

ASPARTAME, METHYLEUGENOL, AND ISOEUGENOL

VOLUME 134



This publication represents the views and expert opinions of an IARC Working Group on the Identification of Carcinogenic Hazards to Humans, which met in Lyon, France, 6–13 June 2023

LYON, FRANCE - 2024

IARC MONOGRAPHS
ON THE IDENTIFICATION
OF CARCINOGENIC HAZARDS
TO HUMANS

Advance publication, 29 April 2024

International Agency for Research on Cancer



Table S1.2 Exposure assessment review and critique for epidemiological studies on cancer in humans exposed to aspartame

Reference and outcome	What was the study design?	What methods were used for the exposure assessment? (incl. data source, environmental and biological measurements, etc.)	What was the exposure context? Specify period over which exposure data were gathered, and how historical exposures were accounted for (if relevant)	Was estimate of exposure qualitative, semiquantitative, or quantitative?	Which exposure sources were assessed?	What exposure metrics were derived for use in analyses (e.g. average exposure, exposure duration, cumulative exposure, etc.)? (specify units)	What was the timing of exposure relative to the outcome?	Which other potential carcinogens, confounders, or effect modifiers were assessed?	Was there potential for differential exposure misclassification? Was there potential for non-differential exposure misclassification? (Likely/unlikely)
Andreatta et al. (2008) Urinary tract tumours	Case-control	Interview by a nutritionist Habitual use of AS in the past 5 yr: ever consumption (yes/no), brand name, duration of consumption Classification of participants in 3 categories: non-AS consumers, AS short-term consumers (1–9 years), and AS long-term consumers (10 or more years)	What: artificial sweeteners (two subgroups: saccharine/cyclamate and aspartame/acesulfame-K used for description but not for analyses) Where: Argentina When: 1999 to 2006 Context: 14% of the population regularly use AS to sweeten drinks and foods, saccharin and cyclamate are the most frequently consumed, aspartame and acesulfame-K used by a smaller percentage	Qualitative (ever use) Quantitative (duration of use)	Use of AS in infusions (tea, coffee, mate) No data on other sources (soft drinks, dietetic foods)	Ever use and duration of use (years)	Usual diet assessed for the 5 yr before diagnosis or hospitalization	Potential co-exposure measured and considered in analyses: smoking, BMI, tobacco use, mate/infusion drinking ("hot beverage")	Differential likely: case-control study; retrospective assessment of AS consumption Non-differential likely: memory bias; only one source of AS considered; no specific assessment of aspartame
Bao et al. (2008) Pancreatic cancer	Cohort (NIH-AARP Diet and Health Study)	Self-administered baseline FFQ (124 items, past 12 months) validated against two 24-hour recalls Consumption of 3 types of soft drinks assessed through 10 frequencies ("never" to "6+ times per day"), 3 portion size ranges and the frequency of sugar-free (diet) or regular-calorie version of these beverages (usually, or more than half the time)	What: diet soft drinks When: diet data collected in 1995–1996, follow-up until 2003 Where: USA Context: *limited history of use of aspartame before study baseline: aspartame use started in 1981 for dry foods (incl. tabletop sweetener), in 1983 for carbonated beverages, in 1993 for other beverages, baked goods, and confections, and in 1996 for all foods and beverages *soft drinks > 70% of aspartame sales in the USA in early 2000s *aspartame as main artificial sweetener in beverages in the 1980s and 1990s (before 1983: only saccharin, after 1983: mainly aspartame in soft drinks, 1998–2002: acesulfame-K, sucralose and neotame approved)	Quantitative	3 potentially aspartame-containing beverages: sugar-free or "diet" version of soda, fruit drinks, and iced tea No data on other potential sources: "diet" version of foods, such as yogurt, gelatin/pudding, ice cream and frozen desserts, and hot chocolate (50 mg or more aspartame per serving in the early 2000s)	Average daily consumption Quintiles or never drinkers and quintiles in drinkers	Usual diet assessed in 1995–1996, follow-up until 2003	Potential co-exposure measured and considered in analyses: BMI, alcohol, smoking, physical activity, energy-adjusted intakes of total fat, saturated fat, red meat and folate, multivitamins, regular soft drinks, diabetes	Differential unlikely: cohort study; diet soft drink consumption assessed before cancer diagnosis Non-differential likely: only one potential source of aspartame considered (diet soft drinks), uncertainty regarding the content of the beverages in aspartame
Bassett et al. (2020) Cancers not related to obesity	Prospective cohort study (Melbourne Collaborative Cohort Study)	Self-administered 121-item FFQ with separate questions on frequency of consumption in the past year of diet (artificially sweetened) soft drinks	What: Artificially sweetened soft drink Where: Australia When: Baseline data collected 1990–1994	Semiquantitative	Artificially sweetened soft drink	Frequency of consumption (Never or < 1/month, 1–3/month, 1–6/week, 1/day, > 1/day)	Baseline data collected 1990–1994 on consumption in previous 12 months with follow-up to 2015	Other co-exposures: Mediterranean diet score, BMI, Waist, smoking, leisure time physical activity, alcoholic beverages	Differential unlikely: cohort study with assessment before diagnosis Non-differential likely: only ASB as a proxy measure
Bosetti et al. (2009) Stomach, pancreatic and endometrial cancers	Case-control	Reproducible and valid FFQ (78 items, past 2 yr before diagnosis or hospital admission) Weekly consumption of sachets or tablets of saccharin and other sweeteners	What: sweeteners (saccharin and 'other sweeteners', described as "mainly aspartame" by the authors) Where: Italy When: 1997–2007 (stomach), 1991–2007 (pancreas), 1992–2006 (endometrium) Context: recent introduction of diet soft drinks and low frequency of consumption in middle age and elderly in this population (unlikely to have a major contribution to cancer development)	Qualitative (low-calorie sweeteners, saccharin and other sweeteners) Semiquantitative (low-calorie sweeteners)	-sachets or tablets of sweeteners Other sources of sweeteners (ASB) not considered but not widespread at the time of the study	Average daily consumption in sachets or tablets/day Ever users/non-users of low-calorie sweeteners, saccharin and other sweeteners; > 2 vs 0 sachets or tablets per day of low-calorie sweeteners	Usual diet assessed for the 2 yr before diagnosis (cases) or hospital admission (controls)	Potential co-exposure measured and considered in analyses: BMI, smoking, alcohol, diabetes, hot beverages (incl. coffee, decaffeinated coffee, tea)	Differential likely: case-control study; retrospective assessment of sweeteners consumption Non-differential likely: memory bias; only one source of aspartame considered; no specific assessment of aspartame ('other sweeteners' although mainly aspartame)

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Cabaniols et al. (2011) Brain cancer	Case-control study	Self-administered questionnaire on gender, date of birth, socioeconomic and marital status, stress, hobbies, diet and place of residence; question on aspartame consumption frequency for the past 5 yr. Person-to-person interview for medical questionnaire and missing data from self-administered questionnaire	What: Aspartame consumption frequency Where: France When: Data collected 2005	Semiquantitative	Aspartame	Non-consumers (< 1 per week) and regular consumers (\geq 1 per week)	Previous 5 yr before diagnosis	Other co-exposures: BMI, other dietary habits (vegetables, fruit); Two daily meals; skipping meals; vitamin supplement; physical activity, smoking, alcohol, cannabis	Differential likely: case-control study; retrospective assessment Non-differential likely: only frequency collected, measurement validity of questions unclear
Chan et al. (2009) Pancreatic cancer	Population-based case-control study	131-item food validated questionnaire via in-person interviews, previous 1 months	What: total sugar-free carbonated beverages/day Where: California, USA When: data collected 1995 and 1999	Semiquantitative	Total sugar-free carbonated beverages/day (low-calorie colas, low-calorie caffeine-free colas, and other low-calorie carbonated beverages such as Diet 7-up, Fresca, diet ginger ale, etc.) By type of carbonated beverage: < 1/month, 1–3/month, 1–6/week, \geq 1/day	Total sugar-free carbonated beverages/day (0, < 1, \geq 1) By type of carbonated beverage: < 1/month, 1–3/month, 1–6/week, \geq 1/day	Previous 12 months before diagnosis	Other co-exposures: BMI, cigarette smoking, physical activity, other food groups (red meat, white meat, dairy, vegetable and fruit, eggs, fish, whole grain, and refined grain), history of diabetes, sugar-sweetened beverages and sweets	Differential likely: case-control study; retrospective assessment Non-differential likely: only ASB as a proxy measure
Chazelas et al. (2019) All cancers combined, breast, colorectal, prostate	Prospective cohort study (Nutrinet-Santé cohort)	Participants are asked every 6 months to complete a series of 3 validated web-based 24 h dietary records randomly assigned over a two-week period (2 weekdays, 1 weekend day) At least 2 24-hour dietary records during the first 2 yr of follow-up considered in analyses (mean \pm SD, 5.6 \pm 3.0)	What: Artificially sweetened soft drink Where: France When: Data collected from 2009–2017, follow-up to Jan 2018, median follow-up time 5.1 yr	Quantitative	12 ASB items all beverages containing non-nutritive sweeteners, such as diet soft drinks, sugar-free syrups, and diet milk-based beverages	ASBs (mL/d); sex-specific cut-offs for quartiles of artificially sweetened beverages intake were 2.7, 4.7, and 7.9 mL/d in men and 4.6, 7.7, and 11.6 mL/d in women	Data collected from 2009–2017, follow-up to Jan 2018, median follow-up time, 5.1 yr	Other co-exposures: sugar intake from other dietary sources (all sources except sugary drinks), alcohol, sodium, fat and fruit and vegetable intakes, BMI, physical activity, smoking status	Differential unlikely: cohort study with assessment before diagnosis Non-differential likely: only ASB as a proxy measure
Davis et al. (2023) Pancreatic cancer and mortality	Case-control	46-item FFQ regarding general dietary habits (incl. daily consumption of ASB) in the few years before diagnosis	What: ASB When: retrospective assessment of diet before diagnosis between 1982 and 1998 Where: USA (Buffalo, NY) Hospital-based	Semiquantitative	Diet cola	3 categories: never, occasional (< 1 drink/day), and habitual (1+ drinks/day) consumers	Retrospective assessment of exposure in the few years before diagnosis between 1982 and 1998	Potential co-exposure measured and considered in analyses: smoking status, BMI, vegetable intake, processed meat intake, family history of pancreatic cancer, radiation status	Differential likely: retrospective assessment; case-control study Non-differential likely: no details on aspartame; only ASB (diet cola) consumption as potential source
Debras et al. (2022) All cancers combined, breast, prostate, all obesity-related cancers combined (colorectal, stomach, liver, mouth, pharynx, larynx, oesophageal, breast, ovarian, endometrial, prostate)	Prospective cohort study (Nutrinet-Santé cohort)	Participants are asked every 6 months to complete a series of 3 validated web-based 24 h dietary records randomly assigned over a 2-wk period (2 weekdays, 1 weekend day) At least 2 24-hour dietary records during the first 2 yr of follow-up considered in analyses (mean (SD) of 5.6 (3.0)) Sensitivity analyses conducted using all 24 h dietary records available during follow-up	What: aspartame When: baseline data collected 2009–2021, median follow-up time = 7.8 yr. Context: date of consumption of each food or beverage declared by each participant was used to match the product to the closest composition data, thus accounting for potential reformulations.	Quantitative	Aspartame	Aspartame mg/day	Baseline dietary intakes were evaluated by averaging all 24-hour dietary records provided during the first 2 yr of follow-up. Sensitivity analysis with time-dependent aspartame exposure	Other co-exposures: physical activity, smoking, BMI; alcohol, other dietary exposures (sodium, saturated fatty acids, fibre, sugar, fruit and vegetables, whole-grain foods, and dairy products)	Differential unlikely: cohort study with assessment before diagnosis Non-differential unlikely: measurement of aspartame with food composition data adjusted with changes over time

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Ewertz and Gill (1990) Breast	Case-control study	Self-administered, semiquantitative food frequency questionnaire with additional questions on consumption of tea, coffee, sugar, and artificial sweeteners	What: usage of Sweeteners in coffee and tea Where: Denmark. When: 1 March 1983 to 29 February 1984	Qualitative	Usage of sweeteners in coffee and tea	Usage of sweeteners in coffee and tea (yes/no)	Previous 12 months before diagnosis		Differential likely: case-control study; retrospective assessment Non-differential likely: only sweeteners in tea and coffee as a proxy measure
Fulgoni and Drewnowski (2022) Cancer mortality	Cohort (NHANES)	One or two 24 h recalls by a trained interviewer Identification of products containing low-calorie sweeteners (no separation by brand name: e.g. Aspartame, sucralose, saccharin) Less than 2% ($n = 165$) of food items were classified as containing low-calorie sweeteners In NHANES 1988–1994: specific questions regarding aspartame or saccharin (sodas, added sweeteners, etc.)	What: low-calorie sweeteners When: cross-sectional surveillance studies in 1988–1994 and 1999–2018 Where: USA Context: low-calorie sweeteners consumed by 41.4% of US adults in NHANES cycles 2009–2012	Quantitative	Diet beverages, including diet sodas and other diet beverages (fruit-based and other), tabletop sweeteners, and low-calorie sugar-free foods such as yogurts, ice cream, grain-based desserts, and candies	Non-consumers and tertiles of gram weight of low-calorie sweetener beverages and foods in consumers Tertiles of aspartame only in NHANES 1988–1994; tertiles of low-calorie sweetener products in NHANES 1988–1994, 1999–2018, and 1988–2018	Aspartame exposure assessed in 1988–1994; low-calorie sweetener assessed in 1988–1994 or 1999–2018 Follow-up until 2019	Potential co-exposure measured and considered in analyses: current smoking status, alcohol consumption, physical activity, BMI	Differential unlikely: prospective design Non-differential likely: only one or maximum 2 dietary recalls; no specific assessment of aspartame in cycles 1999–2018
Gallus et al. (2007) Cancers of the oral cavity and pharynx, oesophagus, colon, rectum, larynx, breast, ovary, prostate, kidney	Case-control	Reproducible and valid FFQ (78 items, past 2 yr before diagnosis or hospital admission) Weekly consumption of sachets or tablets of saccharin and other sweeteners	What: sweeteners (saccharin and others including mainly aspartame) Where: Italy When: 1991 to 2004 Context: recent introduction of diet soft drinks and low frequency of consumption in middle age and elderly in this population (unlikely to have a major contribution to cancer development)	Qualitative (low-calorie sweeteners, saccharin and other sweeteners) Semiquantitative (low-calorie sweeteners)	Sachets or tablets of sweeteners No data on other sources (soft drinks, dietetic foods)	Average daily consumption in sachets or tablets/day Ever users/non-users of low-calorie sweeteners, saccharin and other sweeteners; > 2 vs 0 sachets or tablets per day of low-calorie sweeteners	Usual diet assessed for the 2 yr before diagnosis (cases) or hospital admission (controls)	Potential co-exposure measured and considered in analyses: alcohol, tobacco smoking, BMI, hot beverages, sugar	Differential likely: case-control study; retrospective assessment of sweeteners consumption Non-differential likely: memory bias; only one source of sweeteners considered; no specific assessment of aspartame ('other sweeteners' although mainly aspartame)
Gurney et al. (1997) Childhood brain tumours	Case-control	In-person interview of biological mothers on: Children's consumption of aspartame before the date of diagnosis (cases) or comparable reference date (controls) Mother's consumption of aspartame during pregnancy and breastfeeding	What: aspartame When: cases and controls born in 1981 or later; cases diagnosed with a primary brain tumour between 1984 and 1991 Where: USA Exposure assessed from the introduction of aspartame on the US market, but contains 3 yr in which aspartame was not used in beverages (1981–1984)	Semiquantitative	Any food, chewing gum, or diet drink containing aspartame; Nutrasweet	Children: age at first consumption, time period of consumption, frequency of consumption Mothers: trimesters of consumption, time period of consumption, frequency of consumption during pregnancy or while breastfeeding	Exposure to aspartame before cancer diagnosis (between 1984 and 1991) of children born or in utero in 1981 and later	Potential co-exposure measured and considered in analyses: maternal vitamin use, cured meat consumption, passive smoke exposure, X-ray exposure	Differential likely: case-control study; retrospective assessment: memory bias for the assessment of aspartame consumption (children and mother during their pregnancy) several years in the past Non-differential likely: only frequency and period of consumption (no dose); unclear and unspecific sources of aspartame; mothers assess children's consumption
Heath et al. (2021) Renal cell carcinoma incidence and mortality	Cohort (EPIC)	Usual diet over the previous 12 months Country-specific instruments developed and validated within the various source populations and including hundreds of	What: artificially sweetened soft drinks When: ASB assessed at inclusion between 1992 and 2000 Where: western European countries (Denmark, France, Germany, Italy, Netherlands, Spain, Sweden, United	Quantitative	Carbonated/ soft/ isotonic drinks, and diluted syrups: "low-calorie or diet fizzy soft drinks", "fizzy soft drinks, e.g. cola, lemonade", and "fruit squash or cordial"	Mean daily intakes over the past 12 months Risk estimates per 100 g/day -mean follow-up of 15 yr for incidence of	Diet questionnaires covering the past year between 1991 and 2000 -mean follow-up of 15 yr for incidence of	Potential co-exposure measured and considered in analyses: smoking, alcohol, physical activity, juice intake, total soft drink, BMI, fruit and vegetable intake,	Differential unlikely: cohort study; exposure assessed before cancer diagnosis Non-differential likely: no details on aspartame; only ASB as potential sources of

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Hodge et al. (2018) Obesity-related cancers	Prospective cohort study (Melbourne Collaborative cohort)	country- and region-specific foods. These extensive self-administered quantitative dietary questionnaires collected usual portions and frequency of consumption of up to 260 food items food and drinks during different seasons of the year. Soft drink consumption: number of glasses (typical glass sizes in each centre, \approx 250 mL) per month, week, or day	Kingdom); data on artificially sweetened soft drinks not available in Spain, Italy (Florence, Turin, Ragusa, Varese) and Sweden (Umea) -context: multiple European countries and associated context of consumption, no information on historical exposure	Total soft drinks: sugar-sweetened/artificially sweetened	renal cell carcinoma and 16 yr for mortality	diabetes, sugar-sweetened soft drinks	aspartame; uncertainty regarding the content of the beverages in aspartame; diet only assessed at baseline in a context of low consumption of AS soft drinks; potential variations of the content of AS soft drinks in aspartame; measurement errors		
Hur et al. (2021) Early-onset colorectal cancer	Cohort (NHSII)	Self-administered 121-item FFQ with separate questions on frequency of consumption in the past year of diet (artificially sweetened) soft drinks	What: artificially sweetened soft drink Where: Australia When: Baseline data collected 1990–1994	Semiquantitative	Artificially sweetened soft drink	Frequency of consumption (Never or < 1/month, 1–3/month, 1–6/week, 1/day, > 1/day)	Baseline data collected 1990–1994 on consumption in previous 12 months with follow-up to 2015	Other co-exposures: Mediterranean diet score, BMI, waist circumference, smoking, leisure time physical activity, alcoholic beverages	Differential unlikely: cohort study with assessment before diagnosis Non-differential likely: only ASB as a proxy measure
Inoue-Choi et al. (2013) Endometrial cancer	Cohort (Iowa Women's Health Study (IWHS))	Validated, semiquantitative FFQ (130 items, past 12 months) every 4 yr since 1991 Dietary intake in adolescence assessed in 1998 through a high-school (HS)-FFQ (124 items typically consumed between 1960 and 1982)	What: artificially sweetened beverages When: adult diet assessed every 4 yr since 1991; adolescent diet (between 1960 and 1982) assessed in 1998 Where: USA Context: no aspartame in soft drinks before 1983	Semiquantitative	Low-calorie carbonated beverages	Cumulative average of beverage intake collected across all available FFQs from the study baseline up to each questionnaire cycle ASBs categorized as < 1 serving/week, 1 serving/week to < 1 serving/day, 1 to < 2 servings/day, \geq 2 servings/day + per each serving/day; one standard serving size in adults: 12 ounces (oz), in adolescence: 8 oz	FFQ in 1991 and then every 4 yr, follow-up until 2015	Potential co-exposure measured and considered in analyses (adulthood and adolescence): BMI, menopausal hormone, smoking, physical activity, aspirin or NSAIDS, multivitamins, alcohol, red and processed meat, dietary fibre, total folate and total calcium, diet quality (AHEI-2010), sugar-sweetened beverages, diabetes (low proportion) Reduction in milk consumption concomitant to an increase in soft drink consumption	Differential unlikely: cohort study; exposure assessed before cancer diagnosis Non-differential likely: no details on aspartame; only ASB as potential sources of aspartame; uncertainty regarding the content of the beverages in aspartame; potential variations of the content of AS soft drinks in aspartame; measurement errors

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Joh et al. (2021) Colorectal cancer precursors (polyp, adenoma)	Cohort (NHSII)	Adolescent diet assessed in 1998 using a self-administered HS-FFQ (124-item, food items commonly consumed between 1960 and 1982 when participants were in high school (13–18 yr old)) Adult diet assessed every 4 yr since 1991 using a validated FFQ (131 items) Standard serving sizes: 1 glass, a bottle, or a can (12 ounces)	What: ASB When: adolescence between 1960 and 1982 Where: USA Context: no aspartame in soft drinks before 1983	Semiquantitative	Carbonated and non-carbonated low-calorie or diet beverages	Estimates for adolescent ASB intake per 1 serving/d increase and from 4 categories: < 1 serving/week, 1–6 servings/week, 1 serving/day, and ≥ 2 servings/day Adult diet: cumulative updated intake (average of the repeated measures from all available FFQs up to 2 yr before the most recent endoscopy)	Adolescence intake between 1960 and 1982, follow-up between 1998 and 2015	Potential co-exposure measured and considered in analyses: menopausal hormone, aspirin, diabetes, BMI, smoking, alcohol, physical activity, adolescent and adult dietary intakes of total calcium, vitamin D, total folate, total fibre, fruits, vegetables, and dairy, adult intake of total red meat, western dietary pattern score during adolescence, adult intake of ASB, IBD	Differential unlikely: cohort study; exposure assessed before diagnosis Non-differential likely: recall bias from adult recall of adolescent diet; no details on aspartame; only ASB as potential sources of aspartame; ASB in the time period of adolescence likely contained no aspartame; measurement errors; recalled adolescent diet only weakly correlated with adult diet
Jones et al. (2022) Liver and biliary duct cancer	Pooled analysis of 2 cohort studies: NIH-AARP Diet and Health Study, and Prostate Lung, Colorectal and Ovarian cancer screening trial (PLCO)	NIH-AARP: FFQ at baseline in 1995–1996 PLCO: diet history questionnaire (DHQ) in 1998 Frequency of consumption of ASB (from no consumption to 6+ times per day) No information on the volume consumed	What: ASB When: diet assessed in 1995–1996 (NIH-AARP) and 1998 (PLCO) Where: USA	Quantitative	Soda, fruit punches	Mean daily frequency, estimates for an increase of one consumption frequency per day	Diet assessed in 1995–1996 (NIH-AARP) or 1998 (PLCO), follow-up until 2011 (NIH-AARP) or 2017 (PLCO)	Potential co-exposure measured and considered in analyses: BMI, smoking, alcohol, diabetes	Differential unlikely: cohort study; exposure assessed before cancer diagnosis Non-differential likely: no details on aspartame; only ASB as potential sources of aspartame; uncertainty regarding the content of the beverages in aspartame; potential variations of the content of ASB in aspartame over time; only one dietary assessment at baseline; possible variations of ASB consumption over time; measurement errors
Kobeissi et al. (2013) Urinary bladder cancer	Case-control	-face to-face interview questionnaires “artificial sweetener consumption”	What: artificial sweeteners When: between 2002 and 2008 Where: Lebanon	Qualitative	Artificial sweeteners	Frequency of artificial sweetener intake: never, rarely, frequently, always	Before diagnosis	Potential co-exposure measured and considered in analyses: smoking, UTD (infections and stones), hair dyes, occupational chemical exposure, passive smoking	Differential likely: retrospective assessment; not possible to mask the interviewers on the subject's status Non-differential likely: no details on aspartame; unclear source “artificial sweeteners”; only broad frequency of use; measurement errors
Larsson et al. (2016) Cancers of the biliary tract and the gallbladder	Cohort (Swedish Mammography Cohort (SMC) and Cohort of Swedish Men (COSM))	Self-administered semiquantitative FFQ (96 items, past year) Usual consumption of a standard glass (200 mL) of sweetened beverages No distinction between sugar-sweetened and artificially sweetened (low-calorie) beverages	What: sweetened beverages When: FFQ in 1997 Where: Sweden Context: low-calorie soft drinks and “juice” drinks accounted for 9.9% (men) to 19.2% (women) of total soft drink and “juice” drink consumption in 1997 (Swedish national consumption data)	Semiquantitative	Sweetened beverage (not including fruit juices, energy and sports drinks, or sweetened coffee, tea, or milk) without distinction between sugar-sweetened and artificially sweetened beverages	Mean daily intake Non-consumers and quartiles of consumption among consumers (0.1–0.4, 0.5–1.9, and 2 servings/day); per 1 serving per day	FFQ in 1997, follow-up until 2012 (mean follow-up of 13.4 yr)	Potential co-exposure measured and considered in analyses: smoking, BMI, protein, total fat, carbohydrates, fruit juice, coffee, tea, and milk, alcohol, physical activity, diabetes	Differential unlikely: cohort study; exposure assessed before cancer diagnosis Non-differential likely: no distinction between sugar-sweetened and artificially sweetened beverages; no details on aspartame; only sugar-sweetened beverage as potential sources of aspartame; uncertainty regarding the content of the beverages in aspartame;

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Lim et al. (2006) Haematopoietic cancers and gliomas	Prospective Cohort (NIH-AARP Diet and Health Study)	Self-administered baseline FFQ (124 items, past 12 months) validated against two 24-hour recalls Consumption of 3 types of soft drinks assessed through 10 frequencies ("never" to "6+ times per day"), 3 portion size ranges and the frequency of sugar-free (diet) or regular-calorie version of these beverages (usually, or more than half the time) Tabletop packet of aspartame added to cups of coffee and hot tea *soft drinks > 70% of aspartame sales in the USA in early 2000s *aspartame as main artificial sweetener in beverages in the 1980s and 1990s (before 1983: only saccharin, after 1983: mainly aspartame in soft drinks, 1998–2002: acesulfame-K, sucralose and neotame approved)	What: aspartame When: diet data collected in 1995–1996, follow-up until 2000 Where: USA Context: *limited history of use of aspartame before study baseline: aspartame use started in 1981 for dry foods (incl. tabletop sweetener), in 1983 for carbonated beverages, in 1993 for other beverages, baked goods, and confections, and in 1996 for all foods and beverages *soft drinks > 70% of aspartame sales in the USA in early 2000s *aspartame as main artificial sweetener in beverages in the 1980s and 1990s (before 1983: only saccharin, after 1983: mainly aspartame in soft drinks, 1998–2002: acesulfame-K, sucralose and neotame approved)	(Semi-) quantitative	3 potentially aspartame-containing beverages: sugar-free or "diet" version of soda, fruit drinks, and iced tea Tabletop aspartame-containing packets No data on other potential sources: "diet" version of foods, such as yogurt, gelatin/pudding, ice cream and frozen desserts, and hot chocolate (50 mg or more aspartame per serving in the early 2000s)	Average daily consumption of aspartame in mg/day derived from consumption frequency, portion size and aspartame content Values of aspartame content used (source: Nutrition Data System for Research) and literature search: *per 100 g of beverage: 50 mg for diet soda, 14.95 mg for diet fruit drink, 25.55 mg for diet iced tea *per tabletop packet: 35 mg Categories of aspartame intake used in analyses: none, > 0 to < 100, ≥ 100 to < 200, ≥ 200 to < 400, ≥ 400 to < 600, ≥ 600 mg/day	Aspartame exposure assessed in 1995–1996 for the past 12 months, follow-up until 2000	Potential co-exposure measured and considered in analyses: BMI, diabetes, alcohol, smoking, physical activity, caffeine	Differential unlikely: prospective cohort study; aspartame exposure assessed before cancer diagnosis Non-differential likely: uncertainty regarding actual aspartame exposure (actual content of aspartame in the considered sources, aspartame content in other not considered sources); diet only assessed at baseline; measurement errors: assessment of the frequency of consumption of soft drinks and then of the diet version of these soft drinks
Liu et al. (2022) Cancer mortality	Cohort (United Kingdom Biobank)	Validated web-based 24-hour dietary recall questionnaire (Oxford WebQ) At least 1 questionnaire completed out of 5 maximum occasions over 1 yr (seasonal variations) between April 2009 and June 2012 (mean completed 24-hour dietary recalls (SD), n 2.2 (1.2)) Number of drinks of coffee in the previous 24 hours, number of teaspoons of added sugar or artificial sweeteners (any brand) Standard portion size (e.g. mug or cup)	What: artificially sweetened coffee When: diet assessed between 2009 and 2012 Where: United Kingdom	Semiquantitative	Artificial sweeteners added in coffee	Classification as non-consumers, sole consumers (same kind of coffee over the dietary recalls: unsweetened, sugar-sweetened, artificially sweetened), overlapped consumers Average number of drinks across multiple dietary recalls; one drink ≈ 250 mL; 5 groups: ≥ 0 to 1.5 drinks/d, ≥ 1.5 to 2.5 drinks/d, ≥ 2.5 to 3.5 drinks/d, ≥ 3.5 to 4.5 drinks/d, and ≥ 4.5 drinks/day (averages of 1, 2, 3, 4, and 5 or more drinks/d, respectively)	Diet assessed in 2009–2012, follow-up until 2017–2018 (median of 7.0 yr)	Potential co-exposure measured and considered in analyses: smoking, physical activity, BMI, waist circumference, hypertension, diabetes, long-standing illness, cholesterol-lowering drug, blood pressure drug, vitamin and mineral supplements, dietary intake of, total sugar, fresh fruit, vegetables, red meat, processed meat, alcohol, milk, tea, SSBs, ASBs, environmental factors (particulate matter, nitrogen dioxide, average 24-hour sound level of noise pollution, proximity to a major road, green space percentage, distance to coast)	Differential unlikely: cohort study; prospective assessment of exposure Non-differential likely: no details on aspartame; only artificially sweetened coffee as potential sources of aspartame and no other sources; uncertainty whether the artificial sweeteners used contained aspartame; only one dietary assessment at baseline: possible variations of AS consumption over time; measurement errors
Mahfouz et al. (2014) Colorectal cancer	Case-control	FFQ Melbourne University? (8 items, 2 yr before cancer diagnosis)	What: soft drinks and artificial sweeteners When: between 2010 and 2011 Where: Egypt	Qualitative	Soft drinks, use of artificial sweeteners	Consumption of soft drinks (yes/no) Use of artificial sweeteners (yes/no)	2 yr before cancer diagnosis	Potential co-exposure measured and considered in analyses: red meat, preserved food, fast foods, smoking,	Differential likely: retrospective assessment; case-control study

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Malik et al. (2019) Cancer mortality	Cohort (NHS and HPFS)	Frequency of intake daily, weekly or monthly; number of servings Validated self-administered semiquantitative FFQ every 4 yr: since 1980 in the NHS and 1986 in the HPFS (61 items in 1980 to 131 and 166 items in subsequent questionnaire cycles)	What: artificially sweetened beverages When: diet assessed from 1980–1986 to 2010, follow-up until 2014 Where: USA Context: aspartame as primary artificial sweetener in ASBs	Semiquantitative	Caffeinated, caffeine-free, and non-carbonated low-calorie or diet beverages	Frequency of intake: < 1/mo, 1 to 4/mo, 2 to 6/wk, 1 to < 2/d, 2 to < 4/d, and ≥ 4/d Update of dietary intakes at the beginning of each FFQ cycle (main analysis) and cumulative average (secondary analysis; mean intake from all FFQs up to the beginning of a follow-up interval); no update after report of diabetes, stroke, CHD, or cancer Substitution of 1 serving/d of SSB with an equivalent amount of ASB	Diet assessed every 4 yr from 1980 or 1986 until 2014 Secondary analyses with an 8-yr lag (exposures evaluated in relation to outcomes 8 yr later)	Potential co-exposure measured and considered in analyses: smoking, hormone use, alcohol, physical activity, multivitamins, aspirin, hypertension or hypercholesterolemia, intakes of whole grains, fruit, vegetables, and red and processed meat, diet quality (AHEI score), BMI, SSB, diabetes, CVD, cancer	Non-differential likely: no details on aspartame; qualitative assessment of soft drink consumption and use of artificial sweeteners; measurement errors Differential unlikely: cohort study; prospective assessment of exposure Non-differential likely: no details on aspartame; only ASB as potential sources of aspartame; uncertainty regarding the content of the beverages in aspartame; potential variations of the content of ASB in aspartame over time; measurement errors
Mayne et al. (2006) Oesophageal and gastric cancers	Population-based case-control study	Interviewer administered, in-person structured questionnaire (30% proxy interviews for cases, 3% for controls)	What: diet soft drinks Where: Connecticut (USA) When: 1993–1995	Semiquantitative	Usual frequency of consumption of “diet soft drinks or soda” (per day, week, month, or year)	Diet soft drinks or soda, top 20% of consumers vs others	3–5 yr before diagnosis	BMI, beer, wine, and liquor, meat; smoking	Differential likely: case-control study; retrospective assessment Non-differential likely: only ASB as a proxy measure
McCullough et al. (2014) Lymphoid neoplasms	Cohort (CPS-II Nutrition Cohort)	Self-administered modified Willett FFQ (152 item) in 1999 and 2003 Artificially sweetened carbonated beverage consumption including subtypes (cola with caffeine, other carbonated beverages with or without caffeine): frequency categories ranging from “never” to “≥4 per day”, standard serving size (“1 glass, bottle, or can (355 mL)”) Question regarding the use of aspartame packets (Nutrasweet or Equal): frequency ranging from “never” to “≥6 per day”	What: aspartame When: diet assessed in 1999 and 2003 Where: USA Long-term soda consumption patterns examined from data collected in 1982 (CPS-II mortality cohort) but aspartame not calculated (not included in soft drinks at that time)	Quantitative	Artificially sweetened carbonated beverage and aspartame packets (main contributors) Other sources not considered	Mean exposure over the past year (in mg/day) assessed in 1999 and 2003 Estimates from 1999 used to predict risk for 1999–2003, mean of 1999 and 2003 used to predict risk for 2003–2009 Continuous intake (per 50 mg/d), non-consumption and gender-specific quartiles Values of aspartame assigned: *180 mg/355 mL for low-calorie cola with caffeine, 90 mg/355 mL for other low-calorie soda with caffeine, and 70 mg/355 mL for other low-calorie soda without caffeine	Diet assessed in 1999, updated in 2003 and follow-up until 2009	Potential co-exposure measured and considered in analyses: smoking, BMI, diabetes, sugar-sweetened beverages, weight, waist circumference, physical activity, sitting time, hormone replacement therapy, NSAID, cholesterol-lowering medication, alcohol, intake of beef, processed meat, animal protein, total milk, saturated fat, fruits, vegetables, and tea or coffee	Differential unlikely: cohort study; aspartame exposure assessed before cancer diagnosis Non-differential likely: uncertain sources of aspartame (values assigned to all beverages actually containing aspartame or not, aspartame being the most widely used sweetener in diet carbonated beverages in the USA); some sources of aspartame not considered (artificially sweetened non-carbonated beverages, yogurts, ice cream) but more minor compared to ASB and tabletop packets

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McCullough et al. (2022) Mortality from all cancers combined, obesity-related cancers combined, and 20 individual cancer types	Cohort (CPS-II)	Question regarding the usual number of cups, glasses, or drinks per day, and duration for “diet soda or diet iced teas” Previous intake inquired in case of a change in consumption during the past 10 yr Exclusion of former drinkers (no current intake but non-zero amount for previous intake)	What: artificially sweetened beverages When: assessment at study baseline in 1982 Where: USA Context: aspartame not included in ASB at the time of baseline questionnaire	Semiquantitative	Diet soda or diet iced teas	*20 mg/packet of Nutrasweet or Equal	Usual daily consumption: Categorical: never drinkers (no past or current consumption), < 1 drink/day, 1 drink/day, 2+ drinks/day Continuous per 1 drink/day	Questionnaire on ASB consumption in 1982, end of follow-up in 2016 Median follow-up of 27.7 yr Follow-up censored at age 90 for men and 95 for women	Potential co-exposure measured and considered in analyses: smoking, red and processed meat, fruit and vegetable, alcohol consumption, SSB, for female cancers: estrogen, oral contraceptive Other co-exposures considered but not included in analyses: aspirin, multivitamin, physical activity	Differential unlikely: cohort study; exposure assessed before cancer diagnosis Non-differential likely: no details on aspartame, only ASB consumption as potential source of aspartame, ASB consumption assessed in 1982 at a time when ASB did not contain aspartame, no information on the stability of ASB consumption through the up to 34 yr of follow-up [some data in the CPS-II Nutrition cohort (McCullough et al., 2014) suggested a stable ranking of participants as regards ASB consumption between 1982 and 1999 for the subsample ($n = 100\,442$) providing data at both time points].
Mullee et al. (2019) Cancer mortality	Cohort (EPIC)	Usual diet over the previous 12 months Country-specific instruments developed and validated within the various source populations and including hundreds of country- and region-specific foods. These extensive self-administered quantitative dietary questionnaires collected usual portions and frequency of consumption of up to 260 food items food and drinks during different seasons of the year. Soft drink consumption: number of glasses (typical glass sizes in each centre, ≈ 250 mL) per month, week, or day	What: artificially sweetened soft drinks When: diet assessed at inclusion between 1991 and 2000 Where: western European countries (Denmark, France, Germany, Italy, Netherlands, Spain, Sweden, United Kingdom); data on artificially sweetened soft drinks not available in Spain, Italy (Florence, Turin, Ragusa, Varese) and Sweden (Umeå) Context: multiple European countries and associated context of consumption, no information on historical exposure	Semiquantitative	Carbonated/ soft/ isotonic drinks, and diluted syrups: “low-calorie or diet fizzy soft drinks”, “fizzy soft drinks, e.g. cola, lemonade”, and “fruit squash or cordial” Total soft drinks: sugar-sweetened/artificially sweetened	Mean daily intakes over the past 12 months Estimates per frequency of glasses consumed (< 1 glass per month, 1 to 4 glasses per month, > 1 to 6 glasses per week, 1 to < 2 glasses per day, or ≥ 2 glasses per day), 1 glass = 250 mL	Diet questionnaires covering the past year between 1991 and 2000 Mean (range) follow-up of 16.4 (11.1 to 19.2) years	Potential co-exposure measured and considered in analyses: alcohol, smoking, BMI, physical activity, menopausal hormone therapy, dietary intakes of red and processed meats, coffee, fruit and vegetable juices, and fruits and vegetables, dietary fibre, sugar-sweetened soft drinks, cancer, heart disease, stroke, diabetes	Differential unlikely: cohort study; exposure assessed before cancer diagnosis Non-differential likely: no details on aspartame; uncertainty regarding the content of the beverages in aspartame; diet only assessed at baseline in a context of low consumption of ASB; potential variations of the content of ASB in aspartame; measurement errors	
Navarrete-Muñoz et al. (2016) Pancreatic cancer	Cohort (EPIC)	Usual diet over the previous 12 months Country-specific instruments developed and validated within the various source populations and including hundreds of country- and region-specific foods. These extensive self-administered quantitative dietary questionnaires collected usual	What: artificially sweetened soft drinks When: diet assessed at inclusion between 1991 and 2000 Where: western European countries (Denmark, France, Germany, Italy, Netherlands, Spain, Sweden, United Kingdom); data on artificially sweetened soft drinks not available in Spain, Italy	Quantitative	Carbonated/ soft/ isotonic drinks, and diluted syrups: “low-calorie or diet fizzy soft drinks”, “fizzy soft drinks, e.g. Cola, lemonade”, and “fruit squash or cordial” Total soft drinks: sugar-sweetened/artificially sweetened	Mean daily intakes over the past 12 months Estimates per 100 g/d and 12 oz (336 g/d) increments, for categorization into non-consumers and cohort-wide quintiles in consumers, and for alternative categorizations (i.e. 0.0, 0.1–124.9, 125.0–249.9, or	Diet questionnaires covering the past year between 1991 and 2000 Median follow-up of 11.6 y	Potential co-exposure measured and considered in analyses: alcohol, physical activity, smoking, diabetes, BMI, intakes of red meat, fruit and vegetables, dietary sugar, coffee, folate, waist circumference, sugar-sweetened soft drinks, juice and nectar	Differential unlikely: cohort study; exposure assessed before cancer diagnosis Non-differential likely: no details on aspartame; uncertainty regarding the content of the beverages in aspartame; diet only assessed at baseline in a context of low consumption of ASB;	

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Nomura et al. (1991) Bladder	Case-control study	portions and frequency of consumption of up to 260 food items food and drinks during different seasons of the year). Soft drink consumption: number of glasses (typical glass sizes in each centre, \approx 250 mL) per month, week, or day	(Florence, Turin, Ragusa, Varese) and Sweden (Umeå) Context: multiple European countries and associated context of consumption, no information on historical exposure			$\geq 250.0 \text{ g/d}$ or $< 1 \text{ glass/mo}$, 1–4 glasses/mo, $> 1\text{--}6$ glasses/wk, or $\geq 1 \text{ glass/d}$			potential variations of the content of ASB in aspartame; measurement errors
Norell et al. (1986) Pancreas	Population-based case-control study	Interviews, diet history of 29 food items consumed during a usual week (or usual month for less frequently consumed items), usual diet 1 yr before diagnosis	What: artificially Sweetened beverages Where: Hawaii When: 1977 and 1986	Qualitative	Artificially sweetened beverages, such as diet or low-calorie sodas Use and frequency of saccharin, cyclamates and other artificial sweeteners (analysis for saccharin use only)	Diet beverages: Non-user, User (1–2 can-years, 3+ can-years)	Usual diet 1 year before diagnosis	Smoking	Differential likely: case-control study; retrospective assessment, Interviewers not blinded to case-control status Non-differential likely: only ASB as a proxy measure
Palomar-Cros et al. (2023) Colorectal, breast, prostate, stomach cancer, chronic lymphocytic leukaemia	Case-control study	Self-administered, semiquantitative FFQ, 140 food items, assessing usual dietary intake during the previous year	What: Categorized intake of aspartame-containing products (low- or no-calorie soft drinks and tabletop sweeteners other than saccharin), and other AS (saccharin and Gaseosa). Where: Spain When: 2008–2013	Semiquantitative	Consumption of AS was estimated from four questions in the FFQ: (i) Low- or no-calorie soft drinks (ii) Gaseosa (AS soft drink, contains saccharin and cyclamate) (iii) Tabletop sweeteners (saccharin) (iv) Tabletop sweetener (others)	Portions per day (derived from frequency data) of aspartame-containing vs other AS products. Intake of each group of products were categorized for analysis as: - Non-consumers - Medium intake - High intake These categories were based on sex-specific quartiles among consumers in controls, With 3rd and 4th quartiles used as medium and high intake and compared to non-consumers for both groups of products	Usual dietary intake during the previous year	Smoking, radiation exposure, total WCRF score (lifestyle), total energy intake, sugar intake Models for intake of aspartame products were adjusted for consumption of products containing other AS	Differential likely: case-control study; retrospective assessment Non-differential likely: two main sources considered, but rest of food supply not included (reported that other foods in Spain do contain AS e.g. Dairy products, during period studied).
Ringel et al. (2022) Urinary tract cancers, bladder and kidney cancers	Cohort (WHI-OS)	Question regarding the frequency of consumption of ASB during the past 3 months Reference serving size (12 fl. oz can) Nine frequency of servings: never or $< 1/\text{month}$, 1–3/month, 1/week, 2–4/week, 5–6/week, 1/day, 2–3/day, 4–5/day, and 6+/day.	What: artificially sweetened beverages When: assessment 3 yr after study baseline in 1993–1998 Where: USA	Semiquantitative	Diet drinks such as Diet Coke or diet fruit drinks	3 categories: never or fewer than one serving per week (reference), one to six servings per week, and one or more servings per day (rare, frequent, and daily consumption)	Questionnaire on ASB in 1996–2001, end of follow-up in 2020	Potential co-exposure measured and considered in analyses: smoking, water consumption, BMI, history of hypertension, diet quality	Differential unlikely: cohort study; exposure assessed before cancer diagnosis Non-differential likely: no details on aspartame, only ASB consumption as potential source of aspartame, no information on the stability of ASB consumption over

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Romanos-Nanclares et al. (2021) Breast cancer	Cohort (NHS and NHS II)	Validated semiquantitative FFQ (past year) administered every 4 yr since 1980 (NHS, 61 items in 1980, 116 items in 1984 and 1986, and ≥ 130 items thereafter) or 1991 (NHSII, ≥ 130 items) Frequency of consumption for a standard 355 mL (12 oz) serving (1 glass/can/bottle) of each ASB: 9 possible responses ranging from “never/almost never” to “6 or more times per day”	What: ASB When: diet assessed every 4 yr between 1980/1991 and 2016/2017 Where: USA	Semiquantitative	Caffeinated, non-caffeinated, and non-carbonated low-calorie or diet beverages	Cumulative averages (mean intake from all FFQs up to the beginning of a 2-yr follow-up interval) Estimates for categories of frequencies of intake: < 1/month, ≥ 1 to ≤ 4/month, > 1 to < 7/week, and ≥ 1/day Other models used: simple update (consumption reported on the most recent FFQ before each follow-up interval) and latency (consumptions reported at different latencies (i.e. 4–8, 8–12, 12–16, and 16–20 yr) before a cancer diagnosis)) Changes in consumption updated every 4 yr to estimate the risk in the subsequent 4-yr period: 5 categories (no change or relatively stable, increase or decrease from 1.0 serving/week to 0.50 serving/day, and increase or decrease by > 0.50 serving/day)	Diet assessed every 4 yr between 1980 and 2016 (NHS) or between 1991 and 2017 (NHSII) Follow-up until 2006 for molecular subtypes Cumulative average, simple update, latency or changes in consumption models	Potential co-exposure measured and considered in analyses: postmenopausal hormone, oral contraceptive, alcohol, physical activity, BMI at age 18, diet quality (AHEI score), SSB	time (up to 24 yr of follow-up)
Schernhammer et al. (2005) Pancreatic cancer	Cohort (NHS and HPFS)	Validated self-administered semiquantitative FFQ every 4 yr: since 1980 in the NHS and 1986 in the HPFS Diet soft drink consumption: 1 item (low-calorie carbonated drink) in 1980, 3 items (low-calorie cola, low-calorie caffeine-free cola, other low-calorie carbonated beverage) in 1984 and subsequent questionnaire cycles	What: artificially sweetened beverages When: from 1980–1986 to 2000 Where: USA Context: aspartame as primary artificial sweetener in ASBs	Semiquantitative	Low-calorie carbonated drinks: low-calorie cola, low-calorie caffeine-free cola, other low-calorie carbonated beverage	Cumulative average (average of all measures up to the start of each follow-up interval) 3 categories (less than once monthly, 1–12 times monthly, and > 3 times weekly)	Diet assessed every 4 yr since 1980/1986, follow-up until 2000	Potential co-exposure measured and considered in analyses: smoking, BMI, physical activity, diabetes, sugar-sweetened soft drinks, caffeine	Differential unlikely: cohort study; prospective assessment of exposure Non-differential likely: no details on aspartame; only some ASB as potential sources of aspartame; uncertainty regarding the content of the beverages in aspartame; potential variations of the content of ASB in aspartame over time; measurement errors
Schernhammer et al. (2012) Lymphoma and leukaemia	Cohort (NHS and HPFS)	Validated self-administered semiquantitative FFQ (≈ 130 items) Frequency of consumption (9 frequencies from never to ≥ 6 times/d) with one serving size (355 mL) of 3 types of diet sodas: diet cola with caffeine, diet cola	What: aspartame Where: USA When: diet sodas assessed every 4 yr since 1984 (NHS) and 1986 (both cohorts); tabletop sweeteners assessed every 4 yr since 1994 Context: aspartame approved in 1981, sole artificial sweetener in Diet Coke soda (most	Quantitative	Diet soda and aspartame packet (main contributors) Other sources not considered: breakfast cereals collected by brand name but not considered in analysis (no breakfast cereals containing aspartame in the early years, only 4% at the end of follow-up)	Cumulative average (intakes updated after every FFQ with the mean of all reported intakes up to that time) Assigned values of aspartame content: *aspartame packet: 20 mg	Diet sodas: follow-up between 1984 (NHS), 1986 (HPFS) and 2006 Aspartame: follow-up between 1994 and 2006	Potential co-exposure measured and considered in analyses: fruit and vegetable, multivitamins, alcohol, total sugar, saturated fat, animal protein, BMI, physical activity, smoking, hormone replacement therapy, diabetes, waist-to-hip ratio	Differential unlikely: cohort study; aspartame exposure assessed before cancer diagnosis Non-differential likely: uncertainty regarding the content of the beverages in aspartame; other possible sources of aspartame not

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Singh et al. (2020) Thyroid cancer	Case-control study	without caffeine, and other diet soda Dietary collected every 4 yr since 1984 (NHS) and 1986 (both cohorts) Use of aspartame sweeteners added at the table (Nutrasweet and Equal) assessed every 4 yr since 1994	commonly used diet soda) from 1983, most other diet sodas in the 1980s used both aspartame and saccharin; aspartame most broadly used in sodas from 1992 Lifetime exposure to aspartame from diet sodas captured	Quantitative	Artificial sweetener consumption as tabletop sweetener and beverages (beverages included in assessment were as carbonated beverages, multiple colas, Sprite, Mountain Dew, Fresca) Consumption of artificial sweetener in the form of snacks/ice creams was not considered. Intake of the mixture of artificial sweeteners in products was assessed and used in the analysis.	*diet soda: weighted average of the representative sodas in that category (70–180 mg/serving) Zero intakes as the lowest category and cohort specific exact quartiles	Total amount and duration of artificial sweetener consumed	Average duration of 5 yr before diagnosis	Other co-exposures: BMI; alcohol; irradiation in childhood	Differential likely: case-control study; retrospective assessment Non-differential likely: no specific assessment of aspartame alone, only total artificial sweeteners and only in beverages
Stepien et al. (2016) Hepatocellular cancers	Cohort (EPIC)	Usual diet over the previous 12 months Country-specific instruments developed and validated within the various source populations and including hundreds of country- and region-specific foods. These extensive self-administered quantitative dietary questionnaires collected usual portions and frequency of consumption of up to 260 food items food and drinks during different seasons of the year. Soft drink consumption: number of glasses (typical glass sizes in each centre, \approx 250 mL) per month, week, or day	What: artificially sweetened soft drinks When: diet assessed at inclusion between 1991 and 2000 Where: western European countries (Denmark, France, Germany, Italy, Netherlands, Spain, Sweden, United Kingdom); data on artificially sweetened soft drinks not available in Spain, Italy (Florence, Turin, Ragusa, Varese) and Sweden (Umea) Context: multiple European countries and associated context of consumption, no information on historical exposure	Quantitative	Carbonated/ soft/ isotonic drinks, and diluted syrups: “low-calorie or diet fizzy soft drinks”, “fizzy soft drinks, e.g. Cola, lemonade”, and “fruit squash or cordial” Total soft drinks: sugar-sweetened/artificially sweetened	Mean daily intakes over the past 12 months Estimates per serving (330 g, equivalent to a soft drink can size in Europe: 330 mL)	Diet questionnaires covering the past year between 1991 and 2000 11.4 yr of follow-up	Potential co-exposure measured and considered in analyses: smoking, alcohol (at recruitment and lifetime pattern), BMI, physical activity, diabetes, liver function, waist-to-hip ratio, intakes of sugar, meats, fish, fruit and vegetables, other non-alcoholic beverages intake (i.e. Coffee and tea), gallstones, SSB	Differential unlikely: cohort study; exposure assessed before cancer diagnosis Non-differential likely: no details on aspartame; uncertainty regarding the content of the beverages in aspartame; diet only assessed at baseline in a context of low consumption of AS soft drinks; potential variations of the content of AS soft drinks in aspartame; measurement errors	
Wang et al. (2021) Colorectal cancer	Cohort (NHS, NHSII and HPFS)	Validated self-administered semiquantitative FFQ every 4 yr: since 1984 (NHS), 1986 (HPFS) and 1991 (NHSII)	What: sulfur microbial diet score When: diet assessed every 4 yr since 1984 (NHS), 1986 (HPFS) and 1991 (NHSII) until 2014 (HPFS), 2016 (NHS) and 2017 (NHSII) Where: USA	Quantitative	Low-calorie beverages	Sulfur microbial diet score: weighted sum of standardized consumption of food groups with positive weights for low-calorie beverages, French fries, red meats, and processed meats, and negative weights for fruits, yellow vegetables, whole grains, legumes, leafy vegetables, and cruciferous vegetables (positive and negative correlation with most of the	Diet assessed every 4 yr since 1984 (NHS), 1986 (HPFS) and 1991 (NHSII) until 2014 (NHS), 2016 (HPFS) and 2017 (NHSII)	Potential co-exposure measured and considered in analyses: BMI, smoking, physical activity, aspirin, NSAID, menopausal hormone therapy, western dietary pattern	Differential unlikely: cohort study; prospective assessment of exposure Non-differential likely: no details on aspartame; ASB (potential source of aspartame) as a component of the sulfur microbial diet score; uncertainty regarding the content of ASB in aspartame; potential variations of the content of ASB in aspartame over time; measurement errors	

Table S1.2 Exposure assessment review and critique for epidemiological studies on cancer in humans exposed to aspartame

Reference and outcome	What was the study design?	What methods were used for the exposure assessment? (incl. data source, environmental and biological measurements, etc.)	What was the exposure context? Specify period over which exposure data were gathered, and how historical exposures were accounted for (if relevant)	Was estimate of exposure qualitative, semiquantitative, or quantitative?	Which exposure sources were assessed?	What exposure metrics were derived for use in analyses (e.g. average exposure, exposure duration, cumulative exposure, etc.)? (specify units)	What was the timing of exposure relative to the outcome?	Which other potential carcinogens, confounders, or effect modifiers were assessed?	Was there potential for differential exposure misclassification? Was there potential for non-differential exposure misclassification? (Likely/unlikely)		
You et al. (2022) Lung cancer All cancer	Prospective cohort study (PLCO cohort)	Diet history questionnaire: Food frequency questionnaire with 156 items	What: Diet soft drinks Where: 10 study centres in the USA When: Baseline data collected 1993–2001; follow-up until 2009; median follow-up time 11.3 yrs	Qualitative	Daily gram of consumption of regular and diet/sugar-free soft drinks using frequency and serve size	sulfur-metabolizing bacteria respectively)	Cumulative average of the sulfur microbial diet score (updated at each questionnaire cycle), categorization into quintiles	Consumption of soft drink was categorized as: 1. “None”: No regular drinks or diet/sugar-free soft drinks; 2. “Regular only”: Only regular soft drinks; 3. “Diet only”: only diet/sugar-free soft drinks; 4. “Both”: Both regular and diet/sugar-free soft drinks.	Baseline dietary data collected referring to the previous 12 months. Patients with any cancer before baseline excluded from this analysis.	Included in multivariable models: (BMI) types at baseline, smoking status, physical activity status, daily energy consumption, red meat, fruits, vegetables and coffee, alcohol consumption, estrogen use (females only)	Differential unlikely: cohort study with assessment before diagnosis Non-differential likely: only ASB as a proxy measure
Yuan et al. (2022) Colorectal cancer incidence and mortality	Cohort (NHS and HPFS)	Validated self-administered semiquantitative FFQ (past year) every 4 yr: since 1980 (NHS) and 1986 (HPFS) Frequency of consumption of 61 items (1980) up to 131–169 items in 1984 9 possible responses ranging from “never or less than once per month” to “6 or more times per day”	What: ASB When: diet assessed every 4 yr since 1980 (NHS) or 1986 (HPFS) until 2014 Where: USA	Quantitative	Caffeinated, caffeine-free, and non-carbonated low-calorie or diet beverages	Substitution of 1 serving of SSBs per day with an equivalent amount of ASBs; no estimates for ASB as such	Diet assessed every 4 yr since 1980 (NHS) or 1986 (HPFS) until 2014 Secondary analyses with recent and distant periods	Potential co-exposure measured and considered in analyses: BMI, physical activity, smoking, alcohol, aspirin, diabetes, menopausal hormone therapy, intakes of dietary fibre, total calcium, total folate, red meat, and processed meat, diet quality (AHEI-2010), fruit intake	Potential co-exposure measured and considered in analyses: BMI, physical activity, smoking, alcohol, aspirin, diabetes, menopausal hormone therapy, intakes of dietary fibre, total calcium, total folate, red meat, and processed meat, diet quality (AHEI-2010), fruit intake	Differential unlikely: cohort study; prospective assessment of exposure Non-differential likely: no details on aspartame; only ASB as potential sources of aspartame; uncertainty regarding the content of the beverages in aspartame; potential variations of the content of ASB in aspartame over time; measurement errors	
Zamora-Ros et al. (2022) Thyroid cancer	Cohort (EPIC)	Usual diet over the previous 12 months Country-specific instruments developed and validated within the various source populations and including hundreds of country- and region-specific foods. These extensive self-administered quantitative dietary questionnaires collected usual portions and frequency of consumption of up to 260 food items food and drinks during different seasons of the year). Soft drink consumption: number of glasses (typical glass sizes in	What: artificially sweetened soft drinks When: diet assessed at inclusion between 1991 and 2000 Where: western European countries (Denmark, France, Germany, Italy, Netherlands, Spain, Sweden, United Kingdom); data on artificially sweetened soft drinks not available in Spain, Italy (Florence, Turin, Ragusa, Varese) and Sweden (Umeå) Context: multiple European countries and associated context of consumption, no information on historical exposure; consumption of ASB relatively low in the 90s (baseline): < 25% of total soft drinks	Quantitative	Carbonated/ soft/ isotonic drinks, and diluted syrups: “low-calorie or diet fizzy soft drinks”, “fizzy soft drinks, e.g. Cola, lemonade”, and “fruit squash or cordial” Total soft drinks: sugar-sweetened/artificially sweetened	Mean daily intakes over the past 12 months Estimates per 100 mL/d and for non-consumers/tertiles of consumers	Diet questionnaires covering the past year between 1991 and 2000 Mean follow-up of 14 yr	Potential co-exposure measured and considered in analyses: BMI, smoking, physical activity, oral contraceptive, infertility problems, alcohol	Potential co-exposure measured and considered in analyses: BMI, smoking, physical activity, oral contraceptive, infertility problems, alcohol	Differential unlikely: cohort study; exposure assessed before cancer diagnosis Non-differential likely: no details on aspartame; uncertainty regarding the content of the beverages in aspartame; diet only assessed at baseline in a context of low consumption of AS soft drinks; potential variations of the content of AS soft drinks in aspartame; measurement errors	

Table S1.2 Exposure assessment review and critique for epidemiological studies on cancer in humans exposed to aspartame

Reference and outcome	What was the study design?	What methods were used for the exposure assessment? (incl. data source, environmental and biological measurements, etc.)	What was the exposure context? Specify period over which exposure data were gathered, and how historical exposures were accounted for (if relevant)	Was estimate of exposure qualitative, semiquantitative, or quantitative?	Which exposure sources were assessed?	What exposure metrics were derived for use in analyses (e.g. average exposure, exposure duration, cumulative exposure, etc.)? (specify units)	What was the timing of exposure relative to the outcome?	Which other potential carcinogens, confounders, or effect modifiers were assessed?	Was there potential for differential exposure misclassification? (Likely/unlikely)
Zhang et al. (2021) Cancer mortality	Cohort (NHANES)	each centre, ≈ 250 mL) per month, week, or day 24-hour dietary recalls: before 2003, only one 24-hour dietary recall administered in-person, since 2003, two 24-hour dietary recalls (1 in-person and 1 by telephone after 3–10 days) Trained investigators Main Food List with over 2600 food items	What: artificially sweetened beverages When: inclusion between 1999 and 2014, follow-up until 2015 Where: USA Context: ASB consumptions increased from 1999 to 2006 but declined afterwards	Semiquantitative	Sugar-free soft drinks and carbonated water (no sugar, only AS)	Mean intake from up to two 24-hour dietary recalls Standard 12-oz serving defined Estimates per 12-oz serving/d and for categories: none, > 0 to < 1 serving/d, 1 to < 2 servings/d, and ≥ 2 servings/d Substitution of one serving/d of SSB with equivalent amounts of ASBs	Diet estimated once between 1999 and 2014, follow-up (registries) until 2015	Potential co-exposure measured and considered in analyses: alcohol, smoking, physical activity, BMI, high-cholesterol, hypertension, diabetes, CVD, cancer, diet quality (HEI-2015), intakes of major food groups (i.e. Vegetable, fruit, whole grain, red meat, and processed meat), macronutrients, SSBs	Differential unlikely: cohort study; prospective assessment of exposure Non-differential likely: no details on aspartame; uncertainty regarding the content of the beverages in aspartame; diet only assessed at baseline through 1 or max. 2 24-hour recalls; potential variations of the content of ASB; measurement errors

acesulfame-K, acesulfame potassium; AS, artificial sweetener; ASB, artificially sweetened beverage; BMI, body mass index; CPS, Cancer Prevention Study; CVD, cardiovascular disease; d, day(s); EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, food frequency questionnaire; HPFS, Health Professionals Follow-up Study; IBD, inflammatory bowel disease; NHANES, National Health and Nutrition Examination Survey; NIH-AARP, National Institutes of Health-American Association of Retired Persons Diet and Health Study; NHS, Nurses' Health Study; NNS, non-nutritive sweetener; NR, not reported; PLCO, Prostate Lung, Colorectal and Ovarian cancer screening trial; SD, standard deviation; SSB, sugar-sweetened beverage; US, United States; UTD, urinary tract disease; vs, versus; wk, wee(s); yr, year(s).

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