Routledge
Taylor & Francis Group

Nutrition and Cancer

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/hnuc20

Vegetable, Fruit Consumption and Risk of Biliary Cancer: Evidence from a Meta-Analysis

Jiaping Huai & Xiaohua Ye

To cite this article: Jiaping Huai & Xiaohua Ye (2020): Vegetable, Fruit Consumption and Risk of Biliary Cancer: Evidence from a Meta-Analysis, Nutrition and Cancer, DOI: 10.1080/01635581.2020.1800767

To link to this article: https://doi.org/10.1080/01635581.2020.1800767

Published online: 31 Jul 2020.

NUTRITION AND CANCER
https://doi.org/10.1080/01635581.2020.1800767

Taylor & Francis
Taylor & Francis Group

REVIEW

Vegetable, Fruit Consumption and Risk of Biliary Cancer: Evidence from a Meta-Analysis

Jiaping Huai[a] and Xiaohua Ye[b]

[a]Department of Critical Care Medicine, Jinhua Municipal Central Hospital, Jinhua Hospital of Zhejiang University, Jinhua, China; [b]Department of Gastroenterology and Hepatology, Jinhua Municipal Central Hospital, Jinhua Hospital of Zhejiang University, Jinhua, China

ABSTRACT

Background and objective: This meta-analysis was performed to assess the association between vegetable and fruit (VF) consumption and biliary cancer risk.

Method: Relevant studies were identified by a search of MEDLINE and Embase databases. The summary relative risks (RRs) with 95% confidence intervals (CIs) for the highest vs. lowest consumption and dose-response analyses were assessed.

Results: Fourteen studies were eligible. The summary RRs associated with the risk of biliary cancer for the highest vs. lowest were 0.48 ($n = 10$; 95% CI: 0.22-0.74; $Q = 68.27$, $P_{heterogeneity} < 0.001$, $I^2 = 86.8\%$) for vegetable consumption and 0.47 ($n = 13$; 95% CI: 0.32-0.61; $Q = 32.68$, $P_{heterogeneity} = 0.001$, $I^2 = 63.3\%$) for fruit consumption. Dose-response associations were analyzed for every 100 gram/day increment: for vegetable ($n = 8$; RR = 0.31, 95%CI: 0.20–0.47; $P_{non\text{-}linearity} = 0.35$) and for fruit ($n = 8$; RR = 0.89, 95%CI: 0.66–1.18; $P_{non\text{-}linearity} = 0.20$). There was no publication bias among studies ($P_{Begg} = 0.53$, $P_{Egger} = 0.84$ for vegetable; $P_{Begg} = 0.95$, $P_{Egger} = 0.64$ for fruit).

Conclusion: This meta-analysis indicated that VF consumption may significantly reduce the risk of biliary cancer. Further well-designed prospective studies are warranted to confirm our findings.

ARTICLE HISTORY
Received 24 November 2019
Accepted 29 June 2020

Introduction

Biliary cancers, including gallbladder cancer (GBC), intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC), are relatively rare but highly lethal malignancies (1–3). Despite the global incidence rates of biliary tract cancers are low; there are notable geographical variations (1,4). Although gallstone disease, primary sclerosing cholangitis, and biliary tract infection have been identified as the risk factors of biliary cancer (5,6), the exact etiology remains largely unknown.

Vegetable and fruit (VF) consumption may have protective effects against several types of cancer. The World Cancer Research Fund/American Institute for Cancer Research reported in 2018 that VF may probably reduce the risks of cancer in the mouth, pharynx, larynx, nasopharynx, esophagus, lung, stomach, breast and bladder (7). Moreover, there is evidence that VF consumption is associated with a reduced risk of total cancer incidence and mortality (8). Regarding biliary cancer, it is generally accepted the fact that higher intake of VF is beneficial for cancer prevention because of the putative anticarcinogenic and antimutagenic micronutrients including vitamin C, vitamin E, folate, carotenoids and flavonoids (9). Prior studies investigating associations between VF consumption and biliary cancer have yielded inconsistent or inconclusive results (9–22). Some studies showed an inverse correlation between VF and risk of biliary cancer (9–11,13–15,18,21,22), whereas others failed to demonstrate such an association. The lack of consistency across studies may be due to small sample size, differences in the study populations and methodological designs, or variation in quantity of VF consumption, thus limiting the ability to detect modest associations and to perform analyses individually by anatomic site. Previous meta-analyses only reported data concerning cholangiocarcinoma within Thailand and almost exclusively assessed ever vs. never VF consumption (23,24).

CONTACT Xiaohua Ye yexiaohuare@qq.com Department of Gastroenterology and Hepatology, Jinhua Municipal Central Hospital, Jinhua Hospital of Zhejiang University, 365#, Renmin East Road, Jinhua 321000, China

Knowledge of VF consumption as a potential protective factor would allow positive prevention for patients with a high risk of developing biliary cancer and would be helpful for exploring intervention strategies. To investigate the association between VF and biliary cancer, we performed a meta-analysis of published studies following the meta-analysis of observational studies in epidemiology guidelines (25).

Methods

Search Strategy and Data Extraction

Two investigators (Ye XH and Huai JP) independently performed a computerized search of MEDLINE (from one January 1966 to 31 May 2020) and Embase (from one January 1974 to 31 May 2020) databases to identify potentially relevant articles. The following search terms were used: "*fruit*", "*fruits*", "*vegetable*", "*vegetables*", "*diet*", "*dietary*", "*food*" and "*foods*" combined with "*biliary cancer*", "*bile duct cancer*", "*gallbladder cancer*" and "*cholangiocarcinoma*". Manual searches on the bibliographies of all potential articles were also conducted to identify additional studies relevant to the review. Only citations from English-language literature were included. Studies were included if they met the following inclusion criteria: (1) case-control or cohort design and published in manuscript form; (2) vegetable and/or fruit included as an exposure of interest; (3) biliary cancer included as an outcome of interest; (4) studies reported relative risks (RR) or odds ratios (OR) and their corresponding 95% confidence intervals (CI). If multiple reports based on the same population were retrieved, the most informative study was selected. Studies were excluded if: (1) the definition of biliary cancer was not specified; (2) data were not meta-analyzable (i.e., letter, review, practice guideline, editorial, case report, consensus statement, etc.); or (3) duplicated reports. Moreover, we used studies that evaluated fruit or vegetable groups classified as "all" or "total". Also, we included studies that reported "fresh fruit" or "cooked vegetables", because fresh fruit or cooked vegetables accounts for a large proportion of the total consumption (26). Exposures were excluded while presented as green-yellow vegetables, green leafy vegetables, other vegetables, citrus fruit, or other specific types of fruits.

Data were independently extracted by two authors (Ye XH and Huai JP) using a standardized data collection form. For each eligible study, the following data were extracted: first author's last name, publication year, region of the study population, study design, number of subjects, dietary data ascertainment, variables adjusted in the analysis, and RR with corresponding 95% CI for the highest vs. the lowest level. When different types of adjusted RRs were presented, we extracted the one that controlled for the most confounders. If RR was not reported, it was calculated using the original data (number of case and control subjects exposed to VF) from the study. Any disagreement was resolved by consensus.

Assessment of Study Quality

The well-established, validated Newcastle-Ottawa scale (NOS) was used for assessing the quality of the included studies (27). It allocates a maximum of nine points according to three categories: (1) patient selection (three items); (2) comparability of the two study arms (two items); and (3) assessment of outcome (two items). Studies with 7–9 points were considered of high quality, studies with 5–6 points were considered of moderate quality, and studies with 0–4 points were considered of poor quality. The NOS score was assessed independently by two reviewers. Discrepancies were resolved through discussion between the reviewers.

Statistical Analysis

Different measures of RR were included in this meta-analysis: case-control studies (OR) and cohort studies (RR). Because clinical heterogeneity existed among the definitions of exposure, we calculated the summary RRs with their corresponding 95%CIs for the comparison between the study-specific highest category of consumption vs. the lowest using a random-effects model (28). Heterogeneity was evaluated using the Q-statistic and quantified using I^2. For the Q test, $P < 0.10$ was considered to imply statistical heterogeneity. I^2 is the proportion of total variation contributed by between-study variation. We conducted further analyses stratified by study design, geographic region, source, cancer type by anatomic site and adjustments for smoking and alcohol intake. Publication bias was evaluated using Begg's funnel plot and Egger's test (29,30).

For dose-response analysis, we used a one-stage robust error meta-regression model described by Xu and Doi (31). Estimates of RRs with 95% CIs for at least two categories of VF consumption were required. The mean or median VF consumption for each category was assigned to the corresponding RR for individual study. When the data were not provided, the midpoint of the upper and lower boundaries in each category was assigned as the average consumption. If the lowest category was open-ended, we assumed the

lowest boundary to be 0 (32). When the highest category was open-ended, the value is 1.5 times the low end of the interval (33). For studies that reported results by frequency (10–12,14,16,18–20), we defined a time or a serving size or a portion equal to 80 gram for vegetables and 100 gram for fruit according to previous studies (26,34).

All analyses were performed using STATA software (version 12.0; College Station, Texas, USA). A P value of < 0.05 was considered to be statistically significant.

Results

Study Identification and Characteristics

A total of 735 unique citations were retrieved based on the search strategy, and 708 were excluded by inspection of the titles or abstracts because they were reviews, experimental studies, meta-analyses, and other irrelevant articles. Of the remaining 27 articles, 13 articles were subsequently excluded from the meta-analysis: six reported irrelevant exposures, five were not meta-analyzable, one did not evaluate the association between VF and biliary cancer (35) and one was based on the same cohort (24). As a result, 14 studies (12 case-control, 1 nested case-control, and one prospective studies) were identified in this meta-analysis (Figure 1) (9–22).

The characteristics of the included studies are listed in Table 1. The 14 studies were published between 1989 and 2020 and were performed in 8 countries. Of the 14 studies, 10 were conducted in Asia (9–11,14,16,18–22), 3 in Europe (12,13,17), and 1 in South America (15). There were a total of 1858 cases with GBC, 1034 cases with CC and 195 cases with biliary tract cancer (BTC). Adjustments were made for potential confounders of one or more factors in 10 of 14 studies. The qualities of the included studies were shown in Table 2.

Vegetable Consumption and Biliary Cancer

Ten studies showed the results for the highest vs. lowest consumption (9,12–14,16–18,20,24). Study data collection occurred from 1995 to 2020. The summary RR associated with vegetable consumption was 0.48 (95%CI: 0.22, 0.74) (Figure 2A). There was significant heterogeneity among studies ($Q = 68.27$, $P_{\text{heterogeneity}} < 0.001$, $I^2 = 86.8\%$).

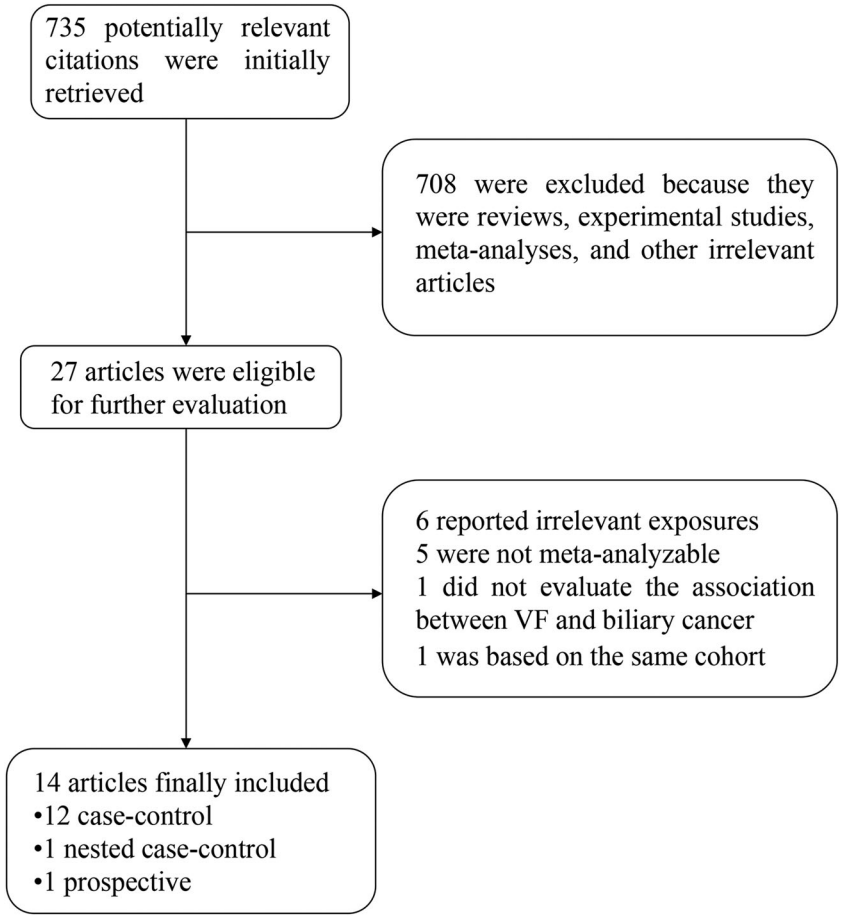

Figure 1. Flow chart of the study selection.

Table 1. Characteristics of included studies.

Author/year	Country	Cancer type/No.	Controls	Design	Source of control	Case ascertainment	Dietary assessment	Exposure details	RR (95% CI) (highest vs. lowest)	Adjustments
Kato et al. 1989	Japan	GBC: 109 BTC: 84	386	CC	Population	Histologically	Self-administered questionnaire	Vegetable (≥ 3 times/week) Fruit (daily)	Vegetable: GBC: 0.37 (0.19, 0.75)[a] Fruit: GBC: 0.26 (0.13, 0.50) BTC: 0.48 (0.28, 0.81)[a]	Marital status and intakes of pickels, fresh fish, salted fish, river fish and eggs in addition to intakes of fruit, coffee and broiled fish and preference of oily foods
Parkin et al. 1991	Thailand	CC: 103	103	CC	Hospital	Histologically or non-histologically	Structured questionnaire	Fruit (3 times/month)	0.5 (0.3, 0.9)[a]	NA
Negri et al. 1991	Italy	GBC: 41	6,147	CC	Hospital	Histologically	Questionnaire	Vegetable (T3 vs. T1) Fruit (T3 vs. T1)	Vegetable: 0.5 (0.2, 1.2) Fruit: 0.8 (0.3, 2.1)	Age, area of residence, education, smoking and (when required) sex
Moerman et al. 1995	Netherland	BTC:111	480	CC	Population	Histologically and ICD code	Semiquantitative food frequency questionnaire	Vegetable (T3 vs. T1)	0.4 (0.2, 0.8)	Sex, age class, response status, BMI and smoking status
Chernrungroj et al. 2000	Thailand	CC: 200	200	CC	Hospital	Histologically or non-histologically	Food-frequency questionnaire	Vegetable (> 2.8 vs. < 1.7 portions/day) Fruit (> 2.08 vs. 1.0 portions/day)	Vegetable: 0.06 (0.02, 0.14) Fruit: 0.34 (0.17, 0.70)	Age, gender, education, household income, alcohol consumption, cigarette smoking, praziquantel use, O. viverrini infestation and total energy intake
Serra et al. 2002	Chili	GBC: 114	114	CC	Hospital	surgically and histologically	Food-frequency questionnaire	Fruit (> 2 fruits/day vs. < 1 fruit /week)	Fruit: 0.32 (0.12, 0.84)[a]	NA
Honjo et al. 2005	Thailand	CC: 129	129	CC	Population	Non-histologically	Structured questionnaire	Vegetable (≥ 1 time/day vs. < 3 times/week) Fruit (≥ 2 times/week vs. < 1 time/week)	Vegetable: 1.48 (0.62, 3.51) Fruit: 1.63 (0.64, 4.12)	Anti-OV Ab, smoking and alcohol drinking
Nakadaira et al. 2009	Hungary	GBC: 41	30	CC	Hospital	NA	Questionnaire	Vegetable (3-7 vs. < 3 days/week) Fruit (2-7 vs. < 2 days/week)	Vegetable: 3.80 (0.75, 18.70) Fruit: 1.50 (0.29, 8.92)	Age
Songserm et al. 2012	Thailand	CC: 219	438	nested CC	Population	Histologically or non-histologically	Food-frequency questionnaire	Vegetable (≥ 52 vs. < 52 times/month) Fruit (≥ 35 vs. < 35 times/month)	Vegetable: 0.40 (0.23, 0.76) Fruit: 0.60 (0.33, 0.98)	Education level, MTHFR C677T polymorphism, MTHFR A1298C polymorphism, cigarette smoking, units of alcohol per

										month of all alcohol drinking, dish of raw freshwater fish, processed beef, frequency of Somtam consumption
Jain et al. 2012	India	GBC: 200	200	CC	Population	Histologically	Food-frequency questionnaire	Fruit ($\geq$ 3 vs. $<$ 3 times/week)	Fruit: 0.5 (0.3, 0.7)	NA
Manwong et al. 2013	Thailand	CC: 123	123	CC	Hospital	Histologically	Structured questionnaire	Vegetable (3 times/week vs. $<$ 1 times/month) Fruit (3 times/week vs. $<$ 1 times/month)	Vegetable: 1.67 (0.54, 5.12) Fruit: 1.72 (0.85, 3.47)[a]	Age, sex and residential area
Tamrakar et al. 2016	Nepal	GBC: 50	100	CC	Hospital	histologically or cytologically	Semi structured questionnaire	Fruit (1 vs. $<$ 1 day/week)	Fruit: 0.101 (0.03, 0.35)	NA
Makiuchi et al. 2017	Japan	GBC: 133 ICC: 99 ECC: 161	80,371	Prospective cohort	Population	ICD code	Food-frequency questionnaire	Vegetable (Q4 vs. Q1) Fruit (Q4 vs. Q1)	Vegetable: GBC: 1.45 (0.83, 2.52) ICC: 1.18 (0.66, 2.12) ECC: 0.55 (0.34, 0.90) Fruit: GBC: 1.16 (0.66, 2.02) ICC: 1.20 (0.64, 2.24) ECC: 0.63 (0.38, 1.04)	Age, study area, sex, BMI; history of cholelithiasis, history of diabetes mellitus, history of chronic hepatitis or cirrhosis, history of smoking, alcohol drinking frequency, physical activity, green tea consumption, energy-adjusted consumption of fish, red meat
Mhatre et al. 2020	India	GBC: 1,170	2,525	CC	Hospital	Histologically	Food-frequency questionnaire	Vegetable (Frequency: Q4 vs. Q1) Fruit (Frequency: Q4 vs. Q1)	Vegetable: 0.62 (0.49, 0.79) Fruit: 0.53 (0.41, 0.68)	Age, education, current residential regions, gender, waist to hip ratio, gallstones history, tobacco chewing and tobacco smoking, any meat consumption, per person per week mustard oil consumption

[a]Univariate RR was calculated; RR relative risk; CC case-control; NA not available.

Table 2. Methodological quality of included studies.

	Selection				Comparability		Assessment of outcome			
Author	Ia	Ib	Ic	Id	IIa	IIb	IIIa	IIIb	IIIc	NOS score
Kato et al. 1989	*	*	*	*	*	*	*	*	*	9
Parkin et al. 1991	*	*	*	*	*	*	*	*		8
Negri et al. 1991	*	*	*		*	*	*	*	*	8
Moerman et al. 1995	*	*			*	*	*	*	*	7
Chernrungroj et al. 2000	*	*	*	*	*	*	*	*		8
Serra et al. 2002	*	*	*	*	*		*	*		7
Honjo et al. 2005	*	*	*		*	*	*	*		7
Nakadaira et al. 2009	*	*	*		*	*	*	*		7
Songserm et al. 2012	*	*	*	*		*	*	*	*	8
Jain et al. 2012	*	*	*	*	*	*	*	*		8
Manwong et al. 2013	*	*	*	*	*		*	*		7
Tamrakar et al. 2016	*	*	*	*	*	*	*	*		8
Makiuchi et al. 2017	*		*	*	*	*	*	*	*	8
Mhatre et al. 2020	*	*		*	*	*	*	*	*	8

For case-control studies: (Ia) indicates cases with independent validation; (Ib) indicates consecutive or representative cases; (Ic) indicates community controls; (Id) indicates controls with no history of biliary cancer ; (IIa) indicates that study controls were comparable for age and sex; (IIb) indicates that study controls were comparable on all additional factor(s) reported; (IIIa) indicates that the same method of ascertainment was used for cases and controls; (IIIb) indicates that assessment of exposure was from a secure record; and (IIIc) indicates that the non-response rate was similar in both groups. For cohort studies: (Ia) indicates that the exposed cohort was representative of the population; (Ib) indicates that the non-exposed cohort was drawn from the same population; (Ic) indicates that the exposure ascertainment was from secure records or a structured interview; (Id) indicates that biliary cancer was not present at start of study; (IIa) indicates that the cohorts were comparable for age and sex; (IIb) indicates that the cohorts were comparable on all additional factor(s) reported; (IIIa) indicates that biliary cancer was assessed from a secure record; (IIIb) indicates that follow-up was long enough for biliary cancer to occur; and (IIIc) indicates that follow-up was complete. NOS: Newcastle-Ottawa score.

For dose-response analysis, eight studies were included (9,10,12–14,16,18,20) and there was no evidence of a nonlinear dose-response association between vegetable consumption and biliary cancer ($P_{\text{non-linearity}} = 0.35$). As shown in Figure 3A, the risk of biliary cancer decreased by 69% (RR = 0.31, 95%CI: 0.20–0.47, $P < 0.001$) for every 100-gram increment per day in vegetable consumption.

Fruit Consumption and Biliary Cancer

Thirteen studies investigated the association between fruit and the development of biliary cancer (Figure 2B) (9–12,14–22). Study data collection occurred from 1989 to 2020. Meta-analysis of 13 studies associated with the highest vs. lowest fruit consumption showed an inverse association of developing biliary cancer (RR = 0.47; 95% CI: 0.32-0.61). Significant heterogeneity was detected among studies (Q = 32.68, $P_{\text{heterogeneity}} = 0.001$, $I^2 = 63.3\%$).

Dose-response analysis was achieved by including 8 studies (Figure 3B) (9,11,12,14,16,18–20). The summary RR per 100-gram increment per day was 0.89 (95% CI: 0.66–1.18, $P = 0.35$) with a linear association between fruit and biliary cancer risk ($P_{\text{non-linearity}} = 0.20$).

Subgroup Analysis

The summary RRs of subgroup analyses based on a number of study characteristics are presented in Table 3. For high vs. low consumption of vegetables, the meta-analytical results remained significant in all subgroup analyses. In addition, subgroup analyses according to region, source and cancer type reduced or eliminated the heterogeneity of association between vegetable and biliary cancer.

In subgroup analyses for high vs. low consumption of fruit, there were statistically inverse associations for biliary cancer risk in most of the strata except for region (Europe). Also, fruit consumption was significantly associated with reduced risk of different subtypes of biliary cancer (GBC, CC and BTC).

We also limited the analysis to studies that adjusted for smoking and alcohol intake. The summary RRs did not significantly change for both vegetable and fruit consumption.

Publication Bias

There is no evidence of significant publication bias ($P_{\text{Begg}} = 0.53$ and $P_{\text{Egger}} = 0.84$ for vegetable; $P_{\text{Begg}} = 0.95$ and $P_{\text{Egger}} = 0.64$ for fruit), indicating that publication bias probably had little effect on summary estimates (Figure 4).

Discussion

To the best of our knowledge, this systematic review and meta-analysis is the most comprehensive to summarize recent studies investigating the relationship between consumption of VF and risk of biliary cancer. We included 14 studies with a total sample size of 1858 cases with GBC, 1034 cases with CC and 195 cases with biliary tract cancer (BTC) (9–22). Our main finding was that higher consumption of VF was

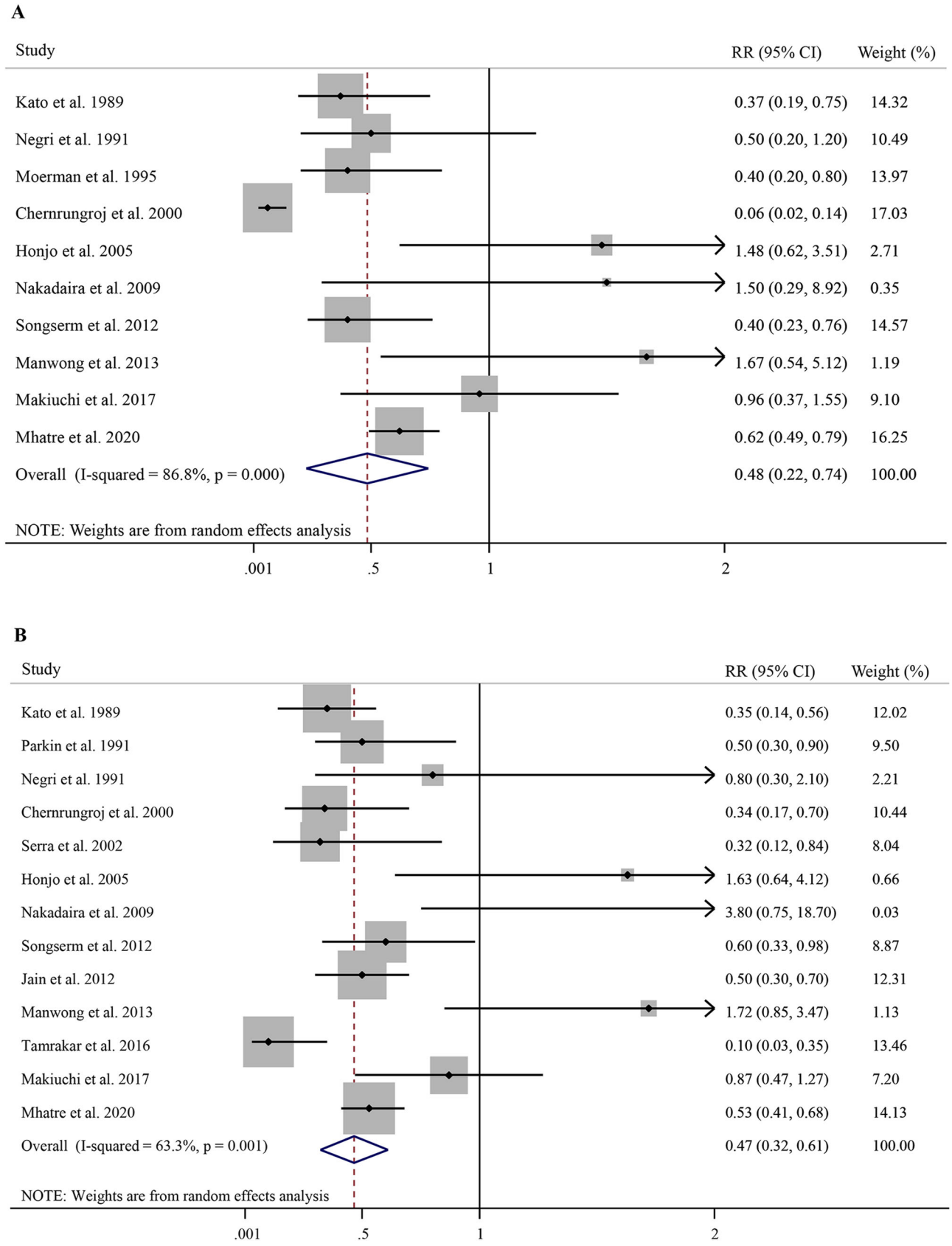

Figure 2. Forest plots of vegetable (A) and fruit (B) consumption (highest *vs.* lowest) and risk of biliary cancer.

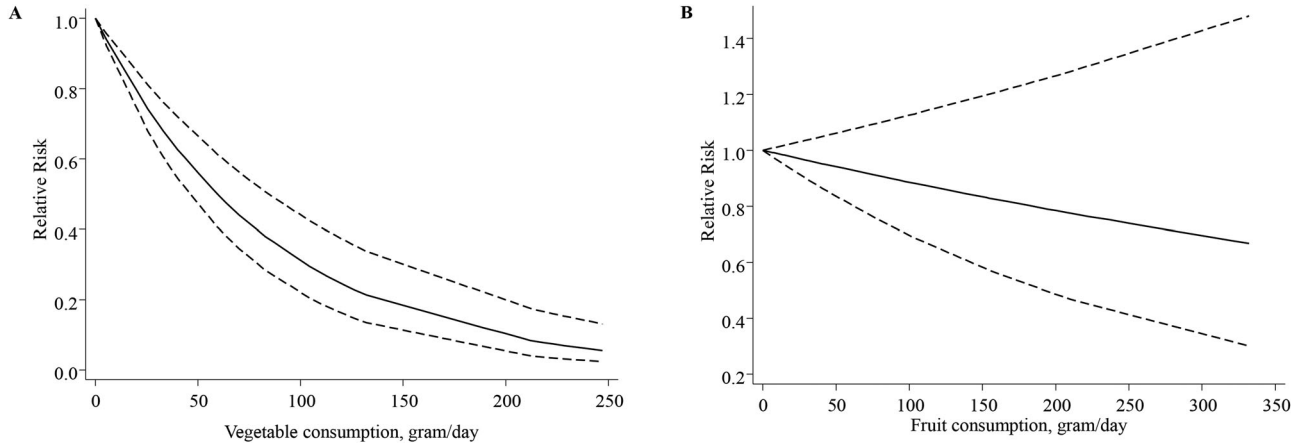

Figure 3. The dose-response analysis between vegetable (A) and fruit (B) consumption and risk of biliary cancer.

Table 3. Subgroup analyses for the association between vegetable, fruit consumption and risk of biliary cancer.

	Vegetable					Fruit				
			Tests for heterogeneity					Tests for heterogeneity		
Subgroups	No. of studies	RR (95% CIs)	Q	*P*	I^2(%)	No. of studies	RR (95% CIs)	Q	*P*	I^2(%)
Geographical region										
Europe	3	0.43 (0.17, 0.69)	0.35	0.84	0.0	2	0.83 (-0.07, 1.73)	0.42	0.51	0.0
Asia	7	0.50 (0.18, 0.82)	64	< 0.001	90.6	10	0.47 (0.31, 0.63)	31.16	< 0.001	71.1
South America	—	—	—	—	—	1	0.32 (0.12, 0.84)	—	—	—
Study design										
Case-control	8	0.45 (0.14, 0.75)	58.44	< 0.001	88.0	11	0.41 (0.26, 0.56)	26.03	0.004	61.6
Nested Case-control	1	0.40 (0.23, 0.76)	—	—	—	1	0.60 (0.33, 0.98)	—	—	—
Cohort	1	0.96 (0.37, 1.55)	—	—	—	1	0.87 (0.47, 1.27)	—	—	—
Source										
Population	5	0.46 (0.27, 0.66)	5.37	0.25	25.5	5	0.54 (0.35, 0.74)	7.23	0.12	44.7
Hospital	5	0.43 (-0.01, 0.88)	50.24	< 0.001	92.0	8	0.41 (0.20, 0.62)	22.61	0.002	69.0
Cancer type by anatomic site										
GBC	5	0.58 (0.35, 0.82)	6.78	0.15	41.0	7	0.40 (0.17, 0.63)	24.04	0.001	75.0
CC	5	0.44 (0.06, 0.82)	16.69	0.002	76.0	7	0.53 (0.37, 0.69)	7.94	0.24	24.4
BTC	1	0.40 (0.20, 0.80)	—	—	—	1	0.48 (0.28, 0.81)	—	—	—
Smoking-adjusted										
Yes	7	0.49 (0.19, 0.79)	64.35	< 0.001	90.7	6	0.56 (0.40, 0.71)	6.78	0.24	26.3
No	3	0.39 (0.12, 0.67)	1.47	0.48	0.0	7	0.37 (0.18, 0.57)	16.73	0.01	64.1
Alcohol-adjusted										
Yes	4	0.47 (0.05, 0.88)	18.12	< 0.001	83.4	4	0.61 (0.30, 0.91)	6.44	0.09	53.4
No	6	0.54 (0.42, 0.66)	4.50	0.48	0.0	9	0.42 (0.25, 0.58)	23.94	0.002	66.6

Abbreviations: *RR* relative risk; *No.* number; *GBC* gallbladder cancer; *CC* cholangicarcinoma; *BTC* biliary tract cancer.

associated with a reduced risk of biliary cancer (RR = 0.48; 95% CI: 0.22-0.74 for vegetable; RR = 0.47; 95% CI: 0.32-0.61 for fruit). Moreover, subgroup analyses according to subtype of biliary cancer yielded similar results. In addition, the dose-response analysis indicated a significant lower risk of biliary cancer for each 100 gram per day increment of vegetable ($n = 8$; RR = 0.31, 95%CI: 0.20–0.47), whereas a nonsignificant decreasing trend was observed for fruit ($n = 8$; RR = 0.89, 95%CI: 0.66–1.18).

Our results carry substantial clinical and public health implications. Although a nonsignificant decreasing trend was observed for fruit in the dose-response analysis, understanding of VF consumption as a possible protective factor for biliary cancer should still be improved due to its highly fatal nature (1–3). Awareness of this beneficial factor would allow enabling proactive implementation of preventive strategies. Therefore, early and constant publicity and education of the potential benefit of VF consumption should be the responsibility of clinical physicians. Moreover, physicians who are capable of stratifying risk will also be better placed to help individuals and their families understand the significance of VF consumption and potential outcomes.

It has been hypothesized that several micronutrients may be involved in decreasing the risk of cancer development. Carotenoids might protect DNA, mutagenesis, tumor growth, malignant transformation from oxidative damaging (36). Secondly, folate plays a pivotal role in DNA methylation and synthesis/repair, and its deficiency causes genomic DNA

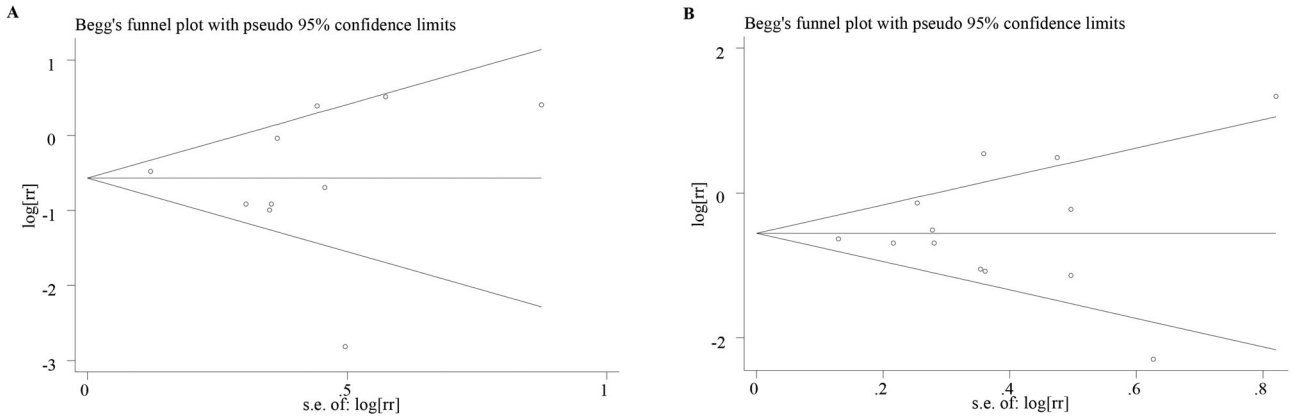

Figure 4. Begg's funnel plot with pseudo 95% confidence limits showing the symmetrical distribution of included studies for vegetable (A) and fruit (B) consumption.

hypomethylation as well as defects in DNA synthesis, which result in carcinogenesis in several types of tumors (37–39). Furthermore, vitamin C is one of the major antioxidants contained in diet, and has shown its protective role in certain types of malignancies (40). Finally, fiber rich in VF consumption may also be relevant to the reduced risk of biliary cancer. Multiple potential mechanisms were suggested for a cancer-protective effect of fiber including improvement of insulin-resistance, amelioration of IGF activity, generation of an anti-inflammatory effect by producing butylate, and optimization of the colonic micro-biota reinforcing the intestinal barrier (41,42). However, a prior study showed there was no association between total fiber and biliary tract cancer (43). Indeed, the protective mechanism of VF against biliary cancer is unclear due to data paucity of laboratory studies, further researches are warranted to elucidate the association.

An advantage of this study is that our quantitative risk assessment for biliary cancer has been controlled for both smoking and alcohol consumption. A recent meta-analysis published in 2019 has provided evidence that smoking and alcohol intake may be potentially strong risk factors for biliary cancer development (1). Indeed, the role of lower intake of VF may be compromised if smoking and alcohol intake acts as a primary risk factor in the occurrence of biliary cancer. However, the protective effect for both vegetable and fruit remained significant and had little variations after we separately combined studies that reported the smoking-adjusted or alcohol-adjusted RR (Table 3). Another strength of our study is we performed dose-response analyses with a novel model described by Xu and Doi (31) in addition to exclusively performing comparisons of the highest vs. lowest categories. Using this model, distribution of cases and person-years (non-cases) for each level of exposure is not required. Therefore, more studies could be included in dose-response analysis and a more accurate estimate could reach.

As with all meta-analyses of observational studies, our results have several limitations. First, there was significant heterogeneity among certain results. The included studies were heterogeneous according to study region, design, source, cancer type by anatomic site and adjustments. We used a random effects model assuming that the true effects were normally distributed, and more weight was assigned to small-sized studies compared with that in the fixed-effect model (44). Subgroup analyses were also conducted to address heterogeneity (Table 3). Subgroup analyses based on study design and source reduced or eliminated the heterogeneity for both vegetable and fruit consumption. Also, the majority of studies included in this meta-analysis were case-control studies, which are more susceptible to selection and recall bias. Therefore, caution is needed to interpret the results from the case-control studies. Thirdly, the misclassification and different exposure ranges from the lowest to highest categories were probably a weak point across the included studies and this might contribute to incomparable results and heterogeneity to some extent. Last, we could not further perform analysis based on specified fruits or vegetables because of the miscellaneous definition and data paucity.

In summary, the results from this meta-analysis suggest that VF consumption is associated with a reduced risk of biliary cancer. Moreover, the dose-response analysis indicated a significant lower risk of biliary cancer for each 100 gram per day increment of vegetable, whereas a nonsignificant decreasing trend

was observed for fruit. Therefore, more well-designed, prospective studies are urgently required to further validate the dose-response relationship.

Disclosure Statement

No potential conflict of interest was reported by the author(s).

Author Contribution Statement

Jiaping Huai contributed to data collection and manuscript drafting; Xiaohua Ye contributed to study design and data analysis.

Funding

This work was supported by Natural Science Foundation of Zhejiang Province (LQ19H030003) and Key Project of Jinhua Science and Technology Bureau (2018A32022).

References

1. McGee EE, Jackson SS, Petrick JL, Van Dyke AL, Adami HO, et al. Smoking, alcohol, and biliary tract cancer risk: A pooling project of 26 prospective studies. J Nat Cancer Inst. 2019;111(12):1263-1278. doi: 10.1093/jnci/djz103
2. Xiong J, Lin J, Wang A, Wang Y, Zheng Y, Sang X, Xu Y, Lu X, Zhao H. Tea consumption and the risk of biliary tract cancer: a systematic review and dose-response meta-analysis of observational studies. Oncotarget. 2017;8(24):39649–57. doi:10.18632/oncotarget.16963
3. Godos J, Micek A, Marranzano M, Salomone F, Rio D, Ray S. Coffee consumption and risk of biliary tract cancers and liver cancer: A dose-response meta-analysis of prospective cohort studies. Nutrients. 2017; 9(9):950. doi:10.3390/nu9090950
4. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359–386. doi:10.1002/ijc.29210
5. Palmer WC, Patel T. Are common factors involved in the pathogenesis of primary liver cancers? A meta-analysis of risk factors for intrahepatic cholangiocarcinoma. J Hepatol. 2012;57(1):69–76. doi:10.1016/j.jhep.2012.02.022
6. Ishiguro S, Inoue M, Kurahashi N, Iwasaki M, Sasazuki S, Tsugane S. Risk factors of biliary tract cancer in a large-scale population-based cohort study in Japan (JPHC study); with special focus on cholelithiasis, body mass index, and their effect modification. Cancer Causes Control. 2008;19(1):33–41. doi:10.1007/s10552-007-9067-8
7. WCRF/AICR. Diet, Nutrition, Physical Activity and Cancer: a Global perspective. Continuous Update Project Expert Report. 2018.
8. Aune D, Giovannucci E, Boffetta P, Fadnes LT, Keum NNa, Norat T, Greenwood DC, Riboli E, Vatten LJ, Tonstad S, et al. Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality-a systematic review and dose-response meta-analysis of prospective studies. Int J Epidemiol. 2017;46(3):1029–56. doi:10.1093/ije/dyw319
9. Makiuchi T, Sobue T, Kitamura T, Ishihara J, Sawada N, Iwasaki M, Sasazuki S, Yamaji T, Shimazu T, Tsugane S, et al. The relationship between vegetable/fruit consumption and gallbladder/bile duct cancer: A population-based cohort study in Japan. Int J Cancer. 2017;140(5):1009–19. doi:10.1002/ijc.30492
10. Kato K, Akai S, Tominaga S, Kato I. A case-control study of biliary tract cancer in Niigata Prefecture, Japan. Jpn J Cancer Res. 1989;80(10):932–8. doi:10.1111/j.1349-7006.1989.tb01629.x
11. Parkin DM, Srivatanakul P, Khlat M, Chenvidhya D, Chotiwan P, Insiripong S, L'Abbé KA, Wild CP. Liver cancer in Thailand. I. A case-control study of cholangiocarcinoma. Int J Cancer. 1991;48(3):323–8. doi:10.1002/ijc.2910480302
12. Negri E, La Vecchia C, Franceschi S, D'Avanzo B, Parazzini F. Vegetable and fruit consumption and cancer risk. Int J Cancer. 1991;48(3):350–4. doi:10.1002/ijc.2910480307
13. Moerman CJ, Demesquita HBB, Smeets FWM, Runia S. Consumption of foods and micronutrients and the risk of cancer of the biliary tract. Preventive Med. 1995;24(6):591–602. doi:10.1006/pmed.1995.1094
14. Chernrungroj G. Risk factors for cholangiocarcinoma: a case-control study. Ann Arbor: Yale University; 2000.
15. Serra I, Yamamoto M, Calvo A, Cavada G, Báez S, Endoh K, Watanabe H, Tajima K. Association of chili pepper consumption, low socioeconomic status and longstanding gallstones with gallbladder cancer in a Chilean population. Int J Cancer. 2002;102(4):407–11. doi:10.1002/ijc.10716
16. Honjo S, Srivatanakul P, Sriplung H, Kikukawa H, Hanai S, Uchida K, Todoroki T, Jedpiyawongse A, Kittiwatanachot P, Sripa B, et al. Genetic and environmental determinants of risk for cholangiocarcinoma via Opisthorchis viverrini in a densely infested area in Nakhon Phanom, northeast Thailand. Int J Cancer. 2005;117(5):854–60. doi:10.1002/ijc.21146
17. Nakadaira H, Lang I, Szentirmay Z, Hitre E, Kaster M, et al. A case-control study of gallbladder cancer in Hungary. Asian Pacific J Cancer Prevention: APJCP. 2009;10(5):833–6.
18. Songserm N, Promthet S, Sithithaworn P, Pientong C, Ekalaksananan T, Chopjitt P, Parkin DM. Risk factors for cholangiocarcinoma in high-risk area of Thailand: role of lifestyle, diet and methylenetetrahydrofolate reductase polymorphisms. Cancer Epidemiol. 2012; 36(2):e89–e94. doi:10.1016/j.canep.2011.11.007
19. Jain K, Sreenivas V, Velpandian T, Kapil U, Garg PK. Risk factors for gallbladder cancer: a case-control study. Int J Cancer. 2013;132(7):1660–6. doi:10.1002/ijc.27777
20. Manwong M, Songserm N, Promthet S, Matsuo K. Risk factors for cholangiocarcinoma in the lower part

of Northeast Thailand: a hospital-based case-control study. Asian Pac J Cancer Prev. 2013;14(10):5953–6. doi:10.7314/apjcp.2013.14.10.5953
21. Tamrakar D, Paudel I, Adhikary S, Rauniyar B, Pokharel P. Risk Factors for Gallbladder Cancer in Nepal a Case Control Study. Asian Pacific J Cancer Prevention: APJCP. 2016;17(7):3447–53.
22. Mhatre S, Rajaraman P, Chatterjee N, Bray F, Goel M, Patkar S, Ostwal V, Patil P, Manjrekar A, Shrikhande S, et al. Mustard oil consumption, cooking method, diet and gallbladder cancer risk in high- and low-risk regions of India. Int J Cancer. 2020;147(6): 1621-1628. doi:10.1002/ijc.32952
23. Songserm N, Woradet S, Charoenbut P. Fruit and vegetables consumption: A pointer for Cholangiocarcinoma prevention in Northeast Thailand, the highest incidence area in the world. Nutr Cancer. 2016;68(8):1289–94. doi:10.1080/01635581.2016.1225101
24. Poomphakwaen K, Promthet S, Suwanrungruang K, Kamsa-Ard S, Wiangnon S. Risk factors for cholangiocarcinoma in Thailand: A systematic review and meta-analysis. Asian Pacific J Cancer Prev: APJCP. 2015;16(14):6105–614. doi:10.7314/APJCP.2015.16.14.6105
25. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15): 2008–12. doi:10.1001/jama.283.15.2008
26. Riboli E, Norat T. Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. Am J Clin Nutr. 2003;78(3 Suppl):559S–69S. doi:10.1093/ajcn/78.3.559S
27. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010; 25(9):603–5. doi:10.1007/s10654-010-9491-z
28. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003; 327(7414):557–60. doi:10.1136/bmj.327.7414.557
29. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1088–101. doi:10.2307/2533446
30. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629–34. doi:10.1136/bmj.315.7109.629
31. Xu C, Doi SAR. The robust error meta-regression method for dose-response meta-analysis. Int J Evid Based Healthc. 2018;16(3):138–44. doi:10.1097/XEB.0000000000000132
32. Aune D, Lau R, Chan DSM, Vieira R, Greenwood DC, Kampman E, Norat T. Nonlinear reduction in risk for colorectal cancer by fruit and vegetable intake based on meta-analysis of prospective studies. Gastroenterology. 2011;141(1):106–18. doi:10.1053/j.gastro.2011.04.013
33. Zhao W, Tang H, Yang X, Luo X, Wang X, Shao C, He J. Fish consumption and stroke risk: A meta-analysis of prospective cohort studies. J Stroke Cerebrovasc Dis. 2019;28(3):604–11. doi:10.1016/j.jstrokecerebrovasdis.2018.10.036
34. Liu H, Wang X-C, Hu G-H, Guo Z-F, Lai P, Xu L, Huang T-B, Xu Y-F. Fruit and vegetable consumption and risk of bladder cancer: an updated meta-analysis of observational studies. Eur J Cancer Prev. 2015; 24(6):508–16. doi:10.1097/CEJ.0000000000000119
35. Petrick JL, Campbell PT, Koshiol J, Thistle JE, Andreotti G, Beane-Freeman LE, Buring JE, Chan AT, Chong DQ, Doody MM, et al. Tobacco, alcohol use and risk of hepatocellular carcinoma and intrahepatic cholangiocarcinoma: The Liver Cancer Pooling Project. Br J Cancer. 2018;118(7):1005–12. doi:10.1038/s41416-018-0007-z
36. Janakiram NB, Mohammed A, Madka V, Kumar G, Rao CV. Prevention and treatment of cancers by immune modulating nutrients. Mol Nutr Food Res. 2016;60(6):1275–94. doi:10.1002/mnfr.201500884
37. Czeizel AE, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med. 1992;327(26): 1832–5. doi:10.1056/NEJM199212243272602
38. Kim YI. Folate and carcinogenesis: evidence, mechanisms, and implications. J Nutr Biochem. 1999;10(2): 66–88. doi:10.1016/S0955-2863(98)00074-6
39. Song M, Garrett WS, Chan AT. Nutrients, foods, and colorectal cancer prevention. Gastroenterology. 2015; 148(6):1244–60. e1216. doi:10.1053/j.gastro.2014.12.035
40. Block G. Epidemiologic evidence regarding vitamin C and cancer. Am J Clin Nutr. 1991;54(6 Suppl): 1310S–4S. doi:10.1093/ajcn/54.6.1310s
41. Canani RB, Costanzo MD, Leone L, Pedata M, Meli R, Calignano A. Potential beneficial effects of butyrate in intestinal and extraintestinal diseases. World J Gastroenterol. 2011;17(12):1519–28. doi:10.3748/wjg.v17.i12.1519
42. Kaczmarczyk MM, Miller MJ, Freund GG. The health benefits of dietary fiber: beyond the usual suspects of type 2 diabetes mellitus, cardiovascular disease and colon cancer. Metab Clin Exp. 2012;61(8):1058–66. doi:10.1016/j.metabol.2012.01.017
43. Bradbury KE, Appleby PN, Key TJ. Fruit, vegetable, and fiber intake in relation to cancer risk: findings from the European Prospective Investigation into Cancer and Nutrition (EPIC). Am J Clin Nutr. 2014; 100(Suppl 1):394S–8S. doi:10.3945/ajcn.113.071357
44. Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. Stat Med. 1999;18(20):2693–708. doi:10.1002/(SICI)1097-0258(19991030)18:20<2693::AID-SIM235>3.0.CO;2-V