

Response to Review Comments

(Manuscript ID: 107723)

Dear editor,

We are very much thankful to the reviewers for their complete and thorough review. We have revised the manuscript in light of their useful suggestions and comments. We hope our revision has improved the manuscript to the level of your satisfaction. Number-wise answers to the specific comments/suggestions/queries are as follows.

Reviewer #1:

1. Clarity in Some Sections: While the manuscript is generally well-written, some sections could benefit from clearer explanations. For example, the discussion on the molecular mechanisms underlying the effects of dietary factors (such as aflatoxins or polyunsaturated fatty acids) could be more concise and structured to avoid potential confusion. Consider summarizing the mechanisms in bullet points or tables for easier comprehension.

Response: Thanks for the recognition of our work. The related sections are revised as suggested:

“AFB1 exerts hepatocarcinogenic effects primarily through cytochrome P450-mediated metabolic activation, generating the reactive AFB1-8,9-epoxide that forms DNA adducts (e.g., AFB1-N7-guanine)[13]. These lesions drive characteristic TP53 mutations, notably G→T transversions at codon 249, and genomic analyses reveal AFB1-specific mutational signatures including C>A transversions in GCN sequences and recurrent adhesion G protein-coupled receptor B1 mutations linked to tumor angiogenesis [14, 15]. Crucially, AFB1 synergizes with HBV infection, evidenced by accelerated HCC progression (odds ratio=5.47) in individuals with elevated AFB1-albumin adducts[16]. Independent carcinogenicity persists in HCV/non-viral HCC cases, with alcohol consumption exacerbating risks [17].”

“Current evidence supports prioritizing unsaturated fats over saturated fats for

HCC prevention, though n-6 PUFA effects may depend on viral hepatitis status.”

“β-Carotene metabolizes to retinol, activating RAR/RXR receptors; all-trans retinoic acid inhibits HCC proliferation via RXR dephosphorylation through Ras/Erk suppression[25], while vitamin A derivatives block metastasis by reversing epithelial-mesenchymal transition[26].”

2. Addressing Heterogeneity in Studies: The manuscript frequently references studies with large sample sizes but does not delve into the potential heterogeneity in study populations or study design that could influence the results. More discussion is needed on the challenges of comparing studies with different geographic populations, dietary habits, and diagnostic methods. This would enhance the critical appraisal of the evidence presented.

Response: We sincerely appreciate your valuable feedback and fully agree with your perspective. The information has now been incorporated into the relevant paragraph as follows:

“The NIH-AARP prospective observational cohort study (n=485,717) in the United States, found highest quintile fiber consumers had 31% lower HCC risk (hazard ratio, HR=0.69, 95%CI:0.53-0.90) [7]”

“The EPIC prospective observational cohort study (n=477,206) in Europe reported a 43%...”

“Large cohort studies reveal complex associations: while the Nurses’ Health Study and the Health Professionals Follow-up Study cohorts (~~n=138,483~~), which prospectively recruited 138,483 healthy adults, found...”

“Conversely, a Chinese prospective cohort (n=510,048) observed no overall association between red meat...”

“...while a U.S. prospective cohort study of health professionals (n=125,455) noted that whole grain and cereal fiber intake...”

“A Finnish randomized controlled cohort study (27,037 male smokers), originally designed to assess the effect of vitamin E on lung cancer risk, found

that each daily cup of coffee reduced HCC risk by 18% (RR=0.82, 95% CI: 0.73–0.93) [41].”

“The Shanghai Women's Health Study (~~n=71,841~~), a prospective cohort of 71,841 middle-aged Chinese women, provided compelling longitudinal evidence...”

“A nationwide prospective cohort study of 119,316 ~~participants~~ health professionals found that higher dietary inflammatory...”

3. Inclusion of Additional Lifestyle Factors: While the manuscript covers a broad range of lifestyle factors, there could be a brief mention of other emerging factors influencing liver cancer, such as environmental toxins, exposure to pollutants, and their cumulative impact with lifestyle habits. These factors are becoming increasingly important in public health discussions and could enrich the manuscript.

Response: Thank you for your suggestions. We have supplemented the relevant content in the document accordingly.

“Beyond the lifestyle factors discussed in this review, such as diet, smoking, metabolic health, physical activity, mental status, and sleep, emerging environmental exposures, including particulate matter, polycyclic aromatic hydrocarbons, heavy metals, industrial chemicals, and electromagnetic radiation, may influence HCC development and prognosis. Future studies should evaluate the roles of these emerging environmental exposures...”

*4. More Discussion on Treatment Implications: While the manuscript discusses lifestyle modifications as a preventive measure, the implications of these factors on treatment outcomes (including those undergoing surgery, chemotherapy, or immunotherapy) could be expanded. How might lifestyle interventions improve the efficacy of current treatments or reduce treatment-related side effects? Conclusion and Future Directions: The conclusion could be strengthened by including **a call for future research directions**. Specifically, there could be more emphasis on the need for randomized controlled trials to confirm the causal relationships between lifestyle factors*

and HCC. Additionally, exploring the role of socioeconomic factors in lifestyle choices and HCC risk could be an important area for future studies.

Response: We appreciate the reviewer's valuable suggestion. In our manuscript, we have specifically addressed the impact of lifestyle factors on HCC treatment outcomes through multiple dimensions. As highlighted in our analysis: (1) Dietary interventions may enhance therapeutic efficacy - tea-derived EGCG improves 5-FU chemosensitivity and inhibits metastasis, while coffee polyphenols and folate optimization reduce treatment-related inflammation and support immune function. (2) Physical activity demonstrates synergistic effects with immunotherapy, as evidenced by patients maintaining exercise during Lenvatinib/anti-PD-1 therapy showing 4.57-fold higher objective response rates and prolonged survival, potentially through exercise-induced immunomodulation and prevention of muscle wasting. (3) Mental health management addresses critical biological-psychological interactions, where psychiatric comorbidities worsen survival and depression exacerbates treatment resistance via chronic inflammation pathways. (4) Sleep optimization may further modulate inflammation networks associated with tumor progression. While current evidence supports their adjunctive potential across treatment modalities (chemotherapy, immunotherapy, and supportive care), we acknowledge that deeper mechanistic insights into lifestyle-treatment interactions remain limited by existing preclinical and clinical study designs. Therefore, we fully endorse incorporating recommendations to prioritize randomized controlled trials to confirm causal relationships between lifestyle factors and HCC outcomes, as well as exploring socioeconomic influences on lifestyle choices and HCC risk, and have revised relevant sections accordingly. Future research should prioritize standardized protocols to validate these multimodal synergies and optimize their integration into comprehensive HCC management strategies.

“Future studies should evaluate the roles of these emerging environmental exposures, refine lifestyle assessments with quantitative measures, explore

diet-treatment interactions, and prioritize randomized controlled trials to establish causality between modifiable lifestyle factors and HCC risk. Additionally, personalized interventions must integrate genetic profiles and socioeconomic influences, particularly how income disparities and healthcare access mediate lifestyle behaviors and hepatocarcinogenesis explore lifestyle interactions with HCC treatments and refine risk assessment methods”

5. *Minor Edits: There are a few minor grammatical and typographical errors throughout the manuscript that should be addressed. The references to tables and figures could be better integrated into the text, ensuring that the reader can easily navigate between them.*

Response: Based on this suggestion and the requirements of the journal, we have selected an optimal service provider (i.e., MedE) from the recommended language editing service providers and conducted English polishing as well as grammar revision for this manuscript, obtaining the relevant certificate in the process. Additionally, the references to tables and figures have been integrated into the text as advised.

“According to current evidences, key dietary strategies include avoiding aflatoxin exposure, increasing fiber and vegetable intake, and consuming coffee, green tea, and n-3 PUFA-rich fish, while limiting alcohol and processed red meats-(Table 1), as summarized in Table 1.”

Reviewer #2:

1. *In the introduction part, authors have claimed that “major risk factors include chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, alcoholic liver disease, non-alcoholic steatohepatitis (NASH), and aflatoxin exposure. Although targeted therapies (e.g., Sorafenib, Lenvatinib) and immune checkpoint inhibitors (e.g., Atezolizumab combined with Bevacizumab) have improved outcomes for some patients, overall therapeutic efficacy remains limited, with no significant breakthrough in 5-year survival rates [4]”. I suggest that it’s not have a close relationship with lifestyles.*

Response: Thank you for your suggestion. After carefully reviewing the context, we realized that this paragraph indeed has limited relevance to the main topic. Therefore, we have followed your advice and removed this text.

2. For the part of dietary components, there are big different between east and west, however, authors have not taken it into consideration, it's a significant limitation in this review. I suggest that authors should compare different lifestyles between east and west.

Response: We fully agree with your insightful observations regarding East-West dietary differences. Precisely for this reason, we have dedicated a "Dietary Patterns" section to systematically analyze how various eating habits influence HCC incidence and prognosis. This section specifically examines three distinct dietary frameworks: Western-leaning patterns (e.g., Mediterranean diet), Eastern-leaning patterns (e.g., Chinese Healthy Eating Index), and neutral patterns (e.g., empirical dietary inflammatory pattern). While we have emphasized these dietary frameworks, we acknowledge that the limited available literature restricts direct comparative analyses across cultural contexts. It is possible that our original phrasing did not explicitly highlight these aspects, and we have therefore refined this section to enhance clarity regarding these geographically distinct dietary influences on HCC."

"Emerging evidence demonstrates significant associations between dietary patterns and HCC risk, with distinct protective effects observed across cultural contexts."

"In contrast, Chinese studies yielded culturally specific insights: comparable results, with higher Chinese Healthy Eating Index (CHEI) scores were associated with 26% lower..."

"These findings consistently demonstrate that adherence to culturally rooted healthy dietary patterns can reduce HCC risk across diverse populations."

"Public health strategies promoting regionally tailored dietary guidelines ~~these dietary patterns~~ may substantially impact HCC prevention, especially in high-

risk groups.”

3. For the part for “TOBACCO USE AND HCC”, there are little new findings in this review, I suggest that authors should make it shorten.

Response: This section has been condensed from 234 words to 108 words as suggested.

“A meta-analysis of 81 epidemiological studies revealed current smokers have had 55% higher HCC incidence (OR=1.55, 95% CI: 1.46-1.65) and 29% greater HCC mortality (OR=1.29, 95% CI: 1.23-1.34) compared to non-smokers, with heavy smokers showing 90% increased risk (OR=1.90, 95% CI: 1.68-2.14) [72]. These findings are Subsequent research corroborated by recent studies showing current smokers have a 2.46-fold higher HCC risk in current smokers (HR=2.46, 95% CI: 1.77-3.43) in a dose-dependent manner [60]. Effects were most pronounced in viral hepatitis patientsThe detrimental effects are particularly pronounced in viral hepatitis patients. A Swiss cohort study found smokers with HBV/HCV-related HCC had nearly triple the mortality risk of non-smokers (HR=2.99, 95% CI: 1.70-5.23) [73, 74]. Similarly, Chinese research demonstrated smoking increases HCC risk by 49% in long-term smokers (>40 years). Mechanistically, Smoking promotes HCC through multiple pathways: (1) direct DNA damage/p53 inactivation carcinogenesis via tobacco constituents that damage DNA and inactivate tumor suppressors like p53 [75]; (2) immunosuppressive effects in HBV carriers by elevating viral load while reducing interferon- γ and impairing NK cell function, HBV-related immunosuppression (elevated viral load, impaired natural killer cells) [76], and inflammation/fibrosis (stellate cell activation, iron overload); (3) pro-inflammatory and fibrogenic actions through stellate cell activation and cytokines that accelerate cirrhosis, along with erythropoietin-mediated iron overload exacerbating oxidative stress [75]. It synergizes with viral hepatitis but not alcoholNotably, smoking interacts synergistically with viral hepatitis but not necessarily with alcohol, suggesting distinct pathogenic mechanisms

[60]. While some studies show mixed survival outcomes Although certain studies have failed to demonstrate significant survival differences based on smoking status in HCC patients with mixed etiologies [77], the overwhelming body of evidence shows that tobacco use substantially elevates HCC risk and adversely impacts disease progression."

4. For the part for "EMERGING RESEARCH FRONTIERS", I suggest that there is not close relationship with the topic for this review- "Lifestyle Factors in Hepatocellular Carcinoma: From Pathogenesis to Prognosis".

Response: Thank you for your suggestion. We agree with your viewpoint and have accordingly streamlined and removed the relevant content.

"5. EMERGING RESEARCH FRONTIERS

5.1 Refining Lifestyle Assessments Beyond Simple Classifications

~~Current categorizations (e.g., "ever/never" smoker) are overly simplistic and fail to capture dose-response relationships, particularly in prognostic studies [24]. Future research must incorporate quantitative measures and account for synergistic effects between lifestyle factors. For instance, smoking combined with low education and physical inactivity exacerbates unhealthy dietary patterns, whereas moderate wine consumption is often linked to healthier overall behaviors, including higher fruit/vegetable intake and reduced red meat consumption [109]. Additionally, dietary patterns should be evaluated holistically, considering sociocultural influences (e.g., Mediterranean vs. Asian diets) rather than isolated nutrients [110].~~

5.2 Lifestyle Interactions with HCC Treatment Modalities

~~Emerging evidence suggests that dietary habits may influence treatment responses in HCC patients. A priori dietary patterns (e.g., Mediterranean, Dietary Approaches to Stop Hypertension, or plant-based diets) have demonstrated benefits in metabolic and cardiovascular health, potentially improving outcomes in HCC patients undergoing surgery, chemotherapy, or immunotherapy [68, 111]. However, these patterns must be culturally~~

adapted—for example, Asian diets emphasize soy and rice, whereas Western diets include more dairy and red meat. Future studies should explore whether specific diets enhance immunotherapy efficacy or reduce chemotherapy toxicity.

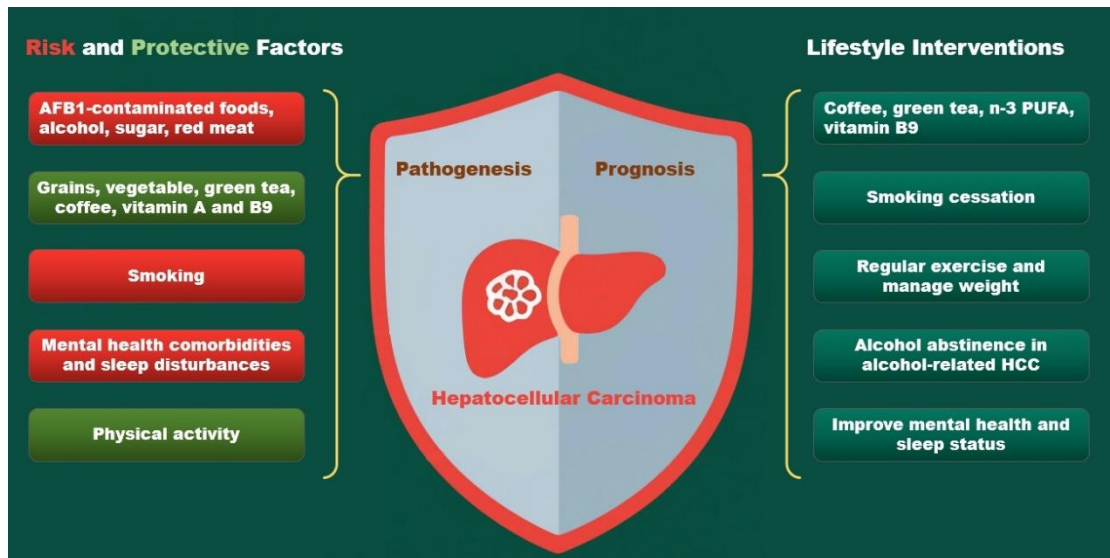
5.3 Personalized Lifestyle Interventions

Given the heterogeneity in HCC risk factors, such as viral hepatitis, metabolic syndrome, or alcohol-related cirrhosis, tailored prevention strategies are needed. Genetic predispositions may interact with lifestyle, necessitating precision nutrition approaches. Furthermore, socioeconomic status and education influence lifestyle behaviors, suggesting that interventions should be stratified by risk profiles rather than adopting a one-size-fits-all approach.”

“Future studies should evaluate the roles of these emerging environmental exposures, refine lifestyle assessments with quantitative measures, explore diet-treatment interactions, and prioritize randomized controlled trials to establish causality between modifiable lifestyle factors and HCC risk. Additionally, personalized interventions must integrate genetic profiles and socioeconomic influences, particularly how income disparities and healthcare access mediate lifestyle behaviors and hepatocarcinogenesis ~~explore lifestyle interactions with HCC treatments and refine risk assessment methods”~~

5. From Pathogenesis to Prognosis, I think it's one of the most important points in this review, I suggest that authors should make figure(s) to show how lifestyles “from pathogenesis to prognosis” in HCC, it would be better to make readers understand.

Response: We fully agree with your perspective and have added a schematic diagram as suggested to illustrate how lifestyles influence HCC from pathogenesis to prognosis.



“Figure 1. Hepatocellular carcinoma and lifestyle. AFB1, aflatoxin B1; HCC, hepatocellular carcinoma; PUFA, polyunsaturated fatty acids.”

In the revision manuscript, authors have revised and edited their manuscript according to the editors’ comments and suggestions, and now, I think that it’s ready for publication.

Response: Thanks for your comments.