

Addendum

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Shortly after a draft of this report was transmitted to Congress on June 7, 1977, OTA learned of a Canadian epidemiological study that showed a positive correlation between consumption of artificial sweeteners and bladder cancer in human males (74). At almost the same time, an American epidemiological study found no correlation between bladder cancer and consumption of artificial sweeteners (192). In order to allow full examination and public discussion of these studies, FDA Commissioner Donald Kennedy announced on June 27, 1977, that the comment period on the proposal to ban saccharin would be extended to August 31, 1977 (77). Summaries of these two studies have recently been made available to OTA.

THE (POSITIVE) CANADIAN EXPERIMENT

Experimental Design

A total of 821 newly diagnosed cases of primary bladder cancer were identified in three Canadian provinces between April 1974 and June 1977. Of these cases, 632 people (480 males and 152 females) were personally interviewed in their homes and asked questions about their use of artificial sweetener drops or tablets. The information from these interviews was compared to information obtained from interviewing an equal number of controls. Each case was matched with a control of the same sex and same age (within 5 years) who lived in the same neighborhood.

Results

The average ages for all bladder cancer cases were: males, 67.7 years; male controls, 67.2; females, 69.1; female controls, 68.4. For males, 69 cases (compared to 43 controls) had ever used artificial sweeteners; and for females, 18 cases (compared to 30 controls) had ever used artificial sweeteners. The conclusions drawn from these data are that artificial sweetener use increases the risk of bladder cancer in males by a factor of 1.6 (i.e., $69/43=1.6$) and that there is no association between sweetener use and bladder cancer in females (i.e., $18/30=0.6$). However, too few cases of female bladder cancer were found to conclude with any statistical assurance that sweeteners had any effect on cancer incidence in women.

The authors made an effort to separate saccharin users from users of other sweeteners. Although they have reservations about the accuracy of separating these groups (some cases and controls did not recall whether they had used saccharin or cyclamates, or both), the males identified as saccharin users had a risk of 1.7, and female users had no increased risk. Males who used more than seven tablets or drops of saccharin a day for more than 3 years were at a greater risk than less frequent users. The authors concluded that these data showed a dose-response relationship.

Male diabetics were at greater risk from the use of sweeteners, including saccharin, than male diabetics who did not use sweeteners. This conclusion was complicated because male diabetics who never used sweeteners were at a reduced risk (0.8 as compared to nondiabetic nonusers), and diabetic users had essentially the same risk as nondiabetic users (1.9).

The cases and control populations differed from one another in a number of ways: educational levels, occupations, and infection histories. The authors state that these differences were taken into consideration and did not alter the conclusion that sweetener use was associated with higher risk.

Summary

Male users of sweeteners were more frequently found among bladder cancer cases than among controls. Male users of sweeteners and male diabetic users of saccharin were both at increased risk; females were not.

THE (NEGATIVE) AMERICAN HEALTH FOUNDATION STUDY

Experimental Design

Over a 15-year span, bladder cancer patients were identified in 17 hospitals in six U.S. cities. Each bladder cancer case was matched with a control on the basis of age, race, and sex. Because bladder cancer had been associated with tobacco use, the controls were selected from people hospitalized for cancers that are not associated with tobacco use.

Beginning in 1973, each case-control pair was questioned about artificial sweetener consumption. Although 574 males and 158 females were included in the 15-year study, a smaller number (132 males and 31 females) were questioned about sweetener consumption.

Results

The average age of male cases was 61; female cases 62. Thirteen of 132 male cases and 5 of 31 female cases had ever used sweeteners. These numbers do not differ significantly from 16 of 124 male controls and 5 of 29 female controls who had used sweeteners. The conclusion drawn from these data is that sweetener consumption was not found to be associated with increased risk. There were no statistically significant differences in marital status, education, or places of residence between the cases and controls.

Diabetics may consume more sweeteners than do nondiabetics in the general population. In this study, 40 male and 11 female cases were found to be diabetic. This frequency was not statistically different from the 38 male and 8 female diabetics found in the control population. Thus, diabetics were not overrepresented in cases compared with controls.

Summary

No correlation was found between sweetener consumption and occurrence of bladder cancer.

COMPARISON OF THE TWO STUDIES

The Canadian paper is in press in the journal, *Lancet*, and the American Health Foundation paper will appear in *Cancer*. The most striking differences between the two methods were the origins of the cases and the choice of controls. In the Canadian study, all cases from three provinces were included and compared to controls who

resided in the same neighborhood. In the American study, cases were obtained in selected hospitals and compared to controls who were sick with other cancers in the same hospitals.

The Canadians found that cases and controls differed in educational levels. No such difference was found in the American study, probably because the cases and controls were of "high social class," based on hospital selection. These differences in selection of cases and controls may account for the difference in results. Ernest Wynder (191) has informed FDA Commissioner Kennedy that he will have data on more than 400 users and 4,000 controls by the end of September 1977.

If more extensive data and evaluation support the Canadian conclusions, the saccharin experience would be an additional example of animal testing predicting a human risk. Specifically, the results of the Canadian epidemiology study, if confirmed, show that saccharin causes bladder cancer in males. This finding parallels the rat experiments, which also showed that only males "are affected. Furthermore, the risk estimated by assuming 1) a mg/kg dose relationship between rats and humans, and 2) a linear extrapolation between rats and humans was 600 to 1,200 cases per year. This estimate from rat studies agrees with the 1,000 to 2,000 cases estimated from human studies.