

## Soft drinks, aspartame, and the risk of cancer and cardiovascular disease<sup>1,2</sup>

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The consumption of sugar-sweetened soft drinks has been associated with excess weight and an increased risk of type 2 diabetes in systematic reviews and meta-analyses of the evidence (1, 2), and these conditions are by themselves related to an increased risk of mortality, cardiovascular disease, some cancers, and other chronic diseases. Evidence for an association between soft drink intake and risk of cardiovascular disease and cancer is, however, more limited (3–7). Sugar-sweetened soft drinks are the primary source of added sugars in the American diet and contribute 9.2% of total energy intake in the United States (8).

Recently, the American Heart Association released recommendations to reduce the intake of added sugar to no more than 100–150 kcal/d for most Americans (9). Replacing sugar-sweetened beverages with non- or low-caloric beverages could be used to reduce sugar intake, and artificially sweetened diet soft drinks have been marketed as a healthier alternative due to their lack of calories. However, it is unclear whether they should be recommended as a replacement for sugar-sweetened soft drinks because some studies have found increased risk of type 2 diabetes, cardiovascular disease, or the metabolic syndrome with higher intake of diet soft drinks (10–12), although it is possible that these findings may be due to reverse causation (4).

Most manufacturers have used aspartame as an artificial sweetener in diet soft drinks. Although many short-term animal studies have suggested the safety of aspartame, a recent large study that assessed aspartame intake throughout the life span in rats suggested an increased risk of lymphomas, leukemias, and transitional cell carcinomas of the pelvis, ureter, and bladder in a dose-dependent manner within ranges that are considered to be safe for human consumption (doses as low as 20 mg/kg body weight) (13). However, epidemiologic studies in humans on the health effects of diet soft drinks or aspartame intake are sparse and have not suggested an association with cancer risk [see references in (14)], but they have some limitations that include either retrospective design with potential recall and selection biases or only one baseline dietary assessment and short follow-up in the only other prospective study published on the subject. In addition, because diet soft drinks are often consumed by persons with excess weight and type 2 diabetes with the aim of reducing caloric intake and facilitating weight loss and because these 2 conditions are associated with an increased risk of several cancers including lymphomas and leukemias, studies need to be conducted and interpreted carefully because of the potential for residual confounding.

In this issue of the Journal, Schernhammer et al (14) investigate the association between artificially sweetened and sugar-containing sodas and the risk of hematopoietic cancers in the Nurses' Health Study and the Health Professionals Follow-Up Study. Both studies have important strengths, including the prospective design (which avoids recall bias and reduces the potential for selection bias that may affect retrospective studies), repeated dietary assessments (which reduces random measurement error due to changes in diet during follow-up), and >20 y of follow-up, which results in a considerable number of cancer cases. Schernhammer et al found that among men greater intake of diet sodas ( $\geq 1$  serving/d) was associated with an increased risk of non-Hodgkin lymphoma (NHL; RR: 1.31; 95% CI: 1.01, 1.72) and multiple myeloma (RR: 2.02; 95% CI: 1.20, 3.40) compared with no intake. Intake of regular sugar-sweetened sodas was associated with an increased risk of NHL (RR: 1.66; 95% CI: 1.10, 2.51) in men, but no association was found for multiple myeloma or leukemia. None of the analyses showed a significant association among women only. In addition, the authors observed an increased risk of leukemia with a high compared with a low intake of diet soft drinks in the combined cohorts (RR: 1.42; 95% CI: 1.00, 2.02), with similar risk estimates but limited power in the sex-specific analyses. Intake of aspartame was directly associated with risk of NHL and multiple myeloma and suggestively associated with leukemia in men, although not in women.

With regard to the mechanism that may explain the findings for diet soft drinks, it is known that aspartame breaks down to methanol, aspartic acid, and phenylalanine if stored near or above room temperature. The authors suggested that higher enzymatic activity of alcohol dehydrogenase type 1 (ADH) in men, which induces higher conversion rates from methanol to carcinogenic formaldehyde, could explain the sex differences in the results for NHL and multiple myeloma. Because ethanol intake inhibits methanol metabolism, persons with a low ethanol intake might have more unbound ADH activity and higher formaldehyde conversion rates.

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Indeed, a significant interaction was observed when results for diet soda intake were stratified by alcohol intake ( $P = 0.03$ ), with an increased risk of NHL (RR: 2.34; 95% CI: 1.46, 3.76) among men who consume <6 g alcohol/d but not among men with higher alcohol intake (RR: 0.96; 95% CI: 0.48, 1.90). However, given the positive association between regular sodas and NHL, other mechanisms might be involved as well.

The authors found no modification of the results by BMI, which would be important to examine because of the strong association between BMI and diet soft drink consumption, but further large-scale studies will be needed to explore this issue. In addition, adjustment for diabetes and waist-to-hip ratio did not alter the results.

Although the studies had a large number of NHL cases, there were more modest numbers of multiple myeloma and leukemia cases, and when further categorized by frequency or quintile of intake it can be seen that some of the positive associations observed were based on relatively low or modest numbers of cases. Thus, at present, it cannot be excluded that the findings may simply have been due to chance.

In a second study in this issue, Drake et al (15) investigated the association between dietary carbohydrates, fiber, and their food sources and risk of prostate cancer in 8128 Swedish men (817 cases) from the Malmö Diet and Cancer cohort. It has been hypothesized that dietary carbohydrates could affect prostate cancer risk through alterations in the insulin and insulin-like growth factor endocrine axis. However, consistent with most of the available data to date, the study found no association between intake of total carbohydrates, dietary fiber, whole grains, vegetables, fruit and berries, potatoes or low- or high-fiber bread, and sweets and sugar and prostate cancer risk. However, greater intake of cakes and biscuits (RR: 1.42; 95% CI: 1.03, 1.97) and rice and pasta (RR: 1.33; 95% CI: 1.04, 1.70) was associated with an increased risk of low-risk prostate cancer, low-fiber cereals were associated with an increased prostate cancer risk overall (RR: 1.24; 95% CI: 1.01, 1.52); and sugar-sweetened beverages were associated with an increased risk of symptomatic prostate cancer (RR: 1.41; 95% CI: 1.06, 1.88). Given the numerous analyses that were conducted in this study, it is possible that some of these results may be due to chance. Nevertheless, this study shows that although overall intake of carbohydrates or most carbohydrate-rich foods may not be related to prostate cancer risk, some individual items may still be associated with risk, and it will be important for other studies to further investigate these findings.

In a third study in this issue, Eshak et al (16) investigated the association between soft drink intake and ischemic heart disease and stroke in a Japanese population (16). The few studies already published on the subject have been conducted in the United States (3–5), but replication in studies from other geographic areas with different dietary patterns and lifestyles would lend further support to the hypothesis. During 18 y of follow-up, 453 cases of ischemic heart disease and 1922 stroke cases were ascertained among 39,786 men and women participating in the Japan Public Health Center–based study cohort I.

The study found a suggestive inverse association between almost-daily soft drink intake compared with rare or never consumers and stroke risk in men (RR: 0.76; 95% CI: 0.62, 1.06;  $P$ -trend = 0.07) and no association for ischemic heart disease (RR: 1.04; 95% CI: 0.74, 1.48), whereas for women there was a positive association with stroke (RR: 1.21; 95% CI: 0.88, 1.68;

$P$ -trend = 0.02), which was restricted to ischemic strokes (RR: 1.83; 95% CI: 1.22, 2.75;  $P$ -trend = 0.001), but no association for ischemic heart disease (RR: 0.88; 95% CI: 0.30, 2.60). When excluding subjects with morbidities and early follow-up, the result in men was closer to the null and the result in women was slightly strengthened. This suggests that reverse causation, where subjects with baseline morbidities may have altered their soft drink intake as a result of their disease, could have affected the results. The results for stroke are consistent with American studies that found an increased risk of stroke among women but not among men (5), but the null results for ischemic heart disease are inconsistent with the results from the United States (3, 4). However, soft drink intake in the Japanese studies was lower both in terms of frequency and portion sizes than that in the American studies, and this may partly explain the differences in the results.

These 3 studies add to a growing body of evidence on the adverse health effects of soft drinks; however, given the limited and conflicting data available, these findings can at the present time be considered only suggestive, not conclusive, but they warrant further investigation in other prospective studies with data on long-term intake of soft drinks, diet soft drinks, and aspartame.

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