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# The burden of illness associated with hepatocellular carcinoma in the United States☆

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***Background/Aims*: Despite the rising prevalence of hepatocellular carcinoma (HCC), data on its economic consequences are limited. This study was undertaken to estimate the aggregate annual financial burden associated with HCC in the United States, including healthcare costs and the value of lost productivity.**

***Methods*: Annual prevalence of HCC and incidence and survival were estimated using SEER data. The linked SEER-Medicare database was used to estimate distributions of healthcare utilization, quantities of treatment, and unit costs among 392 HCC patients. An age- and sex-matched cohort of non-cancer controls was used to estimate background non-cancer-related resource use and costs.**

***Results*: We determined the annual cost of HCC in the United States to be $454.9 million, with per-patient costs of $32,907. Healthcare costs and lost productivity accounted for 89.2% and 10.8% of total cost, respectively. Costs associated with localized HCC accounted for the highest portion (44.5%) of the total cost of illness, at $202.5 million. Regional, distant, and unstaged HCC accounted for 31.0%, 13.9%, and 10.6%, respectively.**

***Conclusions*: Our results exhibit a considerable economic impact of HCC and substantial national spending on this disease.**



***Keywords*: Hepatocellular carcinoma (HCC); Cost of illness; Burden of illness; Prevalence; Outcomes; Treatment pattern**

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*Abbreviations:* HCC, hepatocellular carcinoma; SEER, surveillance epidemiology and end results; ICD, international classification of diseases; NCI, National Cancer Institute; TACE, transarterial chemoembolization; HCPS, Health Care Financing Administration's Common Procedure Coding System.

## 1. Introduction

Hepatocellular carcinoma (HCC) is the predominant histologic subtype of liver cancer in adults, comprising approximately 65% of all cases of primary liver cancer [1]. Worldwide, it is the sixth most common neoplasm, with more than half a million new cases diagnosed each year [2]. HCC is the third most common cause of cancer mortality [3] and the main cause of death among cirrhotic patients [2]. The overall incidence rate of HCC has been estimated at 2.99 per 100,000 [1], with accruing evidence over the past 5–8 years, indicating that the incidence is rising in several countries [4]. In

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2000, approximately 564,000 HCC cases were reported globally, with 11,500 cases in the United States and 50,000 in Europe [5].

Although HCC has predominantly affected persons in the developing world (where >80% of liver cancer cases occur) [6,7], Western countries have seen rising numbers of cases over the past two decades – an increase largely attributed to the high prevalence of hepatitis B and C virus (HBV and HCV) infections [1,8]. Chronic infection with hepatitis C virus is the predominant risk factor for HCC in Western countries and Japan, and hepatitis B virus is the predominant risk factor for HCC in Southeast Asia and Africa [9]. Incidence and mortality rates associated with HCC have doubled in the United States over the past 25 years, and given the current prevalence of HCV among persons aged 30–50 years, the US incidence and mortality rates of HCC are expected to double over the next 10–20 years [10].

Historically, treatment of HCC has been problematic, primarily due to tumor identification at an advanced stage—although the more recent trend has been encouraging, as HCC is being diagnosed at an earlier stage (i.e., when liver function is preserved and cancer-related symptoms are absent) in many patients [4]. Another obstacle to effective treatment is that most patients with HCC also have cirrhosis, which limits the use of surgical resection [11]. Although liver transplantation has achieved increasing success in the treatment of HCC, many clinicians consider the high risk of tumor recurrence and hepatitis infection to be a contraindication to transplantation—and moreover its cost-effectiveness has been questioned when it is performed in patients who do not meet the appropriate selection criteria [11]. Nevertheless, due to advances over the past two decades – such as the use of transarterial catheter chemoembolization (TACE) and radiofrequency ablation, transplantation is now recognized as one of the few curative treatment modalities for HCC patients [12]. Encouragingly, significant survival benefit has been shown with arterial chemoembolization in a subset of patients with unresectable HCC [13]. The treatment response to systemic chemotherapy among HCC patients has been estimated to be lower than 10%, and no clear impact on overall survival has been observed [11]. Only recently, angiogenesis inhibitors such as sorafenib, which was recently approved by the US Food and Drug Administration for the treatment of unresectable HCC, have been shown to increase overall survival in advanced-stage HCC patients [14,15].

Given the rising prevalence of HCC and the limited treatment options for patients with advanced disease, it is important to know the financial burden associated with HCC in the United States. However, data on its economic consequences are limited. Most of the literature on HCC-related costs pertains to cost-effectiveness of screening for the disease [16–20] or cost-analyses of specific treatments [21–24]. Other studies have assessed the economic burden of several types of cancer [25–27], but these studies either did not include data on HCC or addressed inpatient care only or did not include data on lost productivity. Our study was undertaken to estimate the aggregate annual financial burden associated with HCC in the United States from a societal perspective, including healthcare costs and the value of lost productivity (i.e., lost workdays due to cancer).

## 2. Materials and methods

### 2.1. General model structure

Key relationships presented in the model include annual numbers of patients treated for HCC by age group and cancer stage; utilization of various cancer-specific treatments among these patients; unit costs of these treatments; workdays missed; and wage rates.

The general modeling approach is illustrated in Figs. 1 and 2. The model begins with all HCC patients alive in a given year (i.e., the prevalence of HCC), stratified by factors expected to influence resource utilization and burden of illness, including age (<65, 65+), gender, and cancer stage as categorized in the SEER database (i.e., localized, regional, distant [metastasized], and unstaged). Localized cancer is defined as disease that is limited to the organ in which it originated; regional cancer is defined as having spread beyond the primary site to nearby lymph nodes, organs, and tissues; and distant cancer is defined as having spread beyond the primary site to distant organs and lymph nodes (i.e., metastatic) [28]. Patients in each age-, gender- and stage-specific stratum are assumed to use cancer-related healthcare resources, which translate to healthcare costs attributable to cancer. They also are assumed to have missed workdays (e.g., absenteeism and unemployment), which translate to lost productivity attributable to cancer.

These figures constitute simplified versions of the structural equations estimated in the model. Multiplying stratum- (i.e., age-, gender-, and cancer stage-) specific distributions of treatment by annual quantities of HCC treatments and unit costs yields stratum-specific estimates of annual healthcare costs associated with HCC. Similarly, multiplying stratum-specific estimates of annual workdays missed by average wage rates yields stratum-specific estimates of lost productivity associated with HCC. Summing these estimates across strata yields an estimate of the total annual burden attributable to HCC.

### 2.2. Data sources

Data sources used to estimate the model include the Surveillance Epidemiology and End Results (SEER)-Stat data file, the linked SEER-Medicare database, the US Bureau of Labor Statistics, published literature, and other secondary sources.

The SEER Program of the National Cancer Institute (NCI) [29] is an epidemiologic surveillance system designed to track cancer incidence and survival in the United States. It comprises population-based tumor registries that collect demographic and diagnostic information on cancer patients in geographically defined metropolitan areas, currently representative of roughly 25% of the US population [30]. The SEER-Stat database contains summary data on cancer incidence and survival from population-based cancer registries belonging to the SEER Program, The linked SEER-Medicare database is a collaborative effort of the NCI, the SEER cancer registries, and the Centers for Medicare and Medicaid Services. The Medicare administrative claims files include detailed information on the use of inpatient, outpatient, home health, hospice, and skilled nursing facility (SNF) services, including dates and type of service, diagnosis codes, Medicare payment amounts, primary insurer payments, and patient deductibles and copayments. Age- and sex-specific salary data from the Bureau of Labor Statistics were used to estimate wage rates.