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Original article

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A pooled analysis of dietary sugar/carbohydrate intake and esophageal and gastric cardia adenocarcinoma incidence and survival in the USA

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Abstract

Background: During the past 40 years, esophageal/gastric cardia adenocarcinoma (EA/GCA) incidence increased in Westernized countries, but survival remained low. A parallel increase in sugar intake, which may facilitate carcinogenesis by promoting hyperglycaemia, led us to examine sugar/carbohydrate intake in association with EA/GCA incidence and survival.

Methods: We pooled 500 EA cases, 529 GCA cases and 2027 controls from two US population-based case-control studies with cases followed for vital status. Dietary intake, assessed by study-specific food frequency questionnaires, was harmonized and pooled to estimate 12 measures of sugar/carbohydrate intake. Multivariable-adjusted odds ratios (ORs) and hazard ratios [95% confidence intervals (CIs)] were calculated using multinomial logistic regression and Cox proportional hazards regression, respectively.

Results: EA incidence was increased by 51–58% in association with sucrose ($OR_{Q5vs.Q1} = 1.51$, 95% CI = 1.01–2.27), sweetened desserts/beverages ($OR_{Q5vs.Q1} = 1.55$, 95% CI = 1.06–2.27) and the dietary glycaemic index ($OR_{Q5vs.Q1} = 1.58$, 95% CI = 1.13–2.21). Body mass index (BMI) and gastro-esophageal reflux disease (GERD) modified these associations ($P_{multiplicative\text{-interaction}} \leq 0.05$). For associations with sucrose and sweetened

desserts/beverages, respectively, the OR was elevated for BMI < 25 ($OR_{Q4–5vs.Q1–3}$ = 1.79, 95% CI = 1.26–2.56 and $OR_{Q4–5vs.Q1–3}$ = 1.45, 95% CI = 1.03–2.06), but not BMI ≥ 25 ($OR_{Q4–5vs.Q1–3}$ = 1.05, 95% CI = 0.76–1.44 and $OR_{Q4–5vs.Q1–3}$ = 0.85, 95% CI = 0.62–1.16). The EA-glycaemic index association was elevated for BMI ≥ 25 ($OR_{Q4–5vs.Q1–3}$ = 1.38, 95% CI = 1.03–1.85), but not BMI < 25 ($OR_{Q4–5vs.Q1–3}$ = 0.88, 95% CI = 0.62–1.24). The sucrose-EA association OR for GERD < weekly was 1.58 (95% CI = 1.16–2.14), but for GERD ≥ weekly was 1.01 (95% CI = 0.70–1.47). Sugar/carbohydrate measures were not associated with GCA incidence or EA/GCA survival.

Conclusions: If confirmed, limiting intake of sucrose (e.g. table sugar), sweetened desserts/beverages, and foods that contribute to a high glycaemic index, may be plausible EA risk reduction strategies.

Key words: Sucrose, sweetened desserts/beverages, glycaemic index, esophageal adenocarcinoma

Key Messages

- The risk of developing esophageal adenocarcinoma was increased by 51% to 58% in association with sucrose intake, sweetened desserts/beverages and glycaemic index, comparing the intake in the highest with the lowest quintile.
- Obesity may modify the associations between sucrose intake, sweetened desserts/beverages and glycaemic index, with esophageal adenocarcinoma incidence; and gastro-esophageal reflux disease may modify the association between sucrose intake and esophageal adenocarcinoma incidence.
- If confirmed in prospective studies, reducing intake of sucrose (particularly table sugar), sweetened desserts/beverages and foods that contribute to a high dietary glycaemic index, may be plausible risk reduction strategies for esophageal adenocarcinoma.

Introduction

Incidences of esophageal adenocarcinoma (EA), and the adjacently located gastric cardia adenocarcinoma (GCA), have increased dramatically in Westernized countries during the past four decades.[1–9] The incidence of EA was 28 per million in the USA in 2012, with overall 5-year survival remaining low at < 20%.[10–12] Identification of safe and practical intervention strategies to reduce risk of developing or dying from these lethal cancers is a pressing clinical and public health need.

Obesity, gastro-esophageal reflux disease (GERD) and cigarette smoking are established EA/GCA risk factors.[13–15] Thus, exploring the role of glucose metabolism in the development of EA/GCA appears warranted.[16–18] Long-term high sugar/carbohydrate intake may lead to chronic hyperinsulinaemia, which may decrease cell apoptosis and prolong healing time after esophageal mucosal injury, thereby promoting carcinogenesis.[18–21] Intake of refined sugar leads to acute fluctuations in blood glucose, which may induce oxidative stress and modulate carcinogenesis pathways.[22–24] Sugar intake, which has also increased dramatically since the 1960 s,[25] is inconsistently associated with risk of developing EA in several epidemiological studies.[17,26,27] Only one study has examined the role of sugar/carbohydrate intake in association with survival following EA.[28]

In this study, we harmonized and pooled individual-level data from two case-control studies conducted within the USA, with cases followed for vital status, to investigate whether sugar/carbohydrate intake is associated with the risk of developing EA/GCA or mortality after diagnosis of EA/GCA.

Methods

This pooled analysis comprises two case-control studies of esophageal and gastric cancer: the US Multi-Center study and the Los Angeles (LA) Multi-Ethnic study,[29,30] selected from the International Barrett's and Esophageal Adenocarcinoma Consortium (BEACON) because both are population-based, used incidence density sampling and collected follow-up information on vital status. The institutional review boards of participating institutions approved this study.

Study population

The US Multi-Center study was conducted in Connecticut, New Jersey, and western Washington state.[29] Eligible cases

were 30–79-year-old English-speaking men and women diagnosed with first primary invasive cancer of the esophagus or stomach during 1993–95. Cases were identified through population-based cancer registries using established rapid-reporting systems; a diagnosis of EA or GCA was confirmed through review of pathology materials. Controls were identified using a random digit-dialling method for those aged 30–64 years, and Health Care Financing Administration rosters for those aged 65–79 years. Controls were frequency-matched to the expected case distribution by 5-year age group, sex, state of residence and, in New Jersey, by race.

The LA Multi-Ethnic study was conducted in LA County, California.[30] Cases were 30–74-year-old men and women diagnosed with first primary cancer of esophagus or stomach during 1992–97. Cases were identified through the LA County cancer registry; EA or GCA diagnosis was confirmed by reviewing all available pathology reports. Controls were selected from a case's neighbourhood and individually matched by date of birth (±5 years), sex and race.

Respondents from the two studies included 513 EA cases, 538 GCA cases and 2051 controls. We excluded individuals with no information on dietary intake and those who reported extreme total energy intake values (defined by beyond ± 3 standard deviations from study-specific $\log_e$-transformed mean total energy intake), yielding 500 EA cases, 529 GCA cases and 2027 controls for this pooled analysis.[31]

Dietary assessment

In both studies, dietary information was collected using validated semi-quantitative food frequency questionnaires (FFQs) during structured in-person interviews.[32,33] When subjects were unable to participate in the interview due to illness/death, interviews were administered to their closest next of kin, usually the spouse.[32,33] The US Multi-Center study used a 104-item FFQ, a modification of the Fred Hutchinson Cancer Research Center instrument, which assessed frequency of intake.[34] Participants were asked to report their usual diet in the 3–5 years before diagnosis (cases) or interview (controls).[32] The LA Multi-Ethnic study used a 124-item FFQ developed at the University of Hawaii, which assessed portion size and frequency of intake of each line item.[33] Cases were asked to report their diet in the year before diagnosis, and controls were asked to report their diet during the same time period as their matched case.[33] The two FFQs similarly assessed dietary intake (food items, frequency) (Table 1), which enhanced our ability to harmonize and pool data.

Sugar/carbohydrate intake assessment

We estimated 12 intake measures including: sugar components (free glucose, free fructose, sucrose); total sugar; added sugar; total carbohydrate; starch; glycaemic index; glycaemic load; and servings of sweetened desserts, sweetened beverages and sweetened desserts/beverages (Table S1, available as Supplementary data at *IJE* online). Added sugar was defined as sugars and syrups that were added to foods during food preparation/processing.[35] For this pooled study, the study-specific FFQ information was linked with the University of Minnesota Nutrition Coordinating Center Food and Nutrient Database, to determine sugar/carbohydrate intake.[35] During harmonization, we assumed a medium serving size for the US Multi-Center study. For example, daily starch intake from an FFQ line item was calculated as follows:[36]

$$\text{amount of food consumed each time (g)} \times \text{frequency (/day)} \times \text{starch}\,\frac{\text{g}}{\text{g}}\,\text{food}.$$

Daily intake of starch was calculated by summing starch intake across all FFQ line items. When FFQ line items represented > 1 food item, the nutrient contents of the FFQ line item were weighted according to their weights estimated based on the national consumption pattern.[36–38]

Dietary glycaemic index and glycaemic load estimate the effect of diet on blood glucose. For this study, the

Table 1. Comparison between the two studies of esophageal and gastric cardia adenocarcinoma (EA/GCA)

	US Multi-Center study	LA Multi-Ethnic study
Study design	Population-based case-control study	Population-based case-control study
Time and location	CT, NJ, WA, 1993–95	Los Angeles county, CA, 1992–97
Sample size	282 EA cases, 256 GCA cases, 684 controls	218 EA cases, 273 GCA cases, 1343 controls
Food Frequency Questionnaire (# items)	Modified Fred Hutchinson Cancer Research Center (104)	University of Hawaii (124)
Frequency of consumption	_ times per D W M Y	_ times per D W M Y
Serving size	Assumed medium serving size	1/2 cup, 1 cup, 1½ cups

US, United States; LA, Los Angeles county; CT, Connecticut; NJ, New Jersey; WA, Washington; CA, California; D, day; W, week; M, month; Y, year.

following formulas were used to calculate dietary glycaemic index and glycaemic load,[39–41] respectively:

$$\frac{\sum(\text{amount of food consumed(g)/day} \times \text{carbohydrate contents(g)/g food} \times \text{glycaemic index of food})}{\text{total carbohydrate consumed(g)/day}}$$

$$\frac{\sum(\text{amount of food consumed(g)/day} \times \text{carbohydrate contents(g)/g food} \times \text{glycaemic index of food})}{100}$$

Covariate assessment

Information on non-dietary covariates was collected in-person by each study using interviewer-administered questionnaires.[29,30] Covariates were harmonized, as previously described.[13–15]

Outcome assessment

Vital status and date of death for EA/GCA cases were determined by linking participants with the National Death Index.[42] An event was defined as death from any cause during follow-up. The maximum length of follow-up was 90 months in the US Multi-Center study and 129 months in the LA Multi-Ethnic study.

Statistical analysis

Estimated sugar/carbohydrate intake from each study was pooled on study-specific quintiles (Q), based on the study-specific intake distributions among the controls (case-control analysis) or EA/GCA patients (survival analysis).[31,43]

We used multinomial logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between sugar/carbohydrate intake and EA/GCA incidence.[44] We explored whether body mass index (BMI $< 25/\geq 25$ kg/m^2 during adulthood[45] or year before interview[30]), or GERD frequency (< weekly/≥ weekly) were effect measure modifiers of the sugar/carbohydrate intake (comparing Q1–3 vs Q4–5) and EA/GCA incidence associations. Effect measure modification was assessed using the likelihood ratio test (multiplicative scale) and the interaction contrast ratio (ICR) and 95% CI (additive scale)[46]

Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95% CIs for the association between sugar/carbohydrate intake and EA/GCA survival.[46] The proportional hazards assumption was evaluated using product terms with log-time and exposure or covariate; no violations were found.

Potential confounders were first identified using directed acyclic graphs.[47] After the initial adjustment set was identified, only those covariates that changed the effect estimate (on a $\log_e$ scale) by $\geq 10\%$ were included in final model.[46] Case-control adjustment sets included adjustment for age (continuous), sex (male/female), race (White/other), study indicator (US Multi-Center/LA Multi-Ethnic), cigarette smoking (ever/never), fruit/vegetable intake (servings,<median/≥median), GERD frequency (<weekly/≥weekly), total energy intake (continuous kcal/day) and BMI ($<25/\geq 25$ kg/m^2). Survival adjustment sets included age, education (≤high school/some college or technical school/≥college graduate), study indicator and total energy intake. BMI and education were not included in some measure-specific case-control ($n = 2$) and survival ($n = 1$) models, respectively, because inclusion/removal of these covariates changed the effect estimate on a $\log_e$ scale by<10%.[46] Linear trends were examined by modelling sugar/carbohydrate intake as continuous variables.

Sensitivity analyses for case-control and survival analyses were conducted as follows. First, we pooled study-specific effect estimates using a meta-analytic approach (fixed effect, Table S2, available as Supplementary data at *IJE* online). Second, we also examined pooled individual-level intake based on absolute cut-points derived from intake distributions among all controls (case-control analysis) or all EA/GCA patients (survival analysis).[31,43] Third, we used wider exclusion criteria for extreme total energy intake (lower/upper 2.5%). Fourth, we excluded participants with proxy interviews. Fifth, we compared effect estimates derived using carbohydrate intake values estimated based on the University of Minnesota nutrient database, with effect estimates derived using carbohydrate intake previously calculated by study-specific nutrient data processing centres. For the case-control analysis only, we: additionally adjusted for potential confounding by physical activity and diabetes; explored diabetes as an effect measure modifier in the LA Multi-Ethnic study (since this information was unavailable from the Multi-Center study); examined fructose from fruits/vegetables vs other fructose; used a nutrient density energy adjustment method (which would help to standardize responses); and removed energy intake from the models.

SAS (version 9.3; SAS Institute Inc., Cary, NC) and STATA software (version 14.0; StataCorp LP, College Station, TX) were used for the statistical analysis.

Results

As presented in Table 2, participants in the LA Multi-Ethnic study were more likely to be younger, non-White, obese, experience frequent GERD, consume more fruits/vegetables and have higher total energy intake, compared

Table 2. Distribution of demographic and other relevant characteristics among 500 EA cases, 529 GCA cases and 2027 controls from two US case-control studies of esophageal and gastric cardia adenocarcinoma

	US Multi-Center study			LA Multi-Ethnic study		
	Controls $N = 684$	EA cases $N = 282$	GCA cases $N = 256$	Controls $N = 1343$	EA cases $N = 218$	GCA cases $N = 273$
Age, years, mean (SD)	62.74 (10.66)	64.34 (10.69)	63.14 (10.91)	61.52 (11.25)	61.08 (9.47)	60.73 (10.19)
Sex, *n* (%)						
Male	548 (80.12)	235 (83.33)	218 (85.16)	991 (73.79)	198 (90.83)	227 (83.15)
Female	136 (19.88)	47 (16.67)	38 (14.84)	352 (26.21)	20 (9.17)	46 (16.85)
Race, *n* (%)						
White	615 (89.91)	268 (95.04)	243 (94.92)	838 (62.40)	169 (77.52)	208 (76.19)
Other	69 (10.09)	14 (4.96)	13 (5.08)	505 (37.60)	49 (22.48)	65 (23.81)
Education, *n* (%)						
≤High school	302 (44.15)	152 (54.09)	138 (54.12)	498 (37.08)	97 (44.50)	119 (43.59)
Some college/technical	172 (25.15)	75 (26.69)	59 (23.14)	386 (28.74)	62 (28.44)	86 (31.50)
≥College graduate	210 (30.70)	54 (19.22)	58 (22.75)	459 (34.18)	59 (27.06)	68 (24.91)
Cigarette smoking, *n* (%)						
Ever	443 (64.74)	220 (79.71)	202 (82.11)	806 (60.01)	170 (77.98)	195 (71.43)
Never	211 (32.26)	56 (20.29)	44 (17.89)	537 (39.99)	48 (22.02)	78 (28.57)
GERD, *n* (%)						
Ever	356 (52.05)	183 (65.12)	110 (42.97)	890 (66.32)	176 (80.73)	185 (68.52)
Never	328 (47.95)	98 (34.88)	146 (57.03)	452 (33.68)	42 (19.27)	85 (31.48)
GERD frequency, *n* (%)						
<Weekly	553 (81.20)	157 (56.47)	192 (75.00)	1068 (79.58)	101 (46.54)	166 (61.48)
≥Weekly	128 (18.80)	121 (43.53)	64 (25.00)	274 (20.42)	116 (53.46)	104 (38.52)
BMI (kg/m^2)						
<25	379 (55.65)	118 (41.99)	113 (44.14)	652 (49.43)	78 (36.97)	111 (42.21)
25-<30	253 (37.15)	122 (43.42)	105 (41.02)	486 (36.85)	87 (41.23)	93 (35.36)
≥30	49 (7.20)	41 (14.59)	38 (14.84)	181 (13.72)	46 (21.80)	59 (22.43)
Diabetes, *n* (%)						
Yes	–	–	–	113 (8.43)	32 (14.75)	25 (9.23)
No	–	–	–	1227 (91.57)	185 (85.25)	246 (90.77)
Total energy intake,[a] kcal/day, mean (SD)	1838.13 (663.60)	2027.42 (644.03)	1999.68 (711.85)	2593.07 (1224.59)	2926.66 (1343.77)	2836.06 (1467.32)
Fruit/vegetable intake, servings/day,[a] median (SD)	2.00 (1.17)	1.71 (1.19)	1.86 (1.15)	6.96 (5.32)	6.10 (4.21)	6.95 (4.48)

[a]Based on study-specific serving sizes and study-specific food frequency questionnaires.
Missing values ([n]): education (2), GERD (5), GERD frequency (12), smoking (46), BMI (45), fruits and vegetables intake (28).

with participants in the US Multi-Center study (which was conducted in New Jersey, Connecticut, and western Washington state). As shown in Table 3, in both the US Multi-Center study and the LA Multi-Ethnic study, respectively, EA/GCA cases compared with controls had higher mean intake of sucrose (g/day: 49.91/50.69 vs 45.78; 47.16/41.99 vs 41.42) and sweetened desserts/beverages (servings/day: 4.33/4.42 vs 3.94; 3.66/3.30 vs 3.18).

Multivariable-adjusted ORs for EA (comparing the highest with the lowest quintile) were increased by 51% to 58% in association with intake of sucrose ($OR_{Q5vs.Q1} = 1.51$, 95% CI = 1.01–2.27, $P_{trend} = 0.19$), sweetened desserts/beverages ($OR_{Q5vs.Q1} = 1.55$, 95% CI = 1.06–2.27, $P_{trend} = 0.28$) and dietary glycaemic index ($OR_{Q5vs.Q1} = 1.58$, 95% CI = 1.13–2.21, $P_{trend} = 0.32$) (Table 4). Fructose intake was inversely associated with risk of developing EA ($OR_{Q5vs.Q1} = 0.60$, 95% CI = 0.41–0.89, $P_{trend} = 0.08$), which remained when examining intake of natural fructose ($OR_{Q5vs.Q1} = 0.52$, 95% CI = 0.34–0.82), but not for intake of other fructose ($OR_{Q5vs.Q1} = 0.89$, 95% CI = 0.60–1.32). The fourth quintile of glucose intake was associated with 39% decrease in the OR for EA ($P_{trend} = 0.08$). For carbohydrate intake, the individual ORs were close to null. However, there was a significant trend for these associations with EA and GCA ($P_{trend} \leq 0.02$), which appeared to be driven by very high intake of carbohydrate among some controls (data not shown). In sensitivity analyses, most findings were similar to those shown in Table 4

Table 3. Daily mean (standard deviation) intake of sugar/carbohydrate among 500 EA cases, 529 GCA cases and 2027 controls in two US case-control studies of esophageal and gastric cardia adenocarcinoma

Measure	US Multi-Center Study			LA Multi-Ethnic Study		
	Controls $N = 684$	EA cases $N = 282$	GCA cases $N = 256$	Controls $N = 1343$	EA cases $N = 218$	GCA cases $N = 273$
Free glucose (g/day)	20.97 (12.90)	20.24 (13.72)	21.96 (11.38)	30.06 (19.67)	30.15 (18.72)	30.62 (17.89)
Sucrose (g/day)	45.78 (27.83)	49.91 (27.50)	50.69 (28.64)	41.42 (27.17)	47.16 (32.89)	41.99 (25.79)
Free fructose (g/day)	22.56 (15.31)	21.50 (16.61)	23.18 (13.69)	29.63 (19.49)	29.46 (19.28)	29.80 (18.61)
Total sugar[a] (g/day)	99.49 (48.02)	103.26 (50.85)	107.06 (46.06)	120.62 (64.86)	129.32 (68.93)	123.04 (62.38)
Added sugar[b] (g/day)	48.83 (31.97)	54.78 (32.88)	55.27 (31.80)	50.18 (34.86)	60.37 (46.82)	54.25 (35.83)
Starch (g/day)	79.15 (29.24)	85.40 (30.15)	87.89 (32.29)	126.25 (68.14)	130.27 (65.90)	128.31 (77.01)
Total carbohydrate (g/day)	220.34 (78.67)	232.54 (77.52)	241.48 (80.87)	307.54 (139.17)	321.44 (144.92)	315.20 (152.56)
% Carbohydrate calories	47.11 (7.95)	44.41 (6.83)	45.41 (7.25)	48.58 (9.17)	44.69 (7.83)	45.81 (8.56)
Glycaemic index	61.03 (5.05)	60.60 (7.28)	60.92 (5.82)	59.73 (4.88)	59.46 (5.06)	59.04 (5.57)
Glycaemic load	123.06 (45.79)	129.65 (46.78)	134.71 (46.78)	166.26 (77.04)	174.51 (81.75)	169.29 (85.70)
All sweetened desserts/ beverages[c] (servings/day)	3.94 (2.74)	4.33 (2.70)	4.42 (2.75)	3.18 (2.48)	3.66 (2.62)	3.30 (2.14)
Sweetened desserts[c] (servings/day)	1.95 (1.27)	2.12 (1.15)	2.25 (1.38)	1.99 (1.88)	2.41 (1.92)	2.11 (1.68)
Sweetened beverages[c] (servings/day)	1.99 (2.37)	2.21 (2.20)	2.17 (2.25)	1.19 (1.42)	1.26 (1.35)	1.19 (1.11)

[a]Total sugar is defined as the sum of the individual monosaccharides (glucose, fructose and galactose) and disaccharides (sucrose, lactose and maltose), including both added sugar and naturally occurring sugar.

[b]Added sugar is defined as sugars and syrups that were added to foods during food preparation or processing, such as white sugar, powdered sugar, brown sugar, corn syrups, high fructose corn syrups, pancake syrup, honey and molasses.

[c]The differences in intake of all sweetened desserts/beverages, sweetened desserts and sweetened beverages between the two studies may be attributed to the utilization of study-specific FFQs. Both the serving sizes, and the number of FFQ line items that contained sweetened desserts/beverages, varied by study. There were 17 FFQ line items that contain sweetened desserts/beverages (12 line items contain sweetened desserts and 5 line items contain sweetened beverages) in the US Multi-Center Study. There were 19 FFQ line items that contain sweetened desserts/beverages (12 line items contain sweetened desserts and 7 line items contain sweetened beverages) in the LA Multi-Ethnic Study.

with several exceptions, including attenuation of positive sucrose-EA association and more pronounced inverse association with carbohydrate intake (Table S3, available as Supplementary data at *IJE* online). Moreover, after removing energy intake from the models, ORs were more pronounced for most measures (Table S4 available as Supplementary data at *IJE* online).

BMI modified, on the multiplicative scale, associations between sucrose, sweetened desserts/beverages or glycaemic index, and risk of developing EA. The OR for the sucrose-EA association was elevated among participants with BMI < 25 (OR = 1.79, 95% CI = 1.26–2.56), but not among those with BMI ≥ 25 (OR = 1.05, 95% CI = 0.76–1.44) ($P_{interaction} = 0.02$). Similarly, for the sweetened desserts/beverage-EA association, an elevated OR was found for BMI < 25 (OR = 1.45, 95% CI = 1.03–2.06), but not for BMI ≥ 25 (OR = 0.85, 95% CI = 0.62–1.16) ($P_{interaction} = 0.02$). In contrast, the glycaemic index-EA association was elevated for BMI ≥ 25 (OR = 1.38, 95% CI = 1.03–1.85), but not for BMI < 25 (OR = 0.88, 95% CI = 0.62–1.24) ($P_{interaction} = 0.05$). On the additive scale, effect measure modification by BMI on the glycaemic index-EA association was also evident (ICR = 0.62, 95% CI = 0.08–1.15). GERD modified, on the multiplicative scale, the sucrose-EA association: the OR was elevated for GERD < weekly (OR = 1.58, 95% CI = 1.16–2.14), but not for GERD ≥ weekly (OR = 1.01, 95% CI = 0.70–1.47) ($P_{interaction} = 0.05$). In the LA Multi-Ethnic study, there was no strong indication that diabetes was an effect measure modifier in any of the significant associations between sugar/carbohydrate and risk of developing EA (data not shown).

None of the sugar/carbohydrate measures was associated with increased risk of developing GCA (Table 4), or mortality after EA/GCA (Table S5, available as Supplementary data at *IJE* online).

Discussion

In this pooled study, the risk of developing EA was increased 51% to 58% in association with sucrose, sweetened desserts/beverages and glycaemic index; these associations were modified by BMI or frequency of GERD. Sugar/carbohydrate intake was not associated with GCA incidence or mortality after EA/GCA. Our study suggests that reducing intake of sucrose and sweetened desserts/beverages (especially among those with BMI < 25 or GERD < weekly)

Table 4. Multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between sugar/carbohydrate intake and risk of developing esophageal and gastric cardia adenocarcinoma among 500 EA cases, 529 GCA cases and 2027 controls from two US case-control studies (pooled approach, based on study-specific quintiles)

		Esophageal adenocarcinoma		Gastric cardia adenocarcinoma	
Measure	Controls (*N*)	Cases (*N*)	OR (95% CI)	Cases (*N*)	OR (95% CI)
Free glucose (g/day)[a]					
Q1	385	104	Ref.	75	Ref.
Q2	384	96	0.91 (0.65–1.27)	96	1.28 (0.90–1.80)
Q3	396	96	0.88 (0.63–1.25)	104	1.36 (0.96–1.93)
Q4	398	74	0.61 (0.42–0.89)	102	1.26 (0.88–1.82)
Q5	393	103	0.74 (0.50–1.09)	122	1.43 (0.97–2.11)
P_{trend}			0.08		0.37
Sucrose (g/day)[a]					
Q1	391	69	Ref.	78	Ref.
Q2	394	83	1.22 (0.85–1.77)	103	1.30 (0.93–1.82)
Q3	393	90	1.16 (0.80–1.68)	99	1.15 (0.81–1.62)
Q4	387	105	1.45 (1.00–2.12)	107	1.24 (0.87–1.76)
Q5	391	126	1.51 (1.01–2.27)	112	1.10 (0.74–1.61)
P_{trend}			0.19		0.69
Free fructose (g/day)[a]					
Q1	382	110	Ref.	89	Ref.
Q2	387	96	0.84 (0.60–1.17)	103	1.13 (0.81–1.56)
Q3	398	91	0.74 (0.52–1.04)	88	0.90 (0.64–1.28)
Q4	393	88	0.70 (0.49–1.01)	104	1.07 (0.75–1.52)
Q5	396	88	0.60 (0.41–0.89)	115	1.07 (0.74–1.56)
P_{trend}			0.08		0.25
Total sugar (g/day)[a]					
Q1	385	82	Ref.	82	Ref.
Q2	396	85	0.98 (0.69–1.40)	90	1.00 (0.72–1.42)
Q3	393	103	1.13 (0.79–1.61)	107	1.16 (0.82–1.62)
Q4	390	90	0.89 (0.61–1.30)	102	1.03 (0.72–1.48)
Q5	392	113	0.98 (0.65–1.50)	118	1.05 (0.70–1.57)
P_{trend}			0.79		0.26
Added sugar (g/day)[a]					
Q1	385	70	Ref.	76	Ref.
Q2	399	73	0.92 (0.63–1.35)	75	0.90 (0.63–1.29)
Q3	392	96	1.08 (0.75–1.55)	106	1.18 (0.84–1.66)
Q4	389	116	1.33 (0.92–1.92)	119	1.33 (0.94–1.87)
Q5	391	118	1.06 (0.71–1.59)	123	1.14 (0.77–1.67)
P_{trend}			0.14		0.96
Starch (g/day)[a]					
Q1	389	70	Ref.	85	Ref.
Q2	390	81	1.04 (0.72–1.51)	87	0.92 (0.65–1.29)
Q3	390	109	1.33 (0.93–1.92)	117	1.17 (0.84–1.64)
Q4	394	103	1.04 (0.71–1.54)	102	0.89 (0.62–1.28)
Q5	393	110	1.03 (0.66–1.62)	108	0.84 (0.55–1.29)
P_{trend}			0.34		0.11
Total carbohydrate (g/day)[a]					
Q1	386	79	Ref.	88	Ref.
Q2	390	81	0.98 (0.68–1.41)	89	0.94 (0.67–1.32)
Q3	393	88	0.91 (0.62–1.33)	83	0.79 (0.55–1.13)
Q4	393	101	0.93 (0.62–1.39)	112	0.97 (0.67–1.41)
Q5	394	124	0.93 (0.56–1.54)	127	0.94 (0.59–1.52)
P_{trend}			0.02		0.01

(continued)

Table 4. Continued

Measure	Controls (*N*)	Esophageal adenocarcinoma		Gastric cardia adenocarcinoma	
		Cases (*N*)	OR (95% CI)	Cases (*N*)	OR (95% CI)
Glycaemic index[b]					
Q1	399	94	Ref.	106	Ref.
Q2	397	95	1.29 (0.92–1.81)	86	0.98 (0.71–1.36)
Q3	398	96	1.31 (0.93–1.84)	103	1.17 (0.85–1.61)
Q4	395	85	1.09 (0.77–1.55)	114	1.28 (0.94–1.75)
Q5	394	111	1.58 (1.13–2.21)	98	1.21 (0.88–1.67)
P_{trend}			0.32		0.69
Glycaemic load[a]					
Q1	387	86	Ref.	91	Ref.
Q2	390	79	0.84 (0.59–1.21)	80	0.80 (0.57–1.13)
Q3	395	87	0.85 (0.59–1.23)	90	0.85 (0.60–1.21)
Q4	390	105	0.93 (0.63–1.36)	121	1.07 (0.75–1.54)
Q5	394	116	0.81 (0.51–1.29)	117	0.86 (0.55–1.35)
P_{trend}			0.32		0.07
All sweetened desserts/beverages (servings/day)[a]					
Q1	382	69	Ref.	75	Ref.
Q2	392	79	1.09 (0.75–1.58)	90	1.13 (0.80–1.60)
Q3	401	102	1.43 (0.99–2.05)	108	1.38 (0.98–1.93)
Q4	391	87	1.02 (0.70–1.50)	105	1.16 (0.82–1.64)
Q5	390	136	1.55 (1.06–2.27)	121	1.24 (0.86–1.79)
P_{trend}			0.28		0.88
Sweetened desserts (servings/day)[a]					
Q1	383	65	Ref.	74	Ref.
Q2	392	72	1.01 (0.69–1.49)	96	1.20 (0.85–1.70)
Q3	393	104	1.31 (0.91–1.89)	100	1.16 (0.82–1.63)
Q4	399	103	1.28 (0.88–1.85)	112	1.26 (0.90–1.78)
Q5	389	129	1.38 (0.94–2.03)	117	1.13 (0.78–1.62)
P_{trend}			0.48		0.92
Sweetened beverages (servings/day)[b]					
Q1	394	97	Ref.	86	Ref.
Q2	398	88	0.97 (0.69–1.36)	100	1.18 (0.85–1.64)
Q3	396	91	1.02 (0.73–1.43)	92	1.10 (0.79–1.54)
Q4	400	83	0.84 (0.60–1.19)	116	1.31 (0.95–1.81)
Q5	395	122	1.22 (0.87–1.70)	113	1.21 (0.86–1.69)
P_{trend}			0.60		0.93

[a]Adjusted for age, sex, race, study indicator, BMI, fruits and vegetables intake, cigarette smoking, GERD frequency and total energy intake. [b]Adjusted for age, sex, race, study indicator, fruits and vegetables intake, cigarette smoking, GERD frequency and total energy intake.

and dietary glycaemic index (especially among those with BMI $\geq$ 25), may be plausible EA risk reduction strategies.

Ours is the first study to report that sweetened desserts/beverages are associated with increased risk of developing EA. Positive, but non-significant, findings were reported by a small US case-control study,[48] based on assessment of only five dessert line items. In contrast, our larger pooled study included a more comprehensive dessert/beverage assessment based on 17–19 line items. Others,[49–51] focused only on carbonated beverages, found no positive associations; however, our category of sweetened beverages enlarges the number of sugar-containing food items considered. Compared with other sugar/carbohydrate measures, sweetened desserts/beverages are relatively easier for the general population to identify when implementing risk reduction strategies. Thus our finding, if confirmed, has potential public health implications.

Several studies have examined the association between glycaemic index and risk of developing EA, but with inconsistent results.[17,26,27] An Australian case-control study reported no association.[17] In contrast, two studies–an Irish case-control study of EA[26] and the prospective NIH-AARP study (combining EA and esophageal squamous cell carcinoma (ESCC))[52]–reported significant 42% and 50% increases in the effect estimates, respectively. Results of the

latter two investigations are consistent with our finding of a 58% increased OR for the glycaemic index-EA association.

Sucrose intake was positively associated with EA incidence in our study, but the NIH-AARP study reported no association.[27] However, the NIH-AARP study did not distinguish between the two types of esophageal cancer (EA/ESCC) that have different aetiologies,[53] and adjusted for different confounder sets than did our study. Sucrose exists naturally in fruits/vegetables, but is also commonly present as table sugar, which can be added by the consumer or in preparation of processed foods/beverages.[54] Sucrose in fruits/vegetables co-exists with vitamins/minerals and fibre, which can preserve cell integrity and slow the rate of sucrose digestion.[54–56] In contrast, table sugar is present in foods/beverages that are low in fibre and micronutrients and are rapidly digestible.[54] The quick digestion of concentrated table sugar induces acute glucose fluctuations, which may increase oxidative stress and cancer risk.[22–24] Therefore, it is possible that the positive sucrose-EA association we found was driven by table sugar intake.

We are first to report that free fructose was inversely associated with EA incidence, which in sensitivity analyses appeared to be driven by natural fructose. Reasons for our findings are unclear. They could be spurious, given that in animal studies fructose has been shown to induce hyperinsulinaemia by raising serum uric acid.[57] In addition to the anti-carcinogenic substances found in foods with natural fructose, another possible explanation for the inverse finding is the potential for under-reporting of fructose intake in EA patients. EA patients may have confused their current diet with their previous diet, although they were instructed otherwise. As dysphagia is a common symptom of EA, patients may experience difficulty swallowing and therefore may reduce raw fruit intake.[58] Added sugar, which mainly consists of added sucrose and added fructose, was positively associated with EA incidence in the NIH-AARP study[27] but was not associated with EA incidence in our study. Future studies with refined measures of added sugar are needed.

In our study, glycaemic index was associated with an increased risk of developing EA among participants with BMI ≥ 25, but not among those with BMI < 25. This finding suggests a synergistic effect of high glycaemic index diet and obesity on carcinogenesis, possibly via insulin resistance.[21,59] Our finding is comparable to the NIH-AARP study finding of a positive glycaemic index-esophageal cancer association in the high BMI group; and the Irish study's finding of a positive association presents only in the BMI ≥ 25 and high waist-to-hip ratio group; although no significant interactions were found in either study.[26,52] We are first to report that both sucrose and sweetened desserts/beverages were associated with an elevated risk of developing EA among participants with BMI < 25, but not among those with BMI ≥ 25. There are two possible explanations: participants with BMI ≥ 25 may be more likely to unde-rreport their sweets intake due to social desirability; or obesity is such a strong, metabolically active risk factor for EA, that the metabolic impact of sucrose or sweetened desserts/beverages intake on carcinogenesis is less evident among the obese. Future studies should consider examining effect modification by waist-to-hip ratio.

There are several limitations to our study. First, recall bias is a possibility. Although the participants were instructed to report dietary intake during time periods before diagnosis/interview, some patients may have confused their previous diet with their current diet, as discussed above. Second, non-differential misclassification may be of concern, given dietary intake was collected using FFQs, particularly those which include a detailed assessment of the exposure of interest. Non-differential misclassification may have been introduced by data harmonization and pooling, given the discrepancies in data collection and variable definitions between the two studies. To mitigate this possibility, we appropriately pooled intake estimates based on relative rankings of intake in each study. Third, we chose not to adjust for multiple comparisons. Instead, we focused on internal and external consistencies and biological plausibility. Fourth, we observed no association between sugar/carbohydrate intake and GCA, which could be due to potential misclassification of the outcome. Finally, we were unable to fully assess the impact of diabetes, given this information was unavailable in one of the two pooled studies. But in sensitivity analysis within the LA Multi-Ethnic study, diabetes did not confound or modify the EA associations with sucrose, sweetened desserts/beverages or glycaemic index.

There are several strengths to our study. Ours is the first to comprehensively investigate the role of sugar/carbohydrate intake in relation to EA/GCA incidence and mortality. Harmonizing and pooling of individual-level study data minimized potential sources of heterogeneity between studies and improved study power. Consideration of multiple measures allowed us to more fully capture the complexity of sugar/carbohydrate intake. Finally, the population-based design enhances generalizability of our findings.

In conclusion, we found increases in the risk of developing EA in association with three measures of sugar/carbohydrate intake assessed in our study. None of the sugar/carbohydrate measures was associated with survival. If confirmed in large prospective studies, limiting intake of sucrose, sweetened desserts/beverages and foods that contribute to a high dietary glycaemic index, may be plausible risk reduction strategies for EA incidence.

Supplementary Data

Supplementary data are available at *IJE* online.

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