SUGAR/CARBOHYDRATE INTAKE AND THE BARRETT'S ESOPHAGUS-ADENOCARCINOMA CONTINUUM

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ABSTRACT

Nan Li: Sugar/carbohydrate intake and the Barrett's esophagus-adenocarcinoma continuum
(Under the direction of Marilie D. Gammon)

The incidence of esophageal and gastric cardia adenocarcinoma (EA/GCA) has increased rapidly in Westernized countries during the past few decades, whereas survival remains low. Barrett's esophagus (BE), the only known precursor lesion of EA/GCA, has been increasing. Long-term high sugar/carbohydrate intake may promote carcinogenesis by inducing hyperinsulinemia. In this dissertation, four United States-based case-control studies were pooled to examine the associations between sugar/carbohydrate intake and risk of developing BE, risk of developing EA/GCA, and mortality after a diagnosis of EA/GCA. In total, there were 513 BE cases/528 controls, and 513 EA cases/538 GCA cases/2051 controls. EA/GCA cases were followed for vital status. Dietary intake was assessed by study-specific food frequency questionnaires, and then linked with the University of Minnesota Nutrient Database to harmonize and estimate intake of twelve sugar/carbohydrate measures. Sugar/carbohydrate intake was then pooled using study-specific quantiles and absolute cut-points. Odds ratios and 95% confidence intervals were calculated using: logistic regression for BE incidence; and multinomial logistic regression for EA incidence and GCA incidence as distinct outcomes. Hazard ratios and their 95%CIs were calculated using Cox proportional hazards regression for EA/GCA survival analysis. Sucrose was found to be associated with 79% and 51% increase in risk of developing BE and EA, respectively. Intake of sweetened desserts/beverages was associated with 71% and 55% increase in risk of developing BE and EA, respectively. Added sugar was associated with 71% increase in risk of developing BE, but not with EA. Glycemic index was associated with 58% increase in risk of developing EA, but not with BE. Waist

circumference modified the sweetened desserts/beverages-BE association, and body mass index (BMI) modified all of the above positive associations with EA incidence. The sucrose-EA association was modified by frequency of gastroesophageal reflux disease (GERD). If the results from this dissertation are confirmed, there could be potential to reduce risk of BE/EA by reducing intake of sucrose (especially among those with BMI<25 or GERD<weekly) and sweetened desserts/beverages (especially among those with lower waist circumference or BMI<25). Reducing added sugar intake and dietary glycemic index (especially among those with BMI≥25), may also be plausible risk reduction strategies.

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LIST OF ABBREVIATIONS AND SYMBOLS

BE	Barrett's esophagus
BEACON	International Barrett's and Esophageal Adenocarcinoma Consortium
BMI	Body mass index
CI	Confidence interval
DAG	Directed acyclic graphs
EA	Esophageal adenocarcinoma
EGJAC	Gastro-esophageal junction adenocarcinoma
EMM	Effect measure modification
ESCC	Esophageal squamous cell carcinoma
FFQ	Food frequency questionnaire
FHCRC	Fred Hutchinson Cancer Research Center
GCA	Gastric cardia adenocarcinoma
GE	Gastroesophageal
GERD	Gastroesophageal reflux disease
H. Pylori	Helicobacter Pylori
HR	Hazard ratio
ICR	Interaction contrast ratio
IGF-I	Insulin-like growth factor-I
KPNC	Kaiser Permanente Northern California
LA	Los Angeles
LSBE	Long-segment Barrett's esophagus
NHANES	National Health and Nutrition Examination Survey
NIH-AARP	National Institutes of Health-American Association for Retired Persons

NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
PH	Proportional hazards
RDD	Random digit dialing
SEER	Surveillance Epidemiology and End Results
SES	Socioeconomic status
SD	Standard deviation
SSBE	Short-segment Barrett's esophagus
US	United States
USDA	United States Department of Agriculture
Σ	Summation

CHAPTER 1: BACKGROUND

Introduction

The incidence of esophageal and gastric cardia adenocarcinoma (EA/GCA) has been increasing in many Westernized countries since 1970s.[1-5] Prognosis remains poor, with a 5-year survival of less than 20%.[6, 7] The only known potential precursor lesion of esophageal adenocarcinoma is Barrett's esophagus (BE), which has also been increasing.[8-12] Given the rapid increase in incidence and the sustained poor survival, instead of focusing on reducing the risk of developing invasive cancer alone, identification of key windows of susceptibility along the entire cancer continuum (normal tissue → precancerous condition → invasive cancer → mortality) could potentially be more fruitful. This approach may identify optimal times that could be targeted for intervention with specific risk reduction strategies.

Thus, this dissertation aimed to determine the role of dietary sugar/carbohydrate intake along the cancer development and progression continuum by examining whether dietary sugar/carbohydrate intake increases the risk of developing BE, the risk of developing esophageal and gastric cardia adenocarcinoma, or the risk of dying once diagnosed with these deadly tumors.

Sugar/sweetener intake (per capita) is much higher in Western populations than Asian populations,[13] which corresponds to the global distribution of EA/GCA - higher incidence of EA/GCA in Western countries compared to developing countries (**Figure 1.1**).[14, 15] Intake of caloric sweeteners has increased dramatically since 1960s,[16] which corresponds to the rapid increase in the EA/GCA incidence in the past few decades. The hypothesis of this study was

that sugar/carbohydrate intake is associated with increased risk of developing esophageal and gastric cardia adenocarcinoma. The potential underlying mechanism is that long-term consumption of a high-sugar/carbohydrate diet may lead to chronic hyperglycemia and hyperinsulinemia, and the elevated levels of insulin and insulin-like growth factor 1 (IGF-I) may promote carcinogenesis by stimulating cell proliferation and inhibiting apoptosis.[17-20] Therefore excess dietary intake of sugar/carbohydrate may play a role in the etiology of BE-EA/GCA cancer continuum outcomes.

Specific aims of this study included the following. Aim 1: Determine if sugar/carbohydrate intake is associated with the development of Barrett's esophagus (with aim 1A: Explore whether overweight/obesity [measured by body mass index] or gastroesophageal reflux disease [GERD] are effect measure modifications [EMMs] of the significant associations between sugar/carbohydrate intake and risk of developing BE). Aim 2: Determine if sugar/carbohydrate intake is associated with the development of EA/GCA (with aim 2A: Explore whether overweight/obesity [measured by body mass index] or GERD are EMMs of the significant associations between sugar/carbohydrate intake and risk of developing EA/GCA). Aim 3: Determine if sugar/carbohydrate intake is associated with survival following a diagnosis of EA/GCA. The study is significant because the increasing incidence and poor prognosis of EA/GCA underscore the importance of identifying modifiable risk factors and relevant risk reduction strategies. However, the currently well-established risk factors, GERD, obesity, and smoking, may be difficult to modify: weight loss and smoking cessation are difficult to achieve or maintain;[21, 22] and GERD is a chronic disease that usually requires continued therapy to prevent relapse.[23] Because dietary sugar intake is a modifiable factor, there might be potential to reduce the disease burden by limiting sugar intake. The study is innovative because the entire cancer continuum from BE, invasive cancer by subtype, to mortality, was considered. If we find that sugar/carbohydrate, or a specific type of sugar, are associated with risk of BE, or

incidence/mortality of EA/GCA, there is potential to reduce the disease burden of these lethal cancers by implementing a risk reduction strategy of limiting dietary sugar/carbohydrate intake.

Esophageal and Gastric Cancer

Esophageal Cancer: Squamous Cell Carcinoma vs. Adenocarcinoma

Esophageal cancer was the eighth most common cancer worldwide with 456,000 new cases estimated in 2012 (most recently published), and also was the sixth most common cause of death from cancer with an estimated 400,000 deaths in 2012.[24] Esophageal cancer is a lethal cancer with a very poor prognosis, and the overall ratio of mortality to incidence was 0.88.[24] As a result, the geographical distribution pattern for esophageal cancer mortality closely follows the pattern for esophageal cancer incidence.[24] The major histological types of esophageal cancer include esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma, with other sub-types occurring only very rarely.[1, 25] ESCCs generally occur in the upper or middle third of the esophagus, whereas EAs occur in the lower third of the esophagus or at the gastroesophageal junction.[26] ESCC is the predominant histological type of esophageal cancer worldwide.[1, 25] ESCC mainly occurs in less-developed regions such as Eastern Asia, Southern Africa, and Eastern Africa, whereas EA predominantly occurs in more-developed regions such as the United States (US) and many Western countries.[1] Although the global incidence of esophageal squamous cell carcinoma has slightly decreased in the past four decades, the incidence of esophageal adenocarcinoma has been increasing rapidly in the US and some Western countries.[1-5] As a result, adenocarcinoma has slowly replaced squamous cell carcinoma as the most common type of esophageal cancer in the US and many Western countries.[3, 27-29]

Gastric Cancer: Cardia vs. Non-Cardia

Gastric cancer was the fifth most common cancer worldwide with almost one million new cases estimated in 2012, and also was the third most common cause of death from cancer with an estimated 723,000 deaths in 2012.[24] The vast majority of gastric cancers are adenocarcinomas.[30] Because the differences between gastric cardia and non-cardia cancer were once not evident, not until the 8th revision of the International Classification of Diseases (1968) that cancer of the gastric cardia was coded separately from other gastric cancers.[31] Based on the new classification, gastric cancers are usually anatomically classified as noncardia and cardia cancers.[1] Gastric cardia cancer occurs in the proximal portion of the stomach next to or at the gastroesophageal junction, whereas the gastric non-cardia cancer occurs at the distal portion of the stomach.[32] Non-cardia cancers constitute the majority of gastric cancer cases worldwide.[1] Gastric cardia and non-cardia cancers are epidemiologically distinct: the incidence of non-cardia gastric cancer has remarkably decreased in the past 50 years particularly in developed countries,[33-36] whereas the incidence of gastric cardia cancer increased rapidly in the US and many Western countries in the past four decades.[26, 33, 37-39]

Summary. Cancers of esophageal and gastric are among the most common causes of cancer morbidity and mortality worldwide.[24] Among different sub-types of esophageal and gastric cancers, esophageal adenocarcinoma and gastric cardia adenocarcinoma are most similar in incidence trends and global distributions.[26, 33, 37-39] The increasing incidence and poor survival of esophageal and gastric cardia adenocarcinoma calls for identification of modifiable risk factors for these cancers so that relevant risk reduction strategies could be implemented.

Esophageal and Gastric Cardia Adenocarcinoma

Esophageal and Gastric Cardia Adenocarcinoma Incidence and Survival

Esophageal and gastric cardia adenocarcinoma were once rare, however, a rapid increase in the incidence for esophageal and gastric cardia adenocarcinoma was reported

during the past four decades from many population-based cancer registries, including United States, New Zealand, the United Kingdom, Norway, Denmark, Finland, and some other Western countries.[3, 25, 26, 37, 40-43] As a result of the dramatic increase, EA/GCA was among the most rapidly increasing cancer types in the US and some Western countries.[14, 44]

In the United States, according to the analysis based on data collected from Surveillance Epidemiology and End Results (SEER) 9 regions, the overall incidence of adenocarcinoma of the esophagus and the gastric cardia increased from 13.4 per million in 1973 to 51.4 per million in 2009, with a nearly 400 % increase.[45] The incidence continued to increase in early twenty-first centuries, although the increase somewhat slowed down during 1987-2009 compared to the increase during 1973-1987.[45]

Stratified by anatomic sites, the incidence of GCA increased rapidly since 1973, from 9.5 per million to >20 per million in late 1980s, with an annual increase of 5.2%.[45] However, the incidence seems to have reached a plateau in late 1980s, and the incidence remained more or less stable from 1987 to 2009.[45] In contrast, the incidence of EA kept increasing from 3.9 per million in 1973 to 28.9 per million in 2009, surpassing the incidence of GCA in 1996.[45]

Stratified by race and sex, the most prominent increase in the incidence of EA was observed among white men, with a yearly increase in incidence of 2.3 per million reaching 107.3 per million in 2009.[45] A smaller yearly increase was observed in white women (0.7 per million before 1988 to 0.4 per million after 1988).[45] In contrast to the continuous rise among both white men and women, the incidence remained stable or even declined in non-white men and women.[45] The incidence of EA in non-white men increased before 1992, and has been slightly decreasing since 1992, reached 30 per million in 2009.[45] EA incidence in non-white females remained relatively constant between 7 and 17 per million.[45]

Stratified by stage, esophageal and gastric cardia adenocarcinoma at all of the stages continued to rise between 1973 and 2009, except for non-invasive cancer (in situ carcinoma, makes up no more than 2.5% of the all EA/GCA cancers), which decreased with a yearly

decrease of 0.22 per million since 2003 and reached 0.25 per million in 2009.[45] Yearly increase of incidence of localized disease slowed down after 1999, and the incidence was approximately 13 per million in 2009.[45] Similarly, the increase in regional disease slowed down after 1985, and the incidence was slightly over 13 per million in 2009.[45] In contrast, the incidence of metastatic disease, which makes up 38% of all EA/GCA cancers, has been increasing constantly and was slightly over 20 per million in 2009.[45]

According to SEER9 data collected from 1975 to 2009, EA mortality has been rapidly increasing, from around 4 per million in 1977 to 23 per million in 2009.[46] The mortality trends followed a similar pattern to that of EA incidence - a rapid increase since late 1970s followed by a less rapid increase since mid-1990s.[46] Noticeably, different from the overall pattern, mortality and incidence of localized disease have diverged beginning in the late 1990s due to the fact that the mortality increased less rapidly then incidence, possibly due to the great improvement in the 5-year relative survival in people diagnosed with localized disease.[46] The 5-year relative survival was around 2.1% in patients diagnosed with localized disease in 1975, compared to a rate of >50% in all patients diagnosed with localized EA in 2004.[46] Although the 5-year relative survival in patients diagnosed with regional and distant stage has also been improving since 1975, the 5-year survival remains low.[46] The 5-year relative survival were 20% and 2.8%, respectively, in patients diagnosed with regional staged and distant staged EA in 2004.[46] EA and GCA were shown to have little survival difference.[47, 48] It is noteworthy that because early-stage esophageal and gastric cardia adenocarcinomas are often asymptomatic, most of the patients were diagnosed at a late stage.[45, 46, 49] The local staged EA/GCA makes up 20-30% of all diagnosed cases, whereas the distant staged EA/GCA makes up approximately 40% of all EA/GCA cases.[45, 46, 49] As a result, the 5-year relative survival rate for all patients diagnosed with different stages remains less than 20%.[6, 7] Median survival times in local, regional, and distant esophageal and gastric cancers were 11, 10, and 4 months respectively in the 1970s, and 35, 15, and 6 months respectively after 2000.[49]

Summary. The incidence of EA/GCA has been increasing since 1970s, although at a slightly slower rate in recent years.[45] The mortality trends followed a similar pattern to the incidence trends.[46] Although the survival of EA/GCA has been improved in the past few decades, the 5-year relative survival remains lower than 20%.[6, 7] Given the continuing increase in incidence and persistent poor prognosis, identification of potentially modifiable risk factors may help to develop and/or refine relevant risk reduction strategies.

Esophageal and Gastric Cardia Adenocarcinoma Risk Factors and Risk Reduction Factors

Esophageal adenocarcinoma and gastric cardia adenocarcinoma are often considered as one clinical entity because they occur contiguously at or near the gastroesophageal (GE) junction and have comparable 5-year survival rates.[47] In addition, esophageal and gastric cardia adenocarcinomas share many risk factors, as presented in the sections below.

Medical Conditions. GERD and Barrett's esophagus are two well-established risk factors for esophageal and gastric cardia adenocarcinoma.[50-55] Barrett's esophagus is a precursor lesion of EA, and usually arises from GERD.[52, 55, 56] GERD not only increases the risk of EA/GCA by increasing the risk of BE development, but appears to increase the risk of EA/GCA in the absence of BE as well.[54, 57] Diabetes mellitus (DM), has also been evaluated as a risk factor for EA/GCA.[58-63]

Gastroesophageal Reflux Disease. GERD develops when the lower esophageal sphincter allows gastric acid and other gastric contents to flow back into the esophagus and subsequently causes troublesome symptoms or complications.[64] GERD is common in Western populations, with highest prevalence in the US.[65] The prevalence of at least weekly GERD symptoms in the US is approximately 20%.[65] In the pooled analysis of five studies from the international Barrett's and Esophageal Adenocarcinoma Consortium (BEACON), both frequency and duration of heartburn/regurgitation symptoms were found to be independently associated

with increased risk of EA and esophagogastric junction adenocarcinoma.[66] Recurrent symptoms of heartburn/regurgitation was reported to be associated with an increased risk of EA (OR and 95%CI: 4.81 [3.39−6.82]).[66] The study also suggested that the risk of EA increased with the increase of the frequency of regurgitation/heartburn (ORs and 95%CIs were 7.96 [4.51-14.04], 5.07[3.07-8.38], and 2.08[1.14-3.79] for >daily, >weekly to daily, and ≤weekly, respectively, all compared with those had never experienced symptoms).[66] It was suggested that risk of EA also increased with increased duration of heartburn/regurgitation symptoms (ORs and 95%CIs were 2.80[1.60-4.91], 3.85[2.93-5.07], and 6.24[3.37-11.55] for symptom durations of <10 years, 10 to <20 years, and ≥20 years, respectively).[66] Frequency and duration of heartburn/regurgitation symptoms were also found to be positively associated with increased risk of esophagogastric junction adenocarcinoma, although the associations were slightly weaker.[66] A meta-analysis reported that GERD symptoms were associated with elevated risk of EA (pooled ORs and 95%CIs were 4.92[3.90-6.22] and 7.40[4.94-11.1], for at least weekly symptoms and daily symptoms, respectively).[50] Another study examined the association between GERD and EA/GCA also suggested that the risk of EA/GCA increased with the frequency, severity, and duration of symptomatic GERD.[54] Consistent with the pooled analysis, the association between GERD and EA was found to be stronger than that between GERD and GCA.[54]

One hypothesized mechanism for the GERD-EA/GCA association is that the acid reflux injures the esophageal epithelium and subsequently results in inflammation and cell proliferation.[67] Another potential mechanism is that acid reflux causes the production of nitrous oxide, which results in elevated levels of DNA damage.[68]

Barrett's Esophagus. Barrett's esophagus is a metaplastic change of the lining of the esophagus, and it is characterized by the replacement of the normal squamous epithelium by specialized or intestinalized columnar epithelium.[69] BE is the precursor lesion of EA, and is associated with an increased risk of EA.[70-73] Earlier studies reported that the incidence rate of adenocarcinoma was around 5-10 cases per 1000 person-years among patients with BE.[70-72] In

addition, the risk of EA in patients with BE was estimated to be approximately 30-500 times of the risk in the general population.[73] A recent large cohort study conducted within the entire Danish population studies reported a lower incidence rate and lower risk ratio.[74] The annual risk of esophageal adenocarcinoma was found to be 1.2 cases per 1000 person-years (95%CI, 0.9-1.5) among patients with BE.[74] The risk ratio of adenocarcinoma among patients with BE was reported to be 11.3 (95%CI, 8.8-14.4), compared with the risk in the general population.[74] Although the earlier studies might have overestimated the incidence rates and risk ratio due to the smaller sample size, both earlier and recent studies suggested that BE increases the risk of EA.[71, 75]

As the adenocarcinoma arises through a progressive sequence (from metaplasia to low-grade dysplasia, to high-grade dysplasia, to adenocarcinoma), risk of developing adenocarcinoma is associated with the histologic grade of the dysplasia in BE.[76] In the Danish study, the incidence rate among patients with low-grade dysplasia (LGD) was 5.1 cases per 1000 person-years, compared to 1.0 case per 1000 person-years among patients without dysplasia.[74] In a Dutch population-based study, the EA incidence rate among patients with high-grade dysplasia (HGD) was reported to be 42 cases per 1000 person-years.[77] Another characteristic of BE that is associated with the risk of developing adenocarcinoma is the length of BE segment.[78-80] In a large cohort study of patients with non-dysplastic BE, the length of BE was longer in patients who progressed to HGD or EA compared to those who did not progress.[80] It was also estimated that 1 cm increase in the length of BE was associated with 28% increased risk of progression.[80] They also found that it took patients with a BE length of ≤3 cm longer to progress to HGD or EA compared to patients with a BE length of >4 cm (6 years versus 4 years).[80] Another population-based study conducted in Northern Ireland found that BE patients with a long-segment BE (LSBE, defined as ≥3 cm) have an increased risk of progressing to high-grade dysplasia or EA.[79]

Diabetes Mellitus. A few studies have investigated the association between DM and esophageal cancer, however, not all have distinguished EA from ESCC.[61, 63] The results from these studies are inconsistent. Most of the case-control studies suggested a positive association between DM and EA,[58-62] whereas the only prospective study (HR and 95%CI, 0.98 [0.73-1.31]) and one case-control study (OR and 95%CI, 1.1 [0.8-1.5]) suggested little or no association.[63, 81] The results from studies that investigated the DM-GCA associations also yield inconsistent results.[61, 63] The prospective study suggested a positive association,[63] whereas a large case-control study suggested no association.[61] In the prospective study, DM was associated with risk of GCA even when restricted to only overweight subjects (HR and 95%CI, 1.83 [1.18-2.85]).[63] Further prospective studies are needed to investigate the association between DM, EA, and GCA.

Demographic Factors. Several demographic factors, including age, sex, race/ethnicity, were found to be associated with risk of EA/GCA.[82-85] Some studies also suggest an association between socioeconomic status (SES) and risk of EA/GCA.[86-89]

Age, Sex, Race/Ethnicity. Consistent with other cancers, risk of developing EA/GCA increases with increasing age.[82, 83] Based on SEER data, the EA/GCA incidence was low among younger people, and then increases rapidly starting at around 45 years old of age, until 75-79 and 80-84 years of age for EA and GCA, respectively, then starts to decline in the older age groups.[82] Men are associated with a higher risk of EA/GCA compared to women.[82, 84, 85] Non-Hispanic whites are associated with a higher risk compared to non-Hispanic blacks, Hispanics, Asians, and other races/ethnicities.[82, 84, 85] Based on SEER data, between 1977 and 1996, the age-adjusted incidence of EA was six to eight times higher in men than in women, and three to four times higher in whites than in blacks.[82] Compared with EA, the sex and race/ethnicity discrepancy was less pronounced in GCA incidence.[82] The age-adjusted

incidence of GCA was three to five times higher in men than in women, and no more than twice higher in whites than in blacks.[82]

Socioeconomic Status. Several studies suggested that low income and low education were associated with an increased risk of EA/GCA.[86-89] In the US Multi-Center Study, comparing study subjects with an income of ≥ $75,000 to those with an income of <$15,000 per year, the odds ratios (ORs) and 95% confidence intervals (CIs) were 0.5 (0.3-1.0) and 0.8 (0.4-1.6) for EA and GCA, respectively.[89] Comparing study subjects who completed graduate school to those with less than high school education, the ORs and 95%CIs were 0.7 (0.3-1.3) and 0.8 (0.4-1.6) for EA and GCA, respectively.[89]

Epidemiologic Factors. Obesity and cigarette smoking are two well-established epidemiologic factors for EA/GCA.[51, 89-92] Alcohol has been evaluated as a risk factor, but most studies suggested no association between alcohol and EA/GCA.[93] Dietary fat has also been evaluated as a risk factor, but the results were inconsistent.[94-96]

Obesity. Elevated body mass index (BMI, defined as weight in kilograms/height in meters squared) has consistently been shown to be associated with an increased risk of EA/GCA.[51, 90-92] In a pooled analysis of BEACON studies, the risk of EA was found to increase with increasing BMI (ORs and 95%CIs were 1.54 [1.26–1.88], 2.39[1.86–3.06], 2.79[1.89–4.12] and 4.76[2.96–7.66] for BMI of 25.0-29.9, 30.0-34.9, 35.0-39.9, and ≥40.0, respectively, all compared with those with a BMI of <25.0).[92] Similarly, the risk of esophagogastric junction adenocarcinoma also increases with increasing BMI (ORs and 95%CIs were and 1.28[1.13–1.45], 2.08[1.75–2.47], 2.36[1.75–3.17], and 3.07[1.89–4.99] for BMI of 25.0-29.9, 30.0-34.9, 35.0-39.9, and ≥40.0, respectively, all compared with those with a BMI of <25.0).[92]

Recent studies have focused more on body fat distribution and have reported that increased central adiposity (measured by waist circumference, waist-to-hip ratio, etc.) were strongly associated with increased BE/EA/GCA risk, after adjusting for BMI.[97-100] The large prospective cohort study - National Institutes of Health-American Association for Retired

Persons (NIH-AARP) Diet and Health Study suggested that waist circumference was positively associated with both EA (hazard ratios [HRs] and 95%CIs: Q_{4th} vs. Q_{1st}, 2.01[1.35-3.00]; Q_{3rd} vs. Q_{1st}, 1.51[1.02–2.25]; Q_{2nd} vs. Q_{1st}, 1.36[0.89–2.09]) and GCA risk (HRs and 95%CIs: Q_{4th} vs. Q_{1st}, 2.22[1.43-3.47]; Q_{3rd} vs. Q_{1st}, 1.29[0.82–2.04]; Q_{2nd} vs. Q_{1st}, 1.32 [0.82–2.14]).[101] It was also suggested in this study that the waist-to-hip ratio was positively associated with both EA and GCA risk (HRs and 95%CIs: highest vs. referent, 1.81 [1.24 - 2.64] and 1.37 [0.92–2.05], respectively).[101] Abdominal obesity was found to be associated with increased risk of EA even in patients with normal BMI (18.5-<25 kg/m^2).[101] Abdominal obesity may increase intra-abdominal pressure and subsequently relax the lower esophageal sphincter, which may promote GERD and increase the risk of EA/GCA.[92] However, this may only partly explain the mechanism since a pooled analysis of BEACON studies suggested that obesity was associated with increased risk of EA in absence of GERD.[92] Another potential mechanism could be that abdominal obesity may lead to insulin resistance and chronic inflammation, which may increase the risk of EA/GCA.[102]

Although obesity was found to be associated with risk of EA/GCA and the rapid increase in obesity in the general population is in parallel to the increasing EA/GCA incidence, studies suggested that the rise in EA incidence was prior to the rise in obesity and the rise in obesity cannot fully explain the rise in EA/GCA incidence.[103, 104]

Cigarette Smoking. Studies have consistently found an association between cigarette smoking and increased EA/GCA risk.[87, 89, 105-107] In a pooled analysis of cigarette smoking from twelve BEACON studies, the risk of adenocarcinomas among ever smokers was approximately two times the risk of adenocarcinomas among never smokers (summary ORs were 1.96 [1.64 - 2.34] and 2.18 [1.84-2.58], for EA and gastroesophageal junction adenocarcinoma, respectively).[108] In addition, the results suggested a trend of increasing risk of EA with increased pack-years smoked (ORs and 95%CIs were 1.25 [1.02-1.53], 1.96 [1.58-2.45], 2.07 [1.66-2.58], and 2.71 [2.16-3.40] for pack-years of smoking <15, 15-<30, 30-<45, and ≥45, respectively, all

compared with non-smokers).[108] A similar trend was suggested for GE junction adenocarcinoma, with the corresponding ORs (95%CIs) of 1.32 (0.99-1.75), 2.44 (1.98-3.00), 2.64 (2.07-3.38), and 2.68 (2.23-3.23), respectively.[108] Cigarette smoking has also been reported to increase the risk of progression from BE to EA/GCA or high-grade dysplasia (HR with 95%CI was 2.03 [1.29-3.17], current smoker vs. never smoker).[109]

Alcohol. Alcohol has been evaluated as a risk factor in previous studies. Most studies suggested no association between alcohol consumption and EA.[93] Several studies reported an increased risk of EA/GCA among alcohol drinkers,[110-112] whereas a slight decrease of EA/GCA risk among wine drinkers and drinkers with moderate alcohol intake was found in some studies.[52, 113] A pooled analysis from the BEACON consortium found that there was little or no strong evidence that heavy alcohol consumption was associated with increased risk of esophageal adenocarcinoma or adjacent adenocarcinomas of the esophagogastric junction (ORs and 95%CIs for the highest frequency category [≥7 drinks/day] were 0.97 [0.68-1.36] and 0.77 [0.54-1.10], respectively, for EA and adjacent adenocarcinomas of the esophagogastric junction, all compared to non-drinkers).[52, 113] Additional studies are needed to further elucidate the association between alcohol consumption and EA/GCA.

Dietary Fat. Dietary fat has been evaluated as a risk factor in previous studies, and the results were inconsistent.[94-96] Some studies have not shown an association between dietary fat and EA whereas others suggested a positive association.[94-96] However, it is possible that some important associations were masked due to the fact that most studies had not differentiated the various types of fatty acid.[94] For instance, omega-3 and omega-6 are different types of polyunsaturated fatty acids.[114-116] Omega-3 fatty acids may decrease cancer risk whereas omega-6 fatty acids may increase the risk.[114-116] The large prospective cohort study, NIH-AARP study, has comprehensively investigated fat intake by various types, however, little or no association was found between dietary fat, regardless of the definitions used, and EA/GCA.[95] More studies are needed to examine the association between various types of fat and EA/GCA.

Risk Reduction Factors. Fruits and vegetables are well-established risk reduction factors for EA/GCA.[117-121] Other dietary factors, such as fiber intake[122], dietary antioxidants (including vitamin C, vitamin E, β-carotene)[94, 123-127], and folate[94, 126, 127] have also been suggested to be risk reduction factors for EA/GCA. Non-steroidal anti-inflammatory drugs use is also established risk reduction factor for EA/GCA.[128-130] *Helicobacter Pylori* infection has been evaluated as a risk factor in several studies, and perhaps, it is a risk reduction factor.[131-134]

Dietary Intake.

*Fruits and Vegetables***.** Studies suggested that fruit and vegetable intake were inversely associated with EA and GCA.[117-121, 135] A recent meta-analysis reported an EA risk reduction of 32% (summary RR and 95%CI, 0.68 [0.49-0.93]) at higher level of intake.[121] The risk reduction remained when examining fruit and vegetables separately.[121]

*Fiber***.** The highest level of total fiber intake was associated with a 34% decreased EA risk (summary OR and 95%CI 0.66[0.44-0.98]), as suggested in a recent meta-analysis.[122]

*Dietary Antioxidants***.** Studies suggested that dietary antioxidants, including β-carotene, vitamin C, and vitamin E, were associated with reduced risk of EA/GCA.[94, 123-127, 135] A meta-analysis has reported a 54% reduction in EA risk with higher intake of β-carotene (summary OR and 95%CI, 0.46 [0.36-0.58]).[124] Higher intake of vitamin C was also suggested to be associated with a 35% reduction in risk of EA/GCA in a meta-analysis (summary OR and 95%CI, 0.65 [0.54-0.78].[123] As summarized in a recent qualitative review, vitamin E was found to be inversely associated with EA risk reductions ranging from 10-87% in case-control studies.[135]

Folate. Studies reported that higher dietary folate intake was associated with an approximately 30-50% decreased EA risk.[94, 126, 127, 135]

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Use. In a pooled analysis of NSAIDs use from BEACON studies, risks were reduced for the association between NSAID use and EA (OR and 95%CI, 0.68[0.56-0.83]) and esophagogastric junctional adenocarcinoma (OR and 95%CI, 0.83[0.66-1.03]).[128] The reductions in risk were similar when examining the effect of

aspirin and non-aspirin NSAIDs intake respectively.[128] The highest level of frequency (daily or more frequently) and the second highest level of frequency (occasionally-<daily) of NSAIDs use were associated with 44% and 34% reduction in risk of EA, respectively (ORs and 95%CIs were 0.56 [0.43-0.73] and 0.66[0.44-1.00]).[128] A meta-analysis also suggested that aspirin was associated with reduced risk of EA (OR and 95%CI, 0.64[0.52-0.79]) and GCA (OR and 95%CI, 0.82 [0.65-1.04]).[130] Similarly, non-aspirin NSAIDs were also associated with reduced risk of EA (OR and 95%CI, 0.65[0.50-0.85]) and GCA (OR and 95%CI, 0.80[0.67-0.95]).[130] NSAID use has also been reported to reduce the risk of progression from BE to adenocarcinoma in a prospective study (HR and 95%CI, 0.32[0.14-0.76]).[129]

Helicobacter Pylori (*H. pylori*) Infection. *H. pylori* is a bacterium that colonizes the human stomach, and is a major cause of non-cardia gastric cancer.[32, 136] Several studies have reported that *H. pylori* infection was associated with reduced risk of EA/GCA.[131-134] In an Australian, population-based study, *H. pylori* infection was inversely associated with risks of EA (OR and 95%CI, 0.45[0.30-0.67]) and esophagogastric junctional adenocarcinoma (OR and 95%CI, 0.41[0.27-0.60]).[132] If *H. pylori* infection is indeed a risk reduction factor for EA, then the increase in EA incidence in Western population may, perhaps, be partly explained by the decline in rate of *H. pylori* infection.[137] The potential underlying mechanisms might be: (1) *H. pylori* may decrease risk of acid reflux by reducing acid production in the stomach;[138] and/or (2) *H. pylori* may reduce EA risk by decreasing the production of the hormone ghrelin, which may in turn lead to lower rates of obesity.[51, 139]

Summary. Risk factors for EA/GCA include GERD[66], Barrett's esophagus[70-73], obesity[51, 89-92], cigarette smoking[87, 89, 105-107], and some demographic factors (age, sex, race/ethnicity, and SES) [82, 85-89]. Risk reduction factors include fruits and vegetables[117-121], dietary fiber[122], dietary antioxidants (including vitamin C, vitamin E, β-carotene) and folate[94, 123-127], NSAIDs use,[128-130] and, perhaps, *H. pylori* infection.[131-134] These factors were important to consider when

examining the association between sugar/carbohydrate and development of EA/GCA since they are potential confounders, mediators, or effect measure modifiers.

Esophageal and Gastric Cardia Adenocarcinoma Prognostic Factors

Many factors (e.g. demographics, clinical characteristics, epidemiologic factors) have been explored as prognostic factors for EA/GCA, and a few were found to be predictors of prognosis.[140-146] However, most factors are still understudied and more studies are needed to elucidate or confirm the association, especially with epidemiologic factors.

Demographic Factors. Two previous studies suggested that age, sex, and education were not associated with EA/GCA survival.[140, 142] In a recent US study, sex was also not associated with superficial (T1) esophageal adenocarcinoma survival, however, age was associated with a decrease in overall survival (HR and 95%CI, 1.71 [1.36–2.17], per 10-year increment).[141] Higher household income (≥$15,000) was found to be associated with better EA and GCA survival (HRs and 95%CIs were 0.64 [0.48-0.87] and 0.62 [0.43-0.88], for EA and GCA, respectively, both compared to <$15,000 income).[140]

Clinical Characteristics. Tumor site has been suggested to be associated with long-term survival.[142] Cancer in the esophagus has a better prognosis than in cardia, possibly due to earlier detection resulted from post-BE surveillance and earlier presentation of dysphagia in cancers of esophagus.[142] Stage was found to be a predictor of prognosis in several studies,[140, 142] regardless of the staging systems used. In the US Multi-Center Study, compared with distant stage, patients diagnosed at regionalized, localized, or unknown stage have a better survival (the corresponding HRs and 95%CIs were 0.32 [0.23-0.45], 0.22 [0.15-0.31], and 0.42 [0.30-0.60] for EA and 0.48 [0.35-0.65], 0.18 [0.11-0.31], and 0.54 [0.35-0.83] for GCA.[140] Tumor grade was not associated with overall survival in EA and GCA.[140, 141]

Presence of lymphovascular invasion was found to be associated with reduced overall survival in patients with T1 EA.[141, 143] In a recent US study, an HR of 1.95 was reported (95%CI,

1.18–3.22) for overall mortality in patients with T1 EA.[141] Leggett et al. reported that deep margin involvement by carcinoma was associated with reduced overall survival in patients with T1 EA (HR and 95%CI, 1.67[1.09–2.55]).[141] In a prospective study, Dexter et al. found that the presence of tumor cells within 1 mm of the circumferential margin was an independent prognostic factor for survival.[144]

Medical Conditions/Treatment Several studies have found that patients with BE appeared to have a better survival compared to those without BE.[147-149] It was also suggested in several studies that tumors without BE may not be of a different origin, but were larger tumors that may have overgrown areas of BE.[150-152] Therefore, the better prognosis among patients with a prior diagnosis of BE is likely due to the fact that tumors with BE were detected earlier and have a smaller diameter.[142]

Gastroesophageal reflux disease may be associated with EA and GCA survival (unadjusted HRs and 95%CIs were 0.80 [0.63-1.03] and 0.74 [0.56-0.98] for EA and GCA, respectively, both compared to those without GERD).[140] More studies are needed to further elucidate the association. In addition, the presence of dysphagia at diagnosis was associated with an advanced disease and worse prognosis.[142]

Another important prognostic factor is treatment. Analysis based on SEER data suggested that patients who received esophagectomy had longer overall survival than those without esophagectomy.[145] In another population-based study, patients who received chemoradiation had a better survival among both patients treated with surgery (HR and 95%CI, 0.56 [0.35-0.89]) and patients treated without surgery (HR and 95%CI, 0.62 [0.43-0.92]).[146]

Epidemiologic Factors. In the US Multi-Center Study, cigarette consumption, alcohol use, and NSAIDs use were found to be not associated with EA and GCA survival.[140] Overweight individuals (BMI 25-29.9 kg/m^2) appeared to have better overall survival compared to individuals who were normal weight (BMI <25 kg/m^2) or obese (BMI ≥30 kg/m^2).[140] BMI appeared to be possibly associated with EA survival (the HRs and 95%CIs were 0.78 [0.55-1.12] and 0.67

[0.51-0.88], for obese and overweight, respectively, both compared to those who were normal weight) but not GCA survival (the unadjusted HRs and 95%CIs were 0.98 [0.67-1.43] and 0.90 [0.67-1.20], for obese and overweight, respectively, both compared to normal weight participants).[140] Weight loss is another important prognostic factor. Several studies have suggested that weight loss was associated with advanced disease and worse prognoses.[142, 153-155]

Summary. Income[140], BE[147-149], presence of dysphagia[140, 142], BMI[140], weight loss[142, 153-155], tumor location (tubular esophagus)[142], stage[140, 142], presence of lymphovascular invasion[141], surgical margin involvement by carcinoma[141], and treatment[145], are likely to be prognostic factors of EA/GCA survival. These factors were important to consider when examining the association between sugar/carbohydrate and EA/GCA survival since they are potential confounders, mediators, or effect measure modifiers. If sugar/carbohydrate intake is found to increase the risk of mortality after EA/GCA diagnosis, we would be able to improve EA/GCA survival by limiting sugar/carbohydrate intake.

Sugar/Carbohydrate and Esophageal/Gastric Cardia Adenocarcinoma: Potential Biologic Mechanisms

The three main types of carbohydrate are starch, fiber, and sugar.[156] Based on chemical structure, starch and fiber are complex carbohydrate, whereas sugar is simple carbohydrate.[156] Starch is digestible carbohydrate, and foods high in starch include grains (wheat, rice, oats, barley, etc.), starchy vegetables (potatoes, taro root, etc.), and legumes (beans, peas, etc.).[156] Fiber is indigestible carbohydrate, and foods high in fiber include vegetables, fruits, whole grains, legumes, and nuts. Sugar includes naturally occurring sugar (e.g., sucrose, fructose, and glucose in fruits and vegetables, lactose in milk, etc.) and sugar added during food processing and preparation (table sugar, syrup, molasses, honey, etc.).[156]

Sugar/Carbohydrate and EA/GCA Development. Frequent over-consumption of high-sugar/carbohydrate food may lead to hyperglycemia and hyperinsulinemia. Chronically elevated levels of insulin reduces the production of IGF binding proteins, which normally bind to IGF-I and inhibit its action, and consequently result in elevated circulating concentration of bioactive IGF-I.[17-19] Several cellular actions of IGF-I support tumor growth, including mitogenic action, inhibition of apoptosis, induction of vascular endothelial growth factor, and promoting tumor cell migration.[17, 19, 20] In addition, postprandial hyperglycemia (especially acute glucose fluctuations) may increase oxidative stress and subsequently promote carcinogenesis.[157-160] The potential biological mechanism between sugar/carbohydrate consumption and EA/GCA development is illustrated in **Figure 1.2**.

Human studies suggested associations between blood glucose/insulin resistance and development of esophageal cancer.[161, 162] A large prospective cohort study in Korean reported that men with a fasting serum glucose level 110-125 mg/dL had increased risk of esophageal cancer after controlling for multiple confounders (HR and 95%CI, 1.37 [1.20-1.80], compared to men with a fasting serum glucose level <90 mg/dL).[161] A US study of patients with BE has reported that homeostatic model assessment scores (a measure of insulin sensitivity) were significantly associated with increased risk of EA 3 years and 6 years after entering the study, and full follow-up (HRs and 95%CIs, 2.45 [1.43–4.19], 2.06 [1.30–3.25] and 1.64 [1.08–2.48], respectively).[162]

Obesity is a known risk factor for EA, and one of the potential mechanisms is that obesity promotes carcinogenesis by inducing insulin resistance.[102] However, a large population-based case-control study in UK found that type 2 diabetes mellitus (T2DM) was associated with increased BE, after controlling for obesity (as measured by BMI) and other risk factors (smoking and GERD) (OR and 95%CI, 1.49 [1.16-1.91]).[163] The study suggested that obesity may not necessarily mediate the association between sugar/carbohydrate intake and BE-EA cancer

continuum. However, it was not a formal test of mediation, and therefore the results need to be interpreted cautiously.

Foods with carbohydrate increase postprandial blood glucose level and insulin secretion at different rates, depending on the chemical structure of the carbohydrate, presence of fiber and other nutrients, and the food processing method. For instance, fiber has the ability to alter the glycemic response by slowing digestion and absorption of carbohydrates.[164] Starch, which contains a large number of monosaccharide molecules, takes longer to break down and digest, and therefore enters the bloodstream slowly and causes a flattened blood glucose rise.[156] Sugar that is naturally found in whole food, is a simple carbohydrate with one or two molecules, usually comes with vitamins, minerals, protein, and fiber, which may slow down the absorption of sugar and moderate its impact on blood glucose. In contrast, added sugar, which is added during food processing and preparation, can be quickly digested and absorbed, and thus usually causes a spike in blood glucose and insulin level. Therefore, it is commonly accepted that refined sugars affect glucose metabolism more detrimentally than naturally occurring sugar, starches and fiber.[165] Evidence from studies of both humans and animals suggested that the high intake of refined sugars had deleterious effects on glucose metabolism.[165] For example, the quick absorption of a large amount of refined sugar may lead to acute glucose fluctuations, which may increase the oxidative stress and thereby promoting carcinogenesis.[159, 160, 166]

Glucose, sucrose, and fructose are common types of sugar that are found naturally in many fruits and vegetables.[156] Sucrose is also found in table sugar, brown sugar, and molasses, all of which are added to foods and drinks during food processing and preparation. Fructose is also often added to beverages and prepared foods in the US in the form of high fructose corn syrups (HFCS).[167] Sucrose is broken down into free glucose and free fructose after consumption.[168] Glucose is the body's preferred energy source, and it stays in the blood stream for cells in the body to use.[168] In contrast, fructose is cleared on its first pass through the liver.[168] Fructose is almost exclusively metabolized in the liver, and has a different metabolic pathway

than glucose.[169, 170] The metabolism of fructose may contribute to metabolic abnormalities by inducing impaired liver functions, generation of reactive oxygen species, reduced copper, and elevated iron.[165] Evidence from biomedical and epidemiologic studies suggested that the high intake of fructose increases the risk of metabolic syndrome.[171] The different metabolisms of glucose, sucrose, and fructose may have different impact on carcinogenesis.

High levels of postprandial glucose and insulin were suggested to be involved in the etiology of several obesity-related cancers, including colorectal cancer, breast cancer, and endometrial cancer.[172-175] In particular, a carbohydrate-rich diet may play a role in the etiology of colon cancer by inducing hyperglycemia and hyperinsulinemia.[172, 173] Sucrose and fructose were suggested to be associated with increased colonic proliferation and aberrant crypt foci in most animal experiments, possibly by interfering with levels of blood glucose/triglycerides (directly or through insulin and others).[176] Epidemiologic studies indicate a suggestive association between sugar/carbohydrate intake and colorectal cancer.[176] A recent meta-analysis suggested that high intake of added sugar was associated with colorectal cancer (pooled RR and 95%CI, 1.25 [1.03-1.50], the highest vs. the lowest added sugar intake).[177] However, the results were subject to presence of high heterogeneity (I^2 = 74%, P < 0.001), and the only cohort study included suggested a non-association.[177] It was also suggested in this study that glycemic index was associated with colorectal cancer (pooled RR and 95%CI, 1.17 [1.00–1.36], the highest vs. the lowest category of dietary glycemic index).[177] This positive association was also subject to presence of heterogeneity (I^2 = 73%, P < 0.001), with the pooled estimate among cohort studies suggesting non-association (pooled RR and 95%CI, 1.01 [0.88–1.16]).[177] These epidemiologic studies suggested that high levels of glucose and insulin might be involved in the etiology of obesity-related cancer, which further supported the potential mechanisms underlying the association between high sugar/carbohydrate consumption and development of EA/GCA.

Sugar/Carbohydrate and EA/GCA Survival. Glucose acts as an energy source for the development of cells.[178] Tumor cells have increased glucose uptake and elevated glycolysis

compared to benign cells of the same tissue.[178] It was suggested that many cancer cells may express insulin receptors (IRs) and show hyperactivation of the IGF-I receptor (IGF-IR) - IR pathway.[178] A clinical study reported that 75% (90 out of 120) of adenocarcinoma specimens displayed overexpression of IGF-IR, and suggested that IGF-IR was associated with reduced overall survival for EA ($p = 0.05$).[179] Chronically elevated levels of blood glucose, insulin, and IGF-I were suggested to worsen the outcome in cancer patients.[178] The Korean study mentioned above suggested that among a cohort of men, who were initially cancer-free at baseline and with a fasting serum glucose level of >140 mg/dL had increased risk of death from esophageal cancer (HR and 95%CI, 1.44 [1.08-1.93], compared to men who were initially cancer-free at baseline and with a fasting serum glucose level <90 mg/dL).[161] Studies have proposed to restrict carbohydrate intake/control hyperglycemia as an adjunct to cancer therapy.[178, 180, 181] An animal study suggested that a high amylose containing low carbohydrate slowed tumor growth.[181]

Summary. Sugar/carbohydrate intake may promote carcinogenesis by inducing hyperglycemia and hyperinsulinmia.[17-20] This potential mechanism supports the hypothesis of a positive association between sugar/carbohydrate intake and risk of developing EA/GCA, and survival among EA/GCA cases. If an association between sugar/carbohydrate intake and risk of developing EA/GCA, or survival among EA/GCA cases, is found, there could be potential to reduce disease burden by limiting sugar/carbohydrate intake.

Epidemiology of Sugar/Carbohydrate and Esophageal/Gastric Cardia Adenocarcinoma

Several studies, as summarized in **Tables 1.1-1.5** and **Figure 1.3** have investigated on the association between sugar/carbohydrate consumption and Barrett's esophagus and/or esophageal adenocarcinoma, and different measures of the exposure were used, including food groups, total carbohydrate, starch, total sugar, sucrose, fructose, added sugar, glycemic index, and glycemic load.[182-193] In total, there were one study examined the association with risk of

developing BE, one study examined the association with EA survival, and several studies examined the association with risk of developing EA/GCA.

Total Carbohydrate. As shown in **Table 1.1**, most of the few studies that have examined total carbohydrate with EA report an inverse association.[182, 183, 187, 189, 190] A case-control study conducted in Northern Ireland and the Republic of Ireland recruited 224 BE cases and 260 population controls.[182] It was found in this Irish study that total carbohydrate intake was inversely associated with risk of EA (OR and 95%CI, 0.39[0.16-0.98], >=340.3 g/day vs. <264.8 g/day).[182] Another population-based case-control study examining this association was conducted in Australia, and had recruited 299 EA cases, 337 gastro-esophageal junction adenocarcinoma (EGJAC) cases, 245 squamous cell carcinoma cases, and 1507 controls.[183] This Australian study suggested that total carbohydrate intake possibly decreased the risk of EA and EGJAC ($OR_{Q4th\ vs.\ Q1st}$ and 95%CIs, 0.79[0.49-1.25] and 0.75[0.48-1.16], respectively).[183] A nationwide Swedish population-based case-control study also suggested that a high dietary proportion of carbohydrates decreased the risk of EA and EGJAC (OR and 95%CI, 0.50[0.34-0.73]).[194]

The inverse association may be driven by the risk reduction effect of fiber, which is also part of total carbohydrate. Fiber has several anti-carcinogenic properties, such as binding or diluting bile acids, reducing levels of circulating markers of inflammation, removing carcinogenic cells from the esophageal epithelium, altering the glycemic response by slowing digestion and absorption of carbohydrates.[164, 195] Many studies have reported an inverse association between fiber and EA/GCA, and a recent meta-analysis suggested that the highest level of total fiber intake was associated with a 34% decreased EA risk (summary OR and 95%CI 0.66[0.44-0.98]).[122]

Starch. As shown in **Table 1.2**, three studies have examined the association between starch intake and EA.[182, 183, 189] Two of the three studies suggested an inverse association,[182, 183] whereas one study suggested no reduced association.[189] The latter is a multicenter study, which

suggested that starch intake was positively associated with GCA but not EA (ORs and 95%CIs were 1.12[0.80-1.59] and 1.61[1.14-2.28] for EA and GCA, respectively).[189] In the Australian study, the starch intake was possibly associated with decreased risk of EGJAC ($OR_{Q4th\ vs.\ Q1st}$ and 95%CI, 0.71 [0.48-1.06]), although the association with esophageal adenocarcinoma was attenuated ($OR_{Q4th\ vs.\ Q1st}$ and 95%CI, 0.80 [0.53-1.21]).[183] The Irish study reported possible association between starch and EA, although the CI was wide and include the null value (OR and 95%CI, 0.76 [0.36-1.60], ≥175.0g/day vs. <136.0g/day).[182] Similarly, the inverse association may also be somewhat affected by the risk reduction effect of fiber, which often occurs in whole grains and starchy vegetables, and thus is associated with starch intake.

Total Sugar. As shown in **Table 1.3**, two case-control studies and one cohort study have examined the association between total sugar intake and EA, and the results were inconsistent.[182-184] In the Australian study, a positive association was suggested between total sugar intake and EA, although the OR might be imprecise ($OR_{Q4th\ vs.\ Q1st}$ and 95%CI, 1.22 [0.77-1.92]), but not with EGJAC ($OR_{Q4th\ vs.\ Q1st}$ and 95%CI, 0.88 [0.58-1.35]).[183] In contrast, the Irish study suggested an inverse association between total sugar intake and EA (OR and 95%CI, 0.47 [0.21-1.05], ≥162.9g/day vs. <115.9g/day).[182] In the prospective cohort study of NIH-AARP (452 esophageal cancer cases including both EA and ESCC), total sugar intake was possibly associated with increased risk in women ($HR_{T3rd\ vs.\ T1st}$ and 95%CI, 1.41[0.69-2.91]), but not in men ($HR_{Q5th\ vs.\ Q1st}$ and 95%CI, 1.09 [0.73-1.63]).[184] The naturally occurring sugar intake is highly associated with intake of fruits and vegetables, which was suggested to have a risk reduction effect on EA/GCA (due to the large variety of potentially anticarcinogenic substances contained in fruits and vegetables).[121, 196, 197] Therefore, the association between total sugar intake and EA/GCA may be affected by the effect of fruits and vegetable intake.

Individual Sugar Components (Fructose, Sucrose). Two studies have examined the association between individual sugar components and esophageal cancer (see **Table 1.3**).[184, 190] Fructose, but not sucrose, was possibly associated with risk of esophageal cancer.[184, 190] In

the NIH-AARP Diet and Health Study, total fructose was possibly weakly associated with increased risk of esophageal adenocarcinoma in men ($HR_{Q5th vs. Q1st}$ and 95%CI, 1.28 [0.87-1.87]) and in women ($HR_{T3rd vs. T1st}$ and 95%CI, 1.71 [0.83-3.54]), whereas sucrose was possibly not associated with esophageal cancer either in men ($HR_{Q5th vs. Q1st}$ and 95%CI, 1.05 [0.75-1.48]) or in women ($HR_{T3rd vs. T1st}$ and 95%CI, 1.13[0.58-2.20]).[184]

Added Sugar. Only one study has examined the association between added sugar intake and EA, and a positive association was found (see **Table 1.3).**[184] In the NIH-AARP Diet and Health Study, added sugar increased the risk of esophageal adenocarcinoma by 62% ($HR_{Q5th vs. Q1st}$ and 95%CI, 1.62[1.07-2.45]).[184]

Sweetened Desserts/Beverages. Only one study to-date has examined the association between desserts and EA development, and no association was found (see **Table 1.4**).[186] This study is a population-based case-control study that recruited 124 EA cases, 124 distal stomach adenocarcinoma cases, and 449 control subjects.[186] They found that high-dessert dietary pattern was possibly associated with risk of EA, however the CI was wide and included null value (ORs and 95%CIs, 1.6 [0.39, 6.9]).[186] Desserts intake was possibly not associated with EA ($OR_{Q4th vs. Q1st}$ and 95%CI, 1.1 [0.44, 2.7]).[186] In their study, desserts were simply defined as doughnuts, cookies, cakes, pastry, and pie, and thus they may not be able to capture intake of all added sugar.[186] A small hospital-based case-control study conducted in Athens suggested that sugars and syrups were positively associated with EA incidence ($OR_{Q5th vs. Q1st}$ and 95%CI, 1.23 [0.96-1.59]).[190]

Three large population-based case-control studies and one prospective cohort study have examined the association between carbonated soft drink intake and the risk of EA and GCA/EGJAC.[188, 191-193] The two case-control studies in Sweden and Australia, and the prospective cohort study in the US (NIH-AARP) suggested no association,[188, 192, 193] In contrast, one US multicenter case-control study suggested an inverse association between carbonated soft drink intake and EA (OR and 95%CI, 0.47[0.29-0.76]).[191]

One small US case-control study has examined the association between sugary beverages and EA survival, and found increased but non-significant association (HRs and 95%CIs: soft drinks, 1.84 [0.92-3.68]; fruit juices, 1.60 [0.79-3.25]; sugar from soft drinks and fruit juices, 1.51 [0.72–3.16]; sugar from all sweetened beverages, 1.44 [0.57–3.62]).[198]

Glycemic Index and Glycemic Load. Glycemic index and glycemic load are proxy measures designed to estimate the effect of diet on blood glucose levels.[199, 200] The glycemic index is an assessment of foods based on the incremental glucose response and insulin demand they produce for a given amount of carbohydrate.[201, 202] Glycemic load estimates the impact of carbohydrate consumption using the glycemic index while taking into account the amount of carbohydrate that is consumed.[199] Glycemic index is calculated by summing the products of the carbohydrate content per serving for each food times the average number of servings of that food per day, times its glycemic index (based on International Tables of glycemic index,[203] all divided by the total amount of carbohydrate daily intake.[199, 200] Glycemic load is calculated by multiplying the carbohydrate content of each food by its glycemic index, then multiplying this value by the frequency of consumption and summing the values from all foods.[199]

One cohort study and two case-control study have examined the association between glycemic index/glycemic load and EA (See **Table 1.5**).[182, 183, 185] In another analysis based on data collected in NIH-AARP Diet and Health Study, glycemic index possibly increased risk of esophageal cancer in both men and women ($RRs_{Q5th\ vs.\ Q1st}$ and 95%CIs, 1.50[1.10-2.05] and 1.27[0.60-2.67], respectively).[185] Glycemic load was found to possibly decrease the risk of esophageal cancer in men but increase risk of esophageal cancer in women ($RRs_{Q5th\ vs.\ Q1st}$ and 95%CIs, 0.65[0.38-1.11] and 2.18[0.57-8.32], respectively).[185] In the Australian study, glycemic index and glycemic load were found to possibly slightly decrease the risk of EA ($ORs_{Q4th\ vs.\ Q1st}$ and 95%CIs, 0.82 (0.54-1.26) and 0.73 (0.48-1.13), for glycemic index and glycemic load, respectively).[183] The associations with EGJAC were similar.[183] In the Irish study, glycemic index

was possibly associated with increased risk of EA, although the OR might be imprecise (OR and 95%CI, 1.44 (0.78-2.63), ≥44.2 vs. <36.5).[182] Glycemic load was possibly not associated with risk of EA (OR and 95%CI, 1.11 [0.53-2.32], ≥135.6 vs. <102.3).[182]

The inconsistent results may be partially explained by the use of the glycemic index/glycemic load measures themselves. The use of glycemic index/glycemic load has been controversial.[204] First, glycemic index/glycemic load pertains only to individual foods but not food combinations, and therefore may not accurately reflect the glycemic effect of a mixed meal.[205, 206] In addition, the effects of concurrent intake of non-carbohydrate contents on blood glucose are not taken into account in the current formula for glycemic index/glycemic load calculation.[207] Therefore, postprandial insulin responses may not be proportional to the carbohydrate content of a meal. One study suggested that the postprandial glycemic response to foods explains only approximately 23% of the variation in insulin levels.[208] A recent study suggested that glycemic index may even fail to capture the variation in insulin response between slowly digestible starch and rapidly digestible starch.[209] Further, considering the effect on a mixed meal, the glycemic index/glycemic load may be more appropriated when derived from 24-hour diet recall than a FFQ, however, FFQ was used to measure food intake in the previous studies examining the association between glycemic index/glycemic load and BE/EA/GCA. In addition, glycemic index measurements have been found to differ both between individuals and within individuals,[210] which may lead to exposure misclassifications. This may also partly explain the inconsistency in the results.

Effect Measure Modification by Obesity or GERD. Two studies have previous examined the EMM by obesity (measured by BMI).[182, 184] The Irish study and the NIH-AARP study reported difference in effect estimates respectively for glycemic index and added sugar stratified by obesity, but the interaction was not statistically significant,[182, 184] mostly likely due to the small number of cases within ideal-weight (n=51 and n=54 in the two studies, respectively), which was the high-risk subgroup. I hypothesized that obesity and sugar were two individual

markers of the insulin resistance/IGF-1 pathway – and I assumed that obesity would be the stronger marker. Thus, I expected the effects would be most evident among those that were of ideal weight rather than among those who were obese. This hypothesis is consistent with observations from studies of sugar with other tumors (such as breast cancer)[211], and the Irish study[182]. Other than this dissertation, no studies to-date have examined effect measure modification by GERD.

Summary. Total carbohydrate and starch have been reported to decrease the risk of developing EA.[182, 183, 187, 189, 190] Added sugar and fructose were found to increase the risk of EA in one study.[184] Studies examining the associations between glycemic index/glycemic load, total sugar, desserts, carbonated soft drinks, and EA/GCA were inconsistent. This may be partly explained by consideration of fruits and vegetables intake as confounders, accuracy of glycemic index/glycemic load measures, or perhaps the different distribution of the sources of sugar intake by sex or geographic regions (e.g., Australia, US, European countries). In addition, previous studies either had incomplete consideration or inadequate assessment of dietary sugar/carbohydrate intake[182-193], or had inadequate consideration of a specific underlying biological model which would influence consideration of specific confounders and effect modifiers to include in a statistical model[182-193]. Further, no population studies have considered the impact of these dietary compounds on mortality among EA/GCA patients.[182-193] Therefore, additional studies are needed to further explore the association between sugar/carbohydrate and EA/GCA, by including multiple measures of sugar/carbohydrate exposure, establishing statistical models on the basis of the underlying biological mechanism, and fully examining the impact on the entire cancer development continuum. Although the different distribution of the sources of sugar intake by sex or geographic regions cannot be examined in this study due to power considerations and the similar origins of the four parent study populations, the different distribution of the sources of sugar intake may be resolved by using multiple measures of sugar/carbohydrate exposure.

Precursor Lesion of Esophageal Adenocarcinoma: Barrett's Esophagus

The only known potential precursor of EA is BE.[212] Barrett's esophagus is characterized by a metaplastic change in the epithelium of the distal esophagus from the normal squamous mucosa to intestinalized columnar mucosa.[213] The process of metaplastic change is intestinal metaplasia, which is thought to arise as a protective response (wound healing) to chronic tissue inflammation, such as the inflammation caused by GERD.[214] GERD develops when gastric acid and other gastric contents flow back into the esophagus and subsequently causes troublesome symptoms or complications.[64] GERD is common in Western population, and the prevalence of GERD symptoms in the US is approximately 20%.[65] BE is thought to progress to adenocarcinoma in a stepwise process from metaplasia to low-grade dysplasia, to high-grade dysplasia, to adenocarcinoma.[76] It is unknown if BE is a necessary precursor to all EA cases.[213] GCA was postulated to arise from intestinal metaplasia of the gastric cardia following a similar process, however, it is still controversial.[215-219]

Study of the precursor lesion of BE could help to elucidate the etiology and progression of EA, which could help to reduce the burden of disease associated with these fatal tumors. For example, if we are able to demonstrate an association between the exposure of interest and BE development, there would be potential to implement prevention strategies early in disease onset to reduce the risk of developing lethal cancers. Another strength of studying BE, besides the potential to prevent cancers early in disease onset, is that studying relative shorter time period (from normal tissue to precursor lesion vs. from normal tissue to adenocarcinoma) may mitigate recall error and loss to follow-up.[220] The exposure of interest may be found to be associated with BE only, adenocarcinoma only, or both. These three conditions separately indicate the exposure of interest was involved in early stage of carcinogenesis (cancer initiation/promotion), later stage of carcinogenesis (cancer progression), or both. Therefore, studying BE helps us better

understand the underlying mechanisms, and identify at which stages along the cancer development continuum the exposure of interest plays a role.

Summary. The development of EA appears to be a stepwise process, from normal squamous mucosa to GERD, followed by BE development (metaplasia → low-grade dysplasia → high-grade dysplasia), and then to neoplasia.[76] GCA was postulated to arise from intestinal metaplasia of the gastric cardia following a similar process, however, it is still controversial.[215-219] It is of great importance to study the precursor lesion of BE since it may offer potential to implement prevention strategies early in disease onset to reduce the risk of developing lethal cancers.

Epidemiology of Barrett's Esophagus

Because BE is frequently asymptomatic and many individuals live with undiagnosed BE for years, the actual incidence and prevalence of BE is largely unknown.[221] BE develops more frequently in older people, and the most common age for BE diagnosis was approximately 65 years old.[222] Similar to EAC, BE is more common in Caucasians and men, compared to non-Caucasians and women.[222]

Several studies have tried to evaluate the prevalence of Barrett's esophagus.[223-226] One of the best estimates was from a Swedish study which surveyed a random sample (n = 3000) of the adult population in two municipalities and applied upper endoscopy in a random subsample (n = 1000).[223] BE prevalence was estimated to be 1.6% in general Swedish population.[223] The prevalence of BE were 2.3% and 1.2% in those with reflux symptoms and those without, respectively (P =0.18).[223] Another study conducted among adults from two Italian villages reported a BE prevalence of 1.3%, which is similar to that of Swedish study.[224] However, estimates reported from US studies were relatively high.[225] Based on a simulation model, an estimated BE prevalence of 5.6% (5.49-5.70%) best aligns with the EA incidence in SEER registry.[225] A screening test for BE in colonoscopy patients reported a BE prevalence of 6.8%.[226]

Consistent to the Swedish study, BE prevalence did not differ by heartburn symptoms.[226] The BE prevalence were 8.3% and 5.6% among those who had a history of any heartburn and those who had never had a heartburn, respectively (p=0.1).[226]

Studies suggested that the incidence of BE had increased during the past few decades.[8-12] Although the increased use of diagnostic upper gastrointestinal endoscopy may contribute to the observed increase in BE diagnosis, a true increase in the incidence of BE seems likely since the increase was found to be independent of the increasing endoscopies.[8-10] A cohort study in the Netherlands reported that the incidence of BE increased from 14.3 per 100,000 person-years in 1997 to 23.1 per 100,000 person-years in 2002 in the general population, independent of the number of endoscopies that were performed.[8] The incidence of BE increased most markedly in men younger than 60 years, followed by women younger than 60 years.[8] Another study based on the national registry data of the Netherlands reported a 40% increase in the incidence of BE among men and a 17% increase among women during 1992-2003.[10] They also found that the increase in the number of BE diagnoses was greater than the increase in the total number of biopsies during the same time period.[10] Consistent to the Netherlands studies, a population-based study in Northern Ireland reported an average annual increase of 159% in BE incidence from the time period of 1993-1997 to 2002-2005, which exceeded the corresponding increases in rates of endoscopies and biopsies.[9]

Summary. The incidence of EA/GCA has been increasing rapidly in the US and other Western countries in the past 40 years.[1-5] BE is the only known precursor of EA.[8-12] Therefore, it is important to identify risk factors for BE so that relevant risk reduction strategies could be implemented.

Barrett's Esophagus Risk Factors and Risk Reduction Factors

Because Barrett's esophagus is the only precursor lesion of EA, identifying risk factors for BE may offer potential to reduce the risk of developing lethal cancers. Many factors (e.g.

demographics, clinical characteristics, epidemiologic factors) have been explored as the risk factors for BE, as presented in the sections below.

Medical Conditions. Several studies suggested that GERD/reflux symptom is a major risk factor for BE.[227-230] Both frequency and duration of GERD were found to be associated with risk of developing BE.[229, 230] In a study of GERD patients, individuals who had heartburn more often than once a week were more likely to have BE (OR and 95%CI, 3.01 [1.35–6.73]).[231] In a prospective, community-based study, compared with individuals with GERD symptoms for < 1 year, the ORs for BE in individuals with GERD symptoms for 1-5 years and >10 years were 3.0 and 6.4, respectively.[229]

Demographic Factors. Several demographic factors, including age, sex, and race/ethnicity, were shown to be associated with risk of developing BE.[222, 231-234] Studies examining the association between SES and risk of developing BE yield inconsistent results.

Age, Sex, Race/Ethnicity. The risk of developing BE was found to increase steadily with age, to a peak at 61-70 years of age.[222] In a study of GERD patients, it was found that the risk of BE increased 30% (95%CI, 1.02–1.67) for each 10-year increment of age.[231] Many studies have found that BE occurred more commonly in men than women.[222, 232-234] A meta-analysis of the men to women sex ratio for Barrett's esophagus reported an overall pooled estimate of 1.96 (95%CI, 1.77-2.17).[234] BE was found to be more common among non-Hispanic whites than other race/ethnicity groups.[222, 232] In a large community-based study, the annual incidence of BE was found to be highest among non-Hispanic whites (39 per 100,000 member-years), followed by Hispanics (22 per 100,000 member-years), Asians (16 per 100,000 member-years), and blacks (6 per 100,000 member-years).[222]

Socioeconomic Status. In a US study conducted in northern California, individuals with at least a college education was found to have a decreased risk of developing BE compared to individuals with high school or less education (OR and 95%CI, 0.47 [0.27-0.82]).[235] Individuals with an income of >$75,000 were at a possibly decreased risk of developing BE (OR and 95%CI,

0.68 [0.42-1.11]), compared to individuals with an income of <$50,000.[235] This finding is consistent with the inverse association between low income, low education, and EA/GCA risk.[89] However, in a large study conducted in United Kingdom, it was found that patients with BE were more likely to be of higher SES ($OR_{T1st\ vs.\ T3rd}$ and 95%CI: 1.58 [1.16, 2.15]).[232] Further studies are needed to examine the association between SES and BE.

Epidemiologic Factors. Obesity is a well-established risk factor for BE.[98, 99, 236, 237] Cigarette smoking and alcohol has been evaluated as risk factor, but the results were inconsistent. Dietary fat has also been evaluated as a risk factor, but the results were inconsistent.

Obesity. Abdominal obesity was found to be a more important risk factor for development of BE than BMI.[98, 99, 236, 237] In a pooled analysis from BEACON consortium, waist circumference, after adjusting for BMI, was found to be associated with risk of developing BE among both men and women ($ORs_{Q4th\ vs.\ Q1st}$ and 95%CIs were 2.24 [1.08 to 4.65] and 3.75 [1.47 to 9.56], respectively, among men and women).[236] In contrast, BMI was moderately associated with risk of BE, and the association was attenuated after adjusting for waist circumstance.[236]

Cigarette Smoking. Cigarette smoking is a risk factor for BE, although the association was not very strong.[106, 238-240] A pooled analysis of BEACON studies suggested that cigarette smoking was associated with BE (OR and 95%CI: 1.67 [1.04-2.67], ever vs. never).[238] In addition, the results suggested increased risk of BE with increased pack-years smoked (ORs and 95%CIs were 1.59 [1.02-2.47], 1.44 [0.78-2.69], 1.99 [1.21-3.29], and 1.92 [1.05-3.51] for pack-years of smoking <15, 15-<30, 30-<45, and ≥45, respectively, all compared with non-smokers).[238]

Alcohol. Earlier studies suggested alcohol as a potential risk factor for BE[223, 227, 230, 241] whereas recent large population-based studies reported no overall effect of alcohol intake on the risk of BE.[52, 235, 242] In addition, several studies found that wine consumption was associated with a decreased risk of BE.[52, 235, 242] A recent pooled analysis of BEACON studies suggested

that alcohol consumption was possibly associated with decreased risk of BE (summary OR and 95%CI: 0.77 [0.60-1.00], any consumption vs. none).[242] Among alcohol types, wine consumption was found to be associated with a decreased risk of BE (OR and 95%CI, 0.71 [0.52-0.98], any consumption vs. none).[242] Further studies are needed to further elucidate the associations between alcohol and BE.

Dietary Fat. The association between fat intake and BE was under studied and the results were inconsistent. An Irish study found that neither intake of total fat nor any specific fat subtype were associated with the risk of BE.[96] In contrast, a US study found saturated fat was associated with an increased risk of LSBE (OR and 95%CI, 1.05 [1.01–1.09], per gram per day).[115] Jiao et al. also reported an increased risk associated with saturated fat (OR and 95%CI, 1.80 [1.02–3.16]).[243]

Risk Reduction Factors. Many dietary factors, such as fruits and vegetables intake[106, 120, 244, 245], and dietary antioxidants (including vitamin C, vitamin E, β-carotene)[125, 127, 244], have been examined as risk reduction factors. Besides dietary factors, NSAIDs use[246, 247] and *Helicobacter Pylori* infection[133, 248, 249] have also been examined as risk reduction factors.

Dietary Intake.

Fruits and Vegetables. Studies suggested that intake of fruits and vegetables combined were associated with decreased risk of BE.[106, 120, 244, 245] Jiao et al. found that vegetables consumption was possibly associated with a risk reduction of 39% ($OR_{T3rd\ vs.\ T1st}$ and 95%CI, 0.61 [0.35-1.06]).[127] They also found a possibly inverse association between fruit intake and BE, although the OR might be imprecise ($OR_{T3rd\ vs.\ T1st}$ and 95%CI, 0.81 [0.47-1.38]).[127] Similarly, reduced risk of BE was found to be possibly associated with vegetables consumption ($HR_{Q5th\ vs.\ Q1st}$ and 95%CI, 0.66 [0.43, 1.01]), but not fruits consumption ($HR_{Q5th\ vs.\ Q1st}$ and 95%CI, 1.00 [0.65-1.53]) among men in a Dutch study.[250] A recent qualitative review summarized that fruits and vegetables consumption or vegetables consumption alone was associated with reduced risk of EA.[135]

Dietary Antioxidants. Several studies suggested risk reductions associated with intake of vitamin C, vitamin E, and/or β-carotene.[125, 127, 244] Jiao et al. found that vitamin E intake was associated with a 54% of reduced risk ($OR_{T3rd\ vs.\ T1st}$ and 95%CI, 0.46 [0.26-0.83]), and β-carotene intake was possibly associated with a 36% of reduced risk ($OR_{T3rd\ vs.\ T1st}$ and 95%CI, 0.64 [0.37-1.10]).[127] Intake of vitamin C was possibly inversely associated with risk of BE, although the OR might be imprecise ($OR_{T3rd\ vs.\ T1st}$ and 95%CI, 0.79 [0.47-1.34]).[127] Kubo et al. found that dietary intake of vitamin C, vitamin E, and β-carotene were all inversely associated with the risk of BE ($ORs_{Q4th\ vs.\ Q1st}$ and 95%CIs were 0.48 [0.26-0.90], 0.25 [0.11-0.59], and OR 0.56 [0.32-0.99], respectively).[244]

NSAIDs Use. Some studies found an inverse association between Aspirin/NSAIDs use and BE,[246, 247] whereas other studies found no association.[251, 252] A US study by Schneider et al. reported that individuals with BE were less likely to use aspirin than population controls (OR and 95%CI, 0.59 [0.39-0.87]).[247] A study conducted in Ireland reported that use of aspirin and NSAIDs were both associated with a reduced risk of BE [ORs and 95%CIs were 0.53 [0.31-0.90] and 0.40 [0.19-0.81], respectively].[246] In contrast, a US study of individuals who underwent esophagogastroduodenoscopy suggested that the use of any NSAIDs, aspirin, and non-aspirin NSAIDs were not associated with BE (ORs and 95%CIs were 0.89 [0.75-1.28], 1.16 [0.90-1.51], 0.88 [0.55-1.39], respectively, all compared to never use).[252] The association between NSAIDs and BE remains to be examined.

H. Pylori Infection. Several studies have found that *H. Pylori* infection was inversely associated with BE.[133, 248, 249] A meta-analysis by Rokkas et al. reported an inverse association between and BE (pooled OR and 95%CI, 0.64 [0.43-0.94]).[133] The association was stronger with *H. pylori* cagA+ strain (pooled OR and 95%CI, 0.39 [0.21-0.76]).[133]

Summary. Risk factors for BE include GERD[227-230], abdominal obesity[98, 99, 236, 237], cigarette smoking[106, 238-240], and some demographic factors (age, sex, race/ethnicity)[222, 232]. Risk reduction factors include vegetables[127], dietary antioxidants (including vitamin C, vitamin E, β-

carotene)[125, 127, 244], and perhaps *H. Pylori* infection[133, 248, 249]. These factors were important to consider when examining the association between sugar/carbohydrate and development of BE since they are potential confounders, mediators, or effect measure modifiers.

Sugar/Carbohydrate and Barrett's Esophagus: Biologic Mechanisms

Similarly to the carcinogenesis of EA, sugar/carbohydrate intake may also promote pathogenesis of the precursor lesion (Barrett's esophagus), by inducing hyperglycemia and hyperinsulinmia. Greer et al. reported that both serum insulin and IGF-I levels were associated with an increased risk of BE ($ORs_{T3rd\ vs.\ T1st}$ and 95%CIs, 2.02 [1.15-3.54] and 4.05 [2.01-8.17], respectively).[253] Level of insulin-like growth factor binding protein-1 (which normally binds to IGF-I and inhibits its action) was reported to be inversely associated with risk of BE ($ORs_{T3rd\ vs.\ T1st}$ and 95%CIs, 0.11 [0.05- 0.24]).[253] All of these results suggested that the insulin/IGF signaling pathways have a role in BE development.[253] A large population-based case-control study in UK found that type 2 diabetes mellitus was associated with an increase of 49% in BE, after controlling for BMI, smoking, and GERD (OR and 95%CI, 1.49 [1.16-1.91]), which also suggested that metabolic pathways related to type 2 diabetes mellitus may play a role in BE pathogenesis.[163] In addition, the metabolic syndrome was found to be associated with the length of BE.[254] In an Irish study, 60% of patients with LSBE had metabolic syndrome, compared with 23.8% of patients with short-segment BE (SSBE) (P = 0.007).[254] A higher proportion of patients with LSBE had hyperinsulinemia compared with SSBE (20% vs. 0%, P=0.026).[254] The results suggested that the metabolic syndrome may be associated with the continuum of metaplasia within BE, and may play a role in the development of BE.[254]

Summary. Sugar/carbohydrate intake may promote BE pathogenesis by inducing hyperglycemia and hyperinsulinmia. Therefore the hypothesis of a positive association between sugar/carbohydrate intake and risk of developing BE is biologically plausible. An association between sugar/carbohydrate intake and BE development would suggest potential to

implementing prevention strategies early in disease onset to reduce the risk of developing lethal cancers.

Epidemiology of Sugar/carbohydrate and Barrett's Esophagus

Other than this dissertation, only one epidemiologic study has examined the association between sugar/carbohydrate intake and risk of developing Barrett's esophagus (see **Tables 1.1-1.5**).[182] This case-control study recruited 224 BE cases and 260 population controls from Northern Ireland and the Republic of Ireland.[182] The study considered total carbohydrate, total sugars, glycemic index, glycemic load, and starch as exposures, and found none of these exposures were associated with risk of BE.[182]

Summary. The only study (other than this dissertation) that has investigated the association between sugar/carbohydrate intake and risk of BE found non-association.[182] However, in their study, total sugar did not distinguish between added sugar and naturally occurring sugar, which may have confounded the results since naturally occurring sugar were mostly from fruits and vegetables which may reduce risk of BE.[182] Therefore, further studies are needed to investigate the association between sugar/carbohydrate intake and BE.

Specific Aims

This dissertation aimed to determine the role of dietary sugar/carbohydrate intake along the cancer development and progression continuum (normal tissue → BE → EA/GCA → mortality). By examining if dietary sugar/carbohydrate intake increases the risk of developing BE, risk of developing or dying from EA/GCA, optimal times were identified and targeted for intervention with a specific risk reduction strategy.

The hypotheses of this dissertation were as follows.

Hypothesis 1: Sugar/carbohydrate intake is positively associated with BE incidence, EA/GCA incidence, and/or mortality among patients diagnosed with EA/GCA. The strength of

this association will vary by: (1) the definition of sugar/carbohydrate intake (defined as sweetened desserts, sweetened beverages, sweetened desserts/beverages; added sugar; total sugar; sugar components (dietary free glucose, free fructose, sucrose); glycemic index, glycemic load; starch; or total carbohydrate) in this ancillary analysis because of the differences in foods and beverages that contribute to different type of sugar; and (2) disease type (BE/EA/GCA); and (3) disease severity of BE (LSBE/SSBE).

Hypothesis 2: Obesity is an effect measure modifier of added sugar - risk of developing EA/GCA association. Obesity is a major risk factor for BE and EA/GCA, and was associated with an increased EA/GCA risk of 2-5 times.[53, 92] Obesity may enhance tumor development by increasing the risk of insulin resistance and metabolic syndrome.[255] Because diets high in sugar/carbohydrate may also promote carcinogenesis by inducing chronic hyperglycemia and hyperinsulinemia, it is important to explore if there exists any complicated associations, such as effect modification by obesity. Among the multiple measures of sugar/carbohydrate intake, added sugar is most likely to interact with obesity, since added sugar can be quickly digested/absorbed and cause peaks and valleys in levels of blood glucose and insulin. Therefore, the EMMs will be examined in the association between added sugar and EA/GCA incidence. However, if other measures are found to be more strongly associated with the outcome, those measures will be used instead of added sugar.

Hypothesis 3: GERD is an effect measure modifier of the added sugar – risk of developing EA/GCA association. One major risk factor for BE and EA/GCA is GERD, which was associated with an increased EA risk of 2.6-7 times, depending on the severity and duration of the disease.[53, 66] However, only 10% of patients with chronic GERD develop BE or EA/GCA.[53] It is likely that GERD interacts with other risk factors to increase tumor risk.[53] This study will explore if there is interaction between GERD and added sugar (which has a greater impact on levels of blood glucose and insulin and is most likely to interact with GERD among multiple

measures of sugar/carbohydrate intake). Similarly, if other measures are found to be more strongly associated with the outcome, those measures will be used instead of added sugar.

Specific Aim 1: Determine if sugar/carbohydrate intake is associated with the development of BE. **Specific Aim 1A**. Explore whether overweight/obesity (measured by BMI) or GERD are EMMs of the significant associations between sugar/carbohydrate intake and risk of BE development.

Specific Aim 2: Determine if sugar/carbohydrate intake is associated with the development of EA/GCA. **Specific Aim 2A**. Explore whether overweight/obesity (measured by BMI) or GERD are EMMs of the significant associations between sugar/carbohydrate intake and risk of EA/GCA development.

Specific Aim 3: Determine if sugar/carbohydrate intake is associated with survival following a diagnosis of EA/GCA.

Summary

The incidence of esophageal and gastric cardia adenocarcinoma has been increasing in the US and many Western countries since 1970s.[2-5] However, the prognosis remains poor, with a 5-year survival of less than 20%.[6, 7] The only known potential precursor lesion of esophageal adenocarcinoma is Barrett's esophagus, which has also been increasing.[8-12] Studying the cancer development and progression continuum (normal tissue → precancerous condition → invasive cancer → mortality) would provide a better understanding of the underlying mechanisms and the potential to implement prevention strategies early in disease onset to reduce the risk of developing lethal cancers. Epidemiologic studies suggest that diabetes mellitus/metabolic syndromes/insulin resistance are associated with esophageal and gastric cancer and BE.[58-62, 161-163] Long-term consumption of diets high in sugar/carbohydrate are thought to induce hyperglycemia and hyperinsulinemia, stimulate insulin/IGF-I signaling pathways, and subsequently increase risk of esophageal/gastric cancer and BE.[17-20] Previous

studies examining the associations between sugar/carbohydrate intake and risk of BE-EA/GCA continuum have several limitations. The studies either had incomplete consideration or inadequate assessment of dietary sugar/carbohydrate intake,[182-193] or had inadequate consideration of a specific underlying biological model which would influence consideration of specific confounders and effect modifiers to include in a statistical model.[182-193] In addition, no population studies have considered the impact of these dietary compounds on mortality among EA/GCA patients.[182-193]

By pooling data from four US studies (with similar dietary intake methods), this dissertation is the largest study to date to examine the association between sugar/carbohydrate intake and BE-EA/GCA cancer continuum (including 513 BE cases, 513 EA cases, 538 GCA cases, and 2579 controls).[118, 244, 245, 256] This study is innovative because it is the first study to consider the entire cancer continuum from BE, invasive cancer by subtype, to mortality. Further, multiple measures of exposure were used to capture the complexity of sugar/carbohydrate intake. In addition, this study is the first to explore if the sugar/carbohydrate-cancer association is modified by GERD.

This dissertation is significant because Barrett's esophagus and esophageal adenocarcinoma have been increasing rapidly and the survival of esophageal and gastric cardia adenocarcinoma remains poor. Further, the currently well-established risk factors are difficult to modify. Some risk reduction factors, such as NSAIDs use and perhaps *H. Pylori* infection, may not be applicable as intervention strategies since the risks may outweigh the benefits given the rarity of EA/GCA in general population and the harmful side effects (H. Pylori infection as a major risk factor for gastric cancer and NSAIDs use is associated with increased bleeding and perforation in gastrointestinal tract, increased risk of cardiovascular disease, etc.).[257-259] In contrast, dietary sugar intake is a modifiable factor, and limiting dietary sugar intake would also provide the potential to reduce the risks of obesity and obesity-related diseases.

In sum, this dissertation investigated the association between dietary sugar/carbohydrate intake and the Barrett's esophagus-esophageal/gastric cardia adenocarcinoma continuum. If I demonstrate an association between sugar/carbohydrate intake and risk of developing BE, risk of developing or dying from esophageal and gastric cardia adenocarcinoma, there would be potential to implement prevention strategies (e.g. limiting sugar/carbohydrate intake) to reduce the disease burden associated with these lethal cancers.

Figure 1.1. Worldwide sugar and sweetener consumption (grams per capita per day) in 2004 vs. age-standardized incidence rate (per 100,000) of esophageal adenocarcinoma in men.[13, 15]

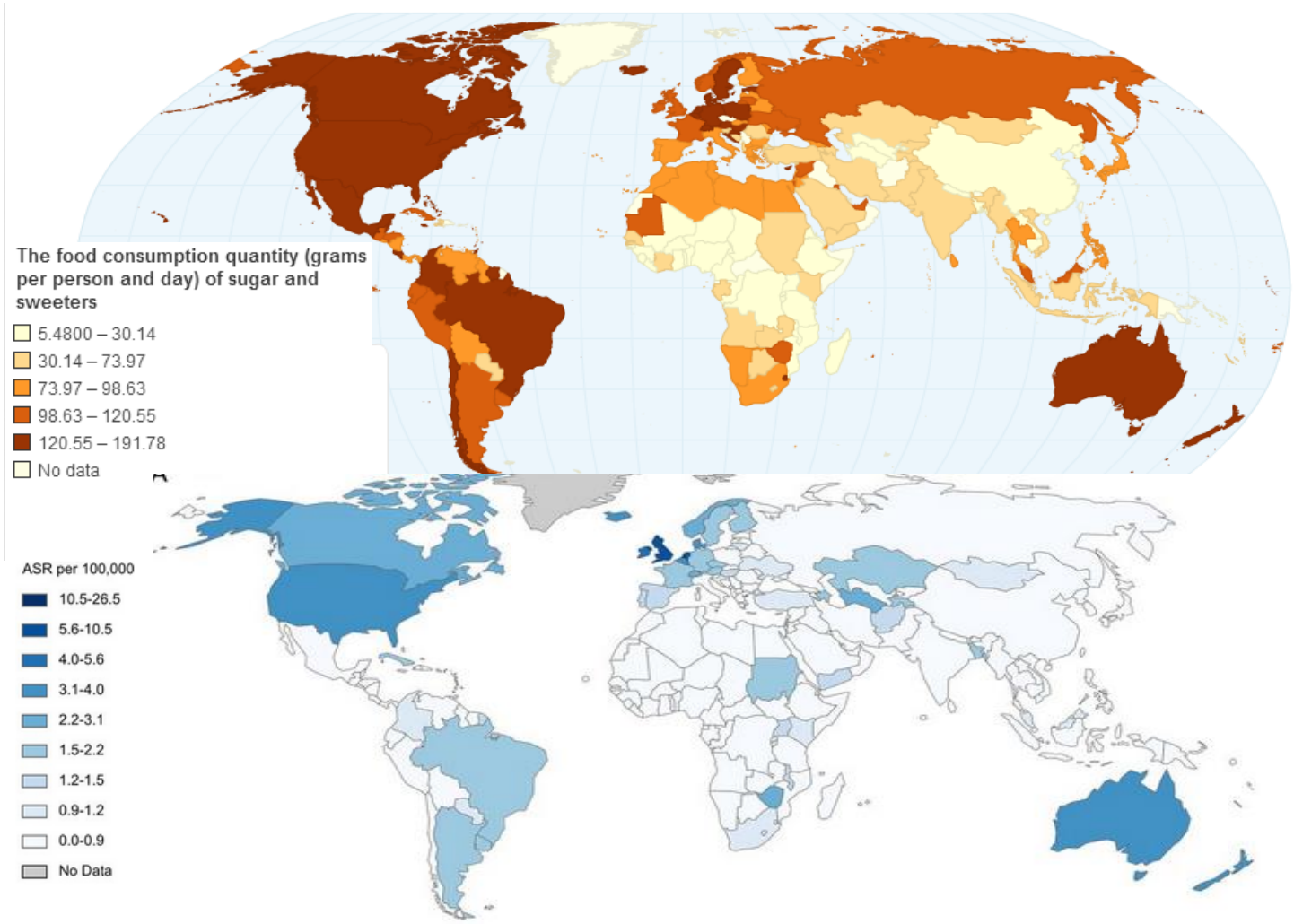

Figure 1.2. Potential mechanisms underlying the association between sugar/carbohydrate intake and the Barrett's esophagus-adenocarcinoma development.

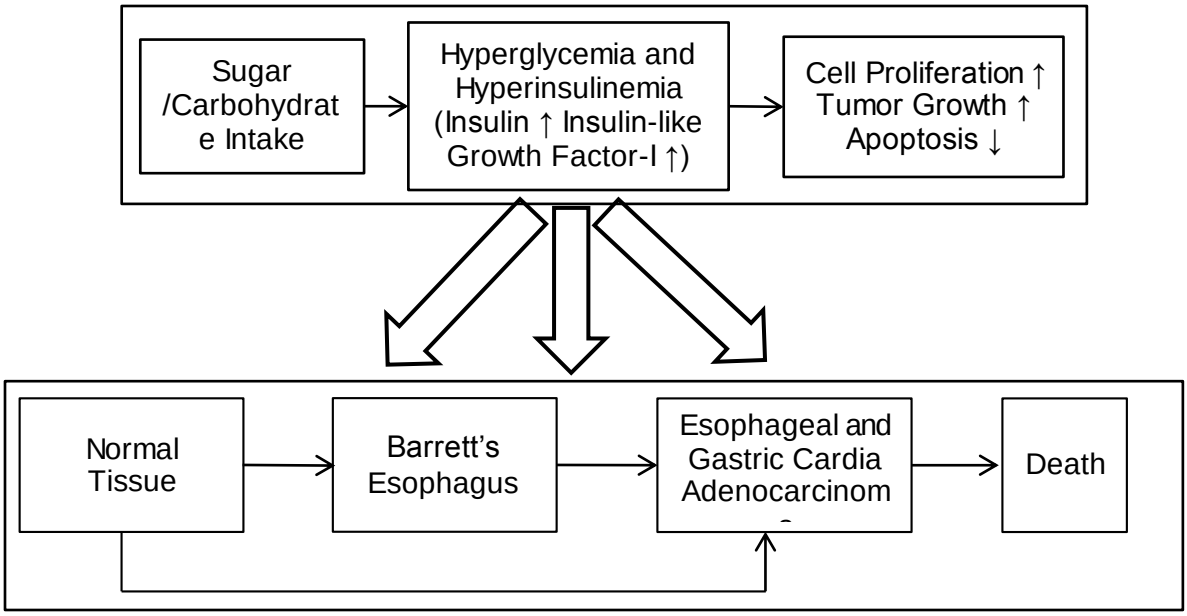

Figure 1.3. Epidemiologic studies supporting examination of the association between sugar/carbohydrate intake and the Barrett's esophagus-adenocarcinoma continuum.

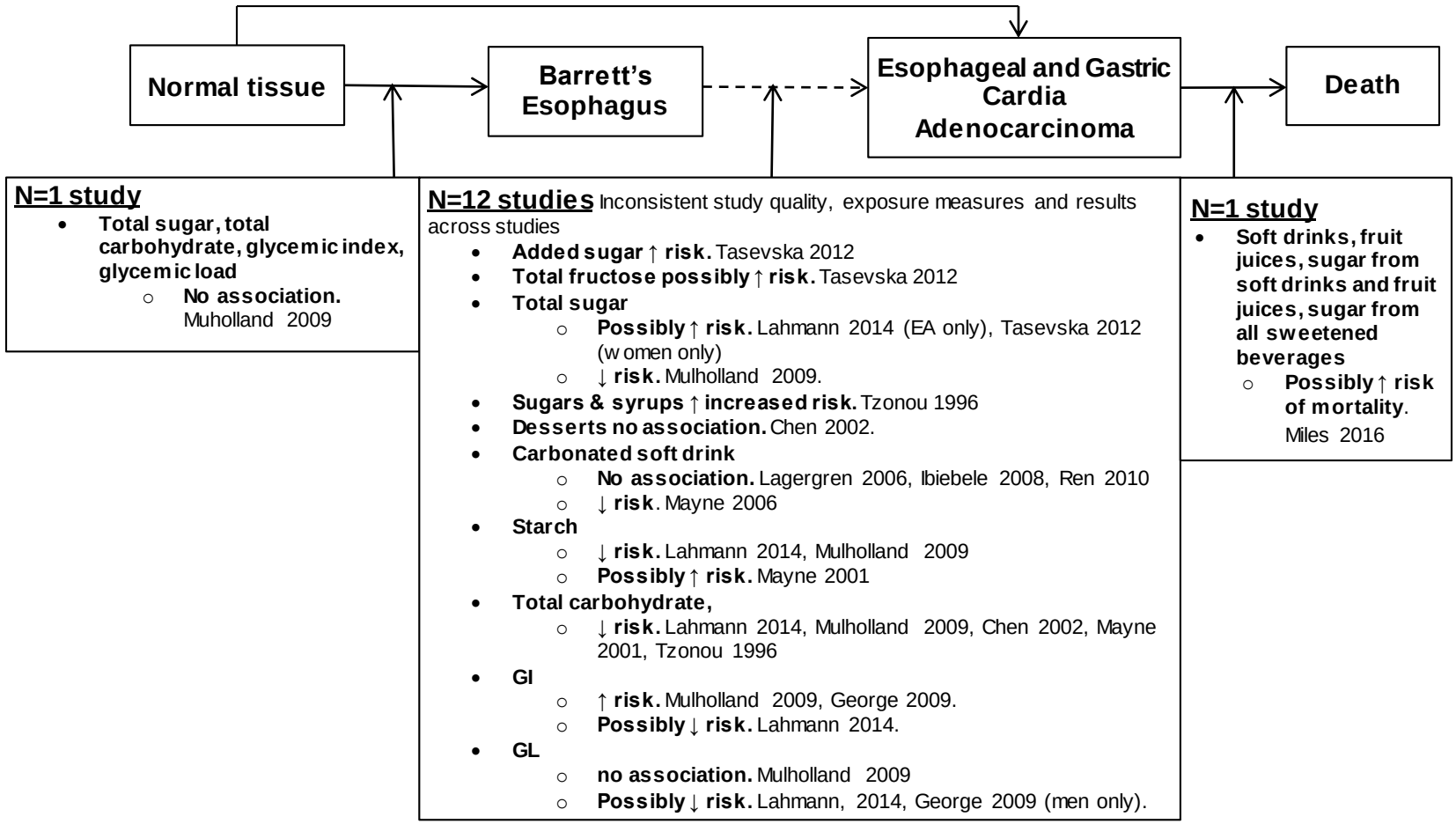

Table 1.1. Epidemiologic studies of total carbohydrate and development of Barrett's esophagus, esophageal and gastric cardia adenocarcinoma.

Author, Year	Population	Study Design & Sample Size	Cancer Continuum outcome	Exposure Assessment & Categorization	Results, Adjusted HR or OR (95%CI), & Covariates
Mulholland et al., 2009	Northern Ireland and the Republic of Ireland	Case-control population-based controls 220 BE cases; 224 EA cases; 256 controls	BE	101-item FFQ Categories	**Total carbohydrate** ≥340.3g/day vs. <264.8g/day 1.02 (0.44-2.35) Covariates: age, sex, energy intake (standard multivariate approach), smoking status, BMI 5 years prior, education, occupation, alcohol, regular NSAID use, location
Tzonou et al., 1996	Athens	Case-control hospital-based controls 56 EA cases; 43 ESCC cases; 200 controls	EA	115-item FFQ Quintiles	**Total carbohydrate** (Q5 vs. Q1) 0.84(0.59-1.19) Covariates: gender, age, birthplace, schooling, height, analgesics, coffee drinking, alcohol intake, tobacco smoking and energy intake
Mayne et al., 2001	US: Multicenter EA study	Case-control population-based controls 282 EA cases; 255 GCA cases; 687 controls	EA and GCA	124-item FFQ Quartiles	**Total carbohydrate** (75th vs. 25th) EA: 0.34 (0.20–0.58) GCA: 0.70 (0.42–1.17) Covariates: sex, site, age, race, proxy status, income, education, usual body mass index, cigarettes, years of consuming beer/wine/liquor, and energy intake (standard multivariate approach)

Table 1.1. (cont.) Epidemiologic studies of total carbohydrate and development of Barrett's esophagus, esophageal and gastric cardia adenocarcinoma.

Author, Year	Population	Study Design & Sample Size	Cancer Continuum outcome	Exposure Assessment & Categorization	Results, Adjusted HR or OR (95%CI), & Covariates
Chen et al., 2002	US: eastern Nebraska	Case-control population-based controls 124 EA cases; 154 stomach cancer cases; 449 controls	EA	A modified version of the short Health Habits and History Questionnaire Quartiles	**Total carbohydrate** Q4 vs. Q1 0.4 (0.2-0.9) Covariates: age, age squared, gender, respondent type, BMI, alcohol use, tobacco use, education level, family history of respective cancers, and vitamin supplement use
Mulholland et al., 2009	Northern Ireland and the Republic of Ireland	Case-control population-based controls 220 BE cases; 224 EA cases; 256 controls	EA	101-item FFQ Categories	**Total carbohydrate** ≥340.3 g/day vs. <264.8 g/day 0.39 (0.16-0.94) Covariates: age, sex, energy intake (standard multivariate approach), smoking status, BMI 5 years prior, education, occupation, alcohol, regular NSAID use, location
Lahmann et al., 2014	Australia	Case-control population-based controls 288 EA cases; 318 EGJAC cases; 1490 controls	EA and EGJAC	135-item FFQ Quartiles	**Total carbohydrate** [g/day (median, range)] Q4 [273 (256-438)] vs. Q1 [196 (94-212)]: EA: 0.79 (0.49-1.25) EGJAC: 0.75 (0.48-1.16) Covariates: age, sex, education, BMI, smoking, physical activity, lifetime mean alcohol intake, acid reflux symptoms in last 10 years, non-steroidal anti-inflammatory drug use, presence of diabetes, total fruit intake (except for fiber intake), red meat, processed meat, and total energy (nutrient residual model)

Table 1.2. Epidemiologic studies of starch and development of Barrett's esophagus, esophageal and gastric cardia adenocarcinoma.

Author, Year	Population	Study Design & Sample Size	Cancer Continuum outcome	Exposure Assessment & Categorization	Results, Adjusted HR or OR (95%CI), & Covariates
Mulholland et al., 2009	Northern Ireland and the Republic of Ireland	Case-control population-based controls 220 BE cases; 224 EA cases; 256 controls	BE	101-item FFQ Categories	**Starch** ≥175.0 g/day vs. <136.0 g/day 1.08 (0.52-2.22) Covariates: age, sex, energy intake (standard multivariate approach), smoking status, BMI 5 years prior, education, occupation, alcohol, regular NSAID use, location
Mayne et al., 2001	US: Multicenter EA study	Case-control population-based controls 282 EA cases; 255 GCA cases; 687 controls	EA and GCA	124-item FFQ Quartiles	**Starch** (75th vs. 25th) EA: 1.12 (0.80-1.59) GCA: 1.61 (1.14-2.28) Covariates: sex, site, age, race, proxy status, income, education, usual body mass index, cigarettes, beer/wine/liquor consumption, and energy intake (standard multivariate approach)
Mulholland et al., 2009	Northern Ireland and the Republic of Ireland	Case-control population-based controls 220 BE cases; 224 EA cases; 256 controls	EA	101-item FFQ Categories	**Starch** ≥175.0g/day vs. <136.0g/day 0.84 (0.40-1.76) Covariates: age, sex, energy intake (standard multivariate approach), smoking status, BMI 5 years prior, education, occupation, alcohol, regular NSAID use, location

Table 1.2. (cont.) Epidemiologic studies of starch and development of Barrett's esophagus, esophageal and gastric cardia adenocarcinoma.

Author, Year	Population	Study Design & Sample Size	Cancer Continuum outcome	Exposure Assessment & Categorization	Results, Adjusted HR or OR (95%CI), & Covariates
Lahmann et al., 2014	Australia	Case-control population-based controls 288 EA cases; 318 EGJAC cases; 1490 controls	EA and EGJAC	135-item FFQ Quartiles	**Starch** [g/day (median, range)] Q4 [128 (116-249)] vs. Q1 [74 (31-85)]: EA: 0.80 (0.53-1.21) EGJAC: 0.71 (0.48-1.06) Covariates: age, sex, education, BMI, smoking, physical activity, lifetime mean alcohol intake, acid reflux symptoms in last 10 years, non-steroidal anti-inflammatory drug use, presence of diabetes, total fruit intake (except for fiber intake), red meat, processed meat, and total energy (nutrient residual model)

Table 1.3. Epidemiologic studies of sugar and development of Barrett's esophagus, esophageal and gastric cardia adenocarcinoma.

Author, Year	Population	Study Design & Sample Size	Cancer Continuum outcome	Exposure Assessment & Categorization	Results, Adjusted HR or OR (95%CI), & Covariates
Mulholland et al., 2009	Northern Ireland and the Republic of Ireland	Case-control population-based controls 220 BE cases; 224 EA cases; 256 controls	BE	101-item FFQ Categories	**Total sugar** ≥162.9g/day vs. <115.9g/day 1.12 (0.53-2.37) Covariates: age, sex, energy intake (standard multivariate approach), smoking status, BMI 5 years prior, education, occupation, alcohol, regular NSAID use, location
Mulholland et al., 2009	Northern Ireland and the Republic of Ireland	Case-control population-based controls 220 BE cases; 224 EA cases; 256 controls	EA	101-item FFQ Categories	**Total sugar** ≥162.9g/day vs. <115.9 g/day 0.43 (0.19-0.94) Covariates: age, sex, energy intake (standard multivariate approach), smoking status, BMI 5 years prior, education, occupation, alcohol, regular NSAID use, location
Tasevska et al.,2012	US: NIH-AARP study	Cohort study 435674 participants aged 50-71 years 452 esophageal cancer cases, 7.2 years of follow up	Esophageal cancer (including both EA and ESCC)	124-item FFQ Quintiles for men Tertiles for women	**Total sugar** Men: Q5 vs. Q1: 1.09 (0.73-1.63) Women: T3 vs. T1: 1.41 (0.69-2.91) Covariates: age, BMI, family history of cancer, marital status, smoking, race, education, physical activity, energy intake (nutrient density method), alcohol intake, and vegetables intake. Additionally adjusted for red meat, beta-carotene and vitamin C intake for women

Table 1.3. (cont.) Epidemiologic studies of sugar and development of Barrett's esophagus, esophageal and gastric cardia adenocarcinoma.

Author, Year	Population	Study Design & Sample Size	Cancer Continuum outcome	Exposure Assessment & Categorization	Results, Adjusted HR or OR (95%CI), & Covariates
Lahmann et al., 2014	Australia	Case-control population-based controls 288 EA cases; 318 EGJAC cases; 1490 controls	EA and EGJAC	135-item FFQ Quartiles	**Total sugar** [g/day (median, range)] Q4 [168 (148-395)] vs. Q1 [90 (25-106)]: EA: 1.22 (0.77-1.92) EGJAC: 0.88 (0.58-1.35) Covariates: age, sex, education, BMI, smoking, physical activity, lifetime mean alcohol intake, acid reflux symptoms in last 10 years, non-steroidal anti-inflammatory drug use, presence of diabetes, total fruit intake (except for fiber intake), red meat, processed meat, and total energy (nutrient residual model)
Tzonou et al., 1996	Athens	Case-control hospital-based controls 56 EA cases; 43 ESCC cases; 200 controls	EA	115-item FFQ Quintiles	**Sucrose** (Q5 vs. Q1) 0.93(0.68-1.26) Covariates: gender, age, birthplace, schooling, height, analgesics, coffec drinking, alcohol intake, tobacco smoking and energy intake

Table 1.3. (cont.) Epidemiologic studies of sugar and development of Barrett's esophagus, esophageal and gastric cardia adenocarcinoma.

Author, Year	Population	Study Design & Sample Size	Cancer Continuum outcome	Exposure Assessment & Categorization	Results, Adjusted HR or OR (95%CI), & Covariates
Tasevska et al.,2012	US: NIH-AARP study	Cohort study 435674 participants aged 50-71 years 452 esophageal cancer cases, 7.2 years of follow up	Esophageal cancer (including both EA and ESCC)	124-item FFQ Quintiles for men Tertiles for women	**Added sugar** Overall (EA only): Q5 vs. Q1: 1.62 (1.07-2.45) Men: Q5 vs. Q1: 1.44 (1.03-2.03) Women: T3 vs. T1: 1.04 (0.56-1.93) **Total fructose** Men: Q5 vs. Q1: 1.28 (0.87-1.87) Women: T3 vs. T1: 1.71 (0.83-3.54) **Sucrose** Men: Q5 vs. Q1: 1.05 (0.75-1.48) Women: T3 vs. T1: 1.13 (0.58-2.20) Covariates: age, BMI, family history of cancer, marital status, smoking, race, education, physical activity, energy intake (nutrient density method), alcohol intake, and vegetables intake. Additionally adjusted for red meat, beta-carotene and vitamin C intake for women. Additionally adjusted for fruit without juice and fruit juice for added sugar

Table 1.4. Epidemiologic studies of sweetened desserts/beverages and development of Barrett's esophagus, esophageal and gastric cardia adenocarcinoma.

Author, Year	Population	Study Design & Sample Size	Cancer Continuum outcome	Exposure Assessment & Categorization	Results, Adjusted HR or OR (95%CI), & Covariates
Tzonou et al., 1996	Athens	Case-control hospital-based controls 56 EA cases; 43 ESCC cases; 200 controls	EA	115-item FFQ Quintiles	**Sugars and syrups** (Q5 vs. Q1) 1.23 (0.96-1.59) Covariates: gender, age, birthplace, schooling, height, analgesics, coffee drinking, alcohol intake, tobacco smoking and energy intake
Chen et al., 2002	US: eastern Nebraska	Case-control population-based controls 124 EA cases; 124 distal gastric adenocarcinoma cases; 449 controls	EA	A modified version of the short Health Habits and History Questionnaire Quartiles	**Desserts:** Q4 vs. Q1 1.1 (0.44-2.7) **High dessert dietary pattern:** 1.6 (0.39-6.9) Covariates: age, sex, energy intake, respondent type, BMI, alcohol use, tobacco use, education, family history, and vitamin supplement use
Lagergren et al., 2006	Sweden	Case-control population-based controls 189 EA cases; 262 GCA cases; 820 controls	EA and GCA	FFQ Categories	**Carbonated soft drinks** (>6 times/week vs. none) EA: 0.89 (0.49 -1.64) GCA: 1.09 (0.64 -1.85) Covariates: age and sex (matching factors), and adjusted for tobacco smoking status, alcohol use, socioeconomic status, and dietary intake of fruits and vegetables

Table 1.4.(cont.) Epidemiologic studies of sweetened desserts/beverages and development of Barrett's esophagus, esophageal and gastric cardia adenocarcinoma.

Author, Year	Population	Study Design & Sample Size	Cancer Continuum outcome	Exposure Assessment & Categorization	Results, Adjusted HR or OR (95%CI), & Covariates
Mayne et al., 2006	US: Multicenter EA study	Case-control population-based controls 282 EA cases; 255 GCA cases; 687 controls	EA and GCA	124-item FFQ Quartiles	**Carbonated soft drink** (Q4 vs. Q1) EA: 0.47 (0.29-0.76) GCA: 0.74 (0.46-1.16) Covariates: age, sex, center, race, proxy interview status, average adult body mass index, mean caloric intake, consumption of beer/wine/liquor, consumption of meat, cigarettes per day, education, income, and frequency of reflux symptoms
Ibiebele et al., 2008	Australia	Case-control population-based controls 294 EA cases; 325 EGJAC cases; 1484 controls	EA and EGJAC	135-item FFQ Categories	**Carbonated soft drink** (ever vs. never) EA: 1.06 (0.72-1.56) EGJAC: 0.71 (0.51-0.99) Covariates: adjusted for age, gender, body mass index, heartburn and acid reflux symptoms, cumulative history of smoking in pack years, alcohol intake status, educational status, total energy intake, and total vegetable intake
Ren et al., 2010	US: NIH-AARP study	Cohort study 481563 participants aged 50-71 years 305 EA cases, 231 GCA cases	EA and GCA	124-item FFQ Categories	**Carbonated soft drinks** (≥1 can/day vs. none) EA: 1.11 (0.66, 1.85) GCA: 0.89 (0.55, 1.45) Covariates: age, sex, tobacco smoking, alcohol drinking, BMI, education, ethnicity, usual physical activity throughout the day, vigorous physical activity, and the daily intake of fruit, vegetables, red meat, white meat, and calories

Table 1.4.(cont.) Epidemiologic studies of sweetened desserts/beverages and development of Barrett's esophagus, esophageal and gastric cardia adenocarcinoma.

Author, Year	Population	Study Design & Sample Size	Cancer Continuum outcome	Exposure Assessment & Categorization	Results, Adjusted HR or OR (95%CI), & Covariates
Miles et al., 2016	US	Case-control population-based controls with follow-up approach 42 EA deaths; 74 EA cases.	EA survival	Brief Block FFQ Medians	**Soft drink** (upper vs. lower median) EA: 1.84 (0.92-3.68) **Fruit juice** (upper vs. lower median) EA: 1.60 (0.79-3.25) **Sugar from soft drink and fruit juice** (upper vs. lower median) EA: 1.51 (0.72–3.16) **Sugar from all sweetened beverages** (upper vs. lower median) EA: 1.44 (0.57–3.62) Covariates: age, gender, ethnicity, education, smoking, alcohol drinking, caloric intake, pathology type, and tumor differentiation grade.

Table 1.5. Epidemiologic studies of glycemic Index, glycemic Load, and development of Barrett's esophagus, esophageal and gastric cardia adenocarcinoma.

Author, Year	Population	Study Design & Sample Size	Cancer Continuum outcome	Exposure Assessment & Categorization	Results, Adjusted HR or OR (95%CI), & Covariates
Mulholland et al., 2009	Northern Ireland and the Republic of Ireland	Case-control population-based controls 220 BE cases; 224 EA cases; 256 controls	BE	101-item FFQ Categories	**Glycemic index** ≥44.2 vs.<36.5 0.93 (0.53-1.64) **Glycemic load** ≥135.6 vs. <102.3 0.79 (0.39-1.58) Covariates: age, sex, energy intake (standard multivariate approach), smoking status, BMI 5 years prior, education, occupation, alcohol, regular NSAID use, location
Mulholland et al., 2009	Northern Ireland and the Republic of Ireland	Case-control population-based controls 220 BE cases; 224 EA cases; 256 controls	EA	101-item FFQ Categories	**Glycemic index** ≥44.2 vs. <36.5 1.52 (0.84-2.76) **Glycemic load** ≥135.6 vs. <102.3 1.14 (0.55-2.33) Covariates: age, sex, energy intake (standard multivariate approach), smoking status, BMI 5 years prior, education, occupation, alcohol, regular NSAID use, location
George et al., 2009	US: NIH-AARP study	Cohort study 446177 participants aged 50-71 years 501 Esophageal cancer cases, 6.89 years of follow up	Esophageal cancer (including both EA and ESCC)	124-item FFQ Quintiles for men Tertiles for women	**Men:** **Glycemic index** ≥44.2 vs. <36.5 1.52 (0.84-2.76) **Glycemic load** ≥135.6 vs. <102.3 1.14 (0.55-2.33) **Women:** **Glycemic index** ≥44.2 vs. <36.5 1.52 (0.84-2.76) **Glycemic load** ≥135.6 vs. <102.3 1.14 (0.55-2.33) Covariates: age, race/ethnicity, education, marital status, body mass index, family history of any cancer, physical activity, smoking, alcohol consumption, and total energy intake. Additionally adjust for menopausal hormone therapy use for women

Table 1.5.(cont.) Epidemiologic studies of glycemic index, glycemic load, and development of Barrett's esophagus, esophageal and gastric cardia adenocarcinoma.

Author, Year	Population	Study Design & Sample Size	Cancer Continuum outcome	Exposure Assessment & Categorization	Results, Adjusted HR or OR (95%CI), & Covariates
Lahmann et al., 2014	Australia	Case-control population-based controls 288 EA cases; 318 EGJAC cases; 1490 controls	EA and EGJAC	135-item FFQ Quartiles	**Glycemic index** [median, range] Q4 [57 (54-71)] vs. Q1 [46 (27-49)]: EA: 0.82 (0.54-1.26) EGJAC: 0.78 (0.52-1.18) **Glycemic load** [median, range] Q4 [146 (135-259)] vs. Q1 [95 (21-105)]: EA: 0.73 (0.48-1.13) EGJAC: 0.72 (0.49-1.08) Covariates: age, sex, education, BMI, smoking, physical activity, lifetime mean alcohol intake, acid reflux symptoms in last 10 years, non-steroidal anti-inflammatory drug use, presence of diabetes, total fruit intake (except for fiber intake), red meat, processed meat, and total energy (nutrient residual model)

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CHAPTER 2: METHODS

Overview

This dissertation aimed to determine the associations between dietary intake of sugar/carbohydrate and (1) the risk of developing Barrett's esophagus (BE), (2) the risk of developing esophageal and gastric cardia adenocarcinoma (EA/GCA), and (3) survival among esophageal and gastric cardia adenocarcinoma cases. To address these aims, this study incorporated both case-control and follow-up designs. The case-control design was used to address the research questions focused on determine whether sugar/carbohydrate intake are associated with tumor development, and the follow-up approach was used to address the questions focused on survival. A pooled analysis of four existing United States (US) case-control studies[1-4] was conducted to complete the following three steps. Step 1: Estimation of sugar/carbohydrate intake for each participant. The four study-specific food frequency questionnaires (FFQs) were linked with the University of Minnesota nutrient database. Frequency of consumption, serving size, and nutrient contents, were utilized to determine sugar/carbohydrate consumption. Step 2: Pooling of the sugar/carbohydrate intake across studies. Both study-specific quantiles and identical absolute intake cut-points across studies were used to identify intake categories. Step 3: Estimation of the odds ratios for the associations between sugar/carbohydrate intake and the risk of developing BE and esophageal/gastric cardia adenocarcinoma, and the hazard ratios for the association between sugar/carbohydrate intake and survival among cases of esophageal/gastric cardia adenocarcinoma. Whether risk varies by different measures of sugar/carbohydrate intake,

the severity of BE, or tumor location, were also explored. In addition, obesity and gastroesophageal reflux disease (GERD) were examined as effect measure modifiers (EMMs) in the associations between sugar/carbohydrate intake and BE-EA/GCA cancer continuum outcomes.

Study Populations

To address the study aims, I pooled resources from: (1) two parent case-control studies of EA/GCA (US Multi-Center Study[1] and Los Angeles (LA) County Multi-Ethnic Case-Control Study[2]), both of which included a follow-up component to determine vital status; and (2) two parent case-control studies of BE (Study of Reflux Disease[3], and Epidemiology and Incidence of BE Study[4]) (**Table 2.1**).

The US Multi-Center Study was conducted in the state of Connecticut, a 15-county area of New Jersey, and a three-county area of western Washington State during 1993-1995.[5] The LA Multi-Ethnic Case-Control Study was conducted in Los Angeles county during 1992-1997.[2] In both parent EA/GCA studies, cases were identified by the population-based cancer registries of their residing geographic areas.[2,5] Cases included those who were histologically diagnosed with invasive cancer of the esophagus or stomach during the study period.[2,5]

In US Multi-Center Study, cases were identified through rapid-reporting systems.[5] Eligible cases were English-speaking men and women, aged 30-79 years, who were diagnosed with primary invasive cancer of the esophagus or stomach between 1993 and 1995.[5] Initial subject selections were based on the review of pathology reports. Case-subject eligibility was determined based on a systematic review by the study pathologists using standardized criteria.[5] The site of tumor origin was determined by review of pathology slides and medical records including endoscopic, surgical, and pathologic data.[5] Population-based controls were frequency matched to the cases on 5-year age group and sex.[5] Controls aged 30-64 years were identified by Waksberg's random digit-dialing (RDD) method, and random sampling of Health Care

Financing Administration rosters identified controls aged 65-79 years.[5] The trained interviewers used a structured questionnaire to collect information on demographics, tobacco and alcohol, medical history, medication use, diet, etc. from cases/proxies and controls during a face-to-face interview.[5] The average time to complete interview was 130 minutes.[5] The average lengths of time between cancer diagnosis and the interview were 3.7 months and 8.5 months, when the interview was conducted with the case himself/herself and a proxy, respectively.[5]

In LA Multi-Ethnic Study, cases were men and women who were 30-74 years of age and were histologically diagnosed with first cancer of esophagus or stomach during 1992-1997.[2] Pathology reports were used to identify the histological classification or the sub-site of the gastric cancer.[6] Controls were individually matched to cases by date of birth (±5 years), sex, and race.[2] A systematic algorithm based on the address of the case was used to seek neighborhood control for the case, and two controls were sought for each case whenever possible.[2] An in-person interview was administered using structured questionnaire to collect information on smoking habits, alcoholic beverages intake, body size characteristics, family history, and diet history from cases or their next-of-kin (when patients were unable to participate the interview due to illness or death).[2]

The Study of Reflux Disease was conducted in western Washington state.[7] Eligible cases were selected from men and women, aged 20-80 years, without previously diagnosed BE who were undergoing an upper endoscopy for GERD symptoms at one of four community gastroenterology clinics between 1997 and 2000.[7] A four-quadrant biopsy specimen was collected for consenting participants and was evaluated by one of three pathologists.[7] Cases were those with specialized intestinal metaplasia on at least one of the four biopsy specimens.[7] Population controls were selected among current residents of western Washington using a modified Waksberg RDD technique.[7] Controls were individually matched to cases by age (±3 years) and sex.[7] Cases and controls underwent structured interviews by trained interviewer, and the interview covered demographics, tobacco and alcohol use, diet, medical history, and

medication use.[7] Detailed diet information was collected through self-administered food frequency questionnaire.[7] The length of interview was approximately 45 minutes.[7] The interview occurred approximately 1-2 months after endoscopy for cases.[7]

The Epidemiology and Incidence of BE Study was conducted within the Kaiser Permanente Northern California (KPNC, an integrated health services delivery organization) population.[8] Cases and controls were selected from 18-79 years-old KPNC members who were continuously enrolled for at least 2 years before their index period, were able to understand spoken and written English, and met the case or control criteria.[8] Cases were eligible KPNC members who were diagnosed with incident BE between 2002 and 2005.[8] BE cases were identified using the International Classification of Disease, Ninth Revision code 530.2.[8] To identify cases, endoscopy and pathology records of potentially eligible cases were reviewed by a gastroenterologist (DAC) to determine if they met the stated Barrett's esophagus definition.[8] A separate review of pathologic slides was subsequently conducted by an independent gastrointestinal pathologist to evaluate for the presence of intestinal metaplasia.[8] Patients were excluded if they had a prior diagnosis of BE, only gastric-type metaplasia of the esophagus on all pathologic evaluations, didn't have a biopsy specimen of esophageal origin, or their columnar metaplasia demonstrated no features of intestinal metaplasia on any pathologic evaluation.[8] Population controls were randomly selected from the KPNC members without previous diagnosis of Barrett's esophagus using risk set sampling.[8] An in-person interview was conducted by trained interviewers to collect information on GERD symptoms, tobacco and alcohol use, medication use, medical history, diet, and body size.[8]

Demographics of the four parent studies have been previously published[5-8] and are summarized in **Table 2.2-2.3**. In all parent studies, the majority of participants were Caucasian males. For the parent studies of EA, the median age at diagnosis was 66 years old in US Multi-Center Study and the mean age at diagnosis was 61 years old in LA Multi-Ethnic Study. For the parent studies of BE, the mean age at diagnosis were 55 and 62 years old, respectively, in

Study of Reflux Disease and Epidemiology and Incidence of BE Study. In all of the four parent studies, control participants were more likely to be well educated than cases.

In addition to the inclusion criteria of the parent studies, only cases and controls that have completed a FFQ were included. Completed FFQs were obtained for: 96% of EA cases, 98% of GCA cases, and 99% of controls in US Multi-Center Study; 93% of EA cases, 93% of GCA cases, and 96% of controls in LA Multi-Ethnic Study; 88% of BE cases and 86% of controls in Study of Reflux Disease; 93% of BE cases and 97% of controls in Epidemiology and Incidence of BE Study.[1-8] Therefore, combining the two EA/GCA studies yielded 513 EA cases, 538 GCA cases, and 2051 non-cases, combining the two BE studies yielded 513 BE cases and 528 controls.[1-4] Distribution of age, sex, race/ethnicity, and geographic area were not significantly different between the subjects included in the parent study and those that were included in this ancillary study.[1-8]

The study population for this dissertation is of great generalizability. The four parent studies were either population-based[1-3] or community-based case-control studies.[8] This pooled analysis had a wide coverage of US population, which greatly extended the generalizability of this study compared to a single case-control study. In addition, the mortality data of EA/GCA patients allowed this study to be the first to determine if sugar/carbohydrate intake is associated with the entire cancer continuum. Because BE and EA/GCA are rare diseases, there are not many existing large studies of BE or EA/GCA in the US that have collected dietary data, and a pooled analysis of existing studies would be more efficient. Parent studies were selected from international Barrett's and Esophageal Adenocarcinoma Consortium (BEACON, formed in 2005 by an international group of investigators to provide an open scientific forum for epidemiological research by facilitating the sharing of data across studies, http://beacon.tlvnet.net/), based on the similarities in: (a) targeting US source populations; (b) study designs employed; (c) structure of their food frequency questionnaires; and (d) covariate assessment through in-person interviews. The NIH-AARP cohort study in the BEACON consortium was not selected because

of the differences in study design and FFQ management.[9]

Exposure Assessment

All parent studies collected dietary information using a food frequency questionnaire (FFQ), during a structured interview by trained interviewers[1, 2, 4] or a self-administered questionnaire.[3] Relative validity of the FFQs utilized using diet records and/or multiple 24-hour recall instruments has been reported.[10-15] The FFQs included both frequency and portion size questions in three of the studies. Only frequency questions were used in the US Multi-Center Study, however, medium serving sizes were assumed for the food items, which is consistent with Fred Hutchinson Cancer Research Center (FHCRC) procedures.

The US Multi-Center Study utilized a 104-item FFQ that was modified from the FFQ developed by investigators at the FHCRC.[1] Participants were asked to report their usual diet in the 3-5 years before diagnosis (cases) or interview (controls).[1] The LA Multi-Ethnic Study utilized a 124-items FFQ developed by investigators at University of Hawaii.[2] Cases were asked to report their diet in 1 year prior to diagnosis, and their matched controls were asked to report their diet at the same time as cases.[2] The Study of Reflux Disease utilized the standard 131-item FFQ developed by FHCRC.[3] Both cases and controls were asked to report their dietary intake for the year before interview.[3] The Epidemiology and Incidence of BE Study utilized a 110-item FFQ (Block 98) to assess nutritional intake. The participants were asked to report their diet over the year before the index date.[4] The index date was the date of diagnosis for cases.[4] For controls, the index date was the midpoint of the 2-3 month selection interval for the cases.[4] Although the parent studies utilized different FFQs, these FFQs share similarities in food items, FFQ structure, and nutrient database. Nutrient intake was assessed using University of Minnesota nutrient database (US Multi-Center EA/GCA Study and Study of Reflux Disease)[3, 16] or University of Hawaii nutrient database (LA Multi-Ethnic EA/GCA Study)[2], both of which were developed based on United States Department of Agriculture (USDA) nutrient database.

Nutrient intake for Epidemiology and Incidence of BE Study was assessed using Block dietary nutrient system, [4] which is also similar to the USDA nutrient database.

In US Multi-Center Study, in-person interviews (including target subjects and proxies) were conducted for 80.6% (n=554) of the eligible cases, and 73.7% (n=695) of the eligible controls.[5] Interviews were administered to the closest next of kin (usually the spouse) when the patient was unable to be interviewed due to illness or death.[5] Proxy interviews were conducted for 29.6% of the target cases, and 3.4% of the controls.[5] In the LA Multi-Ethnic Study, interviews were conducted for 77% (947/1230) of the cases that were approached (77% for EA, 74% for GCA, and 78% for distal gastric cancer).[6] In-person next of kin (NOK) interviews accounted for 29% of interviews with case patients (66 for EA, 85 for GCA, and 125 for distal gastric cancer patients).[6] Combining the two EA studies, complete dietary data were available for 1038 EA/GCA cases and 2045 EA/GCA controls.[1, 2] Previous studies have examined reliability and validity of proxy versus self-report for many factors including dietary intake.[17, 18] The agreement between next-of-kin recall and self-report was shown to be fair/moderate for fruits and vegetables intake.[17, 18] In addition, an ancillary study of the US Multi-Center Study examining the association between micronutrients and esophageal and gastric cancer reported that, results from analyses including versus excluding proxy interview data were almost identical.[16] In the Study of the Reflux Disease, 92.8% (n=193) of the BE cases and 68.7% (n=211) of the controls were successfully interviewed.[7] In the Epidemiology and Incidence of BE Study, 47% (n=320) of the eligible BE cases and 37% (n=317) of eligible controls were interviewed.[8] Neither of the BE parents studies conducted interviews with proxy respondents. Combining the two BE studies, complete dietary data were available for 479 BE cases and 501 BE controls.[3, 4]

Twelve measures were used to capture the complex dietary exposure of sugar/carbohydrate, including sweetened desserts, sweetened beverages, sweetened desserts/beverages; added sugar; total sugar; sugar components (dietary free glucose, free fructose, sucrose); glycemic index, glycemic load; starch; or total carbohydrate (**Table 2.4**).

Examining the effect of added sugar was important because it is added during food processing/preparation and the absorption may be different from naturally occurring sugar. Studying the effects of different sugar component was important because each sugar component has different metabolism which may lead to different effects on carcinogenesis.[19] Glycemic index and glycemic load are approximate measures of the effect of diet on blood glucose and insulin levels.[20] Sweetened desserts/beverages was also an important measure because they may be easier to be identified by the general population when implementing risk reduction strategies. Therefore, examining multiple measures helped us better understand the underlying mechanism and provide guidance in intervention.

Data Harmonization

Because most of the sugar/carbohydrate measures of interest are not available in the originally processed nutrient data from parent studies, each of the four study-specific FFQs were linked with the University of Minnesota nutrient database,[21] utilizing frequency of consumption, serving size, and nutrient contents, to determine sugar/carbohydrate consumption. Although USDA database also contains sugar/carbohydrate values (e.g. total sugar, total carbohydrate, glucose, sucrose, fructose, starch), data were not complete for some of the FFQ food items.[22] In addition, the only version of added sugar database released by USDA was removed from their website due to the constant changes in formulations for commercial foods, multi-ingredient foods, and the primary contributor of added sugar to the diet.[23]

University of Minnesota nutrient database was created primarily based on the USDA database.[24] Additional resources used to create the University of Minnesota nutrient database include values from other food and nutrient databases and articles in scientific journals containing values for food products were utilized when values for some nutrients, food components, and brand name food products were not available from USDA.[24] In addition, several standardized procedures were utilized to impute or logically calculate estimations of

nutrient values. The steps followed by the University of Minnesota for the nutrient database include: (1) use of a proxy value from a different but similar food item; (2) calculate an estimate using the value for another form of the same food; (3) calculate an estimate of the value using other components in the same food; (4) calculate an estimate of the value using household recipes or commercial food product formulations for multi-component foods.[24]

University of Minnesota nutrient database contains more food items, minimal missing nutrient values, and values of all nutrients of interest (including total carbohydrate, starch, total sugar, glucose, sucrose, fructose, added sugar, glycemic index, and glycemic load), and therefore was utilized in this study. Although a unified nutrient database, rather than study-specific nutrient database was used to determine sugar/carbohydrate intake, it is unlikely it would alter the study results since intake was essentially measured by relative intake (ranking) rather than the absolute values. Bingham et al. reported that the study results were similar using unified vs. study-specific nutrient database.[25] A sensitivity analysis was conducted to compare the results based on the unified nutrient database with the results based on study-specific nutrient database to examine the robustness of this method (see sensitivity analysis section).

To estimate sugar/carbohydrate intake, frequency of consumption and portion size of FFQ line items from each of the four study-specific FFQs were linked with the nutrients per 100 grams of food from University of Minnesota nutrient database. For each of the four parent studies, participants were asked how often they consumed the food items. For both EA parent studies, participants gave the number of times the food item was consumed per day, week, month, or year. For both BE parent studies, different categorizes of frequency were pr ovided for the participants to choose from, such as never or less than once per month, 1 per month, 2-3 per month, 1 per week, 2 per week, 3-4 per week, 5-6 per week, 1 per day, etc.

The FFQs include portion size questions in three of the parent studies, but not in the US Multi-Center Study. However, medium serving sizes were assumed for the food items, which is consistent with procedures of the original nutrient data processing center - FHCRC. In the LA

Multi-Ethnic Study, participants were given what each of the serving size represents specifically for each of the FFQ line items. For example, the three options for the line item 'orange juice' were 1/2 cup or 4 oz., 1 cup or 8 oz., and 1 ½ cups or 12 oz. Participants were asked to report both the usual serving size and the number of servings each time they consumed each line item. In the Study of Reflux Disease conducted in Seattle, participants were given a definition of medium serving size and asked to report the serving size of the FFQ line item they usually consumed. There options were provided for serving size, including small (≤ 1/2 of the medium serving), medium, and large (≥1 ½ of the medium serving). In the Epidemiology and Incidence of BE Study conducted in Kaiser in Northern California, four options were provided for serving size. Participants were given what each of the serving size represents for each of the FFQ line items respectively. For example, the four options for the line item 'grapefruit' were 1/2 cup, 1 cup, 2 cups, and 3 cups. Participants were asked to report the serving size they usually consumed.

For most of the FFQ items, serving size was defined in units other than grams (e.g. cups, glasses, slices, etc.). Therefore, the portion size files documenting the conversions between other units to grams for FFQ items were obtained from each of the original nutrient data processing centers and were used for this ancillary study. In the LA Multi-Ethnic Study conducted in Los Angeles, portion size conversions were missing for a few FFQ items. Because the original data were processed based on University of Hawaii nutrient database, which was developed based on USDA nutrient database, the USDA database for portion size conversions for those items were utilized.[22] In the Kaiser Epidemiology and Incidence of BE Study, portion size conversions were provided based on FFQ line items rather than individual items. For most of the line items, the individual items were listed in a line item separately or the multiple foods in a line item were all similar in sizes, and therefore the portion size conversions from the file were used. However, there were a few line items that include multiple food items and are probably different in sizes, and therefore the USDA for portion size conversions were utilized.[22] For

example, for the line item 'raw peaches, apricots, nectarines', the smallest serving size option in the FFQ was 1/2 of the fruit. The portion size file provided by original nutrition data processing center gave 49 grams for 1/2 of the fruit for this line item. However, the gram weight for 1/2 of peach or nectarine should be different from the weight for 1/2 of apricot. Therefore, I looked up in USDA to determine the grams weight for 1/2 of peach, apricot, and nectarine, respectively.

Some FFQ line items represent multiple foods (e.g. 'pancakes or waffles'), and therefore the nutrient contents of the FFQ line item were weighted according to the assigned weights (e.g. 0.65 for 'pancakes' and 0.35 for 'waffles'). The relative weights were based on nationally consumed patterns of consumption as compiled by each of the studies. The files that documented the weights were provided by the original nutrition data processing centers for the LA Multi-Ethnic Study and the Seattle Study of Reflux Disease. For the US Multi-Center Study conducted in Connecticut, New Jersey and Western Washington, the FHCRC was unable to locate records of the weights that were originally utilized in processing nutrient data. However, verification of the weighting scheme was done previously by using the weighting scheme of a similar FHCRC FFQ and examining the correlations between the newly calculated total energy and the FHCRC originally reported total energy.[26] The new weights that were used in this study were shown to be close to how the FHCRC originally weighted the FFQ items (the Pearson correlation coefficient was 0.97). For the Kaiser Epidemiology and Incidence of BE Study, weights file is unavailable and thus the weights (percentages) were determined by referring to the weights used by investigators that have utilized the FFQs of the other three parent studies. If the weight percentages were unavailable in the other FFQs, the weights for the foods in one FFQ line item were evenly split.[27] The Block 98 FFQ utilized in the Kaiser Epidemiology and Incidence of BE Study was originally processed based on the 'icon' method (Dr. Doug Corley, personal communication, 2015), which is different from the standard method utilized by the other three parent studies. According to the 'icon' method, one USDA nutrient database food that represents the FFQ line item was selected based on the relative frequency of reports of

those foods in National Health and Nutrition Examination Survey (NHANES) (e.g. for "apples and pears" it would have been apples). Some items may have been constructed from more than one SR food. In contrast, the standard method is to use the food intake provided by national published surveys (e.g., NHANES) to weight line items that correspond to the years the study FFQ assessed intake (e.g. for "apples and pears" it would have been 60% apples and 40% pears) (FHCRC, personal communication 2015). However, values estimated using the 'icon' method and the standard method (using NHANES data) were compared, and have yielded highly correlated estimates (unpublished data, Dr. Doug Corley, personal communication 2015). Because the other three studies were originally processed based on the more commonly used standard method, I used the standard method rather than 'icon' method to estimate intake for this ancillary analysis.

FFQ items that were categorized as sweetened desserts/beverages based on previous studies[28-30] were listed in **Table 2.5**. To calculate the total intake of sweetened desserts/beverages, the number of times of consumption per day were multiplied by the number of medium servings each time, and then summed across all high-added sugar FFQ line items. Medium servings in US Multi-Center Study FFQs and Seattle Study of Reflux Disease FFQs were defined by the investigators from FHCRC, and medium servings were defined as the second answer options in the study-specific FFQs for LA Multi-Ethnic Study and Epidemiology and Incidence of BE Study. In addition, sweetened desserts/beverages were divided into two groups including sweetened desserts group and sweetened beverages group. The intake of each group of items was estimated respectively.

Intake of total carbohydrate, starch, total sugar, free glucose, sucrose, free fructose, and added sugar was estimated by linking FFQ data with nutrient contents in University of Minnesota nutrient database.[21] For example, intake of total sugar was calculated as follows: total sugar intake per day from an FFQ line item = the number of times of consumption per day * amount of consumption each time in grams * grams of total sugar per 100 grams of food. Intake

of total sugar per day for each person was calculated by repeating the calculation above for each of the FFQ line items and summing up the sugar intake values across all FFQ line items. When FFQ line items represent multiple foods, the nutrient contents of the FFQ line item were weighted according to the assigned weights. For example, the FFQ line item of 'pancakes or waffles' was assigned a weight of 0.65 for 'pancakes' and 0.35 for 'waffles'. To calculate the total sugar intake, the weight assigned to each food in the FFQ item were multiplied by the total sugar content of one medium serving of that food, summed across all foods in the FFQ line item, and then multiplied by the number of times consumed per day and the number of medium servings. In this example, 100 grams of pancakes contains 8.32 grams of total sugar and 100 grams of waffles contains 4.91 grams of total sugar. A medium serving size of pancakes and waffles were 76 grams and 22 grams, respectively. If a participant reported consuming one medium serving of pancakes or waffles per day, the participant's daily intake of total sugars from pancakes and waffles was calculated as: 1 serving of pancakes or waffles /day * [(0.65 * 76 g * 8.32 g/100g pancakes) + (0.35 *22 g * 4.91 g/100g waffles)] = 4.49 g total sugar/day.

Glycemic index and glycemic load were calculated as follows[20, 31]: glycemic index of a person's diet per day = SUM (times of consumption per day * the amount of consumption in grams * carbohydrate contents/gram of food * glycemic index of individual food) / total carbohydrate consumption in grams / day; glycemic load of a person's diet per day = SUM (times of consumption per day * the amount of consumption in grams * carbohydrate contents/gram of food * glycemic index of individual food) /100. Similarly, when FFQ line items represent multiple foods or beverages, glycemic index/glycemic load calculation were weighted according to the assigned weights of individual foods or beverages.

Outcome Assessment: Vital Status

For the follow-up component of the EA/GCA studies, the vital status and date of death of EA/GCA cases were determined by linking participants with the National Death Index.[32] An

event was defined as death from any cause during the follow-up period and patients alive at the end of the follow-up period were censored.[32] Because EA/GCA are lethal diseases with median survival time of approximately 1 year,[32] I used all-cause death as an approximate of EA/GCA specific death. The maximum lengths of follow-up were 90 months and 129 months, for the US Multi-Center study and the LA Multi-Ethnic study, respectively.

Covariate Assessment

Covariate information (excluding dietary intake) was collected by each parent study during a structured in-person interview conducted by trained research interviewers.[5-8] The majority of covariates have already been harmonized by Drs. Wong-Ho Chow and Michael Cook, and other colleagues at the National Cancer Institute, for the purpose of previous BEACON pooled analyses.[33-37] Covariates that may potentially confound the sugar/carbohydrate intake - BE/EA/GCA outcomes association include proxy status, age, sex, race, income, education, smoking, GERD frequency, body mass index (BMI), fruits and/or vegetables intake, tumor stage, treatment, and total energy intake. Directed acyclic graphs (DAGs, **Figures 2.1-2.3**) and hand-driven backward elimination were utilized to identify potential confounders.[38] First, covariates were determined whether to be included in the DAGs based on prior knowledge and existing literature.[38-43] Further, potential confounders were determined using DAG rules. Finally, due to power considerations, hand-driven backward elimination was conducted starting with the adjustment sets identified from DAG analysis to identify a more parsimonious subset of confounders. Confounders identified from DAG analysis were assessed if inclusion of the confounder changed the $\log_e$ form of the effect estimate by >10%.[38] In sum, the covariates were included in the statistical model if both criteria (DAG analysis and change-in-estimate >10%) were met.

Obesity (measured by BMI) and GERD were examined as potential effect measure modifiers of the positive association between specific type of sugar/carbohydrate measurement

and specific tumor outcome. Obesity and GERD were selected because they are two currently well-established risk factors for BE and EA/GCA, and they are strongly associated with BE and EA/GCA. BMI (weight in kg/ height in m^2) was calculated based on assessments that were obtained either by measuring participant's height and weight using established protocols, [7, 8] or asking the participant about their height and usual weight one year prior to the diagnosis (cases) or interview (controls).[6, 44] BMI was dichotomized in the EMM analysis (<25/≥25 kg/m^2). GERD refers to the combined exposure of heartburn or regurgitation because heartburn and regurgitation symptoms essentially reflect a similar exposure of the esophagus to gastric juice.[34] GERD frequency (categorized at the median), rather than GERD (ever/never) was used to better reflect the impact of GERD. GERD frequency was not adjusted for antacid medication use due to the limited information on antacid medication use and heterogeneity of antacid medications by study/over time.

Study Design

This dissertation incorporated both case-control and follow-up designs to address the study aims. The case-control design was used to address the research questions focused on determine whether sugar/carbohydrate intake is associated with tumor development, and the follow-up approach was used to address the questions focused on survival. Because BE and EA/GCA are rare disease and require a long induction period for tumor development, [25, 45] a case-control study design is more efficient for addressing the aims focused on elucidating factors associated with disease incidence. This study pooled data from four existing case-control studies,[1-4] which not only greatly enlarged the sample size, but also improve time-efficiency and cost-effectiveness because the dietary, covariates, and outcome data have been previously collected. Because the four studies share a lot of similarities, instead of pooling published risk estimates via a meta-analytical approach, this study pooled individual-level study data, which allowed for standardization of the epidemiologic models and harmonization of the

variables. Because EA and GCA are lethal cancers and the median survival time is approximately 1 year,[32] for the aims focused on mortality, I used this harmonized data and appropriately employ a follow-up approach.

One possible alternative, when I addressed the research questions focused on disease development, would be to utilize a cohort study design. Although a cohort study design would enable me to more accurately capture the dietary exposure (e.g. measuring sugar/carbohydrate intake at various time points prior to disease development), it is less time-efficient and less cost-effective than a case-control design due to the lengthy follow-up given that the study outcomes are rare. Therefore, a case-control design would be more practical and suitable for the aims focused on identifying whether sugar/carbohydrate intake is associated with the BE-adenocarcinoma continuum.

Results from Previous Analyses

Of the four parent studies, only the US Multi-Center Study has published results on the association between sugar/carbohydrate intake and cancer development.[16] It was suggested that starch intake was positively associated with GCA but not EA (ORs and 95%CIs were 1.12[0.80-1.59] and 1.61[1.14-2.28] for EA and GCA, respectively).[16] Total carbohydrate intake was suggested to be inversely associated with development of EA and GCA (ORs and 95%CIs were 0.34[0.20–0.58] and 0.70[0.42–1.17], respectively).[16]

Statistical Analysis

The first aim was to determine if sugar/carbohydrate intake is associated with the development of Barrett's esophagus, utilizing existing data from two parent BE studies (the Study of Reflux Disease, and Epidemiology and Incidence of BE Study). The second aim was to determine if sugar/carbohydrate intake is associated with the development of EA/GCA, utilizing existing data from two parent EA studies (the US Multi-Center Study and the LA Multi-Ethnic

Study). In addition, obesity (measured by BMI) or GERD (measured by frequency) was explored as EMMs of the significant associations between sugar/carbohydrate intake and risk of developing BE or EA/GCA. The third aim was to determine if sugar/carbohydrate intake is associated with survival following a diagnosis of EA/GCA, utilizing existing follow-up data from the two parent EA studies. Multiple measures of exposure (sugar/carbohydrate) were considered separately in this ancillary analysis, including sweetened desserts, sweetened beverages, sweetened desserts/beverages; added sugar; total sugar; sugar components (dietary free glucose, free fructose, sucrose); glycemic index, glycemic load; starch; or total carbohydrate.

Data Management

The parent studies were population-based[1-3] or community-based[8]. Dietary data for the parent studies was collected during a structured paper-based interview by trained interviewers[1, 2, 4] or using a self-administered questionnaire.[3] In the US Multi-Center Study, the principal investigators from different study sites (Dr. Marilie Gammon - NJ, Dr. Harvey Risch - CT, and Dr. Thomas Vaughan - WA) collaborated closely to ensure that the study methods were implemented and the same questionnaire was used at each study site. Similarly, Dr. Anna Wu and colleagues specifically designed the Los Angeles study to be compatible with the US Multi-Center Study (personal communication). Each parent study conducted quality control, and discrepancies were resolved by referencing the original interview documents.[1-8] The validated data were then linked with nutrient databases for the analyses of nutrient intake and total energy intake.[1-4]

Descriptive Analysis

The distributions of exposure, outcome, and covariates by each study were first examined, followed by examination on the distribution of harmonized exposure, outcome, and

covariates after pooling. For both the pooled analysis of BE and EA/GCA, the distribution of sex, race, BMI, GERD frequency, cigarette smoking, income, education, fruits and/or vegetables intake, sugar/carbohydrate intake, by case-control status were assessed as categorical measures using frequency (n) and relative frequency (%). In addition, age, fruits/vegetables intake, sugar/carbohydrate intake, and total energy intake were also assessed as continuous measures using histograms and descriptive statistics.

Exposure Variable Construction (Pooling)

The sugar/carbohydrate intake values I obtained after linking FFQs with University of Minnesota nutrient database were in continuous form. First, for each individual study, each measures of sugar/carbohydrate intake were examined both in the continuous form and a categorized form. For the continuous form, the amount of added sugar, total sugar, free glucose, free fructose, sucrose, starch, and total carbohydrate, was modeled using a unit of g/day. Sweetened desserts/beverages were modeled using a unit of serving/day, and the continuous form of glycemic index and glycemic load was examined based on the numbers (no unit are available). For the categorical form, quantiles was used to divide each type of the exposure measure, based on the intake distribution of each study's control group (case-control analysis) or case group (survival analysis), and the lowest quantile was used as the reference group.[25] I explored the quantile cut-offs (quartiles, tertiles, etc.) and spline models to determine the optimal categorization of these data. Further, raw FFQ data were pooled from existing studies on sugar/carbohydrate intake based on the study-specific quantiles, where respondent intake were ranked and quantiled within study before pooling.[25] In addition, I also tried pooling raw FFQ data based on absolute values, where respondent intake were ranked and quantiled with all studies combined. As described by Smith-Warner et al., I pooled FFQ data according to the identical cut-points based on absolute values from controls from both BE parent studies or both parent EA studies together.[46] I used both categories based on study-specific quantiles, and

categories defined by identical absolute intake cut-points across studies, because both of the two approaches have strengths. True differences in population intake were considered when using identical absolute intake cut-points but not study-specific quantiles. However, because reported sweetened desserts/beverages intake may increase with the number of high-added sugar food items on each FFQ, which is likely to vary across studies, study-specific quantiles may be a better approach than absolute intake cut-points to account for the variations in FFQ design. In Smith-Warner's pooled study,[46] the inverse fruit/vegetable intake-cancer risk associations were similar for both approaches. Thus, for this dissertation, I used study-specific quantiles as my primary approach, and considered absolute intake cut-points in a sensitivity analysis.

Analysis to Address Specific Aim 1

The multiple measures of dietary sugar/carbohydrate exposure were used separately to determine the association with risk of developing BE. After pooling the two parent BE studies based on study-specific quantiles or identical absolute intake cut-points, unconditional logistic regression was utilized to calculate odds ratios (ORs) and 95% confidence intervals (CIs).[47] Additionally, the associations with short-segment BE (SSBE, BE segment length <3cm) and long-segment BE (LSBE, BE segment length ≥3cm) were analyzed respectively, to cross-sectionally examine the continuum within BE development. The Wald Test was used to formally evaluate differences by segment length (<3cm/≥3 cm).[47] The best measure for the continuum of BE severity would be histologic type (defined by intestinal metaplasia, low-grade dysplasia, high-grade dysplasia), however, data on histologic type is unavailable. I therefore used BE length as a surrogate.

Potential confounders were assessed using both DAGs (**Figure 2.1**) and hand-driven backward elimination method (examine if inclusion of the confounder changed the $\log_e$ form of the effect estimate by >10%).[38] The minimal sufficient set identified by DAG analysis included

age (continuous), sex (male/female), race (white/other), BMI (<25/≥25 kg/m^2), fruit/vegetable intake (≤study-specific median/>study-specific median), frequency of GERD (≤weekly/>weekly), and total energy intake (kcal/day). Study (Study of Reflux Disease/Epidemiology and Incidence of BE) was adjusted in all models.

Obesity and GERD frequency were assessed in the significant sugar/carbohydrate - BE incidence associations as EMMs. Multiplicative effect measure modification was first assessed using likelihood ratio tests to compare regression models that include a multiplicative term compared to a model without that term, using $p<0.10$ as a priori criteria. Subsequently, additive effect modification was assessed using interaction contrast ratios (ICRs, also referred as relative excess risk due to interaction). ICR was calculated as follows: $ICR = OR_{11}-OR_{01}-OR_{10}+1$. The doubly unexposed group (exposed to neither the exposure nor the effect modifier) serves as the referent group. OR_{01} and OR_{10} refer to the OR contrasts between those singly exposed to those doubly unexposed. OR_{11} refers to OR contrasts between those doubly exposed to those doubly unexposed. ICRs that were significantly different from zero suggest the presence of additive interaction.

Analysis to Address Specific Aim 2

Similarly, the multiple measures of dietary sugar/carbohydrate exposure were used separately to determine the association with risk of developing EA and GCA. After pooling the two parent EA studies based on study-specific quantiles or identical absolute intake cut-points, polytomous logistic regression was used to calculate ORs and 95%CIs for EA and GCA as distinct outcomes.[48] Similarly, potential confounders were assessed using both DAGs (**Figure 2.2**) and hand-driven backward elimination. The minimal sufficient set identified by DAG analysis included age (continuous), sex (male/female), race (white/other), cigarette smoking (ever, never), fruit/vegetable intake (<median/≥median), GERD frequency (<weekly/≥weekly), BMI (<25/≥25 kg/m^2), and total energy intake (kcal/day, continuous). Study indicator (US Multi-

Center/LA Multi-Ethnic) was adjusted in all models. I assessed the role of obesity and GERD frequency respectively as EMMs in the significant sugar/carbohydrate - EA/GCA incidence associations. The details on EMM assessment were stated previously in the "analysis to address specific aim 1" section.

Analysis to Address Specific Aim 3

To determine if sugar/carbohydrate intake is associated with survival among EA/GCA cases, Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95%CIs for EA and GCA as distinct outcomes.[38] The proportional hazards (PH) assumption was evaluated using cross-product terms with log-time and exposure, and cross-product terms with log-time and each of the confounder. PH assumption was not violated in any of the models. The minimal sufficient set identified by DAG analysis included age (continuous), education (≤high school/some college or technical school/≥college graduate), study indicator, and total energy intake (kcal/day, continuous) (**Figure 2.3**).

All Models

In all models, linear trends were tested by modeling the sugar/carbohydrate measures as continuous variables.

Because total energy intake is often positively correlated with absolute intake of a specific nutrient, and may confound relationships between specific nutrients and the outcome, it was adjusted in all models for each of the specific aims.[49] The standard multivariate model (including a term for nutrient intake and total energy intake) was used for energy adjustment, which held energy constant when modeling nutrient intake in relation to the outcome.[49] Individuals with implausible reporting of total energy (beyond ±3 standard deviations (SDs) from study-specific $\log_e$-transformed mean energy intake) was excluded.[49]

Previous pooled analysis used a meta-analytic approach[46, 50-52] where the study-specific ORs/HRs (by quantiles) were calculated, and then pooled using random effect and/or fixed effect model. In this ancillary analysis, I pooled study-specific quantiles or categories defined by identical absolute intake cut-points across studies to calculate ORs/HRs, rather than using the meta-analytic approach. There are several reasons, as outlined here. (1) The number of studies to pool - two BE studies and two EA studies - is much smaller in this study compared to previous pooling studies focused on dietary intake. (2) The individual studies are all US studies, and the study subjects are primarily white and residents of highly educated and/or high-income areas in the US, and therefore may share similar diet, cultural, and environmental factors (e.g. Seattle BE study and KAISER BE study were conducted in western Washington and Northern California, respectively). (3) The four studies have very similar FFQ structures; for example, there is little variation in the number of food items covered in FFQ (ranging from 104 to 131), and the majority of food items were same/similar among the four studies. (4) Nutrient intake was assessed using a unified source - University of Minnesota nutrient database. Therefore, given the similarities in study approach and populations, I used a pooled approach. A sensitivity analysis was conducted using a meta-analytic approach to examine the robustness of the results. If study heterogeneity was present, for the pooled approach, an interaction term for study and the exposure variable was used to determine study heterogeneity, and the interaction term was included in the model if statistically significant (and was omitted if it is not statistically significant).

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Sensitivity Analyses

In addition to the sensitivity analyses mentioned above (examination of individual absolute cut-points in addition to study-specific cut-points, and consideration of a meta-analytic analysis), I also conducted the following sensitivity analyses.

A unified source - University of Minnesota nutrient database was used to estimate sugar/carbohydrate intake in this study since the majority of measures were not available from the originally processed nutrient data. However, carbohydrate intake values were available in the processed data from each of the four studies, and therefore a sensitivity analysis was conducted to estimate the ORs/HRs for the association between total carbohydrate intake and outcomes. The effect estimates based on study - specific nutrient database were compared with the estimates obtained by utilizing the unified source to examine if utilizing a unified nutrient database substantially altered the results.

Both parent EA studies have included proxy responses since some patients were unable to participate in the interview due to illness or death. A sensitivity analysis was conducted by excluding data obtained from proxy interviews. If the effect estimates are similar to the estimates obtained without exclusion, proxy responses were included to increase power. Given that most of the cases were male, and recall/reporting by wives may be better than that by husbands because wives do more of the food preparation,[53] it is unlikely the effect estimates were altered due to the proxy responses. Due to power considerations, this sensitivity analysis was not conducted by differentiating sex.

Income data were available for the US Multi-Center Study and the two BE parent studies, but not for the LA Multi-Ethnic Study. Therefore, in the aim 2 analysis, income variable was not adjusted in the models. Therefore, a sensitivity analysis was conducted to consider income as a potential confounder in US Multi-Center Study to examine whether the results were altered.

Individuals with implausible reporting of total energy (as defined by beyond ±3 standard deviations (SDs) from study-specific $\log_e$-transformed mean energy intake) were excluded in the analysis. A sensitivity analysis was conducted to allow a wider exclusion, such as upper/lower 2.5%.[49]

To be consistent with previous studies and examine the robustness of the results based on the pooled approach described above (pooling study-specific quantiles or absolute intake

categories to calculate ORs/HRs), a meta-analytic approach was also utilized to calculate summary ORs/HRs. First, study-specific ORs/HRs and 95%CIs were estimated for the association between exposure and outcome in each study, adjusting for harmonized covariates. Then, summary ORs/HRs were generated by pooling study-specific ORs/HRs using both random-effects and fixed-effects meta-analysis.[54] The results based on pooled approach and meta-analytic approach were compared.

For the pooled analysis of BE parent studies and EA/GCA parent studies, I also (1) excluded total energy intake (as it may be on the causal pathway) from the covariate sets to see if the results were altered; and (2) considered an alternative energy adjustment method - nutrient density method. For the EA/GCA case-control analysis, I also adjusted for potential confounding by physical activity and diabetes, and explored ever history of diabetes as an EMM (using data from the LA Multi-Ethnic study (which included a limited number of positive responses), since this information was not available from the US Multi-Center study). However, I was not able to examine the associations by length of time with diabetes due to the small number of participants with diabetes. I further explored the effect of fructose from natural sources (fruits/vegetables) versus other fructose (mostly from added high-fructose corn syrup) on EA development. For examination of EMM in both BE and EA/GCA studies, I have used different cut-points to categorize the sugar/carbohydrate intake variables. For example, to maximize study power, I relied primarily on using medians as cut-points when examining EMM on sugar/carbohydrate-BE incidence associations. I also used the extreme quantiles (highest versus lowest) of sugar/carbohydrate intake when examining EMM on sugar/carbohydrate-BE incidence, and sugar/carbohydrate-EA incidence.

All analyses in this study were conducted using SAS version 9.3 (SAS Institute, Cary, NC) and Stata version 14.0 (StataCorp LP, College Station, TX). Results from the main data analyses as well as the sensitivity analyses are shown in **Tables 3.2-3.8**, **Tables 4.2-4.9**, and **Tables A.1-A.27**.

Statistical Power

This study was a pooled analysis of four existing US case-control studies. The specific aims are: (1) Determine if sugar/carbohydrate intake is associated with the risk of BE development (with aim 1A: explore whether overweight/obesity or GERD are effect measure modifiers [EMMs] of the significant associations between sugar/carbohydrate intake and risk of BE). (2) Determine if sugar/carbohydrate intake is associated with the development of EA/GCA (with aim 2A: explore whether overweight/obesity or GERD are EMMs of the significant associations between sugar/carbohydrate intake and risk of developing EA/GCA). (3) Determine if sugar/carbohydrate intake is associated with survival following a diagnosis of EA/GCA. In addition to employing the case-control designs, which focus on the association between sugar/carbohydrate intake and BE/EA/GCA development, I also used the follow-up approach to address the questions focused on survival. The sample size used for power calculations was based on the number of individuals who have completed a study-specific FFQ. Combining the two EA/GCA studies yielded 504 EA cases, 534 GCA cases, and 2045 non-cases; combining the two BE studies yielded 479 BE cases and 501 controls. Power calculations shown below have combined the EA and GCA cases. Power (1-β) for aim 1-3 and aim 1a/2a were estimated using SAS version 9.3 (SAS Institute, Cary, NC) and NCI Power Version 3.0, respectively, assuming a two-sided test at 5% significance level (α).

Aim 1 Study Power

Multiple measures were used to capture the dietary exposure of sugar/carbohydrate, including sweetened desserts, sweetened beverages, sweetened desserts/beverages; added sugar; total sugar; sugar components (dietary free glucose, free fructose, sucrose); glycemic index, glycemic load; starch; or total carbohydrate. Since quantiles (quartiles, tertiles, median) were used to divide each type of the exposure measure, the percentage of controls in the

highest level of exposure were 25%, 33%, or 50%, respectively. The effect estimates used (OR) to calculate the power for the main effects of sugar/carbohydrate intake on risk of developing BE ranges from 1.5-1.7, which is consistent with the effect of added sugar on EA risk as reported by Tasevska et al. (OR=1.62).[9] As shown in **Table 2.6**, for the effect on BE development, study power was good (>85%) when the exposure is dichotomized.

Aim 2 Study Power

Similar to aim 1, the percentage of controls in the highest level of exposure were 25%, 33%, or 50%, respectively. The effect estimates used to calculate the power for the main effects of sugar/carbohydrate intake on EA/GCA incidence ranges from 1.5-1.7.[9] As shown in **Table 2.6**, for the effect on EA/GCA incidence, study power was good (>90%).

The strongest positive association that I expect to find in the specific aim 2 analysis was added sugar-EA/GCA incidence association, and thus I assessed if there was interaction between obesity and added sugar on EA/GCA incidence, or interaction between GERD and added sugar on EA/GCA incidence. GERD and added sugar consumption were also used as dichotomous variables in this power calculation. The prevalence of obesity (BMI≥30kg/m^2) was estimated to range from 0.10 to 0.20, and the prevalence of GERD was estimated to range from 0.20 to 0.50. As shown in **Table 2.7**, power was good to evaluate both interactions with obesity and interactions with GERD (power 85% and >90%, respectively).

Aim 3 Study Power

Similar to aim 1 & aim 2, the percentages of controls in the highest level of exposure were 25%, 33%, or 50%, respectively, and the effect estimates ranges from 1.5-1.7.[9] Power calculations were based on the assumption that 13% of EA/GCA cases survived after a follow-up of 7.5 years.[32] As shown in **Table 2.6**, for the effect on EA/GCA survival, study power was excellent (>95%).

Data Interpretation Issues

A 30%-60% of increased risk in BE/EA/GCA outcome among participants who had higher sugar/carbohydrate consumption was expected. However, my results should be interpreted with caution.

Because the main exposure (sugar/carbohydrate intake) was assessed by FFQs, there are possibilities of misclassifications. Differential recall between cases and controls is possible due to the case-control study design of the parent studies. Another concern was that cases may alter their dietary habits when they experience some clinical symptoms. However, all of the parent studies attempted to capture the participants' usual diet 1-5 years prior to diagnosis or interview.[1-4] In addition, the foods that GERD patients are commonly recommended to omit comprise a small portion of foods that contribute to sugar/carbohydrate intake.[55] There is also possibility of errors in recall or report since the dietary intake was assessed a few years later. However, previous studies have reported a good correlation varying from 0.5 to 0.7 between dietary intake originally assessed and assessed by recall 3-10 years later.[56-59] Therefore, the dietary intake captured using FFQ is likely to be an appropriate estimate of the subjects' normal diet before disease initiation.

Another limitation is that since this study was a pooled analysis of multiple studies, there might be minor discrepancies in the original data collection, variable definitions, and data management, which may introduce misclassifications of exposure, covariates, or outcome. However, the demographic factors, the BMI, cigarettes smoking, alcohol drinking, nonsteroidal anti-inflammatory drug use, and GERD data have been successfully pooled in previous BEACON studies,[35-37, 60-62] which show promise in pooled analysis.

The four parent studies were conducted in late 1990s or early 2000s, whereas the University of Minnesota nutrient database I utilized was released in 2014. Therefore, there might be changes in sugar/carbohydrate contents in certain food items, especially in prepared foods

such as desserts. However, because University of Minnesota nutrient database was used as a unified source for all of the four studies and intake was compared based on relative values (ranking) rather than absolute values, it is unlikely the effect estimates would be altered. In addition, as discussed earlier, a sensitivity analysis was conducted by comparing the effect estimates based on study - specific nutrient database with the estimates obtained by utilizing the unified source to examine the robustness of the results.

Multiple comparisons issues also need to be considered. Twelve different measures of sugar/carbohydrate intake exposure and the outcomes of BE development, EA/GCA incidence, and survival among EA/GCA cases, were examined, which yielded 36 comparisons. It is possible that some statistically significant results were due to chance. I did not adjust for multiple comparisons due to power considerations. However, I evaluated associations individually based on consistency with published results, consistency of associations between studies included in this pooled analysis, and consistency across the continuum of cancer development.[49, 63, 64]

This study also has several strengths. By pooling data from four US studies I had an enlarged sample size to evaluate EMMs and was the first to explore EMM by GERD. By considering multiple measures of sugar/carbohydrate consumption, the complexity of this dietary exposure was better captured to help further understand the biological mechanisms. Another strength of this study is that multiple outcomes (BE incidence, EA/GCA incidence, and EA/GCA mortality) were examined, which allowed me to identify when along the cancer continuum (normal tissue → BE → EA/GCA → mortality) that sugar/carbohydrate intake intervenes and risk reduction strategies could be implemented. In addition, this study was the first to comprehensively examine the association between sugar/carbohydrate and EA/GCA survival.

Summary

The goal of this dissertation was to examine the association between sugar/carbohydrate intake and BE-EA/GCA cancer outcomes by conducting a pooled analysis of four existing case-control studies. To address the study aims, this study incorporated both case-control (to address the association with tumor development) and follow-up designs (to address the association with survival). Misclassifications of exposure, covariates, or outcome are possible due to the data collection method (using FFQs), data harmonization and pooling, proxy-responses, etc. However, several sensitivity analyses were conducted to examine the robustness of the results. Overall, this study is significant and the strengths of this study outweighed its limitations. Because sugar/carbohydrate intake is a modifiable factor, demonstration of an association between sugar/carbohydrate intake and risk of developing BE, risk of developing or dying from esophageal and gastric cardia adenocarcinoma may suggest potential to reduce cancer burden by limiting sugar/carbohydrate intake.

Figure 2.1. Directed acyclic graph of potential confounders of the association between sugar/carbohydrate intake and Barrett's esophagus development.

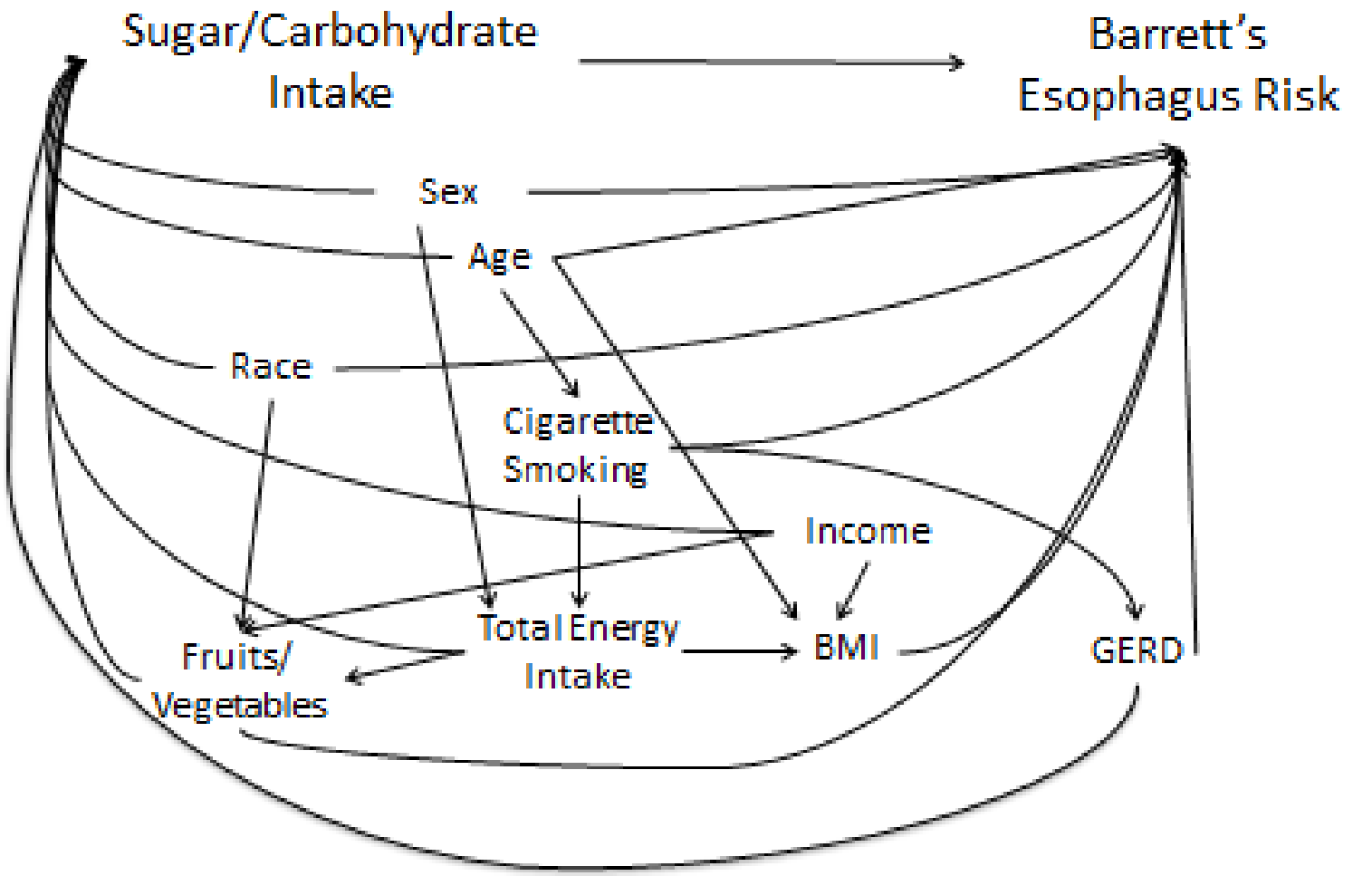

Figure 2.2. Directed acyclic graph of potential confounders of the association between sugar/carbohydrate intake and esophageal/gastric cardia adenocarcinoma development.

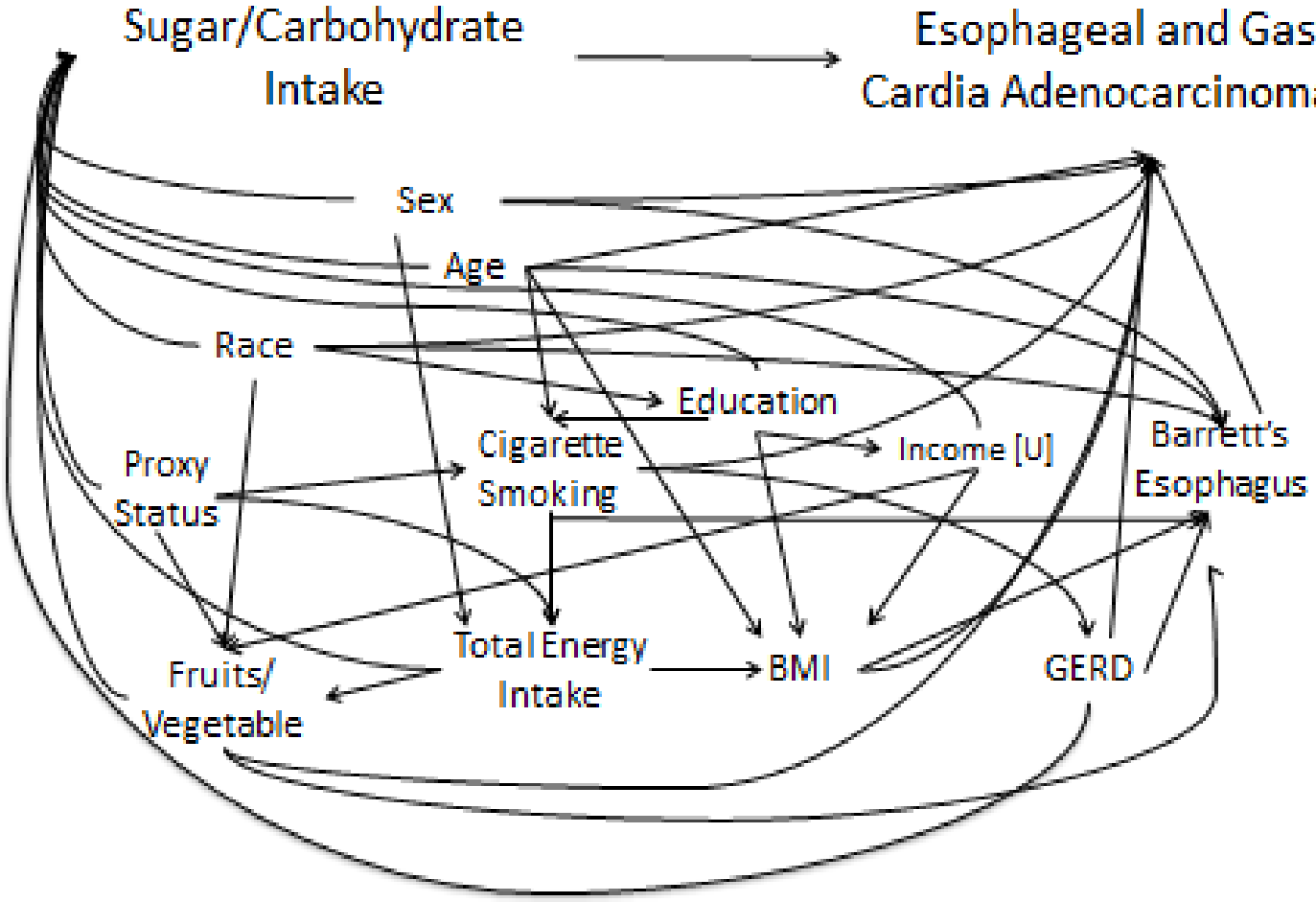

Figure 2.3. Directed acyclic graph of potential confounders of the association between sugar/carbohydrate intake and survival among cases of esophageal/gastric cardia adenocarcinoma.

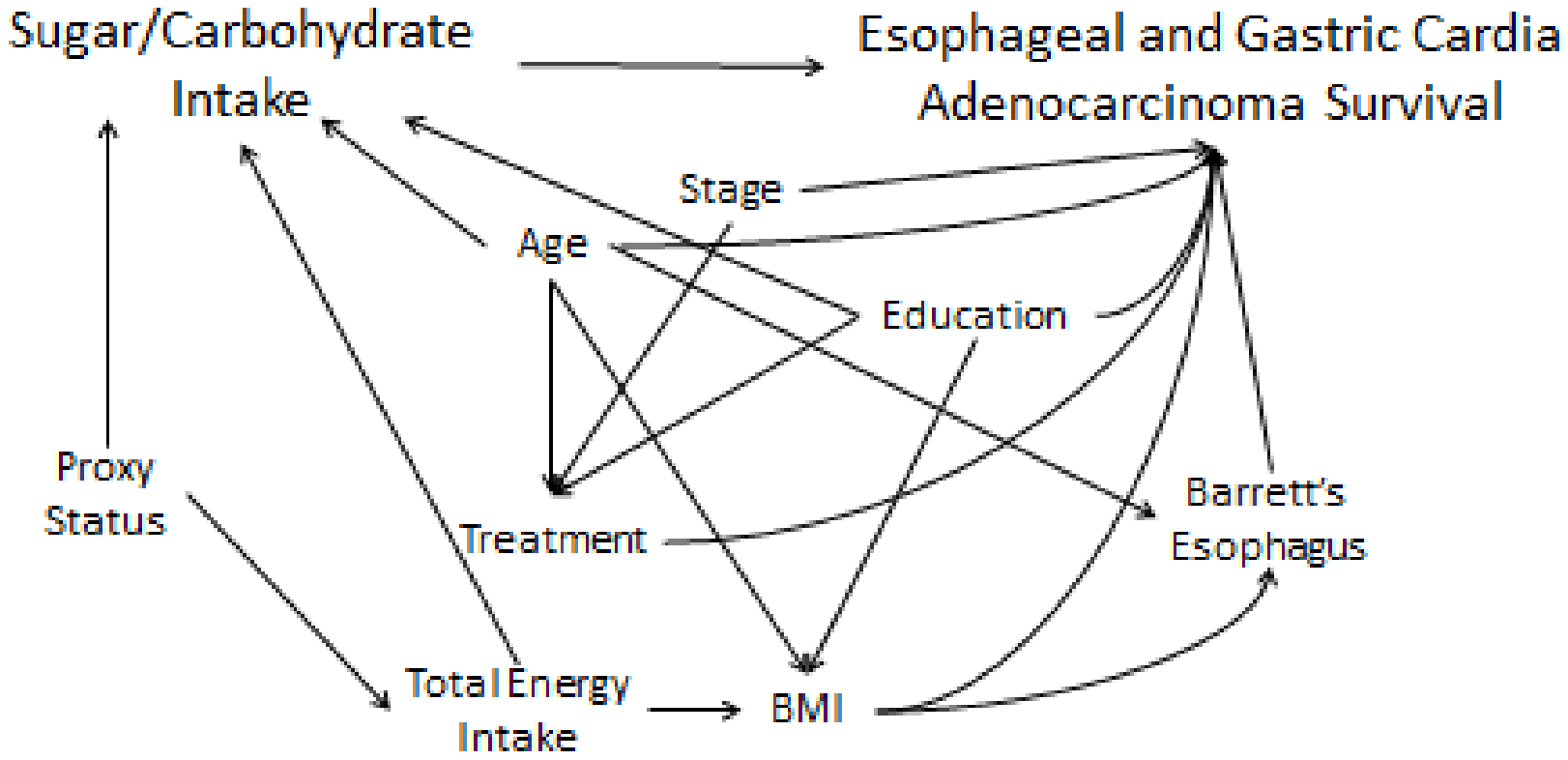

Table 2.1. Description of four parent studies and the sample sizes.

Name of the Study	Location	Study Period	Cases			Controls	Nutrient Database	# of FFQ Items
			BE	EA	GCA			
US Multi-Center Study[1]	CT, NJ, WA	1993-1995	-	293	261	695	University of Minnesota	104
LA Multi-Ethnic Study[2]	Southern CA	1992-1997	-	220	277	1356	University of Hawaii	124
Study of Reflux Disease[3]	Western WA	1997-2000	193	-	-	211	University of Minnesota	131
Epidemiology and Incidence of BE[4]	Northern CA	2002-2005	317	-	-	320	Block 98	110

Table 2.2. Distribution of demographic characteristics among case and control participants in the parent EA studies.

	US Multi-Center Study				LA Multi-Ethnic Study		
Characteristic	Control Participants N=695	Esophageal Adeno-carcinoma N=293	Gastric Cardia Adeno-carcinoma N=261	Characteristic	Control Participants N=1356	Esophageal Adeno-carcinoma N=222	Gastric Cardia Adeno-carcinoma N=277
Age, years				Age, years			
<57	179 (25.8)	76 (25.9)	65 (24.9)	<49	291 (21.4)	23 (10.4)	36 (13.0)
57-64	178 (25.6)	48 (16.4)	56 (21.5)	50-59	343 (25.3)	57 (25.7)	73 (26.4)
65-71	176 (25.3)	79 (27.0)	71 (27.2)	60-69	466 (34.4)	96 (43.2)	108 (39.0)
>71	162 (23.3)	90 (30.7)	69 (26.4)	70+	256 (18.9)	46 (20.7)	60 (21.7)
Sex				Sex			
Male	555 (79.9)	245 (83.6)	223 (85.4)	Male	999 (73.7)	202 (91.0)	231 (83.4)
Female	140 (20.1)	48 (16.4)	38 (14.6)	Female	357 (26.3)	20 (9.0)	46 (16.6)
Race				Race			
White	646 (93.0)	289 (98.6)	252 (96.6)	White	841 (62.0)	172 (77.5)	210 (75.8)
Black	34 (4.9)	2 (0.7)	4 (1.5)	African-American	90 (6.6)	3 (1.4)	10 (3.6)
Other	15 (2.2)	2 (0.7)	5 (1.9)	Latino-American	308 (22.7)	40 (18.0)	40 (14.4)
				Asian-American	117 (8.6)	7 (3.2)	17 (6.1)
Education				Education			
≤High School	308 (44.3)	158 (53.9)	141(54.0)	≤High School	504 (37.2)	99 (44.6)	121 (43.6)
Technical	175 (25.2)	78 (26.6)	61 (23.4)	Some College	392 (28.9)	64 (28.8)	86 (31.0)
≥College Graduate	212 (30.5)	57 (19.5)	59 (22.6)	≥College Graduate	460 (33.9)	59 (26.6)	70 (25.3)
Geographic Center				Geographic Center			
Connecticut	206 (29.6)	80 (27.3)	82 (31.4)	LA county	1356 (100.0)	222 (100.0)	277 (100.0)
New Jersey	333 (47.9)	138 (47.1)	113 (43.3)				
Washington	156 (22.5)	75(25.6)	66 (25.3)				

Table 2.3. Distribution of demographic characteristics among case and control participants in the parent BE studies.

	Study of Reflux Disease			Epidemiology and Incidence of BE	
	Controls	Barrett's Esophagus		Controls	Barrett's Esophagus
Characteristic	N=211	N=193	Characteristic	N=309	N=296
Age, years			Age, years		
20-39	31 (14.7)	27 (14.0)	Mean (SD)	62.3 (10.3)	62.3 (10.7)
40-49	53 (25.1)	49 (25.4)			
50-59	64 (30.3)	57 (29.5)			
60-80	63 (29.9)	60 (31.1)			
Sex			Sex		
Male	133 (63.0)	118 (61.1)	Male	208 (67)	218 (74)
Female	78 (37.0)	75 (38.9)	Female	101 (33)	77 (26)
Race			Race		
White	192 (91.0)	172 (89.1)	White	262 (85)	255 (86)
Black	5 (2.4)	3 (1.6)	Black	16 (5)	5 (2)
Other	14 (6.6)	18 (9.3)	Other	31 (10)	36 (12)
Education			Education		
≤High school	42 (19.9)	49 (25.4)	≤High school	85 (29)	77 (26)
Technical	9 (4.2)	9 (4.7)	Some college	105 (34)	134 (45)
≥College graduate	160 (75.8)	135 (70.0)	≥College graduate	132 (43)	85 (29)
Income			Income		
<$45,000	61 (28.9)	57 (29.5)	<$50,000	104 (36)	125 (46)
$45,000-$74,999	68 (27.0)	56 (29.0)	$50,000-$75,000	67 (23)	61 (22)
≥$75000	77 (36.5)	61 (31.6)	>$75,000	119 (41)	87 (32)
Unknown	16 (7.6)	19 (9.8)		173 (56)	197 (67)

Table 2.4. Comparison of the sugar/carbohydrate measures of the exposure.

Exposure Measurement	Definition/What the estimation was based on	What it represents/Why use this measure
Total sugar	Estimated based on nutrient intake analyses of each parent study; including naturally occurring sugar and added sugar	Representing the impact of total sugar
Sugar components (free glucose, free fructose, sucrose)	Estimated based on nutrient intake analyses of each parent study	Each sugar component has different metabolisms, which may lead to different effects on carcinogenesis.[19]
The amount of added sugar	Sugars and syrups that are added to foods during processing or preparation; estimated based on University of Minnesota nutrient database	Representing the impact of added sugar, which has different metabolisms than naturally occurring sugar
Sweetened desserts/beverages	Including sweetened desserts and sweetened beverages (**Table 2.5**)	More closely parallel the real world in which nutrients and foods are consumed in combination
Total carbohydrate	Estimated based on nutrient intake analyses of each parent study; including sugar, complex carbohydrate, and dietary fiber	Representing the impact of carbohydrate consumption, which affects blood glucose and insulin levels
Starch	Estimated based on nutrient intake analyses of each parent study	Representing the impact of starch - a common type of carbohydrate that is rich in cereal, bread, and pasta
Glycemic index	Calculated by summing the products of the carbohydrate content per serving for each food times the average number of servings of that food per day, times its glycemic index, all divided by the total amount of carbohydrate daily intake.[20, 31]	The glycemic index is an assessment of foods based on the incremental glucose response and insulin demand they produce for a given amount of carbohydrate.[65, 66]
Glycemic load	Calculated by multiplying the carbohydrate content of each food by its glycemic index, then multiplied this value by the frequency of consumption and summed the values from all foods.[20, 31]	Glycemic load estimates the impact of carbohydrate consumption using the glycemic index while taking into account the amount of carbohydrate that is consumed. Glycemic index and glycemic load are best measures of the effect of diet on blood glucose and insulin levels.

Table 2.5. Food frequency questionnaire items that were categorized as sweetened desserts/beverages.

US Multi-Center Study

Cereals, cold or cooked
Pancakes or waffles
Yogurt, all types, except frozen
Ice cream or milkshakes
Low-fat frozen desserts,
including frozen yogurt, sherbet, or ice milk
Pudding, custard, or flan
Jello, any flavor
Doughnuts, cakes, or pastries
Cookies
Pies
Chocolate candy or candy bars
Hard candy, jelly, jam, honey, or syrup
Sugar in coffee or tea or on cereal
Regular soft drinks or soda, not diet
Orange juice, grapefruit juice or Vitamin C enriched fruit drinks
Other fruit juices and fruit juice drinks
Kool-Aid

Study of Reflux Disease

Cold cereal
Pancakes and waffles
Nonfat yogurt (not frozen)
All other yogurt (not frozen)
Ice cream
Pudding, custard, and flan
Low-fat or non-fat frozen desserts,
such as frozen yogurt, Sherbet, ice milk, etc.
Doughnuts, cakes, pastries, Pop-Tarts, pan dulce
Cookies
Pumpkin and sweet potato pie
All other pies, fried pastries, pastelitos, and fruit empanadas
Chocolate candy and candy bars
Hard candy, jam, jelly, honey, or syrup
Sugar in coffee or tea and on cereal
Regular Soft drinks (not diet)
Orange juice and grape fruit juice
Tang, Kool-Aid, Hi-C, and other fruit drinks
Other fruit juices such as apple, grape

LA Multi-Ethnic Study

High fiber cereal such as bran, All-Bran, bran flakes, oat bran
Highly fortified cereals, such as Special K, Total
Other dry cereals, e.g. Cornflakes, Rice Krispies, granola, etc.
Chocolate milk, cocoa or ovaltine
Pancakes, waffles, French toast
Doughnuts, cookies, cakes, pastries, cinnamon rolls, danishes
Pumpkin or sweet potato pie
Other non-fruit pies
Chocolate candy
Other candy
Jellies, jam, honey syrup
Ice cream
Orange juice
Other citrus juice such as grapefruit, tangerine, lemonade
Other fruit juices including grape, cranberry, pineapple, etc.
Any type of fruit pie, cobbler
Caffeine-free soda (e.g. Pepsi-free, 7-up, Sprite, etc.)
Sodas with caffeine (Coca Cola, Pepsi, Dr. Pepper, etc.)
Other carbonated drinks including mineral water, fruit drinks, etc.

Epidemiology and Incidence of BE

Pancakes, waffles, French toast, Pop Tarts
Breakfast bars, granola bars, power bars
High-fiber cereals like All Bran, Raisin Bran, Fruit-n-Fiber
Product 19, Just Right or Total cereal
Any other cold cereal, like Corn Flakes, Cheerios, Special K
Yogurt or frozen yogurt
Doughnuts, Danish pastry
Cake, sweet rolls, coffee cake
Cookies
Ice cream, ice milk, ice cream, bars
Pumpkin pie, sweet potato pie
Any other pie or cobbler
Chocolate candy, candy bars
Other candy, not chocolate, like hard candy, caramel, jelly beans
Jelly, jam, or syrup
Sugar on coffee, sugar on tea
Regular soft drinks, or bottled drinks like Snapple (not diet drinks)
Real 100% orange or grapefruit juice, including fresh, frozen, or bottled
Other real fruit juices like apple juice, prune juice, lemonade
Kool-Aid, Hi-C, or other drinks with added vitamin C
Drinks with some juice in them, like Sunny Delight, Juice Squeeze
Instant breakfast milkshakes, diet shakes, or liquid supplements

Table 2.6. Power calculations for risk of Barrett's esophagus, esophageal and gastric cardia adenocarcinoma and survival among esophageal and gastric cardia adenocarcinoma cases.

	Barrett's Esophagus Development			**Risk of Esophageal and Gastric Cardia Adenocarcinoma**			**Survival among Esophageal and Gastric Cardia Adenocarcinoma Cases**		
Exposure Quantiles	Dichotomous	Tertile	Quartile	Dichotomous	Tertile	Quartile	Dichotomous	Tertile	Quartile
Minimum detectable odds/hazard Ratio									
1.7	98%	91%	82%	>99%	>99%	>99%	>99%	>99%	>99%
1.6	95%	84%	72%	>99%	>99%	99%	>99%	>99%	>99%
1.5	88%	72%	60%	99%	99%	96%	>99%	>99%	>99%

Table 2.7. Power calculations for interactions between added sugar and obesity or gastroesophageal reflux disease on risk of esophageal and gastric cardia adenocarcinomas.

Prevalence of Exposure		Theta[1]=2	Theta=3	Theta=0.5	Theta=0.3
Obesity	Added sugar intake	OR (x, y)=6.4	OR (x, y)=9.6	OR (x, y)=1.6	OR (x, y)=0.96
0.10	0.50	91%	>99%	85%	>99%
0.15	0.50	95%	>99%	93%	>99%
0.20	0.50	98%	>99%	97%	>99%
Gastroesophageal reflux disease	Added sugar intake	OR (x, y)=8.3	OR (x, y)=12.5	OR (x, y)=2.1	OR (x, y)=1.2
0.20	0.50	98%	>99%	98%	>99%
0.30	0.50	98%	>99%	>99%	>99%
0.50	0.50	94%	>99%	>99%	>99%

[1]Theta=OR (x, y)/ [OR (x)*OR (y)], where OR (x)=the odds ratio for high relative to low category of exposure to added sugar intake; OR (y)= the odds ratio for high (≥30) relative to low BMI or for GERD positive relative to GERD negative; OR (x, y)=the hypothesized OR for persons with the high category of added sugar intake and BMI or GERD positive.

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CHAPTER 3: DIETARY SUGAR/CARBOHYDRATE INTAKE AND BARRETT'S ESOPHAGUS - A POOLED ANALYSIS

Introduction

Incidence of esophageal adenocarcinoma (EA) has increased rapidly in many Westernized countries.[1-3] However, EA prognosis remains poor, with a 5-year survival of less than 20%.[4, 5] Barrett's esophagus (BE) is a key precursor lesion of EA.[6] The increasing incidence and poor prognosis of EA points to the importance of identifying modifiable risk factors that act early during carcinogenesis.

Known modifiable risk factors for BE are gastro-esophageal reflux disease (GERD), obesity, and cigarette smoking.[7-9] However, GERD usually requires continued medical therapy to control, and many interventions, particularly weight loss, are difficult to achieve or maintain.[10-12] Therefore, additional modifiable risk factors need to be identified.

Caloric sweetener intake has increased dramatically since 1960s,[13] corresponding to the increase in BE/EA risk in the last four decades. However, few studies have examined the associations between sugar/carbohydrate and BE/EA.[14-16] The link between sugar and cancer risk is biologically plausible. Long-term high intake of dietary sugar/carbohydrate may alter levels of insulin-like growth factor compounds, and subsequently promote carcinogenesis.[17-19] Specifically, insulin resistance may hamper the healing of esophageal mucosal injury and decrease cell apoptosis.[20] Thus, exposure to sugar/carbohydrate intake may be associated with development of EA and its precursor BE.

To comprehensively examine associations between multiple measures of sugar/carbohydrate intake and BE risk, we harmonized, pooled, and analyzed individual-level

participant data from two United States (US)-based case-control studies. If sugar/carbohydrate intake is found to be associated with BE risk, there is potential to reduce BE risk by providing clinical recommendations on limiting sugar/carbohydrate intake.

Methods

This study pooled data from two US community-based case-control studies of Barrett's esophagus, including the western Washington-based Study of Reflux Disease[21] and the Epidemiology and northern California-based Incidence of BE Study.[8] The two parent studies, from the International Barrett's and Esophageal Adenocarcinoma Consortium, were chosen due to their similarities in study design, study population, and data collection methodology (**Table 3.1**). This study was approved by the institutional review boards of the participating institutions.

Study Population. The Study of Reflux Disease was conducted in western Washington state.[21] Eligible cases were between 20-80 years of age, without a previous BE diagnosis, and who underwent an upper endoscopy for GERD symptoms at one of four community gastroenterology clinics during 1997-2000. Cases were those with endoscopic findings of BE and specialized intestinal metaplasia on at least one of the four biopsy specimens taken within the tubular esophagus. Controls were residents of western Washington state identified using a random digit dialing technique during the same period that cases were diagnosed.

The Epidemiology and Incidence of BE Study was conducted within the Kaiser Permanente Northern California (KPNC) population.[8] Cases and controls were 18-79 year-old KPNC members who were continuously enrolled (in KPNC) for at least 2 years, and were able to understand spoken and written English. Cases comprised individuals diagnosed with incident BE (endoscopic findings and biopsies with intestinal metaplasia) during 2002-2005. BE cases were identified using the International Classification of Disease, Ninth Revision code 530.2 and confirmed by review of endoscopy and pathology records. Controls were randomly selected

from the eligible KPNC members without a prior diagnosis of BE at the time the cases were diagnosed.

In total, the two studies provided 513 BE cases and 528 controls. We excluded individuals who did not complete a dietary intake assessment, or if their reported energy intake was beyond ±3 standard deviations from study-specific $\log_e$-transformed mean energy intake.[22] After exclusions there remained 472 BE cases and 492 controls for this pooled study.

Dietary Assessment. Both BE studies collected dietary information using a validated food frequency questionnaire (FFQ), either during a structured interview by trained interviewers[23] or through a self-administered questionnaire.[24] Participants were asked to report their dietary intake for the year before diagnosis (cases) or interview (controls).[23, 24] The Study of Reflux Disease utilized the 131-item FFQ developed by Fred Hutchison Cancer Research Center[23], and the Epidemiology and Incidence of BE Study utilized the 110-item FFQ (Block 98).[24] The two FFQs were similar in design and structure, including number of food items and frequency/portion size questions, which enhanced our ability to harmonize the diet data.

Assessment of Sugar/Carbohydrate Intake. Twelve measures were used to assess sugar/carbohydrate intake, including: sugar components (free glucose, free fructose, sucrose); added sugar; total sugar; starch; total carbohydrate; glycemic index; glycemic load; servings of sweetened desserts/beverages (servings of sweetened desserts; servings of sweetened beverages, and servings of sweetened desserts/beverages). Added sugar was defined as sugars and syrups added to foods during food preparation or commercial food processing, including white sugar, brown sugar, powdered sugar, honey, pancake syrup, corn syrups, high fructose corn syrups, and molasses.[25]

Primary data from the two study-specific FFQs were harmonized and linked with the University of Minnesota Nutrition Coordinating Center Food and Nutrient Database to estimate individual-level intake.[25] For example, sucrose intake was calculated as follows.

$$\text{Sucrose intake/day from an FFQ line item} = \text{amount of food consumed each time(g)} \times \text{frequency (/day)} \times \text{sucrose/g food}$$

Intake of sucrose per day was calculated by summing up the sucrose intake values across all line items in the FFQ.[26] When a FFQ line item represented multiple foods, the nutrient contents of the line item were weighted according to the estimated relative national distribution of intake for each food.[26]

FFQ items categorized as sweetened desserts/beverages were based on previous studies as listed in **Table 3.6**.[27-29] Dietary glycemic index and glycemic load were developed to reflect the putative effect of diet on blood glucose.[30, 31] For this pooled study, dietary glycemic index was calculated using the following formula.[30-32]

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

Similarly, dietary glycemic load was calculated as follows.[30-32]

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

Covariate Assessment. Covariate information for non-dietary factors was collected by each parent study during a structured in-person interview.[8, 21] Responses were harmonized in preparation for pooled analyses, as previously described.[9, 33, 34] Potential confounders were identified through the use of directed acyclic graphs (DAGs),[35] and included age (continuous), sex (male/female), race (white/other), fruit/vegetable intake (≤study-specific median/>study-specific median), body mass index (BMI, <25/≥25 kg/m^2), frequency of GERD (≤weekly/>weekly), and total energy intake (kcal/day). We adjusted for study (Study of Reflux Disease/Epidemiology and Incidence of BE) in all models.

Statistical Analysis. Estimated intake of sugar/carbohydrate from each BE study was pooled based on study-specific quartiles, which were determined by the distributions of intake among the controls in each study (**Table 3.7)**.[36] The individual-level intake values were also

pooled based on using absolute cut-points, which were determined by the intake distributions among all controls from both studies.[36] The results from both approaches were similar, and thus only the results based on the study-specific quartiles are shown.

Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between sugar/carbohydrate intake (categorized in quartiles) and BE risk, with each intake measure modeled separately.[35] Linear trends were tested by modeling the sugar/carbohydrate measures as continuous variables. All final models included adjustment for age, sex, study indicator, and total energy intake. Adjustment sets also included race, BMI, GERD frequency, and fruit/vegetable intake for select sugar/carbohydrate measures, if inclusion of the covariate changed the effect estimate on a $\log_e$ scale by ≥10%.[35] Cigarette smoking was considered, but not identified as a confounder by DAG analysis; also, inclusion of this covariate did not change the effect estimates by ≥10%. We evaluated effect measure modification on a multiplicative scale by BMI at interview (<25/≥25 kg/m^2), waist circumference at interview (≤101.6/>101.6 cm for male, ≤89.0/>89.0 cm for female), and frequency of GERD (≤weekly/>weekly) for any significant associations between sugar/carbohydrate (categorized at the median) and BE using the likelihood ratio test, by comparing models with and without interaction terms.[35]

Multinomial logistic regression was used to calculate ORs and 95%CIs for the associations between sugar/carbohydrate intake (categorized at the median) and BE by segment length (defined as short-segment BE (SSBE, <3 cm, n=248) and long-segment BE (LSBE, ≥3 cm, n=165)).[35, 37] The Wald Test was used to formally evaluate differences by segment length (<3cm/≥3 cm).[38] BE cases with unknown segment length (n=59) were not included in these models.

We conducted sensitivity analyses by: (1) pooling study-specific ORs using a meta-analytic approach[9, 36] (fixed effect, **Table 3.8**); (2) excluding total energy intake (as it may be on the causal pathway) from the covariate sets; (3) using nutrient density energy adjustment

method; (4) utilizing wider exclusion criteria for plausible total energy intake values (lower/upper 2.5%); (5) comparing effect estimates (ORs and CIs for carbohydrate intake-BE associations) derived using the intake values in the current study (estimated based on University of Minnesota nutrient database) versus the effect estimates derived using the previously calculated carbohydrate values by study-specific nutrient data processing center; and (6) categorizing the sugar/carbohydrate intake variables using cut-points other than the median, when examining effect measure modification. Our results were not substantially altered in any of the sensitivity analyses (data not shown for (2)-(6)).

SAS version 9.3 (SAS Institute, Inc., Cary, NC) was used for all analyses except for meta-analysis, which was analyzed using Stata version 14.0 (StataCorp LP, College Station, TX).

Results

Distributions of demographic factors by study and case-control status are shown in **Table 3.2**. Participants in the Northern California-based Epidemiology and Incidence of BE study were more likely to be older, male, non-White, with LSBE and higher prevalence of proton pump inhibitors use, consume more servings of fruits/vegetables, and were less likely to report frequent GERD (>weekly), compared to participants in the western Washington-based Study of Reflux Disease.

In both BE studies, the intake of sucrose, added sugar, and sweetened desserts/beverages, was higher in cases compared to controls (**Table 3.3**). In the Study of Reflux Disease, the intake of sucrose (g/day) was 36.07 and 33.51, the intake of added sugar (g/day) was 46.15 and 41.01, and the intake of sweetened desserts/beverages (servings/day) was 3.13 and 2.81, in cases and controls, respectively. In the Epidemiology and Incidence of BE study, the intake of sucrose (g/day) was 36.80 and 35.06, the intake of added sugar (g/day) was 44.18 and 40.68, and the intake of sweetened desserts/beverages (servings/day) was 2.26 and

2.10, in cases and controls, respectively.

After adjustment, BE risk was increased 79% and 71%, respectively, among those in the highest vs. lowest quartiles of sucrose ($OR_{Q4vs.Q1}$=1.79, 95%CI=1.07-3.02, P_{trend}=0.004) and added sugar intake ($OR_{Q4vs.Q1}$=1.71, 95%CI=1.05-2.80, P_{trend}=0.15) (**Table 3.4**). Sweetened desserts/beverages were associated with 71% increase in BE risk ($OR_{Q4vs.Q1}$=1.71, 95%CI=1.07-2.73, P_{trend}=0.04). The OR was also elevated for intake of sweetened beverages ($OR_{Q4vs.Q1}$=1.47, 95%CI=0.95-2.26, P_{trend}=0.29), although the 95%CI included the null. There were little or no associations between other measures of sugar/carbohydrate intake and BE risk. The association with sweetened desserts/beverages was elevated among those with lower waist circumference (OR=1.63, 95%CI=1.06-2.50), but not among those with higher waist circumference (OR=0.91, 95%CI=0.59-1.41, $P_{interaction}$=0.05). Other statistically significant associations were not modified by BMI, waist circumference, or GERD frequency (data not shown).

As shown in **Table 3.5**, associations with most sugar/carbohydrate intake measures differed significantly by segment length. Risk of SSBE was associated with increased intake of sucrose, total sugar, starch, total carbohydrate, glycemic load, sweetened desserts, or sweetened beverages. In contrast, the risk of LSBE was not associated with sugar/carbohydrate intake, except for glycemic load ($OR_{\geq median\ vs.<median}$=0.42, 95%CI=0.24-0.74). These findings did not vary by study site (data not shown).

Discussion

In this pooled US-based study, BE risk was increased by 71%-79% in association with added sugar, sucrose, and sweetened desserts/beverages for intake in the highest compared to the lowest quartile. Risk increased in a dose-dependent manner (P_{trend}<0.05) for both sucrose and sweetened desserts/beverages. Waist circumference appeared to modify the sweetened desserts/beverages-BE association. Thus, altering diet to reduce intake of added sugar or

sweetened desserts/beverages (especially among those with lower waist circumference) may be a potential risk reduction strategy.

Ours is the first study to investigate the role of added sugar, individual sugar components, and sweetened desserts/beverages in relation to BE risk. Our finding that added sugar was associated with increased risk of BE is consistent with a US-based cohort study that found that added sugar was associated with a 62% increase in EA risk.[16] Thus, from the perspective of the cancer development continuum, added sugar may either play a role during the early (development of BE), or at both early and later (development of EA) stages of carcinogenesis.

One previous BE study from Ireland considered several sugar/carbohydrate measures that were also examined in our study, including total sugar, starch, total carbohydrate, glycemic index, and glycemic load.[14] However, none of these other measures were associated with BE in either the Irish study or in our pooled study. It is possible that it is easier for participants to recall intake of foods with added sugar, than foods with naturally occurring sugar, and that this improved measurement yields stronger observed associations for intake of added sugar and sweetened desserts/beverages. However, even though added sugar and naturally occurring sugar are chemically identical, their physiological effects may differ. Naturally occurring sugar is an integral part of a cellular structure of whole foods (e.g., fruit), and is usually accompanied with vitamins, minerals, and fiber, which may slow down the absorption of sugar and moderate its impact on blood glucose.[39-41] Moreover, some of these substances can decrease inflammation or oxidative stress, and thus are potentially anti-carcinogenic.[40,42] In contrast, added sugar is usually present in processed foods that are low in micronutrients and fiber, more energy-dense, and are rapidly digestible. The quick absorption may lead to acute glucose fluctuations, which have been suggested to increase oxidative stress and subsequently to promote carcinogenesis.[43,44] Thus, our findings of a positive association between added sugar/ sweetened desserts/beverages and BE risk, but no association with the other

sugar/carbohydrate measures we considered, are biologically plausible.

We found a positive association between sucrose and BE. Sucrose was not associated with esophageal cancer in a US cohort study.[16] However, in that study, EA was not differentiated from esophageal squamous cell carcinoma. Because the epidemiology of these two tumor types differs substantially,[1, 2] it is unclear whether sucrose may have been associated with EA in the US cohort study. Many fruits/vegetables contain sucrose, but mostly in small amounts.[39] Sucrose is largely found in the form of table sugar that is added in preparation of baked goods, processed foods, and sweetened beverages.[25] Given that naturally occurring sucrose only contributes a small proportion of total sucrose, and the source of natural sucrose (fruits/vegetables) is associated with BE risk reduction, it is likely that the association between sucrose and BE we observed was driven by added sucrose. Consequently, our results suggest that clinical recommendations could target limiting table sugar intake, by reducing the intake of foods and beverages that are high in table sugar.

Multiple measures of sugar/carbohydrate intake were associated with SSBE, but were not associated (or in one instance, inversely associated), with LSBE. Given the small sample size for examining BE length despite our pooling efforts, our results regarding segment length may be spurious, and should be interpreted with caution. In addition, it remains unclear whether LSBE and SSBE have the same pathogenesis and natural history, or whether length of BE segment increases over time.[45] Nonetheless, our findings suggest that it is possible that SSBE may be more susceptible to sugar/carbohydrate intake than LSBE. Further studies are needed to explore these associations.

There are several limitations to our study. First, recall bias is possible due to the case-control design. However, the general lack of awareness of the sugar/carbohydrate-BE risk association by participants at the time of data collection may reduce the possibility of recall bias. Second, there may be non-differential measurement error (introduced by utilization of FFQ) and non-differential misclassification error (introduced by data harmonization and pooling). Thus, to

reduce the impact from these potential non-differential errors, we appropriately pooled and compared intake data based on relative rankings of sugar/carbohydrate intake within each study, instead of the absolute values. Third, because information on diabetes mellitus was not collected as part of the two parent studies, we were not able to assess the influence of diabetes on the associations between sugar/carbohydrate intake and BE. However, obesity is a strong risk factor for diabetes,[46] yet, we found a stronger association between sweetened desserts/beverages and BE risk only among those with lower waist circumference but not among those with generalized obesity, suggesting that sweetened desserts/beverages intake, independent of obesity (or potentially diabetes), may be a risk factor for BE. Further well-powered studies are needed to more formally evaluate the role of diabetes in the associations between sugar/carbohydrate and BE.

There are several strengths to our study. This is the first US study to comprehensively examine associations between sugar/carbohydrate intake and BE. To better capture the complexity of sugar/carbohydrate intake, improve understanding of the underlying mechanisms, and provide support for specific evidence-based dietary recommendations, we examined multiple measures, among which added sugar, individual sugar components, and sweetened desserts/beverages, had not been examined in previous BE studies. Moreover, by pooling individual-level data from two existing studies, we increased our sample size, which yielded more precise estimates of association. Further, harmonization of the exposure variables and covariates, and standardization of the statistical models have minimized potential sources of heterogeneity between studies. Most importantly, food selection is a non-pharmaceutical and potentially sustainable method for disease prevention, and is of interest to patients.[47]

In summary, our pooled study examined multiple measures of sugar/carbohydrate intake in relation to the risk of developing BE, and we are the first to report that added sugar, sucrose, and sweetened desserts/beverages were associated with a 71%-79% increase in BE risk. Our results suggest that clinical recommendations to limit intake of foods and beverages that are

high in added sugar (especially table sugar) could potentially reduce the risk of developing BE, a precursor to the lethal tumor EA.

Table 3.1. Comparison between the two studies of Barrett's esophagus.

	Study of Reflux Disease	Epidemiology and Incidence of BE
Study design	Community-based case-control study	Community-based case-control study
Time and location	Western WA, 1997-2000	Northern CA, 2002-2005
Sample size	193 BE cases, 211 controls	320 BE cases, 317 controls
FFQ (# items)	FHCRC (131)	Block 98 (110)
Frequency of consumption	Never or less than once per month, 1 per month, 2-3 per month, 1 per week, 2 per week, 3-4 per week, 5-6 per week, 1 per day	Never or less than once per month, 1 per month, 2-3 per month, 1 per week, 2 per week, 3-4 per week, 5-6 per week, 1 per day
Serving size	Small, medium, large	1/4 cup, 1/2 cup, 1 cup, 2 cups

FFQ: food frequency questionnaire
FHCRC: Fred Hutchinson Cancer Research Center

Table 3.2. Demographic characteristics among 472 cases and 492 controls from two US case-control studies of Barrett's esophagus.

	Study of Reflux Disease		Epidemiology and Incidence of BE	
Characteristic	**Controls N=191**	**Cases N=176**	**Controls N=301**	**Cases N=296**
Age, years, mean (SD)	53.37 (12.08)	54.75 (12.77)	62.35 (10.26)	62.28 (10.71)
Sex, n (%)				
Male	119 (62.30)	105 (59.66)	203 (67.44)	217 (73.31)
Female	72 (37.70)	71 (40.34)	98 (32.56)	79 (26.69)
Race, n (%)				
White	175 (91.62)	157 (89.20)	256 (85.05)	256 (86.49)
Other	16 (8.38)	19 (10.80)	45 (14.95)	40 (13.51)
BE segment length, n (%)				
<3cm	--	139 (84.76)	--	109 (43.78)
≥3cm	--	25 (15.24)	--	140 (56.22)
Cigarette smoking, n (%)				
Ever	92 (48.17)	114 (64.77)	170 (56.48)	198 (67.12)
Never	99 (51.83)	62 (35.23)	131 (43.52)	97 (32.88)
Gastro-esophageal reflux disease, n (%)				
Ever	126 (65.97)	160 (90.91)	138 (45.85)	250 (84.46)
Never	65 (34.03)	16 (9.09)	163 (54.15)	46 (15.54)
GERD frequency, n (%)				
≤Weekly	144 (75.79)	47 (26.70)	259 (86.05)	141 (47.64)
>Weekly	46 (24.21)	129 (73.30)	42 (13.95)	155 (52.36)
Proton pump inhibitors use, n (%)				
Ever	12 (6.32)	79 (44.89)	41 (13.71)	201 (68.37)
Never	178 (93.68)	97 (55.11)	258 (86.29)	93 (31.63)
Body mass index (kg/m^2)				
<25	62 (33.33)	35 (20.12)	70 (23.25)	59 (19.93)
25-<30	76 (40.86)	73 (41.95)	111 (36.88)	121 (40.88)
≥30	48 (25.81)	66 (37.93)	120 (39.87)	116 (39.19)
Fruit/vegetable intake, servings/day[1], median (SD)	1.71 (1.49)	1.71 (1.43)	4.40 (2.92)	3.65 (2.54)

[1]Based on study-specific serving sizes and study-specific food frequency questionnaires.
Missing values (N): GERD frequency (1), smoking (1), Proton Pump Inhibitors use (5), BMI (7), fruit/vegetable intake (32), BE segment length (59).

Table 3.3. Daily mean (SD) intake of sugar/carbohydrate among 472 cases and 492 controls in two US case-control studies of Barrett's esophagus.

Measure	Study of Reflux Disease		Epidemiology and Incidence of BE	
	Controls N=191	Cases N=176	Controls N=301	Cases N=296
Free glucose (g/day)	16.79 (13.42)	16.80 (11.57)	23.93 (14.48)	22.49 (13.91)
Sucrose (g/day)	33.51 (22.75)	36.07 (23.26)	35.06 (19.38)	36.80 (21.77)
Free fructose (g/day)	18.64 (17.16)	18.82 (14.69)	26.84 (17.89)	24.68 (17.06)
Total sugar (g/day)	86.30 (54.08)	91.14 (50.95)	100.56 (50.03)	99.38 (49.90)
Added sugar (g/day)	41.01 (42.96)	46.15 (36.00)	40.68 (32.12)	44.18 (33.23)
Starch (g/day)	75.84 (38.16)	74.97 (36.13)	68.40 (37.53)	66.30 (38.22)
Total carbohydrate (g/day)	196.95 (92.43)	200.92 (88.68)	215.44 (93.77)	209.17 (95.55)
Glycemic index	60.62 (4.43)	60.25 (4.68)	60.96 (3.54)	60.62 (4.29)
Glycemic load	109.23 (55.02)	111.34 (51.57)	116.63 (52.79)	113.28 (53.06)
All sweetened desserts/beverages[1] (servings/day)	2.81 (2.26)	3.13 (2.18)	2.10 (1.29)	2.26 (1.43)
Sweetened desserts[1] (servings/day)	1.58 (1.06)	1.76 (1.22)	1.45 (1.08)	1.53 (1.21)
Sweetened beverages[1] (servings/day)	1.23 (1.84)	1.37 (1.57)	0.64 (0.64)	0.73 (0.74)

[1]The differences in intakes 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 23 FFQ line items that contain sweetened desserts/beverages (15 line items contain sweetened desserts and 8 line items contain sweetened beverages) in Study of Reflux Disease. There were 18 FFQ line items that contain sweetened desserts/beverages (13 line items contain sweetened desserts and 5 line items contain sweetened beverages) in Epidemiology and Incidence of BE.

Table 3.4. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing Barrett's esophagus among 472 cases and 492 controls from two US case-control studies (pooled approach, based on study-specific quartiles).

Measure	Controls (N)	Cases (N)	OR (95%CI)	P_{trend}
Free glucose (g/day)[1]				
Q1	116	107	Ref.	
Q2	120	134	1.44 (0.94-2.21)	
Q3	123	115	1.26 (0.80-1.99)	
Q4	122	94	1.29 (0.77-2.17)	0.85
Sucrose (g/day)[2]				
Q1	117	105	Ref.	
Q2	120	108	1.07 (0.69-1.64)	
Q3	117	97	1.17 (0.74-1.86)	
Q4	122	138	1.79 (1.07-3.02)	<0.01
Free fructose (g/day)[1]				
Q1	115	108	Ref.	
Q2	123	131	1.35 (0.88-2.07)	
Q3	121	113	1.28 (0.81-2.03)	
Q4	122	98	1.26 (0.77-2.05)	0.66
Total sugar (g/day)[1]				
Q1	117	109	Ref.	
Q2	120	116	1.15 (0.75-1.78)	
Q3	122	103	1.09 (0.68-1.73)	
Q4	122	122	1.54 (0.89-2.67)	0.15
Added sugar (g/day)[2]				
Q1	119	97	Ref.	
Q2	118	100	1.12 (0.73-1.72)	
Q3	120	112	1.14 (0.73-1.80)	
Q4	119	139	1.71 (1.05-2.80)	0.15
Starch (g/day)[2]				
Q1	117	103	Ref.	
Q2	118	109	1.00 (0.65-1.56)	
Q3	121	133	1.36 (0.84-2.19)	
Q4	120	103	1.00 (0.52-1.90)	0.74
Total carbohydrate (g/day)[1]				
Q1	117	109	Ref.	
Q2	119	115	1.12 (0.72-1.75)	
Q3	123	127	1.29 (0.78-2.16)	
Q4	122	99	1.25 (0.61-2.54)	0.39

Glycemic index[3]				
Q1	122	112	Ref.	
Q2	122	109	0.83 (0.55-1.26)	
Q3	119	113	0.93 (0.62-1.41)	
Q4	118	116	0.93 (0.62-1.41)	0.39
Glycemic load[4]				
Q1	115	108	Ref.	
Q2	119	124	1.18 (0.76-1.84)	
Q3	123	109	1.12 (0.67-1.86)	
Q4	119	107	1.39 (0.71-2.70)	0.35
All sweetened desserts/beverages (servings/day)[5]				
Q1	123	94	Ref.	
Q2	123	124	1.33 (0.88-2.02)	
Q3	122	116	1.27 (0.82-1.95)	
Q4	123	138	1.71 (1.07-2.73)	0.04
Sweetened desserts (servings/day)[6]				
Q1	122	123	Ref.	
Q2	122	81	0.63 (0.41-0.96)	
Q3	121	126	1.12 (0.74-1.70)	
Q4	121	140	1.26 (0.80-1.99)	0.10
Sweetened beverages (servings/day)[3]				
Q1	118	97	Ref.	
Q2	121	108	1.11 (0.73-1.69)	
Q3	120	107	1.29 (0.84-1.98)	
Q4	122	138	1.47 (0.95-2.26)	0.29

[1]Adjusted for age, sex, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
[2]Adjusted for age, sex, race, study indicator, BMI, fruit/vegetable intake, GERD frequency, and total energy intake
[3]Adjusted for age, sex, race, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
[4]Adjusted for age, sex, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
[5]Adjusted for age, sex, study indicator, GERD frequency, and total energy intake
[6]Adjusted for age, sex, study indicator, BMI, GERD frequency, and total energy intake

Table 3.5. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing Barrett's esophagus by BE segment length among 413 cases and 492 controls from two US case-control studies (pooled approach, based on study-specific medians).

		Short-segment BE(<3cm)		Long-segment BE (≥3cm)		*P-value**
Measure	**Controls (N)**	**Cases (N)**	**OR (95%CI)**	**Cases (N)**	**OR (95%CI)**	
Free glucose (g/day)[1]						
<median	236	116	Ref.	96	Ref.	
≥median	245	117	1.23 (0.83-1.83)	65	0.74 (0.47-1.16)	0.04
Sucrose (g/day)[1]						
<median	239	98	Ref.	91	Ref.	
≥median	242	135	1.70 (1.12-2.58)	70	0.82 (0.51-1.31)	<0.01
Free fructose (g/day)[1]						
<median	238	118	Ref.	91	Ref.	
≥median	243	115	1.21 (0.82-1.79)	70	0.92 (0.59-1.43)	0.27
Total sugar (g/day)[1]						
<median	237	102	Ref.	95	Ref.	
≥median	244	131	1.57 (1.03-2.39)	66	0.72 (0.45-1.17)	<0.01
Added sugar (g/day)[2]						
<median	237	96	Ref.	78	Ref.	
≥median	239	135	1.50 (0.99-2.26)	83	0.95 (0.60-1.50)	0.07
Starch (g/day)[1]						
<median	237	99	Ref.	91	Ref.	
≥median	244	134	1.65 (1.05-2.58)	70	0.76 (0.45-1.26)	<0.01
Total carbohydrate (g/day)[1]						
<median	236	102	Ref.	96	Ref.	
≥median	245	131	1.72 (1.07-2.77)	65	0.63 (0.37-1.10)	<0.01
Glycemic index[3]						
<median	244	108	Ref.	86	Ref.	
≥median	232	123	1.06 (0.75-1.50)	75	0.90 (0.60-1.33)	0.44
Glycemic load[1]						

<median	236	99	Ref.	104	Ref.	
≥median	245	134	1.76 (1.10-2.82)	57	0.42 (0.24-0.74)	0.01
All sweetened desserts/beverages (servings/day)[4]						
<median	236	104	Ref.	79	Ref.	
≥median	241	127	1.22 (0.84-1.75)	82	1.04 (0.68-1.57)	0.51
Sweetened desserts (servings/day)[2]						
<median	238	91	Ref.	81	Ref.	
≥median	238	140	1.81 (1.20-2.71)	80	1.08 (0.69-1.68)	0.04
Sweetened beverages (servings/day)[5]						
<median	245	104	Ref.	78	Ref.	
≥median	246	144	1.48 (1.05-2.11)	87	1.27 (0.85-1.89)	0.47

[1]Adjusted for age, sex, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
[2]Adjusted for age, sex, race, study indicator, BMI, fruit/vegetable intake, GERD frequency, and total energy intake
[3]Adjusted for age, sex, study indicator, BMI, fruit/vegetable intake, GERD frequency, and total energy intake
[4]Adjusted for age, sex, study indicator, BMI, fruit/vegetable intake, and total energy intake
[5]Adjusted for age, sex, race, study indicator, fruit/vegetable intake, and total energy intake
*P value for Wald test of equality of effect across the different outcome types

Table 3.6. Food frequency questionnaire items that were categorized as sweetened desserts/beverages in each of the two US case control studies of Barrett's esophagus.

Study of Reflux Disease (Western Washington State)	**Epidemiology and Incidence of BE (Northern California)**
Cold cereal	Pancakes, waffles, French toast, Pop Tarts
Pancakes and waffles	Breakfast bars, granola bars, power bars
Nonfat yogurt (not frozen)	High-fiber cereals like All Bran, Raisin Bran, Fruit-n-Fiber
All other yogurt (not frozen)	Product 19, Just Right or Total cereal
Ice cream	Any other cold cereal, like Corn Flakes, Cheerios, Special K
Pudding, custard, and flan	Yogurt or frozen yogurt
Low-fat or non-fat frozen desserts	Doughnuts, Danish pastry
Doughnuts, cakes, pastries, Pop-Tarts, pan dulce	Cake, sweet rolls, coffee cake
Cookies	Cookies
Pumpkin and sweet potato pie	Ice cream, ice milk, ice cream, bars
All other pies, fried pastries, pastelitos, and fruit empanadas	Pumpkin pie, sweet potato pie
Chocolate candy and candy bars	Any other pie or cobbler
Hard candy, jam, jelly, honey, or syrup	Chocolate candy, candy bars
Sugar in coffee or tea and on cereal	Other candy, not chocolate, like hard candy, caramel, jelly beans
Regular Soft drinks (not diet)	Jelly, jam, or syrup
Orange juice and grape fruit juice	Sugar on coffee, sugar on tea
Tang, Kool-Aid, Hi-C, and other fruit drinks	Regular soft drinks, or bottled drinks like Snapple (not diet drinks)
Other fruit juices such as apple, grape	Real 100% orange or grapefruit juice, including fresh, frozen, or bottled
	Other real fruit juices like apple juice, prune juice, lemonade
	Kool-Aid, Hi-C, or other drinks with added vitamin C
	Other fruit juices such as apple, grape

Table 3.7. Study-specific sugar/carbohydrate intake quartiles defined by the intake distribution of the controls from each of the two US case-control studies of Barrett's esophagus.

Measure	Study of Reflux Disease	Epidemiology and Incidence of BE	Controls (N=492)	Cases (N=472)
Free glucose (g/day)				
Q1	1.61-<9.45	2.93-<13.17	123	115
Q2	9.45-<14.12	13.17-<20.89	123	135
Q3	14.12-<19.93	20.89-<30.63	123	123
Q4	≥19.93	≥30.63	123	99
Sucrose (g/day)				
Q1	2.26-<17.71	4.16-<22.14	123	111
Q2	17.71-<30.30	22.14-<31.85	123	117
Q3	30.30-<42.19	31.85-<44.17	123	100
Q4	≥42.19	≥44.17	123	144
Free fructose (g/day)				
Q1	1.48-<9.69	1.92-<13.74	123	116
Q2	9.69-<15.23	13.74-<22.50	123	134
Q3	15.23-<22.04	22.50-<34.99	123	118
Q4	≥22.04	≥34.99	123	104
Total sugar (g/day)				
Q1	10.85-<52.18	14.55-<65.72	123	115
Q2	52.18-<79.96	65.72-<93.47	123	122
Q3	79.96-<107.09	93.47-<123.44	123	105
Q4	≥107.09	≥123.44	123	130
Added sugar (g/day)				
Q1	1.77-<19.08	1.77-<20.11	123	106
Q2	19.08-<33.20	20.11-<32.15	123	101
Q3	33.20-<50.32	32.15-<50.25	123	116
Q4	≥50.32	≥50.25	123	149
Starch (g/day)				
Q1	4.48-<47.94	7.05-<41.29	123	113
Q2	47.95-<69.39	41.29-<58.63	123	117
Q3	69.39-<98.56	58.63-<86.34	123	136
Q4	≥98.56	≥86.34	123	106
Total carbohydrate (g/day)				
Q1	35.56-<129.08	38.13-149.58	123	114
Q2	129.09-<180.00	149.58-202.76	123	121
Q3	180.00-<251.16	202.76-265.03	123	135
Q4	≥251.16	≥265.03	123	102
Glycemic index				
Q1	22.27-<59.08	35.36-<58.77	123	122
Q2	59.08-<61.01	58.77-<61.11	123	113

Q3	61.01-<63.10	61.11-<63.13	123	116
Q4	≥63.10	≥63.13	123	121
Glycemic load				
Q1	16.69-<70.97	21.61-<78.20	123	117
Q2	70.97-<97.77	78.20-<111.72	123	126
Q3	97.77-<138.37	111.72-<142.48	123	119
Q4	≥138.37	≥142.48	123	110
All sweetened desserts/beverages (servings/day)				
Q1	0-<1.29	0.06-<1.13	123	94
Q2	1.29-<2.44	1.13-<1.88	123	124
Q3	2.44-<3.75	1.88-<2.81	123	116
Q4	≥3.75	≥2.81	123	138
Sweetened desserts (servings/day)				
Q1	0-<0.78	0-<0.68	123	124
Q2	0.78-<1.36	0.68-<1.14	123	81
Q3	1.36-<2.22	1.14-<1.98	123	127
Q4	≥2.22	≥1.98	123	140
Sweetened beverages (servings/day)				
Q1	0-<0.20	0-<0.12	123	102
Q2	0.20-<0.71	0.12-<0.52	123	109
Q3	0.71-<1.47	0.52-<1.00	123	116
Q4	≥1.47	≥1.00	123	145

Table 3.8. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing Barrett's esophagus among 472 cases and 492 controls from two US case-control studies (meta-analytic approach, fixed effect).

Measure	Controls (N)	Cases (N)	OR (95%CI)	I^2 (%)	$P_{heterogeneity}$
Free glucose (g/day)[1]					
Q1	116	107	Ref.		
Q2	120	134	1.43 (0.93-2.21)	0	0.68
Q3	123	115	1.27 (0.80-2.02)	0	0.38
Q4	122	94	1.28 (0.75-2.16)	0	0.32
P_{trend}			0.78	0	0.79
Sucrose (g/day)[2]					
Q1	117	105	Ref.		
Q2	120	108	1.07 (0.69-1.66)	4.4	0.31
Q3	117	97	1.17 (0.73-1.86)	0	0.85
Q4	122	138	1.78 (1.05-3.01)	0	0.997
P_{trend}			0.08	51.1	0.15
Free fructose (g/day)[1]					
Q1	115	108	Ref.		
Q2	123	131	1.36 (0.88-2.09)	0	0.70
Q3	121	113	1.28 (0.81-2.05)	0	0.75
Q4	122	98	1.23 (0.74-2.03)	43.4	0.18
P_{trend}			0.63	0	0.66
Total sugar (g/day)[1]					
Q1	117	109	Ref.		
Q2	120	116	1.17 (0.75-1.80)	28.1	0.24
Q3	122	103	1.08 (0.67-1.73)	0	0.59
Q4	122	122	1.57 (0.90-2.75)	0	0.76
P_{trend}			0.24	0	0.83
Added sugar (g/day)[2]					
Q1	119	97	Ref.		
Q2	118	100	1.11 (0.72-1.70)	0	0.78
Q3	120	112	1.15 (0.73-1.82)	0	0.72
Q4	119	139	1.69 (1.03-2.77)	0	0.81
P_{trend}			0.22	0	0.46
Starch (g/day)[2]					
Q1	117	103	Ref.		
Q2	118	109	0.99 (0.64-1.54)	0	0.43
Q3	121	133	1.37 (0.84-2.21)	0	0.92
Q4	120	103	0.98 (0.51-1.89)	0	0.69
P_{trend}			0.76	0	0.81
Total carbohydrate (g/day)[1]					
Q1	117	109	Ref.		

Q2	119	115	1.13 (0.72-1.78)	0	0.81
Q3	123	127	1.31 (0.78-2.20)	0	0.61
Q4	122	99	1.26 (0.61-2.61)	0	0.38
P_{trend}			0.34	0	>0.99
Glycemic index[3]					
Q1	122	112	Ref.		
Q2	122	109	0.83 (0.55-1.26)	0	0.36
Q3	119	113	0.93 (0.61-1.40)	0	0.34
Q4	118	116	0.93 (0.61-1.41)	0	0.72
P_{trend}			0.36	0	0.82
Glycemic load[4]					
Q1	115	108	Ref.		
Q2	119	124	1.18 (0.75-1.84)	0	0.89
Q3	123	109	1.13 (0.67-1.89)	0	0.36
Q4	119	107	1.36 (0.69-2.68)	26.8	0.24
P_{trend}					
All sweetened desserts/beverages (servings/day)[5]					
Q1	123	94	Ref.		
Q2	123	124	1.33 (0.88-2.01)	0	0.37
Q3	122	116	1.25 (0.81-1.93)	0	0.79
Q4	123	138	1.69 (1.06-2.72)	0	0.51
P_{trend}			0.05	39.7	0.20
Sweetened desserts (servings/day)[6]					
Q1	122	123	Ref.		
Q2	122	81	0.62 (0.40-0.95)	55.1	0.14
Q3	121	126	1.11 (0.73-1.69)	38.3	0.20
Q4	121	140	1.22 (0.77-1.93)	0	0.39
P_{trend}			0.12	0	0.35
Sweetened beverages (servings/day)[3]					
Q1	118	97	Ref.		
Q2	121	108	1.12 (0.73-1.72)	0.0	0.49
Q3	120	107	1.30 (0.84-1.99)	0.0	0.45
Q4	122	138	1.50 (0.97-2.30)	48.0	0.17
P_{trend}			0.29	0	0.41

[1]Adjusted for age, sex, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
[2]Adjusted for age, sex, race, study indicator, BMI, fruit/vegetable intake, GERD frequency, and total energy intake
[3]Adjusted for age, sex, race, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
[4]Adjusted for age, sex, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
[5]Adjusted for age, sex, study indicator, GERD frequency, and total energy intake
[6]Adjusted for age, sex, study indicator, BMI, GERD frequency, and total energy intake

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CHAPTER 4: A POOLED ANALYSIS OF DIETARY SUGAR/CARBOHYDRATE INTAKE AND ESOPHAGEAL AND GASTRIC CARDIA ADENOCARCINOMA IN THE UNITED STATES (US)

Introduction

Incidence 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 overall 5-year survival for these cancers remains low at <20%.[10, 11] Therefore, 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.

In addition to gastro-esophageal reflux disease (GERD) and cigarette smoking, obesity is an established EA/GCA risk factor.[12-14] As such, exploration of the role of glucose metabolism in the development of EA/GCA appears warranted.[15-17] Long-term high sugar/carbohydrate intake may lead to chronic hyperinsulinemia, which may decrease esophageal cell apoptosis and prolong healing time after esophageal mucosal injury thereby promoting carcinogenesis.[17-20] Intake of foods high in refined sugar leads to acute fluctuations in blood glucose, which may induce oxidative stress and modulate the carcinogenesis pathways.[21-23] Whether sugar intake, which has also increased dramatically since 1960s,[24] is associated with risk of developing EA has been investigated in several epidemiologic studies, with inconsistent results.[16, 25, 26] Only one study has examined the role of sugar/carbohydrate intake in association with survival among individuals diagnosed with EA.[27]

In this study, we harmonized and pooled individual-level data from two case-control studies conducted within the US, 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, [28, 29] selected from the International Barrett's and Esophageal Adenocarcinoma Consortium (BEACON) because both are population-based with follow-up information on vital status and are similar in data collection methodology. The institutional review boards of all participating institutions approved this study.

Study Population. The US Multi-Center study was conducted in Connecticut, New Jersey, and western Washington state.[28] Eligible cases were 30-79 year-old English-speaking men and women diagnosed with first primary invasive cancer of the esophagus or stomach during 1993-1995. 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 random digit-dialing 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, race.

The LA Multi-Ethnic study was conducted in LA County, California.[29] Cases were 30-74 year-old men and women diagnosed with first primary cancer of esophagus or stomach during 1992-1997. 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 neighborhood 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 or 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.[30]

Dietary Assessment. In both studies, dietary information was collected using validated food frequency questionnaires (FFQs) during structured in-person interviews.[31, 32] 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.[31, 32] The US Multi-Center Study utilized a 104-item FFQ, a modification of the Fred Hutchinson Cancer Research Center instrument.[33] Participants were asked to report their usual diet in the 3-5 years before diagnosis (cases) or interview (controls).[31] The LA Multi-Ethnic Study utilized a 124-item FFQ developed at University of Hawaii.[32] Cases were asked to report their diet in the year before the date of diagnosis, and controls were asked to report their diet during the same time period as their matched case.[32] The two FFQs similarly assessed dietary intake (food items, frequency, and total number of food items) (**Table 4.1**), which enhanced our ability to harmonize and pool data.

Sugar/Carbohydrate Intake Assessment. We estimated twelve intake measures including sugar components (free glucose, free fructose, sucrose); total sugar; added sugar; total carbohydrate; starch; glycemic index; glycemic load; servings of sweetened desserts, sweetened beverages, and sweetened desserts/beverages (**Table 4.5**). Added sugar was defined as sugars and syrups that were added to foods during food preparation/processing.[34] 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.[34] For example, daily starch intake from an FFQ line item was calculated as follows.[35]

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

Daily intake of starch was calculated by summing up 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 national consumption pattern.[35-37]

Dietary glycemic index and glycemic load were developed to estimate the effect of diet on blood glucose. For this study, the following formulas were used to calculate dietary glycemic index and dietary glycemic load,[38-40] respectively.

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

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

Covariate Assessment. Information on non-dietary covariates was collected in-person by each study using interviewer-administered questionnaires.[28, 29] Covariates were harmonized, as previously described.[12-14]

Outcome Assessment. Vital status and date of death for EA/GCA cases were determined by linking participants with the National Death Index.[41] 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 based on study-specific quintiles (Q), based on the study-specific intake distributions among the controls (case-control analysis) or EA/GCA patients (survival analysis).[30, 42]

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, with each of the intake measures and outcomes modeled separately.[43] We explored whether body mass index (BMI<25/≥25kg/m^2 during adulthood[44] or year before interview[29]), or frequency of GERD (<weekly/≥weekly) were effect measure modifiers of the associations between sugar/carbohydrate intake(comparing Q1-3 vs. Q4-5) and EA/GCA incidence. Effect

measure modification was assessed using the likelihood ratio test (multiplicative scale) and the interaction contrast ratio (ICR) and 95%CI (additive scale)[45]

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, with each intake measure and outcome modeled separately.[45] The proportional hazards assumption was evaluated using product terms with log-time and exposure, and product terms with log-time and each covariate. The assumption was not violated in any of the models.

Potential confounders were first identified using directed acyclic graphs.[46] After the initial adjustment set was identified, only those covariates that changed the effect estimate (on a $\log_e$ scale) by ≥10% were included in final models.[45] Case-control models 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), and total energy intake (continuous kcal/day). Survival models 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 of the models, because inclusion/removal of these covariates changed the effect estimate on a $\log_e$ scale by <10%.[45] Linear trends were examined by modeling sugar/carbohydrate intake as continuous variables.

Sensitivity analyses for both case-control and survival analyses were conducted as follows. First, we pooled study-specific effect estimates using a meta-analytic approach (fixed effect, **Table 4.6)**. 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).[30,42] Third, we utilized wider exclusion criteria for extreme total energy intake values (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 values previously calculated by study-specific nutrient data processing centers. 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 not available from the other study); explored the effect of fructose from fruits/vegetables versus other fructose; used nutrient density energy adjustment method; and removed energy intake from the model.

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 4.2**, participants in the LA Multi-Ethnic study were more likely to be younger, non-White, obese (BMI>30), experience frequent GERD, consume more fruits/vegetables, and have higher total energy intake, compared to participants in the US Multi-Center study (which was conducted in New Jersey, Connecticut, and western Washington state). As shown in **Table 4.3**, in both the US Multi-Center study and the LA Multi-Ethnic study, respectively, EA/GCA cases, compared to 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 to 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 glycemic index ($OR_{Q5vs.Q1}$=1.58, 95%CI=1.13-2.21, P_{trend}=0.32) (**Table 4.4**). 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 4th 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}≤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 4.4.,** with several exceptions, including attenuation of positive sucrose-EA association, and more pronounced inverse association with carbohydrate intake (**Table 4.7**). In addition, after removing energy intake from the models, ORs were more pronounced for most measures (**Table 4.8**).

BMI modified, on the multiplicative scale, associations between sucrose, sweetened desserts/beverages, or glycemic 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 glycemic 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 glycemic 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).

Other sugar/carbohydrate measures were not associated with increased risk of developing GCA (**Table 4.4**), or mortality after EA/GCA (**Table 4.9**).

Discussion

In this pooled study, the risk of developing EA was increased 51% to 58% in association with sucrose, sweetened desserts/beverages, and glycemic index; these associations were modified by BMI or frequency of GERD. Other sugar/carbohydrate measures were not associated with EA/GCA incidence nor 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), and dietary glycemic index (especially among those with BMI≥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 of EA,[47] 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,[48-50] 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 to 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/clinical implications.

Several studies have examined the association between glycemic index and risk of developing EA, but with inconsistent results.[16, 25, 26] An Australian case-control study reported no association.[16] In contrast, two studies - an Irish case-control study of EA[25] and the prospective NIH-AARP study (combining EA and esophageal squamous cell carcinoma (ESCC))[51] - 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 glycemic index-EA association.

Sucrose intake was positively associated with EA incidence in our study, but the NIH-AARP study reported no association.[26] However, the NIH-AARP study did not distinguish the two types of esophageal cancer (EA/ESCC) that have different etiologies,[52] and adjusted for different confounder sets than our study. However, the NIH-AARP study[26] reported a positive association between added sugar and EA incidence, which contrasts with our finding of no association with added sugar. 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.[53] Sucrose in fruits/vegetables co-exists with vitamins, protein, minerals, and fiber, which can preserve cell integrity and slow the rate of sucrose digestion.[53-55] In contrast, table sugar is present in foods/beverages that are low in fiber and micronutrients, and are rapidly digestible.[53] The quick digestion of concentrated table sugar induces acute glucose fluctuations, which may increase oxidative stress and cancer risk.[21-23] Therefore, it is possible that the positive sucrose-EA association we found was driven by table sugar intake.

We are the 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 hyperinsulinemia by raising serum uric acid.[56] 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. Although instructed otherwise, EA patients may have confused their current diet with their previous diet. As dysphagia is a common symptom of EA, patients may experience difficulty swallowing and therefore may reduce raw fruit intake.[57] Further adequately-powered studies are needed to explore the appropriate window of exposure for fructose in association with EA incidence.

In our study, glycemic 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 glycemic index diet and obesity on carcinogenesis, possibly via insulin

resistance.[20, 58] Similarly, in the stratified analysis, the positive glycemic index-esophageal cancer association reported in NIH-AARP study only remained in the high BMI group, and the positive association reported by the Irish study only remained in the BMI≥25 and high waist-to-hip ratio group, although no significant interactions were found in either study.[25, 51] 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 underreport 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 therefore less evident among the obese.

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, it is possible that 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. Non-differential misclassification may have been introduced by data harmonization and pooling, given the discrepancies in data collection, variable definitions, and data management between the two studies. To mitigate this possibility, we appropriately pooled intake estimates based on relative rankings of intake in each study. Third, we were unable to fully assess the impact of diabetes, given that information on diabetes was available in one of the two pooled studies. But in sensitivity analysis within the LA Multi-Ethnic study only, diabetes did not confound or modify the EA associations with sucrose, sweetened desserts/beverages, or glycemic index. Further adequately-powered studies are needed to explore the role of diabetes in these associations.

There are also 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 after diagnosis of EA/GCA. 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 pooled study. Our results suggest that limiting intake of sucrose (especially table sugar), sweetened desserts/beverages, along with foods that contribute to a high dietary glycemic index, may be plausible risk reduction strategies for EA incidence.

Table 4.1. Comparison between the two studies of esophageal and gastric adenocarcinoma.

	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, 1993-1995	Los Angeles county, CA, 1992-1997
Sample size	282 EA cases, 256 GCA cases, 684 controls	218 EA cases, 273 GCA cases, 1343 controls
FFQ (# items)	Modified FHCRC (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, 1 ½ cups

FFQ: food frequency questionnaire; FHCRC: Fred Hutchinson Cancer Research Center

Table 4.2. 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		
Characteristic	**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[1], 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[1], 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)

[1]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).

Table 4.3. Daily mean (standard deviation) intakes 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[1] (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[2] (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)
Glycemic 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)
Glycemic 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[3] (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[3] (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[3] (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)

[1] 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.

[2] 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.

[3] The differences in intakes 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 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 LA Multi-Ethnic Study.

Table 4.4. Multivariable-adjusted ORs and 95%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)[1]					
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)[1]					
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)[1]					
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)[1]					
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)[1]					
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)[1]					

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)[1]					
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
Glycemic index[2]					
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
Glycemic load[1]					
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)[1]					
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)[1]					
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)[2]					

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

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

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

Table 4.5. Food frequency questionnaire items that were categorized as sweetened desserts/beverages in each of the two US case control studies of the esophageal and gastric cardia adenocarcinoma.

US Multi-Center Study (CT, NJ, Western WA)	**LA Multi-Ethnic Study (Southern CA)**
Cereals, cold or cooked	High fiber cereal such as bran, All-Bran, bran flakes, oat bran
Pancakes or waffles	Highly fortified cereals, such as Special K, Total
Yogurt, all types, except frozen	Other dry cereals, e.g. Cornflakes, Rice Krispies, granola, etc.
Ice cream or milkshakes	Chocolate milk, cocoa or ovaltine
Low-fat frozen desserts,	Pancakes, waffles, French toast
including frozen yogurt, sherbet, or ice milk	Doughnuts, cookies, cakes, pastries, cinnamon rolls, danishes
Pudding, custard, or flan	Pumpkin or sweet potato pie
Jello, any flavor	Other non-fruit pies
Doughnuts, cakes, or pastries	Chocolate candy
Cookies	Other candy
Pies	Jellies, jam, honey syrup
Chocolate candy or candy bars	Ice cream
Hard candy, jelly, jam, honey, or syrup	Orange juice
Sugar in coffee or tea or on cereal	Other citrus juice such as grapefruit, tangerine, lemonade
Regular soft drinks or soda, not diet	Other fruit juices including grape, cranberry, pineapple, etc.
Orange juice, grapefruit juice or Vitamin C enriched fruit drinks	Any type of fruit pie, cobbler
Other fruit juices and fruit juice drinks	Caffeine-free soda (e.g. Pepsi-free, 7-up, Sprite, etc.)
Kool-Aid	Sodas with caffeine (Coca Cola, Pepsi, Dr. Pepper, etc.)
	Other carbonated drinks including mineral water, fruit drinks, etc.

Table 4.6. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing EA/GCA among 500 EA cases, 529 GCA cases, and 2027 controls from two US case-control studies (meta-analytic approach, fixed effect).

		Esophageal Adenocarcinoma				Gastric Cardia Adenocarcinoma			
Measure	**Controls (N)**	**Cases (N)**	**OR (95%CI)**	**I^2 (%)**	**$P_{hetero-geneity}$**	**Cases (N)**	**OR (95%CI)**	**I^2 (%)**	**$P_{hetero-geneity}$**
Free glucose (g/day)[1]									
Q1	385	104	Ref.			75	Ref.		
Q2	384	96	0.92 (0.65-1.30)	13.0	0.28	96	1.23 (0.87-1.74)	0	0.71
Q3	396	96	0.86 (0.61-1.24)	0	0.38	104	1.29 (0.90-1.84)	0	0.64
Q4	398	74	0.58 (0.39-0.86)	78.0	0.03	102	1.15 (0.79-1.67)	0	0.96
Q5	393	103	0.64 (0.42-0.97)	71.3	0.06	122	1.25 (1.04-1.50)	0	0.39
P_{trend}			0.06	36.9	0.21		0.42	0	0.82
Sucrose (g/day)[1]									
Q1	391	69	Ref.			78	Ref.		
Q2	394	83	1.26 (0.87-1.84)	50.9	0.15	103	1.22 (0.87-1.72)	0	0.44
Q3	393	90	1.14 (0.77-1.68)	34.7	0.22	99	1.12 (0.79-1.59)	0	0.77
Q4	387	105	1.48 (1.00-2.19)	0	0.78	107	1.12 (0.78-1.60)	0	0.77
Q5	391	126	1.51 (0.99-2.30)	0	0.54	112	0.97 (0.65-1.45)	0	0.54
P_{trend}			0.26	62.9	0.10		0.24	0	0.96
Free fructose (g/day)[1]									
Q1	382	110	Ref.			89	Ref.		
Q2	387	96	0.84 (0.60-1.18)	1.4	0.31	103	1.08 (0.78-1.51)	0	0.47
Q3	398	91	0.68 (0.47-0.97)	0	0.70	88	0.86 (0.61-1.23)	0	0.99
Q4	393	88	0.69 (0.47-1.01)	76.1	0.04	104	0.98 (0.69-1.41)	0	0.61
Q5	396	88	0.52 (0.34-0.78)	81.2	0.02	115	1.02 (0.70-1.49)	0	0.65
P_{trend}			0.04	0	0.38		0.26	0	0.79
Total sugar (g/day)[1]									
Q1	385	82	Ref.			82	Ref.		
Q2	396	85	0.97 (0.67-1.40)	0	0.41	90	0.97 (0.68-1.37)	0	0.38
Q3	393	103	1.08 (0.74-1.56)	0	0.40	107	1.10 (0.78-1.56)	36.2	0.21

Q4	390	90	0.85 (0.57-1.26)	0	0.65	102	0.92 (0.63-1.33)	25.0	0.25
Q5	392	113	0.89 (0.57-1.40)	33.6	0.22	118	0.98 (0.82-1.18)	0	0.43
P_{trend}			0.72	59.3	0.12		0.25	0	0.73
Added sugar (g/day)[1]									
Q1	385	70	Ref.			76	Ref.		
Q2	399	73	0.90 (0.61-1.32)	0	0.50	75	0.87 (0.60-1.25)	0	0.77
Q3	392	96	1.08 (0.73-1.58)	84.7	0.01	106	1.17 (0.83-1.65)	0	0.61
Q4	389	116	1.26 (0.87-1.85)	0	0.32	119	1.24 (0.87-1.77)	0	0.98
Q5	391	118	0.98 (0.64-1.51)	0	0.37	123	1.03 (0.69-1.54)	0	0.50
P_{trend}			0.27	0	0.62		0.61	0	>0.99
Starch (g/day)[1]									
Q1	389	70	Ref.			85	Ref.		
Q2	390	81	1.01 (0.69-1.48)	0	0.64	87	0.87 (0.62-1.24)	75.8	0.04
Q3	390	109	1.26 (0.86-1.83)	0	0.81	117	1.06 (0.75-1.50)	82.2	0.02
Q4	394	103	0.94 (0.62-1.41)	0	0.91	102	0.78 (0.54-1.14)	64.7	0.09
Q5	393	110	0.87 (0.54-1.42)	0	0.95	108	0.68 (0.43-1.08)	83.2	0.02
P_{trend}			0.32	0	0.82		0.18	20.9	0.26
Total carbohydrate (g/day)[1]									
Q1	386	79	Ref.			88	Ref.		
Q2	390	81	0.93 (0.64-1.36)	0	0.38	89	0.88 (0.62-1.24)	0	0.94
Q3	393	88	0.81 (0.54-1.22)	0	0.76	83	0.69 (0.48-1.01)	69.9	0.07
Q4	393	101	0.77 (0.49-1.20)	0	0.79	112	0.80 (0.54-1.19)	62.0	0.11
Q5	394	124	0.68 (0.38-1.22)	0	0.71	127	0.68 (0.40-1.16)	60.2	0.11
P_{trend}			0.01	56.8	0.13		<0.01	0	0.22
Glycemic index[2]									
Q1	399	94	Ref.			106	Ref.		
Q2	397	95	1.23 (0.87-1.74)	0	0.89	86	1.01 (0.73-1.41)	0	0.60
Q3	398	96	1.26 (0.89-1.79)	0	0.86	103	1.18 (0.85-1.62)	38.1	0.20
Q4	395	85	1.09 (0.77-1.56)	5.1	0.31	114	1.30 (0.94-1.79)	87.2	0.01
Q5	394	111	1.57 (1.11-2.22)	0	0.72	98	1.27 (0.91-1.76)	0	0.37

P_{trend}			0.25	0	0.48		0.61	38.4	0.20
Glycemic load[1]									
Q1	387	86	Ref.			91	Ref.		
Q2	390	79	0.82 (0.57-1.20)	0	0.35	80	0.74 (0.52-1.05)	0	0.90
Q3	395	87	0.81 (0.55-1.18)	0	0.69	90	0.79 (0.55-1.13)	78.5	0.03
Q4	390	105	0.83 (0.55-1.26)	0	0.86	121	0.93 (0.64-1.36)	81.4	0.02
Q5	394	116	0.69 (0.42-1.15)	0	0.35	117	0.72 (0.44-1.16)	61.6	0.11
P_{trend}			0.22	0	0.37		0.05	21.6	0.26
All sweetened desserts/beverages (servings/day)[1]									
Q1	382	69	Ref.			75	Ref.		
Q2	392	79	1.07 (0.73-1.57)	0	0.77	90	1.08 (0.76-1.54)	0	0.69
Q3	401	102	1.40 (0.97-2.03)	0	0.47	108	1.36 (0.96-1.91)	0	0.51
Q4	391	87	0.99 (0.66-1.47)	58.5	0.12	105	1.08 (0.76-1.55)	0	0.33
Q5	390	136	1.57 (1.05-2.33)	0	0.57	121	1.13 (0.77-1.66)	0	0.47
P_{trend}			0.34	0	0.46		0.66	0	0.49
Sweetened desserts (servings/day)[1]									
Q1	383	65	Ref.			74	Ref.		
Q2	392	72	0.97 (0.65-1.43)	0	0.92	96	1.16 (0.82-1.64)	0	0.69
Q3	393	104	1.25 (0.86-1.81)	0	0.90	100	1.13 (0.80-1.60)	0	0.95
Q4	399	103	1.19 (0.81-1.75)	18.9	0.27	112	1.19 (0.84-1.68)	0	0.55
Q5	389	129	1.33 (0.89-1.98)	41.7	0.19	117	1.01 (0.69-1.48)	0	0.85
P_{trend}			0.51	41.8	0.19		0.70	0	0.57
Sweetened beverages (servings/day)[2]									
Q1	394	97	Ref.			86	Ref.		
Q2	398	88	0.91 (0.64-1.29)	47.7	0.17	100	1.13 (0.81-1.58)	25.7	0.25
Q3	396	91	0.97 (0.68-1.37)	0	0.48	92	1.06 (0.76-1.49)	36.0	0.21
Q4	400	83	0.80 (0.56-1.15)	0	0.94	116	1.26 (0.91-1.76)	10.7	0.29
Q5	395	122	1.17 (0.82-1.66)	0	0.82	113	1.13 (0.80-1.60)	0	0.37
P_{trend}			0.67	0	0.89		0.67	0	0.78

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

Table 4.7. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing EA, derived from sensitivity analyses: (1) based on identical absolute intake cut-points; (2) after excluding proxy interviews; (3) using ±2.5% as exclusion criteria); or (4) using nutrient density energy adjustment method.

Measure	Controls (N)	Cases (N)	OR[1] (95%CI)
(1) Pooling on identical absolute intake cut-points			
Sucrose (g/day)			
Q1	390	71	Ref.
Q2	396	78	1.04 (0.71-1.51)
Q3	396	80	0.95 (0.65-1.39)
Q4	383	113	1.39 (0.96-2.03)
Q5	391	131	1.33 (0.89-1.99)
P_{trend}			0.19
(2) Excludes proxy interviews			
Sucrose (g/day)			
Q1	391	54	Ref.
Q2	394	58	1.07 (0.70-1.63)
Q3	393	67	1.13 (0.75-1.72)
Q4	387	73	1.28 (0.84-1.96)
Q5	391	82	1.26 (0.79-1.99)
P_{trend}			0.67
(3) Increased exclusion criteria for total energy intake			
Sucrose (g/day)			
Q1	377	77	Ref.
Q2	378	72	0.92 (0.63-1.33)
Q3	376	87	1.00 (0.69-1.45)
Q4	371	101	1.21 (0.83-1.75)
Q5	373	123	1.28 (0.85-1.91)
P_{trend}			0.13
(4) Nutrient density energy adjustment method			
Sucrose (g/day)			
Q1	395	106	Ref.
Q2	393	96	1.01 (0.72-1.40)
Q3	391	88	1.02 (0.73-1.43)
Q4	393	86	1.00 (0.71-1.41)
Q5	384	97	1.16 (0.83-1.62)
P_{trend}			0.33
Total carbohydrate (g/day)			
Q1	389	143	Ref.
Q2	393	123	0.99 (0.74-1.34)
Q3	394	96	0.86 (0.63-1.19)
Q4	394	70	0.65 (0.46-0.93)
Q5	386	41	0.47 (0.31-0.71)
P_{trend}			<0.01

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

Table 4.8. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing EA/GCA among 500 EA cases, 529 GCA cases, and 2027 controls from two US case-control studies (pooled approach, based on study- specific quartiles, without adjusting for total energy intake).

		EA		GCA	
Measure	Controls (N)	Cases (N)	OR (95%CI)	Cases (N)	OR (95%CI)
Free glucose (g/day)[1]					
Q1: 0.12-<14.58	381	135	Ref.	99	Ref.
Q2: 14.58-<19.96	384	93	0.98 (0.70-1.37)	89	1.33 (0.94-1.87)
Q3: 19.96-<25.95	396	83	1.01 (0.72-1.41)	101	1.45 (1.03-2.04)
Q4: 25.95-<36.21	394	83	0.74 (0.51-1.07)	113	1.39 (0.98-1.98)
Q5: ≥36.21	401	79	1.03 (0.72-1.46)	97	1.69 (1.19-2.41)
P_{trend}			0.95		0.54
Sucrose (g/day)[1]					
Q1: 0.97-<21.62	390	71	Ref.	84	Ref.
Q2: 21.62-<31.46	396	78	1.26 (0.87-1.82)	90	1.34 (0.96-1.87)
Q3: 31.46-<42.33	396	80	1.24 (0.86-1.78)	96	1.24 (0.88-1.74)
Q4: 42.33-<59.76	383	113	1.62 (1.13-2.32)	104	1.41 (1.01-1.98)
Q5: ≥59.76	391	131	1.85 (1.30-2.63)	125	1.40 (1.00-1.96)
P_{trend}			<0.01		0.14
Free fructose (g/day)[1]					
Q1: 0.001-<14.25	381	126	Ref.	98	Ref.
Q2: 14.25-<20.29	387	113	0.90 (0.65-1.25)	109	1.17 (0.84-1.62)
Q3: 20.29-<26.00	392	71	0.83 (0.59-1.17)	86	0.97 (0.69-1.37)
Q4: 26.00-<36.77	397	80	0.83 (0.58-1.19)	101	1.18 (0.84-1.67)
Q5: ≥36.77	399	83	0.82 (0.57-1.17)	105	1.29 (0.91-1.82)
P_{trend}			0.82		0.87
Total sugar (g/day)[1]					
Q1: 2.40-<66.65	385	84	Ref.	78	Ref.
Q2: 66.65-<89.47	392	104	1.03 (0.72-1.47)	102	1.05 (0.75-1.47)
Q3: 89.47-<114.64	391	96	1.26 (0.89-1.78)	113	1.25 (0.90-1.75)
Q4: 114.64-<150.37	390	86	1.09 (0.76-1.57)	102	1.19 (0.85-1.68)
Q5: ≥150.37	398	103	1.41 (0.98-2.01)	104	1.36 (0.97-1.92)
P_{trend}			0.03		0.25
Added sugar (g/day)[1]					
Q1: 0.38-<23.52	386	68	Ref.	76	Ref.
Q2: 23.52-<35.02	397	77	0.98 (0.67-1.42)	77	0.93 (0.65-1.33)
Q3: 35.02-<48.57	393	92	1.18 (0.82-1.69)	102	1.25 (0.89-1.76)
Q4: 48.57-<70.68	389	120	1.54 (1.08-2.19)	121	1.46 (1.05-2.04)
Q5: ≥70.68	391	116	1.40 (0.99-2.00)	123	1.38 (0.99-1.93)
P_{trend}			<0.01		0.07
Starch (g/day)[1]					
Q1: 1.75-<63.69	383	87	Ref.	89	Ref.

Q2: 63.69-<85.40	385	106	1.12 (0.77-1.61)	123	0.98 (0.70-1.37)
Q3: 85.40-<109.99	396	115	1.54 (1.08-2.19)	109	1.33 (0.97-1.84)
Q4: 109.99-<145.37	393	84	1.31 (0.91-1.87)	96	1.09 (0.78-1.53)
Q5: ≥145.37	399	81	1.54 (1.07-2.21)	82	1.23 (0.87-1.72)
P_{trend}			0.03		0.22
Total carbohydrate (g/day)[1]					
Q1: 40.83-<178.96	380	88	Ref.	88	Ref.
Q2: 178.96-<226.96	390	102	1.07 (0.75-1.53)	108	0.99 (0.71-1.39)
Q3: 226.96-<279.63	393	105	1.08 (0.76-1.55)	99	0.89 (0.63-1.26)
Q4: 279.63-<356.57	393	89	1.20 (0.84-1.72)	115	1.17 (0.84-1.63)
Q5: ≥356.57	400	89	1.51 (1.06-2.16)	89	1.34 (0.96-1.89)
P_{trend}			0.03		0.14
Glycemic index[2]					
Q1: 2.50-<57.40	401	85	Ref.	108	Ref.
Q2: 57.40-<60.10	401	88	1.20 (0.86-1.68)	79	0.93 (0.67-1.28)
Q3: 60.10-<61.82	398	82	1.20 (0.86-1.69)	85	1.10 (0.81-1.51)
Q4: 61.82-<63.64	393	105	1.03 (0.73-1.45)	122	1.23 (0.90-1.67)
Q5: ≥63.64	390	121	1.46 (1.05-2.04)	113	1.14 (0.83-1.58)
P_{trend}			0.73		0.89
Glycemic load[1]					
Q1: 2.03-<96.51	382	95	Ref.	86	Ref.
Q2: 96.51-<122.52	389	89	0.92 (0.64-1.31)	104	0.85 (0.61-1.20)
Q3: 122.52-<153.57	394	113	1.00 (0.71-1.43)	107	0.95 (0.68-1.33)
Q4: 153.57-<196.57	394	86	1.19 (0.84-1.69)	112	1.28 (0.93-1.77)
Q5: ≥196.57	397	90	1.31 (0.92-1.86)	90	1.22 (0.87-1.71)
P_{trend}			0.01		0.15
Sweetened desserts/beverages (servings/day)[1]					
Q1: 0-<1.57	385	61	Ref.	65	Ref.
Q2: 1.57-<2.48	393	93	1.12 (0.77-1.63)	100	1.17 (0.82-1.65)
Q3: 2.48-<3.43	397	83	1.50 (1.05-2.15)	100	1.44 (1.03-2.02)
Q4: 3.43-<4.81	395	87	1.12 (0.78-1.63)	96	1.27 (0.90-1.78)
Q5: ≥4.81	386	149	1.87 (1.32-2.64)	138	1.49 (1.07-2.08)
P_{trend}			0.01		0.11
Sweetened desserts (servings/day)[1]					
Q1: 0-<0.75	387	64	Ref.	70	Ref.
Q2: 0.75-<1.33	392	68	1.02 (0.70-1.50)	94	1.22 (0.86-1.72)
Q3: 1.33-<1.98	389	105	1.37 (0.96-1.97)	99	1.21 (0.86-1.71)
Q4: 1.98-<2.94	399	107	1.39 (0.97-2.00)	119	1.37 (0.98-1.92)
Q5: ≥2.94	389	129	1.67 (1.17-2.38)	117	1.36 (0.97-1.90)
P_{trend}			0.01		0.15
Sweetened beverages (servings/day)[2]					
Q1: 0-<0.35	396	82	Ref.	75	Ref.

Q2: 0.35-<0.85	399	89	0.98 (0.70-1.37)	100	1.19 (0.86-1.65)
Q3: 0.85-<1.27	399	83	1.04 (0.74-1.46)	100	1.11 (0.80-1.56)
Q4: 1.27-<2.07	401	83	0.88 (0.63-1.25)	116	1.36 (0.98-1.87)
Q5: ≥2.07	388	144	1.39 (1.00-1.92)	116	1.35 (0.97-1.88)
P_{trend}			0.14		0.36

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

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

Table 4.9. Multivariable-adjusted HRs and 95%CIs for the associations between sugar/carbohydrate intake and overall survival in esophageal and gastric cardia adenocarcinoma among 500 EA cases and 529 GCA cases from two US case-control studies (pooled approach, based on study-specific quintiles).

	Esophageal Adenocarcinoma			Gastric Cardia Adenocarcinoma		
Measure	Deaths (N)	EA Cases (N)	HR (95%CI)	Deaths (N)	GCA Cases (N)	HR (95%CI)
Free glucose[1] (g/day)						
Q1	87	100	Ref.	86	104	Ref.
Q2	89	100	0.96 (0.71-1.30)	95	106	1.05 (0.79-1.42)
Q3	87	98	0.94 (0.70-1.28)	90	105	1.00 (0.74-1.36)
Q4	86	98	1.00 (0.73-1.37)	89	106	0.82 (0.60-1.12)
Q5	85	100	1.04 (0.74-1.46)	90	105	0.95 (0.69-1.31)
P_{trend}			0.64			0.86
Sucrose[1] (g/day)						
Q1	86	99	Ref.	90	106	Ref.
Q2	85	99	0.99 (0.73-1.34)	89	106	1.01 (0.75-1.35)
Q3	85	99	1.02 (0.74-1.40)	92	104	1.06 (0.79-1.43)
Q4	91	100	1.28 (0.93-1.76)	90	105	0.94 (0.68-1.29)
Q5	87	99	1.21 (0.84-1.74)	89	105	0.87 (0.61-1.22)
P_{trend}			0.39			0.57
Free fructose[1] (g/day)						
Q1	89	100	Ref.	87	106	Ref.
Q2	86	100	0.86 (0.64-1.16)	96	105	1.24 (0.93-1.67)
Q3	89	98	1.03 (0.76-1.39)	87	104	0.97 (0.72-1.31)
Q4	85	99	0.92 (0.67-1.25)	90	106	0.90 (0.66-1.22)
Q5	85	99	1.07 (0.76-1.49)	90	105	0.99 (0.72-1.35)
P_{trend}			0.47			0.79
Total sugar[2] (g/day)						
Q1	86	100	Ref.	89	106	Ref.
Q2	90	99	1.29 (0.96-1.75)	86	105	0.92 (0.68-1.23)
Q3	84	100	1.03 (0.75-1.41)	93	105	1.12 (0.83-1.50)
Q4	89	99	1.22 (0.87-1.70)	99	106	1.12 (0.81-1.53)
Q5	86	99	1.31 (0.90-1.91)	84	105	0.77 (0.54-1.09)
P_{trend}			0.72			0.77
Added sugar[1] (g/day)						
Q1	90	100	Ref.	88	106	Ref.
Q2	85	99	0.89 (0.66-1.20)	92	106	1.20 (0.89-1.62)
Q3	82	99	0.79 (0.58-1.08)	87	103	1.00 (0.74-1.36)
Q4	89	99	1.11 (0.82-1.52)	93	105	1.06 (0.78-1.45)
Q5	88	99	1.09 (0.76-1.55)	90	106	0.94 (0.67-1.33)
P_{trend}			0.67			0.70
Starch[1]						

(g/day)						
Q1	91	100	Ref.	89	106	Ref.
Q2	83	98	0.88 (0.65-1.18)	91	104	1.11 (0.83-1.50)
Q3	87	100	0.99 (0.73-1.35)	88	105	0.96 (0.70-1.32)
Q4	83	99	0.98 (0.70-1.37)	94	106	1.06 (0.77-1.47)
Q5	90	99	1.33 (0.91-1.94)	88	105	0.99 (0.67-1.44)
P_{trend}			0.18			0.32
Total carbohydrate[1] (g/day)						
Q1	89	100	Ref.	89	107	Ref.
Q2	82	98	0.86 (0.63-1.17)	91	106	1.03 (0.77-1.39)
Q3	90	100	1.21 (0.87-1.68)	93	104	1.12 (0.82-1.52)
Q4	90	99	1.14 (0.79-1.64)	91	105	0.90 (0.64-1.25)
Q5	83	99	1.07 (0.68-1.71)	86	104	0.67 (0.43-1.04)
P_{trend}			0.36			0.82
Glycemic index[1]						
Q1	88	100	Ref.	91	106	Ref.
Q2	84	100	0.96 (0.71-1.31)	90	106	1.24 (0.92-1.67)
Q3	90	98	1.16 (0.86-1.57)	90	104	1.18 (0.87-1.58)
Q4	91	100	1.03 (0.76-1.39)	95	106	1.22 (0.91-1.63)
Q5	81	98	0.97 (0.72-1.33)	84	104	1.01 (0.75-1.37)
P_{trend}			0.87			0.29
Glycemic load[1]						
Q1	91	100	Ref.	89	106	Ref.
Q2	78	98	0.77 (0.56-1.06)	88	106	0.90 (0.66-1.21)
Q3	89	100	1.05 (0.77-1.44)	94	104	1.13 (0.83-1.53)
Q4	90	99	1.12 (0.79-1.58)	93	104	0.94 (0.68-1.29)
Q5	86	99	1.24 (0.82-1.87)	86	106	0.73 (0.49-1.08)
P_{trend}			0.34			0.93
All sweetened desserts/beverages [1] (servings/day)						
Q1	86	98	Ref.	92	106	Ref.
Q2	88	100	0.95 (0.70-1.28)	89	106	0.94 (0.70-1.27)
Q3	84	100	0.89 (0.66-1.21)	85	103	0.86 (0.63-1.15)
Q4	92	99	1.13 (0.83-1.53)	95	105	1.00 (0.74-1.35)
Q5	84	99	1.02 (0.72-1.43)	89	106	0.80 (0.58-1.10)
P_{trend}			0.54			0.55
Sweetened desserts[1] (servings/day)						
Q1	88	99	Ref.	92	106	Ref.
Q2	83	100	0.91 (0.67-1.24)	90	106	1.01 (0.75-1.35)
Q3	91	99	1.18 (0.87-1.59)	88	102	0.97 (0.72-1.30)
Q4	83	98	0.95 (0.69-1.31)	89	106	0.92 (0.68-1.24)
Q5	89	100	0.94 (0.68-1.30)	91	106	0.83 (0.60-1.14)
P_{trend}			0.69			0.26

Sweetened beverages[1] (servings/day)						
Q1	84	96	Ref.	86	105	Ref.
Q2	90	99	1.12 (0.83-1.51)	98	107	1.14 (0.85-1.53)
Q3	87	101	0.95 (0.70-1.29)	95	112	1.01 (0.75-1.35)
Q4	86	100	1.01 (0.75-1.38)	81	97	0.86 (0.63-1.16)
Q5	87	100	1.07 (0.79-1.47)	90	105	0.99 (0.73-1.35)
P_{trend}			0.60			0.84

[1]Adjusted for age, education, study indicator, and total energy intake
[2]Adjusted for age, study indicator, and total energy intake

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CHAPTER 5: DISCUSSION

Overview

This dissertation examines the role of sugar/carbohydrate intake in relation to the Barrett's esophagus (BE) - esophageal/gastric cardia adenocarcinoma (EA/GCA) continuum (normal tissue→Barrett's esophagus→adenocarcinoma→death). Chapter 1 and Chapter 2 describe the background and methods, Chapter 3 reports the findings on the association between intake of sugar/carbohydrate and risk of developing BE, and Chapter 4 reports the findings on the association between intake of sugar/carbohydrate and risk of developing or dying from EA/GCA. In Chapter 5, I: summarize my dissertation findings, emphasizing commonalities across the BE-EA/GCA continuum and briefly compare my results to those from other studies; discuss the weaknesses and the strengths of my approach, which impact interpretation of my findings; and, finally, I propose possible future directions for addressing my study hypotheses.

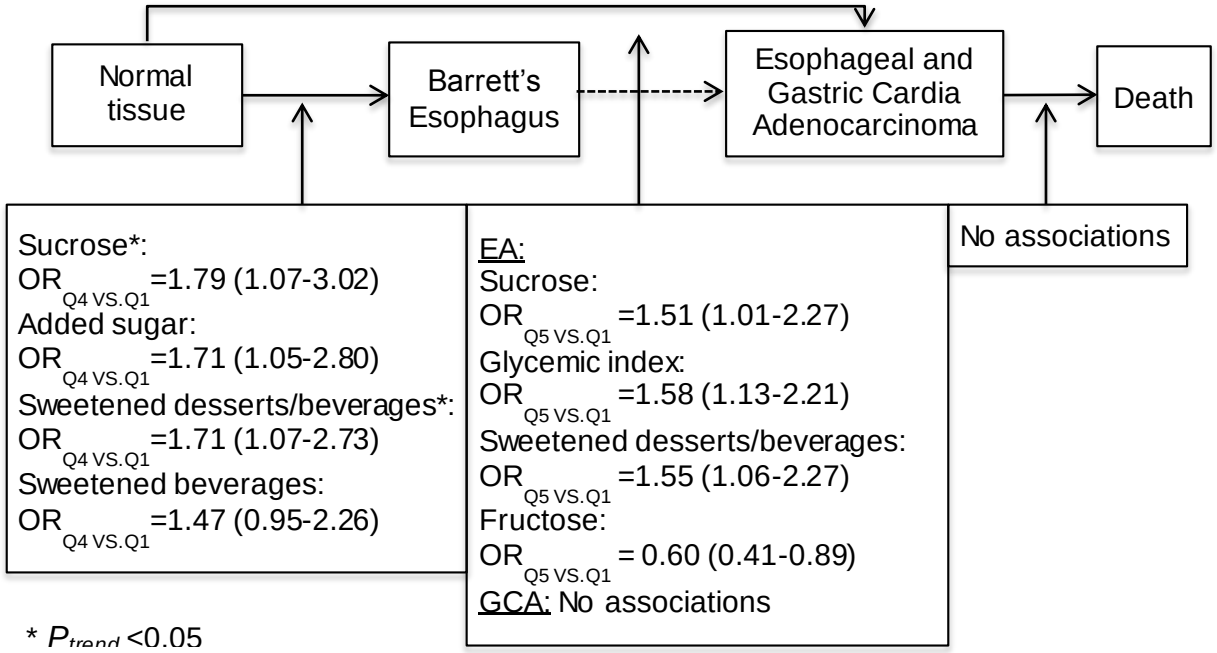
The overarching goal of this dissertation is to identify where along the cancer continuum sugar/carbohydrate intake may play a detrimental role and thereby potential risk reduction strategies could be implemented. The significance of this dissertation is that EA incidence is rapidly increasing, and the disease is highly fatal. Identification of potential risk reduction strategies could help to reduce the high clinical and public health burden associated with this disease. The innovation of this dissertation is that I considered twelve measures of sugar/carbohydrate intake in order to better capture the complexity inherent in the intake of these foods and the subsequent potential biologic response. Also, harmonizing and pooling data

from multiple high quality studies with similar methodological approaches increased study power providing more stable effect estimates and facilitated examination of high risk subgroups across the BE-EA/GCA continuum. Finally, this is the first study to consider associations between sugar/carbohydrate intake and mortality after diagnosis with esophageal/gastric cardia adenocarcinoma.

Summary of Results and Comparison with Previous Literature

My dissertation findings across the BE-EA continuum are summarized in **Figure 5.1**.

Figure 5.1. Summary results for sugar/carbohydrate intake and Barrett's-esophageal/gastric cardia adenocarcinoma continuum.



In my dissertation, sucrose was associated with 79% and 51% increase in risk of developing BE and EA, respectively, comparing the highest to the lowest intake quantile (**Figure 5.1**). Similarly, intake of sweetened desserts/beverages was associated with both increased risk of developing BE ($OR_{Q4\ VS.Q1}$=1.71, 95%CI=1.07-2.73) and EA ($OR_{Q5\ VS.Q1}$ =1.55, 95%CI=1.06-2.27). Sweetened beverages alone, may be associated with increased risk of developing BE ($OR_{Q4\ VS.Q1}$=1.47, 95%CI=0.95-2.26), although the 95%CI included the null. Added sugar was positively associated with risk of developing BE ($OR_{Q4\ VS.Q1}$=1.71, 95%CI=1.05-2.80), but not

with EA. In contrast, glycemic index was associated with 58% increase in risk of developing EA, but not with BE. Fructose appeared to be inversely associated with risk of developing EA. Other sugar/carbohydrate intake measures were not associated with risk of developing BE or EA. Neither risk of developing GCA nor mortality after EA/GCA was associated with intake of sugar/carbohydrate. Not illustrated in **Figure 5.1** are my findings regarding effect measure modification. I observed that waist circumference appeared to modify the association between sweetened desserts/beverages and BE, body mass index (BMI) modified all of the above positive associations with EA, and gastro-esophageal reflux disease (GERD) modified the sucrose-EA incidence association. My results suggest that reducing intake of sucrose (especially among those with BMI<25 or with GERD<weekly) and sweetened desserts/beverages (especially among those with lower waist circumference or BMI<25) may be plausible BE/EA risk reduction strategies. Reducing added sugar intake and dietary glycemic index (especially among those with BMI≥25), respectively, may be plausible risk reduction strategies for BE and EA.

An Irish case-control study previously examined associations between sugar/carbohydrate intake and risk of developing BE and EA, using only some of the intake measures considered in my dissertation.[1] The Irish investigators found glycemic index was positively associated with EA incidence (but not with BE incidence), which is consistent with my findings. An Australian case-control study also examined associations between a limited number of measures of sugar/carbohydrate intake and risk of developing EA, but found no associations.[2] Neither of the two studies examined individual sugar components (e.g. sucrose), sweetened desserts/beverages, or differentiated added sugar from naturally occurring sugar. A summary of findings from previous studies can be found in Figure 1.3.

Limitations

There are several limitations to this dissertation and therefore the results need to be interpreted with caution. First, there might be recall bias due to the case-control design. For example, in the pooled analysis of EA/GCA studies, the participants were instructed to report their dietary intake during the time period before diagnosis (cases) or interview (controls). However, patients may alter their diet due to EA/GCA-related symptoms such as dysphasia (i.e. avoid eating raw fruits that are difficult to swallow and may stick in throat), and therefore they may confuse their previous diet with their current diet and tend to report their current dietary intake.[3]

Further, there are potential non-differential misclassification errors, given that food frequency questionnaires (FFQs) were used to collect dietary intake data. Dietary assessment may be limited by the food items covered by the FFQ, and the participants (regardless of their case/control status) may not be able to accurately recall their average intake.[4] However, each of the study-specific FFQs included more than 100 FFQ line items, with most line items representing more than one food item, and therefore the FFQs have a wide coverage of food items. In addition, in this pooled analysis, effect estimates were calculated based on the relative ranking of dietary intake rather than absolute intake, and therefore the effect estimates were less likely to be affected by the limitations of FFQ.

There is also potential non-differential misclassification introduced by the data harmonization and pooling process, due to the minor discrepancies in data collection, data management, and variable definitions among the parent studies. However, the above two sources of misclassification would most likely result in attenuation of the effect estimates.[5]

Another limitation is that the nutrient database utilized in this dissertation was released in 2014, whereas the parent studies were conducted over a couple of decades ago. Therefore, there may be changes in sugar/carbohydrate contents in certain food items. However, because the nutrient intakes were harmonized based on a unified nutrient database and intake was

pooled and compared based on relative rankings rather than absolute values, it is unlikely the effect estimates were substantially altered. The sensitivity analysis of using original calculated carbohydrate values by study-specific nutrient data processing center had shown similar results as my main findings, which further confirmed the robustness of my results.

Multiple comparisons might be of concern given that the associations between 12 measures of exposure and three outcomes were examined. However, adjusting for multiple comparisons may undeservedly reduce statistical power.[6] In this dissertation, the significant results were consistent across the cancer development continuum (sucrose and sweetened desserts/beverages), across the parent studies (sucrose, sweetened desserts/beverages, added sugar, and glycemic index), or were consistent with previous published results (glycemic index). Therefore, it is unlikely that the significant results were purely due to chance.

Because EA and GCA are lethal cancers with poor prognoses, proxy interviews were administered to the closest next of kin (usually the spouse) when participants were unable to be interviewed due to illness/death.[7,8] Therefore, there might be potential misclassification due to proxy interviews. However, a sensitivity analysis was conducted by excluding participants with proxy interviews, and the results were not substantially altered except for attenuation of the sucrose-EA incidence association.

In addition, the information on diabetes was available in only one parent study, and therefore the impact of diabetes cannot be fully assessed. A sensitivity analysis was conducted within the Los Angeles Multi-Ethnic study by additionally adjusting for or stratifying by diabetes. Diabetes did not appear to confound or modify the significant associations between sugar/carbohydrate intake and risk of developing EA. Further well-powered studies are needed to more formally evaluate the role of diabetes in the associations between sugar/carbohydrate intake and incidence of BE and EA/GCA.

Finally, although this pooled study has a larger sample size to examine the associations with BE and EA/GCA, the sample size was still limited when examining the associations by BE

segment length. Further well-powered studies are needed to confirm the relevant findings in this dissertation.

Strengths

There are several strengths to this study. This is the first United States (US) study to comprehensively examine the role of sugar/carbohydrate intake in associations with BE-EA/GCA cancer development continuum (normal tissue→BE→adenocarcinoma→death). To better capture the complexity of sugar/carbohydrate intake and provide support for clinical dietary recommendations/public health risk reduction strategies, twelve measures of the exposure were examined. Previous studies used inadequate measurement of the sugar/carbohydrate intake, and usually focused on EA incidence as outcome.[1, 2, 9-11] As a result, the associations with BE incidence, GCA incidence, and EA/GCA survival were rarely studied in previous studies. Examination of the entire cancer continuum allows identification of key windows along the cancer development continuum that potential risk reduction strategies could be implemented. Food selection, as a non-pharmaceutical and potentially sustainable method for disease prevention, affects almost everyone in their daily life, and is of interest to patients.[12] If findings from this dissertation are confirmed, there could be potential to reduce the disease burden from these lethal cancers by helping individuals limit sugar/carbohydrate intake.

Further, the study-specific FFQs used to collect dietary intake data are valid and reliable, and include 17-23 line items that contain sweetened desserts or beverages, which allows for better assessment of sugar/carbohydrate intake (e.g. added sugar, sweets) than previous studies. The two FFQs from BE parent studies and the two FFQs from the EA/GCA studies share a lot of similarities, which enhanced my ability to harmonize dietary intake data. The estimates of sugar/carbohydrate intake were calculated by linking with the most recent University of Minnesota nutrient database, which contains more food items compared to other

databases, includes minimal missing nutrient values, and provides values of all nutrients of interest in this dissertation.[13]

In addition, by pooling two similarly-conducted BE studies and two similar-designed EA/GCA studies, the sample size of my dissertation was enlarged, which enabled more precise estimates. With a larger sample size than relevant studies published previously, this is the first study to report that BMI modifies the sucrose-EA incidence, glycemic index-EA incidence, and sweetened desserts/beverages-EA incidence associations, and the first to report that waist circumference modifies the sweetened desserts/beverages-BE incidence association. Also, my dissertation is the first study to report GERD as an effect measure modifier of the sucrose-EA incidence association.

In this dissertation, individual-level participant data, rather than published effect estimates, were pooled, which allowed for standardization of the statistical models and harmonization of the exposure variables and covariates, and therefore the heterogeneity between the studies were minimized. For example, there was a difference in sweetened desserts/beverages intake by study, which may be partly attributed to the differences in the study-specific serving sizes and the number of FFQ line items that contained sweets, and partly explained by the true differences in sweets intake. This study is also more time-/cost-efficient by pooling existing studies.

Multiple sensitivity analyses were conducted to examine the robustness of my results. For example, I primarily pooled sugar/carbohydrate intake on study-specific quantiles, although I also considered pooling on absolute cut-points.[14, 15] Additionally, study-specific ORs were pooled using a meta-analytic approach, wider exclusion criteria for plausible total energy intake values (lower/upper 2.5%) were utilized, and effect estimates derived using the intake values in the current study were compared with the effect estimates derived using the previously calculated intake values by study-specific nutrient data processing center. The results were not

substantially altered in most of the sensitivity analyses, which support the robustness of my findings.

Finally, this dissertation benefits from the four well-conducted parent studies. The parent studies were either population-based or community-based case-control studies, with incident BE or EA/GCA cases identified through population-based cancer registries or clinical settings with wide coverage, which allows for stronger inferences regarding BE or EA/GCA incidence.[5, 8, 16-18] Vital status of EA/GCA patients were determined by linking with national death index (NDI), which is a standard, high-sensitivity resource for assessing mortality in the US[19] In addition, this pooled study has a wide coverage of US population, which greatly enhances generalizability of my findings.

Public Health/Clinical Implications

The rapid increase in incidence and the sustained poor prognoses of EA/GCA underscore the importance of identifying risk reduction strategies for BE and EA. If findings from this dissertation are confirmed, there could be potential to reduce the risk of developing BE or EA by helping individuals limit intake of sweetened desserts/beverages, or reduce the table sugar contents in commercial and homemade desserts/beverages.

Future Directions

To confirm whether select measures of sugar/carbohydrate intake are associated with BE-EA/GCA continuum outcomes along specific windows of exposure, future studies should consider improvements in the following areas: study design; exposure assessment; windows of exposure; sample size; and examination of potential high-risk subgroups (BE segment length, fat/fat patterning, history of diabetes, and frequency of GERD). These issues are discussed in more detail below.

Study Design. The case-control study design usually examines one disease outcome. Although multiple disease outcomes were examined in this dissertation by pooling four case-control studies, I was not able to examine how sugar/carbohydrate intake impacts the progression from BE to EA/GCA in this study within the same study subjects. Therefore, to identify the key windows of susceptibility along the entire cancer development continuum, a prospective cohort study that follows participants who are free of BE/EA/GCA at baseline for BE outcomes, EA/GCA outcomes, and mortality after a diagnosis of EA/GCA, would be a better study design.

Exposure Assessment Method. Future studies should consider a comprehensive battery of measures to capture the complexity of sugar/carbohydrate intake, as was done in this dissertation. This approach is dependent upon the quality of the methods used to assess dietary intake in an epidemiologic study.

Potential measurement of sugar/carbohydrate intake in an epidemiologic study includes utilizing a FFQ, 24-hour recalls, or biomarkers, but each of these assessment methods has its strengths and limitations. A FFQ captures usual intake, whereas 24-hour recall and biomarker assessment reflect short-term intake, and therefore are subject to day-to-day variations in dietary intake.[4] 24-hour recalls may provide more accuracy in dietary intake reporting, but may not reflect dietary patterns that vary by season, or even by the day of the week;[4] although this drawback can be overcome by the administration of repeated 24-hour recalls throughout the year. Biomarkers could provide an objective measure of dietary intake, however, biomarkers for sugar intake are still understudied.[20] Because the development of cancer is more likely to be associated with long-term (rather than short-term) exposure to sugar/carbohydrate intake, a FFQ which reflects usual dietary intake may be the better exposure assessment method, particularly if repeated 24-hour recalls over an extended period of time (for example over multiple years) are not feasible.

Windows of Exposure. To more accurately capture dietary intake, and identify the windows of exposure that impacts carcinogenesis along the BE-EA/GCA continuum, future studies should assess dietary sugar/carbohydrate intake with repeated 24-hour recalls or FFQs to capture the dietary intake at different time periods. To be specific, participants should be asked to self-report their dietary intake using a validated FFQ at baseline and every 5 years thereafter (or, if feasible, collect 24 hours recalls up to six times per year every year on a quintennial basis). In addition, future studies should incorporate additional questions inquiring diet change in the FFQs to help BE or EA/GCA patients disentangle their previous vs. current diet.

Sample Size. Despite of the rapid increase, the incidence of BE and EA/GCA remains relatively low in the general population.[21, 22] Given the long induction period of cancer outcomes, the ideal cohort study would by necessity last more than a decade, and therefore there might be a large number of participants who are lost to follow-up. Thus, the rarity of these cancer outcomes, the lost to follow-up, and the need to examine effect measure modification, would require an extraordinarily large sample size to guarantee sufficient statistical power.

High-Risk Subgroup: Segment Length of Barrett's Esophagus. In this dissertation, the sample size to examine the sugar/carbohydrate intake and BE incidence by segment length – a possible measure of disease severity -- was restricted, and therefore the results need to be interpreted with caution. Future well-powered studies with BE segment length information collected are needed to confirm my findings.

High-Risk Subgroup: Fat/Fat Patterning. Obesity, and perhaps abdominal obesity, is consistently associated with BE and EA/GCA, and one potential mechanism is via insulin resistance pathway.[23] Long-term high sugar/carbohydrate intake may also increase the risk of developing BE/EA/GCA by promoting insulin resistance.[24-26] Therefore, it is plausible that obesity and/or abdominal obesity confound, mediate, or modify the sugar/carbohydrate-cancer association. Common measures for obesity and abdominal obesity include BMI and waist

circumference, respectively. Both measures have been found to be associated with EA/GCA incidence, with waist circumference more consistently associated with risk of developing BE.[27, 28] However, in this dissertation, data on waist circumference were collected in the BE parent studies, but not in the EA/GCA parent studies. I am the first to report effect measure modification by BMI, and perhaps waist circumference, in some of the sugar/carbohydrate-cancer associations; further studies are needed to confirm my findings. Therefore, future well-powered cohort studies should collect data on BMI and waist circumference (preferably adulthood BMI and waist circumference prior to symptomatic disease onset), and formally evaluate their role in the associations between sugar/carbohydrate and outcomes in the BE-adenocarcinoma continuum.

High-Risk Subgroup: Diabetes Mellitus. One potential underlying biological mechanism is that sugar/carbohydrate intake may promote carcinogenesis though the insulin resistance pathway. Therefore, it is of interest to know the role of diabetes (which is strongly associated with insulin resistance), in the sugar/carbohydrate-cancer association.[29] In this dissertation, data on diabetes was only collected in one parent study, and therefore I was not able to fully evaluate its role in the associations between sugar/carbohydrate intake and Barrett's esophagus-adenocarcinoma continuum. Future cohort studies with diabetes data collected are needed to evaluate the role of diabetes, whether as a mediator, confounder, or an effect measure modifier.

High-Risk Subgroup: Frequency of GERD. This dissertation is the first to report that frequency of GERD (<weekly/≥weekly) modified the association between sucrose intake and risk of developing EA, and a higher risk was found among those with less frequent GERD (<weekly). As discussed in Chapter 1, GERD symptomology (frequency, intensity and duration) – both current and historical – is difficult to assess in an epidemiologic study, due to cultural and individual variations in the experience of GERD symptoms.[30-33] Future studies, with improved

GERD measures, are needed to confirm our findings, and to explore the role of GERD as an effect measure modifier.

In summary, given the large sample size needed and the long induction period of BE and EA/GCA, the ideal cohort study design is likely to be very costly and inefficient. Although the study design used in this dissertation was less than ideal, it was much more practical and time-/cost-efficient when compared to the ideal study approach proposed above.

Conclusions

This dissertation is the first to examine whether multiple measures of sugar/carbohydrate intake are associated with multiple outcomes in the BE-EA/GCA continuum in the US. I conducted a pooled analysis drawing upon the resources of four case-control studies (of which two included a follow-up component to assess mortality after EA/GCA) that were conducted using similar methodologies, which facilitated harmonization of the study responses. I considered a comprehensive number of exposure measures to better capture the intake of these complex foods. I found that dietary intake of sucrose and sweetened desserts/beverages was positively associated with both BE and EA incidence. Added sugar intake and the glycemic index were associated with increased incidence of BE and EA, respectively. If these findings are confirmed by future studies, limiting intake of sweetened desserts/beverages may be a potential risk reduction strategy for BE and EA incidence.

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APPENDIX: ADDITIONAL TABLES

Table A.1. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing Barrett's esophagus, stratified by BMI, among 472 cases and 492 controls from two US case-control studies.

BMI (kg/m^2)	Measure	Controls (N)	Cases (N)	Multiplicative scale		Additive scale	
				Stratified ORs (95%CIs)	$P_{interaction}$	Single referent ORs (95%CIs)	Interaction contrast ratio (95%CI)
	Sucrose						
<25	<median	61	39	1.00		1.00	
	≥median	70	50	1.55 (0.81-2.95)		1.55 (0.81-2.95)	
≥25	<median	176	174	1.00		1.37 (0.81-2.30)	
	≥median	169	185	1.27 (0.86-1.88)	0.58	1.74 (0.99-3.05)	-0.18 (-1.16, 0.80)
	Added sugar						
<25	<median	68	32	1.00		1.00	
	≥median	63	57	1.97 (1.03-3.78)		1.97 (1.03-3.78)	
≥25	<median	169	165	1.00		1.68 (0.99-2.86)	
	≥median	176	194	1.12 (0.77-1.64)	0.12	1.89 (1.07-3.33)	-0.76 (-2.06, 0.54)
	Sweetened desserts/beverages						
<25	<median	62	38	1.00		1.00	
	≥median	70	56	1.48 (0.80-2.73)		1.48 (0.80-2.73)	
≥25	<median	181	178	1.00		1.40 (0.84-2.33)	
	≥median	173	198	1.18 (0.83-1.70)	0.52	1.66 (0.97-2.82)	-0.22 (-1.17, 0.72)

Table A.2. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing Barrett's esophagus, stratified by waist circumference categories, among 472 cases and 492 controls from two US case-control studies.

Waist circumference[1]	Measure	Controls (N)	Cases (N)	Multiplicative scale		Additive scale	
				Stratified ORs (95%CIs)	$P_{interaction}$	Single referent ORs (95%CIs)	Interaction contrast ratio (95%CI)
	Sucrose						
<median	<median	120	91	1.00		1.00	
	≥median	137	125	1.39 (0.88-2.19)		1.39 (0.88-2.19)	
≥median	<median	118	121	1.00		1.09 (0.71-1.66)	
	≥median	103	109	1.21 (0.76-1.92)	0.64	1.31 (0.81-2.14)	-0.16 (-0.89, 0.57)
	Added sugar						
<median	<median	124	87	1.00		1.00	
	≥median	133	129	1.41 (0.90-2.22)		1.41 (0.90-2.22)	
≥median	<median	114	109	1.00		1.15 (0.75-1.77)	
	≥median	107	121	1.09 (0.70-1.72)	0.39	1.26 (0.78-2.02)	-0.30 (-1.06, 0.45)
	Sweetened desserts/beverages						
<median	<median	125	88	1.00		1.00	
	≥median	136	138	1.63 (1.06-2.50)		1.63 (1.06-2.50)	
≥median	<median	119	127	1.00		1.43 (0.94-2.17)	
	≥median	108	115	0.91 (0.59-1.41)	0.05	1.31 (0.83-2.06)	-0.75 (-1.64, 0.14)

[1]Sex-specific waist circumference category

Table A.3. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing Barrett's esophagus, stratified by GERD frequency, among 472 cases and 492 controls from two US case-control studies.

GERD frequency	Measure	Controls (N)	Cases (N)	Multiplicative scale		Additive scale	
				Stratified ORs (95%CIs)	$P_{interaction}$	Single referent ORs (95%CIs)	Interaction contrast ratio (95%CI)
	Sucrose						
≤Weekly	<median	195	81	1.00		1.00	
	≥median	198	99	1.40 (0.93-2.10)		1.40 (0.93-2.10)	
>Weekly	<median	42	132	1.00		8.71 (5.56-13.65)	
	≥median	41	136	1.22 (0.71-2.08)	0.66	10.59 (6.41-17.49)	1.48 (-3.75, 6.71)
	Added sugar						
≤Weekly	<median	198	82	1.00		1.00	
	≥median	195	98	1.31 (0.88-1.96)		1.31 (0.88-1.96)	
>Weekly	<median	39	115	1.00		8.35 (5.25-13.29)	
	≥median	44	153	1.20 (0.71-2.05)	0.79	10.05 (6.26-16.13)	1.39 (-3.48, 6.26)
	Sweetened desserts/beverages						
≤Weekly	<median	203	87	1.00		1.00	
	≥median	200	101	1.24 (0.85-1.81)		1.24 (0.85-1.81)	
>Weekly	<median	43	131	1.00		8.11 (5.23-12.58)	
	≥median	45	153	1.17 (0.71-1.94)	0.84	9.50 (6.02-14.99)	1.14 (-3.31, 5.60)

Table A.4. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing BE among 472 cases and 492 controls from two US case-control studies (pooled approach, based on identical absolute intake cut-points).

Measure	Controls (N)	Cases (N)	OR (95%CI)
Free glucose (g/day)[1]			
Q1: 1.61-<11.53	115	113	Ref.
Q2: 11.53-<17.88	121	107	0.82 (0.53-1.26)
Q3: 17.88-<26.28	122	121	1.23 (0.78-1.93)
Q4: ≥26.28	123	109	1.08 (0.64-1.81)
P_{trend}			0.85
Sucrose (g/day)[2]			
Q1: 2.26-<20.24	117	98	Ref.
Q2: 20.24-<31.69	119	120	1.26 (0.82-1.94)
Q3: 31.69-<43.81	118	93	1.21 (0.76-1.94)
Q4: ≥43.81	122	137	1.90 (1.12-3.21)
P_{trend}			<0.01
Free fructose (g/day)[1]			
Q1: 1.48-<11.19	115	98	Ref.
Q2: 11.19-<18.90	121	126	1.26 (0.82-1.94)
Q3: 18.90-<29.73	122	130	1.55 (0.99-2.45)
Q4: ≥29.73	123	96	1.14 (0.69-1.90)
P_{trend}			0.66
Total sugar (g/day)[1]			
Q1: 10.85-<58.54	115	101	Ref.
Q2: 58.54-<86.74	122	114	1.29 (0.83-2.00)
Q3: 86.74-<118.73	122	117	1.37 (0.86-2.20)
Q4: ≥118.73	122	118	1.69 (0.96-2.97)
P_{trend}			0.15
Added sugar (g/day)[2]			
Q1: 1.77-<19.97	119	97	Ref.
Q2: 19.97-<32.55	118	100	1.06 (0.69-1.63)
Q3: 32.55-<50.28	120	112	1.16 (0.74-1.83)
Q4: ≥50.28	119	139	1.70 (1.04-2.78)
P_{trend}			0.15
Starch (g/day)[2]			
Q1: 4.48-<43.22	117	103	Ref.
Q2: 43.22-<61.84	118	109	0.84 (0.54-1.30)
Q3: 61.84-<91.87	121	133	1.28 (0.80-2.07)
Q4: ≥91.87	120	103	0.98 (0.51-1.90)
P_{trend}			0.74
Total carbohydrate (g/day)[1]			
Q1: 35.56-<142.13	116	107	Ref.
Q2: 142.13-<196.04	120	121	1.13 (0.72-1.75)

Q3: 196.04-<260.82	123	122	1.17 (0.70-1.94)
Q4: ≥260.82	122	100	1.26 (0.62-2.54)
P_{trend}			0.39
Glycemic index[3]			
Q1: 22.27-<58.93	122	110	Ref.
Q2: 58.93-<61.10	122	114	0.92 (0.61-1.39)
Q3: 61.10-<63.12	119	110	0.95 (0.63-1.44)
Q4: ≥63.12	118	116	0.97 (0.64-1.47)
P_{trend}			0.39
Glycemic load[4]			
Q1: 16.69-<75.64	115	107	Ref.
Q2: 75.64-<106.06	119	121	1.13 (0.73-1.76)
Q3: 106.06-<141.08	123	115	1.17 (0.71-1.94)
Q4: ≥141.08	119	105	1.34 (0.69-2.61)
P_{trend}			0.35
Sweetened desserts/beverages (servings/day)[5]			
Q1: 0-<1.20	123	98	Ref.
Q2: 1.20-<2.00	123	112	1.12 (0.74-1.70)
Q3: 2.00-<3.10	122	124	1.27 (0.83-1.95)
Q4: ≥3.10	123	138	1.65 (1.03-2.64)
P_{trend}			0.04
Sweetened desserts (servings/day)[6]			
Q1: 0-<0.72	121	124	Ref.
Q2: 0.72-<1.22	123	85	0.65 (0.43-0.99)
Q3: 1.22-<2.08	121	124	1.07 (0.71-1.63)
Q4: ≥2.08	121	137	1.14 (0.73-1.79)
P_{trend}			0.10
Sweetened beverages (servings/day)[3]			
Q1: 0-<0.15	118	98	Ref.
Q2: 0.15-<0.53	120	112	1.21 (0.79-1.84)
Q3: 0.53-<1.11	123	117	1.24 (0.81-1.89)
Q4: >1.11	120	123	1.46 (0.94-2.28)
P_{trend}			0.29

[1]Adjusted for age, sex, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
[2]Adjusted for age, sex, race, study indicator, BMI, fruit/vegetable intake, GERD frequency, and total energy intake
[3]Adjusted for age, sex, race, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
[4]Adjusted for age, sex, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
[5]Adjusted for age, sex, study indicator, GERD frequency, and total energy intake
[6]Adjusted for age, sex, study indicator, BMI, GERD frequency, and total energy intake

Table A.5. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing BE among 448 cases and 472 controls from two US case-control studies (using lower and upper 2.5% as exclusion criteria).

Measure	Controls (N)	Cases (N)	OR (95%CI)
Free glucose (g/day)[1]			
Q1			Ref.
Q2	111	107	1.36 (0.87-2.11)
Q3	115	122	1.24 (0.78-1.97)
Q4	118	111	1.26 (0.75-2.10)
P_{trend}	118	87	0.47
Sucrose (g/day)[2]			
Q1	112	96	Ref.
Q2	115	107	1.12 (0.72-1.74)
Q3	112	92	1.21 (0.75-1.96)
Q4	118	130	2.01 (1.18-3.43)
P_{trend}			<0.01
Free fructose (g/day)[1]			
Q1	110	100	Ref.
Q2	119	127	1.43 (0.92-2.22)
Q3	116	105	1.35 (0.85-2.16)
Q4	117	95	1.39 (0.84-2.29)
P_{trend}			0.59
Total sugar (g/day)[1]			
Q1	112	101	Ref.
Q2	116	114	1.23 (0.79-1.92)
Q3	116	100	1.21 (0.74-1.96)
Q4	118	112	1.60 (0.91-2.81)
P_{trend}			0.02
Added sugar (g/day)[2]			
Q1	114	92	Ref.
Q2	113	95	1.11 (0.71-1.72)
Q3	115	107	1.17 (0.73-1.86)
Q4	115	131	1.75 (1.06-2.90)
P_{trend}			0.01
Starch (g/day)[2]			
Q1	112	99	Ref.
Q2	113	103	0.96 (0.61-1.51)
Q3	116	129	1.40 (0.84-2.31)
Q4	116	94	1.06 (0.53-2.10)
P_{trend}			0.62
Total carbohydrate (g/day)[1]			
Q1	112	102	Ref.
Q2	115	112	1.28 (0.80-2.04)

Q3	117	123	1.56 (0.89-2.74)
Q4	118	90	1.66 (0.75-3.65)
P_{trend}			0.09
Glycemic index[3]			
Q1	116	105	Ref.
Q2	118	105	0.85 (0.56-1.30)
Q3	115	101	0.88 (0.58-1.34)
Q4	113	116	0.93 (0.61-1.43)
P_{trend}			0.39
Glycemic load[4]			
Q1	110	103	Ref.
Q2	115	119	1.18 (0.74-1.87)
Q3	117	106	1.19 (0.69-2.05)
Q4	115	97	1.50 (0.73-3.08)
P_{trend}			0.07
Sweetened desserts/beverages (servings/day)[5]			
Q1	117	90	Ref.
Q2	118	120	1.33 (0.87-2.03)
Q3	118	103	1.18 (0.75-1.84)
Q4	118	135	1.79 (1.11-2.88)
P_{trend}			<0.01
Sweetened desserts (servings/day)[6]			
Q1	116	116	Ref.
Q2	118	80	0.63 (0.41-0.98)
Q3	116	118	1.12 (0.73-1.72)
Q4	116	132	1.31 (0.83-2.08)
P_{trend}			0.12
Sweetened beverages (servings/day)[3]			
Q1	114	89	Ref.
Q2	118	104	1.12 (0.72-1.72)
Q3	115	104	1.40 (0.90-2.18)
Q4	115	130	1.60 (1.03-2.50)
P_{trend}			0.02

[1]Adjusted for age, sex, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
[2]Adjusted for age, sex, race, study indicator, BMI, fruit/vegetable intake, GERD frequency, and total energy intake
[3]Adjusted for age, sex, race, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
[4]Adjusted for age, sex, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
[5]Adjusted for age, sex, study indicator, GERD frequency, and total energy intake
[6]Adjusted for age, sex, study indicator, BMI, GERD frequency, and total energy intake

Table A.6. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing Barrett's esophagus among 472 cases and 492 controls from two US case-control studies (pooled approach, based on study-specific quartiles, without adjusting for total energy intake).

Measure	Controls (N)	Cases (N)	OR (95%CI)	P_{trend}
Free glucose (g/day)[1]				
Q1	116	107	Ref.	
Q2	120	134	1.42 (0.94-2.15)	
Q3	123	115	1.24 (0.80-1.91)	
Q4	122	94	1.26 (0.79-1.99)	0.95
Sucrose (g/day)[2]				
Q1	117	105	Ref.	
Q2	120	108	1.02 (0.67-1.56)	
Q3	117	97	1.07 (0.69-1.65)	
Q4	122	138	1.50 (0.99-2.29)	0.02
Free fructose (g/day)[1]				
Q1	115	108	Ref.	
Q2	123	131	1.34 (0.88-2.04)	
Q3	121	113	1.27 (0.82-1.97)	
Q4	122	98	1.24 (0.78-1.95)	0.76
Total sugar (g/day)[1]				
Q1	117	109	Ref.	
Q2	120	116	1.11 (0.73-1.68)	
Q3	122	103	1.01 (0.66-1.55)	
Q4	122	122	1.35 (0.88-2.08)	0.24
Added sugar (g/day)[2]				
Q1	119	97	Ref.	
Q2	118	100	1.09 (0.71-1.67)	
Q3	120	112	1.07 (0.70-1.64)	
Q4	119	139	1.53 (1.01-2.33)	0.16
Starch (g/day)[2]				
Q1	117	103	Ref.	
Q2	118	109	1.01 (0.66-1.55)	
Q3	121	133	1.39 (0.91-2.12)	
Q4	120	103	1.05 (0.67-1.65)	0.89
Total carbohydrate (g/day)[1]				
Q1	117	109	Ref.	
Q2	119	115	1.09 (0.72-1.66)	
Q3	123	127	1.23 (0.81-1.88)	
Q4	122	99	1.13 (0.72-1.79)	0.57

Glycemic index[3]				
Q1	122	112	Ref.	
Q2	122	109	0.83 (0.55-1.26)	
Q3	119	113	0.93 (0.62-1.41)	
Q4	118	116	0.93 (0.62-1.41)	0.38
Glycemic load[4]				
Q1	115	108	Ref.	
Q2	119	124	1.15 (0.76-1.75)	
Q3	123	109	1.07 (0.69-1.64)	
Q4	119	107	1.26 (0.80-1.99)	0.41
Sweetened desserts/beverages (servings/day)[5]				
Q1	123	94	Ref.	
Q2	123	124	1.28 (0.85-1.93)	
Q3	122	116	1.17 (0.77-1.77)	
Q4	123	138	1.45 (0.96-2.18)	0.13
Sweetened desserts (servings/day)[6]				
Q1	122	123	Ref.	
Q2	122	81	0.61 (0.40-0.93)	
Q3	121	126	1.04 (0.70-1.55)	
Q4	121	140	1.10 (0.74-1.63)	0.22
Sweetened beverages (servings/day)[3]				
Q1	118	97	Ref.	
Q2	121	108	1.10 (0.72-1.69)	
Q3	120	107	1.28 (0.84-1.97)	
Q4	122	138	1.45 (0.95-2.20)	0.29

[1]Adjusted for age, sex, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
[2]Adjusted for age, sex, race, study indicator, BMI, fruit/vegetable intake, GERD frequency, and total energy intake
[3]Adjusted for age, sex, race, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
[4]Adjusted for age, sex, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
[5]Adjusted for age, sex, study indicator, GERD frequency, and total energy intake
[6]Adjusted for age, sex, study indicator, BMI, GERD frequency, and total energy intake

Table A.7. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing Barrett's esophagus among 472 cases and 492 controls from two US case-control studies (nutrient density energy adjustment method).

Measure	Controls (N)	Cases (N)	OR (95%CI)	P_{trend}
Free glucose (g/day)[1]				
Q1	118	117	Ref.	
Q2	118	130	1.27 (0.85-1.91)	
Q3	123	102	0.97 (0.63-1.49)	
Q4	122	101	1.07 (0.69-1.65)	0.98
Sucrose (g/day)[2]				
Q1	117	92	Ref.	
Q2	119	108	1.10 (0.71-1.69)	
Q3	121	103	1.07 (0.70-1.65)	
Q4	119	145	1.84 (1.21-2.79)	<0.01
Free fructose (g/day)[1]				
Q1	118	120	Ref.	
Q2	118	121	1.11 (0.74-1.66)	
Q3	123	117	1.12 (0.73-1.70)	
Q4	122	92	0.90 (0.58-1.40)	0.85
Total sugar (g/day)[1]				
Q1	119	102	Ref.	
Q2	120	116	1.34 (0.89-2.04)	
Q3	121	110	1.18 (0.78-1.80)	
Q4	121	122	1.39 (0.91-2.12)	0.12
Added sugar (g/day)[2]				
Q1	119	94	Ref.	
Q2	120	85	0.89 (0.57-1.37)	
Q3	119	104	1.15 (0.75-1.76)	
Q4	118	165	1.67 (1.11-2.51)	0.05
Starch (g/day)[2]				
Q1	121	120	Ref.	
Q2	118	100	0.88 (0.58-1.33)	
Q3	118	118	0.98 (0.65-1.47)	
Q4	119	110	0.95 (0.63-1.43)	0.55
Total carbohydrate (g/day)[1]				
Q1	118	105	Ref.	
Q2	121	134	1.33 (0.89-1.99)	
Q3	119	105	1.00 (0.65-1.53)	
Q4	123	106	1.22 (0.79-1.87)	0.43

[1]Adjusted for age, sex, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake
[2]Adjusted for age, sex, race, study indicator, BMI, fruit/vegetable intake, GERD frequency, and total energy intake

Table A.8. Multivariable-adjusted ORs and 95%CIs for the associations between carbohydrate intake and risk of developing BE among 472 cases and 492 controls from two US case-control studies (originally calculated carbohydrate values vs. new carbohydrate values).

Measure	Controls (N)	Cases (N)	OR[1] (95%CI)
Old total carbohydrate values (g/day)			
Q1	117	105	Ref.
Q2	119	110	1.01 (0.65-1.58)
Q3	123	128	1.27 (0.77-2.07)
Q4	122	107	1.26 (0.65-2.45)
P_{trend}			0.32
New total carbohydrate values (g/day)			
Q1	117	109	Ref.
Q2	119	115	1.12 (0.72-1.75)
Q3	123	127	1.29 (0.78-2.16)
Q4	122	99	1.25 (0.61-2.54)
P_{trend}			0.39

[1]Adjusted for age, sex, study indicator, fruit/vegetable intake, GERD frequency, and total energy intake

Table A.9. Multivariable-adjusted ORs and 95%CIs for the associations between sweetened desserts/beverages intake and risk of developing Barrett's esophagus, stratified by waist circumference categories, among 472 cases and 492 controls from two US case-control studies (using extreme quartiles for sweetened desserts/beverages measure).

Waist circumference[1]	Sweetened desserts /beverages	Controls (N)	Cases (N)	Multiplicative scale		Additive scale	
				Stratified ORs (95%CIs)	$P_{interaction}$	Single referent ORs (95%CIs)	Interaction contrast ratio (95%CI)
<median	Q1	61	35	1.00		1.00	
	Q4	73	76	2.07 (1.08-3.96)		2.07 (1.08-3.96)	
≥median	Q1	62	58	1.00		1.54 (0.84-2.84)	
	Q4	49	61	1.28 (0.65-2.52)	0.25	1.98 (0.96-4.08)	-0.63 (-2.11, 0.85)

[1]Sex-specific waist circumference category

Table A.10. Study-specific sugar/carbohydrate intake quintiles defined by the intake distribution of the controls from each of the two US case-control studies of EA/GCA (quintiles for case-control analysis).

Measure	US Multi-Center Study	LA Multi-Ethnic Study	EA cases (N=500)	GCA cases (N=529)	Controls (N=2027)
Free glucose (g/day)					
Q1	0.12-<13.29	1.21-<16.11	118	83	406
Q2	13.29-<16.11	16.11-<22.64	98	100	405
Q3	16.11-<20.69	22.64-<29.12	99	111	405
Q4	20.69-<26.29	29.12-<39.83	79	106	406
Q5	≥26.29	≥39.83	106	129	405
Sucrose (g/day)					
Q1	2.26-<23.90	0.97-<20.09	75	82	405
Q2	26.90-<34.45	20.09-<30.23	88	107	406
Q3	34.45-<45.71	30.23-<40.90	95	104	405
Q4	45.71-<64.25	40.90-<58.08	110	115	406
Q5	≥64.25	≥58.08	132	121	405
Free fructose (g/day)					
Q1	0.00-<12.18	0.61-<15.91	123	98	405
Q2	12.18-<16.88	15.91-<22.24	98	108	406
Q3	16.88-<22.03	22.24-<28.37	95	94	405
Q4	22.03-29.58	28.37-<40.19	93	107	405
Q5	≥29.58	≥40.19	91	122	406
Total sugar (g/day)					
Q1	2.40-<61.31	3.75-<69.99	89	88	405
Q2	61.31-<79.47	69.99-<95.79	92	93	406
Q3	79.47-<121.58	95.79-<122.55	108	116	405
Q4	102.75-130.24	122.55-<160.64	94	106	406
Q5	≥130.24	≥160.64	117	126	405
Added sugar (g/day)					
Q1	1.10-<23.84	0.38-<23.28	75	81	405
Q2	23.84-<34.59	23.28-<35.26	80	78	406

Q3	34.59-<49.50	35.26-<47.94	101	112	405
Q4	49.50-<69.27	47.94-71.86	120	125	406
Q5	≥69.27	≥71.86	124	133	405
Starch (g/day)					
Q1	1.75-<54.43	3.73-<72.92	77	89	405
Q2	54.43-<69.03	72.92-<99.91	87	90	406
Q3	69.03-<83.73	99.91-<126.58	113	122	405
Q4	83.73-101.44	≥126.58	104	109	406
Q5	≥101.44		119	119	405
Total carbohydrate (g/day)					
Q1	54.70-<155.09	40.83-<195.80	85	95	405
Q2	155.09-<190.36	195.80-<254.03	90	90	406
Q3	190.36-<228.77	254.03-<311.53	92	89	406
Q4	228.77-277.00	311.53-399.25	102	117	405
Q5	≥277.00	≥399.25	131	138	405
Glycemic index					
Q1	2.50-<59.00	19.93-<56.83	96	110	405
Q2	59.00-<61.38	56.83-<59.53	99	89	405
Q3	61.38-<62.84	59.53-<61.28	98	108	406
Q4	62.84-64.28	61.28-<63.09	87	117	406
Q5	≥64.28	≥63.09	120	105	405
Glycemic load					
Q1	2.03-<86.29	7.21-<105.08	93	96	405
Q2	86.29-<104.58	105.08-<136.65	85	85	406
Q3	104.58-<127.22	136.65-<167.90	92	95	405
Q4	127.22-157.79	≥167.90-<216.01	107	125	405
Q5	≥157.79	≥216.01	123	128	406
Sweetened desserts/beverages (servings/day)					
Q1	0-<1.98	0-<1.39	77	80	405
Q2	1.98-<2.92	1.39-<2.21	84	93	407
Q3	2.92-<3.90	2.21-<3.17	107	114	405

Q4	3.90-5.41	3.17-<4.51	88	112	406
Q5	≥5.41	≥4.51	144	130	404
Sweetened desserts (servings/day)					
Q1	0-<0.88	0-<0.66	74	80	404
Q2	0.88-<1.46	0.66-<1.25	76	99	406
Q3	1.46-<2.04	1.25-<1.95	108	105	406
Q4	2.04-2.94	1.95-<2.94	108	119	406
Q5	≥2.94	≥2.94	134	126	405
Sweetened beverages (servings/day)					
Q1	0-<0.57	0-<0.31	101	91	404
Q2	0.57-<1.04	0.31-<0.66	92	101	407
Q3	1.04-<1.71	0.66-<1.12	93	96	405
Q4	1.71-3.00	1.12-<1.75	87	121	407
Q5	≥3.00	≥1.75	127	120	404

Table A.11. Study-specific sugar/carbohydrate intake quintiles defined by the intake distribution of the EA/GCA from each of the two US case-control studies of EA/GCA (quintiles for survival analysis).

	EA cases			GCA cases		
Measure	**US Multi-Center Study**	**LA Multi-Ethnic Study**	**N**	**US Multi-Center Study**	**LA Multi-Ethnic Study**	**N**
Free glucose (g/day)						
Q1	0.12-<10.73	4.16-<16.17	100	3.76-<12.99	1.38-<17.68	105
Q2	10.73-<14.89	16.17-<22.36	100	12.99-<17.81	17.68-<23.31	106
Q3	14.89-<19.08	22.36-<29.13	100	17.81-<22.09	23.31-<30.48	106
Q4	19.08-<26.34	29.13-<41.49	100	22.09-<29.24	30.48-<41.23	106
Q5	≥26.34	≥41.49	100	≥29.24	≥41.23	106
Sucrose (g/day)						
Q1	2.26-<28.10	3.30-<20.91	100	6.00-<26.23	4.32-<21.46	106
Q2	28.10-<40.19	20.91-<31.30	100	26.23-<40.15	21.46-<30.53	106
Q3	40.19-<50.26	31.30-<46.40	100	40.15-<52.51	30.53-<40.81	106
Q4	50.26-<68.86	46.40-<71.99	100	52.51-<71.99	40.81-<57.98	105
Q5	≥68.86	≥71.99	100	≥71.99	≥57.98	106
Free fructose (g/day)						
Q1	0-<10.50	3.63-<15.47	100	2.75-<12.64	0.61-<16.28	106
Q2	10.50-<15.04	15.47-<21.60	100	12.64-<17.17	16.28-<22.68	106
Q3	15.04-<19.80	21.60-<28.66	100	17.17-<23.18	22.68-<29.34	105
Q4	19.80-<28.31	28.66-<40.29	100	23.18-<32.21	29.34-<41.62	106
Q5	≥28.31	≥40.29	100	≥32.21	≥41.62	106
Total sugar (g/day)						
Q1	2.40-<65.89	27.85-<73.44	100	17.97-<71.05	25.82-<76.02	106
Q2	65.89-<84.05	73.44-<96.99	100	71.05-<90.28	76.02-<97.02	105
Q3	84.05-<103.11	96.99-<129.87	100	90.28-<113.58	97.02-<122.55	106
Q4	103.11-<134.78	129.87-<170.80	100	113.58-<141.66	122.55-<165.79	106
Q5	≥134.78	≥170.80	100	≥141.66	≥165.79	106
Added sugar (g/day)						
Q1	1.10-29.48	4.03-<25.37	100	7.93-<28.09	4.39-<27.05	106

Q2	29.48-<42.51	25.37-<37.99	100	28.09-<43.04	27.05-<39.28	106
Q3	42.51-<53.65	-37.99<58.49	100	43.04-<58.94	39.28-<54.43	105
Q4	53.65-<74.67	58.49-<86.37	100	58.94-<79.80	54.43-<75.22	106
Q5	≥74.67	≥86.37	100	≥79.80	≥75.22	106
Starch (g/day)						
Q1	1.75-<60.20	21.15-<78.85	100	21.13-<63.21	20.63-<70.09	106
Q2	60.20-<77.44	78.85-<103.50	100	63.21-<78.17	70.09-<100.55	105
Q3	77.44-<89.63	103.50-<130.02	100	78.17-<90.57	100.55-<125.01	106
Q4	89.63-<107.37	130.02-<172.82	100	90.57-<108.77	125.01-<163.29	106
Q5	≥107.37	≥172.82	100	≥108.77	≥163.29	106
Total carbohydrate (g/day)						
Q1	71.30-<164.25	84.31-<201.49	100	77.47-<175.11	94.82-<197.24	107
Q2	164.25-<204.85	201.49-<259.63	100	175.11-<216.62	197.24-<253.10	107
Q3	204.85-<244.70	259.63-<331.54	100	216.62-<255.35	253.10-<325.11	105
Q4	244.70-<298.57	331.54-<420.39	100	255.35-<302.61	325.11-<415.59	106
Q5	≥298.57	≥420.39	100	≥302.61	≥415.59	104
Glycemic index						
Q1	2.50-<59.15	32.52-<57.53	100	35.01-<59.57	29.77-<55.63	106
Q2	59.15-<61.68	57.53-<59.54	100	59.57-<62.03	55.63-<59.19	106
Q3	61.68-<63.10	59.54-<60.97	100	62.03-<63.21	59.19-<60.95	106
Q4	63.10-<64.69	60.97-<63.15	100	63.21-<64.33	60.95-<62.89	106
Q5	≥64.69	≥63.15	100	≥64.33	≥62.89	105
Glycemic load						
Q1	2.03-<89.59	45.36-<106.54	-<	38.87-<96.86	41.53-<101.35	106
Q2	89.59-<112.37	106.54-<137.77	100	96.86-<119.66	101.35-<131.53	106
Q3	112.37-<134.67	137.77-<176.03	100	119.66-<143.09	131.53-<172.41	105
Q4	134.67-<166.29	176.03-<228.82	100	143.09-<173.37	172.41-<222.97	106
Q5	≥166.29	≥228.82	100	≥173.37	≥222.97	106
Sweetened desserts/beverages (servings/day)						
Q1	0-<2.29	0.03-<1.62	100	0.08-<2.30	0-<1.72	106

Q2	2.29-<3.35	1.62-<2.36	100	2.30-<3.46	1.72-<2.45	106
Q3	3.35-<4.41	2.36-<3.45	100	33.46-<4.51	2.45-<3.17	105
Q4	4.41-<6.11	3.45-<5.57	100	4.51-<5.93	3.17-<4.69	106
Q5	≥6.11	≥5.57	100	≥5.93	≥4.69	106
Sweetened desserts (servings/day)						
Q1	0-<1.11	0.01-<0.80	100	0.06-<1.08	0-<0.82	106
Q2	1.11-<1.73	0.80-<1.53	100	1.08-<1.72	0.82-<1.38	106
Q3	1.73-<2.34	1.53-<2.28	100	1.72-<2.34	1.38-<2.06	105
Q4	2.34-<3.12	2.28-<4.04	99	2.34-<3.28	2.06-<3.16	106
Q5	≥3.12	≥4.04	101	≥3.28	≥3.16	106
Sweetened beverages (servings/day)						
Q1	0-<0.57	0-<0.33	97	0-<0.63	0-<0.39	105
Q2	0.57-<1.14	0.33-<0.64	100	0.63-<1.13	0.39-<0.73	107
Q3	1.14-<2.14	0.64-<1.09	102	1.13-<2.00	0.73-<1.21	112
Q4	2.14-<3.46	1.09-<1.96	100	2.00-<3.16	1.21-<1.79	99
Q5	≥3.46	≥1.96	101	≥3.16	≥1.79	106

Table A.12. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing EA, stratified by BMI, among 500 EA cases, 529 GCA cases, and 2027 controls from two US case-control studies.

BMI (kg/m^2)	Measure	Controls(N)	Cases (N)	Multiplicative scale		Additive scale	
				Stratified ORs (95%CIs)	$P_{interaction}$	Single referent ORs (95%CIs)	Interaction contrast ratio (95%CI)
	Sucrose						
<25	Q1-Q3	636	88	1.00		1.00	
	Q4-Q5	367	100	1.79 (1.26-2.56)		1.79 (1.26-2.56)	
≥25	Q1-Q3	542	154	1.00		2.00 (1.48-2.72)	
	Q4-Q5	411	131	1.05 (0.76-1.44)	0.02	2.10 (1.48-2.98)	-0.70 (-1.54, 0.14)
	Sweetened desserts/beverages						
<25	Q1-Q3	613	86	1.00		1.00	
	Q4-Q5	390	102	1.45 (1.03-2.06)		1.45 (1.03-2.06)	
≥25	Q1-Q3	562	164	1.00		1.99 (1.47-2.70)	
	Q4-Q5	391	121	0.85 (0.62-1.16)	0.02	1.69 (1.19-2.41)	-0.75 (-1.51, 0.01)
	Glycemic index						
<25	Q1-Q3	582	118	1.00		1.00	
	Q4-Q5	421	70	0.88 (0.62-1.24)		0.88 (0.62-1.24)	
≥25	Q1-Q3	597	161	1.00		1.29 (0.97-1.72)	
	Q4-Q5	356	124	1.38 (1.03-1.85)	0.05	1.79 (1.31-2.44)	0.62 (0.08, 1.15)
	Free fructose						
<25	Q1-Q3	629	125	1.00		1.00	
	Q4-Q5	374	63	0.81 (0.56-1.17)		0.81 (0.56-1.17)	
≥25	Q1-Q3	538	172	1.00		1.60 (1.21-2.11)	
	Q4-Q5	415	113	0.75 (0.54-1.04)	0.74	1.20 (0.85-1.68)	-0.21 (-0.74, 0.32)

Table A.13. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing EA, stratified by GERD frequency, among 500 EA cases and 2027 controls from two US case-control studies.

GERD	Measure	Cases (N)	Controls (N)	Multiplicative scale		Additive scale	
				Stratified ORs (95%CIs)	$P_{interaction}$	Single referent ORs (95%CIs)	Additive ICR (95%CI)
	Sucrose						
<Weekly	Q1-Q3	120	962	1.00		1.00	
	Q4-Q5	125	602	1.58 (1.16-2.14)		1.58 (1.16-2.14)	
≥Weekly	Q1-Q3	122	216	1.00		4.47 (3.28-6.08)	
	Q4-Q5	106	176	1.01 (0.70-1.47)	0.05	4.51 (3.18-6.40)	-0.53 (-2.20, 1.14)
	Glycemic index						
<Weekly	Q1-Q3	155	949	1.00		1.00	
	Q4-Q5	94	638	1.01 (0.76-1.35)		1.01 (0.76-1.35)	
≥Weekly	Q1-Q3	130	245	1.00		3.35 (2.52-4.46)	
	Q4-Q5	102	151	1.32 (0.93-1.88)	0.24	4.44 (3.22-6.13)	1.08 (-0.21, 2.36)
	Sweetened desserts/beverages						
<Weekly	Q1-Q3	128	955	1.00		1.00	
	Q4-Q5	117	609	1.21 (0.90-1.64)		1.21 (0.90-1.64)	
≥Weekly	Q1-Q3	122	220	1.00		4.19 (3.08-5.69)	
	Q4-Q5	106	172	0.89 (0.62-1.28)	0.18	3.72 (2.65-5.22)	-0.68 (-2.15, 0.79)
	Free fructose						
<Weekly	Q1-Q3	159	951	1.00		1.00	
	Q4-Q5	86	613	0.81 (0.59-1.12)		0.81 (0.59-1.12)	
≥Weekly	Q1-Q3	138	216	1.00		3.85 (2.89-5.14)	
	Q4-Q5	90	176	0.72 (0.49-1.05)	0.59	2.77 (1.96-3.91)	-0.90 (-2.14, 0.35)

Table A.14. Multivariable-adjusted HRs and 95%CIs for the associations between sugar/carbohydrate intake and overall survival in EA/GCA among 500 EA cases and 529 GCA cases from two US case-control studies (meta-analytic approach, fixed effect).

	Esophageal Adenocarcinoma					Gastric Cardia Adenocarcinoma				
Measure	Deaths (N)	Total EA Cases (N)	HR[1] (95%CI)	I^2 (%)	$P_{heterogeneity}$	Deaths (N)	Total GCA Cases (N)	HR[1] (95%CI)	I^2 (%)	$P_{heterogeneity}$
Free glucose (g/day)[1]										
Q1	87	100	Ref.			86	104	Ref.		
Q2	89	100	0.95 (0.70-1.29)	0	0.68	95	106	1.07 (0.79-1.43)	0	0.38
Q3	87	98	0.89 (0.65-1.22)	70.1	0.07	90	105	1.04 (0.77-1.41)	0	0.63
Q4	86	98	0.96 (0.70-1.33)	0	0.42	89	106	0.86 (0.62-1.18)	11.4	0.29
Q5	85	100	0.95 (0.81-1.11)			90	105	0.99 (0.72-1.37)	0	0.59
P_{trend}			0.49	0	0.89			0.93	0	0.46
Sucrose (g/day)[1]										
Q1	86	99	Ref.			90	106	Ref.		
Q2	85	99	0.96 (0.70-1.30)	6.0	0.30	89	106	1.02 (0.76-1.38)	30.5	0.23
Q3	85	99	1.01 (0.73-1.40)	0	0.56	92	104	1.15 (0.84-1.56)	0	0.62
Q4	91	100	1.25 (0.91-1.73)	0	0.57	90	105	1.04 (0.75-1.45)	0	0.82
Q5	87	99	1.15 (0.79-1.69)	0	0.59	89	105	0.97 (0.68-1.39)	67.3	0.08
P_{trend}			0.48	0	0.81			>0.99	0	0.67
Free fructose (g/day)[1]										
Q1	89	100	Ref.			87	106	Ref.		
Q2	86	100	0.85 (0.63-1.15)	0	0.75	96	105	1.26 (0.94-1.69)	0	0.95
Q3	89	98	0.97 (0.72-1.32)	0	0.83	87	104	1.01 (0.74-1.37)	0	0.53
Q4	85	99	0.87 (0.63-1.20)	18.9	0.27	90	106	0.93 (0.68-1.28)	0	0.34
Q5	85	99	1.03 (0.73-1.45)	0	0.76	90	105	1.03 (0.75-1.41)	0	0.96
P_{trend}			0.40	0	0.87			0.98	0	0.48
Total sugar (g/day)[2]										
Q1	86	100	Ref.			89	106	Ref.		
Q2	90	99	1.30 (0.96-1.75)	0	0.58	86	105	0.95 (0.70-1.28)	77.4	0.04
Q3	84	100	1.08 (0.79-1.49)	67.2	0.08	93	105	1.17 (0.87-1.59)	0	0.78

Q4	89	99	1.26 (0.89-1.78)	0	0.57	99	106	1.20 (0.87-1.66)	0	0.83
Q5	86	99	1.35 (0.91-2.00)	0	0.49	84	105	0.81 (0.57-1.16)	0	0.47
P_{trend}			0.36	0	0.36			0.75	0	0.71
Added sugar (g/day)[1]										
Q1	90	100	Ref.			88	106	Ref.		
Q2	85	99	0.90 (0.67-1.23)	0	0.67	92	106	1.26 (0.94-1.70)	0	0.61
Q3	82	99	0.79 (0.58-1.09)	0	0.95	87	103	1.09(0.79-1.49)	53.9	0.14
Q4	89	99	1.12 (0.81-1.54)	0	0.45	93	105	1.17 (0.85-1.62)	0	0.76
Q5	88	99	1.09 (0.75-1.59)	0	0.55	90	106	1.04 (0.73-1.49)	0	0.53
P_{trend}			0.89	0	0.54			>0.99	0	>0.99
Starch (g/day)[1]										
Q1	91	100	Ref.			89	106	Ref.		
Q2	83	98	0.87 (0.64-1.19)	85.0	0.01	91	104	1.21 (0.89-1.65)	0	0.41
Q3	87	100	0.96 (0.70-1.31)	75.9	0.04	88	105	1.03 (0.74-1.41)	72.5	0.06
Q4	83	99	1.02 (0.72-1.44)	84.0	0.01	94	106	1.15 (0.81-1.62)	80.8	0.02
Q5	90	99	1.26 (0.85-1.88)	71.6	0.06	88	105	1.08 (0.72-1.62)	85.1	0.01
P_{trend}			0.20	21.3	0.26			0.70	86.1	0.01
Total carbohydrate (g/day)[1]										
Q1	89	100	Ref.			89	107	Ref.		
Q2	82	98	0.86 (0.63-1.18)	0	0.89	91	106	1.11 (0.82-1.50)	0	0.85
Q3	90	100	1.23 (0.87-1.75)	0	0.45	93	104	1.25 (0.90-1.74)	63.7	0.10
Q4	90	99	1.17 (0.77-1.77)	0	0.58	91	105	1.02 (0.71-1.46)	0	0.91
Q5	83	99	1.20 (0.69-2.08)	31.7	0.23	86	104	0.80 (0.49-1.29)	0	0.69
P_{trend}			0.51	0	0.38			>0.99	0	>0.99
Glycemic index[1]										
Q1	91	100	Ref.			89	106	Ref.		
Q2	78	98	0.94 (0.69-1.28)	74.2	0.05	88	106	1.23 (0.91-1.66)	29.0	0.24
Q3	89	100	1.16 (0.86-1.57)	0	0.40	94	104	1.15 (0.85-1.55)	30.2	0.23
Q4	90	99	0.99 (0.73-1.35)	20.1	0.26	93	104	1.24 (0.92-1.66)	0	0.46
Q5	86	99	0.94 (0.69-1.28)	37.5	0.21	86	106	0.99 (0.73-1.34)	0	0.47
P_{trend}			0.68	6.3	0.30			0.54	50.1	0.16

Glycemic load[1]										
Q1	91	100	Ref.			89	106	Ref.		
Q2	78	98	0.77 (0.56-1.06)	0	0.63	88	106	0.95 (0.70-1.29)	48.9	0.16
Q3	89	100	1.10 (0.79-1.52)	78.3	0.03	94	104	1.24 (0.90-1.70)	48.8	0.16
Q4	90	99	1.11 (0.76-1.60)	0	0.42	93	104	1.03 (0.74-1.43)	45.3	0.18
Q5	86	99	1.30 (0.82-2.05)	69.6	0.07	86	106	0.81 (0.53-1.22)	41.2	0.19
P_{trend}			0.45	27.6	0.24			0.86	0	0.49
Sweetened desserts/beverages (servings/day)[1]										
Q1	86	98	Ref.			92	106	Ref.		
Q2	88	100	0.95 (0.70-1.29)	0	0.42	89	106	0.98 (0.73-1.32)	0	0.80
Q3	84	100	0.88 (0.65-1.21)	0	0.36	85	103	0.91 (0.67-1.24)	0	0.56
Q4	92	99	1.10 (0.81-1.50)	0	0.97	95	105	1.12 (0.82-1.54)	17.5	0.27
Q5	84	99	0.97 (0.68-1.39)	0	0.91	89	106	0.89 (0.64-1.23)	3.1	0.31
P_{trend}			0.58	0	0.97			0.41	0	0.88
Sweetened desserts (servings/day)[1]										
Q1	88	99	Ref.			92	106	Ref.		
Q2	83	100	0.92 (0.67-1.25)	41.7	0.19	90	106	1.02 (0.76-1.37)	44.2	0.18
Q3	91	99	1.21 (0.89-1.64)	0	0.94	88	102	1.01 (0.75-1.35)	50.6	0.16
Q4	83	98	0.95 (0.69-1.32)	27.2	0.24	89	106	0.96 (0.71-1.29)	0	0.79
Q5	89	100	0.94 (0.67-1.33)	0	0.71	91	106	0.89 (0.64-1.24)	0	0.59
P_{trend}			0.75	0	0.95			0.52	20.9	0.26
Sweetened beverages (servings/day)[1]										
Q1	84	96	Ref.			86	105	Ref.		
Q2	90	99	1.11 (0.82-1.50)	0	0.99	98	107	1.16 (0.86-1.55)	13.3	0.28
Q3	87	101	0.92 (0.68-1.26)	0	0.88	95	112	1.05 (0.78-1.41)	66.7	0.08
Q4	86	100	0.97 (0.71-1.32)	0	0.35	81	97	0.93 (0.68-1.28)	42.1	0.19
Q5	87	100	1.03 (0.75-1.42)	0	0.59	90	105	1.02 (0.75-1.39)	23.1	0.25
P_{trend}			0.60	0	0.97			0.44	0	0.44

[1]Adjusted for age, education, study indicator, and total energy intake
[2]Adjusted for age, study indicator, and total energy intake

Table A.15. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing EA/GCA among 500 EA cases, 529 GCA cases, and 2027 controls from two US case-control studies (pooled approach, based on identical absolute intake cut-points).

		EA		GCA	
Measure	Controls (N)	Cases (N)	OR (95%CI)	Cases (N)	OR (95%CI)
Free glucose (g/day)[1]					
Q1: 0.12-<14.58	381	135	Ref.	99	Ref.
Q2: 14.58-<19.96	384	93	0.74 (0.54-1.03)	89	0.97 (0.70-1.35)
Q3: 19.96-<25.95	396	83	0.63 (0.45-0.89)	101	1.06 (0.76-1.48)
Q4: 25.95-<36.21	394	83	0.67 (0.47-0.96)	113	1.27 (0.90-1.79)
Q5: ≥36.21	401	79	0.61 (0.40-0.93)	97	1.07 (0.72-1.59)
P_{trend}			0.08		0.37
Sucrose (g/day)[1]					
Q1: 0.97-<21.62	390	71	Ref.	84	Ref.
Q2: 21.62-<31.46	396	78	1.04 (0.71-1.51)	90	0.96 (0.69-1.35)
Q3: 31.46-<42.33	396	80	0.95 (0.65-1.39)	96	0.98 (0.70-1.39)
Q4: 42.33-<59.76	383	113	1.39 (0.96-2.03)	104	1.06 (0.75-1.51)
Q5: ≥59.76	391	131	1.33 (0.89-1.99)	125	1.06 (0.72-1.55)
P_{trend}			0.19		0.69
Free fructose (g/day)[1]					
Q1: 0.001-<14.25	381	126	Ref.	98	Ref.
Q2: 14.25-<20.29	387	113	1.01 (0.73-1.38)	109	1.20 (0.87-1.65)
Q3: 20.29-<26.00	392	71	0.61 (0.43-0.88)	86	0.93 (0.66-1.31)
Q4: 26.00-<36.77	397	80	0.68 (0.47-0.98)	101	1.09 (0.77-1.55)
Q5: ≥36.77	399	83	0.67 (0.45-1.01)	105	1.11 (0.76-1.63)
P_{trend}			0.08		0.25
Total sugar (g/day)[1]					
Q1: 2.40-<66.65	385	84	Ref.	78	Ref.
Q2: 66.65-<89.47	392	104	1.24 (0.88-1.74)	102	1.24 (0.89-1.74)
Q3: 89.47-<114.64	391	96	1.07 (0.75-1.54)	113	1.35 (0.96-1.89)
Q4: 114.64-<150.37	390	86	0.93 (0.63-1.37)	102	1.16 (0.81-1.68)
Q5: ≥150.37	398	103	1.11 (0.72-1.72)	104	1.10 (0.72-1.68)
P_{trend}			0.79		0.26
Added sugar (g/day)[1]					
Q1: 0.38-<23.52	386	68	Ref.	76	Ref.
Q2: 23.52-<35.02	397	77	0.97 (0.67-1.42)	77	0.90 (0.63-1.29)
Q3: 35.02-<48.57	393	92	1.06 (0.73-1.54)	102	1.13 (0.80-1.60)
Q4: 48.57-<70.68	389	120	1.37 (0.95-1.98)	121	1.32 (0.93-1.86)
Q5: ≥70.68	391	116	1.09 (0.72-1.64)	123	1.15 (0.78-1.69)
P_{trend}			0.14		0.96
Starch (g/day)[1]					
Q1: 1.75-<63.69	383	87	Ref.	89	Ref.

Q2: 63.69-<85.40	385	106	1.16 (0.82-1.63)	123	1.28 (0.93-1.76)
Q3: 85.40-<109.99	396	115	1.15 (0.81-1.64)	109	1.03 (0.74-1.45)
Q4: 109.99-<145.37	393	84	1.04 (0.70-1.55)	96	0.97 (0.67-1.41)
Q5: ≥145.37	399	81	1.10 (0.66-1.84)	82	0.73 (0.45-1.19)
P_{trend}			0.34		0.11
Total carbohydrate (g/day)[1]					
Q1: 40.83-<178.96	380	88	Ref.	88	Ref.
Q2: 178.96-<226.96	390	102	1.13 (0.80-1.59)	108	1.14 (0.82-1.59)
Q3: 226.96-<279.63	393	105	1.09 (0.75-1.57)	99	0.98 (0.69-1.40)
Q4: 279.63-<356.57	393	89	0.91 (0.60-1.38)	115	1.05 (0.71-1.54)
Q5: ≥356.57	400	89	0.91 (0.51-1.61)	89	0.68 (0.39-1.18)
P_{trend}			0.02		0.01
Glycemic index[2]					
Q1: 2.50-<57.40	401	85	Ref.	108	Ref.
Q2: 57.40-<60.10	401	88	1.37 (0.96-1.94)	79	0.87 (0.63-1.22)
Q3: 60.10-<61.82	398	82	1.16 (0.81-1.65)	85	0.91 (0.66-1.27)
Q4: 61.82-<63.64	393	105	1.42 (1.01-2.01)	122	1.28 (0.94-1.74)
Q5: ≥63.64	390	121	1.53 (1.09-2.16)	113	1.21 (0.88-1.66)
P_{trend}			0.32		0.69
Glycemic load[1]					
Q1: 2.03-<96.51	382	95	Ref.	86	Ref.
Q2: 96.51-<122.52	389	89	0.91 (0.64-1.28)	104	1.15 (0.83-1.60)
Q3: 122.52-<153.57	394	113	1.02 (0.72-1.45)	107	1.10 (0.78-1.55)
Q4: 153.57-<196.57	394	86	0.85 (0.57-1.26)	112	1.13 (0.78-1.64)
Q5: ≥196.57	397	90	0.86 (0.52-1.44)	90	0.81 (0.49-1.33)
P_{trend}			0.32		0.07
Sweetened desserts/beverages (servings/day)[1]					
Q1: 0-<1.57	385	61	Ref.	65	Ref.
Q2: 1.57-<2.48	393	93	1.32 (0.91-1.91)	100	1.34 (0.94-1.91)
Q3: 2.48-<3.43	397	83	1.17 (0.79-1.72)	100	1.33 (0.93-1.90)
Q4: 3.43-<4.81	395	87	0.95 (0.64-1.40)	96	1.08 (0.75-1.55)
Q5: ≥4.81	386	149	1.58 (1.07-2.33)	138	1.47 (1.01-2.14)
P_{trend}			0.28		0.88
Sweetened desserts (servings/day)[1]					
Q1: 0-<0.75	387	64	Ref.	70	Ref.
Q2: 0.75-<1.33	392	68	0.85 (0.58-1.26)	94	1.14 (0.81-1.62)
Q3: 1.33-<1.98	389	105	1.21 (0.84-1.75)	99	1.14 (0.80-1.61)
Q4: 1.98-<2.94	399	107	1.17 (0.81-1.70)	119	1.30 (0.92-1.84)
Q5: ≥2.94	389	129	1.27 (0.86-1.87)	117	1.12 (0.78-1.63)
P_{trend}			0.48		0.92
Sweetened beverages (servings/day)[2]					
Q1: 0-<0.35	396	82	Ref.	75	Ref.

Q2: 0.35-<0.85	399	89	1.30 (0.91-1.84)	100	1.47 (1.05-2.07)
Q3: 0.85-<1.27	399	83	0.97 (0.68-1.38)	100	1.23 (0.87-1.73)
Q4: 1.27-<2.07	401	83	0.96 (0.67-1.37)	116	1.43 (1.03-2.00)
Q5: ≥2.07	388	144	1.36 (0.97-1.93)	116	1.23 (0.87-1.74)
P_{trend}			0.60		0.93

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

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

Table A.16. Multivariable-adjusted HRs and 95%CIs for the associations between sugar/carbohydrate intake and overall survival in esophageal and gastric cardia adenocarcinoma among 500 EA cases and 529 GCA cases from two US case-control studies (pooled approach, based on identical absolute intake cut-points).

	Esophageal Adenocarcinoma			Gastric Cardia Adenocarcinoma		
Measure	Deaths (N)	Total EA Cases (N)	HR[1] (95%CI)	Deaths (N)	Total GCA Cases (N)	HR[1] (95%CI)
Free glucose (g/day)[1]						
Q1	90	100	Ref.	90	105	Ref.
Q2	84	99	0.93 (0.68-1.25)	90	105	0.95 (0.70-1.27)
Q3	89	100	1.04 (0.77-1.41)	87	106	0.79 (0.58-1.07)
Q4	85	98	0.99 (0.72-1.36)	92	106	0.95 (0.70-1.29)
Q5	86	99	0.79 (0.74-1.49)	91	104	0.85 (0.61-1.19)
P_{trend}			0.64			0.86
Sucrose (g/day)[1]						
Q1	85	99	Ref.	87	106	Ref.
Q2	88	99	1.05 (0.77-1.43)	91	105	1.15 (0.86-1.55)
Q3	84	99	0.93 (0.67-1.29)	92	106	1.13 (0.83-1.54)
Q4	90	100	1.33 (0.95-1.84)	93	104	1.18 (0.85-1.63)
Q5	87	99	1.17 (0.81-1.69)	87	105	0.94 (0.66-1.35)
P_{trend}			0.39			0.57
Free fructose (g/day)[1]						
Q1	92	100	Ref.	91	106	Ref.
Q2	84	100	0.82 (0.61-1.11)	90	104	0.97 (0.72-1.31)
Q3	88	99	0.96 (0.71-1.30)	91	107	0.85 (0.63-1.14)
Q4	85	98	0.85 (0.62-1.16)	87	105	0.77 (0.57-1.05)
Q5	85	99	0.95 (0.67-1.34)	91	104	0.85 (0.61-1.18)
P_{trend}			0.47			0.79
Total sugar (g/day)[2]						
Q1	85	100	Ref.	88	106	Ref.
Q2	92	99	1.25 (0.92-1.69)	89	106	1.05 (0.78-1.41)
Q3	82	100	1.05 (0.76-1.43)	93	105	1.13 (0.84-1.53)
Q4	90	99	1.28 (0.92-1.78)	95	106	1.10 (0.80-1.51)
Q5	86	99	1.22 (0.83-1.79)	86	104	0.81 (0.56-1.15)
P_{trend}			0.70			0.80
Added sugar (g/day)[1]						
Q1	90	100	Ref.	88	106	Ref.
Q2	84	98	0.91 (0.68-1.23)	91	105	1.17 (0.87-1.57)
Q3	84	100	0.81 (0.59-1.13)	90	105	1.06 (0.78-1.43)
Q4	88	99	1.08 (0.79-1.47)	92	105	1.04 (0.76-1.42)
Q5	88	99	1.06 (0.74-1.51)	89	105	0.92 (0.65-1.29)
P_{trend}			0.67			0.70

Starch (g/day)[1]						
Q1	92	100	Ref.	87	106	Ref.
Q2	81	99	0.70 (0.51-0.94)	97	106	1.43 (1.06-1.92)
Q3	83	99	0.83 (0.61-1.13)	84	103	1.05 (0.74-1.44)
Q4	90	100	1.09 (0.79-1.50)	92	105	1.14 (0.82-1.58)
Q5	88	98	1.20 (0.81-1.78)	90	106	0.99 (0.66-1.47)
P_{trend}			0.18			0.32
Total carbohydrate (g/day)[1]						
Q1	88	99	Ref.	86	105	Ref.
Q2	82	99	0.89 (0.66-1.21)	94	107	1.17 (0.87-1.58)
Q3	88	100	1.08 (0.78-1.49)	92	104	1.19 (0.87-1.62)
Q4	90	99	1.18 (0.83-1.68)	90	105	0.86 (0.61-1.20)
Q5	86	99	1.16 (0.73-1.85)	88	105	0.76 (0.49-1.20)
P_{trend}			0.36			0.82
Glycemic index[1]						
Q1	87	100	Ref.	91	105	Ref.
Q2	88	99	1.02 (0.76-1.39)	90	104	1.28 (0.95-1.72)
Q3	88	99	1.12 (0.82-1.51)	96	107	1.23 (0.92-1.64)
Q4	89	99	1.00 (0.74-1.36)	86	105	1.00 (0.74-1.36)
Q5	82	99	0.95 (0.70-1.31)	87	105	1.05 (0.78-1.42)
P_{trend}			0.87			0.29
Glycemic load[1]						
Q1	91	100	Ref.	89	106	Ref.
Q2	82	98	0.84 (0.62-1.14)	91	106	1.00 (0.75-1.35)
Q3	82	100	0.77 (0.56-1.07)	92	103	1.14 (0.84-1.56)
Q4	95	100	1.31 (0.94-1.82)	87	106	0.82 (0.59-1.12)
Q5	84	98	0.94 (0.61-1.45)	91	105	0.86 (0.57-1.29)
P_{trend}			0.34			0.93
Sweetened desserts/beverages (servings/day)[1]						
Q1	86	99	Ref.	91	105	Ref.
Q2	88	99	1.09 (0.81-1.47)	89	106	0.88 (0.66-1.18)
Q3	86	100	1.00 (0.73-1.37)	89	106	0.86 (0.63-1.16)
Q4	88	98	1.08 (0.79-1.49)	94	104	0.99 (0.72-1.36)
Q5	86	100	1.13 (0.80-1.60)	87	105	0.78 (0.56-1.09)
P_{trend}			0.67			0.50
Sweetened desserts (servings/day)[1]						
Q1	89	99	Ref.	91	107	Ref.
Q2	83	100	0.82 (0.61-1.11)	90	104	1.06 (0.79-1.42)
Q3	90	99	1.15 (0.85-1.55)	89	104	0.94 (0.70-1.27)
Q4	85	99	0.88 (0.64-1.21)	89	105	0.98 (0.73-1.33)
Q5	87	99	0.92 (0.66-1.28)	91	106	0.85 (0.62-1.17)
P_{trend}			0.90			0.77

Sweetened beverages (servings/day)[1]						
Q1	90	102	Ref.	85	105	Ref.
Q2	76	85	0.89 (0.66-1.21)	87	96	1.23 (0.91-1.67)
Q3	96	110	0.96 (0.72-1.29)	106	121	1.06 (0.79-1.41)
Q4	87	99	1.06 (0.79-1.43)	84	99	1.06 (0.78-1.43)
Q5	85	100	0.98 (0.71-1.34)	88	105	0.99 (0.72-1.36)
P_{trend}			0.51			0.40

[1]Adjusted for age, education, study indicator, and total energy intake
[2]Adjusted for age, study indicator, and total energy intake

Table A.17. Multivariable-adjusted ORs and 95%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 (nutrient density energy adjustment method).

		Esophageal Adenocarcinoma		Gastric Cardia Adenocarcinoma	
Measure	Controls (N)	Cases (N)	OR (95%CI)	Cases (N)	OR (95%CI)
Free glucose (g/day)[1]					
Q1	389	144	Ref.	120	Ref.
Q2	390	109	0.92 (0.68-1.26)	109	1.04 (0.76-1.41)
Q3	391	96	0.85 (0.61-1.17)	86	0.87 (0.63-1.21)
Q4	390	66	0.67 (0.47-0.95)	87	0.97 (0.69-1.35)
Q5	396	58	0.59 (0.40-0.85)	97	1.09 (0.78-1.52)
P_{trend}			0.01		0.89
Sucrose (g/day)[1]					
Q1	395	106	Ref.	112	Ref.
Q2	393	96	1.01 (0.72-1.40)	97	0.94 (0.68-1.28)
Q3	391	88	1.02 (0.73-1.43)	108	1.13 (0.83-1.53)
Q4	393	86	1.00 (0.71-1.41)	99	1.05 (0.76-1.44)
Q5	384	97	1.16 (0.83-1.62)	83	0.91 (0.66-1.27)
P_{trend}			0.33		0.74
Free fructose (g/day)[1]					
Q1	387	141	Ref.	128	Ref.
Q2	395	113	0.92 (0.68-1.25)	108	0.92 (0.68-1.25)
Q3	389	96	0.92 (0.67-1.28)	90	0.86 (0.62-1.19)
Q4	393	68	0.66 (0.46-0.94)	78	0.77 (0.55-1.08)
Q5	392	55	0.55 (0.38-0.81)	95	0.96 (0.69-1.35)
P_{trend}			0.01		0.55
Total sugar (g/day)[1]					
Q1	395	124	Ref.	116	Ref.
Q2	389	102	0.94 (0.69-1.30)	111	1.06 (0.78-1.44)
Q3	391	101	0.99 (0.72-1.36)	99	0.98 (0.71-1.34)
Q4	392	76	0.82 (0.58-1.16)	87	0.94 (0.68-1.31)
Q5	389	70	0.81 (0.57-1.16)	86	0.98 (0.70-1.37)
P_{trend}			0.21		0.51
Added sugar (g/day)[1]					
Q1	392	86	Ref.	102	Ref.
Q2	390	110	1.34 (0.96-1.88)	90	0.92 (0.67-1.28)
Q3	391	78	0.90 (0.63-1.29)	100	1.00 (0.72-1.37)
Q4	397	90	1.00 (0.71-1.41)	93	0.87 (0.63-1.20)
Q5	386	109	1.28 (0.91-1.79)	114	1.16 (0.85-1.58)
P_{trend}			0.30		0.56
Starch (g/day)[1]					

Q1	391	116	Ref.	133	Ref.
Q2	392	102	0.98 (0.71-1.35)	116	0.95 (0.71-1.27)
Q3	391	107	1.11 (0.80-1.52)	94	0.80 (0.59-1.09)
Q4	396	91	1.00 (0.72-1.40)	93	0.85 (0.62-1.16)
Q5	386	57	0.71 (0.49-1.05)	63	0.67 (0.47-0.96)
P_{trend}			0.19		0.03
Total carbohydrate (g/day)[1]					
Q1	389	143	Ref.	151	Ref.
Q2	393	123	0.99 (0.74-1.34)	105	0.77 (0.58-1.04)
Q3	394	96	0.86 (0.63-1.19)	90	0.71 (0.52-0.97)
Q4	394	70	0.65 (0.46-0.93)	91	0.77 (0.56-1.05)
Q5	386	41	0.47 (0.31-0.71)	62	0.61 (0.43-0.88)
P_{trend}			<0.01		0.01

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

Table A.18. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing EA/GCA among 348 EA cases, 379 GCA cases, and 2027 controls from two US case-control studies (after excluding cases with proxy interviews).

		Esophageal Adenocarcinoma		Gastric Cardia Adenocarcinoma	
Measure	Controls (N)	Cases (N)	OR (95%CI)	Cases (N)	OR (95%CI)
Free glucose (g/day)[1]					
Q1	385	74	Ref.	54	Ref.
Q2	384	70	0.95 (0.65-1.39)	68	1.27 (0.86-1.89)
Q3	396	70	0.91 (0.61-1.35)	78	1.42 (0.96-2.11)
Q4	398	50	0.60 (0.38-0.93)	75	1.31 (0.87-2.00)
Q5	393	70	0.72 (0.46-1.13)	89	1.48 (0.96-2.30)
P_{trend}			0.07		0.43
Sucrose (g/day)[1]					
Q1	391	54	Ref.	57	Ref.
Q2	394	58	1.07 (0.70-1.63)	76	1.31 (0.90-1.92)
Q3	393	67	1.13 (0.75-1.72)	68	1.11 (0.74-1.65)
Q4	387	73	1.28 (0.84-1.96)	78	1.27 (0.85-1.90)
Q5	391	82	1.26 (0.79-1.99)	85	1.20 (0.78-1.86)
P_{trend}			0.67		0.88
Free fructose (g/day)[1]					
Q1	382	77	Ref.	65	Ref.
Q2	387	74	0.93 (0.64-1.35)	75	1.13 (0.78-1.65)
Q3	398	60	0.69 (0.46-1.03)	62	0.87 (0.58-1.29)
Q4	393	67	0.79 (0.52-1.19)	79	1.13 (0.76-1.68)
Q5	396	56	0.55 (0.35-0.86)	83	1.07 (0.70-1.62)
P_{trend}			0.07		0.37
Total sugar (g/day)[1]					
Q1	385	62	Ref.	60	Ref.
Q2	396	60	0.89 (0.60-1.34)	65	0.98 (0.67-1.45)
Q3	393	76	1.09 (0.73-1.62)	76	1.13 (0.76-1.66)
Q4	390	65	0.84 (0.54-1.30)	74	1.05 (0.69-1.58)
Q5	392	71	1.12 (0.71-1.77)	89	0.84 (0.54-1.30)
P_{trend}			0.27		0.36
Added sugar (g/day)[1]					
Q1	385	52	Ref.	57	Ref.
Q2	399	52	0.91 (0.59-1.41)	51	0.84 (0.55-1.27)
Q3	392	70	1.11 (0.73-1.68)	76	1.17 (0.80-1.73)
Q4	389	81	1.30 (0.85-1.97)	88	1.35 (0.92-2.00)
Q5	391	79	1.00 (0.63-1.59)	92	1.22 (0.79-1.88)
P_{trend}			0.61		0.54
Starch (g/day)[1]					

Q1	389	54	Ref.	59	Ref.
Q2	390	58	0.98 (0.64-1.49)	67	1.04 (0.71-1.54)
Q3	390	80	1.29 (0.85-1.95)	90	1.34 (0.92-1.97)
Q4	394	72	0.95 (0.61-1.48)	71	0.92 (0.61-1.40)
Q5	393	70	0.85 (0.51-1.44)	77	0.91 (0.56-1.49)
P_{trend}			0.06		0.03
Total carbohydrate (g/day)[1]					
Q1	386	63	Ref.	59	Ref.
Q2	390	54	0.80 (0.53-1.22)	72	1.16 (0.79-1.71)
Q3	393	63	0.78 (0.51-1.20)	54	0.80 (0.52-1.22)
Q4	393	76	0.85 (0.54-1.33)	85	1.18 (0.77-1.82)
Q5	394	78	0.65 (0.36-1.15)	94	1.17 (0.68-2.02)
P_{trend}			<0.01		0.01
Glycemic index[2]					
Q1	399	70	Ref.	82	Ref.
Q2	397	72	1.33 (0.91-1.95)	62	0.92 (0.63-1.33)
Q3	398	59	1.08 (0.72-1.60)	72	1.05 (0.73-1.51)
Q4	395	60	1.03 (0.70-1.54)	82	1.20 (0.85-1.70)
Q5	394	78	1.49 (1.02-2.17)	69	1.11 (0.77-1.60)
P_{trend}			0.61		0.98
Glycemic load[1]					
Q1	387	65	Ref.	65	Ref.
Q2	390	57	0.78 (0.51-1.17)	59	0.83 (0.56-1.24)
Q3	395	61	0.78 (0.51-1.18)	62	0.84 (0.82-1.70)
Q4	390	79	0.90 (0.58-1.38)	93	1.21 (0.81-1.82)
Q5	394	72	0.61 (0.36-1.05)	85	0.95 (0.57-1.58)
P_{trend}			0.04		0.09
Sweetened desserts/beverages (servings/day)[1]					
Q1	382	51	Ref.	54	Ref.
Q2	392	60	1.14 (0.75-1.74)	65	1.17 (0.78-1.74)
Q3	401	72	1.41 (0.93-2.13)	77	1.41 (0.95-2.08)
Q4	391	60	1.00 (0.65-1.54)	72	1.15 (0.77-1.72)
Q5	390	91	1.47 (0.95-2.28)	96	1.47 (0.97-2.23)
P_{trend}			0.66		0.38
Sweetened desserts (servings/day)[1]					
Q1	383	50	Ref.	53	Ref.
Q2	392	55	0.99 (0.65-1.53)	67	1.17 (0.78-1.74)
Q3	393	67	1.12 (0.74-1.70)	78	1.28 (0.87-1.89)
Q4	399	71	1.20 (0.79-1.83)	73	1.19 (0.80-1.77)
Q5	389	91	1.35 (0.87-2.08)	93	1.32 (0.87-1.99)
P_{trend}			0.51		0.61
Sweetened beverages (servings/day)[2]					

Q1	394	70	Ref.	61	Ref.
Q2	398	60	0.89 (0.60-1.31)	70	1.16 (0.80-1.70)
Q3	396	67	1.06 (0.72-1.55)	68	1.16 (0.79-1.70)
Q4	400	58	0.83 (0.56-1.24)	84	1.36 (0.94-1.97)
Q5	395	84	1.17 (0.80-1.73)	84	1.30 (0.88-1.90)
P_{trend}			0.80		0.59

*Adjusted for age, sex, race, study indicator, BMI, fruits and vegetables intake, cigarette smoking, GERD frequency, and total energy intake

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

Table A.19. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing EA/GCA among 485 EA cases, 503 GCA cases, and 1939 controls from two US case-control studies (using lower and upper 2.5% as exclusion criteria).

		Esophageal Adenocarcinoma		Gastric Cardia Adenocarcinoma	
Measure	Controls (N)	Cases (N)	OR (95%CI)	Cases (N)	OR (95%CI)
Free glucose (g/day)[1]					
Q1	372	106	Ref.	81	Ref.
Q2	368	94	0.86 (0.62-1.21)	95	1.22 (0.86-1.71)
Q3	378	91	0.80 (0.56-1.13)	94	1.20 (0.85-1.70)
Q4	381	72	0.56 (0.38-0.82)	97	1.20 (0.83-1.74)
Q5	376	97	0.68 (0.46-1.00)	108	1.35 (0.92-1.98)
P_{trend}			0.13		0.41
Sucrose (g/day)[1]					
Q1	377	77	Ref.	86	Ref.
Q2	378	72	0.92 (0.63-1.33)	94	1.08 (0.77-1.51)
Q3	376	87	1.00 (0.69-1.45)	92	1.04 (0.74-1.47)
Q4	371	101	1.21 (0.83-1.75)	96	1.11 (0.78-1.59)
Q5	373	123	1.28 (0.85-1.91)	107	1.16 (0.78-1.71)
P_{trend}			0.13		0.94
Free fructose (g/day)[1]					
Q1	370	110	Ref.	98	Ref.
Q2	371	90	0.78 (0.56-1.10)	93	0.95 (0.69-1.33)
Q3	381	91	0.74 (0.53-1.06)	83	0.82 (0.58-1.16)
Q4	374	83	0.67 (0.46-0.97)	92	0.94 (0.66-1.35)
Q5	379	86	0.61 (0.41-0.90)	109	1.06 (0.73-1.53)
P_{trend}			0.12		0.30
Total sugar (g/day)[1]					
Q1	373	79	Ref.	85	Ref.
Q2	378	88	1.06 (0.74-1.52)	88	1.00 (0.71-1.41)
Q3	377	97	1.10 (0.77-1.59)	102	1.16 (0.82-1.64)
Q4	372	79	0.81 (0.54-1.21)	92	1.03 (0.71-1.49)
Q5	375	117	1.05 (0.68-1.61)	108	1.15 (0.76-1.75)
P_{trend}			0.93		0.40
Added sugar (g/day)[1]					
Q1	345	63	Ref.	74	Ref.
Q2	389	76	0.93 (0.64-1.37)	74	0.94 (0.65-1.34)
Q3	392	92	1.05 (0.72-1.52)	99	1.17 (0.83-1.65)
Q4	384	118	1.27 (0.88-1.85)	116	1.37 (0.96-1.94)
Q5	365	111	1.04 (0.69-1.57)	112	1.32 (0.89-1.95)
P_{trend}			0.09		0.58
Starch (g/day)[1]					

Q1	337	82	Ref.	86	Ref.
Q2	383	106	1.03 (0.71-1.50)	122	0.86 (0.61-1.21)
Q3	392	114	1.26 (0.87-1.83)	107	1.10 (0.78-1.55)
Q4	386	80	0.90 (0.60-1.35)	92	0.87 (0.60-1.27)
Q5	377	78	1.00 (0.63-1.58)	68	0.85 (0.55-1.32)
P_{trend}			0.47		0.07
Total carbohydrate (g/day)[1]					
Q1	374	84	Ref.	96	Ref.
Q2	373	76	0.82 (0.56-1.19)	79	0.83 (0.58-1.17)
Q3	376	82	0.71 (0.48-1.05)	82	0.82 (0.57-1.19)
Q4	375	101	0.76 (0.50-1.90)	102	1.00 (0.66-1.50)
Q5	377	117	0.65 (0.38-1.11)	116	1.13 (0.67-1.90)
P_{trend}			0.04		0.01
Glycemic index[2]					
Q1	382	89	Ref.	99	Ref.
Q2	380	88	1.24 (0.88-1.76)	80	0.94 (0.67-1.31)
Q3	379	97	1.38 (0.98-1.95)	98	1.15 (0.83-1.59)
Q4	380	84	1.12 (0.79-1.59)	111	1.29 (0.94-1.77)
Q5	377	109	1.58 (1.12-2.22)	94	1.16 (0.84-1.61)
P_{trend}			0.26		0.70
Glycemic load[1]					
Q1	376	87	Ref.	96	Ref.
Q2	372	77	0.83 (0.58-1.20)	76	0.80 (0.56-1.13)
Q3	378	81	0.77 (0.53-1.13)	84	0.85 (0.60-1.22)
Q4	372	103	0.84 (0.57-1.26)	115	1.15 (0.79-1.68)
Q5	377	112	0.71 (0.44-1.15)	104	0.99 (0.62-1.59)
P_{trend}			0.48		0.07
Sweetened desserts/beverages (servings/day)[1]					
Q1	369	69	Ref.	78	Ref.
Q2	375	79	1.18 (0.81-1.71)	87	1.12 (0.80-1.59)
Q3	383	96	1.40 (0.97-2.02)	101	1.33 (0.95-1.87)
Q4	374	83	1.00 (0.68-1.47)	95	1.12 (0.79-1.60)
Q5	374	133	1.56 (1.07-2.29)	114	1.35 (0.93-1.95)
P_{trend}			0.24		0.81
Sweetened desserts (servings/day)[1]					
Q1	370	67	Ref.	76	Ref.
Q2	377	71	0.94 (0.64-1.38)	92	1.12 (0.79-1.58)
Q3	375	96	1.20 (0.83-1.73)	94	1.12 (0.79-1.58)
Q4	379	98	1.18 (0.82-1.72)	100	1.19 (0.84-1.68)
Q5	374	128	1.32 (0.90-1.94)	113	1.23 (0.85-1.77)
P_{trend}			0.50		0.81
Sweetened beverages (servings/day)[2]					

Q1	382	94	Ref.	86	Ref.
Q2	378	83	0.94 (0.66-1.33)	98	1.18 (0.85-1.64)
Q3	373	91	1.06 (0.75-1.50)	86	1.07 (0.76-1.50)
Q4	390	81	0.84 (0.59-1.19)	111	1.28 (0.92-1.77)
Q5	375	118	1.22 (0.87-1.72)	101	1.19 (0.84-1.67)
P_{trend}			0.51		0.91

*Adjusted for age, sex, race, study indicator, BMI, fruits and vegetables intake, cigarette smoking, GERD frequency, and total energy intake

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

Table A.20. Multivariable-adjusted ORs and 95%CIs for the associations between carbohydrate intake and risk of developing EA/GCA among 500 EA cases, 529 GCA cases, and 2027 controls from two US case-control studies (originally calculated carbohydrate values vs. new carbohydrate values).

		Esophageal Adenocarcinoma		Gastric Cardia Adenocarcinoma	
Measure	Controls (N)	Cases (N)	OR[1] (95%CI)	Cases (N)	OR[1] (95%CI)
Old total carbohydrate values (g/day)					
Q1	385	96	Ref.	101	Ref.
Q2	395	86	0.86 (0.61-1.22)	100	0.92 (0.66-1.27)
Q3	389	95	0.86 (0.60-1.24)	96	0.84 (0.59-1.20)
Q4	390	102	0.81 (0.55-1.21)	102	0.83 (0.57-1.21)
Q5	397	94	0.60 (0.36-1.02)	100	0.67 (0.41-1.11)
P_{trend}			0.01		0.01
New total carbohydrate values (g/day)					
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

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

Table A.21. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing EA, stratified by BMI, among 500 EA cases, 529 GCA cases, and 2027 controls from two US case-control studies (using medians as cut-points for sugar/carbohydrate measures).

BMI (kg/m^2)	Measure	Controls(N)	Cases (N)	Multiplicative scale		Additive scale	
				Stratified ORs (95%CIs)	$P_{interaction}$	Single referent ORs (95%CIs)	Interaction contrast ratio (95%CI)
	Sucrose						
<25	<median	523	73	1.00		1.00	
	≥median	480	115	1.48 (1.04-2.11)		1.48 (1.04-2.11)	
≥25	<median	460	124	1.00		1.90 (1.36-2.65)	
	≥median	493	161	1.04 (0.76-1.43)	0.13	1.98 (1.39-2.82)	-0.40 (-1.14, 0.35)
	Sweetened desserts/beverages						
<25	<median	501	71	1.00		1.00	
	≥median	502	117	1.29 (0.91-1.84)		1.29 (0.91-1.84)	
≥25	<median	473	133	1.00		1.92 (1.38-2.69)	
	≥median	480	152	0.88 (0.65-1.19)	0.09	1.69 (1.19-2.40)	-0.53 (-1.24, 0.19)
	Glycemic index						
<25	<median	472	99	1.00		1.00	
	≥median	531	89	0.88 (0.63-1.22)		0.88 (0.63-1.22)	
≥25	<median	512	139	1.00		1.28 (0.94-1.74)	
	≥median	441	146	1.30 (0.98-1.74)	0.08	1.66 (1.22-2.27)	0.51 (0.02, 1.00)

Table A.22. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing EA, stratified by BMI, among 500 EA cases, 529 GCA cases, and 2027 controls from two US case-control studies (using extreme quintiles for sugar/carbohydrate measures).

BMI (kg/m^2)	Measure	Controls(N)	Cases (N)	Multiplicative scale		Additive scale	
				Stratified ORs (95%CIs)	$P_{interaction}$	Single referent ORs (95%CIs)	Interaction contrast ratio (95%CI)
	Sucrose						
<25	Q1	212	23	1.00		1.00	
	Q5	181	48	2.31 (1.23-4.32)		2.31 (1.23-4.32)	
≥25	Q1	179	46	1.00		2.51 (1.42-4.43)	
	Q5	210	78	1.60 (0.93-2.77)	0.32	4.02 (2.13-7.58)	0.20 (-1.61, 2.02)
	Sweetened desserts/beverages						
<25	Q1	188	23	1.00		1.00	
	Q5	203	55	1.96 (1.08-3.56)		1.96 (1.08-3.56)	
≥25	Q1	194	46	1.00		2.11 (1.19-3.75)	
	Q5	187	81	1.73 (1.04-2.87)	0.72	3.65 (1.98-6.72)	0.57 (-0.96, 2.10)
	Glycemic index						
<25	Q1	179	41	1.00		1.00	
	Q5	219	40	1.07 (0.64-1.79)		1.07 (0.64-1.79)	
≥25	Q1	216	52	1.00		1.05 (0.64-1.71)	
	Q5	167	69	2.22 (1.39-3.55)	0.04	2.32 (1.42-3.81)	1.21 (0.30, 2.12)

Table A.23. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing EA, stratified by GERD frequency, among 500 EA cases and 2027 controls from two US case-control studies (using extreme quintiles or medians for sucrose intake).

GERD	Sucrose	Controls (N)	Cases (N)	Multiplicative scale		Additive scale	
				Stratified ORs (95%CIs)	$P_{interaction}$	Single referent ORs (95%CIs)	Additive ICR (95%CI)
	Sucrose						
<Weekly	<median	806	107	1.00		1.00	
	≥median	758	138	1.28 (0.94-1.73)		1.28 (0.94-1.73)	
≥Weekly	<median	177	90	1.00		3.88 (2.75-5.46)	
	≥median	215	138	1.12 (0.77-1.63)	0.58	4.35 (3.12-6.06)	0.19 (-1.33, 1.72)
	Sucrose						
<Weekly	Q1	318	38	1.00		1.00	
	Q5	293	62	1.91 (1.11-3.26)		1.91 (1.11-3.26)	
≥Weekly	Q1	73	31	1.00		3.45 (1.96-6.08)	
	Q5	98	64	1.80 (0.95-3.41)	0.88	6.22 (3.55-10.90)	1.86 (-1.12, 4.83)

Table A.24. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing EA/GCA among 218 EA cases, 273 GCA cases, and 1343 controls from the LA Multi-Ethnic study (results additionally adjusted for diabetes).

		Esophageal Adenocarcinoma			Gastric Cardia Adenocarcinoma	
Measure	Controls (N)	Cases (N)	OR (95%CI)	OR (95%CI)[3]	Cases (N)	OR (95%CI)	OR (95%CI)[3]
Free glucose (g/day)[1]							
Q1	259	40	Ref.	Ref.	41	Ref.	Ref.
Q2	259	43	1.09 (0.67-1.80)	1.11 (0.67-1.82)	50	1.16 (0.73-1.84)	1.16 (0.73-1.85)
Q3	266	41	1.03 (0.61-1.72)	1.03 (0.61-1.72)	55	1.20 (0.75-1.92)	1.20 (0.75-1.92)
Q4	266	37	0.89 (0.51-1.57)	0.91 (0.52-1.59)	57	1.19 (0.72-1.95)	1.19 (0.72-1.96)
Q5	264	48	1.10 (0.59-2.04)	1.11 (0.59-2.06)	56	1.08 (0.62-1.91)	1.09 (0.62-1.92)
P_{trend}			0.56	0.55		0.35	0.36
Sucrose (g/day)[1]							
Q1	261	34	Ref.	Ref.	42	Ref.	Ref.
Q2	265	47	1.44 (0.87-2.39)	1.46 (0.88-2.41)	62	1.38 (0.88-2.14)	1.37 (0.88-2.14)
Q3	262	29	0.79 (0.45-1.39)	0.81 (0.46-1.43)	53	1.07 (0.67-1.70)	1.07 (0.67-1.70)
Q4	262	39	1.26 (0.73-2.19)	1.27 (0.73-2.21)	52	1.08 (0.66-1.74)	1.08 (0.67-1.75)
Q5	264	60	1.61 (0.90-2.88)	1.66 (0.93-2.97)	50	0.83 (0.48-1.44)	0.84 (0.48-1.45)
P_{trend}			0.05	0.04		0.19	0.20
Free fructose (g/day)[1]							
Q1	259	43	Ref.	Ref.	48	Ref.	Ref.
Q2	258	42	1.01 (0.62-1.65)	1.01 (0.62-1.65)	50	0.99 (0.63-1.55)	0.99 (0.63-1.56)
Q3	265	34	0.77 (0.46-1.31)	0.75 (0.44-1.27)	49	0.87 (0.55-1.39)	0.87 (0.55-1.39)
Q4	267	46	1.03 (0.60-1.75)	1.02 (0.60-1.74)	55	0.92 (0.57-1.50)	0.92 (0.57-1.50)
Q5	265	44	0.97 (0.53-1.76)	0.96 (0.53-1.76)	57	0.93 (0.54-1.58)	0.93 (0.54-1.59)
P_{trend}			0.52	0.48		0.24	0.24
Total sugar (g/day)[1]							
Q1	259	37	Ref.	Ref.	46	Ref.	Ref.
Q2	265	43	1.10 (0.67-1.82)	1.11 (0.67-1.83)	57	1.08 (0.69-1.68)	1.08 (0.69-1.68)
Q3	262	35	0.91 (0.54-1.56)	0.90 (0.53-1.54)	51	0.91 (0.58-1.45)	0.91 (0.58-1.45)

Q4	264	40	0.95 (0.54-1.66)	0.97 (0.56-1.70)	49	0.77 (0.47-1.27)	0.77 (0.47-1.27)
Q5	264	54	1.28 (0.68-2.39)	1.28 (0.69-2.40)	56	0.77 (0.43-1.36)	0.77 (0.44-1.37)
P_{trend}			0.42	0.40		0.15	0.15
Added sugar (g/day)[1]							
Q1	257	38	Ref.	Ref.	41	Ref.	Ref.
Q2	267	36	0.82 (0.49-1.37)	0.82 (0.49-1.39)	42	0.88 (0.55-1.42)	0.88 (0.55-1.42)
Q3	262	28	0.59 (0.34-1.02)	0.58 (0.33-1.01)	54	1.09 (0.68-1.72)	1.08 (0.68-1.72)
Q4	265	50	1.07 (0.64-1.78)	1.09 (0.66-1.82)	64	1.23 (0.77-1.95)	1.23 (0.77-1.96)
Q5	263	57	0.84 (0.48-1.49)	0.86 (0.48-1.51)	58	0.87 (0.51-1.49)	0.88 (0.51-1.49)
P_{trend}			0.16	0.16		0.55	0.56
Starch (g/day)[1]							
Q1	261	34	Ref.	Ref.	58	Ref.	Ref.
Q2	265	39	0.98 (0.58-1.67)	1.01 (0.60-1.71)	45	0.63 (0.41-0.99)	0.64 (0.41-0.99)
Q3	264	50	1.25 (0.75-2.10)	1.25 (0.75-2.10)	57	0.75 (0.48-1.16)	0.75 (0.48-1.16)
Q4	262	41	0.86 (0.48-1.51)	0.85 (0.48-1.51)	53	0.59 (0.36-0.95)	0.58 (0.36-0.94)
Q5	262	45	0.79 (0.40-1.60)	0.78 (0.39-1.57)	46	0.39 (0.21-0.72)	0.39 (0.21-0.72)
P_{trend}			0.18	0.19		0.03	0.03
Total carbohydrate (g/day)[1]							
Q1	258	38	Ref.	Ref.	52	Ref.	Ref.
Q2	266	41	0.99 (0.59-1.65)	0.98 (0.59-1.64)	56	0.90 (0.58-1.40)	0.90 (0.58-1.39)
Q3	264	38	0.80 (0.46-1.38)	0.79 (0.46-1.38)	38	0.52 (0.32-0.86)	0.52 (0.32-0.86)
Q4	265	42	0.72 (0.40-1.32)	0.72 (0.40-1.32)	58	0.63 (0.38-1.06)	0.63 (0.38-1.06)
Q5	261	50	0.76 (0.34-1.68)	0.76 (0.34-1.70)	55	0.47 (0.23-0.96)	0.47 (0.23-0.97)
P_{trend}			0.16	0.17		<0.01	<0.01
Glycemic index[2]							
Q1	267	41	Ref.	Ref.	64	Ref.	Ref.
Q2	266	45	1.33 (0.82-2.15)	1.32 (0.81-2.14)	51	0.90 (0.59-1.37)	0.90 (0.59-1.37)
Q3	268	44	1.35 (0.83-2.19)	1.34 (0.82-2.17)	55	0.96 (0.63-1.45)	0.96 (0.63-1.45)
Q4	268	42	1.29 (0.79-2.11)	1.29 (0.79-2.11)	46	0.83 (0.54-1.27)	0.83 (0.54-1.27)
Q5	269	44	1.65 (1.01-2.71)	1.66 (1.01-2.73)	51	1.08 (0.70-1.65)	1.08 (0.70-1.66)

P_{trend}			0.27	0.27		0.52	0.52
Glycemic load[1]							
Q1	259	40	Ref.	Ref.	56	Ref.	Ref.
Q2	265	41	0.90 (0.54-1.50)	0.92 (0.55-1.53)	52	0.76 (0.49-1.17)	0.75 (0.49-1.17)
Q3	265	38	0.85 (0.50-1.45)	0.85 (0.50-1.44)	41	0.56 (0.35-0.91)	0.57 (0.35-0.91)
Q4	263	38	0.77 (0.43-1.36)	0.77 (0.43-1.36)	56	0.66 (0.40-1.08)	0.66 (0.40-1.08)
Q5	262	52	0.89 (0.43-1.81)	0.91 (0.44-1.86)	54	0.49 (0.26-0.95)	0.50 (0.26-0.96)
P_{trend}			0.68	0.72		0.01	0.01
Sweetened desserts/beverages (servings/day)[1]							
Q1	256	31	Ref.	Ref.	39	Ref.	Ref.
Q2	261	37	1.01 (0.59-1.73)	1.03 (0.60-1.76)	53	1.15 (0.73-1.83)	1.16 (0.73-1.83)
Q3	267	48	1.50 (0.90-2.51)	1.53 (0.92-2.56)	63	1.42 (0.91-2.22)	1.42 (0.91-2.23)
Q4	268	26	0.68 (0.38-1.22)	0.70 (0.39-1.27)	49	0.92 (0.57-1.49)	0.93 (0.58-1.51)
Q5	262	67	1.76 (1.01-3.05)	1.85 (1.06-3.22)	55	0.95 (0.57-1.59)	0.96 (0.57-1.61)
P_{trend}			0.20	0.16		0.31	0.33
Sweetened desserts (servings/day)[1]							
Q1	256	29	Ref.	Ref.	39	Ref.	Ref.
Q2	264	33	0.95 (0.55-1.66)	0.95 (0.55-1.66)	56	1.25 (0.79-1.98)	1.25 (0.79-1.97)
Q3	262	46	1.25 (0.74-2.12)	1.27 (0.75-2.16)	53	1.11 (0.70-1.77)	1.11 (0.70-1.77)
Q4	267	33	0.92 (0.53-1.61)	0.95 (0.54-1.66)	52	1.06 (0.67-1.70)	1.07 (0.67-1.71)
Q5	265	68	1.61 (0.95-2.75)	1.68 (0.98-2.88)	59	1.02 (0.62-1.66)	1.02 (0.63-1.67)
P_{trend}			0.22	0.17		0.38	0.40
Sweetened beverages (servings/day)[2]							
Q1	265	41	Ref.	Ref.	40	Ref.	Ref.
Q2	269	49	1.14 (0.71-1.83)	1.12 (0.70-1.80)	55	1.32 (0.84-2.07)	1.32 (0.84-2.07)
Q3	268	40	1.06 (0.65-1.74)	1.06 (0.65-1.74)	51	1.28 (0.81-2.03)	1.28 (0.81-2.03)
Q4	265	33	0.82 (0.48-1.38)	0.81 (0.48-1.37)	62	1.47 (0.93-2.31)	1.47 (0.93-2.31)
Q5	271	53	1.22 (0.74-2.02)	1.21 (0.73-2.01)	59	1.31 (0.81-2.11)	1.31 (0.81-2.11)
P_{trend}			0.64	0.65		0.65	0.66

[1]Adjusted for age, sex, race, study indicator, BMI, fruits and vegetables intake, cigarette smoking, GERD frequency, and total energy intake
[2]Adjusted for age, sex, race, study indicator, fruits and vegetables intake, cigarette smoking, GERD frequency, and total energy intake
[3]Additionally adjusted for diabetes

Table A.25. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing EA/GCA among 282 EA cases, 256 GCA cases, and 684 controls from the US Multi-Center study (results additionally adjusted for income category).

		Esophageal Adenocarcinoma			Gastric Cardia Adenocarcinoma	
Measure	Controls (N)	Cases (N)	OR (95%CI)	OR[3] (95%CI)	Cases (N)	OR (95%CI)	OR[3] (95%CI)
Free glucose (g/day)[1]							
Q1	126	64	Ref.	Ref.	34	Ref.	Ref.
Q2	124	52	0.77 (0.48-1.23)	0.78 (0.49-1.26)	45	1.31 (0.78-2.21)	1.34 (0.79-2.26)
Q3	128	55	0.71 (0.43-1.15)	0.72 (0.44-1.17)	49	1.38 (0.81-2.34)	1.41 (0.83-2.40)
Q4	132	37	0.39 (0.23-0.67)	0.40 (0.23-0.68)	45	1.10 (0.63-1.92)	1.13 (0.65-1.98)
Q5	129	55	0.50 (0.29-0.85)	0.50 (0.30-0.85)	65	1.52 (0.88-2.64)	1.53 (0.89-2.66)
P_{trend}			0.04	0.04		0.61	0.57
Sucrose (g/day)[1]							
Q1	130	35	Ref.	Ref.	36	Ref.	Ref.
Q2	128	35	0.91 (0.52-1.58)	0.92 (0.53-1.60)	40	1.04 (0.61-1.76)	1.05 (0.62-1.78)
Q3	130	61	1.45 (0.86-2.45)	1.47 (0.87-2.48)	46	1.14 (0.68-1.94)	1.16 (0.68-1.97)
Q4	124	66	1.50 (0.88-2.58)	1.50 (0.88-2.58)	55	1.21 (0.71-2.07)	1.21 (0.71-2.07)
Q5	127	66	1.30 (0.72-2.36)	1.29 (0.71-2.34)	61	1.09 (0.61-1.97)	1.08 (0.60-1.95)
P_{trend}			0.75	0.74		0.66	0.66
Free fructose (g/day)[1]							
Q1	123	67	Ref.	Ref.	41	Ref.	Ref.
Q2	128	53	0.73 (0.46-1.17)	0.75 (0.47-1.20)	52	1.22 (0.75-1.99)	1.25 (0.77-2.05)
Q3	131	57	0.65 (0.40-1.05)	0.66 (0.41-1.06)	39	0.84 (0.49-1.43)	0.85 (0.50-1.44)
Q4	126	42	0.47 (0.28-0.80)	0.48 (0.28-0.82)	49	1.07 (0.63-1.82)	1.09 (0.64-1.86)
Q5	131	44	0.39 (0.23-0.66)	0.39 (0.23-0.66)	57	1.05 (0.62-1.78)	1.05 (0.62-1.78)
P_{trend}			0.05	0.05		0.50	0.45
Total sugar (g/day)[1]							
Q1	126	45	Ref.	Ref.	36	Ref.	Ref.
Q2	131	41	0.81 (0.48-1.35)	0.81 (0.48-1.36)	32	0.79 (0.46-1.37)	0.79 (0.46-1.38)
Q3	129	68	1.25 (0.76-2.06)	1.25 (0.76-2.07)	56	1.37 (0.81-2.30)	1.37 (0.82-2.31)
Q4	126	50	0.74 (0.42-1.29)	0.75 (0.43-1.30)	53	1.14 (0.65-1.99)	1.15 (0.66-2.01)

Q5	127	59	0.69 (0.37-1.27)	0.68 (0.37-1.25)	61	1.08 (0.58-2.00)	1.06 (0.57-1.96)
P_{trend}			0.15	0.14		0.43	0.42
Added sugar (g/day)[1]							
Q1	128	32	Ref.	Ref.	35	Ref.	Ref.
Q2	131	37	0.98 (0.56-1.72)	0.99 (0.57-1.73)	32	0.82 (0.47-1.43)	0.82 (0.47-1.44)
Q3	129	67	1.65 (0.97-2.79)	1.64 (0.97-2.79)	52	1.25 (0.74-2.12)	1.25 (0.74-2.11)
Q4	123	66	1.47 (0.84-2.55)	1.46 (0.84-2.53)	55	1.22 (0.71-2.11)	1.21 (0.70-2.09)
Q5	128	51	1.13 (0.61-2.10)	1.12 (0.60-2.08)	64	1.16 (0.64-2.12)	1.14 (0.63-2.08)
P_{trend}			0.96	>0.99		0.84	0.79
Starch (g/day)[1]							
Q1	128	36	Ref.	Ref.	27	Ref.	Ref.
Q2	125	41	0.98 (0.57-1.68)	0.97 (0.56-1.67)	41	1.34 (0.76-2.36)	1.34 (0.76-2.36)
Q3	126	59	1.23 (0.72-2.10)	1.22 (0.72-2.09)	60	1.81 (1.04-3.16)	1.79 (1.03-3.12)
Q4	130	62	0.97 (0.55-1.72)	0.97 (0.55-1.72)	49	1.14 (0.62-2.09)	1.14 (0.62-2.08)
Q5	130	65	0.90 (0.47-1.75)	0.89 (0.46-1.72)	61	1.26 (0.64-2.51)	1.24 (0.62-2.47)
P_{trend}			0.95	0.92		0.55	0.59
Total carbohydrate (g/day)[1]							
Q1	128	41	Ref.	Ref.	35	Ref.	Ref.
Q2	124	39	0.81 (0.47-1.40)	0.81 (0.47-1.39)	33	0.83 (0.47-1.47)	0.83 (0.47-1.45)
Q3	129	50	0.82 (0.46-1.45)	0.82 (0.46-1.44)	45	0.96 (0.54-1.71)	0.95 (0.53-1.70)
Q4	126	59	0.83 (0.44-1.55)	0.83 (0.44-1.54)	54	1.12 (0.60-2.11)	1.11 (0.59-2.09)
Q5	132	74	0.66 (0.30-1.49)	0.65 (0.29-1.46)	71	0.98 (0.44-2.20)	0.95 (0.42-2.14)
P_{trend}			0.35	0.32		0.01	0.01
Glycemic index[2]							
Q1	131	53	Ref.	Ref.	42	Ref.	Ref.
Q2	129	50	1.23 (0.75-2.02)	1.24 (0.76-2.04)	34	1.12 (0.65-1.91)	1.13 (0.67-1.94)
Q3	130	51	1.21 (0.74-1.96)	1.23 (0.75-2.01)	47	1.56 (0.94-2.60)	1.58 (0.95-2.63)
Q4	127	43	0.98 (0.59-1.62)	0.98 (0.59-1.61)	68	2.15 (1.33-3.47)	2.14 (1.32-3.45)
Q5	125	67	1.52 (0.95-2.44)	1.51 (0.94-2.41)	47	1.49 (0.90-2.47)	1.47 (0.89-2.44)
P_{trend}			0.63	0.62		0.17	0.17

Glycemic load[1]							
Q1	128	46	Ref.	Ref.	34	Ref.	Ref.
Q2	125	37	0.69 (0.41-1.17)	0.69 (0.40-1.17)	28	0.75 (0.42-1.33)	0.74 (0.42-1.33)
Q3	130	49	0.75 (0.44-1.28)	0.75 (0.44-1.27)	49	1.18 (0.68-2.04)	1.17 (0.67-2.02)
Q4	125	67	0.87 (0.49-1.52)	0.80 (0.44-1.47)	65	1.51 (0.85-2.71)	1.50 (0.84-2.69)
Q5	131	64	0.55 (0.28-1.09)	0.54 (0.27-1.07)	62	1.01 (0.50-2.05)	0.99 (0.49-2.01)
P_{trend}			0.13	0.12		0.83	0.79
Sweetened desserts/beverages (servings/day)[1]							
Q1	126	38	Ref.	Ref.	36	Ref.	Ref.
Q2	129	42	1.09 (0.64-1.86)	1.12 (0.65-1.90)	37	1.03 (0.60-1.77)	1.06 (0.62-1.81)
Q3	134	53	1.21 (0.72-2.04)	1.23 (0.73-2.07)	44	1.16 (0.68-1.97)	1.18 (0.69-2.00)
Q4	122	61	1.26 (0.74-2.14)	1.27 (0.75-2.16)	56	1.33 (0.78-2.25)	1.34 (0.79-2.28)
Q5	128	69	1.28 (0.73-2.22)	1.26 (0.73-2.20)	65	1.32 (0.76-2.31)	1.30 (0.75-2.28)
P_{trend}			0.95	0.98		0.84	0.88
Sweetened desserts (servings/day)[1]							
Q1	127	36	Ref.	Ref.	35	Ref.	Ref.
Q2	127	39	1.01 (0.59-1.73)	1.03 (0.60-1.76)	40	1.06 (0.63-1.81)	1.08 (0.64-1.84)
Q3	130	57	1.24 (0.74-2.08)	1.26 (0.75-2.12)	47	1.11 (0.66-1.88)	1.13 (0.67-1.91)
Q4	131	70	1.45 (0.86-2.46)	1.47 (0.87-2.49)	59	1.33 (0.78-2.25)	1.35 (0.79-2.28)
Q5	124	61	0.94 (0.53-1.69)	0.96 (0.54-1.73)	57	0.97 (0.54-1.74)	1.00 (0.55-1.79)
P_{trend}			0.31	0.31		0.66	0.66
Sweetened beverages (servings/day)[2]							
Q1	128	56	Ref.	Ref.	46	Ref.	Ref.
Q2	127	39	0.73 (0.45-1.21)	0.74 (0.45-1.22)	44	0.92 (0.56-1.50)	0.94 (0.57-1.53)
Q3	128	50	0.90 (0.56-1.45)	0.91 (0.56-1.46)	41	0.83 (0.51-1.38)	0.85 (0.51-1.40)
Q4	135	50	0.80 (0.50-1.30)	0.81 (0.50-1.30)	54	1.05 (0.65-1.70)	1.06 (0.66-1.71)
Q5	124	69	1.12 (0.70-1.80)	1.11 (0.69-1.78)	53	0.93 (0.57-1.53)	0.92 (0.56-1.51)
P_{trend}			0.78	0.82		0.79	0.74

[1]Adjusted for age, sex, race, study indicator, BMI, fruits and vegetables intake, cigarette smoking, GERD frequency, and total energy intake
[2]Adjusted for age, sex, race, study indicator, fruits and vegetables intake, cigarette smoking, GERD frequency, and total energy intake
[3]Additionally adjusted for income

Table A.26. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing EA/GCA among 218 EA cases, 273 GCA cases, and 1343 controls from the LA Multi-Ethnic study (results additionally adjusted for physical activity).

		Esophageal Adenocarcinoma			Gastric Cardia Adenocarcinoma	
Measure	Controls (N)	Cases (N)	OR (95%CI)	OR (95%CI)[3]	Cases (N)	OR (95%CI)	OR (95%CI)[3]
Free glucose (g/day)[1]							
Q1	259	40	Ref.	Ref.	41	Ref.	Ref.
Q2	259	44	1.11 (0.68-1.83)	1.11 (0.68-1.83)	50	1.14 (0.72-1.82)	1.14 (0.72-1.82)
Q3	268	41	1.03 (0.61-1.71)	1.03 (0.61-1.72)	55	1.17 (0.73-1.88)	1.17 (0.73-1.87)
Q4	266	37	0.91 (0.52-1.58)	0.91 (0.52-1.58)	56	1.14 (0.69-1.89)	1.15 (0.70-1.90)
Q5	264	48	1.11 (0.60-2.07)	1.11 (0.60-2.07)	57	1.08 (0.61-1.90)	1.08 (0.61-1.89)
P_{trend}			0.58	0.57		0.33	0.34
Sucrose (g/day)[1]							
Q1	261	34	Ref.	Ref.	42	Ref.	Ref.
Q2	265	48	1.47 (0.89-2.42)	1.46 (0.89-2.42)	63	1.38 (0.89-2.14)	1.38 (0.89-2.15)
Q3	263	29	0.79 (0.45-1.39)	0.79 (0.45-1.40)	53	1.05 (0.66-1.67)	1.05 (0.66-1.67)
Q4	263	39	1.27 (0.73-2.19)	1.27 (0.73-2.21)	51	1.03 (0.64-1.68)	1.02 (0.63-1.66)
Q5	264	60	1.64 (0.92-2.94)	1.66 (0.93-2.96)	50	0.82 (0.47-1.42)	0.81 (0.47-1.40)
P_{trend}			0.05	0.05		0.19	0.17
Free fructose (g/day)[1]							
Q1	259	43	Ref.	Ref.	48	Ref.	Ref.
Q2	258	43	1.02 (0.63-1.67)	1.02 (0.62-1.66)	50	0.98 (0.62-1.53)	0.98 (0.63-1.54)
Q3	267	34	0.77 (0.45-1.30)	0.77 (0.46-1.31)	49	0.85 (0.53-1.36)	0.84 (0.53-1.35)
Q4	267	46	1.04 (0.61-1.77)	1.03 (0.61-1.76)	54	0.88 (0.54-1.44)	0.89 (0.55-1.46)
Q5	265	44	0.98 (0.54-1.79)	0.98 (0.54-1.78)	58	0.92 (0.54-1.56)	0.91 (0.53-1.56)
P_{trend}			0.54	0.53		0.22	0.22
Total sugar (g/day)[1]							
Q1	259	37	Ref.	Ref.	46	Ref.	Ref.
Q2	264	44	1.13 (0.68-1.86)	1.13 (0.69-1.87)	58	1.09 (0.70-1.69)	1.07 (0.69-1.67)
Q3	264	35	0.91 (0.53-1.55)	0.91 (0.53-1.55)	50	0.87 (0.55-1.39)	0.88 (0.55-1.39)
Q4	264	40	0.96 (0.55-1.67)	0.96 (0.55-1.68)	48	0.74 (0.45-1.22)	0.74 (0.45-1.21)

Q5	265	54	1.28 (0.69-2.40)	1.28 (0.69-2.40)	57	0.76 (0.43-1.35)	0.76 (0.43-1.34)
P_{trend}			0.43	0.44		0.14	0.14
Added sugar (g/day)[1]							
Q1	257	38	Ref.	Ref.	41	Ref.	Ref.
Q2	268	36	0.81 (0.48-1.37)	0.82 (0.49-1.38)	43	0.89 (0.55-1.43)	0.88 (0.55-1.42)
Q3	262	29	0.60 (0.35-1.05)	0.60 (0.35-1.05)	54	1.07 (0.68-1.70)	1.06 (0.67-1.69)
Q4	266	50	1.07 (0.65-1.78)	1.08 (0.65-1.80)	64	1.20 (0.76-1.91)	1.18 (0.74-1.87)
Q5	263	57	0.86 (0.48-1.51)	0.86 (0.49-1.53)	57	0.84 (0.49-1.44)	0.83 (0.48-1.41)
P_{trend}			0.16	0.14		0.55	0.49
Starch (g/day)[1]							
Q1	261	34	Ref.	Ref.	58	Ref.	Ref.
Q2	264	40	1.01 (0.60-1.70)	1.01 (0.60-1.69)	46	0.65 (0.42-1.00)	0.65 (0.42-1.01)
Q3	264	50	1.25 (0.75-2.10)	1.25 (0.75-2.10)	56	0.73 (0.47-1.13)	0.73 (0.47-1.13)
Q4	264	41	0.85 (0.48-1.51)	0.85 (0.48-1.50)	53	0.57 (0.36-0.93)	0.57 (0.35-0.93)
Q5	263	45	0.80 (0.40-1.61)	0.80 (0.40-1.60)	46	0.38 (0.20-0.71)	0.38 (0.20-0.71)
P_{trend}			0.18	0.17		0.02	0.03
Total carbohydrate (g/day)[1]							
Q1	258	38	Ref.	Ref.	53	Ref.	Ref.
Q2	265	42	1.01 (0.61-1.68)	1.01 (0.61-1.68)	56	0.87 (0.57-1.35)	0.87 (0.57-1.35)
Q3	264	38	0.80 (0.46-1.38)	0.80 (0.46-1.39)	37	0.48 (0.29-0.80)	0.48 (0.29-0.80)
Q4	267	42	0.72 (0.39-1.31)	0.72 (0.39-1.31)	58	0.59 (0.35-0.99)	0.59 (0.35-0.98)
Q5	262	50	0.76 (0.34-1.69)	0.76 (0.34-1.69)	55	0.43 (0.21-0.88)	0.43 (0.21-0.88)
P_{trend}			0.16	0.15		<0.01	<0.01
Glycemic index[2]							
Q1	267	41	Ref.	Ref.	64	Ref.	Ref.
Q2	266	45	1.31 (0.81-2.12)	1.31 (0.81-2.13)	51	0.91 (0.60-1.38)	0.91 (0.60-1.38)
Q3	268	44	1.38 (0.85-2.24)	1.38 (0.85-2.24)	55	0.98 (0.65-1.48)	0.98 (0.65-1.48)
Q4	268	42	1.30 (0.79-2.12)	1.29 (0.79-2.11)	46	0.83 (0.54-1.27)	0.83 (0.54-1.28)
Q5	269	44	1.62 (0.99-2.66)	1.62 (0.99-2.66)	51	1.04 (0.68-1.60)	1.04 (0.68-1.61)
P_{trend}			0.29	0.29		0.44	0.48

Glycemic load[1]							
Q1	259	40	Ref.	Ref.	57	Ref.	Ref.
Q2	264	42	0.92 (0.56-1.53)	0.92 (0.56-1.53)	52	0.73 (0.47-1.13)	0.73 (0.47-1.14)
Q3	265	38	0.85 (0.50-1.45)	0.85 (0.50-1.44)	40	0.53 (0.33-0.86)	0.53 (0.33-0.86)
Q4	265	38	0.76 (0.43-1.36)	0.76 (0.43-1.36)	56	0.62 (0.38-1.02)	0.63 (0.38-1.02)
Q5	263	52	0.89 (0.43-1.83)	0.89 (0.43-1.83)	54	0.46 (0.24-0.89)	0.50 (0.24-0.89)
P_{trend}			0.69	0.68		0.01	0.08
Sweetened desserts/beverages (servings/day)[1]							
Q1	256	31	Ref.	Ref.	39	Ref.	Ref.
Q2	263	37	1.01 (0.59-1.72)	1.01 (0.59-1.72)	52	1.12 (0.71-1.78)	1.11 (0.70-1.77)
Q3	266	49	1.53 (0.92-2.56)	1.53 (0.92-2.55)	64	1.44 (0.92-2.26)	1.45 (0.93-2.27)
Q4	269	26	0.68 (0.38-1.22)	0.68 (0.38-1.22)	48	0.90 (0.56-1.45)	0.90 (0.56-1.46)
Q5	262	67	1.78 (1.03-3.09)	1.78 (1.03-3.09)	56	0.97 (0.58-1.62)	0.97 (0.58-1.62)
P_{trend}			0.19	0.19		0.35	0.35
Sweetened desserts (servings/day)[1]							
Q1	256	29	Ref.	Ref.	38	Ref.	Ref.
Q2	265	33	0.94 (0.54-1.63)	0.95 (0.55-1.66)	56	1.29 (0.82-2.05)	1.25 (0.79-1.97)
Q3	263	47	1.25 (0.74-2.12)	1.27 (0.75-2.16)	53	1.14 (0.71-1.81)	1.11 (0.70-1.77)
Q4	267	33	0.91 (0.52-1.60)	0.95 (0.54-1.66)	53	1.12 (0.70-1.79)	1.07 (0.67-1.71)
Q5	265	68	1.62 (0.95-2.76)	1.68 (0.98-2.88)	59	1.04 (0.64-1.71)	1.02 (0.63-1.67)
P_{trend}			0.20	0.17		0.44	0.40
Sweetened beverages (servings/day)[2]							
Q1	266	41	Ref.	Ref.	40	Ref.	Ref.
Q2	271	48	1.12 (0.69-1.80)	1.12 (0.69-1.81)	55	1.31 (0.84-2.06)	1.30 (0.83-2.04)
Q3	267	41	1.10 (0.67-1.80)	1.10 (0.67-1.80)	51	1.29 (0.81-2.04)	1.29 (0.82-2.04)
Q4	265	33	0.83 (0.49-1.40)	0.83 (0.49-1.40)	62	1.47 (0.94-2.31)	1.48 (0.94-2.34)
Q5	271	53	1.26 (0.76-2.09)	1.26 (0.76-2.09)	59	1.30 (0.81-2.10)	1.30 (0.81-2.09)
P_{trend}			0.57	0.57		0.64	0.65

[1]Adjusted for age, sex, race, study indicator, BMI, fruits and vegetables intake, cigarette smoking, GERD frequency, and total energy intake
[2]Adjusted for age, sex, race, study indicator, fruits and vegetables intake, cigarette smoking, GERD frequency, and total energy intake
[3]Additionally adjusted for physical activity

Table A.27. Multivariable-adjusted ORs and 95%CIs for the associations between sugar/carbohydrate intake and risk of developing EA, stratified by diabetes, among 218 EA cases, 273 GCA cases, and 1343 controls from the LA Multi-Ethnic study.

Diabetes	Measure	Cases (N)	Controls (N)	Multiplicative scale		Additive scale	
				Stratified ORs (95%CIs)	$P_{interaction}$	Single referent ORs (95%CIs)	Additive ICR (95%CI)
	Sucrose						
No	Q1-Q3	96	715	1.00		1.00	
	Q4-Q5	82	486	1.30 (0.88-1.93)		1.30 (0.88-1.93)	
Yes	Q1-Q3	14	73	1.00		1.50 (0.78-2.89)	
	Q4-Q5	17	40	1.66 (0.67-4.11)	0.62	2.48 (1.22-5.07)	0.68 (-1.20, 2.56)
	Glycemic index						
No	Q1-Q3	112	729	1.00		1.00	
	Q4-Q5	72	496	1.20 (0.85-1.69)		1.20 (0.85-1.69)	
Yes	Q1-Q3	18	72	1.00		1.49 (0.81-2.73)	
	Q4-Q5	14	41	1.62 (0.67-3.92)	0.53	2.41 (1.18-4.91)	0.72 (-1.15, 2.59)
	Sweetened desserts/beverages						
No	Q1-Q3	99	705	1.00		1.00	
	Q4-Q5	79	496	0.91 (0.62-1.32)		0.91 (0.62-1.32)	
Yes	Q1-Q3	17	79	1.00		1.45 (0.79-2.67)	
	Q4-Q5	14	34	1.29 (0.51-3.27)	0.48	1.86 (0.86, 4.05)	0.51 (-1.09, 2.11)
	Free fructose						
No	Q1-Q3	104	714	1.00		1.00	
	Q4-Q5	74	487	1.04 (0.70-1.55)		1.04 (0.70-1.55)	
Yes	Q1-Q3	15	68	1.00		1.40 (0.74-2.66)	
	Q4-Q5	16	45	1.55 (0.63-3.82)	0.41	2.17 (1.06-4.44)	0.73 (-0.94, 2.40)