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VIRAL HEPATITIS, TOBACCO AND ALCOHOL USE AND RISK OF LIVER CANCER IN THE EASTERN MEDITERRANEAN REGION (EMRO) COUNTRIES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT – *Objective:* Hepatocellular carcinoma (HCC) is one of the most prevalent cancers worldwide. In this review we aimed at investigating the severe and challenging risk factors for HCC in Eastern Mediterranean region.

Materials and Methods: A systematic search was conducted from 2000 to December 2022 using the Scopus, PubMed, and Web of Science databases. Joanna Briggs Institute Critical appraisal checklist served as the basis for assessing quality. For the analysis, CMA software version 3 was used.

Results: Finally, the meta-analysis included 16 articles. Based on the development, the incidence of HCC significantly decreased from 2000 to 2022 in EMRO countries. There was a significant association between HCC and viral hepatitis (OR=7.8, 95% CI: 4.7-12.9, p<0.001). Also, no meaningful correlation was observed between alcohol users and the development of HCC based on the results. Cigarettes play a non-significant protective role in HCC development (OR: 0.90, 95% CI: 0.55-1.48, p=0.7).

Conclusions: Alcohol consumption and smoking, unlike the virus, have no significant relationship with HCC. There is a possibility that the effect of factors affecting HCC may vary in different geographical areas.

KEYWORDS: Hepatocellular carcinoma, Eastern Mediterranean region, Alcohol, hepatitis, Smoking.

LIST OF ABBREVIATIONS: HCC: Hepatocellular Carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NAFLD: Non-alcoholic fatty liver disease; EMRO: Eastern Mediterranean region Office; CMA: Comprehensive meta-analysis; AhR: Aryl hydrocarbon receptor; OR: Odds Ratio.

INTRODUCTION

Hepatocellular Carcinoma (HCC) represents one of the cancers with the highest prevalence worldwide and with a high-rated cause of cancer death[1,2]. Liver cancer prevalence is growing incredibly fast in the world; HCC includes 90% of liver cancer cases[3,4], So focusing on the risk factors of HHC is necessary. HCC occurs in 80-90% of patients with cirrhosis. They can occur together with a probability of 2-4% [5]. The risk factors leading to HCC are hepatitis C virus (HCV), hepatitis B virus (HBV), non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, liver steatohepatitis, obesity, smoking, and diabetes[6]. The association between

metabolic syndrome and liver disease has evolved ever closer in recent years, leading to an increased focus on metabolic-associated liver diseases (MALDs). A connection between the diseases appears to be insulin resistance, which leads to type 2 diabetes (T2D). Patients with NASH cirrhosis are more likely to develop HCC due to these complications[7,8]. NAFLD, along with its development into non-alcoholic steatohepatitis (NASH) and cirrhosis, is mediated by several pathophysiological mechanisms. These include pro-inflammatory molecules, apoptosis, oxidative stress, adipokines, immunomodulation, JNK-1 stimulation, and alterations in gut microbiota, increased IGF-1 activity, which in turn can increase HCC risk as well[9].

Viral infections such as HBV and HCV are the most frequently identified causes of HCC[10,11]. HBV and HCV are hepatotropic viruses that can damage the liver through hepatic inflammation, oxidative stress, and disruption of cellular signaling pathways[12]. HCV and HBV can cause a massive decrease in antioxidant enzymes; as a result, they can increase free oxygen radicals in the long term[10,13]. Another mechanism that can damage the liver is steatohepatitis, which increases triglycerides in the liver. HCV can cause steatohepatitis by increasing lipogenesis and inducing lipotoxicity in the liver, which leads to an increased risk of HCC[10,14]. However, there are differences between HBV and HCV's oncogenic mechanism, such as the HBV potency in merging its DNA in hepatocyte DNA and causing functional disorders. Still, HCV is an RNA virus and can't connect with the host DNA. Finally, all these damages progress toward cirrhosis and HCC[12].

Alcohol is one of liver disease's most significant risk factors[15]. It is expected that 25% of cirrhosis deaths are related to alcohol. Drinking alcohol for ten years or longer at a measured dose can progress to advanced liver disease[16]. Alcohol drinkers are more susceptible to HCC[15]. Alcohol gets absorbed in the gastrointestinal tract, and its metabolism occurs in the liver[17]. Metabolites of alcohol can lead to fatty liver disease, cellular apoptosis, endoplasmic reticulum stress, peroxidation, increased synthesis of cytokines, and reduced immune surveillance[18].

Smoking can import over 4000 toxic chemicals affecting approximately every body organ[19]. Smoking can accelerate HCC progression in individuals who are chronically infected with HBV or HCV [20]. It is considered that smoking individually, without correlating with other risk factors, leads to liver fibrosis and HCC. Systemic inflammation, oxidative stress, free radical damage, and increased transcription of P-53RS are harmful effects of smoking[21].

In this review, our objective was to examine the severe and challenging risk factors of HCC, such as alcohol and cigarettes, in the last two decades in Eastern Mediterranean region (EMRO) countries.

MATERIALS AND METHODS

Search strategy

The current systematic review and meta-analysis was conducted using guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We used Scopus, PubMed, and Web of Science databases for our systematic search. The search terms used in the database included: ("liver cancer" OR "hepatocellular carcinoma" OR "HCC") AND ("risk factor" OR "cigarette" OR "smoking" OR "alcohol" OR "virus" OR "epidemiology" OR "prevalence" OR "incidence") AND ("case-control") AND ("Iran" OR "Afghanistan" OR "Morocco" OR "Bahrain" OR "Djibouti" OR "Egypt" OR "Iraq" OR "Qatar" OR "Jordan" OR "Kuwait" OR "Yemen" OR "Lebanon" OR "Libya" OR "Oman" OR "Tunisia" OR "Pakistan" OR "Saudi Arabia" OR "Somalia" OR "Sudan" OR "Syria" OR "United Arab Emirates"). We searched English publications in EMRO (Eastern Mediterranean Regional Office) countries and stored and checked articles using Endnote software as a citation manager. All selected papers were published from 2000 to December 2022. In reviewing the search results, our team considered the title, abstract, and full text of the articles for study selection to determine inclusion criteria. Inclusion criteria contained any case-control studies in three categories of liver cancer risk factors, including alcohol, cigarette, and hepatitis. Reviews, case reports, cross-sectional studies, and duplicate studies are the exclusion criteria in this systematic review.

Quality assessment and data extraction

Based on the nine-point Joanna Briggs Institute Critical appraisal checklist for studies, two researchers assessed the research's quality and resolved disagreements through consensus. In total, over 50% of the quality parameters were met by the selected articles. Among the studies in Table 1, we extracted the author's name, publication year, country, number of patients, and population origin. We got the following information: study design and research question, number of articles and types of studies, language and country of study, the device used, characteristics of patients, and statistical analysis.

Table 1. The main characteristics of studies included in the meta-analysis.

Number	Author	Year	Country	Design	Sample size		Population	Reference
					Case	Control		
1	Ezzat	2005	Egypt	Case-Control	236	236	National Cancer Institute, Cairo University	49
2	Schieffelin	2014	Egypt	Case-Control	148	148	Tanta Cancer Center and the Gharbiah Cancer Society	50
3	Ayoola	2004	Saudi Arabia	Case-Control	118	118	Regional hospital in Saudi Arabia	51
4	Manal	2001	Egypt	Case-Control	35	35	The University of Cairo National Cancer Institute	52
5	Ezzikouri	2007	Morocco	Case-Control	96	222	The Hospital University Center Ibn-Sina,	53
6	Soliman	2009	Egypt	Case-Control	150	150	Gharbiah Cancer Society and Tanta Cancer Center	54
7	Montasser	2021	Egypt	Case-Control	100	100	-	55
8	Nasim Habibi	2015	Iran	Case-Control	41	41	Imam Khomeini Hospital of Tehran and Namazi Hospital of Shiraz	56
9	Israa T. Ismail	2011	Egypt	Case-Control	15	15	General population	57
10	Anis Khan	2009	Pakistan	Case-Control	82	102	General population	58
11	Manal	2015	Egypt	Case-Control	662	660	General population	59
12	Ghias Un Nabi Tayyab	2020	Pakistan	Case-Control	42	620	Two centers in Pakistan	60
13	Davod Javanmard	2020	Iran	Case-Control	105	32	Iran University of Medical Sciences.	61
14	Asma Gulnaz	2012	Pakistan	Case-Control	74	50	Institute Biotechnology, Bahaudin Zakriya University, Multan.	62
15	R. E. Omer	2001	Sudan	Case-Control	115	199	From West Sudan and Central Sudan	63
16	Ines Dhifallah	2011	Tunisia	Case-Control	73	70	Two departments of gastroenterology at La Rabta Hospital and Tahar Maamouri Hospital and one department of surgery at Mongi Slim Hospital	64

Statistical analysis

To analyse the data and construct graphs, a comprehensive meta-analysis (CMA) version 3 (Biostat Inc., Englewood, NJ) with a random effect model plotted on forest plots was employed. The summary estimate was based on the pooled standard deviation with a 95% confidence interval. We use the I-squared (I^2) test (with a value greater than 50%) to test heterogeneity. We assessed the visual bias employing a funnel plot, and Egger's regression test confirmed it (considering $p<$ 0.05 as a signification of publication bias). Also, a power analysis was performed using the average sample size and Hedges' g statistic.

RESULTS

Search outcome and study characteristics

Our search identified 1431 studies found in the Scopus, PubMed, and Web of Science databases. Following deduplication and screening based on inclusion and exclusion criteria, 16 studies qualified for inclusion in this review. Included articles have been conducted in the following countries: Egypt (7), Pakistan (3), Iran (2), and one study from Morocco, Saudi Arabia, Sudan, and Tunisia. All selected studies were little in design (Figure 1).

Association between major risk factors and HCC development in EMRO countries

This study demonstrated an observable correlation between HCC and viral hepatitis; the pooled Odds Ratio (OR) for HCC in viral infection reached 7.8. Therefore, it can be stated that viral infections were the leading risk factor for HCC in EMRO countries (OR: 7.8, 95% CI: 4.7-12.9, p <0.001). Also, according to Figure 2A, no statistically meaningful relationship was found between alcohol users and the development of HCC in EMRO countries (OR: 1.38, 95% CI: 0.76-2.47, p = 0.28). Therefore, unlike in other countries, alcohol did not have a significant effect on HCC in EMRO countries. All heterogeneity analyses were collected in Table 2.

Smoking and its association with liver cancer in EMRO countries

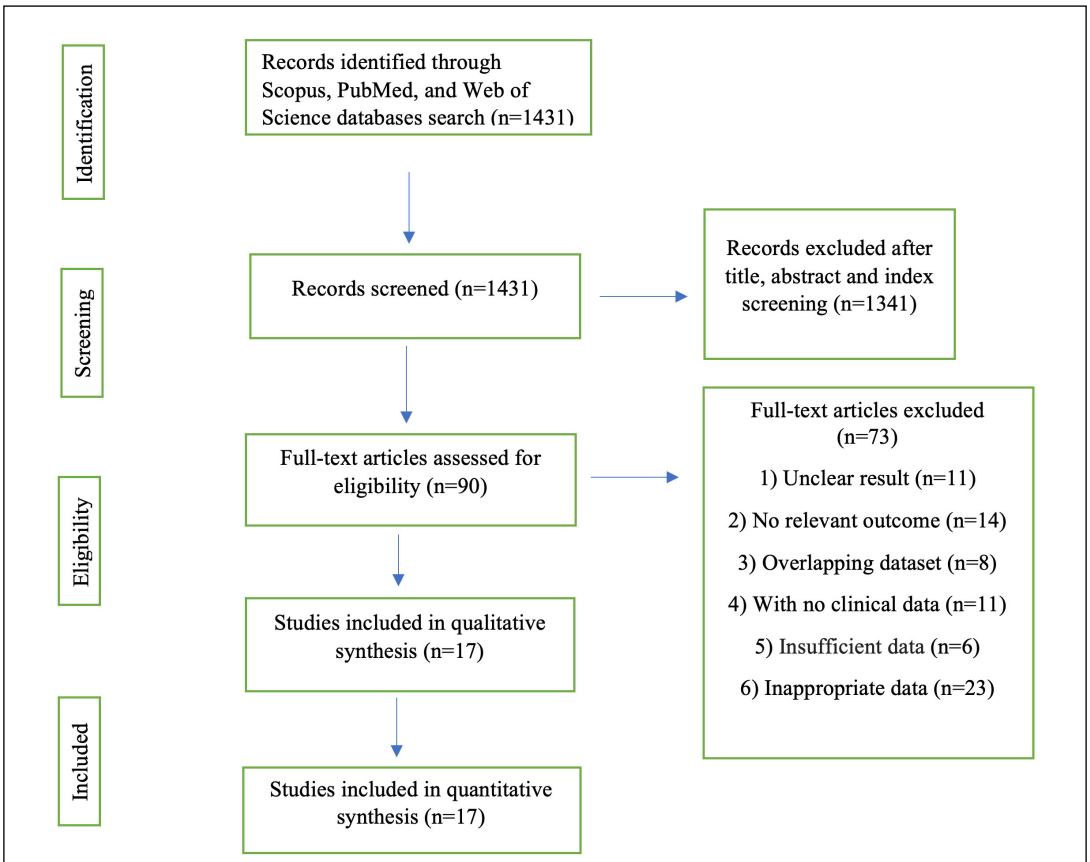
The analysis showed that in some countries, smoking has a protective effect on liver cancer, and pooled OR confirms it. Based on the result, smoking does not negatively influence HCC development because the pooled OR for HCC in smokers was 0.9. However, based on the impact of the analysis in Figure 2A, they had no significant relationship (OR: 0.9, 95% CI: 0.55-1.48, p=0.7).

Progress of HCC incidence from 2000 to 2022 in EMRO countries

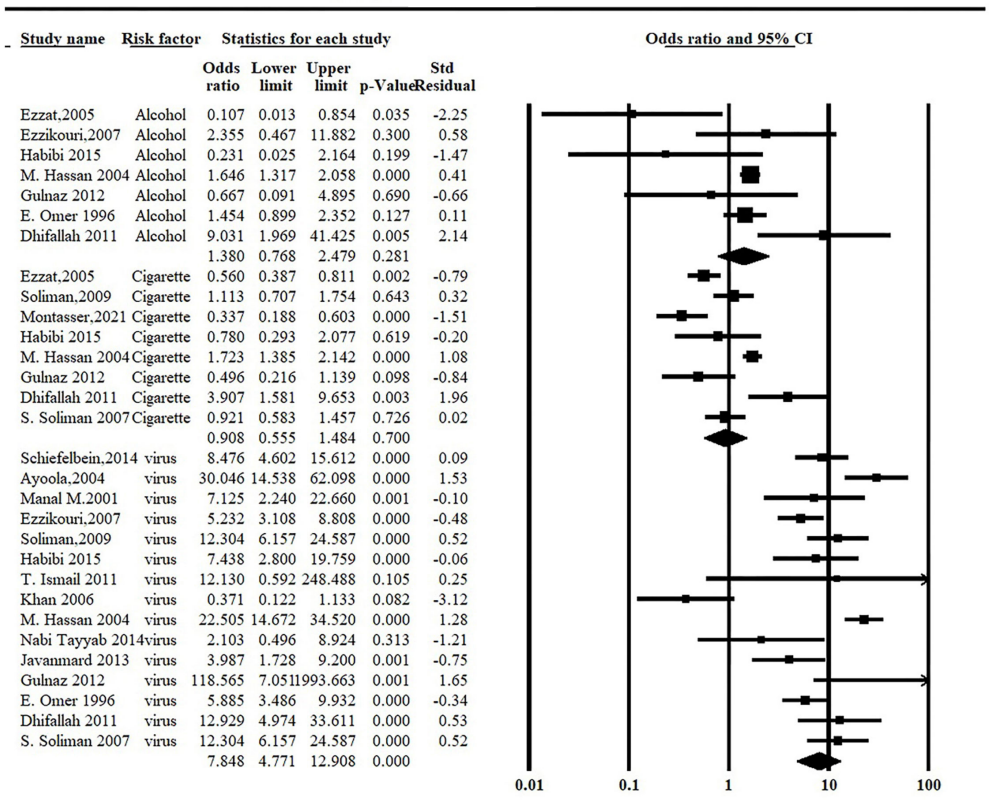
The progression of HCC incidence was examined in this study. Based on the results, the incidence of HCC significantly decreased from 2000 to 2022 in EMRO countries (Figure 3) because the meta-regression showed that the coefficient of progression was -0.02 (p<0.05).

Publication bias and sensitivity analysis

As for sensitivity analysis and publication bias, the study exclusion did not affect the results. Funnel plots were used for visual evaluation, and Egger's test was used to determine bias in Table 2. Funnel plots were symmetric, and according to Egger's test, no publication bias was found in this study (Figure 4). In sensitivity analysis, all three variables indicated no publication bias. Also, a power analysis was performed using Hedges' g statistic (Figure 2A, B, and C).



A



Study name	Risk factor	Odds ratio	Lower limit	Upper limit	p-Value	Std Residual
Ezzat,2005	Alcohol	0.107	0.013	0.854	0.035	-2.25
Ezzikouri,2007	Alcohol	2.355	0.467	11.882	0.300	0.58
Habibi 2015	Alcohol	0.231	0.025	2.164	0.199	-1.47
M. Hassan 2004	Alcohol	1.646	1.317	2.058	0.000	0.41
Gulnaz 2012	Alcohol	0.667	0.091	4.895	0.690	-0.66
E. Omer 1996	Alcohol	1.454	0.899	2.352	0.127	0.11
Dhifallah 2011	Alcohol	9.031	1.969	41.425	0.005	2.14
		1.380	0.768	2.479	0.281	
Ezzat,2005	Cigarette	0.560	0.387	0.811	0.002	-0.79
Soliman,2009	Cigarette	1.113	0.707	1.754	0.643	0.32
Montasser,2021	Cigarette	0.337	0.188	0.603	0.000	-1.51
Habibi 2015	Cigarette	0.780	0.293	2.077	0.619	-0.20
M. Hassan 2004	Cigarette	1.723	1.385	2.142	0.000	1.08
Gulnaz 2012	Cigarette	0.496	0.216	1.139	0.098	-0.84
Dhifallah 2011	Cigarette	3.907	1.581	9.653	0.003	1.96
S. Soliman 2007	Cigarette	0.921	0.583	1.457	0.726	0.02
		0.908	0.555	1.484	0.700	
Schiefelbein,2014	virus	8.476	4.602	15.612	0.000	0.09
Ayoola,2004	virus	30.046	14.538	62.098	0.000	1.53
Manal M.2001	virus	7.125	2.240	22.660	0.001	-0.10
Ezzikouri,2007	virus	5.232	3.108	8.808	0.000	-0.48
Soliman,2009	virus	12.304	6.157	24.587	0.000	0.52
Habibi 2015	virus	7.438	2.800	19.759	0.000	-0.06
T. Ismail 2011	virus	12.130	0.592	248.488	0.105	0.25
Khan 2006	virus	0.371	0.122	1.133	0.082	-3.12
M. Hassan 2004	virus	22.505	14.672	34.520	0.000	1.28
Nabi Tayyab 2014	virus	2.103	0.496	8.924	0.313	-1.21
Javanmard 2013	virus	3.987	1.728	9.200	0.001	-0.75
Gulnaz 2012	virus	118.565	7.051	1993.663	0.001	1.65
E. Omer 1996	virus	5.885	3.486	9.932	0.000	-0.34
Dhifallah 2011	virus	12.929	4.974	33.611	0.000	0.53
S. Soliman 2007	virus	12.304	6.157	24.587	0.000	0.52
		7.848	4.771	12.908	0.000	

B

Figure 1. PRISMA flow chart of study selection (**A**) and statistics (**B**).

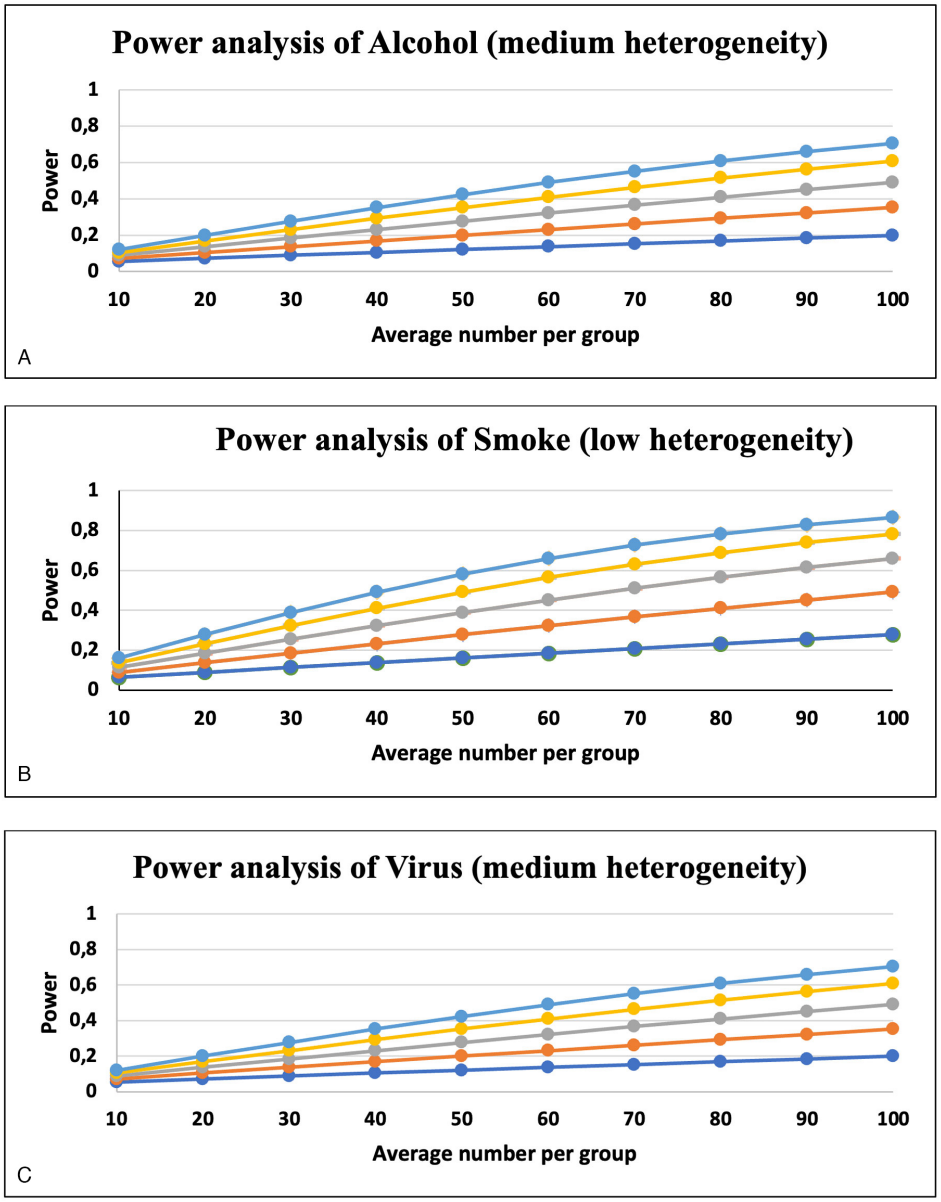


Figure 2. Association between HCC incidence and three major risk factors and power analysis (**A**, Alcohol, **B**, Smoke, and **C**, Virus).

Table 2. The complete results of heterogeneity and publication bias examination.

Variable	Number of report/s	Effect size	95% CI		Heterogeneity			Egger's regression	
			Lower limit	Upper limit	X^2	*p*-value	I^2	*p*-value	*t*-value
Alcohol and liver cancer	7	1.38	0.76	2.47	15.2	<0.017	61.3	0.483	0.75
Virus and liver cancer	15	7.8	4.77	12.9	79.4	<0.001	82.3	0.41	0.84
Cigarette and liver cancer	8	0.9	0.55	1.48	57.01	<0.001	87.72	0.29	1.15

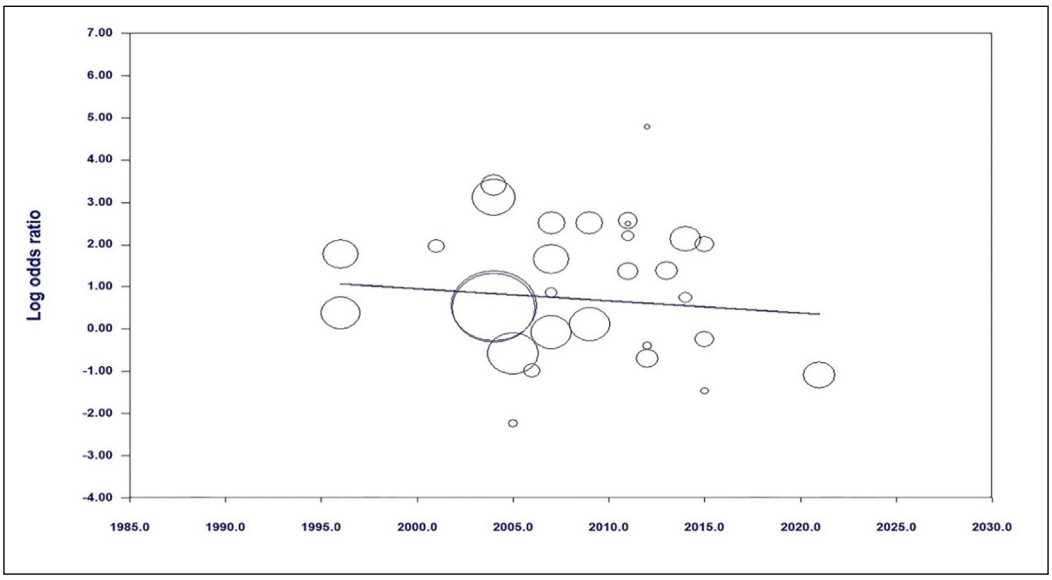


Figure 3. The incidence of HCC in EMRO countries in the last two decades.

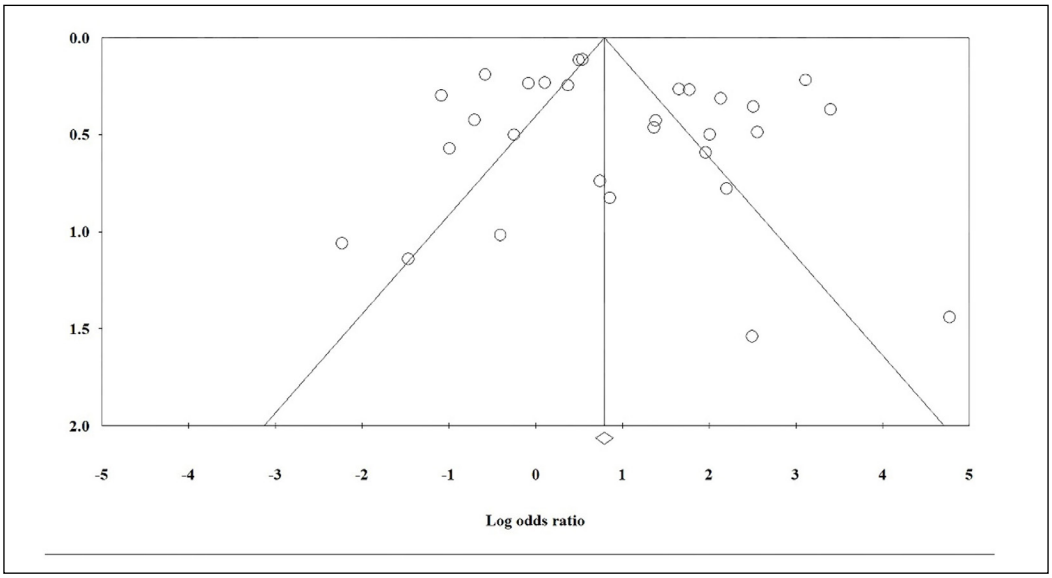


Figure 4. Funnel plot for assessing possible publication bias.

DISCUSSION

HCC is a dangerous tumor, only curable in the early stages of the disease, accounting for only 20% of cases[22]. Therefore, preventing this disease is a much more effective strategy than treating it after it has manifested [23]. Preventing HBV and HCV infections is regarded as the mainstay in preventing HCC. However, alcohol consumption, smoking cessation, and other potentially modifiable factors are also significant factors in HCC incidence[24,25]. It is believed that several factors affect the occurrence of HCC worldwide. It is critical to investigate the relationship between factors such as viral infection, alcohol consumption, smoking, and HCC, especially in EMRO countries which are muslim countries with unique lifestyles[26,27].

The incidence of HCC in various regions can be different[28]. However, the incidence of HCC has been decreasing from 2000 to 2022 in EMRO countries. Some suggest that lifestyle and food habits contributed to the decrease in HCC incidence during this period[29]. Evaluation of critical risk factors in the EMRO region over the

last 22 years sometimes reveals unexpected points. For example, Park et al[30] emphasized in a meta-analysis study conducted in 2020 in East Asia that alcohol consumption led to liver cancer and was thus introduced as a risk factor. However, the summary of the data extracted during the last 22 years in the present review indicates no significant association between alcohol and HCC incidence in EMRO countries. The amount of alcohol intake was calculated through the following formulas: average alcohol intake each time (g) = average alcoholic drink consumption each time (ml) × alcohol concentration (%) × 0.8 (alcohol density). Weekly alcohol intake (g) = average alcoholic drink consumption each time (ml) × alcohol concentration (%) × 0.8 (alcohol density) × average weekly drinking frequency (times/week)[31]. It is possible that this can be attributed to lower levels of alcohol drinking among Muslim nations[32]. Statistics indicate that only a small percentage of Muslims consume alcohol, and if they do, the quantity and frequency are extremely low.

Globally, HCV is the most common cause of liver cancer. Infection with chronic viral hepatitis is the most significant risk factor for HCC development[33]. Through the deregulation of host cell cycle checkpoints, HCV proteins have a direct carcinogenic activity[34]. Often, HBV and HCV infections in advanced stages are not eliminated by the immune system. As a result, cancer develops from chronic liver inflammation caused by ongoing interactions between the host and the virus[35]. Furthermore, Aljumah et al[36] confirmed that infection with the virus is prominent in human cancer development in Saudi Arabia. In the European cohort, Trichopoulos et al[37] stated that chronic HBV and HCV infection is the most potent risk factor for HCC. Finally, the analysis of the total data extracted from EMRO countries demonstrated a significant relationship between the virus and HCC. Li et al[34] evaluated how statins affect HCC risk in a patient with HBV or HCV. They stated that in patients with HBV or HCV, statin administration was independently linked to decreased risk of HCC because of the potential pleiotropy of statins, including anti-inflammation, immunomodulation, and anti-invasion, which all contribute to carcinogenesis.

In cancer prevention, smoking is regarded as one of the most significant causes, and quitting smoking can reduce the risk of a wide variety of cancers (including lung and head and neck cancer)[38]. According to studies, smoking can increase cancer risk and carcinogens or free radicals in the liver[39]. Nonetheless, some studies do not confirm these findings and emphasize that smoking is an ineffective factor[40,41]. Also, clinical and laboratory studies have reported such effects of smoking on other conditions or cancers. For instance, Daniluk et al[42] noted one of the beneficial effects of smoking on colitis. They stated that this phenomenon was associated with alterations in the CD4/CD8 ratio and the level of B cells in the peripheral blood and colon. These processes may underlie smoking's protective properties in ulcerative colitis. Wang et al[43] emphasized smoking's protective properties in preeclampsia through increasing trophoblast invasion and reducing placental oxidative damage through Aryl hydrocarbon receptor (AhR) activation. Agostini et al[44] also reported the anti-apoptotic effect of smoking in mouse lung cancer. Despite Chuang et al[45] and Zhang et al[46] studies examining smoking as a risk factor in China, our analysis suggests no significant relationship between tobacco use and HCC in EMRO countries. This shows that the effect of smoking on HCC can be influenced by factors including sex, geographical region, smoking rate, and other risk factors.

Smoking is generally regarded as a modifiable risk factor that increases the risk of HCC in individuals with HBV, HCV, or alcohol consumption[47]. It is possible that smoking can intensify the harmful effects of alcohol, viruses, and other risk factors[48]. The amount of smoking independently can affect the occurrence of HCC. The impact of factors, such as the amount and duration of cigarette exposure, should be investigated. Therefore, we suggest future studies comparing the effect of smoking in the presence and absence of other risk factors or different geographical areas.

CONCLUSIONS

Finally, according to the analysed data from EMRO regions, alcohol consumption, and smoking, unlike the virus, have no significant relationship with HCC. Also, the incidence of HCC in EMRO countries has decreased over the past 20 years. According to the findings of this study, the effect of factors affecting HCC may vary in different geographical areas.

Ethics approval and consent to participate:
Not applicable

Availability of data and material:
The authors confirm that the data supporting the findings of this study are available within the article and its supplementary material. Raw data supporting this study's findings are available from the corresponding author upon reasonable request.

Conflict of interest:
The authors have no conflict of interest to declare.

Authors' contributions:
M.A: Design, Literature search, Data collection/processing, and Writing; F.A: Design, Data collection/processing, and Writing; A.B: Concept development, Data collection/processing, and Writing; M.J.A: Literature search, Data collection/processing, and Writing; S.H: Concept development, Design, Supervision, and Writing.

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