Title

A 30-year time trend analysis of primary liver cancer incidence in Canada, Mongolia, and the United Kingdom, (1990 - 2019)

Author

Palmer, Duane

Publication Date

2022

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

A 30-year time trend analysis of primary liver cancer incidence in Canada, Mongolia, and the United Kingdom, (1990 - 2019)

A thesis submitted in partial satisfaction

of the requirements for the degree Master of Science

in Epidemiology

by

Duane Philip Palmer

2022

ABSTRACT OF THE THESIS

A 30-year time trend analysis

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and the United Kingdom, (1990 - 2019)

by

Duane Philip Palmer

Master of Science in Epidemiology

University of California, Los Angeles, 2022

Professor ZuoFeng Zhang, Chair

Background: As one of the leading causes of cancer deaths, reducing primary liver cancer incidence remains a top global health priority. Overall, the most common causes of liver cancer are chronic hepatitis B and hepatitis C viral infections, dietary alcohol abuse, and non-alcoholic fatty steatohepatitis. Countries with historically high disease burden, such as China, have implemented public health strategies to reduce primary liver cancer incidence significantly. Conversely, countries like Mongolia have not experienced the same declines despite prolonged public health intervention. Historically, Western countries have largely avoided substantial disease burden, only to see upticks in incidence rates as etiology and populations have shifted. This study examines primary liver cancer incidence in Canada and the United Kingdom, representative of low burden North American and European populations, and Mongolia, a

representative of a high burden Asian population, to analyze incidence trends over 30 years and evaluate for signs of disease reduction.

Methods: Data on liver cancer incidence estimates were retrieved from the Global Burden of Disease 2019, covering 30 years from 1990 to 2019. Crude and age-standardized incidence rates and a web-based Age-Period-Cohort tool were calculated to determine age, period, and cohort effects. Hypothesis testing using Wald chi-squared testing was implemented to determine the statistical significance of the time trends observed.

Results: Overall, populations in Canada, Mongolia, and the United Kingdom experienced increasing age-standardized incidence rates of primary liver cancer over the 30 years. Plotted longitudinal ASIR estimates reveal that Canadian and UK populations experienced steady increases in age-standardized incidence rates. In contrast, Mongolia peaked around 2010, withdrawing slightly to finish with a net increase. All populations experienced statistically significant positive increases in net drift and period effects. Regardless of gender, all UK populations experienced increased PLC risk after the 1955 reference cohort, while Canada mostly saw statistically significant increases.

Conclusion: Exacerbated by shifting causal factors, asymptomatic disease progression, and limited early-detection strategies, liver cancer incidence continues to increase globally. Surveillance must guide data-driven public awareness campaigns, promote preventative lifestyle behaviors, and reduce liver cancer incidence among populations at highest risk.

The thesis of Duane Philip Palmer is approved.

Jian Yu Rao

Donatello Telesca

ZuoFeng Zhang, Committee Chair

University of California, Los Angeles

2022

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List of Acronyms

APC: Age-Period-Cohort;

ASIR: Age-Standardized Incidence Rate;

CIR: Crude Incidence Rate;

dsDNA: double-stranded DNA;

GBD: Global Burden of Disease;

HBV: Hepatitis B Virus;

HCV: Hepatitis C Virus;

LCAL: Liver Cancer due to Alcohol;

LCHB: Liver Cancer due to Hepatitis B Virus;

LCHC: Liver Cancer due to Hepatitis C Virus;

LCNASH: Liver Cancer due to Non-Alcoholic Steatohepatitis;

LC_OTHER: Liver Cancer due to Other causes;

NASH: Non-Alcoholic Steatohepatitis;

PAF: Percent Attributable Fraction;

PLC: Primary Liver Cancer;

Introduction

Primary liver cancer (PLC) remains one of the most common malignancies found worldwide, despite it also being one of the most preventable [1]. According to 2020 global estimates, liver cancer was the sixth most diagnosed cancer and third most common among cancer-related deaths, after lung and colorectal cancers [2]. After diagnosis, disease progression is often rapid and fatal [1]. Late-stage treatment is generally ineffective [1], and the 5-year survival rate remains less than 20% [3, 4]. Therapies may be available during early disease stages and often rely on aggressive procedures to improve prognosis, including surgical resection, liver transplantation, and localized ablative techniques [4, 5]. As such, substantial regional and global health resources have been committed over decades to developing surveillance and management strategies to reduce PLC incidence rates over time. From an international perspective, successful national public health interventions are studied closely in hopes of applying similar principles to other areas of high regional PLC burdens and reduce overall cancer incidence.

Historically, the distribution of international liver cancer incidence rates has been highly variable, with roughly 83% of all PLC cases occurring in low- and middle-income countries [6]. Regions such as Sub-Saharan Africa and Eastern Asia have experienced decades of heightened disease burden, while Western countries have experienced relatively low levels [7, 8]. Intra-country rates can vary widely as different populations accumulate different risk exposure profiles and longitudinal exposure histories [9]. Diverging incidence rates have also been observed in different urban settings, even in countries with historically low disease burden [10]. Additionally, men typically have higher incidence rates than women, especially in countries with higher disease burden [6]. With respect to age, those younger than 45 typically shoulder higher risk of incident PLC than those in countries with a lower disease burden [1].

Decades of epidemiological research have established several well-confirmed, high-impact risk factors for incident PLC, including the presence of gallbladder cancer, chronic viral infection, alcoholic cirrhosis, dietary aflatoxins, and non-alcoholic steatohepatitis (NASH) [1]. Given a direct anatomical connection to the intestine via the portal vein, researchers have also suggested a relationship between the gut microbiome and the occurrence and development of PLC [11, 12]. Interestingly, PLC was one of the first common cancers which was shown to have viral etiology. Hepatitis B virus (HBV) and hepatitis C virus (HCV) can have both asymptomatic courses of infection, eventually leading to chronic infection and persistent inflammation of the liver [5]. HBV infection is characterized by integrating viral dsDNA into the host chromosome, promoting genomic instability, and accelerating the likelihood of field cancerization of infected tissues. HCV infection involves metabolic reprogramming leading to abnormal retention of lipids in the liver [14]. Consequences of both viral infections are immune-mediated oxidative stress and deregulation of cellular signaling pathways by viral proteins to further destabilize tissues and lead to an increased likelihood of carcinogenesis [15]. Alcoholic cirrhosis and NASH similarly achieve chronic liver inflammation through related pathways to destabilize liver tissue and promote hepatocarcinogenesis over time [16].

Several international surveillance programs and databases, such as the Global Burden of Disease (GBD), have been established to help monitor, evaluate, and direct public health efforts to reduce the incidence of liver cancer worldwide. To enhance public health efforts, research groups have shifted away from non-parametric descriptive epidemiology measures instead to adopt parametric statistical models to better interpret PLC disease burden over time [17]. One such method, the Age-Period-Cohort (APC) analysis, has been used effectively to evaluate racial disparity in breast cancer rates, testicular and ovary cancers, pancreas, and lung cancers [18-22].

As international surveillance programs chart changing PLC incidence rates, researchers and public health officials can identify increasing or decreasing trends that can be used to evaluate the effectiveness of any associated public health intervention efforts. Furthermore, parametric statistical models, such as the APC method, can robustly power these institutions to detect and analyze any estimated trends' statistical significance. Historically, disease etiology has been geographically varied. Researchers have described falling PLC incidence rates in regions with historically high disease burdens; within the same time, however, other regions have experienced increases or persistently high rates. This study selects countries for analysis with either historically high PLC incidence burdens resistant to public health interventions or historically low PLC incidence that are now seeing increased rates. Populations in Canada, Mongolia, and the United Kingdom were selected because management strategies to control their respective disease burdens reflect public health officials' current challenges to reduce incident PLC going forward. Historically, the incident PLC burden in Mongolia has been some of the highest globally [23], whereas Canada and the UK have been at low risk but are now among regions showing increasing rates [10]. Together, these three countries represent areas with high and low disease burdens struggling to reduce PLC incidence over time in Asian, North American, and European populations. An analysis of these countries may highlight shifting proportions among etiologies and differential responses to public health intervention strategies to apply elsewhere to lower the disease burden. Together, an analysis of PLC incidence rates in Canada, Mongolia, and the UK, will provide a statistically robust way to determine shifting APC effects and provide a means for future disease surveillance, and evaluation of applied interventions as effective cancer prevention strategy.

Data Sources and Methods

Data Sources:

All data used in this retrospective, registry-based study were retrieved from the GBD study available through the Global Health Data Exchange (http://ghdx.healthdata.org/gbd-results-tool; accessed December 2021). Commissioned in 1990 by the World Bank, the GBD was established to estimate mortality and disability from major communicable and non-communicable diseases, injuries, and risk factors. As of 2021, the GBD has grown to include 204 countries and territories, 369 diseases and injuries, and 87 risk factors through collaboration with the WHO and researchers across the world [24]. Previous studies have utilized this data source to estimate liver cancer incidence trends [25, 26].

Disease diagnosis of primary liver cancer at the local level were made in accordance with the International Classification of Diseases and Injuries 9th and 10th revisions, specifically all ICD9 and ICD10 codes pertaining to PLC 155.0-155.963 and C22.0-C22.9. Careful attention was made to diagnose according to pathology reports using patient biopsy samples, which limit the inclusion of secondary liver cancer cases in the sub-national statistics. Data were then reported to the appropriate national or regional cancer registry for consolidation and reporting [27]. At the national level, procedures are in place to routinely monitor, correct for, and standardize methodologies to address data completeness, presence of case duplicates, inconsistencies for reporting multiple cancers from the same individual [28]. As a result, cases of incident PLC and specific subtypes, including Liver cancer due to HBV infection (LCHB), liver cancer due to HCV infection (LCHC), liver cancer due to alcohol (LCAL), liver cancer due to NASH (LCNASH), and liver cancer due to other causes (LC_OTHER) were made publicly available for research purposes and overall disease surveillance.

Statistical Analysis:

To obtain all incidence-related liver cancer data, the following search terms were submitted to the GBD Results Tool, on the Overview Page: Measure: Incidence; Cause: B.1.7 Liver Cancer, B.1.7.1 Liver cancer due to hepatitis B, B.1.7.2, Liver cancer due to hepatitis C, B.1.7.3 Liver cancer due to alcohol use, B.1.7.4 Liver cancer due to NASH, B.1.7.5 Liver cancer due to other causes; Context: Cause; Location: Mongolia, Canada, United Kingdom; Sex: Male, Female; Metric: Number. In addition to the above terms, ages were selected using 5-year age groups from 15 to 79 years old, with individuals outside of that range being censored. Lastly, all available years, from 1990 to 2019, in the database were selected and individually exported to ensure a complete dataset as values can be lost if search criteria are too large. After obtaining data for each year, using the above conditions, CSV files were consolidated into Microsoft Excel, version 16.57, for data management and analysis. From the complete dataset, data by country and sex were parsed into respective tabs using data filter.

Similarly, population data were obtained from the GBD Study 2019 and Population Estimates 1950-2019 (http://ghdx.healthdata.org/record/ihme-data/gbd-2019-population-estimates-1950-2019). Population data estimates were extracted from the CSV files titled "Population estimates: Single-Year Age Groups, 1990-1999 [CSV]", "Population estimates: Single-Year Age Groups, 2000-2009 [CSV]", and "Population estimates: Single-Year Age Groups, 2010-2019 [CSV]", and stored in excel. Next, data were filter-parsed to consolidate all years and corresponding variables by country and sex into separate tabs. Finally, estimates were tabulated by 5-year age groups and individual year over the 30-year period.

To calculate age-standardized incidence rates (ASIR) for each country, 5-year age groups for primary liver and subtype incidence counts were calculated using the direct standardized method. For each year, age-specific incidence counts were divided by corresponding population estimates to obtain age-specific rates per population. Next, those rates were multiplied by the 2019 GBD standard 'both sex' population counts, categorized into the same 5-year age groupings, and divided by 100,000 to achieve an ASIR value per 100k of population. This was done using point, upper, and lower estimates corresponding to the appropriate 95% confidence interval. These results are shown for PLC rates, as well as by PLC subtype. In other words, the rates of each country by gender were multiplied by the weights of standard population and divided by 100k. The generalized formula to calculate the ASIR values can be seen here:

(Equation 1) ASIR (per 100,000) = $\Sigma(I_K^A \times W_K^*)$

Where: A = Country and gender of interest

K = Age-specific 5-year grouping

I_K^A = Age-specific incidence rate of country, per 100k

T_K^*= Number of persons by age group in standard population

$W_k = (T_K^*)/(\Sigma_k T_K^*)$ = Weights for each age group

Crude incidence rates (CIR) were determined using the same data but summing across all age groupings both incidence and population estimates, dividing cumulative incidence by cumulative population, and multiplying the resulting rate by total count of the 2019 GBD 'both sex' standard population, and dividing by 100k. CIR calculations can be generalized by the function below:

(Equation 2) CIR (per 100,000) = $I^A \times T^* \times 100{,}000$

Where:

I^A= Incidence rate [(incidence cases)/(total count of country-specific population)]

T^*= Total count of standard population

To perform the age-period-cohort analysis, separate CSV files by country and sex were made and submitted to the APC webtool (https://analysistools.cancer.gov/apc/). There, alternating incidence, and population estimates for each 5-year period were tabulated against 5-year age groups from 15-79 years of age. For future applications of the APC webtool, the age and year periods must be identical in length, matching as either 1, 5, or 10-year increments, for example. The start year was set to 1990, starting age set to 15, and the interval (Years) set to 5. References were determined manually by the user, setting Reference Year to 2000-2004 and Reference Age to 45-49. After computation, results were exported to Excel. Wald chi-squared tests of heterogeneity were applied to detect the significance of estimated drift, cohort, and period effects relative to null values. All statistical tests were two-sided, and p-values less that 0.05 were considered statistically significant.

Results

Table 1: Country characteristics

From 1990 to 2019, Canada, Mongolia, and the United Kingdom, and experienced growth across respective male and female populations, despite holding stable percentages of the total global population over the same period. Similarly, all three national populations maintained slight female over-representation with respect to male counterparts. In terms of PLC incidence, simple count data increased for both sexes in all three countries over the thirty years. When

direct standardized, ASIR per 100k estimates maintained increased disease burden across males and females of all three countries. In Mongolia, males' overall PLC disease burden increased 25%, while female cases increased by almost 85%. Canadian and UK males and females saw larger increases. Canadian male and female PLC incidence rates more than doubled, at 221% and 230%, respectively. In the United Kingdom, male and female ASIR estimates more than doubled, 232% and 225%, respectively.

Table 2: PLC subtype analysis

ASIR rates and counts of primary liver cancer, as summarized in Table 1, are further detailed by subtype in Table 2 for the years 1990 and 2019. ASIR results are summarized by gender for either country or PLC subtype, as seen below:

In the UK, the overall PLC disease burden essentially doubles in males, and nearly triples in females across the 30 years, as measured by ASIR per 100k. UK males were most at risk for LCAL, while UK females were most at risk for LCHC. Both UK males and females were least at risk for LCNASH.

In Canada, the disease burden of each PLC subtype roughly doubled for both male and female populations. Canadian males were most at risk for LCAL. At the same time, female populations were most at risk for LCAL or LCHC. Baseline risk was observed for LCHB and LCNASH across both genders.

In Mongolia, ASIR rates were considerably elevated compared to all other PLC subtype ASIR estimates observed in Canada or the UK. Similar to Canadian and UK populations, Mongolian males appear to hold at least double the risk for LCHB and LCAL over females. Interestingly, however, Mongolian females have a slightly elevated LCHC and

LCNASH than their male counterparts. ASIR rates for LCHC and LCNASH, once slightly below male rates in 1990, were now estimated to be slightly above corresponding male rates in 2019 for females. For both Mongolian males and females, the PLC disease burden appears to be split among LCHB, LCHC, and LCAL. Males saw roughly consistent disease burden across PLC subtypes, except for LCAL, while females saw considerable increases across every subtype except for LCNASH.

Overall, Mongolian male and female populations carry the highest disease burden across every PLC subtype category. Canada and the UK, however, exhibit higher rates of percent ASIR increase across PLC subtypes, except for cases of LCAL and LCNASH among Mongolian females. The highest percent attributable fraction (PAF) of PLC subtype incidence is found in males from the United Kingdom and Canada, with estimates LCAL at 50% and 70%, respectively. The next highest PAF was observed amongst LCHC cases in females from the United Kingdom and Mongolia. Interestingly, females in Canada showed elevated PAF due to LCNASH, contrary to those in the UK or Mongolia. The highest percent changes in ASIR by PLC subtype were observed for cases of LCHB among males and females in the UK and for cases of LCNASH among males and females in Canada, both of which tripled. From 1990 to 2019, the lowest percent change was observed in Mongolian males for cases of LCHB and LCHC, which showed a modest increase of roughly 5-10%.

Figure 1: Longitudinal time trends of PLC incidence rates

For each country, male and female ASIR and CIR estimates are plotted over time, from 1990 to 2019. Supplementing the book-end analysis in Table 2, Figure 1 illustrates how CIR and ASIR trends evolve yearly. The highest PLC disease burden magnitudes are among Mongolian

males and females, followed by males from Canada and the UK. Canadian and UK populations generally display a monotonal increase over time, with few variations from the overall trend. The UK does exhibit a plateauing of ASIR across both male and female populations. Similarly, Canadian males and females showed a slight decrease in upward trajectory around 2005, only to recover the overall upward trend. Interestingly, both male and female populations in Mongolia show a persistent upwards trajectory in ASIR, followed by plateauing by 2010 and slight retraction by 2019. Additionally, with CIR estimates larger in magnitude than the corresponding ASIR estimates in the UK and Canada, there appears to be some degree of confounding brought on by intrinsic differences within age structures amongst male and female populations of those countries.

Figure 2: Net drifts and local drifts effects on incidence rates of different age groups

Overall, all evaluated male and female populations experienced statistically significant increasing PLC burden, as suggested by point estimates of net drift, the overall annual percentage change of all age groups across the 30 years (Figure 2, Table 3), and the corresponding 95% confidence intervals. In terms of greatest disparity between male and female populations within the same country, Mongolian females, 2.20 (1.12, 3.30), experienced roughly twice the increase in disease burden as their male counterparts, 0.92 (0.08, 1.76), though the difference isn't formally statistically significant (Table 3). Conversely, Canadian and UK male and female populations saw roughly similar overall increases in disease burden (Table 3).

Using a Wald chi-squared test for heterogeneity, each calculated net drift estimate was subjected to formal hypothesis testing. The "Net Drift = 0" test tested the validity of the null hypothesis that each estimated net drift value was the same as zero, statistically speaking.

Conversely, the alternate hypothesis was that each estimated net drift value showed to be statistically different from zero. The resulting p-values shown in Table 3 were all less than alpha of 0.05, indicating rejection of the null in favor of the alternate hypothesis that each net drift estimate is different from zero. All populations evaluated had net drift estimates that were statistically different from zero, indicating increases in PLC disease burden over the 30 years.

In terms of local drift, the estimator of age-specific annual percentage change, there is a high degree of overlap between male and female estimates (Figure 2). When examining if all local drifts are statistically different from the static net drift value with a Wald chi-squared test for heterogeneity, resulting p-values suggest a failure to reject the null hypothesis (Table 3). This indicates that local drift estimates are not statistically different from estimates of the net drift. Interestingly, Mongolian females had a p-value of roughly 0.10, suggesting an emerging informal difference between respective net and local drifts. All other populations had a very large p-value, indicating high agreement with the null hypothesis. Canadian males had a p-value of 0.33, representing the second-lowest p-value observed, suggesting a lesser degree of separation between local and net drifts than the Mongolian female population (Table 3).

Figure 3: Period effects on PLC incidence

The period effect reflects variation in risk estimates under specific calendar years that affects all age groups relative to the rate ratio present during the 2000-2004 period. When considering the complete period effect profile, UK and Canadian populations are roughly consistent across males and females, with a statistically significant upwards trend shown after the reference period (Figure 3). Male and female populations in Mongolia show similar profiles in period effect to Canada and the UK, although a more informal separation exists between Mongolian males and females (Figure 3). For all three countries, there exists a protective period

effect relative to the PLC rate ratio between 1990 and 1999 and an increasing disease burden associated with the years between 2005 and 2019.

Similarly, with other facets of the APC model, a Wald chi-squared test for heterogeneity was applied to determine if the estimated period rate ratios differed from RR=1. Table 3 depicts the Wald chi-squared test statistic, degrees of freedom, and corresponding p-value. All populations examined had p-values smaller than alpha, suggesting a rejection of the null hypothesis that all period rate ratios equal one. This result confirms a statistically significant difference between a rate ratio of no change and period effects on PLC incidence observed.

Figure 4: Cohort effects on PLC incidence

The cohort effect reflects the overall observed PLC risk for individuals belonging to the same birth year. All populations except for Mongolian males show highly similar, upwards linear trends across the range of cohort birth years when observed on a logarithmic scale (Figure 4). Relative to the reference cohort born in 1955, more senior cohorts show lowered rate ratio, while cohorts born after show increasing rate ratios of incident PLC. Mongolian males, however, show cohort effects that are much closer to the null rate ratio (ex: RR=1).
When applying the Wald chi-squared test for heterogeneity, all populations show statistically significant differences between observed cohort PLC rate ratios and the null rate ratio, even among Mongolian males, despite their closer visual proximity with the null (Table 3).

Discussion

This study evaluates the incidence of primary liver cancer in Canada, the United Kingdom, and Mongolia using non-parametric ASIR methods and parametric models to separate

longitudinal time trends and age, period, and cohort effects. Previous work has estimated the global PLC burden from 1990 to 2019 [29], revealing that total ASIR trends continually decreased, likely resulting from successful public health interventions in China and Southeast Asia [30, 31]. At the same time, interestingly, global mortality counts for all four PLC subtypes increased, possibly due to population growth and aging [29]. Despite overall declines in global counts, much public health work remains. This study suggests substantial resiliency in historically disease-burdened populations, increasing disease burden, and shifting etiology in formerly low-risk countries. To mitigate these trends, data-driven public health interventions will be required to help limit future PLC burdens.

Incident PLC burden was not equal across male and female populations in Canada, Mongolia, and the UK, much in line with previous studies [33-35]. This study found that males have at least twice the risk of incident PLC than their female counterparts. Interestingly, males and females tended to show mirrored longitudinal ASIR profiles. Sex-specific hormones [35] immune responses, more significant accumulations of risk factors exposure histories to behaviors such as drinking and smoking in males [36-38] can explain this resilient global difference in PLC burden between sexes over time. Increased rates among female populations are fueled by shifting proportions in underlying disease etiology prevalence. In Canada and the UK, countries at historically low risk for PLC, females have increased ASIR rates due to LCHC and LCAL. In Mongolia, females experienced a more significant risk from LCNASH than their male counterparts. Within UK females, chronic hepatitis C infection produced the largest percent increase in ASIR estimates from 1990 to 2019. All populations evaluated showed positive net drift estimates indicating a statistically significant increase in incident PLC, with Canada and the UK showing the largest increases.

Interestingly, Mongolian females had a net drift that was much greater than their male counterparts, representing the most significant male-female disparity observed in this study. In terms of period and cohort effects, male and female populations in Canada and the UK showed the most significant increases, consistent with studies showing increases in ASIR rates in formerly low-risk countries across Europe, North America, and Australia [39, 40]. Furthermore, females in the UK demonstrated increases in ASIR due to LCNASH, which has also been reported previously [41, 42].

In theory, primary liver cancer incidence is a prime target for public health intervention as its development and onset is associated with largely preventable risk factors. Control of incident PLC would reduce the prevalence of one of the fastest-rising causes of cancer-related deaths worldwide [43] and help to reduce overall cancer burden. In practice, however, the actual surveillance and management of incidence PLC represents a significant public health challenge. Clinical progression is often asymptomatic, underlying etiology varying, and life-saving treatment options are limited if diagnosed outside of early stages. Factors promoting chronic liver inflammation, such as chronic HBV infections and associated genomic instability, chronic HBV infection, heavy alcohol use, and tobacco use [36] all have associated challenges in managing rates over a national population.

The risk of new HBV infections can be negated by a 3-dose vaccination regimen for neonates [44, 45], while current infections in older individuals can only be alleviated, not cured, by antiviral medication. There are no vaccinations available for HCV infection, although infections can be treated with direct-acting antivirals that can cure over 90% of chronic carriers [5]. Unsafe need usage and blood transfusions represent another route that facilitates HCV spread [46]. Reducing heavy alcohol and tobacco usage is also challenging from a public health perspective,

as individuals would need to be receptive of and willing to change long term behaviors from a public health awareness campaign to make a meaningful impact. Quitting is most complicated by the addictive qualities of nicotine and alcohol. Previous work has shown that study participants with thirty years or more of drinking exposure had an increased cancer risk odds ratio compared to those with less than thirty years of exposure [47]. Normalized social drinking, alcohol dependence and addictions, and long latency between exposure accumulation and disease onset all represent significant hurdles to build overall public urgency and reduce harmful alcohol consumption. Lastly, to combat increases in NASH prevalence within a population, only long-term behavioral changes, such as reducing cholesterol intake, maintaining a healthy weight, control of diabetes, and regular exercise, are available to help manage conditions and reduce chances of further complications [48].

Compounding the above issues is unequal coverage of healthcare across countries struggling to manage with incident PLC burdens and shifting etiologies. Transitioned countries such as Canada and the UK, while historically having the lowest PLC burden, have the greatest available healthcare resources to devote to reducing disease burden. Mongolia, and other similar transitioning countries, have historically experienced highest rates of PLC burden [49] with fewer public health resources available manage and intervene.

In fact, there is an interesting case-study to be made that compares the public health interventions and measurable outcomes in terms of disease incidence. China and Mongolia have had decades of high PLC burden, largely coming from chronic HBV infections [50]. Over the 30-year period from 1990 to 2019, other studies have documented China's drastic reduction in overall PLC incidence, thanks largely to aggressive and widespread public health campaigns directed towards vaccination [51]. A series of programs, such as free-of-charge HBV vaccinations

for all neonates and young children aged 8-15 [51, 52] without previous HBV exposure, have helped to reduce prevalence of chronic liver inflammation and drive down overall PLC burden over time in China. Despite a national HBV vaccination program for newborns in place since 1991, Mongolia, however, has been unable to see a similar decrease in disease burden decades after implementation of these programs, as neighboring China was. This discrepancy is likely due to limited coverage of HBV vaccinations, varied program adoption and adherence, and uneven access to healthcare across Mongolian populations.

Conversely, most countries in North America and Europe have experienced low levels of PLC burden historically but have now observed increased rates in recent years [31, 40]. This study confirms previous work, finding increasing ASIR trends and age, period, and cohort effects associated with both males and females from Canada and the UK. This phenomenon is likely due to changing prevalence of etiological factors such as harmful alcohol consumption, excess body weight, and diabetes. Within formerly low-risk countries, such as the US, diverging trends have been reported for PLC in rural and urban settings, with rates slowing in urban settings and increasing across rural America [10]. In addition, variation in disease distribution is likely when evaluating racial groups. A study looking at HBV and HCV infection prevalence among Mongolian-born individuals living in Washington DC reported that nearly 13% had chronic HBV, HCV infection, or both [53], which is lower than prevalence estimates in Mongolia of 19% and higher than general US estimates [54]. These studies expose differential distribution of PLC risk factors and disease burden across racial and geographic groups and highlight the need to commit resources to sub-populations otherwise hidden or marginalized by overall national burden trends.

There are several limitations to consider in this study. First, as a secondary analysis relying on GBD data over a 30-year observation period, this study is subject to the same accuracy and robustness issues as the GBD data itself, namely the accuracy and integrity of extrapolated incidence counts to the country which reported them. For example, the ability to diagnose disease with high sensitivity and specificity directly impacts reported estimates. Second, the GBD database reports incident PLC due to either HBV, HCV, alcohol, NASH, or other factors. While this covers the most common causes of PLC, the level of granularity for more regionally specific causal factors may be lost at the expense of a standardized global codebook. For example, the other category refers to other causes such as tobacco use, exposure to dietary aflatoxin b1, or liver flukes. Lastly, this study evaluates the PLC burden across the three decades prior to the SARS-CoV-2 pandemic, which abruptly changed the accessibility and functionality of healthcare systems globally.

Conclusions

Liver cancer remains a globally important public health issue, but its effective control is complicated by uneven, and oftentimes shifting disease etiology and burden. Thankfully, there exist effective public health tools to reduce prevalence of the major causes of liver cancer, although decades are required to observe any positive effects on incidence PLC. Through effective vaccination programs, chronic HBV infections can be avoided. By utilizing direct-acting antivirals and implementing safe blood transfusion and needle sharing programs, HCV infections can be minimized. Harmful alcohol and poor dietary behaviors can be addressed through public awareness campaigns, although challenges remain. Together, incidence liver cancer can be a largely avoided, thereby reducing one of the leading causes of cancer-related deaths globally. Results from this study highlight countries attempting to manage PLC incidence

from opposite ends of the burden spectrum and identifies etiological targets for public health intervention. Going forward, cost-effective, and nuanced prevention strategies are needed as future cancer burdens are expected to increase in the coming decade.

Table 1: Incidence of primary liver cancer in Canada, Mongolia, and the UK, from 1990 to 2019

	Population (millions)		Percent of global population (%)		PLC incidence		30-year change (%)
Characteristics	1990	2019	1990	2019	1990	2019	
United Kingdom							
Males	27.9 (26.1, 29.7)	33.3 (29.9, 36.6)	1.04 (0.99, 1.08)	0.86 (0.80, 0.91)			
ASIR (per 100k)					3.42 (3.39, 3.44)	7.95 (6.68, 9.39)	232.5 (197.1, 273.0)
Incidence count					900 (850, 950)	2,921 (2,218, 3,781)	324.5 (260.9, 398.0)
Females	29.6 (27.7, 31.5)	34.0 (30.6, 37.3)	1.11 (1.07, 1.16)	0.88 (0.82, 0.94)			
ASIR (per 100k)					1.63 (1.62, 1.64)	3.68 (3.17, 4.26)	225.8 (195.7, 259.8)
Incidence count					520 (491, 550)	1,466 (1,144, 1,850)	281.9 (233.0, 336.4)
Canada							
Males	13.5 (12.4, 14.5)	18.0 (19.5, 16.4)	0.5 (0.47, 0.53)	0.46 (0.44, 0.49)			
ASIR (per 100k)					3.82 (3.59, 4.08)	8.45 (5.89, 11.54)	221.2 (164.1, 282.8)
Incidence count					387 (336, 446)	1,745 (1,125, 2,559)	450.9 (334.8, 573.8)
Females	13.8 (12.8, 14.9)	18.6 (16.9, 20.1)	0.52 (0.49, 0.55)	0.48 (0.45, 0.50)			
ASIR (per 100k)					1.46 (1.31, 1.63)	3.36 (2.34, 4.69)	230.1 (178.6, 287.7)
Incidence count					173 (144, 207)	747 (481, 1,120)	431.8 (334.0, 541.1)
Mongolia							
Males	1.07 (1.00, 1.16)	1.67 (1.47, 1.87)	0.040 (0.038, 0.042)	0.043 (0.039, 0.047)			
ASIR (per 100k)					129.02 (87.27, 180.67)	162 (111.04, 223.45)	125.6 (127.2, 123.7)
Incidence count					444 (276, 676)	1,265 (738, 2,004)	284.9 (267.4, 294.5)
Females	1.08 (1.00, 1.16)	1.72 (1.51, 1.92)	0.041 (0.038, 0.043)	0.045 (0.040, 0.048)			
ASIR (per 100k)					50.92 (32.29, 75.01)	93.84 (64.06, 129.16)	184.3 (172.2, 198.4)
Incidence count					198 (116, 315)	816 (485, 1,272)	412.1 (403.8, 418.1)

Footnote: Age-Standardized Incidence Rates (ASIR) were calculated for 5-year age-groupings, from 15-79, using the Global Burden of Disease (GBD) database, the direct standardization method, and either the 1990 or 2019 GBD 'Both Sex' standard populations. Percent 30-year change was calculated by dividing point estimates for 1990 ASIR values by 2019 values. All single values represent point estimates, with adjacent ranges corresponding to lower and upper 95% confidence intervals estimates. Incidence counts reflect raw incidence count data from GBD. Subtype abbreviations are as follows: LCHB= Liver Cancer from Hepatitis B virus, LCHC= Liver Cancer from Hepatitis C virus, LCAL= Liver Cancer from Alcohol, and LCNASH =Liver Cancer from Non-Alcoholic Steatohepatitis.

Table 2: Incidence of primary liver cancer subtype in Canada, Mongolia, and the UK, from 1990 to 2019

	LCHB incidence		LCHC incidence		LCAL incidence		LCNASH incidence	
Characteristics	1990	2019	1990	2019	1990	2019	1990	2019
United Kingdom								
Males								
ASIR (per 100k)	0.6 (0.46, 0.75)	1.84 (1.3, 2.46)	0.83 (0.67, 1)	1.88 (1.41, 2.44)	1.72 (1.51, 1.91)	3.98 (3.14, 4.89)	0.14 (0.11, 0.17)	0.37 (0.27, 0.48)
Incidence count	161(133, 193)	554 (400, 727)	279 (239, 324)	1,100 (833, 1435)	519 (463, 572)	1,880 (1428, 2423)	44 (37, 53)	197 (146, 260)
(%) PLC incidence	18 (13, 22)	23 (19, 26)	24 (19, 30)	24 (21, 26)	50 (44, 56)	50 (47, 52)	4 (3, 5)	5 (4, 5)
Females								
ASIR (per 100k)	0.25 (0.19, 0.32)	0.74 (0.52, 0.99)	0.77 (0.68, 0.86)	1.71 (1.38, 2.04)	0.33 (0.26, 0.41)	0.75 (0.56, 0.97)	0.14 (0.11, 0.17)	0.38 (0.29, 0.49)
Incidence count	85 (71, 102)	250 (181, 329)	391 (352, 426)	1,241 (987, 1539)	135 (114, 158)	416 (313, 540)	68 (57, 81)	255 (193, 335)
(%) PLC incidence	15 (12, 20)	20 (17, 23)	47 (41, 53)	46 (43, 48)	20 (16, 25)	20 (18, 23)	9 (7, 11)	10 (9, 12)
Canada								
Males								
ASIR (per 100k)	0.36 (0.19, 0.6)	0.72 (0.33, 1.36)	0.39 (0.21, 0.64)	0.88 (0.42, 1.58)	2.69 (2.26, 3.04)	5.9 (3.97, 8.25)	0.22 (0.13, 0.36)	0.63 (0.32, 1.11)
Incidence count	39 (27, 57)	154 (244, 92)	46 (28, 69)	242 (140, 390)	299 (264, 332)	1,432 (1013, 1901)	27 (18, 40)	173 (105, 272)
(%) PLC incidence	9 (5, 15)	8 (6, 12)	10 (6, 16)	10 (7, 14)	70 (63, 74)	70 (67, 71)	6 (4, 9)	7 (5, 10)
Females								
ASIR (per 100k)	0.13 (0.07, 0.21)	0.25 (0.12, 0.46)	0.44 (0.27, 0.61)	1 (0.55, 1.61)	0.5 (0.32, 0.69)	1.09 (0.6, 1.75)	0.24 (0.15, 0.36)	0.65 (0.36, 1.09)
Incidence count	17 (11, 24)	61 (37, 96)	70 (51, 90)	336 (220, 478)	71 (52, 91)	310 (197, 444)	40 (29, 55)	221 (145, 324)
(%) PLC incidence	9 (5, 13)	7 (5, 10)	30 (21, 37)	30 (23, 34)	17 (12, 20)	22 (17, 27)	16 (11, 22)	19 (15, 23)
Mongolia								
Males								
ASIR (per 100k)	50.6 (27.86, 81.37)	55.9 (30.3, 90.27)	29.76 (15.13, 50.44)	31.2 (16.09, 51.63)	41.21 (21.99, 66.6)	64.82 (37.2, 98.85)	4.58 (2.27, 8.27)	6.74 (3.49, 11.54)
Incidence count	185 (128, 259)	506 (325, 751)	106 (66, 161)	256 (151, 388)	144 (90, 205)	517 (337, 747)	17 (10, 26)	56 (34, 87)
(%) PLC incidence	39 (32, 45)	35 (27, 40)	23 (17, 28)	19 (14, 23)	32 (25, 37)	40 (33, 44)	4 (3, 5)	4 (3, 5)
Females								
ASIR (per 100k)	13.05 (6.29, 23.13)	20.29 (10.37, 34.08)	23 (12.74, 36.77)	39.43 (23.03, 58.63)	8.45 (3.98, 15)	20.72 (10.64, 34.48)	3.81 (1.85, 6.93)	8.74 (4.72, 14.76)
Incidence count	54 (34, 81)	209 (133, 311)	99 (68, 138)	401 (271, 545)	35 (20, 55)	197 (118, 303)	17 (10, 26)	90 (138, 58)
(%) PLC incidence	26 (19, 31)	22 (16, 26)	45 (39, 49)	42 (36, 45)	17 (12, 20)	22 (17, 27)	7 (6, 9)	9 (7, 11)

Footnote: Age-Standardized Incidence Rates (ASIR) were calculated for 5-year age-groupings, from 15-79, using the Global Burden of Disease (GBD) database, the direct standardization method, and either the 1990 or 2019 GBD 'Both Sex' standard populations. The (%) PLC incidence results are calculated as the proportion of ASIR by PLC subtype to the total PLC ASIR value. All single values represent point estimates, with adjacent ranges corresponding to lower and upper 95% confidence intervals estimates. Incidence counts reflect raw incidence count data from GBD. Subtype abbreviations are as follows: LCHB= Liver Cancer from Hepatitis B virus, LCHC= Liver Cancer from Hepatitis C virus, LCAL= Liver Cancer from alcohol consumption, and LCNASH =Liver Cancer from Non-Alcoholic Steatohepatitis.

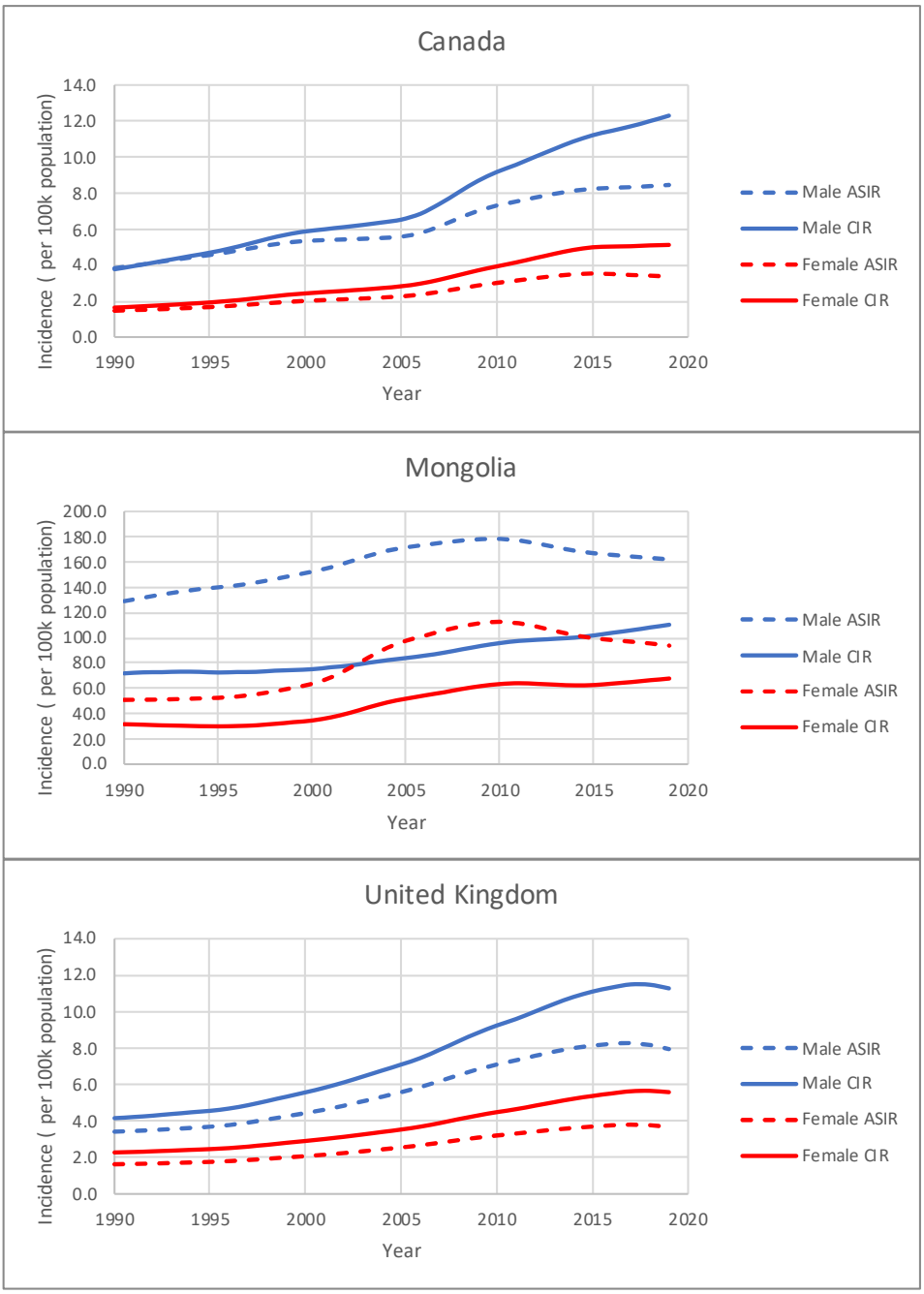
Table 3: Summary of net drift estimates and Wald chi-squared tests for heterogeneity across APC functions

	Point estimate (95% CI)	Wald χ^2 test statistic	df	P-value	
United Kingdom					
Males					
Net drift (% / year)	3.80 (3.27, 4.32)				
Net drift = 0		206.85	1	6.68E-47	*
All local drifts = net drift		5.02	13	0.97	
All period RR =1		232.41	5	3.25E-48	*
All cohort RR = 1		846.86	17	4.67E-169	*
Females					
Net drift (% / year)	3.47 (2.77, 4.17)				
Net drift = 0		96.30	1	9.86E-23	*
All local drifts = net drift		6.61	13	0.92	
All period RR =1		110.71	5	2.89E-22	*
All cohort RR = 1		440.08	17	7.50E-83	*
Canada					
Males					
Net drift (% / year)	2.89 (2.17, 3.62)				
Net drift = 0		62.80	1	2.29E-15	*
All local drifts = net drift		14.65	13	0.33	
All period RR =1		73.87	5	1.60E-14	*
All cohort RR = 1		272.31	17	5.63E-48	*
Females					
Net drift (% / year)	3.63 (2.63, 4.63)				
Net drift = 0		52.15	1	5.13E-13	*
All local drifts = net drift		1.47	13	1.00	
All period RR =1		60.96	5	7.70E-12	*
All cohort RR = 1		164.15	17	4.03E-26	*
Mongolia					
Males					
Net drift (% / year)	0.92 (0.08, 1.76)				
Net drift = 0		4.65	1	3.11E-02	*
All local drifts = net drift		6.07	13	0.94	
All period RR =1		16.08	5	6.61E-03	*
All cohort RR = 1		33.03	17	1.12E-02	*
Females					
Net drift (% / year)	2.20 (1.12, 3.30)				
Net drift = 0		16.19	1	5.72E-05	*
All local drifts = net drift		19.99	13	0.10	
All period RR =1		41.01	5	9.34E-08	*
All cohort RR = 1		144.00	17	3.63E-22	*

* denotes statistical significance (alpha = 0.05)

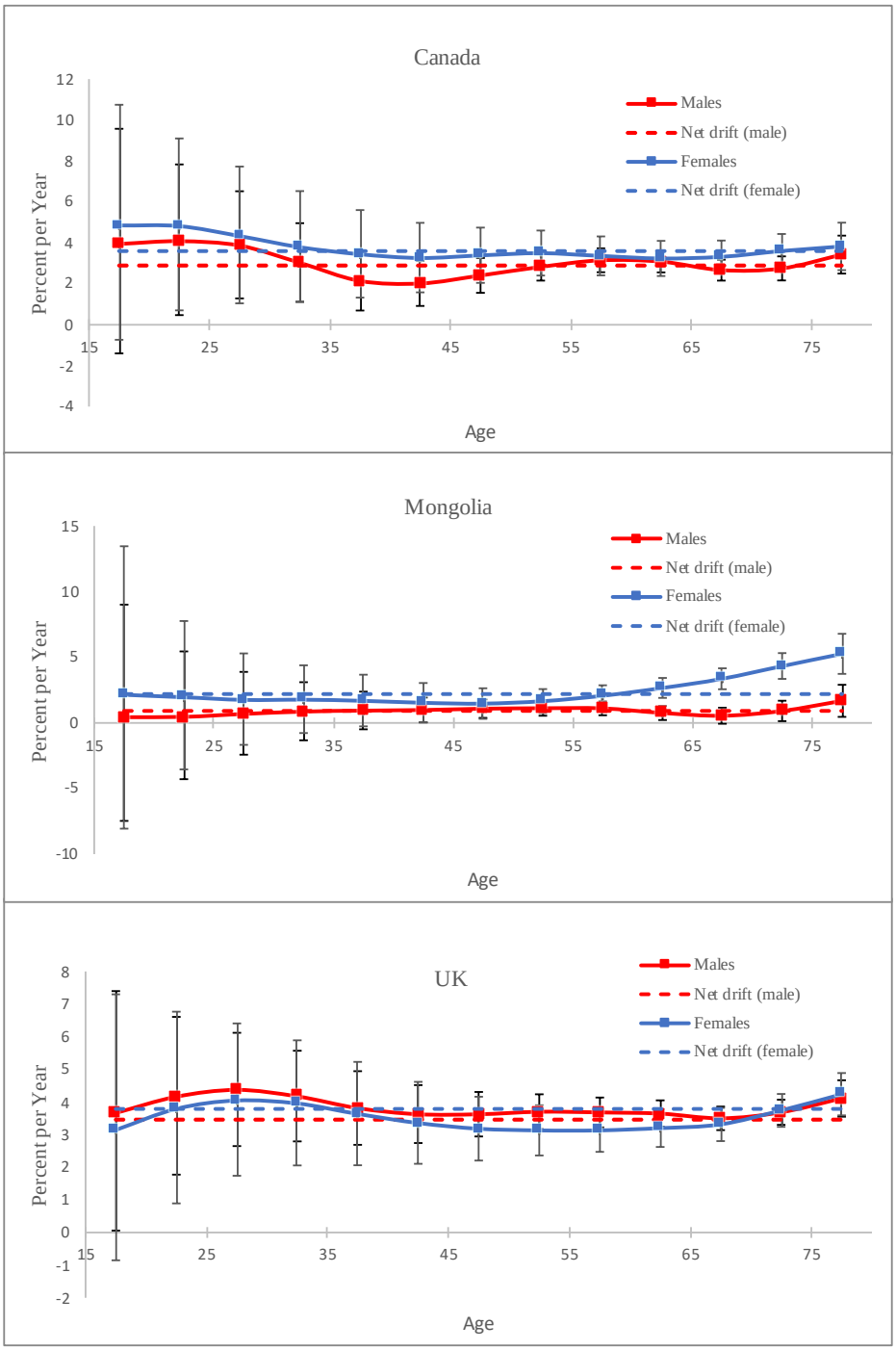
Footnote: Net drift is a single point estimate of the annualized percentage change of the age-standardized incidence rate over the 30-year observation period. Local drift, conversely, is the estimated annual change per year specific to an age group. The remaining features represent several null hypotheses and results associated with key Wald tests for heterogeneity generated the APC webtool.

Figure 1: Crude incidence rates and age-standardized incidence rates in Canada, Mongola, and the UK, from 1990 to 2019



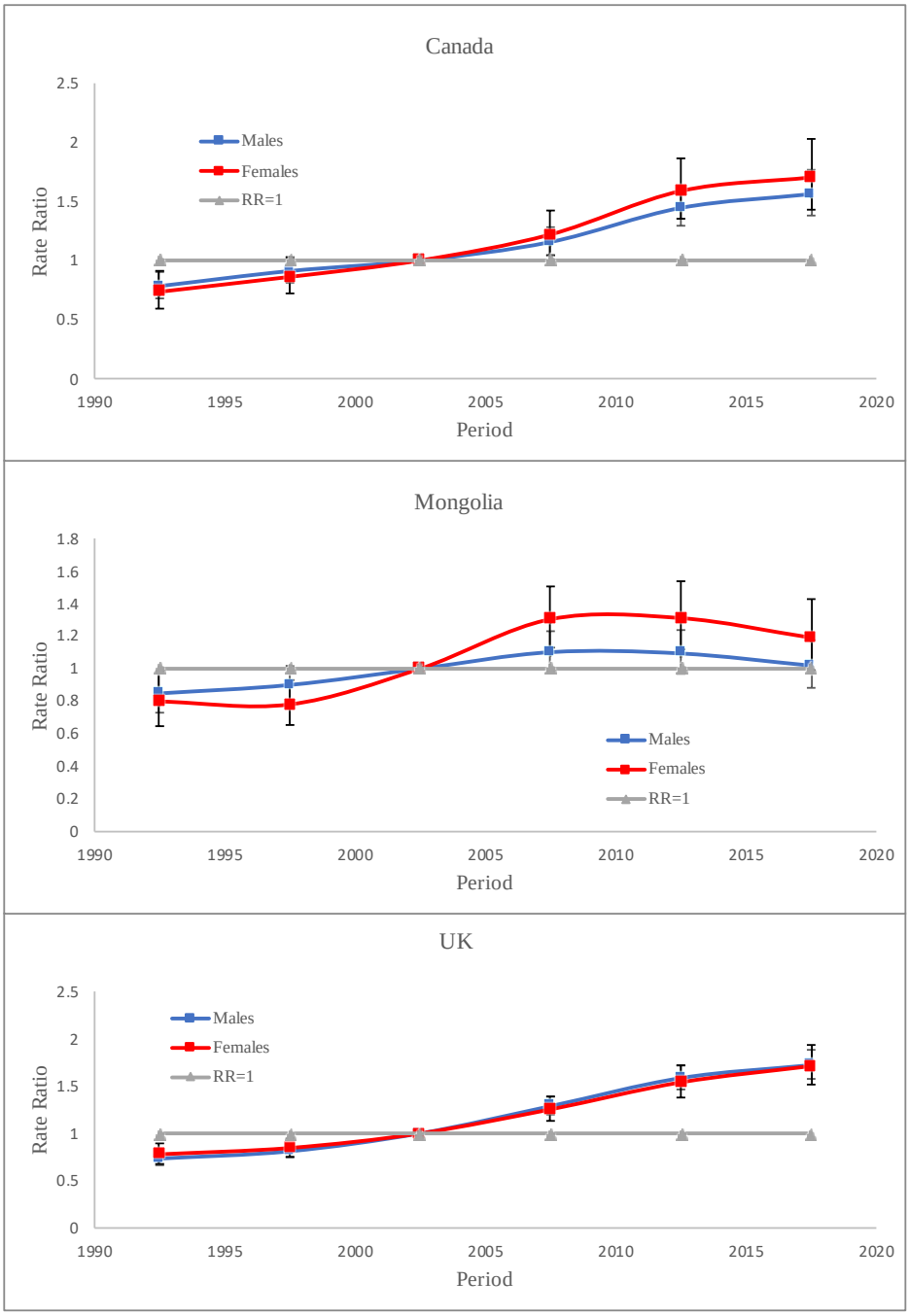
Footnote: Age-Standardized Incidence Rates (ASIR) were calculated for 5-year age-groupings, from 15-79, using the Global Burden of Disease (GBD) database, the direct standardization method, and either the 1990 or 2019 GBD 'Both Sex' standard populations. All single values represent point estimates.

Figure 2: Net and local drift estimates of incident primary liver cancer by country and sex



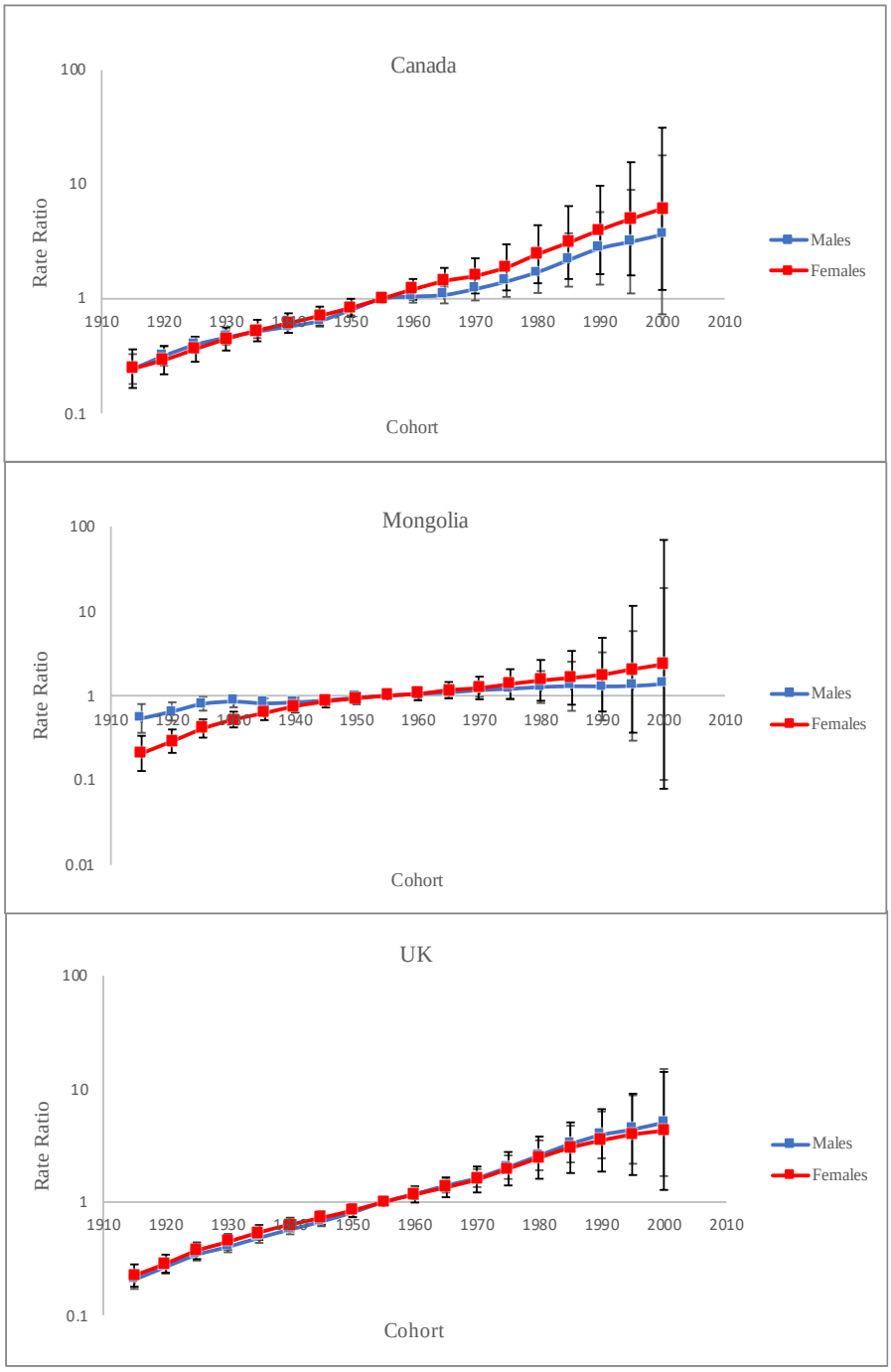
Footnote: Results generated using GBD PLC incidence and population data from 1990 to 2019, and the APC webtool (NIH Division of Cancer Epidemiology & Genetics). Error bars represent upper and lower estimates for 95% confidence intervals.

Figure 3: Estimated period effects of primary liver cancer incidence by sex in Canada, Mongolia, and the UK, from 1990 to 2019



Footnote: Results generated using GBD PLC incidence and population data from 1990 to 2019, and the APC webtool (NIH Division of Cancer Epidemiology & Genetics). Error bars represent upper and lower estimates for 95% confidence intervals.

Figure 4: Estimated cohort effects of primary liver cancer incidence by sex in Canada, Mongolia, and the UK, from 1990 to 2019



Footnote: Results generated using GBD PLC incidence and population data from 1990 to 2019, and the APC webtool (NIH Division of Cancer Epidemiology & Genetics). Error bars represent upper and lower estimates for 95% confidence intervals.

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