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Review

Landscape of dietary factors associated with risk of gastric cancer: A systematic review and dose-response meta-analysis of prospective cohort studies

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Abstract ***Background:*** The associations between dietary factors and gastric cancer risk have been analysed by many studies, but with inconclusive results. We conducted a meta-analysis of prospective studies to systematically investigate the associations.
Methods: Relevant studies were identified through searching Medline, Embase, and Web of Science up to June 30, 2015. We included prospective cohort studies of intake of dietary factors with risk estimates and 95% confidence intervals for gastric cancer.
Results: Seventy-six prospective cohort studies were eligible and included in the analysis. We ascertained 32,758 gastric cancer cases out of 6,316,385 participants in relations to intake of 67 dietary factors, covering a wide ranging of vegetables, fruit, meat, fish, salt, alcohol, tea, coffee, and nutrients, during 3.3 to 30 years of follow-up. Evidence from this study indicates that consumption of total fruit and white vegetables, but not total vegetables, was inversely associated with gastric cancer risk. Both fruit and white vegetables are rich sources of vitamin C,

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which showed significant protective effect against gastric cancer by our analysis too. Furthermore, we found concordant positive associations between high-salt foods and gastric cancer risk. In addition, a strong effect of alcohol consumption, particularly beer and liquor but not wine, on gastric cancer risk was observed compared with nondrinkers. Dose-response analysis indicated that risk of gastric cancer was increased by 12% per 5 g/day increment of dietary salt intake or 5% per 10 g/day increment of alcohol consumption, and that a 100 g/day increment of fruit consumption was inversely associated with 5% reduction of risk.
Conclusion: This study provides comprehensive and strong evidence that there are a number of protective and risk factors for gastric cancer in diet. Our findings may have significant public health implications with regard to prevention of gastric cancer and provide insights into future cohort studies and the design of related clinical trials.

1. Introduction

Although its incidence has decreased for several decades, gastric cancer is still one major public health concern worldwide [1]. Epidemiological data from the American Cancer Society suggest that gastric cancer is the fourth most common cancer in males and the fifth most common cancer in females, accounting for 6.8% of the total cancer cases and 8.8% of total cancer-related deaths in 2012 globally [2]. Because of this still significant mortality, there is a pressing need to develop gastric cancer specific prevention strategies.

Helicobacter pylori infection is a World Health Organisation class I carcinogen for gastric cancer, but only less than 0.5% of those infected people develop gastric cancer, suggesting a considerable contribution of other factors [3,4]. Dietary factors have been recognised to play a very critical role in the prevention of cancer, including gastric cancer [5]. The decreasing incidence of gastric cancer in developed countries may be partly the results of increased use of refrigeration, availability of fresh fruit and vegetables, and decreased reliance on salted or preserved foods [6]. Although many dietary factors were suggested to affect the risk of gastric cancer, the conclusions remain inconsistent and lack firm scientific evidence [7].

In recent decades, quite a number of prospective cohort studies, such as the European Prospective Investigation into Cancer and Nutrition (EPIC) study, have been performed to investigate the association between various dietary factors and gastric cancer. In order to develop effective dietary and nutritional prevention strategies for gastric cancer, we conducted meta-analyses of the evidence across all existing prospective cohort studies. We aimed to provide a comprehensive evaluation of the associations of gastric cancer with a diversity of dietary factors.

2. Methods

The design, implementation, analysis, and reporting of our meta-analysis were performed in accordance with the Meta-Analysis of Observational Studies in Epidemiology protocol [8].

2.1. Search strategy and selection criteria

We systematically searched multiple literature databases, including Medline, Embase, and Web of Science, from inception to 30 June 2015 for prospective cohort studies of gastric cancer. The following keywords were used for the literature search: ("gastric cancer" OR "gastric neoplasm" OR "stomach cancer" OR "stomach neoplasm") AND (cohort OR "prospective study" OR "follow-up study" OR "longitudinal study"). No restrictions were imposed on language of publications. The references of retrieved relevant articles, especially meta-analyses, were reviewed to identify potential studies.

Studies that satisfied the following four criteria were included in our meta-analysis: 1) published prospective cohort studies; 2) the exposure of interest was dietary factors, including foods, beverages, and nutrients; 3) the outcome was the risk of gastric cancer; and 4) the authors reported the relative risk estimates, including 95% confidence intervals (CIs). In addition, we excluded reviews, meta-analyses, retrospective studies, non-human studies, and letters without sufficient data.

2.2. Data extraction and quality assessment

Two investigators (XF and PA) independently conducted the literature search, identified potential studies, and extracted detailed information from each included article. Discrepancies were resolved through group discussion with the third investigator (FW). Using a standardised data collection form, we recorded the following information in the identified studies: first author, year of publication, study location, study name, duration of follow-up, gender, sample size (number of cases and participants), dietary exposures and corresponding risk estimates with 95% CIs. We extracted risk estimates with the most adjustment.

Quality assessment was performed according to the Newcastle-Ottawa scale for non-randomised studies [9]. This scale assigns a maximum of nine points to each study: four for selection of participants and measurement of exposure, two for comparability, and three for assessment of outcomes and adequacy of follow-up. We regarded scores of 0–3, 4–6, and 7–9 as low, moderate, and high quality, respectively.

2.3. Statistical analysis

In this meta-analysis, the relative risks (RRs) and 95% CIs were considered as the effect size for all studies, and the hazard ratios (HRs) were deemed equivalent to RRs. Any results stratified by gender were treated as two separate reports. Those articles reporting both gastric cardia cancer (GCC) and gastric non-cardia cancer (GNCC) were also treated as two separate reports.

Whenever more than one cohort study had been performed on the same exposure, we examined whether the main reported conclusions were concordant. For each dietary factor, we pooled the RRs with corresponding CIs by using a random effects model (DerSimonianand-Laird method) that combines within-study variations with between-study heterogeneity [10]. Populations were categorised into three groups: North America, Europe, and Asia-Pacific (including Hawaii). Regarding the differences between cancers of the gastric cardia and non-cardia subsites, we also conducted corresponding subgroup analyses as far as possible.

The dose-response relations were estimated by using generalised least squares trend estimation, according to the methods developed by Greenland and Longnecker [11,12]. For this method, the doses of dietary factor intake, distributions of cases and person-years, and RRs with 95% CIs were required for at least three quantitative exposure categories. If the total number of cases or person-years was reported (but not the distribution), we estimated the distribution based on the definitions of the quantiles. When neither medians nor means were reported, we used the categorical midpoint. If the highest or lowest category was open-ended, the midpoint of the category was set by assuming that the width of the category is the same as the next adjacent category. In addition, we evaluated a potential curvilinear association of significant risk and protective factors with incidence of gastric cancer, using restricted cubic splines with three knots at percentiles 10%, 50%, and 90% of the distribution [13].

Heterogeneity among the studies was estimated using the I^2 statistic, with values of 25%, 50%, and 75% representing low, moderate, and high degrees of heterogeneity, respectively [14]. Publication bias was evaluated by the application of Egger's linear regression test and Begg's rank correlation test with significance set to $P < 0.10$ [15].

All statistical analyses were performed with Stata version 12 (StataCorp LP, College Station, TX, USA). All tests were two tailed and statistical significance was defined as $P < 0.05$.

3. Results

3.1. Literature search and study characteristics

Fig. 1 shows the study selection process and results from the literature search. We identified 2,123 articles from Medline, 4,221 articles from Embase, and 2,422 articles from Web of Science prior to June 30, 2015. After exclusion of duplicates and studies that did not meet the inclusion criteria, 67 remaining articles appeared to be eligible for this study. Meanwhile, nine additional studies were identified through checking reference lists of previous published reviews and meta-analyses.

Table 1 and Supplementary Table 1 show the characteristics of the 76 selected studies, all of which had prospective cohort design and participants with no prior diagnoses of gastric cancer at baseline. During a mean of 11.4 years of follow-up (from 3.3 to 30), we documented 6,316,385 participants in total and ascertained 32,758 incident cases of gastric cancer. Among these

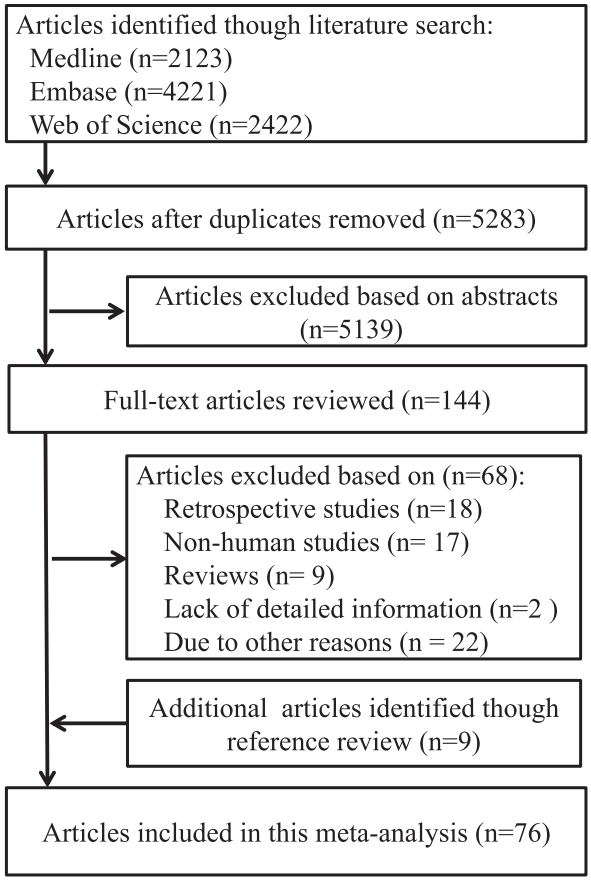

Fig. 1. Flow diagram of literature search and study selection.

Table 1
Characteristics of the including 76 prospective cohort studies of dietary factors in relation to gastric cancer.

Study name	Author, year	Location	Period of observation	Follow-up (years)	Gender	Cases/ participants	Main exposure
a-Tocopherol, β-Carotene Cancer Prevention Study	Nouraie et al., 2005	Finland	1964–1992	13.7	Both	122/28,463	Alcohol, wine, beer, and spirits
Cancer Prevention Study	McCullough et al., 2001	United States	1953–2006	18	Both	299/60,041	Coffee
Copenhagen Centre for Prospective Population Study	Barstad et al., 2005	Denmark	1986–1992	6.3	Both	282/120,852	Vegetables and fruit
European Prospective Investigation into Cancer and Nutrition (EPIC)	Buckland et al., 2010	Europe	1986–1992	6.3	Both	282/120,852	Vitamins, carotenoids, and dietary fibre
EPIC	Duell et al., 2011	Europe	1992–2006	8.9	Both	449/485,044	Mediterranean diet
EPIC	González et al., 2006	Europe	1995–2003	8	Both	647/566,402	Vitamin E
EPIC	González et al., 2006	Europe	1966–1983	18	Male	111/8006	Selected foods and nutrients
EPIC	González et al., 2012	Europe	1995–2006	10	Both	532/303,156	Meat
EPIC	Jakszyn et al., 2006	Europe	1986–1989	3.3	Both	139/120,852	Onions
EPIC	Jakszyn et al., 2012	Europe	1992–2004	8.4	Both	444/478,459	Alcohol
EPIC	M.A et al., 2007	Europe	1996–2000	4	Female	206/73,064	Fruits and vegetables
EPIC	Zamora-Ros et al., 2012	Europe	2002–2006	4	Male	132/59,247	Fruits and vegetables
Higashi-Yamanashi Study	Kurosawa et al., 2006	Japan	1978–2008	30	Male	185/7150	Alcohol, beer, wine, and vodka
Hisayama Study	Miyazaki et al., 2012	Japan	1995–2000	4.5	Both	375/474,606	Alcohol
Hisayama Study	Shikata et al., 2006	Japan	1995–2000	4.5	Both	394/490,802	Fruits and vegetables
Hokkaido Study	Khan et al., 2004	Japan	1988–1997	2.5	Both	379/44,930	Selected foods, alcohol, and green tea
Honolulu Heart Program	Stemmermann et al., 1990	Hawaii	1975–1994	14.8	Both	108/11,907	Selected foods and beverages
Iowa Women's Health Study	Zheng et al., 1995	United States	1986–1990	4.3	Both	200/12,0852	Black tea
Japan Collaborative Cohort Study (JACC)	Fujino et al., 2002	Japan	1992–2002	6.5	Both	330/521,451	Meat
JACC	Tokui et al., 2005	Japan	1992–2002	6.5	Both	330/521,451	Fruits and vegetables
Japan Collaborative Study for Evaluation of Cancer Risk	Hoshiyama et al., 2002	Japan	1992–2010	11	Both	683/477,312	Fruits and vegetables
Japan Public Health Center (JPHC) Prospective Study	Hara et al., 2012	Japan	2001–2006	5	Both	1,249/84,881	Isoflavones
JPHC-based Prospective Study	Kobayashi et al., 2002	Japan	1988–1997	8.1	Both	359/72,851	Green tea
JPHC-based Prospective Study	Sasazuki et al., 2004	Japan	1985–1995	6	Both	69/5373	Selected foods

(*continued on next page*)

Table 1 (*continued*)

Study name	Author, year	Location	Period of observation	Follow-up (years)	Gender	Cases/ participants	Main exposure
JPHC-based Prospective Study	Takachi et al., 2010	Japan	1988–2004	10.4	Both	3,577/219,080	Green tea
JPHC-based Prospective Study	Tsugane et al., 2004	Japan	1992–2002	6.6	Both	314/521,457	*N*-nitroso compounds
Kaunas Rotterdam Intervention Study & Multifactorial Ischemic Heart Disease Prevention Study	Everatt et al., 2012	Lithuania	1992–2002	8.7	Both	444/481,419	Haem iron
Korean Multi-Center Cancer Cohort	Ko et al., 2013	Korea	1958–1989	25	Male	267/12,763	Plant foods
Life Span Study	Sauvaget et al., 2005	Japan	1997–2004	5.7	Female	153/74,942	Ginseng
Linxian General Population Trial	Tran et al., 2005	China	1985–1991	6	Both	57/9753	Selected foods and alcohol
Miyagi Cohort Study	Nakaya et al., 2005	Japan	1986–2002	16.3	Both	652/120,852	Meat
Miyako Study	Murata et al., 2010	Japan	1984–2002	14.3	Both	51/3158	Selected foods
National Health Insurance Corporation Study	Sung et al., 2007	Korea	1996–2003	7	Both	12,393/2,248,129	Meat and salt
Netherlands Cohort Study (NCS)	Botterweck et al., 1998	Netherlands	1967–1990	24	Both	189/9985	Nitrates, nitrites, and *N*-nitroso compounds
NCS	Botterweck et al., 2000	Netherlands	1966–1986	20	Male	75/17,633	Selected foods
NCS	Dorant et al., 1996	Netherlands	1993–2008	8.5	Both	166/19,688	Soy products and other foods
NCS	Goldbohm et al., 1996	Netherlands	1990–1999	10	Both	404/39,993	Fruits and vegetables
NCS	Keszei et al., 2012	Netherlands	1989–1999	11	Both	76/8035	Highly salted food and mountain herbs
NCS	Steevens et al., 2010	Netherlands	1987–2005	15.7	Female	160/61,433	Alcoholic beverage
NCS	Steevens et al., 2011	Netherlands	1998–2005	7.2	Both	139/82,002	Fruits and vegetables
NCS	van den Brandt 2003	Netherlands	1987–2005	15.7	Female	160/61,433	Coffee
NCS	van Loona et al., 1997	Netherlands	1987–2004	18	Female	160/61,433	Meat, fish, and nitrosamines
NCS	van Loona et al., 1998	Netherlands	1997–2005	18	Female	156/61,433	Folate
NIH-AARP Diet and Health Study	Carman et al., 2009	United States	1987–2004	18	Female	156/61,433	Total carbohydrate
NIH-AARP Diet and Health Study	Cross et al., 2011	United States	1987–2004	7.2	Female	139/82,002	Vitamin A, retinol, and carotenoids
NIH-AARP Diet and Health Study	Freedman et al., 2007	United States	1998–2002	9.9	Both	128/81,670	Lignans
NIH-AARP Diet and Health Study	Freedman et al., 2008	United States	1982–1996	14	Both	1349/970,045	Selected foods
NIH-AARP Diet and Health Study	O'Doherty et al., 2012	United States	1992–1999	6.7	Both	312/435,000	Cereal fibre
NIH-AARP Diet and Health Study	Xiao et al., 2014	United States	1988–2002	14	Both	93/2467	Vitamin A

Table 1 (*continued*)

Study name	Author, year	Location	Period of observation	Follow-up (years)	Gender	Cases/ participants	Main exposure
Seven Countries Study	Jansen et al., 1999	United States, Finland, Netherlands, Italy, Croatia, Serbia, Greece, and Japan	1986–2005	20	Male	391/18,244	Alcohol
Shanghai Cohort Study	Moy et al., 2010	China	1986–2003	8.9	Both	87/6830	Salted foods
Shanghai Men's Health Study (SMHS)			1992–1999	7	Both	121/30,304	Soy products
Shanghai Women's Health Study (SWHS)	Epplein et al., 2010	China	1990–1997	8	Male	882/21,201	Alcohol
Six cohorts combined	Inoue et al., 2009	Japan	1986–1999	10.5	Both	116/13,250	Selected foods
Swedish Mammography Cohort (SMC) Selected foods and alcohol	Larsson et al., 2006	Sweden	1965–1986	17.6	Male	150/7990	
SMC	Larsson et al., 2006	Sweden	1985–1999	12	Male	243/29,133	Fruits, vegetables, and antioxidants
SMC	Larsson et al., 2006	Sweden	1995–2006	10	Both	955/494,978	Fat
SMC	Larsson et al., 2006	Sweden	1990–2001	11	Both	892/72,943	Green tea
SMC	Larsson et al., 2006	Sweden	1950–1981	20	Both	1270/38,576	Selected food and green tea
SMC	Larsson et al., 2007	Sweden	1988–2002	14	Both	93/2476	Salt
SMC & Cohort of Swedish Men (COSM)	Larsson et al., 2006	Sweden	1984–2002	15.4	Both	577/73,133	Salt and salted food
SMC & COSM	Lin et al., 2013	Sweden	1986–2002	16.3	Both	655/120,852	Alcohol
Swedish Twin Registry	Terry et al., 1998	Sweden	1986–2002	16.3	Both	616/120,852	Fruits and vegetables
SWHS	Kamangar et al., 2007	China	1940–1968	20	Male	174/8006	Alcohol
Takayama Study	Nagata et al., 2002	Japan	1996–2002	6.5	Male	3452/669,570	Alcohol
Not available	Bidel et al., 2013	Finland	1995–2004	7.7	Both	869/77,500	Sodium and salted foods
Not available	Chyou et al., 1990	Hawaii	1967–1992	21	Both	116/11,546	Alcohol
Not available	Galanis et al., 1998	United States	1988–1990	11	Both	859/110,792	Selected foods
Not available	Inoue et al., 1996	Japan	1984–1991	15	Both	1452/29,584	Selected foods
Not available	Kato et al., 1992	Japan	1984–1992	9	Both	419/26,311	Green tea
Not available	Kim et al., 2010	Korea	1990–2001	11	Both	486/39,065	Salt and salted foods
Not available	Knekt et al., 1999	Finland	1986–1992	6.3	Both	282/120,852	Salt and salted foods
Not available	Kneller et al., 1991	United States	1986–1990	4.3	Both	203/120,852	Nitrate
Not available	Ngoan et al., 2002	Japan	1986–1992	6.3	Both	282/120,852	Nitrate
Not available	Nomura et al., 1990	Hawaii	1995–2006	9.1	Both	939/492,293	Folate, methionine, vitamin B6, and vitamin B12
Not available	Sjödahl et al., 2008	Norway	1992–2010	11	Both	683/477,312	Flavonoids and lignans
Not available	Tsubono et al., 2001	Japan	1986–1992	7	Female	26/34,691	Retinol and antioxidant vitamins

studies, 37 were conducted in Europe, 21 in Japan, 11 in the United States, 4 in China, and 3 in Korea.

Assessment of study quality yielded an average score of 7.7 (± 0.92), and the score for all the studies was five or above (moderate or high quality). The detailed quality scores of all including studies were provided in Supplementary Table 2.

3.2. Effects of vegetable and fruit consumption on risk of gastric cancer

Fig. 2 shows an advanced forest plot that summarises the effects of various vegetables and fruit on the risk of gastric cancer. Based on the high versus low analysis, consumption of white vegetables (RR: 0.67, 95% CI:

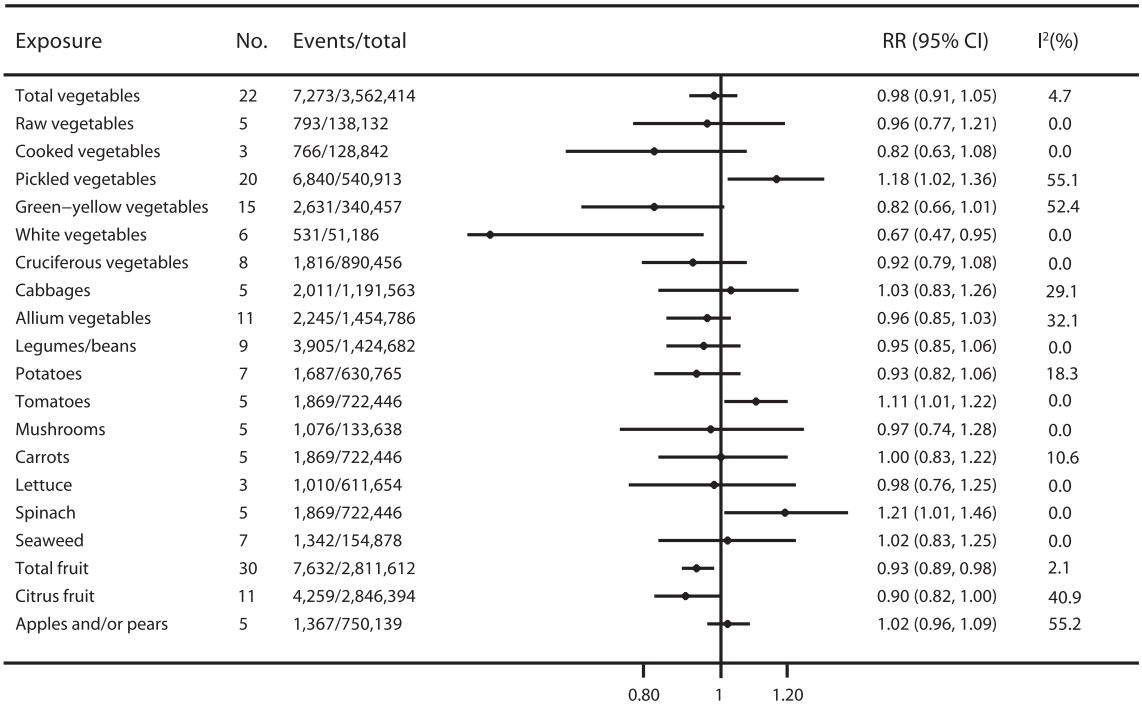

Fig. 2. Forest plot of associations between vegetable and fruit consumption and gastric cancer risk.

0.47 to 0.95), but not total vegetables (RR: 0.98, 95% CI: 0.91 to 1.05), reduced the risk for gastric cancer significantly. The consumption of pickled vegetable (RR: 1.18, 95% CI: 1.02 to 1.36), tomato (RR: 1.11, 95% CI: 1.01 to 1.22), and spinach (RR: 1.21, 95% CI: 1.01 to 1.46) was associated with a greater risk of gastric cancer. Meanwhile, the combined RRs of gastric cancer were 0.93 (95% CI: 0.89 to 0.98) for total fruit consumption, and 0.90 (95% CI: 0.82 to 1.00) for citrus fruit consumption, suggesting evident protective effects. Other categories showed no significant association.

3.3. Effects of meat, fish, and other food consumption on risk of gastric cancer

Fig. 3 summarises associations of meat, fish, and other foods consumption for the risk of gastric cancer. The highest, compared with the lowest, consumption of both processed meat (RR: 1.15, 95% CI: 1.03 to 1.29) and salted fish (RR: 1.25, 95% CI: 1.07 to 1.47) were associated with an increase in gastric cancer risk. We also identified similar positive findings for ham, bacon, and sausage (RR: 1.21, 95% CI: 1.01 to 1.49). In addition, excess dietary salt intake may increase risk for gastric cancer significantly (RR: 1.11, 95% CI: 1.05 to 1.16), and higher consumption of high-salt foods was also associated with a greater risk (RR: 1.55, 95% CI: 1.17 to 2.05). Other categories showed no significant association.

3.4. Effects of alcohol, coffee, tea, and other beverage consumption on risk of gastric cancer

Fig. 4 summarises associations of different kinds of beverage consumption for gastric cancer risk. Compared with nondrinkers, a strong effect of alcohol consumption on gastric cancer risk was observed among 24 identified studies (RR: 1.15, 95% CI: 1.01 to 1.31). In the analysis of gastric cancer by alcoholic beverage type, higher consumption of beer (RR: 1.21, 95% CI: 1.02 to 1.43) and liquor (RR: 1.22, 95% CI: 1.05 to 1.43), but not wine (RR: 1.02, 95% CI: 0.77 to 1.34), was significantly associated with gastric cancer risk. Coffee, green tea, and other categories showed no significant association.

3.5. Effects of nutrient intake on risk of gastric cancer

Fig. 5 summarises associations of different kinds of nutrients intake for gastric cancer risk. Dietary intake of vitamin C (RR: 0.89, 95% CI: 0.85 to 0.93) was inversely associated with the risk of gastric cancer. Other nutrients, either macro or micro, showed no significant association.

3.6. Dose-response analyses

Table 2 showed the results of dose-response analyses of above protective and risk factors. A 100 g/day increment of fruit consumption was inversely associated with 5%

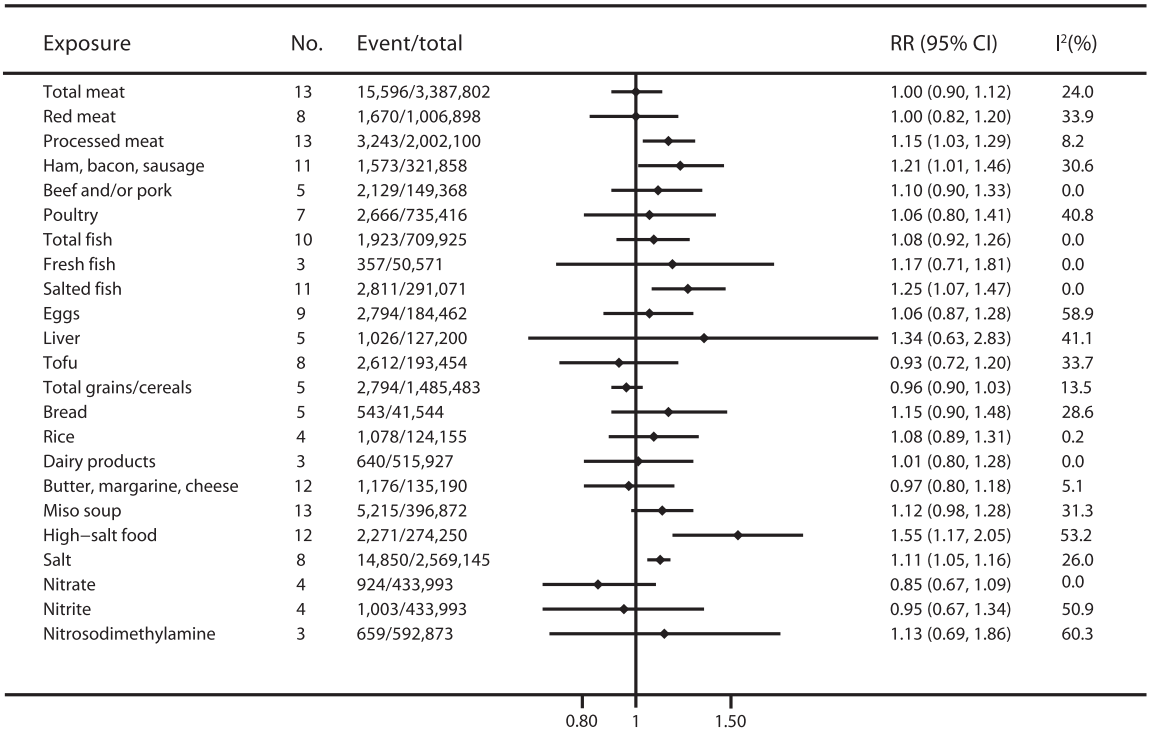

Fig. 3. Forest plot of associations between meat, fish, and other foods consumption and gastric cancer risk.

reduction of risk (RR: 0.95, 95% CI: 0.92 to 0.99). Conversely, these results also indicated that risk of gastric cancer was increased by 12% per 5 g/day increment of dietary salt intake (RR: 1.12, 95% CI: 1.02 to 1.23), and 5% per 10 g/day increment of alcohol consumption (RR: 1.05, 95% CI: 1.02 to 1.08).

Using a restricted cubic splines model, we observed significant evidence of a curvilinear association between consumption of total fruit ($P = 0.01$ for non-linearity; Fig. 6A), salt ($P = 0.02$ for non-linearity; Fig. 6B), and alcohol ($P < 0.01$ for non-linearity; Fig. 6C) and risk of gastric cancer.

3.7. Subgroup analyses by continents and cancer anatomical subsites

We examined whether estimates varied among populations for both protective and risk factors in which we

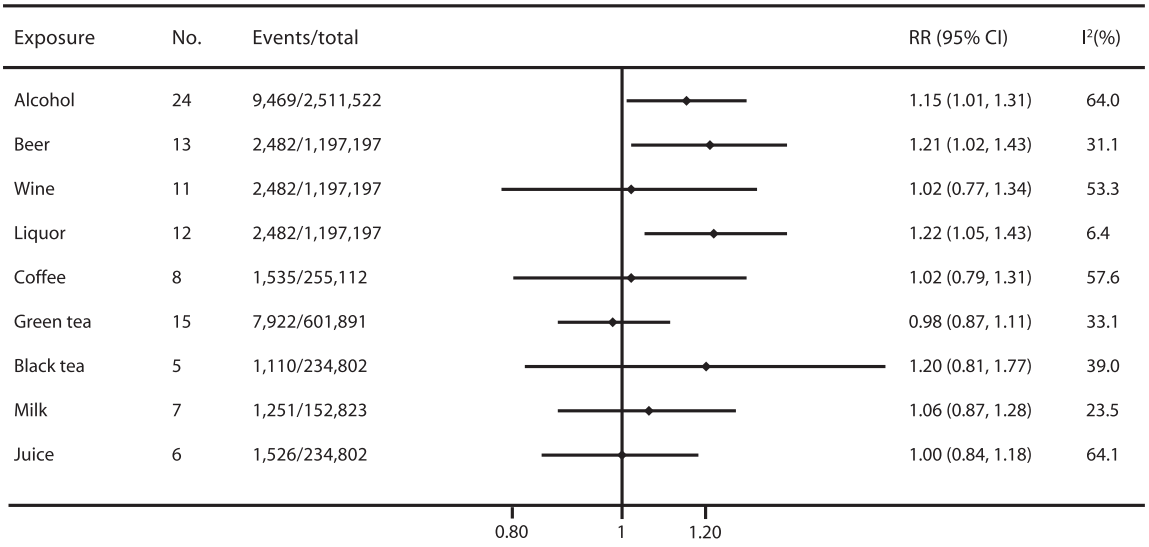

Fig. 4. Forest plot of associations between alcohol, coffee, tea, and other beverage consumption and gastric cancer risk.

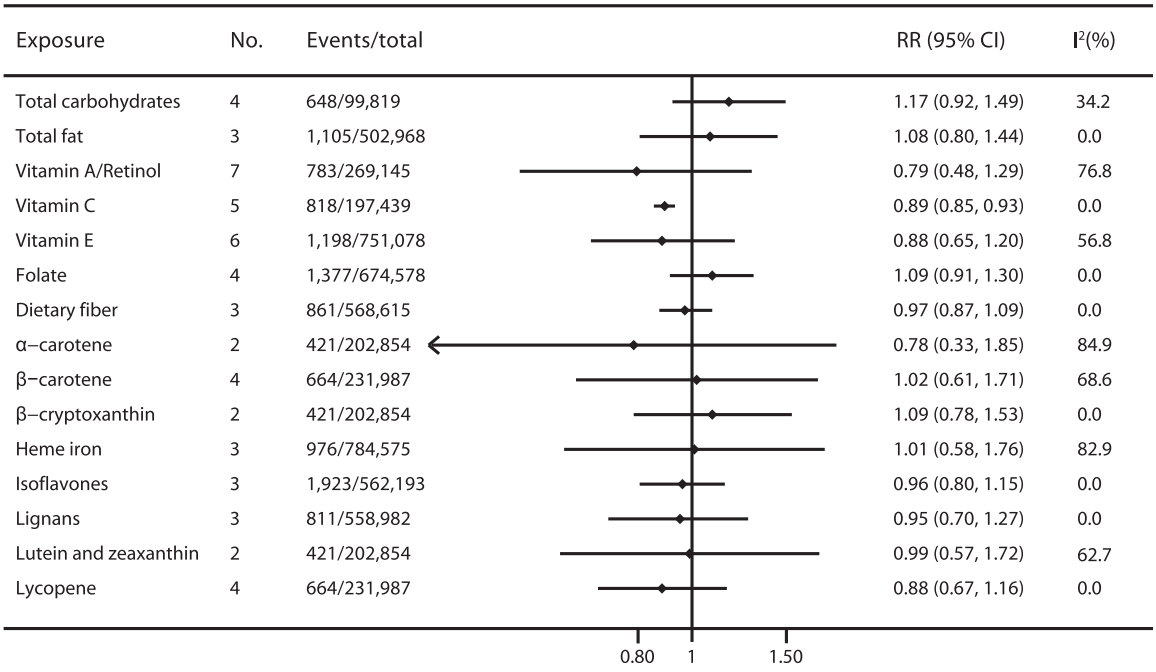

Fig. 5. Forest plot of associations between dietary intake of nutrients and gastric cancer risk.

had at least two reports across continents (Table 3). For many dietary factors, the associations observed in the study were consistent across populations. However, there are some notable differences of some food and drinks might account for high-observed heterogeneity recorded among studies. Specifically, either the protective effect of fruit intake or the risk factor of alcohol consumption was significantly recorded in European populations but not in other two continents.

As shown in Table 4, we also analysed the effect of dietary factor exposures on GCC and GNCC. The results suggest no significant differences between GCC and GNCC in total vegetables, fruit, alcohol, red and processed meat.

3.8. Heterogeneity and publication bias

Between-study heterogeneity for each dietary factor can be found in Figs. 2–5. For more than half dietary factors observed, there is no or low study heterogeneity ($I^2 < 25\%$). Both Egger and Begg test did not suggest publication bias for associations for any dietary factor consumption and risk of gastric cancer.

4. Discussion

The present meta-analyses of 76 prospective cohort studies provide the most comprehensive assessment so far of the association between diet and gastric cancer.

Table 2
Dose-response analyses of both protective and risk factors in relation to gastric cancer.

Exposure	Comparison	Relative risk (95% confidence interval)	I^2	*P* for Begg's test	*P* for Egger's test
Protective factors					
White vegetables	Per 1/week	0.98 (0.93 to 1.02)	0.0%	1.000	–
Total fruit	Per 100 g/day	0.95 (0.92 to 0.99)	0.0%	0.536	0.431
Citrus fruit	Per 30 g/day	0.97 (0.94 to 0.99)	34.6%	0.133	0.276
Vitamin C	Per 50 mg/day	0.92 (0.84 to 1.01)	6.9%	1.000	0.949
Risk factors					
Pickled vegetables	Per 1/week	1.01 (0.99 to 1.03)	23.3%	0.562	0.668
Processed meat	Per 1/week	1.03 (0.99 to 1.06)	37.5%	0.089	0.347
Ham, bacon, sausage	Per 1/week	1.00 (0.98 to 1.02)	57.7%	0.133	0.020
Salted fish	Per 1/week	1.04 (1.01 to 1.08)	53.6%	0.806	0.559
High-salt food	Per 1/week	1.10 (1.05 to 1.16)	79.4%	1.000	0.399
Salt	Per 5 g/day	1.12 (1.02 to 1.23)	44.7%	0.806	0.912
Alcohol	Per 10 g/day	1.05 (1.02 to 1.08)	65.1%	0.548	0.468
Beer	Per 1 /day	1.04 (0.97 to 1.10)	6.6%	0.548	0.505
Liquor	Per 1 /day	1.05 (0.99 to 1.11)	64.8%	1.000	0.618

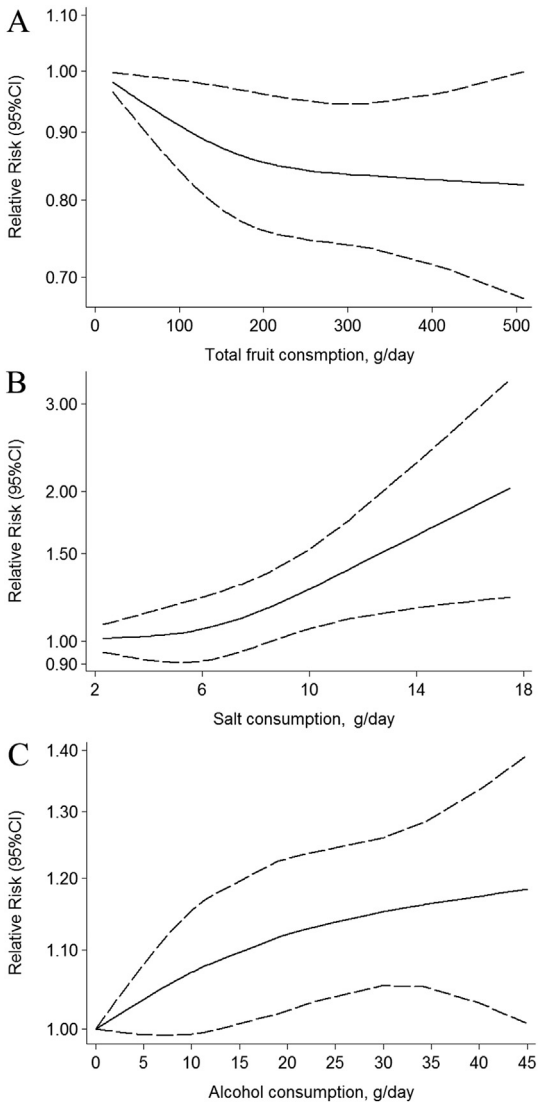

Fig. 6. Curvilinear association between consumption of total fruit (A), salt (B), and alcohol (C) and risk of gastric cancer.

The risk of gastric cancer has been explored in relation to an impressive number of dietary factors (67 in total), including vegetables, fruit, meat, fish, salt, alcohol, tea, coffee, and nutrients. Evidence from this study indicates that consumption of total fruit and white vegetables, but not total vegetables, was inversely associated with the risk. Importantly, we found concordant positive associations between high-salt foods and gastric cancer risk: elevated consumption of pickled vegetables, processed meat, salt fish, and salt were in relation to respectively 18%, 15%, 25%, and 11% greater risk of gastric cancer. Our findings also indicated that alcohol drinking is associated with a 15% increased gastric cancer risk when the highest reported intake was compared with the lowest. In addition, similar associations were identified in consumption of beer and liquor, instead of wine.

4.1. Results in relation to other studies

Adherence to a Mediterranean diet, with a relatively high consumption of fruit, has been shown to significantly decrease the risk of incident gastric cancer [16]. In order to investigate and quantify the relation between fruit consumption and gastric cancer risk, Jansen *et al.* collected 16 cohorts from seven countries and followed these 12,763 participants for 25 years [17]. After adjusting for energy and smoking, an inverse association was observed for total fruit. Similar to a previous meta-analysis [18], our studies demonstrated the protective effect for total fruit consumption on gastric cancer risk, but not for total vegetable consumption. Nevertheless, we found that an increase in white vegetable consumption is associated with decreased risk of gastric cancer. White vegetables have been of particular interest due to their effects on glycaemia and satiety [19], but our work is the first meta-analysis to report the important anticancer property.

As for the mechanisms for the inverse association between consumption of fruit and white vegetables and gastric cancer risk, antioxidant vitamin intake may play an important role in reducing tissue and/or DNA damage [20]. Both fruit and white vegetables are rich sources of vitamin C that have been reported to have significant protective effect against gastric cancer. Besides of their effect as antioxidants, high dietary intake

Table 3
Subgroup analyses by geographic location.

Exposure	Europe			North America			Asia-Pacific		
	No.	RR (95% CI)	I^2 (%)	No.	RR (95% CI)	I^2 (%)	No.	RR (95% CI)	I^2 (%)
Protective factors									
Total fruit	9	0.81 (0.71 to 0.92)	0	4	0.91(0.64 to 1.29)	41.8	15	0.94 (0.86 to 1.03)	0
Citrus fruit	5	0.79 (0.63 to 0.97)	41.6	3	1.00 (0.81 to 1.23)	59.4	2	0.84 (0.61 to 1.16)	0
Risk factors									
Processed meat	6	1.39 (1.15 to 1.68)	0	6	1.05 (0.93 to 1.19)	0	–	–	–
Ham, bacon, sausage	5	1.18 (0.87 to 1.60)	64.1	–	–	–	5	1.30 (1.01 to 1.68)	0
Salt	2	1.07 (0.82 to 1.40)	0	–	–	–	6	1.17 (0.99 to 1.40)	44.7
Alcohol	11	1.35 (1.03 to 1.77)	64.4	3	0.98 (0.52 to 1.87)	59.9	10	1.06 (0.90 to 1.25)	69.2
Beer	8	1.32 (1.02 to 1.72)	57.0	2	1.11 (0.61 to 2.00)	0	3	1.09 (0.82 to 1.44)	0
Liquor	8	1.18 (1.00 to 1.40)	0	2	0.84 (0.11 to 6.36)	85.5	2	1.28 (0.89 to 1.85)	0

RR = relative risk; CI = confidence interval.

Table 4
Subgroup analyses by anatomical subsites of gastric cancer.

Exposure	GCC			GNCC		
	N	RR (95% CI)	I^2 (%)	N	RR (95% CI)	I^2 (%)
Total vegetables	6	0.88 (0.76 to 1.01)	0.0	6	0.92 (0.77 to 1.09)	18.5
Total fruit	7	1.08 (0.93 to 1.26)	0.0	7	0.98 (0.82 to 1.16)	0.0
Red meat	4	0.98 (0.74 to 1.29)	0.0	4	1.01 (0.74 to 1.37)	56.8
Processed meat	4	0.98 (0.74 to 1.29)	3.8	4	1.21 (0.98 to 1.49)	10.1
Alcohol	5	1.08 (0.81 to 1.43)	53.5	5	1.05 (0.72 to 1.54)	86.2

GCC = gastric cardia cancer; GNCC = gastric non-cardia cancer; RR = relative risk; CI = confidence interval.

of vitamin C has been shown to inhibit *H. pylori* growth and colonisation via impairing the microenvironment created by the bacteria and via facilitating the diffusion of antibiotics into gastric mucosa [21,22]. In addition, vitamin C from diet also acts as a scavenger of cancerigenic *N*-nitroso compounds in the stomach [23,24].

While fruit and white vegetables are observed to be protective, salt is associated with an increase in gastric cancer morbidity and mortality [25,26]. Although salt intake is necessary to life and not directly carcinogenic, excess salt is present in brine or cured, pickled vegetables, processed meat, and salt fish and may act as an irritant to the gastric mucosa, causing atrophic gastritis, increased DNA synthesis, and cell proliferation [27,28]. It is important to elucidate the role that salt plays in the causal link between *H. pylori* infection and gastric cancer. Chronic salt intake may potentiate *H. pylori*-associated carcinogenesis by inducing proliferation, colonisation, and glandular atrophy [29]. In addition to having plenty of salt, these high-salt foods often contain too much nitrate and nitrite, which contribute to the formation of cancerigenic *N*-nitroso compounds along with sodium chloride itself [30,31].

The role that alcohol consumption plays in carcinogenesis has been heeded for decades. In 2007, the International Agency for Research on Cancer classified alcohol as group 1 human carcinogen [32]. As to gastric cancer, a previous meta-analysis based on both case-control and cohort studies provided evidence of a lack of association between moderate alcohol drinking and gastric cancer risk. There was, however, a positive association with heavy alcohol drinking [33]. The ethanol in alcoholic beverages induces various reactive oxygen species and oxidative stress, which damage the DNA and affect its repair [34]. Acetaldehyde, the first metabolite produced during alcohol degradation, may play a more important role for the carcinogenic effect of ethanol on the mucosa owing to its multiple mutagenic effects on DNA [35]. Wine has relatively high ethanol and acetaldehyde content, but it also contains substances thought to be protective [36,37].

Evidence from case-control studies suggested that green tea has a preventive effect on gastric cancer [38–40], but we did not find significant association between them in the present meta-analysis of cohort studies [41]. Caffeine, kahweol, and cafestol in coffee may contribute to a protective effect against cancer. Based on the evaluation of eight independent prospective studies, there was no apparent evidence that coffee consumption has any effect on the risk of gastric cancer [42].

Notably, in the summary performed by the World Cancer Research Fund and the American Institute for Cancer Research in 2007, fruits and vegetables (especially non-starchy vegetables) probably protect against gastric cancer. And salt, including salt-preserved foods, are probably causes of this cancer [43]. However, the data of other exposures were either of low quality and inconsistent, or the limited number of studies to reach to the conclusions.

4.2. Strengths and limitations

The present study provides the most comprehensive summary in relation to the impacts of diet on gastric cancer for several reasons. As in all meta-analyses and literature reviews, the quality is directly related to the quality of the included studies. First, we included only prospective cohort studies with large sample size and long duration of follow-up, in order to increase the statistical power by detecting modest associations. Second, the prospective nature of these included studies minimised recall bias and reduced the likelihood of selection bias. Finally, we used the estimates from models adjusting most established covariates to reduce the potential of confounding factors. Additionally, the high scores of Newcastle-Ottawa assessment (7.7 on average) ensure the overall quality of evidence.

However, our study might have several limitations. First, given the observational nature of the studies, the possibility of residual confounding cannot be excluded even in the fully adjusted models. Second, because the consumption of various dietary factors was assessed by food frequency questionnaires in almost every cohort, errors in measurement seemed inevitable and may attenuate true associations toward the null. Third, during the long follow-up, participants may have changed their diet, and quite a number of included studies did not update the death information from food frequency questionnaires. In addition, there was substantial heterogeneity between analyses examining the associations of several dietary factors, which could not be further explored because of the limited number of studies.

5. Conclusions

Our results indicate that a 100 g/day increment of fruit consumption was inversely associated with 5% reduction of gastric cancer risk. In contrast, a 5 g/day increment of dietary salt intake could increase 12% risk of gastric cancer, and 5% increasing risk of gastric cancer if one consumes 10 g/day increment of alcohol. These findings have important public health implications. Our results provide further support for public health recommendations to increase the intake of dietary fruits and white vegetables, while reduce intake of high-salt food, beer and liquor, in the prevention of gastric cancer. These findings may also provide valuable insights into further cohort studies and the design of informative clinical trials.

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Conflict of interest statement

None declared.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2015.09.010.

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