The Meducator

Volume 1 | Issue 15 Article 8

1-18-2012

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Recommended Citation
Lin, Dolly (2009) "Examining the Increasing Prevalence of Hepatocellular Carcinoma in Canada," *The Meducator*: Vol. 1: Iss. 15, Article 8.
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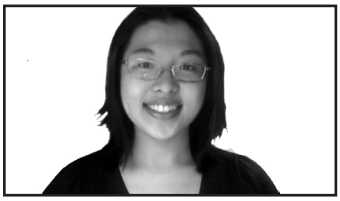
Examining the Increasing Prevalence of Hepatocellular Carcinoma in Canada



Dolly Lin

With over 550,000 newly diagnosed cases each year, liver cancer or hepatocellular carcinoma ranks among the ten most common malignancies worldwide (WHO, 2008). Its increasing prevalence in Canada has prompted a re-evaluation of the burden of the disease. This article will examine the possible explanations behind liver cancer's rising incidence; its epidemiology, etiology, and implications to the Canadian health care system.

Hepatocellular carcinoma causes approximately 660,000 deaths per annum, and accounts for more than 5% of all cancers (WHO, 2008; Ribes et al., 2004). Underlying causes range widely from genetic diseases, parasites, viral infections, to fatty liver disease caused by a high cholesterol diet (El-serag et al., 2001). Damage to the liver through cirrhosis may cause acute liver failure. However, many cases progress towards tumour formation before liver failure occurs.

Despite improvements in screening, transplantation and surgical resection the prognosis of hepatocellular carcinoma is poor. While the five year post-operative survival rate is 60-70% in most developed countries, tumour recurrence occurs in more than half of the patients (Davis et al., 2008; Song et al., 2004). Advanced disease progression at the time of diagnosis also accounts for the low survival rates (Dusheiko et al., 1992; Bosch et al, 2004). Only 13% of males and 15% of females diagnosed survive five years past their diagnosis.

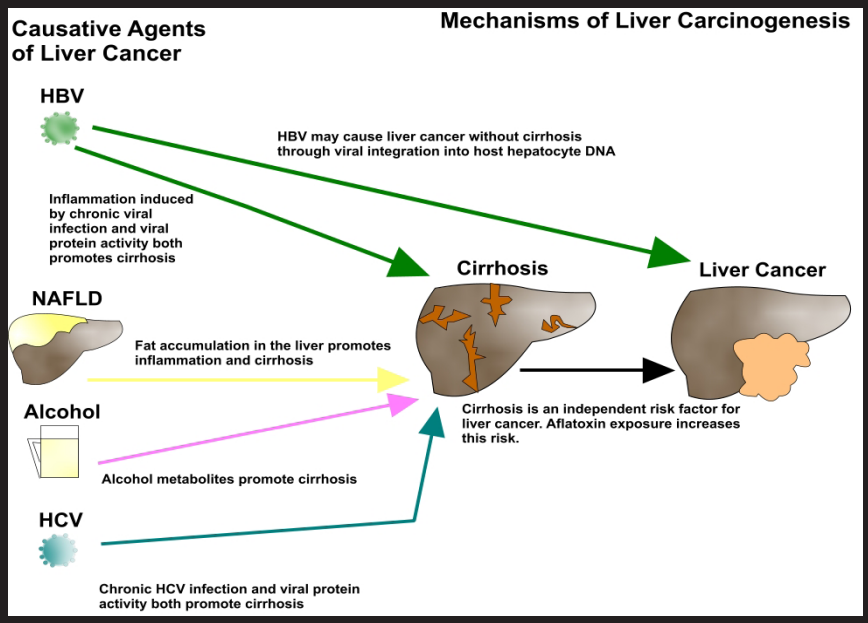


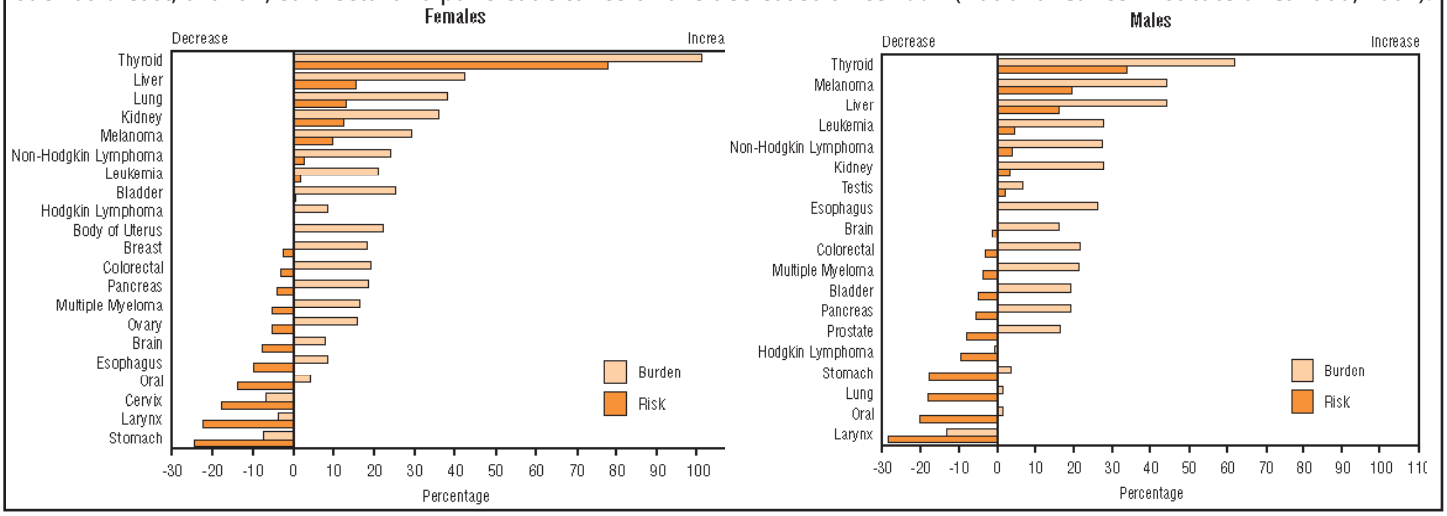
Figure 1 Common causative agents of liver cancer are summarized figuratively with their methods of carcinogenesis. Many factors listed above, such as alcohol and HCV, can work together in synergy in promoting liver cancer. HBV: Hepatitis B, NAFLD: Non-Alcoholic Fatty Liver Disease; HCV: Hepatitis C.

Liver Cancer Epidimiology and Etiology

Liver cancer is generally considered an uncommon problem in Canada. Incidence rates, once among the lowest in the world at less than 3.3 per 100,000, have seen an unfortunate increase of 2.5% annually since 1997 (Bosch et al., 2004; Canadian Cancer Statistics 2007). It now ranks as the 19th most common cancer in the country. Assessment of the relative burden and risk find that while the rates of breast, ovary, and pancreatic cancers are all decreasing, the burden of liver cancer is increasing significantly (Figure 2).

Among the many factors that contribute to liver carcinogenesis worldwide, 80 to 85% of all cases are a result of chronic hepatitis B and C infections (Davis et al., 2008). Due to

Figure 2 Evaluation of cancer incidence burdens for specific cancers, through the total number of new cases, and cancer risk, through age-standardized incidence rates, shows that liver cancer burden has increased dramatically since 1994 for Canadians. Liver cancer burden and risk increase is in the top 3 for both male and female Canadians, while the risk of many common cancers such as breast, ovarian, colorectal and pancreatic cancers have decreased since 1994 (National Cancer Institute of Canada, 2007).



their scarcity in Canada, the role of genetic factors and liver parasites will not be addressed in this article. The incidence rates due to non-alcoholic fatty liver disease have not been extensively documented, they will be discussed here due to their relevance in North America (Figure 1).

Cirrhosis is the scarring of the liver due to connective tissue integration in response to heavy damage. This state of liver damage promotes cancer due to the abnormally high hepatocyte division rates, which increase the risk of mutations in this typically non-mitotic cell population (Anzola, 2004). Most etiologic factors promote carcinogenesis by promoting cirrhosis. Prominent examples are non-alcoholic fatty liver disease, fat accumulation causing liver inflammation and scarring and alcoholic liver disease, in which alcoholic metabolites damage liver tissue (Cai et al., 2005; WHO, 2004). On the other hand, hepatitis B and C induce cirrhosis by triggering inflammation through infection, which further promotes mutations in hepatocytes through viral protein activity (Gurtsevitch, 2008; Benard, Douc-Rasy & Ahomadegbe, 2003). The hepatitis B virus (HBV) directly mutates liver cells through integrating viral DNA into the host and accounts for the most cases of all non-cirrhotic liver cancer (Brechot, 2004).

Causes of Liver Cancer Increase in Canada

Hepatitis B

HBV is a prime suspect for the increased prevalence of hepatocellular carcinoma. As vaccines for the virus become available, the spread of HBV is most likely attributable to immigration from areas of high viral prevalence. Hepatitis B infection occurs when individuals are exposed to the virus through bodily fluid transmissions. Infection is characterized by jaundice and flares of abnormal liver activity. While 90% of exposed adults regain normal liver function (Rehermann et al., 2005), HBV infection in children is far more problematic. This often occurs during delivery or in early infancy through transmission of the mother's bodily fluids. As many as 90% of these individuals develop chronic infection. This develops into cirrhosis and liver cancer (Seeger et al., 2000). From the integration of HBV DNA into host cells, it is becoming evident that even infected individuals who recover normal liver activity are at higher risk for the development of liver cancer (Mulrooney-Cousins & Michalak, 2007).

To assess the effect of immigration, an Australian study modelled the future burden of Hepatocellular Carcinoma (HCC) based on a) the number of immigrants from each HBV endemic country currently settling in Australia, b) the rates of HBV in their native country, and c) the rates of HCC in chronic HBV carriers. The result was a linear rise in projected cancer rates until at least 2025 (Nguyen 2007). Canada receives more Asian immigrants than Australia. Similar, if not greater HCC increases from HBV infection should also be also expected. In fact, immigration in Australia peaked in the early 1990s, while Canadian Asian immigration continues to rise after 2000. Therefore, HBV-attributed cancer cases are unlikely to decline in the near future. However, concrete support for this hypothesis is unavailable due to the scarcity of Canadian HBV-related epidemiological statistics, the asymptomatic state of most chronic HBV infections, and varying HBV reporting protocols across the country (Zhang, Zou, & Giulivi, 2001).

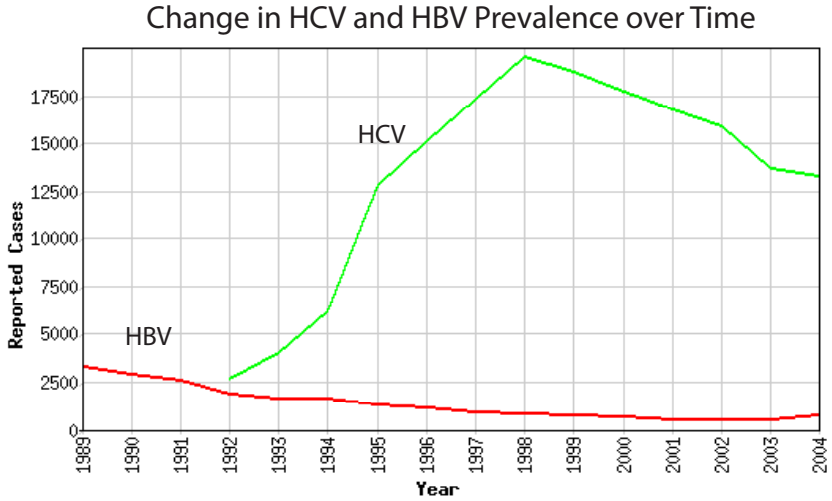


Figure 3 This chart was automatically generated from data collected by the Public Health Agency of Canada, showing the total number of reported cases of HCV in grey, and the total number of reported cases of HBV in black (Public Health Agency of Canada, 2005).

Hepatitis C

Like HBV, Hepatitis C (HCV) is transmitted through bodily fluids though transmission from mother-to-child is virtually nonexistent. Transmission among adults results in chronic infection in 60-80% of exposed individuals (Rehermann & Nascimbendi, 2005). The rate of cirrhosis development in chronic HCV carriers is highly variable, with 3-4% of cirrhotic cases leading to cancer (Anzola, 2004; Gurtsevitch, 2008). The average time span between viral infection and cancer development is around 30 years (Tong, El-Farra, Reikes, & Co., 1995).

In the United States, there are an estimated 3.9 million individuals infected with HCV (Razali et al., 2007). A 51% increase in incidence of HCC in the greater Houston area did not correlate with immigration or population aging, but did correlate with HCV infection (Kulkarni, Barcak, El-Serag & Goodgame, 2004). In addition, HCV has been identified as a major risk factor for HCC in Caucasians and African Americans (Di Bisceglie et al., 2004). It is estimated that 50% of the increase in liver cancer observed in the US between 1975 and 1998 is attributable to HCV infection (El-Serag, Davilda, Peterson & McGlynn, 2003). Modelling within Canada in 1998 predicted that HCC prevalence will increase by 102% by 2008 due to HCV infection alone (Zou, Tepper & El Saadany, 2000). Although HCV infection rates had reached their highest levels to date in Canada in the late 1990s, the number of people living with HCV is still increasing (Figure 3).

Non-Alcoholic Fatty Liver Disease

The contribution of Non-Alcoholic Fatty Liver Disease (NAFLD) to hepatocellular carcinoma is not well documented, as this disease has only recently emerged as a health concern. Its association with obesity makes it a pressing topic in North America. Based on the calculated risk of NAFLD in obese individuals, an estimated 20-30% of the adult population living in developed countries has, or will develop, NAFLD. Cirrhosis will occur in 2-3% of these cases (Preiss et al., 2008).

Implications for the Canadian Healthcare System

Given the national gastroenterologist shortage, the unique profile of high-risk individuals and the stigma related to the diseases, rising rates of liver cancer has various implications for the Canadian health care system.

The Canadian Association of Gastroenterology has identified human resource planning as a priority for the past two years. The number of gastroenterologists in Canada stands at 1.83 per 100,000 people, and is one of the lowest specialist-to-populations ratios in the G8 countries (Paterson et al., 2006). This ratio is only expected to drop when one third of all practising gastroenterologists reach retirement age over the next 19 years (Leddin et al, 2008). By 2015, Canadians will have 10% less gastroenterologists than they do now (Wait Time Alliance, 2008). This is very alarming considering the excessive wait times already encountered by referred individuals. Less than 33% of patients referred for probable cancer cases were seen by gastroenterologists within target wait times. Overall, the national median wait time has been extended to over 13 weeks, with 25% of patients waiting more than 29 weeks (Leddin et al., 2008).

Documented as cost-effective, screening and surveillance programs are vital for individuals with high risks of liver cancer, as all viable treatments are limited to targetting non-metastatic tumours at the time of discovery (Dusheiko, Hobbs, Dick & Burroughs, 1992; Bartlett & Heaton, 2008; Kemp, Pianko, Nguyen, Bailey & Roberts, 2005; Bolondi et al., 2001). Given the specialist's role in issuing

surveillance exams, the shortage of gastroenterologists does not bode well for the increase in prevalence of liver cancer patients expected in future years.

While HBV infection rate ranges from 0.02 to 0.5% in the Canadian population, infection rates in the immigrant population is as high as 4.3%. Areas of concern for this demographic include documented low levels of HBV awareness and possible language barriers preventing health care access (Cheng, Lee, Teh, Wang & Kwan, 2005).

As for Hepatitis C, the rigorous protocols regarding health care equipment today means that viral transmission occurs mainly through intravenous drug use. Because there is a perception that the disease is self-inflicted, controversy exists over the use of taxation as a form of public financing to provide treatment for the disease. For example, the existence of InSite is a source of provocation in the public fora; InSite is North America's first safe injection site aiming to limit infection disease transmission (The Ottawa Citizen, 2008).

Stigma surrounding the diseases HBV and HCV is also a problem for viral carriers seeking aid. Hepatitis carriers surveyed in the United States reveal that 20% have experienced job discrimination over their viral status, while 13% felt social stigma and alienation from their community (Hepatitis Central, 2007).

Conclusion

Increasing liver cancer incidence in Canada reveals a potential public health problem easily overlooked due to its low prevalence in Canada. Several common factors such HBV, HCV, and NAFLD, are projected to continue in future risk. The projected worsening shortage of gastroenterologists is another concern for increasing liver cancer rates, especially given the established relationship between regular screening and liver cancer survival rates. Research into the main causes of accelerating rates and future incidence projections would be useful in determining whether timely interventions could alleviate future burdens on the Canadian healthcare system.

Acknowledgements

Special thanks to Dr. Mel Krajden from the BC Center for Disease Control, Hepatitis Division, for taking the time to answer my questions. Further gratitude is due to the Public Health Agency of Canada for allowing me access to archived data regarding Hepatitis B incidence.

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