Dec. 13, 1979

PROGRESS REPORT TO THE FOOD AND DRUG ADMINISTRATION FROM THE NATIONAL CANCER INSTITUTE CONCERNING THE NATIONAL BLADDER CANCER STUDY

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ACKNOWLEDGEMENTS

We wish to thank all of the participants in this study, the physicians, the patients, and the members of the general public whose time and cooperation made this study possible.

For their hard work and careful attention to the standards of epidemiologic research, we wish to thank the field supervisors: Ms. Juanita Burroughs, Ms. Joanne Bill, Ms. Delores Chavez, Ms. Hazel Cook, Ms. Cindee George, Ms. Helen Gregory, Mr. Jack Hollahan, Ms. Janice Hunter, Ms. Mary Lovell, Ms. Joan Miller, Ms. Virginia Osterlund, Ms. Kathleen Stock, Ms. Judith Woolridge.

We also wish to thank the co-investigators who, with the authors of the report, designed and conducted the study: Dr. Samuel Albert, Dr. Martin Goldfield, Ms. Mary Hauck, Dr. Lorraine Marrett, Dr. J. Meigs, Dr. Paul Scherr, and Ms. Barbara Ziegler.

We also wish to thank the Health Care Financing Administration and former Administrator Robert A. Derzon whose cooperation greatly assisted us in collecting information from the general population.

For their vital role in coordinating the field activities, conducting telephone screening, and coding the data, we thank memebers of the staff of Westat, Inc.: Mr. John Cahill, Mr. Robert Daley, Ms. Eileen Horan, Ms. Sandra Hendricks, and Mr. Phil Whitt.

For their computer assistance in programming and manuscript preparation, we thank Ms. Diane Mueller and Dr. B. J. Stone of NCI and Ms. Elizabeth Martin, Mr. Robert Weinstock, and Ms. Sharon Wheatley of Operations Research, Inc.

For their valuable guidance and suggestions, we thank our advisors: Drs. Gilbert Friedell, Alan Gittelsohn, Evelyn Kitagawa, Alan Morrison, Nicholas Petrakis, Charles Platz, Carol Redmond, and Noel Weiss.

For their advice and assistance, we also wish to thank Drs. Arthur Upton, Guy Newell, Marvin Schneiderman, and Joseph F. Fraumeni, Jr. of the National Cancer Institute and Dr. Frank Cordle and Albert Kolbye of the Food and Drug Administration, former Commissioner of the FDA Dr. Donald Kennedy, and all of the members of the FDA/NCI Saccharin Working Group.

Finally, we wish to offer our gratitude to Mrs. Nancy Guerin. She graciously bore the burdens of producing this oft-revised report under the press of time. The responsibility for any errors that remain rests with us, the credit for eliminating those that are gone rests with her.

INTRODUCTION

In 1977, results of a Canadian epidemiologic investigation of bladder cancer were published,[1] reporting a 60% excess risk of bladder cancer associated with the use of artificial sweeteners (AS). The positive association was restricted to males, with a non-significant deficit noted among females. The excess risk in males was noted for table-top AS (sweeteners added directly to food or drink), but no excess risk was noted for the use of diet drinks or diet foods. Although based on a relatively small number of observations, the risk in males increased with more intense and long-term use of AS. These results followed closely a laboratory investigation[2] reporting an excess of bladder tumors in rats that were exposed to saccharin *in utero* and throughout life. Because results of the Canadian epidemiologic investigation implied a level of risk greater than that extrapolated from the animal data and were at variance with other human studies,[3-6] the Commissioner of Food and Drugs requested a joint Food and Drug Administration (FDA)-National Cancer Institute (NCI) review of all the available human evidence. A joint FDA/NCI group, the Saccharin Working Group, was formed and submitted its report to the Commissioner in December 1977.[7] Their conclusion was:

"At the present time, there is neither enough evidence to accept or to reject the hypothesis that the use of artificial sweeteners, specifically saccharin, increases the risk of bladder cancer in humans."

Since that time, several events have supported that equivocal conclusion. In 1978, a case-control study of bladder cancer confirmed

an earlier preliminary observation indicating no association with AS use.[8] However, a progress report of an ongoing case-control study (with previously reported negative results) showed a significant 80% excess risk of bladder cancer among men associated with the use of table-top AS, along with some evidence of a dose-response relationship.[9] Reviews of the laboratory studies have led to the conclusion that saccharin itself is a carcinogen.[10-11] It is generally thought to be a weak carcinogen when given alone. Recent work suggests that saccharin is also a "promoter"; that is, animals given saccharin along with another carcinogen develop many more tumors than do those who receive the other carcinogen alone.[12,13]

When the Saccharin Working Group submitted its report in 1977, it indicated the desirability of a large-scale investigation which would meet the criticisms of earlier efforts and perhaps resolve some of the apparently conflicting results of various studies.

Toward this end the Saccharin Working Group proposed a large population-based, case-control interview study of bladder cancer, including incident cases as close to the time of diagnosis as possible, and covering populations with various baseline bladder cancer risks. The study was to have high response rates, obtain detailed histories of AS use, and probe into other known or suspected bladder cancer risk factors. This paper is a preliminary report of the findings of that study.

The specific objectives of this study were:

(1) To test specifically the hypothesis raised by two studies[1,9] that there is an increase of at least 60% in the risk of bladder cancer, in males only, with evidence of a dose-response relationship, associated with the use of table-top AS.

(2) To investigate generally the possibility of any of several kinds of association between AS use and bladder cancer in the aggregate data set, incorporating appropriate control for other relevant factors. As part of this objective, the study was designed specifically to test the two hypotheses raised by the laboratory experiments. In order to determine if AS was a relatively weak carcinogen when given alone, the study was designed to be large enough both to evaluate the effects of very heavy use of AS and to allow separate analysis of a low-risk subgroup of the entire study population (i.e., a subgroup having none of the recognized bladder cancer risk factors). In such a subgroup, the influence of a carcinogen might be more readily identifiable even if it were relatively weak. To evaluate whether AS was also a cancer-promoting agent (i.e., whether it enhanced the effects of other carcinogens), the study was designed to include substantial numbers of subjects who had been exposed to relatively high doses of recognized bladder carcinogens.

(3) To utilize the detailed exposure information collected on AS, in order to investigate the effects of several exposure variables (cyclamates vs. saccharin, total dose in milligrams, continuous vs. intermittant use, etc.).

(4) To use certain methodological aspects of this study to resolve some of the differences seen in previous studies.

The study was not designed to evaluate the second-generation effect (the result of in utero exposure) seen in the most recent animal studies.

A study design incorporating these objectives was accepted by the NCI, the Commissioner of the FDA, and the Interagency Regulatory Liaison Group. The NCI, the FDA, the Environmental Protection Agency and the Health Care Financing Administration joined in sponsoring the study. The first interview in this study was conducted in January of 1978, and data from the last interviews were delivered to NCI in June of 1979.

Because of the potential utility of even preliminary observations in current decision-making processes, we are submitting this report, albeit with a caveat. These are only initial analyses of the data, they are directed toward meeting the first two objectives stated above, and they are the responsibility of the listed authors only. This report is preliminary. There are a number of analyses yet to be done which could alter some of the observations presented or their interpretations.

METHODS

Cases

The case series included all residents of ten geographic areas (Table 2) who met these criteria: aged 21-84; first diagnosed with cancer of the urinary bladder in 1978; tumor histologically confirmed

and classified as either a carcinoma or a papilloma not specified as benign; and absence of prior cancer of the lower urinary tract.

The ten areas chosen represented populations with a range in risk of bladder cancer. Each area had an existing system for rapid identification of cases (the NCI-funded system of population-based cancer registries in the Surveillance, Epidemiology and End Results (SEER) network, and the registry maintained by the New Jersey State Department of Health). The study was confined to newly diagnosed cases to ensure consideration only of factors related to risk of disease and not those related to chance of survival. By including all cases occurring in defined geographic areas, the case series was by definition representative of all of the cases arising from the general population of these areas in a one-year period. Including papillomas that were not specifically called benign reflected the current opinion of expert pathologists that such tumors are early stage carcinomas. We interviewed cases as soon as possible after their diagnoses, to reduce the number of interviews lost to death and disability.

Controls

The control series was a sex-, age-stratified random sample of the general population in the ten geographic areas (weighted at a 2:1 ratio of controls to anticipated cases, with controls selected to reflect the expected anticipated distribution of the cases by sex and by 5-year age groups). The only planned variation in the stratification criteria was in Detroit. There only one general population control was chosen for each anticipated case. In addition, one hospital

control was chosen for each case. This was done to test certain methodological issues raised by previous studies. These hospital controls have not been included in this report.

We chose general population controls to assure that the AS histories in the control series reflected the experience of the population from which the cases came. Two methods of drawing controls, both relatively new to epidemiologic research, were used. A sample of persons aged 65-84 was derived from the files of the Health Care Financing Administration, which provided a nearly complete census of individuals over age 65. We drew controls aged 21-64 using a three-stage process: (1) a group of telephone numbers was drawn at random from all of the residential telephones in the geographic area; (2) an interviewer called each telephone number and obtained the age and sex of every household member aged 21-64 and the address of the household; (3) a stratified random sample of individuals was drawn from the pooled censuses of the households.

Data Collection

Data were collected in a personal interview conducted in the respondent's home. Interviewers from the ten areas received the same training and used identical questionnaires. While it was impossible to conceal the case or control status of each respondent from the interviewer, both the instructions for conducting the interview and the training procedures stressed a standardized approach to the collection of the information. The questionnaire (Appendix A) elicited detailed history of exposure to AS (table-top, diet drinks, and diet foods),

including data on brand, dose, frequency, and timing. The questionnaire also covered questions about tobacco use, occupation, medical history, residence, source of drinking water, consumption of coffee and other beverages, and a number of other variables.

Strict standards in design and conduct were followed to reduce the chance of missing a small elevation of risk because of methodological flaws. Special efforts were made to achieve a high response rate. Appendix B is a protocol for the study which gives more detail concerning the design and conduct of the study.

Exposure Definitions

Throughout the analysis, the unexposed groups included only subjects unexposed to any form of AS. In tables that refer to only one form of sweetener, the exposed group included all those subjects, and only those, who used that form of AS. (Some of the exposed may also have used other forms of AS). Some subjects were excluded altogether. For example, in analyses of diet drink exposures, subjects who never used diet drink but who did use diet food or table-top sweeteners were excluded, since they properly belonged neither with those exposed to diet drink nor with those unexposed to AS.

Subjects with information missing were also excluded from the analyses. In most analyses, the proportion of cases with missing data was similar to the proportion of controls. Exceptions are noted in the text. Of the subjects who ever used diet drinks, 13% were excluded from analyses of average use, 11% from analyses of years of use, and 22% from analyses of lifetime servings, because of missing data. For

table-top sweeteners, the corresponding figures were 17%, 13%, and 13% respectively.

For diet drinks, the respondent was asked to report his usual weekly consumption and his years of use. Total consumption was estimated by multiplying these two figures. For table-top sweeteners, the respondent was asked about each combination of a brand with a food that he ever used. From this detailed historical profile, total consumption and average consumption were calculated. The average number of daily uses was calculated using only those periods for which the respondent was able to estimate his consumption. If the respondent characterized all his use as irregular, the average value was treated as missing.

Statistical Methods

The measure of strength of association between bladder cancer and various exposures used in this paper is the relative risk (RR). For a retrospective case-control study such as this one, the odds ratio is used as an estimate of the RR.[14] The RR is a measure of the risk of bladder cancer among those exposed to a particular factor under study, relative to the risk among those not so exposed. An RR of 1.0 would indicate no difference in the risk of bladder cancer between those exposed to a particular factor and those not exposed. An RR above 1.0 would indicate an increased risk for those exposed (e.g., an RR of 2.0 means that the exposed have 2 times the risk of those not exposed), and an RR below 1.0 would indicate a decreased risk among the exposed (e.g., an RR of 0.5 means that the exposed have one-half the risk of those not exposed).

Many of the estimates of RR presented herein are controlled for the influence of other variables. The method usually used to derive these estimates was a standard multiple contingency table analysis.[15] In addition, when it seemed desirable to control for the potential influences of a large number of other variables, a logistic regression analysis was also used to develop estimates of RR.[16]

The test for whether there is a statistically significant difference between an RR and 1.0 is the χ^2 test for a simple comparison, and the Mantel-Haenszel summary χ^2 test was used when the data were controlled for the influence of other variables.[17] When multiple, naturally-ordered levels of an exposure variable were evaluated (e.g., when testing for dose-response relationships) the test of statistical significance used was the χ^2 test for linear trend. This tests the likelihood that a linearly increasing or decreasing trend in the RR with increasing dose could be due to chance alone. When the estimates of RR were controlled for the influence of other variables, the test for linear trend in these estimates was the Mantel Extension of the Mantel-Haenszel test, performed after the data were stratified on the control variables.[18]

The p-values given to estimate the likelihood that the difference between any RR and an RR of 1.0 could be due to chance, in the absence of any real association, are p-values corresponding to one-tailed significance tests. These seemed appropriate for regulatory purposes since increased risks, not decreased risks, are the principal concern. However, many scientists prefer the more "conservative" two-tailed tests for estimating the probability that an observed association

could be due to chance alone. Two-tailed p-values can be obtained by doubling the p-values given. An association is considered statistically significant in this report if the p-value is less than 0.05.

Ninety-five percent confidence intervals (CI) have been calculated for a number of the RR's. These can be interpreted as indicating that, after taking account of the possibility of random errors (chance), 95% of the time the "true" value for the RR will lie within this CI. When the 95% CI is calculated for an RR that is controlled for other variables, the CI is controlled for these variables also.[15]

RESULTS

Four thousand and thirty-five eligible cases were identified. One percent of these were histologically characterized as "papillomas" while 99% were called carcinomas. Seven percent of the cases died before they could be interviewed and another 7% were too ill to be interviewed. Eighty-seven percent of the remaining cases were interviewed (13% were not found or refused) (Table 1).

One percent of the controls died before they could be interviewed and another 3% were too ill to be interviewed. Of the remaining identified controls, 86% were interviewed (14% were not found or refused) (Table 1). Among the younger controls (ages 21-64) another level of non-response existed, i.e., those eligible controls in households where no census was obtained. Estimating the number of such refusals based on the known refusal rate yields an overall cooperation rate among the controls of 81%. (Appendix C gives a more detailed discussion of the response rates in the younger controls.)

Table 2 shows the cases and controls interviewed by geographic area, age, and sex. Among the cases there were 3 times as many males as females and the median age was 67 years. The predominance of males and the late age of onset reflect the patterns already described in incidence surveys.[19] The designed 2:1 sample of controls to cases and similarity in their age distribution was achieved in most areas. This ratio was lower in Detroit, 1.4:1, for the reason noted above (see Methods). The ratio was also lower in New Jersey, 1.8:1. In this instance, the actual number of cases identified exceeded the predictions used to estimate the numbers of controls needed. All analyses in this report relate to the combined data for all of the areas. Some of the analyses have been controlled for individual area or region of the country, as noted in the text.

Table 3 compares some demographic features of the case and control series. Blacks, orientals and American indians are at lower risk of bladder cancer compared to whites (they represent smaller fractions of the cases than of the controls); this is consistent with race-specific incidence data.[19] Cases have a somewhat higher proportion of people with 9-12 years of education. This pattern has been seen before and may be related to the types of occupation associated with exposure to bladder carcinogens.[21]

The two major known risk factors for bladder cancer are cigarette smoking and occupational exposures.[21] Table 4 shows the association of bladder cancer with the estimated lifetime consumption of cigarettes. The RR's found here agree with those reported elsewhere [20]. Persons

who smoked 40 pack-years or more had a 3-fold excess risk of bladder cancer and the dose-response trend was statistically significant.

Comparisons between cases and controls for several other known or suspected risk factors are given in Table 5. Those with occupational exposure to known or highly suspect bladder carcinogens had a 30% increased risk. This was also comparable to the risk reported among groups similarly categorized in other studies.[22] The "exposure" was to dyes, rubber, leather, ink, or paint in any job held during a respondent's lifetime. These materials have been linked to bladder cancer in a number of studies. It is likely that not all "occupationally-exposed" individuals had meaningful contact with carcinogens, so that further analyses are needed to delineate specific occupational subgroups who are at higher risk than this aggregate group. However, this measure of occupational exposure is useful for the limited purpose of controlling for potential confounding of AS associations by occupation.

Coffee drinkers in this study had an elevated risk of bladder cancer. Other reports have found such an elevation but consistent dose-response relationships have not been noted.[23] This has been interpreted as evidence that the association is merely an indication of some other aspect of the lifestyle of non-coffee drinkers that places them at lower risk.

In summary, this study of bladder cancer revealed a median age of 67, a 3:1 excess of males to females, an excess risk of whites versus nonwhites, an excess risk among those with 9 to 12 years of formal education, a strongly positive dose-response relationship to cigarette

smoking, and an excess risk among those exposed on the job to dyes, rubber, ink, and paints. These results are similar to those of other population-based studies of bladder cancer.[21]

Table 6 shows how intake of AS in any form varied among subgroups of the control population as defined by certain risk factors. These data give some idea of the pattern of AS use in the general population and indicate which factors might confound an association between AS use and bladder cancer. Younger people were more likely than older people to have used AS. Cigarette smoking, which increased the risk of bladder cancer, was not correlated with AS exposure. A reported history of diabetes was strongly correlated with AS exposure, but the proportion of diabetics among the cases was only slightly greater than among the controls (10% vs. 9%). The degree of possible confounding for these factors is correspondingly small.

There are several reasons to distinguish the three common forms of AS. Most saccharin in the American diet today comes from diet soft drinks. The typical 12 oz. can of diet soft drink contains about 120 mg. of saccharin, whereas two tablets or one packet of granulated sweetener contains about 30 mg. Table-top sweeteners have been in general use for 80 years, while diet soft drinks have been widely consumed for 20 years. Different segments of the population tend to use the different forms of AS. Finally, as noted, the earlier positive findings reported an association between bladder cancer and AS use only for table-top sweeteners.

Throughout this report, we have referred to associations with AS. Future analyses will attempt to evaluate separately, to the extent possible, saccharin and cyclamates. We have, however, repeated most of the major analyses considering the 1960's (the era when cyclamates were used) separately. None of the associations presented derived solely from exposures in the 1960's.

Figure 1 shows the percent of the control group who ever used each of the three major forms of AS singly or in combination. Forty-two percent used at least one form. Most of the users of diet food were also users of diet drink or table-top sweeteners.

Most of the analyses presented in this report concern table-top AS and diet drinks, the major sources of AS in the diet in the past. Future analyses will include evaluations of diet foods.

Table 7 gives the RR's of bladder cancer associated with the use of each form of AS and all forms combined. The point estimates are all close to 1.0, and the 95% confidence intervals are narrow. As previously indicated, the evidence was that other factors were not likely to confound this association. Such was the case, as the estimates were unchanged by fine control for a variety of factors, alone or in combinations (including age, race, number of cigarettes smoked, number of cups of coffee drunk, history of diabetes, geographic area, occupation, and education). For example, simultaneous control for age, race, sex, cigarette smoking, occupational exposure, history of diabetes, region, and educational level in logistic regression analysis yielded an RR of

1.00 for a history of use of any form of AS, with a 95% CI of 0.91 to 1.10. The estimates of RR presented in this report were controlled for the major bladder cancer risk factors but were rarely different from the uncontrolled estimates.

Earlier positive studies showed some evidence of an increasing relative risk of bladder cancer with increasing dose and duration of AS use [1,9]. Tables 8-10 give data on these measures.

Table 8 shows the average daily frequency of use of table-top sweeteners, a measure of intensity of use. Among males there was no clear-cut or statistically significant dose-response relationship, although a slight elevation in RR was present in the heaviest exposure category. In females, the risk appeared slightly decreased among lighter users and slightly increased among heavier users. The trend in these RR's was variable but statistically significant. For the sexes combined, there were slightly higher risks at higher doses. There was no statistically significant dose-response relationship.

One of the few instances where RR's adjusted for other variables differed somewhat from the unadjusted estimates occurred in the most extreme dose category. Whether these differences represent some element of confounding operating only among very heavy users or whether they simply reflect the influence of random variation when the group with the fewest subjects was extensively subdivided cannot be determined from inspection of the stratum-specific RR's. For this reason, both the unadjusted and adjusted estimates of RR are presented.

One serving could mean a variable number of tablets, drops, or packets. Further analyses will be necessary to account for these differences and will provide an estimation of exposure in milligrams of saccharin and cyclamate. However, in practice, uses-per-day is a good index of relative exposure. For the vast majority of subjects, a serving was 2 tablets or one packet (30 mg.). In interpreting these results one should keep in mind that one of the positive studies found an association mainly because of a two-fold excess risk in men using $\geq$2500 tablets a year [1]. This is roughly equivalent to the measure of $\geq$3 servings per day in the present study.

Table 9 shows daily servings of diet drinks as a measure of intensity of diet drink use. Among males, no consistent or clear-cut trend was seen with increasing dose, although some elevations in risk again occurred among the more heavily exposed. Among the females, heavier users also showed slight elevations in risk, but there was also no clear-cut, consistent, or statistically significant trend with increased dose.

Since there was some evidence of increased risk among heavier users of both table-top sweeteners and diet drinks (more prominent in females than males), these two measures were considered jointly to assess the effects of exposure to both forms of AS (Table 10). The categories were chosen to reflect the fact that the average serving of diet drink (8 oz.) contains 2-3 times the dose of AS present in the average serving of table-top sweetener. Among the heaviest users of either type of AS, there was evidence of an increasing RR with increasing

dose of the other type, progressing to the highest RR among the heaviest users of both types of AS. Additional control for other variables did not alter this pattern. For example, the uncontrolled RR for users of both forms who drank ≧2 diet drinks or used ≧6 servings of table-top AS was 1.45. Simultaneous control for sex, age, race, cigarette smoking, occupational exposure, geographic region, and formal education in a logistic regression analysis yielded an RR of 1.43. However, there were few heavy users of both types of AS, so that there was substantial variability in the RR's for heavy use, and none of the individual RR's in Table 10 taken by itself would be statistically significant. The higher risks for the intense users of both forms were present for both sexes, but they were slightly more elevated in females. The risk among users of both forms in the 3 most extreme categories of use in Table 10 was 1.56 for males and 1.73 for females. These observations will receive more attention in subsequent analyses, to evaluate whether these heavy users had some other characteristics which might be responsible for their apparently increased risk of bladder cancer. The more refined measures of dose now being developed might also help to sharpen some of these observations.

Another measure of the degree of exposure is the duration of use. Table 11 shows the relative risks for users of diet drinks and users of table-top sweeteners according to the number of years of use. No pattern emerged in either sex for either form of AS, although the lowest risk occurred in the group with longest duration. In one of the positive studies, the excess was greatest among those who had used

sweeteners for 3 years or more [1]; in the other study the excess was seen mainly in those with over 10 years of use [9].

A measure of exposure that combines intensity and duration is estimated lifetime consumption. Table 12 shows the estimated number of lifetime uses of table-top AS. No pattern appeared among males, but females show some elevated RR's with increased total consumption. The trend in the RR among females was significant (p=0.039).

Table 12 also gives the corresponding figures for lifetime consumption of diet drink. There was no consistent or statistically significant trend with increasing dose in either males or females.

Table 13 separates users into groups according to the time since first exposure. Because many carcinogens have a long latent period, it is possible than an effect among users whose first exposure was many years ago would be lost if all users of AS were considered together. However, there was no tendency for the relative risks to rise with increasing time since first exposure to diet drinks, diet foods, or table-top sweeteners taken separately. In fact, for females the highest RR was seen in the group with the least time since first exposure to any form of AS.

When separate analyses were done for those who used two or more diet drinks daily, and for those who used table-top AS two or more times daily, no trend was seen for duration of exposure or for length of time since first exposure, thus mirroring results in the total group. The slight reductions in risk among those exposed for the longest period and among those first exposed the longest time ago,

which were seen in the total group, were not seen in these more heavily exposed.

The subgroups discussed above are of interest because of the intensity, duration, timing, or total extent of their exposure to AS. Other subgroups are of interest because of their special risks of bladder cancer apart from any exposure to AS. As noted at the outset, the evidence from animal experimentation points in two directions -- toward saccharin being a weak carcinogen when given alone and a promoter of the effects of other carcinogens. The influence of a weak carcinogen may be detected more readily among people who are otherwise at low risk of bladder cancer. Only against such a background of low risk might one be able to discover a slight elevation in risk from weak agents. To detect promotion, one would look at the opposite end of the spectrum of risk, i.e., among "high-risk" persons. Only among individuals exposed to other carcinogens and at high probability of having had a tumor initiated by such exposure would one be likely to discover the effect of promoting agents. In fact, the major reason for undertaking a study of this size was to develop a data base that would allow us to explore relationships in these two types of subgroups.

An adequate evaluation for promotional effects will require more extensive analyses. It will be necessary to distinguish the specific exposures that convey excess risk in this study and then to investigate the timing of these exposures in relation to exposures to AS. For this report, therefore, the only information about possible promotion of the effects of other carcinogens is some information concerning AS

use and bladder cancer among heavy smokers. Heavy use of cigarettes is a well-known cause of bladder cancer that is confirmed by the data in this study as well. Since heavy cigarette smokers tend to be lifelong smokers, one can safely assume that most of the subjects were smoking before any exposure to AS occurred.

It is somewhat easier to investigate the low-risk persons exposed to no other known or suspect bladder carcinogen since the nature and timing of exposures other than AS do not need to be considered. We initially defined the "low-risk group" as white females who never smoked, drank coffee, or handled dye, rubber, leather, ink, or paint on any job. As shown in Table 14, a significantly elevated risk was associated with the use of table-top sweeteners in this low-risk group. The small sample size (80 women) precluded any detailed examination for dose-response relationships.

It is possible that finding an increased risk in this small subgroup was merely due to chance. A larger low-risk group that provided more stable estimates of risk and permitted a more refined evaluation of dose-response relationships was assembled by relaxing the criteria used to define the low-risk group. The addition of coffee drinkers to the low-risk group resulted in the smallest modification of risk (among non-smokers, those who ever drank coffee were at 28% higher risk than non-drinkers) but by far the greatest increase in numbers (from 80 to 987). In previous studies, coffee drinking has shown an inconsistent relationship with bladder cancer with little evidence of dose-response.[21] In this study, while there was a

slight difference in risk between coffee drinkers and non-coffee drinkers among non-smoking females, there was no dose-response relationship with the number of cups of coffee per day. For these reasons, AS use was examined in a modified "low-risk group" which included coffee drinkers.

There were 250 case and 737 control women who neither smoked nor reported any exposure to a hazardous occupation. In this group the RR associated with having ever used any form of AS was 1.14 (p=0.186). However, there was evidence of increasing risk with increasing average daily consumption of table-top sweeteners and diet beverages, rising to a 60 to 80% excess risk in the highest dose categories (Table 15).* The trend in the RR was positive and statistically significant for table-top AS but not diet beverages. There was no linear relationship with duration of use (the highest risk occurring in the intermediate category both for table-top sweeteners and for diet beverages). There was a significant dose-response relationship with total lifetime servings of table-top AS, rising to twofold among those with 10,000 or more uses (Table 16). In addition, when attention was restricted to those whose usual use of table-top AS or diet drinks was two or more

* In Table 15, the proportion of controls with missing data for years of use of table-top sweetener and average number of daily uses of table-top sweetener was higher than the proportion of cases with missing data. Most of the missing data came from those who used sweetener sporadically. Thus the findings from the group of heavy users would probably not be affected.

servings per day (those showing an excess risk in the low-risk group), the relationships with duration of use were somewhat different than those in the total group (Table 17). Among these heavy users there was a significant positive trend in the RR with increasing duration of use of both table-top AS and diet drinks . The RR among heavy users of table-top AS who used them longer than 10 years was 2.7 times that of those who never used AS.

To determine if variables which were not confounding in the aggregate data were confounding in the low-risk group and responsible for these AS associations, a number of RR's were computed controlling for diabetes, coffee drinking, education, region, obesity, hair dye use, and urinary-tract infections. The RR for heavy users in the low-risk group remained essentially unchanged by any of these controlling procedures. For example, logistic regression analysis incorporating simultaneous control for age, coffee drinking, history of diabetes, region (east,west), and formal education yielded an RR of 1.74 (with a 95% CI of 1.11 to 2.74) for those who used 2 or more servings of table-top AS or diet drinks daily.

As noted, an evaluation for possible promotional effects of AS on the action of other carcinogens was conducted among heavy smokers. RR's for various dose levels of AS among smokers according to the average number of cigarettes smoked per day are given in Tables 18 and 19. No consistent or significant evidence of a dose-response relationship is noted with either table-top sweeteners or diet drinks in smokers of one pack per day or less of either sex. However, among heavy smokers

who used diet drinks, there is some evidence of increasing RR with increasing dose of AS for both sexes. In addition, evidence of a dose-response relationship for AS used as table-top sweeteners was seen among heavy-smoking females. Among males who were the heaviest smokers, users of table-top sweeteners had an increased RR compared to non-users, but there was no evidence of an increasing trend in RR with increasing dose of AS. Further analyses will be needed to describe fully the relationships of risk with AS among heavy smokers. Interpretation of these findings should also be aided by analyses of other groups at high risk because of extensive exposure to other bladder carcinogens. These analyses will be performed when more of the other risk factors have been thoroughly evaluated.

DISCUSSION

In interpreting the results of this preliminary analysis, one must bear in mind several points. The evidence from experimentation with laboratory animals indicates that saccharin, like cyclamates, has the biologic capability of inducing cancer. The current study is not a general examination of that capability, for several reasons. First of all, cancer risk is evaluated at only one anatomic site, the bladder. Secondly, a carcinogen producing, for example, a 1% or 2% elevation in risk among all those exposed and a 4% to 5% excess in those most heavily exposed could not be detected by this study. Even a much larger study would be hard pressed to address such low levels of risk, which are obscured in the presence of more potent risk factors for bladder cancer. The problems in uncovering relatively small increases

in risk are not unique to epidemiologic studies. Experiments with laboratory animals are conducted with large doses to assess high levels of risk precisely because of the practical impossibility of evaluating relatively small elevations in risk. Finally, the most persuasive experimental evidence that saccharin given alone is a carcinogen comes from the studies of animals that were exposed while in utero and then throughout their lives. The current study is not a test of the effect of exposure in utero.

Although this study does not examine whether AS can cause any increase, however small, in the risk of bladder cancer in humans, it is capable of testing the hypothesis, raised in two earlier studies, that men who use table-top AS have an average risk of bladder cancer that is 60% or more above the risk of men who do not use it. In addition, the large number of subjects involved in the current study and the detailed information on AS and other risk factors permit us to conduct an unusually powerful search for many different kinds of evidence of an association. For example, the data allow detailed analysis of the effects of dose, of duration of exposure, and of several other facets of exposure. In particular, assessment of risk is possible among heavy users of AS. The size of the study also permits a detailed evaluation of AS use among specific subgroups of the study population. Of special interest at the outset of the study were low-risk individuals (in whom the action of a relatively weak carcinogen given alone might be most detectable) and high-risk individuals (in whom a promotional effect of AS might be most apparent).

Men who had a history of any use of table-top AS showed a relative risk of 1.04, with a 95% confidence interval of 0.84 to 1.18. These data provide no support for earlier reports of a relative risk as high as 1.6 among males who used table-top AS. There was also no evidence of an excess risk as high as two-fold or greater at the dose levels showing these elevations in prior studies.

Analysis of the entire data set, controlling for relevant risk factors, ruled out evidence for a strong or moderate carcinogenic effect of AS on the human bladder at the average doses of AS used in the past in the United States. The relative risk for a history of use of any form of AS was 1.01, with a 95% confidence interval of 0.92 to 1.11. In other words, these results are not consistent with a risk among users of AS in excess of 11% over that among non-users. In the total study group, there was no evidence of increased risk with long-term use of AS in any form or with use that began decades ago.

However, an excess risk was seen among subjects who used table-top AS or diet drinks heavily (6 or more servings of table-top AS, or 2 or more glasses of diet drinks per day), particularly when both forms of AS were consumed at these levels. These excesses were relatively small in epidemiologic terms (with relative risks rising to 1.6 in the heaviest users of both forms), were more apparent in females than males, and did not show a consistent dose-response relationship. In addition, the estimates of RR for very heavy users were based on relatively small numbers of subjects.

The inconsistencies associated with the relatively small increases in risk among heavy users suggest caution in their interpretation and a need for further analyses. However, for two reasons the preliminary findings in heavy users are a cause for concern. First of all, the study was designed to include large numbers of subjects in order to assess the effect of just such heavy use. This was done since the effect of a relatively weak carcinogen might be apparent only at high doses. Secondly, as noted, the apparent lack of an association overall relates to risks at the average dose levels of AS used in the past. There has been a recent trend toward increased consumption of AS, so in the future the overall association between AS use and bladder cancer may be better approximated by considering the risks involved at higher doses.

This importance of relating the level of average risk to the average dose received is illustrated by another bladder cancer risk factor, cigarette smoking. The increased risk of bladder cancer associated with cigarette smoking is two-fold. This reflects the increased risk of the average smoker, who in this study smoked 25 cigarettes per day. Using these data, one can estimate that the RR associated with a dose of one cigarette per day might be 1.04. Thus, if the study had been done in a population in which the smokers averaged 1 cigarette per day and the heavy smokers averaged twice this amount, then the anticipated excess risks would be 4% for all smokers and 8% for heavy smokers. As noted previously these risks would be essentially undetectable in this type of study. The reason we can detect an

association between cigarette smoking and bladder cancer is that smokers commonly consume large "doses" of cigarettes. The degree to which consumption of AS is increasing, especially among children who have yet to reach an age when bladder cancer appears, is a measure of the degree to which the findings for the heavier users in this study need to be given more weight.

These preliminary analyses also searched for associations in subgroups of the study population determined in advance on the basis of the experimental evidence. When saccharin alone was given to laboratory animals, it appeared to be weakly carcinogenic. We infer that the effect was weak because the excesses of bladder cancer were seen only among animals receiving high doses, and this was not consistently observed in all studies. In addition, the excess risk was most apparent following exposure of particularly susceptible animals (i.e., those exposed in utero). We reasoned that if this were also true for humans, such a low-level effect might be most clearly seen among heavily exposed persons with an otherwise low background risk of bladder cancer (e.g., females who never smoked, never were occupationally exposed to bladder carcinogens, and never drank coffee). In this "low-risk" group there was evidence of an overall increased risk associated with AS use. However, since this subgroup was small it was difficult to establish or exclude any dose-response relationships. Enlarging this group by including coffee drinkers led to the finding of a (non-significant) 14% excess risk associated with a history of AS use. However, there was evidence of higher risks among heavy users of

table-top AS and heavy users of diet drinks. Among such heavy users there was also a significant positive trend in the RR's with increasing duration of use. The RR for those who used over 2 daily servings of table-top AS for 10 years or more was 2.7 times that of the group who never used AS.

The potential value of using this low-risk group to identify relatively weak effects can be seen by estimating rates of bladder cancer in subgroups. Women in the low-risk group who did not use AS had a crude risk of bladder cancer of 4.6 cases per 100,000 such women per year. If the 60% increased risk with heavier use of table-top AS or diet drinks reflects a causal relationship, then the amount of disease produced by such use would be approximately 2.9 cases per 100,000 heavy users per year. An effect of this magnitude would be undetected in other groups because of their higher background risks. For example, this amount of disease would be reflected as a 13% increase in the rate for all males who used AS at similarly high doses. This is consistent with the RR's noted in this study.

Subjects at high risk are of interest because of the possibility of evaluating whether saccharin promotes the carcinogenic activity of other agents, as has been observed in some animal experiments. Promotion is difficult to demonstrate in humans since little is known about the expected timing of the contributing risk factors. Furthermore, an adequate analysis of promotion effects will require an extensive evaluation of the data set in order to identify those specific exposures that elevate the risk of bladder cancer. In our initial evaluation,

we found no relationship between any form of AS use and bladder cancer among light-to-moderate smokers. However, among the heaviest smokers (men and women) there was evidence of increased risk among those who were relatively heavy users of table-top AS and diet drinks. These associations should be clarified by a more complete delineation of smoking and other risk factors in this population and by analyses to evaluate interactions with AS use.

While the RR's observed in this study may reflect biological reality, other interpretations need to be considered. In order to assess etiologic influences and not those associated only with prognosis, this study was restricted to newly incident cases, and an attempt was made to identify and interview the cases promptly. However, 14% of the case series were either dead or too ill to be interviewed by the time an attempt was made to approach them. If these cases were markedly different from the majority with respect to use of AS, our estimates of RR would be biased. We also made extensive attempts to obtain a high cooperation rate among the patients and comparison individuals we approached. However, some subjects selected for study did refuse to be interviewed. To the extent that the proportion refusing differed between the case and control groups, and to the extent that those who refused might use AS differently from respondents, some of our estimates of association may have been affected. The likelihood that either of these potential sources of bias has affected the results will be assessed by future analyses. We will examine the AS associations according to the stage of the tumor and survival characteristics of

the cases. We will also compare the respondents and nonrespondents. Another potential source of bias that cannot be addressed directly is the possibility that cases may have recalled past AS use differently from controls. Such a "recall bias" could operate in opposite ways. Possibly patients with bladder cancer were aware of reports linking AS and bladder cancer and therefore took more time to reflect on and remember their prior usage of AS. Alternatively, patients with bladder cancer concerned about personal responsibility for their cancer might suppress memory of voluntary exposures that they think could be related to their disease. Cancer patients in general do not seem to report a pattern of AS usage different from that of other patients.[24] In addition, we think it unlikely that such a bias would have produced the patterns of associations seen in this study (associations in some groups of subjects and not in others). Another concern in some studies is diagnostic bias. In this study, such a bias would exist if AS users were more or less likely to be followed for symptoms of bladder cancer than non-users would be. Since blood in the urine is the first symptom of bladder cancer for the vast majority of patients, and since this symptom is generally rapidly brought to a physician's attention by the affected patient, we think it unlikely that diagnostic bias affects this study.

We think that the apparent lack of association with the average use of AS and the pattern of positive RR's for heavy users are unlikely to be due to any obvious source of bias. It is more difficult, however, to exclude the possibility of chance. By chance alone, we could have

missed a small but important risk associated with AS use at the levels commonly used in the past. In addition, the pattern of positive RR's described (at high doses, and particularly evident in a low-risk subgroup and among heavy smokers) could be ascribed to chance variation in subgroups of a study which, overall, shows no association between AS use and bladder cancer. While most of the positive associations noted are "statistically significant," or form significant trends, some of them could be chance observations. While this is possible, we do not think that the pattern of positive associations arises from a "multiple comparison problem." If a large number of independent tests are performed on the same data set, some will be "statistically significant" on a chance basis alone. While the positive risks in this study emerged from a large number of analyses, all associations occurred in subgroups that were specified prior to the study as being most likely to reveal an underlying relationship between AS use and bladder cancer, if indeed one existed.

We are reasonably confident that the lack of an overall association among all those having ever used AS, along with narrow confidence intervals for these estimates, has ruled out a strong or moderate carcinogenic effect on the human bladder of AS at the doses and under the conditions in which they were commonly used in the past. Earlier suggestions of an increased risk of approximately 60% or more among men who used table-top AS could not be confirmed. However, the increases in risk at high dose levels of AS, the fact that the increases in risk are higher for any particular dose level among a subgroup of study

subjects who have a very low background risk, and the apparent interactive effect of heavy use of AS and heavy smoking can all be interpreted as consistent with the results of animal experimentation. These experiments suggest that saccharin is weakly carcinogenic when given alone and a promoter of the carcinogenic effects of other agents.

Obviously, a cause-and-effect relationship between AS use and bladder cancer in humans has not been established by the positive associations in this study. Understanding of the results presented in this report will be enhanced by further analyses and by critical review and comparison of these results with those of other studies (published and ongoing). In the meantime, we believe it is prudent to assume that the findings of this study are consistent with the associations seen with experiments in laboratory animals which imply that AS consumption is a potential risk factor for human bladder cancer.

SUMMARY

A case-control interview study of bladder cancer involving almost 9000 people was conducted in 5 states and 5 metropolitan areas in order to evaluate the possible risks associated with the use of artificial sweeteners (AS). 3010 newly diagnosed cases of bladder cancer occurring during 1978 in these areas were interviewed, along with 5783 controls from a stratified random sample of the population.

Averaged over all persons who ever used any form of AS, the relative risk of bladder cancer was 1.01, with a 95% confidence interval of 0.92 to 1.11. This relative risk is not significantly different from 1.00 and suggests that if an elevated risk exists for users at

the doses consumed in the past, it is not more than 11% above the risk among non-users. Among all males who ever used table-top AS, the relative risk of bladder cancer was 1.04, with a 95% confidence interval of 0.84 to 1.18. This suggests that the average risk for males using this form of AS at the doses consumed in the past is not in excess of 18% above the risk in non-users. This result is not consistent with the 60% excess risk reported among males using table-top AS from 2 earlier studies.

However, an excess risk was seen among subjects who used table-top AS or diet drinks heavily (6 or more daily servings of table-top AS, or 2 or more daily servings of diet drink), particularly among subjects who consumed both forms at those higher levels. These increased risks were relatively small in epidemiologic terms, more apparent in females than in males, and without a consistent dose-response relationship.

In a subgroup of individuals with a low background incidence of bladder cancer (non-smoking females with no occupational exposure to potentially hazardous substances), the relative risks for bladder cancer were higher than in the total group for each level of exposure to table-top AS or diet drinks, and the dose-response relationships were more consistent. Among the heavier consumers (2 or more daily uses of table-top AS or servings of diet drinks), the relative risks rose with increasing duration of use. In this subgroup, women who used table-top AS twice or more daily for at least ten years had 2.7 times the risk of similar women who never used AS.

In a preliminary evaluation, we found no relationship between any form of AS use and bladder cancer among light-to-moderate smokers. However, among the heaviest smokers (men and women) there was some evidence of elevated risk among those who used table-top AS and diet drinks most heavily. These findings will be clarified by a thorough delineation of the role of cigarette smoking and other risk factors and a fuller examination of their interactions with AS use.

The positive associations in this study do not by themselves establish a causal link between AS use and bladder cancer. It is noteworthy, however, that they are consistent with experiments in laboratory animals, which have suggested that artificial sweeteners given alone are weakly carcinogenic and can also promote the carcinogenic action of other agents. On the other hand, the possibility cannot be excluded that the positive associations seen herein represent merely chance variations in subgroups of a study which, overall, fails to demonstrate an association between AS use and bladder cancer.

Determining the most valid interpretation from among the alternatives is a difficult task and will require further analysis of the results in light of other evidence. In the meantime, we believe the data presented in this report are helpful in giving an approximation of the maximum impact past AS use may have had on current patterns of human bladder cancer in the U.S. Pending further evaluation, we also believe the associations observed in this study among heavy users of AS lend support to experimental data implicating AS as a potential risk factor for human bladder cancer.

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Table 1

Response Rates

	Cases	Controls		Total
		21-64	65-84	
Not Approached For Interview				
Dead	7%	0%	2%	3%
Disabled	7%	1%	4%	4%
Non-Response in Telephone Screening	--	12%*	--	--
Approached For Interview	3479	2899	3790	10168
Interviewed	3010	2470	3314	8794
Percent Interviewed	87%	85%	87%	86%
Estimated Response Rate	87%	75%**	87%	83%***

* See Bladder Cancer Study Controls Aged 21-64: Review of Methods and Results

** Product of screening response rate and interviewing response rate

*** Adjusted for telephone screening response rate

Table 2

Numbers of Cases and Controls,

By Age and Sex, and

By Geographic Area

	Males				Females			
	Cases		Controls		Cases		Controls	
	No.	%	No.	%	No.	%	No.	%
21-24	3	-	14	-	2	-	9	1
25-29	5	-	19	-	7	1	11	1
30-34	13	1	39	1	8	1	19	1
35-39	18	1	36	1	11	1	16	1
40-44	54	2	95	2	13	2	37	2
45-49	94	4	200	5	30	4	56	4
50-54	154	7	326	8	54	7	120	8
55-59	251	11	481	11	82	11	156	10
60-64	356	16	629	15	108	15	170	11
65-69	419	18	698	16	124	17	241	16
70-74	385	17	758	18	114	15	262	17
75-79	317	14	585	14	114	15	218	15
80-84	197	9	403	9	79	11	185	12
Total	2266	100	4283	100	744	100	1500	99

	Cases		Controls	
	No.	%	No.	%
New Mexico	68	2	173	3
New Orleans	82	3	168	3
Atlanta	106	4	267	5
Utah	118	4	285	5
Seattle	179	6	332	6
Iowa	354	12	749	13
San Francisco	361	12	731	13
Detroit	378	13	520	9
Connecticut	414	14	878	15
New Jersey	950	32	1680	29
Total	3010	100	5783	99

Table 3

Percent of Cases and Controls,

By Demographic Features

	Cases	Controls
Race		
White	94.1%	91.0%
Black	4.3%	7.0%
Oriental	0.5%	1.0%
Indian	0.4%	0.5%
Other	0.7%	0.5%
Years of School		
1-8	30%	31%
9-12	46%	42%
13-16	18%	19%
17+	4%	8%
Religion		
Protestant	50%	52%
Catholic	38%	35%
Jewish	5%	4%
Mormon	3%	4%
Marital Status		
Married	74%	73%
Widowed	15%	17%
Divorced	5%	4%
Separated	2%	1%
Never Married	5%	4%

Table 4

Lifetime Cigarette Consumption

Pack-Years*	Cases	Controls	R.R.**
Non-Smoker	659	2193	1.00
<1	42	111	1.27
1-9	271	644	1.48
10-19	346	632	1.93
20-29	346	540	2.25
30-39	342	484	2.46
40-49	317	364	3.04
50-59	206	240	2.96
60+	394	427	3.31

(χ = 18.394; p = <0.001)

* 1 pack-year = 365 packs of cigarettes

** Adjusted for race and sex

Table 5

Percent of Cases and Controls,

By Selected Exposures

	Cases	Controls
[illegible] cigarettes	78%	62%
[illegible]	83%	71%
[illegible], Rubber, Leather [illegible] on a Job	34%	28%
[illegible] Coffee	3%	6%	
[illegible] of Diabetes	10%	9%
[illegible] Residence in [illegible]	37%	35%

Table 6

History of Use of Artificial Sweeteners,

Controls Only,

Selected Groups

Selected Group	Percent Ever Used AS*
Aged 21-44	55%
Aged 45-64	50%
Aged 65-84	37%
Never Smoked Cigarettes	45%
Smoked <20 Cigarettes Per Day	42%
Smoked 20-39 Cigarettes Per Day	41%
Smoked ≥40 Cigarettes Per Day	44%
Never Drank Coffee	40%
Drank <2 Cups of Coffee Per Day	42%
Drank 2-3 Cups of Coffee Per Day	42%
Drank ≥4 Cups of Coffee Per Day	43%
Handled Dye, Rubber, Leather, Ink or Paint on a Job	47%
Had Diabetes	81%
Had Longest Residence in Large City	45%
All Controls	42%

* Adjusted for age, sex, and race

Table 7

History of Use of Artificial Sweeteners, By Sex

	Cases	Controls	R.R.*	95% Confidence Limits
Males				
Never Used AS	1349	2554	1.00	
Ever Used Diet Drink	607	1204	0.95	(0.84, 1.07)
Ever Used Table Top	592	1066	1.04	(0.92, 1.18)
Ever Used Diet Food	240	442	1.02	(0.85, 1.22)
Ever Used Any Form	909	1723	0.99	(0.89, 1.10)
Females				
Never Used AS	358	767	1.00	
Ever Used Diet Drink	262	504	1.02	(0.83, 1.25)
Ever Used Table Top	236	474	1.04	(0.84, 1.28)
Ever Used Diet Food	130	239	1.13	(0.87, 1.47)
Ever Used Any Form	384	732	1.07	(0.89, 1.29)
Both Sexes				
Never Used AS	1707	3321	1.00	
Ever Used Diet Drink	869	1708	0.97	(0.87, 1.07)
Ever Used Table Top	828	1540	1.04	(0.93, 1.16)
Ever Used Diet Food	370	681	1.05	(0.91, 1.22)
Ever Used Any Form	1293	2455	1.01	(0.92, 1.11)

* Adjusted for race, cigarette smoking, coffee drinking, occupational exposure

Table 8

Average Number of Daily Uses of Table-Top Sweeteners

By Sex

	Cases	Controls	R.R.	
			Unadjusted	Adjusted*
Males				
Never Used AS	1349	2554	1.00	1.00
<1 Use	109	190	1.09	1.09
1-1.9 Uses	105	229	0.87	0.88
2-3.9 Uses	164	299	1.04	1.08
4-5.9 Uses	62	118	0.99	0.97
6-7.9 Uses	20	34	1.11	0.99
≥8 Uses	19	25	1.44	1.12
	(χ = 0.186; p = 0.426)			
Females				
Never Used AS	358	767	1.00	1.00
<1 Use	39	113	0.74	0.73
1-1.9 Uses	56	96	1.25	1.28
2-3.9 Uses	72	110	1.40	1.42
4-5.9 Uses	22	45	1.05	0.99
≥6 Uses	16	20	1.71	1.36
	(χ = 1.938; p = 0.026)			
Both Sexes				
Never Used AS	1707	3321	1.00	1.00
<1 Use	148	303	0.95	0.97
1-1.9 Uses	161	325	0.96	0.99
2-3.9 Uses	236	409	1.12	1.17
4-5.0 Uses	84	163	1.00	0.98
≥6 Uses	55	79	1.35	1.12
	(χ = 1.146; p = 0.126)			

* Adjusted for age, race, sex, cigarette smoking

Table 9

Average Number of Daily Servings of Diet Drink

By Sex

	Cases	Controls	R.R.*	
			Unadjusted	Adjusted
Males				
Never Used AS	1349	2554	1.00	1.00
<1 Servings	349	723	0.91	0.93
1-1.9 Servings	107	207	0.98	0.93
2-2.9 Servings	48	63	1.44	1.44
≥3 Servings	25	41	1.15	1.01
	(χ = 0.352; p = 0.362)			
Females				
Never Used AS	358	767	1.00	1.00
<1 Servings	146	294	1.06	1.01
1-1.9 Servings	44	108	0.87	0.83
2-2.9 Servings	24	29	1.77	1.72
≥3 Servings	15	20	1.60	1.37
	(χ = 0.942; p = 0.173)			
Both Sexes				
Never Used AS	1707	3321	1.00	1.00
<1 Servings	495	1017	0.95	0.95
1-1.9 Servings	151	315	0.93	0.90
2-2.9 Servings	72	92	1.52	1.52
≥3 Servings	40	61	1.28	1.12
	(χ = 0.805; p = 0.210)			

* Adjusted for age, sex, race, cigarette smoking

Table 10

Average Number of Daily Uses of Table-Top Sweeteners by Average Number of Daily Servings of Diet Drink

Males and Females Combined

	Diet Drinks Daily		
	None	<2	≥2
Uses of Table Top Daily			
None	1.00* (1707, 3321)**	0.94 (314, 638)	1.21 (38, 60)
<3	1.02 (189, 367)	0.98 (212, 417)	1.26 (35, 54)
3-6	1.15 (80, 136)	0.76 (59, 146)	1.56 (20, 25)
≥6	0.99 (18, 34)	1.53 (28, 34)	1.64 (7, 8)

* Relative risk adjusted for age, race, sex

** (Number of cases, number of controls)

Table 11

Number of Years of Using Table-Top Sweeteners and Number of Years of Drinking Diet Drinks, By Sex

	Cases	Controls	R.R.*
Table-Top Sweeteners			
Males			
Never Used AS	1349	2554	1.00
<5 Years	208	373	1.05
5-9 Years	134	251	1.02
≥10 Years	157	314	0.97
	(χ =-0.132; p = 0.447)		
Females			
Never Used AS	358	767	1.00
<5 Years	83	168	1.04
5-9 Years	68	101	1.39
≥10 Years	62	137	0.96
	(χ = 0.665; p = 0.253)		
Diet Drinks			
Males			
Never Used AS	1349	2554	1.00
<5 Years	175	334	0.99
5-9 Years	137	265	0.99
10-14 Years	131	248	1.01
≥15 Years	84	220	0.75
	(χ= -1.381; p = 0.084)		
Females			
Never Used AS	358	767	1.00
<5 Years	87	157	1.12
5-9 Years	63	117	1.06
10-14 Years	56	96	1.14
≥15 Years	33	91	0.77
	(χ = -0.184; p = 0.427)		

* Adjusted for race, age, cigarette smoking

Table 12

Number of Total Lifetime Uses of Table-Top Sweeteners and Number of Total Lifetime Servings of Diet Drinks By Sex

	Cases	Controls	R.R.*
Table-Top Sweeteners			
Males			
Never Used AS	1349	2554	1.00
<1000 Uses	111	200	1.06
1000-2499 Uses	100	205	0.92
2500-4999 Uses	90	178	0.96
5000-9999 Uses	92	150	1.18
≥10000 Uses	106	205	0.96
	(χ = 0.067; p = 0.473)		
Females			
Never Used AS	358	767	1.00
<1000 Uses	46	105	0.91
1000-2499 Uses	41	96	0.91
2500-4999 Uses	41	67	1.35
5000-9999 Uses	38	68	1.22
≥10000 Uses	47	70	1.32
	(χ = 1.763; p = 0.039)		
Diet Drinks			
Males			
Never Used AS	1349	2554	1.00
<500 Servings	116	230	0.95
500-999 Servings	83	189	0.81
1000-2499 Servings	119	252	0.92
2500-4999 Servings	77	127	1.15
≥5000 Servings	66	128	0.93
	(χ =-0.430; p = 0.334)		
Females			
Never Used AS	358	767	1.00
<500 Servings	61	118	0.99
500-999 Servings	43	68	1.31
1000-2499 Servings	44	96	0.94
2500-4999 Servings	22	71	0.61
≥5000 Servings	38	60	1.25
	(χ =-0.060; p = 0.476)		

* Adjusted for race, cigarette smoking

Table 13

Number of Years Since First Use of Artificial Sweeteners in Any Form

By Sex

	Cases	Controls	R.R.*
Males			
Never Used AS	1349	2554	1.00
<5 Years	206	368	1.04
5-9 Years	209	391	1.00
10-19 Years	273	526	1.01
≥20 Years	153	315	0.95
	(χ= -0.265; p = 0.395)		
Females			
Never Used AS	358	767	1.00
<5 Years	97	161	1.22
5-9 Years	101	182	1.16
10-19 Years	111	221	1.02
≥20 Years	54	132	0.89
	(χ = -0.134; p = 0.447)		
Both Sexes			
Never Used AS	1707	3321	1.00
<5 Years	303	529	1.09
5-9 Years	310	573	1.04
10-19 Years	384	747	1.01
≥20 Years	207	447	0.94
	(χ = -0.297; p = 0.383)		

* Adjusted for race, age and cigarette smoking

Table 14

History of Use, Average Number of Servings Daily, and Number of Years of Use of Table-Top Sweeteners and of Diet Drinks Among Very Low-Risk* White Females

	Table-Top Sweeteners			Diet Drinks		
	Cases	Controls	R.R.**	Cases	Controls	R.R.**
Never Used AS	7	34	1.0	7	35	1.0
Ever Used Table-Top/ Diet Drinks	9	15	3.0	5	19	1.1
	(χ = 1.845; p = 0.033)			(χ = 0.190; p = 0.425)		

* Never smoked cigarettes; never drank coffee; never handled dye, rubber, leather, ink or paint on any job

** Adjusted for age

Table 15

History of Use, Average Number of Servings Daily, and Number of Years of Use of Table-Top Sweeteners and of Diet Drinks Among Low-Risk* White Females

	Table-Top Sweeteners			Diet Drinks		
	Cases	Controls	R.R.**	Cases	Controls	R.R.**
Never Used AS	130	402	1.0	130	402	1.0
Ever Used Table-Top/ Diet Drink	82	210	1.2	71	219	1.1
	(χ = 1.163; p = 0.122)			(χ = 0.387; p = 0.349)		
<1 Use/Serving	15	53	0.9	36	132	0.9
1-1.9 Uses/Servings	17	43	1.2	16	43	1.2
2-2.9 Uses/Servings	21	36	1.8	7	14	1.6
≥3 Uses/Servings	22	38	1.8	3	6	1.6
	(χ= 2.630; p = 0.004)			(χ= 1.075; p = 0.141)		
<5 Years	34	85	1.2	18	77	0.8
5-9 Years	22	43	1.6	19	45	1.4
≥10 Years	21	51	1.3	27	83	1.1
	(χ = 1.589; p = 0.056)			(χ = 0.605; p = 0.273)		

* Never smoked cigarettes and never handled dye, rubber, leather, ink or paint on any job

** Adjusted for age

Table 16

Number of Total Lifetime Uses of Table-Top Sweeteners
and of Total Lifetime Servings of Diet Drink
Among Low-Risk* White Females

	Cases	Controls	R.R.**
Sweeteners			
Used AS	130	402	1.0
[illegible]	9	25	1.1
[illegible] Uses	10	25	1.3
[illegible] Uses	12	48	0.8
[illegible] Uses	12	28	1.4
[illegible] Uses	18	30	1.9
[illegible] Uses	16	24	2.1
	(χ = 2.408; p = 0.008)		
[illegible]			
Used AS	130	402	1.00
[illegible] Servings	24	85	0.95
[illegible] Servings	9	41	0.71
[illegible] Servings	6	33	0.58
[illegible] Servings	17	22	2.60
	(χ = 1.258; p = 0.104)		

[illegible] smoked cigarettes and never handled dye, rubber, leather, ink on any job

[illegible] for age

Table 17

Number of Years of Using Table-Top Sweeteners
and of Drinking Diet Drinks
Among Low-Risk* White Females
Who Used Twice Daily or More

	Cases	Controls	R.R.**
Table-Top Sweeteners			
Never Used AS	130	402	1.0
<5 Years	14	34	1.3
5-9 Years	13	22	1.8
≥10 Years	16	18	2.7
	(χ = 3.240; p = 0.001)		
Diet Drinks			
Never Used AS	130	402	1.0
<5 Years	1	6	0.5
5-9 Years	3	7	1.4
≥10 Years	6	7	3.0
	(χ = 1.654; p = 0.049)		

* Never smoked cigarettes and never handled dye, rubber, leather, ink or paint on any job

** Adjusted for age

Table 18

Average Number of Daily Uses of Table-Top Sweeteners and Average Number of Daily Servings of Diet Drink Among White Males By Usual Number of Cigarettes Smoked

	Uses of Table-Top Sweeteners				Servings of Diet Drink		
	Cases	Controls	R.R.*		Cases	Controls	R.R.*
Never Smoked							
Never Used AS	194	638	1.00	Never Used AS	194	638	1.00
<1 Use	22	56	1.36	<1 Serving	56	231	0.83
1-1.9 Uses	13	65	0.67	1-1.9 Servings	13	57	0.80
2-3.9 Uses	29	106	0.92	2-2.9 Servings	3	22	0.49
4-5.9 Uses	8	34	0.81	≥3 Servings	1	5	0.75
≥6 Uses	3	7	1.46		(χ = -1.501; p = 0.067)		
	(χ = -0.598; p = 0.275)						
Smoked ≤20 Cigarettes Daily							
Never Used AS	576	1028	1.00	Never Used AS	576	1028	1.00
<1 Use	41	75	0.98	<1 Serving	148	226	1.17
1-1.9 Uses	45	75	1.08	1-1.9 Servings	40	63	1.13
2-3.9 Uses	68	99	1.24	2-2.9 Servings	15	21	1.30
4-5.9 Uses	25	43	1.05	≥3 Servings	7	15	0.83
≥6 Uses	13	23	1.01		(χ = 0.972; p = 0.166)		
	(χ = 0.901; p = 0.184)						
21-40 Cigarettes Daily							
Never Used AS	379	461	1.00	Never Used As	379	461	1.00
<1 Use	33	35	1.14	<1 Serving	96	162	0.70
1-1.9 Uses	20	49	0.49	1-1.9 Servings	37	54	0.80
2-3.9 Uses	46	62	0.91	2-2.9 Servings	16	12	1.55
4-5.9 Uses	20	24	1.03	≥3 Servings	11	10	1.26
≥6 Uses	15	22	0.81		(χ=-0.390; p = 0.348)		
	(χ = -1.073; p = 0.142)						
>40 Cigarettes Daily							
Never Used AS	104	167	1.00	Never Used AS	104	167	1.00
<1 Use	12	15	1.28	<1 Serving	39	53	1.20
1-1.9 Uses	19	14	2.07	1-1.9 Servings	14	19	1.20
2-3.9 Uses	16	13	1.96	2-2.9 Servings	10	5	3.33
4-5.9 Uses	8	10	1.33	≥3 Servings	6	4	2.62
≥6 Uses	7	7	1.86		(χ = 2.339; p = 0.010)		
	(χ = 2.220; p = 0.013)						

* Adjusted for age

Table 19

Average Number of Daily Uses of Table-Top Sweeteners and Average Number of Daily Servings of Diet Drink Among White Females By Usual Number of Cigarettes Smoked

	Uses of Table-Top Sweeteners				Servings of Diet Drinks		
	Cases	Controls	R.R.*		Cases	Controls	R.R.*
Never Smoked							
Never Used AS	151	441	1.00	Never Used AS	151	441	1.00
<1 Use	16	67	0.71	<1 Serving	47	164	0.88
1-1.9 Uses	24	52	1.35	1-1.9 Servings	17	53	0.96
2-3.9 Uses	37	60	1.82	2-2.9 Servings	7	16	1.35
4-5.9 Uses	8	21	1.14	≥3 Servings	4	7	1.76
≥6 Uses	4	7	1.66		(χ = 0.560; p = 0.288)		
	(χ = 2.298; p = 0.011)						
Smoked <20 Cigarettes Daily							
Never Used AS	140	189	1.00	Never Used AS	140	189	1.00
<1 Use	13	31	0.55	<1 Serving	69	92	1.00
1-1.9 Uses	25	21	1.60	1-1.9 Servings	15	34	0.57
2-3.9 Uses	24	33	0.95	2-2.9 Servings	8	5	2.02
4-5.9 Uses	7	13	0.69	≥3 Servings	4	8	0.61
≥6 Uses	5	10	0.64		(χ = -0.666; p = 0.253)		
	(χ = -0.388; p = 0.349)						
Smoked ≥20 Cigarettes Daily							
Never Used AS	45	63	1.00	Never Used AS	45	63	1.00
<1 Use	7	9	1.08	<1 Serving	26	21	1.74
1-1.9 Uses	2	9	0.31	1-1.9 Servings	8	12	0.93
2-3.9 Uses	7	6	1.66	2-2.9 Servings	7	3	3.13
4-5.9 Uses	7	4	2.48	≥3 Servings	6	3	2.81
≥6 Uses	5	3	2.25		(χ = 1.827; p = 0.034)		
	(χ = 1.451; p = 0.073)						

* Adjusted for age