Artificial Sweeteners and the Risk of Gastric, Pancreatic, and Endometrial Cancers in Italy

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Abstract

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 artificial or low-calorie sweeteners (mainly aspartame), we updated the analysis of an integrated network of case-control studies conducted in Italy between 1991 and 2004 including data on cancers of the stomach, pancreas, and endometrium.**

Patients and Methods: **Cases were 230 patients with incident, histologically confirmed cancers of the stomach and 547 corresponding controls, 326 of the pancreas and 652 controls, and 454 of the endometrium and 908 controls. All controls were patients admitted to the same hospitals as cases for acute, non-neoplastic disorders. Odds ratios (OR) and corresponding confidence intervals (CI) were derived by unconditional logistic regression models.**

Results: **After allowance for various confounding factors, ORs for ever users of sweeteners versus nonusers were 0.80 (95% CI, 0.45-1.43) for gastric cancer, 0.62 (95% CI, 0.37-1.04) for pancreatic cancer, and 0.96 (95% CI, 0.67-1.40) for endometrial cancer. Corresponding ORs for saccharin were 0.65, 0.19, and 0.71, and for other sweeteners were 0.86, 1.16, and 1.07, respectively, for the three cancer sites.**

Conclusions: **The present study adds further evidence on the absence of an adverse effect of low-calorie sweetener (including aspartame) consumption on the risk of common neoplams in the Italian population.** (Cancer Epidemiol Biomarkers Prev 2009;18(8):2235–8)

Introduction

The role of sweeteners on cancer risk has been widely debated since the 1970s, when animal studies found an excess risk of bladder cancer in rodents treated with extremely high doses of saccharin (1). A few epidemiologic studies also found some associations between saccharin and bladder cancer risk in humans (2-4), but most epidemiologic studies did not support the association (5-12). Subsequently, it was shown that the carcinogenic effect of saccharin is species specific (13).

With reference to aspartame and other sweeteners, animal studies have failed to show a carcinogenic activity (1, 14). Only two recent studies on rats treated with variable doses of aspartame and followed until natural death found an excess of malignant neoplams, mainly lymphomas and leukemias in females, but not in males (15, 16). Such an apparent excess can, however, be explained by the longer life of animals treated with aspartame, as well as by the higher rates of infections in the study animals (17).

Epidemiologic data on the role of aspartame in humans are scanty (1, 18). An ecologic analysis of data from the U.S. National Cancer Institute's Surveillance, Epidemiology, and End Results suggested that an increase in brain cancer incidence was related to the introduction of aspartame in the market (19). However, such study was later criticized mainly because of uncertainties on brain cancer trends and the intrinsic limitations of ecologic investigations (20). Moreover, a few subsequent case-control studies on brain cancer found no consistent evidence of an excess risk in relation to aspartame (21, 22) and aspartame-based soft drinks (23). Likewise, a cohort study from the United States found no association between aspartame-containing beverages and the risk of brain, as well as of hematopoietic cancers (24).

With reference to other cancer sites, a case-control study from Denmark reported no association with breast cancer risk (25); two case-control studies from the United States found nonsignificant and inconsistent increased risk of renal cell cancer (26, 27); and a study based on an integrated network of case-control studies conducted in Italy found no association between saccharin and other sweeteners on the risk of cancers of the oral cavity and pharynx, esophagus, colorectum, larynx, breast, ovary, prostate, and kidney (28).

To provide additional information on the role of artificial or low-calorie sweeteners on the risk of cancer, we updated the analysis of the Italian case-control studies (28), including data on cancers of the stomach, pancreas, and endometrium.

Materials and Methods

Data were derived from three Italian hospital-based case-control studies including, respectively, 230 cases

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Table 1. Distributionof cases of selected cancers and corresponding controls according to consumption of low-calorie sweeteners, with corresponding ORs and 95% CIs

Cancer site	All low-calorie sweeteners		Saccharin		Other sweeteners	
	Nonusers	Users	Nonusers	Users	Nonusers	Users
Gastric cancer						
Cases/controls	207:471	23:71	224:521	6:23	213:491	17:51
OR* (95% CI)	1†	0.78 (0.47-1.30)	1†	0.62 (0.25-1.55)	1†	0.83 (0.46-1.49)
OR*‡ (95% CI)	1†	0.80 (0.45-1.43)	1†	0.65 (0.25-1.68)	1†	0.86 (0.45-1.67)
Pancreatic cancer						
Cases/controls	281:571	45:80	316:618	10:34	291:602	35:49
OR* (95% CI)	1†	1.15 (0.77-1.70)	1†	0.57 (0.28-1.18)	1†	1.49 (0.94-2.35)
OR*‡ (95% CI)	1†	0.62 (0.37-1.04)	1†	0.19 (0.08-0.46)	1†	1.16 (0.66-2.04)
Endometrial cancer						
Cases/controls	378:780	73:123	436:867	16:39	394:816	58:87
OR* (95% CI)	1†	1.21 (0.88-1.66)	1†	0.80 (0.44-1.45)	1†	1.37 (0.96-1.95)
OR*‡ (95% CI)	1†	0.96 (0.67-1.40)	1†	0.71 (0.36-1.38)	1†	1.07 (0.71-1.61)

NOTE: The sum does not add up to the total because of missing values.
*Estimated by unconditional multiple logistic regression models adjusted for age, sex (when appropriate), and study center (when appropriate).
†Reference category.
‡Further adjusted for year of interview, education, BMI, tobacco smoking, history of diabetes, consumption of hot beverages, and total energy intake.

with incident, histologically confirmed stomach cancer (143 males, 87 females; median age, 63 y; range, 22-80 y) and 547 corresponding controls (286 males, 261 females; median age, 63 y; range, 22-80 y) enrolled between 1997 and 2007 in the greater Milan area (northern Italy; ref. 29); 326 cases with pancreatic cancer (174 males, 152 females; median age, 63 y; range, 34-80 y) and 652 corresponding controls (348 males, 304 females; median age, 63 y; range, 34-80 y) enrolled between 1991 and 2007 in the greater Milan area and the province of Pordenone (northern Italy); 454 cases with endometrial cancer (median age, 60 y; range, 18-79 y) and 908 corresponding female controls (median age, 61 y; range, 19-80 y) enrolled between 1992 and 2006 in the greater Milan area, the provinces of Udine and Pordenone (northern Italy), and the urban area of Naples (southern Italy; ref. 30).

Controls were selected among patients admitted to the same network of general and teaching hospitals as cases for acute, non-neoplastic disorders, and were frequency matched to cases by age, sex, and study center. Overall, 25% of the controls were admitted for traumas, 32% for other nontraumatic orthopaedic conditions, 15% for acute surgical disorders, and 27% 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 the same structured questionnaire, including information on sociodemographic factors, anthropometric characteristics, tobacco smoking, and other life-style habits. The subjects' usual diet in the 2 y before diagnosis (or hospital admission for controls) was investigated using a valid (31) and reproducible (32) 78-items food frequency questionnaire. The food frequency questionnaire included specific questions on weekly consumption of saccharin and other low-calorie sweeteners (mainly aspartame) expressed in sachets or tablets per week, as well of sugar expressed in teaspoons per week. Total energy intake was estimated using Italian food composition tables (33, 34).

Odds ratios (OR) and the corresponding 95% confidence intervals (CI) for consumption of sweeteners (and, for comparative purpose, for consumption of sugar) were derived by unconditional multiple logistic regression models (35). Two models were considered: the former included terms for the matching variables, i.e., age (seven categories), sex (when appropriate), and study center (when appropriate); the latter included additional terms for year of interview (continuous term); education (<7/7-12/≥12 y); body mass index (BMI in kg/m^2, <20/20-24.9/25-29.9/≥30); tobacco smoking (never smokers/ex-smokers/current smokers of <15/15-24/≥25 cigarettes/d); history of diabetes (no/yes); consumption of hot beverages, including coffee, decaffeinated coffee, and tea (approximate quartiles); and total energy intake (approximate quintiles). Findings from the last (fully adjusted) models only are described in the Results section. Analyses across strata of selected covariates (i.e., sex, age, education, BMI, total energy intake, history of diabetes, smoking status, and hot beverages) were also conducted. In the stratum of subjects with a history of diabetes, a more parsimonious model was used because of the limited number of subjects. To test for interactions, the differences in −2log(likelihood) of the models with and without an interaction term were compared with the χ^2 distribution with one degree of freedom.

Results

Table 1 gives the distribution of various cancer cases and controls according to consumption of all low-calorie sweeteners, saccharin, and other sweeteners, and the corresponding ORs. After allowance for selected covariates, the ORs for ever users of low-calorie sweeteners versus nonusers were 0.80 (95% CI, 0.45-1.43) for gastric cancer, 0.62 (95% CI, 0.37-1.04) for pancreatic cancer, and 0.96 (95% CI, 0.67-1.40) for endometrial cancer. Corresponding ORs for saccharin were 0.65 (95% CI, 0.25-1.68), 0.19 (95% CI, 0.08-0.46), and 0.71 (95% CI, 0.36-1.38), and for other sweeteners were 0.86 (95% CI, 0.45-1.67), 1.16 (95% CI, 0.66-2.04), and 1.07 (95% CI, 0.71-1.61), respectively, for the three cancer sites. The OR for endometrial cancer after further allowance for menopausal status, parity, and use of oral contraceptives and hormone replacement therapy was 0.98 (95% CI, 0.67-1.44). The ORs for consumption of >2 versus 0 sachets or tablets per day of all low-calorie

sweeteners were 0.58 (95% CI, 0.27-1.25) for stomach cancer, 0.84 (95% CI, 0.42-1.65) for pancreatic, and 0.88 (95% CI, 0.56-1.40) for endometrial cancer, in the absence of a trend in risk for all the cancer sites considered. When we excluded diabetic cases and controls, the ORs for all low-calorie sweetener users were 0.71 (95% CI, 0.36-1.38) for gastric cancer, 0.59 (95% CI, 0.32-1.09) for pancreatic, and 1.03 (95% CI, 0.69-1.54) for endometrial cancer. The multivariate ORs for ever users versus never users of sugar were 1.46 (95% CI, 0.92-2.30) for gastric cancer, 2.13 (95% CI, 1.40-3.26) for pancreatic, and 1.18 (95% CI, 0.85-1.63) for endometrial cancer.

Table 2 shows the ORs for ever users of low-calorie sweeteners in strata of selected covariates, including sex, age, education, BMI, total energy intake, history of diabetes, smoking status, and hot beverages. There was no heterogeneity across the strata of the covariates considered, the apparent differences in risk being likely due to the play of chance, giving the small number of sweetener users.

Discussion

The results of the present study indicate that the consumption of sweeteners is not associated to the risk of cancer of the stomach, pancreas, and endometrium. No other epidemiologic studies that addressed the role of sweeteners on cancer risk have considered these neoplasms (18, 19, 21-24).

Allowance for various confounding factors did not meaningfully alter the ORs for gastric cancer, whereas the estimates for pancreatic and endometrial cancers were reduced particularly after allowance for history of diabetes, which is a recognized risk factor for these two neoplasms (36). In any case, when we excluded from the analyses diabetic subjects—which are more likely to use low-calorie sweeteners as a substitute for sugar—we obtained similar results.

In the same data set, consumption of sugar (which is inversely correlated with that of sweeteners) was directly associated with the risk of gastric (29) and of pancreatic cancer, but not with that of endometrial cancer (30). Most other case-control studies reported a direct association between sugar intake and pancreatic cancer (37), as well as gastric cancer (38), whereas the evidence is less consistent in cohort studies (39). These findings need, however, to be cautiously interpreted due to the possibility of reverse causation, i.e., the subclinical disease causing changes in food intake, which can be particularly relevant for pancreatic and other gastrointestinal cancers, and in case-control studies.

Among the limitations of the study, there is the relatively low frequency of low-calorie sweetener consumption in this Italian population, and, consequently, its relatively low statistical power to detect weak associations. Nevertheless, the study size is relatively large for such neoplasms, and most associations were inverse or very close to the null, which makes it unlikely that larger sample sizes would have resulted in statistically significant positive associations. Moreover, we did not collect information on light soft drinks (nor on other products containing low-calorie sweeteners). However, their use is quite recent in Italy is rare in middle age and elderly population, and they are therefore unlikely to have been frequently consumed in the past by subjects in our study. We also had no information on specific sweeteners other than saccharin. In Italy, the prevalence of aspartame users has

Table 2. ORs and corresponding 95% CIs of gastric, pancreatic, and endometrial cancers, according to ever consumption of low-calorie sweeteners in strata of selected covariates

Covariates	Low-calorie sweeteners (ever vs never users), OR* (95% CI)		
	Gastric cancer	Pancreatic cancer	Endometrial cancer
Sex			
Males	0.76 (0.32-1.79)	0.66 (0.31-1.38)	—
Females	0.93 (0.39-2.18)	0.62 (0.29-1.34)	—
Age (y)			
<60	0.32 (0.08-1.22)	0.99 (0.39-2.49)	0.84 (0.49-1.44)
≥60	1.12 (0.57-2.21)	0.47 (0.24-0.91)	1.14 (0.68-1.91)
Education (y)			
<7	0.58 (0.22-1.51)	0.52 (0.23-1.19)	1.16 (0.69-1.93)
≥7	1.06 (0.50-2.26)	0.68 (0.34-1.36)	0.82 (0.47-1.43)
BMI (kg/m^2)			
<25	0.49 (0.18-1.32)	0.62 (0.23-1.67)	1.03 (0.47-2.25)
≥25	1.13 (0.54-2.37)	0.72 (0.39-1.34)	1.03 (0.67-1.57)
Total energy intake (calories)			
<2100	0.63 (0.29-1.37)	0.69 (0.28-1.66)	1.07 (0.66-1.73)
≥2100	1.19 (0.47-3.01)	0.47 (0.24-0.92)	0.75 (0.40-1.38)
History of diabetes			
No	0.71 (0.36-1.38)	0.59 (0.32-1.09)	1.03 (0.69-1.54)
Yes	1.37 (0.34-5.55)†	0.95 (0.38-2.36)†	0.69 (0.24-1.95)†
Smoking status			
Never smokers	0.56 (0.20-1.53)	0.91 (0.42-1.99)	1.01 (0.64-1.57)
Current/ex-smokers	1.09 (0.52-2.28)	0.53 (0.26-1.05)	0.98 (0.49-1.96)
Hot beverages (cups/week)			
<17	0.72 (0.27-1.91)	0.53 (0.24-1.13)	1.17 (0.68-2.02)
≥17	0.98 (0.47-2.06)	0.81 (0.38-1.69)	0.86 (0.51-1.44)

*Estimated by unconditional multiple logistic regression models adjusted for age, sex (when appropriate), study center (when appropriate), year of interview, education, BMI, tobacco smoking, history of diabetes, consumption of hot beverages, and total energy intake.
†Estimated by unconditional multiple logistic regression models adjusted for age, sex (when appropriate), study center (when appropriate), and year of interview.

been shown to be higher than that of other sweeteners (40). Ascertainment of dietary factors in case-control studies may be subject to recall bias, which usually shows spurious associations between the exposure and case-control status; however, there is little evidence here for the presence of such bias.

The strengths of our study include the similar interview setting, the comparable catchment areas, and the high participation rate of cases and controls. Moreover, we selected controls admitted for a large number of diseases unrelated to tobacco smoking, alcohol drinking, and diet. It is in any case unlikely that use of low-calorie sweeteners is associated with any of the outcomes used as controls (trauma, acute surgical conditions, etc). Information on saccharin and other sweeteners was satisfactorily reproducible (Spearman correlation coefficient was 0.47 for saccharin and 0.81 for other sweeteners; ref. 32). Furthermore, we controlled our estimates for various potential confounding factors, including education, alcohol and tobacco, energy intake, as well as BMI and history of diabetes, and we did not find consistent heterogeneity across strata of various covariates.

In conclusion, the present study adds further evidence on the absence of an association between low-calorie sweetener (including aspartame) consumption and the risk of common neoplams in the Italian population.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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