Artificial Sweetener Use and Bladder Cancer: A Case-Control Study

Abstract. *In a case-control study of 302 male and 65 female bladder cancer patients and an equal number of other patients matched to them in age, sex, hospital, and hospital-room status, no association was found between use of artificial sweeteners or diet beverages and bladder cancer. No dose-response was observed with respect to quantity or duration of use or the two combined. No evidence was found to suggest that artificial sweeteners or diet beverages promote the tumorigenic effect of tobacco smoking. Artificial sweetner and diet beverage use strongly reflected socioeconomic status among controls with various diagnoses.*

The relation between saccharin and bladder cancer in humans is a matter of both public and scientific controversy, extending even into the arena of legislative debate and regulatory processes. Experimental and epidemiological evidence to date has provided contradictory results. Several feeding studies have demonstrated a statistically significant increase in bladder tumors in male rats (*1*), and tumor-promoting effects have been observed in vitro (*2*) and in vivo (*3*). Published epidemiological studies have been uniformly negative (*4*), except for one in which an increased risk was reported for males only (*5*).

We present here data on the relation between artificial sweetener (AS) and diet beverage (DB) use and bladder cancer collected in an ongoing case-control study of smoking and disease (*6–8*) by means of interviews of patients in hospitals in New York and several other cities. Cases eligible for the present study were 312 male and 79 female patients admitted with a first diagnosis of bladder cancer who were interviewed between August 1977 and June 1979. The population from which the controls were drawn consisted of 3798 male and 1799 female patients admitted for other conditions, neoplastic and nonneoplastic (*9*), and interviewed in the same period. All diagnoses were verified histopathologically.

The interviews were conducted in the hospitals by professional interviewers. Data were obtained on a variety of demographic variables and on the use of tobacco, alcohol, coffee, tea, and other beverages, including those containing artificial sweeteners.

Comparison of background variables indicated, as in our previous studies, that the male bladder cancer cases tended to be of much higher professional and educational levels than the males in the control pool and the female cases were much lower than female controls (*10*). A substantial proportion in the control pool had diseases linked to lower socioeconomic background, especially cancer of the lung, the larynx, and the mouth (*7, 11*). Several variables indicative of socioeconomic level were strongly associated with both AS and DB use. Therefore a subset of controls was chosen (by computer) which matched the cases on a one-to-one basis not only in age (in decades) and sex but also in hospital and hospital-room status (private, semiprivate, or ward), these being found to be an excellent indicator of socioeconomic status. Matches were found for all but 10 male and 14 female cases. The diagnoses of the male matched controls were tobacco-related cancers (lung, larynx, mouth, and esophagus), 23 percent; other cancers, 38 percent; benign neoplastic diseases, 5 percent; and nonneoplastic conditions, 34 percent. Among the women the corresponding figures were 14, 36, 7, and 43 percent.

The quantity of regular AS intake (*12*) is reported here in terms of units per day, a unit being roughly equal to 20 to 40 mg of saccharin, depending upon which commercial product is used; no attempt was made to identify dosages more precisely. Canned diet beverages usually contain 8 to 11 mg of saccharin per ounce. The unit of DB consumption was taken to be a 12-ounce can, that being the most popular size. Information on use of diet foods was not obtained (*13*).

Among males, 25.2 percent of the cases and 26.5 percent of the matched controls reported current or past regular use of AS; among females, 21.5 percent and 29.2 percent (Table 1). Among male users, more controls than cases (43 percent versus 25 percent, $P < .05$) were or had been heavy (4+ units a day) AS users; no other statistically significant differences in duration or amount were found between cases and controls of either sex (Tables 2 and 3).

Of particular interest are those who used AS or DB in large quantities for long periods of time. If AS enhances carcinogenesis in the bladder, then these persons should be overrepresented among the cases. We classified AS users as either having or not having consumed at least 2 units per day for at least 10 years. There were no statistically significant differences between cases and controls classified on this measure or on an analogous DB measure.

We computed the average quantity and duration of AS usage for cases and controls, as well as the mean of the product of quantity (units per day) and duration of use in years as a measure of cumulative dose. There were no statistically significant differences between cases and controls for any of these variables. We also attempted to quantify lifetime AS intake, estimated as grams of saccharin, with a composite AS and DB measure. For this calculation, the lifetime saccharin consumption for each regular user of AS or DB was estimated as (AS units per day × 30 mg × 365 × years of AS use) + (DB cans per week × 110 mg × 52 × years of DB use). The lifetime saccharin intake estimated in this way was about 20 percent lower for cases than for controls (408 g for male cas-

Table 1. Regular users of artificial sweeteners and diet beverages among bladder cancer patients and matched controls. Regular use was defined as continued use for at least 1 month. The reported frequency of regular use lasting less than 1 year was < 1 percent.

When regularly used	Males (%)		Females (%)	
	Cases (N = 302)	Controls (N = 302)	Cases (N = 65)	Controls (N = 65)
	Artificial sweeteners			
Never	74.8	73.5	78.5	70.8
Currently	16.6	18.9	16.9	21.5
Formerly				
Quit ≤1 year ago	2.3	3.3		3.1
Quit >1 year ago	6.3	4.3	4.6	4.6
	Diet beverages			
Never	85.1	82.8	84.6	75.4
Currently	13.6	16.2	13.8	20.0
Formerly				
Quit ≤1 year ago		0.3	1.5	
Quit >1 year ago	1.3	0.7		4.6

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Table 2. Quantity of artificial sweeteners (per day) and diet beverages (per week) used regularly by bladder cancer patients and matched controls. Artificial sweeteners are estimated in units of 20 to 40 mg of saccharin, diet beverages in 12-ounce cans or equivalent (see text).

Number of units	Males (%)		Females (%)	
	Cases (N = 302)	Controls (N = 302)	Cases (N = 65)	Controls (N = 65)
	Artificial sweeteners			
None	74.8	73.5	78.5	70.8
<1 a day	1.0	1.7		6.1
1	8.3	5.6	7.7	10.8
2	6.6	7.0	3.1	3.1
3	3.0	1.7	3.1	3.1
4	1.0	4.3	4.6	
5–10	3.3	4.3	1.5	3.1
11+	2.0	1.0	1.5	3.1
Not stated		1.0		
	Diet beverages			
None	85.1	82.8	84.6	75.4
<1 a week				3.1
1–3	6.3	5.3	9.2	10.8
4–7	5.3	8.3	4.6	6.2
8–14	1.3	2.0		4.6
15–21	1.3	0.7		
22+	0.7	1.0	1.5	

Table 3. Duration of regular use of artificial sweeteners and diet beverages by bladder cancer patients and matched controls.

Number of years	Males (%)		Females (%)	
	Cases (N = 302)	Controls (N = 302)	Cases (N = 65)	Controls (N = 65)
	Artificial sweeteners			
None	74.8	73.5	78.5	70.8
1–4	10.3	10.3	9.2	12.3
5–9	6.3	8.9	4.6	4.6
10	4.3	2.6	4.6	3.1
11–15	2.0	1.3	3.1	4.6
16+	2.3	2.6		4.6
Not stated		0.7		
	Diet beverages			
None	85.1	82.8	84.6	75.4
< 1		0.3		3.1
1–4	5.3	6.0	7.7	12.3
5	0.7	3.3	1.5	3.1
6–9	1.3	2.0	1.5	
10	4.6	2.3	1.5	4.6
11–15	2.3	2.6	3.1	1.5
16+	0.3	0.3		
Not stated	0.3	0.3		

es, 496 g for male controls; 372 g for female cases, 455 g for female controls). The differences were not statistically significant.

Risk ratios (*RR*) for bladder cancer among AS and DB consumers (Table 4) were estimated by the matched-pair procedure described by Miettinen (*14*). No changes of any substance were produced by differentiating current and former users. The *RR* (and 95 percent confidence interval) among men was 0.93 (0.68–1.28) for AS and 0.85 (0.55–1.17) for DB, and among women 0.62 (0.26–1.40) and 0.60 (0.27–1.29), respectively. The *RR* estimates did not vary appreciably when further controlled for a number of potentially confounding variables, such as history of diabetes, obesity, occupation, education, religion, and coffee or tea consumption (*15*).

The possibility that AS plays the role of a promoter rather than a primary carcinogen was investigated by computing *RR*'s by the Mantel-Haenszel method (*16*) for subjects who were current long-term (≥ 10 years) smokers of cigarettes (*17*). In men the *RR* was 0.56 (0.29–1.09), in women 1.04 (0.21–5.09); similar results were obtained for DB. No statistically significant changes occurred when smokers were further classified by the number of cigarettes smoked per day.

For completeness, the association between cigarette smoking and bladder cancer was examined, as in our previous studies (*6, 7*), by estimating *RR*'s among present smokers relative to nonsmokers. For men the *RR* was 2.53 ($P < .001$); for women 2.19 ($P \cong .05$). These estimates are probably somewhat low because of inclusion of controls with tobacco-related cancers, but they are consistent with our previous reports.

It is possible, of course, that the absence of a demonstrable association in our data between AS or DB use and bladder cancer is due to insufficient sample size. At levels of 5 percent significance and 80 percent power, and with an AS usage rate of 25 percent among the male controls, the minimum *RR* detectable with the given sample size is about 1.5 (*18*). For women the corresponding figure is about 2.8. The estimated *RR*'s are not significantly different from 1, but the upper limits of their 95 percent confidence intervals are 1.28 (men) and 1.40 (women). However, the lack of a dose-response in this study and the repeated findings of a negative association between AS or DB consumption and bladder cancer in women in this and other studies (*4–6*) are inconsistent with a causal hypothesis, as is the low bladder cancer rate among diabetics (*19*), a group which consumes large quantities of saccharin. Furthermore, while we found obesity to be a major correlate of AS and DB use, obesity has never been reported as a risk factor for bladder cancer (*20*).

The often-raised question of the risk for children, especially those exposed in utero, is not addressed here, nor can we assess risks for older persons with lifelong DB use, because these high-saccharin products have not been on the market sufficiently long. Furthermore, because of the wide variation of saccharin consumption observed among patients with

Table 4. Matched-pair comparisons of use of artificial sweeteners and diet beverages by bladder cancer patients and controls. *RR*, risk ratio; *CI*, confidence interval.

Male cases	Male controls		Female cases	Female controls	
	Used	Never used		Used	Never used
	Artificial sweeteners				
Used	19	57	Used	6	8
Never used	61	165	Never used	13	38
	RR = 57/61 = 0.93			RR = 8/13 = 0.62	
	95 percent CI = 0.68–1.28			95 percent CI = 0.26–1.40	
	Diet beverages				
Used	6	39	Used	1	9
Never used	46	211	Never used	15	40
	RR = 39/46 = 0.85			RR = 9/15 = 0.60	
	95 percent CI = 0.55–1.17			95 percent CI = 0.27–1.29	

various types of cancers, surveillance of AS and DB usage in hospital populations should be continued.

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9. Nonneoplastic tobacco-related diseases eligible for interview are myocardial infarction, abdominal aortic aneurysm, peripheral vascular disease, chronic obstructive pulmonary disease, chronic bronchitis, emphysema, gastric ulcer, and cirrhosis of the liver. In addition, many other nonneoplastic diseases are eligible as control diagnoses, including fractures, burns, infections, cataracts, surgical procedures, and so forth.
10. This apparent selection bias for males is likely to be due in part to the relative difficulty of treatment of bladder cancer, and the tendency of patients in higher socioeconomic strata to be referred to specialized hospitals, such as Memorial Hospital in New York, for primary care.
11. Proper interpretation of the data requires judgment as to whether bias in selection of control patients has been minimized and confounding reduced. The extent to which confounding factors are associated with the exposure of interest and also differ among cases and controls may profoundly influence estimates of association between exposure and disease. Both AS and DB use were strongly associated with socioeconomic status indicators such as occupation level (27 percent of professionals used AS compared to 12 percent of unskilled workers) and higher education (26 percent of college graduates used AS compared to 16 percent of those without high school). AS use was also greater among ex-smokers than smokers, owing partly to the higher degree of education among ex-smokers (and possibly to their fear of weight gain), but was low among heavy consumers of alcohol, users of nonfilter cigarettes, and male ward patients; among female ward patients AS use was higher, owing possibly to the greater level of obesity in this group.
12. Regular use was defined as continued use for at least one month. The reported frequency of "regular" AS or DB use lasting less than one year was < 1 percent.
13. Questions were also asked about use of cyclamates, which, in combination with saccharin, were contained in nearly all artificial sweeteners between 1960 and 1969. Saccharin has been the only AS permitted by federal law since the banning of cyclamates as a carcinogen in 1969. The number of subjects specifically recalling cyclamate use, as distinct from saccharin, was too small for analysis. However, since cyclamates would have been used by nearly all who used AS for 10 years or more, and since no increased bladder cancer risk was observed among this group, it is highly unlikely that cyclamate consumption contributed to excess cancer risk in our study population.
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15. Exclusion of patients with diabetes from the analysis resulted in negligible lowering of *RR*'s. Exclusion of patients with cardiovascular diseases also resulted in trivial changes; patients with cardiovascular disease in our study did not, as has often been suggested, consume larger amounts of AS or DB than other groups of controls.

These findings are essentially in agreement with results obtained during an earlier phase of the study, in which a less elaborate questionnaire was used. In that version, three questions (history of regular AS use [yes or no], quantity, duration) were added in 1974 to a bladder cancer study already in progress, in response to widespread public interest in possible health effects of saccharin. That study, published in 1977 (6), found no association between AS and bladder cancer based on the rather limited numbers then available: 132 male and 31 female cases and equal numbers of matched controls. As data collection proceeded, an interim, preliminary analysis was submitted in a progress report to the National Cancer Institute in October 1977, based on 260 male and 86 female patients with bladder cancer. It gave crude *RR* estimates of 1.87 for males and 0.9 for females. Reservations were expressed at the time that a causal hypothesis might not be supported by the data for several reasons: (i) Substantial socioeconomic differences existed between cases and controls, with 29 percent of all male controls coming from Veterans Administration and county hospitals (notably Los Angeles County) compared with only 8 percent of male cases; opposite patterns of socioeconomic confounding appeared to explain much of the opposite female *RR* estimates. (ii) For a given substance to produce opposite risks for men and women would be highly unusual. (iii) *RR* estimates varied substantially from one city to another.

When data collection terminated in 1977, bladder cancer cases numbered 402 males and 122 females, with 7200 male and 3777 female controls. Final crude *RR* estimates (and 95 percent confidence intervals) were 1.85 (1.45–2.36) for males and 0.99 (0.61–1.59) for females. When adjusted for age, hospital, hospital-room status, and year of interview, these *RR*'s fell to 1.43 (1.10–1.86) and 0.89 (0.48–1.64), respectively. A matched-pair analysis, with matching based on the above variables plus education, further reduced the *RR* estimates to the statistically not significant values of 1.13 (0.60–2.09) and 0.80 (0.20–2.98). An equivalent result was obtained by matching on occupation instead of education. There were no noteworthy or statistically significant differences between cases and controls with respect either to quantity or duration of AS use.
16. N. Mantel and W. Haenszel, *J. Natl. Cancer Inst.* **22**, 719 (1959).
17. All cigarette smokers interviewed had smoked for at least 10 years.
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19. I. I. Kessler, *J. Natl. Cancer Inst.* **44**, 673 (1970); B. Armstrong and R. Doll, *Br. J. Prev. Soc. Med.* **28**, 233 (1974).
20. An additional observation of a strong association between obesity and kidney cancer in both men and women leads to the prediction that these patients use substantial amounts of AS. Use of AS was in fact higher in the current series of 65 male kidney cancer patients, but not among the 88 male kidney cancer patients interviewed in 1974–1977. This epidemiological lead merits further investigation.
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