The past, present and future of liver cancer control for Māori

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ABSTRACT

Liver cancer is among the most commonly diagnosed and least-survivable cancers in New Zealand. There are stark disparities between the Indigenous Māori population in incidence of and mortality from liver cancer relative to non-Māori. In this review, we have summarised the key risk factors for liver cancer, and the key activities undertaken in New Zealand, over time, to control this disease, with a focus on how risk factors and interventions aimed at reducing them differentially impact Māori.

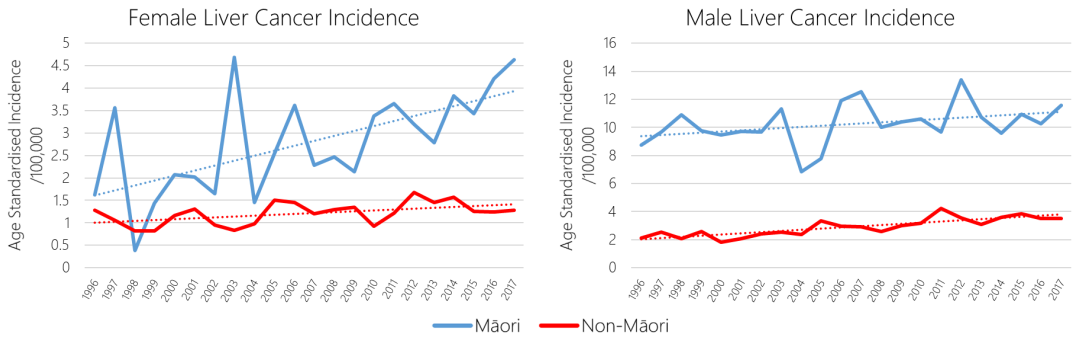
We have conducted a narrative literature review. The disproportionate burden of liver cancer experienced by Māori is primarily driven by disparities in viral exposure to hepatitis B and C between ethnic groups. Efforts to control hepatitis-associated liver cancer in New Zealand have lacked national coordination, further driving disparities in liver cancer survival between Māori and NZ Europeans.

A national primary care-based programme to detect and treat hepatitis B and C and to screen for liver cancer among high-risk patients, along with renewed effort to maximise hepatitis B vaccination rates, has the potential to substantially reduce the burden of hepatitis-associated liver cancer and address a significant health disparity between Māori and non-Māori.

Primary liver cancer (hereafter liver cancer) is the seventh most common cancer globally, with 906,000 cases occurring in 2020.[1] Liver cancer is also among the most deadly cancers, having the third highest cancer mortality rate globally (behind lung and breast cancer) and with 830,000 deaths in 2020.[1] This high mortality rate is driven by poor survival among those diagnosed with liver cancer, of whom approximately 40% will survive one year post diagnosis, and 20% will survive five years.[2] Liver cancer is curable if diagnosed early; curative treatments for early stage disease include liver resection, liver transplantation, and targeted ablation to small lesions. Unfortunately, most patients present with intermediate or advanced stage disease. Treatment for intermediate stage disease include therapies such as chemoembolisation or systemic therapies,[3] while patients who present with symptomatic advanced stage disease are generally only treated with supportive palliative care.[4] As such, the importance of early diagnosis cannot be overstated.

Liver cancer is one of the top 10 most common cancers among New Zealand's Indigenous Māori population, and one of the top 5 most common causes of Māori cancer death.[5,6] The most common causes of liver cancer are well known and preventable, and yet liver cancer incidence and mortality rates continue to increase over time for Māori (see Figure 1).[6] Māori remain substantially more likely to be diagnosed with liver cancer than non-Māori, and less likely to survive once diagnosed.[2,5]

Figure 1: Incidence of primary liver cancer in NZ for Māori and non-Māori between 1996–2017, by sex.[6]



How did we get here? What can we learn from the history of liver cancer control in New Zealand that might help to explain current liver cancer incidence and mortality rates for Māori? What is New Zealand's current approach to liver cancer control, and what future approaches might yield significant gains in this area for Māori, and therefore deserve our consideration? In this manuscript, we summarise relevant literature regarding liver cancer risk factors and prevention in New Zealand, with a focus on Māori. We then consider, where evidence exists, previous and current liver cancer prevention activities, and the extent to which these have focussed on Māori. Finally, we consider the future direction of liver cancer control for Māori in New Zealand and make some key recommendations for next steps.

Types of liver cancer

There are two primary types of liver cancer: hepatocellular carcinoma (HCC), in which a primary cancer develops within liver cancer cells (hepatocytes); and intrahepatic cholangiocarcinoma (ICC), which forms within cholangiocytes lining small intrahepatic bile ducts.[7] HCC is the most common of the two, accounting for 71% of liver cancer cases diagnosed in New Zealand.[8] While the aetiology of ICC is poorly understood, the key risk factors for HCC are well described—with the distribution of these risk factors intrinsically linked to the substantial disparity in liver cancer burden observed between Māori and non-Māori New Zealanders.[5]

There are four key categories of risk factors for HCC: viral hepatitis, alcohol-related liver disease, non-alcohol-related liver disease, and other risk factors (including aflatoxin). Chronic hepatitis B virus (Hep-B) and hepatitis C virus (Hep-C) infections are by far the most frequent cause of hepatocellular carcinoma (HCC), accounting for ~80% of HCC globally.[9] As such, the most important of the risk factors for HCC (by a substantial margin) in terms of both absolute disease burden and as a driver of inequity for Māori are the Hep-B and Hep-C viruses. For the purposes of brevity and focus, this review will focus on the prevention of hepatitis and viral hepatitis-associated HCC within New Zealand. We have presented an extended review of the additional risk factors, and their relevance to Māori, within Appendix 1.

The hepatitis B virus

Hep-B is a DNA virus that is the most prominent risk factor for the development of HCC, with approximately 55% of HCC cases worldwide occurring due to Hep-B chronic infection.[10] Those with Hep-B infection are 30–60 times more likely to develop HCC than those without Hep-B infection.[11–13]

Hep-B is one of the most common chronic infections globally, with 5% of the world's population infected (240–350 million people),[14] of which 35–87 million will die due to HCC.[15] Hep-B is not yet curable, but vaccination has successfully contributed to a reduction in the incidence of HCC,[16] although many Hep-B infected unvaccinated individuals (257 million globally in 2015) are still at risk for developing HCC.[16]

Two mechanisms of the causal pathway from Hep-B to HCC have been proposed. The first involves Hep-B inducing inflammation and cirrhosis-promoting carcinogenesis by up-regulating hepatocyte regeneration, DNA damage, and reactive oxygen species (ROS) production. The second mechanism involves Hep-B DNA incorporation into the host genome, thus affecting activation of proto-oncogenes, chromosomal instability, and transcription of pro-carcinogenic Hep-B genes.[17] It remains unclear as to which of these is the most dominant mechanism, by which chronic Hep-B infection leads to HCC.[18]

The hepatitis C virus

Hep-C, which is an RNA virus, is the second most prominent risk factor in HCC development—accounting for approximately 10–25% of all cases internationally. It is the main cause of HCC in Western countries.[16]

Chronic Hep-C infection is associated with a 20–30-fold risk of developing HCC.[19] However, due to effective treatment using direct-acting antiviral drugs, the risk of HCC attributed to Hep-C has significantly decreased.[20] The World Health Organization (WHO) launched a Global Health Sector Strategy of Viral Hepatitis 2016–2021 aimed at reducing new Hep-C infections by 90%, and at reducing deaths due to all-cause viral hepatitis by 65% by 2030;[21] however, the achievement of these goals will likely be impacted by the COVID-19 pandemic.[20]

The mechanism of Hep-C-associated HCC carcinogenesis occurs progressively over 20–30 years of chronic Hep-C infection.[22] The infection promotes a wide range of changes within the liver from lipid

accumulation within hepatocytes, impaired oxidative stress metabolism, and architectural changes associated with fibrogenesis which impacts liver function.[18] Over time, repeated cell cycles under the influence of oxidative stress induced by the virus and the host immune response leads to the accumulation of mutations in the hepatocytes, ultimately leading to the development of HCC.[23]

Prevention of viral hepatitis-associated HCC

Transmission of hepatitis B and C

Despite their preventable nature and some efforts to reduce the national burden of disease, Hep-B and Hep-C are endemic within New Zealand.[24–27] Hep-B is commonly spread through physical contact, perinatally from mother to child, and through contact with blood and other bodily fluids.[28] Similarly, Hep-C is primarily a blood borne virus which is largely transmitted parenterally through needles or other sharp instruments.[27,29] Those most at risk of contracting Hep-C are injecting drug users; people receiving blood; blood products or organs that are not screened—particularly prior to the introduction of robust screening protocols (see below); those in the prison population; and healthcare workers due to exposure to sharp instruments.[30] Screening of blood products prior to transfusion and a safe, sterile environment when using needles or other sharps are crucial to stop the transmission of Hep-B or Hep-C.[28,30]

Prevention of hepatitis B

Hepatitis B can be prevented at a population level through vaccination, with 90%+ effectiveness against chronic illness achievable via immunisation during childhood.[31] New Zealand first introduced neonatal vaccination against Hep-B in 1985, subsequently making it available for people of all ages in 1988, being one of the first countries to do so internationally.[25] There are still many New Zealanders who were born before the introduction of the neonatal vaccination programme who are unvaccinated and may already be infected, albeit unaware: as of 2018, approximately 3.2 million New Zealanders remained unvaccinated for Hep-B and from this, 93,609 are thought to have chronic Hep-B infection.[26] Additionally, Gane et al. found that 4% of children under the age of 15 were infected with chronic Hep-B.[32] Considering the effectiveness of the vaccine in delivering immunity from chronic Hep-B, it is probable that these children never received a vaccine at birth.[32]

There is also a high risk of transmission to infants from mothers who are carriers of Hep-B. To prevent transmission of Hep-B during labour, Hep-B immunoglobulin can be administered promptly within the first few hours post-delivery.[25] Antiviral treatment late in pregnancy is also recommended for women with a high viral load.[33] Furthermore, administration of the Hep-B vaccine within three days of life was shown to prevent transmission in 91–94% of cases.[25] Hep-B immunoglobulin can also be administered to anyone following exposure to bodily fluid of someone with Hep-B, to prevent infection.[34] Together, neonatal vaccination and Hep-B immunoglobulin for infants of Hep-B-positive mothers, as well as targeted Hep-B vaccination of high-risk individuals,[31] could eradicate Hep-B in New Zealand and reduce the burden of disease caused by Hep-B-associated HCC.[34]

Relevance to Māori

It is widely supported that the burden of Hep-B disease is disproportionate among Māori and Pacific peoples compared to NZ Europeans, and the high incidence of liver cancer among Māori is largely attributable to the incidence of Hep-B.[35–37] Māori also had the lowest Hep-B vaccination rates in 2018, with 333,906 Māori over the age of 30 remaining unvaccinated.[26] One of the major barriers to Māori being vaccinated is likely to be a mistrust in the healthcare system due to institutionalised racism and culturally unsafe service provision, with one in four Māori having experienced discrimination in the previous 12 months.[37] As demonstrated with COVID-19 vaccinations, Māori-led campaigns are more successful than taking a "one-size-fits-all" approach, which often results in poorer access to vaccination for Māori.[38–43]

Reducing social inequities continues to be an important, unmet area of concern.[26] Māori are over-represented in areas of higher deprivation, which is associated with increased transmission of infectious diseases.[26] Hep-B is transmitted horizontally in families, especially those living in overcrowded conditions, where just one person needs to be infected with Hep-B to spread it to other unvaccinated whānau. Horsfall et al. found that among 17,000 Hep-B patients, over 25% lived in areas of highest deprivation, and Māori and Pacific peoples had the highest median deprivation level.[26]

Prevention of hepatitis C

Unfortunately, there is no vaccine available for hepatitis C, emphasising the importance of

other preventative measures.[31] According to the New Zealand Ministry of Health's *"Action Plan on Hepatitis C Prevention"*, current preventative strategies are divided into primary and secondary categories.[27] Primary prevention strategies include: a) controlling injectable drug availability via border control and local and international police activities;[29,44] b) educating the population regarding issues such as needle exchange and the risk of spread of infectious diseases;[29] c) supporting safe injectable drug use by providing environments where injecting equipment can be used safely;[27,29] d) screening blood products to guarantee blood safety;[29,45] and e) workplace legislation to either directly or indirectly reduce the transmission of Hep-C in the workplace.[29] Secondary prevention strategies are closely linked to screening and surveillance, but also include activities such as research into risk factors, transmission and changes in disease incidence, along with providing further training and education to healthcare professionals.[29]

Relevance to Māori

Patients with a history of injecting drug use have an increased likelihood of being marginalised and stigmatised.[46] When this is combined with the high incidence of discrimination Māori also face in healthcare,[37] engaging with services such as the Needle Exchange Programme can be an arduous and difficult experience. Furthermore, patients with Hep-C-associated HCC are commonly the major income earners providing for large families in low decile areas.[48] As noted previously, Māori have a higher median deprivation level compared to non-Māori, making access to these prevention services, such as needle exchange centres and primary healthcare, increasingly difficult.[26] This is often due to a multitude of factors such as lack of transport, inability to get time off work, and childcare commitments.

Screening for hepatitis B

Since the 1980s, Hepatitis B Surface Antigen (HBsAg) has been included in antenatal and blood donor screening.[48] Initially, screening for Hep-B was done in an ad hoc way, which is not effective considering the large number of people who remained undiagnosed.[49] Estimates suggest about 50% of the approximately 100,000 people living with chronic Hep-B, and 40% of the 45,000 chronic Hep-C patients, still remain undiagnosed or have been lost to follow-up.[47] Because of concerns regarding the ramifications of undiagnosed and untreated hepatitis, in 1994 the New Zealand Hepatitis Foundation, a non-governmental organisation (NGO) based in Whakatāne campaigned for organised Hep-B screening to reduce the burden of chronic Hep-B infection, but this was not rolled out nationally at the time.[48]

In 1998, the Government funded a Hep-B screening programme, which set out to target Māori, Pacific and Asian communities in Northland and wider Auckland regions over the age of 15—those who were unlikely to be protected by the Hep-B vaccine.[32] The screening programme was executed by two different providers: 1) the Northern Region Hepatitis Consortium, which was made up of Auckland District Health Board staff, Ngāti Whātua (a tribal entity based in central west Auckland) and Māori and Pacific primary care and public health organisations; and 2) the Hepatitis Foundation. Both agencies were responsible for screening and follow-up, and the Northern Consortium also offered immunisation, counselling and surveillance services.[48] The South Island was not covered, with this approach rationalised at the time by relative differences in the Māori, Pacific and Asian populations between the North and South Islands.[48]

The Hepatitis Foundation led screening in the Northland and Auckland regions from July 1999 to 2002, and largely worked out of purpose-built screening centres and marae (traditional meeting houses). Additionally, from April 2000 to December 2002, the Northern Consortium was up and running—largely focussing on supporting practitioners along with Māori and Pacific Health providers to recruit individuals opportunistically through invitation, phone call, and local advertisement via radio, churches and marae.[48]

In terms of the screening test itself, a blood sample was taken after gaining informed consent from the participant and transported to a designated laboratory for testing. Each blood sample was analysed for HBsAg and those who were positive were further tested for e-antigen (HBeAg), along with alanine aminotransferase (ALT) and alpha-fetoprotein (AFP), which are markers of active hepatitis and HCC, respectively.[48]

This short-lived screening programme tested 177,000 people and found that 4,081 people (6%) were positive for HBsAg.[48,49] Later analysis suggested that had the programme continued and completed screening the total target population,

an estimated 80,000 people would have been identified as positive for HBsAg—with subsequent ramifications in terms of HCC surveillance and prevention.[24]

Importantly, 40% of patients diagnosed with advanced stage HCC associated with Hep-B are unaware of their Hep-B status at their initial presentation.[24] A pressing issue arising from this screening programme is ensuring that the remaining people with chronic Hep-B are receiving effective follow-up and surveillance. This has proven difficult for several reasons: largely because primary care providers struggle to access specialist services for referral of patients, and some patients are lost to follow-up or hard to trace.[48]

Relevance to Māori

When the Hep-B Screening Programme was up and running, only 27% of eligible Māori (aged over 15 years) were screened for Hep-B. Disappointingly, this was significantly below the goal of 70% coverage rate, despite engaging with Māori healthcare providers and marae.[35,48] Gane et al. suggests the poor recruitment of Māori could reflect perceptions on mass screening, which may stem from previous negative publicity around screening programmes.[32]

Surveillance of hepatitis B and C

HCC tumours are largely asymptomatic in the early stages, making them difficult to detect during this period without effective surveillance following a diagnosis of Hep-B or Hep-C.[50] When viral hepatitis-associated HCC is caught at an early stage, it is more likely to be treatable.[26,51] However, most cases of Hep-B or Hep-C-associated HCC in New Zealand are picked up at later stages where curative treatment is often not an option.[47] As such, monitoring high risk patients such as those with chronic liver disease from hepatitis is extremely important.

Ideally, all patients with chronic Hep-B infection should be recruited on to a monitoring programme (such as the programme run by the Hepatitis Foundation), to receive regular monitoring of serum ALT and Hep-B DNA. This will identify any potential need for Hep-B suppression therapy to reduce the risk of HCC.[26] For higher risk patients, six monthly imaging of the liver and analysis of AFP in viral hepatitis patients will also help detect HCC at an earlier stage and improve survival.[47]

The number of HCC cases increased substantially between 1998 (introduction of the surveillance programme) and 2017, with the most common causes of HCC in these patients being Hep-B (42%) and Hep-C (28%).[47] In support of this, Mules et al. also found the rate of Hep-B-associated HCC had increased over time in New Zealand.[24] Furthermore, those who had been previously diagnosed with Hep-B but not recruited on to a surveillance programme presented with advanced stage HCC and had poor prognoses; several factors were found to be contributing to this late presentation, including a lack of initial Hep-B diagnosis, and/or poor follow-up and surveillance.[24] In November 2019, only 19% of New Zealanders with Hep-B had been recruited onto the national monitoring programme.[26]

However, Mules et al. also noted that some patients who were receiving "optimal surveillance" still presented with advanced disease, which emphasises the limitations of our current surveillance methods.[24] Firstly, measurements of serum AFP have a low sensitivity and specificity as nearly one-third of HCC cases will have a measured AFP in the normal range, and healthy patients may also produce an elevated AFP (mostly caused by pregnancy). Secondly, the sensitivity and specificity of abdominal ultrasounds (USS) are also low, as 15% of HCC tumours may only be detected by USS when they are large, and other imaging methods such as MRI or CT may be required to differentiate HCC tumours from benign abnormalities.[24]

Relevance to Māori

It is estimated that a Māori male with chronic Hep-B infection has a 10–15% chance of developing HCC by the time they are 70 years of age.[48] Schauer et al. found that majority of patients (92%) with Hep-B-associated HCC were Māori, Pacific or Asian, with NZ European only making up 5% of cases.[47] Furthermore, Māori were largely over-represented in patients with advanced stage HCC due to viral hepatitis infection, with 45% of Māori cases from Hep-B and 23% from Hep-C.[24,47] In support of this, Mules et al. found that 143 out of 368 eligible HCC patients presenting with late stage HCC associated with Hep-B at the New Zealand Liver Transplant Unit were Māori.[24]

Crucially, Chamberlain et al. found that only around 40% of Māori who developed HCC from either Hep-B or Hep-C were on surveillance.[35] As such, there is clearly a strong need to ensure adequate access to surveillance services for Māori.[47] Māori are also over-represented in areas of higher deprivation, where barriers to medical

care and treatment are abundant, and they are more likely to experience poorer health literacy and understanding of the risks involved with viral hepatitis and HCC.[24,47,50]

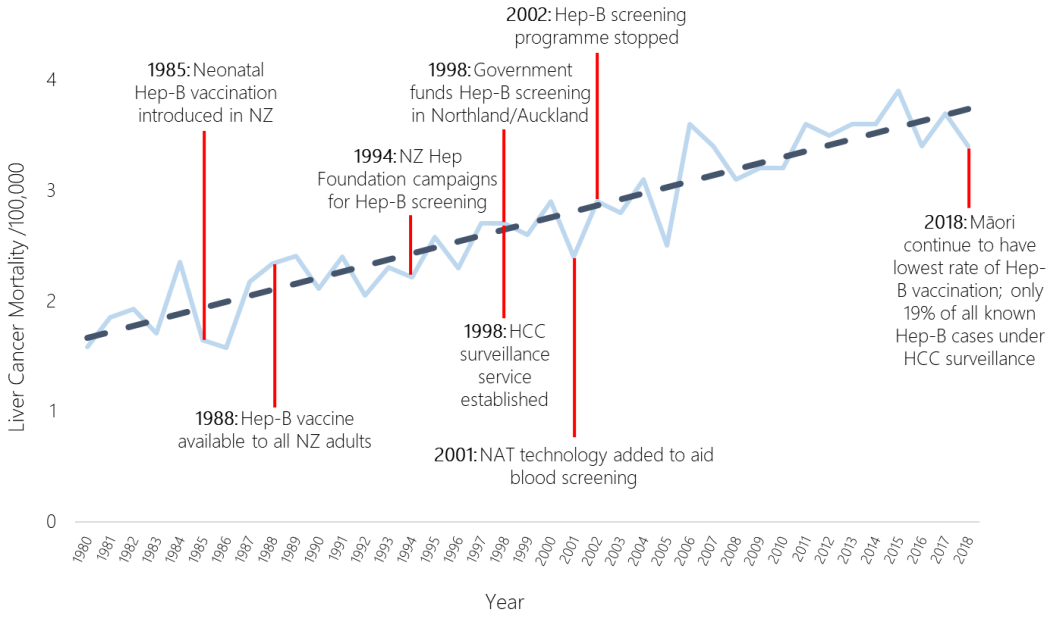
Key lessons and recommendations

This review has summarised the public health efforts aimed at detecting and treating patients with chronic hepatitis B and C in New Zealand over the last 25 years (see Figure 2). Chronic infection with Hep-B and Hep-C remains a significant health issue in New Zealand, with many patients currently undiagnosed and untreated, particularly within Māori and Pacific communities. As presented by Horsfall et al., an estimated 2 million Europeans, 333,000 Māori and 215,000 Pacific peoples in New Zealand remain unvaccinated for Hep-B, while an estimated 10,000 Europeans, 19,000 Māori and 15,000 Pacific have chronic Hep-B infection.[26] Around 40% of the 45,000 chronic Hep-C patients still remain undiagnosed or have been lost to follow-up.[47]

The neonatal Hep-B vaccination program has been successful in reducing transmission in the neonatal period through use of immunoglobulin in Hep-B positive mothers presenting for delivery;[25,26] however, unvaccinated children are most likely to become infected between the ages of 1 and 4 years.[25] In addition, there remains a significant reservoir of adults with chronic active Hep-B infections in the community who are an important cause of horizontal transmission within family groups. An additional issue is that vaccination funding ceases at 18 years of age, meaning that adults will likely need to pay for their own vaccination. While no vaccination exists for Hep-C, contemporary antiviral therapy will result in viral elimination in over 99% of affected patients.[27]

While the neonatal vaccination program has been successful, public health initiatives aimed at adults with these conditions have been episodic and undertaken without a national focus or national coordination. This is despite the conditions and their sequelae, such as HCC, being very much national healthcare issues, if not emergencies. There is now excellent data that confirms the prevalence and lethality of hepatitis and HCC in Māori and similar, although less complete, data in Pacific peoples residing in New Zealand. Addressing the disproportionate effects of these largely preventable conditions in these populations must be an important part of any health

Figure 2: Rate of liver cancer mortality per 100,000 New Zealanders between 1980 and 2018, overlaid by a chronology of actions taken to control hepatitis-associated liver cancer. Mortality data sourced from the Ministry of Health.[54]



strategy that is attempting to address issues of health equity for these populations.

There is a clear pathway by which we can achieve improvements in liver cancer control for all New Zealanders, and for Māori in particular. A programme to detect and treat Hep-B and Hep-C, as well as screen for HCC, could be undertaken through primary care. All enrolled patients over 18 years of age should undergo testing for Hep-B (HBsAg) and Hep-C (Hep-C Ab); those with positive results should undergo further testing including Hep-B/Hep-C viral load, liver function and platelet count. HBsAg positive patients will additionally be tested for Hep-B e-antigen and α-fetoprotein. Patients can then be started on appropriate antiviral therapy, and those with a higher risk of HCC based on the screening tests, or those with an initial positive serum α-fetoprotein, will be referred for specialist assessment at regional public hospitals and considered for HCC surveillance screening—with six monthly liver ultrasound scans and serum α-fetoprotein.[52]

The success of adequately resourced and empowered Māori and Pacific health providers in reaching their communities during the COVID-19 pandemic, and in their ongoing facilitation of vaccination and healthcare, is evidence that a nationally led, but grassroots driven, campaign would be successful.[39–42] For Māori such a program would resonate, reinforcing the importance of whānau (extended family) and the handing-on of good health from one generation to another. In 18 years (2040), or a little under one generation, New Zealand will celebrate the bicentenary of Te Tiriti o Waitangi, the founding document of our nation. If work begins now, hepatitis B and C-associated liver cancer could be largely eliminated from our population by 2040—sparing, without exaggeration, hundreds of lives each year and putting an end to a significant cause of health disparity for our Indigenous Māori population. This would be a cause for considerable celebration.

Conclusions

In this review, we have summarised the key risk factors for liver cancer, and the key activities undertaken in New Zealand to control this disease. Māori suffer a disproportionate burden of liver cancer in New Zealand, and there is evidence of systemic inadequacies in the prevention of, and outcomes from, liver cancer for our Māori population. The majority of the liver cancer burden for Māori is driven by disparities in viral exposure to hepatitis B and C; however, efforts to control hepatitis-associated liver cancer in New Zealand have been uncoordinated to date, and this remains a cause of the enduring disparity in liver cancer survival between Māori and NZ Europeans. We recommend the implementation of a national programme to detect and treat hepatitis B and C, and to screen for HCC among high-risk patients, with this programme to be delivered through primary care (including Māori health providers). Such a programme should be coupled with renewed effort to maximise hepatitis B vaccination rates, particularly for Māori. In combination, these efforts could result in the near elimination of hepatitis-associated liver cancer from Māori (and non-Māori) communities within a few generations.

COMPETING INTERESTS
Nil.

ACKNOWLEDGEMENTS
We would like to thank the following individuals for providing assistance with the literature review for this manuscript: Professor Chris Bullen, Professor Ed Gane, Ms Susan Hay, Mr John Hornell, Professor John McCall.

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Appendix 1: Non-hepatitis risk factors for hepatocellular carcinoma (HCC).

Alcohol-related liver disease

Alcohol and alcohol abuse is responsible for an estimated 30% of global incident cases of HCC and is expected to increase.[1–3] A meta-analysis of 19 cohort studies found a dose-response relationship between alcohol consumption and the risk of HCC.[4–6] Another meta-analysis of 19 prospective studies estimated an increased risk of 16% of HCC with alcohol consumption of three or more drinks per day, and a 22% increase with six or more drinks per day.[7,8] There is further evidence of an increased rate of HCC with alcohol consumption as low as 10g per day, relative to no consumption.[9,10] Moreover, evidence suggests that alcohol in conjunction with HBV and HCV has an additive synergistic effect on HCC risk.[1,7]

Chronic and sustained alcohol intake drives hepatocarcinogenesis by altering the architecture and functional capacity of the liver (steatosis, steatohepatitis, and cirrhosis) thereby generating a carcinogenic tissue microenvironment.[3,5] A pivotal pathophysiological factor implicated is oxidative stress, secondary to the production of ROS derived from alcohol metabolism, inflammation, and iron metabolism.[3]

Alcohol and hepatocellular carcinoma among Māori

The 2020/2021 New Zealand Health Survey shows that 20% of the population have hazardous drinking patterns (alcohol consumption that indicates a high risk of mental or physical damage).[11] Māori (33%) had a higher rate of hazardous drinking compared to NZ European/Other (21%).[11] However, the largest published study analysing the differences in patterns of alcohol consumption between Māori and non-Māori involving 6,926 Māori participants and 37,904 non-Māori demonstrated that Māori are less likely to drink alcohol, drink less often but consume a larger amount on one drinking occasion when compared with non-Māori.[12] Thus, the average alcohol consumption per day overall is similar between Māori and non-Māori [12]. These results are consistent with the 2013/14 New Zealand Health Survey which found that non-Māori were more likely to have consumed alcohol four or more times a week in the past year (RR 0.60) compared to Māori. However, of those who have consumed alcohol in the past year, Māori were more likely than non-Māori to have consumed a large amount of alcohol at least weekly (RR 1.75).[13]

A New Zealand study conducted over 24 years (1981–2004) found that 40% of individuals with HCC also had documented heavy alcohol use. Heavy alcohol use was similarly common for both Māori and non-Māori.[14] Based on available evidence, it appears unlikely that the strong disparities in liver cancer incidence observed between Māori and non-Māori in New Zealand is driven by differences in alcohol-related liver disease.

Non-alcohol-related liver disease

Non-alcohol fatty liver disease (NAFLD) is considered to be the hepatic manifestation of obesity, metabolic syndrome, and diabetes. It is the fourth most common aetiology of HCC[15–20] with the global prevalence forecasted to increase from 83 million (2015) to 101 million (2030).[21] It is becoming the most common liver disease contributing to hepatocarcinogenesis in developed countries.[22] However, it should be noted that the RR of NAFLD-related HCC is not comparable to the RR of HBV-HCC and HCV-HCC.[7]

The hallmark of NAFLD is triglyceride build-up in which sustained accumulation can lead to the development of HCC occurring as a sequential pathophysiological process; steatosis, steatohepatitis, fibrosis, cirrhosis, and eventually HCC.[16] The NAFLD-carcinogenic environment is promoted by sustained cycles of hepatocellular destruction and compensatory proliferation as a response to metabolic and oxidative toxicity, pathological inflammatory response, altered immune response, and altered endocrine/adipokine signalling.[23,24]

Non-alcohol-related liver disease and hepatocellular carcinoma among Māori

In New Zealand, the prevalence of NAFLD is 13%[25] with no existing data on the prevalence of NAFLD in Māori, or HCC attributable to NAFLD. Overall, the burden of obesity, metabolic syndrome, and diabetes is higher in Māori compared to non-Māori.[26,27] Although there is no data to demonstrate the prevalence of NAFLD induced HCC in Māori, we may infer that the increased exposure for NAFLD clinical risk factors may con-

fer an increased incidence of NAFLD-HCC among Māori compared to non-Māori.

Other causes of hepatocellular carcinoma

Aflatoxin and hepatocellular carcinoma

Aflatoxin is a mycotoxin produced by the *Aspergillus* fungus found in contaminated food such as groundnuts, tree nuts, and corn stored in damp, warm environments.[2,7] It has been estimated that 25,000–155,000 cases of HCC worldwide may be attributable to aflatoxin exposure, primarily in those regions where it is mostly found (sub-Saharan Africa, Southeast Asia and China).[28] AFB1, the most potent aflatoxin, is classed as a group 1 human carcinogen by the International Agency for Research on Cancer[29] and increases HCC risk by four-fold.[7,22] AFB1 has shown to have a synergistic association when combined with HBV, increasing HCC risk by sixty-fold compared to persons with neither risk factor.[7,30,31] There are concerns arising around the impact of climate change (driving increasing temperatures) and increased levels of aflatoxin.[28] It is expected that aflatoxin levels are to become more frequent in the future.[28,32]

A New Zealand Ministry for Primary Industries assessment determined that the overall population is exposed to low levels of aflatoxin compared to the international average. It was determined that liver cancer attributed to AFB1 would be less than 0.1 per year, thus indicating that dietary aflatoxin exposure is an insignificant contributor to HCC in New Zealand.[33] There is insufficient information available on aflatoxin exposure in Māori, although due to the insignificant AFB1 levels in New Zealand, it is unlikely that AFB1 exposure is an important contributor to the increased HCC incidence in this population.

Smoking and hepatocellular carcinoma

Tobacco smoking is responsible for 13% of global HCC cases.[9,34] The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort with more than 4.4 million person-years of follow-up found that smoking has a RR of 4.55 for HCC, while a meta-analysis found an RR of 1.5 in smokers compared to non-smokers and an RR of 1.12 for previous smokers. The large RR variation can likely be explained by differences in study designs and exposure to smoking.[35,32] Smoking and tobacco exposure have also been shown to accelerate disease progression in other HCC-related diseases such as HBV and HCV infection.[35]

In New Zealand, the prevalence of adult daily smokers is 13% (2018/2019) of which 31% are Māori.[36] There is insufficient information on the prevalence of smoking and tobacco exposure attributable to hepatocarcinogenesis in Māori; however, due to increased smoking rates, we may be able to assume that smoking contributes to increased HCC prevalence in Māori. Further research is required to understand the extent to which smoking is a contributing driver of inequities in HCC incidence for Māori.

Helicobacter Pylori and hepatocellular carcinoma

Approximately 50% of the global population has been infected with the bacterium *Helicobacter Pylori* (*H. Pylori*).[37] Although principally associated with stomach cancer, several studies have found an association between *H. pylori* and HCC. A meta-analysis found the OR for the association between *H. pylori* infection and risk for HCC was 13.6.[37,38] By contrast, several high-quality studies have found a negative correlation between *H. pylori* and HCC, and evidence on the direct carcinogenic effect of *H. pylori* on hepatocytes has yet to be found.[37] Thus, as of yet, it is unclear whether *H. pylori* infections are unlikely to contribute to hepatocarcinogenesis.

Despite contrasting studies on the association of *H. pylori* infections and HCC, it is known that Māori have a greater prevalence of *H. pylori* infection (35%) compared to NZ Europeans (18%).[39] If the association of *H. pylori* induced HCC were to be proven, we can assume that it would disproportionately affect Māori compared to non-Māori.

The "other" other causes of hepatocellular carcinoma

Several studies have found an association between exposures other than those listed above and HCC. Some compounds/chemicals such as aristolochic acid,[22] areca nut (nitrosamines), betel leaves (safrole), vinyl chloride, and dichlorodiphenyltrichloroethane have been shown to increase the risk of HCC. Other studies have linked groundwater contaminants, organic solvents to hepatotoxicity.[2] However, given the insufficient body of evidence supporting these exposures and HCC, it is likely that these are not important contributors towards HCC for Māori.

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