Detailed Study Notes: Episode 449

Do Artificial Sweeteners Increase Cancer Risk?: The NutriNet-Santé Study

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Introduction to this Episode

In March 2022, a study was published in PLOS Medicine titled “Artificial sweeteners and cancer risk: Results from the NutriNet-Santé population-based cohort study”. This study, from Charlotte Debras and colleagues, suggested higher consumers of artificial sweeteners had a 13% increased risk of cancer compared to those who were non-consumers.

And the study picked up quite a lot of news coverage, and within health circles it was noted as being a source of evidence (in humans) that sweetener use could pose a health risk.

One of our Premium subscribers asked for our thoughts on this study and whether it really does confirm a connection that has long been claimed, but usually on the basis of mechanisms or animal studies. And so in this episode Alan Flanagan, Niamh Aspell and Danny Lennon discuss this study.

Connection to Previous Episodes

In episode 431 of the podcast we discussed the general topic of artificial sweeteners and human health. This episode gives a really good grounding in how acceptable/safe intakes are determined by food safety authorities, how they compare with evidence showing harm, and what the overall evidence base says about sweeteners and health outcomes.

If you haven’t had a chance to listen to that episode yet, then it will prove to be really useful adjunct material to this current episode. There are also show notes available for that episode which you can read through to further understand some of these details.

Overview

Our Premium subscriber Zachary Wenger asks:

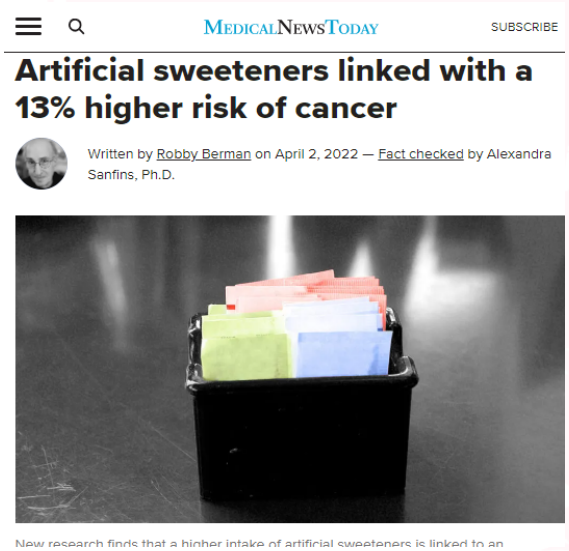
> *"What are your thoughts on this recent publication? Adjustment model, follow-up time, contrast in exposure, etc, all appeared sufficient."*

This study was published in PLOS Medicine titled *"Artificial sweeteners and cancer risk: Results from the NutriNet-Santé population-based cohort study"*.

Charlotte Debras and colleagues published the study - Nutritional Epidemiology Research Team, University of Paris

This study suggested higher consumers of artificial sweeteners had a **13% increased risk of cancer** compared to those who were non-consumers.

And the study picked up quite a lot of news coverage, and within health circles it was noted as being a source of evidence (in humans) that sweetener use could pose a health risk.



Study Finds

CANCER NEWS, HEALTH & MEDICAL NEWS

Artificial sweeteners can increase cancer risk, study warns

MARCH 28, 2022

by Jocelyn Solis-Moreira

Share Tweet

PARIS, France — If you think picking a packet of zero-calorie Splenda is going to let you have your cake and eat it too, think again. New research from France reveals that consuming common artificial sweeteners can increase your risk for cancer.

Objective:
To investigate the association between artificial sweetener (AS) intake and cancer risk.

AS intakes were assessed as:

- Total dietary sources*, AND
- Most frequently consumed (Aspartame, Acesulfame-K, Sucralose)

**Most epi studies are focused on AS-beverages only. Aspartame is found in nearly 1,400 food products on the French market, and more than 6,000 worldwide. Previous studies limited by 'true' exposure.*

Cancer Risk assessed for

- Overall
- Site specific

Importance of this evidence - [EFSA re-evaluation sweeteners]

Background Research To This Point

All previous regulatory evaluations concluded more evidence was required in humans.

Studies showing increase in cancer incidence with artificial sweetener use nearly all coming from animal studies. Caution needed when taking conclusions and trying to apply to humans.

For example:

- An animal study was conducted in mice who were exposed to aspartame (Soffritti et al, 2010). But EFSA largely dismissed this finding (in their 2013 risk assessment), due to it being an animal model, which used mice who were followed over their lifetime.
    - Older animals are more prone to illness and if carcinogenicity studies in mice >104 weeks, age related changes confound the results.
    - Also the breed of mice used in the study are known to have a high incidence of spontaneous tumors.
- As mentioned in episode 431, controversy regarding aspartame stems from 3 studies from the same research group in Europe, all of which purported to show carcinogenicity in rats and mice. But…
    - EFSA rejected findings as researchers misdiagnosed hyperplasia as malignant tumours and violated OECD testing protocols by administering aspartame during fetal development.
- In relation to saccharin, concerns were from early animal toxicology studies in the 1970's showing bladder cancer developed in rats administered high doses.
    - But further research found that the carcinogenic mechanisms identified in rodents were not applicable to humans.

When looking at human trials, previous to NutriNet-Sante, there seemed to be no increased risk. For example, Liu et al. (2021) meta-analysis of case–control studies consumption of artificial sweeteners was not associated with an increase in cancer when all types of cancers are analyzed comprehensively (OR 0.91, 95% CI 0.75–1.11).

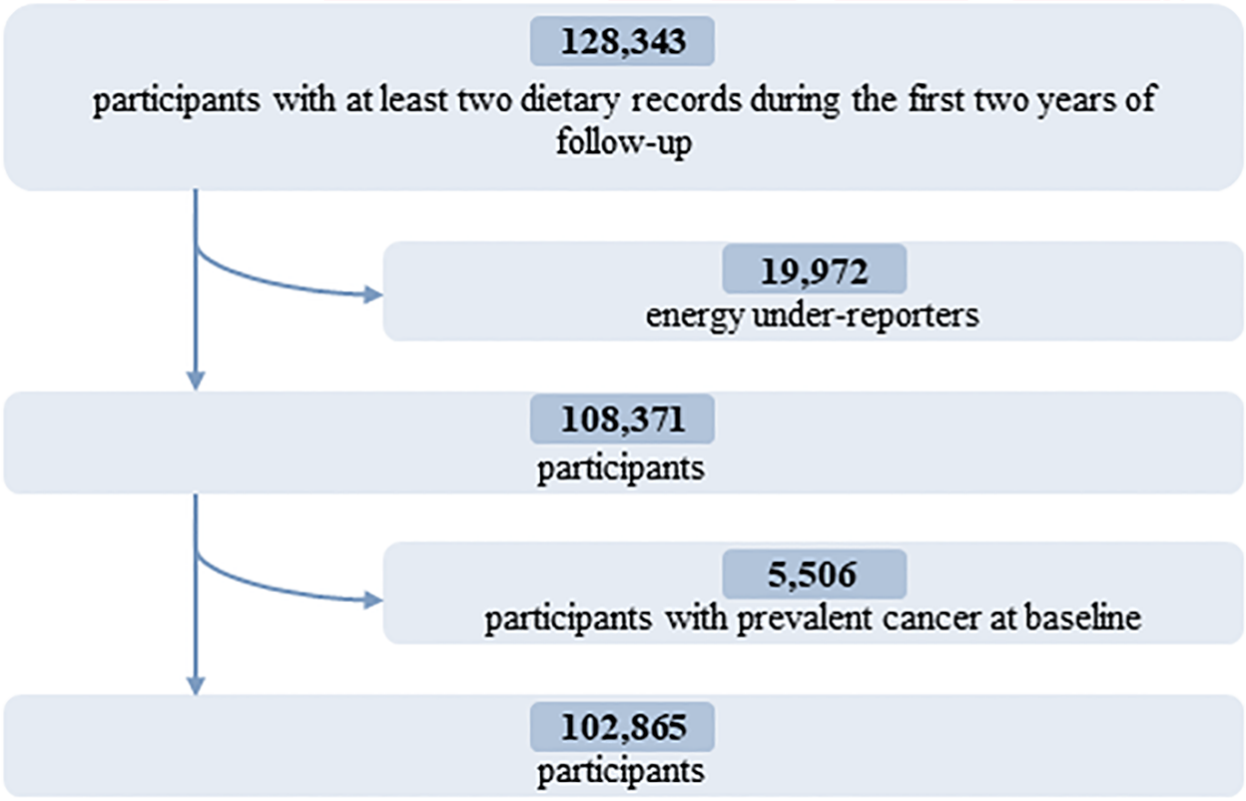
Large health agencies have echoed the same conclusions:

- Both Cancer Research UK and the US National Cancer Institute have said sweeteners don't cause cancer.
- World Cancer Research Fund: *"There is no strong evidence in humans to suggest that artificially sweetened drinks with minimal energy content, such as diet sodas, are a cause of cancer."*

Study Design

Study population:

- French population (NutriNet-Sante cohort)
- Total participants – 102, 865 (78.5% women)
- Adults (average 42.2 ± 14.5 years)
- Began in 2009 (this study data is from 2009 - 2021)
- When looking at the results (discussed later), it is noted:
    - Higher consumers (vs. non-consumers) tended to be more often women, younger, smokers, less physically active, more educated, and more likely to have prevalent diabetes.
    - They had lower energy, alcohol, saturated fatty acid, fibre, fruit and vegetables, and whole-grain food intakes and higher intakes of sodium, total sugar, dairy products, sugary foods and drinks, and unsweetened non-alcoholic beverages.



As seen in the image above, there are approximately 20,000 excluded *'energy under-reporters'*. For more on this, see the section on the Goldberg cut-off method later in these notes.

Data collection

- Yearly data collection
- Web-based
- Modules: health status, anthro data, physical activity, lifestyle and sociodemographic data and diet.

Dietary Assessment

- Web-based self-administered dietary record tool
- Every 6 months: 3 non-consecutive days based on 24-hr dietary records, randomly assigned over 15 days.
- Portion sizes: validated photographs or standard serving containers.
- Records were also validated by a trained dietitian and against blood and urinary biomarkers.
- Example: Web-Based Nonconsecutive Dietary Records and Respective Biomarkers (Lassale *et al*., 2015)
- Self-reported intake of fish, fruit and vegetables, and selected micronutrient intakes assessed against the following concentration biomarkers:
    - plasma beta carotene
    - vitamin C
    - n-3 polyunsaturated fatty acids
- Simple and adjusted Spearman rank correlations – overall demonstrated acceptable validity.

Goldberg cut-off method

- Dietary energy under-reported identified using basal metabolic rate and the Goldberg cut-off method.
    - *Approx 20,000 excluded 'energy under-reporters'*
- Black *et al*., 2000: Critical evaluation of energy intake using the Goldberg cut-off for energy intake:basal metabolic rate. A practical guide to its calculation, use and limitations
- *"Goldberg cut-off can be used to evaluate the mean population bias in reported energy intake, but information on the activity or lifestyle of the population is needed to choose a suitable PAL energy requirement for comparison. Sensitivity for identifying under-reporters at the individual level is limited. In epidemiological studies information*

on home, leisure and occupational activity is essential in order to assign subjects to low, medium or high PAL levels before calculating the cut-offs."

Quantifying AS Intakes

- Based on assessing the AS intake of different brands, routinely collected to determine exposure to each food additive.
- Used 3 large compositional databases, two in France and one global database
- Products were cross referenced by date of consumption as declared by participants and composition of the food product at that time, to factor in any possible re-formulations.
- Finally, the measurable dose of additives were estimated by around 2,700 lab assays on different foods for primary food sources.

From the paper:

"This methodology allowed us to assess exposure for the following artificial sweeteners: acesulfame-K, aspartame, cyclamates, saccharin, sucralose, thaumati, neohesperi- dine dihydrochalcon, steviol glycosides, and salt of aspartame-acesulfame; the quantities consumed of all these artificial sweeteners were summed to calculate the variable 'total artificial sweeteners"

Three groups:

1. Non-consumers (reference category)
2. Lower consumers
3. Higher consumers

[36% of participants consumed AS]

- Specific analyses were performed for the most represented artificial sweeteners in the cohort (see diagram on next page):
    - Aspartame
    - Acesulfame-K
    - Sucralose
- All other artificial sweeteners were consumed by less than 3.5% of participants.

Level of intake reported in results:

- All participants' intakes of aspartame and acesulfame-K were below the ADIs of 40 mg/kg body weight/ day and 9 mg/kg body weight/day, respectively
- Only 5 participants exceeded the ADI of 15 mg/kg body weight/day for sucralose

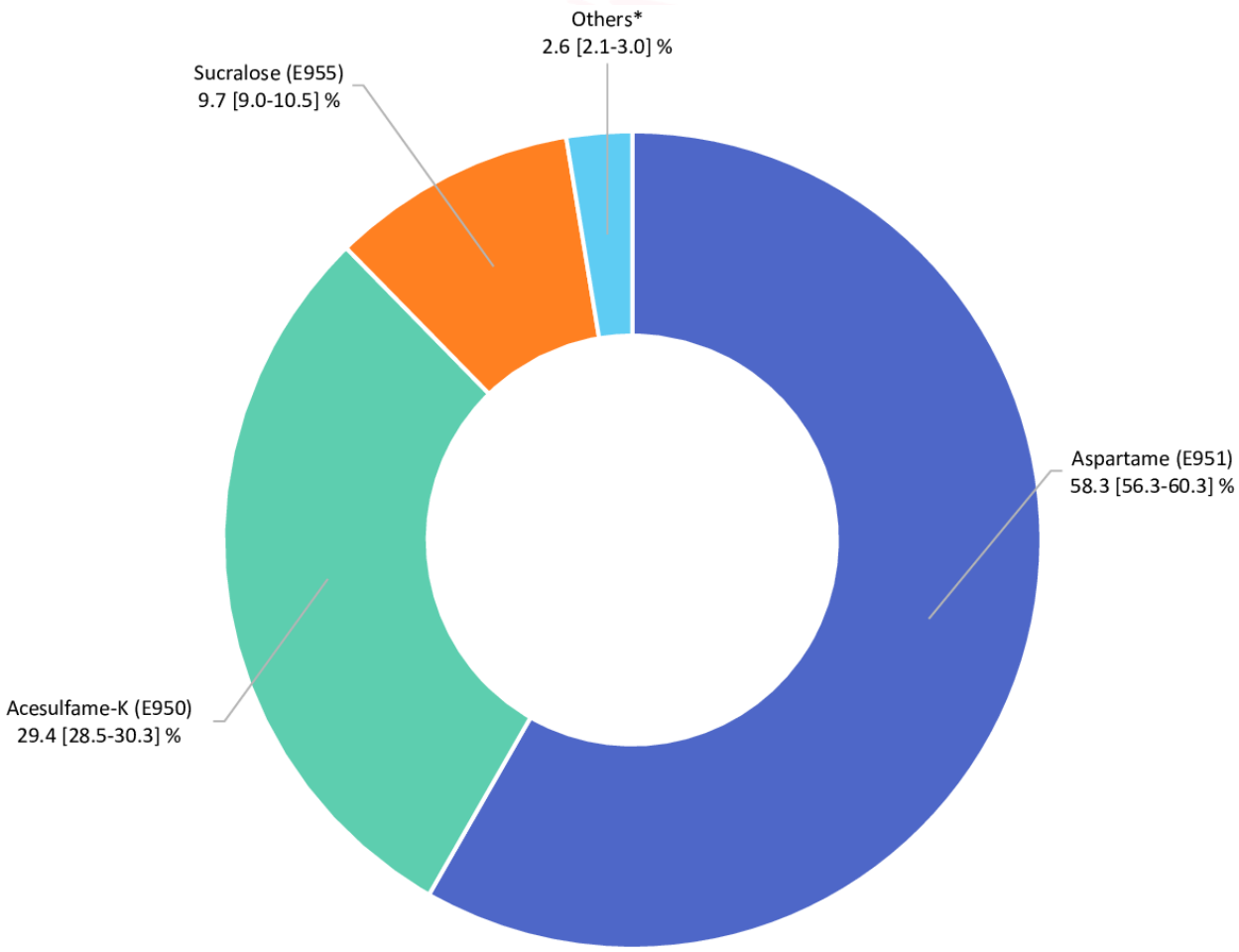


Image from: Debras et al., PLoS Med. 2022 Mar 24;19(3):e1003950

Sources of sweeteners in the diet

The main contributors to total artificial sweetener intake were:

1. Soft drinks with no added sugars - 53%
2. Table-top sweeteners - 29%
3. Yogurt/cottage cheese - 8%

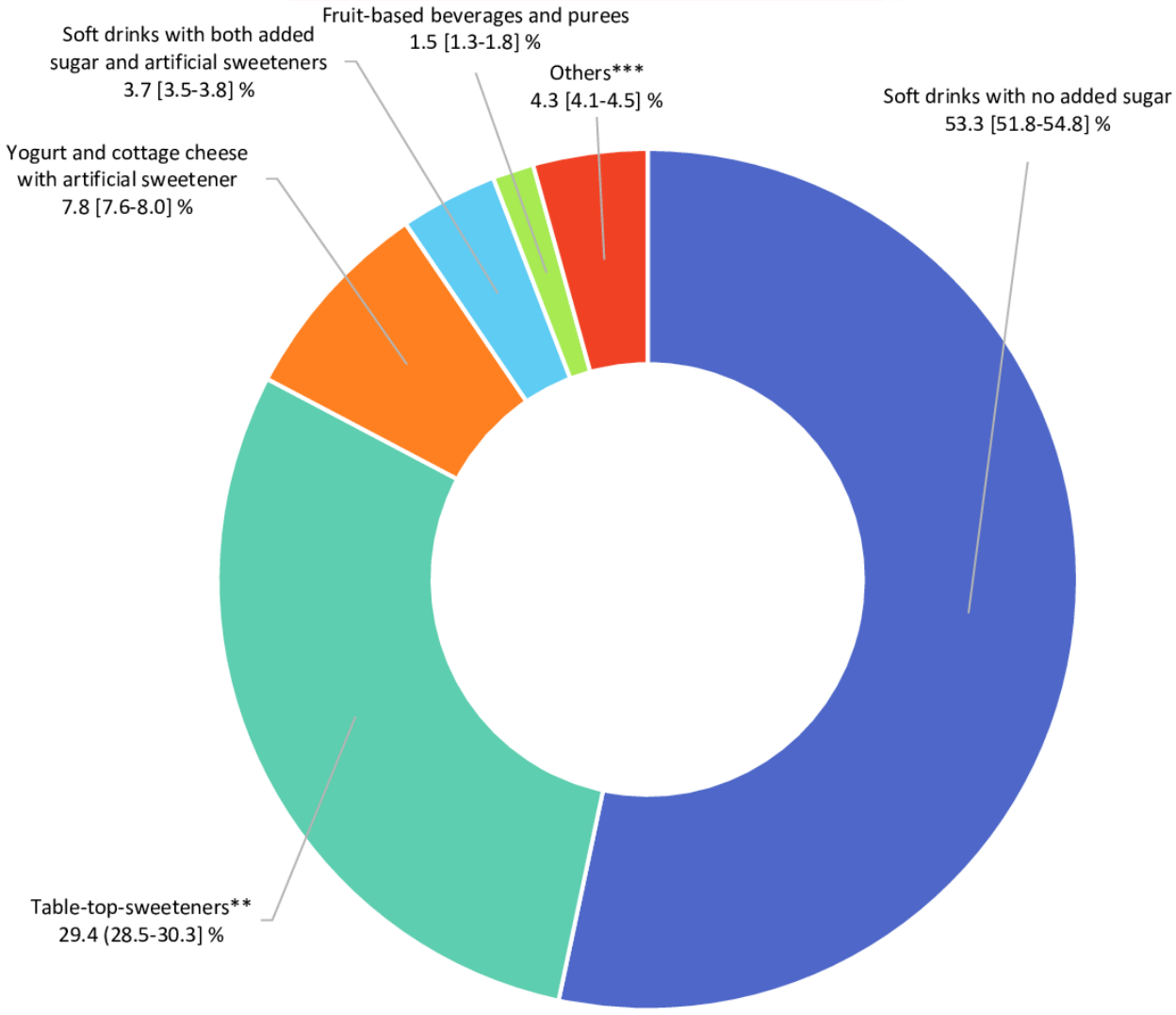


Image from: Debras et al., PLoS Med. 2022 Mar 24;19(3):e1003950

Determination of Cancer Cases

- Annual health questionnaire:
    - all meds and treatments, major health events, check up Q every 6 months.
    - Or anytime on the portal, if they wished to report a new update.
- Validation of cancer incidence
    - Follow up with physician – medical report, including pathology reports.
    - Some unclear cases, follow up confirmation with the participant's physician.
- Data are also linked with medical administrative databases of the national health insurance system database and national mortality registry. Limiting biases with unreported cases.
- 90% of the cases had corresponding medical information (95% of this was validated and included).
- All first primary cancers diagnosed (ICD-10) were considered cases.
- Obesity related cancer (cancer where obesity is involved in their etiology as one of the risk or protective factors);
    - colorectal, stomach, liver, mouth, pharynx, larynx, oesophageal, breast (with opposite associations pre- and postmenopause), ovarian, endometrial, and prostate cancers.

Results

- 3,358 incident cancer cases were diagnosed
    - 59.5 ± 12.2 years
- AS intake was positively associated with the risk of overall cancer:
    - Hazard Ratio (HR) for higher consumers versus non-consumers = 1.13 [95% CI 1.03 to 1.25]
    - **Meaning: higher intake is associated with a 13% increased risk of cancer, compared to non-consumers**
- Increased risks were observed for:
    - Aspartame & breast cancer - 22% increased risk
        - HR = 1.22 [95% CI 1.01 to 1.48]
    - Total artificial sweeteners & obesity-related cancers - 13% increased risk
        - HR = 1.13 [95% CI 1.00 to 1.28]
    - Aspartame & obesity-related cancers - 15% increased risk
        - HR = 1.15 [95% CI 1.01 to 1.32]
- No association was found with prostate cancer.
- No interaction was detected for any cancer outcome between artificial sweetener exposures and BMI, nor between the 3 main artificial sweeteners.
- Using a 6-category composite variable, combining artificial sweetener and sugar intakes, it was seen that increased cancer risk was associated with both artificial sweetener and sugar intakes.

For all cancers:

Exposure (mg/day)	Measure	Non-consumers	Lower consumers[2]	Higher consumers[2]	*P*-trend
Total artificial sweeteners	Participants/incident cases	64,892/2,013	18,986/744	18,987/601	
	HR (95% CI)—minimally adjusted[3]	1	1.26 (1.16 to 1.37)	1.19 (1.08 to 1.30)	<0.001
	HR (95% CI)—fully adjusted[4]	1	1.14 (1.05 to 1.25)	1.13 (1.03 to 1.25)	0.002
Aspartame	Participants/incident cases	74,169/2,309	14,345/572	14,351/477	
	HR (95% CI)—minimally adjusted	1	1.21 (1.11 to 1.33)	1.18 (1.07 to 1.31)	<0.001
	HR (95% CI)—fully adjusted	1	1.12 (1.02 to 1.23)	1.15 (1.03 to 1.28)	0.002
Acesulfame-K	Participants/incident cases	67,662/2,096	17,601/766	17,602/496	
	HR (95% CI)—minimally adjusted	1	1.22 (1.12 to 1.33)	1.19 (1.07 to 1.33)	<0.001
	HR (95% CI)—fully adjusted	1	1.12 (1.03 to 1.22)	1.13 (1.01 to 1.26)	0.007
Sucralose	Participants/incident cases	88,867/2,883	7,005/288	6,993/187	
	HR (95% CI)—minimally adjusted	1	1.20 (1.06 to 1.35)	1.00 (0.86 to 1.17)	0.177
	HR (95% CI)—fully adjusted	1	1.03 (0.91 to 1.17)	0.96 (0.82 to 1.12)	0.823

Table adapted from: Debras et al., PLoS Med. 2022 Mar 24;19(3):e1003950

Statistical Analysis

For those of you who want to get into the nerdy details of the stats…

- Associations with intake and cancer risk – Cox proportional hazard models, with age modeled as the time scale.
- Cancer types – breast, prostate (most prev in FR and this study cohort) and obesity related.
- 5,500, excluded at baseline for prevalent cancer
- The proportional hazards assumption of the Cox model was confirmed with the rescaled Schoenfeld-type residuals method.
- Missing values for any covariates were handled using the multiple imputation by chained equations (MICE) method (15 imputed data- sets).
    - Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls

Multiple imputation is a general approach to the problem of missing data.

- It aims to allow for the uncertainty about the missing data by creating several different plausible imputed data sets and appropriately combining results obtained from each of them.
- Multiple imputation has potential to improve the validity of medical research.
- However, the validity of results from multiple imputation depends on such modeling being done carefully and appropriately.

Adjustments

1. Sociodemographic characteristics (age, sex [except for breast and prostate cancer analyses], educational level)
2. Lifestyle characteristics (physical activity, smoking)
3. Anthropometric characteristics (BMI, height, percentage weight gain during follow-up),
4. Personal and family medical history
5. Number of 24-hour dietary records
6. Baseline intakes of energy and food groups/key nutrients for which a direct or indirect role in cancer etiology has been strongly suggested:
    a. Alcohol, sodium, saturated fatty acids, fiber, total sugar, fruit and vegetables, whole-grain foods, and dairy products

Our Conclusions

1. Better designed study than other epidemiological studies in this area.
2. Adds to the data available for EFSA to make a re-evaluation on sweeteners, but as a single study still does not confirm cause/effect.
3. Other attributes of the population present the possibility that other factors may also be the driver of these results:
    a. This needs to be extrapolated beyond a national cohort
    b. The prevalence of consumption in this cohort differs largely with the national consumption rates (highlighting the typical health research participant profile – i.e. healthy, middle-aged, white, females)
4. There's a lot of heterogeneity across the 3 AS groups:
    a. Consumers were more likely to be women, smokers, younger, diabetic, more likely to take oral contraception, and a number of dietary differences (more dairy, more UP foods), had lost weight in first 2 years of FU, vs non-consumers.
    b. Even with adjustments (and many adjustments in the models were applied), many of the associations remained in the adjusted model but this doesn't mean that every potential factor has been adjusted for (e.g. no information on environmental or occupational exposures, etc.)
5. Measurement error in explanatory variables and unmeasured confounders can cause considerable problems.
    a. When the confounders are uncorrelated, bias in the exposure effect estimate increases as the amount of residual and unmeasured confounding increases.
    b. Patterns are more complex for correlated confounders.
    c. With plausible assumptions, effect sizes of the magnitude frequently reported in observational epidemiologic studies can be generated by residual and/or unmeasured confounding alone.
    d. For more, see: The Impact of Residual and Unmeasured Confounding in Epidemiologic Studies: A Simulation Study
6. Pragmatically, we must ask "how big is the difference in risk?"
    a. Consider that, in the people studied, about two-thirds said they did not consume any artificial sweeteners at all.
    b. Out of every thousand participants who said they consumed no sweeteners, about 31 (3.09%) had a new cancer diagnosis during the follow-up period of about 8 years (on average).
    c. If we adjusted for all factors (i.e. took people with the same characteristics as the 1,000 people mentioned above) but with one exception; rather than not

consuming sweeteners at all, they were instead AS consumers, how many would get a cancer diagnosis in that group of 1,000? Approx. 32-33 (less the adjustment-margin of error?)

i. Difference isn't negligible, but it's not very large.

7. There was a low rate of cancer incidence, but this is likely due to the age of the participants in this cohort.
8. Dose-response relationship was not strong.
    a. For a lot of the findings, risk of cancer was higher in the lower AS consumer group than the higher consumer group, despite higher consumers reporting 10 times the total AS consumption than lower consumers.

Implications for Practice

1. While this is a well-done PCS, that is a welcome addition to the literature base using human outcome data, it shouldn't be used in isolation to make strong conclusions or decisions on individuals' diets.
2. Causation cannot be determined for this study, and the limitations (which all studies have) mean that it needs to be followed up by further research.
3. To make decisions about our diet, in this case whether artificial sweeteners are safe or not, we need to look at the overall evidence base.
4. Based on the human evidence to date, in line with the current position of virtually all public health agencies and organizations, it seems that consuming artificial sweeteners in the amounts typical in the population diet does not pose a health concern with respect to increasing cancer risk.
5. Therefore, it is highly likely that consuming artificial sweeteners, within currently suggested limits, is safe for humans.
6. At this time, it is ***not*** evidence-based to recommend that people avoid artificial sweeteners on account of cancer risk.