Original article

Citrus fruit intake and stomach cancer risk: a quantitative systematic review

JONG-MYON BAE^{1,2}, EUN JA LEE³, and GORDON GUYATT²

¹Department of Preventive Medicine, Cheju National University College of Medicine, No. 1 Ara-1-dong, Jeju, Jeju-do 690-756, Korea

²CLARITY Research Group, Department of Clinical Epidemiology & Biostatistics, Health Sciences Centre, McMaster University, Hamilton, Ontario, Canada

³Department of Radiology, Myongji Hospital, Kwandong University, College of Medicine, Koyang, Korea

Abstract

Background. The purpose of this systematic review was to investigate the association between dietary intake of citrus fruits and gastric cancer risk.

Methods. We searched electronic databases and the reference lists of publications on diet and stomach cancer studies until April 2007. All of the epidemiological studies that obtained individual data on dietary intake of citrus fruits and presented risk estimates of the association between intake of citrus fruits and risk of stomach cancer were identified and included in this review. Using general variance-based methods, study-specific odds ratio (OR)/ relative risk (RR) and associated confidence interval (CI)/ standard error (SE) for highest versus lowest intake of citrus fruits level were extracted from each article.

Results. Fourteen articles, including six hospital-based case-control studies, six community-based case-control studies, and two cohort studies, proved eligible. Overall summary OR using a fixed-effect model showed a 28% reduction in risk of stomach cancer associated with high intake of citrus fruits (summary OR = 0.72; 95% CI = 0.64–0.81; *P* value <0.0001); results were consistent across studies ($I^2 = 0$, where I^2 describes the percentage of total variation across studies because of heterogeneity rather than chance). Also, visual inspection of the results did not suggest a publication bias.

Conclusion. Pooled results from observational studies support a protective effect of high citrus fruit intake in the risk of stomach cancer.

Key words Citrus fruits · Stomach neoplasm · Metaanalysis · Cancer risk · Prevention

tables is associated with a lower risk of cancer [1–2], the effect of high consumption of fruits and vegetables on the incidence of gastric cancer remains controversial in spite of over 40 years of epidemiological research [3, 4]. The reason for this is that most retrospective studies have shown that a high intake of fruits and vegetables is associated with a moderate reduction in risk of gastric cancer, but the results of prospective studies have not shown as strong an effect [5, 6].

Based on the finding that a high consumption of fruit and vegetables is inversely related to risk of gastric cancer [7], scientists have suggested possible anticarcinogenic mechanisms of substances in fruits and vegetables [8, 9]. In particular, ascorbic acid (vitamin C) acts as an antioxidant and can quench reactive oxygen species produced in the gastric environment [10]. And high-dose vitamin C is effective in inhibiting *Helicobacter pylori* infection [11]. However, some randomized trials have reported that dietary supplementation with antioxidant micronutrients including vitamin C is not an effective tool for gastric cancer control [12–15].

On the other hand, Gonzalez et al. [16] found an inverse but nonsignificant association between citrus fruit intake and cancer of the stomach cardia by a collaborative prospective cohort study. And Taylor et al. [17] suggested that low intake of citrus fruits led to inadequate vitamin C intake among adults. These considerations suggest a hypothesis that dietary intake of citrus fruits, rather than vitamin C supplements, would reduce stomach cancer risk. We conducted a systematic review to explore this hypothesis.

Introduction

Although one of the most important messages of modern nutrition research is that a diet rich in fruits and vege-

Materials and methods

Search strategy

A computerized search of the PubMed English-language literature on citrus fruit and stomach (or

gastric) cancer yielded no relevant publication to April 2007. We therefore decided to use the key word “fruits” as well as “citrus”. Thus, the search terms were [(stomach) OR (gastric)] AND [(neoplasm) OR (cancer)] AND [(Fruit) OR (Citrus)] AND [(Prevention) OR (Risk) OR (Etiology)]. We limited the search to studies of human adults, without language restrictions. We searched the following electronic databases: PubMed, Ovid Medline, and EMBASE. In addition, we manually searched the references cited in the full-text articles and in the relevant review articles or metaanalyses identified in the search.

Study selection

We chose the following inclusion criteria: (1) epidemiological studies including case-control or cohort studies; (2) human adult participants; and (3) studies addressing the association between fruit intake and gastric cancer. The full-text articles of all references selected after applying the inclusion criteria were collected. To full-text articles including potential references listed by hand-search, reviewers applied the following exclusion criteria: (1) no original data, i.e., reviews, metaanalyses; (2) studies of mortality instead of incidence of gastric cancer; (3) studies not measuring citrus fruit intake at the individual level; and (4) studies providing insufficient information on the odds ratio (OR) or relative risk (RR), and their corresponding 95% confidence intervals (CIs), for highest versus lowest level of citrus intake.

The eligibility of each abstract or full-text article was assessed independently in a standardized manner by two reviewers (J.-M. Bae and L.J. Lee). Disagreements between reviewers were resolved by consensus.

Data abstraction

The following information was extracted for all eligible studies: study design, country of origin, years of enrollment, sampling frame, number of subjects, age range, sex distribution, kinds of citrus fruits, level of comparison, and potential confounding variables considered. From the eligible studies that met the inclusion criteria, estimates of ORs/RR, and their associated 95% CIs, were extracted relating to intake of citrus fruits.

If separate reports from the same study were published, the report showing more detailed information on citrus fruit consumption was selected for inclusion.

Statistical analyses

For using general variance-based methods, study-specific OR/RR and 95% CIs for highest versus lowest intake of citrus fruit level were extracted from each

article. For all studies, the reported OR/RR estimate was adjusted for age and sex, if applicable. The standard errors (SEs) of the log OR were calculated from the extracted OR estimates and 95% CIs by using the following equation: $SE = [\ln(OR_{upper}) - \ln(OR_{lower})] / 3.92$. Where ORs were only given by subsites or histological types (e.g., cardia versus noncardia, or intestinal versus diffuse) [18–20], separate estimates were obtained by fixed-effects metaanalysis, though the results for the subgroups were also considered [21].

We assessed heterogeneity with I^2 , which describes the percentage of total variation across studies because of heterogeneity rather than chance [17]. I^2 lies between 0% (no observed heterogeneity) and 100%. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. We used a fixed effect model to calculate the summary OR and its 95% CI [22–23]. In an attempt to detect publication bias, we first visually explored asymmetry in funnel plots [24]. If the funnel plots were skewed, we then tested the degree of asymmetry of the funnel plot using Egger’s regression asymmetry test [23]. We considered the funnel plot to be asymmetrical if the intercept of the regression line deviated from zero with a P value of <0.10 . Sensitivity analyses were conducted by entering studies based on degree of adjustment (crude or adjusted OR) and then evaluating the impact of the changes on the pooled OR and heterogeneity.

We used The Cochrane Collaboration software RevMan 8.2 to analyze the extracted data with both fixed-effect and random-effect model analysis [25]. STATA was used to conduct the Egger’s regression asymmetry test by using the metabias command [26].

Results

Search results

The computerized search yielded 105 references, and 234 articles identified from citations were added. Of these articles, 287 were included after abstract review by the inclusion criteria. We excluded 268 articles, based on the exclusion criteria, from articles that were obtained for full-text review (Fig. 1).

Among the 19 eligible articles, 5 were excluded because of sharing the same database. For example, the results of Palli et al. [19] were selected instead of those of La Vecchia et al. [27], Buiatti et al. [28], and Munoz et al. [29] for the case-control study in Northern Italy. For the case-control study in Montevideo, Uruguay, the results of De Stefani et al. [30] were included instead of those of De Stefani et al. [31]. Lastly, the results of Lagiou et al. [32] replaced those of Trichopoulos et al. [33] for the case-control study in Greece.

Fig. 1. Literature flow. *DB*, database

Finally, 14 articles were included in the metaanalysis, consisting of six hospital-based case-control studies [30, 34–38], six community-based case-control studies [18–20, 39–41], and two cohort studies [16, 42].

Study characteristics

Table 1 presents some details of the eligible studies. Three articles were not published in English, but in Serbian Cyrillic script [34], Korean [36], and Lithuanian [38]. Seven studies were conducted among residents of Europe [16, 18–19, 34–35, 38, 42], another five studies were conducted in North and South America [20, 30, 39–41], and the remaining two studies were conducted in Asia [36–37]. Eight of the studies recruited study subjects in the 1980s, five in the 1990s, and one between 2000 and 2004.

All of the studies matched or adjusted for age and sex, eight adjusted for total energy intake [16, 18–20, 30, 39–41], and eight adjusted for tobacco smoking [16, 18, 20, 30, 38, 40–42]. Other adjustment factors included ethnic group, area of residence, hospital, education, body mass index, alcohol drinking, physical activity, use of a refrigerator, family history of cancer, multivitamin supply, salt use, and vegetable or meat intake.

In all of the studies, intake of citrus fruits was part of a broader dietary assessment, and the relation between citrus fruit intake and stomach cancer had not been a primary hypothesis. The adjusted ORs/RR for the highest category for citrus fruit intake in all of the studies were associated with a decreased risk of stomach cancer compared to the lowest category of intake, with the ORs/RRs ranging from 0.2 to 0.88. Four studies

reached the usual threshold P value of 0.05 [19, 30, 35, 39].

Heterogeneity and pooled results

There was no significant heterogeneity among the study results ($I^2 = 0$; $P = 0.49$). Overall summary OR using the fixed-effect model showed a 28%, statistically significant reduction in risk of stomach cancer associated with high intake of citrus fruits (summary OR = 0.72; 95% CI = 0.64–0.81; Fig. 2).

Publication bias

Visualization of Begg's funnel plot did not suggest publication bias (Fig. 3). Formal testing using Egger's method also did not support the notion of a publication bias (intercept = -0.268 ; $P = 0.685$).

Discussion

Although all articles describing observational studies conducted with control groups showed low quality rating when applying the GRADE system [43], the overall summary OR suggested an inverse association between citrus fruit intake and stomach cancer (RR = 28%; 95% CI = 19%–36%; $P < 0.0001$). The results of this study would suggest conducting an epidemiological study and/or clinical trial for an association of citrus fruit intake and gastric cancer risk because it remains unclear which constituents in fruits and vegetables play a significant role in gastric cancer prevention [4].

Table 1. Summary of cohort (CO) and case-control (CC) studies selected in metaanalysis

Study, country, year of enrollment (year of publication)	Study design, no. of subjects (year of FU: CO)	CO Population or sources of controls	Age range in years Men (%)	Factors controlled for in analysis of citrus fruit intake	Type of citrus fruit	Comparison of exposure level	RR/OR (95% CI)	P value of χ^2 trend
Jarebinski [34] Yugoslavia (now Serbia), 1984–6 (1994)	CC; 80/80	Hospital	67, median 58	Age, sex, living place	Lemon	Less than 2 vs 3+ times/month	0.8 (0.2–3.1)	
Boeing [35] Germany, 1985–6 (1991)	CC; 143/579	Hospital	32–80 ND	Age, sex, hospital	Citrus fruit	Q1 vs Q3	0.46 (0.27–0.78)	<0.01
Park [36] Korea, 1996 (1998)	CC; 126/234	Hospital	30–69 69	Age, sex, education, economic status, residence	Citrus fruit	2–3 times/month vs 3+ times/week	0.2 (0.1–0.5)	<0.0001
De Stefani [30] Uruguay, 1996–2000 (2004)	CC; 240/960	Hospital	30–89 70	Age, sex, residence, education, BMI, tobacco, alcohol, total energy intake	Citrus fruit	Q1 vs Q3	0.45 (0.30–0.68)	0.0002
Kim [37] Korea 1997–8 (2002)	CC; 136/136	Hospital	55–74 68	Age, sex, socioeconomic status, family history, refrigerator use	Citrus fruit	Q1 vs Q3	0.66 (0.31–1.41)	0.27
Zickute [38] Lithuania 2002–4 (2005)	CC; 379/1137	Hospital	ND 60	Age, sex, smoking, alcohol, family history, education, residence	Citrus fruit	Less than 3 times/month vs 1+ times/week	0.81 (0.55–1.20)	0.35
Risch [39] Canada, 1979–82 (1985)	CC; 246/246	Community	35–79 66	Age, sex, area of residence, total food consumption, ethnicity	Citrus fruit	100 g/day	0.75 (0.60–0.92)	0.0056
Palli [19] Italy, 1985–7 (1992)	CC; 68 (cardia) + 819 (all others) /1159	Community	ND 65 (cases)	Age, sex, area of residence, migration, socioeconomic status, family history, Quetelet index, total calorie intake	Citrus fruit	Q1 vs Q3	0.3 for cardia (0.2–0.6) 0.6 for all others (0.4–0.7)	ND

Chen [40] USA, 1986–7 (2002)	CC; 124/449	Community	70.3 (mean of case) 54	Age, sex, proxy status, energy intake, BMI, alcohol, tobacco, education, vitamin supply, family history	Citrus fruits and juices	Q1 vs Q4	0.84 (0.40–1.70)	NS
Ward [41] Mexico 1989–90 (1999)	CC; 220/752	Community	ND ND	Age, sex, total calories, chili pepper, added salt, history of peptic ulcer, smoking, socioeconomic status	Citrus fruit	Less than 2 vs 9+ times/ week	0.7 (0.3–1.5)	0.07
Ekstrom [18] Sweden, 1989–95 (2000)	CC; 505/1116	Community	67.9 (mean) 67	Age, sex, total caloric intake, tobacco, BMI, resident area, no of siblings, no of meals/ day, multivitamin supplement, table salt use, urban	Citrus fruit	Less than 1/ month vs 3+ times/ week	0.8 in cardia (0.4–2.0) / 0.8 in noncardia (0.5–1.2)	0.26/ 0.04
Harrison [20] USA, 1992–4 (1997)	CC; 132/132	Community	62.0 (mean of case) 58	Age, sex, caloric intake, race, education, smoking, alcohol, BMI	Citrus fruit	g/Day	0.7 in intestinal (0.4–1.3) 0.8 in diffuse (0.4–1.4)	0.20
Botterweck [42] Netherlands, 1986 (1998)	CO; 282 (6.3)	120,852	55–69 48	Age, sex, smoking, education, stomach disorders, family history, total vegetable intake	Citrus fruit	Q1 vs Q5	0.86 (0.57–1.29)	
Gonzalez [16] Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, UK, 1992–8 (2006)	CO; 330 (6.5)	521,457	35–70 71	Age, center, sex, height, weight, education, smoking, physical activity, alcohol, energy intake, meat intake	Citrus fruit	Q1 vs Q4	0.88 (0.63–1.24)	0.21

ND, not described; FU, follow-up; Q1, baseline level by rank distribution; Q3, tertile level; Q4, quartile level; Q5, quintile level

Fig. 2. Summary estimates of the association between citrus fruit intake and gastric cancer risk sorted by effect estimate. *CI*, confidence interval; *df*, degrees of freedom; χ^2 , χ^2 statistic; *I*², the percentage of total variation across studies that is due to heterogeneity rather than chance; *OR*, odds ratio; *RR*, relative risk; *fixed*, using fixed-effect model

Fig. 3. Funnel plot of studies evaluating the association between citrus fruit intake and gastric cancer risk. *Dotted lines*, 95% pseudo-confidence intervals

In addition to vitamin C, citrus fruits are the main dietary source of β -cryptoxanthin, another major carotenoid in human plasma [44], which showed a protective effect for lung cancer [45]. While investigators have undertaken several randomized chemoprevention trials of the supplementation of antioxidants [15, 46–49], these studies have found no relationship between such supplementation and stomach cancer [50]. The results of these randomized trials as well as the present systematic review lend support to the hypothesis that antioxidants may be protective at the doses available from dietary intake alone rather than from megadoses in supplement form [51].

Conclusions from the results of the present study need to be drawn cautiously, because the body of evidence on this topic has limitations. First of all, only supplementary data from individual studies were obtained for this metaanalysis, because there were no primary studies of the intake of citrus fruit and stomach

cancer risk. In other words, none of the studies were originally designed to test the citrus fruit/stomach cancer hypothesis. Thus, the extreme diversity of study designs and populations in terms of epidemiology, as well as potential biases in the original studies, makes the interpretation of simple summaries problematic [52]. Different types of control groups could also be among the potential causes of variations in the studies' estimates [53]. Especially, measurement errors in dietary intake should be considered because the consumption pattern of fruits and vegetables may be different among countries. In addition, methodological issues related specifically to metaanalysis, such as publication bias, could have particular impact when combining the results of observational studies [54–56].

While stringent criteria would make selected studies homogeneous, these could bring about an inclusion bias [54, 57]. When the selection criteria in this study were considered, omitting six studies sharing the same source

Table 2. Summary of six articles excluded from metaanalysis because of insufficient information

Study, country, year of enrollment (year of publication)	Study design, no. of subjects (year of FU; CO)	CO Population or sources of controls	Age range, in years Men (%)	Factors controlled for in analysis of citrus fruit intake	Type of citrus fruit	Comparison levels (unit)	RR/OR (95% CI)	P value of χ^2 trend
Chyou [67] Hawaiian Japanese 1965–68 (1990)	Case-cohort; 111/361	Cohort	57.7; mean 100	age	Citrus fruit	g/Day	52.9 (mean) 12.0 (SD) in cases	
Tajima [64] Japan, 1981–83 (1985)	CC; 93/186	Hospital	40–70 63	Age, sex	Orange	Less than 1 time/ week vs 4+ times/week	0.90 (ND)	ND
Lagiou [32] Greece, 1981–4 (2004)	CC; 110/100	Hospital	34–85 76	ND	Citrus fruit	Q1 vs Q5	ND (ND)	<0.001
Ramon [65] Spain 1986–9 (1993)	CC; 117/234	Community	31–80 85	Age, sex	Citrus fruit	Q1 vs Q3	0.65 (ND)	<0.01
Gonzalez [66] Spain 1987–9 (1991)	CC; 354/354	Hospital	65 (mean) 66	Total calories	Citrus fruit	Q1 vs Q4	0.99 (ND)	0.89
Ye [68] China 1994–5 (1998)	CC; 272/544	Community	30–78 86	ND	Citrus fruit	>2.5 kg/year vs 2.5+ kg/year	1.41 (1.03, 1.92)	

population was rational because the inclusion of duplicated data may lead to overestimation of exposure effects [58]. Selecting only studies of incidence outcome is not an issue of metaanalysis, but of cancer statistics. While remnant primary gastric cancer is defined as cancer in the remnant stomach that is detected over 10 years after the initial gastric resection [59], cancer deaths reflect the failure of treatment as well as the occurrence of the cancer [60]. Thus, incidence rates are preferable as an early indicator of the impact of a risk factor. Several articles on studies conducted in Japanese people, whose occurrence of stomach cancer is highest in the world, were omitted based on this criterion [61–63]. Six articles were excluded because of insufficient information to obtain a summary estimate (Fig. 1 and Table 2). Four of these articles did not state the SE of adjusted OR [32, 64–66], and the article by Chyou et al. [67] stated the mean and standard deviation (SD) of citrus intake instead of the OR. The article by Ye et al. [68], published in Chinese, showed an OR above 1 but did not define it as crude or adjusted. The most appropriate way of handling the selection of studies is to perform sensitivity analyses with regard to the different possible entry criteria [57]. Thus, we conducted a metaanalysis of a new model, adding the article by Ye et al. [68] to the 14 selected studies listed in Table 1, so that heterogeneity was introduced ($I^2 = 50.1\%$ from 0%) and the summary OR based on the random-effect model was 0.76 (95% CI = 0.64–0.91). This finding showed that statistical significance, as well as the protective effect of citrus fruit on stomach cancer risk, was kept although heterogeneity occurred. Crude ORs and the SE for four studies having unknown SE [32, 64–66] could be estimated based on the published numbers of cases and controls per category of citrus intake [53], or by the exact P value [69]. However, we did not calculate the crude OR and its SE from the study of Chyou et al. [67] because we were not convinced of the assumption of normality, even though Greenland [69] has suggested a method for estimating the crude OR and its SE from reports presenting only means, by the linear discriminant function method. When we performed another metaanalysis, including the total of 19 studies listed in Tables 1 and 3 (except for the study of Chyou et al. [67]), I^2 was 52.0% and the summary OR based on the random-effect model was 0.76 (95% CI = 0.65–0.89). These results of sensitivity analysis mean that the protective effect of citrus fruit on stomach cancer risk was still kept even when we also selected the five excluded articles. While this consistency increases confidence in the results, we decided to exclude these five studies having only estimated crude ORs because they are more prone to bias [70].

As vitamin C was inversely associated with all subtypes and subtypes of gastric cancer in a significant dose-

Table 3. Summary of odds ratios (ORs) and their 95% confidence intervals (CIs) by study design

Study design	Reference numbers of studies included in metaanalysis	I ² (%)	Summary OR, fixed (95% CI)
Hospital-based case-control studies	30, 34–38	0	0.58 (0.47–0.73)
Community-based case-control studies	18–20, 39–41	0	0.74 (0.63–0.87)
Prospective cohort studies	16, 42	0	0.87 (0.67–1.13)
All articles	16, 18–20, 30, 34–42	0	0.72 (0.64–0.81)

I² (%), the percentage of total variation across studies because of heterogeneity rather than chance

response manner, with risk reductions between 40% and 60% [4, 18], we conducted subgroup analysis, applying a random-effect model, to the results of Palli et al. [19] and Ekstrom et al [18]. The summary ORs in cardia and noncardia were 0.47 (95% CI = 0.18–1.22; I² = 74.3%) and 0.81 (95% CI = 0.62–0.83; I² = 15.2%), respectively. But the role of anatomical localization (cardia versus noncardia) or the histological subtype (intestinal versus diffuse) of gastric cancer should be evaluated with caution in the present study, because only 3 of the 14 selected articles showed these results. Meanwhile, the summary OR based on the two cohort studies exhibited somewhat weaker association than that in the case-control studies, showing no statistical significance (Table 3). The findings in this metaanalysis accorded with some previous reports [5, 6]. The discrepancies between study results can be explained by recall and selection biases in case-control studies and by imprecise dietary measurements and limited variability of dietary intake in cohort studies [71]. The reasons for in the present study might be that there were only two selected cohort studies and these had follow-up of about 6.4 years, so that further cohort studies would be needed to interpret some effects stratified by study design [72].

In summary, the results of the present study provide evidence of the decreased risk of gastric cancer associated with citrus fruit intake. However, this metaanalysis evaluated the association between citrus fruit intake and stomach cancer risk based on published results from epidemiological studies, but, from the relatively small number of epidemiological studies, we can conclude that there is insufficient information to provide a definitive assessment on the relationship between citrus fruit intake and stomach cancer risk in humans. As the main concern of this metaanalysis was to pose a new hypothesis for an exploratory metaanalysis [73], we hope that this metaanalysis will be used to shape future research questions by helping us understand the results from past studies. Because it remains unknown which constituents in citrus fruits play a significant role in gastric cancer prevention [74].

Acknowledgments We thank our colleague, Diane Heels-Ansdell, for her valuable comments on the analy-

sis. And we are grateful to Byung-Joo Park at Seoul National University College of Medicine for serving as a scientific advisor. This work was supported by a research grant from the Chuongbong Academic Research Fund of the Cheju National University in 2007.

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