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Estimating the Incidence and Prevalence of Chronic Hepatitis C Infection in Taiwan Using Back Projection

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ABSTRACT

Objective: Hepatitis C virus (HCV) infection is the leading cause of liver disease, and Taiwan has among the highest prevalence of HCV infection in the general population in Northeast Asia, estimated at between 2% and 4%. The aim of this study was to estimate the number of patients living with chronic HCV infection in Taiwan and quantify the expected numbers in each of the five Metavir fibrosis stages. **Methods:** We applied a back-projection approach, using observed hepatocellular carcinoma incidence between 1979 and 2008 and a smoothed Expectation-Maximization algorithm to maximize a Poisson likelihood to estimate the previous incidence of HCV infection. The algorithm was coded in Excel and combined with the MOdelling the NAtural histoRy and Cost-effectiveness of Hepatitis model (a hepatitis C natural history markov model) to predict the past and future numbers in each Metavir fibrosis stage. **Results:** Incident cases were predicted to have peaked in 1972 at 56,634 annually, with the prevalence peaking in 1986 at 763,737 infections and falling to 578,203 infections in 2012. It was estimated that in 2012, 127,795 (23.0%), 105,545 (19.0%), 81,211 (14.6%), 123,939 (22.3%), and 116,823 (21.1%) subjects were in fibrosis stages F0, F1, F2, F3, and F4, respectively. **Discussion:** Our study provides HCV infection prevalence estimates, stratified by Metavir fibrosis stage, in Taiwan for 2012. This has potential implications for budget planning, particularly with the availability of emerging therapies because fibrosis stage is predictive of both rapid and sustained virological response; therefore, planning expected treatment response in a given population could be enhanced with this additional information.

Keywords: chronic, cirrhosis, fibrosis, hepatocellular, liver.

Introduction

Hepatitis C virus (HCV) infection is the leading cause of liver disease and a major public health burden; approximately 130 to 170 million people are estimated to be infected globally [1]. Incidence rates across the world fluctuate, and accurate estimates are difficult to obtain because of the asymptomatic, often latent nature of the disease before clinical presentation. The World Health Organization estimates that HCV infects 3 to 4 million people every year [2]; of these, approximately 20% to 30% will spontaneously clear the virus; the remaining develop chronic HCV infection and are at risk of progressing to compensated cirrhosis, decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), and premature death. Taiwan has among the highest prevalence of HCV infection in the general population in Northeast Asia [3], estimated at between 2% and 4% (463,000 and 927,000) [4].

The period between infection and end-stage liver disease (ESLD) is highly variable [5]. On average, around 10% to 20% of the subjects with HCV infection will progress to ESLD within 10 to 20 years following infection [6]. This has important implications because the current health care burden associated with treating HCV infection and managing ESLD complications is relatively small compared with the potential future cost associated with treating those progressing over the coming years. Furthermore, as patients age and their disease progresses, the number presenting either with ESLD or for treatment will increase substantially. Consequently, knowledge of historic infection rates and disease prevalence estimates is informative for developing effective public health management strategies for screening and treatment. Estimates of the number of subjects living with chronic HCV infection and the extent of fibrosis are important because treatment response is reduced in patients with advanced fibrosis. Identifying treatment-eligible patients and initiating the most cost-effective treatment option will become increasingly relevant in the very near future.

The aim of this study was to estimate the number of patients living with chronic HCV infection in Taiwan and quantify the expected numbers in each of the five Metavir fibrosis stages.

Conflicts of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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Methods

Back Projection

Back projection, also known as back-calculation, is a technique that has been used extensively to estimate historic HIV infection levels given knowledge of AIDS incidence [5]. The technique has also been applied to estimate the incidence and prevalence of hepatitis C infection in the United Kingdom [7], France [8], and Australia [9]. Estimating chronic HCV infection incidence and prevalence via back projection typically uses routinely coded HCV-related ESLD events, such as DC or HCC, together with an estimate of the time between chronic infection and progression to ESLD to calculate the unobserved infections that must have occurred in the past.

The technique can be implemented in a number of ways, ranging from statistical to deterministic [10–12]. The approach taken in this study was to use a smoothed Expectation-Maximization algorithm to maximize a Poisson likelihood. We assume that the incidence of chronic HCV infection cases occurs as an independent random process in which the number of individuals developing chronic HCV infection following infection in period t is denoted as N_t and the number of subjects with HCV-related HCC is denoted as Y_t, where $t=1,2,\ldots,T$. In the current implementation, T represents the last year of recorded HCC included in the analysis (2008) and each t is equivalent to one calendar year. The number of expected HCV-related HCC cases in year t is given by

$$E[Y|N_1,N_2,\ldots,N_t]=\sum_{i=1}^{t} N_i f_{t-i}$$

The mean number of HCC cases in year t is then given by

$$\mu_t=\sum_{i=1}^{t} \lambda_i f_{t-i}$$

where $\mu_i=E[Y_t]$ and $\lambda_i=E[N_i]$

Assuming that all HCV infections are independent Poisson variates, the log likelihood function is given by

$$\log L(\lambda|y)=\sum_{t=1}^{T}[y_t \log(\mu_t)-\mu_t]$$

where μ is given by the second equation.

The Expectation-Maximization algorithm was coded in Visual Basic for Applications within Microsoft Excel.

Data

Data on HCC incidence for the period 1979 to 2008 were obtained from the Taiwan National Cancer Registration Database. Our analysis required HCV-specific HCC event data; therefore, an adjustment was made that accommodated secular trends in hepatitis B virus (HBV) and HCV-associated HCC in line with reported male- and female-specific HBV-related HCC over the period 1981 to 2001 [4]. In men, HBV-related HCC decreased from 81.5% in the period 1981 to 1983 to 66.2% in the period 1999 to 2001. In women, HBV-related HCC decreased from 66.7% in the period 1981 to 1983 to 41.4% in the period 1999 to 2001. We further assumed that 10.5% (males) and 11.3% (females) of the HCC cases were unrelated to either HBV or HCV. Figure 1 shows the unadjusted HCC data alongside estimated HCV-specific HCC incidence data. The upper and lower limits for estimated HCV-specific HCC were obtained by using reported confidence intervals for secular trends in HBV-related HCC in Taiwan.

Back projection is relatively inaccurate at predicting recent infection rates; as such, it was necessary to provide a minimum HCV incidence within the model. Because information on HCV incidence within Taiwan is extremely limited, the infection rate was estimated from US data and applied to the Taiwan population. It was estimated that 5.437 people in every 100,000 are infected with HCV each year [13]. This rate was applied to the Taiwan population to give an annual incidence of 1260.

Model

The natural history of progression from chronic infection to HCC was obtained by using the MOdelling the NAtural histoRy and Cost-effectiveness of Hepatitis model. This is a cohort-based Markov lifetime simulation that has previously been described in detail [14]. In brief, the model iterates a cohort through annual cycles starting at Metavir disease stage F0 (no fibrosis) and progressing though F1 (portal fibrosis with no septa), F2 (portal fibrosis with few septa), F3 (portal fibrosis with numerous septa), and F4 (compensated cirrhosis). The model flow diagram is shown in Figure 2. Progression through fibrosis stages is controlled via stage-specific transition probabilities influenced by the duration of HCV infection, age at infection, sex, genotype, source of infection, and excessive alcohol consumption [15]. Table 1 reports the transition rates used in the model. We assumed that 54% of the infections were genotype 1 [3].

In addition to estimating the number of chronic HCV infection cases (F0), the number of individuals progressing through fibrosis

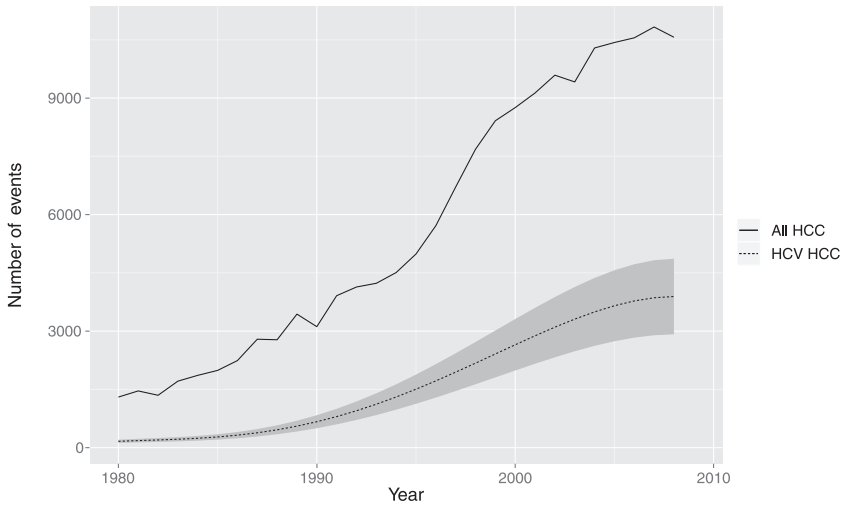

Fig. 1 – Incident cases of confirmed HCC in Taiwan with estimated HCV-related HCC. HCV, hepatitis C virus.

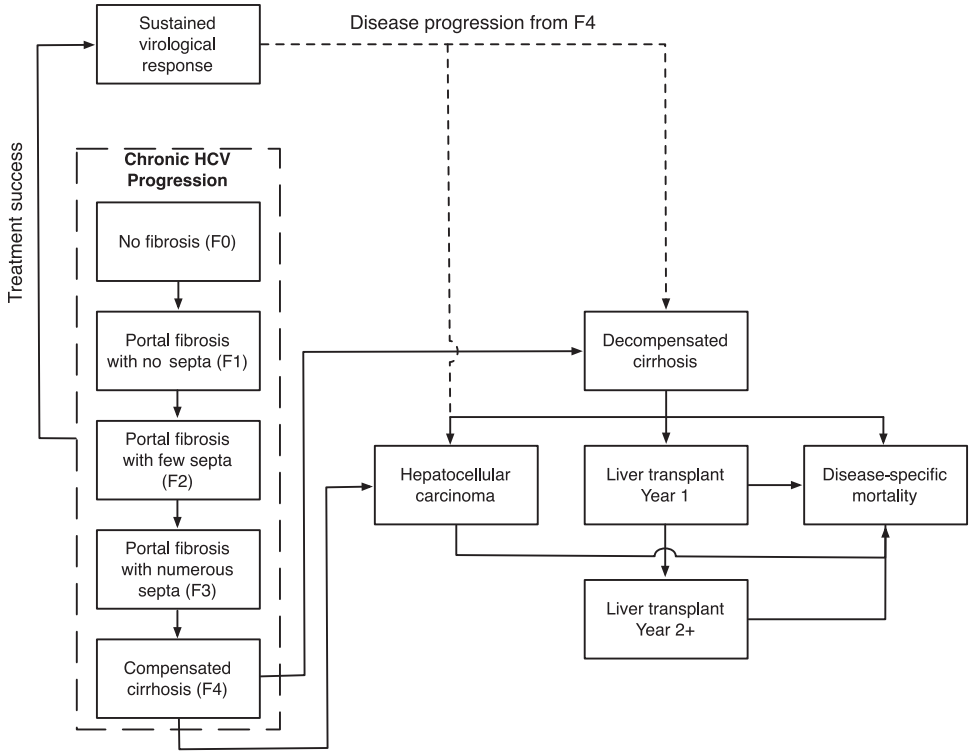

Fig. 2 – Flow diagram of the MONARCH model. Annual transition probabilities control progression through disease states. HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

Table 1 – Annual disease progression rates, distribution type, and parameters used in the model.

Disease progression	Mean	SE	Distribution	Parameters	Source
F0 to F1	0.079		Normal*	$\exp[-2.0124-(0.07589 \times HCVD) + (0.3247 \times Design)+(0.5063 \times Male)+(0.4839 \times GT1)]$	[15]
F1 to F2	0.073		Normal*	$\exp[-1.5387-(0.06146 \times HCVD)+(0.8001 \times Alchohol)]$	[15]
F2 to F3	0.111		Normal*	$\exp[-1.6038+(0.0172 \times HCV\ Age)-(0.05939 \times HCVD)+ (0.4539 \times Alchohol)]$	[15]
F3 to F4	0.051		Normal*	$\exp[-2.2898+(0.01689 \times HCV\ Age)-(0.03694 \times HCVD)+(0.5963 \times IDU)+ (1.1682 \times BT)-(0.4652 \times GT1)]$	[15]
				Minimum	**Maximum**	
F3 to HCC	0.002	0.013	Normal	0.001	0.028	[16]
F4 to DC	0.030	0.010	Normal	0.010	0.050	[16]
F4 to HCC	0.017	0.014	Normal	0.008	0.045	[16]
DC to LT	0.031	0.008	Normal	0.016	0.047	[16]
DC to death	0.100	0.051	Normal	0.1	0.2	[16]
HCC to death	0.700	0.102	Normal	0.55	0.9	[16]
				Alpha	**Beta**	
DC to HCC	0.079	0.011	Beta	45.583	531.417	[16]
LT (year 1) to death	0.150	0.005	Beta	669.750	3795.250	[16]
LT (year 2+) to death	0.030	0.003	Beta	133.950	4331.050	[16]

Alcohol, proportion of cohort with excess alcohol consumption; BT, proportion of cohort infected via blood transfusion; DC, decompensated cirrhosis; design, observational or trial setting; GT1, proportion of cohort genotype 1; HCC, hepatocellular carcinoma; HCV Age, age at HCV infection; HCVD, HCV duration of infection (y); IDU, proportion of cohort infected via intravenous drug use; LT liver transplant; male, proportion of cohort male; SE, standard error.

* SEs for coefficients obtained from Thein et al. [15] (Table 6) and sampled from a normal distribution.

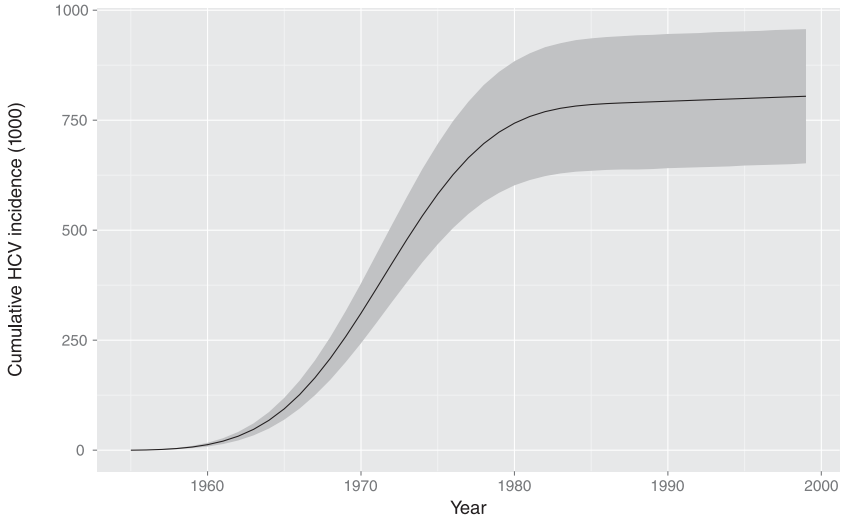

Fig. 3 – Estimated cumulative number of chronic hepatitis C infections with bootstrapped 95% confidence intervals. HCV, hepatitis C virus.

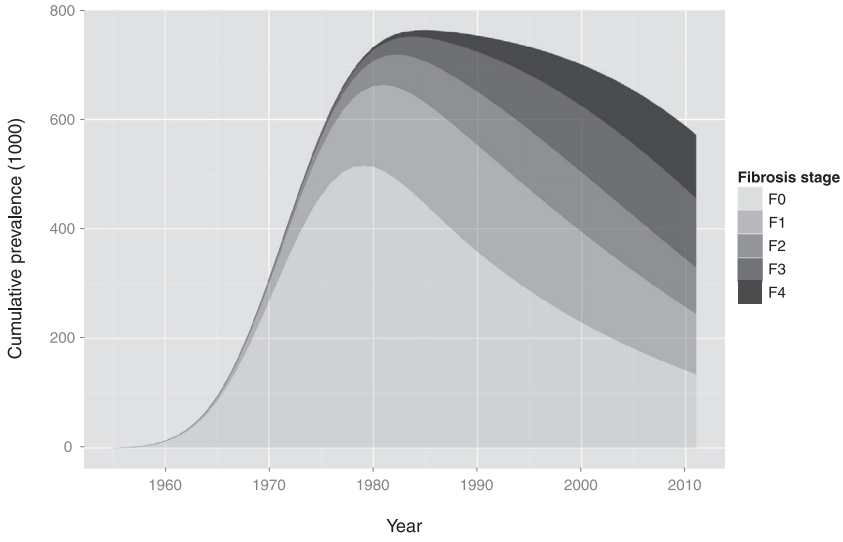

Fig. 4 – Cumulative estimated prevalence of chronic HCV by fibrosis stage. As of 2012, it is estimated that 23.0%, 19.0%, 14.6%, 22.3%, and 21.1% of the 555,313 patients with chronic HCV are in fibrosis sages F1, F2, F3, and F4, respectively.

stages F1 to F4 was estimated and used to project the future incidence of HCV-related complications.

Results

As of 2012, the model estimates that a cumulative total of 1.2 million people have been chronically infected with HCV infection in Taiwan. The initial incidence of chronic HCV infection cases was predicted to have occurred during the late 1950s, with the most rapid period of growth in incidence occurring during the 1960s and 1970s (Fig. 3). New cases were predicted to have peaked in 1972 at 56,634 annually. Figure 4 shows prevalent cases stratified by fibrosis stages estimated historically over the period 1955 to 2012. These projections assume that the natural history of disease progression is static over time. In 2012, it was estimated that 127,795 (23.0%), 105,545 (19.0%), 81,211 (14.6%), 123,939 (22.3%), and 116,823 (21.1%) subjects were in fibrosis stages F0, F1, F2, F3, and F4, respectively.

Figure 5 shows the estimated prevalence of chronic HCV infection over time of four different scenarios. The base-case estimate (solid line) shows the prevalence of HCV assuming a minimum HCV incidence of 1,260. It is predicted that a peak prevalence of 763,737 occurs in 1986, with prevalence falling to 578,203 in 2012. The other plots represent the prevalence of HCV assuming a minimum incidence of 10,000 (vertical crosses), 5,000 (diagonal crosses), and 0 (stars). Without accurate information, we have predicted the current incidence of HCV in Taiwan at a constant rate of 1,260 on the basis of information from the United States. It is clear that to accurately predict the future prevalence of HCV, accurate estimates of current incidence are needed because the incidence of HCV has a strong influence on future prevalence.

Figure 6 shows the predicted incidence of DC, HCC, HCV-related liver transplants, and deaths historically and projected over the period 2012 to 2030. Assuming current natural history disease progression, the incidence of subjects living with DC is expected to increase from 3463 in 2012 to a peak of 3540 in 2015; importantly, the model suggests that these numbers would

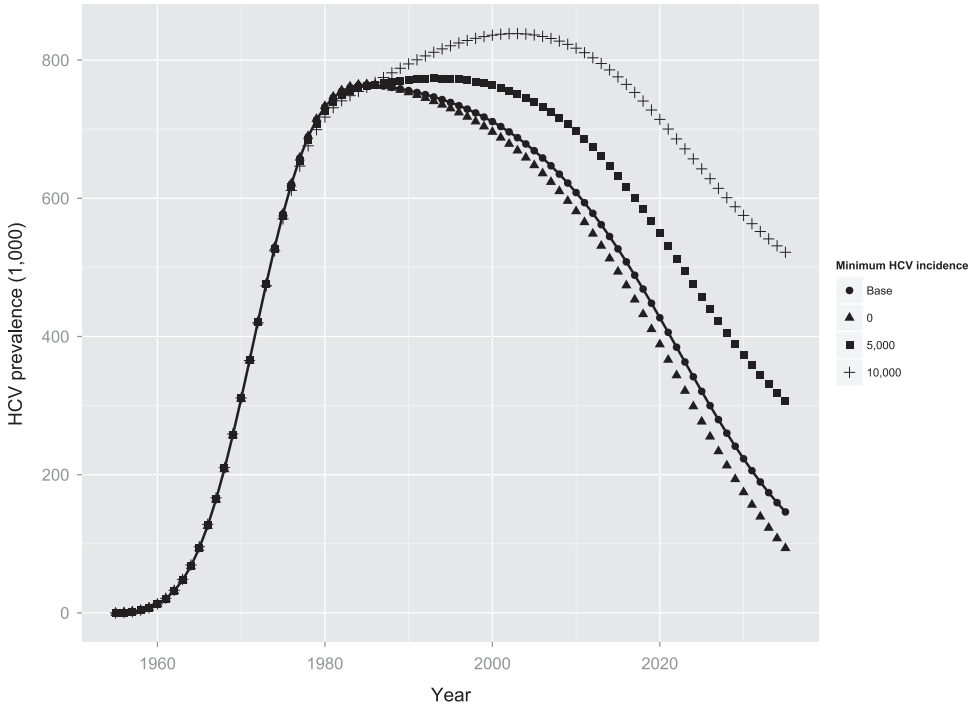

Fig. 5 – Estimated prevalence of chronic HCV with varying 'minimum incidence caps.' HCV, hepatitis C virus.

continue to decrease after this point, as we approach 2030. The projected incidence of HCC similarly increases initially, peaking at 2939 cases in 2016 and then decreasing to an estimated 1891 cases in 2030. By 2030, it is projected that the incidence of HCV-related liver transplants will have decreased to 384, with approximately 9000 transplants required over the period 2012 to 2030.

Discussion

This study used a contemporary HCV natural history disease progression model to characterize the development of chronic HCV infection to HCC, thereby enabling past infection rates to be estimated. This study provides HCV prevalence estimates in Taiwan for 2012 that are consistent with those previously reported. In addition, this study provides further granularity by partitioning those chronically infected with HCV into fibrosis stages. This has potential implications for budget planning, particularly with the availability of emerging therapies because fibrosis stage is predictive of both rapid and sustained virological response [17]; therefore, planning expected treatment response in a given population should be enhanced with this additional information. Furthermore, the step change in efficacy observed with protease inhibitors is associated with a substantial increase in drug acquisition cost; therefore, future optimal treatment strategies may need to consider patient phenotype, expected sustained virological response, and therapy cost in combination when planning budgets. Importantly, this study demonstrated that the potential excess health care expenditure required to manage future ESLD complications is substantial; therefore, the value associated with successful treatment is also high. Consequently, emerging HCV therapies will be both costly and highly cost-effective.

There are inherent limitations to the modeling approach undertaken in this analysis. Back projection requires accurate estimates of ESLD end points. The source data used for this analysis were HCC data drawn from the Taiwan National Cancer Registration, and it was necessary for us to estimate the percentage of HCC cases that were HCV specific; this is subject to some uncertainty. Furthermore, given the latency of HCV disease progression, back projection is unable to provide estimates of recent (last 10 years) infection levels; other techniques are required for this, for example, unlinked anonymous testing programs. A consequence of unreliable recent infection rates will have an insignificant effect on future projections over the short term but may have an impact on longer-term projections. The main objective of this approach, however, is not to provide definitive estimates of disease burden over the long term but rather to provide an insight into potential outcomes. The emergence of protease inhibitors and the imminent profusion of available therapies that have the potential to cure HCV infection will lead to clinical outcomes very different from those projected here. As such, our analysis is designed to facilitate an understanding of possible future scenarios and the clinical and economic consequences of changing clinical practice today, or, as presented here, maintaining current practice.

Our estimates are based on published disease progression parameters that are consistent with the natural history of HCV infection progression. The relatively recent uptake in the treatment for HCV, with associated sustained virological response rates, will have a very limited impact on our back-projected HCV incidence due to the long duration between chronic HCV infection and HCV infection end points, but clearly future incidence will be dependent on both future treatment uptake rates and treatment efficacy; consequently, our results should be interpreted with this limitation in mind.

Recent evidence from the United States suggests that screening and treating hepatitis C is highly cost-effective [18]; earlier work from a UK perspective demonstrated only borderline cost-effectiveness in screening for HCV in intravenous drug users and universal screening was found to be not cost-effective [19]. Given the expected costs of maintaining the current clinical practice patterns that this study predicts, the improved efficacy of newer therapies, and the potential for a cure that would prevent

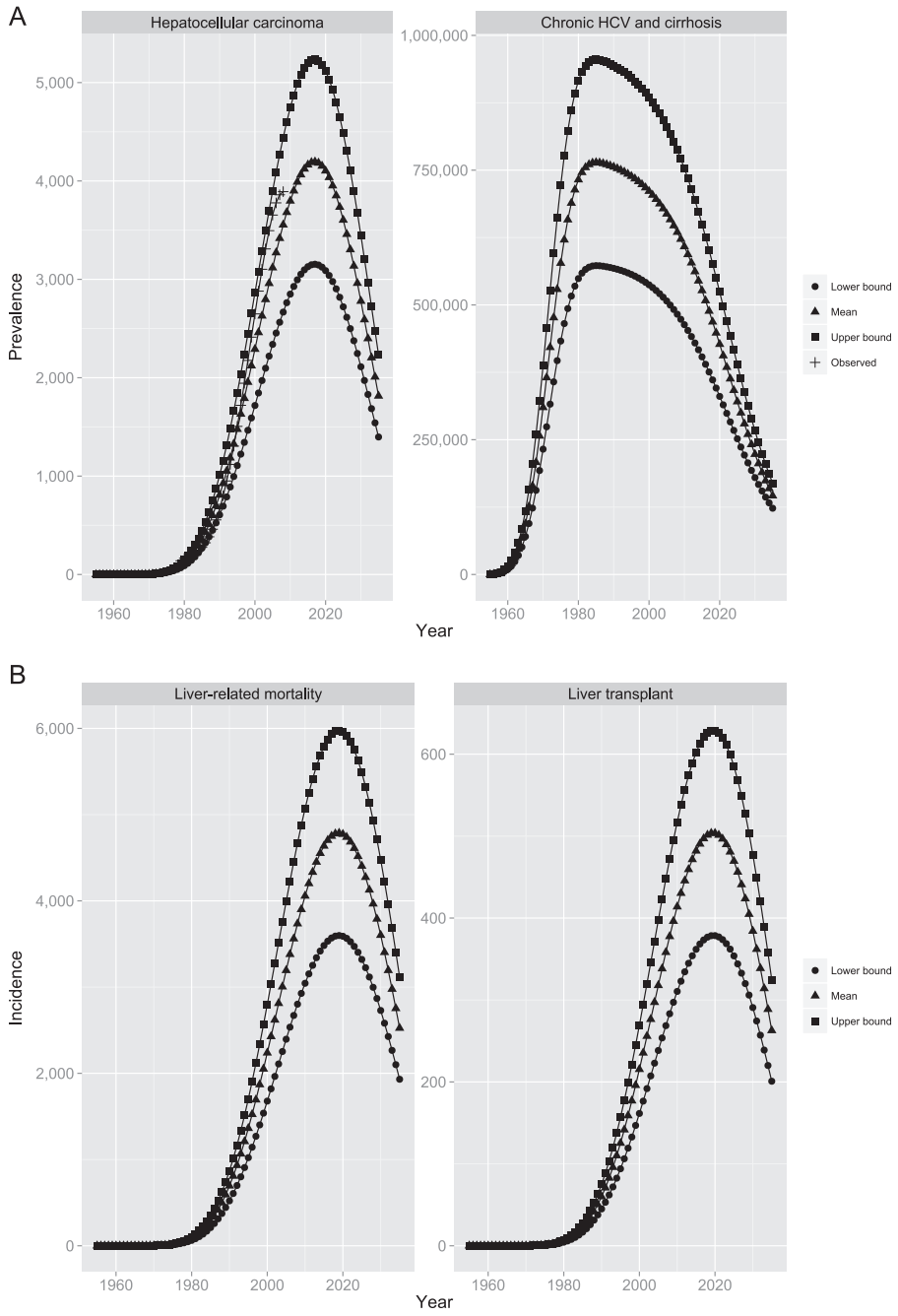

Fig. 6 – (A) Estimated prevalence of hepatocellular carcinoma and chronic HCV per year. (B) Estimated incidence of liver transplants and liver-related deaths per year. HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

reinfections and improve patient quality of life, the evaluation of a screening strategy for Taiwan may be warranted.

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