Using Epidemiology to Regulate Food Additives: Saccharin Case-Control Studies

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Synopsis

The increasing use of nonnutritive sweeteners and the widely publicized 1969 ban on cyclamate led to additional investigations in rodents of the carcinogenic potential of saccharin. Preliminary results of a long-term feeding study indicated formation of bladder tumors in rodents, and collective experimental evidence has demonstrated that high doses of the synthetic sweetener saccharin can cause bladder cancer in rodents.

Based on the results of that and other rodent studies indicating an increased risk of bladder cancer associated with saccharin, the Commissioner of the Food and Drug Administration announced the agency's intention to propose a ban on saccharin. This intention was made known in April 1977 under the Delaney Clause of the Food, Drug, and Cosmetic Act. The clause essentially states that no additive shall be deemed safe if it is found to induce cancer in man or animals, or if it is found, after tests appropriate for the evaluation of the safety of food additives, to induce cancer in man or animals.

Also in 1977, a group of epidemiologists began to assess the available epidemiologic information to determine the potential human risk. This report describes the assessment of several human epidemiologic studies available then and the results of more recent epidemiologic studies.

SACCHARIN IS A NONNUTRITIVE sweetener that was discovered in 1879, and it has been used since the turn of the century (*1*). Prior to 1972, it was classified by the Food and Drug Administration (FDA) as "generally recognized as safe" (GRAS), a classification meaning that saccharin was not considered a food additive for the purposes of the Food, Drug, and Cosmetic Act and therefore did not need FDA approval.

Saccharin Ban Proposal

Nine Federal statutes are important to the regulation of clinical substances. The Food, Drug, and Cosmetic Act generally takes precedence over other Federal laws in regard to the carcinogenicity of substances that may be ingested. Of these laws, only the Food, Drug, and Cosmetic Act contains a provision like the Delaney Clause, which in essence states that no additive shall be deemed safe if it is found to induce cancer in man or animals or if it is found, after tests appropriate for evaluation of the safety of food additives, to induce cancer in man or animals. Other provisions regulate substances in animal feed. However, the importance of the Delaney Clause is that it allows no regulatory discretion. When a substance such as saccharin, which is regulated by the Delaney Clause, is found to be a carcinogen, it must be banned. No other law mandates such specific obligatory action to ban.

The increasing use of nonnutritive sweeteners and the widely publicized 1969 ban on cyclamate led to investigations of the carcinogenic potential of saccharin. Preliminary results of a long-term feeding study indicated formation of bladder tumors in rodents, and collective experimental evidence demonstrated that high doses of the synthetic sweetener saccharin can cause bladder cancer in rodents (*2–6*). This information was also discussed in 1977 at the Toxicology Forum of Saccharin held at the University of Nebraska Medical Center, May 9, 1977.

In April 1977, the FDA Commissioner announced in the Federal Register the agency's intention to propose a ban on saccharin (*7*). The proposed ban would:

- Revoke the interim food additive regulation under which saccharin and its salts were permitted as ingredients in foods, thereby banning its use in foods and beverages.
- Allow the marketing of saccharin as a single ingredient, over-the-counter drug.
- Remove saccharin from cosmetics that are likely to be ingested, such as toothpastes, mouthwashes, and lipstick.

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- Remove saccharin as a nonmedical ingredient in drugs.
- Prohibit saccharin in animal drugs and animal feeds.

Epidemiologic Studies

Also in 1977, the Saccharin Working Group, led by FDA epidemiologists and composed of epidemiologists from several other Federal agencies, was convened. To make specific recommendations for future epidemiologic studies, the group considered the available human data from epidemiologic studies concerned with increased risk of cancer associated with consumption of artificial sweeteners and the factors known or suspected to be associated with bladder cancer. The group considered both descriptive and analytic studies.

Descriptive studies. This approach is mainly observational and can suggest causal relationships, but can seldom prove them. To investigate the relationship of artificial sweeteners to bladder cancer in humans, two types of descriptive studies are used:

1. Comparison of time trends between use of artificial sweeteners (analogous to cigarette smoking) and occurrence of bladder cancer in humans (analogous to lung cancer). Two such studies of time trends have been conducted, the first by Burbank and Fraumeni (*8*) and the second by Armstrong and Doll (*9*).

2. Comparison of persons with diabetes, who are more likely to consume artificial sweeteners, with persons without diabetes, who are more likely to use regular sweetening products. Three of these types of studies have been conducted: by Kessler (*10*), Armstrong and Doll (*11*), and Armstrong and associates (*12*).

No association between use of artificial sweeteners and bladder cancer was found in these five descriptive studies. However, it would be hard to rule out such an association on the basis of these indirect studies, because of the limitations of both the methods used and the studies themselves, as described in the following section.

Analytic studies. The second type of epidemiologic studies are analytic studies, which can be used to test specific hypotheses. Basically, these approaches consist of (*a*) a cohort study that follows a population exposed to a suspected carcinogen such as saccharin and comparing it with an unexposed population to determine if the frequency of a disease such as bladder cancer is greater in the exposed group and (*b*) a case-control study in which saccharin use by bladder cancer patients and controls is compared. Descriptions of several case-control studies follow, including those by Kessler (*13*), Wynder and Goldsmith (*14*), and Howe and coworkers (*15*). Two other analytic studies are generally recognized as giving no support to a saccharin-bladder cancer association (*16,17*).

Studies reviewed by Saccharin Working Group. Kessler (*13*) compared all bladder cancer patients discharged from participating Baltimore hospitals (not just those with newly diagnosed cases) with control patients. The controls were selected from cancer-free patients discharged from the same hospitals as the bladder cancer patients. Controls were without bladder conditions and had been hospitalized at about the same time as the patients with bladder cancer. Controls and cancer patients were matched for sex, race, age (within 3 years), and marital status. All patients in the study were interviewed about their occupational history, smoking habits, and use of artificial sweeteners. Those sweeteners were categorized as being in table sweeteners, diet beverages, diet foods, or total intake. For each specific nonnutritive sweetener-containing substance, data were sought on the frequency and duration of use and the quantity ingested. For purposes of analysis, ingestion of nonnutritive sweeteners within 1 year of the date of cancer diagnosis was not considered for each patient. Matching was not taken into account in the analysis.

Findings among the 418 bladder cancer patients, both when the data were combined and when separated by sex, failed to demonstrate any significant excesses in amounts of artificial sweeteners used by bladder cancer patients as compared with controls. Additional analyses controlling for case-control differences in diabetes or smoking histories yielded similar results.

Three features in the design of this study could have easily masked an association between saccharin and bladder cancer (*13*). First, the use of hospital patients as controls might have introduced selection factors not found in the general population with respect to artificial sweetener use. For example, people with obesity-related conditions may be overrepresented among the controls; they would have both a greater chance of being hospitalized and a greater disposition toward the use of artificial sweeteners than people from the general population. An indication of such a bias is the high rate of sweetener use among the controls—about 30 percent of the group, which is two to three times the rate observed

in the two other studies (*14,15*) and about equal to the rate reported by Armstrong and Doll (*9,11*) among persons with diabetes.

Wynder and Goldsmith (*14*) studied patients with recently diagnosed diseases, including bladder cancer, that were suspected to have been caused by smoking or alcohol. Although interviews were conducted in 17 hospitals in 6 cities in the United States, 46 percent of the study patients were from Memorial Hospital, New York City. Controls, matched by sex, race, hospital status, and age at diagnosis (within 5 years), were hospital patients with no previous history of tobacco- or alcohol-related illness. Bladder cancer cases were selected for study as a subset of the cases of tobacco- and alcohol-related diseases. The questionnaire used was originally designed to obtain histories of smoking and alcohol use, but it was later modified to obtain data on other factors, including the use of artificial sweeteners.

As with the Kessler study (*13*), matching was not considered in the analysis, and the resulting sample sizes were small: 132 male and 31 female patients with tobacco- or alcohol-related disease and 124 male and 29 female controls (*14*). The data did not demonstrate a significant relationship between bladder cancer and artificial sweeteners, though a strong relationship between bladder cancer and smoking was observed. Duration and frequency of use of sweeteners were accounted for in the analysis but not the time between exposure and diagnosis of the disease. Besides the small sample size, other aspects of the Wynder and Goldsmith study might lead to a bias that could affect an association between bladder cancer and artificial sweetener use. The way cases and controls were selected from each hospital was not reported in detail, nor was it stated whether this selection was uniform from hospital to hospital. A meeting with those working on the study indicated that complete ascertainment of bladder cancer cases may have been a problem and that the manner in which followup was conducted led to a mixture of prevalence and incidence cases favoring those patients with more protracted hospitalization. The removal of patients with cardiovascular disease, however, from the control population (because their disease may have been caused by smoking and alcohol) decreased the bias of using hospital patients as controls. The rate of artificial sweetener use in this study was comparable to that observed in the general population controls employed by Howe and coworkers (*15*).

Though the 4 percent nonresponse rate reported by Wynder and Goldsmith appears excellent (*14*), the Saccharin Working Group's meeting with the investigators also revealed that the nonresponse rate applies only to those patients whose physicians had granted permission for the interview and who were still in the hospital at the time. The overall nonresponse rate, including that of the cancer patients whose physicians did not permit interviews and those who had left the hospital, is very much in excess of 4 percent. This nonresponse bias may have an effect on the possible association between artificial sweeteners and bladder cancer.

At that time the epidemiologic evidence available to the Saccharin Working Group was equivocal. The group recommended further study.

Howe and coworkers (*15*) studied 632 recently diagnosed bladder cancer patients—480 men and 152 women—in three Canadian Provinces. An equal number of controls from the general population were individually matched to the patients by sex, age (within 5 years), and neighborhood of residence. The study subjects were asked about demographic variables, residential history, use of nonpublic water supply, occupational history, use of analgesics, and smoking history.

In a matched pair analysis, the authors observed a significant association between bladder cancer and the use of artificial sweeteners with a risk ratio of 1.6 ($P < .001$). In the same group studied by Howe and associates (*15*), A. B. Miller and associates reported differences observed for several important variables between bladder cancer patients and controls (Presentation to the Society for Epidemiologic Research, Seattle, May 1977). The variables included occupational history, water supply, cigarette smoking, industrial fumes, hair dyes, and coffee consumption. The association between bladder cancer and use of artificial sweeteners was still significant when adjustments for these variables were made one at a time.

As with the other two studies, features of Canadian case-control study (*15*) may lead to a bias in a saccharin-bladder cancer relationship. First, the nonresponse rate for the controls was not reported. In a meeting with the authors, the Saccharin Working Group found that information from all three Provinces was not available, and that British Columbia had generated most of the data. Of the 4,000 households selected, no one was home when 1,200 households were visited, residents of 100 households refused to answer the door, and 2,200 households were not eligible. Of the 500 eligible households that remained, residents of 20 percent refused to participate. These rates of nonresponse would, in effect, weaken the authors' strong emphasis on the use of population-based controls.

Another feature that caused some difficulty involves the classification of artificial sweetener use by "ever used" and "never used" categories. If ingestion of ar-

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tificial sweetener in one tablet or soft drink in a lifetime qualifies patients as "ever used," the strength of any causal suggestion is severely diminished. Our meeting with the authors indicated that the original study was not designed specifically to test the possible association between saccharin and bladder cancer but to investigate the possible associations between bladder cancer and smoking, occupation, coffee consumption, or use of public versus nonpublic water supply. Thus, specific questions regarding latency cannot be answered because of the lack of appropriate data from the questionnaire.

In summary, one epidemiologic case-control study suggested an association between bladder cancer and saccharin in males. Two other case-control studies failed to demonstrate for either sex an association between bladder cancer and saccharin. There are, however, aspects in each study that could result in biases sizable enough to reverse the given finding. Thus, at that time the totality of the epidemiologic evidence available to the Saccharin Working Group was equivocal. The group recommended that further studies be conducted.

More recent studies. In 1978, the National Cancer Institute (NCI) began a case-control study (*18*) involving almost 9,000 people in 5 States and 5 metropolitan areas to investigate the possible risks associated with the use of artificial sweeteners. About 3,000 patients with newly diagnosed cases of bladder cancer and 6,000 controls were interviewed. Averaged for all the persons who had ever used any form of artificial sweetener, there was a relative risk of 1.01. This risk is not significantly different from 1.00, and it suggests that if an elevated risk exists for users at the doses consumed in the past, it is not more than 11 percent above the risk of nonusers. A slight excess in risk was observed in subjects who used tabletop artificial sweeteners or who drank diet beverages heavily and in a subgroup of persons with a low incidence of bladder cancer.

Several other case-control studies support the conclusions that, as a group, users of artificial sweeteners have little or no excess risk of bladder cancer. In two reports Morrison and coworkers (*19,20*) described studies in Boston, Japan, and the United Kingdom. The Boston study consisted of 592 patients with bladder cancer and 536 controls drawn from the Boston standard metropolitan statistical area (SMSA); there was an overall relative risk of 0.9 for users of artificial sweeteners in the patients compared with controls. For males, the comparative risks were 0.8 for those drinking diet beverages and 0.8 for those using sugar substitutes. For females, the risks were 1.6 and 1.5, respectively.

In the other study by Morrison and coworkers (*20*), a high proportion of subjects in both Japan and the United Kingdom used saccharin in the years during and following the Second World War. For the 555 patients with bladder cancer and 735 controls in Manchester and the 203 patients and 589 controls in Japan, the risk of bladder cancer did not increase regularly with the duration or frequency of artificial sweetener use.

Other case-control studies, such as Jensen and Kamby (*21*) in Denmark and Cartwright and coworkers in England (*22*), failed to demonstrate an increased risk of bladder cancer associated with the use of artificial sweeteners.

The Jensen-Kamby report is of special interest because it addressed the risk of bladder cancer among persons exposed to artificial sweeteners in utero and during the first years of life. In the study, the risk of bladder cancer over a period of 30–35 years was evaluated in Danes born during the Second World War. This group experienced increased intrauterine exposure compared with people born before the war. The study provides no evidence of an increased risk of bladder cancer during the first 30–35 years of life associated with in utero exposure to saccharin.

Conclusion

Although animal studies appear to have shown an excess risk of bladder cancer when rats were exposed to saccharin and cyclamate, the results of human epidemiologic studies tend to support the conclusion that human users of artificial sweeteners—saccharin and cyclamate—do not have an increased risk of cancer of the lower urinary tract. Whether variables such as latency, the strength of the artificial sweeteners as carcinogens, or other, as yet unknown variables may manifest their effects in a consistent, mearsurable manner remains to be seen.

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Thyroid Tumors Associated with Radiation Exposure

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Synopsis

Epidemiologic studies of medically and environmentally exposed populations have been central to establishing ionizing radiation as a cause of malignant and benign thyroid tumors. Issues currently under investigation concern low dose effects, age sensitivity, the relative effectiveness of X-rays and iodine-131 in inducing thyroid cancer, and other risk factors. Excess thyroid tumors continue to appear in irradiated populations under study more than three decades after exposure.

THREE HISTORICAL EVENTS are related to the study of radiation-induced thyroid disease:

- the discovery of X-rays (external radiation) and radioactivity (internal and external radiation) at the end of the 19th century, followed almost immediately by worldwide medical applications;
- the discovery of nuclear fission in 1939, followed by atomic bomb explosions in 1945 and later atmospheric tests; and
- the production of radioactive iodine in 1942, followed by manufacture and widespread use of iodine-131 in 1946.

Beginning in the early 1920s, for more than 30 years it was common medical practice to use ionizing radiation to treat a variety of benign nonthyroid conditions of the head, neck, and upper thorax of infants and children. These conditions included enlarged thymus gland, hypertrophic tonsils and adenoids, cervical adenitis, ringworm, and acne. Unfortunately, the thyroid gland fre-