Citrus fruit intake and gastric cancer: the Stomach cancer Pooling (StoP) project consortium

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Abbreviations: CI, confidence intervals; EPIC, European Prospective Investigation into Cancer and Nutrition cohort; FFQ, food frequency questionnaire; OR, odds ratio; StoP, Stomach cancer Pooling Project

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Conflict of interest

The authors declare no conflicts of interest.

Novelty and Impact

The association between citrus fruit intake and cardia cancer was classified as limited/suggestive, whereas no conclusions could be drawn on non-cardia cancer. Our pooled analysis within a global consortium of case-control studies indicates and quantifies a protective effect of citrus fruits on both cardia and non-cardia cancers.

Abstract

Diets rich in vegetables and fruit have been associated with reduced risk of gastric cancer, and there is suggestive evidence that citrus fruits have a protective role. This study aimed at evaluating and quantifying the association between citrus fruit consumption and gastric cancer risk. We conducted a one-stage pooled analysis including 6340 cases and 14,490 controls from 15 case-control studies from the Stomach cancer Pooling (StoP) Project consortium. Odds ratio (OR) and the corresponding 95% confidence intervals (CI) of gastric cancer across study-specific tertiles of citrus fruit intake (grams/week) were estimated by generalized linear mixed effect models, with logistic link function and random intercept for each study. The models were adjusted for sex, age, and the main recognized risk factors for gastric cancer. Compared to the first third of the distribution, the adjusted pooled ORs (95% CI) for the highest third was 0.80 (0.73-0.87). The protective effect of citrus fruits increased progressively until three servings/week and levelled off thereafter. The magnitude of the association was similar between cancer sub-sites and histotype. The analysis by geographic area showed no association in studies from the Americas. Our data confirm an inverse association between citrus fruit intake and gastric cancer and provide precise estimates of the magnitude of the association. However, the null association found in studies from America and in some previous cohort studies prevent to draw definite conclusions on a protective effect of citrus fruit consumption.

Introduction

Gastric cancer is the fifth most common cancer worldwide and the third cancer-related cause of death [1]. It can originate from two different anatomic areas of the organ, i.e. the proximal part of the stomach (cardia cancers) or the mid and distal part (non-cardia cancers), with distinct etiology and epidemiology. Gastroesophageal reflux and obesity have been identified as risk factors for cardia cancers, while *Helicobacter pylori* infection, low socio-economic status, smoking, heavy alcohol drinking, consumption of food preserved by salt and processed meat are the main risk factors for non-cardia cancers [2].

Cardia cancer incidence has been stable or increasing[3–6], while non-cardia cancers have been substantially decreasing, likely as a consequence of reduced of *Helicobacter pylori* infection prevalence, improvements in diet, and advances in food preservation technology [7].

Healthy dietary patterns, rich in vegetables and fruit, have been associated with reduced risk of gastric cancer [8,9] and there is suggestive evidence that citrus fruits could have a protective role [2,10,11]. Such a favourable effect has been related to bioactive compounds contained in citrus fruits, including, among others, vitamin C and flavonoids. Vitamin C, an enzymatic cofactor and scavenger of reactive oxygen species, inhibits nitrosamine formation in the stomach, thus reducing oxidative damage of the gastric mucosa [12,13]. Flavonoids are aromatic secondary plant metabolites, which have antioxidant, radical scavenging and immunomodulatory activity [14].

This study aims at verifying and quantifying the strength of the association between citrus fruit intake and the risk of gastric cancer through the analysis of the Stomach cancer Pooling (StoP) Project consortium [15].

Materials and Methods

Study population

This study is based on the second release of the StoP Project consortium (http://www.stop-project.org/), which included 31 case-control studies of gastric cancer conducted worldwide. Detailed information on the aims and methods of the StoP Project has been given elsewhere [16]. Participating studies were involved

through personal contacts of participating investigators. Principal investigators of these studies who agreed to participate provided a signed data transfer agreement and, thereafter, the complete original data set of the study. We collected and harmonized all data according to a pre-specified format. For these analyses, we selected 15 case-control studies with data on citrus fruit intake including one study from Greece [17], three from Italy [18–20], one from Portugal [21], one from Russia [22], one from Spain [23], two from Iran [24,25], one from Japan [26], one from Canada [27], one from the USA [28], and three from Mexico [29–31].

Studies' quality was assessed by the Newcastle-Ottawa quality assessment scale for case-control studies. The scale evaluates the study quality on the basis of three different categories: selection, exposure and comparability. A study can be awarded a maximum of nine stars that indicates the highest quality.

The original studies were approved by their Institutional Review Board and the StoP Project received ethical approval from the University of Milan Review Board (reference 19/15 on 01/04/2015).

Citrus fruit intake

Citrus fruit consumption was measured through food frequency questionnaires (FFQs) that asked participants to indicate food and beverage consumption before the diagnosis of gastric cancer, for all the studies. Of the 15 studies included, 9 defined exposure on citrus fruits one year before diagnosis/interview, 2 two years, and 4 two to five years. Citrus fruit consumption was expressed in grams per week, by taking into account the serving and frequency of consumption indicated in each study-specific FFQ. When the FFQ did not contain a specific variable for the whole citrus fruit group, we combined the available information on the consumption of single food items, including oranges, lemons, tangerines, grapefruits and citrus fruit juices. Fruit juices containing a mixture of citrus and non-citrus fruits were not considered. When the consumption of the food item was not expressed in grams, we converted the amount of fruit reported into grams by considering the following average weight for each fruit: 150g for oranges and citrus fruit juices, 300g for grapefruits, 50g for tangerines, and 30g for lemons.

Data analysis

We carried out an individual participant data pooled analysis using a one-stage approach [32]. We run generalized linear mixed effect models with logistic link function and random intercept for each study, to estimate the odds ratio (OR) and corresponding 95% confidence intervals (CI) of gastric cancer across study-specific tertiles of citrus fruit consumption. Tertiles were derived from the distribution of citrus fruit consumption among controls. ORs and corresponding 95% CIs were estimated also for the number of servings per week that was included in the model as categorical variable, ranging from 0 to 7 or more servings per week. The number of servings per week was computed by considering an average serving of 150g. The models were adjusted for sex, 5-year age groups, socioeconomic status (low, intermediate, high), tobacco smoking (never, former, current low, current intermediate, current high), alcohol drinking (never, low: ≤ 12 g/day, intermediate: > 12 to <48 g/day, high: ≥48 g/day), study-specific salt, other fruit and vegetable intake (low, intermediate, high), and family history of gastric cancer. Information on these covariates were collected by structured questionnaires, self-administered or administered by trained interviewers. Subjects with missing values for a given covariate were retained in the model by including them in a separate category of the variable.

A dose-risk relationship was modelled using polynomial models. This flexible class of models allowed to evaluate the possible non-linear trends of the dose-risk relationship by fitting several functional forms, including the linear one. The Akaike information criterion was used to select the model that provided the best fit with the data.

We performed stratified analyses by sex, age group, socioeconomic status, geographic area, smoking status, alcohol drinking, total fruit intake, salt intake, family history of gastric cancer, *Helicobacter pylori* infection, type of controls, cancer sub-site and histotype. For the strata of sub-site and histotype, we used multinomial mixed effect models to estimate the ORs for each type of cancer separately (i.e., cardia and non-cardia or intestinal and diffuse). For each stratifying variable, the Q statistics was computed to test the heterogeneity across strata.

We also carried out a series of sensitivity analyses: 1) we excluded citrus fruit juices from the evaluation of citrus fruit consumption in studies that had this item listed in the FFQ, since the fruit content may vary in fruit juices, 2) we estimated the ORs of gastric cancer across thirds of the distribution of citrus fruit intake

using a two-stage approach[32], 3) we restricted the analysis to the studies that scored more than five stars at the Newcastle-Ottawa quality assessment score, 4) we removed from the analysis the studies that evaluated citrus fruit consumption by self-administered FFQ, 5) to evaluate if the time window for dietary information modified our results we provided two separate estimates for studies who collected citrus fruit consumption 1 year before and 2 to 5 years before diagnosis of gastric cancer.

Results

Table 1 gives the distribution of the sociodemographic characteristics and the main lifestyle risk factors of the 6340 gastric cancer cases and 14,490 controls. Almost 60% of cases came from Europe, about one third from the Americas, and the remaining cases from Asia. Cases were more likely than controls to be males, older, of low socioeconomic status, heavy smokers and alcohol drinkers, and to have a positive family history of gastric cancer. Fruit intake was lower among cases as compared to controls.

Table 2 shows the distribution of citrus fruit consumption (including and excluding citrus fruit juices) for cases and controls by study. Most studies showed higher citrus fruit intake in controls than in cases. In cases, median citrus fruit intakes ranged between 56g per week in the Iran 1 study and 789g per week in the study from Canada, while in controls they ranged between 200g per week in the Iran 2 study to over 1 kg per week in the study from Greece. Most of the citrus fruit intake in the studies from the USA and Canada came from citrus fruit juices (around 80%).

The risk of gastric cancer was inversely related to citrus fruit consumption (**Table 3**). Compared to the 1st third of the distribution of citrus fruit intake, the adjusted pooled ORs (95% CI) for the 2nd and 3rd third were: 0.80 (0.74-0.86) and 0.80 (0.73-0.87), respectively. **Figure 1** shows the ORs for the highest compared to the lowest third of citrus fruit intake for each study along with the pooled estimate. Heterogeneity emerged across studies.

The inverse relationship between citrus fruits and gastric cancer risk increased progressively until three servings per week and levelled off thereafter (**Table 3**). **Figure 2** shows the dose-risk relationship between citrus fruit consumption and gastric cancer risk estimated by a model including the natural logarithm of citrus fruit

intake as exposure variable. The best fitting dose-risk relationship between citrus consumption and gastric cancer risk was: ln(OR) = -0.05535 · ln(citrus fruit consumption in grams per week).

The stratified analysis showed similar effects of citrus fruit intake among strata of sex, age group, smoking status, alcohol drinking, total fruit, salt intake, family history of gastric cancer, *Helicobacter pylori* infection, type of controls, cancer sub-site and histotype, while the protective effect was greater in people from low socio-economic status (Q= 4.6, p= 0.032). There were also significant differences across geographic areas (Q= 18.6, p<0.0001) with a no association in studies from America (**Figure 3**).

The results of the sensitivity analysis excluding citrus fruit juices from the estimation of citrus fruit consumption did not materially differ from those of the main analysis. The pooled OR for the highest compared to the lowest citrus fruit intake (excluding juices) was 0.81 (0.74-0.89). Similarly, using the two-stage approach the pooled estimate of the OR for the highest compared to the lowest citrus fruit intake was similar to that obtained by the one-stage approach (OR: 0.79, 95% CI: 0.64-0.97).

When applying the Newcastle-Ottawa quality assessment scale to the included studies, four of them was awarded seven stars, seven studies scored six stars, and two studies (Greece and Canada) scored five stars. Removing the latter studies from the analysis did not changed substantively the magnitude of the association (OR for the last compared to the first third of citrus fruit consumption: 0.74, 95% CI: 0.66-0.82). Similar results were obtained when removing the studies (Canada, USA 1 and Russia) that evaluated citrus fruit consumption by self-administered FFQs instead of trained interviewers (OR for the last compared to the first third of citrus fruit consumption: 0.74, 95% CI: 0.67-0.83).

The inverse association was slightly stronger in studies that collected citrus fruit consumption one year before diagnosis as compared to those that collected it between 2 to 5 years before diagnosis (ORs for the last compared to the first third of citrus fruit consumption: 0.74, 95% CI: 0.64-0.85 *vs.* 0.82, 95% CI: 0.68-0.86, respectively).

Discussion

In this uniquely large study, we found an inverse association between citrus fruit intake and gastric cancer. The magnitude of the association was similar between cancer sub-sites (cardia and non-cardia) and histotype (intestinal and diffuse), while it was stronger in people from low socio-economic status and in studies from Asia.

A recent meta-analysis [33] including 4907 cases of gastric cancer from 6 cohort studies (two from the USA, two from Japan, one from China, one from the Netherlands and one from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort) did not find a significant association between citrus fruit intake and gastric cancer. Three of the included studies reported cardia cancer incidence and two of them (one from the Netherlands and the other one from the EPIC cohort) found a protective effect, while the study from the USA did not show any association. However, evidence of a decreased risk of gastric cancer with increasing citrus fruit intake was also reported in hospital- and community-based case-control studies [10,34].

The mechanisms underneath this potential protective effect were investigated in studies based on gastric cancer cell lines and animal-models. These showed anticancer effects of flavanones, a class of flavonoids contained almost exclusively in citrus fruits and juices [35–39]. Hesperitin and naringenin, two of the major flavanones compounds contained in oranges and mandarins, inhibit human gastric cancer cell proliferation, migration and invasion in a dose- and time-dependent manner [35,37]. Moreover, naringenin showed a combinative effect on human gastric cell lines when administered in combination with ABT-737, an inhibitor of the antiapoptotic protein B-cell lymphoma [38]. These findings were confirmed in a study based on albino rats, in which the administration of naringenin simultaneously with and subsequently to the gastric carcinogen N-methyl-*N'-nitroce*-nitroso-guanidine reduced the tumor mass via its antioxidant potential [36]. However, the plasma concentrations used in these studies (from 20 to 400 μmol/L) are far higher than those reached by humans even in cases of very high citrus fruit consumption [40,41]. Dietary intake of flavanones varies according to population and dietary habits, and some studies reported mean intakes ranging between 15 and 40 mg/day [41–44]. In a group of 37 Finnish women [40], mean plasma concentrations of hesperitin was 0.48 μmol/L during their habitual diet and reached 3.26 μmol/L after 5-week diet containing high amounts of vegetables

and fruit, including citrus fruit. Corresponding figures for naringenin were 0.05 μmol/L during habitual diet, and 1.13 μmol/L after the 5-week high vegetables and fruit diet.

In a Greek case-control study, flavanones from citrus fruit were inversely associated with gastric cancer risk [17]. Moreover, citrus fruit are also a good source of vitamin C and high levels of plasma vitamin C were associated with reduced gastric cancer risk in a case-control study nested within the EPIC cohort. [45].

The lack of significant association when pooling the studies from the Americas is attributable to the remarkable high contribution of the study from Canada, which enrolled 70% of all participants from the Americas. In that study, the FFQ was mailed to cancer cases and controls, while in most of the studies included in this pooled analysis the investigators used trained interviewers to collect dietary information. This could result in a less accurate assessment of citrus fruit consumption. Low socio-economic status is a well-recognized risk factor for gastric cancer partly as consequence of unfavorable distribution of risk factors including *Helicobacter pylori* infection, tobacco smoking, alcohol drinking and poor diet [46]. In our study, the stronger inverse association between citrus fruit intake and gastric cancer in people from low socio-economic status suggests that a diet rich in citrus fruits could counteract the negative effects of the lifestyle risk factors related to low social class.

The main limitations of our study lie in the potential inaccurate measure of citrus consumption in a case-control design and the challenging separation of the effect of citrus fruit from that of other dietary factors.

The multicenter nature of our study entailed the evaluation of citrus fruit consumption through different FFQs with different lists of food items. This could have resulted in underestimation of citrus fruit intake in some studies, which did not collect information on different types of citrus fruits. However, the results were consistent between hospital- and population-based studies, as well as across strata of sex, age, and other major covariates.

The inverse association between citrus fruit consumption and gastric cancer risk can be at least partially attributable to a generally healthier diet associated to high consumption of fruit and vegetables. In fact, high citrus fruit consumers have also a high consumption of other fruits and vegetables that contain dietary components with potential anticarcinogenic effects. However, our results were virtually unmodified after adjust-

ment for other fruit and vegetable intake. With reference to other potential confounders, we considered the dietary factors most strongly correlated to citrus fruit consumption, such as salt and alcohol. We also checked the additional inclusion of meat and pickled vegetables (whenever available), but these did not materially modify any of the estimates.

This study provides more precise and valid evidence than previously available of an inverse relationship between citrus fruit consumption and gastric cancer obtained from a large consortium of case-control studies, in relation to different anatomic sub-sites and histologic types of gastric cancers, as well as to consider the majority of risk factors that could act as confounders in the relationship between citrus fruit intake and gastric cancer.

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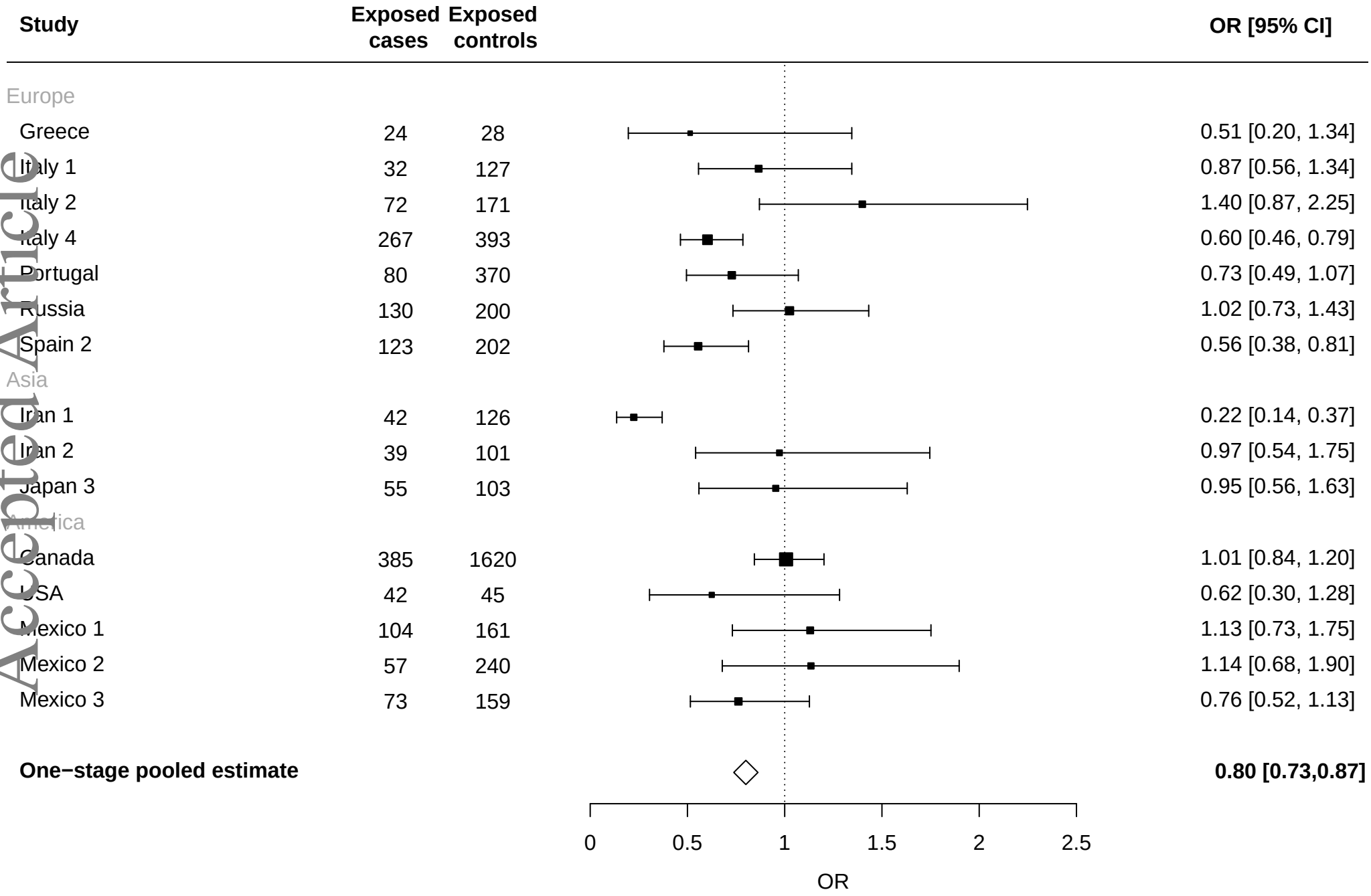
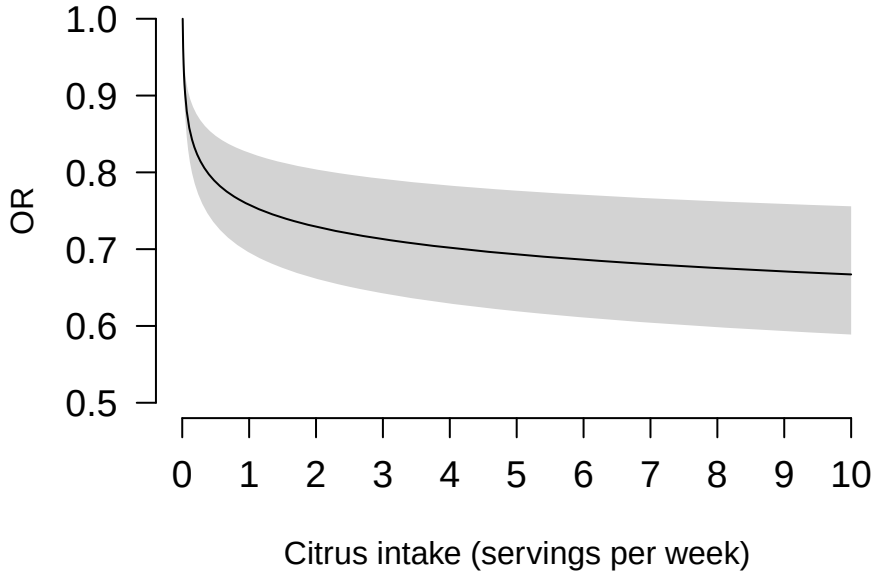
Figure legends

Figure 1. Study-specific and pooled odds ratio of gastric cancer for the highest compared to the lowest study-specific third of the distribution of citrus fruit consumption.

Figure 2. Dose-risk relationship between citrus fruit consumption and gastric cancer, obtained by a logistic mixed effects model including the natural logarithm of citrus fruit intake as exposure variable. Citrus fruit consumption was converted in servings per week by considering one serving equal to 150g of fruit or juice.

Figure 3. Pooled odds ratio of gastric cancer for the highest compared to the lowest study-specific third of the distribution of citrus fruit consumption, according to strata of selected variables.





Stratum	Exposed cases	Exposed controls	OR [95% CI]
Sex			
Males	946	2077	0.82 [0.73, 0.92]
Females	579	1969	0.78 [0.67, 0.89]
Age (years)			
<65	796	2435	0.78 [0.69, 0.88]
>=65	729	1611	0.84 [0.73, 0.95]
Socioeconomic status			
Low SES	706	1471	0.72 [0.63, 0.82]
Intermediate SES	520	1410	0.87 [0.75, 1.02]
High SES	270	1113	0.89 [0.72, 1.12]
Geographic area			
Europe	728	1491	0.73 [0.64, 0.83]
Asia	136	330	0.52 [0.39, 0.69]
America	661	2225	0.97 [0.85, 1.12]
Smoking status			
Never smokers	648	1943	0.77 [0.67, 0.88]
Former smokers	466	1144	0.86 [0.73, 1.01]
Current smokers	338	871	0.79 [0.65, 0.95]
Alcohol drinking			
<1 drink/day	810	2528	0.84 [0.74, 0.94]
1−3 drinks/day	448	898	0.69 [0.58, 0.82]
>=4 drinks/day	161	286	0.87 [0.67, 1.13]
Fruit intake			
Low fruit intake	111	307	0.75 [0.58, 0.96]
Intermediate fruit intake	455	1158	0.78 [0.67, 0.91]
High fruit intake	886	2422	0.89 [0.76, 1.05]
Salt intake			
Low salt intake	492	1540	0.81 [0.70, 0.94]
Intermediate salt intake	425	1119	0.80 [0.68, 0.95]
High salt intake	317	869	0.97 [0.79, 1.18]
Family history			
Family history No	565	1270	0.68 [0.59, 0.78]
Family history Yes	134	145	0.64 [0.46, 0.89]
H. pylori infection			
H. pylori negative	118	280	0.68 [0.50, 0.93]
H. pylori positive	349	818	0.78 [0.65, 0.93]
Type of control			
Hospital−based	551	1035	0.81 [0.70, 0.94]
Population−based	974	3011	0.81 [0.72, 0.90]
Site			
Cardia	223	4046	0.77 [0.63, 0.94]
Non−cardia	820	4046	0.79 [0.69, 0.89]
Histotype			
Intestinal	409	4046	0.70 [0.60, 0.83]
Diffuse	315	4046	0.74 [0.62, 0.89]

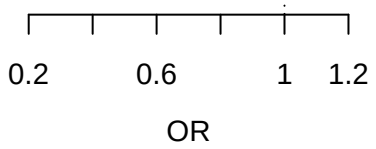


Table 1. Distribution of gastric cases and controls according to study center, sex, age, and other selected covariates. Stomach Cancer Pooling Project (StoP) consortium.

	Case		Control	
	N	%	N	%
Total	6340	100.0	14490	100.0
Study				
Europe				
Greece[17]	110	1.7	100	0.7
Italy 1[18]	769	12.1	2081	14.4
Italy 2[19]	230	3.6	547	3.8
Italy 4[20]	1016	16.0	1159	8.0
Portugal[21]	692	10.9	1667	11.5
Russia[22]	450	7.1	611	4.2
Spain 2[23]	401	6.3	455	3.1
Asia				
Iran 1[24]	217	3.4	394	2.7
Iran 2[25]	286	4.5	304	2.1
Japan 3[26]	153	2.4	303	2.1
The Americas				
Canada[27]	1182	18.6	5039	34.8
USA 1[28]	132	2.1	132	0.9
Mexico 1[29]	248	3.9	478	3.3
Mexico 2[30]	220	3.5	752	5.2
Mexico 3[31]	234	3.7	468	3.2
Sex				
Men	3995	63.0	7747	53.5
Women	2345	37.0	6743	46.5
Age (years)				
<40	265	4.2	1401	9.7
40-44	261	4.1	1035	7.1
45-49	429	6.8	1307	9.0
50-54	570	9.0	1500	10.4

	Case		Control	
	N	%	N	%
55-59	781	12.3	1678	11.6
60-64	996	15.7	2132	14.7
65-69	1203	19.0	2364	16.3
70-74	1209	19.1	2142	14.8
≥75	626	9.9	931	6.4
Social class (study-specific)				
Low	3533	55.7	5952	41.1
Intermediate	1861	29.4	4853	33.5
High	827	13.0	3505	24.2
Missing	*119*	*1.9*	*180*	*1.2*
Tobacco smoking				
Never	2670	42.1	6522	45.0
Former	1739	27.4	3889	26.8
Current				
Low	448	7.1	1360	9.4
Intermediate	630	9.9	1389	9.6
High	566	8.9	981	6.8
Missing	*287*	*4.5*	*349*	*2.4*
Alcohol drinking status				
Never	1885	29.7	4650	32.1
Ever	4373	69.0	9550	65.9
Missing	*82*	*1.3*	*290*	*2.0*
Alcohol drinking (gr/day)[b]				
Low (≤12)	1349	30.3	4156	42.3
Intermediate (>12 and ≤47)	1915	43.1	3307	33.6
High (>47)	932	21.0	1535	15.6
Missing	*251*	*5.6*	*835*	*8.5*
History of stomach cancer in first degree relatives[c]				

	Case		Control	
	N	%	N	%
No	2988	67.1	5219	67.3
Yes	645	14.5	842	10.9
Missing	*823*	*18.5*	*1692*	*21.8*
Total fruit intake (study-specific tertiles)[d]				
Low	2114	34.6	4063	29.0
Intermediate	2089	34.2	4871	34.7
High	1831	30.0	5010	35.7
Missing	*72*	*1.2*	*78*	*0.6*
Salt intake (study-specific tertiles)[e]				
Low	2081	39.9	5356	40.5
Intermediate	1679	32.2	3987	30.1
High	1244	23.9	3119	23.6
Intermediate or high	160	3.1	308	2.3
Missing	*50*	*1.0*	*461*	*3.5*

[a] Between-group comparison by Chi-squared test.

[b] Data not available for the study Iran 2.

[c] Data not available for the following studies: Canada, Mexico 1, Mexico 2, and Mexico 3.

[d] Data not available for the study Mexico 3.

[e] Data not available for the studies Italy 4 and Greece.

[f] Data not available for the following studies: Italy 1, Italy 2, Italy 4, Greece, Canada, USA 1, and Mexico 2.

Table 2. Characteristics of the case-control studies included and distribution of citrus fruit consumption, by study

Study	Study period	Controls	Citrus consumption, gr/week, median (33th – 66th centile)		Citrus consumption (excluding juices), gr/week, median (33th – 66th centile)	
			Cases	Controls	Cases	Controls
Europe						
Greece[17]	1981-1984	Hospital-based	545 (360; 1110)	1160 (487; 1360)	-	-
Italy 1[18]	1985-1997	Hospital-based	225 (75; 300)	300 (150; 525)	-	-
Italy 2[19]	1997-2007	Matched hospital-based	525 (375; 675)	525 (300; 750)	-	-
Italy 4[20]	1985-1987	Population-based	280 (143; 454)	380 (222; 565)	-	-
Portugal[21]	1999-2006	Matched population-based	98 (0; 179)	228 (98; 390)	-	-
Russia[22]	1996-1997	Hospital-based	298 (213; 420)	315 (240; 465)	215 (170; 320)	235 (170; 350)
Spain 2[23]	1995-1999	Matched hospital-based	423 (363; 726)	666 (363; 847)		
Asia						
Iran 1[24]	2004-2005	Matched population-based	56 (56; 225)	225 (225; 525)	-	-
Iran 2[25]	2005-2007	Population-based	156 (107; 194)	200 (135; 313)	-	-
Japan 3[26]	1998-2002	Matched hospital-based	344 (244; 550)	379 (273; 523)	-	-
America						
Canada[27]	1994-1997	Matched population-based	789 (410; 1050)	789 (450; 1050)	150 (70; 450)	150 (70; 450)
USA 1[28]	1992-1994	Hospital-based	750 (369; 1143)	675 (351; 1200)	188 (58; 421)	150 (41; 375)
Mexico 1[29]	2004-2005	Matched population-based	286 (171; 469)	257 (164; 343)	158 (116; 285)	89 (72; 148)
Mexico 2[30]	1989-1990	Matched population-based	450 (171; 512)	471 (171; 512)	-	-
Mexico 3[31]	1994-1996	Matched hospital-based	563 (284; 1050)	610 (420; 1077)	416 (149; 560)	434 (196; 762)

Frequency matching on age and sex for the Italy 2, Portugal, Iran 1, Canada, Mexico 1, and Mexico 2 studies; on age, sex, and area of residence for the Spain 2, Japan 3 and Mexico 3 studies.

Table 3. Distribution of cases and controls according to citrus fruit intake (expressed as study-specific tertiles and servings per week), odds ratios (OR) and corresponding 95% confidence intervals (CI) for gastric cancer.

	Cases		Controls		OR (95% CI)[a]	OR (95% CI)[b]
	N	%	N	%		
Study-specific tertiles						
[min-T1)	2654	42.5	4890	34.0	1[c]	1[c]
[T1-T2)	2070	33.1	5436	37.8	0.72 (0.67-0.77)	0.80 (0.74-0.86)
[T3-max]	1525	24.4	4046	28.2	0.68 (0.62-0.73)	0.80 (0.73-0.87)
Servings per week						
0	1964	31.4	3407	23.7	1[c]	1[c]
1	1050	16.8	2156	15.0	0.81 (0.74-0.89)	0.85 (0.77-0.94)
2	756	12.1	1517	10.6	0.76 (0.69-0.85)	0.85 (0.76-0.95)
3	692	11.1	2116	14.7	0.61 (0.55-0.68)	0.71 (0.64-0.80)
4	276	4.4	651	4.5	0.62 (0.53-0.72)	0.70 (0.59-0.82)
5	354	5.7	1024	7.1	0.63 (0.54-0.72)	0.73 (0.63-0.85)
6	227	3.6	674	4.7	0.62 (0.53-0.74)	0.80 (0.67-0.95)
≥7	930	14.9	2827	19.7	0.67 (0.61-0.74)	0.82 (0.73-0.92)

[a] Estimated by logistic mixed effect model with a random intercept for each study.
[b] Further adjusted for sex, age category, social class, smoking status, salt intake, alcohol intake, other fruit and vegetable intake and family history of gastric cancer.
[c] Reference category.

Novelty and Impact:

Diets rich in fruit and vegetables have been associated with reduced risk of gastric cancer, and citrus fruits especially may provide protection. In this global, case-control study, the authors found that citrus may indeed confer some protective effect for cardia (proximal) gastric cancer, although the picture for non-cardia cancer was less clear.