A Systematic Review and Meta-analysis of the Effect of Hepatitis B, Hepatitis C, Smoking, Alcohol Consumption, and Aflatoxin B1 on Chronic Liver Cancer

Abstract

Liver cancer is a life-treating illness due to growing tumors in the human liver. This systematic review and meta-analysis were designed based on literature spanning between 1982 and 2022 to assess the interaction between the risk factors (chronic hepatitis B virus (HBV), chronic hepatitis C virus (HCV), tobacco smoking, alcohol consumption, and aflatoxin B1 (AFB1)) and hepatocellular carcinoma (HCC). A random effect model is utilized to pool the effect size from the results of individual studies, with subsequent tests for publication bias, heterogeneity, and sensitivity analyses. Among the 55 case-control and cohort studies, 17 were on chronic HBV (with a total of 1220 cases), 15 studies on chronic HCV (with 1377 cases), 10 studies on smoking (with 3669 cases), 10 studies on alcohol (with 2581 cases), and 3 studies on AFB1 (with 208 cases) were used for meta-analysis. The summary odds ratio (OR) for chronic HBV and chronic HCV were 6.78 (95% CI: 5.35-8.60), and 8.91 (95% CI: 7.10-11.18), with heterogeneity I^2= 25% (p>0.05) and 17% (p>0.05), respectively. The calculated pooled effect size for tobacco and smoking was 1.50 (95% CI: 1.27-1.76) with I^2=0% (p>0.05). The summary effect size obtained from random effect meta-analysis models revealed for alcohol consumption and AFB1 were 1.57 (95% CI: 1.30-1.90), and 1.95 (95% CI:1.33-2.58), with I^2= 21%(p>0.05), and 0% (p>0.05), respectively. The result of this meta-analysis suggested a positive association betweenchronic HBV, chronic HCV, tobacco smoking, alcohol consumption, and AFB1 with HCC. This study also revealed low heterogeneity and minimal publication bias.

Keywords: Liver Cancer, Meta-Analysis, Hepatitis, Alcohol Consumption, Aflatoxin

1. introduction

Liver cancer is a chronic tumor that often develops in conjunction with liver cirrhosis and liver dysfunction. (Liu, Chen, and Chen 2015). The extraordinary heterogeneity of liver cancer causes a complex molecular and cellular landscape of the interactions between different molecules and cells, whichmakes it difficult to prevent (Li and Wang 2016). Early identification through diagnosis, screening, and treatment can help reduce infections and mortality (WHO (World Health Organization) 2022). Despite advanced treatments, liver cancer remains a formidable global challenge. Around 10 million people died, and 19.3 million new cases were reported globally in 2020 (Bosch et al. 2004;Sung et al. 2021). Shockingly, new cases are projected to increase by 55.0% from 2020 to 2040, with an estimated 1.4 million new diagnoses (Rumgay, Arnold, et al.

2022).

Liver cancer can either originate within the liver, referred to as primary liver cancer (PLC), or result from the spread of tumors from other regions, leading to secondary liver cancer (Shen et al. 2012). In most cases, two types of PLC include hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) (Rumgay, Ferlay, et al. 2022). HCC is often caused by liver cirrhosis, biliary cirrhosis, hemochromatosis, and Wilson's disease, while ICC is associated with cholangitis, cholelithiasis, choledochal cysts, and inflammatory bowel disease (Welzel et al. 2011). However, the prevalence of HCC is higher than the prevalence of ICC, with 70%85% instances of HCC and 10% to 20% of ICC (Mohammadian et al. 2018; Palmer and Patel 2012; Srivatanakul, Sriplung, and Deerasamee 2004). The incidence rate of liver cancer varies globally, with lower rates in certain regions like South-Central and Western Asia and higher rates in East and Southeast Asia, the Middle East, and Western Africa (Liu et al. 2015).

Since the beginning, researchers have been striving to ascertain the incidence and risk factors and suggested control strategies for liver cancer. Key risk factors of liver cancer comprise HBV (hepatitis B virus), HCV (hepatitis C virus), alcohol consumption, tobacco use, excess body fat, and aflatoxins (Akinyemiju et al. 2017; Lu et al. 1999). The World Health Organization stated human papillomavirus (HPV) and hepatitis together cause about 30% of cancer cases in low and lower-middle-income countries (WHO (World Health Organization) 2022). In 2019, hepatitis B, hepatitis C, and alcohol consumption were significant contributors to liver cancer-related fatalities, accounting for 39.57%, 29.26%, and 18.73%, respectively (Yang et al. 2022). Recent investigations identified that alcohol consumption, diabetes, obesity, and chronic viral hepatitis B and C elevate the incidence of ICC (Orcutt and Anaya 2018). Moreover, a study in Southern China revealed that HBV significantly impacts the infection of HCC (Gao et al. 2004). Another study in the USA suggested HCV infection is a significant risk factor for ICC and discovered a substantial positive correlation between smoking and ICC (Shaib et al. 2005). In Italy, it was revealed that HCV and HBV are the leading causes of ICC (Donato et al. 2001). In addition, excessive drinking and cigarette smoking significantly increase the risk of HCC (Shen et al. 2020) (Tanaka, Hirohata, and Takeshita 1988; Yu et al. 1988). Multiple investigations have established a linear relationship between blood AFB1 dietary intake and the risk of HCC (Anitha et al. 2014; Long et al. 2009, 2011).

A comprehensive review giving pooled estimates of cancer-related prevalence has not been broadly conducted, and this study aims to address those limitations. By analyzing existing literature, the goal is to provide insights into the effects of various risk factors, including chronic HBV, chronic HCV, smoking, alcohol consumption, and aflatoxin B1 (AFB1). The findings aim to contribute valuable information for better recognition, control, and treatment of cancer-related issues, guiding future interventions. Researchers and policymakers can utilize the findings to comprehensively understand the current state of cancer, including new developments, challenges, and research limitations.

2. Methods

2.1. Data sources and paper selection

This study carried out a systematic review by applying the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist of items. A comprehensive survey of the literature was carried out, including the published articles till October 7, 2023, concentrating on the impact of various risk factors (HBV, HCV, smoking, alcohol consumption, and AFB1) on liver cancer. The articles were collected from different publishers like Elsevier, Wiley, Springer, SAGE, Nature, Oxford University Press, Taylor & Francis, PLOS, and BMJ based on the combination of keywords such as the impact of chronic HBV on liver cancer, the impact of chronic HCV on liver cancer, the effect of smoking on liver cancer, the impact of alcohol consumption on liver cancer, Impact of AFB1 on liver cancer.

A total of 3,33,115 papers were initially obtained from different publishers based on the initial searched keywords. All the papers were independently screened by 2 reviewers and included only 39 relevant papers following the four-phase diagram of PRISMA (Figure 1). Among the 39 articles, most of the studies were taken from Willy (12) and Elsevier (12), 7 from Springers, 2 from both Taylor & Francis and 2 from Nature, and 1 from Oxford University Press, SAGE, PLOS, and BMJ, respectively. There were other factors like oral contraceptives, type 2 diabetes mellitus, gender, race, inherited metabolic diseases, exposure to carcinogenic substances, and geographic variation impacting liver cancer. However, in this meta-analysis, we only considered the five most impacting factors: chronic HBV and HCV, smoking, alcohol consumption, and AFB1. Selected studies conducted in different countries are presented in Figure 2. Most of the studies were performed in China (10), USA (9) and Italy (7). It also included countries Taiwan (5), Japan (3), West Africa (2), Serbia (1), Guatemala (1), and India (1). The publication years of the papers were also presented in Figure 3. Most of the studies were published between 2000-2008 and 2009-2018 year.

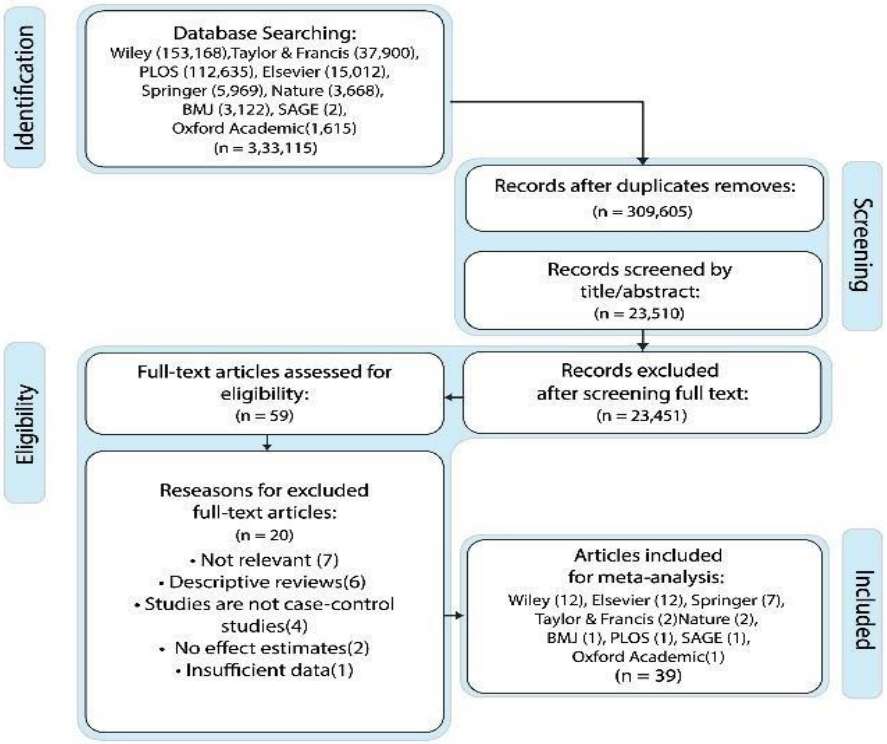

Figure 1: Four-phase flow diagram of the study search and selection.

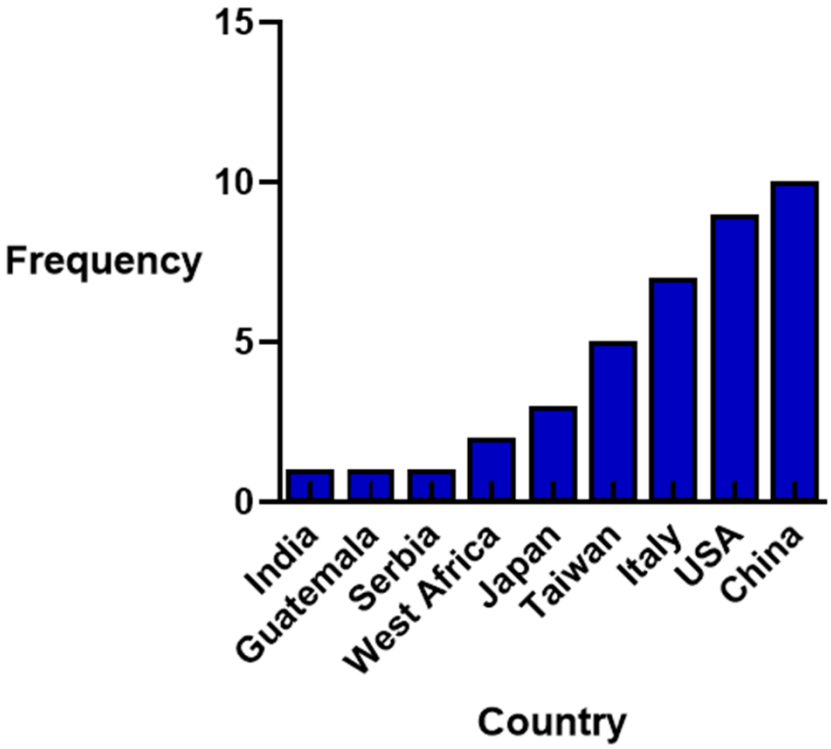

Figure 2: The number of articles found in different countries.

2.2. Inclusion and exclusion criteria

Studies that reflected the following requirements were added to the meta-analysis: (1) Case-control studies with HCC/ICC patients as cases and subjects without chronic liver diseases as controls; (2) Tested with hepatitis B surface antigen (HBsAg) for chronic HBV infection, serum anti-HCV+ for chronic HCV infection;(3) Frequency of data on smoking (tobacco use), alcohol consumption, AFB1; and (4) odds ratio with corresponding 95% confidence intervals (CIs). Exclusion criteria were: 1) Studies that did not have a case-control study, 2) Studies without HBsAg and Anti-HCV infection test for chronic HBV and HCV, respectively, and 3) Insufficient data on Alcohol consumption, Smoking, and AFB1.

2.3. Data extraction and quality assessment

Two authors systematically stored and independently extracted all the selected papers into pre-defined forms. The following extracted data was recorded in an Excel sheet containing the first column with author's name, the second with year of publication, subsequent columns were sample size, nation where the study was conducted, journal name, publisher, and number of individuals with HCC/ICC (cases) or without HCC/ICC (controls) who either had or did not have the relevant risk factor. The third investigator's decision resolved discrepancies between the two investigators.

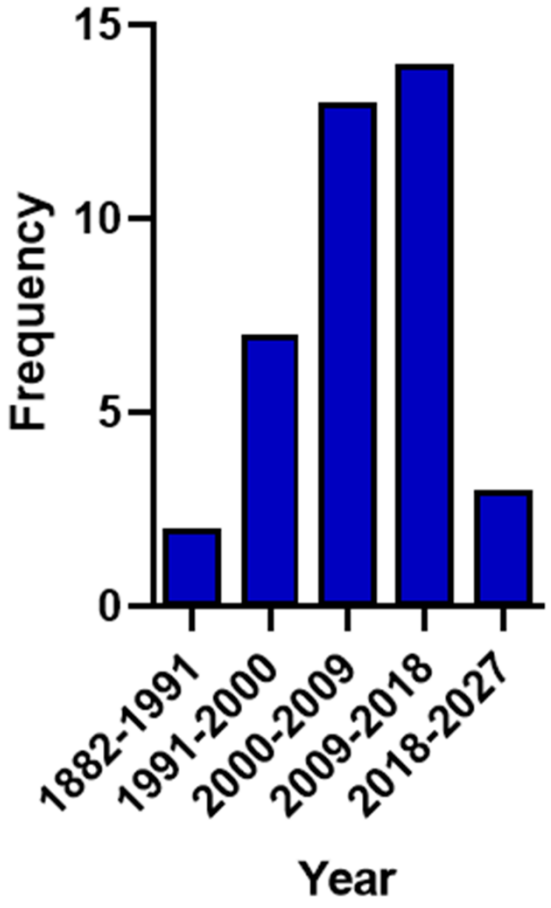

Figure 3 Number of articles published in different years.

2.4. Data synthesis

A meta-analysis was performed by combining various studies of each risk factor, calculating summary odds ratio (OR) to compare the incidence of case groups between different control groups with 95% confidence interval (CI). The risk of liver cancer among different factor types was pooled by the random-effects model Der Simonian and Laird described. The Hartung-Knapp adjustment method was used to reduce the study bias. Study heterogeneity was assessed using Higgins & Thompson's I^2 Statistic (directly based on Cochran's Q) and interpreted with the widely used and accepted rule of thumb $I^2 \leq 25\%$, indicating low, moderate, substantial, and considerable heterogeneity, respectively [21]. The High heterogeneity was removed by the basic outlier removal method and influential analysis with the leave-one-out method (sorted by I^2). Forest plots were also constructed for each risk factor analyzed. Statistical software R programming language (R version 4.3.1) was used to perform all analyses. The R package {meta} function metabin() was used to estimate the pooled effect size and associated confidence interval.

3 Results

3.1 Methodologies

Among 39 studies, 26 found chronic HBV infection has a significant impact on PLC, 23 found chronic HCV infection associated with PLC, 17 articles found an association of PLC with smoking, 21 with alcohol consumption, and 5 with AFB1 factors. The summary effect size was calculated for odds ratio (OR) in studies, followed by adjusted odds ratio (AOR) (9), risk ratio (RR) (3), and incidence rate ratio (IRR). The effect sizes of each factor were calculated using many statistical methods. Logistic regression analysis was used by 34 studies to calculate OR, RR, and AOR. One study used the Mantel-Haenszel estimate to calculate OR. RR using the log-linear model. IRR was calculated using the Poisson Regression model. This systematic review and meta-analysis were performed by reducing the study heterogeneity in each factor shown in (Supplement 1) and detecting publication bias shown in (Supplement 2).

3.2 Chronic HBV infection

Chronic infection with HBV has been confirmed by positive HBsAg in all studies. Among 26 case-control studies on chronic HBV infection, 9 were excluded for outliers. Then, the remaining 17 case-control studies of risk factor HBV were selected for meta-analysis. These studies provided 1,220 cases and 14,198 controls. A high chronic HBV seemed to be associated with the presence of HCC in most studies. In that case, we use OR to summarize multiple studies' results using a random effect model and constructing a forest plot (**Error! Reference source not found.**).Based on 95% CI for all respective studies, it is concluded that all studies are statistically significant except first (Francesco Donato), because the CI of odds ratio included value 1. Combined data from all 17 studies showed a trend for a positive association between HBV and HCC (OR: 6.78, 95% CI: 5.35-8.60). The odds ratio indicates, on average, that the chance of developing HCC is 6.78 times higher in those with chronic HBV than in individuals without HBV.However, a high p-value (0.16>0.05) indicates no heterogeneity among the studies considered in the meta-analysis. The random effect forest plot proves the positive association between HBV and HCC. A forest plot with

I^2=25% indicates low to moderate variability among the included studies. This indicates an acceptable level of consistency in the estimations across the papers in the meta-analysis. The higher weight indicates that studies likely have higher sample sizes and lower variability, making them more influential in pooled estimates. In this case, the study with a higher weight (>10) has a greater influence on the pooled estimate than the other studies. The larger length prediction interval (3.58-12.84) indicates higher uncertainty for further research.

The funnel plot presented in Figure 9a does not show any clear indication of publication bias as the maximum study is inside the funnel line, but one study is outside of the line, and studies are not close to the summary effect line. However, Egger's regression test (p-value 0.0472) suggests publication bias in this study.

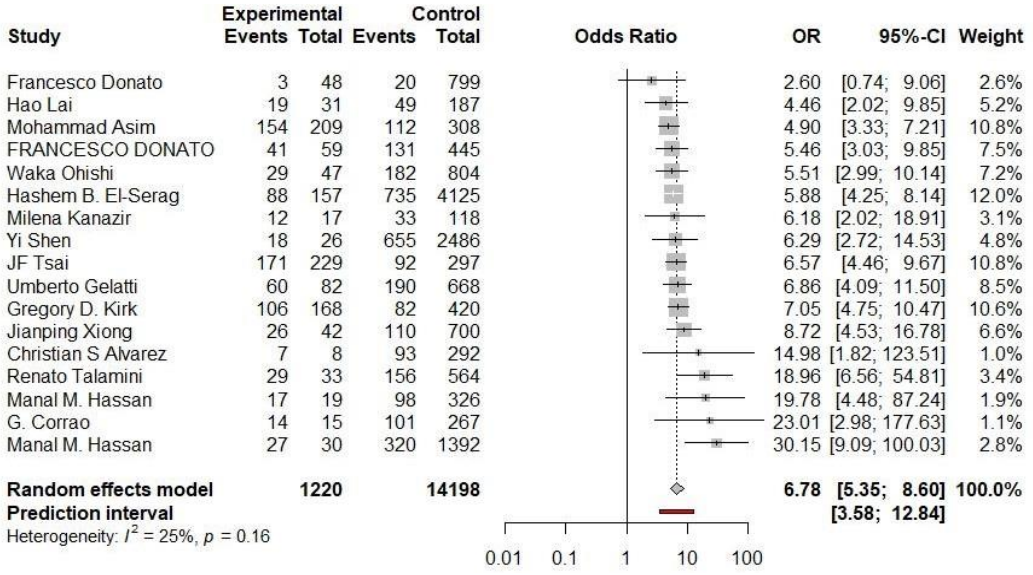

Figure 4: Random effects forest plot of case-control studies for the association of selected chronic HBV infection with HCC.

3.3 Chronic HCV infection

In this study, among 23 case-control studies on chronic HCV infection, 8 studies were excludedfor outliers. Then, the remaining 15 case-control studies of risk factor HBV were selected for meta-analysis. These studies provided 1,377 cases and 102952 without controls. Most of the studies depicted a positive association between chronic HCV and the presence of HCC. In that case, we use OR to summarize the results from multiple studies due to dichotomous outcomes using a random effect forest plot (Figure 5). Based on 95% CI for all respective studies, it is concluded that among 15 studies, 13 studies were statistically significant, and only 2 were conducted by Jianping Xiong and Christian S Alvarez. Combined data from all 15 studies showed a positive association between chronic HCV and HCC (OR: 8.91, 95% CI: 7.10-11.18). The odds ratio indicates, on average, that the chance of developing HCC is 8.91 times higher in those with chronic

HCV than in individuals without HCV. Although a high p-value (0.26>0.05) indicates a weaker association, the random effect forest plot provides strong evidence of the positive association between HCV and HCC. A forest plot with I^2=17% indicates low to moderate variability among the included studies. This indicates an acceptable level of consistency in the estimations across the papers in the meta-analysis. The higher weight indicates that studies likely have higher sample sizes and lower variability, making them more influential in pooled estimates. In this case, the study with a higher weight (>10) has a greater influence on the pooled estimate than the other studies. From Figure 9b, it is observed that no publication bias exists among the studies. However, the statistical significance of Egger's regression test (p-value 0.3767) suggests no publication bias among the studies considered in the meta-analysis.

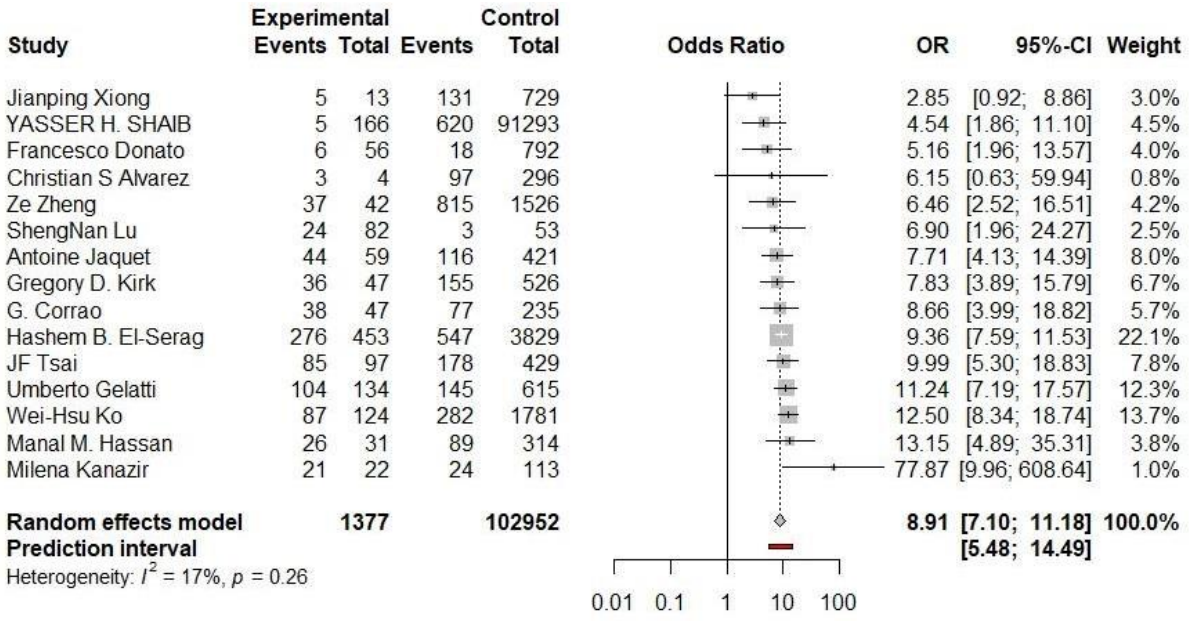

Figure 5 Random effects forest plot of case-control studies for the association of chronic HCV infection with HCC.

3.4 Smoking

Smoking is another risk factor for HCC. Out of 17 case-control studies on smoking, 7 were excluded for outliers to perform a meta-analysis. Then, the remaining 10 case-control studies of risk factor HBV were selected to build a random effect forest plot. These studies provided 3,669 cases and 90,484 controls. All the studies depicted a positive association between smokingand the presence of HCC. In that case, we use OR to summarize the results from multiple studies due to dichotomous outcomes using a random effect forest plot (Figure 6). Based on 95% CI for all respective studies, it is concluded that among 10 studies, only 3 studies were statistically significant. Interestingly, combined data from all 10 studies showed a positive association between

smoking and HCC (OR: 1.50, 95% CI: 1.27-1.76). The odds ratio indicates, on average, that the chanceof developing HCC is 1.50 times higher in those who smoke a cigarette than those who do not smoke. Although a high p-value (0.61>0.05) indicates a weaker association, the random effect forest plot provides strong evidence of the positive association between smoking and HCC. A forest plot with I^2=0% indicates no heterogeneity was observed among the included studies. This indicates a high level of consistency in the estimations across the papers in the meta-analysis. The higher weight indicates that studies likely have higher sample sizes and lower variability, makingthem more influential in the pooled estimates. In this case, the study with a higher weight (>10) has a greater influence on the pooled estimate than the other studies. Figure 9c also detects the presence of publication bias. The plot clearly shows that all studies are plotted inside the funnel, which means that there is no publication bias in this study.

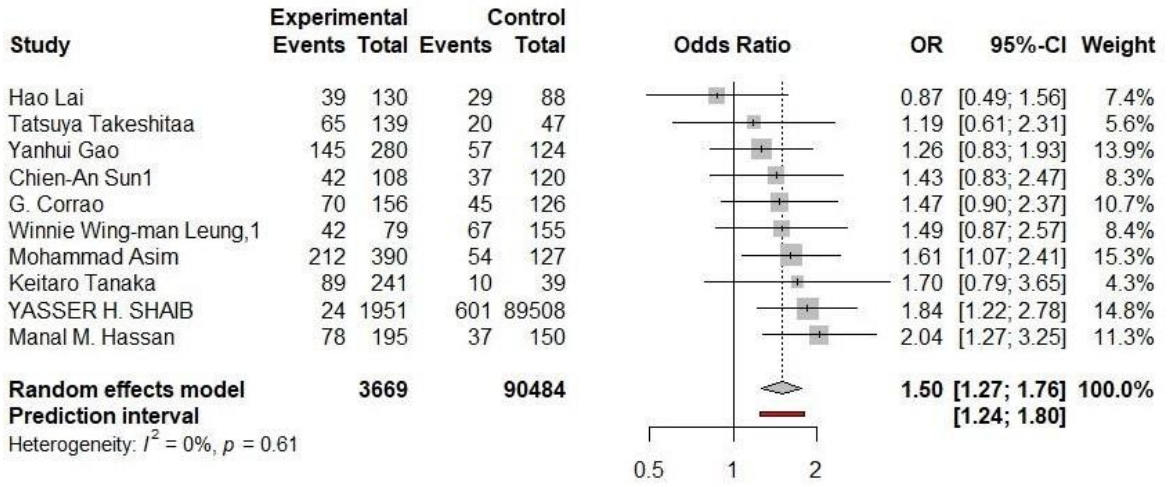

Figure 6 Random effects forest plot of case-control studies for the assessment of association of smoking and HCC.

3.5 Alcohol Consumption

To provide a comprehensive review, we summarize 21 case-control studies on alcohol consumption and liver cancer disease. Among 21 studies, 11 studies were excluded for outliers. Then, the remaining 10 studies were selected for meta-analysis. These studies provided 2581 cases and 2078 without controls. Most of the studies depicted a positive association between chronic alcohol consumption and the presence of HCC. Similarly, using a random effect forest plot, we use OR to summarize multiple studies' results due to dichotomous outcomes (Figure 7). Based on 95% CI for all respective studies, it is concluded that among 10 studies, 4 studies were statistically significant. But combined data from all 10 studies showed a positive association between alcohol consumption and HCC (OR: 1.57, 95% CI: 1.30-1.90). The odds ratio indicates, on average, that the chance of developing HCC is 1.57 times higher in those who consume alcohol than in

individuals who don't. Although a high p-value (0.25>0.05) indicates a weaker association, the random effect forest plot provides strong evidence of the positive association between alcohol consumption and occurring HCC. A forest plot with I^2=21% indicates low to moderate variability among the included studies. The higher weight indicates that studies likely have higher sample sizes and lower variability, making them more influential in pooled estimates. In this case, the study with a higher weight (>10) has a greater influence on the pooled estimate than the other studies. Figure 9d does not clearly indicate publication bias as the maximum study is inside the funnel line, but few studies are outside. However, the statistical significance of Egger's regression test (p-value 0.57) suggests no publication bias in this study.

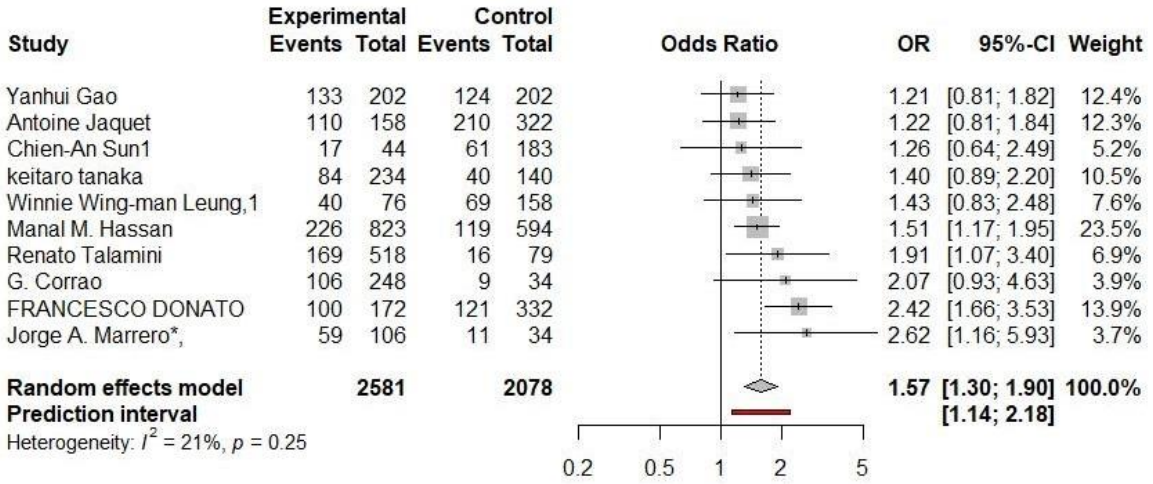

Figure 7 Random effects forest plot of case-control studies for the association of selected alcohol consumption factors with HCC.

3.6 *AFB1*

To determine the pooled estimate of AFB1 on liver cancer, we took four case-control studies, all of which confirmed AFB1 as a risk factor. Among 4 studies, 1 of the studies was excluded for outliers. Then, 3 studies were selected for performed meta-analysis, and the result is represented in Figure 8. These studies provided 208 cases and 609 without controls. All the studies indicated an increased risk of HCC with AFB1. The 95% CI of the odds ratio confirmed that among 3 studies first 2 studies were statistically significant. Moreover, combined data from all 3 studies showed a positive association between AFB1 and HCC (OR: 1.95, 95% CI: 1.33-2.58). The funnel plot could not be plotted because of a small study. The model heterogeneity (I^2=0%) indicates no heterogeneity in the included investigations. This suggests that the estimations in the studies included in the meta-analysis have a high degree of consistency.

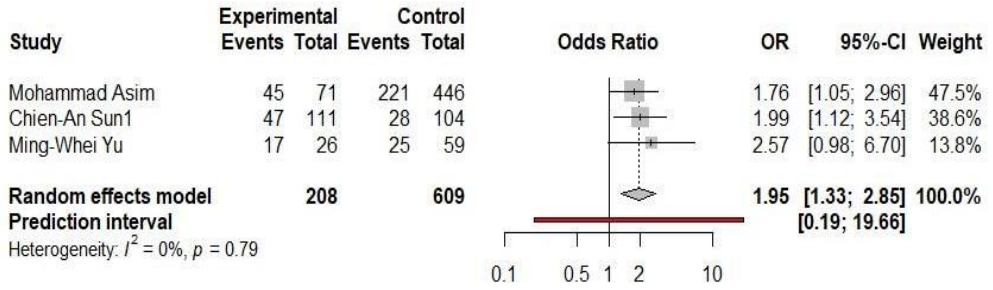

Figure 8 Random effects forest plot of case-control studies for the association of selected afb1 factors with HCC.

4. Discussion

This study extensively conducted systematic reviews and meta-analyses of 5 risk factors associated with HCC. For analysis purposes, 55 case-control studies were included in determining the association between chronic HBV and PLC, chronic HCV and PLC, smoking and PLC, alcohol consumption and PLC, AFB1, and PLC. The meta-analysis combined 17 case-control studies on chronic HBV to explore the pooled odds ratio with PLC, 15 studies on chronic HCV, 10 studieson smoking, 10 studies on alcohol, and only 3 studies on AFB1, respectively. Pearson chi-square, Fisher exact test, Binary logistic regression, Univariate logistic regression, Multivariate logistic regression, Stepwise logistic regression, conditional logistic regression, unconditional logistic regression, spline regression, and Spearman rank correlation were applied to explore the relationship between risk factors and HCC. Most of them showed a significant positive association between included risk factors and PLC.

This study found a pooled OR of 6.78 (95% CI: 5.35-8.60) of chronic HBV with PLC. This implies that, on average, the likelihood of developing HCC is 6.78 times higher in those with chronic HBVthan in individuals without HBV. Another study demonstrated a slightly lower OR (5.10 (95% CI:2.91–8.95)) for HBV, suggesting a parallel investigation (Palmer and Patel 2012). Furthermore, Patients with hepatitis B virus in Japan had a nearly sevenfold increase in the chance of developing liver cancer (OR: 6.92; 95 %CI: 2.92 to 16.39) (Tsukuma et al. 1993). A study conducted in WestAfrica, especially in the Gambia, revealed a higher OR of 16.7 (95% CI: 9.7-28.7) (Kirk et al. 2004). Another study in West Africa also reported a substantially higher OR of 62.5 (95% CI: 20.5-190.7) for HBV infection, indicating a higher risk associated with HBV in the African population (Jaquet et al. 2018). In conclusion, the populations in the Gambia and West Africa reported higher ORs, suggesting a greater risk of HCC associated with chronic HBV infection. Incontrast, a prior study reported a higher OR of 14.1 (95% CI: 10.6 -18.8), indicating a more significant risk association (Shi et al. 2005).

This study revealed chronic HCV as a significant risk factor in the occurrence of HCC with a pooled OR of 8.91 (95% CI: 7.10-11.18). In other words, the chance of developing HCC is 8.91 times higher in those with chronic HCV infection than in individuals without HCV. A case-control study conducted in Serbia confirmed a stronger association between HCV and HCC (OR = 24.6, P = 0.001) (Kanazir et al. 2010). In contrast, a study in northern India discovered a non-significant association between HCV infection and HCC (Asim et al. 2011). In West Africa, chronic HCV (OR: 16.7; 95% CI :6.9-40.1) showed a highly significant association with an increased HCC risk, and this study highlighted that HCV patients were much older and more likely to be female (Kirk et al. 2004). Another case-control study in West Africa exhibited a much higher OR (OR: 35.9 [CI 95%: 10.0-130.3]) (Jaquet et al. 2018). Additionally, a cohort study found that both HBV and HCV infections independently contribute to a greater chance of HCC (Ohishi et al. 2011). Comparatively, the Chaina and northern India populations reported lower ORs, indicating a potentially lower risk of HCC associated with chronic HCV infection. In contrast, the population in Serbia and West Africa, especially in West Africa, exhibited higher ORs, suggesting a potentially greater risk of HCC associated with chronic HCV infection. In contrast, a prior investigation reported a weaker association with a lower OR (4.09, 95 CI: 1.30 - 12.85) (Tsukuma et al. 1993). Conversely, a study in China reported a lower OR of 4.6 (95% CI: 3.6 – 5.9), indicating a weaker association between Chronic HCV and HCC (Shi et al. 2005). William C. Palmer suggested an overall OR for HCV positive in HCC of 4.84 (95% CI: 2.41-9.71) (Palmer and Patel 2012).

This study on HCC identified smoking as a significant risk factor, with an estimated pooled OR of OR: 1.50 (95% CI: 1.27-1.76). This suggests that individuals who smoke have 1.50 times higher odds of developing HCC compared to non-smokers. In comparison, a meta-analysis combining data from 11 studies reported a slightly lower OR estimate of 1.31 (95% CI: 0.95–1.82) (Palmer and Patel 2012). Furthermore, Kangmin Zhu et al. (2007) found that the likelihood of developing HCC was 1.85 (95% CI: 1.05–3.25) times higher for former smokers compared to non-smokers (Zhu et al. 2007). Additionally, Kanazir et al. (2010) demonstrated a highly significant association between hepatocellular carcinoma and a smoking duration of ≥25 years (OR = 3.8, P = 0.020) (Kanazir et al. 2010).

This investigation into HCC identified alcohol consumption as a significant risk factor, revealing a positive impact with a pooled OR of 1.57 (95% CI: 1.30-1.90). This suggested that individuals who consume alcohol have 1.57 times higher odds of developing HCC compared to non-drinkers. A prior meta-analysis study showed an overall odds ratio of 2.81 (95% CI:1.52–5.21) for the positive association between alcohol consumption and HCC (Palmer and Patel 2012). Additionally, Shu-Chun Chuang et al. (2015) conducted a meta-analysis by including 112 publications that concluded a significant positive association between alcohol drink and liver cancer (Chuang et al. 2015). In the Japanese population, a comprehensive analysis by Tanaka et al. (2008) revealed that drinking alcohol raises the risk of liver cancer (Tanaka et al. 2008). In America, a study by Marrero et al. explored risk factors in HCC patients, indicating that alcohol consumption and smoking cigarettes increased the risk, with estimated ORs of 5.7 (95% CI: 2.4–13.7) and 4.9 (95% CI: 2.2–10.6) respectively (Marrero et al. 2005). Conversely, Asim et al. reported a non-significant association between alcohol consumption (OR = 1.18) and HCC (Asim

et al. 2011). In North Italy, there was a high risk among HCC patients with alcohol intake exceeding 40g per day, reflecting a higher OR of 7.1 (95% CI:4.1–12.2) (Tagger et al. 1999). Furthermore, studies confirmed hazardous alcohol consumption as a risk factor for HCC with a higher OR of 4.5 (95% CI: 1.1-18.5) (Jaquet et al. 2018).

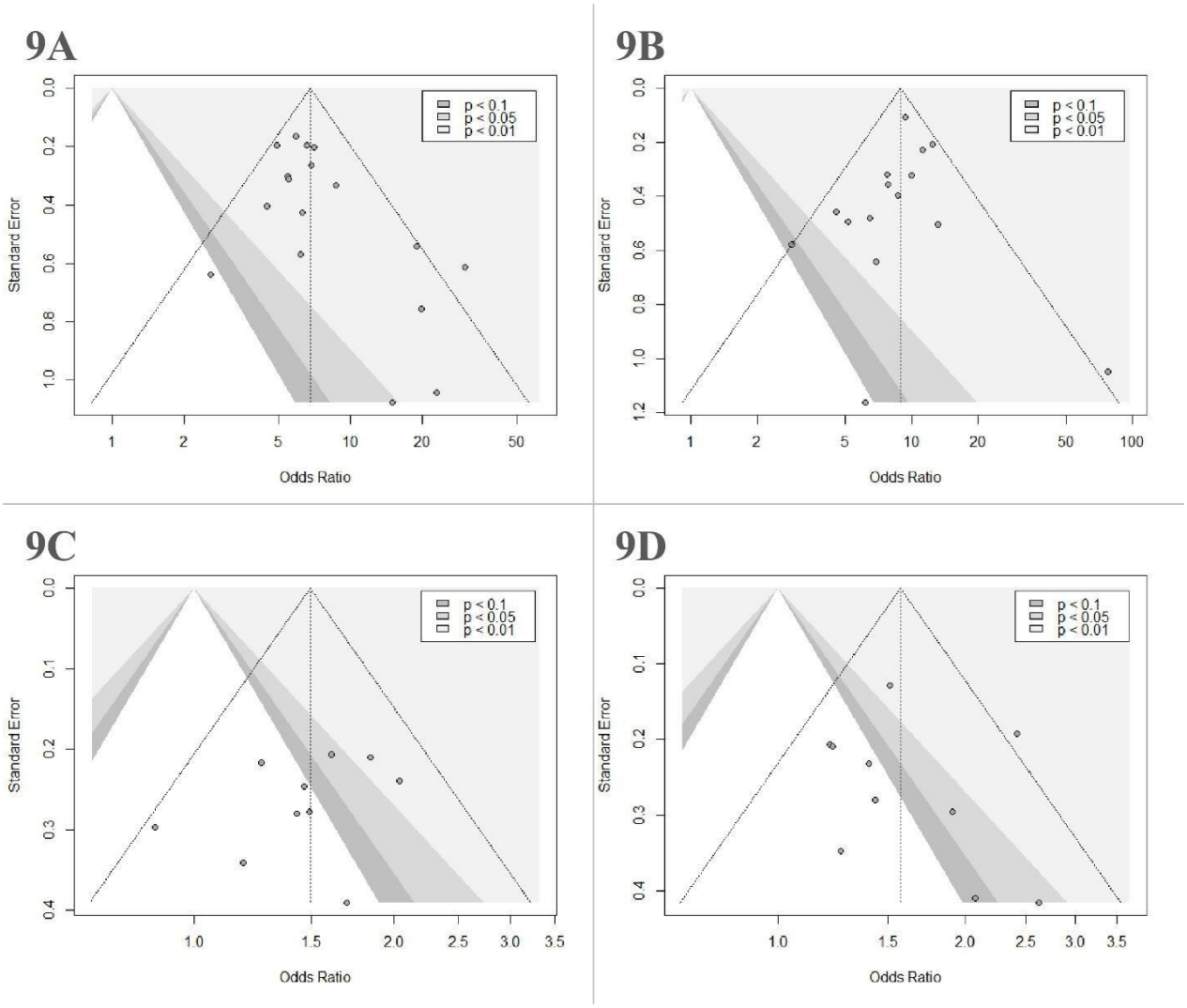

Figure 9 Assessment of publication bias with funnel plots

This study identified AFB1 as a risk factor for HCC, revealing a pooled OR of 1.95 (95% CI: 1.33-2.58). A case-control study conducted by Lai et al., 2014 reported a substantially higher OR of 5.24 (95 % CI :2.77–9.88), indicating a highly significant association between AFB1 and HCC occurrences (Lai et al. 2014). Moreover, another study observed a remarkably high positive association between AFB1 exposure and cirrhosis, with an elevated OR of 11.55 (95%CI 4.05 - 32.89) (Alvarez et al. 2020). In northern India, Asim et al. discovered a substantially high 5-fold greater risk of HCC (OR: 5.47) in individuals with AFB1 exposure (Asim et al. 2011). Similarly, a case-control study in Taiwan showed a high OR of 3.65 (95% CI: 1.32–10.10) for AFB1 exposure (Chu et al. 2018).

This study meticulously examines diverse investigations, revealing a consistent and significant association between identified risk factors and the development of HCC. However, the observed odds ratio (OR) scores and their respective 95% CI exhibit variability across studies, attributed to distinct study designs and varying sample sizes.

5. Conclusion

This systematic review and meta-analysis explored various risk factors, including chronic HBV, chronic HCV, smoking cigarettes, alcohol consumption, and aflatoxin B1 (AFB1) influencing the development of hepatocellular carcinoma (HCC). The literature reveals significant associations between these risk factors and hepatocellular carcinoma (HCC). Studies consistently demonstrated a positive association between chronic HBV infection and the occurrence of hepatocellular carcinoma (HCC). Patients with chronic HCV exhibited a notably higher risk of developing hepatocellular carcinoma (HCC). Behavioral factors such as smoking and alcohol consumption were also found to be significantly associated with more active liver cancer. The aflatoxin B1 (AFB1), another major risk factor, displayed a significant relationship in this study. In summary, chronic HCV is associated with a higher risk of hepatocellular carcinoma (HCC) than chronic HBV, smoking cigarettes, alcohol consumption, and aflatoxin B1 (AFB1). This study could assist policymakers and researchers in developing effective public health strategies and improve overall healthcare planning for preventing, diagnosing, and treating liver cancer.

References

Akinyemiju, Tomi, Semaw Abera, Muktar Ahmed, Noore Alam, Mulubirhan Assefa Alemayohu, Christine Allen, Rajaa Al-Raddadi, Nelson Alvis-Guzman, Yaw Amoako, and Al Artaman. 2017. "The Burden of Primary Liver Cancer and Underlying Etiologies from 1990 to 2015 at the Global, Regional, and National Level: Results from the Global Burden of Disease Study 2015." *JAMA Oncology* 3(12):1683–91.

Alvarez, Christian S., Elisa Hernández, Kira Escobar, Carmen I. Villagrán, María F. Kroker-Lobos, Alvaro Rivera-Andrade, Joshua W. Smith, Patricia A. Egner, Mariana Lazo, and Neal D. Freedman. 2020. "Aflatoxin B1 Exposure and Liver Cirrhosis in Guatemala: A Case–Control Study." *BMJ Open Gastroenterology* 7(1):e000380.

Anitha, S., D. Raghunadharao, F. Waliyar, H. Sudini, M. Parveen, Ratna Rao, and P. Lava Kumar. 2014. "The Association between Exposure to Aflatoxin, Mutation in TP53, Infection with Hepatitis B Virus, and Occurrence of Liver Disease in a Selected Population in Hyderabad, India." *Mutation Research/Genetic Toxicology and Environmental Mutagenesis* 766:23–28.

Asim, Mohammad, Manash P. Sarma, L. Thayumanavan, and P. Kar. 2011. "Role of Aflatoxin B1 as a Risk for Primary Liver Cancer in North Indian Population." *Clinical Biochemistry* 44(14–15):1235–40.

Bosch, F. Xavier, Josepa Ribes, Mireia Díaz, and Ramon Cléries. 2004. "Primary Liver Cancer: Worldwide Incidence and Trends." *Gastroenterology* 127(5):S5–16.

Chu, Yu-Ju, Hwai-I. Yang, Hui-Chen Wu, Mei-Hsuan Lee, Jessica Liu, Li-Yu Wang, Sheng-Nan Lu, Chin-Lan Jen, San-Lin You, and Regina M. Santella. 2018. "Aflatoxin B1 Exposure Increases the Risk of Hepatocellular Carcinoma Associated with Hepatitis C Virus Infection or Alcohol Consumption." *European Journal of Cancer* 94:37–46.

Chuang, Shu-Chun, Yuan-Chin Amy Lee, Guo-Jie Wu, Kurt Straif, and Mia Hashibe. 2015. "Alcohol Consumption and Liver Cancer Risk: A Meta-Analysis." *Cancer Causes & Control* 26:1205–31.

Donato, Francesco, Umberto Gelatti, Alessandro Tagger, Maurizio Favret, Maria Lisa Ribero, Francesco Callea, Claudia Martelli, Antonella Savio, Paola Trevisi, and Giuseppe Nardi. 2001. "Intrahepatic Cholangiocarcinoma and Hepatitis C and B Virus Infection, Alcohol Intake, and Hepatolithiasis: A Case–Control Study in Italy." *Cancer Causes & Control* 12:959–64.

Gao, Yanhui, Qingwu Jiang, Xuefu Zhou, Baoguo Ding, Ruhong Wang, Genming Zhao, and Yue Chen. 2004. "HBV Infection and Familial Aggregation of Liver Cancer: An Analysis of Case-Control Family Study." *Cancer Causes & Control* 15:845–50.

Jaquet, Antoine, Boris Tchounga, Aristophane Tanon, Aklesso Bagny, Didier K. Ekouevi, Hamar A. Traore, Annie J. Sasco, Moussa Maiga, and François Dabis. 2018. "Etiology of Hepatocellular Carcinoma in W Est A Frica, a Case–Control Study." *International Journal of Cancer* 143(4):869–77.

Kanazir, Milena, Ivan Boricic, Dragan Delic, Darija Kisic Tepavcevic, Aleksandra Knezevic, Tanja Jovanovic, and Tatjana Pekmezovic. 2010. "Risk Factors for Hepatocellular Carcinoma: A Case-Control Study in Belgrade (Serbia)." *Tumori Journal* 96(6):911–17.

Kirk, Gregory D., Olufunmilayo A. Lesi, Maimuna Mendy, Aliu O. Akano, Omar Sam, James J. Goedert, Pierre Hainaut, Andrew J. Hall, Hilton Whittle, and Ruggero Montesano. 2004. "The Gambia Liver Cancer Study: Infection with Hepatitis B and C and the Risk of Hepatocellular Carcinoma in West Africa." *Hepatology* 39(1):211–19.

Lai, Hao, Xianwei Mo, Yang Yang, Ke He, Jun Xiao, Chao Liu, Jiansi Chen, and Yuan Lin. 2014. "Association between Aflatoxin B1 Occupational Airway Exposure and Risk of Hepatocellular Carcinoma: A Case-Control Study." *Tumor Biology* 35:9577–84.

Li, Liang, and Hongyang Wang. 2016. "Heterogeneity of Liver Cancer and Personalized Therapy." *Cancer Letters* 379(2):191–97.

Liu, Chun-Yu, Kuen-Feng Chen, and Pei-Jer Chen. 2015. "Treatment of Liver Cancer." *Cold Spring Harbor Perspectives in Medicine* 5(9).

Long, Xi Dai, Yun Ma, Yun Feng Zhou, Jin Guang Yao, Fu Zhi Ban, Yong Zhi Huang, and Bing Cheng Huang. 2009. "XPD Codon 312 and 751 Polymorphisms, and AFB1 Exposure, and Hepatocellular Carcinoma Risk." *BMC Cancer* 9:1–9.

Long, Xi-Dai, Jin-Guang Yao, Yong-Zhi Huang, Xiao-Ying Huang, Fu-Zhi Ban, Li-Ming Yao, and Lu-Dan Fan. 2011. "DNA Repair Gene XRCC7 Polymorphisms (Rs# 7003908 and Rs# 10109984) and Hepatocellular Carcinoma Related to AFB1 Exposure among Guangxi Population, China." *Hepatology Research* 41(11):1085–93.

Lu, Sheng-Nan, Chuan-Mo Lee, Chi-Sin Changchien, and Chien-Jen Chen. 1999. "Excess Mortality from Hepatocellular Carcinoma in an HCV-Endemic Township of an HBV-Endemic Country (Taiwan)." *Transactions of the Royal Society of Tropical Medicine and Hygiene* 93(6):600–602.

Marrero, Jorge A., Robert J. Fontana, Sherry Fu, Hari S. Conjeevaram, Grace L. Su, and Anna S. Lok. 2005. "Alcohol, Tobacco and Obesity Are Synergistic Risk Factors for Hepatocellular Carcinoma." *Journal of Hepatology* 42(2):218–24.

Mohammadian, M., N. Mahdavifar, A. Mohammadian-Hafshejani, and H. Salehiniya. 2018. "Liver Cancer in the World: Epidemiology, Incidence, Mortality and Risk Factors." *World Cancer Res J* 5(2):e1082.

Ohishi, Waka, Saeko Fujiwara, John B. Cologne, Gen Suzuki, Masazumi Akahoshi, Nobuo Nishi, Masataka Tsuge, and Kazuaki Chayama. 2011. "Impact of Radiation and Hepatitis Virus Infection on Risk of Hepatocellular Carcinoma." *Hepatology* 53(4):1237–45.

Orcutt, Sonia T., and Daniel A. Anaya. 2018. "Liver Resection and Surgical Strategies for Management of Primary Liver Cancer." *Cancer Control* 25(1):1073274817744621.

Palmer, William C., and Tushar Patel. 2012. "Are Common Factors Involved in the Pathogenesis of Primary Liver Cancers? A Meta-Analysis of Risk Factors for Intrahepatic Cholangiocarcinoma." *Journal of Hepatology* 57(1):69–76.

Rumgay, Harriet, Melina Arnold, Jacques Ferlay, Olufunmilayo Lesi, Citadel J. Cabasag, Jérôme Vignat, Mathieu Laversanne, Katherine A. McGlynn, and Isabelle Soerjomataram. 2022. "Global Burden of Primary Liver Cancer in 2020 and Predictions to 2040." *Journal of Hepatology* 77(6):1598–1606.

Rumgay, Harriet, Jacques Ferlay, Catherine de Martel, Damien Georges, Amal Samy Ibrahim, Rongshou Zheng, Wenqiang Wei, Valery EPP Lemmens, and Isabelle Soerjomataram. 2022. "Global, Regional and National Burden of Primary Liver Cancer by Subtype." *European Journal of Cancer* 161:108–18.

Shaib, Yasser H., Hashem B. El-Serag, Jessica A. Davila, Robert Morgan, and Katherine A. McGlynn. 2005. "Risk Factors of Intrahepatic Cholangiocarcinoma in the United States: A Case-Control Study." *Gastroenterology* 128(3):620–26.

Shen, Qiujin, Jia Fan, Xin-Rong Yang, Yexiong Tan, Weifeng Zhao, Yang Xu, Ning Wang, Yongdong Niu, Zheng Wu, and Jian Zhou. 2012. "Serum DKK1 as a Protein Biomarker for the Diagnosis of Hepatocellular Carcinoma: A Large-Scale, Multicentre Study." *The Lancet Oncology* 13(8):817–26.

Shen, Yi, Harvey Risch, Lingeng Lu, Xiaomei Ma, Melinda L. Irwin, Joseph K. Lim, Tamar Taddei, Karen Pawlish, Antoinette Stroup, and Robert Brown. 2020. "Risk Factors for Hepatocellular Carcinoma (HCC) in the Northeast of the United States: Results of a Case–Control Study." *Cancer Causes & Control* 31:321–32.

Shi, J., L. Zhu, S. Liu, and WF Xie. 2005. "A Meta-Analysis of Case–Control Studies on the Combined Effect of Hepatitis B and C Virus Infections in Causing Hepatocellular Carcinoma in China." *British Journal of Cancer* 92(3):607–12.

Srivatanakul, Petcharin, Hutcha Sriplung, and Somyos Deerasamee. 2004. "Epidemiology of Liver Cancer: An Overview." *Asian Pacific Journal of Cancer Prevention* 5(2):118–25.

Sung, Hyuna, Jacques Ferlay, Rebecca L. Siegel, Mathieu Laversanne, Isabelle Soerjomataram, Ahmedin Jemal, and Freddie Bray. 2021. "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries." *CA: A Cancer Journal for Clinicians* 71(3):209–49.

Tagger, Alessandro, Francesco Donato, Maria L. Ribero, Roberta Chiesa, Giuseppe Portera, Umberto Gelatti, Alberto Albertini, Michele Fasola, Paolo Boffetta, and Giuseppe Nardi. 1999. "Case-control Study on Hepatitis C Virus (HCV) as a Risk Factor for Hepatocellular Carcinoma: The Role of HCV Genotypes and the Synergism with Hepatitis B Virus and Alcohol." *International Journal of Cancer* 81(5):695–99.

Tanaka, Keitaro, Tomio Hirohata, and Setsuko Takeshita. 1988. "Blood Transfusion, Alcohol Consumption, and Cigarette Smoking in Causation of Hepatocellular Carcinoma: A Case-control Study in Fukuoka, Japan." *Japanese Journal of Cancer Research* 79(10):1075–82.

Tanaka, Keitaro, Ichiro Tsuji, Kenji Wakai, Chisato Nagata, Tetsuya Mizoue, Manami Inoue, and Shoichiro Tsugane. 2008. "Alcohol Drinking and Liver Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence among the Japanese Population." *Japanese Journal of Clinical Oncology* 38(12):816–38.

Tsukuma, Hideaki, Tomohiko Hiyama, Sachiko Tanaka, Miho Nakao, Takako Yabuuchi, Tsugio Kitamura, Katsumi Nakanishi, Isaburo Fujimoto, Atsuo Inoue, and Hideo Yamazaki. 1993. "Risk Factors for Hepatocellular Carcinoma among Patients with Chronic Liver Disease." *New England Journal of Medicine* 328(25):1797–1801.

Welzel, Tania M., Barry I. Graubard, Stefan Zeuzem, Hashem B. El-Serag, Jessica A. Davila, and Katherine A. McGlynn. 2011. "Metabolic Syndrome Increases the Risk of Primary Liver Cancer in the United States: A Population-Based Case-Control Study." *Hepatology (Baltimore, Md.)* 54(2):463.

WHO (World Health Organization). 2022. "Overview of Cancer." doi: https://gco.iarc.fr/today.

Yang, Jianqing, Guangdong Pan, Linjing Guan, Zhipeng Liu, Yongrong Wu, Zhen Liu, Wuchang Lu, Shuai Li, Honglai Xu, and Guoqing Ouyang. 2022. "The Burden of Primary Liver Cancer Caused by Specific Etiologies from 1990 to 2019 at the Global, Regional, and National Levels." *Cancer Medicine* 11(5):1357–70.

Yu, HE, Randall E. Harris, Geoffrey C. Kabat, and Ernst L. Wynder. 1988. "Cigarette Smoking, Alcohol Consumption and Primary Liver Cancer: A Case-control Study in the USA." *International Journal of Cancer* 42(3):325–28.

Zhu, Kangmin, Cynthia Moriarty, Lee S. Caplan, and Robert S. Levine. 2007. "Cigarette Smoking and Primary Liver Cancer: A Population-Based Case–Control Study in US Men." *Cancer Causes & Control* 18:315–21.