NUTRITION AND CANCER
https://doi.org/10.1080/01635581.2023.2180823

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LETTER TO THE EDITOR

Continuing the Conversation on Artificial Sweeteners and the Risk of Cancer: Results from the NutriNet-Santé Cohort Study

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Introduction

While several world agencies reevaluate the safety of artificial sweeteners (AS), Debras and coworkers estimated their association with overall and site-specific cancer using data from the NutriNet-Santé cohort in France (1). Results revealed that higher consumers (above the population median) of total AS had a 13% higher risk of cancer than non-consumers. This association was most notable for aspartame and acesulfame-K and when evaluating breast and obesity-related cancers.

The study has several strengths. The authors used prospective data from 102,865 participants, where 3,358 incident cancer cases were diagnosed. The analysis accounted for within-person variability occurring throughout follow-up time by collecting repeated measures of AS intake. These repeated measures improve upon less valid single baseline assessments from observational studies attempting to predict disease risk. The study provided separate analyses for specific AS types, a methodological enhancement that complements previous assessments evaluating a broad category of AS (e.g., artificially sweetened beverages). Estimates for synergistic effects and interactions (e.g., AS and sugar) and effect modification introduced by AS dosage were also ascertained in supplementary findings.

Considering the relevance of this study and the well-deserved media coverage it has received, it is worth framing some declared and undeclared limitations.

Limited Generalizability

As explained by the authors, selection bias is likely to be present. The NutriNet-Santé cohort is mainly constituted of women (78.46%; aged 42.2 ± 14.5 y at baseline) with a healthy body mass (BMI at baseline = 23.69 ± 4.48 kg/m2), high educational status (65% with more than two years after high school), low prevalence of diabetes mellitus type 1 (0.25%) and 2 (1.48%), and with moderate-to-high physical activity level (65%). Such characteristics might differ from the French and world general population (e.g., the prevalence of overweight, obesity, and type 2 diabetes in France approximates 59.5, 23.2, and 5.3%, respectively) (2, 3) to the extent that AS intake and cancer risk might also differ.

Future research could benefit from including a broader, sex-balanced, and diverse sociodemographic sample with different prevailing health statuses (e.g., diverse body weights and conditions) to better explore the risk of cancer associated with AS consumption. For example, results suggested that AS consumption was particularly associated with obesity-related cancers, although participants living with obesity were underrepresented in this cohort. Longer follow-up periods (7.8 years in Debras et al. study) are also warranted to comprehensively detect cancer cases, given that most cancers, such as breast cancer, reach their peak of incidence in the 60–69 years group (4).

Residual and Time-varying Confounding

While the analysis estimated the risk of cancer by adjusting for numerous confounders at baseline, regression models did not always account for changes in lifestyle and dietary factors occurring during follow-up (e.g., interval increments/decrements in smoking status, alcohol intake, servings of dairy products, fried foods, whole- and refined grains, sweets, processed meats, and red meats, along with other relevant covariates). Introducing time-varying variables into analyses to mitigate time-varying confounding

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has been considered in other large prospective cohorts evaluating AS concerning health-related outcomes (5).

Furthermore, residual confounding is likely present in models estimating the AS-breast cancer association because breastfeeding, a well-known factor that reduces the risk for breast cancer, was not included as a covariate. Breastfeeding also might be associated with changes in usual AS consumption patterns because health professionals usually recommend avoiding artificial additives during pregnancy and lactation, hypothesizing potential damage to the infant's health (6).

Exposure Assessment

Diet was evaluated using three 24-h recalls repeated every six months during the first two years of follow-up (i.e., up to 15 recalls). AS intake was then estimated by averaging all 24-h dietary records. This approach relies on the assumption that the exposure remained constant over time. However, long-term dietary data are best computed as changes in each dietary factor between repeated assessments to account for intake variability, which is not captured by a simple average. Data from the Nurses' Health Study II revealed that the consumption of AS-containing beverages varies from −0.73 to 0.52 servings/day between 4-year intervals (5). Evaluating changes in exposure rather than baseline or prevalent exposure appears to provide more consistent, robust, and biologically plausible associations (7).

Measurement Error Correction

Measurement error could lead to inaccurate exposure quantification when using food frequency questionnaires (FFQ) or 24 h recalls. The NutriNet-Santé study did not apply measurement error correction, and estimates could be imprecise. We encourage measurement error calibration reliant on a subsample with diet records or biomarkers of consumption (considered the standard of reference). Regression calibration methods for Cox proportional hazard models to correct measurement error bias in nutritional epidemiology (specifically when evaluating breast cancer) are available elsewhere (8). Such methodological precautions might estimate disease risk more accurately.

Despite these limitations, which the authors aptly acknowledged, this article provides comprehensive evidence on this topic. We applaud Debras and et al., for this exhaustive assessment of the role of AS consumption in total and site-specific cancer risks. We agree with the authors that causality cannot be established, which must be incorporated in press communications and considered by the general public and regulatory authorities.

Disclosure Statement

The authors report there are no competing interests to declare

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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