Editorial

See corresponding article on page 1267.

Sugar intake and cancer risk: when epidemiologic uncertainty meets biological plausibility

Mingyang Song[1,2,3,4]

[1]Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, MA; [2]Department of Nutrition, Harvard TH Chan School of Public Health, Boston, MA; [3]Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA; and [4]Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, MA

Reprogramming metabolism is an emerging hallmark of cancer cells, with glycolysis as the main pathway of energy production, even when sufficient oxygen is present, a phenomenon referred to as the Warburg effect. Owing to this metabolic adaptation, cancer cells consume large quantities of glucose to survive through hypoxic conditions, commonly found in tumors, and support their anabolic requirements for uncontrolled growth and division. Therefore, dietary restriction of carbohydrates and pharmacologic agents that decrease insulin production or inhibit insulin signals have been exploited as potential therapeutic methods for cancer prevention or treatment. On the other hand, how carbohydrate intake may influence the incidence of cancer in the general population remains unclear.

Meta-analyses of prospective studies have largely reported a null association between carbohydrate intake and cancer incidence. Similar null associations with cancer risk have also been reported for glycemic index and glycemic load, indicators of carbohydrate quality based on the ability of foods to raise postprandial blood glucose concentrations. Although these results suggest no major influence of total carbohydrate on cancer development, the possibility that specific groups of carbohydrates or carbohydrate-contributing foods may affect cancer risk cannot be ruled out. Among them, sugar has received growing attention due to its known effect on weight gain and the established link of sugar-sweetened beverages with cardiometabolic health. Given the important role of obesity and metabolic disturbances in cancer, it is reasonable to hypothesize that higher sugar intake may increase cancer risk. However, again, epidemiologic evidence thus far has indicated a null association of total sugar, sucrose, and fructose intake with cancer risk, although some reported studies showed positive associations with cancer risk for added sugar and sugary beverages (1).

In the current issue of the Journal, Debras and colleagues (2) report the findings of a prospective analysis of total and added sugars, specific sugar types (glucose, fructose, galactose, maltose, lactose, and sucrose), and food sources of sugar in relation to cancer risk in the NutriNet-Santé cohort (2009–2019). Participants reported their dietary intake through web-based 24-h dietary records administered at baseline and every 6 mo. Total, but not added, sugar intake, was associated with a modest increase in overall cancer risk (HR for comparison of quartiles Q4 to Q1: 1.17; 95% CI: 1.00, 1.37). Among specific cancer types, only breast cancer showed a positive association with total and added sugar intake. The associations were more pronounced for sucrose, non–fruit-derived sugars, and added and natural sugars present in sugary drinks.

Major strengths of the study include the large sample size and rigorous control for potential dietary and lifestyle confounders, the inclusion of a series of sensitivity analyses that indicate the robustness of the findings, and most uniquely, the comprehensive analysis according to sugar types and food sources that have variable nutritional values. However, some limitations of the study need to be considered as well. First, although the web-based 24-h dietary records have been validated against blood and urinary markers and 24-h dietary recall conducted by dietitian interviews, the validity of the instrument for assessing the participants' usual diets and accounting for the day-to-day variation remains uncertain. Although repeated dietary assessments were conducted every 6 mo, it is unclear whether the time-varying dietary exposures were modeled throughout the follow-up. Moreover, while the web-based dietary recording has interactive features and facilitates real-time assessment of eating practices and portion sizes, compliance and accuracy have to be considered with great care. In a prior validation study, nearly 20% of participants completed the dietary record within 10 min and another 30% in 11–20 min (3). Compared with a median of 20–30 min needed to complete other web-based dietary assessments, the short completion time raises questions about the completeness and quality of reporting. Nevertheless, given the prospective study design, any measurement error is likely to have biased the associations toward the null. Another limitation is the relatively short duration of follow-up (median 5.9 y) for examination of cancer that can take decades to develop. Because of this shortcomong, the numbers of cases for nonbreast cancers are fairly small, precluding examination of less common cancers

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Address correspondence to MS (e-mail: mis911@mail.harvard.edu).

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for which metabolic disturbances are particularly important (e.g., pancreatic and endometrial cancers).

Despite these limitations, several of the study findings are noteworthy. First, the findings of positive associations of total and added sugar with breast cancer contrast with the findings in prior studies for which largely null associations were reported. Such a discrepancy may be related to the distinct characteristics of the NutriNet-Santé cohort participants, including their higher sugar intake [mean 89.7 g/d compared with 79.8 g/d for the Canadian National Breast Screening Study (4)], younger age [mean 42.2 y compared with 63.1 y for the Women's Health Initiative (5)], and lower body mass index (BMI, kg/m^2; mean 23–24 compared with 26–27 for the NIH-AARP cohort (6)]. It is possible that high adiposity in other cohorts may have diluted any of the metabolic effects of sugar on cancer risk. Also, interestingly, when study participants were stratified by age, Debras et al. (2) found a particularly strong positive association of sugar intake with breast cancer in individuals aged <45 y (HR comparing extreme quartiles: 2.45; 95% CI: 1.37, 4.39) but found no significant association in those aged ≥45 y (HR: 1.27; 95% CI: 0.92, 1.74). These findings are consistent with the meta-analysis data for a positive association of carbohydrate intake and glycemic load with risk of estrogen receptor–negative breast cancer (7), which is more commonly diagnosed in younger women. Therefore, the modifying role of age and hormonal factors in the effects of sugar intake on breast cancer warrants further studies.

Another important finding by Debras et al. (2) was that increased adiposity did not appear to explain the higher cancer risk associated with sugar intake. Adjustment for BMI or weight gain during follow-up had no material impact on the results. Also, no association was found for obesity-related cancers other than breast cancer. These results suggest an adiposity-independent pathway underlying the sugar–cancer relation. Prior studies have linked sugar and sugary drinks, independent of adiposity, with altered lipid profiles, inflammatory markers, and insulin resistance. Moreover, in support of the observation by Debras et al. of a particularly strong association of sucrose with breast cancer (2), a high-sucrose diet has been shown to promote tumorigenesis in mammary glands in mice through the 12-lipoxygenase pathway (8). In addition, dietary fructose, a component of sucrose, may promote lipogenesis and tumorigenesis by gut microbial production of acetate and tumor cell production of fructose-1-phosphate (9, 10). Therefore, further studies on the interplay between specific sugar types, the gut microbiome, and tumor metabolism are needed.

Like many questions in nutrition, strong biological plausibility does not necessarily lead to positive findings in epidemiology. This is particularly true when it comes to the sugar–cancer relation. The reasons are multifaceted and related to the challenges of accurate dietary assessment over a long period of time, adequate control for confounding by other dietary/lifestyle exposures, identification of the most relevant time window for exposure assessment, consideration of potential effect modifications by population characteristics, and heterogeneity between and within cancer types. Exemplifying and attempting to address these challenges, the study by Debras et al. (2) provides significant insight into the potential effect of sugar on cancer development. Because only <30% of adults currently meet the 2015 Dietary Guidelines for Americans for consuming ≤10% of calories from added sugar (11), a better understanding of the health effects of sugar is critical to increase our knowledge and develop new strategies to mitigate any potential adverse effects.

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