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Artificial sweeteners and cancer risk in a network of case–control studies

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Background: The role of sweeteners on cancer risk has been widely debated over the last few decades. To provide additional information on saccharin and other sweeteners (mainly aspartame), we considered data from a large network of case–control studies.

Methods: An integrated network of case–control studies has been conducted between 1991 and 2004 in Italy. Cases were 598 patients with incident, histologically confirmed cancers of the oral cavity and pharynx, 304 of the oesophagus, 1225 of the colon, 728 of the rectum, 460 of the larynx, 2569 of the breast, 1031 of the ovary, 1294 of the prostate and 767 of the kidney (renal cell carcinoma). Controls were 7028 patients (3301 men and 3727 women) admitted to the same hospitals as cases for acute, non-neoplastic disorders. Odds ratios (ORs), and the corresponding 95% confidence intervals (CIs), were derived by unconditional logistic regression models.

Results: The ORs for consumption of saccharin were 0.83 (95% CI 0.30–2.29) for cancers of the oral cavity and pharynx, 1.58 (95% CI 0.59–4.25) for oesophageal, 0.95 (95% CI 0.67–1.35) for colon, 0.93 (95% CI 0.60–1.45) for rectal, 1.55 (95% CI 0.76–3.16) for laryngeal, 1.01 (95% CI 0.77–1.33) for breast, 0.46 (95% CI 0.29–0.74) for ovarian, 0.91 (95% CI 0.59–1.40) for prostate and 0.79 (95% CI 0.49–1.28) for kidney cancer. The ORs for consumption of other sweeteners, mainly aspartame, were 0.77 (95% CI 0.39–1.53) for cancers of the oral cavity and pharynx, 0.77 (95% CI 0.34–1.75) for oesophageal, 0.90 (95% CI 0.70–1.16) for colon, 0.71 (95% CI 0.50–1.02) for rectal, 1.62 (95% CI 0.84–3.14) for laryngeal, 0.80 (95% CI 0.65–0.97) for breast, 0.75 (95% CI 0.56–1.00) for ovarian, 1.23 (95% CI 0.86–1.76) for prostate and 1.03 (95% CI 0.73–1.46) for kidney cancer. A significant inverse trend in risk for increasing categories of total sweeteners was found for breast and ovarian cancer, and a direct one for laryngeal cancer.

Conclusion: The present work indicates a lack of association between saccharin, aspartame and other sweeteners and the risk of several common neoplasms.

Key words: cancer, case–control study, risk factor, sweeteners

introduction

The role of sweeteners on cancer risk has been widely debated since the 1970s, when animal studies found an excess bladder cancer risk in more than one generation of rodents treated with extremely high doses of saccharin [1], and a few earlier epidemiological studies found some association with bladder cancer risk in humans [2, 3]. Larger epidemiological studies in humans failed, however, to reproduce these findings [4–6], and it was subsequently shown that the metabolism of saccharin was species specific, and that saccharin did not lead to the formation of either urinary tract stones or epithelial lesions in humans [7].

Less is known on other sweeteners, including cyclamate and mainly aspartame [1].

With reference to aspartame, a study based on 900 male and 900 female Sprague–Dawley rats treated with variable doses of aspartame (from 0 to 100 000 p.p.m.) and followed until natural death found an apparent excess of lymphatic neoplasms in females only, in the absence of a linear trend in risk [8]. Animals treated with aspartame, however, tended to live longer than untreated ones, and—in the absence of a life-table analysis—such an apparent excess may simply be due to advancing age in treated animals. Some inconsistent excess was reported also for dysplastic lesions and carcinoma of the renal

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pelvis and ureter, and for schwannomas, again in the absence of any trend in risk with dose or exposure pattern [8]. These animal data have received widespread attention [9], in the presence of limited epidemiological data on sweeteners other than saccharin and specifically aspartame on humans [1].

To provide additional information on the role of artificial sweeteners on the risk of cancer at several sites in humans, we considered data from a large and integrated network of case–control studies conducted in Italy [10–12].

materials and methods

An integrated network of case–control studies has been conducted between 1991 and 2004 in four Italian areas, including northern, central and southern regions. The studies included a total of 598 cases with incident, histologically confirmed cancers of the oral cavity and pharynx (512 males, 86 females, median age 58 years) and corresponding 1491 controls (1008 males, 483 females, median age 57 years) [13], 304 of the oesophagus (275 males, 29 females, median age 60 years) and 743 controls (593 males, 150 females, median age 60 years) [14], 1953 of the colorectum (1225 of the colon and 728 of the rectum; 1125 males, 828 females, median age 62 years) and 4154 controls (2073 males, 2081 females, median age 58 years) [15], 460 of the larynx (415 males, 45 females, median age 61 years) and 1088 controls (863 males, 225 females, median age 61 years) [16], 2569 of the female breast (median age 55 years) and 2588 controls (median age 56 years) [11], 1031 of the ovary (median age 56 years) and 2411 controls (median age 57 years) [17], 1294 of the prostate (median age 66 years) and 1451 controls (median age 63 years) [18] and 767 of the kidney (renal cell carcinoma; 494 males, 273 females, median age 62 years) and 1534 controls (988 males, 564 females, median age 62 years) [12]. In each study, controls were admitted to the same network of general and teaching hospitals as cases for acute, non-neoplastic disorders.

Controls enrolled in the network of studies were a total of 7028 patients (3301 men and 3727 women; 4838 controls were included in more than one study). Of these, 24% were admitted for traumas, 31% for other nontraumatic orthopaedic conditions, 17% for acute surgical disorders and 28% for miscellaneous other diseases. Less than 5% of both cases and controls contacted refused to participate.

Cases and controls were interviewed during their hospital stay, using a structured questionnaire, including information on sociodemographic factors, anthropometric variables, tobacco and alcohol consumption and other lifestyle habits. The subjects' usual diet in the 2 years before diagnosis (or hospital admission for controls) was investigated using a reproducible [19] and valid [20] 78-item food-frequency questionnaire (FFQ). From this, we derived total energy intake using Italian food composition tables [21]. The FFQ included specific questions on weekly consumption of sugar expressed in teaspoons/week, saccharin, and other sweeteners, expressed in sachets or tablets/week. For the present analyses, categories of consumption were expressed in sachets or tablets/day.

Odds ratios (ORs), and the corresponding 95% confidence intervals (CIs), for consumption of sweeteners were derived by unconditional multiple logistic regression models [22], including terms for age (quinquennia), sex, study centre, education (<7, 7–12, ≥12 years), alcohol drinking (<14, 14–27, ≥28 drinks/week), tobacco smoking (never smokers, ex-smokers, current smokers of <15, 15–24, ≥25 cigarettes/day), body mass index (BMI in kg/m^2, tertiles), total energy intake (quintiles) and consumption of hot beverages (quartiles). For breast and ovarian cancers, estimates were further adjusted for parity and menopausal status/age at menopause.

results

Table 1 shows the distribution of various cancer cases and controls according to consumption of saccharin and other sweeteners. The percentage of users of saccharin or other sweeteners ranged between 3% and 13% for the various groups of cases, and between 7% and 15% among corresponding groups of control subjects.

Table 2 shows the ORs of the cancers considered for consumption of saccharin, other sweeteners and all sweeteners. The ORs for >2 versus 0 sachets or tablets/day of all sweeteners were 0.77 (95% CI 0.36–1.64) for cancers of the oral cavity and pharynx, 1.24 (0.54–2.81) for oesophageal, 0.89 (95% CI 0.65–1.21) for colon, 0.80 (95% CI 0.54–1.19) for rectal, 2.34 (95% CI 1.20–4.55) for laryngeal, 0.70 (95% CI 0.54–0.91) for breast, 0.56 (95% CI 0.38–0.81) for ovarian, 1.19 (95% CI 0.80–1.79) for prostate and 0.96 (95% CI 0.64–1.42) for kidney cancer. The trends in risk and the continuous terms for an increment of one sachet or tablet/day were significant for laryngeal (direct), breast and ovarian cancer (inverse). The ORs for consumption of saccharin were 0.83 (95% CI 0.30–2.29) for cancers of the oral cavity and pharynx, 1.58

Table 1. Distribution[a] of cases of selected cancers and corresponding controls according to consumption of sweeteners

Cancer site	Number of cases : number of controls						
	Artificial sweeteners			Saccharin		Other sweeteners	
	Sachet or tablet/day			Sachet or tablet/day		Sachet or tablet/day	
	0	>0–2	>2	0	>0	0	>0
Oral cavity and pharynx	580 : 1380	8 : 51	10 : 60	592 : 1465	6 : 26	586 : 1405	12 : 86
Oesophagus	286 : 683	6 : 31	12 : 28	296 : 724	8 : 19	294 : 702	10 : 40
Colon	1096 : 3683	70 : 245	59 : 226	1181 : 4004	44 : 150	1137 : 3827	88 : 327
Rectum	664 : 3683	32 : 245	32 : 226	703 : 4004	25 : 150	689 : 3827	39 : 327
Larynx	423 : 1006	13 : 47	24 : 35	443 : 1059	17 : 29	439 : 1033	21 : 55
Breast	2244 : 2206	210 : 216	115 : 166	2456 : 2468	113 : 120	2350 : 2318	219 : 270
Ovary	936 : 2053	55 : 182	40 : 176	1007 : 2285	24 : 126	958 : 2175	73 : 236
Prostate	1179 : 1335	56 : 63	59 : 52	1252 : 1402	42 : 49	1217 : 1382	77 : 68
Renal cell carcinoma	687 : 1368	39 : 81	41 : 85	741 : 1474	26 : 60	710 : 1425	57 : 109

[a]In some of the cancer sites considered, the sum does not add up to the total because of missing values.

(95% CI 0.59–4.25) for oesophageal, 0.95 (95% CI 0.67–1.35) for colon, 0.93 (95% CI 0.60–1.45) for rectal, 1.55 (95% CI 0.76–3.16) for laryngeal, 1.01 (95% CI 0.77–1.33) for breast, 0.46 (95% CI 0.29–0.74) for ovarian, 0.91 (95% CI 0.59–1.40) for prostate and 0.79 (95% CI 0.49–1.28) for kidney cancer. The ORs for users versus nonusers of other sweeteners, mainly aspartame, were 0.77 (95% CI 0.39–1.53) for cancers of the oral cavity and pharynx, 0.77 (95% CI 0.34–1.75) for oesophageal, 0.90 (95% CI 0.70–1.16) for colon, 0.71 (95% CI 0.50–1.02) for rectal, 1.62 (95% CI 0.84–3.14) for laryngeal, 0.80 (95% CI 0.65–0.97) for breast, 0.75 (95% CI 0.56–1.00) for ovarian, 1.23 (95% CI 0.86–1.76) for prostate and 1.03 (95% CI 0.73–1.46) for kidney cancer.

Table 3 shows the OR for the continuous term for an increment of one sweetener sachet or tablet/day in strata of age, sex and BMI. There was no consistent heterogeneity across most of the strata considered, the only significant differences being observed for strata of sex for kidney and of BMI for oral and pharyngeal cancers. Likewise, apart from the differences in risk found in strata of hot beverages for laryngeal, and of smoking for oesophageal cancer, no systematic heterogeneity was observed across strata of alcohol and hot beverage consumption, smoking and history of weight-reduction diet.

The multivariate ORs for ≥5 versus <1 teaspoon/day of sugar were 1.41 (95% CI 0.95–2.11) for cancers of the oral cavity and pharynx, 1.61 (95% CI 0.97–2.70) for oesophageal, 1.30 (95% CI 1.05–1.62) for colon, 1.43 (95% CI 1.09–1.87) for rectal, 1.46 (95% CI 0.98–2.17) for laryngeal, 1.22 (95% CI 1.02–1.47) for breast, 1.58 (95% CI 1.23–2.04) for ovarian, 0.86 (95% CI 0.67–1.11) for prostate and 1.06 (95% CI 0.80–1.41) for kidney cancer.

Table 2. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) of selected cancers according to consumption of saccharin and other sweeteners

Cancer site	Artificial sweeteners				Saccharin	Other sweeteners
	Sachet or tablet/day		χ^2 trend, *P* value	Continuous term, increment of one sachet or tablet/day OR[a] (95% CI)	Sachet or tablet/day >0 OR[a,b] (95% CI)	Sachet or tablet/day >0 OR[a,b] (95% CI)
	>0–2 OR[a,b] (95% CI)	>2 OR[a,b] (95% CI)				
Oral cavity and pharynx	0.81 (0.35–1.90)	0.77 (0.36–1.64)	0.64, 0.424	0.89 (0.76–1.06)	0.83 (0.30–2.29)	0.77 (0.39–1.53)
Oesophagus	0.78 (0.29–2.11)	1.24 (0.54–2.81)	0.08, 0.784	1.01 (0.85–1.21)	1.58 (0.59–4.25)	0.77 (0.34–1.75)
Colon	0.91 (0.68–1.21)	0.89 (0.65–1.21)	0.92, 0.338	0.96 (0.90–1.02)	0.95 (0.67–1.35)	0.90 (0.70–1.16)
Rectum	0.77 (0.52–1.13)	0.80 (0.54–1.19)	2.33, 0.127	0.94 (0.86–1.02)	0.93 (0.60–1.45)	0.71 (0.50–1.02)
Larynx	1.23 (0.59–2.57)	2.34 (1.20–4.55)	6.11, 0.014	1.16 (1.04–1.30)	1.55 (0.76–3.16)	1.62 (0.84–3.14)
Breast[c]	0.97 (0.79–1.19)	0.70 (0.54–0.91)	5.92, 0.015	0.94 (0.89–0.99)	1.01 (0.77–1.33)	0.80 (0.65–0.97)
Ovary[c]	0.68 (0.49–0.95)	0.56 (0.38–0.81)	13.61, <0.001	0.87 (0.80–0.94)	0.46 (0.29–0.74)	0.75 (0.56–1.00)
Prostate	0.97 (0.66–1.43)	1.19 (0.80–1.79)	0.47, 0.492	1.03 (0.95–1.12)	0.91 (0.59–1.40)	1.23 (0.86–1.76)
Renal cell carcinoma	0.87 (0.58–1.30)	0.96 (0.64–1.42)	0.23, 0.632	0.99 (0.91–1.07)	0.79 (0.49–1.28)	1.03 (0.73–1.46)

[a]Estimated by unconditional multiple logistic regression models, after allowance for quinquennia of age, sex, study centre, education, tobacco smoking, alcohol drinking, body mass index, total energy intake and consumption of hot beverages.
[b]Reference category is sweetener nonconsumers.
[c]Further allowed for parity and menopausal status/age at menopause.

Table 3. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) of selected cancers, according to consumption of sweeteners in strata of body mass index (BMI), sex and age

Cancer site	Artificial sweeteners					
	Continuous term, increment of one sachet or tablet/day, OR[a] (95% CI)					
	BMI (kg/m^2)		Sex		Age (years)	
	<25	≥25	Men	Women	<60	≥60
Oral cavity and pharynx	0.60 (0.34–1.09)	0.95 (0.79–1.13)	0.97 (0.78–1.20)	0.78 (0.55–1.13)	0.78 (0.56–1.08)	0.99 (0.81–1.23)
Oesophagus	0.95 (0.63–1.44)	1.02 (0.84–1.24)	1.07 (0.88–1.32)	0.80 (0.48–1.31)	0.96 (0.73–1.26)	1.06 (0.84–1.34)
Colon	1.02 (0.92–1.13)	0.92 (0.85–1.01)	1.00 (0.91–1.10)	0.92 (0.84–1.01)	0.92 (0.82–1.03)	0.98 (0.90–1.06)
Rectum	1.04 (0.92–1.17)	0.89 (0.79–1.00)	0.98 (0.87–1.10)	0.92 (0.81–1.03)	0.95 (0.84–1.08)	0.93 (0.83–1.04)
Larynx	1.05 (0.80–1.38)	1.18 (1.03–1.34)	1.22 (1.07–1.39)	0.95 (0.71–1.28)	1.20 (1.00–1.42)	1.13 (0.97–1.32)
Breast[b]	0.90 (0.83–0.99)	0.95 (0.89–1.01)			0.94 (0.88–1.00)	0.93 (0.85–1.01)
Ovary[b]	0.80 (0.69–0.93)	0.91 (0.82–0.99)			0.88 (0.79–0.96)	0.85 (0.74–0.98)
Prostate	1.09 (0.91–1.32)	1.03 (0.94–1.13)			1.14 (0.95–1.38)	1.02 (0.93–1.11)
Renal cell carcinoma	0.96 (0.82–1.12)	1.01 (0.92–1.11)	1.10 (0.99–1.23)	0.87 (0.75–1.00)	0.95 (0.83–1.09)	1.02 (0.92–1.14)

[a]Estimated by unconditional multiple logistic regression models, after allowance for quinquennia of age, sex, study centre, education, tobacco smoking, alcohol drinking, BMI, total energy intake and consumption of hot beverages.
[b]Further allowed for parity and menopausal status/age at menopause.

discussion

Most previous epidemiological studies of sweeteners and cancer risk in humans refers to bladder and brain cancers. A case–control study including 408 cases [3] showed a 60% increased risk for bladder cancer in men (but not in women) who used artificial sweeteners, and a case–control study from the UK, including 841 cases of bladder cancer, found a slight excess risk in nonsmokers only [1, 5]. However, at least seven case–control studies of bladder or low urinary tract cancers from the United States [1, 4, 6, 23–28] found no significant association with consumption of sweeteners, and the largest case–control study analysing the issue, conducted in the United States, including 3010 cases of bladder cancer, found no relation with all sweeteners (OR = 1.01; 95% CI 0.92–1.11 for ever versus never use) [4].

An ecological study indicated a direct correlation between aspartame consumption and the incidence of brain cancer [29], but such ecological studies are known to be subject to ecological fallacy [30]. Further, this hypothesis was not confirmed by studies in animals or humans [31, 32]. Moreover, a case–control study including 56 children with brain cancer from the United States found no excess risk for all sources of aspartame (OR = 1.1; 95% CI 0.5–2.6), age at first aspartame consumption (OR = 1.2; 95% CI 0.4–3.6), duration (OR = 1.1; 95% CI 0.3–3.4) and frequency of consumption (OR = 0.9; 95% CI 0.3–2.4) [31]. The National Institute of Health—American Association of Retired Persons Diet and Health Study, a cohort study including >500 000 subjects, 2106 hematopoietic and 376 brain cancer cases, found no association with aspartame-containing beverages, the adjusted relative risk for ≥600 mg/day versus none being 0.93 (95% CI 0.72–1.19) for all hematopoietic cancers combined, and the relative risk for ≥400 mg/day versus none being 0.74 (95% CI 0.49–1.13) for brain cancer [33].

Scantier information is available on humans with reference to other cancer sites. The present study provides, to our knowledge, the first data on the relation between sweeteners and digestive tract cancers. Since the use of sweeteners is inversely correlated with sugar (Spearman correlation coefficient was −0.27 among the control group), the role of sugar on carcinogenesis should be taken into account. In our data, sugar was directly associated to the risk of digestive tract cancers. Likewise, added sugar was directly related to the risk of gastric cancer in a study conducted in northern Italy [34].

In the present data, there was a direct association between consumption of sweeteners and laryngeal cancer risk. However, we found a borderline significant association also between sugar consumption and laryngeal cancer risk.

Whereas sugar consumption was directly associated with breast cancer, we found a significant inverse association between sweeteners and breast cancer risk, in agreement with a case–control study from Denmark including 1486 breast cancer cases (OR = 0.9; 95% CI 0.7–1.2 for users versus nonusers of artificial sweeteners) [35].

Ovarian cancer risk was also inversely associated to saccharin and other sweeteners. This is even more relevant, considering the direct association found in our data between sugar consumption and ovarian cancer risk.

We found an inverse association between sweeteners and kidney cancer risk in women, but a lack of association in men. A case–control study from the United States on 315 cases found an increased risk in men (age–weight–education adjusted OR = 2.4, 95% CI 1.4–4.0 for all sweeteners), but not in women (OR = 1.3, 95% CI 0.7–2.4) [36]. Another study from the United States including 267 cases of renal cell carcinoma found no association for saccharin consumption and lifetime consumption of artificial sweeteners (OR 1.3, 95% CI 0.9–1.9 for both sexes combined) [37].

The results of the present network of studies provide a broad picture on the relation between sweeteners and cancer risk. Among the limitations of the study, there is the relatively low frequency of consumption of sweeteners in this Italian population [38], and, consequently, despite the large sample size, the relatively limited statistical power. Moreover, we did not collect information on dietetic soft drinks (containing sweeteners). However, their use is recent in Italy, and they are therefore unlikely to have appreciably contributed to the cancers in the age groups investigated. We also had no information on specific sweeteners other than saccharin. However, in a study on 212 Italian teenagers, the prevalence of aspartame users was by far the highest (76% of the whole sample versus only 6% for cyclamate) [38].

The questionnaire was administered to both cases and controls by the same interviewer under similar conditions. We also selected controls admitted for a large number of diseases unrelated to tobacco smoking, alcohol drinking and changes in diet. Information on saccharin and other sweeteners was satisfactorily reproducible (Spearman correlation coefficient was 0.47 for saccharin and 0.81 for other sweeteners) [19]. Users of sweeteners were heavier than nonusers (mean BMI 27.0 versus 25.7 kg/m^2), but strict allowance was made for BMI in the analyses. Among other strengths of our study, are the high participation rate of cases and controls, the comparable catchment areas of study subjects, the strict control for tobacco and alcohol, as well as other potential confounding factors, including education, alcohol and tobacco, total energy intake and hot beverage consumption. Moreover, after further adjustment for a measure of occupational physical activity, the estimates did not appreciably change. Given the high number of risk estimates considered in the present study, some significant results could arise by chance only. However, we did not find consistent heterogeneity across strata of age, sex, BMI, alcohol and hot beverage consumption, smoking and history of weight-reduction diet. Moreover, we compared cases with the corresponding controls within each study in order to have comparable distribution in terms of age, sex, area of residence and calendar period. This accounts for the difference in prevalence of use of sweeteners among various comparison groups.

In conclusion, therefore, this study provides no evidence that saccharin or other sweeteners (mainly aspartame) increase the risk of cancer at several common sites in humans.

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