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Article *in* Journal of Evidence-Based Medicine · September 2017

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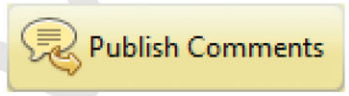

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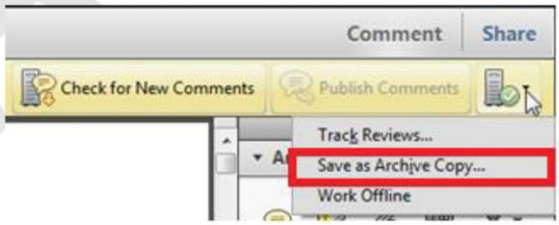

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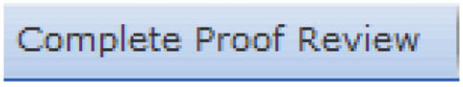

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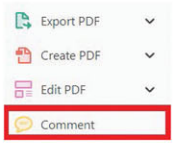

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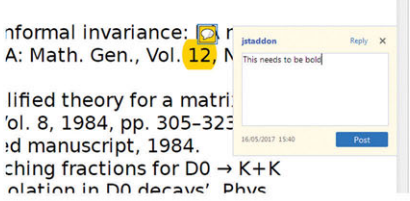

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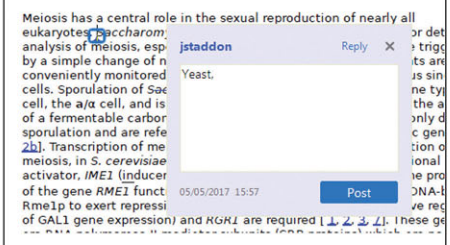

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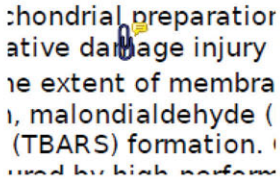

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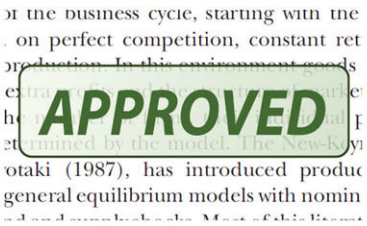

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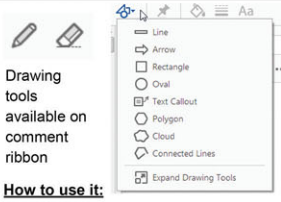

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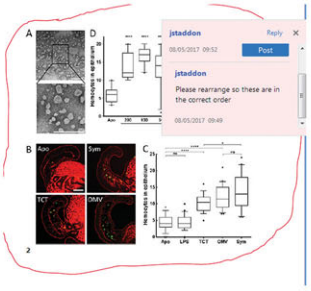

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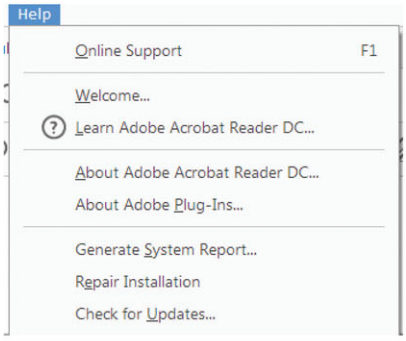

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Received: 5 March 2017 | Accepted: 13 August 2017

DOI: 10.1111/jebm.12270

ARTICLE

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Cigarette smoking as a risk factor for the development of and mortality from hepatocellular carcinoma: An updated systematic review of 81 epidemiological studies

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Abstract

Background and aims: Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and its incidence has increased during the past decade. While hepatitis B and C virus infections and alcohol were established risk factors, the impact of smoking on the incidence and mortality of HCC was needed to be confirmed.

Methods: We reviewed cohort and case–control studies evaluating the association between cigarette smoking and incidence and mortality of HCC from MEDLINE and Google Scholar. We also checked reference lists of original studies and review articles manually for cross-references up to February 2016. We extracted the relevant information on participant characteristics and study outcomes, as well as information on the methodology of the studies. We also assessed the quality of the included trials using critical appraisal skills program checklists. Meta-analysis was performed by using RevMan 5.3 software.

Results: A total of 81 studies were included in the systematic review. Pooled OR for HCC development with current smokers was 1.55 (95% CI: 1.46 to 1.65; $P < 0.00001$). Pooled OR for HCC development with former smokers was 1.39 (95% CI: 1.26 to 1.52; $P < 0.00001$) and pooled OR for HCC development with heavy smokers was 1.90 (95% CI: 1.68 to 2.14; $P < 0.00001$). Pooled OR for the mortality of current smokers with HCC was 1.29 (95% CI: 1.23 to 1.34; $P < 0.00001$); and for former smokers with HCC, it was 1.20 (95% CI: 1.00 to 1.42; $P = 0.04$).

Conclusions: Cigarette smoking increases the incidence and mortality of HCC. Further studies are needed to evaluate possible impact of quitting smoking on decreasing this risk.

KEYWORDS

cigarette, epidemiological study, hepatocellular carcinoma, meta-analysis, risk factor, smoking, systematic review

1 | INTRODUCTION

Worldwide, hepatocellular carcinoma (HCC) is the sixth most commonly occurring cancer and the second greatest contributor to cancer mortality.[1–3] Wide geographic differences exist among different ethnic groups of the world with the majority of new cases occurring in less developed areas of the world.[4] Diverse etiological factors have been proved to play important roles in the development of this disease.[4] In the majority of cases, HCC develops in an already chronically damaged liver, often cirrhosis-related. In most geographical areas, posthepatitis cirrhosis due to either hepatitis B virus (HBV) or hepatitis C virus (HCV) is the principal cause of HCC.[5]

HCV is a major cause of liver cancer cases globally; north and middle African countries are the areas of highest prevalence.[6,7] Moreover, HCV is the most common viral etiology of HCC in Europe and North America.[8]

HBV is another major cause of liver cancer cases globally; the majority of these cases are diagnosed in Asia/western Pacific regions.[9]

Other potential contributing factors including fatty liver/non-alcoholic steatohepatitis,[10] metabolic syndrome, obesity, aflatoxin exposure, and diabetes mellitus.[11–13] Another important factor is alcohol consumption.[14] The causal association between alcohol and HCC has been proven in many studies and confirmed by the International Agency for Research on Cancer (IARC) working group (IARC monographs, 1988, 2010).[15]

Smoking has been reported to increase the risk of development of HCC in people with HCV, HBV, as well as alcoholics; a meta-analysis has reported a more than additive effect between smoking and HBV or HCV in HCC development.[16] Moreover, another meta-analysis published in 2009 and two previous IARC monographs published in 2004 and 2012 suggested that smoking is an independent risk factor for HCC development.[15,17] What remains to be elucidated is the potential role of smoking as an independent risk factor for mortality after diagnosis of HCC. Moreover, the potential impact of quitting smoking on amelioration of the above risks is not yet clear.

The objective of the current meta-analysis is to provide an update on the existing evidence of cigarette smoking and development of HCC, and to provide a quantitative assessment of the association between cigarette smoking and mortality of HCC.

2 | METHOD

2.1 | Search strategy

A comprehensive search for literature published in English was performed in the following databases: Pubmed/Medline and Google Scholar in order to identify all relevant citations. The date of the last search was the 13 February 2016. Citations with the following words in their titles or abstracts were assessed: ("smoking" [All Fields] OR "cigarette smoking" [All Fields]) AND ("hepatocellular carcinoma" [All Fields] OR "liver cancer" [All Fields] OR "HCC" [All Fields]).

2.2 | Selection criteria

Inclusion criteria: (a) Case–control and cohort studies that evaluate the association between cigarette smoking and HCC risk and mortality; (b) Association is being reported by hazard ratio (HR), odds ratio (OR), or relative risk (RR).

2.3 | Data extraction

Data were extracted by three review authors (OA, ME, and HM). All eligible articles underwent initial evaluation for relevance. The following data were extracted where available: study authors, study design, country of accrual, accrual period, smoking habits, number of cases/controls or cases/overall cohort, covariates for which adjustment has been done, and outcome measures. The outcome measures of interest were HR, RR, and OR. We also checked reference lists of original studies and review articles manually for cross-references up to February 2016. This meta-analysis adheres to the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses report.[18,19]

2.4 | Data analysis

ORs were employed to assess association across studies. When HRs or RRs were used, they were directly considered as ORs. Pooled ORs and relevant 95% CIs were then computed using the inverse variance calculation method. ORs in some studies were adjusted with relevant confounders (eg, alcohol history, HCV, or HBV status) and this was detailed in the data extraction tables (Supplement Table S1). These adjusted OR was utilized in the pooling where available. Heterogeneity was assessed with Cochrane Chi^2 statistic and P values. We planned to use both random-effects model as well as fixed-effect model. In case of discrepancy between the two models (eg, one giving a significant effect, the other no significant effect), we planned to report both results; otherwise, we planned to report only the results from the fixed-effect model.[20] We performed a sensitivity analysis by performing planned subgroup analysis according to the study design (cohort vs. case–control) as well as according to adjustment for confounders (adjusted vs. non-adjusted OR). We assessed publication bias by visual inspection of funnel plots. All statistical analyses were conducted using the program RevMan 5.3 (Copenhagen, Denmark). Quality of the included studies was assessed using critical appraisal skills program (CASP) checklists for cohort and case–control studies.[21]

3 | RESULTS

3.1 | Search results

Figure 1 summarizes the PRISMA diagram for study selection; 914 results were obtained from the searches in PubMed (n = 703) and other databases (n = 211). Of these results, 205 were duplicates and 607 did not meet the eligibility criteria and were therefore excluded. Of the 102 possibly eligible studies after the initial screening, the full text search that ensued resulted in removal of 21 studies. Hence, 81 studies were included in the systematic review.[22–102] Seventy-two studies assessed the association between smoking and risk of development of HCC and nine studies assessed the association between smoking and the risk of mortality in HCC patients. Among the 81 studies included in the qualitative analysis, 55 studies were included in the quantitative analysis; while the other 26 studies were not included in the quantitative analysis because of either not reporting the 95% CI of the relevant measure (OR, RR, HR) or because of the reporting the risk of ever smokers (combining all patients together) rather than differentiating between current smokers and former smokers.

Among the studies assessing the risk of development, there were 24 cohort studies and 48 case–control studies; while among the studies assessing the mortality risk, there were six prospective cohort studies, two retrospective cohort studies, and one case–control study (Supplement Table S1). Among the reported studies in our analysis, 52 studies were conducted in Asian countries (27 studies were conducted in Japan, 18 studies in China, 6 studies in South Korea, 1 study in Singapore), 13 studies in European countries (6 studies in Italy, 2 studies in Greece, 2 studies in Germany, 1 study conducted in multiple

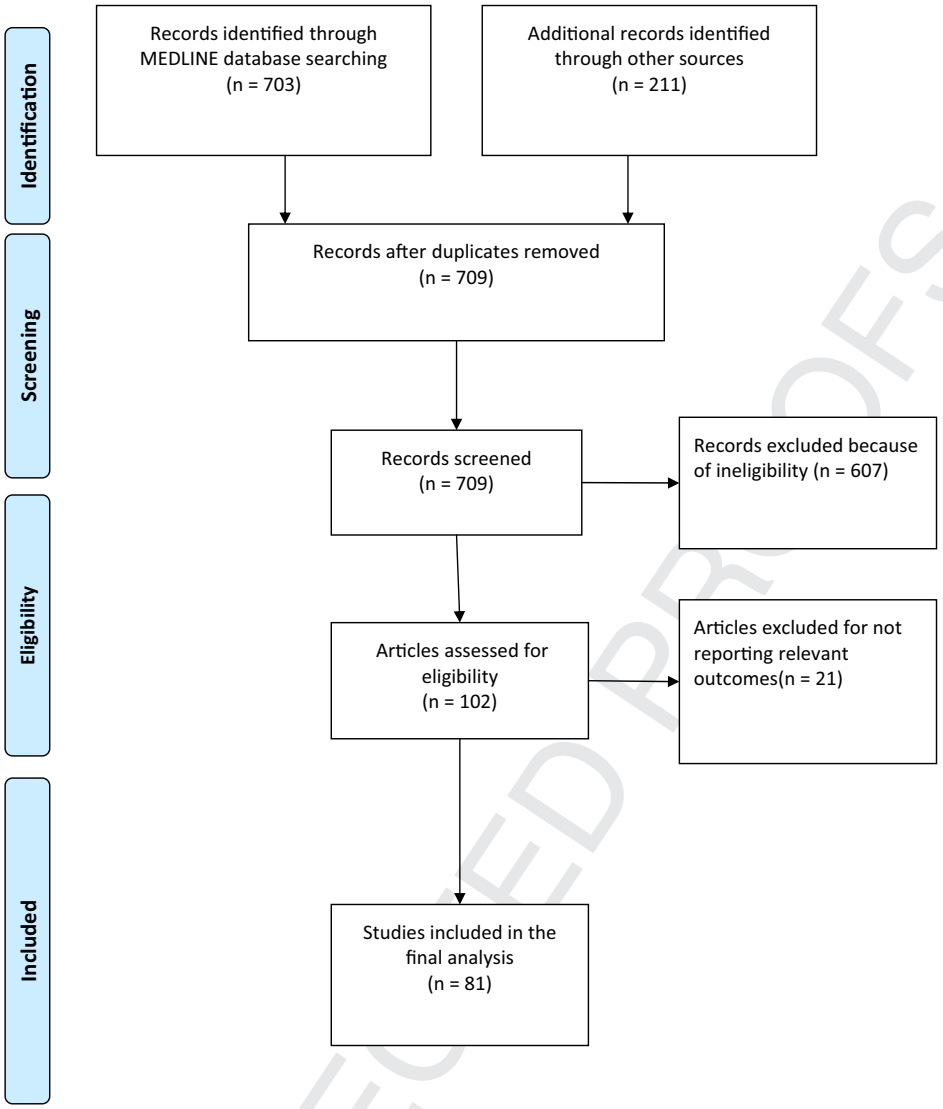

FIGURE 1 Flowchart of study selection procedure

European countries, 1 study in Sweden, 1 study in Serbia), 4 studies in African countries (1 study in Egypt, 1 study in Nigeria, 2 studies in South Africa), and 12 studies in North American countries (11 studies in the United States, 1 study in Canada). CASP quality scores of the included studies have been detailed in Supplement Table S1. HCC diagnosis in the included studies was based on the histopathology and standard radiological criteria.

3.2 | Overall estimates for the association between smoking and development of HCC

Pooled OR for HCC development with current smoking was 1.55 (95% CI: 1.46 to 1.65; P < 0.00001), pooled OR for HCC development with former smoking was 1.39 (95% CI: 1.26 to 1.52; P < 0.00001) and pooled OR for HCC development with heavy smoking was 1.90 (95% CI: 1.68 to 2.14; P < 0.00001) (Figs. 2A–C). Heavy smoking was defined in the majority of included studies as either more than 20 cigarettes/day or more than one pack/year. The significant P value was maintained when conducting the meta-analysis by either fixed-effects or random-effects models; and thus, the above data were reported according to fixed-effects model. Funnel plot did not reveal an evidence of a significant publication bias (Fig. 3). Thus, the current data point out to an enhanced risk of HCC development risk in people with current or former history of smoking.

3.3 | Overall estimates for the mortality risk in smokers diagnosed with HCC

Pooled OR for the mortality of current smokers with HCC was 1.29 (95% CI: 1.23 to 1.34; P < 0.00001); and for former smokers with HCC, it was 1.20 (95% CI: 1.00 to 1.42; P = 0.02) (Figs. 4A and B). The significant P value was maintained when conducting the meta-analysis by either fixed-effects or random-effects models; and thus, the above data were reported according to the fixed-effects model. Thus, the current data point out to an enhanced mortality risk in HCC patients with current or former history of smoking. We planned to conduct an additional analysis to evaluate the impact of duration of smoking and quitting smoking on the overall mortality risk; however, due to insufficiency of these specific data in the included studies, we cannot conduct this analysis.

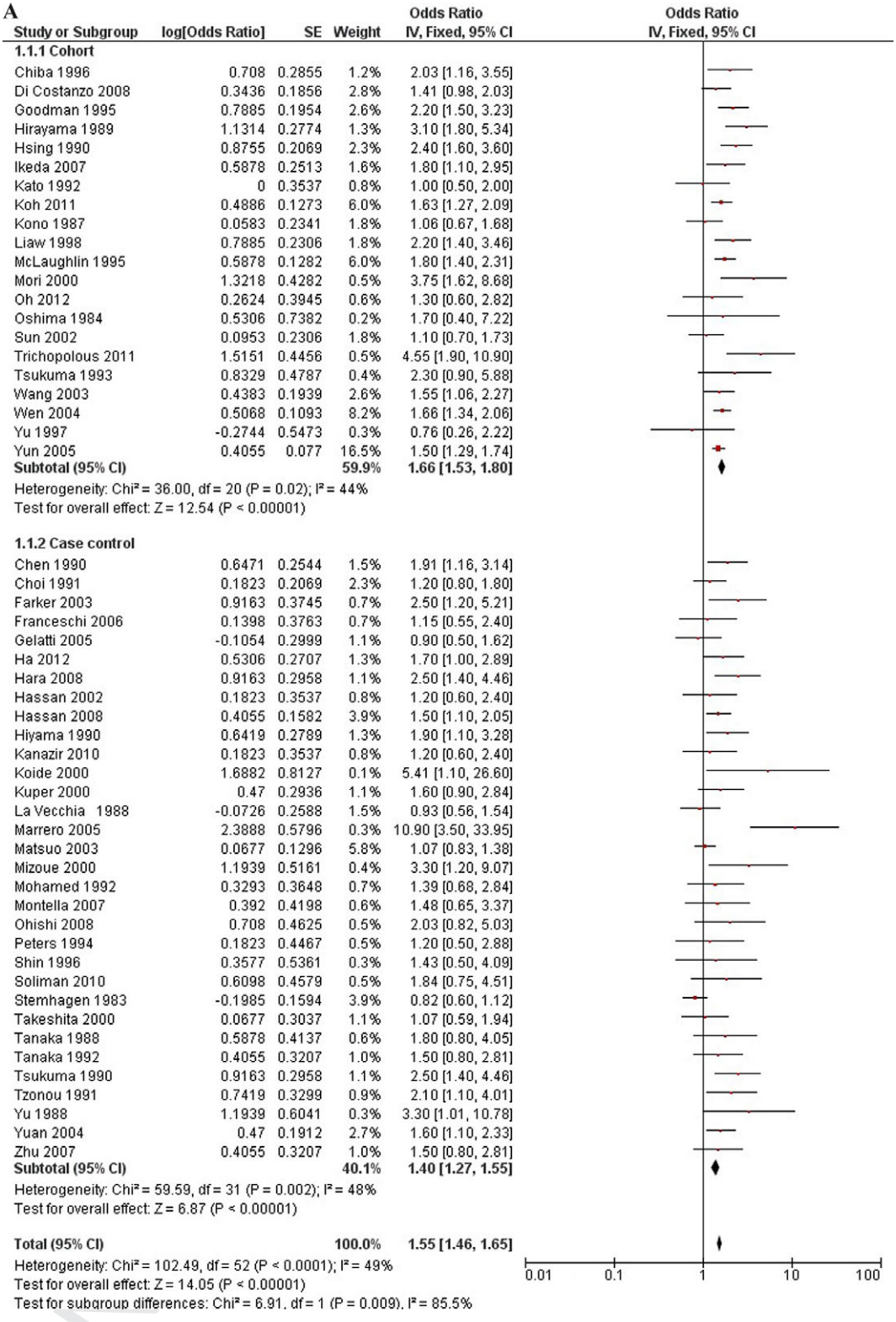

FIGURE 2 Forest plots of pooled odds ratio (ORs) for HCC development risk for: (A) current smokers; (B) former smokers; and (C) heavy smokers

3.4 | Subgroup analysis

We detected a significant subgroup difference between cohort and case–control studies in the risk of development of HCC (for current smokers: P = 0.009 and for former smokers: P = 0.004) (Fig. 2). We have conducted an additional analysis for the subset of studies providing summary measures adjusted for HBV and HCV status and the pooled OR for the risk of HCC development with current smoking was 1.64 (95% CI: 1.44 to 1.88; P < 0.00001) (data not shown).

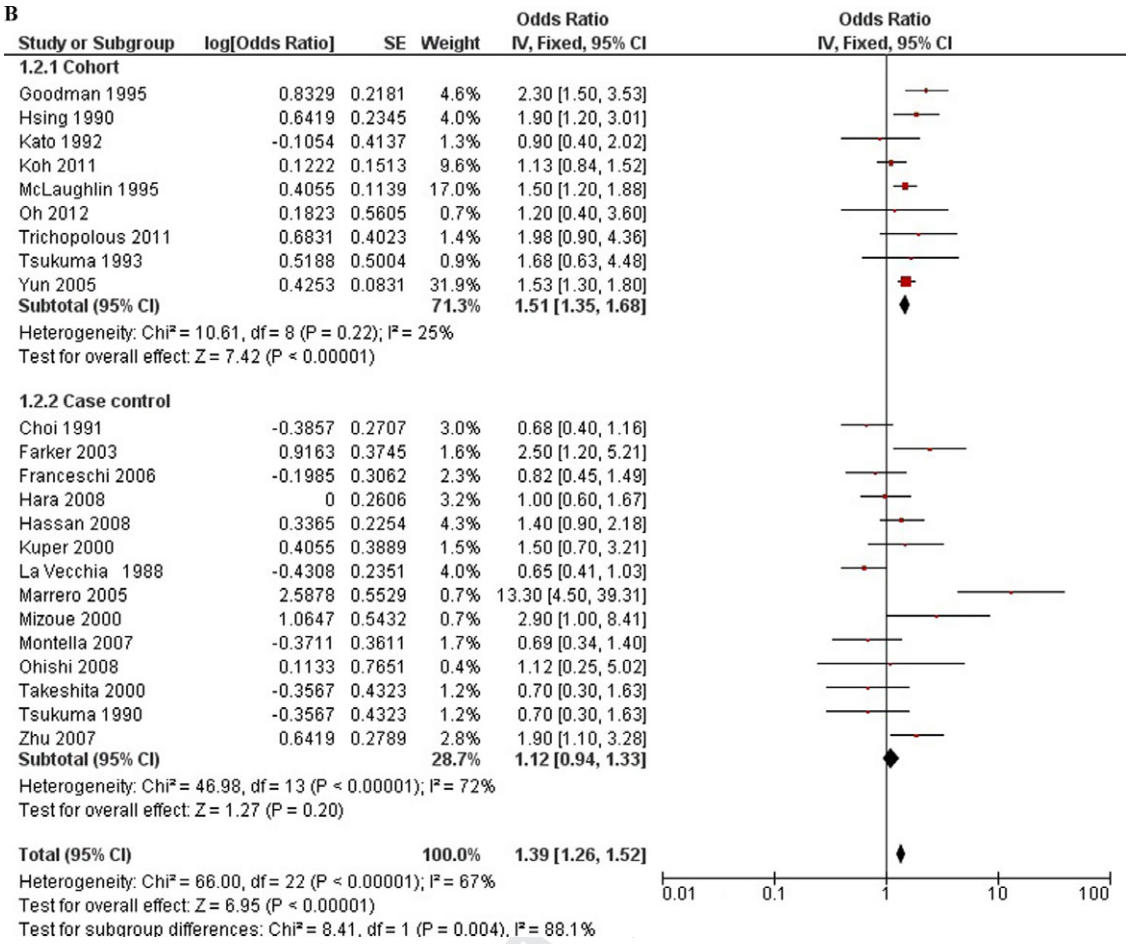

FIGURE 2 Continued

4 | DISCUSSION

To our knowledge, this is the most updated meta-analysis to provide an assessment of the impact of cigarette smoking on the incidence and mortality risk of HCC. Our analysis of observational data demonstrated that cigarette smoking increases the risk of development of and mortality from HCC.

HCC is an aggressive tumor with curable treatment options only in the earliest stages of the disease which constitute no more 20% of the total cases.[103,104] Prevention of this disease has thus been considered a much more effective strategy than treatment after development of the disease. Although prevention and treatment of HBV and HCV infections is considered the main pillar of HCC prevention, prevention of other potentially modifiable factors, for example, alcoholic consumption and smoking is also important in the overall preventive strategy for at-risk patients.[105,106]

Smoking has been considered one of the most important preventive causes of cancer and quitting smoking has been shown to lower the risks of many cancers; particularly lung cancer and head and neck cancer.[107,108]

A number of mechanisms may be hypothesized to explain tobacco-induced hepatic carcinogenesis. These include the observation of high DNA adducts in liver tissues of smokers compared to non-smokers.[109] Another mechanism involves the production of reactive oxygen species which leads to DNA damage and increased susceptibility to HCC.[110]

Smoking has been established as a modifying risk factor increasing the risk of HCC development in people with HBV, HCV, or alcohol consumption. A previously published meta-analysis has shown a more than additive interaction between HBV and smoking (S = 1.44; 95% CI: 1.00 to 2.06) and a more than multiplicative interaction (V = 1.60; 95% CI: 1.16 to 2.20) between HCV and smoking.[16]

Moreover, the meta-analysis by Lee and co-workers showed that it can work as an independent risk factor for liver cancer development.[17] The Lee and co-workers work has included 38 cohort studies and 58 case–control studies; however, it has to be noted that they included studies evaluating different categories of liver cancer (ie, studies evaluating HCC, cholangiocarcinoma, and mixed populations), while our study focuses only on HCC studies and thus we included a lower number of studies (81 studies). Our current analysis confirms and updates the findings from Lee and co-workers study; moreover, it shows that it increases mortality after diagnosis of HCC.

Such conclusions have widespread impact on the preventive policies to combat this disease and, in our viewpoint, it is important to counsel every smoker (particularly if at risk for HCC development) to quit smoking. Moreover, for people diagnosed with HCC, they are strongly advised to stop smoking and healthcare providers are

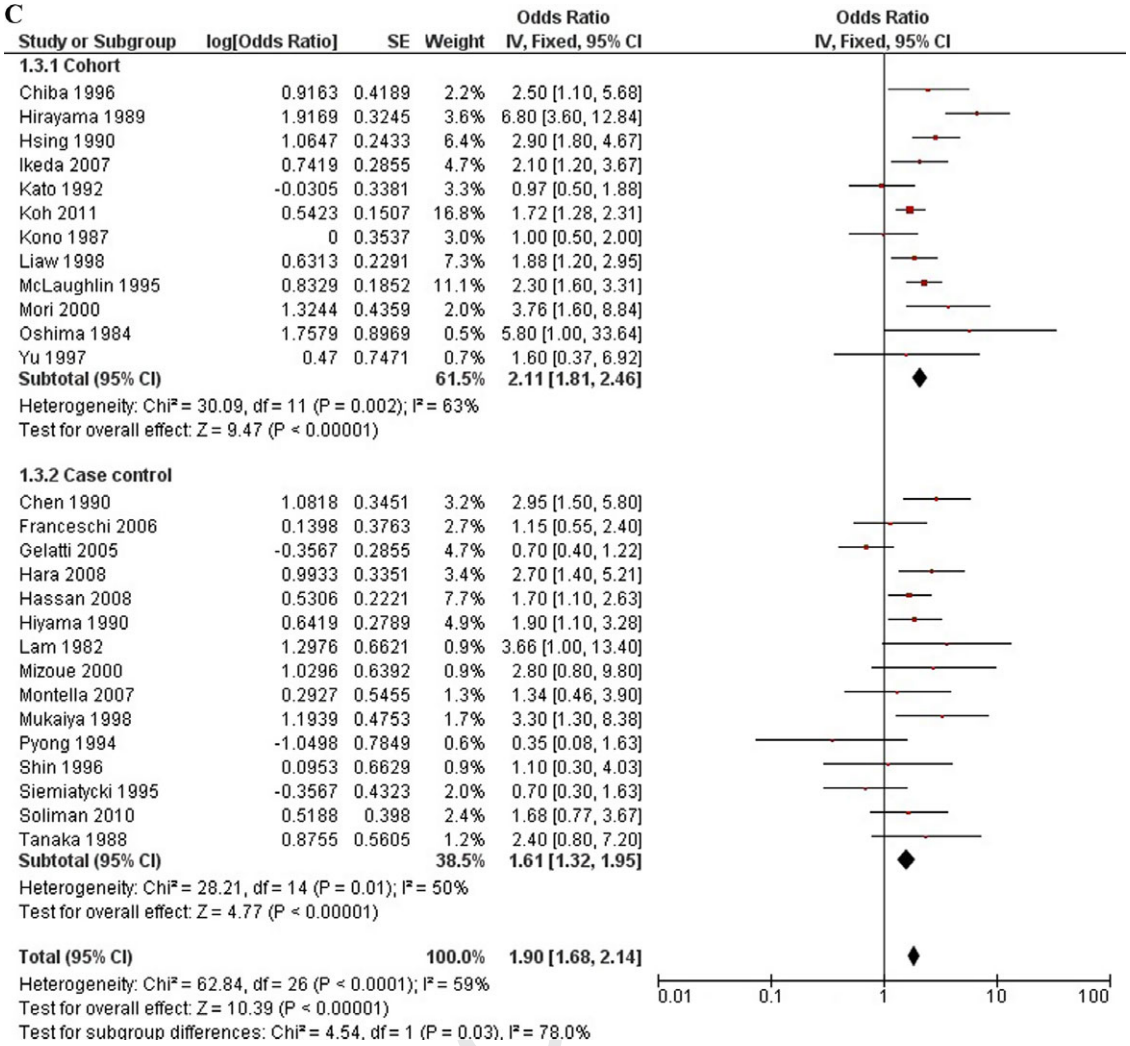

FIGURE 2 Continued

encouraged to counsel them on the potential deleterious effects on survival if they continue to smoke.

Some pharmacogenetic factors have been claimed to play an important role in the development of smoking-related HCC. In a meta-analysis conducted by Yu and colleagues, significant associations were found between both the Ile–Val and MspI polymorphisms of CYP1A1 and HCC risk among smokers (Ile-Val: OR = 1.40, 95% CI: 1.06 to 1.85; MspI: OR = 2.65, 95% CI: 1.47 to 4.77).[111] This may point out to differential genetic susceptibility among smokers to develop HCC. However, this point needs further clarification in future genetic epidemiology studies.

Among the setbacks of our meta-analysis is the difference in the adjustment procedure for each group of studies. In order to overcome this, we conducted a subgroup analysis for studies adjusted for HBV and HCV. Moreover, another setback is the existing heterogeneity of some of the included studies in terms of study designs; we conducted an additional subgroup analysis according to the study design in order to overcome the effect of this heterogeneity. Moreover, some additional confounding factors are not available in the majority of the studies like the duration of smoking (for current smokers) and the duration of abstinence of smoking (for former smokers).

In conclusion, our analysis of data demonstrated that cigarette smoking increases the risk of development of and mortality from HCC. Further, properly conducted observational studies are needed to further confirm the dose-effect and time-effect relations. Further success in the field of smoking prevention will hopefully contribute to declining incidence and mortality of liver cancer. This is combined with improved preventive strategies of other confirmed etiologic factors, for example, HBV and HCV as well as early diagnosis and better locoregional and systemic therapies for this fatal disease.

COMPLIANCE WITH ETHICAL STANDARDS

This study has not funded by any organizational body.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

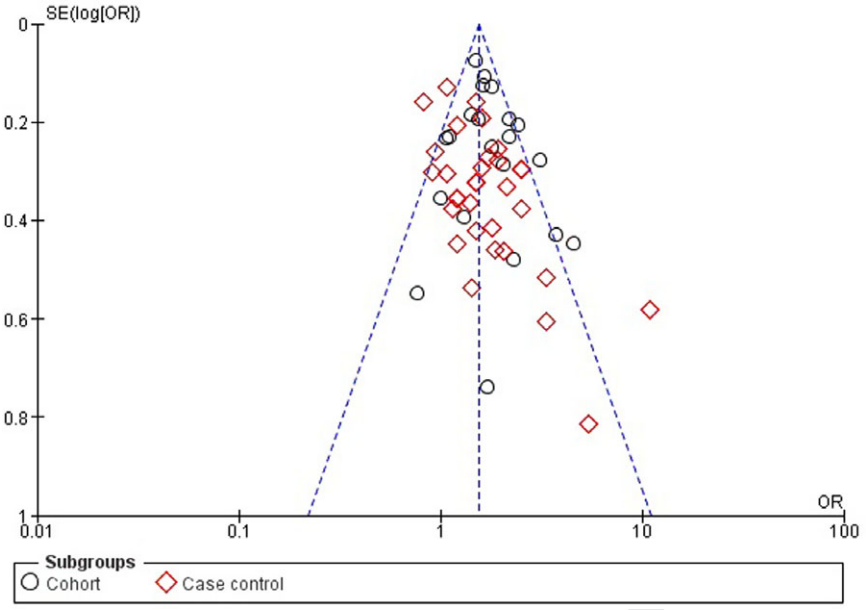

FIGURE 3 Funnel plot for publication bias

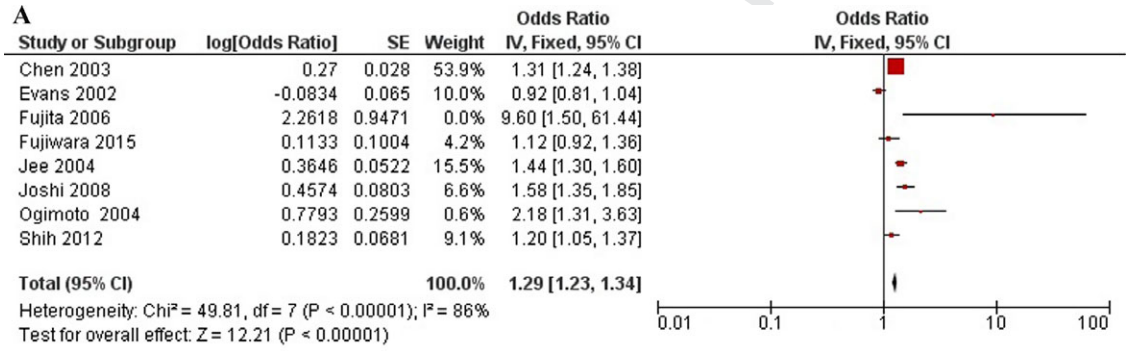

FIGURE 4 Forest plots of pooled odds ratio (ORs) for HCC mortality risk for: (A) current smokers; (B) former smokers

ETHICAL APPROVAL

This article does not contain any studies with human participants performed by any of the authors.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Abdel-Rahman O, Helbling D, Schöb O, et al. Cigarette smoking as a risk factor for the development of and mortality from hepatocellular carcinoma: An updated systematic review of 81 epidemiological studies. *J Evid Based Med*. 2017;00:1–10. https://doi.org/10.1111/jebm.12270