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The Association between Dietary Polyphenols Intake and Risk of Liver Cancer: A Systematic Review and Meta-Analysis of Observational Studies

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SYSTEMATIC REVIEW and META-ANALYSIS

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ABSTRACT

Background: The current data on the association between dietary polyphenols intake and liver cancer are not conclusive. Therefore, we aimed to perform a systematic review and meta-analysis of observational studies on the association between dietary polyphenol intake and liver cancer. **Methods:** A systematic search of online databases, including PubMed/MEDLINE, Scopus, and Web of Science, was conducted until August 2024. Observational studies that investigated the association between dietary intake of polyphenols and the risk of liver cancer were included. The overall effects were assessed using the random effects model. **Results:** Totally, four studies were eligible to be included in the systematic review, and for meta-analysis, 3 studies with 4 effect sizes were included. The overall association between dietary intake of isoflavones and the risk of liver cancer was not significant (P=0.35, 95% CI: 0.58-1.21). **Conclusion:** No significant association was found between dietary polyphenols intake and liver cancer risk. Further observational studies are suggested to confirm these findings.

Introduction

Liver cancer is the third leading cause of cancer-related death worldwide (Sung *et al.*, 2021). The prevalence of liver cancer is highly increasing, and new-diagnosed cases and cancer mortality in 2017 were more than twice the statistics in 1990 (Lin *et al.*, 2020). Although the prevalence of this cancer is decreasing in Asia, it still has a higher rate than in European and American countries (Dasgupta *et al.*, 2020). About 75 to 90% of primary liver cancers are hepatocellular carcinomas (HCC), which are often malignant and have a poor prognosis (London and

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McGlynn, 2006). One of the reasons for the high prevalence of liver cancer in Asia, especially in East and Southeast Asia, is the endemicity of hepatitis B virus infection, which is an important risk factor for this cancer (Petrick *et al.*, 2020). Contamination of food with toxins such as aflatoxin, alcohol drinking, smoking, non-alcoholic fatty liver disease, obesity, and diabetes, genetic and also dietary factors are mentioned as other risk factors in the incidence of liver cancer (Mohammadian *et al.*, 2018).

Evidence suggests that plant-based dietary patterns are associated with a reduced risk of liver cancer (Zhang *et al.*, 2013). A study in Chinese adults found that adherence to a dietary pattern rich in fruits, vegetables, fish, and herbal tea may diminish the risk of liver cancer (Lan *et al.*, 2018). Studies have also shown that the intake of certain food items, such as tea, coffee, and soy products which are rich sources of polyphenols, may be inversely related to the risk of liver cancer (Yang *et al.*, 2020). Polyphenols are compounds that have been claimed to have numerous benefits, including antioxidant, anti-inflammatory, anti-atherosclerosis, and anti-cancer activities (Costea *et al.*, 2019). So far, many polyphenols are known, which are divided into 4 main structural groups including flavonoids, phenolic acids, lignans, and stilbenes (Papuc *et al.*, 2017, Wu *et al.*, 2021). Due to their pharmacological effects on oxidative stress, lipid metabolism, and inflammation (Li *et al.*, 2014), nowadays, polyphenols are considered an adjuvant treatment for liver diseases. However, few human studies have been conducted on the association between dietary polyphenols and the risk of liver cancer. An in-vitro study stated that flavonoids can increase the apoptosis of liver cancer cells (Mansoor *et al.*, 2011). A randomized, double-blinded, and placebo-controlled trial demonstrated that green tea polyphenols may be protective for liver cancer by decreasing oxidative DNA damage in high-risk individuals (Luo *et al.*, 2005). It was also suggested by Lagiou *et al*. that flavones intake may be inversely related to HCC risks (Lagiou *et al.*, 2008). However, another study showed an increased risk of HCC in women with isoflavone consumption (Kurahashi *et al.*, 2009). Moreover, recent studies have suggested conducting a systematic review to find out the association between different polyphenols and liver disease (Li *et al.*, 2018).

To the best of our knowledge, no systematic review and meta-analysis has been conducted on the association between polyphenols and liver cancer risk. Therefore, the present study investigated the relationship between dietary intake of polyphenols and risk of liver cancer.

Materials and Methods

The present study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher *et al.*, 2015). The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (http://www.crd. york.ac.uk/PROSPERO) with the following registration number: CRD42023487302

Search strategy

The search strategy was applied in online databases until August 2024, including, PubMed/MEDLINE, Web of Science, and Scopus. To find related articles, two authors screened titles and abstracts independently (B Forootani & H Yekrang Safakar). The references of the selected articles were also checked to find additional studies.

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Table 1. Characteristics of studies that assessed the association between dietary polyphenols intake and risk of liver cancer

First author, year	Country	Design/follow up (year)	Cases/Controls or cohort size	Dietary assessment	Polyphenols	Contrast	Adjusted OR	Adjustments	Quality score
Raul Zamora-Ros *et al.*, 2013	Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, the Netherlands and United Kingdom	Cohort/11.4	191/477015	FFQ[a]	Total flavonoids Flavanols Flavan-3-ol monomers Proanthocyanidins Theaflavins Anthocyanidins Flavonols Flavanones Flavones Isoflavones Lignans	T3[b] vs. T1	0.65 (0.4-1.04) 0.62 (0.39-0.99) 0.65 (0.39-1.07) 1.1 (0.72-1.7) 0.6 (0.35-1.03) 1.2 (0.78-1.87) 0.79 (0.47-1.32) 1.1 (0.75-1.62) 1.06 (0.69-1.62) 0.74 (0.44-1.26) 1.37 (0.8-2.35)	Center, sex, age, total energy, educational level, smoke intensity, alcohol lifetime and alcohol baseline, body mass index, self-reported diabetes at baseline, physical activity, fiber and coffee intake.	9
Pagona Lagiou *et al.*, 2008	Greece	Case-Control	250/360	FFQ	Flavanones Flavan-3-ols Flavonols Anthocyanidins Flavones Isoflavones Total flavonoids	Q5[c] vs. Q1	1.18 (0.56-2.47) 1.14 (0.5-2.58) 1.11 (0.51-2.43) 1.73 (0.74-4.04) 0.41 (0.16-1.06) 0.85 (0.39-1.86) 0.96 (0.43-2.12)	Gender, age, education, tobacco smoking, and total energy intake	6
Norie Kurahashi *et al.*, 2008 (men)	Japan	Cohort/11.8	69/7146	FFQ	Genistein Daidzein	T3 vs. T1	1.13 (0.6-2.11) 1.09 (0.58-2.05)	Age, area, HCV, HBsAg, smoking status, alcohol consumption, and intake of coffee and vegetables	9
Norie Kurahashi *et al.*, 2008 (women)	Japan	Cohort/11.8	32/12751	FFQ	Genistein Daidzein	T3 vs T1	3.19 (1.13-9) 3.9 (1.3-11.69)	Age, area, HCV, HBsAg, smoking status, alcohol consumption, and intake of coffee and vegetables	9
Wei Zhang *et al.*, 2019 (men)	China	Nested case-control	131/262	FFQ	Isoflavone Daidzein Genistein Glycitein	Q4[d] vs. Q1	1.36 (0.57-3.21) 1.27 (0.55-2.96) 1.24 (0.52-2.93) 0.72 (0.3-1.74)	Total energy intake, education level, regular physical activity during past 5 years, history of viral	8

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									hepatitis, history of chronic liver disease or cirrhosis, history of diabetes, history of cholelithiasis or cholecystectomy, and family history of liver cancer, regular alcohol drinker, body mass index, dietary fat intake	
Wei Zhang *et al*., 2019 (women)	China	Nested case-control	86/165	FFQ	Isoflavone Daidzein Genistein Glycitein	Q4 Q1	vs.	0.63 (0.2-1.97) 0.68 (0.22-2.08) 0.64 (0.21-1.96) 0.63 (0.18-2.26)	Total energy intake, education level, regular physical activity during past 5 years, history of viral hepatitis, history of chronic liver disease or cirrhosis, history of diabetes, history of cholelithiasis or cholecystectomy, and family history of liver cancer, regular alcohol drinker, body mass index, dietary fat intake	8

[a]: Food frequency questionnaire ; [b:]P-tertile; [c]: Quintile; [d]: Quartile .

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Eligibility criteria

Articles were included in the study if they: 1) were a cohort, case-control, or cross-sectional study; 2) assessed the association between dietary polyphenols and risk of liver cancer; 3) reported risk estimates with a 95% confidence interval (CI); and, 4) were performed on adults. Articles were excluded if they: 1) examined polyphenols in plasma or urine, 2) had a review or trial design; or 3) were done on animals.

Data extraction

The following characteristics were extracted from each included study: the last name of the first author, publication year, study location, study design, gender, number of participants, age, type and the average intake of polyphenols, hazard ratio (HR), relative risk (RR) or odds ratio (OR) of the fully adjusted models with their 95% CI for each level of polyphenol intake. A.E extracted the data, and it was rechecked by the second author (F Mirjalili).

Risk of bias assessment

The Newcastle-Ottawa Scale was used to assess the quality of the eligible studies (Wells, 2000). In this scale, there are three main domains, including "selection", "comparability", and "outcome" to evaluate the quality of the studies. Studies would be classified as high quality if they got 7 stars or more. If a study got less than 5 stars, it would be classified as low quality. A study with 6 stars would be in the moderate quality category (Wells, 2000). Two authors (AS Emrani & F Mirjalili) performed the quality assessment independently.

The overall quality of the meta-analysis

The Grading of Recommendation Assessment, Development and Evaluation (GRADE) system was used to assess the overall quality of the present meta-analysis (Guyatt *et al.*, 2008). The GRADE system evaluates the certainty of the evidence according to the risk of bias, consistency, directness, precision, publication bias, and study design of the included articles in the meta-analysis.

Data analysis

All statistical analysis was performed using Stata version 17 (STATA Corp., College Station, Texas). All reported HRs, RRs, and ORs (with their 95% CI) were used to calculate RR and its standard error. The overall effect size was calculated by using a random effects model. Using Cochran's Q test and I^2 statistic, between-study heterogeneity was assessed. Publication bias was checked by looking over Begg's funnel plot and asymmetry tests (Begg's test and Egger's test). P-values less than 0.05 were considered statistically significant.

Results

Literature search

In this systematic search, 14230 articles were identified from PubMed/MEDLINE, Scopus, and Web of Science. There were 3790 duplicates and 9521 ineligible articles after screening through the title and abstract. By reading 919 full texts of potentially relevant studies, 651 irrelevant records were excluded, and 268 related reports were assessed for eligibility. Finally, 264 articles were excluded for the following reasons: 237 studies were performed on other cancers, 4 studies were reviews, 4 studies reported urinary or plasma concentration, 3 articles did not report any data for polyphenols or reported mixed polyphenols, and 16 articles were not observational studies. Therefore, 4 studies were included in the present systematic review and meta-analysis (Kurahashi *et al.*, 2009, Lagiou *et al.*, 2008, Zamora-Ros *et al.*, 2013, Zhang *et al.*, 2013) (**Figure 1**).

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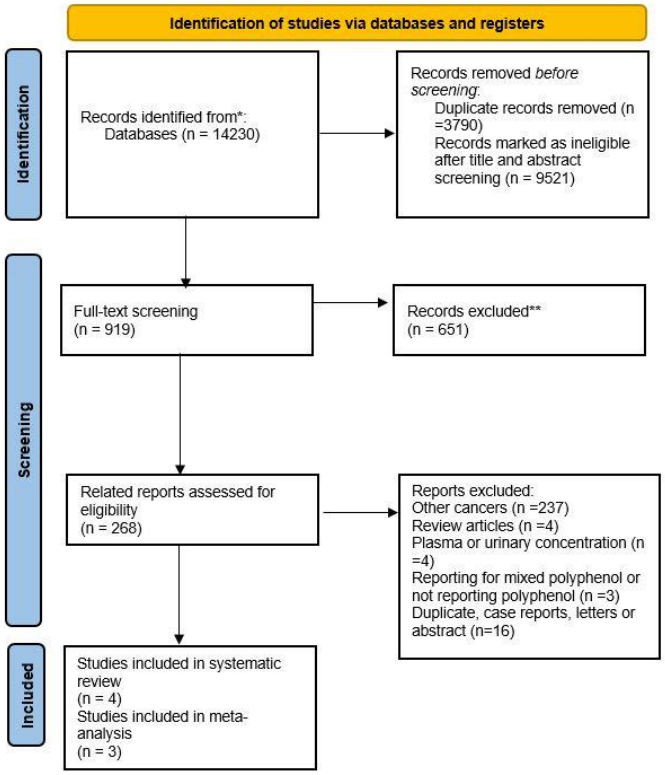

Figure 1. Flow diagram for the study selection process.

Characteristics of the included studies

The characteristics of all four eligible studies are presented in **Table 1**. These studies were published between 2008 and 2019. One study was conducted in China (Zhang *et al.*, 2013), one in Japan (Kurahashi *et al.*, 2009), one in Greece (Lagiou *et al.*, 2008), and one of the studies was multi-center research conducted in Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, the Netherlands, and United Kingdom (Zamora-Ros *et al.*, 2013). Two studies were cohorts (Kurahashi *et al.*, 2009, Zamora-Ros *et al.*, 2013), one study had a case-control design (Lagiou *et al.*, 2008) and one of them was a nested case-control (Zhang *et al.*, 2013). All studies were performed on both genders. However, in the studies conducted by Norie Kurahashi *et al*. (Kurahashi *et al.*, 2009) and Wei Zhang *et al*. (Zhang *et al.*, 2013), results were reported for men and women separately; therefore, we obtained two effect sizes from the study by Wei Zhang *et al*.. This meta-analysis was only conducted for the association between dietary intake of isoflavones and liver cancer risk. Since Norie Kurahashi *et al*. (Kurahashi *et al.*, 2009) did not report any data for total isoflavones, this study was not included in the present meta-analysis.

Risk of bias assessment

According to the Newcastle-Ottawa quality assessment scale, all studies were categorized as high quality except one. This case-control study (Lagiou *et al.*, 2008) had moderate quality, mainly because the non-response rate was different in the case and control groups.

The overall quality of the meta-analysis

We assessed the certainty of the evidence for the association between isoflavone intake and the risk of liver cancer based on the GRADE system. The GRADE certainty of evidence was very low for this association.

Findings from systematic review

In a study conducted by Raul Zamora-Ros *et al*. (Zamora-Ros *et al.*, 2013), the association between total flavonoids, flavanols, flavan-3-ol

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monomers, proanthocyanidins, theaflavins, anthocyanidins, flavonols, flavanones, flavones, and lignans and the risk of liver cancer was assessed. In this study, only dietary intake of flavanols was inversely related to liver cancer risk. In a case-control study (Lagiou *et al.*, 2008), Pagona Lagiou *et al*. examined the role of flavanones, flavan-3-ols, flavonols, anthocyanidins, flavones, and total flavonoids in the etiology of liver cancer. They found that flavones may be related to the reduced risk of hepatocellular carcinoma. Another cohort study in Japan investigated the relationship between isoflavones (genistein and daidzein) and the incidence of hepatocellular carcinoma (Kurahashi *et al.*, 2009). They concluded that genistein and daidzein may be related to an increased risk of liver cancer in women. However, this relation was non-significant in men. Finally, a nested case-control study evaluated the association between dietary and urinary isoflavones (genistein, daidzein, and glycitein) and the odds of liver cancer (Zhang *et al.*, 2013). They did not observe any significant relation between dietary intake of isoflavones and liver cancer risk.

Findings from meta-analysis

Three articles reported data on the relationship between dietary intake of isoflavones and liver cancer risk (Lagiou *et al.*, 2008, Zamora-Ros *et al.*, 2013, Zhang *et al.*, 2013). The overall results did not show any significant association between dietary consumption of isoflavones and the odds of liver cancer (*P*=0.35, 95% CI: 0.58-1.21, **Figure 2**). Between-study heterogeneity was not significant (*P*=0.65, I^2=0.00%).

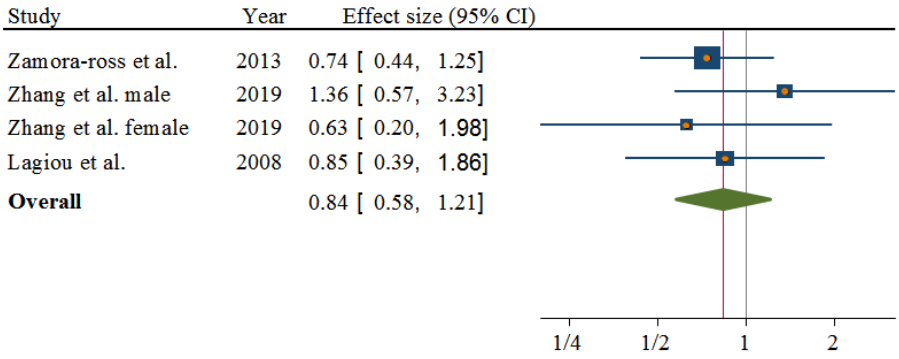

Figure 2. Forest plot of the association between dietary isoflavones intake and risk of liver cancer.

Publication bias

There was no publication bias for the meta-analysis of the association between dietary intake of isoflavones and the risk of liver cancer (Begg's test, *P*=0.73; Egger's tests, *P*=0.75).

Discussion

In the present systematic review and meta-analysis, no significant association was found between dietary intake of isoflavones and the risk of liver cancer. Many health properties have been attributed to isoflavones, such as hormone-like properties, immunity, antioxidant, anti-tumor, and anti-inflammatory functions (Ko, 2014). Evidence has shown that isoflavones may have a protective association with cancer due to their anti-tumor and antioxidant properties (Ko, 2014). These protective effects occur through blocking endoplasmic reticulum (ER-a) protein, suppression of DNA transcription, and stopping carcinogenesis pathways by protein tyrosine kinase inhibition (Ko, 2014). A review has stated that polyphenols have protective effects on the liver, and by affecting the metabolism they can inhibit liver cancer (Li *et al.*, 2023). Moreover, this review suggested that flavonoids enter the liver by binding to albumin and cause changes in glucose uptake, gene expression of glucose transporter, and its metabolism in the liver (Li *et al.*, 2023). Another review study in 2018 showed

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that polyphenols through different mechanisms such as regulating mitochondrial and signaling pathways can induce apoptosis in liver cancer cells (Li *et al.*, 2018).

In the case of liver cancer, there are few human studies, the results of in-vitro studies showed the reducing effects of isoflavones on the proliferation of hepatocellular cancer cells in rats (Gu *et al.*, 2005, Su *et al.*, 2003). Researchers found higher levels of genistein and daidzein (which are common isoflavones) in rats' liver than in plasma (Janning *et al.*, 2000, McClain *et al.*, 2006). Moreover, genistein may be used as an adjuvant treatment for liver disease, since it has shown protective effects on liver fibrosis in rat models (Leija Salas *et al.*, 2007, Salas *et al.*, 2007). Contrary to the results obtained in the present meta-analysis, a case-control study found a decreasing association between the intake of miso soup and tofu (which contain a high amount of soybeans) and the risk of HCC (Sharp *et al.*, 2005). In a cohort study conducted on the Japanese population, unlike the current study, intake of genistein and daidzein was positively related to the HCC risk in women, while this relationship was non-significant in men (Kurahashi *et al.*, 2009). This study suggests that the effects of isoflavones intake may differ in populations based on gender. Studies have shown that estrogen can be effective in HCC prevention (Kurahashi *et al.*, 2009). On the other hand, isoflavones can have anti-estrogenic effects due to competition with estradiol (Bingham *et al.*, 1998), and this may be one of the reasons for the difference in isoflavones impact in men and women. Consistent with the present study results, two observational studies found no association between dietary isoflavone intake and the risk of liver cancer (Lagiou *et al.*, 2008, Zamora-Ros *et al.*, 2013).

The present study is the first systematic review and meta-analysis to investigate the association between dietary polyphenols intake and liver cancer risk. A complete and unrestricted search was performed in the study. However, this study has some limitations. Since the studies relating to dietary polyphenol intake and liver cancer risk were limited, a meta-analysis could not be performed for all polyphenols. Meta-analysis was only possible for the relationship between dietary intake of isoflavones and the incidence of liver cancer. In addition, the small number of included articles made it impossible to perform subgroup analysis. Moreover, the design of the included studies was observational, which can lead to recall bias. Finally, the range of polyphenol intake and confounding variables adjusted in the final models were different in the included studies.

Conclusion

There was no significant association between dietary isoflavones intake and the risk of liver cancer. There are limited observational studies assessing the relationship between polyphenol intake and the odds of liver cancer. On the other hand, liver cancer is one of the most fatal cancers worldwide, and it is important to examine its risk and protective factors. Therefore, it is highly recommended that future research investigate the relationship between polyphenols and liver cancer risk.

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Authors' contributions

B Forootani and A Salehi-abargouei conceived the study. H Yekrang Safakar and B Forootani designed the search strategy and conducted the systematic search and study selection. AS Emrani and F Mirjalili did data extraction and statistical analyses. AS Emrani wrote the first draft of the manuscript. A Salehi-abargouei critically revised the manuscript. All authors read and approved the final version of the manuscript.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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