Editorial Commentary

Sugary drinks and cancer risk

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Consumption of sugars has been increasing worldwide and parallels the rising prevalence of obesity, type 2 diabetes and cancers. Whether there is a cause-effect relationship is a complex issue for several reasons.

First reason, there are many different sugars. In the present article, sugars refer to a group of sweet-tasting and soluble carbohydrates among which the main molecules are the monosaccharides and disaccharides. Fructose, galactose, and glucose are *simple sugars*, or monosaccharides, while lactose, maltose, and sucrose are all compound sugars, disaccharides, formed by the combination of two monosaccharides. For instance, sucrose (the most common sugar, also called *table sugar*) is composed of two monosaccharides: glucose and fructose.

Second reason, there are many different sources of sugars in our diets. For instance, until the 20th century, the main dietary sources of simple sugars were honey, sugarcane and sugar beet. After the 2nd world war, "manufactured foods" (including *table sugar*) and sugary drinks are the main food sources of simple sugars in the diet of most populations over the world, in particular the Western populations.

Although all sugars are chemically indistinguishable, their physiologic effects greatly depend on the physical properties of the foods in which they are included. For example, sugars that are built into a food's cellular structure (fruits and vegetables) are inserted into a fibrous matrix and accompanied with bioactive compounds (vitamins and micronutrients) and thereby have metabolic consequences different from those of readily available sugars occurring in large concentrations (or even free in solution) in highly processed rapidly digestible foods and beverages, such as sugary drinks.

It is therefore critical in any study examining the effect of nutrients (such as sugars) on cancer risk to focus the analyses on specific foods or beverages; and to control for the many (dietary or nondietary) confounders that can obscure the results. Double-blinded randomised trial is the only technique to unequivocally demonstrate cause-effect relationship in medical sciences. In addition, in the field of cancers, and contrary to the cardiovascular field, long-term exposure is required to observe the clinical surfacing of any tumor and also a long follow-up is needed for the diagnostics to be validated. It appears thereby that one of the basic principles of randomised trials—with a specific *primary hypothesis*—is not compatible with the long duration of exposure and follow-up required to demonstrate, for instance, the protective (anticancer) effects of any nutrient. Many confounders can interfere with the analyses. Thus, in nutrition, observational epidemiology is the main technique used by scientists to explore whether things we eat might be positively or negatively associated with cancer risk. But again, in such prospective or case-control studies, duration of exposure is a critical issue.

Nutritional epidemiology is a highly prolific field but, because of the weakness of these studies, controversies on associations (not causation) of some nutrients with cancer risk frequently arise, attracting attention in the public media. Indeed, in the absence of well-conducted randomised trials, interpretation of the multitude of observational studies in this area is difficult and is strongly dependent on the accurate assessment of the credibility of the published data (1). Additionally, when "significant" results are reported, the majority of the claims are based on weak statistical evidence leading to individual significant

studies usually reporting larger effect sizes than do the meta-analyses (1).

Lastly, an important consideration is that when it comes to sugary drinks, there are clear conflicts between public health interests and those of the food and beverage industry. Studies are more likely to conclude there is no relationship between sugar consumption and health outcomes when investigators receive financial support from food industry (2). On the other hand, authoritative organizations have issued public health guidance that consistently focuses on limiting and reducing sugar consumption, especially sugary drinks. But then, and still more confusing, these respected organizations themselves issued conflicting recommendations that result in confusion and raise concern about the quality of the guidelines and the underlying evidence (3).

Considering this context, we must analyse and interpret with caution the results of a recent study (NutriNet-Santé study) claiming that the consumption of sugary drinks may increase the risk of cancers, in particular breast cancers (4).

The authors assessed the prospective associations between consumption of sugary drinks (100% fruit juices and sugar-sweetened drinks) and artificially sweetened beverages—also called LCS (low calorie sweetened) beverages—with the risk of cancer. The consumption of these various beverages was assessed by using repeated 24-hour dietary records—the best technique so far to evaluate dietary habits of any population—designed to register individuals' usual consumption for 3,300 food and beverage items. Overall, 101,257 participants were included and the median follow-up time was about 5 years. Despite a quite short follow-up, this is a remarkable study with a large sample size. But then, in such a prospective diet/cancer study, duration of follow-up does not reflect duration of exposure. Follow-up is the time period during which tumors are identified by the investigators while duration of exposure to the supposed carcinogenetic nutrients (sugary drinks in this study) is not determined by measuring sugary drink consumptions during the 5-year follow-up. However, it is considered that, in average, the sugary drink intakes measured at the beginning of follow-up represent the chronic consumptions of these beverages over a much longer period of time, compatible with the time needed for cancer appearance and progression to be diagnosed during the follow-up.

An important issue in a study analysing relations between specific food/beverage consumption and health outcome is that this outcome is potentially influenced by many (including lifestyle) confounding factors that have to be controlled for. For instance, in the NutriNet-Santé study (4), heavy consumers of sugary drinks were younger—mean age in quartile 4 was 34.2 versus 52.6 years in the quartile 1 of light consumers of sugary drinks—and more often current smokers and diabetics. As older age, diabetes and smoking are major causal factors of several cancers, it is indispensable to control for these factors in the analyses.

Before extrapolating these data—obtained in a French homogeneous middle-aged population—to other populations, it is very important to quantitatively consider the mean consumption of sugary drinks. From the first to the fourth quartile, mean total sugary drinks intake (including 100% fruit juice) was 27.6 mL per day in quartile 1, 57 mL in quartile 2, 101.4 in quartile 3 and 185.8 in quartile 4. Thus, in average, the mean daily sugary drinks intake was lower than 100 mL. This is considerably lower than those measured in other populations, for instance in USA, where the average daily per capita consumption of soft drinks was higher than 440 mL in 2018 (5). In terms of sugar intakes, sugary drinks in the NutriNet-Santé study provided (respectively in quartile 1 to 4) 3.1, 6.1, 10.5 and 19.1 grams of sugars per day (4) which again is quite low compared with populations from other developed countries (5).

In the NutriNet-Santé study (4), more than half of the sugary drinks intakes were from 100% fruit juices, the consumption of which was: 16.2, 33.7, 66 and 107.5 mL/day in quartile 1 to 4 respectively. In the same time, intake of artificially-sweetened beverages (no sugar, low calorie) in the same sugary drink quartiles was: 15.3, 25.3, 24.5 and 32 mL per day per person. Thus, consumptions of sugary drinks and artificially-sweetened beverages were low to moderate in the study population. Showing significant associations between sugary drinks and cancer risk in that context of low to moderate exposure to potential carcinogens is epidemiologically relevant in terms of public health.

During the follow-up, 2,193 cancer cases occurred. Despite the limitations of an observational study, a significant association was shown between sugary drinks and the risk of overall cancer. It was calculated that for each 100 mL/day increase of sugary drinks, there was an 18% relative risk increase of any cancer (95% confidence intervals, 10% to 27%, $P<0.001$). There was also a significant association with breast cancers (693 cases), both premenopausal and postmenopausal breast cancers. In contrast, there was no significant association with colorectal cancer (166 cases) and prostate cancer (291 cases) which is less interpretable in view of the quite small number of cases.

Significant associations were also found between the consumption of 100% fruit juice and overall cancer rate. For each 100 mL/day increase, there was a 12% relative risk increase of any cancer (95% confidence intervals, 3% to 23%, P=0.007), being thereby consistent with the total sugary drinks data.

Interestingly, artificially sweetened beverages were not associated with the risk of cancer for any cancer site, despite the presence in some of these beverages of substances (aspartame for instance) that have been controversially accused of favouring cancer development (6). It is noteworthy that heavy drinkers of artificially-sweetened beverages were also, in average, heavy drinkers of sugary drinks. As the non-harmful artificially-sweetened beverages do not contain sugars, this would suggest that it is the sugars present in sugary drinks that play a significant role in the association with cancer risk. And indeed, increase of sugars from sugary drinks was positively associated with overall cancer. It was calculated that for each increase of 10 g/day of sugars from sugary drinks, there was a 16% relative risk increase of cancer from all cancer sites (P<0.001).

According to the investigators (4), adjustments for potential confounders—age, body mass index, diabetes, smoking status, several indicators of diet quality—did not substantially modify the findings. As mentioned, heavy consumers of artificially-sweetened beverages (no sugar) were, in average, also heavy consumers of sugary drinks. If the above mentioned confounders—in particular older age, smoking status and diabetes—have been preponderant in the higher risk of cancers among heavy drinkers of sugary drinks, we would probably have found a higher risk of cancer (at least a trend) among the heavy consumers of artificially-sweetened beverages. This is not the case and indirectly suggests that the sugars contained in sugary drinks (but totally absent from the artificially-sweetened beverages) were the main substances associated with cancer risk.

These rather robust data raise two additional questions: is there any other study showing similar associations between sugary drinks and cancer risk, supporting the NutriNet-Santé data? And, is there a biological mechanism supporting these data?

Regarding previous studies, we must differentiate studies analysing sugary drinks specifically—including 100% fruit juices—from studies analysing all soft drinks i.e., including artificially-sweetened beverages. We have retained only studies with high quality methods and significant durations of exposure and follow-up, significant numbers of cases and rigorous evaluation of individual chronic sugary drink consumption. In a pooled analysis from 14 prospective cohort studies—with 2,185 pancreatic cancer cases identified among 853,894 individuals—Genkinger observed a nonsignificant increased risk of pancreatic cancer associated with sugar sweetened carbonated soft drink consumption (7) whereas Navarrete-Muñoz (8) and colleagues observed no association at all in the EPIC cohort between sugar-sweetened soft-drink consumption and pancreatic cancer risk (865 cases with a median follow-up of 11.60 years). In the Melbourne Collaborative Cohort Study, with 41,514 men and women aged 40–69 years, Hodge and colleagues observed an increased risk of breast cancer associated with sugary drinks (9). This association was only observed for postmenopausal breast cancer (946 cases) and there was no significant association with any other cancer site. It is noteworthy however that, apart from colorectal cancer (1,055 cases), the numbers of cases were quite small. Interestingly, for artificially-sweetened beverages, there was no association with cancer risk—as observed in NutriNet-Santé study (4) —and the results were not changed by including total energy intake in the models. In the Framingham Offspring Cohort study, total consumption of sugary beverages was not associated with overall cancer risk. However, higher intakes of fruit juice were associated with an increased risk of prostate cancer (157 cases, relative risk 1.58; 95% confidence intervals, 1.04–2.41) in multivariable-adjusted models (10). Other associations were not significant but, in general, the numbers of cases were small. Fuchs and colleagues (11) assessed the association between sugar-sweetened beverage consumption on cancer recurrence and mortality in 1,011 stage III colon cancer patients who completed food frequency questionnaires as part of a U.S. National Cancer Institute-sponsored adjuvant chemotherapy trial. They found that patients consuming 2 servings or more of sugar-sweetened beverages per day experienced an adjusted increased relative risk for disease recurrence or mortality of 67% compared with those consuming less than 2 servings per month (P trend =0.02). In contrast, they observed that consumption of artificially sweetened beverages was associated with a decreased relative risk of 54% for cancer recurrence or mortality compared to those who largely abstained (P trend =0.004) (12). The authors hypothesized that this inverse association might be mediated by decreased consumption of sugar-sweetened alternatives. Finally, in a recent population-based cohort study involving a very large cohort (n=451,743) in the European Prospective Investigation into Cancer and

Nutrition (EPIC), investigators did not find significant association between consumption of sugar-sweetened beverages and mortality from cancers of several sites (13). However, the study was not prospectively designed to test the sugary drink/cancer hypothesis and many confounders were not included into the analyses.

The last question regards the possible mechanisms by which sugary drinks may increase cancer risk. Several hypotheses have been proposed in relation with overweight/obesity, high visceral adiposity, insulin resistance (or chronic high glycaemic load). Also, sugary drinks with high fructose content, induces hepatic steatosis and triggers progression of non-alcoholic fatty liver disease (NAFLD) which in turn increases the risk of cancer (14,15). Finally, chemical compounds present in sugary drinks may play a role in cancer development. For instance, pesticides in fruit juices and caramel colorants—such as methylimidazole (16)—in soda are known carcinogenic substances.

We conclude that the recent high-quality data—the NutriNet-Santé study (4)—although they do not prove a causal relationship, are consistent with the hypothesis that sugary drinks increase cancer risk.

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Footnote

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