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TOPIC HIGHLIGHT

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Dietary flavonoid intake and risk of stomach and colorectal cancer

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Abstract

Stomach and colorectal cancers are common cancers and leading causes of cancer deaths. Because the alimentary tract can interact directly with dietary components, stomach and colorectal cancer may be closely related to dietary intake. We systematically searched published literature written in English *via* PubMed by searching for terms related to stomach and colorectal cancer risk and dietary flavonoids up to June 30, 2012. Twenty-three studies out of 209 identified articles were finally selected for the analysis. Log point effect estimates and the corresponding standard errors were calculated using covariate-adjusted point effect estimates and 95%CIs from the selected studies. Total dietary flavonoid intake was not associated with a reduced risk of colorectal or stomach cancer [odds ratio (OR) (95%CI) = 1.00 (0.90-1.11) and 1.07 (0.70-1.61), respectively]. Among flavonoid subclasses, the intake of flavonols, flavan-3-ols, anthocyanidins, and proanthocyanidins showed a significant inverse association with colorectal cancer risk [OR (95%CI) = 0.71 (0.63-0.81), 0.88 (0.79-0.97), 0.68 (0.56-0.82), and 0.72 (0.61-0.85), respectively]. A significant association was found only between flavonols and stomach cancer risk based on a limited number of selected studies [OR (95%CI) = 0.68 (0.46-0.99)]. In the summary estimates from case-control studies, all flavonoid subclasses except flavones and flavanones were inversely associated with colorectal cancer risk, whereas neither total flavonoids nor any subclasses of flavonoids were associated with colorectal cancer risk in the summary estimates based on the cohort studies. The significant association between flavonoid subclasses and cancer risk might be closely related to bias derived from the case-control design. There was no clear evidence that dietary flavonoids are associated with reduced risk of stomach and colorectal cancer.

Key words: Flavonoids; Flavonols; Flavones; Flavanones; Flavan-3-ols; Anthocyanidins; Proanthocyanidins; Cancer risk; Meta-analysis

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INTRODUCTION

Stomach and colorectal cancer are common cancers and leading causes of cancer deaths[1]. Because the alimentary tract can interact directly with dietary components, stomach and colorectal cancer may be closely related to dietary intake. The consumption of meat, especially of red and processed meats that produce N-nitrosamine, was positively associated with stomach and colorectal cancer risk in a previous meta-analyses[2-4]. However, fruit and vegetable intakes were inversely associated with

colorectal cancer risk in people with high intakes of red and processed meat[5], and inverse association between vitamin C intake and stomach cancer risk was stronger in high red and processed meat intake group[6]. High fruit and vegetable intakes are associated with beneficial health effects, and these effects have been partly attributed to the high flavonoid content of these foods. Flavonoids are polyphenolic compounds that are abundant in fruits and vegetables. The beneficial health effects of flavonoids have been attributed to their free radical scavenging properties. In addition to their antioxidant properties, flavonoids have antiviral, antiallergic, antiinflammatory, and antitumor activities[7,8]. Flavonoids are generally classified as flavonols, flavones, flavanones, flavanols, isoflavones or anthocyanidins based on their chemical structure[9-11]. The antioxidant activities of the dietary flavonoids and their subclasses vary due to the differences in their chemical structures. Flavonols, the most common flavonoids in foods, include kaempferol, myricetin, quercetin, and isorhamnetin. Among them, quercetin is abundant in onions and apples, and has been studied extensively due to its high bioavailability and strong antioxidant effects. Flavones, such as apigenin and luteolin, are abundant in green leafy spices (*e.g.*, parsley, thyme, and celery), and the flavanones naringenin, hesperetin, and eriodictyol are found in citrus fruits. Flavanols, often referred to as flavan-3-ols, include catechin, gallocatechin, and epicatechin, which are abundant in teas, red wine, and apples. Isoflavones, especially genistein, are found in soy foods and have been studied widely due to their antitumor properties. Anthocyanidins are found in cherries, strawberries, and red wine.

A reduced risk of cardiovascular disease associated with flavonoid intake has been observed in many epidemiological studies[12,13]. Flavonoids have been suggested to reduce the risk of cardiovascular disease by modulating various mechanisms[14]. However, the association between cancer risk and dietary flavonoid intake has less supportive evidence from epidemiological studies, and the results have been inconsistent. To date, meta-analyses have focused mainly on dietary flavonoids and cardiovascular disease[12,13] or tea flavonoids and lung cancer[15,16]. Thus, we performed a meta-analysis of summary data to calculate the effect estimates of dietary flavonoid intake, including individual subclasses of flavonoids, on stomach and colorectal cancer risk.

DIETARY FLAVONOID INTAKE AND RISK OF STOMACH AND COLORECTAL CANCER

English-language studies were systemically searched using PubMed with the phrase "cancer risk and (stomach or gastric or colorectal or colon or bowel or rectal) and (flavonoid or flavonol or quercetin or kaempferol or myricetin or isorhamnetin or flavone or luteolin or apigenin or flavanone or eriodictyol or hesperetin or naringenin or flavan-3-ol or catechin or epicatechin or theaflavin or anthocyanidin or cyanidin or delphinidin or malvidin or pelargonidin or peonidin or petunidin or proanthocyanidin or isoflavone)" up to June 30, 2012. The inclusion criteria were as follows: (1) original articles with a case-control or cohort design; (2) articles reporting intake of either total flavonoids or subclasses of flavonoids and stomach or colorectal cancer; (3) articles with at least 3 categories of dietary flavonoid intake; and (4) studies reporting adjusted odds ratios (OR) or relative risks (RR) with 95%CIs for the risk of stomach or colorectal cancer in subjects with the highest dietary flavonoid intake compared with those with the lowest intake of dietary flavonoids.

The retrieved studies were reviewed independently by two investigators (Woo HD and Kim J). Data on authors, publication year, types of flavonoids, cancer sites, country in which the study was performed, number of cases and controls, categories of flavonoids or subclasses of flavonoids, subclasses included in the calculation of total flavonoids, and adjusted OR/RR and 95%CI were collected for the meta-analysis. The multivariate-adjusted values for OR/RR and 95%CI were selected for the meta-analysis to reduce the effects of potential confounding variables. If there was additional adjustment for fruit and vegetable intake, the adjusted values were selected.

All statistical analyses were performed using the STATA software package (version 10; Stata Corp, College Station, TX, United States). Log point effect estimates and the corresponding standard errors were calculated using the covariate-adjusted point effect estimates and 95%CI from selected studies and weighted by the inverse variance to calculate the summary estimates[17]. The heterogeneity across studies was measured using the Q-test based on the χ^2 statistic. Heterogeneity was considered statistically significant when $P < 0.1$ for the Q-test and was quantified using the I^2 test as described by Higgins *et al*[18]. Based on the heterogeneity of the included studies, fixed or random effects models were selected to calculate the pooled effect measures. Sensitivity analyses were performed to test the robustness of the results of the combined effects.

A total of 209 studies were identified, and 160 studies were excluded based on the titles and abstracts. The full texts of the remaining 49 studies were reviewed, and 25 studies were excluded for the following reasons: 7 studies were not related to dietary flavonoid intake or any of the flavonoid subclasses; 5 studies presented only recurrence or survival analysis data; 5 studies were not related to stomach or colorectal cancer: 4 studies did not report cancer risk; 2 studies were review articles; and 2 studies reported plasma concentrations instead of dietary flavonoid intake.

Sensitivity tests were conducted for the remaining 24 studies of total flavonoids and each subclass of flavonoids. One study showing substantial influence on the summary estimates in the sensitivity tests was excluded[19]. Thus, 23 studies, comprising 13 case-control

studies and 10 cohort studies, were finally selected to estimate the overall effects of total dietary flavonoid or flavonoid subclass intake on stomach and colorectal cancer risk (Table 1)[20-42]. Begg's funnel plot and Egger's test were used to evaluate the publication bias in studies of total flavonoids and each subclass of flavonoids. Egger's test showed no significant bias.

The summary estimates for the risk of cancer in subjects with the highest dietary flavonoid intake, compared with that in subjects with the lowest flavonoid intake, are presented in Table 2. The heterogeneity was low in the overall results, but heterogeneity was found in several summary estimates of the studies that included mostly case-control design. Total dietary flavonoids were not associated with a reduced risk of colorectal or stomach cancer [OR (95%CI) = 1.00 (0.90-1.11) and 1.07 (0.70-1.61), respectively]. However, flavonol, flavan-3-ol, anthocyanidin, and proanthocyanidin intakes showed a significant inverse association with colorectal cancer risk among flavonoid subclasses [OR (95%CI) = 0.71 (0.63-0.81), 0.88 (0.79-0.97), 0.68 (0.56-0.82), and 0.72 (0.61-0.85), respectively]. A significant association was found only for flavonol intake and stomach cancer risk in a limited number of selected studies [OR (95%CI) = 0.68 (0.46-0.99)].

Subgroup analyses by study design or sex were conducted for each subclass of flavonoids. In case-control studies, all flavonoid subclasses except flavones and flavanones were inversely associated with colorectal cancer risk. However, neither total flavonoids nor any subclasses of flavonoids were associated with colorectal cancer risk in the cohort studies. Colorectal cancer showed a statistically significant association for the summary estimate of flavonols in both female and male subjects [OR (95%CI) = 0.84 (0.75-0.93) and 0.87 (0.79-0.96), respectively] and isoflavones in male subjects [OR (95%CI) = 0.90 (0.83-0.99)]. A reduced risk of colorectal cancer was not observed for the subclasses of flavonols.

The preventative effects of flavonoids on stomach and colorectal cancer risk were estimated by pooling the estimates based on the published observational studies. Total dietary flavonoid intake was not associated with a reduced risk of stomach and colorectal cancer, but several subclasses of flavonoids, mostly in case-control studies, showed protective effects against stomach and colorectal cancer risk.

Flavonoids could affect cancer risk through their antiinflammatory and antitumor activities. Flavonoids exert their antiinflammatory activities by inhibiting cycloxygenase-2 (COX2) in colon cancer cells, and this is associated with a reduced risk of colorectal cancer[43]. Plant flavonoids induce apoptosis and suppress the growth of colon cancer cells by inhibiting the COX2- and Wnt/epidermal growth factor receptor/nuclear factor-κB-signaling pathways, which play crucial roles in colorectal cancer[44]. Quercetin inhibits tyrosine kinase activity, thus downregulating cell proliferation[45]. The antitumor effects of flavonoids have not been demonstrated conclusively, but it has been suggested that the free radical scavenging properties of flavonoids are closely related to beneficial effects on cancer risk, as flavonoids are more effective antioxidants than vitamin C, vitamin E and carotenoids[46]. Hydroxylation at the 3-position on the C ring, the increased number of hydroxyl groups in ring B, and a saturated 2-3 bond on the C ring showed enhanced scavenging activities[47,48].

Reduced risks of colorectal cancer were observed in the summary estimates for flavonols, flavan-3-ols, anthocyanidins, and proanthocyanidins in the present study, as well as in subgroup analyses. The intake of total dietary flavonols and dietary quercetin were associated with a significant reduction of stomach cancer risk. These results might be attributed to the antiinflammatory and antitumor effects of those nutrients. However, no reduced risk of stomach and colorectal cancer was observed in the summary estimates of total dietary flavonoids, including the subgroup analyses by sex and study design, in the present meta-analysis. The subclasses of flavonoids included in the calculations of total flavonoids were different across studies, as shown in Table 1. All studies included flavonols and flavones among the total dietary flavonoids, but flavan-3-ols, proanthocyanidins, which can contribute a considerable proportion of the total flavonoid intake, were not considered in most studies. These discrepancies can lead to highly heterogeneous results. However, the overall results were homogenous in terms of the effects of total flavonoids, except for the summary estimate of case-control studies, which showed moderate heterogeneity. Thus, dietary flavonoid intake might not be truly associated with stomach or colorectal cancer risk. Furthermore, dietary intake of quercetin, kaempferol, and myricetin showed no significant association with colorectal cancer risk, whereas total dietary flavonols showed statistically significant results for both cancer types. These results might be closely related to the design of the selected studies. The studies that investigated total flavonoids as well as the flavonols quercetin, kaempferol and myricetin were mostly cohort designs, while the studies that investigated total flavonols were mostly case-control designs. Case-control studies are more subject to recall bias, resulting in either an underestimate or overestimate of the risk estimates. Especially in stomach and colorectal cancer, patients might have intestinal discomfort prior to diagnosis, resulting in changes in dietary habits. Similar results were found in a meta-analysis of fruit and vegetable consumption[49]. A statistically significant association between the risk of stomach and colorectal cancer and fruit and vegetable consumption was observed only in the summary estimate of case-control studies. This summary risk estimate was highly heterogeneous, unlike that of the cohort studies, suggesting that bias might be introduced in case-control studies. Another explanation for the lack of association in cohort studies is the typically short follow-up times. In a meta-analysis of association between fruit and vegetable consumption and gastric cancer risk[50], a

Table 1 Selected studies on dietary flavonoids and risk of stomach and colorectal cancer

Ref.	Cancer site	Country	Study period	Case/control (*n*/*n*)	Dietary assessment method	Reported flavonoids	Included subclasses for total flavonoids	Intake comparison High *vs* low (mg/d)[1]	Controlled confounders
Garcia-Closas *et al*[20]	Stomach	Spain	1987-1989	354/354	Diet history	Q, K, M		Q4 *vs* Q1 mean (SD), Q: 7.1 (6.5), K: 1.2 (1.9), M: 0.65 (1.17)	Total energy intake, intake of nitrites, nitrosamines, vitamin C, total carotenoids (α-carotene, β-carotene, lutein, and lycopene) and other specific favonoids (quercetin, kaempferol, myricetin, and luteolin)
Lagiou *et al*[21]	Stomach	Greece	1981-1984	110/100	FFQ	F1, F2, F3, F4, An, I		F1: per 10.0, F2: per 0.3, F3: per 19.8, F4: per 135.1, An: per 40.4, I: per 2.0.	Age, gender, total energy intake, place of birth, BMI, height, years of education, smoking habits and duration of smoking, alcohol consumption, and fruit and vegetable consumption
Cotterchio *et al*[22]	Colorectum	Canada	1997-2000	1095/1890	FFQ	I		> 1.097 *vs* < 0.289.	Age, sex, and total energy intake
Rossi *et al*[23]	Colorectum	Italy	1992-1996	1953/4154	FFQ	T, F1, F2, F3, F4, An, I	F1, F2, F3, F4, An, I	T: > 191.1 *vs* < 75.3, F1: > 28.5 *vs* < 13.2, F2: > 0.7 *vs* < 0.3, F3: > 67.0 *vs* < 12.5, F4: > 88.5 *vs* < 20.8, An: > 31.7 *vs* < 5.3, I: > 33.9 *vs* < 14.4	Age, sex, energy intake, study center, family history of colorectal cancer, education, alcohol consumption, BMI, and occupational physical activity
Theodoratou *et al*[24]	Colorectum	Scotland	-	1456/1456	FFQ	F1, F2, F3, F4, Q, H, N, C, E		F1: > 36.75 *vs* < 16, F2: > 1.9 *vs* < 0.5, F3: > 45.2 *vs* < 16.7, F4: > 162.1 *vs* < 42.6, Q: > 22.9 *vs* < 11.7, H: > 21.1 *vs* < 3.95, N: > 19.7 *vs* < 3.8	Total energy intake, family history of colorectal cancer, total fiber intake, alcohol intake, NSAID intake, smoking, BMI, physical activity, and fruit and vegetable intake
Akhter *et al*[25]	Colorectum	Japan	2004-2005	721/697	FFQ	I		> 62.41 *vs* < 24.77	Age, sex, total energy intake, screening period, family history of colorectal cancer, cigarette smoking, alcohol consumption, BMI, physical activity, supplement use and non-steroidal anti-inflammatory drug use
Kyle *et al*[26]	Colorectum	United Kingdom	1998-2000	261/404	FFQ	F1, F3, F4		F1: > 40.4 *vs* < 19.3, F3: > 32.2 *vs* < 2.73, F4: > 188.8 *vs* < 67.1	Age, energy, family history, non-steroidal anti-inflammatory drugs, aspirin, Mn, riboflavin, vitamin C, folate
Rossi *et al*[27]	Stomach	Italy	1997-2007	230/547	FFQ	F1, F2, F3, F4, An, I, P		F1: > 32.3 *vs* < 13.2, F2: > 0.7 *vs* < 0.3, F3: > 56.8 *vs* < 12.9, F4: > 79.2 *vs* < 21.6, An: > 21.5 *vs* < 6.2, I: > 34.3 *vs* < 15.0, P: > 373.0 *vs* < 339.6	Age, sex, education, year of interview, BMI, tobacco smoking, and total energy intake
Rossi *et al*[28]	Colorectum	Italy	1992-1996	1953/4154	FFQ	P		> 486.6 *vs* < 202.5	Age, sex, study center, family history, education, alcohol consumption, BMI, physical activity and energy intake
Budhathoki *et al*[29]	Colorectum	Japan	2003-2003	816/815	FFQ	I		74.4 *vs* 15.5 (median)	Age, sex, total energy intake, resident area, parental colorectal cancer, smoking, alcohol use, BMI, type of job, and leisure time physical activity
Ekström *et al*[30]	Stomach (cardia and non cardia)	Sweden	1989-1995	C81, Non; 420 /1116	FFQ	Q		> 11.89 *vs* < 3.88	Age, sex, socioeconomic status, number of siblings, BMI, smoking and energy and salt intake

Zamora-Ros *et al*[31]	Colorectum	Spain	1996-1998	424/401	FFQ	T, F1, F2, F3, F4, An, I, P	F1, F2, F3, F4, An, I, P, Th	T: > 167.9 *vs* < 68.9, F1: > 11.5 *vs* < 5.1, F2: > 2.1 *vs* < 0.7, F3: > 17.7 *vs* < 3.7, F4: > 12.9 *vs* < 4.9, An: > 10.6 *vs* < 3.3, I: > 0.17 *vs* < 0.07, P: > 112.3 *vs* < 40.9	Age, sex, energy intake, BMI, alcohol and fiber intake, red and processed meat intake, tobacco consumption, physical activity, regular drugs, and family history of colorectal cancer
Djuric *et al*[32]	Colorectum	United States	2003-2005	1163/1501	FFQ	Q		> 10.29 *vs* < 4.33	Age, sex, physical activity at age 30-39, BMI, family history of colorectal cancer, highest education achieved, and nonsteroidal antiinflammatory drug use (NSAID) use, red meat, and total calcium intake
			Follow-up (yr)	Case (*n*)					
Hirvonen *et al*[33]	Colorectum, Stomach	Finland	6.1 (median)	C 133 S 111	Diet history	T	F1, F2	16.3 *vs* 4.2 (median)	Age and supplementation group
Knekt *et al*[34]	Colorectum, Stomach	Finland	30 (maximum)	C 90 S 74	Diet history	T, Q, K, M, H, N	F1, F2, F3	T: > 39.5 (F), 26.9 (M) *vs* < 8.5 (F), 4.3 (M), Q: > 4.7 (F), 3.9 (M) *vs* < 1.8 (F), 1.5 (M), K: > 0.9 (F), 0.8 (M) *vs* < 0.2 (F), 0.1 (M), M: > 0.2 (F), 0.11 (M) *vs* < 0.03 (F), 0.06 (M), H:> 26.8 (F), 15.4 (M) *vs* < 3.2 (F), 0 (M), N: > 7.7 (F), 4.7 (M) *vs* < 0.9 (F), 0 (M)	Age, sex, geographic area, occupation, smoking, and BMI
Lin *et al*[35]	Colorectum	United States	-	878	FFQ	T, Q, K, M	F1, F2	Q5 *vs* Q1 (NHS: > 31.1 *vs* < 9.6, HPFS: > 30.5 *vs* < 10.7)	Age, BMI, family history of colorectal cancer, history of colorectal polyps, prior sigmoidoscopy screening, physical activity, smoking status, red meat intake, alcohol consumption, total energy intake, total calcium intake, total folate intake, total fiber intake, aspirin use, and multivitamin use
Akhter *et al*[36]	Colorectum	Japan	7.6 (mean)	886	FFQ	I		Q4 *vs* Q1	Age, public health center area, history of diabetes mellitus, BMI, leisure time physical activity, cigarette smoking, alcohol drinking, and intake of vitamin D, dairy products, meat, fruit, vegetable, and fish, (F) + menopausal status and current use of female hormones
Mursu *et al*[37]	Colorectum	Finland	16.2 (mean)	55	Food recording	T, F1, F2, F3, F4, An	F1, F2, F3, F4, An	Q4 *vs* Q1 T: 416.3 *vs* 265.0 (mean)	Age and examination years, BMI, smoking status, pack-years of smoking, physical activity, intakes of alcohol, total fat and saturated fat, and energy adjusted intake of fiber, vitamin C and E
Simon *et al*[38]	Colorectum	Nether-lands	13.3	1271	FFQ	T, F4	F1, F2	T: > 36 *vs* < 16 (M), F4: > 84.3 *vs* < 44.4 (M), T: > 38.3 *vs* < 18.4 (F), F4: > 95.9 *vs* < 51.6 (F)	Age, family history of colorectal cancer, smoking status, alcohol intake, occupational physical activity at longest held job, BMI and processed meat intake
Wang *et al*[39]	Colorectum	United States	11.5 (mean)	305	FFQ	T	F1, F2	T: > 34.6 *vs* < 11.6	Age, race, total energy intake, and randomized treatment assignment, smoking, alcohol use, physical activity, postmenopausal status, hormone replacement therapy use, multivitamin use, BMI, family history of colorectal cancer, ovary cancer, and breast cancer, and intake of fruit and vegetables, fiber, folate, and saturated fat
Yang *et al*[40]	Colorectum	United States	6.4 (mean)	321	FFQ	I		T3 *vs* T1 34.8 *vs* 20.9 (mean)	Age, education, household income, BMI, physical activity, menopausal status, family history of colorectal cancer, total calorie intake, and average intakes of fruit, vegetables, red meat, nonsoy calcium, nonsoy fiber, and nonsoy folic acid

Ward *et al*[41]	Colorectum	Unitd States	9 (mean)	221	Food recording	I	Continuous	Age, height, weight, family history of colorectal cancer, smoking status, aspirin use, physical activity, and average daily intake of fat, energy, calcium, alcohol, and red and processed meats, (F) + oral contraceptive use, menopausal status, menopausal hormone therapy use, parity, breastfeeding, and surgical removal of ovaries
Hara *et al*[42]	Stomach	Japan		1249	FFQ	I	Q4 *vs* Q1 (median) 42.3 *vs* 9.2 (M) 41.8 *vs* 9.4 (F)	Age, public center area, BMI, smoking status, ethanol intake, family history of gastric cancer, vegetable, fruit, fish, salt, and total energy intake

[1]M and F represent male and female in this row. Q: Querectin; K: Kaempferol; M: Myricetin; H: Hesperidin; N: Naringenin; C: Catechin; E: Epicatechin; F1: Flavonols; F2: Flavones; F3: Flavanones; F4: Flavan-3-ols; An: Anthocyanidins; I: Isoflavones; P: Proanthocyanidins; Th: Theaflavins; BMI: Body mass index.

Table 2 Summary estimates of dietary flavonoids and stomach and colorectal cancer risk

	Combined					Colorectum					Stomach				
				Heterogeneity					Heterogeneity					Heterogeneity	
	n[a]	RR	95%CI	I^2	*P*[b]	*n*	RR	95%CI	I^2	*P*[b]	*n*	RR	95%CI	I^2	*P*[b]
Total flavonoids	11	1.00	0.91-1.11	15.0%	0.301	9	1.00	0.90-1.11	28.2%	0.194	2	1.07	0.70-1.61	0%	0.464
Cohort	9	1.05	0.93-1.18	0%	0.517	7	1.04	0.92-1.18	9.6%	0.355	2	-	-	-	-
Case-control	-	-	-	-	-	2	0.81	0.50-1.29	67.9%	0.078[c]	0				
Female	-	-	-	-	-	3	0.93	0.84-1.04	0%	0.890	0				
Male	5	1.05	0.96-1.15	0%	0.514	4	1.05	0.96-1.15	18.6%	0.298	1				
Flavonols	7	0.71	0.63-0.80	10.7%	0.348	5	0.71	0.63-0.81	37.0%	0.175	2	0.68	0.46-0.99	0%	0.586
Case-control	6	0.70	0.62-0.79	0%	0.755	4	0.70	0.62-0.79	0%	0.510	2	-	-	-	-
Female	-	-	-	-	-	2	0.84	0.75-0.93	0%	0.361	0				
Male	-	-	-	-	-	3	0.87	0.79-0.96	45.4%	0.160	0				
Quercetin	8	0.81	0.68-0.97	44.1%	0.085[c]	4	0.90	0.80-1.03	42.2%	0.159	4	0.66	0.51-0.85	0%	0.472
Kaempferol	4	0.95	0.65-1.37	55.2%	0.082[c]	2	1.12	0.91-1.38	0%	0.979	2	0.73	0.31-1.71	71.8%	0.060[c]
Myricetin	4	1.15	0.87-1.51	0%	0.965	2	1.15	0.80-1.67	0%	0.607	2	1.13	0.75-1.71	0%	0.935
Flavones	6	0.84	0.74-0.96	44.8%	0.107	4	0.83	0.63-1.09	64.4%	0.038[c]	2	0.76	0.54-1.08	0%	0.635
Case-control	5	0.82	0.66-1.02	55.0%	0.064[c]	3	0.83	0.61-1.14	87.9%	0.016[c]	2	-	-	-	-
Female	-	-	-	-	-	2	0.94	0.84-1.04	0%	0.353	0				
Male	-	-	-	-	-	3	0.92	0.84-1.02	0%	0.477	0				
Flavanones	7	1.04	0.86-1.27	44.5%	0.094[c]	5	1.08	0.95-1.22	28.2%	0.234	2	0.72	0.49-1.07	38.3%	0.203
Case-control	6	1.05	0.85-1.30	53.3%	0.057[c]	4	1.08	0.95-1.23	46.4%	0.144	2	-	-	-	-
Female	-	-	-	-	-	2	1.01	0.89-1.14	0%	0.734	0				
Male	-	-	-	-	-	3	0.99	0.89-1.11	0%	0.583	0				
Hesperidin	3	1.12	0.90-1.40	0%	0.675	2	1.15	0.91-1.45	0%	0.587	1				
Naringenin	3	1.11	0.89-1.38	0%	0.732	2	1.13	0.90-1.42	0%	0.539	1				
Flavan-3-ols	9	0.88	0.80-0.97	16.3%	0.297	7	0.88	0.79-0.97	30.1%	0.198	2	0.91	0.66-1.26	0%	0.335
Cohort	-	-	-	-	-	3	0.91	0.76-1.08	26.9%	0.254	0				
Case-control	6	0.87	0.77-0.98	24.7%	0.249	4	0.86	0.76-0.98	46.6%	0.132	2	-	-	-	-
Female	-	-	-	-	-	3	0.94	0.87-1.02	54.7%	0.110	0				
Male	-	-	-	-	-	4	1.07	0.99-1.15	23.5%	0.270	0				
Anthocyanidines	5	0.75	0.64-0.89	21.9%	0.275	3	0.68	0.56-0.82	0%	0.868	2	1.03	0.73-1.43	0%	0.509
Case-control	4	0.76	0.64-0.90	37.9%	0.185	2	0.68	0.56-0.83	0%	0.668	2	-	-	-	-
Proanthocyanidines	3	0.55	0.35-0.87	74.4%	0.020[c]	2	0.72	0.61-0.85	0%	0.372	1				
Isoflavones	14	0.90	0.80-1.01	54.4%	0.008[c]	10	0.89	0.77-1.02	65.1%	0.003[c]	4	0.91	0.78-1.06	5.5%	0.206
Cohort	7	0.98	0.85-1.12	44.0%	0.098	5	1.02	0.90-1.15	43.1%	0.135	2	0.88	0.74-1.05	48.7%	0.163
Case-control	7	0.78	0.70-0.87	37.5%	0.143	5	0.76	0.68-0.85	36.2%	0.180	2	1.02	0.73-1.44	0%	0.430
Female	7	0.95	0.81-1.11	47.7%	0.075[c]	6	0.93	0.78-1.11	54.3%	0.052[c]	1				
Male	6	0.89	0.82-0.96	35.7%	0.170	5	0.90	0.83-0.99	42.0%	0.141	1				

[a]Selected study numbers; [b]*P* values for heterogeneity from *Q*-test; [c]Random effects model was used if $P < 0.1$. RR: Relative risk.

significant association was observed only in the meta-analyses of studies with more than 10 years of follow-up. Meta-regression also revealed that longer follow-up time was associated with lower risk of gastric cancer. The mean follow-up times were more than 10 years for all cohort studies reporting total dietary flavonoid intake in our study, except for Hirvonen *et al*[35]. A meta-analysis performed after excluding this study did not change the results. Thus, the hypothesis of an inverse association between dietary flavonoids and risk of stomach and colorectal cancer cannot be supported by our results.

Although this meta-analysis provided little evidence of an inverse association between stomach and colorectal cancer risk and flavonoid intake, several mechanisms supported by *in vitro* and animal studies remain biologically plausible. Antitumor effects were shown for quercetin, luteolin, and myricetin[51-54], and polyphenols extracted from apple and olive oil had a chemopreven-

tive effect in colon cancer cell lines or mice[55-57] and antioxidant activities in gastric mucosa[58,59]. Most subclasses of flavonoids were inversely associated in the present meta-analyses, although some bias might have been introduced. Thus, it is thought that dietary flavonoids are inversely associated with stomach or colorectal cancer risk, but this association is very small, making it difficult to detect. The United States Department of Agriculture (USDA) database for food flavonoids has been updated several times since 2003[60]. Most total dietary flavonoids are flavan-3-ols (82.5%), as estimated by USDA database and 24 h dietary records provided by United States adults[61]. The second greatest contributor was flavanones (7.6%), followed by flavonols (6.8%), anthocyanidins (1.6%), flavones (0.8%), and isoflavones (0.6%). However, the bioavailability of these compounds might be different. For example, tea flavonoids showed low absorption rates, whereas quercetin and isoflavones showed strong bioavailability. The main source of dietary flavonoid subclasses in Scotland in a database by Kyle *et al*[62] was tea[24], whereas the main sources of total flavonoids in Spain[31], calculated using the USDA database[60], were fruits (65.1%), followed by wine (14.4%), legumes (6.3%), and vegetables (4.2%). The methods used to estimate total flavonoids from dietary intake are poorly established[61]. Levels of exact individual flavonoid intake from food should be determined to confirm the true association between flavonoids and stomach and colorectal cancer risk.

The main limitation of this study is the small number of publications included. Especially in the case of stomach cancer, summary estimates could not be calculated in several subgroup analyses due to the limited number of studies. Because a significant association was found in the analyses of case-control studies which were subject to bias, the inverse association between subclasses of dietary flavonoid intake and cancer risk may be overestimated.

CONCLUSION

There was no clear evidence that dietary flavonoids are associated with reduced risk of stomach and colorectal cancer in the present meta-analysis. However, there is a possibility that there may be a weak association with stomach and colorectal cancer based on consistent associations for subclasses of flavonoids. The association of flavonoids with stomach and colorectal cancer could be relatively small and thus might only be detected with better methods of estimating true dietary flavonoid intake.

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