only.

Risk factors included in this analysis include viral hepatitis (types B and C), genetic conditions, autoimmune conditions, alcohol abuse, obesity, diabetes, and tobacco use. Risk factors were measured for the 12 months before HCC diagnosis. The metabolic and genetic risk factor category was not included in individual outcome comparisons because less than 1 % of cases had a risk of this type identified. It was included in the count of total number of risk factors. Diagnosis for risk factors for HCC was based on International Classification of Diseases, Ninth Edition (ICD-9), diagnosis codes that were identified from at least one hospitalization (MedPar) record or two Outpatient (OP) or Carrier (NCH) records on separate dates. Risk factors for HCV infection were found using ICD-9 codes as described in Appendix B and for each risk individual cases were classified as having the risk factor or not having the risk factor. Year of diagnosis was taken from the Patient Entitlement and Diagnosis Summary File (PEDSF) using date of HCC diagnosis from SEER sources. The cases were divided into two equal time periods, those diagnosed from 2000 to 2004 and those diagnosed from 2005 to 2009.

### **2.2.3 Demographic characteristics**

The demographic characteristics of interest for this analysis were sex, race, and age at diagnosis. Demographic variables were all taken from the Patient Entitlement and Diagnosis Summary File using items collected from SEER sources.

### **2.2.4 Tumor characteristics**

Cancer stage was determined using SEER historic stage (i.e., localized, regional, distant, and unstaged). The American Joint Committee on Cancer (AJCC) stage was unavailable for almost half of the cases but AJCC stage and historic stage were largely consistent. The majority of HCC cases in the analysis data set were not histologically confirmed. We did not include information in our analysis about grade as it was unavailable for over 40 % of cases.

### **2.2.5 Treatment**

First course of treatment for HCC included surgical resection, radiation, chemotherapy, and/or liver transplant. We used SEER variables for surgical resection (sxprif1–sxprif10) and radiation (rad1–rad10). Surgery was defined as surgery of the primary site using the site-specific codes for liver and intrahepatic bile ducts.<sup>73</sup> Radiation therapy was defined as having received radiation therapy for the liver cancer instance. Chemotherapy was found in the Medicare Outpatient (OP) and Carrier (NCH) files during the first six months after diagnosis and was defined as Healthcare Common Procedure Coding System (HCPCS) codes 96400–96549 and Q0083–Q0085.<sup>74</sup> Cases with an ICD-9 code of V42.7 (liver replaced by transplant) or 996.82 (complications of transplanted liver) in the Medicare Hospitalization (MedPar) file within three months of diagnosis were considered to have received a liver transplant as part of cancer treatment.

### **2.2.6 Analysis**

Data were analyzed using SAS 9.3 (SAS Institute, Cary, NC). HCC cases were compared across two HCC diagnosis periods from 2000 to 2004 and from 2005 to 2009. Risk factors were grouped into categories (i.e., HBV infection, HCV infection, genetic and autoimmune conditions, obesity, tobacco use, alcohol abuse, and diabetes) and the proportion of HCC cases with each risk factor were compared across time periods. Stage at diagnosis was compared between time periods, by risk group, and by stage at diagnosis over time stratified by risk factor. Tumor characteristics and demographic characteristics were described within risk groups for the entire time period examined. Models were adjusted for risk factors and demographic characteristics as indicated. Chi-squared tests were used. All tests of statistical significance were two-sided and with a *p* value of <0.05 considered statistically significant. A Kaplan-Meier analysis was used to calculate median survival with (95 %) confidence intervals by risk-factor groups and stage at diagnosis, and log-rank testing was used to determine statistical significance.

## **2.3 Results**

### **2.3.1 Demographic characteristics by risk factor**

Cases with identified risks were younger than cases without an identified risk factor. The median age of those with one or more identified risk factor was 75.0 years and the median age of those with no risk factor was 76.9 years ( $p < 0.001$ ). Sex varied by risk factor from the overall proportion of 67 % male and 33 % female. The proportion of males was highest among HCC cases with HBV infection (74 % male,  $p < 0.001$ ), tobacco use (79 % male,  $p < 0.001$ ), and alcohol abuse (85 % male,  $p < 0.001$ ). The proportion among females was highest among HCC cases with HCV infection (44 % female,  $p < 0.001$ ), obesity (40 % female,  $p = 0.04$ ), and cirrhosis (38 % female,  $p < 0.001$ ). The distribution of diabetes cases by sex did not vary significantly from the overall distribution among HCC cases (67 % male and 33 % female,  $p = 0.22$ ).

### **2.3.2 Stage at diagnosis by risk factor**

Over the entire period of study, 2000 to 2009, certain identified HCC risk factors were associated with being diagnosed at an earlier stage of HCC. Having identified HCV infection ( $p < 0.001$ ), identified HBV infection ( $p < 0.001$ ), and cirrhosis ( $p < 0.001$ ) were associated with diagnosis at an earlier stage. Having a history of alcohol abuse was associated with diagnosis at a later stage ( $p = 0.008$ ). Tobacco use and obesity were not significantly associated with stage at diagnosis.

### **2.3.3 Risk factors over time**

From the first time period, 2000 to 2004, to the second time period, 2005 to 2009, the proportion of HCC cases with HCV infection increased from 13 % to 17 % ( $p < 0.001$ ) and the proportion of cases with HBV increased from 4 % to 5 % ( $p = 0.013$ ) (Table 2.1). The proportion of HCC cases with diabetes increased from 43 % to 49 % ( $p < 0.001$ ), alcohol abuse from 4 % to 6 % ( $p < 0.001$ ), obesity from 2 % to 3 % ( $p < 0.001$ ), and tobacco use from 3 % to 5 % from the first time period to the second time period. Fewer HCC cases had no risk factor identified in the second time period with 39 % of those diagnosed from 2000 to 2004 with no identified risk factor compared to 31 % of

those diagnosed from 2005 to 2009 ( $p < 0.001$ ). The proportion of HCC cases with two risk factors increased from 15 % to 19 % and proportion with three or more risk factors increased from 7 % to 10 % from the first time period to the second.

**Table 2.1:** Case characteristics of hepatocellular carcinoma cases by year of diagnosis

	Total		2000–2004		2005–2009		<i>p</i> -value
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
HCC cases	9860		4298		5562		
<b>By gender</b>							0.979
Male	6574	67	2865	67	3709	67	
Female	3286	33	1433	33	1853	33	
<b>By race</b>							0.683
White	6863	70	3023	70	3840	69	
Black	774	8	321	7	453	8	
Other	504	5	217	5	287	5	
Asian	1206	12	520	12	686	12	
Hispanic	420	4	179	4	241	4	
American Indian	74	1	28	1	46	1	
Unknown <sup>†</sup>	19	0	NA		NA		
<b>By age at diagnosis</b>							0.103
65–69	1925	20	819	19	1106	20	
70–74	2680	27	1215	28	1465	26	
75–79	2525	26	1116	26	1409	25	
80–85	1762	18	750	17	1012	18	
85+	968	10	398	9	570	10	
<b>By HCV status</b>							<0.001
HCV case	1505	15	564	13	941	17	
Not HCV case	8355	85	3734	87	4621	83	
<b>By HBV status</b>							0.013
HBV case	495	5	189	4	306	5	
Not HBV case	9365	95	4109	96	5256	95	
<b>By risk-factor group</b>							
Diabetes	4515	46	1828	43	2687	48	<0.001
Cirrhosis	2324	24	915	21	1409	25	<0.001
Hepatitis C	1505	15	564	13	941	17	<0.001
Hepatitis B	495	5	189	4	306	5	0.013
Alcohol abuse	478	5	172	4	306	5	<0.001
Tobacco use	424	4	135	3	289	5	<0.001
Obesity	211	2	58	1	153	3	<0.001
Metabolic or genetic factor <sup>†</sup>	14	0	NA		NA		0.552
<b>Number of risks identified</b>							<0.001
One risk	3948	40	1719	40	2229	40	
Two risks	1707	17	629	15	1078	19	
Three risks or more	815	8	281	7	534	10	
No risk identified	3390	34	1669	39	1721	31	

**Table 2.1, continued**

	Total		2000–2004		2005–2009		<i>p</i> -value
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
<b>Any treatment</b>							<0.001
Treatment	3237	33	1331	31	1906	34	
No treatment	6623	67	2967	69	3656	66	
<b>Stage at diagnosis</b>							<0.001
Localized	4522	46	1776	41	2746	49	
Regional	2442	25	1063	25	1379	25	
Distant	1577	16	728	17	849	15	
Unstaged	1319	13	731	17	588	11	

† Cells with values less than 11 are not presented

### 2.3.4 Stage at diagnosis over time

Stage at diagnosis changed significantly between the two time periods, with diagnosis at earlier stages in the later time period compared to the earlier time period ( $p < 0.001$ ) (Table 2.1). In the time period from 2000 to 2004, 42% of HCC cases were localized and 17% were distant compared to 49% localized and 17% distant in the time period from 2005 to 2009. When unstaged cases were excluded, the proportion of cases diagnosed with HCC at an earlier stage remained higher in the later time period

### 2.3.5 Stage at diagnosis by risk factor over time

Change in stage at diagnosis over time was significant in all HCC cases with more cases being diagnosed at an earlier stage. The relative risk of diagnosis at localized stage in the later time period compared to the earlier time period was 1.15 (CI: 1.11,1.19) for all HCC cases. This difference held across risk groups, but was significant only in those with hepatitis C infection, hepatitis B infection, diabetes, cirrhosis, and no risk. The range of relative risk of diagnosis in an earlier stage was 1.03 to 1.25 suggesting an increase in earlier diagnosis in all groups over time. The risk groups with screening recommendations include at least some of those with HBV infection, HCV infection, and cirrhosis. The relative risk for the HBV group (1.25, CI: 1.07,1.46) and the cirrhosis (1.19, CI: 1.11,1.27) group was slightly higher than in the other risk groups, but the relative risk in the HCV group (1.10, CI: 1.02,1.20) was lower than that of the group with no identified risk.

**Table 2.2:** Risk of being diagnosed at localized stage in 2005–2009 compared to 2000–2004

<b>Race</b>	<b>Relative risk</b>	<b>95 % CI</b>
All HCC cases	1.15	1.11,1.19
Hepatitis C	1.10	0.92,1.20
Hepatitis B	1.25	1.07,1.46
Obesity	1.12	0.95,1.32
Diabetes	1.16	1.11,1.22
Tobacco use	1.04	0.91,1.18
Alcohol abuse	1.03	0.90,1.18
Cirrhosis	1.19	1.11,1.27
No risk	1.14	1.06,1.22

**Table 2.3:** Median survival after diagnosis by stage in days by risk factor

	<b>Median survival without identified risk</b>		<b>Median survival with identified risk</b>	
	<b>Days</b>	<b>95 % CI</b>	<b>Days</b>	<b>95 % CI</b>
All HCC cases	178	170,187	NA	
Hepatitis C	158	151,167	340	310,380
Hepatitis B	169	161,177	554	440,703
Obesity	178	170,188	166	128,229
Diabetes	183	171,195	174	162,186
Tobacco use	180	171,189	142	120,172
Alcohol abuse	180	171,189	160	140,197
Cirrhosis	163	156,173	236	215,258

### 2.3.6 Survival

The results of the Kaplan-Meier analysis showed differences in median survival for those with and without certain risk factors. Median survival for the HCC cohort was 178 days after diagnosis and varied between those with and without HBV infection, HCV infection, and cirrhosis. Median survival was significantly longer in those with HBV at 554 days (CI: 440,703) compared to 169 days (CI: 161,177) in those without HBV. Those with HCV and cirrhosis also had longer median survival. The median survival for those with HCV was 340 days (CI: 310,380) compared to 158 days (CI: 151,167) those without HCV and 236 days (CI: 215,258) in those with cirrhosis and 163 days (CI: 156,173) without cirrhosis. There was no significant difference in survival in any other risk group (Table 2.3).

**Table 2.4:** Median survival by diagnosis group in days

	2000–2004		2005–2009	
	Days	95 % CI	Days	95 % CI
All HCC cases	146	136,154	213	198,226
Hepatitis C	304	254,374	361	320,413
Hepatitis B	371	255,501	761	574,938
Obesity	126	66,201	194	134,279
Diabetes	143	124,156	205	183,225
Tobacco use	144	95,192	141	114,187
Alcohol abuse	118	94,156	175	156,247
Cirrhosis	186	153,214	267	240,299

### 2.3.7 Survival over time

Median survival varied significantly by time period with longer survival in the later diagnosis group (Table 2.4). Median 5-year survival was 146 days (CI: 136,154) in those diagnosed from 2000 to 2004 and 213 days (CI: 198,226) in those diagnosed from 2005 to 2009. Survival increased significantly between the first and second time period within three risk groups: HBV, diabetes, and cirrhosis. The largest increase was in those with identified HBV, from 371 days (CI: 255,501) in the first time period to 761 days (CI: 574,938) in the second time period representing an increase of over a year. There was no significant difference seen between the two time periods for those with HCV, obesity, tobacco use, or alcohol abuse.

## 2.4 Discussion

The results of our analysis are consistent with previous work looking at changes in the proportion of cases of HCC with HCV infection. Two previous studies found increases in the proportion of HCC cases with HCV over time.<sup>60,61</sup> The results of this analysis indicate that this trend is continuing from the early 2000s through the late 2000s. This is consistent with the burden from disease of HCV infection in the United States. The first members of the birth cohort with the highest prevalence of HCV turned 65 years old and became Medicare-eligible due to age in 2010, so increasing HCV infection in the Medicare population will likely continue to increase the proportion of HCC cases with HCV over the next 20 years.



The proportion of cases with HCV infection found in this analysis differed from results in previous analyses.<sup>60,61</sup> We found that 13 % of HCC cases from 2000 to 2004 and 17 % of HCC cases from 2005 to 2009 had evidence of HCV infection while previous estimates for HCV among those with HCC in the SEER-Medicare matched data set found up to 23 % with HCV. This is likely due to differences in case counting. For this analysis we included only one year of claims before HCC diagnosis. In other studies, longer time frames up to three years before diagnosis have been used. The same ICD-9 codes were used for this analysis as were used for previous analyses. A sensitivity analysis was performed using additional years of claims data to identify hepatitis C, and similar rates were identified as in other analyses. The decision to use only one year of claims was based on the ability to include persons as young as 66 years of age in the analysis (See Appendix C, HCV case-counting limitations). Despite these differences, the trend is consistent across the three analyses using this data set. The results from previous analyses used different divisions of time periods with one using two 3.5-year periods and the other using two 6-year periods.<sup>60,61</sup> For this analysis, the time period was split into two equal five year time periods. A sensitivity analysis was done using year of diagnosis as a continuous predictor and no differences were seen in the trends in risk factors over time.

The proportion of female HCC cases varied by risk factor indicating potential differences in HCC risk factors by gender. These findings were consistent with findings in previous studies.<sup>60,61</sup> This analysis was not intended to determine causes of HCC by gender and further investigation into gender specific risks for HCC would be needed to better understand the causes and implications of these differences.

In addition to the differences in the proportion of HCC cases with a history of HCV infection, we found an increase in the proportion of cases with any reported HCC risk. The proportion of cases with no risk decreased from 39 % to 31 %. There was also an increase in those with multiple risk factors identified. The risk factors with the largest increase between the two time periods were hepatitis C, cirrhosis, and diabetes. With all risk factors measured increasing over the time of this study, it is possible that there is a change in the population being diagnosed with HCC or a change in documentation of these risk factors in the Medicare claims. Welzel et al. recently described the

population-attributable fraction, a measure of both the prevalence of the risk factor in the population and the strength of the association between the risk factor and the outcome, for risk factors for HCC using the SEER and Medicare linked data. They found that the population-attributable fraction was greatest for obesity and diabetes in this population.<sup>61</sup> When combined with the results of this analysis, these findings point to at least two potential interventions to reduce the morbidity and mortality associated with HCC in this population. The first, as suggested by Welzel et al., would be to reduce obesity and diabetes in the entire population to reduce the incidence of HCC in the long term.<sup>61</sup> The second would be a targeted approach to identify persons with HCV infection and HBV infection, assure consistent care for their liver disease including identification of cirrhosis, and screening for HCC. These two approaches combined could reduce the incidence of HCC and potentially improve the outcomes from HCC in this population in the near and distant future.

The increasing proportion of cases with a previously identified risk factor is promising for attempts to identify HCC at an earlier stage. Screening is recommended for persons with cirrhosis and HCV infection or HBV infection. We found that HCV infection, HBV infection, and cirrhosis were all associated with diagnosis at an earlier stage. We were not able to measure screening directly, so the role it played in this association is unknown, but screening would be a reasonable explanation for this finding. When examined across time, the relative risk of being diagnosed with localized HCC in the second time period when compared to the first time period was significantly greater than one for all three of these risk factors. The increase among those without any identified risk factor was also greater than 1 and was significant. This indicates that there was a small increase in those diagnosed in the earlier stage for each group over time, but that there were not major differences in improvements in early identification between those with an identified risk and those with no identified risk. The other risk factors examined were associated with shorter survival after diagnosis, but these differences were not significant. Interpretation of the differences in survival in those with tobacco use, obesity, and alcohol abuse in this analysis is limited by the likely underreporting of these risks in the claims data. The findings in this analysis point to a potential difference in survival between those with viral hepatitis infection and those with behavioral risk factors. If those with behavioral risk factors not documented in the Medicare claims make up a large proportion of those

without an identified risk, the apparent protective effect of HCV infection and HBV infection on survival may be explained by difference between those with viral hepatitis infection and those with behavioral risk factors.

Identification at an earlier stage is only important if there are differences in outcomes in those who are identified earlier. We were able to demonstrate that those diagnosed at an earlier stage live significantly longer than those who were diagnosed at any other stage. Those diagnosed in the localized stage lived a median of 295 days longer than those diagnosed at a distant stage. This is a meaningful difference in the context of a range of median survival of 77 to 372 days after diagnosis, but may be due to earlier detection in cases that are screened rather than coming to detection due to symptoms. Over the time period examined in this analysis, we found that survival increased significantly. The median survival in the earlier group was 67 days shorter than in the later group. These gains were seen in both the treatment and no treatment group, so this difference cannot be attributed to treatment alone. Survival improved over time for those with all examined HCC risk factors except tobacco use which remained almost the same (144 days for 2000–2004 and 141 for 2005–2009). For those risk factors where there was an increase in survival, the increase in survival was similar for all risks except HBV infection. Survival for those with HBV doubled from 371 days for 2000–2004 to 761 days for 2005–2009. Some of this difference is explained by stage at diagnosis as HBV cases had the largest increase in cases diagnosed with localized HCC over time. Other factors such as liver health likely play a role in the increase, but were not measured in this analysis.

Measuring risk factors in the Medicare claims data presents many challenges. It is likely that there are some enrollees who have one or more of the risk factors but have no record of these risk factors in the claims data. This is likely especially true for obesity, tobacco use, and alcohol abuse. These are not necessarily conditions that would be documented for a visit even if the condition were present. Given these limitations, these risk factors were likely undercounted. The trends seen with the cases found should still be considered as an indication of potential changes over time. For HCV infection, HCV-related factors and liver health indicators were not available. Cancer staging for HCC is based on factors not measured in SEER. Stage was used to approximate disease progression,

but the BCLC staging recommended by the American Association for the Study of Liver Diseases was not used.<sup>62</sup> Despite these limitations, our findings add to the available information on HCV and other risk factors for HCC in the Medicare population.

In conclusion, both the population with HCC among Medicare beneficiaries and the outcomes of those with HCC are changing over time. Increases in the proportion of cases of HCC with HCV infection in this population are consistent with previous studies. Despite an increasing proportion of cases diagnosed at earlier stages, increases in HCV treatment over time were minimal. This demonstrates opportunities for better HCC outcomes if new therapies become available.

## Chapter 3

# Differences in hepatocellular carcinoma by hepatitis C status in Medicare beneficiaries

**Context** Liver-cancer incidence and mortality are increasing in the United States and hepatitis C is a likely contributor to that increase. The increasing age and duration of infection of the population with hepatitis C has the potential to increase the number of Medicare beneficiaries with HCC caused by hepatitis C over the next 20 years.

**Objective** To describe the outcomes of persons with a diagnosis of HCC who are infected with HCV compared to those who are not infected with HCV

**Design** Cohort study

**Setting** SEER-Medicare matched data

**Patients** Cases of hepatocellular carcinoma diagnosed 2000 to 2009 and reported to SEER

**Main outcome measure** All-cause and liver-cancer-specific mortality

### 3.1 Introduction

HCC, the most common liver cancer, is one of the potential long-term consequences of HCV infection. Certain persons with HCV infection are more likely to get HCC, including men, older persons, persons who use large amounts of alcohol, persons with hepatitis B infection, persons with HIV, and those with evidence of cirrhosis.<sup>29</sup> Estimates of the prevalence of HCC in those with chronic HCV

infection range from 4% to 9% after 10 to 40 years of infection.<sup>30,31</sup> Unfortunately, liver-cancer incidence continues to increase and increased from 5.0 per 100 000 in 1999 to 7.1 per 100 000 in 2010.<sup>59</sup> The American Cancer Society estimates that the 5-year relative survival rate for localized HCC is 28%, for regional HCC it is 10%, and for distant spread it is 3%.<sup>75</sup> HCC screening using ultrasound is recommended for persons with HCV infection with cirrhosis due to elevated risk of HCC.<sup>62</sup>

Past studies examining the outcomes of HCC looked at outcomes of persons with HCV infection and HCC compared to others with HCC alone and found somewhat conflicting results. Reddy et al. compared HCC cases with HCV infection to those with nonalcoholic steatohepatitis and found that HCV infected patients had a shorter overall survival time, but not a significant difference in recurrence-free survival after curative therapy.<sup>44</sup> Takuma et al. found that persons with HCV and HCC in Japan had lower rates of recurrence and lower mortality than those with cirrhosis of an unknown cause and HCC.<sup>45</sup> In contrast, Lee et al. found no difference in survival or treatment between Korean patients with HCV-associated HCC and those with cryptogenic-cirrhosis-associated HCC.<sup>76</sup> In addition, in a study examining the roll of viral load in determining outcomes of HCC after resection, Shindoh et al. found that Japanese patients with low viral load had better long-term outcomes after resection.<sup>46</sup> Other studies have looked at outcomes for persons with HCC, but not looked at HCV-infected patients specifically.

The prevalence of HCV infection varies by age in the United States with the highest rates of reported infection occurring in those born in the 1940s, 1950s, and 1960s.<sup>6</sup> In 2012, CDC recommended screening for all persons born between 1945 and 1965.<sup>6</sup> Data from NHANES was used to estimate the number of cases of chronic hepatitis C in this cohort at 2.06 million.<sup>6</sup> This represents 54–77% of the total estimated infections in the United States, while this age group makes up only 11% of the U.S. population.<sup>1,6,7</sup> Persons born in the early part of this cohort are now eligible for Medicare. Two previous studies using the SEER cancer registry and Medicare-linked database found that the proportion of HCC cases with HCV infection had increased during the 1990s and early 2000s.<sup>60,61</sup> As the population with the highest prevalence of HCV infection reaches Medicare age, the SEER-Medicare database could become more useful as a tool to explore the outcomes of

HCC in persons with HCV infection. In this paper, we will use the SEER-Medicare data to look at differences in treatment for liver cancer, liver cancer mortality, and 5-year survival in HCC cases with and without HCV infection.

## **3.2 Methods**

### **3.2.1 Data**

This analysis was conducted using SEER data linked to Medicare claims data. SEER is a surveillance system made up of a number of population-based tumor registries in states and metropolitan areas. For cases diagnosed in 2000 and later, SEER registries cover 27% of the U.S. population.<sup>70,71</sup> Data are collected on demographic, clinical, and cause-of-death information for persons with cancer in these areas. The data are then linked with Medicare claims and distributed by the National Cancer Institute (Calverton, MD).<sup>72</sup> The cohort for this analysis was persons who were Medicare-enrolled and diagnosed with hepatocellular carcinoma between 2000 and 2009. Medicare claims were available through 2010. Louisiana SEER registry data from 2005 were excluded due to data-collection issues following hurricane Katrina. Rural Georgia SEER registry data were excluded from the analysis due to the small sample size.

### **3.2.2 Case selection**

HCC cases were selected from the SEER database for diagnoses between 2000 and 2009. HCC cases were defined using International Classification of Disease for Oncology codes 8170–8172, 8174–8175, and 8180. All HCC cases diagnosed at age 66 or older with current enrollment based on age were included.

Hepatitis C cases were selected using ICD-9 codes for hepatitis C (i.e., 070.41, 070.44, 070.51, 070.54, 070.70, and 070.71). Diagnosis for hepatitis C and other risk factors were defined as one MedPar diagnosis code or two OP/NCH diagnosis codes on two separate dates. Other risk factors for HCC were found using ICD-9 codes (Appendix B).

We limited cases to those who were likely to have complete claims. That is, they had at least one

year of continuous enrollment in Part A and Part B before the HCC. The cohort was limited to those not enrolled in a health maintenance organization. Cases without a diagnosis date or any Medicare claims prior to diagnosis were excluded. Cases with dates of death or dates of birth varying by more than three months between the SEER death date and Medicare death date were excluded. We limited our cohort to those reported through hospitals, radiation treatment centers or medical oncology centers, laboratories, physician's offices, and hospital outpatient units or surgery centers. We excluded cases who were diagnosed based on death certificate, autopsy, or nursing home reporting only.

### **3.2.3 Treatment**

First course of treatment for HCC included surgical resection, radiation, chemotherapy, and/or liver transplant. We used SEER variables for surgical resection (sxprif1–sxprif10) and radiation (rad1–rad10). Surgery was defined as surgery of the primary site using the site-specific codes for liver and intrahepatic bile ducts.<sup>73</sup> Radiation therapy was defined as having received radiation therapy for the liver cancer instance. Chemotherapy was found in the Medicare Outpatient (OP) and Carrier (NCH) files during the first six months after diagnosis and was defined as Healthcare Common Procedure Coding System (HCPCS) codes 96400–96549 and Q0083–Q0085.<sup>74</sup> Cases with an ICD-9 code of V42.7 (liver replaced by transplant) or 996.82 (complications of transplanted liver) in the Medicare Hospitalization (MedPar) file within three months of diagnosis were considered to have received a liver transplant as part of cancer treatment.

## **3.3 Cancer characteristics**

Tumor characteristics were obtained from SEER sources. For cancer stage, SEER historic stage (i.e., localized, regional, distant, and unstaged) was used because the American Joint Committee on Cancer (AJCC) stage was unavailable for a third of the cases. Historic stage and AJCC stage were largely consistent. The majority of HCC cases in the analysis data set were not histologically confirmed. Size of tumor was calculated from two different variables depending on the year diagnosed (extent of disease tumor size for cases before 2004 and collaborative stage tumor size from 2004 on) and were combined into six categories: no tumor found, <1 cm, 1–2 cm, 2–3 cm, >3 cm, and un-



known tumor size. We did not include information in our analysis about grade as it was unavailable for 59 % of cases.

### **3.3.1 Outcomes**

All-cause mortality and cancer-specific mortality were measured at five years after diagnosis. Date of death is obtained from Medicare sources as SEER sources include month and year of death only. Persons who were deceased according to the Medicare date of death were further classified by cause of death using the cause of death to site recode variable from SEER. Each case of HCC was classified as alive or dead and cases that had died and had cause of death information were classified as liver-cancer-related deaths and deaths from other causes. Specific days-to-death variables were created for liver cancer and all causes. Cases were censored at the most recent claim file date and at death from other causes for the liver-cancer-related death analysis. Persons alive after 5 years were censored as were persons with less than 5 years of follow up as of December 31, 2011.

### **3.3.2 Analysis**

Data were analyzed using SAS 9.3 (SAS Institute, Cary, NC). We compared the frequency of each of the relevant predictors using chi-squared tests. A Kaplan-Meier analysis was used to calculate survival at 5 years stratified by HCV infection status and log-rank testing was used to determine statistical significance. Cox proportional hazard models were used to examine the effect of HCV infection status adjusted for age, gender, and other risk factors for HCC on mortality. We stratified the Cox proportional hazard models by stage at diagnosis and age to further explore the relationship between HCV infection and HCC outcomes within groups.

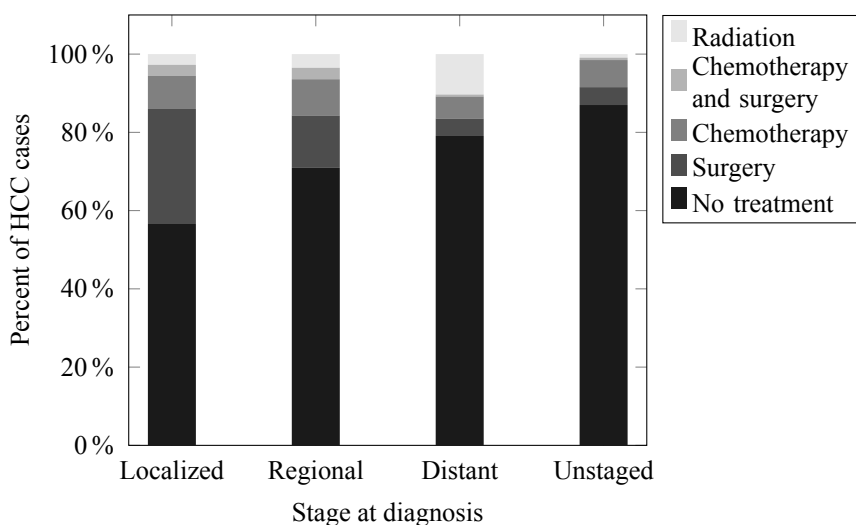
## **3.4 Results**

The linked SEER-Medicare data contained 9860 cases of HCC diagnosed between 2000 and 2009 that met the criteria for inclusion in this analysis (Table 3.1). Of the total number of HCC cases, 1505 (15 %) had a diagnosis of hepatitis C infection. The annual number of cases of HCC increased from 719 in 2000 to 1166 in 2009, while the percent of cases with HCV infection has increased

from 10 % of all HCC cases in 2000 to 18 % of all HCC cases in 2009. Cases of HCC with HCV infection were more evenly divided between genders (56 % male compared to 69 % male with HCC without HCV infection,  $p < 0.001$ ). The median age of HCC cases with HCV infection was younger compared to those without HCV infection (73.5 years versus 75.9 years,  $p < 0.001$ ). Documented cirrhosis varied between HCC cases with and without HCV infection. Just over half of HCV infected HCC cases had cirrhosis documented while only 19 % of HCC cases without HCV infection had documented cirrhosis ( $p < 0.001$ ). The percent of HCV cases with cirrhosis documented was lower than expected, so an additional cirrhosis measure was added for cirrhosis reported from 12 months before HCC diagnosis through the end of the claims data. The proportion of HCC cases with cirrhosis increased when measured after HCC diagnosis and remained higher in HCV cases (84 % of those with HCV infection and 48 % of those without HCV infection,  $p < 0.001$ ); see Appendix G.

The most common stage at diagnosis was localized for both groups, while the percent unstaged is similar across groups (11 % unstaged in those with HCV infection and 14 % unstaged in those without HCV infection). HCC cases with HCV infection were diagnosed at earlier stages than HCC cases without HCV infection (Table 3.1). Tumor size was missing for 32 % of cases. HCC cases with HCV infection were more likely to have a tumor size of less than 1 cm (70 % compared to 50 % for HCC cases without HCV infection). Only 33 % of HCC cases received treatment, with the highest treatment rates in those with localized and regional cancer stage at diagnosis (Table 3.1). HCV-infected cases were more likely to be treated than others at every stage. Given earlier stage at diagnosis, this resulted in HCV-infected cases having higher treatment rates. The most common treatment type was surgery (21 %), followed by chemotherapy (11 %) and radiation (5 %). Treatment type varied by HCV infection status with surgery occurring more commonly in those with HCV infection (30 % in HCV cases and 19 % in HCC cases without HCV infection,  $p < 0.001$ ). A stratified analysis revealed that HCV-infected cases were more likely to be treated at every diagnostic stage but distant (Table 3.3). Treatment type also varied by stage at diagnosis. For localized and regional stages, surgery was the most common treatment (30 % for localized, 13 % for regional, 4 % for distant, and 5 % for unstaged). Radiation was most common at distant stage (3 % of localized, 3 % of regional, 10 % of distant stage, and 1 % of unstaged).

**Figure 3.1:** Treatment by stage at diagnosis



**Table 3.1:** Case characteristics of hepatocellular carcinoma cases by HCV infection status

	Total		Not HCV case		HCV case		<i>p</i> -value
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
<b>HCC cases</b>	9860		8355		1505		
<b>By gender</b>							<0.001
Male	6574	67	5731	69	843	56	
Female	3286	33	2624	31	662	44	
<b>By race</b>							<0.001
White	6863	70	6006	72	857	57	
Black	774	8	601	7	173	12	
Other	504	5	395	5	109	7	
Asian	1206	12	917	11	289	19	
Hispanic	420	4	353	4	67	4	
American Indian <sup>‡</sup>	NA		NA		NA		
Unknown <sup>‡</sup>	NA		NA		NA		
<b>By age at diagnosis</b>							<0.001
65–69	1925	20	1499	18	426	28	
70–74	2680	27	2213	26	467	31	
75–79	2525	26	2157	26	368	24	
80–85	1762	18	1581	19	181	12	
85+	968	10	905	11	63	4	
<b>By HBV status</b>							<0.001
HBV case	495	5	382	5	113	8	
Not HBV case	9365	95	7973	95	1392	92	
<b>By status at 5 years</b>							<0.001
Living	1002	10	792	9	210	14	
Deceased	8858	90	7563	94	1295	86	
<b>By cause of death</b>							0.135
Died of liver cancer	5707	71	4921	71	786	69	
Died of other causes	2373	29	2016	29	357	31	

Table 3.1, continued

	Total		Not HCV case		HCV case		<i>p</i> -value
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
<b>By year diagnosed</b>							<0.001
2000	719	7	650	8	69	5	
2001	778	8	699	8	79	5	
2002	861	9	730	9	131	9	
2003	938	10	797	10	141	9	
2004	1002	10	858	10	144	10	
2005	1060	11	877	11	183	12	
2006	995	10	820	10	175	12	
2007	1166	12	969	12	197	13	
2008	1175	12	996	12	179	12	
2009	1166	12	959	11	207	14	
<b>Percent of census tract below poverty level</b>							0.003
<13.8%	6405	65	5493	66	912	61	
13.8–19.9%	1358	14	1117	13	241	16	
20–39.9%	1737	18	1448	17	289	19	
≥40%	258	3	210	3	48	3	
Unknown	102	1	87	1	15	1	
<b>Median census tract income</b>							0.03
Below U.S. median <42 128	4374	44	3712	44	662	44	
Above U.S. median >42 128	5260	53	4438	53	822	55	
Unknown	226	2	205	2	21	1	
<b>Stage</b>							<0.001
Localized	4522	46	3679	44	843	56	
Regional	2442	25	2098	25	344	23	
Distant	1577	16	1431	17	146	10	
Unstaged	1319	13	1147	14	172	11	
<b>Histology</b>							0.26
8170	9651	98	8169	98	1482	98	
8171 <sup>‡</sup>	16		NA		NA		
8172 <sup>‡</sup>	14		NA		NA		
8174 <sup>‡</sup>	91		NA		NA		
8175 <sup>‡</sup>	NA		NA		NA		
8180	85	1	73	1	12	1	
<b>Grade</b>							<0.001
I	1447		684	13	763	17	
II	1548		628	21	920	21	
III	953		498	10	455	10	
IV	86		42	1	44	1	
Cell type not determined, not stated or not applicable	5826		3613	66	2213	50	
<b>Tumor size</b>							<0.001
No tumor found <sup>‡</sup>	NA		NA		NA		
<1 cm	5226	53	4176	50	1050	70	
1–2 cm	1364	14	1287	15	77	5	
2–3 cm <sup>‡</sup>	67	1	NA		NA		
>3 cm <sup>‡</sup>	26	0	NA		NA		
Unknown	3169	32	2798	33	371	25	

**Table 3.1, continued**

	Total		Not HCV case		HCV case		<i>p</i> -value
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
<b>Treatment</b>							
<b>One or more treatments</b>							<0.001
Any treatment	3237	33	2603	69	634	42	
No treatment	6623	67	5752	31	871	58	
<b>Surgery</b>							<0.001
Surgery	2034	21	1583	19	451	30	
No surgery	7826	79	6772	81	1054	70	
<b>Radiation</b>							0.88
Radiation	471	5	398	5	73	5	
No radiation	9389	95	7957	95	1432	95	
<b>Chemotherapy</b>							0.12
Chemotherapy	1042	11	866	10	176	12	
No chemotherapy	8818	89	7489	90	1329	88	
<b>Multiple treatments</b>							NA
Chemotherapy and surgery	214	2	170	2	44	3	
Chemotherapy and radiation <sup>‡</sup>	42	0	NA		NA		
Surgery and radiation <sup>‡</sup>	44	0	NA		NA		
Chemotherapy, surgery, and radiation <sup>‡</sup>	NA		NA		NA		

<sup>‡</sup> Cells with values less than 11 are not presented

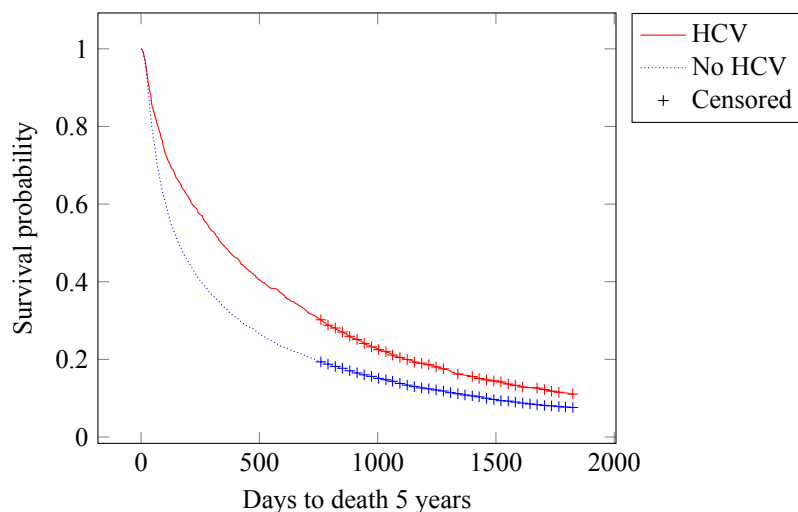
### 3.4.1 Overall 5-year survival

At five years after HCC diagnosis, only 9% of those without HCV infection and 14% of those with HCV infection were still living ( $p < 0.001$ ) (Figure 3.2). Cases of HCC with hepatitis C infection had better unadjusted overall 5-year survival than those without HCV infection (HR = 0.74,  $p < 0.001$ ). HCC cases with hepatitis B infection also had higher unadjusted overall 5-year

**Table 3.2:** Percent treated by HCV infection status stratified by stage at diagnosis

Stage	Percent treated	Percent treated not HCV case	Percent treated HCV case	<i>p</i> -value
Localized	45	42	52	<0.001
Regional	30	28	37	<0.001
Distant	22	22	24	0.629
Unstaged	13	12	19	0.016

**Figure 3.2:** Overall 5-year survival by hepatitis C infection status



**Table 3.3:** Median survival by stage in days unadjusted

Stage	No HCV		HCV		Difference in days	p-value
	Days	95 % CI	Days	95 % CI		
Localized	338	317,361	527	475,614	189	<0.001
Regional	137	126,150	266	216,328	129	<0.001
Distant	77	70, 82	77	61,101	0	0.23
Unstaged	98	86,106	160	97,192	62	0.052

survival (HR = 0.52,  $p < 0.001$ ). HCC cases who were treated had higher unadjusted overall 5-year survival rates than those who did not have treatment (HR = 0.36,  $p < 0.001$ ). Stage at diagnosis significantly impacted overall survival with the lowest survival in those diagnosed at distant stage (HR = 3.00,  $p < 0.001$  compared to localized). The results of the Kaplan-Meier analysis by stage showed a significant advantage for HCV-infected cases compared to HCC cases without HCV infection in survival in days in localized and regional stages only (Table 3.3). Localized HCC cases with HCV infection had a median survival after diagnosis of 189 days longer than those without HCV infection.

When adjusted for stage, race, gender, age at diagnosis, treatment, diabetes, cirrhosis, year of diagnosis, and hepatitis B status, hepatitis C infection was still significantly associated with better overall survival (HR = 0.87,  $p < 0.001$ ) (Table 3.4). The proportional hazards assumption was violated for this model, but the results are presented here without correction. Hepatitis C was signif-

**Table 3.4:** Cox proportional hazard models with covariates for 5-year all-cause mortality

<b>Predictor</b>	<b>HR</b>	<b>p-value</b>
HCV infection	0.87	<0.001
<b>Stage at diagnosis</b>		<0.001
Localized	Reference	
Regional	1.60	
Distant	2.55	
Unstaged	1.59	
<b>Race</b>		<0.001
White	Reference	
Black	1.15	
Other	0.87	
Asian	0.78	
Hispanic	0.95	
American Indian	1.12	
Unknown	0.96	
HBV infection	0.70	<0.001
Male	1.00	1.00
<b>Age at diagnosis</b>		<0.001
65–69	Reference	
70–74	1.09	
75–79	1.16	
80–85	1.22	
85+	1.42	
Receipt of one or more treatment	0.41	<0.001
Diabetes	1.10	<0.001
Cirrhosis	1.10	0.005
Year diagnosed	0.97	<0.001

icantly associated with better overall survival in both the corrected and uncorrected versions. See Appendix H for a Cox proportional hazard model with corrections. When stratified by stage, adjusted overall 5-year survival was only significant in the regional stage (HR = 0.81,  $p = 0.005$ ). There was no significant difference at any other stage, but the hazard ratios remained below one for all stages (Table 3.5). When stratified by age, HCV infection was significantly associated with better survival in the three youngest age groups, but not the two oldest (Table 3.6).

### 3.4.2 Death from liver cancer at five years

Of those HCC cases deceased at five years post diagnosis, 69% of HCV-infected cases and 71% of those without HCV infection died from their liver cancer ( $p = 0.494$ ). The four most common causes of death in those who did not die of their HCC were other cancers, diseases of the heart,

**Table 3.5:** Stage-stratified Cox proportional hazard models adjusted for 5-year all-cause mortality

Stage	HR	<i>p</i> -value
Localized	0.91	0.05
Regional	0.81	<0.001
Distant	0.87	0.133
Unstaged	0.88	0.131

**Table 3.6:** Age-stratified Cox proportional hazard models adjusted for 5-year all-cause mortality

Age at diagnosis	HR	<i>p</i> -value
65–69	0.80	<0.001
70–74	0.84	0.002
75–79	0.83	0.004
80–85	0.93	0.424
85+	0.83	0.174

liver diseases and cirrhosis, and infectious and parasitic diseases including HIV. Cases of HCC with hepatitis C infection have a lower risk of dying from liver cancer in the first five years after diagnosis (HR = 0.73,  $p < 0.001$ ). Earlier stage at diagnosis (localized compared to distant, HR = 0.44,  $p < 0.001$ ), younger age (youngest compared to oldest age group, HR = 0.71,  $p < 0.001$ ), hepatitis B infection (HR = 0.72,  $p < 0.001$ ), cirrhosis (HR = 0.89,  $p < 0.001$ ), and receipt of one or more treatment (HR = 0.42,  $p < 0.001$ ), were significantly associated with lower risk of dying from liver cancer at five years. Those with diabetes (HR = 1.04,  $p = 0.20$ ) had an increased risk of dying from liver cancer. Risk of death increased over time (HR = 1.06,  $p < 0.001$ ). The risk of dying from liver cancer at 5 years varied by race ( $p < 0.001$ ). Male sex (HR = 0.98,  $p = 0.573$ ) was not significantly associated with liver-cancer death.

When adjusted for stage, race, gender, age at diagnosis, treatment, diabetes, cirrhosis, year of diagnosis, and hepatitis B status, the HCV association with liver-cancer death remains statistically significant (HR = 0.83,  $p = 0.001$ ) (Table 3.7). Cirrhosis (HR = 1.01,  $p = 0.77$ ) and age at diagnosis ( $p = 0.13$ ) were not significantly associated with lower risk of liver-cancer death in the adjusted model. All other predictors remained significantly associated with liver-cancer death in the adjusted model.



**Table 3.7:** Cox proportional hazard models with covariates for 5-year liver-cancer mortality

<b>Predictor</b>	<b>HR</b>	<b>p-value</b>
HCV infection	0.85	<0.001
<b>Stage at diagnosis</b>		<0.001
Localized	Reference	
Regional	1.55	
Distant	2.05	
Unstaged	1.50	
<b>Race</b>		0.002
White	Reference	
Black	1.10	
Other	0.96	
Asian	0.88	
Hispanic	0.88	
American Indian	1.31	
Unknown	0.68	
HBV infection	0.83	0.009
Male	0.97	0.249
<b>Age at diagnosis</b>		0.131
65–69	Reference	
70–74	1.07	
75–79	1.06	
80–85	1.07	
85+	1.15	
Receipt of one or more treatment	0.46	<0.001
Diabetes	1.08	0.006
Cirrhosis	1.01	0.766
Year diagnosed	1.05	<0.001

### 3.5 Discussion

Survival differs between Medicare beneficiaries with HCC with evidence of HCV infection and those without evidence of HCV infection. HCC cases with HCV infection have higher 5-year survival and fewer deaths from liver cancer in the first 5 years after diagnosis. Differences in stage at diagnosis and likelihood of treatment may explain some, but not all, of these differences. When stratified by stage, the association between HCV infection status and survival was only significant in those diagnosed at regional stage.

Screening for HCC using abdominal ultrasound is recommended for persons with HCV with cirrhosis based on the elevated risk for HCC in that population.<sup>62,77</sup> Our findings likely reflect this recommendation as persons with HCV infection were diagnosed at earlier stages and smaller tumor sizes. HCC screening was not measured in this study, so the relation between HCC screening and

stage at diagnosis could not be determined directly, but screening would be a likely cause of the observed pattern of earlier stage at diagnosis and smaller tumors. This is consistent with other studies looking at HCC screening and stage at diagnosis.<sup>78,79</sup> It is also possible that both patient and provider awareness of risk of HCC may cause patients to seek evaluation and providers to suspect HCC at a lower threshold than for patients without an identified risk for HCC. This further supports the recommendation for screening in those with HCV infection and cirrhosis.

In most cases, HCC due to hepatitis C infection is thought to occur as a result of cirrhosis of the liver, but there is some evidence that HCC can occur in the absence of cirrhosis in some persons with HCV infection.<sup>29,80,81</sup> In this population, only 51 % of HCV-infected cases had cirrhosis documented before HCC diagnosis and 84 % overall. Although this was higher than in those with HCC alone, there were still cases without documented cirrhosis among those with HCV infection. It is possible that cirrhosis was present in a higher proportion of the HCV cases, but it was not present in the claims data used. In almost half of those with HCV, cirrhosis appears to have been identified after cancer diagnosis rather than before. This raises the possibility of a difference in cases with clinically relevant cirrhosis likely found before HCC diagnosis and cirrhosis discovered at or after HCC diagnosis. Ongoing screening for HCC is recommended for persons with HCV infection only in the presence of cirrhosis. If cirrhosis is present in all or nearly all HCC cases among those with HCV infection, it appears that many of these cases had undiagnosed cirrhosis. Answering the question of whether HCC is occurring in the absence of cirrhosis was beyond the scope of this analysis, but the answer could further the understanding of HCC in persons with HCV infection and recommendation for screening for HCC in persons with HCV infection.

We found that treatment for HCC was associated with better overall 5-year survival and lower mortality at 5 years from liver cancer. This difference remained significant even when adjusted for stage at diagnosis. The effect of treatment on 5-year survival did not vary based on HCV infection status based on the results of the stratified analysis. Based on these results, it appears that hepatitis C infection is not associated with a decreased response to therapy. Evidence from a previous study indicates that higher viral load is associated with poorer outcomes after surgical resection.<sup>46</sup> Further investigation of the association between viral load and HCC outcomes may find differences in

outcomes within HCV-infected HCC cases.

This study is based on data from a population-based cancer registry, SEER, which includes some of the risk factors for HCC, treatments for HCC, and information on cause of death for those who died. There are a number of limitations to the information available in the registry. Some risk factors such as obesity, tobacco use, and rare disorders are poorly documented in Medicare claims data and were not included in this analysis. In addition, HCV-related factors such as viral load, genotype, and mutations and liver-health indicators such as blood bilirubin level and Child-Pugh score were not available from SEER or Medicare sources, and grade was missing in a large proportion of cases. Stage was used to approximate disease progression at diagnosis, but outcomes could not be examined based on the BCLC staging recommended by the American Association for the Study of Liver Diseases because the SEER cancer registries do not collect them.<sup>62</sup> For example, BCLC staging takes Child-Pugh score, portal hypertension, and blood bilirubin levels into consideration. These factors as well as grade may prove to be important in identifying persons with HCV infections who are more or less likely to respond to treatment. Despite these limitations, the findings of this analysis provide further information on the outcomes of HCC in the United States.

In conclusion, there is variation in 5-year mortality among HCC cases with and without HCV infection and it appears to occur primarily in those diagnosed at regional stage. The reasons for this are unclear, but treatment differences and earlier diagnosis may play a role. Treatment only occurs in a small proportion of HCC cases even in those diagnosed in early stages. Improvements in HCC treatment are needed to change the outcomes of HCC in those with and without HCV infection.

## Chapter 4

# The effect of current treatments for hepatitis C on mortality from hepatitis C in persons born between 1945 and 1965, United States

**Context** New HCV treatments were licensed in 2011 and 2013, with more expected in the future.

With better treatments available and many years of surveillance data and HCV experience, some state and local health departments are considering whether to implement strategies to assist HCV-infected persons in finding appropriate health care. If these projects are undertaken, they will have to fit into systems with limited resources. Information is needed on how to prioritize cases, as only a small percentage of cases would be able to be targeted for intervention.

**Objective** To model the effect of treatments for HCV on patient and population outcomes and to identify persons who should be highest priority for linkage to care programs based on the impact of the health of the population

**Design** State-transition model of disease progression with a transmission component and parameter estimates derived from the literature

**Setting** United States

**Patients** People born between 1945 and 1965

**Main outcome measures** Mortality from HCV infection, remaining life years, new HCV infections

## 4.1 Introduction

HCV is the most common blood-borne infection in the United States, with an estimated 2.7 million to 3.9 million Americans living with chronic HCV infection<sup>1</sup> and about 16 500 new HCV infections annually.<sup>2</sup> Chronic HCV infection occurs in the majority of those initially infected and can lead to cirrhosis, hepatocellular carcinoma, and death. The prevalence of HCV infection varies by age in the United States with the highest rates of reported infection occurring in those born in the 1940s, 1950s, and 1960s.<sup>6</sup> In 2012, CDC recommended screening for all persons born between 1945 and 1965.<sup>6</sup> The estimated number of cases of chronic HCV in this cohort is 2.06 million.<sup>6</sup> This represents 54% to 77% of the total estimated infections in the United States, while this age group makes up only 11% of the U.S. population.<sup>1,6,7</sup>

The most commonly reported risk factor for HCV infection in the United States is injection drug use.<sup>2</sup> The percentage of reported cases of new HCV infection reporting injection drug use is higher in younger persons. In those over 40 years of age, injection drug use is the third most frequently reported risk factor after surgery and multiple sexual partners.<sup>82</sup> However, injection drug use is considered to be a higher risk behavior. There is currently no vaccine available for HCV, and prevention consists of encouraging safer injection practices or discontinuation of injection drug use. Continued use of sterile medical equipment, testing of the blood and organ supply, and universal precautions are also prevention strategies.

Treatment for HCV infection has been available for over two decades and has improved dramatically over that time. The goal of HCV treatment is an undetectable viral load at six months after treatment, which is referred to as a SVR. Until 2011, the treatment protocol for HCV involved the use of two drugs, ribavirin and interferon. These medications were taken for six to twelve months and had severe side effects. Since 2011, four new medications have been approved for the treatment of HCV infection and there are a number of additional medications in the approval process.<sup>10</sup> The new medications for HCV have two main benefits: higher rates of SVR and fewer side effects. The availability of these medicines has led to increased interest in treating more people for HCV.

Previous models of HCV treatment in the United States have shown that treating HCV infection reduces morbidity and mortality from HCV.<sup>48,49</sup> In addition, there are a number of modeling studies

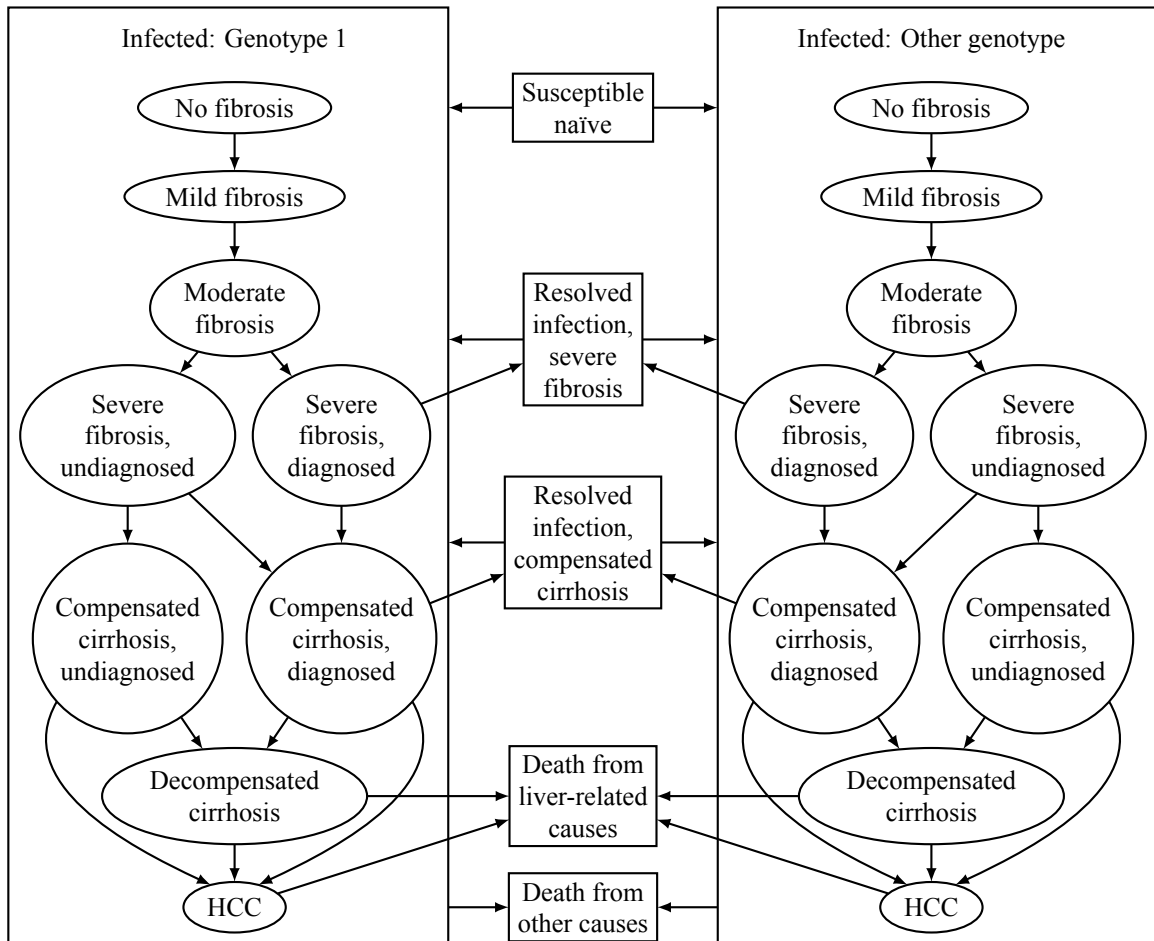
that suggest treatment of HCV infection in those who inject drugs could reduce the transmission of HCV.<sup>50–54,83</sup> Mathematical models have also been used to examine the cost effectiveness of the newer drugs. The first two new drugs approved in the United States, Telaprevir and Boceprevir, were both found to be cost effective in treating those with evidence of liver damage from HCV.<sup>56</sup>

Public health agencies such as CDC and state health departments have focused their limited HCV-related resources on determining the burden of disease in the United States from HCV infection and preventing new HCV infections through education and provision of clean injection-drug equipment. Referral to care and financial assistance for treatments for HCV infection have been limited mostly to those who are co-infected with HIV. With the introduction of new treatments for HCV infection, there is growing interest to provide programs designed to link those with HCV infection to care. The programs would aim to get patients into treatment both for the benefit of the individual and potentially to prevent transmission to others by reducing the reservoir of HCV in the community. It is not known, however, how best to focus limited resources when linking patients to care. In this paper we will consider the potential for treating those in the highest burden population for HCV infection in the United States, those born between 1945 and 1965, and compare the outcomes of treating persons who inject drugs (PWID) with the outcomes of treating those who don't inject drugs (non-PWID).

## **4.2 Methods**

We constructed a state-transition model to represent disease progression and transmission of HCV to evaluate the public health impact of treatment using direct-acting antivirals on mortality from HCV in the United States in two populations. The model builds on a published model used by Salomon and colleagues and Liu and colleagues.<sup>56,84,85</sup> The state-transition model reflects HCV infection progression, infection resolution due to treatment, and mortality under a given treatment policy scenario. We evaluated disease and mortality outcomes over the lifetime of persons living in the United States aged 45 to 65 years in 2010 (i.e. birth years 1945 to 1965). Using currently recommended treatment regimens including simeprevir and sofosbuvir, we considered two treatment policy scenarios, treating PWID and treating non-PWID, and compared these policies to no treatment

**Figure 4.1:** State-transition model of hepatitis C progression



and treatment using only ribavirin and peginterferon alfa for each population.

In the model, persons infected with HCV (existing cases and new infections) move sequentially through six stages of HCV infection (infection with no evidence of fibrosis to three levels of fibrosis, then two levels of cirrhosis) and potentially to HCC. A state-transition diagram of the model is shown in Figure 4.1. Transitions can take place annually. All disease states are divided into two genotype subgroups (type 1 and other) to allow for variation in treatment effectiveness by genotype. The model was run for two populations: PWID and non-PWID. The populations were assumed to be completely separate and no initiation or cessation of injection drug use was assumed. Since not all patients are aware of their HCV status, diagnosis with HCV infection was included in the model for stages eligible for treatment. The likelihood of being aware of diagnosis with HCV infection was

considered to be the same across disease states due to screening recommendations in this population for screening of asymptomatic individuals.

Current guidelines recommend treatment for only some of the HCV-infected persons, those with severe fibrosis (in this model portal fibrosis with several septa) and those with compensated cirrhosis.<sup>3,86</sup> Treatment success is modeled as a transition from an infected state to a resolved state and does not depend on the stage of disease progression. The probability of treatment was assumed to be the same across the two disease states and the two genotype groups. Persons are eligible for treatment each year they are in a treatment-eligible state (shown in Figure 4.1 as those with a transition to resolved infection). Persons who are successfully treated move into disease-free states stratified by the level of liver damage, severe fibrosis, or compensated cirrhosis at the time of treatment. Those who unsuccessfully complete treatment (i.e., undetectable viral load at six months) remain in the appropriate disease state, but are no longer eligible for further treatment. Treatment for HCV is dependent on the patient being aware of his or her HCV infection. Persons were assumed to have varied adherence to the treatment protocol (i.e., did they take all of the doses of medication for the entire treatment period). For each person receiving treatment, there were two possible adherence levels, low adherence and high adherence. Treatment success varied depending on adherence. We assumed that HCC could only occur in those with cirrhosis and that the rate was the same for those with compensated and decompensated cirrhosis. Only those with the latest stages of disease progression, decompensated cirrhosis and HCC, are at risk of liver-related death.

We incorporated transmission of HCV to the model as movement from an uninfected state to HCV infection with no liver damage. The likelihood of infection in this model changes based on injection drug use and the prevalence of HCV in the PWID population. The probability of infection ( $p(\text{Infection})$ ) is modeled as:

$$p(\text{Infection}) = 1 - (1 - q)^{N \cdot P_{\text{HCV}}} \quad (4.1)$$

where  $q$  is the probability of infection per injection,  $N$  is the number of injections per year, and  $P_{\text{HCV}}$  is the prevalence of HCV in the population. HCV prevalence in the population is determined by using the number of persons in the infected states in the last cycle. The equation for transmission



**Table 4.1:** U.S. population estimates for population born between 1945 and 1965

<b>Parameter</b>	<b>Population</b>	<b>Percent of total population born 1945–1965</b>
Total population <sup>5</sup>	84 169 206	100.00 %
Population of PWID <sup>23</sup>	92 586	0.11 %
Infected with HCV <sup>22</sup>	75 752	0.09 %
Not infected with HCV	16 834	0.02 %
Population of non-PWID	84 076 620	99.89 %
Infected with HCV <sup>4</sup>	1 522 996	1.81 %
Not infected with HCV	82 553 624	98.08 %

**Table 4.2:** Initial state probabilities conditional on PWID status<sup>89</sup>

<b>State</b>	<b>Initial probability for non-PWID</b>	<b>Initial probability for PWID</b>
Susceptible	0.981 886	0.225 000
Early infected: Genotype 1	0.006 684	0.284 813
Early infected: Other genotype	0.002 192	0.094 938
Mild fibrosis: Genotype 1	0.004 638	0.197 625
Mild fibrosis: Other genotype	0.001 521	0.065 875
Moderate fibrosis: Genotype 1	0.001 364	0.058 125
Moderate fibrosis: Other genotype	0.000 447	0.019 375
Severe fibrosis: Genotype 1	0.000 682	0.029 063
Severe fibrosis: Other genotype	0.000 224	0.009 688
Compensated cirrhosis: Genotype 1	0.000 103	0.004 377
Compensated cirrhosis: Other genotype	0.000 034	0.001 459
Decompensated cirrhosis	0.000 136	0.005 836
HCC year 1 <sup>56,57,88</sup>	0.000 045	0.001 914
HCC year 2 or greater <sup>56,57,88</sup>	0.000 045	0.001 914
Death from HCV	0	0

Percent with each genotype was assumed to be consistent within each state as disease progression does not differ across genotypes.

was calibrated to an estimated incidence of 6.6 new cases per 100 person-years for persons over 30 from a prospective cohort study.<sup>87</sup> This was used to calibrate Equation 4.1 in the TreeAge model with no treatment and averaged over the first five years of the model. A pair of parameters was chosen for use in the model based confidence in the parameter estimates (see Appendix E).

#### **4.2.1 Parameter estimates and data sources**

We derived population estimates for the United States from the 2010 U.S. Census (Table 4.1).<sup>7</sup> The proportion of the U.S. population infected with HCV was derived separately for persons who

**Table 4.3:** Probability of treatment and sustained virologic response

Parameter	Baseline	Minimum	Maximum
<b>SVR probabilities</b>			
Probability of SVR in genotype 1 with DAA high adherence <sup>13-23</sup>	90	63	100
Probability of SVR in genotype 1 with ribavirin and peginterferon alfa high adherence <sup>94</sup>	50	35	69
Probability of SVR in other genotype high adherence <sup>13-23</sup>	92	90	100
Probability of SVR in genotype 1 with DAA low adherence <sup>95</sup>	25	0	50
Probability of SVR in genotype 1 with ribavirin and peginterferon low adherence <sup>94</sup>	14	0	28
Probability of SVR in other genotype low adherence <sup>95</sup>	25	0	50
<b>Treatment probability</b>			
Probability of treatment per year	25	0	50
Probability of death from treatment <sup>56,57</sup>	0.5	0.05	1.1
Chance of high adherence <sup>56,57</sup>	70	50	80

inject drugs and the general population.<sup>6,90</sup> The proportion of the population who injects drugs was taken from the estimate for those over 50 from the National Survey on Drug Use and Health.<sup>91</sup> The distributions of the starting non-PWID population and PWID population among the different health states is shown in Table 4.2, based on a study of the progression of HCV in those infected by a contaminated blood product over a two year period.<sup>89</sup> The proportion of those infected by genotype 1 (75.3 %) was derived from U.S. general population estimates from NHANES estimates and is incorporated into the estimates shown in Table 4.2.<sup>25</sup> The probability of awareness of HCV diagnosis for the first year was 50 % and was taken from literature estimates of the proportion of those infected that are aware of their infection.<sup>48,92,93</sup> Diagnosis in subsequent years was 1 % per year for the base case. The probability of treatment is based on estimates from Liu et al. (Table 4.3).<sup>56</sup>

Transition probabilities between disease states are taken from previous models when possible (Table 4.4).<sup>56,84,85</sup> Estimates for treatment success were taken from the clinical trials for each drug.<sup>13-20,22,23</sup> Mortality estimates for HCV-related deaths, HCC-related deaths, and mortality from other causes were taken from CDC Wonder and the 2008 U.S. Life Tables. Deaths from HCV infection, excess deaths in those with HCV infection, and excess deaths in those with injection drug use were removed from the all-cause mortality estimates.<sup>96,97</sup> All-cause mortality estimates for those with HCV infection and PWID were considered to be higher than for those without HCV infection and with no injection drug use (Table 4.6). Parameter estimates for transmission of HCV were taken

**Table 4.4:** Transition probabilities between HCV disease states

Parameter	Base case estimate	Minimum	Maximum
Proportion of early infected who never progress	0.24	0.20	0.33
Early infected to mild fibrosis	Varies by age; see Table 4.5		
Mild fibrosis to moderate fibrosis	Varies by age; see Table 4.5		
Moderate fibrosis to severe fibrosis	Varies by age; see Table 4.5		
Severe fibrosis to compensated cirrhosis	Varies by age; see Table 4.5		
Compensated cirrhosis to decompensated cirrhosis	0.044	0.03	0.06
Decompensated cirrhosis to dead for HCV	0.182	0.065	0.4
Compensated cirrhosis to HCC	0.02	0.015	0.03
Decompensated cirrhosis to HCC	0.02	0.015	0.03
Compensated cirrhosis to resolved	See Table 4.3		
Severe fibrosis to resolved	See Table 4.3		
HCC year 1 to death from HCC	0.75	0.3	0.8
HCC year 2 and beyond to death from HCC	0.25	0.5	

Progression variables from previous models.<sup>56,57,84,85</sup>

**Table 4.5:** Fibrosis progression by age<sup>56,57</sup>

Age	Probability of progression	Minimum	Maximum
40–49	0.043	0.03	0.05
50–59	0.099	0.06	0.12
60–69	0.168	0.11	0.2
70–79	0.214	0.14	0.26
80+	0.232	0.2	0.26

from the substance-abuse literature (Table 4.7).<sup>98,99</sup>

## 4.2.2 Analysis

Outcomes for the analysis included number of cases of HCC, deaths from liver-related causes in those with HCV infection, and number of remaining life-years accrued by the population. One-way sensitivity analyses were performed on all variables (Appendix B). The model was constructed in TreeAge Pro, Williamstown, MA: TreeAge Software, 2013. A cycle length of one year was chosen because of the slow progression of HCV infection, the duration of treatment (generally 24 to 48

**Table 4.6:** Multiplier for increased mortality for those with HCV and persons who inject drugs

Parameter	Estimate
HCV infected	3.1 (1.76–5.53) <sup>100</sup>
Person who injects drugs	11.3 (3.6–27.1) <sup>101</sup>

**Table 4.7:** Parameter estimates for infection

<b>Parameter</b>	<b>Base case estimate</b>	<b>Min</b>	<b>Max</b>
Number of needles per month <sup>98</sup>	15	0	67
Number of needles per year	185	2	798
<b>Number of needles shared<sup>99</sup></b>			
Often sharers	46.14	0.6	199.5
Sometimes sharers	23.07	0.3	99.75
Never sharers	0	0	0
<b>Percent of injectors in each group</b>			
Often sharers	0.39		
Sometimes sharers	0.20		
Never sharers	0.41		
Weighed mean of number shared per year	23	0	98
Probability of infection per infected needle	1.2	0.3	3

weeks), and the duration of acute infection (less than 6 months). Three treatment scenarios were considered: no treatment, treatment using ribavirin and peginterferon alfa, and treatment using DAAs. For the treatment scenarios, each HCV-infected person with either severe fibrosis or compensated cirrhosis had an annual probability of treatment of 0.25. Those who failed treatment were not eligible for treatment again. The treatment probabilities and outcomes were assumed to be the same for the PWID and non-PWID groups.

For each scenario, the model was run over a 10-year time horizon, from 2010 to 2020. A 10-year time period was identified as the timeframe for which current treatment guidelines might be relevant. The remaining life expectancy of those alive at the end of the time horizon was estimated using the model with disease progression and state-specific mortality rates without further initiation of HCV treatment. This allowed us to capture the long-term survival benefits of HCV treatment. Because of the slow progression of HCV, the benefits of treatment may take years to realize; only including outcomes in the first 10 years would likely underestimate the benefits of HCV treatments.

### 4.3 Results

The model of disease progression and transmission showed a reduction in the number of deaths for HCV-infected persons for both PWID and non-PWID with treatment using DAAs compared to no treatment or treatment with ribavirin and peginterferon alfa (Table 4.8). The number of cases

**Table 4.8:** Results

	<b>No treatment</b>	<b>Ribavirin and interferon</b>	<b>Direct-acting antivirals</b>
<b>Deaths from HCC</b>			
PWID	734	693	673
Non-PWID	96	89	85
<b>Deaths from HCV-related cirrhosis</b>			
PWID	795	727	693
Non-PWID	116	102	97

treated in the non-PWID cohort was approximately thirty times the number treated in the PWID cohort when treating the same proportion of cases per year. For the PWID cohort, there were 693 deaths per 100 000 population from HCV-related cirrhosis under DAA treatment compared to 727 per 100 000 population from HCV using ribavirin and peginterferon alfa and 795 deaths per 100 000 population under no treatment. For the entire non-PWID cohort, there were 97 deaths per 100 000 population from HCV-related cirrhosis under DAA treatment, 102 deaths per 100 000 population from HCV-related cirrhosis under ribavirin and peginterferon alfa treatment, and 116 per 100 000 population under no treatment. Deaths from HCC were counted separately and were also reduced under treatment. For the PWID cohort, the number of HCC-related deaths was 673 per 100 000 under DAA treatment, 693 per 100 000 under ribavirin and peginterferon alfa treatment, and 734 per 100 000 population under no treatment. For the non-PWID cohort the number of HCC-related deaths under DAA treatment was 85 per 100 000, under ribavirin and peginterferon alfa treatment was 89 per 100 000, and under no treatment were 96 per 100 000.

As expected based on the reduction of number of deaths from HCV and HCC, the predicted number of life years remaining for a 55-year-old in 2010 from the model was higher under treatment. For the PWID cohort, the number of life years remaining was 7.37 under DAA treatment, 7.37 under ribavirin and peginterferon alfa treatment, and 7.36 under no treatment. For the non-PWID cohort, the number of life years remaining was 27.32 under DAA treatment, 27.31 under ribavirin and peginterferon alfa treatment, and 27.31 under no treatment. These numbers were calculated for the entire U.S. population born between 1945 and 1965 with only 1.8% infected with HCV. When only those with HCV infection were included in the non-PWID model, the difference between treatment and no treatment was much greater (22.16 for DAA versus 22.00 for ribavirin and peginterferon alfa and

21.27 for no treatment).

New infections only occurred through injection drug use, so the number of new infections could only be calculated for the PWID cohort. The average annual probability of infection was highest under no treatment and lowest with DAAs. Under DAA treatment there were 7189 new infections compared to 7227 with ribavirin and peginterferon alfa and 7304 under no treatment in the first 10 years. This is a difference of 115 cases in DAA treatment versus no treatment in the PWID cohort born between 1945 and 1965 in the first 10 years.

One-way sensitivity analyses were performed on the probability of resolving each genotype, treatment probability, diagnosis probability, risk of HCC, and mortality from hepatitis and HCC. Two sensitivity analyses were performed for probability of resolving genotype 1 and other genotypes and treatment probability and diagnosis probability (Appendix I). While the number of years of life remaining changed when these parameters varied, the number of life years remaining with treatment was always greater than or equal to no treatment. Additional sensitivity analyses were performed to examine variables that might be targets of policy interventions. These included adherence to different treatment protocols (Appendix K), screening versus treatment (Appendix J), and inputs for the transmission equation (Appendix L).

## **4.4 Discussion**

New HCV drugs shown to improve SVR rates for patients with genotype 1, shorten treatment duration, and reduce side effects were licensed in 2011 and 2013, and it is expected that additional HCV drugs will be licensed in 2014. All of these medications have been shown to be effective in maintaining or increasing rates of SVR for HCV and achieving SVR has been demonstrated to reduce mortality from all causes in persons with HCV.<sup>13–23,102</sup> Previously described models have demonstrated that new HCV treatments are cost effective in treating patients with HCV-related fibrosis and compensated cirrhosis.<sup>53,56,57</sup> Previous modeling studies showed that treating patients for HCV could prevent transmission of HCV in certain populations.<sup>49–55,83</sup> The results of our analysis show that treatment for HCV infection with currently available drug regimens including simeprevir and sofosbuvir decreases deaths from HCV infection, reduces the number of cases of HCC, and increases

the number of life years remaining for persons aged 45 to 65 years for PWID. These reductions are greater than those seen with ribavirin and peginterferon alfa alone.

Decreases in deaths from HCV resulted from halting progression of the natural history of infection before moving into states with a risk of death from cirrhosis. The decrease in HCC cases was the result of preventing progression to cirrhosis in those with severe fibrosis. The decrease in HCC deaths reflected decreasing HCC incidence. For cases successfully treated for HCV infection, mortality from other causes may also be reduced leading to increased life expectancy in those with resolved infection. If HCV treatment does not result in the halting of disease progression, either because of existing liver damage, co-morbidities, or other factors, the benefit will be reduced.

The proportion of patients treated for HCV was assumed to be 0.25 of those eligible per year. This proportion was challenging to estimate given the ongoing changes in medications available to treat HCV. Increasing the proportion of cases treated each year would reduce the number of deaths and cases of HCC even further. Treating the same proportion of infected persons in each population required treatment of over 35 times the number of people in the non-PWID population compared to the PWID population. This would require significantly more resources to implement. Barriers to treating patients with HCV include the identification of persons infected, duration of treatment, side effects of treatment, costs of treatment, and high probability of treatment failure. Current CDC recommendations for screening the cohort of Americans born between 1945 and 1965 are focused on reducing the number of cases of HCV in the age range with the highest prevalence of HCV infection that go unrecognized.<sup>6</sup> While the benefit of treatment using DAAs compared to ribavirin and peginterferon alfa alone was not as great as the benefit of using ribavirin and peginterferon alfa compared to no treatment, the benefits of DAAs for ease of treatment, especially in protocols with interferon, go beyond better outcomes. The introduction of DAAs for HCV has led to reductions in the duration of treatment and increased likelihood of SVR, and it may reduce side effects when used without interferon. In addition, treatment improvements could lead to increased eligibility for treatment at earlier stages in the progression of liver disease. Patients in this cohort are also reaching the age of eligibility for Medicare and may be eligible for treatment once covered. All of these factors will likely result in more patients in this cohort being treated and reductions in deaths from HCV,

**Table 4.9:** Results of calibration for injection equation, pairs using base-case estimates for one parameter (Appendix E)

<b>Pair</b>	<b>Number of injections</b>	<b>Probability of HCV infection per shared injection with HCV+ partner</b>	<b>Cases per 100</b>
Base case	23	0.012	20.9
Base case number of injections per year	23	0.0037	6.6
Base case probability of infection per injection	7	0.012	6.6

cases of HCC, and deaths from HCC.

The results from this model support the findings of previous models that showed treatment for HCV prevents transmission of HCV.<sup>49–55,83</sup> The reduction in new cases of HCV was relatively small due to the population included in the model. While the cohort born between 1945 and 1965 has a high burden of infection from HCV, this cohort is not at high risk of acquiring HCV infection. In the at-risk group for HCV in this model, PWID, only 22.5 % were estimated to be susceptible to HCV infection. This represents only 0.02 % of the overall population in the cohort. Prevention of transmission in this age group is not likely an intended goal for treatment programs in the United States. Only 28.1 % of new HCV infections occurred in those over 40 years of age in 2007.<sup>82</sup> The proportion of persons in this cohort who inject is also relatively small at 0.11 %.<sup>91</sup> The impact of treatment on the incidence of HCV in the population would be greater in a population with low prevalence who are at high risk of HCV infection (e.g., new injection-drug users).

There was a high level of uncertainty in many of the parameters in this model. Sensitivity analyses were used to assess the impact of this uncertainty. The parameters for the transmission equation were particularly challenging to estimate and changes in these parameters led to moderate differences in the number of infections. An assumption in this model was that persons within this cohort only shared injection-drug-use equipment with others in the cohort and that sharing occurred randomly within the cohort. There is likely some sharing of equipment between members of this cohort and those in other age groups. Reducing the prevalence of HCV in the 1945 to 1965 birth cohort could result in the prevention of transmission to younger age groups. In order to better understand



transmission between age groups, more information would be needed on patterns of sharing needles between persons of different ages. In addition, injection drug use is not the only route of transmission of HCV. Reducing the prevalence of HCV may reduce the transmission of HCV in this cohort through other routes (e.g., infection-control breaches or needle-stick injuries). Greater differences might be seen through these routes as more of the non-PWID population is at risk of infection.

In conclusion, in the context of current treatment protocols and resource limitations, the population in this cohort that would benefit most from efforts to link HCV-infected cases to care is PWID. If this is not feasible, there is still a benefit to linking non-PWID cases to care, especially knowing that transmission occurs through other routes.

## Chapter 5

# Overall discussion

We are currently in a time of rapid changes and great possibility in the hepatitis C epidemic in the United States. The population with the highest burden of disease is reaching the point where the progression of their hepatitis C infection may lead to cirrhosis and liver cancer, new drugs have become available to treat hepatitis C, insurance coverage for testing and treatment of hepatitis C is increasing, and HCV incidence is increasing in young persons who inject drugs. While the problem of hepatitis C in the United States has been well described, resources for addressing both the high burden from existing disease and the ongoing transmission of hepatitis C has been limited. All of these factors combine to make this an important moment in hepatitis C virus policy. The combined results of the three analyses contained in this paper add to the body of knowledge available on hepatitis C virus treatment and hepatitis C virus-related liver cancer.

Chapter 2 describes the differences in risk factors for HCC over time and adds to previous work indicating that certain risk factors for HCC make up an increasing proportion of the HCC cases over time and that fewer HCC cases have no identified risk factor before diagnosis. The association between certain identified risk factors and earlier diagnosis indicates that risk-based screening or increased provider awareness of liver cancer risk may be playing a role in HCC diagnosis in those with an identified risk. The risk factors that were significantly associated with earlier diagnosis, HCV infection, HBV infection, and cirrhosis, are those for which HCC screening is currently recommended in at least some cases. Cirrhosis diagnosis occurred after HCC diagnosis in 41 % of HCV cases with cirrhosis documented, demonstrating that cirrhosis may be undiagnosed in many cases with known HCV. Since recommendations for HCC screening in those with HCV infection are limited to HCV cases with cirrhosis, many of those who should be screened may not be. Potential solutions for addressing this gap include increasing evaluation of those with HCV infection for

cirrhosis or broadening HCC screening recommendations for those with HCV infection to include those without documented cirrhosis. More evidence is needed to decide which of these strategies would be preferred.

The number of HCC cases with HCV infection increased over the time examined, indicating that the burden of HCV-related HCC continues to grow. This information is useful in better understanding the burden of disease from HCV infection in the United States. All of the cases of HCC included in this analysis were born before 1945. As the birth cohort with the highest prevalence of HCV reaches the age of eligibility for Medicare, this trend will likely continue for at least the next 20 years. Screening HCV infected persons with cirrhosis is another tool for preventing death from liver cancer. Earlier diagnosis leads to better outcomes from HCC and HCV infected persons in the baby boomer population are a prime target for screening programs. As the population of persons with HCV continues to age, they will likely make up a greater proportion of HCC cases. Outcomes from HCC could be improved through earlier detection of HCC at a point where treatment may be possible.

In Chapter 3, the association between HCV diagnosis and 5-year mortality in those with HCC was examined. Overall, persons with HCV infection and HCC had better 5-year survival than those without HCV infection even when adjusted by stage, age, and treatment. When stratified by stage at diagnosis, this association was only present in those diagnosed with a stage of regional. This may indicate differences in other liver-health-related factors used for staging liver cancer that are not captured. Those with hepatitis C may have less severe liver disease or comorbidities, increasing eligibility for treatment. This relationship could also indicate an important difference in liver cancer outcomes in persons with HCV infection and indicates that those with HCV infection should not be assumed to be the same as others with liver cancer. Further examination into this relationship would require detailed information to better determine cancer stage and liver health. This would appear to be a worthwhile endeavor based on the results in this analysis.

Chapter 4 examines the impact of current treatment of HCV in a population with high burden of HCV infection in the United States. As the standard protocols for treating hepatitis C virus become shorter, easier, and more effective the impact of treatment on outcomes and transmission of hepatitis

could be quite dramatic. Those born between 1945 and 1965 have the highest prevalence of HCV infection of any birth cohort. There are currently efforts underway to screen every person born during this time period for HCV infection once and to link those who are infected into care for their HCV infection. This is a huge undertaking and likely won't be accomplished completely in the near future. Public health efforts to assist in linking HCV infected persons to care need to be focused on the population where the impact would be the greatest. Based on the findings in Chapter 4 and previous work, it appears treating persons who inject drugs would have the most impact. This policy would prevent more deaths, prevent more cases of liver cancer, and prevent transmission of HCV through the most common route. This could be accomplished by treating a smaller number of people in this group than by treating the non-injecting population. Treating persons with HCV infection who are currently injecting will be challenging and other options may be preferred, but it appears that focusing on persons who inject drugs is worth consideration. Despite these findings, treating those with the highest burden of disease, those born between 1945 and 1965, may not be the best strategy for preventing transmission of HCV when compared with younger injection drug users who might have a lower prevalence of HCV infection and prevent the progression of disease at an earlier stage of liver damage. Further examination of treating different populations would allow for better targeting of linkage to care programs

In conclusion, understanding the consequences of hepatitis C virus infection and how to prevent them is vital to creating public health programs and treatment strategies to address HCV infection in the United States. By targeting the highest-impact cases for treatment, screening those with HCV infection and cirrhosis for HCC, and better understanding differences in liver cancer outcomes in those with HCC, we can prevent morbidity and mortality from HCV infection.

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# Appendix A

## Data-source details

Four files were used: (1) Patient Entitlement and Diagnosis Summary File (PEDSF), (2) Medicare Provider Analysis and Review (MedPar), (3) Carrier Claims (NCH), and (4) Outpatient (OP). The PEDSF file was used to obtain information on cancer diagnosis, cancer treatment, and death data. All Medicare files were used to obtain diagnosis information for hepatitis C and other liver-cancer risk factors (e.g., hepatitis B or alcohol abuse). Surgery and radiation therapy data were obtained through the PEDSF file. Chemotherapy data were obtained from the OP and NCH files using standard Healthcare Common Procedure Coding System (HCPCS) codes for chemotherapy (i.e., 964xx, 965xx, and Q0083–Q0085).

**Table A.1:** Sources of variables for Chapter 3

<b>Variable</b>	<b>Data source</b>
Gender	SEER: PEDSF
Race	SEER: PEDSF
Ethnicity	SEER: PEDSF
Age	SEER: PEDSF
Cancer diagnosis	SEER: PEDSF
Cause of death	SEER: PEDSF
Date of death	SEER: PEDSF
Surgical resection	SEER: PEDSF
Radiation therapy	SEER: PEDSF
Chemotherapy	Medicare: MedPar, OP, NCH
Hepatitis C diagnosis	Medicare: MedPar, OP, NCH
Hepatitis B diagnosis	Medicare: MedPar, OP, NCH
Comorbidity	Medicare: MedPar, OP, NCH

## Appendix B

### Codes for other risks and covariates

Hepatitis C is only one of many known risk factors for HCC. A list of risk factors for HCC was created using information from the previous studies on liver cancer risk and the American Cancer Society.<sup>60,61,103</sup> Risk history was examined for claims in the twelve months preceding liver cancer diagnosis. The ICD-9 codes for risk factors are shown in Table B.1 and for covariates are shown in Table B.2. Not all risk factors for HCC were able to be included in the analysis as some risks are not likely to appear in the claim data.

**Table B.1:** ICD-9 codes for risk factors

<b>Risk</b>	<b>Codes used</b>
Hepatitis C infection	070.41, 070.44, 070.51, 070.54, 070.70, 070.71, V02.62
Hepatitis B infection	070.20-.23, 070.30-.33, 070.42, V02.61
Hemochromatosis	275.01-.03
Alpha1-antitrypsin deficiency	273.4
Porphyria cutanea tarda	277.1
Glycogen storage diseases	271
Wilson disease	275.1
Tyrosinemia	270.2
Aflatoxin exposure	989.7
Alcohol abuse	571.0, 571.1, 571.2, 571.3, 291.X, 305.0X, V11.3
Cirrhosis	571.2, 571.5, 571.6
Tobacco use	305.1, 989.84, E869.4, V15.82
Obesity	278.00, 278.01, 278.03
Diabetes <sup>104</sup>	Used CCW diabetes algorithm

**Table B.2:** Covariates

<b>Covariate</b>	<b>Field</b>
Birth year	Medicare year of birth
Gender	Sex
Race/ethnicity	Race
Age at diagnosis	Age at diagnosis recode

## Appendix C

### HCV case-counting limitations

Hepatitis C status was obtained from the claims files from one year before cancer diagnosis from the three claims files, Medicare Provider Analysis and Review (MedPar), Carrier Claims (NCH), and Outpatient Claims (OP). The diagnosis had to be listed on one MedPar claim or two OP or NCH claims on different dates to be counted as a hepatitis C case. The number of cases with only one report from NCH and OP was 374. This represented 20 % of those with one or more report.

One concern with finding cases of hepatitis C in the claims files was misestimating the number of cases. Underestimation of cases could occur if hepatitis C was not noted on claims either because it was not diagnosed or because it was not billed. Based on data found in a recent study looking at risk factors for HCC in the SEER-Medicare data, the number of cases of HCV may be undercounted in this analysis (15 % vs. 23 %).<sup>61</sup> That study looked at risk factors for three or more years before diagnosis, compared to one year for this analysis. When a sensitivity analysis was performed to include three years of claims before HCC diagnosis, similar rates of HCV were found.

Overcounting of hepatitis C cases could occur if hepatitis C were noted frequently as a rule-out diagnosis. A sensitivity analysis was performed to determine whether including cases with only one report of HCV in the outpatient or carrier file would change the results (Table C.1). When these additional cases were included, 19 % of HCC cases had HCV documented in the Medicare claims. The hazard ratio for hepatitis C was 0.87, the same as in the primary analysis (Table 3.4). All other covariates remained largely the same.

**Table C.1:** HCV case counting sensitivity analysis Cox proportional hazard model with covariates for 5-year all-cause mortality

<b>Predictor</b>	<b>HR</b>	<b>p-value</b>
HCV infection	0.87	<0.001
<b>Stage at diagnosis</b>		<0.001
Localized	Reference	
Regional	1.60	
Distant	2.52	
Unstaged	1.59	
<b>Race</b>		<0.001
White	Reference	
Black	1.15	
Other	0.87	
Asian	0.78	
Hispanic	0.96	
American Indian	1.11	
Unknown	0.97	
HBV infection	0.71	<0.001
Male	1.00	0.948
<b>Age at diagnosis</b>		<0.001
65–69	Reference	
70–74	1.09	
75–79	1.16	
80–85	1.22	
85+	1.41	
Receipt of one or more treatment	0.41	<0.001
Diabetes	1.07	0.001
Cirrhosis	1.08	0.003
Year diagnosed	0.97	<0.001



## **Appendix D**

### **State transition model**

A few changes to the model used by Salomon and colleagues and modified by Liu and colleagues were made for this analysis. The liver-transplant state was eliminated, as it was not considered to be relevant to this analysis. In the analysis by Liu and colleagues, patients could be treated in all stages of HCV infection. In this analysis, only those with severe fibrosis and compensated cirrhosis were eligible for treatment based on current recommendations. Race- and gender-specific estimates were not used. Genotype-specific estimates were added because of the variation in treatment recommendations and outcomes across genotypes. Evaluation of treatment effectiveness was outside the scope of this analysis, so estimates of treatment success were taken from clinical trial data.

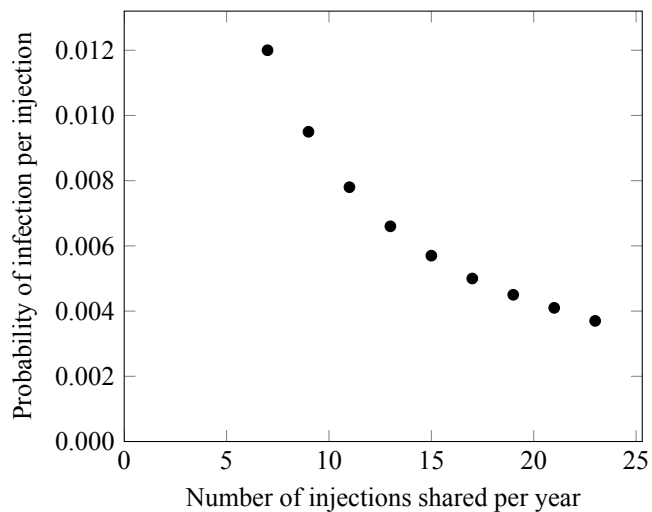
# Appendix E

## Validation and calibration

### E.1 Calibration of risk of transmission

The equation for transmission was calibrated to an estimated incidence of 6.6 new cases per 100 person-years for persons over 30 from a prospective cohort study.<sup>87</sup> This was used to calibrate Equation 4.1 in the TreeAge model with no treatment and averaged over the first five years of the model. After identifying plausible ranges for the parameters from the literature, I determined that the baseline estimates for the parameters produced a much higher than expected rate of HCV incidence in the population. To identify the best combination of parameter estimates, I performed a two-dimensional grid search of the parameter space and found the parameter pairs that minimized the mean squared error between the 5-year average incidence predicted by the model and the literature incidence estimate. Figure E.1 shows a sample of these combinations. There were two estimates that resulted in

**Figure E.1:** Combinations of parameter estimates



an estimated incidence of 6.6 per 100 person-years when added to the model using one of the two baseline estimates from the literature (Table 4.7). The pair with the base case estimate for probability of infection per injection was used due to a higher confidence in that parameter.

The estimates obtained from the model did not vary greatly based on the parameter pair chosen, but the implications for policy would certainly vary depending on differences in these parameters. With a higher likelihood of transmission per injection, reducing transmission of HCV would be much harder as a single shared needle would represent a high risk of HCV infection. If the likelihood of transmission per injection is lower, policies providing clean syringes to PWID will have a greater impact even if the number of shared needles cannot be reduced to zero.

## **E.2 Validation of natural history of hepatitis C**

The natural history portion of the model was calibrated to the models by Liu et al. and Salomon, Weinstein, Hammitt, and Goldie<sup>56,84,85</sup> Altering the model to match the starting age, 40, used by Salomon and Liu, the estimates obtained were similar. The estimated cumulative probability of progressing to cirrhosis in this model was 21 %. In order to compare this estimate to Salomon and Liu, the gender-specific estimates were combined into a weighted average overall estimate. For Salomon the weighted average was 22 % (CI 9,40) and for Liu the weighted average was 19 %.

The initial probabilities were obtained from the literature and then calibrated using the natural history model. The model was run for persons aged 25 in 1980 and was run for the period 1980 through 2010. Infection was assumed to take place at the rates estimated by CDC using national surveillance data.<sup>6,105</sup> The estimates from this model were similar to those used in the base-case estimate. The base case initial probability of being uninfected was 98.1 % and the estimate from the model was 98.5 %. Estimates taken from the model were within the range of the estimates used in sensitivity analyses.

## Appendix F

### Sensitivity analysis using AJCC stage

American Joint Committee on Cancer (AJCC) stage was unavailable for cases diagnosed before 2004 (33 % of cases in this analysis). AJCC stage was compared to SEER historic stage to confirm that they were consistent for cases with both stages available. Table F.1 shows this comparison. In addition, a separate Cox proportional hazard analysis was done for cases with an AJCC stage. The results of this analysis are shown in Table F.2. The hazard ratio for hepatitis C infection is 0.88 compared to 0.87 in the primary analysis. Stage at diagnosis remains significant in this model, but the trend in AJCC stage is not as clear as when using historic stage. The rest of the covariates remain largely the same.

**Table F.1:** Cancer stage consistency

	<b>Localized</b>	<b>Regional</b>	<b>Distant</b>	<b>Unstaged</b>
Stage I	1925	89	0	0
Stage II	594	289	0	0
Stage III NOS	11	68	5	0
Stage IIIA	242	623	0	0
Stage IIIB	0	73	40	0
Stage IIIC	0	168	3	0
Stage IV	0	0	959	0
Not applicable	0	0	0	2
Stage unknown	412	330	10	721

**Table F.2:** AJCC stage sensitivity analysis Cox proportional hazard model with covariates for 5-year all-cause mortality

<b>Predictor</b>	<b>HR</b>	<b>p-value</b>
HCV infection	0.88	<0.001
<b>Stage at diagnosis</b>		<0.001
Stage I	Reference	
Stage II	1.08	
Stage III NOS	2.44	
Stage IIIA	1.69	
Stage IIIB	2.06	
Stage IIIC	1.71	
Stage IV	2.91	
Stage Unknown	1.77	
<b>Race</b>		<0.001
White	Reference	
Black	1.17	
Other	0.88	
Asian	0.78	
Hispanic	0.97	
American Indian	1.13	
Unknown	0.74	
HBV infection	0.68	<0.001
Male	0.99	0.677
<b>Age at diagnosis</b>		<0.001
65–69	Reference	
70–74	1.09	
75–79	1.16	
80–85	1.18	
85+	1.41	
Receipt of one or more treatment	0.43	<0.001
Diabetes	1.06	0.028
Cirrhosis	1.11	0.002
Year diagnosed	0.97	<0.001

## Appendix G

# Cirrhosis sensitivity analysis

The proportion of cases of HCV with cirrhosis documented before HCC diagnosis was smaller than expected. To better describe HCV and cirrhosis in this population, a separate analysis was done using cirrhosis diagnosis both in the 12 months before HCC diagnosis and after HCC diagnosis. It is unlikely that cirrhosis occurred after HCC diagnosis, but this may have occurred in some cases. Those without a diagnosis of cirrhosis before HCC diagnosis would not have been eligible for HCC screening. If cirrhosis affects outcomes from HCC, the timing of diagnosis would not be relevant.

In the sensitivity analysis, the hazard ratio for HCV was 0.92 compared to 0.87 in the primary analysis, and the hazard ratio for cirrhosis was 0.91 compared to 1.10. It appears that when cirrhosis diagnosed before and after HCC diagnosis is included, HCV infection has less of an effect on mortality, and cirrhosis appears to be protective.

**Table G.1:** Proportion of hepatitis C cases with cirrhosis documented before and after HCC diagnosis

	Not HCV case		HCV case	
	<i>n</i>	%	<i>n</i>	%
<b>Before and after diagnosis</b>				
Cirrhosis	4042	48	1261	84
No cirrhosis	4313	52	244	16
<b>Before diagnosis</b>				
Cirrhosis	1550	19	744	50
No cirrhosis	6805	81	731	50

**Table G.2:** Cirrhosis sensitivity analysis Cox proportional hazard model with covariates for 5-year all-cause mortality

<b>Predictor</b>	<b>HR</b>	<b>p-value</b>
HCV infection	0.92	0.006
<b>Stage at diagnosis</b>		<0.001
Localized	Reference	
Regional	1.59	
Distant	2.47	
Unstaged	1.59	
<b>Race</b>		<0.001
White	Reference	
Black	0.96	
Other	1.12	
Asian	0.86	
Hispanic	0.78	
American Indian	0.97	
Unknown	1.09	
HBV infection	0.72	<0.001
Male	1.00	0.948
<b>Age at diagnosis</b>		<0.001
65–69	Reference	
70–74	1.08	
75–79	1.13	
80–85	1.17	
85+	1.34	
Receipt of one or more treatment	0.41	<0.001
Diabetes	1.09	<0.001
Cirrhosis	0.91	<0.001
Year diagnosed	0.98	<0.001

## Appendix H

# Testing the proportional hazards assumption for 5-year all-cause mortality

The test of the proportional hazards assumption was done using time dependent variables for all covariates. Four were found to be significant: HCV infection, treatment, age at diagnosis, and stage at diagnosis. When these variables were included in the model for two time periods (i.e., the first 2 ½ years after diagnosis and the second 2 ½ years after diagnosis), HCV infection was still associated with better survival and the hazard ratio was smaller in the corrected model compared to the original model (0.84 compared to 0.87). The interaction of HCV infection and time was significant, so the effect of HCV infection on survival is not constant over time. For HCV, the hazard ratio for the first time period is 0.84, and for the second period is 1.19, so HCV is protective for the first 2 ½ years after diagnosis, but not during the second 2 ½ years. Over the entire 5-year period, those with HCV are still less likely to die than those without HCV. This makes sense given the shape of the survival curve stratified by HCV case. The same covariates remain significant in this model.



**Table H.1:** Cox proportional hazard model with covariates for 5-year all-cause mortality, test of the proportional hazards assumption

<b>Predictor</b>	<b>HR</b>	<b><i>p</i>-value</b>
HCV infection	0.84	<0.001
<b>Stage at diagnosis</b>		<0.001
Localized	Reference	
Regional	1.60	
Distant	2.54	
Unstaged	1.62	
<b>Race</b>		<0.001
White	Reference	
Black	1.14	
Other	0.87	
Asian	0.78	
Hispanic	0.95	
American Indian	1.12	
Unknown	0.96	
HBV infection	0.71	<0.001
Male	1.00	0.959
<b>Age at diagnosis</b>		<0.001
65–69	Reference	
70–74	1.08	
75–79	1.13	
80–85	1.18	
85+	1.36	
Receipt of one or more treatment	0.39	<0.001
Diabetes	1.07	<0.001
Cirrhosis	1.08	0.004
Year diagnosed	0.97	<0.001
Interaction of HCV infection and time	1.42	<0.001
Interaction of treatment and time	1.53	<0.001
Interaction of age at diagnosis and time	1.16	<0.001
Interaction of stage and time	0.96	0.024

# Appendix I

## Two-way sensitivity analyses

**Table I.1:** Two-way sensitivity analysis for mortality from HCV and HCC. Additional life years remaining with treatment

<b>(a) Persons who do not inject drugs</b>				<b>(b) Persons who inject drugs</b>			
		<b>Mortality from HCV</b>				<b>Mortality from HCV</b>	
		0.065	0.4			0.065	0.4
<b>Mortality</b>	0.3	0	0	<b>Mortality</b>	0.3	0	0.01
<b>from HCC</b>	0.8	0	0	<b>from HCC</b>	0.8	0	0.01

**Table I.2:** Two-way sensitivity analysis for treatment for genotype 1 and other genotypes. Additional life years remaining with treatment

<b>(a) Persons who do not inject drugs</b>				<b>(b) Persons who inject drugs</b>			
		<b>Mortality from HCV</b>				<b>Mortality from HCV</b>	
		0.63	1			0.63	1
<b>Mortality</b>	0.9	0	0	<b>Mortality</b>	0.9	0.01	0.01
<b>from HCC</b>	1	0	0	<b>from HCC</b>	1	0.01	0.01

## Appendix J

# Sensitivity analysis for screening versus treatment to prevent mortality from HCV infection

Two potential policy strategies could be considered to prevent mortality from HCV infection utilizing treatment. One would focus on identifying people with HCV infection and the other would focus on treating persons with HCV infection. With limited resources available, there may be a tradeoff between the two options. When four potential combinations of testing and treating were examined, the outcomes varied. In the context of limited resources, a similar comparison could be used to obtain the preferred strategy. Without costs in the model, choosing parameters for the decrease in treatment due to an increase in resources being allocated to testing is somewhat arbitrary. This analysis does demonstrate that the combination of screening and treatment should be considered together when planning a public health intervention to address hepatitis C.

**Table J.1:** Sensitivity for screening versus treating with DAAs in persons who inject drugs

<b>Percent diagnosed per year</b>	<b>Percent treated per year</b>	<b>Deaths per 100 000 from HCV</b>
0.005	0.30	686
0.010	0.25	693
0.020	0.20	677
0.050	0.10	696

## **Appendix K**

# **Sensitivity analysis for adherence to different treatment protocols**

The two treatment protocols for hepatitis C examined in this analysis have different side effects, which may lead to differing adherence. In general, the DAAs will have the same or fewer side effects compared to ribavirin and peginterferon alfa. A sensitivity analysis was performed to measure the impact of adherence on mortality from HCV in persons who inject drugs. This analysis showed that in order to prevent twice as many deaths with DAAs as with ribavirin and peginterferon alfa, adherence to DAAs would need to be 98%, and adherence to the others would have to be 55%. An adherence level of 98% is unrealistic in this population, so it is unlikely that the marginal benefit of DAAs compared to ribavirin and peginterferon alfa could equal the benefit of ribavirin and peginterferon alfa compared to no treatment.

**Table K.1:** Impact of treatment with varying adherence to treatments in persons who inject drugs

<b>Adherence</b>	<b>Number of deaths from HCV</b>	<b>Deaths prevented</b>
<b>DAA vs. ribavirin and peginterferon alfa</b>		
0.70	693	34
0.75	689	38
0.80	683	44
0.90	673	54
0.95	668	59
0.98	665	62
0.99	664	63
<b>Ribavirin and peginterferon alfa vs. no treatment</b>		
0.70	727	68
0.65	728	67
0.60	730	65
0.55	733	62
0.50	736	59
0.45	739	56
0.40	741	54
0.35	744	51

## Appendix L

# Sensitivity analysis for transmission equation

A sensitivity analysis was performed to show whether choosing a different combination of parameters for the transmission equation (Equation 4.1) affected the number of deaths from HCV in persons who inject drugs. No difference was found.

**Table L.1:** Sensitivity analysis for parameters in the transmission equation

<b>Number of shared injections (<math>N</math>)</b>	<b>Probability of infection per injection (<math>q</math>)</b>	<b>Number of deaths with DAA treatment</b>	<b>Number of deaths without treatment</b>
7	0.0120	693	795
15	0.0057	693	795
23	0.0037	693	795