Journal of Advanced Zoology
ISSN: 0253-7214
Volume 44 Issue S5 Year 2023 Page 2557:2566

A Review On Association Of Diet And Lifestyle With The Occurence Of Hepatocarcinoma

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Article History

Received: 30/09/2023
Revised: 15/10/2023
Accepted:30/10/2023

Abstract

The unrestrained development of malignant cells within the liver characterizes hepatocellular carcinoma, often known as liver cancer, which is a severe global health problem. High consumption of processed foods, sugary drinks, and red meats has been associated with an enhanced risk due to their propensity to generate inflammation and oxidative stress, which promote carcinogenesis. The anti-inflammatory and antioxidant properties of diets rich in fruits, vegetables, whole grains, and lean proteins, on the other hand, have protective effects. Lifestyle decisions further contribute to this malignancy because drinking alcohol directly damages liver cells and raises the chance of cirrhosis. Additionally, obesity, which is commonly linked to poor dietary choices, increases the risk by leading to insulin resistance and fatty liver disease. The risk of liver carcinogenesis is reported to get reduced by regular exercise. Men often experience 2 to 4 times the rate of liver cancer as women. An effort must be made to improve prevention, early diagnosis, and treatment strategies in the fight against this fatal condition. This abstract will concentrate on the epidemiology, risk factors, present treatments, and future research possibilities of liver cancer in order to provide a concise overview of the disease.

Keywords: Hepatocellular carcinoma, liver cancer risk factors, nanotechnology, diet and liver cancer, HCC risk

Introduction:

Liver cancer is the only one of the top five deadliest cancers to have a yearly percentage increase in incidence, and it is the fifth most common cancer in the United States and the most common cancer worldwide (Siegel *et al.*,2019). Liver disorders are more common in developing countries (Starley *et al.*,2010). Hepatitis B and C

viruses, fatty liver disease, alcohol-related cirrhosis, smoking, obesity, diabetes, iron overload, and a number of dietary exposures are risk factors (Center *et al.*,2011). Poor prognosis is associated with liver cancer. Only 5% to 15% of individuals are candidates for surgical removal, which is only appropriate for people in the early stages of the disease and because of impaired hepatic regenerating ability, usually without cirrhosis; right hepatectomy has a higher risk for post-operative complications than left hepatectomy.The following are some treatment options for more advanced stages: (a) Trans-arterial chemoembolization (TACE), which improves 2-year survival for patients with intermediate-stage HCC by 23% compared to conservative therapy. (b) The most popular option for cases in their late stages is oral dosing with the kinase inhibitor sorafenib. However, less than one-third of patients see therapeutic improvement, and medication resistance develops six months after the regimen is started (El-Serag *et al.*,2008). Chemotherapeutic medicines, like sorafenib, pose additional problems with long-term use, including as toxicity and/or medication inefficiency. Because of this, neither current ablation therapies nor chemotherapy significantly improve the course of this deadly disease. More study is required to develop more effective therapies for treating liver cancer.The patient's diet is linked to cancer prevention, development, progression, and treatment. According to a European study, consuming more fruits and vegetables reduces the risk of developing cancer (Soerjomataram*et al.*,2010). Different natural substances found in fruits, vegetables, and spices work to inhibit the development of cancer-causing processes and to boost the development of cancer-prevention mechanisms. The anti-tumor, anti-proliferative, anti-inflammatory, and anti-oxidant systems are activated by these substances, opening up potential therapeutic alternatives for novel cancer therapy regimens (Banerjee *et al.*,2017, Singh *et al.*,2017 & Li *et al.*,2019). Some substances exhibit selectivity in producing cytotoxicity to cancer cells while having no effect on non-cancerous cells (Zhou *et al.*,2016).For instance, substances like piperine block enzymes important for drug metabolism, which may point to a usage of co-administration with present or proposed chemotherapeutic treatments to enhance plasma concentrations in the future (Bhardwaj *et al.*,2002). The effectiveness of present pharmacological regimens might be improved by other natural substances without increasing host toxicity. For instance, polysaccharides from Tricholoma matsutake and Lentinus edodes increase the inhibitory impact of 5-fluorouracil (5-FU) on H22 cells (Ren *et al.*,2014).

Cancer cell eradication frequently involves the immune system. Antigen-presenting cells engage class I and class II major histocompatibility complex (MHC) molecules by delivering tumor fragment peptides. Due to the ability of cancers to circumvent these activities, this method may, however, be ineffectual (Coffelt *et al.*,2016, Boon *et al.*,2006).Additionally, desmoplasia and tumor development biomarkers can be addressed to stop the progression of tumours (Chen *et al.*,2014). Multidrug resistance is a problem with chemotherapeutic drugs. Resistance is brought on by cancer stem-like/cancer starting cells, which also act as a route for metastasis and tumor recurrence. Targeting stem cells, immunotherapy aids in the fight against chemotherapeutic drug resistance (Pan *et al.*,2015). Other effective methods include cancer vaccines and immune checkpoint drugs that target PD-1 and PD-L1 to stop the spread of cancer and destroy cancer cells. Because sorbafenib inhibits immunosuppression, it is reasonable to think about using it in combination therapy (Kudo, 2016, Zhao *et al.*,2015).
Nanotechnology can boost the activity of medications that are only marginally successful at locating and destroying cancer cells. It may be used to develop or improve therapies that have better outcomes for neoplasms.This is done by reducing the possibility of systemic toxicity and side effects by improving the size and surface features of medications and/or using tissue-specific homing devices to target locations (Reddy *et al.*,2011). By enhancing permeability, retention, and pharmacokinetic characteristics, nanotechnology may modify conventional combination therapy techniques and minimize side effects (Singh *et al.*,2017, Davis *et al.*,2008). Through treatment plans that mix several agents to enhance the effects of medications, nanoparticle approaches offer a bright future (Singh *et al.*,2018, Livney *et al.*,2013).

Scientists and medical professionals are looking for novel therapeutic methods to increase patient survival due to the liver cancer patient prognosis. Combining drugs and changing how they are administered or delivered open up new possibilities for improving the prognosis for cancers.The most popular treatments for advanced HCCs, such as chemotherapies, immunotherapies, and nanoparticles, are described in this paper, along with the justification for several ongoing clinical trials.

Material and methods:

By looking for published research papers on liver cancer in PubMed, PubMed Central, the CDC, and Google, the appropriate information for this review article was located. Original studies and review articles from around

the world made up these research projects. Vague descriptions of exposure were discarded, and only published data were taken into account. One of the requirements for inclusion is information gathered from reliable sources of publications on the subject. The study excluded the use of other languages.

Incidence of Liver Cancer:

Overall incidence rate trends: For 5 of the 32 cancer registries taken into account in the analysis, the incidence rates of liver cancer statistically substantially declined for both men and women from 1993 through 2002, whereas they increased for 8 of the 32 cancer registries (Fig. 1). Western Europe, North America, and Oceania saw the majority of the gains while Asia had the majority of the losses. The United Kingdom saw the highest increases in liver cancer incidence between 1993 and 2002, with rates rising by 6.2% and 6.9% year for men and women, respectively (Fig. 1). Saarland (Germany) and France (8 registries) were other Western European registries with rising liver cancer incidence among men and women. Liver cancer incidence mainly stayed steady or slightly rose in Northern and Eastern Europe.Sweden and Poland (2 registries) stand out as major exceptions, where declining rates were seen. In Sweden and Poland (2 registries), the annual incidence rates of liver cancer among men and women fell by 1.6% and 2.3%,
respectively, and by 4.5% and 5.7%, respectively, between 1993 and 2002.

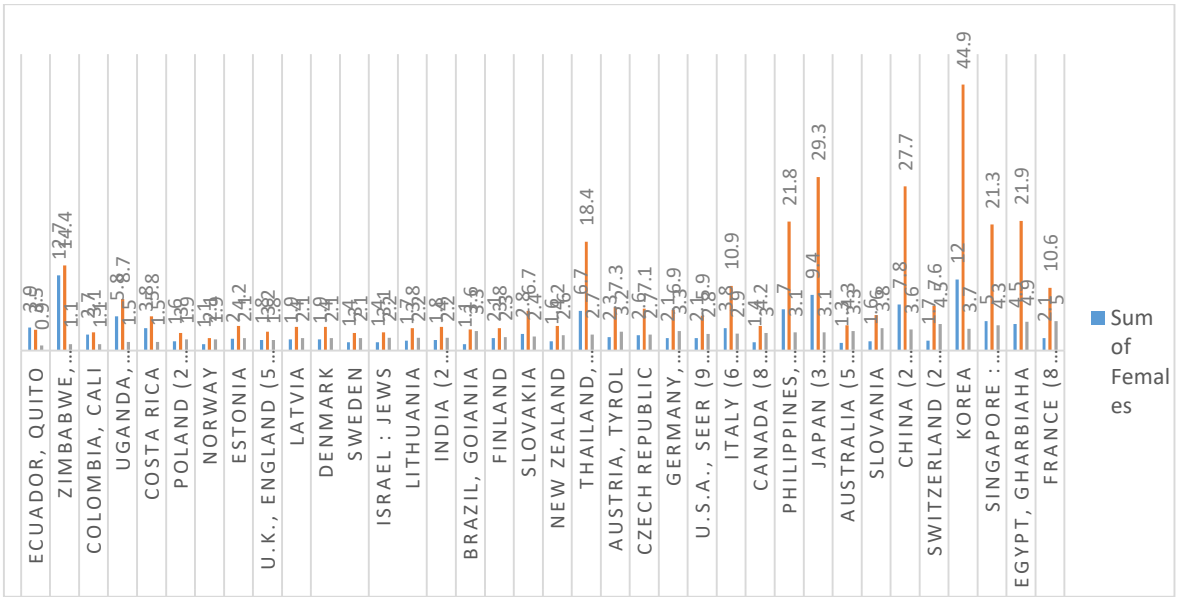

Fig-1: Liver cancer incidence trends among males and females in select registries, 1993–2002.

Incidence rates for liver cancer rose in all registries studied in North America and Oceania, including the United States (SEER 9), Canada, Australia, and New Zealand. The highest increases were seen in Australia, where rates rose 4.3% annually for men and 6.3% annually for women from 1993 to 2002 (Fig. 1). In South America, the incidence trends for liver cancer were more diverse.Both males and women's incidence rates were unchanged in Colombia (Cali) and Ecuador (Quito), however from 1993 to 2002, rates in Brazil (Goiania) declined 7.1% annually for women while remaining stable for men. Contrarily, during the same period, the incidence rates of liver cancer in Costa Rica increased 5.0% for males and 6.0% for women, respectively.

China, the Philippines, and Japan were three of the seven registries or groups of registries that showed declining rates for both men and women in Asia, where liver cancer incidence rates are among the highest in the world (Fig. 1). Incidence rates for both men and women were constant in Singapore (Chinese), Chiang Mai, Thailand, and Israel (Jews).From 1993 to 2002, the incidence of liver cancer in India increased among women but remained steady in men. The trends based on 10 years of data (1988-2002) and 15 years of data (1988-2002) are largely comparable

Incidence rates by age: In each of the five registries we looked at—China (Qidong County), Zimbabwe (Harare), Costa Rica, the United States (SEER 9), and Sweden—liver cancer incidence rates rose with advancing age. Nevertheless, rates for Qidong County, China were incredibly high and substantially above the reported age-specific rates in the other 4 registries in every age category beyond age 29. The incidence rate of

male liver cancer (per 100,000) in Qidong County, China, for the 45–49-year age group in 1993–1997, the most recent years for which data are available, was almost 30 times higher than the rates for the same age and sex in the US, Costa Rica, Sweden, and Harare (Zimbabwe) in 1998–2002

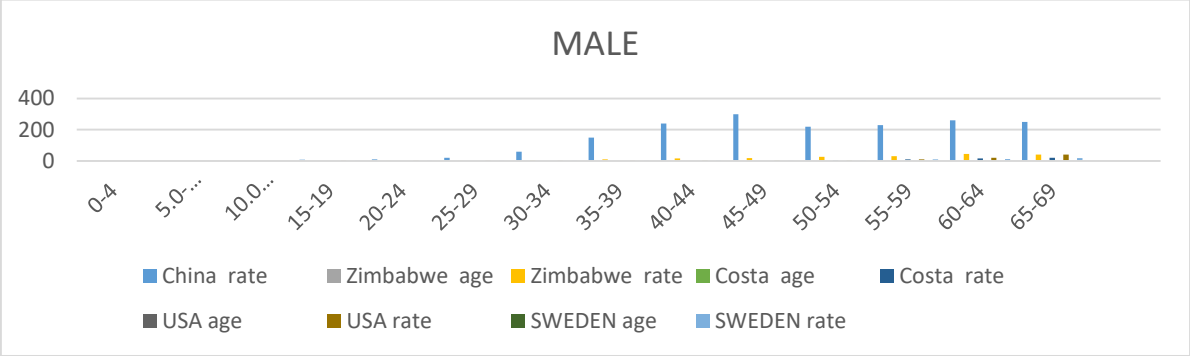

Fig-2: Average annual incidence rates by age group male for select registries, 1998–2002. Data for Qidong County, China are for 1993–1997.

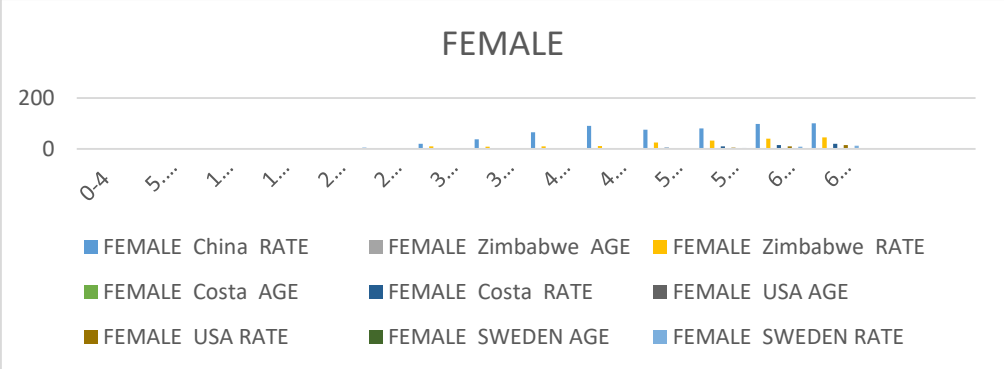

Fig-3: Average annual incidence rates by age group of female for select registries, 1998–2002. Data for Qidong County, China are for 1993–1997

Diet and liver cancer risk: In 2000, liver cancer was thought to have caused 564,000 cases and 549,000 fatalities (Liu *et al.*,2016). Liver cancer rates vary over 20 times between nations, with sub-Saharan Africa and Southeast Asia having substantially higher rates than Europe and North America (Aleksandrova *et al.*,2016); around 75% of liver cancer cases occur in poorer nations. Hepatitis B and, to a lesser extent, hepatitis C virus chronic infection are the main risk factors for hepatocellular carcinoma, the most common kind of liver cancer (de Castro *et al.*,2017). Consuming foods contaminated with the mycotoxin aflatoxin (Shan *et al.*,2012, Di Minno *et al.*,2012) is a significant risk factor for hepatitis virus infection in those living in developing nations. The greatest diet-related risk factor for liver cancer in Western nations is excessive alcohol use, likely as a result of cirrhosis and alcoholic hepatitis (Yang *et al.*,2017). Though little is known about potential dietary cofactors for viral carcinogenesis, this might be a crucial topic for study (Mittal *et al.*,2013).

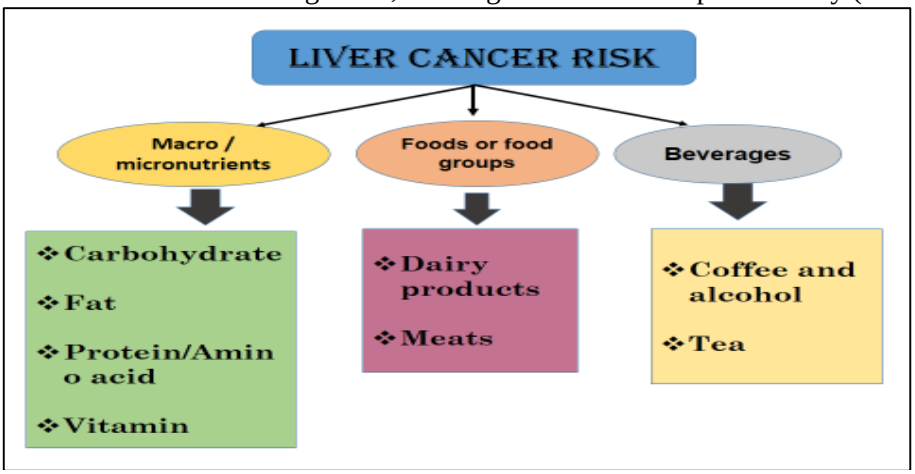

Fig.4: Schematic diagram of diet and liver cancer risk.

Macro-/micronutrients and liver cancer risk:

Carbohydrate: -The link between use of sugar-sweetened beverages and risk of HCC has received mixed epidemiological evidence and is restricted. Only two cohort studies (Fedirko *et al.*,2013, Vogtmann *et al.*,2013)that looked into the relationship between total carbohydrate intake and the risk of developing liver cancer found no link and did not take chronic HBV and/or HCV infection into account. Surprisingly, a case-control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort and the National Institutes of Health-American Association of Retired Persons (NIH-AARP) cohort, respectively, has suggested an inverse association of sucrose and fructose intake with the risk of HCC. Given the small number of liver cancer cases in the two investigations, the outcomes could, however, have been a coincidence. Based on the already scant information, the relationship has not been adequately described overall. Future research should provide additional details on dietary carbohydrate quantity, quality, and HCC risk given that carbs are the primary source of energy for humans. This information may assist people choose meals that contain "good" carbohydrates. A low carbohydrate:fibre ratio in the diet was discovered to be associated with reduced risk of T2D (AlEssa *et al.*,2015) and CHD (AlEssa *et al.*,2018), though its association with liver cancer has not been studied. For instance, a carbohydrate:fibre ratio as a new measure of carbohydrate quality was shown to be more superior to other consumer-oriented methods for selecting more healthful foods (Mozaffarian *et al.*,2013).

Fat:-Only a few studies have examined the relationship between n-3 PUFA and liver cancer risk; both found an inverse link, one in a Japanese cohort (Sawada *et al.*,2012) and the other in an Italian hospital-based case-control study (Polesel *et al.*,2007). Although there may be a potential protective function for plant lipids and unsaturated fats, particularly n-3 PUFA, in the development of liver cancer, no conclusive conclusion was made based on the available information. More epidemiological research in this area is needed, along with consideration of fat subtypes, fat food sources (animal, vegetable, and dairy fat), and the potential substituting effects (Song *et al.*,2018) of various fat subtypes, such as substituting plant fat for animal or dairy fat or substituting unsaturated fat for saturated fat in the development of hepatocarcinogenesis, which may be of public health and aetiological significance.

Protein/Amino acid: - Leucine, isoleucine, and valine, the three BCAAs, are three of the nine necessary amino acids for humans. They have been demonstrated to have an impact on insulin resistance, hepatocyte regeneration, protein metabolism, apoptosis, and gene expression (Takami *et al.*,2016). In vitro studies have also demonstrated that they can stop liver cancer cells from proliferating (Sugiyama *et al.*,1998). Additionally, it was discovered that all three BCAA accelerated the post-transcriptional degradation of insulin-induced vascular endothelial growth factor mRNA, which decreased the expression of vascular endothelial growth factor during the development of HCC (Miuma *et al.*,2012). It's interesting to note that a recent meta-analysis of seven cohort studies and 10 case-control studies found a possible protective relationship between BCAA and HCC risk(Luo *et al.*,2014). To our knowledge, no epidemiological studies have looked specifically at the alleged link between dietary BCAA intake and the chance of developing liver cancer.

Vitamin: - Current experimental evidence supports the roles of a number of vitamins or trace elements (such as vitamins A, C, and E, Se, Fe, Zn, Mn, and Cu) as antioxidants in protection against oxidative stress (such as lipid peroxidation, DNA damage, and protein damage) (Wolonciej *et al.*,2016), which may generate reactive oxygen species and oxygen-free radicals and is linked to carcinogenesis. Nevertheless, more related studies, particularly those conducted in low-risk countries (like those in Europe or North America), are required given the few observational studies that have been conducted so far, all of which were done in China (a high-risk country), with the exception of a cohort study in Finland (Lai *et al.*,2014).

Foods or food groups and liver cancer risk:

Dairy products: -Prior research revealed that consuming a lot of dairy products can raise plasma IGF-1 levels(Ma *et al.*, 2001, Hoppe *et al.*, 2004, Heaney *et al.*, 1999). In experimental studies, including those on HCC, the elevated concentration of IGF-1, a crucial regulator of cell proliferation, differentiation, apoptosis, and carcinogenesis, may have a role in the development of a number of malignancies. According to the evidence, two cohort studies (Duarte-Salles *et al.*, 2014, Yang *et al.*, 2020) but not all demonstrated that higher total dairy product intake (three servings or more per day) was associated with a statistically significant higher risk of HCC, whereas yogurt consumption was suggestively associated with lower HCC risk. These associations persisted among participants who were free of HBV and HCV infections.Despite the fact that dietary Ca, vitamin D, fat, and protein from dairy sources were linked to an elevated risk of HCC in the EPIC

cohort, we were unable to detect these connections in the Nurses' Health Study (NHS) and Health Professionals Follow-Up Study (HPFS).Circulating IGF-1 may be one of the biological processes behind the beneficial links between dairy products and HCC, although additional research in experimental and prospective settings is required. Future research that thoroughly examines the relationship between dairy products and liver cancer according to various food groups (total dairy products, milk, cheese, and yogurt) as well as their main micro- and macronutrient components (Ca, vitamin D, fats, lactose, and protein) is required.

Meats: **-**Red meat consumption was categorized by the International Agency for Research on Cancer in 2015 as "probably carcinogenic to humans" (Group 2A), whereas red meat consumption in processed form was categorized as "carcinogenic to humans" (Group 1) (Bouvard *et al.,* 2015). The possibly carcinogenic chemicals N-nitroso compounds generated endogenously from nitrate or nitrite during meat processing or preservation, as well as heterocyclic amines (HCA) during meat cooking, are other potential underlying processes in addition to the high quantities of saturated fat and Fe found in meats. Contrarily, consumption of white meats (poultry and fish, specifically) has been linked to a lower risk of cancer (Luo *et al.,* 2014, Huang *et al.,* 2015), probably as a result of the long-chain omega-3 PUFAs that are contained in fish, particularly fatty fish. White meat is also a significant source of BCAA, which may act as a preventative measure against hepatocarcinogenesis. White meat includes fish and chicken.

Beverages and liver cancer risk:

Coffee and alcohol: **-**According to WCRF/AICR's 2013 SLR (19), the evidence that coffee prevents liver cancer is "probable" but not "convincing." A total of sixteen pertinent research was published after the 2013 SLR, including eight meta-analyses and eight cohort studies. According to the studies mentioned above, drinking coffee lowers your risk of developing liver cancer. Current meta-analyses (Bravi *et al.,* 2013, Bravi *et al.,* 2017, Godos *et al.,* 2017) consistently demonstrated a 15–20% risk reduction of HCC with an increase in coffee consumption of one cup per day. Men, Asian populations, and case-control studies all showed a larger protective connection between frequent coffee consumption and risk of developing liver cancer than did women, non-Asian groups, and cohort studies. Decaffeinated coffee displayed a lower non-significant inverse connection with the risk of liver cancer compared to caffeinated coffee(Kennedy *et al.,* 2017).According to WCRF/AICR(19), excessive alcohol consumption is a strong risk factor for developing liver cancer. This conclusion was corroborated by the following cohort studies(Loomba *et al.,* 2013, Petrick *et al.,* 2018) and meta-analyses (Turati *et al.,* 2014, Chuang *et al.,* 2015).The 2013 SLR (19) leaves open the question of whether light-to-moderate alcohol consumption (e.g., 3 drinks/d) is related to liver cancer. Recent epidemiological research, including a meta-analysis of 19 cohort studies and a US cohort consortium study, shows a negative correlation between light-to-moderate alcohol consumption and the risk of HCC but not ICC. The consumption of moderate amounts of alcohol is linked to a lower incidence of T2D, probably by improving insulin sensitivity. So, mild to moderate alcohol consumption may lower the risk of HCC through lowering the risk of T2D. More research is required, nevertheless, given to the scant available evidence.

Tea: **-**One of the most popular drinks drunk worldwide, particularly in China, is tea. Due in significant part to the polyphenolic antioxidants in tea, research on animals and in vitro specimens have demonstrated a preventive effect against cancer start and subsequent development(Yang *et al.,* 2009). In a previous meta-analysis of six case-control studies and seven cohort studies, we discovered a significant inverse association for green tea (relative risk 079, 95% CI 068, 093) and a suggestive inverse association for overall tea consumption and the risk of developing liver cancer (relative risk 077, 95% CI 057, 103) (Sing *et al.,* 2011). After that, tea consumption continuously demonstrated a protective link with HCC risk in observational studies (Baima*et al.,* 2015, Huang *et al.,* 2016, Tamura *et al.,* 2018).Though a nested case-control study (211 cases and 1067 matched controls in the Shanghai cohort) (Butler *et al.,* 2015) demonstrating that higher urinary catechin levels (which partly reflect green tea consumption) may not decrease but increase risk of HCC development (online Supplementary Table S3) did not support these findings. Future prospective studies that take different aspects of tea into account, such as tea types, brewing techniques, and tea strength, are required to fully characterize this association. Ideally, these studies would also include useful biomarkers that could more accurately reflect tea consumption in a subset of participants to confirm consistency and, if possible, correct for measurement error.

Conclusion:

In conclusion, despite significant knowledge gaps regarding food and risk for liver cancer, current epidemiological evidence shows an important role for nutrition in the development of liver cancer. Future

large-scale nutritional epidemiological studies on diet and liver cancer are necessary, and they should take the following factors into account: (1) how to best measure diet; (2) the potential etiological heterogeneity between liver cancer subtypes (HCC v. ICC); (3) the potential impact of chronic HBV or HCV infection; (4) high-risk populations (such as those with NAFLD or cirrhosis); and (5) a potential interaction with host gut microbiota or genetic variations. Additionally, more research is also needed to fully understand the underlying mechanisms that relate diet to liver cancer.

Conflict of Interest: There is no conflict of interest related to the study.

Author contributions: Acquisition and interpretation of data is done by Srimika Maira and Samrat Dhar. Conception, design and revising of the article are done by Dr. Pritha Pal.

Acknowledgement: I would like to express my special thanks of gratitude to the higher dignitaries of Swami Vivekananda University for allowing me to carry out the study.

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