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Intake of Anthocyanins and Gastric Cancer Risk: A Comprehensive Meta-Analysis on Cohort and Case-Control Studies

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Summary This meta-analysis aimed to explore the association between anthocyanins intake and the risk of gastric cancer. All the relative articles have been searched in the online databases, including PubMed, EMBASE, Web of Science, and the Cochrane Library until June 11th, 2018. Risk ratios (RRs) or odds ratio (ORs) and their 95% confidence intervals were calculated and pooled through the STATA 12.0. A total of 6 studies were finally selected in the meta-analysis. No significant association was found between total anthocyanins consumption and gastric cancer risk (RR=0.92, 95%CI: 0.81–1.04). Likewise, there was also no significant evidence of the relationship between anthocyanins intake and gastric cancer in tumor site (cardia: RR=0.90, 95%CI: 0.62–1.31; noncardia: RR=0.86, 95%CI: 0.69–1.07) and gender (men: RR=1.02, 95%CI: 0.73–1.40; women: RR=0.80, 95%CI: 0.52–1.23). The dose-response relationship was also not found in this meta-analysis. The Grades of Recommendations Assessment, Development and Evaluation (GRADE) quality in our study was very low. The results of our meta-analysis suggested the intake of anthocyanins had no association with the risk of gastric cancer and further studies are needed.

Key Words anthocyanins, stomach cancer, observational studies, meta-analysis

Gastric cancer is one of the most common malignant tumors in the world, ranking the 4th and 5th respectively in men and women with an estimated 951,600 new cases and also the 3rd and 5th lethal cancer cause in men and women with total 723,100 deaths worldwide in 2012 (*1*). It is also estimated that 26,240 new cases and 10,800 deaths will occur in the US in 2018 (*2*).

From the middle of the 20th century to the early of the 21st century, the incidence and mortality of gastric cancer has shown a stable decline trend in Europe and in some Asian countries where the incidence of gastric cancer was usually high (*3*, *4*). This decline trend has been supposed to be related to several elements, such as diet, life style, and control of *Helicobacter pylori* infection, etc. Among those elements, eradication of *Helicobacter pylori* (*H. pylori*) and the change of diet habit and structure may play an important role (*5*, *6*). For instance, several randomized controlled trials in Japan and some meta-analysis of RCTs revealed the effectiveness of prevention of gastric cancer by eradicating *H. pylori* (*6*). Additionally, intake of vitamin C, which is common in fruits and vegetables, has been reported to be inversely associated with gastric cancer risk in Europeans (*7*).

Besides vitamin C, other natural compounds also have bioactivities like polyphenols, flavonoids, anthocyanins and resveratrol, etc. (*8*, *9*). With the increasing focus on plant-derived polyphenols, anthocyanins have been brought into the wide concern because of their potential benefits for human health (*10*). Anthocyanins, a subgroup of flavonoids, are a kind of water-soluble pigment and occur abundantly in fruits and vegetables, especially blueberries, sweet cherries, black currants, raspberries, strawberries, and red grapes, etc. (*10*, *11*). Anthocyanins can be further divided into 17 types, only 6 of which are widely distributed including cyanidin, delphinidin, petunidin, peonidin, pelargonidin and malvidin (*12*).

Anthocyanins have a basic chemical structure named 2-phenylbenzopyrilium that has a strong capacity of donating electrons, which contributes to their antioxidant benefits (*10*, *13*). It has been reported that anthocyanins have multiple chemopreventive and chemotherapeutic functions, such as antidiabetic, cardioprotective, hepatoprotective, neuroprotective activities, and even anti-carcinogenic effects, especially in lung cancer, colon cancer, prostate cancer and esophageal cancer (*14*). Some in vivo studies in animals showed the inhibitory effect of anthocyanins on the skin cancer (*15*). Furthermore, there were also in vitro studies that illustrated anthocyanins could inhibit gastric cancer via antioxidant or anti-inflammation (*16*), induction of apoptosis (*17*), and blockage of cell cycle (*18*).

However, the association between anthocyanins intake and gastric cancer lacked sufficient epidemiological evidence to support, and the conclusions of several epidemiological studies which had been conducted in human beings did not appear completely consistent (*19–21*). Therefore, this meta-analysis aimed to system-

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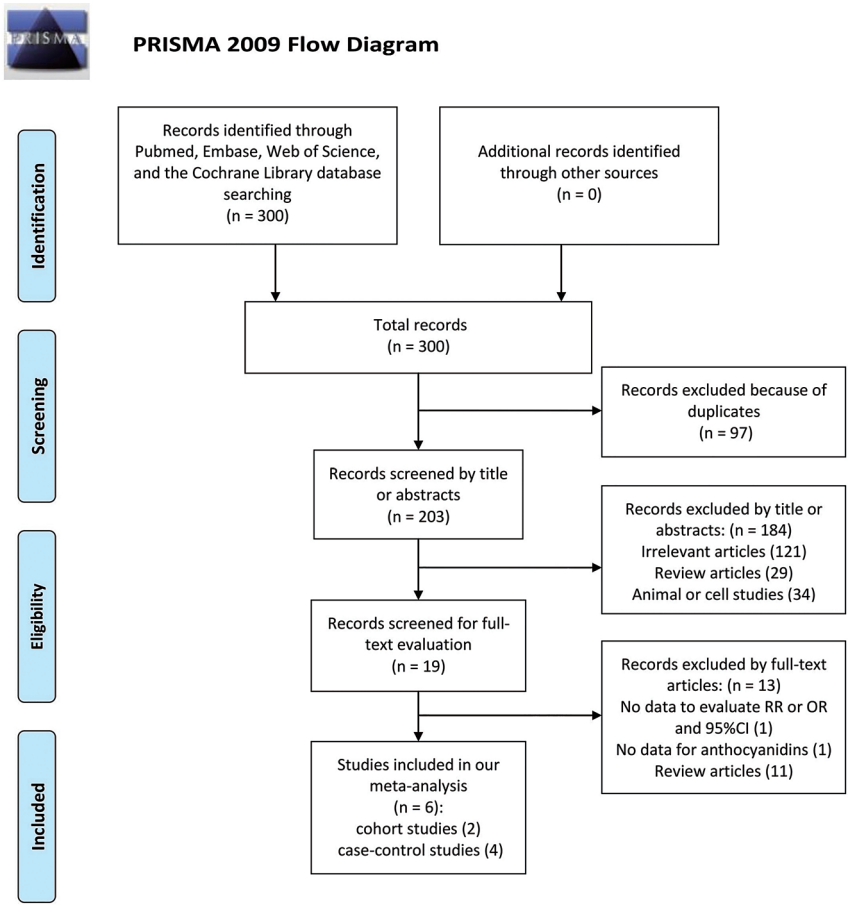

Fig. 1. Flowchart indicating the results of studies for inclusion in the meta-analysis on anthocyanins consumption and the risk of gastric cancer.

atically explore and summarize the association between anthocyanins and gastric cancer based on cohort and case-control studies and we also conducted the subgroup analysis of gender and tumor site and the dose-response analysis. Additionally, we also illustrated the potential mechanisms behind the results. To our best knowledge, our study is the first dose-response meta-analysis to summarize the intake of anthocyanins and the risk of gastric cancer.

SUBJECTS AND METHODS

Search strategy. Our study was guided by the checklist of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (*22*). We performed a systematic literature search in several online databases, including PubMed, EMBASE, Web of Science and the Cochrane Library from up to June 11, 2018.

The following searching strategy was: (anthocyanins OR anthocyanin OR anthocyanidins OR anthocyanidin OR cyanidin) AND (gastric OR stomach) AND (cancer OR carcinoma OR tumor OR neoplasm OR adenocarcinoma). Only articles having been published in English were included in our search range. We also reviewed reference lists from all included articles to identify any additional literature.

Study selection. Eligible studies were included in the meta-analysis according to the following criteria: (1) reviews, animal or cell studies were excluded; (2) only case-control and cohort studies were included; (3) the exposure of interest was anthocyanin consumption with the outcome of gastric cancer; (4) odds ratio (ORs) or relative risks (RRs) or hazard ratios (HRs) with 95% confidence intervals (CIs) should be reported in the articles.

Data extraction. The following data were extracted from each identified study by two authors (DeYi Yang and Xin Wang): the study design; last name of the first author; publication year; study location; participant characteristics; sex; age at baseline; number of cases or controls (participants for cohort studies); study period; multivariate adjusted RRs (ORs for case-control studies) with 95%CIs for each category of anthocyanin consumption, and confounders.

Quality assessment of study and evidence. A 9-star system based on the Newcastle-Ottawa Quality Assessment Scale (NOQAS) was employed for quality assessment by two reviewers (DeYi Yang and Xin Wang) independently. In this system, four stars were allocated to the selection of study participants, two stars were allocated to the comparability of studies based on the design or analysis, and three stars were allocated to the evaluation of exposure in case-control studies or the ascertainment of outcomes in cohort studies. More than 6 stars can be regarded as high quality. Two reviewers (DeYi

Table 1. Characteristics of 6 studies on anthocyanins intake and the risk of gastric cancer.

Reference	Country and age	Design and sample size	Object or subgroup	OR or HR or RR (95%CI)	Measure of intake	Adjustments
Lagiou, P. 2004	Greece 60–65 y	Case-control 110 : 100		1.14 (0.72–1.80)	Per 40.4 mg/d	age, gender, place of birth, body mass index, height, years of education, smoking habits and duration of smoking, alcohol consumption, total energy intake, fruit and vegetable consumption
Petrick, J. L. 2015	America 30–79 y	Case-control GCA, 248 OGA, 341 Controls, 662	Gastric cardia adenocarcinoma (GCA)	1.00 0.98 (0.65–1.47) 0.91 (0.60–1.38) 0.71 (0.46–1.10)	0–7.21 mg/d 7.22–11.53 11.54–18.47 ≥18.48	age (continuous), sex, race (white, other), geographic centre (Connecticut, New Jersey, Washington), cigarette smoking (ever/never), and dietary energy intake (kilocalories, continuous)
			Other gastric adenocarcinoma (OGA)	1.00 0.91 (0.63–1.32) 0.89 (0.61–1.29) 0.70 (0.47–1.03)	0–7.21 7.22–11.53 11.54–18.47 ≥18.48	
Rossi, M. 2010	Italy 22–80 y	Case-control 230 : 547		1.00 0.89 (0.55–1.45) 0.78 (0.47–1.28) 0.53 (0.31–0.91) 0.91 (0.56–1.47)	0–6.2 mg −11.2 −15.7 −21.5 >21.5	sex, age, education, year of interview, body mass index, tobacco smoking, and total energy intake according to the residual model
Sun, L. 2017	America <80 y	Cohort 12-y follow-up 469,008 1,297 gastric (625 cardia and 672 non-cardia) cancer	Cardia	1.00 1.05 (0.81–1.35) 0.97 (0.74–1.27) 0.99 (0.75–1.31) 1.05 (0.80–1.39)	0–3.8 mg/d 3.9–7.0 7.1–11.7 11.8–20.6 20.7–376.6	age at baseline, sex, race, education, smoking status, BMI, alcohol intake, self-reported health, vigorous physical activity of ≥20 min, and total energy intake
			Noncardia	1.00 0.91 (0.71–1.17) 0.84 (0.65–1.10) 0.84 (0.64–1.10) 0.94 (0.72–1.23)	0–3.8 3.9–7.0 7.1–11.7 11.8–20.6 20.7–376.6	
Woo, H. D. 2014	Korea 35–75 y	Case-control 334 : 334	All	1.00 0.86 (0.54–1.35) 1.06 (0.62–1.80)	9.4 14.7 35.1	total energy intake, *H. pylori*, age, sex, education, smoking status, alcohol consumption, BMI, physical activity, and consumption of pickled vegetable and red and processed meat, fruits and vegetable consumption
			Men	1.00 1.01 (0.55–1.83) 1.16 (0.57–2.34)	9.4 14.7 35.1	
			Women	1.00 0.80 (0.37–1.76) 1.22 (0.49–3.01)	9.4 14.7 35.1	
Zamora-Ros, R. 2012	Europe 35–70 y	Cohort 11 y 477,312 683	Men	1.00 1.14 (0.86–1.51) 0.94 (0.69–1.29) 0.98 (0.68–1.41)	<11.7 11.7–20.3 20.4–32.8 >32.8	age, educational level, smoking status, physical activity, BMI, alcohol and energy intake, and daily consumption of fruit, vegetables, and red and processed meat
			Women	1.00 0.69 (0.50–0.95) 0.79 (0.55–1.14) 0.71 (0.44–1.16)	<13.9 13.9–23.6 23.7–38.7 >38.7	

Table 2. Quality assessment according to the Newcastle-Ottawa scale.

Study	Country	Selection	Comparability	Outcome/exposure	Score
Sun, L. 2017[1]	America	4	2	3	9
Petrick, J. L. 2015	America	3	2	1	6
Woo, H. D. 2014	Korea	3	2	2	7
Zamora-Ros, R. 2012[1]	Europe	4	2	2	8
Rossi, M. 2010	Italy	3	2	2	7
Lagiou, P. 2004	Greece	3	2	1	6

[1] Cohort studies.

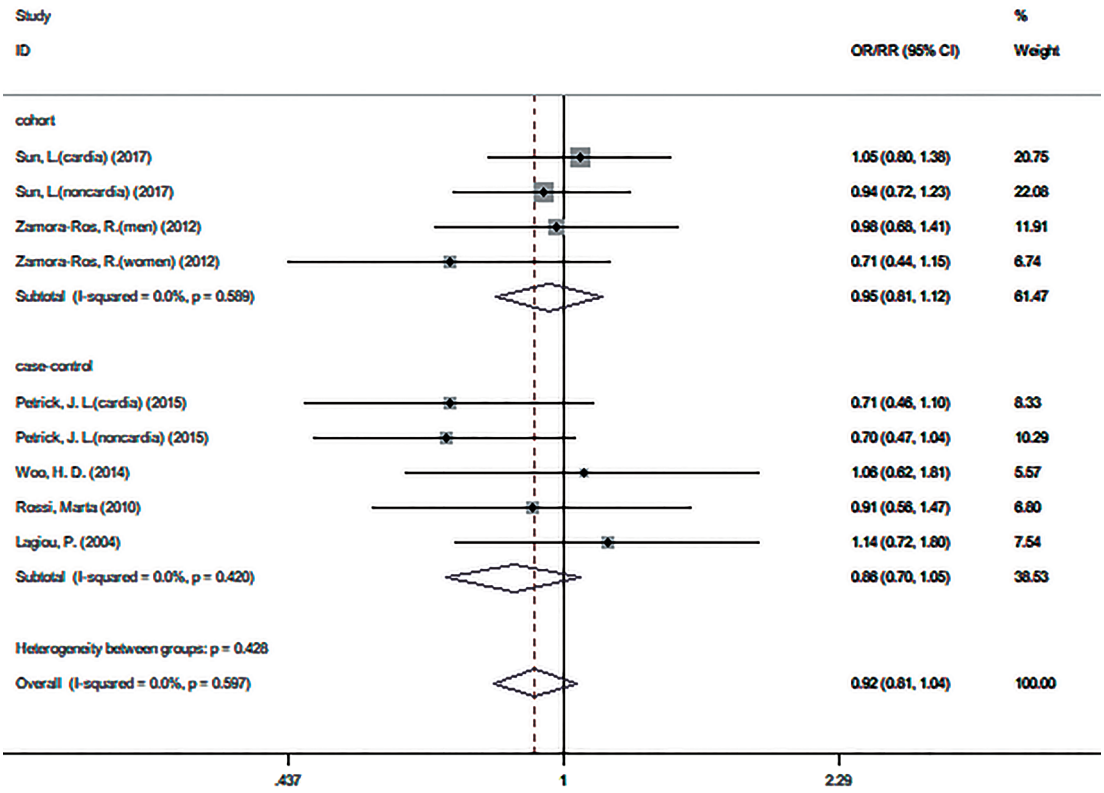

Fig. 2. Forest plot of the highest compared with the lowest categories of anthocyanins intake and gastric cancer risk.

Yang and Xin Wang) evaluated the quality of evidence using the GRADE system (*23*) (GRADE profiler 3.6.1). In this system, the level of an observational study, which is initially regarded as low-quality, could be upgraded for three reasons: a large effect, the presentation of a dose-response gradient, and plausible confounders that would not decrease an apparent treatment effect and could also be downgraded for five reasons: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The evidence grades can be divided into four levels: 1) high, which indicates that further research is unlikely to alter the confidence in the effect estimate; 2) moderate, which indicates that further research is likely to significantly alter confidence in the effect estimate and may change the estimate; 3) low, which indicates that further research is likely to significantly alter confidence in the effect estimate and to change the estimate; and 4) very low, which indicates that any effect estimate is uncertain.

Statistical analysis. Because the incidence of gastric cancer is low (*1*), the ORs can be approximately equal to the RRs (*24*). Thus, all results were reported as RRs simply.

First, we pooled the adjusted RRs/ORs with 95%CIs of gastric cancer by comparing the highest and lowest categories of anthocyanins intake and also displayed the pooled RRs/ORs with 95%CIs of different subgroups. For the dose-response meta-analysis, we used the "generalized least squares for trend estimation" method provided by Greenland and Longnecker (*25*) to evaluate the association between log RR and the exposures.

Based on the rescaling methods of previous dose-response meta-analyses, the upper and lower boundary of anthocyanins intake was transformed into the median or mean values per category. We then assessed the heterogeneity among studies by using the Q test ($p<0.05$) (*26*). The Higgins I^2 statistic (*27*) was also examined, I^2 value $>50\%$ and 75% respectively means

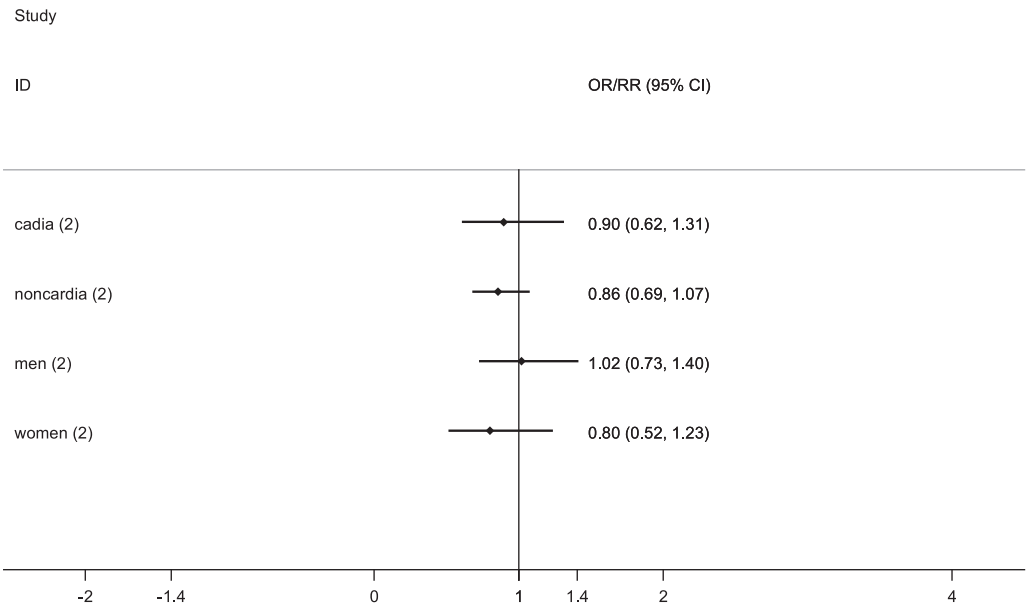

Fig. 3. The summary RR of the highest compared with the lowest categories of anthocyanins intake and gastric cancer risk in subgroups.

substantial heterogeneity and high heterogeneity existed in the trials. A random-effects model was used when significant heterogeneity was detected (*28*); otherwise, a fixed-effects model was preferred. We created funnel plots (*29*) and the Begg's rank correlation test (*30*) or Egger's regression test (*31*) to detect publication bias ($p<0.10$) (*32*). We carried out a sensitivity analysis to exclude one large study that tended to dominate the results. We also carried out subgroup analyses to examine potential sources of heterogeneity by sex, study design and tumor site.

All statistical analyses were performed with the STATA 12.0 statistical software package (Stata Corporation, College Station, Texas, USA). A threshold of $p<0.05$ was considered significant without anything special.

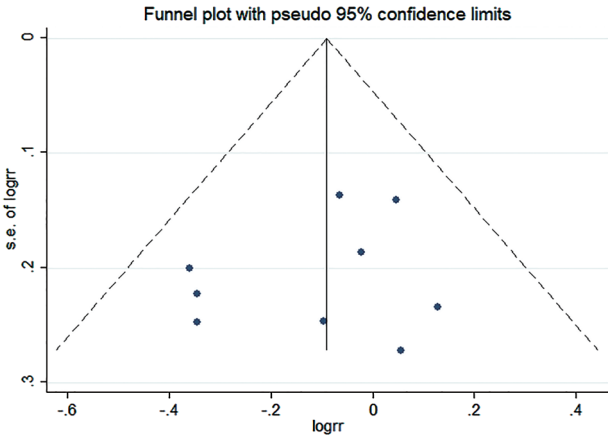

Fig. 4. Funnel plot for evaluation of publication bias.

RESULTS

The process to screen and select the studies has been summarized in Fig. 1. Finally, a total of 6 studies were identified to evaluate the effects of anthocyanins on gastric cancer. The general features of the total 6 studies have been listed in Table 1, of which 4 studies are case-control studies (*21*, *33*–*35*) and 2 are cohort studies (*36*, *37*). The NOQAS ranged from 6 to 9, with a mean of 7.17 stars (Table 2).

Nine sets of data were included in the analysis, and no significant heterogeneity existed among the pooled results (p for heterogeneity=0.597, I^2=0.00%). However, the association was not significant (combined RR: 0.92, 95%CI: 0.81–1.04) (Fig. 2).

According to the study design, we separately analyzed cohort studies (RR=0.95, 95%CI: 0.81–1.12, p for heterogeneity=0.589, I^2=0.0%) and case-control studies (OR=0.86, 95%CI: 0.70–1.05, p for heterogeneity=0.420, I^2=0.0%); males (RR=1.02, 95%CI: 0.73–1.40, p for heterogeneity=0.678, I^2=0.0%) and females (RR=0.80, 95%CI: 0.52–1.23, p for heterogeneity=0.302, I^2=6.0%); cardia (RR=0.90, 95%CI: 0.62–1.31, p for heterogeneity=0.137, I^2=54.7%) and noncardia (RR=0.86, 95%CI: 0.69–1.07, p for heterogeneity=0.224, I^2=32.4%). We did not identify significant associations between anthocyanins intake and gastric cancer risk in these subgroups (Fig. 3).

The incidence of gastric cancer and anthocyanins intake did not exhibit dose-response relationships in the nonlinear (p=0.620; p for heterogeneity=0.85, Q=16.12) and linear (1 mg/d intake of anthocyanins RR=1.000, 95%CI: 0.999–1.001; p for heterogeneity=0.55, Q=23.41) dose-response analysis.

There was not obvious publication bias examined by either Egger's test (p=0.425) or Begg's test (p=0.917) (Fig. 4). The sensitivity analysis that was made by excluding one study at a time also showed a combined RR: 0.88, 95%CI: 0.76–0.99 and no obvious change

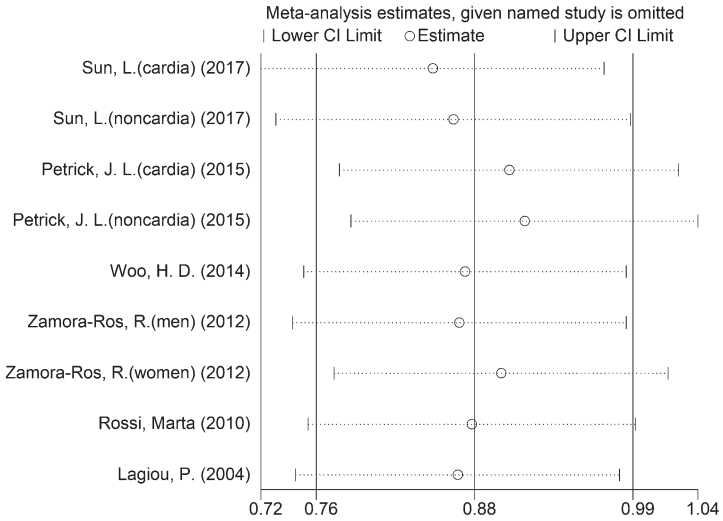

Fig. 5. Sensitivity analysis for dominative weight of each study.

of the overall RR for gastric cancer ranging from 0.85 (95%CI: 0.72–0.97) when excluding Sun et al. (cardia) (*36*) to 0.92 (95%CI: 0.79–1.04) when excluding Petrick et al. (noncardia) (*33*) (Fig. 5).

DISCUSSION

This meta-analysis of 2 cohort studies and 4 case-control studies including 949,226 members (patients and controls) suggested no significant association between anthocyanins intake and gastric cancer risk with no substantial heterogeneity. Furthermore, the subgroup analysis of gender and tumor site (cardia and noncardia) and even the linear and nonlinear dose-response analysis were also found no significant evidence.

Mechanisms

Anthocyanins and anthocyanidins are both subgroups of flavonoids. The basic chemical structure of anthocyanins is 2-phenylbenzopyrilium, also known as flavylium, which consists of two aromatic rings, respectively A and B, and an heterocyclic ring C containing oxygen between them. In fact, anthocyanins occur as the glycosides of polyhydroxy or polymethoxy derivatives of 2-phenylbenzopyrylium and their glycosides of the respective aglycones of anthocyanins are the anthocyanidins (*10*, *38*, *39*).

As is mentioned above, gastric cancer is in direct proportion to infection of *H. pylori* (*6*), so the effects or mechanisms aiming at eradicating *H. pylori* may arouse wide concern. The gastric carcinogenesis of *H. pylori* may be related to oxidative stress, cytotoxin-associated gene A (CagA), and cancer stem cells (CD44+ cells), etc. (*40*)

On the one hand, reactive oxygen species (ROS) is a high risk factor of carcinogenesis because it can cause the mutation and damage of DNA (*41*). The infection of *H. pylori* can cause chemotaxis and activation of neutrophils and the neutrophils can produce the hypochlorous anion (OCl^-) that can react with the ammonia (NH_3), which is produced from urea by *H. pylori* associated urease, to yield monochloramine (NH_2Cl), that can freely penetrate biological membranes to make intracellular components oxidized or make nucleic acids mutated (*42*, *43*). And due to the chemical structure and properties, anthocyanins appear a capability of antioxidant (*13*), which can just deal with the injury of ROS. Kim et al. (*16*) has proved that anthocyanins from black soybean could reduce ROS generation induced by *H. pylori* in gastric epithelial cells. Additionally, Braunlich et al. (*44*) also showed anthocyanins and their derivatives could scavenge diphenylpicrylhydrazyl (DPPH) radical and inhibit 15-lipoxygenase and xanthine oxidase, which are also the sources of ROS (*45*, *46*).

On the other hand, the CagA protein of *H. pylori* can be translocated into host gastric epithelial cells through type IV secretion system and then can induce gastric carcinogenesis by binding Src homology 2-containing protein tyrosine phosphatase (SHP-2) and activating the ERK-MAPK pathway (*40*). Moreover, chronic inflammation caused by infection of *H. pylori* in gastric epithelial cells can induce the expression of CD44, a cell surface marker associated with cancer stem cells (*47*, *48*). And in these CD44-positive gastric cancer stem-like cells, it has been reported by Tsugawa et al. (*47*) that the autophagy of CagA, which can be induced by ROS, could be decreased by suppressing the accumulation of ROS via elevating intracellular glutathione (GSH) levels, in which case CagA maintains a relatively high level in the CD44-positive cells and can lead to their carcinogenesis more easily. Under these circumstances, anthocyanins have also been reported to have anti-microbial and anti-cancer effects. Kim et al. (*49*) has reported that cyanidin 3-O-glucoside (C3G), a kind of anthocyanins, could prevent secretion of CagA produced by *H. pylori* via suppressing the transcription of secA, a cytoplasmic protein that can assist the ATP-driven translocation of bacteria proteins out of the bacterial plasma membrane (*50*).

Besides, the tumor-suppressing effect of anthocyanins can also be seen in other pathways, such as interfering with cell cycle or inducing apoptosis. Wang et al. (*18*)

Table 3. Assessment of quality using the GRADE system.

Outcome	Quality assessment								Quality	Importance
	No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other considerations		
Anthocyanins intake and gastric cancer risk	6	OS[1]	Very serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	None	Very low	Critical

[1] Observational studies.
[2] Only studies with the full text published in English were included; case-control studies have the advantage of being vulnerable to selection and recall bias; anthocyanins consumption was assessed by food frequency questionnaires, errors in measurement were inevitable.

showed the proliferation of gastric cancer cells can be inhibited by a kind of anthocyanins, through upregulating the expression of the KLF6 gene, a novel tumor suppressor gene (*51*), which can increase the expression of p21 and decrease the expression of CDK4 and Cyclin D1 in a p53-independent manner. Moreover, there were also studies that showed the cellular apoptosis can be induced by anthocyanins through p38/p53 and p38/c-jun signaling pathways intrinsically and extrinsically or through caspase-3 related mitochondrial-mediated pathways (*52*).

However, anthocyanins did not decrease the incidence of gastric cancer in our study. And Woo et al. (*21*) also reported that there was no significant evidence that showed dietary anthocyanins could reduce *H. pylori*-positive gastric cancer both in men and women. As for *H. pylori*-negative subjects, the protective effects of anthocyanins on gastric cancer only in women was detected. Therefore, this inconsistency between in vitro studies and epidemiological studies needs explanations. First, the concentration of anthocyanins differs significantly between in vivo and in vitro because of the first-pass effect. Statistically, the study reported that the max plasma levels of total anthocyanins range from 1 to 100 nmol/L after having fruits in human bodies (*12*); however, the concentration of anthocyanins used on AGS cells in some studies can be up to dozens or hundreds micromole (*17*). So, the laboratory data of anthocyanins could not reflect the true concentration in human bodies. Second, the design of epidemiological studies could also underestimate the amount of intake of anthocyanins itself because of missing or insufficient data of food composition (*53*), not specific and comprehensive questionnaires for anthocyanins study (*54*, *55*). Moreover, some other factors might also cause the ambiguity of the results such as the inter-individual variations in absorption and metabolism of anthocyanins (*56*) and dietary modification during the early prediagnostic period of the disease (*37*), etc. Finally, other elements including pH of gastric acid (*57*), different stability in different part of intestinal tract (*10*), vitamin C, salt contents of the food, gender, smoking status (*21*) may also account for this inconsistency. After all, humans are different from animals, so we could not depend on animal or cell studies totally and further well-designed studies should be needed.

Strengths and limitations of this review

The meta-analysis has several strengths. First, our study was the first to analyze the linear and nonlinear dose-response effects of anthocyanins on gastric cancer and also further analyzed the relatively comprehensive subgroups of the included studies. Second, the negative publication bias and sensitivity analysis both guarantee the confidence and reliability of the results. Third, the quality of studies finally identified in our study was high according to the Newcastle-Ottawa Quality Assessment Scale. Nearly all the studies considered the confounding factors such as age, sex, race, dietary energy intake, and smoking status, etc. and we chose the adjusted OR/RRs instead of the crude ones to avoid the possible interfer-

ence. Finally, we only take anthocyanins or anthocyanidins or their subclasses into account instead of fruits, vegetables or some other substances containing anthocyanins, in which case some variations and bias may be controlled and the confidence and consistency of our results may be strengthened to some degree.

However, some limitations were also notable in our study (Table 3). First, the weakest point of our study is the limited number of included studies. Only 6 studies might weaken persuasive power of our results. Similarly, the limited number of studies also confined the sufficient accessible data to make more subgroup analysis and more accurate dose-response analysis. Second, the estimation of anthocyanins intake may produce bias. All the studies evaluated the intake of anthocyanins using the USDA database, which mainly collected data on American regions (*33*); however, the content of anthocyanins can be influenced by multiple variates, such as ripeness, climatic factors, culture types, and storage (*58*). Therefore, the data collected by different studies in different regions may be deviated from the true condition. Finally, there were also other remaining confounding factors that could not be included although all the studies controlled the majority of them, which can also lead to bias of the overall results.

Furthermore, more studies should be conducted to investigate the relationship between the plasma concentrations of anthocyanins and gastric cancer because FFQs (food frequency questionnaires) which were adopted in all the studies could not assess the true concentrations in human bodies. In fact, it is the anthocyanins in blood or tissues that play an important role after absorption, metabolism, and distribution (*58*), and differ from person to person, so biomarkers are becoming the hot issue because they can better and more objectively reflect individual exposure to the targeted substances (*59*). Therefore, more epidemiological studies and more comprehensive and detailed designs should be needed in the future.

CONCLUSIONS

In summary, our meta-analysis indicated no association between the intake of anthocyanins and the risk of gastric cancer. Also, no significant relationship was found in gender and tumor site. Therefore, further studies with better designs and more accurate measurement methods should be made to explore the true value and effects of anthocyanins on gastric tumor.

Author contributions

DeYi Yang and his advisor Professor Chen are responsible for the study design, literature search, systematic review, data collection or analysis, the decision to publish, and manuscript preparation. Dr. Wang helped conduct the dose-response meta-analyses with the STATA program and gave meaningful suggestions. Dr. Yuan helped revise the manuscript and provided valuable advice. All authors made joint efforts to ensure that the final version of this study was reliable and integrated. DeYi Yang serves as a guarantor.

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