Received: 28 July 2023 | Accepted: 25 October 2023

DOI: 10.1002/lci2.77

Liver Cancer INTERNATIONAL WILEY

ORIGINAL ARTICLE

Geographic and temporal trends in aetiology, incidence and mortality from hepatocellular carcinoma in European Union 15+ countries

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Abstract

Background and Aims: Hepatocellular carcinoma (HCC) is the third leading cause of cancer mortality worldwide. This study considers the geographical trends in incidence and mortality from HCC.

Methods: Data were obtained for each EU15+ country from the Global Burden of Disease Study database. Age-standardised incidence rates (ASIRs), mortality rates (ASMRs) and disability-adjusted life years (DALYs) were extracted for each year from 1990 to 2019. Data were subdivided into males and females. Mortality-to-incidence ratios (MIRs) were calculated. All Indices were reported per 100 000 population, and trends were described using Joinpoint regression.

Results: ASIRs increased in 17/19 countries in females and 18/19 countries in males between 1990 and 2019. ASMRs increased in all countries except Italy (for both sexes) and Sweden (for females). MIR decreased in all countries except Denmark in males (+8.0) and females (+1.2). Ireland saw the greatest decline in MIR among females

Abbreviations: ASIRs, age-standardised incidence rates; ASMRs, age-standardised mortality rates; DALYs, disability-adjusted life years; EAPC, estimated annual percentage change; GBD, global burden of disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MIRs, mortality-to-incidence ratios; NAFLD, non-alcoholic fatty liver disease.

(−15.0%) and the United Kingdom for males (−16.4%). DALYs increased in all countries except Italy for males and females and Sweden for females.

Conclusions: The incidence of and mortality from hepatocellular carcinoma are increasing in the majority of EU15+ countries. The rise in mortality and fall in MIR may suggest that outcomes from HCC are improving, despite an increased disease burden.

KEYWORDS
aetiology, disability-adjusted life years, hepatocellular carcinoma, incidence, mortality

1 | INTRODUCTION

Primary liver cancer is the third leading cause of cancer mortality worldwide, causing around 830000 deaths in 2020.[1] It ranks 6th in global incidence, with approximately 900000 new cases diagnosed in 2020. Hepatocellular carcinoma (HCC) accounts for up to 85% of primary liver cancers and represents a major health problem. Among developing nations, hepatitis B virus (HBV) infection is the most common risk factor for HCC. In developed countries, hepatitis C virus (HCV) infection, chronic alcohol dependency and non-alcoholic fatty liver disease (NAFLD) are the most common risk factors for HCC.[2,3]

Trends in HCC incidence and mortality have fluctuated widely over recent decades. Incidence is falling across parts of southern Europe, East Asia and Japan.[4] In contrast, cases are rising across Australia,[5] the United States of America (USA)[6] and some European countries, including Austria, Germany and Switzerland.[7,8] Mortality rates appeared to level off between 2013 and 2015 in some studies, coinciding with the introduction of effective nucleotide/nucleoside analogues against HBV and direct-acting antivirals against HCV.[4,7–12] The main aetiologic factors for chronic liver disease and cirrhosis, the pre-malignant condition that underlies >80% of incident HCC cases, appear to be changing.[13] NAFLD is the fastest-growing cause of HCC in Western countries such as France, the United Kingdom, and the USA, highlighting the importance of identifying and addressing metabolic risk factors.[14] Globally, mortality from HCC remains high, likely resulting from a rising incidence of HCC and population ageing.[6,15]

Obtaining a precise understanding of the evolving trends in HCC incidence and mortality in Europe is important in a disease area characterised most recently by increasing efforts to promote screening and early diagnosis,[16] expanding criteria for radical therapy,[17] and widening options for systemic therapy leading to incremental benefit in survival.[18]

The main aim of this study was to compare the trends in HCC between countries of the European Union (EU) 15+ cohort from 1990 to 2019. The EU15+ grouping collectively refers to the following 19 countries: Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Norway, Portugal, Spain, Sweden, the United Kingdom and the USA. The EU15+ constitutes a comparable group of countries, which we have previously used for comparative analyses of national trends in non-HCC diseases.[19] Data were extracted from the GBD Study in order to evaluate the trends in hepatocellular cancer mortality, incidence and disability-adjusted life years (DALYs) during the period ranging from 1990 to 2019 among EU15+ countries. We used Joinpoint regression analysis to represent mortality, incidence and DALY changes and to assess significant trends during the studied time interval.

Key points

Liver cancer has become increasingly common across Europe. The proportion of people dying of the disease is also increasing but to a lesser extent, suggesting that overall outcomes are improving.

2 | METHODS

2.1 | Characteristics of the data source

This was an observational study looking at epidemiological trends in HCC. Data were obtained from the Global Burden of Disease (GBD) study, which includes annual mortality and morbidity data regarding a range of diseases from over 200 countries worldwide.[20]

Similar methods have previously been employed to track trends in other malignancies, such as thyroid cancer.[21] The GBD data were gathered from various sources, including electronic hospital records, surveillance and insurance data and autopsy reports. Bayesian meta-regression was used to adjust for bias using the DisMod-MR tool.[22] For hepatocellular cancer data, the GBD maps all mortality and incidence data related to the International Classification of Diseases (ICD) codes (codes C22-22.4, C22.7-22.9, Z85.05 from ICD-10 and codes 155-155.9, V10.07 from ICD9).

The quality of mortality data from each country was rated by the GBD methodology in a 5-star system by location-year to enable an assessment of the reliability of the cause of death data. The EU15+ countries have been previously analysed this way, with 10 of 19 scoring 5 stars (85%–100% completeness of mortality data) and the remaining nine countries scoring four stars (65%–84% completeness of mortality data). In spite of the variation in per-capita cost

expenditure by the countries, an internal comparison is conceivable since the health expenditure in these countries is high or equal to that of the United Kingdom, as previously shown by studies on the global burden of disease (GBD) analysis.[23]

2.2 | Handling of the GBD data

We extracted age-standardised incidence rates (ASIRs), age-standardised mortality rates (ASMRs) and disability-adjusted life years (DALYs) for hepatocellular carcinoma from EU15+ countries between 1990 and 2019 using the dedicated GBD Study results tool.[24] Age-standardised rates are used to account for the age structures of each country. The method used by the GBD involves calculating a standard population from the United Nations Population Division's World Population Prospects (2012 revision).[25]

We calculated absolute and relative changes in ASIRs, ASMRs and DALYs from 1990 and 2019 for each sex in each country (Table S1). The mortality-to-incidence indices (MIRs) were calculated by dividing ASMR by ASIR for each year (1990 and 2019) for both sexes in all EU15+ countries. MIRs allow for the crude comparison of disease burden by normalising mortality to incidence. A DALY incorporates morbidity and mortality figures to calculate the number of years lived with and lost from a disability. It is used by the WHO to indicate the overall disease burden on a health system.[26] These measures facilitate our understanding of hepatocellular cancer's varying temporal impact. Global mean trends are also reported for comparison.

2.3 | Statistical analysis

Joinpoint regression analyses of HCC incidence, mortality and DALY were performed using the Joinpoint Command Line Version 4.5.0.154. Trends over time among each domain in each country were modelled using a piecewise linear regression. The model starts with no Joinpoints and then subsequently adds additional Joinpoints where there is a change in the trends. A Monte Carlo permutation method is used to test for significance of each additional Joinpoint, until the addition of Joinpoint does not add a statistically significant improvement in the explanation of these data. Each period between a given Joinpoint is reported as a trend with an associated estimated annual percentage change (EAPC). This provides the opportunity to compare the changing trends over time between countries.

2.4 | Subgroup analysis

GBD sub-classifies HCC data into four sub-sets based on the possible causes, including Hepatitis B, Hepatitis C, alcohol and non-alcoholic hepatic steatosis. To better understand the contribution of individual risk factors to overall trends, we performed a stratified analysis of these four aetiologies for HCC.

3 | RESULTS

Trends in hepatocellular carcinoma (HCC) among EU15+ countries were observed from 1990 to 2019. Age-adjusted incidence, mortality, mortality-incidence ratio and disability-adjusted life years were examined in this study.

3.1 | HCC incidence

The incidence of HCC increased in 17/19 countries for females and 18/19 countries for males. Across the observation period, the greatest increase in age-standardised incidence rate (ASIR) was in Portugal (+211.79%), Ireland (+186.12%) and the United Kingdom (+146.31%) for males. The smallest increase in ASIR for males was in France (+19.06%), Luxembourg (+26.08%) and Austria (+45.66%). A reduction in ASIR was seen in Italy (−10.89%). Among females, a reduction in ASIR was found in Sweden (−7.39%) and Italy (−19.75%). Ireland (+149.92%), Australia (+144.36%) and the United Kingdom (+137.93%) had the greatest increase in ASIR among females. The smallest increase was seen in Belgium (+18.03%), Greece (+18.10%) and Spain (+24.99%). Globally, the incidence of HCC is falling among both males (−25.68%) and females (−30.49%) (Table S1; Figure 1).

3.2 | HCC mortality

An overall increase in mortality was observed in 18/19 countries for males and 17/19 countries for females. An overall reduction in ASMR was seen in Ireland for both males (−25.76%) and females (−30.77%) and in Spain among females (−12.02%). The greatest increase in ASMR was observed in Norway (+183.23%) and Greece (+139.43%) in males. Finland (+4.27%), Italy (+10.63%) and Austria (+25.18%) saw the smallest rise in ASMR over the observation period for males. Among females, Australia (+142.39%), Sweden (+119.97%) and Greece (+115.81%) had the greatest recorded rise in ASMR, with the smallest increase in Belgium (+5.19%), Germany (+7.88%) and Portugal (+12.98%). Globally, the mortality has fallen for both males (−32.30%) and females (−34.95%) (Table S1; Figure 2).

3.3 | HCC mortality-to-incidence ratio (MIR)

MIR decreased in all EU 15+ countries for males (19/19) and 18/19 countries for females. The largest reduction in MIR was observed in

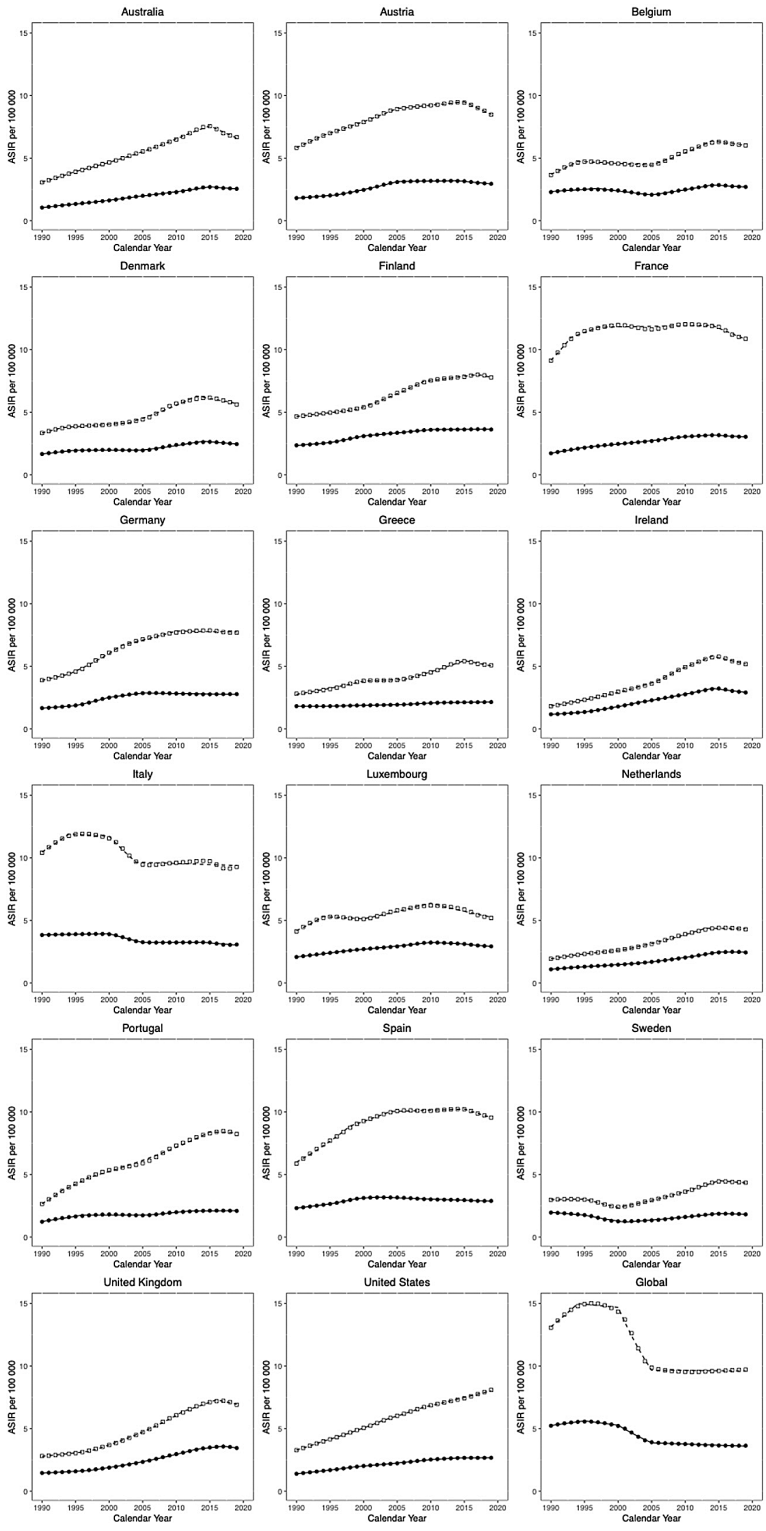

FIGURE 1 Trends in age-standardised incidence rates (ASIRs) for HCC in EU15+ countries between 1990 and 2019.

France (−17.71%) and Ireland (−16.69%), with the smallest reduction seen in Canada (−0.12%) and Spain (−5.07%) for males. In females, MIR increased in Canada (+7.97%) but decreased across Europe. The greatest reduction in MIR for females was in Denmark (−15.19%) and Austria (−14.32%). A slight reduction in MIR was seen in Australia (−0.81%) and Spain (−5.00%) for females. Globally, a fall in MIR was observed in both males (−8.90%) and females (−6.42%) (Table S1; Figure 3).

3.4 | Joinpoint (Males)

Estimated annual percentage change (EAPC) in MIR has fluctuated globally during the study period. By 2019 a more favourable trend was observed. A reduction in EAPC for MIR was identified in the United Kingdom, Norway and Finland. Among the remaining EU15+ nations, the EAPC for MIR decreased initially and then increased during the latter part of the observation period (Table S1).

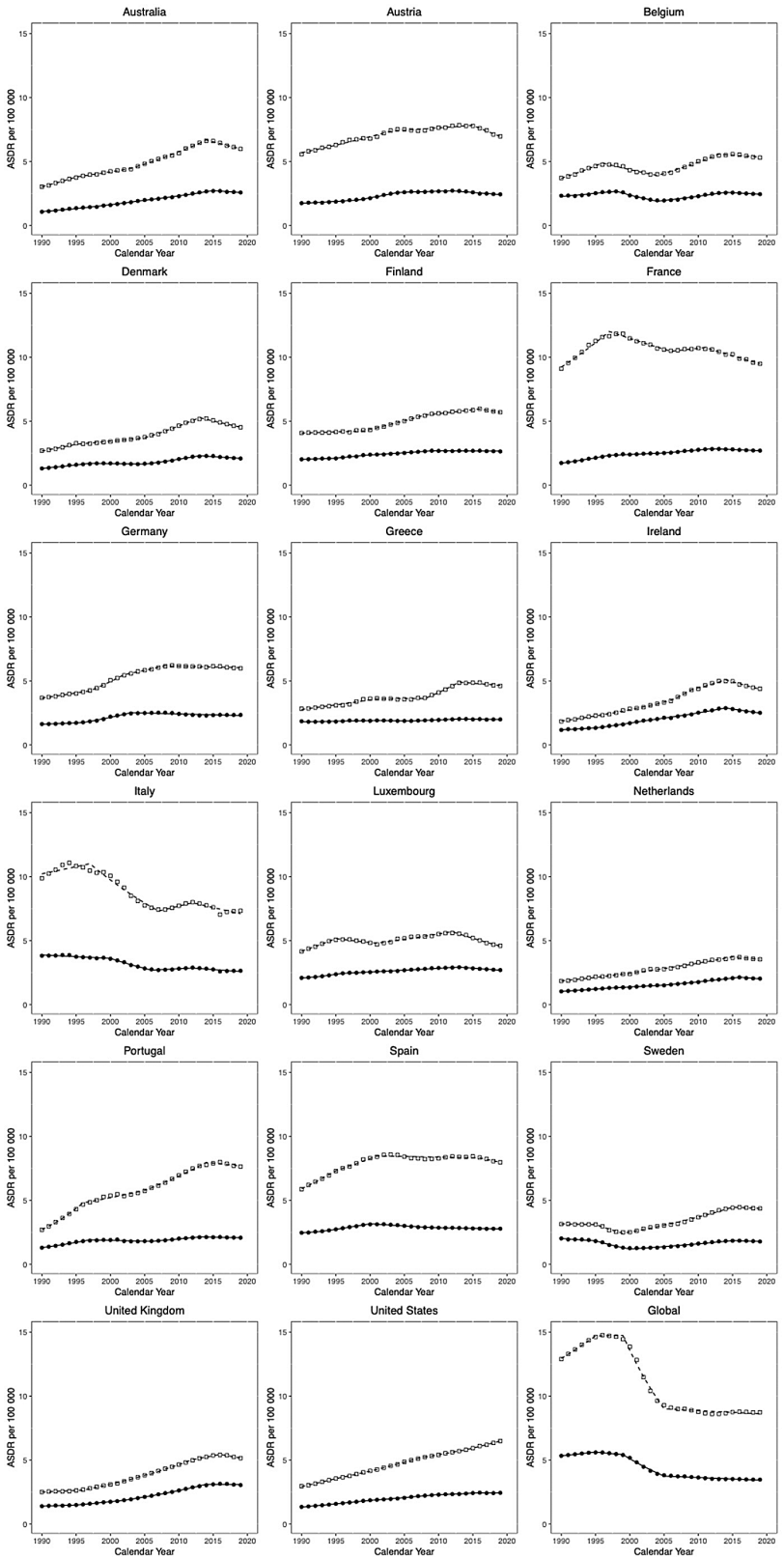

FIGURE 2 Trends in age-standardised mortality rates (ASMRs) for HCC in EU15+ countries between 1990 and 2019.

3.5 | Joinpoint (Female)

The greatest variability in EAPC was observed in Belgium, France, Germany and Portugal. EAPC for MIR fell consistently in Finland −1.1% (1990–2002), −0.2% (2002–2019) and the United Kingdom −0.4% (1990–2008), −0.1% (2008–2019). Among the remaining EU15+ countries, smaller fluctuations in EAPC were observed (Table S1).

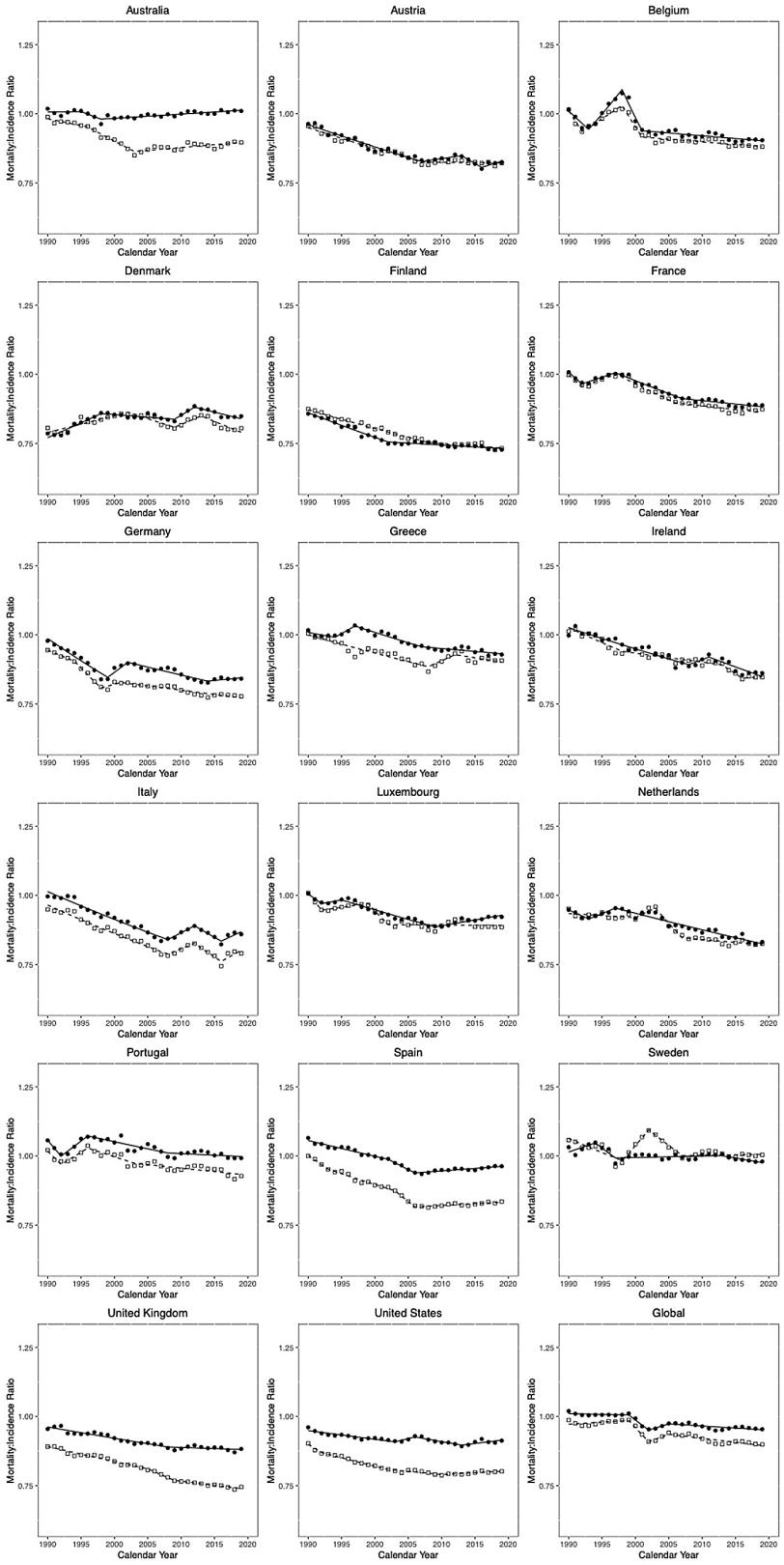

FIGURE 3 Trends in mortality-to-incidence ratios (MIRs) for HCC in EU15+ countries between 1990 and 2019.

3.6 | HCC disability-adjusted life years

Among males, DALYs increased in 18/19 countries between the start and the end of the observation period. In Ireland, however, there was an overall fall in DALYs (−29.61%). The greatest increase was seen in Norway (+174.69%) and Greece (+125.72%). The smallest increase was seen in Finland (+0.03%), Italy (+5.10%) and Austria (+13.04%). Among females, an increase in DALYs was observed in

17/19 countries. A reduction was seen in Ireland (−34.66%) and Spain (−17.46%). For the remaining countries, an overall increase in DALY was observed, with Australia (+120.80%), Sweden (+99.76%) and Greece (+99.18%) having the greatest increase. The smallest increase was seen in Belgium (+5.25%), Portugal (+7.54%) and Germany (+10.25%). Globally, however, there has been an overall reduction in DALYs for both males (−40.43%) and females (−43.31%) (Table S1; Figure 4).

3.7 | Subgroup analysis

3.7.1 | Hepatitis B virus-induced HCC

ASIR has increased in all EU15+ countries for both sexes, apart from Sweden among females (−11.50%) and Italy among males (−17.14%) and females (−26.52%). The greatest increase in male incidence was observed in Portugal, with a rise of 206.05%, followed by Ireland (+172.03%). Among females, the ASIR rose most significantly in Ireland (+132.68%). ASMRs fell across all EU15+ countries in males but only in 3/19 countries in females. Among females, rises in mortality during the observation period were greatest in Australia (+108.57%), Sweden (+105.17%), and Greece (+93.70%). DALY's increased across the majority of EU15+ countries, with 13/19 nations observing an overall increase in percentage change in both males and females. The greatest increase was in Norway in males (+163.04%) and Australia in females (+95.67%). In Ireland, DALY's decreased in both males (−36.07%) and females (−41.57%). MIR fell among all countries and both sexes apart from Canada in females (+4.91%). The greatest reduction in MIR was observed in Australia in males (−88.77%) and Ireland in females (−18.04%) (Table S2).

3.7.2 | Hepatitis C virus-induced HCC

ASIR increased in all nations apart from Italy in males (−5.17%) and females (−17.60%) and Sweden (−8.85%) in females. Portugal observed the greatest rise in males at 231.36% and Ireland in females (+151.84%). ASMR generally increased apart from in Ireland for both males (−19.96%) and females (−27.95%) and in Spain for females (−12.59%). Mortality rose by 202.66% in Norway among males, and the greatest rise among females was observed in Australia (+142.81%). A reduction in MIR was observed in all nations and both sexes apart from Canada (+1.01% in males and +9.00% in females). Among males, DALYs increased in 18/19 countries, with only Ireland observing a reduction (−24.24%). The USA and Greece saw the greatest rise in DALYs at 139.00% and 132.50%, respectively. Among females, DALYs increased in 17/19 countries, with the greatest increase in Australia (+128.38%). Decreases in DALYs were seen among females in Ireland (−31.82%) and Spain (−16.46%) (Table S3).

3.7.3 | Non-alcoholic steatohepatitis (NASH)-induced HCC

Among this cohort, incidence increased in all countries apart from Italy (ASIR −5.32% in males and −17.96% in females). Portugal, Ireland and Australia saw the greatest increase in incidence at 288.53%, 246.11% and 207.27%, respectively. Among females, the greatest rise was in Australia (+231.74%). ASMR's rose in all nations apart from Ireland (−20.13% in males and −28.70% in females). Canada was the only country to have an increasing MIR (+0.04% in males and +8.27% in females). The largest fall in MIR was in France in males (−17.92%) and Denmark in females (−15.64%). DALYs rose across all EU15+ countries apart from Ireland (−24.93% in males, −32.56% in females) and Spain (−4.61% in females). The greatest rise in DALYs was in Norway for males (+246.68%) and Australia for females (+202.78%) (Table S4).

3.7.4 | Alcohol-induced HCC

ASIR's have increased in all EU15+ countries, apart from Italy (−17.06% in males, −27.28% in females) and Sweden (−8.66% in females). The greatest rise in ASIRs was in Portugal for males (+201.68%) and Ireland for females (+155.19%). ASDRs increased in the majority of countries apart from Finland (−3.47%) and Ireland (−30.84%) in males, and Germany (−0.07%), Portugal (−2.51%), Spain (−12.95%) and Ireland (−37.69%) in females. MIR fell in all countries apart from Canada (+0.26% in males and +7.45% in females). DALYs increased in 17/19 countries among males and 16/19 countries for females. A fall in DALYs was seen in Finland (−6.12%) and Ireland (−33.87%) in males. In females, a reduction was observed in Portugal (−5.41%), Spain (−17.83%) and Ireland (−40.27%) (Table S5).

4 | DISCUSSION

In contrast to the decreasing burden of many oncological diagnoses, HCC continues to be a steadily increasing public health problem. In our study, we found that the incidence and mortality from HCC were increasing in the majority of the EU15+ countries. However, although incidence has increased, there is a fall in MIR, suggesting survival from HCC may be improving despite the increased disease burden.

The primary aim of this study was to compare trends among EU15+ countries with respect to mortality, incidence and DALYs associated with hepatocellular carcinoma. Trends from 1990 to 2019 were studied using the GBD study data and Joinpoint regression analysis. The results were consistent with the findings of prior reports.[5–9]

We found the greatest increase in ASIR in Portugal for males and in Ireland and Australia for females. However, these

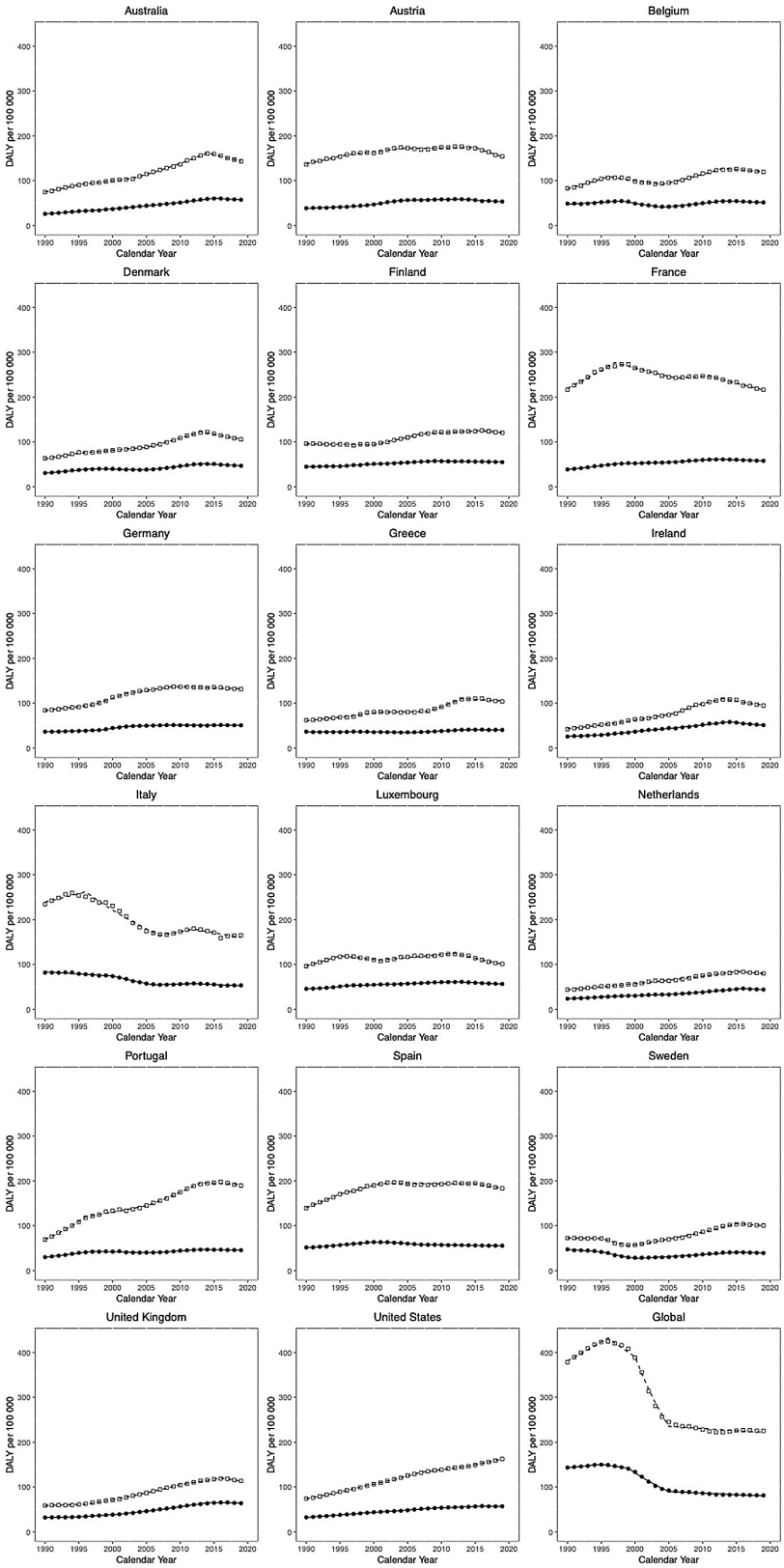

FIGURE 4 Trends in disability-adjusted life years (DALYs) for HCC in EU15+ countries between 1990 and 2019.

countries did not experience the greatest rise in MIR. In fact, Portugal observed the third largest overall percent decrease in MIR among males, while Ireland and Australia decreased from 1990 to 2019 among females. We believe the decrease in MIR to be multicausal. Since 1990, there has been a progressive uptake of screening programmes and surveillance of patients with cirrhosis,[27] leading to an increase in the proportion of patients diagnosed with an early-stage disease where radical therapeutic

approaches are possible. Furthermore, the progressive diffusion and widespread adoption of standardised staging systems such as the Barcelona Clinic Liver Cancer (BCLC) algorithm (first proposed in 1999) have facilitated the optimal allocation of curative and palliative therapies across the various stages of the disease.[28] A previous study conducted in Ireland argued that surgical interventions were central to improving the survival of patients.[29] Lastly, the qualification[30] and subsequent expansion[17] of oncological criteria for liver transplantation in HCC, alongside improvements in multidisciplinary management[31] and approval of systemic therapies capable of prolonging survival in advanced disease,[32] have contributed to significantly expand the life expectancy of patients with HCC despite the ongoing increase in disease burden.

Earlier diagnoses and updates in screening methodologies and guidelines are unlikely to fully account for the increase in the incidence of HCC. HCC is the sequelae to a variety of diseases, including hepatitis B and C viruses, NAFLD and alcohol dependency. Changing patterns in the predominant cause of HCC have previously been documented in the literature. Studies are showing decreasing incidence of HCC in Japan[33] and increasing NAFLD-associated HCC in Western Europe and the USA.[14,34] This is concordant with our results, finding a decrease in the global incidence of HCC caused by HBV and HCV, opposing an increase in the global incidence of HCC related to NAFLD and alcohol dependency. Of note, up to 30% of cases of NAFLD-associated HCC occur in the absence of significant fibrosis, suggesting reduced effectiveness of routine screening protocols in this patient population.[35]

Our study identified a decrease in the global incidence of HBV-related HCC, which may be due to successful vaccination programmes lowering the incidence of HBV infections.[36] ASMR and MIR have decreased in both males and females in the last 20 years. Indeed, a drop of 70% in new HBV infections is expected in the next 20 years as a result of a continued HBV vaccination trend.[2] In contrast, an increase in HCC due to HBV is still present in countries such as Australia, Germany, Sweden, the United Kingdom and the USA. This finding in such high net-migration countries can partly be explained by the weight of undiagnosed and untreated HBV infection in patients from high-prevalence areas.[37] Thus, the management of HBV in these populations has yet to be broadly endorsed. However, a decrease in MIR was reported in all included countries of our study as a result of advancements in the treatment of HBV, such as the use of effective nucleotide/nucleoside analogues.[38,39] Evidence that nucleotide/nucleoside therapy positively influences postoperative recurrence of HCC provides further evidence of improving the utilisation of HBV treatment to reduce mortality outcomes in HCC.[40]

With respect to HCV, although our results showed a global decrease in the incidence of HCC secondary to HCV, we noted an increase in the incidence of HCV-related HCC in the majority of countries. This may be linked to unsafe blood transfusions at first, as the risk of developing HCV from an unidentified blood sample was about 20% in the 1970s, leading to increased cases of HCV in the following period.[41] After implementing screening for HCV in blood donors in 1990, a major contributing route of infection was unsafe injection drug use.[42] It was demonstrated that deaths from prescribed opioids increased in the USA from 2000 to 2010, followed by a continuous increase in heroin overdose mortality since 2010.[43] This may have been reflected in the increased incidence of HCV-related HCC during the studied period, which stresses the importance of prevention of HCV through testing and counselling with follow-up for persons who inject drugs (PWID). As for the treatment of HCV, high efficacy rates of direct-acting antiviral therapies (DAA) probably led to a decrease in MIR globally,[44] which must encourage its easy accessibility in the future, especially for PWID.

Our analysis showed an increase in age-adjusted incidence rates of NAFLD-related HCC in all countries, concordant with previous studies.[14,34] This may be due to population ageing as well as the growing prevalence of obesity and type 2 diabetes mellitus, which are considered risk factors for the progression to cirrhosis.[45] Diagnostic methods for NASH vary between countries. Liver biopsy for a histological diagnosis is widely considered the gold standard; however, noninvasive methods such as the FibroScan are increasingly utilised.[46] Interestingly, the global incidence of NASH in females has decreased, as has the incidence rates for males and females in Italy. Mortality, however, was noted to have decreased for both males and females globally and among individual countries. This will impact the recorded national incidence.

Alcohol dependency was also found to be an increasing cause of HCC in our study, reflecting the importance of designing strategies to tackle harmful alcohol use. Incidence rates for HCC secondary to alcohol use have increased globally and in most EU15+ countries in the last 20 years among males. The exception to this was in Italy, where cultural attitudes towards alcohol may be contributing to this observed trend. Among females, incidence rates globally have decreased. Although the majority of the EU15+ countries are noted to have an increase in the incidence of HCC secondary to alcohol, mortality due to alcohol-related HCC has decreased globally and in individual countries among males and females.

Although survival from an earlier diagnosis of HCC has improved, mortality remains high due to the disease's burden and population ageing.[6,15] DALYs were used to quantify the overall disease burden, which measures the number of years lost due to the disease. In our study, we found that Norway had the greatest increase in DALYs among males, whereas Australia had the greatest increase in DALYs among females. We identified that globally, DALYs were noted to have decreased since 1990 in males and females, with Ireland specifically noted to have the greatest decrease in DALYs among males and females since then. Cause-specific DALYs secondary to HBV and HCV are noted to have the greatest decrease globally among males and females. HCC secondary to NASH shows the greatest burden of disease as observed by the highest DALYs among individual

countries such as, although not limited to, the United Kingdom, USA, Australia and Norway.

Overall, although the incidence of HCC in the EU15+ countries has increased, this may be attributed to a combination of improvements in screening as well as a change in the etiologic factors for chronic liver disease. With this increase, we also note a global decrease in MIR and DALYs. Such trends are seen for HCC overall and are preserved when individual etiologic factors for HCC are considered. It is important to appreciate that changes in screening guidelines as well as techniques to detect HCC earlier, can partially explain these findings. These trends should continue to be followed to determine how the advancements in diagnosis and management, as well as the diverse influence of etiologic factors for HCC, continue to change and affect the incidence and mortality of HCC.

The GBD Study collaborators are transparent with regard to the limitations of using the GBD database,[33] and these limitations have previously been discussed.[9,10] Notable limitations specific to the present analysis include alterations in data coding systems and country-specific practice, including a transition from ICD 9 to ICD 10 over the study period. By mapping mortalities to causes of death lists, the GBD authors attempt to adjust for the different coding systems. Secondly, variability exists both within and across countries in the accuracy of death certification. Errors in death certification range from 39% to 61% worldwide,[47,48] and only 39% of deaths globally were registered in 2012. However, the top performing continents in relation to civil registration and vital statistics were Europe, the Americas and Australasia,[49] which augments the reliability of the data presented from EU15+ countries in this study. The GBD uses under-registration corrections and garbage code distribution algorithms to adjust for under-registration.[12,13] Finally, we stress that this is an observational analysis of the trends in the burden of HCC across 20 years in EU15+ countries. GBD provides subgroup data based on four possible causes. Further causal inferences should not be concluded. As with all observational analyses, there are likely contributory confounders that are not fully accounted for by using sex-specific, age-standardised incidence and mortality rates.

5 | CONCLUSION

In this observational study, we found increasing trends in incidence and mortality from HCC across the majority of the EU15+ countries. However, the observed decrease in MIR suggests that overall survival from HCC may be improving. Furthermore, we demonstrate that the predominant cause of HCC appears to be changing, with declining HBC and HCV-related HCC and increasing NAFLD-associated and alcohol-related HCC. Together, these data are of interest from a health policy and resource planning perspective. Therefore, further research is warranted to prevent ongoing increases in disease incidence from HCC and continue to improve overall survival.

AUTHOR CONTRIBUTIONS

Study concept and design by Georgina Hanbury and Dominic C. Marshall. Dominic C. Marshall acquired the data. All authors contributed to data analysis and interpretation as well as drafting and revising the manuscript. Dominic C. Marshall performed the statistical analysis. Study supervision was by Dominic C. Marshall and David J. Pinato. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

DJP is supported by grant funding from the Wellcome Trust Strategic Fund (PS3416) and infrastructural support from the NIHR Imperial Biomedical Research Centre.

CONFLICT OF INTEREST STATEMENT

DJP received lecture fees from ViiV Healthcare, Bayer Healthcare, EISAI, Roche and BMS; travel expenses from BMS, MSD and Bayer Healthcare; consulting fees for Mina Therapeutics, EISAI, Roche, Astra Zeneca, DaVolterra, Avammune Therapeutics; received research funding (to institution) from MSD and BMS. All remaining authors have declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data set analysed during the current study is available within the World Health Organization's GBD database.

ETHICS STATEMENT

Full ethical approval covers this work which has been carried out in accordance with the principles contained in the Declaration of Helsinki.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Data from the World Health Organization's GBD freely available and use does not require additional consent and approval.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Hanbury G, Jani C, Abdallah N, et al. Geographic and temporal trends in aetiology, incidence and mortality from hepatocellular carcinoma in European Union 15+ countries. *Liver Cancer Int*. 2023;4:109-120. doi:10.1002/lci2.77