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Consumption of Sugars, Sugary Foods, and Sugary Beverages in Relation to Cancer Risk: A Systematic Review of Longitudinal Studies

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systematic review, prospective studies, sugars, sugary foods and beverages, cancer risk

Abstract

High sugar intake may increase cancer risk by promoting insulin–glucose dysregulation, oxidative stress, inflammation, and body adiposity, but epidemiologic evidence is unclear. Associations between dietary sugars and lifestyle-related cancer risk from longitudinal studies were evaluated. We systematically searched PubMed, Embase, and CINAHL and identified 37 prospective cohort studies (1990–2017) reporting multivariable adjusted risk estimates for dietary sugars in relation to cancer. Of 15 and 14 studies on total sugar and sucrose respectively, 11 reported a null association in relation to

cancer. Of 14 studies on fructose, 8 reported null associations, and 2 reported protective and 4 reported detrimental associations. In two of five studies on added sugars, a 60–95% increased cancer risk was observed with higher intakes. In 8 of 15 studies on sugary foods and beverages, a 23–200% higher cancer risk was observed with higher sugary beverage consumption. In conclusion, most studies were indicative of a null association, but suggestive detrimental associations were reported for added sugars and sugary beverages.

Contents

INTRODUCTION

The diets of Americans are characterized by high levels of sugar consumption, with the average American consuming more than 126 g of sugar per day, which is equivalent to approximately three 12-ounce cans of sugar-sweetened soda (**http://www.euromonitor.com/**). The surge in sugar intake is primarily attributed to the consumption of sugary foods and beverages, which are processed or prepared with caloric sweeteners, including sucrose (table sugar) and high-fructose corn syrup, and tend to be calorie-dense and lack essential nutrients (2, 46). Added sugars account for, on average, 270 calories per day, representing >13% of the energy intake of Americans (46). This intake exceeds the recommendations outlined in the 2015–2020 Dietary Guidelines for Americans (46), which emphasized limiting the intake of added sugars to <10% of total caloric intake.

There is increasing concern about the possible role of sugary foods and beverages in displacing or diluting nutrient-dense foods (27, 35, 75). Epidemiologic evidence has consistently linked sugars and their food and beverage sources to increased incidences of obesity, metabolic syndrome, and diabetes (35, 36, 65), all of which are risk factors for cancer (6, 17). In 2007, the second expert report of the World Cancer Research Fund International and the American Institute for Cancer

Table 1 Definitions of dietary sugars and their food and beverage sources

Dietary sugars	Definition	Examples of food and beverage sources
Total sugar	The sum of all free monosaccharides (glucose, fructose, and galactose) and disaccharides (lactose, sucrose, and maltose); total sugar encompasses both naturally occurring and added sugars	Bread, baked goods, cereal products, desserts, fruits and fruit products, milk and other dairy products, candy, and sugar-sweetened beverages
Naturally occurring sugars	Sugars that are found naturally in foods	Fruits and 100% fruit juice, milk, yogurt, and other dairy products
Added sugars	Sugars and syrups that are not naturally found in the food product and are added during food production and processing	Sugar-sweetened beverages, desserts, sweetened fruit products, candy, baked goods, and cereal products
Fructose	A monosaccharide that occurs naturally in fruits; it is also a building block of sucrose and high fructose corn syrup (42–90% fructose, but popular versions are 55% fructose)	The primary sources are sugary foods and beverages sweetened with high-fructose corn syrup, sucrose, honey, or fruit juice; secondary sources are fruits, vegetables, and nuts
Sucrose	A disaccharide (table sugar) made of glucose and fructose units	Sugar beets, sugar cane, and some fruits
Sugary foods	Foods that are high in total and added sugars	Dairy desserts, grain desserts, sugary breakfast snacks, candy, and chocolate
Sugary beverages	Beverages such as fruit juice and sugar-sweetened beverages	Colas, other sodas, 100% fruit juice, calorically sweetened fruit juice and punch, and lemonade

Definitions taken from References 20, 46, and 59.

Research concluded that evidence linking dietary sugars to cancer is "limited suggestive" (75) and that intakes of sugary drinks and energy-dense foods, including processed foods with sugar, should be restricted to avoid overweight and obesity and thereby reduce cancer risk. However, since 2007, 25 additional prospective studies linking dietary sugars to cancer risk have been published (3, 7–9, 12, 15, 19, 22, 24, 25, 28, 32, 37, 38, 41, 42, 44, 45, 53, 57, 61, 64, 66, 68, 76); therefore, this review systematically integrates evidence from 1990 to 2017.

Epidemiologic evidence on the role of dietary sugars and their food and beverage sources (**Table 1**) has been systematically reviewed in relation to obesity, metabolic syndrome, diabetes, and cardiovascular disease (26, 35, 36). However, during the past decade there has been no systematic review of the evidence for a relationship between dietary sugars and most cancers, with the exception of one 2012 review on pancreatic cancer (1). Therefore, the purpose of this systematic review is to comprehensively summarize the evidence from prospective epidemiologic studies evaluating the impact of total sugar and type of sugar (primarily fructose and sucrose) and their food and beverage sources on the risk of cancer. The insights from this review will help identify gaps in the literature and guide clinical practice, dietary guidance, and policy initiatives for preventing cancer, particularly for cancers that are hypothesized to be avertable through lifestyle modification.

POTENTIAL MECHANISMS LINKING DIETARY SUGARS TO CANCER RISK

Sugars as a Source of Energy for Malignant Cells

Sugars may increase cancer risk through a number of plausible biological mechanisms (5, 10, 29, 34, 56) that are summarized in **Figure 1**. Malignant cells have a metabolism that is distinct from normal cells in that sugars are a main source of energy for malignant cells, which rely heavily

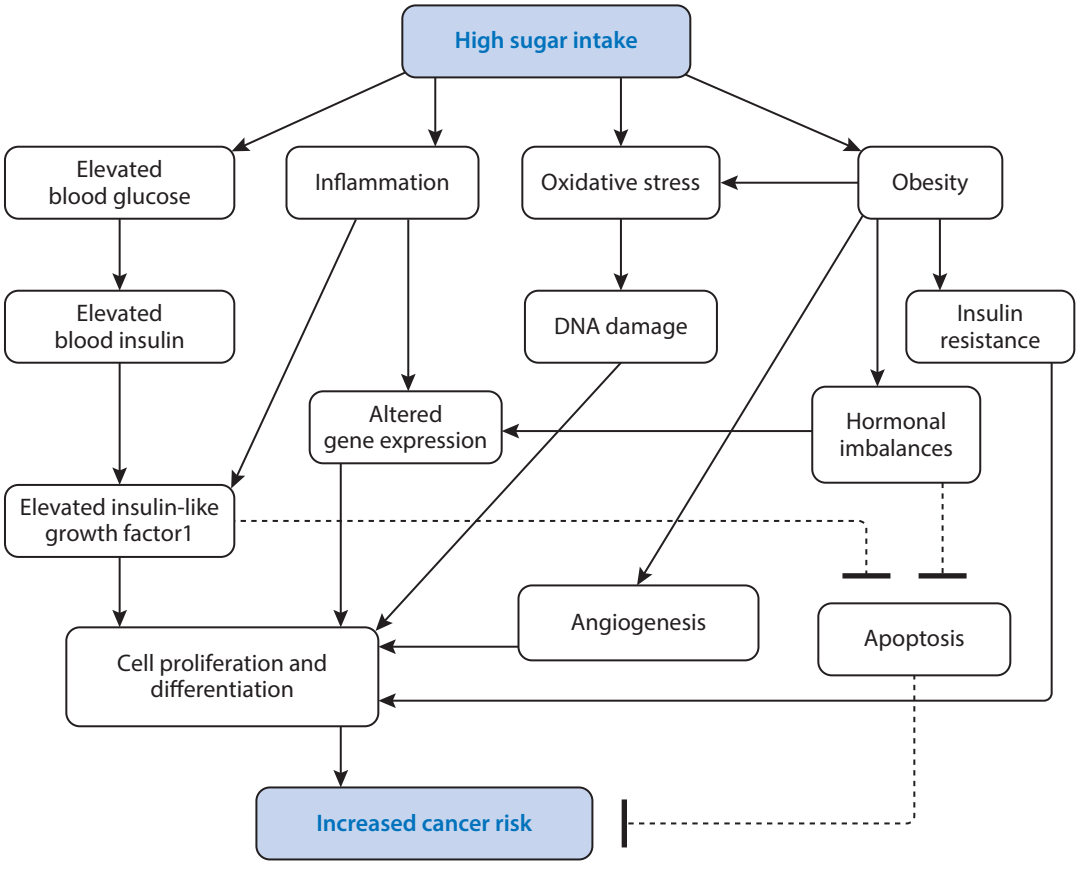

Figure 1

The potential mechanisms supporting the hypothesized association between sugars and cancer risk. The key mechanisms include adiposity-related mechanisms, disruption of the insulin signaling pathway, hormonal imbalances, inflammation, oxidative stress, DNA damage, and alteration of gene expression. Arrows indicate the stimulation of a pathway, and dotted lines indicate the inhibition of a pathway.

on a glucose supply in the blood for growth and proliferation (10, 29, 73). Diets that are high in sugar may potentially cause a metabolic switch from oxidative phosphorylation to glycolysis in tumor cells, which confers the ability to grow in hypoxic environments, fuels tumor growth and invasion, and prevents apoptosis (10, 56). Furthermore, it appears that fructose, particularly, may have adverse effects in cancer etiology. Malignant cells readily utilize fructose to support their growth and proliferation and may actually preferentially use fructose compared with glucose for nucleic acid synthesis (34).

Mechanisms Related to Body Adiposity

High sugar consumption has been linked to overweight and obesity (35, 49), which can promote cancer through adiposity-related mechanisms, including insulin resistance, hyperinsulinemia, increased bioavailability of steroid hormones, oxidative stress, and inflammation (6, 52). Collectively, these metabolic changes create an environment conducive to tumor growth and survival. Obese

individuals experience hormonal imbalances, such as elevations in estradiol, androgens, and leptin, which possess mitogenic, antiapoptotic, and proangiogenic properties, in parallel to decreases in adiponectin, which has inverse effects (52).

Fructose is of particular interest in the context of hormonal imbalances. Fructose is metabolized differently from glucose, and at high concentrations it can serve as a relatively unregulated source of acetyl-coenzyme A, leading to markedly increased rates of de novo lipogenesis (11). Furthermore, chronic consumption of diets high in fructose can lead to decreased insulin response to meals and decreased leptin production, which may have deleterious long-term effects on the regulation of appetite, energy intake, and body adiposity (11, 47). Because of these hormonal effects, diets high in added sugar (sucrose and high-fructose corn syrup) that lead to excessive fructose intake could increase the likelihood of weight gain and its associated metabolic sequelae, as described above, thereby promoting cancer growth (11).

Glucose and Insulin Response to Sugars and Its Metabolic Consequences

Another mechanism by which high-sugar diets can increase cancer risk is through their activation of the insulin signaling pathway by elevating levels of glucose, insulin, and inflammatory cytokines (16, 48). Chronically elevated levels of insulin and insulin-like growth factor 1 (IGF-1) favor survival and proliferation instead of apoptosis in DNA-damaged cells (16, 48). Laboratory evidence suggests that ingesting high concentrations of fructose may be particularly detrimental, as it is more strongly associated with impaired glucose tolerance, thereby contributing to a metabolic environment that supports tumor growth (34). In contrast, under conditions of sugar restriction, the reduction in blood glucose is accompanied by reduced levels of insulin and IGF-1. This suppresses the insulin signaling pathway and its downstream effects, as described above (55).

Inflammation and Oxidative Stress

High-sugar diets lead to excessive postprandial blood glucose excursions, which result in the production of nitric oxide and subsequently peroxynitrite, a potent, long-lived, pro-oxidant molecule that contributes to oxidative stress (5). Moreover, among individuals with excessive sugar intake, the conversion of glucose into other carbohydrates (e.g., fructose) is elevated, resulting in increased formation of advanced glycation end products and consequently increased markers of oxidative stress, which are involved in cancer growth and metastasis (72). Diets that are high in refined sugars have also been associated with higher concentrations of inflammatory markers, including C-reactive protein and interleukin 6; therefore, chronic, low-grade inflammation is a likely intermediary between sugars and cancer risk (5).

METHODS

Approach and Methodology

A comprehensive search of PubMed, Embase, and CINAHL was conducted for articles published in English from January 1, 1990, through September 28, 2017. The population, intervention, comparator, and outcomes (PICO) method (33) was used to formulate and narrow the focus of the research question, Among adults, is consumption of total sugar, fructose, sucrose, glucose, sugary foods, and sugary drinks in the highest versus lowest categories of intake associated with reduced risk of first incident cancer in longitudinal studies (**Table 2**)? The search was limited to longitudinal studies and therefore excluded ecologic, cross-sectional, and case–control studies.

Table 2 The PICO and study design criteria used for the inclusion and exclusion of studies

Parameter	Inclusion criteria	Exclusion criteria
Population	Adults aged ≥18 years who are free of cancer at baseline Sample size ≥200	Participants aged <18 years Participants are cancer survivors Sample size <200
Intervention	Highest category of intake of total sugar, fructose, sucrose, added sugar, sugary food and beverages (quintiles, quartiles, servings/week, servings/day, grams/day)	NA
Comparison	Lowest category of intake of total sugar, fructose, sucrose, added sugar, sugary food and beverages (quintiles, quartiles, servings/week, servings/day, grams/day)	NA
Outcomes	Incidence of first primary lifestyle-related cancer: e.g., female cancers, genitourinary cancers, gastrointestinal cancers, hematologic cancers	Cancer recurrence Cancer mortality Metastases
Study design	Longitudinal studies: observational studies (prospective cohort studies, retrospective cohort studies) Intervention studies (randomized controlled trials, nonrandomized controlled trials)	Editorials Case reports Cross-sectional studies Case–control studies Reviews Meta-analyses

Abbreviation: NA, not applicable.

The PRISMA method (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (33) was used to report the findings of the systematic search for all prospective or retrospective cohort studies and experimental studies that examined the association between dietary sugars and cancer risk among adults. The following search terms were used to find articles that reported risk estimates for dietary sugars and their food and beverage sources in relation to cancer risk: (("sweetening agents" OR "fructose" OR "sucrose" OR "dietary sucrose" OR "sugar" OR "sugars" OR "fructose" OR "sucrose" OR "sugary foods" OR "desserts" OR "sugary drinks" OR "sugary beverages" OR "fruit juice" OR "sugar-sweetened beverages")) AND (("neoplasms" OR "neoplasm" OR "neoplasms by site" OR "cancer" OR "cancers")).

The search process is outlined in **Figure 2**. A total of 2,922 original research articles were retrieved—1,877 from PubMed, 949 from Embase, and 96 from CINAHL—following computer-assisted removal of duplicates. Additionally, the bibliographies of the research articles were manually searched to supplement the online search process, but we did not find any additional studies that had not been captured by the online search. Two independent researchers screened all of the abstracts generated by the search. After the abstract-screening process, 2,841 articles that were not relevant were removed, and 81 full-text manuscripts from prospective cohort studies were reviewed. There were no relevant randomized controlled trials.

Inclusion and Exclusion Criteria and Study Selection

To be included in this systematic review, the studies were required to (*a*) be prospective studies (randomized controlled trials and cohort studies), (*b*) report estimates for the risk of any cancer, (*c*) have a total sample size ≥200 participants and a sufficient number of cancer cases, (*d*) present hazard ratios or rate ratios, and (*e*) present multivariable analyses (not univariate analyses). Editorials, reviews, meta-analyses, cross-sectional studies, and case–control studies were excluded.

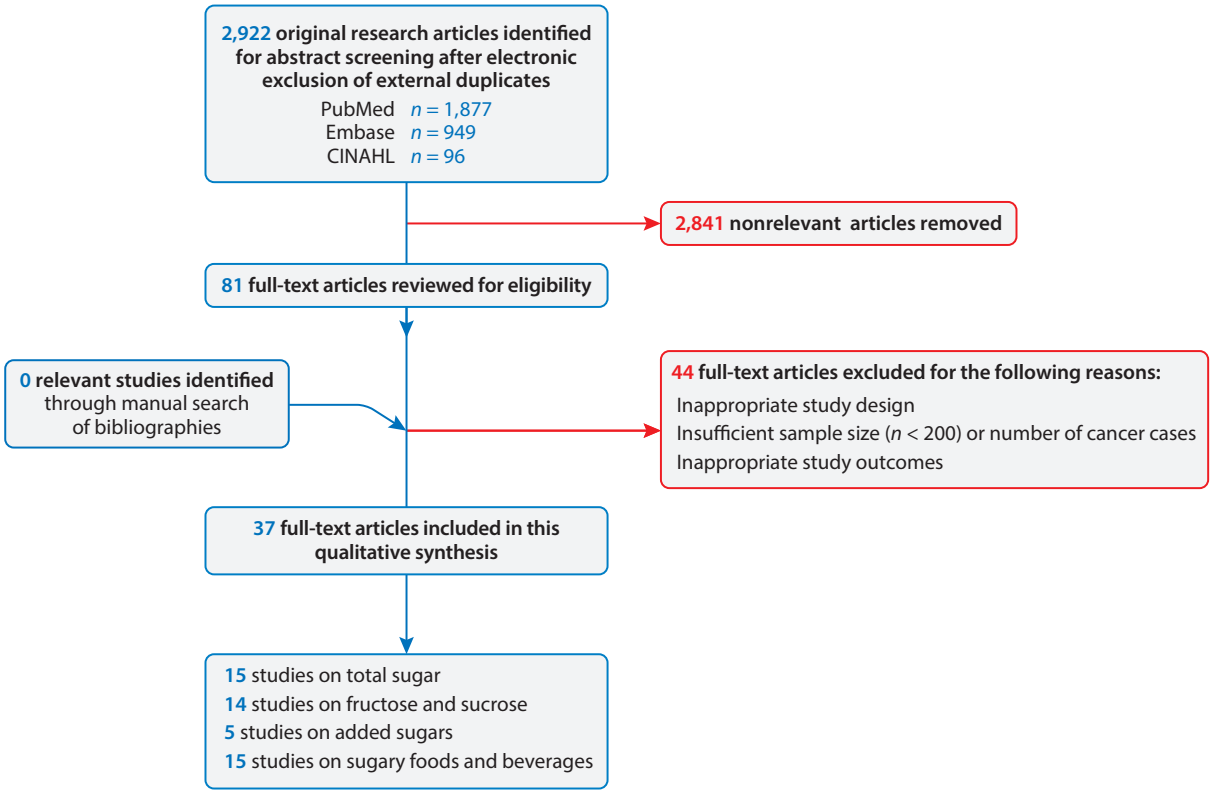

Figure 2

The PubMed, Embase, and CINAHL database search process for original research manuscripts included in this systematic review, following the 2009 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A comprehensive search of the three databases resulted in a total of 2,922 records retrieved for review. Of these records, 2,841 did not pertain to the topic of the review. The full text of the 81 remaining articles was reviewed. After removing 44 articles that did not meet the inclusion criteria, a total of 37 studies from the original search was used in the final review.

We also excluded studies published in a language other than English and not published in the peer-reviewed literature.

A total of 37 prospective cohort studies were selected for this systematic review based on the established inclusion and exclusion criteria: 15 studies reported risk estimates for total sugar, 14 for fructose and sucrose, 5 for added sugar, and 15 for sugary foods and beverages. These studies evaluated dietary sugars in relation to certain lifestyle-related cancers, which included female cancers (breast, endometrial, and ovarian), prostate cancer, gastrointestinal cancers (pancreatic, colorectal, liver, and biliary tract), and hematologic cancers (lymphoma, myeloma, and leukemia).

Data Extraction

The following information was extracted from each relevant original research article: the lead author's last name; year of publication; study location; cohort name; total, mean, or median duration of follow-up; sample size; sex of participants; age; type of cancer and number of incident cancer cases; method of dietary assessment [e.g., food frequency questionnaires (FFQs), diet records, or 24-hour recall]; exposure (total sugar, fructose, sucrose, glucose, sugary foods and beverages);

contrast (highest versus lowest categories of intake, such as tertiles, quartiles, quintiles, or predetermined cutoffs); risk estimates [relative risk or hazard ratio (HR)]; 95% confidence intervals (CIs); and confounders adjusted for in the final reported models.

RESULTS

Female Cancers

A total of 11 North American and European prospective cohort studies (7, 8, 15, 24, 43, 44, 57, 60–62, 68) investigated the intake of total and added sugar, fructose and sucrose, and sugary foods and beverages in relation to the risk of female cancers and reported risk estimates from tertile, quartile, or quintile analysis, or regression analysis (**Table 3**), or a combination of these. There were four studies on breast cancer (43, 44, 57, 60), five studies on endometrial cancer (7, 8, 15, 24, 62), and two studies on ovarian cancer (61, 68). Collectively, five (57, 60–62, 68) out of seven studies (7, 8, 57, 60–62, 68) on total sugar and the risk of female cancers were indicative of a null association, while two studies reported conflicting results (7, 8). One American study—conducted within the US Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (7)—showed that total sugar intake in the highest versus lowest quartiles was associated with a 29% lower risk of endometrial cancer (HR, 0.71; 95% CI, 0.52–0.96; p trend $= 0.02$), and inverse associations were strongest among overweight and obese women. In contrast, an analysis of the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort was suggestive of a 36% higher cancer risk per 50-g increase in total sugar intake (HR, 1.36; 95% CI, 1.05–1.76) (8).

Studies on fructose and sucrose in relation to female cancers reported conflicting results. Three (24, 43, 57) out of four studies (24, 43, 57, 68) on fructose reported null results, while one reported a protective impact (68). In that study (68), conducted within the US National Institutes of Health–American Association of Retired Persons (NIH–AARP) cohort, higher fructose consumption was associated with a 32% lower risk of ovarian cancer (HR, 0.68; 95% CI, 0.49–0.95; p trend $= 0.02$). In studies that investigated sucrose as an exposure, two (24, 43) out of four studies (15, 24, 43, 68) were indicative of a null association. One American cohort study showed that higher sucrose consumption was associated with a 35% lower risk of ovarian cancer (HR, 0.65; 95% CI, 0.47–0.89; p trend $= 0.004$) (68). In contrast, a study of a Swedish cohort reported a 73% higher risk of endometrial cancer with higher sucrose intake (15).

Two studies investigated added sugar in relation to female cancers (breast and ovarian), and both reported null findings (57, 68). Three studies (15, 24, 44) investigated the intake of sugary foods and beverages in relation to female cancer risk and reported conflicting results. An analysis within the Iowa Women's Health Study (24) showed that the consumption of sugary drinks—combined intake of fruit juice and sugar-sweetened beverages (SSB)—and of SSB alone was associated with, respectively, a 54% and 74% higher risk of endometrial cancer (p trend ≤ 0.008), but no association was observed for sugary foods. A recent study within the cohort of the Black Women's Health Study showed that women who did not consume sugary beverages compared with those who had intake levels $\geq$250 g/day had a 27% borderline significant lower risk of breast cancer (HR, 0.73; 95% CI, 0.54–1.00) (44). Contrary to these findings, a Swedish study reported null associations for soft drinks, but sugary foods, including sweet buns and cookies, were associated with $\leq$72% higher risk of endometrial cancer (HR, 1.72; 95% CI, 1.06–2.78) (15).

Gastrointestinal Cancers

A total of 21 prospective cohort studies (3, 4, 12, 19, 21, 22, 25, 28, 31, 32, 38–42, 45, 54, 63, 64, 66, 70) have evaluated dietary sugars and their food and beverage sources in relation to the risk of

Table 3 Cohort studies evaluating the intake of total added and individual sugars, sugary foods, and sugary drinks in relation to the risk of female cancers[a]

Reference	Location and cohort name	Sample (*n*)	Outcome	Contrast	Risk ratio or hazard ratio (95% confidence interval)	Covariates
Breast cancer						
Silvera et al. (60)	Canada National Breast Screening Study	49,613 women Age: 40–59 years Mean follow up: 16.6 years	Breast cancer: 1,461 cases	Total sugar intake: quintile 5 versus 1 (>95 g/day versus <64 g/day)	0.88 (0.70–1.12), p trend = 0.38	Age, BMI, alcohol use, HT use, smoking status, oral contraceptive use, parity, age at menarche, age at first live birth, family history, history of benign breast disease, menopausal status, energy intake, fiber intake, study center, and treatment allocation
Nielsen et al. (43)	Denmark Diet, Cancer, and Health Study	23,870 postmenopausal women Age: 50–65 years Mean follow up: 6.6 years	Breast cancer: 634 cases	Fructose intake: per 10 g/day	0.99 (0.81–1.20)	Parity, number of births, age at first birth, education, HT use, duration of HT use, alcohol use, BMI; adjusted mutually
				Sucrose intake: per 10 g/day	1.01 (0.94–1.08)	
Shikhany et al. (57)	United States Women's Health Initiative	148,767 postmenopausal women Age: 50–79 years Median follow up: 8.0 years	Breast cancer: 6,115 cases	Total sugar intake: quintile 5 versus 1 (median: 155.4 g/day versus 48.5 g/day)	1.06 (0.92–1.21), p trend = 0.60	Age, ethnicity, education level, BMI, alcohol use, HT use, smoking status, oral contraceptive use, parity, age at menarche, age at first birth, menopausal status, energy intake, physical activity, family history, mammogram within 2 years before enrollment, calcium and vitamin D, trial randomization status
				Fructose intake: quintile 5 versus 1 (median: 35 g/day versus 8.5 g/day)	1.07 (0.95–1.21), p trend = 0.71	
				Added sugar intake: quintile 5 versus 1 (median: 85.2 g/day versus 18.1 g/day)	1.01 (0.80–1.16), p trend = 0.71	

(*Continued*)

Table 3 (*Continued*)

Reference	Location and cohort name	Sample (*n*)	Outcome	Contrast	Risk ratio or hazard ratio (95% confidence interval)	Covariates
Nomura et al. (44)	United States Black Women's Health Study	49,103 women Age: 21–69 years Mean follow up: 13.9 years	Breast cancer: 1,827 cases	Sugary beverage intake: 0 g/day versus ≥250 g/day	0.73 (0.54–1.00), p trend = 0.49	Age, geographic region of residence, energy intake, smoking status, family history of breast cancer, education level, menopausal status, oral contraceptive use, parity, and HT use
Endometrial cancer						
Silvera et al. (62)	Canada National Breast Screening Study	49,613 women Age: 40–59 years Mean follow up: 16.4 years	Endometrial cancer: 426 cases	Total sugar intake: quintile 5 versus 1 (>95 g/day versus <64 g/day)	1.26 (0.94–1.68), p trend = 0.10	BMI, alcohol use, HT use, smoking status, oral contraceptive use, parity, age at menarche, menopausal status, energy intake, physical activity, fiber intake, study center, and treatment allocation
Cust et al. (8)[b]	Europe EPIC (1992–2004)	288,428 women Age: 20–85 years Mean follow up: 6.4 years	Endometrial cancer: 710 cases	Total sugar intake: quartile 4 versus 1 (>95 g/day versus <64 g/day)	1.20 (0.97–1.48), p trend = 0.10	Energy intake, BMI, height, and physical activity; stratified by age and study center
				Per 50 g/day	1.36 (1.05–1.76)	
Friberg et al. (15)	Sweden Swedish Mammography Cohort	61,226 women Age: 40–74 years Mean follow up: 18.4 years	Endometrial cancer: 729 cases	Sucrose intake: quintile 5 versus 1 (≥36 g/day versus ≤15 g/day)	1987 diet: 1.36 (1.04–1.77) 1997 diet: 1.73 (1.01–2.97)	Age, BMI, coffee intake, energy intake, diabetes status, smoking status
				Sweet buns and cookies: quintile 5 versus 1 (>3 servings/week versus <0.5 servings/week)	1987 diet: 1.42 (1.15–1.75) 1997 diet: 1.72 (1.06–2.78)	

(*Continued*)

Table 3 (*Continued*)

Reference	Location and cohort name	Sample (*n*)	Outcome	Contrast	Risk ratio or hazard ratio (95% confidence interval)	Covariates
Inoue-Choi et al. (24)	United States Iowa Women's Health Study	23,039 postmenopausal women Age: 52–71 years Mean follow up: 6.4 years	Type I and type II endometrial cancer: 595 cases	Sucrose intake: quintile 5 versus 1 (49.3–165.3 g/day versus 1.3–28.4 g/day)	Data shown for type I: 1.23 (0.90–1.69), *p* trend = 0.06	Energy intake, age, BMI, smoking status, physical activity, alcohol use, estrogen use, age at menarche, age at menopause, number of live births, and coffee intake
				Fructose intake: quintile 5 versus 1 (29.4–129.5 g/day versus 0.9–14.8 g/day)	1.32 (0.96–1.82), *p* trend = 0.11	
				SSB: quintile 5 versus 1 (1.7–60.5 servings/week versus 0 servings/week)	1.74 (1.27–2.38), *p* trend = 0.001	
				Fruit juice: quintile 5 versus 1 (8.4–63.0 servings/week versus 0–0.6 servings/week)	1.18 (0.87–1.61), *p* trend = 0.09	
				SSB and fruit juice: quintile 5 versus 1 (9.9–72.3 servings/week versus 0–1.3 servings/week)	1.54 (1.12–2.12), *p* trend = 0.008	
				Sweets and baked goods: quintile 5 versus 1 (11.9–91.8 servings/week versus 0–2.7 servings/week)	1.08 (0.79–1.48), *p* trend = 0.40	

(*Continued*)

Table 3 *(Continued)*

Reference	Location and cohort name	Sample (*n*)	Outcome	Contrast	Risk ratio or hazard ratio (95% confidence interval)	Covariates
Coleman et al. (7)	United States PLCO Cancer Screening Trial	36,115 women Age: 55–75 years Median follow up: 9.0 years	Endometrial cancer: 386 cases	Total sugar intake: quartile 4 versus 1 (≥87.8 g/1,000 kcal per day versus <61.2 g/1,000 kcal per day)	0.71 (0.52–0.96), *p* trend = 0.02	Age, BMI, age at menarche, age at menopause, race, HT use, and energy intake
Ovarian cancer						
Silvera et al. (61)	Canada National Breast Screening Study	49,613 women Age: 40–59 years Mean follow up: 16.4 years	Ovarian cancer: 264 cases	Total sugar intake: quintile 5 versus 1 (>95 g/day versus <64 g/day)	1.17 (0.76–1.79), *p* trend = 0.21	Age, BMI, alcohol use, HT use, oral contraceptive use, parity, age at menarche, menopausal status, energy intake, physical activity, fiber intake, study center, and treatment allocation
Tasevska et al. (68)	United States NIH–AARP Diet and Health Study	179,990 women Age: 50–71 years Mean follow up: 7.2 years	Ovarian cancer: 457 cases	Total sugar intake: quintile 5 versus 1 (median: 91.5 g/1,000 kcal versus 38.7 g/1,000 kcal)	0.70 (0.51–0.97), *p* trend = 0.03	Age, BMI, family history, marital status, smoking status, race, education level, physical activity, energy intake, alcohol use, and vegetable intake
				Added sugar intake: quintile 5 versus 1 (median: 11.0 tsp/1,000 kcal versus 2.4 tsp/1,000 kcal)	0.72 (0.51–1.00), *p* trend = 0.02	
				Fructose intake: quintile 5 versus 1 (median: 40.6 g/1,000 kcal versus 14.8 g/1,000 kcal)	0.68 (0.49–0.95), *p* trend = 0.02	
				Sucrose intake: quintile 5 versus 1 (median: 37.5 g/1,000 kcal versus 13.6 g/1,000 kcal)	0.65 (0.47–0.89), *p* trend = 0.004	

Abbreviations: BMI, body mass index; EPIC, European Prospective Investigation into Cancer and Nutrition; HT, hormone therapy; NIH–AARP, National Institutes of Health–American Association of Retired Persons; PLCO, Prostate, Lung, Colorectal, and Ovarian; SSB, sugar-sweetened beverages; tsp, teaspoon.

[a]All studies used food frequency questionnaires to assess dietary intake.

[b]Cust et al. (8) also used food records to assess dietary intake.

gastrointestinal cancers (**Supplemental Table 1**). There were 6 studies of colorectal cancer (4, 21, 22, 28, 39, 70), 12 studies of pancreatic cancer (3, 19, 25, 31, 38, 40–42, 45, 54, 63, 64), and 3 studies of liver and biliary tract cancers (12, 32, 66). Most studies reporting risk estimates for total sugar and sucrose intake in relation to gastrointestinal cancers reported a null association (4, 19, 21, 22, 25, 28, 39, 40, 45, 63, 64, 70). However, one analysis (12) within the EPIC cohort reported a detrimental impact of up to an 88% higher risk of hepatocellular carcinoma with higher intakes of total sugar (HR, 1.88; 95% CI, 1.16–3.03; p trend $= 0.008$). Similarly, sucrose was associated with a 68% higher risk of pancreatic cancer in an analysis of the PLCO Cancer Screening Trial (HR, 1.68; 95% CI, 1.11–2.54) (38).

Supplemental Material >

Evidence was mixed for fructose, as five (4, 38, 40, 63, 64) out of nine studies (4, 21, 25, 38–40, 45, 63, 64) reported null findings, while four (21, 25, 39, 45) reported higher risks of pancreatic and colorectal cancer with increased intake. Two cohort studies of Americans (21, 39) in the Health Professionals Follow-Up Study (HPFS) and the Women's Health Study reported, respectively, a 37% increase and a >twofold higher risk of colorectal cancer with higher fructose intake. Similarly, two studies using cohorts from the NIH–AARP (25) and Multiethnic Cohort (45) studies reported 29–35% higher pancreatic cancer risk among participants in the highest versus lowest categories of fructose intake, and a statistically significant linear trend was observed across the categories of intake (p trend ≤ 0.046).

Studies on added sugar (3, 31, 45) reported conflicting results, ranging from no association with pancreatic cancer in two studies (3, 45) to increased risk in one Swedish study (31). In that study (31), the intake of added sugar in the highest versus lowest categories was associated with a 95% higher risk of pancreatic cancer (HR, 1.95; 95% CI, 1.10–3.46; p trend $= 0.03$). Evidence for the role of sugary foods and beverages in gastrointestinal cancer risk was limited to five studies of pancreatic cancer (3, 31, 41, 45, 54). In general, null associations were observed for the relationship between pancreatic cancer and sugary foods, including sweets, fruit soups or stewed fruit, jams and marmalade, dairy desserts, other sugar-sweetened foods, and sugar added to coffee or tea (3, 31).

Studies evaluating sugary beverages in relation to gastrointestinal cancers focused on pancreatic cancer and biliary tract cancers as outcomes. For studies of pancreatic cancer, four US and European studies were suggestive of a null association between pancreatic cancer and SSB and fruit juice (3, 42, 45, 54), although evidence of a detrimental impact was reported in European (31) and Asian cohorts (41). These cohort studies (31, 41) reported approximately a twofold higher risk of pancreatic cancer among participants in the highest versus lowest categories of soft drink intake, and a statistically significant linear trend was detected (p trend ≤ 0.02), but no association was observed for fruit juice in the study among Singaporean Chinese participants (41). In contrast to the mixed evidence for pancreatic cancer, both studies evaluating sugary beverages in relation to biliary tract cancers demonstrated detrimental associations with higher intakes of SSB. In the EPIC cohort, compared with those who did not consume soft drinks, participants who consumed >6 cans/week of soft drinks had an 83% higher risk of biliary tact cancers (HR, 1.83; 95% CI, 1.11–3.02; p trend $= 0.01$), but null results were observed for fruit juice (66). Similarly, within the Swedish Mammography Cohort, women who consumed ≥2 servings/day of SSB had a 79% higher risk of extrahepatic cancers (HR, 1.79; 95% CI, 1.02–3.13; p trend $= 0.05$) and a >twofold higher risk of gallbladder cancer (HR, 2.24; 95% CI, 1.02–4.89; p trend $= 0.02$) (32).

Genitourinary Cancers

Three prospective studies in US and Scandinavian cohorts investigated dietary sugars in relation to prostate cancer (9, 18) and bladder cancer (68) (**Table 4**). In the HPFS, fructose intake in the

highest versus lowest quintiles was associated with a 23% lower risk of prostate cancer (HR, 0.77; 95% CI, 0.62–0.95), and a statistically significant trend across the quintiles of intake was observed (p trend = 0.004) (18). Results from the Malmö Diet and Cancer cohort were indicative of a null association between total risk of prostate cancer and sucrose, sugary foods, fruit juice, and SSB (9). However, a 40% higher risk of symptomatic prostate cancer was observed among participants in the highest versus lowest tertiles of SSB (9). No significant associations were observed between the risk of bladder cancer and intake of total sugar, fructose, sucrose, and added sugar.

Hematologic Cancers and Thyroid Cancer

Three US cohort studies investigated sugar and SSB intake in relation to the risk of hematologic cancers (37, 53, 68) (**Table 4**). Total sugar, fructose, or sucrose consumption was not associated with the risk of leukemia in an analysis of the NIH–AARP cohort (68). However, the intake of added sugar was associated with a 60% higher risk of leukemia only among women (HR, 1.60; 95% CI, 1.03–2.48; p trend = 0.02) (68). Two studies, one that utilized the combined cohorts of the Nurses' Health Study and the HPFS (53) and a second that used the Cancer Prevention Study–II Nutrition Cohort (37), were indicative of a null association between SSB and the risk of non-Hodgkin's lymphoma and leukemia. However, in the HPFS cohort, consuming ≥1 serving/day versus <1 serving/week of sugar-sweetened soda was associated with a 66% higher risk of multiple myeloma (HR, 1.66; 95% CI, 1.10–2.51), and a statistically significant linear trend across the categories of intake was reported (p trend = 0.03) (53).

One study using the EPIC cohort investigated fruit juice in relation to thyroid cancers and reported a nonsignificant increase in risk when comparing those in the highest versus lowest quartiles of fruit juice intake (HR, 1.23; 95% CI, 0.98–1.53; p trend = 0.06) (76).

DISCUSSION

This systematic review integrates observational evidence from prospective cohort studies of the relationship between dietary sugars and their food and beverage sources in relation to cancer. In general, associations between dietary sugars and cancer varied by cancer site. Taken together, the majority of epidemiologic studies are suggestive of a null association between total sugars and sucrose in relation to cancer, although associations varied for sucrose in relation to female cancers. Evidence was mixed for fructose, with approximately half of the studies suggestive of a detrimental impact on the risk of gastrointestinal cancer, although the influence of different dietary sources of fructose was not clearly evaluated. This finding is consistent with a previously published review and meta-analysis of dietary sugars and pancreatic cancer, which reported a 22% higher risk of pancreatic cancer per additional 25g/day of fructose (1).

There were a limited number of studies on added sugar, sugary foods, and sugary beverages in relation to cancer. Conflicting results were reported for added sugar, with some studies indicative of a null association, while other studies were suggestive of an increased risk for gastrointestinal and hematologic cancers with higher intake. Inconsistent results were also reported for sugary foods and beverages in relation to cancer, although detected detrimental associations were primarily observed for SSB.

Findings from the reviewed epidemiologic studies should be interpreted in light of their methodological limitations. Most of the reviewed studies used a single baseline FFQ and assumed that the participants' diets did not change during years of follow up; therefore, the measured sugar intake may not be representative of lifetime intake. Moreover, dietary recall precision is influenced by inconvenience and social desirability, as well as by inaccurate perceptions of portion size (59);

Table 4 Cohort studies evaluating intake of total and individual sugars, and sugary foods and sugary drinks in relation to risks of genitourinary and hematologic cancers[a]

Reference	Location and cohort name	Sample (*n*)	Outcome	Contrast	Risk ratio or hazard ratio (95% confidence interval)	Covariates
Genitourinary cancer						
Giovannucci et al. (18)	United States HPFS	47,781 men Age: 40–75 years Follow up: approximately 8 years	Prostate cancer: 1,414 cases	Fructose intake: quintile 5 versus 1 (>70 g/day versus ≤40 g/day)	0.77 (0.62–0.95), p trend = 0.004	Age, BMI at age 21, energy intake, and intake of total fat, calcium, phosphorus, vitamin D, vitamin E, and lycopene
Tasevska et al. (68)	United States NIH–AARP Diet and Health Study	255,696 men Age: 50–71 years Mean follow up: 7.2 years	Bladder cancer: 1,093 cases	Total sugar intake: quintile 5 versus 1 (median: 91.5 g/1,000 kcal versus 38.7 g/1,000 kcal)	0.85 (0.68–1.05), p trend = 0.23	Age, BMI, family history, marital status, smoking status, race, education level, physical activity, energy intake, alcohol use, and intake of vegetables and red meat
				Added sugar intake: quintile 5 versus 1 (median: 11.0 tsp/1,000 kcal versus 2.4 tsp/1,000 kcal)	1.06 (0.86–1.31), p trend = 0.31	
				Fructose intake: quintile 5 versus 1 (median: 40.6 g/1,000 kcal versus 14.8 g/1,000 kcal)	1.00 (0.82–1.23), p trend = 0.86	
				Sucrose intake: quintile 5 versus 1 (median: 37.5 g/1,000 kcal versus 13.6 g/1,000 kcal)	1.00 (0.82–1.22), p trend = 0.20	
Drake et al. (9)	Sweden Malmö Diet and Cancer cohort	8,128 men Age: 45–73 years Median follow up: 15.0 years	Prostate cancer: 817 cases	Monosaccharide intake: quintile 5 versus 1 (median: 61.5 g/day versus 21.5 g/day)	1.18 (0.92–1.52), p trend = 0.59	Energy intake, age, year of study entry, season of data collection, height, waist circumference, physical activity, smoking status, education level, birthplace, calcium intake, selenium intake, and competing risk for death from all other causes
				Sucrose intake: quintile 5 versus 1 (median: 81.3 g/day versus 23.3 g/day)	0.90 (0.71–1.15), p trend = 0.838	
				Cakes and biscuits: quintile 5 versus 1 (median: 77.5 g/day versus 3.3 g/day)	1.21 (0.94–1.56), p trend = 0.23	

(*Continued*)

Table 4 *(Continued)*

Reference	Location and cohort name	Sample (*n*)	Outcome	Contrast	Risk ratio or hazard ratio (95% confidence interval)	Covariates
				Sweets and sugar: quintile 5 versus 1 (median: 80.7 g/day versus 10.7 g/day)	0.93 (0.73–1.19), *p* trend = 0.634	
				Fruit juice: quintile 5 versus 1 (median: 200.0 g/day versus 0.0 g/day)	0.99 (0.81–1.22), *p* trend = 0.625	
				SSB: quintile 5 versus 1 (median: 297.8 g/day versus 0.0 g/day)	1.13 (0.92–1.38), *p* trend = 0.221	
Hematologic cancers						
Tasevska et al. (68)	United States NIH–AARP Diet and Health Study	435,674 men and women Age: 50–71 years Mean follow up: 7.2 years	Leukemia Men: 584 cases Women: 226 cases	Total sugar intake: quintile 5 versus 1 (median: 91.5 g/1,000 kcal versus 38.7 g/1,000 kcal)	Men: 0.97 (0.73–1.28), *p* trend = 0.96 Women: 1.49 (0.96–2.31), *p* trend = 0.03	Age, BMI, family history, marital status, smoking status, race, education level, physical activity, energy intake, alcohol use, and vegetable intake
				Added sugar intake: quintile 5 versus 1 (median: 11.0 tsp/1,000 kcal versus 2.4 tsp/1,000 kcal)	Men: 1.09 (0.80–1.48), *p* trend = 0.90 Women: 1.60 (1.03–2.48), *p* trend = 0.02	
				Fructose intake: quintile 5 versus 1 (median: 40.6 g/1,000 kcal versus 14.8 g/1,000 kcal)	Men: 1.00 (0.75–1.33), *p* trend = 0.83 Women: 1.34 (0.87–2.08), *p* trend = 0.07	

(*Continued*)

Table 4 (*Continued*)

Reference	Location and cohort name	Sample (*n*)	Outcome	Contrast	Risk ratio or hazard ratio (95% confidence interval)	Covariates
				Sucrose intake: quintile 5 versus 1 (median: 37.5 g/1,000 kcal versus 13.6 g/1,000 kcal)	Men: 1.15 (0.87–1.51), p trend = 0.41 Women: 1.03 (0.66–1.63), p trend = 0.77	
Schernhammer et al. (53)	United States Nurses' Health Study and HPFS	121,701 women and 51,529 men Age: 30–75 years Follow up: 22 years	Lymphoma and leukemia Non-Hodgkin's lymphoma: 1,324 cases Hodgkin's lymphoma: 55 cases Multiple myeloma 285 cases Leukemia: 339 cases	Sugar-sweetened soda: quintile 5 versus 1 (≥1 serving/day versus <1 serving/week)	Non-Hodgkin's lymphoma: 1.34 (0.98–1.83), p trend = 0.05 Multiple myeloma: 1.47 (0.76–2.83), p trend = 0.31 Leukemia: 1.06 (0.56–2.00), p trend = 0.68	Age, questionnaire cycle, diet soda intake, intake of fruits and vegetables, multivitamin use, alcohol use, saturated fat consumption, animal protein consumption, energy, race, BMI, height, physical activity, smoking history, menopausal status, and HT use
McCullough et al. (37)	United States Cancer Prevention Study–II Nutrition Cohort	100,442 men and women Age: 47–95 years Follow up: 10 years	Non-Hodgkin's lymphoma: 1,196 cases	SSB: quintile 5 versus 1 (≥1 can/day versus nondrinkers)	1.10 (0.77–1.58), p trend = 0.62	Age, sex, history of diabetes, BMI, smoking status, energy intake, and intake of artificially sweetened beverages

Abbreviations: BMI, body mass index; HPFS, Health Professionals Follow-Up Study; HT, hormone therapy; NIH–AARP, National Institutes of Health–American Association of Retired Persons; PLCO, Prostate, Lung, Colorectal, and Ovarian; SSB, sugar-sweetened beverages; tsp, teaspoon.

[a]All studies used food frequency questionnaires to assess dietary intake.

for FFQs that do not query portion size, the accuracy of self-reported intake is further compromised. The measurement error associated with self-reported sugar intake, which is particularly prone to misreporting (51, 69), may have resulted in the misclassification of sugar intake and biased risk estimates. It is likely that the measurement error attenuated associations toward the null because FFQs tend to underestimate sugar intake (22, 67). To overcome the measurement error associated with traditional dietary assessment methods, future studies may benefit from using 24-hour urinary sucrose and fructose concentrations as predictive biomarkers for total sugar intake and a calibration equation for the biomarker that provides an unbiased measure of sugar intake (67).

The measurement of added sugars is of particular concern because added sugars from sources beyond the most commonly consumed sugary foods and beverages, such as sugar added to coffee or tea, are difficult to capture (23, 69). For many foods on the FFQs, information about added sugar content is not available in food and nutrient databases in countries where the studies were conducted, in part due to constant changes in formulations of commercial multi-ingredient foods and the need to extrapolate added sugar amounts or obtain them from food companies (59). This inherent limitation of FFQs may account for the limited epidemiologic evidence on the relationship between added sugar and cancer. Therefore, the null associations observed for total sugar intake, which is the sum of added and naturally occurring sugars, may at least in part be ascribed to an underestimation of the intake of added sugar.

One major challenge in quantifying added sugar content is that no analytical laboratory method exists to distinguish between added and naturally occurring sugars (20). Consequently, nutrition labels in most countries cannot distinguish between naturally occurring and added sugars and often reflect only the total sugar content. In addition, when the total sugar content and the content of individual sugars in prepared food products are stated on a label, values are typically calculated from recipes rather than from direct analysis (20, 59). Given that information about the added sugar content in nutrient databases is incomplete, these calculated values are an estimate of the sugar content of foods and may underestimate the actual amount, thereby biasing sugar intake estimates in nutritional epidemiology studies.

The differences in study populations also pose a challenge to interpreting and comparing study findings, particularly when quantifying sugar intake. Many cohort studies were conducted in Scandinavian countries where sucrose is the caloric sweetener added to soft drinks (49). In the United States, high-fructose corn syrup (with fructose typically representing about 45–55% of the sugar) is the major caloric sweetener added to these beverages (50). Therefore, inconsistencies in results may be due to differences in the formulation of sugary foods and beverages and the differential impacts of fructose and sucrose. Another methodological limitation is that the reviewed studies did not consistently adjust for established and potential risk factors for cancer that may be confounders for the hypothesized associations, including body mass index, waist circumference, smoking status, alcohol use, cancer screening habits, education level or socioeconomic status, physical activity, the use of antioxidant supplements, reproductive risk factors, and dietary factors, such as the consumption of red and processed meat, fruits and vegetables, and fat and fiber.

Among the prospective studies reviewed here, it is notable that dietary sugars have primarily been studied in relation to gastrointestinal cancers, particularly pancreatic cancer. Therefore, this review highlights a knowledge gap that remains to be addressed to clarify the role of dietary sugars in the risk of other types of cancer, particularly within US populations for which epidemiologic evidence is nonexistent or limited for the most common cancers. Furthermore, most studies do not comprehensively report risk estimates for cancers in relation to total sugar, added sugar, fructose, and sucrose, thereby limiting our understanding of the role and potential differential impact of dietary sugars in the etiology of these cancers.

For the first time, the Dietary Guidelines for Americans (46) and the World Health Organization (74) have released explicit revised quantitative recommendations with advice to restrict the consumption of added sugar to <10% of total energy intake due to its potential role in nutrient dilution, as based on the modeling of healthy diets, and given its adverse effects on cardiometabolic health. From this review of the evidence, it is notable that the literature is limited about the role of added sugar and the consumption of sugary foods and beverages in cancer risk. Importantly, evidence is limited for the most prevalent nonskin cancers in the United States, including breast, prostate, and colorectal cancers (58). Therefore, additional research is warranted to clarify the role of sugary foods and beverages in the risk of these cancers, especially that evidence on nutrition and cancer is most persuasive and usefully synthesized for foods compared with nutrients and foods constituents (75).

Another research consideration is that most observational studies were conducted in European and primarily Caucasian North American cohorts. Nationally representative data indicate that African Americans and American Indians may have higher intakes of added sugar and Asian American and Hispanic American populations have lower intakes (71). Racial and ethnic minorities may have diminished access to healthful foods and increased access to fast food restaurants and energy-dense foods (30) in addition to distinct metabolism and unique cancer risk profiles due to health disparities (14). Therefore, additional research is warranted in different racial and ethnic groups, for whom associations between dietary sugars and cancer may vary, necessitating health initiatives that are tailored to their needs.

CONCLUSIONS

The results of this qualitative systematic review indicate that associations between dietary sugars and cancer vary by cancer site. Taken together, null results were observed for the consumption of total sugar and sucrose, but some study findings are suggestive of a potential detrimental impact of added sugars, dietary fructose, and sugary beverages on cancer risk. However, prospective evidence that addresses the impact of dietary sugars on site-specific cancers, particularly sugary foods and beverages, is too limited to draw definitive conclusions. These associations are important to clarify, particularly in the United States where sugary foods and beverages—such as grain-based desserts, dairy desserts, soda, and energy and sports drinks—are among the top 10 sources of calories among adults (13).

Therefore, additional well-designed prospective cohort studies that use reliable dietary assessment methods, better estimates of sugar intake based on recent updates in food and nutrient databases, and longer follow-up in diverse populations, particularly including racial and ethnic minorities, are warranted before any associations between dietary sugars and cancer can be confirmed or ruled out. Studies should focus on using food-based approaches for assessing dietary sugars because evidence on foods is more easily translated to public health and clinical dietary guidance. These associations are particularly important to clarify for fructose because detrimental associations are likely due to excessive intake of added sugar and not fruits, which confer numerous health benefits in the context of chronic disease prevention. Future studies should also focus on cancers for which evidence is limited or inconsistent, namely female, genitourinary, hematologic, and gastrointestinal cancers other than pancreatic and colorectal cancer. In the meantime, at the individual and population levels, dietary advice on cancer should focus on encouraging people to limit sugar consumption, particularly from sources of added sugar, such as SSB, primarily due to its detrimental impact on obesity and cardiometabolic health, which are also cancer risk factors.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

AUTHOR CONTRIBUTIONS

N.M. and N.P. conceived this project. N.M. wrote the review, developed the research plan, and assisted with conducting the search for relevant manuscripts. E.V.B. provided insights toward reviewing and revising the manuscript for important intellectual content. J.M.N. conducted the search for relevant manuscripts. N.P. reviewed the manuscript for important intellectual content, was responsible for overseeing the research process, and had primary responsibility for the final content. All coauthors provided substantive comments and editorial review and approved the final version of the manuscript.

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