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Consumption of aspartame and other artificial sweeteners and risk of cancer in the Spanish multicase-control study (MCC-Spain)

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Abstract

Use of artificial sweeteners (AS) such as aspartame, cyclamate, saccharin and sucralose is widespread. We evaluated the association of use of aspartame and other AS with cancer. In total 1881 colorectal, 1510 breast, 972 prostate and 351 stomach cancer and 109 chronic lymphocytic leukaemia (CLL) cases and 3629 population controls from the Spanish Multicase-Control (MCC-Spain) study were recruited (2008-2013). The consumption of AS, from table-top sweeteners and artificially sweetened beverages, was assessed through a self-administered and validated food frequency questionnaire (FFQ). Sex-specific quartiles among controls were determined to compare moderate consumers (<third quartile) and high consumers (≥ third quartile) vs non consumers (reference category), distinguishing aspartame-containing products

Abbreviations: AICR, American Institute of Cancer Research; AS, artificial sweetener; BMI, body-mass index; CESNID, Centro de Enseñanza Superior de Nutrición y Dietética; CI, confidence interval; CLL, chronic lymphocytic leukaemia; FFQ, food frequency questionnaire; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; MCC-Spain, Spanish MultiCase-Control study; OR, odds ratio; WCRF, World Cancer Research Fund; WHO, World Health Organisation.

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and other AS. Unconditional logistic regression models were used to estimate adjusted OR and 95%CI, and results were stratified by diabetes status. Overall, we found no associations between the consumption of aspartame or other AS and cancer. Among participants with diabetes, high consumption of other AS was associated with colorectal cancer (OR = 1.58, 95% CI 1.05-2.41, *P* trend = .03) and stomach cancer (OR = 2.27 [0.99-5.44], *P* trend = .06). High consumption of aspartame, was associated with stomach cancer (OR = 2.04 [0.7-5.4], *P* trend = .05), while a lower risk was observed for breast cancer (OR = 0.28 [0.08-0.83], *P* trend = .03). In some cancers, the number of cases in participants with diabetes were small and results should be interpreted cautiously. We did not find associations between use of AS and cancer, but found associations between high consumption of aspartame and other AS and different cancer types among participants with diabetes.

KEYWORDS
artificial sweeteners, aspartame, cancer risk, case-control

What's new?

Increased awareness of the health impacts of sugar has fuelled a rise in artificial sweetener consumption. Certain artificial sweeteners, including aspartame, however, are suspected of contributing to cancer. Here, associations between cancer risk and aspartame and other artificial sweetener consumption were investigated in cancer patients in Spain. Overall, no associations between artificial sweeteners and cancer risk were detected. For individuals with diabetes, however, high consumption of artificial sweeteners was linked to increased risk of different cancer types. The findings indicate that artificial sweeteners do not increase cancer risk in general but may pose risks for patients with certain health conditions.

1 | INTRODUCTION

The consumption of excessive sugar can have numerous adverse consequences for health, being a major contributor to the global obesity crisis but also increasing the risk of diabetes, cardiometabolic diseases and potentially cancer.[1-4] As awareness of the health risks of sugar intake has increased, the consumption of artificial sweeteners (AS) worldwide has grown.[5] AS, or non-caloric sweeteners, are food additives used to reduce the sugar content of foods because they have a sweetening intensity higher than caloric sweeteners.[6] Much smaller amounts of AS (200-20 000 times less) are needed to reach the same level of sweetness as that of table sugar.[7]

AS were first introduced in the food industry in the 1950s, but since the 2000s, there has been an exponential increase in their consumption.[6] In Europe, there are 19 approved AS[8] and in Spain,[9] the main consumed AS are acesulfame K, aspartame, cyclamate and sucralose. They can be consumed in liquid or powder form directly added by the consumer in beverages or dessert, and otherwise are mainly present in non-alcoholic beverages such as soft drinks and juices, but also chocolates, dairy products and others. It has been estimated that in Spain, 79% of adults consume AS on a daily basis and that 9% of foods and drinks contain AS.[9] The safety of AS has been documented in extensive scientific research, however since their approval, controversies have risen. The consumption of AS has been linked with altered glycaemic control,[6] inflammatory conditions,[6] obesity[5] and cardiovascular disease.[10]

Initial concerns about a potential link between AS and cancer were raised since studies in rats suggested a possible association of two specific AS, cyclamate and saccharin, and bladder cancer.[11] Three studies from the Ramazzini Institute reported a dose-response relationship between aspartame and malignant tumours in multiple organs in rats and mice.[12-14] On the basis of these cancer bioassays, an IARC advisory group recommended to give aspartame high priority for the International Agency for Research on Cancer (IARC) Monographs programme during 2020-2024.[15]

In humans, a meta-analysis commissioned by the World Health Organisation (WHO) showed that overall, there was no association between AS intake and cancer incidence or mortality.[16] Results from this review (from 26 pooled case-control studies) indicate that high intake of AS, mostly coming from saccharin, might be linked to bladder cancer, although with high heterogeneity between studies. Results for other cancers are inconclusive or based on only one or two studies. It appears clearly from this meta-analysis that studies on specific types of AS, and by specific tumour sites are scarce. A recent study in the NutriNet-Santé cohort in France, the largest in terms of exposure assessment which included AS from all dietary sources and obtained by repeated 24-h dietary records, indicated that high aspartame

intake was linked to higher risks of breast cancer and obesity-related cancers.[17] Similarly, in a large prospective cohort, the consumption of artificially sweetened drinks was associated with mortality from obesity-related cancers, but this was confounded by body-mass index (BMI).[18]

The objective of the present study is to investigate whether the consumption of AS, including aspartame, is linked to higher risk of cancer in the Spanish MultiCase-Control study (MCC-Spain). In this study we investigate the association with cancers of the breast, prostate, colorectum and stomach as well as with chronic lymphocytic leukaemia (CLL).

2 | MATERIALS AND METHODS

2.1 | Study population

The MCC-Spain study is a multicase-control study that was conducted in Spain (2008-2013) to investigate etiological factors for common cancers.[19,20] Individuals aged 20 to 85 years with newly diagnosed histologically confirmed cancer were invited to participate in the study. To be included, participants had to have resided in the catchment area for at least 6 months prior to recruitment. Cases of colorectal (International Classification of Diseases 10th Revision [ICD-10]: C18, C19, C20, D01.0, D01.1, D01.2), breast (C50, D05.1, D05.7), stomach (C16, D00.2), or prostate cancer (C61, D07.5) and CLL (C91.1) and with no prior history of their disease were included in this study. Prevalent CLL cases were also recruited and were retained for this analysis if diagnosis was done 1 year prior to the interview. Clinical information on prostate cancer aggressiveness determined by the Gleason score was recorded from medical records. Cases were recruited, as soon as possible after diagnosis, and were frequency-matched by age, sex and region to population-controls. Controls were randomly selected from administrative records of selected primary healthcare centres within the catchment area. A total of 10 106 individuals were recruited. Participants who did not respond to the food frequency questionnaire (FFQ, N = 1354) or who had missing data in some of the covariates were excluded from this study (N = 29). In this study we included 1881 colorectal cancer, 1510 breast cancer, 972 prostate cancer, 351 stomach cancer and 109 CLL cases and 3629 population controls. To avoid reverse causality, we excluded prevalent cases of CLL (having had a diagnosis for ≥1 year) for this analysis.

2.2 | Data collection

At inclusion, participants responded to a computerised epidemiological questionnaire which was administered by trained personnel (https://www.mccspain.org/). The questionnaire included information on socio-demographic factors, smoking, physical activity, night shift history, personal and family medical history and reproductive factors. Participants were asked for their weight the prior year to the inclusion and also at the time of the questionnaire. A semi-quantitative FFQ was self-administered by the participants with a global response rate of 88%.[19] The FFQ included 140 food items, assessing usual dietary intake during the previous year with eight possible frequencies of intake for each food item, ranging from Never or less than once a month to several times per day, and was a modified version from a previously validated questionnaire.[21] Daily consumption of nutrients and energy intake was estimated using the Centro de Enseñanza Superior de Nutrición y Dietética (CESNID) food composition table.[22] Total sugar intake (g/day) was derived from all sugar-containing items in the FFQ.

2.3 | Definition of the exposure and covariates

The consumption of AS was estimated from four questions in the FFQ: (i) low- or no-calorie soft drinks ("refrescos"), (ii) gaseosa (an artificially sweetened soft drink commonly consumed in Spain), (iii) table-top sweeteners (saccharin) and (iv) table-top sweetener (others). We decided to include gaseosa since it also contains AS (usually saccharin and cyclamate).[23] Table-top sweeteners other than saccharin usually contain aspartame. We used public sources of nutritional information (https://es.openfoodfacts.org/) to determine the most common type of sweetener in each of these food items. All items were expressed as number of portions consumed/day, derived from the frequency questions. Then, we distinguished aspartame-containing products (low- or no-calorie soft drinks and table-top sweeteners other than saccharin), and other AS (saccharin and gaseosa). Intake of these two types of products were calculated as the sum of portions/day of each of the two items they included: aspartame-containing (i) + (iv), and other AS (ii) + (iii). Sex-specific quartiles among consumers in controls were determined to compare moderate consumers (<3rd quartile) and high consumers (≥3rd quartile) vs non consumers (reference category) for both groups of products.

A World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) score was derived from information in the main questionnaire and the FFQ. This score was built to set the benchmark for evidence-based guidance on modifiable lifestyle factors to reduce the risk of cancer incidence. The WCRF/AICR score ranged from 0 to 8 and included information on BMI, physical activity, plant foods, animal foods (covering the consumption of red and processed meat), sugar sweetened drinks and alcoholic drinks.[24] Finally, information regarding prevalent diabetes was collected in the baseline questionnaire as part of the personal medical history.

2.4 | Statistical analyses

We explored the distribution of characteristics in individuals highly, moderately and not exposed to AS. We also explored the distribution among controls only to avoid potential bias linked to cancer diagnosis. Unconditional logistic regression models were employed to estimate

OR and 95% CI and investigate associations between AS (aspartame-containing products and other AS) and the risk of cancer. Regression models were adjusted for a priori defined potential confounders. These included age (continuous, years), sex (when applicable, women, men), study centre (Asturias, Barcelona, Cantabria, Girona, Granada, Gipuzkoa, Huelva, León, Madrid, Murcia, Navarra and Valencia), education (less than primary school, primary school, secondary school, university), smoking (never, ex-smoker, current smoker), radiation exposure (never, ever taken radiotherapy), total WCRF score (continuous), total energy intake (continuous, Kcal/day) and simple sugar intake (continuous, g/day). Colorectal, breast and prostate cancer models were further adjusted by family history of site-specific cancer (yes, no) and night shift work (ever, never).[25] The regression models for breast cancer were additionally adjusted for menopausal status (premenopausal, postmenopausal), number of children (nulliparous, one child or more), age at first child (continuous, years) and use of hormonal contraceptives (never, ever). Consumption of aspartame-containing products and other AS were mutually adjusted in the models. Additionally, breast cancer models were stratified by menopausal status when numbers allowed it. This was done because there are clear differences in the aetiology of premenopausal and postmenopausal breast cancer.[26] Results were stratified by diabetes status to account for important differences in risk factor profiles and also in behaviours, as the intake of AS was much higher in participants with diabetes. For example, participants with diabetes have a medical incentive to reduce sugar consumption and are likely to replace sugar with AS resulting in higher AS consumption and stronger exposure contrasts. Moreover, a pooled analysis of two cohort studies reported an effect modification of the association between AS and liver cancer by diabetes status.[27]

In a second set of analyses, we explored combining the intake of all AS and total sugar intake. Sugar intake was categorised as low-to-medium (<100 g/d) and high (≥100 g/d), therefore we created six categories: 1. Low sugar, no AS; 2. Low sugar, medium AS; 3. Low sugar, high AS; 4. High sugar, no AS; 5. High sugar, medium AS and 6. High sugar, high AS.

2.5 | Sensitivity analyses

In a first set of sensitivity analyses, we adjusted for individual confounders instead of the WCRF score: BMI the prior year to the inclusion, dietary fibre, red meat, physical activity and alcohol. We also ran the same model without adjusting for BMI to assess any attenuation in the estimates after adjustment for BMI, and for comparability with other studies. In third set of models, we further included a variable for weight change between the prior year to the inclusion and the inclusion to the study. In another set of analyses, we examined the association between the consumption of low- or no-calorie soft drinks only and cancer risk. We did this separate analysis because we hypothesised that it might be more difficult to recall the frequency of consumption of table-top sweeteners than of these beverages and, therefore, to reduce the impact of a potential recall bias. We also explored the associations for saccharin only. Moreover, dairy products have been linked both with colorectal and prostate cancer[28,29] and given their consumption could be linked to use of table-top sweeteners (eg, yogurts) we explored adjusting the models for this information. Finally, for prostate cancer, we also explored whether the associations were different for low-grade (Gleason score < 7) and high-grade aggressive prostate cancer (Gleason score ≥ 7).

3 | RESULTS

3.1 | Characteristics of the study population

In our study population, 49% of participants consumed AS. The characteristics of the study population (N = 8452) and according to their AS intake, are shown in Table 1. Overall, the mean age of participants was 63 years old, 49% were women and the mean BMI was 26.8 kg/m^2. Compared with non-consumers, individuals consuming more AS were less likely to be never smokers, and more likely to have a higher BMI and have diabetes. High AS consumers had a lower WCRF/AICR score, consumed more energy and more sugar on a daily basis. The characteristics of controls according to their AS intake were similar to those of the whole population (Table S1). The characteristics of the study population by diabetes status are presented in Table S2. Participants with diabetes were more likely to be older, be men, have lower education levels, have a greater BMI and were less likely to be never smokers. Additionally, individuals with diabetes were more likely to consume less energy, less sugar and more AS on a daily basis.

3.2 | Artificial sweeteners, aspartame and cancer risk

In Table 2, we present the results for the associations between the consumption of aspartame and other AS and the risk of cancer in the MCC-Spain study. Overall, we observed that in all participants the consumption of AS was not associated with cancer risk (for colorectal cancer, prostate cancer, stomach cancer, breast cancer and CLL). Among participants in the medium category of consumption of aspartame-containing products, we observed slightly lower odds of colorectal cancer, prostate cancer, CLL and all breast cancers.

Among participants with diabetes, those with a high consumption of other AS had higher odds of colorectal cancer (OR = 1.58, 1.05-2.41, *P* trend = .03) and of stomach cancer (OR = 2.27, 0.99-5.44, *P* trend = .06). We observed similar trends for high consumption of other AS and CLL compared with non-consumers (OR = 2.74, 0.67-12.09, *P* trend = .2), nevertheless, results were not statistically significant. Also, high consumption of aspartame-containing products was associated with higher odds of stomach cancer (OR = 2.04, 0.70-5.40, *P* trend = .05) and non-significantly with prostate cancer (OR = 1.91, 0.87-4.20, *P* trend = .3), but lower odds of all breast cancers compared with non-consumers (OR = 0.28, 0.08-0.83, *P* trend = .03).

TABLE 1 Characteristics of the study population (N = 8452) from the Spanish Multicase-control (MCC-Spain) study.

	All participants	Total artificial sweeteners intake		
		Non-consumer	Low intake	High intake
	N = 8452	N = 4328	N = 3066	N = 1058
	N (%), mean (SD) or median [IQR]	N (%), mean (SD) or median [IQR]	N (%), mean (SD) or median [IQR]	N (%), mean (SD) or median [IQR]
Age	63.07 (11.9)	63.43 (11.8)	62.48 (12.1)	63.33 (11.7)
Women	4110 (48.6)	2084 (48.2)	1517 (49.5)	509 (48.1)
Education				
Less than primary school	1789 (21.2)	932 (21.5)	636 (20.7)	221 (20.9)
Primary school	2940 (34.8)	1495 (34.5)	1082 (35.3)	363 (34.3)
Secondary school	2260 (26.7)	1138 (26.3)	819 (26.7)	303 (28.6)
University	1463 (17.3)	763 (17.6)	529 (17.3)	171 (16.2)
Smoking status				
Never	3697 (43.7)	1970 (45.5)	1352 (44.1)	375 (35.4)
Ex-smoker	3356 (39.7)	1612 (37.2)	1240 (40.4)	504 (47.6)
Current smoker	1399 (16.6)	746 (17.2)	474 (15.5)	179 (16.9)
BMI kg/m^2	26.85 (4.42)	26.28 (4.3)	27.22 (4.4)	28.09 (4.7)
Obesity	1808 (21.4)	754 (17.4)	734 (23.9)	320 (30.2)
Diabetes	1184 (14.0)	284 (6.6)	542 (17.7)	358 (33.8)
Score WCRF	3.57 (1.0)	3.64 (1.0)	3.50 (0.9)	3.44 (0.9)
Night shift	1481 (18.9)	745 (18.7)	537 (18.6)	199 (20.3)
Radiotherapy	335 (4.0)	164 (3.8)	130 (4.2)	41 (3.9)
Energy intake kcal/day	1953.88 (681.0)	1911.46 (629.9)	1950.73 (682.8)	2136.50 (831.1)
Red meat intake g/day	31.39 (25.5)	31.45 (25.7)	31.05 (24.3)	32.16 (27.8)
Fruit & vegetables g/day	530.58 (287.5)	519.02 (269.6)	532.45 (286.9)	572.48 (349.9)
Dairy products g/day	341.55 (186.5)	331.23 (186.7)	333.41 (173.9)	407.34 (206.9)
Alcohol g/day	10.99 (17.0)	10.91 (17.1)	10.97 (16.3)	11.36 (18.4)
Dietary fibre g/day	22.57 (9.9)	22.03 (9.1)	22.79 (9.8)	24.12 (12.8)
Sugar g/day	108.39 (46.5)	107.45 (42.9)	107.64 (46.5)	114.43 (58.8)
Aspartame-containing products[a] (portions/day)	0.12 (0.4), 0.0 [0.0, 0.0]	0.0	0.14 (0.3), 0.0 [0.0, 0.1]	0.56 (1.1), 0.0 [0.0, 0.5]
Other AS (portions/day)	0.48 (0.9), 0.0 [0.0, 0.8]	0.0	0.51 (0.5), 0.4 [0.1, 1.0]	2.38 (0.8), 2.5 [2.5, 2.5]
Total AS (portions/day)	0.60 (1.0), 0.0 [0.0, 1.0]	0.0	0.65 (0.5), 0.7 [0.1, 1.0]	2.94 (0.9), 2.5 [2.5, 2.9]
Pre-menopausal	1122 (27.3)	551 (26.5)	428 (28.2)	143 (28.1)
Nulliparous	755 (18.4)	395 (19.0)	278 (18.3)	82 (16.1)
Ever hormonal contraceptive	1817 (44.2)	897 (43.0)	675 (44.6)	245 (48.1)
Cancer cases				
Colorectal cancer	1881 (35.0)	987 (35.7)	644 (33.5)	250 (36.0)
Breast cancer	1510 (47.4)	775 (48.2)	553 (46.8)	182 (46.1)
Prostate cancer	972 (42.6)	513 (44.6)	354 (41.7)	105 (37.1)
Stomach cancer	351 (10.4)	163 (9.6)	138 (10.9)	50 (11.8)
CLL	109 (6.3)	52 (5.9)	39 (6.2)	18 (7.8)

Abbreviations: AS, artificial sweeteners; BMI, body-mass index; CLL, chronic lymphocytic leukaemia; IQR, interquartile range; N, sample size; WCRF, World Cancer Research Fund.

[a]We distinguished aspartame-containing products (low- or no-calorie soft drinks and table-top sweeteners other than saccharin), and other artificial sweeteners (saccharin and gaseosa). The variable total artificial sweeteners were a combination of both variables.

TABLE 2 Consumption of aspartame and other artificial sweeteners (AS) and cancer risk in the MCC-Spain study (2008-2013, N = 8452).

		All participants			Participants without diabetes			Participants with diabetes		
		N cases/controls	OR (95% CI)[a]	*P* value[b]	N cases/controls	OR (95% CI)	*P* value	N cases/controls	OR (95% CI)	*P* value
Colorectal cancer										
Aspartame containing products	Non-consumers	1620/2796	Ref	.1	1358/2438	Ref	.04	262/358	Ref	1.0
	Medium intake	172/508	0.76 (0.62-0.93)		127/422	0.74 (0.59-0.93)		45/86	0.82 (0.52-1.27)	
	High intake	89/194	0.94 (0.71-1.25)		57/147	0.87 (0.61-1.21)		32/47	1.09 (0.63-1.87)	
Other AS	Non-consumers	1070/2047	Ref	.9	991/1889	Ref	.2	79/158	Ref	.03
	Medium intake	586/1062	1.01 (0.88-1.16)		430/862	0.94 (0.81-1.1)		156/200	1.54 (1.05-2.25)	
	High intake	225/389	0.99 (0.81-1.21)		121/256	0.85 (0.66-1.1)		104/133	1.58 (1.05–2.41)	
Prostate cancer										
Aspartame containing products	Non-consumers	814/1070	Ref	.4	704/873	Ref	.2	110/197	Ref	.3
	Medium intake	110/172	0.81 (0.61-1.07)		87/119	0.84 (0.61-1.15)		23/53	0.85 (0.45-1.56)	
	High intake	48/66	0.96 (0.63-1.46)		30/43	0.82 (0.48-1.36)		18/23	1.91 (0.87–4.2)	
Other AS	Non-consumers	564/727	Ref	.1	520/651	Ref	.4	44/76	Ref	.9
	Medium intake	314/420	0.95 (0.78-1.16)		251/306	0.99 (0.79-1.24)		63/114	1.01 (0.58-1.75)	
	High intake	94/161	0.78 (0.57-1.05)		50/78	0.79 (0.53-1.19)		44/83	0.99 (0.54-1.81)	
Stomach cancer										
Aspartame containing products	Non-consumers	290/2435	Ref	.8	251/2106	Ref	.5	39/329	Ref	.05
	Medium intake	42/430	1.01 (0.69-1.46)		28/352	0.84 (0.53-1.29)		14/78	2.02 (0.92-4.27)	
	High intake	19/165	1.09 (0.62-1.83)		12/129	0.89 (0.43-1.66)		7/36	2.04 (0.70–5.40)	
Other AS	Non-consumers	188/1755	Ref	.2	176/1618	Ref	.7	12/137	Ref	.06
	Medium intake	117/945	1.13 (0.87-1.47)		89/757	1.08 (0.81-1.44)		28/188	1.59 (0.73-3.64)	
	High intake	46/330	1.23 (0.84-1.77)		26/212	1.05 (0.64-1.66)		20/118	2.27 (0.99–5.44)	
Chronic lymphocytic leukaemia										
Aspartame containing products	Non-consumers	89/1294	Ref	.6	75/1105	Ref	.4	14/214	Ref	.4
	Medium intake	9/235	0.56 (0.25-1.08)		7/190	0.56 (0.23-1.18)		2/45	0.55 (0.08-2.37)	
	High intake	11/102	1.76 (0.84-3.41)		9/77	2.15 (0.93–4.51)		2/25	0.63 (0.06-3.41)	
Other AS	Non-consumers	57/961	Ref	.2	52/873	Ref	.4	5/88	Ref	.2
	Medium intake	38/492	1.35 (0.86-2.08)		32/388	1.49 (0.92-2.38)		6/104	1.15 (0.29-4.76)	
	High intake	14/178	1.36 (0.70-2.51)		7/111	1.07 (0.42-2.36)		7/67	2.74 (0.67–12.09)	
All breast cancers										
Aspartame containing products	Non-consumers	1146/1255	Ref	.2	1065/1159	Ref	.4	81/96	Ref	.03
	Medium intake	265/313	0.82 (0.67-1.01)		242/286	0.81 (0.66-1.01)		23/27	0.73 (0.33-1.57)	

TABLE 2 (Continued)

		All participants			Participants without diabetes			Participants with diabetes		
		N cases/ controls	OR (95% CI)[a]	*P* value[b]	N cases/ controls	OR (95% CI)	*P* value	N cases/ controls	OR (95% CI)	*P* value
	High intake	99/106	0.94 (0.69-1.28)		91/89	1.04 (0.75-1.45)		8/17	0.28 (0.08–0.83)	
Other AS	Non-consumers	924/995	Ref	.3	881/947	Ref	.3	43/48	Ref	.6
	Medium intake	434/501	0.95 (0.8-1.13)		387/440	0.95 (0.79-1.13)		47/61	0.90 (0.45-1.8)	
	High intake	152/178	0.90 (0.7-1.16)		130/147	0.91 (0.69-1.19)		22/31	0.82 (0.35-1.87)	
Premenopausal breast cancer										
Aspartame containing products	Non-consumers	377/309	Ref	.1						
	Medium intake	121/126	0.80 (0.57-1.13)							
	High intake	43/48	0.74 (0.45-1.21)							
Other AS	Non-consumers	351/295	Ref	.6						
	Medium intake	136/136	0.86 (0.62-1.20)							
	High intake	54/52	0.97 (0.61-1.55)							
Postmenopausal breast cancer										
Aspartame containing products	Non-consumers	769/946	Ref	.8						
	Medium intake	144/187	0.84 (0.65-1.10)							
	High intake	56/58	1.15 (0.76-1.74)							
Other AS	Non-consumers	573/700	Ref	.4						
	Medium intake	298/365	0.97 (0.79-1.20)							
	High intake	98/126	0.87 (0.63-1.19)							

[a]Models were adjusted for age, sex (when applicable), study centre, education, smoking, radiation exposure, total WCRF score continuous, total energy intake, total sugar intake. Colorectal, breast and prostate cancer models were additionally adjusted for family history of site-specific cancer and night shift work. Breast cancer models were further adjusted for menopause, nulliparity, age at first child and use of hormonal contraceptives. The models for aspartame-containing sweeteners and other artificial sweeteners were mutually adjusted.
[b]*P* value for trend.

TABLE 3 Consumption of artificial sweeteners (AS) and sugar and cancer risk in the MCC-Spain study (2008–2013, N = 8452).

	All participants			Participants without diabetes			Participants with diabetes		
	N cases/controls	OR (95% CI)[a]	*P* value[b]	N cases/controls	OR (95% CI)	*P* value	N cases/controls	OR (95% CI)	*P* value
Colorectal cancer									
Low sugar, no AS	465/851	Ref	.9	420/763	Ref	.6	45/88	Ref	.2
Low sugar, medium AS	310/671	0.84 (0.69-1.02)		210/520	0.76 (0.61-0.94)		100/151	1.41 (0.88-2.29)	
Low sugar, high AS	112/237	0.81 (0.62-1.07)		50/152	0.61 (0.42-0.88)		62/85	1.53 (0.90-2.61)	
High sugar, no AS	522/925	0.98 (0.81-1.18)		497/888	0.94 (0.77-1.14)		25/37	1.42 (0.70-2.85)	
High sugar, medium AS	334/607	0.96 (0.78-1.18)		276/536	0.89 (0.71-1.12)		58/71	1.54 (0.86-2.79)	
High sugar, high AS	138/207	1.00 (0.75-1.33)		89/148	0.92 (0.66-1.29)		49/59	1.64 (0.86-3.10)	
Prostate cancer									
Low sugar, no AS	243/291	Ref	.01	221/250	Ref	.02	22/41	Ref	.5
Low sugar, medium AS	175/250	0.81 (0.61–1.07)		125/170	0.78 (0.57-1.07)		50/80	1.41 (0.69-2.93)	
Low sugar, high AS	47/87	0.70 (0.46-1.06)		21/36	0.64 (0.34-1.18)		26/51	1.27 (0.58-2.81)	
High sugar, no AS	270/345	0.80 (0.60-1.06)		256/326	0.74 (0.54-0.99)		14/19	1.40 (0.52-3.76)	
High sugar, medium AS	179/244	0.69 (0.51-0.94)		161/200	0.71 (0.50-0.99)		18/44	0.67 (0.27-1.61)	
High sugar, high AS	58/91	0.59 (0.38-0.90)		37/53	0.57 (0.33-0.96)		21/38	1.10 (0.45-2.70)	
Stomach cancer									
Low sugar, no AS	61/721	Ref	.2	57/645	Ref	.9	4/76	Ref	.01
Low sugar, medium AS	62/592	1.24 (0.84-1.82)		47/452	1.20 (0.79-1.83)		15/140	2.02 (0.64-7.86)	
Low sugar, high AS	20/199	1.27 (0.72-2.18)		11/123	1.09 (0.51-2.14)		9/76	2.85 (0.81-11.78)	
High sugar, no AS	102/808	1.12 (0.78-1.63)		98/775	1.03 (0.7-1.53)		4/33	2.09 (0.41-10.54)	
High sugar, medium AS	76/534	1.30 (0.87-1.95)		60/466	1.10 (0.71-1.70)		16/68	3.79 (1.13-15.41)	
High sugar, high AS	30/176	1.45 (0.84-2.46)		18/126	1.07 (0.55-2.01)		12/50	5.10 (1.39–22.11)	
Chronic lymphocytic leukaemia									
Low sugar, no AS	30/418	Ref	.1	25/368	Ref	.2			
Low sugar, medium AS	16/320	0.65 (0.34-1.21)		11/239	0.66 (0.3-1.34)				
Low sugar, high AS	8/118	0.97 (0.4-2.12)		5/70	1.14 (0.37-2.92)				
High sugar, no AS	22/409	0.82 (0.43-1.54)		22/387	0.84 (0.43-1.61)				
High sugar, medium AS	23/272	1.41 (0.74-2.67)		22/239	1.51 (0.77-2.96)				
High sugar, high AS	10/94	1.93 (0.78–4.46)		6/69	1.56 (0.51-4.18)				
All breast cancers									
Low sugar, no AS	389/434	Ref	.8	364/408	Ref	.6	25/26	Ref	.5
Low sugar, medium AS	269/332	0.85 (0.68–1.07)		241/280	0.88 (0.69-1.12)		28/52	0.67 (0.29-1.53)	
Low sugar, high AS	81/127	0.66 (0.48-0.93)		71/102	0.73 (0.51-1.05)		10/25	0.31 (0.10-0.88)	

TABLE 3 (Continued)

	All participants			Participants without diabetes			Participants with diabetes		
	N cases/controls	OR (95% CI)[a]	*P* value[b]	N cases/controls	OR (95% CI)	*P* value	N cases/controls	OR (95% CI)	*P* value
High sugar, no AS	386/398	0.96 (0.76-1.21)		373/388	0.95 (0.75-1.21)		13/10	1.54 (0.44-5.45)	
High sugar, medium AS	284/297	0.89 (0.69-1.14)		263/279	0.88 (0.68-1.13)		21/18	0.94 (0.32-2.72)	
High sugar, high AS	101/86	1.09 (0.76-1.57)		86/77	1.03 (0.7-1.52)		15/9	1.52 (0.40-5.81)	
Premenopausal breast cancer									
Low sugar, no AS	128/121	Ref	.9						
Low sugar, medium AS	93/104	0.85 (0.56-1.29)							
Low sugar, high AS	33/46	0.74 (0.42-1.29)							
High sugar, no AS	152/101	1.12 (0.73-1.71)							
High sugar, medium AS	100/91	0.78 (0.49-1.24)							
High sugar, high AS	35/20	1.27 (0.64-2.57)							
Postmenopausal breast cancer									
Low sugar, no AS	261/313	Ref	.9						
Low sugar, medium AS	176/228	0.88 (0.67-1.16)							
Low sugar, high AS	48/81	0.66 (0.43-1.00)							
High sugar, no AS	234/297	0.92 (0.7-1.22)							
High sugar, medium AS	184/206	0.96 (0.71-1.29)							
High sugar, high AS	66/66	1.05 (0.68-1.63)							

Note: The categorisation of sugar was done calculating the median among sugar consumers in controls to compare low consumers (<3rd quartile, 100 g/day) and high consumers (≥3rd quartile).

[a]Models were adjusted for age, sex (when applicable), study centre, education, smoking, radiation exposure, total WCRF score continuous, total energy intake, total sugar intake. Colorectal, breast and prostate cancer models were additionally adjusted for family history of site-specific cancer and night shift work. Breast cancer models were further adjusted for menopause, nulliparity, age at first child and use of hormonal contraceptives. The models for aspartame-containing sweeteners and other artificial sweeteners were mutually adjusted.

[b]*P* value for trend.

In individuals without diabetes, there were lower odds of colorectal cancer, in the medium category of aspartame consumption compared with non-consumers (OR = 0.74, 0.59-0.93, *P* trend = .04). A non-significant association between high consumption of aspartame and CLL (OR = 2.15, 0.93-4.51, *P* trend = .4) was also observed in individuals without diabetes.

3.3 | Sugar and artificial sweeteners and cancer risk

Participants with a highest consumption of AS had also the highest daily consumption of sugar compared with medium AS consumers or non-consumers (Table 1). To disentangle these two effects, we present the results by combining the consumption of all AS and sugar (Table 3).

Overall, we observed no association between AS and sugar consumption and risk of colorectal cancer in all participants and participants without diabetes. Among individuals with diabetes, we observed non-significant higher odds of colorectal cancer associated with high AS intake, similar at low and high sugar intake (*P* trend = .2). Compared with individuals not consuming AS and with a low sugar intake, AS use was associated with a lower risk of prostate cancer (*P* trend = .01), in particular for the high sugar, medium and high AS use. Similar trends were observed among participants without diabetes (*P* trend = .02). Participants consuming high levels of AS had non-significant higher odds of stomach cancer (*P* trend = .2). This association was significant, in combination with a high sugar intake (OR = 5.10, 1.39-22.11, *P* trend = .01) for individuals with diabetes only (although the reference group only includes 4 cases), but not in participants without diabetes. In all participants, a high consumption of AS in combination with sugar was linked with slightly higher odds of CLL, but results were not significant (1.93, 0.78-4.46, *P* trend = .1). For breast cancer, no significant trend was observed, although sugar consumption seemed to be associated with higher odds regardless of AS use in women with diabetes, whereas high AS consumption combined with low-sugar intake was associated with lower odds of breast cancer.

3.4 | Sensitivity analyses

Adjustment for lifestyle factors separately (Table S3), to address more precisely the potential confounding by BMI and other dietary factors, showed that the associations between aspartame and other AS and stomach cancer were no longer statistically significant, although the trend was the same. The associations between other AS and higher colorectal cancer odds and of aspartame and lower breast cancer odds were maintained. Removing adjustment for BMI the year prior to the inclusion did not change the results (Table S4). When including weight change between assessment of exposure to AS and diagnosis, results for aspartame and stomach cancer and other AS and colorectal cancer (Table S5) remained similar to those in our main models (Table 2). We explored the association between consumption of low- or no-calorie soft drinks and cancer risk (Table S6), and inverse associations for breast and colorectal cancer were stronger compared with results for all aspartame-containing products evaluated in Table 3. Results for stomach, CLL and prostate cancer remained similar.

We examined the link between saccharin intake and cancer risk (Table S7). In general, we did not observe an association with cancer risk, although non-significantly higher estimates were observed among participants with diabetes for colorectal cancer (OR = 1.32, 0.89-1.97, *P* trend = .2), stomach cancer (OR = 1.87, 0.86-1.56, *P* trend = .1) and CLL (OR = 2.43, 0.64-9.60, *P* trend = .2). We observed an inverse association between high intake of saccharin and colorectal cancer among participants without diabetes (OR = 0.75, 0.57-1.00, *P* trend = .02) and for prostate cancer in all participants (OR = 0.78, 0.57-1.07, *P* trend = .06).

For prostate and colorectal cancer, further adjustment for consumption of dairy products did not change our results (Table S8). Moreover, results in prostate cancer appeared to be mostly driven by the associations with low-grade tumours, and less clear for high-grade aggressive cancers (Table S9).

4 | DISCUSSION

In this study, we investigated the association between aspartame-containing products and other AS and the risk of cancer with data from the MCC-Spain study. Overall, we observed no association between AS consumption and cancer risk in all participants. In individuals with diabetes, findings suggest that the consumption of aspartame-containing products and other AS might be associated with higher odds of stomach cancer and that a high consumption of AS other than aspartame might be linked with colorectal cancer.

A recent review of human and animal studies concluded that aspartame consumption is not carcinogenic to humans, on the basis of inadequate data.[30] For humans, evidence was based on a large review by the WHO[16] and two later studies.[17,18] The WHO-commissioned review, which included 48 studies on cancer incidence, reported no association between AS-containing beverages and risk of any cancer in prospective studies (9 studies included, HR = 1.02, 0.95-1.09). No statistically significant associations were found for high intakes of primarily AS-containing beverages and brain and breast cancer nor for leukaemia, multiple myeloma, Hodgkin's lymphoma or non-Hodgkin's lymphoma. They reported an association with increased risk of larynx cancer and cancers not related to obesity, based on data from one single study. In one of the largest studies to date with detailed dietary assessment (non-consecutive 24-h diet records, and up-to-date extensive nutritional composition table) using data from the NutriNet-Santé French cohort (2022), an association was found between aspartame consumption (from multiple dietary sources) and breast cancer and obesity-related (combined oesophagus, stomach, colorectal, liver, gallbladder, pancreas, post-menopausal breast, uterus/endometrium, ovary, kidney and multiple myeloma) cancers risk.[17] Possible explanations for this association include genotoxicity, inhibition of cell death processes, induction of angiogenesis and inflammation.[17] In a large

U.S. prospective cohort, the consumption of artificially sweetened drinks (≥2 drinks/day vs never) was associated with mortality from obesity-related cancers (HR, 1.05; 95% CI, 1.01-1.08; *P* trend = .001). This association was null after controlling for BMI suggesting confounding. However, there was an association with mortality from pancreatic cancer that was robust to BMI adjustment.[18]

In our study, participants with diabetes were much more likely to consume AS, so this stronger exposure gradient may explain the results with cancer risk only observed in people with diabetes. Moreover, some AS including aspartame can induce alterations in the gut microbiota,[31,32] and this might be more pronounced in people with diabetes who are more likely to present gut dysbiosis.[32-34] Alterations in the gut microbiota are involved in cancer genesis.[35] To our knowledge this is one of the first studies to explore the heterogeneity of associations of AS and cancer risk by diabetes status. Only one other study has explored this in relation with liver cancer and results suggested that the consumption of artificially sweetened beverages was linked to a higher risk of developing this cancer only in participants with diabetes.[27] Multiple studies have linked diet soda to a higher risk of diabetes.[16,36-39] Findings suggest that this association might be partly explained by BMI. In our study, we observed among individuals with diabetes an association between the consumption of aspartame and other AS and stomach cancer. Noticeably, sugar intake was also associated with stomach cancer, and when considering the joint exposure of AS and sugar intake, there seemed to be an additive effect of high sugar with AS. Few studies have explored the association between AS and stomach cancer, but none considered the interaction with diabetes. A meta-analysis including four prospective and four case-control studies, concluded that consumption of AS was not associated with gastrointestinal cancers overall (eg, pancreatic, hepatocellular or other hepatobiliary), but it was inversely associated with luminal gastrointestinal cancers (eg, colorectal, oesophageal, gastric).[40] The results from the WHO-commissioned revision suggested no association between AS and stomach cancer (results from 2 case-control studies and 1 cohort study).[16]

In our study, high consumption of AS was linked to higher odds of colorectal cancer among individuals with diabetes. Results from the WHO-commissioned review suggested no association with colorectal cancer neither in three case-controls studies (OR = 0.85, 0.68-1.07) nor in three cohorts (HR = 0.80, 0.63-1.01). Noticeably, none of these studies considered the interaction with diabetes status. Then, high consumption of aspartame was non-significantly associated with prostate cancer, nevertheless, when considering sugar intake, this pattern became less clear. For CLL we observed some trends for a higher risk among high consumers of AS, especially of aspartame-containing products. These results were not statistically significant; however, these results were based on very few cases, precision is very low and results have to be interpreted with caution. We chose to report them as we have available data in this study, and they can be used in future reviews or meta-analyses.

We observed that participants without diabetes and with a high consumption of aspartame-containing products had lower odds of colorectal cancer. In sensitivity analyses, when looking only at low- or no-calorie soft drinks this association in medium categories of intake was stronger and also visible in all participants. However, when combining the consumption of AS and sugar, we only observed protective estimates among participants having a low consumption of sugar, therefore we might be observing mostly the effect of overall healthier dietary habits, although we considered several variables capturing these habits (eg, WCRF/AICR score). A similar pattern was also observed for breast cancer. In participants with diabetes, a high consumption of aspartame-containing products was associated with a lower risk of breast cancer. However, this was only observed in participants with a low sugar consumption, which could indicate some residual confounding by a healthier diet. Moreover, results were based on few participants which affected the precision of these analyses. An inverse association has been also observed in one case-control study[41] and one cohort study,[42] however, findings from the WHO-commissioned review on non-sugar sweeteners suggest no overall association.[16]

In models combining the consumption of AS and sugar, we found an inverse association between high sugar and AS intake and risk of prostate cancer. This association was observed in all participants and participants without diabetes, but not in participants with diabetes. In contrast to these findings, a high consumption of sugar has been associated with a higher risk of prostate cancer.[43] The inverse associations that we observed in some cases could also be a result of participants replacing sugary-sweetened soda for artificially sweetened soda.

Finally, in sensitivity analyses we explored the associations with saccharin intake and overall, we observed no association with cancer risk. In terms of statistical significance, there was only some evidence for an inverse association with colorectal cancer risk among participants without diabetes, however, possibly due to some degree of residual confounding.

Our findings suggest that individuals consuming high levels of AS have in general a less healthy lifestyle (smokers, a lower WCRF/AICR score and consuming more energy and sugar). This is similar to what was found in the NutriNet-Santé cohort,[17] participants with the highest consumption of AS being more likely to be in a weight-loss diet, but also having the highest consumption of ultra-processed foods and of sugary drinks. Overall, this indicates that individuals consuming the highest levels of AS have a less healthy lifestyle and residual confounding cannot be completely ruled out. In the NutriNet-Santé study, as in the present study, high consumers of AS tended to have higher BMI and more often prevalent diabetes. The NutriNet-Santé results are not presented by diabetes status and in that study prevalent cases of diabetes were excluded as a sensitivity analysis. Our results indicate that diabetic status should be taken carefully into account in studies on AS and cancer.

In our study, 49% of participants consumed AS. This figure is lower than that of a previous study, where authors showed that in a Spanish adult population (N = 507), 79% of the sample consumed food products containing AS on a daily basis.[9] This difference could be explained because in our study, we could only include AS coming from beverages or table-top sweeteners but no other sources. In the French NutriNet-Santé study, the percentage of AS

consumers was 36.9%, including AS coming from all food sources.[17] Since we observed that high consumers of AS tend to have a less healthy lifestyle, and it has been documented that the NutriNet-Santé cohort overrepresents individuals with healthier behaviours,[44] that might explain partly the low proportion of AS consumers in that cohort.

The strengths of this study are the large sample size which allowed stratification by diabetes, the histopathological confirmation of cancer cases and the extensive assessment of potential confounders. Moreover, the study design of MCC-Spain allowed to investigate five different cancers, something which is unusual in most case-control studies. However, some limitations have to be acknowledged. First, this is a case-control study, moreover, participants reported their consumption of AS the previous year through an FFQ, leading to some recall inaccuracy in exposure assessment. For this particular exposure, the risk of recall bias was unlikely to be differential among cases and controls, due to the lack of general assumptions on the risks of AS and cancer. Second, in this study we only had information on artificially sweetened beverages, table-top sweeteners and consumption of "gaseosa", but we missed information on other sources of AS such as dairy products with AS, therefore, we likely have underestimated the consumption of AS in our participants. However, in the NutriNet-Santé cohort, authors estimated that the biggest source of AS were coming from soft drinks and table top-sweeteners (86% of the AS intake).[17] Third, the assessment of AS consumption through the FFQ in the MCC-Spain study has not been previously validated. Fourth, given the observational nature of this study, we cannot completely rule out residual confounding. Then, early symptoms may perhaps, in some cases, have influenced the consumption over the past year and might have led to some exposure misclassification, but it is not obvious in which direction it would have changed consumption of sugar and AS. Finally, in some cancers, particularly for CLL, the number of cases among individuals with diabetes were small which resulted in a low precision of our results. Given these limited numbers, chance cannot be completely dismissed and results should be interpreted with caution. Further prospective studies with repeated dietary records, with a good assessment of daily consumption of AS coming from multiple sources, could help disentangle these results.

5 | CONCLUSIONS

Our findings show that there is no clear association between consumption of aspartame and other AS and cancer risk in the MCC-Spain study. We find, however, higher risks of stomach and colorectal cancer related to a high consumption of aspartame and other AS among individuals with diabetes, while a lower risk was observed for breast cancer. In some cancers, the number of cases among participants with diabetes were small and, therefore, these results should be interpreted with caution. Given the observational nature of this study, residual confounding cannot be completely ruled out, and results have to be taken cautiously.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Data acquisition was performed by Nuria Aragonés, Gemma Castaño-Vinyals, Vicente Martin, Victor Moreno, Inés Gómez-Acebo, Marcela Guevara, Amaia Aizpurua, Ana Molina-Barceló, José-Juan Jiménez-Moleón, Adonina Tardón, Manuel Contreras-Llanes, Rafael Marcos-Gragera, José Mª Huerta, Beatriz Pérez-Gómez, Ana Espinosa, Natalia Hernández-Segura, Mireia Obón-Santacana, Jessica Alonso-Molero, Rosana Burgui, Pilar Amiano, Marina Pinto-Carbó, Rocio Olmedo-Requena, Guillermo Fernandez-Tardón, Vanessa Santos Sánchez, Nerea Fernández de Larrea-Baz, Tania Fernández Villa, Delphine Casabonne, Trinidad Dierssen-Sotos, Eva Ardanaz, Ane Dorronsoro, Marina Pollán, Manolis Kogevinas. Data curation was performed by Camille Lassale, Anna Palomar-Cros, Gemma Castaño-Vinyals, and Ana Espinosa. Funding acquisition was carried by Marina Pollán, Nuria Aragonés, Vicente Martin, Victor Moreno, José-Juan Jiménez-Moleón, Adonina Tardón, Rafael Marcos-Gragera, Beatriz Pérez-Gómez, Pilar Amiano, Eva Ardanaz, and Manolis Kogevinas. The formal analysis was performed by Camille Lassale and Anna Palomar-Cros. The supervision of the present study was done by Manolis Kogevinas and Kurt Straif. The first draft of the manuscript was written by Anna Palomar-Cros and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data can be provided by contacting the corresponding author and following permission by the participating centres in the MCC-Spain study. All source code is publicly available on GitHub (https://github.com/camillelassale/MCC_ARTSWEET). Further details are available from the corresponding author upon request.

ETHICS STATEMENT

The ethics committees of each included centre reviewed and approved the study protocol and participants had to sign an informed consent to be included in the study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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