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Global and country underestimation of hepatocellular carcinoma (HCC) in 2012 and its implications

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ABSTRACT

Purpose: The problems of screening costs, as well as poor data, potentially lead to the underestimation of the incidence of hepatocellular carcinoma (HCC). In particular, this is problematic in developing countries with limited resources and poor data. The study develops a model to inform policy makers of the true incidence and potential extra cost of HCC in a developing country context.
Methods: Using Globocan 2012 data, we employed an ecological correlation design at country level to associate HCC incidence data with relevant determinant data like HBV–HCV and other exposure factors. A Poisson regression model was used to estimate potentially missed incident cases of HCC by country and region based on the country risk factor covariate values.
Results: The results indicated that HBV and HCV prevalence were significantly associated with HCC incidence ($p < 0.001$) and potentially accounted for 94%% of incident HCC in 2012. We estimated a total of 120,772 potentially missed incident HCC cases in 2012. These cases are largely predicted for South Asia (>21,000), North Asia (>15,000), Western Africa (14,500) and Eastern Africa (12,500).
Conclusions: Developing countries, with poorer quality data and a high historical burden of hepatitis, were predicted to have the majority of missed HCC cases in 2012 based on our model. These countries are, therefore, less able to detect, budget for or manage HCC. The high cost of HCC treatment, as well as its economic implications, poses a challenge in resource poor settings.

1. Introduction

Hepatocellular carcinoma (HCC) continues to be a leading cause of cancer worldwide, and the burden is expected to increase in forthcoming years [1]. Recent cancer incidence data confirms that primary liver cancer (PLC) has a global age standardized rate (ASR) of 10.1 per 100,000 with a male to female ratio of 3:1 [2]. Hepatocellular cancer (HCC) is the fifth and seventh most diagnosed cancer worldwide in men and women respectively [2], however, it accounts for an even higher level of cancer related mortality because HCC is often only diagnosed at an advanced stage [3].

Viral hepatitis (HBV and HCV infection) continues to account for more than 90% of all HCC incidence in developing countries and 40% in developed countries [4]. The risk of developing HBV/HCV related HCC, and the process of its development, has been widely linked to more aggressive genotypes in both HBV (A, D, C) and HCV infection, including the viral load and the presence of co-infection [1,5,6]. The highest incidence of HCC occurs in developing countries like East/South East Asia and Mid-West Africa, however, China (alone) accounts for more than 50% of all HCC related deaths. In more recent decades, the epidemiology of HCC has indicated some changing patterns that indicate a rising trend in western countries that is offset by declining trends in (some) developing country settings [5]. Emerging linkages (HCC) with obesity and diabetes have been associated with non-alcohol related fatty liver disease (NAFLD and its progression to non-alcoholic steatohepatitis (NASH) in many western countries, as well as countries like Japan and Korea [7]. Projected increases of metabolic syndrome in developing countries are also expected to emerge as these countries industrialize and this will translate into a higher risk

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of developing HCC [8,9]. Furthermore, the evidence indicates that the risk of HCC is increased by exposure to toxins (alcohol, aflatoxin, pesticides), metabolic disorders (diabetes mellitus, NAFLD, NASH), hereditary conditions (hemochromatosis), immune related disorders (biliary cirrhosis and autoimmune hepatitis) and lifestyle factors like diet, tobacco use and dietary iron overload [6,10]. Co-infection of HBV/HCV and HIV, in particular, appear to elevate the risk of HCC. Schistosomiasis and liver flukes are also cited as risk factors in specific countries [11–13]. A common denominator across all factors influencing the risk of HCC is that cirrhosis is present in 80–90% of all cases [7,11], however, a small proportion of HCC cases occur in non-cirrhotic livers [5,13,14].

The true incidence of HCC is obscured by the difficulties of detecting the disease in its earlier stages. Although proteomic analyses of early-stage cancers, advanced screening technology and genetic profiling improve the detection of early stage HCC [3,15,16], these facilities are largely unavailable in many (developing) countries at present [17]. The true incidence of HCC is also distorted by a lack of (or poor) data and non-standardized reporting methods in many countries [1]. In the recent Globocan 2012 report, 62 out of 184 countries had no cancer incidence data available and only 66 reported the availability of high quality data to project the incidence rate of HCC using a number of different algorithms [18,19]. The majority of the countries that had no data were in the WHO regions of Africa (19), the Americas (17), Europe (13), South East Asia (5), the Eastern Mediterranean (4) and the Western Pacific (4). The majority of the 62 countries that had no data were also developing countries whose resources for cancer management programmes are likely to be limited.

The problem of poor data is, therefore, compounded by the limited resources that are available to treat costly cancer-related detection and treatment. Two interrelated problems emerge. Firstly, if the detection of HCC is problematic in more affluent countries [3,15,16], what is the possibility of even higher levels of under-estimation in poorer countries because of a combination of data problems, as well as a lack of screening facilities. Secondly, a recent study in the EU indicated that the healthcare systems in these countries were unable to cover all cancer-related costs [20]. If cancer-related costs are not fully covered in more affluent regions of the world (like the EU), the question needs to be asked as to the outcome in poorer countries.

The incidence of cancer in developing countries is expected to increase markedly by 2020 [21,22]. The objective of the paper is to develop a model to quantify the underestimation of HCC incidence in developing countries with limited or no data. The HCC under-estimation model can be used to guide policy to mobilize additional cancer detection and treatment resources especially if these can be utilized for a wider range of cancers. The projected HCC underestimation model could also be used to guide relevant policy to initiate HCC awareness programmes and train healthcare practitioners to establish treatment guidelines in a resource constrained environment. The paper also provides further affirmation of the spatial heterogeneity of liver cancer, as well as identifies 'hotspots' of liver cancer incidence that remain relevant for future planning. In order to achieve this, the paper develops a country-level ecological association model to map and predict the under-estimation of HCC at global, regional and country level. The revised (''true'') incidence of HCC is then compared with HCC incidence in the Globocan 2012 database.

2. Methods

2.1. Data sources

Outcome-Raw counts and age standardized hepatocellular cancer incidence data for 184 countries were extracted from the GLOBOCAN 2012 database [2]. The GLOBOCAN 2012 report also provided a detailed description of the data sources, methodologies and potential limitations. Other reports confirmed a potential underestimation of hepatocellular (liver) cancer incidence in developing regions, specifically sub-Saharan Africa [1,17]. Determinants-The following key determinants of HCC, namely HBV, HCV, alcohol, smoking and Schistosomiasis (bilharzia), were included in this analysis. Largely complete HBV prevalence by country was available for 2006 and was used in this study [23,24]. HCV prevalence by country for 1999 was used [25]. Missing data for countries were supplemented using published studies. Proportion of adults with an alcohol disorder by country in 2004 was extracted from the WHO Global Information System on Alcohol and Health (GISAH) [26]. Data for age standardized prevalence of smoking by country in 1990 were used [27]. Disability-Adjusted Life Years (DALY's) attributed to bilharzia by country in 2004 were used as a proxy for bilharzia prevalence [28]. For interested readers, the relative prevalence of HBV, HCV and alcohol disorder by country are presented in the Supplementary File (S1).

Supplementary Fig. S1 related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.canep.2015.04.006.

2.2. Study design

This study employed a country level ecological correlation design.

2.3. Statistical analysis

Data processing and analyses were performed using STATA software version 13.0 [29]. Using observed numbers of age standardized incident HCC cases and associated population at risk, we calculated incidence rates and associated 95% Poisson confidence limits. Country level HCC incidence was considered significantly above average if the lower 95% CI limit ($\alpha = 0.025$) of the incidence proportion was above the global average [30].

A standard bivariate Poisson regression approach with robust standard errors was used to estimate the associated risk of the determinants with HCC incidence. This was then extended to a multivariable Poisson multivariable model including all potential determinants to account for potential confounding. Model goodness of fit was assessed.

This model was then used to predict ''potentially missed'' incident HCC cases using the observed covariate values specific to each country. The underestimation ratio was calculated by dividing the model predicted number of cases by the observed number of cases (with associated upper and lower 95% confidence limits). A ratio value significantly in excess of 1 was suggestive of potential underestimation in a given country. We only predicted HCC incidence in countries with potentially poor or missing national level cancer data as described in the outcome data section above i.e. ''E-G''.

We also employed a commonly used decomposition approach, namely the Shapley decomposition technique distributional analysis to assess the relative importance (attributability) of the assessed risk factors [31]. This was performed by fitting a robust ecological generalized linear ecological Poisson regression model (equivalent of the above model) to enable us to estimate the Shapley decomposition value for each determinant (risk factor).

2.4. Mapping

Maps of HCC incidence pre and post model adjustment were constructed using MapInfo Professional [32].