Risk of hepatocellular carcinoma among individuals with different aetiologies of cirrhosis: a population-based cohort study

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SUMMARY

Background
Among patients with cirrhosis, only those determined to be at risk for hepatocellular carcinoma (HCC) should undergo surveillance. However, little is known about how different aetiologies of cirrhosis affect risk for HCC.

Aim
To quantify the cumulative incidence of HCC among a representative population of people with cirrhosis of the liver of varying aetiology.

Methods
We identified subjects with hepatic cirrhosis from the UK’s General Practice Research Database (1987–2006). Diagnoses of HCC were obtained from linked national cancer registries (1971–2006). Cox proportional hazards regression was used to estimate hazard ratios. The predicted 10-year cumulative incidence of HCC for each aetiology of cirrhosis was estimated while accounting for competing risks of death from any cause and liver transplant.

Results
Among 3107 people with cirrhosis, the adjusted relative risk of HCC was increased twofold to threefold among people with viral and autoimmune/metabolic aetiologies, compared to those with alcohol-associated cirrhosis. The 10-year predicted cumulative incidence estimates of HCC for each aetiology were alcohol, 1.2%; chronic viral hepatitis, 4.0%; autoimmune or metabolic disease, 3.2%; and cryptogenic, 1.1%.

Conclusions
In a population-based study in the UK, people with cirrhosis have an estimated cumulative 10-year incidence of HCC of 4% or lower. Cumulative incidence varies with aetiology such that individuals with alcohol or cryptogenic cirrhosis have the lowest risk for HCC. These findings provide important information for cost-effectiveness analyses of HCC surveillance.

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**INTRODUCTION**

Surveillance for hepatocellular carcinoma (HCC) has been suggested by some as an explicit indicator of quality of care in patients with cirrhosis. It remains, however, a highly controversial topic and a key aspect of such surveillance activities is whether or not they are cost-effective. It is self-evident that the incidence of HCC critically impacts on whether surveillance is cost-effective, and guidance from the American Association for the Study of Liver Diseases (AASLD) based on studies evaluating cost-effectiveness recommends that surveillance should only be undertaken in those whose risk of HCC is 1.5% per year or greater (or in hepatitis B 0.2% or greater). While cirrhosis is the most common underlying condition associated with HCC, the incidence of HCC in cirrhosis due to different aetiologies is not fully known. Whilst the most recent AASLD guidance suggests that the thresholds for HCC incidence to be cost-effective are exceeded in cirrhosis due to hepatitis B or C, primary biliary cirrhosis – now known as primary biliary cholangitis (PBC), genetic haemochromatosis and alpha-1 antitrypsin deficiency, it is explicitly recognised in this guidance that the risk of HCC is not accurately known in many relevant groups.

There is limited evidence to support the reported incidence of HCC, which may explain some of the documented lack of uptake of these guidelines. The available evidence is based principally on studies conducted in tertiary care centres on a small scale. These studies are prone to significant biases both in case selection, favouring the inclusion of those with more severe cirrhosis, and with respect to HCC ascertainment, employing active case finding. Recently, Danish evidence derived from a large population-based cohort reports 5-year cumulative incidence of only 1% in patients with cirrhosis of an alcoholic aetiology, with HCC barely contributing to the high mortality seen in these patients. Many studies suggest that other aetiologies of cirrhosis, particularly viral hepatitis, carry a greater risk of HCC. However, there is no study to date that has been able to accurately estimate the rate of HCC in patients with cirrhosis of varying aetiologies drawn from the same underlying population.

We therefore carried out a comprehensive population-based study of the risk of HCC in cirrhosis of all aetiologies with a view to improve the evidence-base through which recommendations to current HCC surveillance guidelines can be made to improve their cost-effectiveness.

**METHODS**

We conducted a cohort study using linked data from three sources. The General Practice Research Database (GPRD; now the Clinical Practice Research Datalink – CPRD) is a prospectively gathered, anonymised primary care database using data from more than 600 GP practices in the UK, between 1987 and the present. In brief, it provides all recorded primary care data on patients including clinical diagnoses, treatments and outcomes. Its validity has been tested in numerous studies; for example, a systematic review of 357 validation studies showed that overall, a high proportion of cases were confirmed for all diseases with a median of 89%, that is, 89 of 100 cases with a computerised diagnosis were confirmed based on additional internal or external information. Cancer diagnoses specifically have been validated directly against cancer registration information giving positive predictive values of a GPRD cancer diagnosis of 96% for lung cancer, 92% for urinary tract cancer, 97% for gastro-oesophageal cancer and 98% for colorectal cancer. Hospital Episode Statistics (HES) is a secondary care database containing data for all hospitalisations in England, including diagnoses and procedures. In total, 51% of English GPRD practices are linked to HES, from April 1997 onwards. Cancer registry data are provided by the National Cancer Intelligence Network and consist of two databases; the Merged Cancer Registry data (1990–2006, from English registries only) and the Office for National Statistics minimum cancer dataset (1971–2006).

We identified people with cirrhosis of the liver from subjects in the whole GPRD who had their first incident recording of cirrhosis, oesophageal varices or portal hypertension within their up to research standard GPRD data between 1987 and 2006 as we have previously described. In this previous study, we carried out a validation of the diagnosis in which, in order to assess the accuracy of the recording of the diagnosis of cirrhosis, paper records from the GPs were requested from a stratified random sample of patients with a diagnostic or therapeutic code for cirrhosis. The patients’ paper records (that includes letters from Consultant Hepatologists, liver biopsy results, etc.) were examined by a consultant hepatologist (GPA). Information was gathered on whether there was any record of cirrhosis, whether this had been confirmed by biopsy and whether there was any record of presumed aetiology of the cirrhosis. Three-quarters of these patients had definite evidence of cirrhosis in the available paper records. Of the 25% of cases where cirrhosis could not be confirmed, all bar one had evidence of chronic liver disease; they were cases of PBC,
alcoholic liver disease, Budd-Chari syndrome and autoimmune hepatitis. In subsequent work, we have demonstrated that approximately three-quarters of those people with a diagnosis of cirrhosis in their primary care record have an inpatient hospitalisation related to cirrhosis.\(^9\) Given that there is a reasonably high proportion of cases identified at a compensated stage of their disease and not all patients will require inpatient hospitalisation, this provides further evidence of the robustness for our definition.

We then restricted our population to only those who were registered in practices with linked cancer registry data. Presumed aetiology of cirrhosis of either alcohol-related, viral hepatitis (B and C), autoimmune or metabolic liver disease (i.e. PBC, haemochromatosis, alpha-1 anti-trypsin deficiency) or other unspecified causes of cirrhosis was defined using appropriate Read codes for these aetiologies. We also used information in the available laboratory results (e.g. hepatitis B and C positive results, anti-mitochondrial antibody) and linked HES [using International Classification of Diseases (ICD) 10 codes].\(^{20}\) We defined excess alcohol use if there was evidence in the primary or secondary care records of evidence of, for example, alcohol abuse, addiction or dependence, ‘problem drinking’ or referral to alcohol cessation services. Similarly, if the weekly alcohol consumption in their primary care records exceeded the Chief Medical Officer’s recommended amount (14 units for women, 21 units for men), these patients were ascribed as having alcohol-related cirrhosis. Aetiologies were assigned in a hierarchical fashion ordered chronic viral hepatitis, autoimmune disease, metabolic disease and alcohol excess. Those without any of these aetiologies were grouped together as cryptogenic cirrhosis. Once categorised, these groups were considered mutually exclusive for analysis purposes.

We identified people with HCC using the linked cancer registry data (data available from 1971 to 2006) using ICD 10 and ICD10-O-3 oncology codes.\(^{20}\) Where necessary, ICD\(^9\) codes were mapped to ICD10. We defined incident HCC as the first occurrence of a record in cancer registry data of a diagnosis coded with a four-character ICD10 code of C22.0 (malignant neoplasm, liver cell carcinoma) coupled with a histological classification of either 81703 (HCC NOS) or 80003 (neoplasm, malignant) in ICD-O-3.

**Statistical analysis**

Person-time at risk commenced at the first record of cirrhosis in the people with cirrhosis and ended when patients left a participating GP practice or died or the end of cancer registration follow-up (31 December 2006) or when liver transplant occurred, whichever came first. We assessed several baseline characteristics including whether the person with cirrhosis had evidence of decompensation (prior to and up to 30 days after entry) or diabetes mellitus. Incidence rates of HCC were calculated by dividing the number of cases of HCC by total person years of follow-up and are presented per 1000 person years with 95% confidence intervals. Hazard ratios for HCC were estimated comparing incidence rates by presumed aetiology using Cox proportional hazard’s regression adjusted for sex and age at the start of follow-up, smoking status, body mass index (BMI) and presence of diabetes mellitus, extracted prior to start of follow-up in the study. Model assumptions were checked by plotting proportional hazard and log minus log plots. We fitted a semi-parametric proportional hazards model (Fine–Gray method\(^{22, 23}\)) to estimate the predicted cumulative incidence function for occurrence of HCC accounting for the competing risks of death from any cause and liver transplant. These estimates were calculated at the mean value of all covariates in the model (age, sex, BMI, smoking status and diabetes mellitus) except the primary exposure, that is, aetiology of cirrhosis. All data management and statistical analysis were performed using **STATA** 14 MP2 (Statacorp, College Station, TX, USA).

**RESULTS**

We identified 3107 people with cirrhosis from practices with linked cancer registry data available. These subjects contributed 12 977 person years, respectively, to the analyses. Of the people with cirrhosis, 56% were classified as having a presumed aetiology of alcohol, approximately, 12% chronic viral hepatitis, 11% autoimmune or metabolic disease and the rest (21%) were classified as cryptogenic. Baseline characteristics such as age and sex varied statistically depending on which aetiology category people were in (Table 1). This was also true of all the other factors we measured. As expected, the aetiology with the greatest proportion of those with decompensation was alcohol, and in those with diabetes cryptogenic. More transplants occurred during follow-up in those with chronic viral hepatitis than any other group, whereas more deaths occurred in the alcohol and cryptogenic groups compared to the others.

**Absolute rate of HCC and variation with aetiology**

There were 51 incident cases of HCC in the whole population. Overall, the incidence rate among people with cirrhosis of all causes was 3.9 per 1000 person years or on
average 0.4% per annum. Absolute rates of HCC varied by age, sex and aetiology of disease and are displayed in Table 2. As expected, they were higher in men compared to women, at older ages and among those with a chronic viral aetiology. When mutually adjusted for age, sex, smoking status, BMI, diabetes mellitus and aetiology.

| Table 1 | Baseline characteristics (all in percentages except total number and follow up time), follow-up and events among the cirrhosis cohort, presented by aetiology group (n = 3107) |
|---------|-------------------------------------------------------------------------------------------------|
|          | Viral hepatitis | Autoimmune/metabolic | Alcohol | Cryptogenic | Chi squared |
| Total number | 374 | 343 | 1,743 | 647 |  |
| % Aetiology | 12.0 | 11.0 | 56.1 | 20.8 |  |
| Median follow-up (years) | 2.6 | 3.1 | 2.6 | 3.0 |  |
| Follow-up IQR (years) | 5.0 | 5.1 | 4.9 | 5.6 |  |
| Male | 61.5 | 32.1 | 65.5 | 47.8 | <0.001 |
| Age |  |
| 18 | 27.3 | 10.2 | 18.7 | 10.4 |  |
| 45 | 34.5 | 19.2 | 28.9 | 12.4 |  |
| 55 | 20.6 | 26.2 | 30.6 | 21.0 |  |
| 65 | 17.7 | 44.3 | 21.9 | 56.3 | <0.001 |
| BMI categories |  |
| <25 | 30.0 | 28.6 | 25.7 | 20.4 |  |
| ≥25 to 30 | 23.3 | 26.5 | 20.4 | 22.3 |  |
| ≥30 | 12.8 | 12.0 | 12.3 | 15.9 |  |
| Missing | 34.0 | 32.9 | 41.6 | 41.4 | <0.001 |
| Smoking status |  |
| Current | 35.0 | 16.0 | 39.8 | 13.8 |  |
| Ex | 11.2 | 18.1 | 11.2 | 15.6 |  |
| No | 28.9 | 42.3 | 19.3 | 36.6 |  |
| Missing | 24.9 | 23.6 | 29.8 | 34.0 | <0.001 |
| Diabetes mellitus | 13.6 | 11.1 | 13.0 | 20.1 | <0.001 |
| Decompensated at start of follow-up | 30.8 | 23.0 | 35.6 | 18.7 | <0.001 |
| Events |  |
| None | 65.8 | 61.5 | 57.3 | 55.5 |  |
| Hepatocellular carcinoma | 3.2 | 2.3 | 1.3 | 1.4 |  |
| Death | 27.3 | 33.5 | 40.9 | 42.7 |  |
| Liver transplant | 3.7 | 2.6 | 0.6 | 0.5 | <0.001 |

| Table 2 | Absolute incidence rates of HCC for all follow-up time and hazard ratios (for HCC incidence) and their 95% confidence intervals for the cirrhosis cohort by age, sex and aetiology |
|---------|-------------------------------------------------------------------------------------------------|
|          | Incidence rate per 1000 person years (95% CI) | Hazard ratio (95% CI)* |
| Sex | HCCs during follow up | Person years |  |
| Male | 42 | 7146 | 5.9 (4.3–8.0) | 1 |
| Female | 9 | 5831 | 1.5 (0.8–3.0) | 0.2 (0.10–0.44) |
| Age groups (years) |  |
| 18–44 | 6 | 2390 | 2.5 (1.1–5.6) | 1 |
| 45–54 | 9 | 3292 | 2.7 (1.4–5.2) | 0.85 (0.30–2.41) |
| 55–64 | 13 | 3674 | 3.5 (2.1–6.1) | 1.27 (0.47–3.42) |
| 65+ | 23 | 3621 | 6.4 (4.2–9.6) | 2.73 (1.05–7.10) |
| Aetiology |  |
| Alcohol | 22 | 6977 | 3.2 (2.1–4.8) | 1 |
| Chronic viral hepatitis | 12 | 1572 | 7.6 (4.3–13.4) | 3.22 (1.56–6.65) |
| Autoimmune and metabolic diseases | 8 | 1520 | 5.3 (2.6–10.5) | 2.7 (1.15–6.30) |
| Cryptogenic | 9 | 2908 | 3.1 (1.6–5.9) | 0.92 (0.42–2.05) |

*Adjusted for sex, age groups, smoking status, BMI, diabetes mellitus and aetiology.
using a Cox proportional hazards model, people with a chronic viral aetiology were three times more likely (HR: 3.22; 95% CI: 1.56–6.65) to develop HCC than those with alcohol-related cirrhosis. Those with metabolic or autoimmune diseases were also at increased risk compared to the alcohol group, whereas those with the assignment of cryptogenic cirrhosis had a similar incidence of HCC to the alcohol group.

**Estimated predicted cumulative incidence of HCC by aetiology after accounting for competing risks**

The estimated predicted cumulative incidence of HCC at 1, 5 and 10 years by aetiology among the people with cirrhosis is shown in Table 3. For alcohol and cryptogenic aetiology, the 10-year risk was less than 2%. The cumulative incidence functions for each aetiology are shown in Figure 1.

**DISCUSSION**

In this study, we have quantified the 10-year cumulative incidence of HCC among people with cirrhosis of the liver resulting from alcohol excess; chronic viral hepatitis; autoimmune or metabolic diseases; or of unknown cause using a large, representative, population-based cohort study. Overall, the incidence of HCC in all these groups was low regardless of aetiology. We found the highest 10-year cumulative incidence of HCC among those with cirrhosis due to chronic viral hepatitis; people with either chronic viral hepatitis or autoimmune/metabolic diseases underlying their cirrhosis had a twofold to threefold increased risk of HCC compared to those with alcoholic cirrhosis. However, in those people we identified as having alcohol as the presumed cause of their cirrhosis or no specific cause (i.e. cryptogenic cirrhosis), the 10-year cumulative incidence rates were less than 2% indicating that surveillance for HCC in these particular groups is unlikely to be cost-effective regardless of other parameters that could influence its cost or outcome.

**Strengths and limitations**

If there is imprecision in our definition of cirrhosis, the presumed aetiology we have ascribed or the ascertainment of incident HCC, our results may be incorrect to some extent. If we have either included people without cirrhosis in our disease cohort or missed people with the disease, we may have, respectively, overestimated or underestimated the incidence of HCC. For example, if we have included patients with alcoholic hepatitis or non-alcoholic steatohepatitis incorrectly as having cirrhosis when they do not, we will have underestimated the incidence of HCC in the alcohol and cryptogenic group, respectively. For the definition of cirrhosis, we have relied upon the accuracy of recording made by primary care physicians in the electronic health records of their patients following communication from hepatologists in secondary care about the diagnosis of cirrhosis the latter have made. We have previously validated this approach and shown that it is reliable. In this, the recording of cirrhosis mirrors that of a number of other chronic diseases for which validation studies have been conducted. In addition to this, our cohort is of roughly the same age and sex distribution as those reported previously from similar population based or hospital registries from England, Denmark and Sweden. For these reasons, we think it unlikely we have included many subjects without cirrhosis in our cirrhosis cohort. It is possible, however, that those people diagnosed with decompensated alcoholic cirrhosis via an emergency admission to hospital who then died rapidly while an inpatient may not have had their diagnosis transmitted to primary care for retrospective addition to their records. By this mechanism, we might fail to include some cases of cirrhosis. In the context of our study, that is, determining the risk of HCC for the purposes of deciding whether or not to carry out surveillance among people with alcoholic cirrhosis, the impact of having potentially excluded these individuals is minimal as they would contribute very little person-time at risk and few events during their subsequent follow-up time under surveillance. For the presumed aetiology of disease, we have comprehensively searched the primary and secondary care electronic records of the people with cirrhosis which include not only diagnostic and procedure records but also, where available, laboratory and

| Follow time (years) | Viral hepatitis | Autoimmune/metabolic | Alcohol | Cryptogenic |
|---------------------|-----------------|----------------------|---------|-------------|
| 1                   | 1.0             | 0.8                  | 0.3     | 0.3         |
| 5                   | 2.8             | 2.3                  | 0.9     | 0.8         |
| 10                  | 4.0             | 3.2                  | 1.2     | 1.1         |

Table 3 | Estimated cumulative incidence (%) of HCC accounting for competing risks of death and liver transplant by aetiology at 1, 5 and 10 years of follow-up
test results. However, we must acknowledge that small variations in the number of cancers diagnosed among each of the aetiologies of liver disease due to misclassification of the aetiology could have led to some differences in our findings. However, with respect to the classification of aetiology, our approach is similar if not more comprehensive than previous work. For example, our ascertainment of excess alcohol use is likely to have been more comprehensive than studies reliant solely on secondary care data. Despite the challenges of assigning aetiology, our distribution of the aetiology of cirrhosis is very similar to that reported from northern European countries that have assembled similar cohorts. By assuming that where a specific aetiology is recorded, for example autoimmune liver disease, that it is solely the cause of cirrhosis in a hierarchical manner we will have inevitably introduced some misclassification. We have chosen to do this purposefully as despite the large size of our cohort, it is not large enough to permit us to determine precise rates of HCC among those with multiple aetiologies (e.g. those with a recording of both alcohol excess and an autoimmune liver disease). The effect of our mutually exclusive categorisation is that the rates we have provided may be overestimates of the risk in those with a single aetiology further up our hierarchy if, as has been suggested, those with more than one aetiology have an increased risk. For the ascertainment of incident HCC, we have used the linked national cancer registry data which is a method analogous to that carried out in previous reports from Sweden and Denmark. We have used a specific ICD 10 code for HCC coupled with an oncology classification of histology in our definition to avoid, as far as possible, misclassification of, for example, metastatic liver cancer or cholangiocarcinoma which can otherwise occur.

We were able to adjust for some important confounders (smoking status, BMI and diabetes mellitus) in our multivariate Cox regression model but we did not have good data available on other potential confounding factors such as ethnicity which may have led to some residual confounding being present by this covariate. In addition, due to the small numbers of events within each mutually exclusive aetiological category, we were unable to present meaningful stratified cumulative incidence rates by any of these covariates to assess for evidence of interactions. We have however taken account of the potential competing risks of death from any cause and liver transplant on the incidence of HCC via the predicted cumulative incidence functions estimated in our analysis.

**Other literature**

Few studies have been able to study the risk of HCC for these aetiologies among one cohort identified from the same population-based source in the manner that we have. The best data for comparison we believe are those derived from the Swedish and Danish registry studies. In 1998, Sorensen et al. reported HCC risks among people with cirrhosis diagnosed in Denmark between 1977 and 1989 of alcoholic, chronic hepatitis, PBC and cryptogenic aetiologies. Their approximate crude rates for both alcohol and cryptogenic cirrhosis appear fairly similar to ours (3.4 and 2.5 per 1000 person years, respectively). In addition, a more recent analysis of the same data but limited to patients with alcoholic cirrhosis diagnosed between 1993 and 2005 by Jepsen et al., reported annual and cumulative 5-year incidence rates of 0.4% (95% CI: 0.34–0.47) and 1% (95% CI: 0.8–1.8), respectively, having excluded the first year of follow-up. Kuper et al. carried out a similar study using Swedish data and reported cumulative 15 year risks of HCC of 6.2% (95%: CI 1–12.5) for those with chronic viral hepatitis and 1.1% (95% CI: 0.8–1.5) for those with alcoholic cirrhosis. Studies from elsewhere in Europe, Japan and the United States of America have all reported higher rates of HCC for the
REFERENCES

1. Kanwal F, Kramer J, Asch SM, et al. An explicit quality indicator set for measurement of quality of care in patients with cirrhosis. Clin Gastroenterol Hepatol 2010; 8: 709–17.
2. Lederle FA, Pocha C. Screening for liver cancer: the rush to judgment. Ann Intern Med 2012; 156: 387–9.
3. Sangiovanni A, Colombo M. Surveillance for hepatocellular carcinoma: a standard of care, not a clinical option. Hepatology 2011; 54: 1898–900.
4. Arguedas MR, Chen VK, Eloubeidi MA, Fallon MB. Screening for hepatocellular carcinoma in patients with hepatitis C cirrhosis: a cost-utility analysis. Am J Gastroenterol 2003; 98: 679–90.
5. Lin OS, Keffe EB, Sanders GD, Owens DR. Cost-effectiveness of screening for hepatocellular carcinoma in patients with cirrhosis due to chronic hepatitis C. Aliment Pharmacol Ther 2004; 19: 1159–72.
6. Sarasin FP, Giostra E, Hadengue A. Cost-effectiveness of screening for detection of small hepatocellular carcinoma in western patients with Child-Pugh class A cirrhosis. Am J Med 1996; 101: 422–34.
7. Bruix J, Sherman M. American Association for the Study of Liver D. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020–2.
8. Davila JA, Morgan RO, Richardson PA, Du XL, McGlynn KA, El-Seraq HB. Use of surveillance for hepatocellular carcinoma among patients with cirrhosis in the United States. Hepatology 2010; 52: 132–41.
9. Fattovich G, Pantalena M, Zagni I, Realdi G, Schalm SW, Christensen E. Effect of hepatitis B and C virus infections on the natural history of compensated cirrhosis: a cohort study of 297 patients. Am J Gastroenterol 2002; 97: 2886–95.
10. Velazquez RF, Rodriguez M, Navascues CA, et al. Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. Hepatology 2003; 37: 520–7.
11. Mancebo A, Gonzalez-Diezuz ML, Cadahia V, et al. Annual incidence of hepatocellular carcinoma among patients with alcoholic cirrhosis and identification of risk groups. Clin Gastroenterol Hepatol 2012; 11: 7.

Clinical implications

Our study contributes important information to the on-going debate about the utility and implementation of surveillance for HCC among people with cirrhosis. In the AASLD guidelines on this subject, it is stated that ‘for patients with cirrhosis of varying aetiologies, surveillance should be offered when the risk of HCC is 1.5% per year or greater’ based on cost-effectiveness modelling. In the United Kingdom, a Health Technology Assessment economic model found that annual surveillance with a willingness to pay threshold of £30 000 per Quality Adjusted Life Year was only just cost-effective for alcoholic liver disease. Given that our study has found far lower risks of HCC than were used in these economic models, it seems highly likely that if they were repeated they would find that surveillance was not cost-effective. Although there may be particular patients with combinations of risk factors where surveillance is warranted, our results imply that universal surveillance should not be undertaken on the basis of alcoholic aetiology or in cryptogenic cirrhosis and is likely to be of debatable value in autoimmune and metabolic causes of cirrhosis.

AUTHORSHIP

Guarantor of the article: Joe West.

Author contributions: JW conceived and designed the study, performed the research (acquired the data, carried out the analysis) with contributions from KMF and TRC, and wrote the manuscript; KMF, TRC and GPA all contributed to the interpretation of the study and commented on the manuscript. All authors approved the final version of the manuscript.

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LINKED CONTENT

This article is linked to Brennan and Bathgate papers. To view these articles visit https://doi.org/10.1111/apt.14013.
12. Ikeda K, Saitoh S, Koida I, et al. A multivariate analysis of risk factors for hepatocellular carcinoma: a prospective observation of 795 patients with viral and alcoholic cirrhosis. *Hepatology* 1993; 18: 47–53.

13. Mair RD, Valenzuela A, Ha NB, et al. Incidence of hepatocellular carcinoma among US patients with cirrhosis of viral or nonviral etiologies. *Clin Gastroenterol Hepatol* 2012; 10: 1412–7.

14. Jepsen P, Ott P, Andersen PK, Sorensen HT, Vilstrup H. Risk for hepatocellular carcinoma in patients with alcoholic cirrhosis: a Danish nationwide cohort study. *Ann Intern Med* 2012; 156: 841–7, W295.

15. Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: clinical practice research datalink (CPRD). *Int J Epidemiol* 2015; 44: 827–36.

16. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol* 2010; 69: 4–14.

17. Dregan A, Moller H, Murray-Thomas T, Gulliford MC. Validity of cancer diagnosis in a primary care database compared with linked cancer registrations in England. *Population-based cohort study. Cancer Epidemiol 2012; 36: 425–9*

18. Fleming KM, Aithal GP, Solaymani-Dodaran M, Card TR, West J. Incidence and prevalence of cirrhosis in the United Kingdom, 1992–2001: a general population-based study. *J Hepatol* 2008; 49: 732–8.

19. Ratib S, West J, Crooks CJ, Fleming KM. Diagnosis of liver cirrhosis in England, a cohort study, 1998-2009: a comparison with cancer. *Am J Gastroenterol* 2014; 109: 190–8.

20. International Statistical Classification of Diseases and Related Health Problems. 10th Revision ed. Geneva: World Health Organisation, 1992.

21. International Classification of Diseases: manual of the international statistical classification of diseases, injuries and causes of death. 9th revision ed. Geneva: WHO, 1975.

22. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; 94: 496–509.

23. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation* 2016; 133: 601–9.

24. Sorensen HT, Friis S, Olsen JH, et al. Risk of liver and other types of cancer in patients with cirrhosis: a nationwide cohort study in Denmark. *Hepatology* 1998; 28: 921–5.

25. Kuper H, Ye W, Broome U, et al. The risk of liver and bile duct cancer in patients with chronic viral hepatitis, alcoholism, or cirrhosis. *Hepatology* 2001; 34: 714–8.

26. Roberts SE, Goldacre MJ, Yeates D. Trends in mortality after hospital admission for liver cirrhosis in an English population from 1968 to 1999. *Gut* 2005; 54: 1615–21.

27. Donato F, Tagger A, Gelatti U, et al. Alcohol and hepatocellular carcinoma: the effect of lifetime intake and hepatitis virus infections in men and women. *Am J Epidemiol* 2002; 155: 323–31.

28. West J, Wood H, Logan RF, Quinn M, Aithal GP. Trends in the incidence of primary liver and biliary tract cancers in England and Wales 1971-2001. *Br J Cancer* 2006; 94: 1751–8.

29. Khan SA, Emadossadaty S, Ladep NG, et al. Rising trends in cholangiocarcinoma: is the ICD classification system misleading us? *J Hepatol* 2012; 56: 848–54.

30. Trichopoulos D, Bamia C, Lagiou P, et al. Hepatocellular carcinoma risk factors and disease burden in a European cohort: a nested case-control study. *J Natl Cancer Inst* 2011; 103: 1686–95.

31. Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. *Gut* 2005; 54: 533–9.

32. Thompson Coon J, Rogers G, Hewson P, et al. Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis. *Health Technol Assess* 2007; 11: 1–206.