Risk of Liver Cancer in acute Hepatoporphyria Patients: A Meta-Analysis of Cohort Studies

Chen Zhang*, Yaqian Xiao, Qiaobo Wu

The First Clinical College of Hubei University of Medicine, No. 30, Renmin South Road, Maojian District, Shiyian, Hubei Province, 442000, China.

Abstract

Objective: The intention of this meta-analysis was once to elucidate the impact of hepatic porphyrias on the chance of hepatic carcinoma. Methods: For the current study, three databases, PUBMED, EMBASE, and Cochrane Library, were selected for the literature search until July 31, 2022, using the Medical Subject Headings (MeSH) and keywords, and the required cohort studies, case-control studies, and cross-sectional studies would be included. All statistical analyses were performed using Stata statistical software version 16.0. The Funnel plot and Egger's test were used to evaluate publication bias. Results: In total, 4 cohort studies involving 2838 individuals were included in the final analysis. The occurrence of hepatic porphyria was associated with the development of hepatocellular carcinoma (OR=34.738; 95% CI: 19.310-62.494, I²=65.0%, P=0.036). We found that women with acute hepatic porphyria had a significantly higher risk of hepatocellular carcinoma than men after subgroup analysis using gender. For the male group, the combined OR=22.564 (95% CI: 11.532-44.149, I²=29.1%, P =0.235). For the female group, the combined OR=26.032 (95% CI: 0.823-822.467, I²=95.9%, P=0.000). Conclusions: The development of hepatic porphyria increases the occurrence of hepatocellular carcinoma, and hepatic porphyria evidence is an independent risk factor for the development of liver cancer.

Keywords

Tuberculosis, initial treatment of smear-positive, case management

1. Introduction

Globally, liver cancer is the most frequent fatal malignancy. Because of its anatomical location and tissue structure as well as its unique metabolic and immunosuppressive environment, liver cancer is often accompanied by cancers of other organs [1]. Patients are often diagnosed with liver cancer in advanced stages, contributing to its poor prognosis. Of all liver cancer cases, >90% are hepatocellular carcinomas (HCC) [2]. With an estimated incidence of >1 million cases by 2025 [3]. Primary liver cancer is the third leading cause of cancer-related death worldwide. HCC almost exclusively developed in patients with chronic liver disease, driven by a vicious cycle of liver injury, inflammation and regeneration that typically spans decades [4]. Primary liver cancer (PLC) is one of the most common malignancies, accounting for 9% of all cancer-related mortality worldwide [5]. Thus, identification of modifiable risk factors for primary prevention of liver cancer is urgently needed. The well-established risk factors of liver cancer include chronic infection with hepatitis B virus (HBV) [6] or hepatitis C virus (HCV) [7], heavy alcohol consumption [8], metabolic diseases such as obesity [9] and diabetes [10], and aflatoxin exposure
However, a large proportion of cancer cases worldwide cannot be explained by current known risk factors [12]. Therefore, early identification and intervention of risk factors associated with liver cancer may be a way to prevent the development of liver cancer.

Acute hepatic porphyrias (AHP) are genetically inherited disorders that result from heme biosynthesis enzyme deficiencies and comprise four forms: acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), and ALA-dehydratase porphyria (ALADP) [13]. Currently available studies have explored the risk of developing adipose disease and hepatocellular carcinoma [14] and the treatment of hepatocellular carcinoma [15]. To date, many current studies have explored the link between acute hepatic porphyria and hepatitis virus infection [16]. There are also a small number of cohort studies on acute hepatic porphyrias and the risk of cancer development [17]. However, the effect of acute hepatic porphyria on hepatocellular carcinoma has not received much attention. There was also no meta-analysis of the association between acute hepatic porphyria and the risk of hepatocellular carcinoma. We speculate that acute hepatic porphyria may be associated with an increased risk of liver cancer. Thus, we systematically reviewed existing population-based longitudinal evidence to determine the association between acute hepatic porphyria and liver cancer risk.

2. Methods

This meta-analysis was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021). The protocol was preregistered on the International Prospective Register of Systematic Reviews (PROSPERO) platform, and the approval number is CRD42022348772.

2.1 Data Sources and Searches

Cohort studies, case-control studies, and cross-sectional studies published in PubMed, Embase, and the Cochrane Library from database creation to July 31, 2022 were searched. The search strategy had no language restrictions and used a combination of medical subject headings (MeSH) and keywords. The search terms included Liver Neoplasms; Liver Neoplasm*; Hepatic Neoplasm*; Liver Cancer*; Hepatocellular Cancer*; Hepatic Cancer*; Porphyrias, Hepatic; Hepatic Porphyria*. The full search strategy is in the Supporting Information 1.

2.2 Eligibility Criteria

The inclusion criteria were (1) patients: subjects participating in liver cancer studies; (2) exposure factors: acute hepatoporphyria; (3) controls: healthy individuals; and (4) outcomes: risk of liver cancer. We excluded irrelevant studies based on the following criteria: (1) publications in non-English languages; (2) publications with only abstracts or unpublished studies; (3) review, meta-analysis, and conference abstract articles.

2.3 Study Selection

Two investigators (ZC and XYQ) independently screened the literature according to the inclusion and exclusion criteria. First, we checked the titles and abstracts of the selected papers and excluded irrelevant articles. Second, the complete texts of all included studies were reviewed according to the inclusion and exclusion criteria. Duplicate and irrelevant articles were first excluded according to their titles and abstracts. Thereafter, the full text of the potentially eligible articles was downloaded and read to identify all eligible studies. Any disagreements were resolved by the third reviewer (WQB), who acted as an arbitrator.

2.4 Data Extraction

Data extraction was done independently by the two reviewers mentioned above (ZC and XYQ), who referred to the guidelines for systematic evaluation and meta-analysis data extraction. They used pre-designed tables to extract the first author, year of publication, study type, follow-up time, country, age, risk ratio of developing liver cancer, and confounding factors. Disagreements were resolved through discussions with reviewers (WQB) to reach consensus.

2.5 Risk of Bias Assessment

The quality of the cohort studies was assessed using the Newcastle-Ottawa Scales (Wells et al., 2014). The stars are 0 ~ 9 (cohort studies), 4 (selection of study subjects and exposure measures), 2 (comparability), and 3 (adequacy of outcomes and follow-up), with more stars being associated with higher study quality. We classified 0-3 as low quality, 4-6 as moderate quality, and 7-9 as high quality. The specific scores are in Supporting Information 2.

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2.6 Statistical Analysis

Each trial was adjusted for the Odds Ratio (OR) and 95% Confidence Interval (CI) to assess the association between hepatic porphyria and hepatocellular carcinoma. If P≥0.1 and I²≤50%, a fixed-effects model was adopted. If I²>50% (which indicated great heterogeneity), a random-effects model was adopted. The sensitivity analysis was performed by excluding one study each time and rerunning to verify the robustness of the overall effects. The funnel plot was visually inspected to confirm publication bias, and the Egger’s regression test was used to statistically assess publication bias. We conducted a subgroup analysis based on gender. All statistical analyses were performed using Stata statistical software version 16.0 (Stata Corp, College Station, Texas).

3. Results

3.1 Literature Search

164 outcomes were identified. After title and abstract screening, 15 articles were considered potentially relevant. 4 studies [17-20] were included after full-text review, and all 4 articles reported the incidence of hepatocellular carcinoma at follow-up. The selection process is shown in Figure 1.

3.2 Study Characteristics

This meta-analysis included four cohort studies involving 5454452 individuals published from 1999 to 2022. Four studies were prospective cohort studies. All of the study-worthy individuals in these cohorts were followed up for a longer period of time. The adjusted estimates were available for almost studies even though the adjusted confounders are slightly different. The main characteristics of the included trials are shown in Table 1.

3.3 Quality Assessment

The average score of the included studies was 8.25 stars (9 stars for two studies, 8 stars for one study, and 7 stars for one study), indicating that the cohort studies included in this meta-analysis were of high quality. The scores of the included studies are shown in Table 1.

3.4 Acute Hepatoporphyria and Risk of Liver Cancer

Four cohort studies [17-20] explored the association between hepatic porphyria and hepatocellular carcinoma. Pooled correlational information analysis showed that a history of hepatic porphyria was associated with an increased risk of liver cancer (OR=34.738, 95% CI: 19.310-62.494, I²=65.0%, P=0.036; Figure 2). Sensitivity analysis showed that none of the individual studies had reversed the pooled-effect size, which means that the results are robust.

3.5 Subgroup Analysis

We performed a subgroup analysis by sex and still did not find a source of heterogeneity, and in this subgroup, women with hepatic porphyria had a slightly higher risk of liver cancer than men (Figure 3).

3.6 Publication Bias

The funnel plot of the current study was approximately symmetrical, and a further test of symmetry yielded (P=0.826>0.05), meaning that the funnel plot was symmetrical and there was no evidence of significant publication bias for hepatic porphyria and the risk of developing liver cancer, and there was no publication bias in the current study (Figure 4).

4. Discussion

Four cohort studies involving 2838 subjects were included in this meta-analysis to comprehensively evaluate the relationship between acute hepatic porphyria and hepatocellular carcinoma. We found a significantly increased risk of hepatocellular carcinoma in patients with acute hepatic porphyria, with an overall risk increase of 34.738-fold compared with non-porphyria controls, and more significantly in women than men. This suggests that acute hepatic porphyria may be an independent risk factor for hepatocellular carcinoma. In previous studies, articles have investigated the association between acute hepatic porphyria and the risk of liver cancer and demonstrated that acute hepatic porphyria is an independent risk factor for liver cancer [21], but there is no relevant meta-analysis type literature. Therefore, this is the first meta-analysis to evaluate the risk of acute hepatic porphyria and hepatocellular car-
cinoma.
Porphyrias are a heterogeneous group of diseases that may lead to disabling or life-threatening visceral symptoms and/or cutaneous photosensitivity. Conventional treatment with human hemoglobin, which is effective in reducing symptoms, does not reverse neuropathy in the event of structural nerve damage and may lead to severe phlebitis [22]. Acute hepatic porphyria results from an inborn error in heme synthesis, where a deficiency of a specific enzyme in the heme synthesis pathway causes acute hepatic porphyria. Strong evidence from rodent models supports the role of genetic factors in HCC risk, and this evidence allowed us to identify the number and chromosomal location of loci that influence genetic susceptibility to chemically induced hepatocarcinogenesis in mice and rats. DNA testing identifies familial mutations and enables screening of family members. Management includes eliminating triggers whenever possible, and intravenous hemoglobin is the most effective treatment for acute attacks. Carbohydrate loading is sometimes used for mild seizures. Periodic seizures, if frequent, can be prevented with GnRH analogs. The primary manifestations of acute porphyria are neurologic symptoms, including neurologic abdominal pain, peripheral neuropathy, and psychiatric disturbances. In addition to its highly variable neurologic signs and symptoms, acute porphyrinas differs from other porphyrias by the common overproduction of the porphyrin precursors ALA (an amino acid) and porphyrin bilinogen (a pyrrole). This distinctive biochemical feature has implications for the pathogenesis of neurological manifestations. The triggering of acute attacks is related to environmental or hormonal factors, such as drugs, diet, and steroid hormones that induce ALAS1 leading to excessive production of ALA and porphobilinogen (PBG).

A total of 830,000 liver cancer deaths were reported worldwide, accounting for about 9% of cancer mortality, the third highest. Hepatocarcinogenesis is a very slow process in which genomic changes progressively alter the hepatocyte phenotype. The incidence of hepatocellular carcinoma is increasing due to the prevalence of cirrhosis and chronic hepatitis. Producing cellular intermediates that evolve into hepatocellular carcinoma. During the long pre-tumor stage, where the liver is usually the site of chronic hepatitis, cirrhosis or both, the hepatocyte cycle accelerates this process through upregulation of the mitotic pathway, in part through epigenetic mechanisms. This results in the generation of monoclonal populations of abnormal and dysplastic hepatocytes with telomere erosion and telomerase re-expression, sometimes with microsatellite instability and occasional structural aberrations of genes and chromosomes. The appearance of dysplastic hepatocytes and hepatocellular carcinomas in lesions and nodules is associated with the accumulation of irreversible structural alterations in gene chromosomes, but the genome of the malignant phenotype is heterogeneous. The malignant hepatocyte phenotype may arise due to the disruption of multiple genes that function in different regulatory pathways, resulting in multiple molecular variants of hepatocellular carcinoma. Previous articles have investigated the mechanisms by which AHP leads to HCC: the development of HCC in patients with AHP may be related to the long-term effects of excessive ALA secretion and low melatonin balance levels leading to increased free radical species in the patient's liver tissue.

In the subgroup, women with a history of acute hepatic porphyria had a significantly higher risk of developing liver cancer than men. There is a correlation between the development of acute hepatic porphyria and oral contraceptive use, with this article showing that 25% of women with acute hepatic porphyria are associated with oral contraceptive use. We speculate that the difference in the risk of liver cancer from direct acute hepatic porphyria in men and women may be caused by oral contraceptive use.

To the best of our knowledge, our meta-analysis is a summary of the available evidence suggesting an association between acute hepatic porphyria and the risk of liver cancer. This suggests that we need to pay more attention to the risk of liver cancer in people with acute hepatic porphyria, which also facilitates the early identification of people at high risk of liver cancer.

5. Conclusion
Our meta-analysis suggests that acute hepatic porphyria increases the risk of hepatocellular carcinoma. However, we need more studies to confirm the underlying pathophysiological mechanisms behind this phenomenon. The results of our meta-analysis have great implications for finding new prevention and treatment strategies for hepatocellular carcinoma.

5.1 Contribution to the Field Statement
Our meta-analysis was designed to summarize the available evidence on the association between acute hepatic porphyrias and the risk of liver cancer and to show that acute hepatic porphyrias are a risk factor for liver cancer.

5.2 Conflict of Interest
The authors declare that the study was conducted without any business or financial relationships that could be
interpreted as potential conflicts of interest.

5.3 Authors’ contributions

ZC and WQB conceived the study. ZC and XYQ cell phone data and drafted the manuscript. ZC revised the manuscript and language. XYQ performed the subgroup analysis. All authors have read and approved the manuscript.

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Availability of data and materials

The authors make the raw data supporting the conclusions of this paper available to any qualified researcher without reservation.

References


