EPIDEMIOLOGY 168

Fall 1983

Examination II

November 3, 1983

Instructions:

1. Please do not write your name on this examination. Instead, please write the last four digits of your social security number in the space provided in the upper right-hand corner of each page. (You may do this after the examination.)

2. PLEASE:

   Write all answers and intermediate results on the following pages.
   Write LEGIBLY.
   Indicate clearly if you change your mind about an answer.

3. Read instructions for each question carefully. Some are true-false, some ask you to choose the best answer, some require that you give support for your answer.

4. Pace yourself so that you have time to attempt every question.

5. This examination is closed book. However, you may use:

   - a calculator
   - an English, foreign language, or medical dictionary (a medical dictionary has been provided for your use).

6. When you have finished the examination, please:

   - make certain your code number appears on all pages;
   - sign your name on the signout sheet, under the pledge: "I have neither given nor received help from others in completing this examination."
   - Remove the staple from the examination booklet and place each answer page on the corresponding pile (keep the cover page and the article excerpt).

7. Exams will be returned in Monday's lab. GOOD LUCK.

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SSN: _____

The questions on this examination relate to the article "Artificial sweeteners and lower urinary tract cancer: hospital vs. population controls", by Debra T. Silverman, Robert N. Hoover, and G. Marie Swanson. (Am J Epidemiol 1983;117:326-34). A three-page excerpt consisting of the Introduction, Methods, and Tables 1, 2, and 4 is attached at the end of the examination booklet.

(4 pts) 1. Which of the following statements best characterizes existing knowledge (according to the excerpt) about the relationship of use of artificial sweeteners (UAS) to risk of lower urinary tract cancer (LUTC) at the time the study was initiated? [Choose <u>one best</u> answer]

____ A. The relationship had not been studied epidemiologically;

____ B. Several epidemiologic studies had provided strong support for a positive relationship, but it was suspected that this relationship was due to bias;

____ C. The relationship had received support from several epidemiologic studies, but all of a case-control nature;

____ D. One case-control study indicated a positive association; four others did not.

(5 pts) 2. Give a succinct (one-sentence) statement of the primary study question addressed <u>in this article</u>:

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(4 pts) 3. What is the primary purpose of the control group in a case-control study of LUTC risk and UAS? [choose one best answer]:

____ A. to estimate the risk of LUTC in nonusers of artificial sweeteners;

____ B. to estimate the prevalence of UAS in the population from which the cases of LUTC arose;

____ C. to assess the extent of selection bias in the case group;

____ D. to control for potential confounding.

(4 pts) 4. In the second paragraph of the first text column the authors discuss the controversy over whether hospital controls constitute a valid control group in case-control studies of the effects of UAS and LUTC. Putting the question in the framework of the selection probabilities alpha, beta, gamma, and delta presented in class and in the lab assignment on bias, which of the following statements best identifies the possible problem? [Choose one best answer]

Note: Notation for selection probabilities is:

	UAS	$\overline{\text{UAS}}$
LUTC	alpha	beta
$\overline{\text{LUTC}}$	gamma	delta

____ A. alpha may exceed beta

____ B. alpha may exceed gamma

____ C. gamma may exceed alpha

____ D. gamma may exceed delta

____ E. delta may exceed gamma

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(4 pts) 5. In which direction would the situation discussed in that paragraph most likely influence the observed odds ratio for the relationship between UAS and LUTC risk? Assume that UAS in fact increases risk of LUTC. [Choose <u>one best</u> answer]:

____ A. the observed OR would <u>overstate</u> the true OR;

____ B. the observed OR would <u>understate</u> the true OR;

____ C. the observed OR would be unaffected;

____ D. the direction of the bias <u>cannot</u> be assessed.

(4 pts) 6. State <u>one reason</u> for studying the relationship between UAS and LUTC with the study design used rather than with a cohort design:

_____

_____

(4 pts) 7. State <u>one drawback</u> for studying the relationship between UAS and LUTC of the study design used compared to a cohort design:

_____

_____

(4 pts) 8. What is the purpose of restricting the case group to histologically confirmed cases? [Choose <u>one best</u> answer]

____ A. to minimize false negatives;

____ B. to increase sensitivity;

____ C. to avoid differential misclassification of cases;

____ D. to minimize false positives.

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(6 pts) 9. What are <u>two (2)</u> ways in which eligible population controls might have been missed by the authors' sampling procedure?

a. _____

_____

b. _____

_____

(5 pts) 10. Identify a potential source of <u>differential</u> misclassification bias in the procedure for obtaining the UAS information for the study.

_____

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11. Subjects may have consumed foods (e.g., packaged prepared foods or foods eaten out) without being aware of their artificial sweetener content.

(4 pts) a. Which subjects <u>may have been misclassified by this study</u> if such unintentional artificial sweetener consumption were significant? [Choose <u>one best</u> answer]

____ A. Some subjects <u>whom the study classified</u> as <u>exposed</u>;

____ B. Some subjects <u>whom the study classified</u> as <u>unexposed</u>;

____ C. <u>Controls</u> (only) whom the study classified as <u>exposed</u>;

____ D. Some <u>subjects</u> without regard to their classified status regarding exposure or disease.

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(4 pts) b. What would have been the most likely effect of such misclassification if it had occurred? [Choose one best answer]

____ A. the observed OR would understate the true OR;

____ B. the observed OR would overstate the true OR;

____ C. the observed OR would be unaffected;

____ D. the direction of the bias cannot be assessed.

(4 pts) 12. What was the principal reason for collecting information on "smoking, occupation, coffee consumption, residence, source of water, fluid intake, use of hair dyes, and specific illnesses (i.e., diabetes, bladder, and kidney conditions)" (last paragraph of column 3) [Choose one best answer.]

____ A. A case-control study enables the investigator to assess the effects of various exposures at minimal additional expense;

____ B. One or more of these variables might confound the association between LUTC and UAS;

____ C. This information provides corroborating information for diagnosing the cases.

____ D. To confirm the results found in other studies of LUTC.

(4 pts) 13. In Table 2, 44 percent of male total hospital controls had ever used any artificial sweeteners, compared to 38 percent of of male total population controls and 38 percent of male hospital controls without obesity-related diseases. Therefore it appears that the use of total hospital controls would: [Choose one best answer]

____ A. cause a true (positive) association between LUTC and UAS to be understated;

____ B. cause a true (positive) association between LUTC and UAS to be overstated;

____ C. provide a more nearly valid estimate of the strength of association than would either of the other two control groups;

____ D. not affect the estimate of the strength of association, though its statistical significance might be over- or under-stated.

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(6 pts) 14. If UAS increased the likelihood of hematuria (blood in urine), a UAS - LUTC association might be due to detection bias. State a characteristic of the natural history of LUTC that would be needed for detection bias to occur and briefly explain how the bias might occur:

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(5 pts) 15. Is UAS associated with sex in the data from this study? [Support your answer with the most relevant numbers from Table 2.]

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(4 pts) 16. "Adjustment for these factors [age, smoking, education, and body mass index] had virtually no impact . . . on the estimates of relative risk . . ." (last paragraph of column 4). This result implies that these factors were not: [Choose one best answer]

____ A. risk factors;

____ B. causal risk factors;

____ C. confounders;

____ D. effect modifiers;

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(8 pts) 17. Using the data in Table 4, show the derivation for the relative risk estimate (using total population controls) for LUTC in females who have ever used (versus never used) artificial sweeteners of any type. [Ignore the matched design and the possibility of confounding.] For full credit, your answer should include an appropriately labelled 2 x 2 table, the correct formula, and the correct numbers substituted in the formula.

(4 pts) 18. State in one sentence for the lay reader the meaning of this relative risk.

_____

_____

_____

_____

(4 pts) 19. Is there anything in Table 4 that would be consistent with the possibility that sex is an effect modifier of the LUTC-UAS relationship? [Support your answer with relevant data from the table.]

_____

_____

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(4 pts) 20. Explain how some limitation in the <u>specification or measurement</u> of UAS could have produced an appearance of effect modification when <u>no</u> biological difference in male and female reactions to UAS in fact exists.

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(5 pts) 21. If the suggestion that sex is an effect modifier of the LUTC-UAS relationship <u>were accepted as true</u>, state one public health implication that would follow (for example, a regulation or health education message):

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This is a report of a case-control study of cancer of the lower urinary tract (bladder cancer) conducted in Detroit, Michigan. This study was part of the National Bladder Cancer Study (1), which was a population-based case-control study designed to evaluate the association between artificial sweeteners and the development of bladder cancer. The results of the national study indicated that artificial sweetener users had no overall increased risk of bladder cancer. At the time the study was initiated, the relation between artificial sweeteners and bladder cancer had been examined in five case-control studies (2–7). These studies differed with respect to the type of control group selected: in four studies (2–5), controls were chosen from patients in the same hospital as the cases, and, in the fifth study (6, 7), controls were drawn from the neighborhood of the cases. The results of the hospital-based studies (2–5) provided little or no evidence of an overall positive association between artificial sweetener use and bladder cancer risk, whereas the study based on neighborhood controls (6, 7) indicated a positive association for males.

These conflicting results generated a controversy regarding whether hospital controls constitute a valid control group in case-control studies of the effects of artificial sweeteners (7). Since conditions related to use of artificial sweeteners (such as diabetes and other endocrine and metabolic diseases, hypertension, myocardial infarction, and other cardiovascular diseases) are more highly prevalent in hospital patients than in the general population, the estimate of the artificial sweetener effect based on hospital controls might be biased. In the present study, we selected a hospital control series, in addition to the population control series selected for the national study. We compared the proportions of artificial sweetener users in these two control groups in order to determine the extent of this bias and ways in which it can be eliminated. One approach for eliminating such bias from hospital-based studies is to exclude controls hospitalized for conditions known or suspected of being related to the exposure under study (8–13). However, there has been little formal examination of the effect of such exclusion.

Materials and methods

Subjects

Cases. We attempted to identify all histologically confirmed cases of carcinoma (or papilloma not specified as benign) of the urinary bladder, renal pelvis, ureter, and urethra first diagnosed during a one-year period that began in December, 1977. Only cases that occurred in residents of the metropolitan Detroit area (Macomb, Oakland, and Wayne counties) between the ages of 21 and 84 years were considered eligible for the study.

Hospital controls. For reasons of practicality, we selected hospital controls at only 35 of the 60 hospitals participating in the study. These 35 hospitals contributed 87 per cent of the total cases identified for study. The proportion of artificial sweetener users among cases identified at these 35 hospitals was similar to that in the total case series (males, 37 per cent vs. 40 per cent; females, 58 per cent vs. 57 per cent). For this reason and because of the added precision gained by greater numbers, the total case series was included in the analysis. For each case identified at one of the 35 hospitals, a control was selected (irrespective of diagnosis) from the discharge lists of the same hospital. Cases and hospital controls were also matched for age (within five years), race, sex, and approximate date of discharge. To be eligible, the control had to be a resident of metropolitan Detroit.

Population controls. The population control series was drawn from the general population of the study area. Cases and population controls were frequency matched for age (within five years) and sex. Approximately as many population controls as cases were selected. We chose population controls aged 21–64 years using a method of random digit dialing (14). First, 2368 households were selected at random from all Detroit residences with telephones to obtain the age and sex of every household member between the ages of 21 and 64 years. Of the households identified, 89 per cent gave a household census. Second, we selected a stratified random sample of population controls aged 21–64 years from the household censuses. The population control series aged 65–84 years consisted of a stratified random sample drawn from the Health Care Financing Administration's lists of the Detroit population over age 64 years.

Completeness of interviewing

Interviews were obtained for 445 cases (91 per cent of the total cases approached for interview), 538 population controls (91 per cent), and 347 hospital controls (89 per cent). Interviews were not obtained for 117 cases, 75 population controls, and 143 hospital controls for the reasons indicated in table 1.

The analysis was confined to white subjects because there were too few nonwhite subjects for satisfactory analysis. In addition, 14 cases, six hospital controls, and six population controls were considered ineligible for analysis for several reasons: the subject provided insufficient information to determine an accurate history of artificial sweetener use; the interview was judged by the interviewer to be unreliable; the case had a tumor not specified as transitional or squamous cell carcinoma; or the potential control had lower urinary tract cancer before the study period. A total of 391 cases, 305 hospital controls, and 440 population controls were included in the present analysis.

Data collection

Questionnaires were administered in person by a trained interviewer for most subjects. When this approach was not feasible, the interview was conducted on the telephone (for 35 cases, 51 hospital controls, and 18 population controls). When a subject was either too ill to be interviewed or had died, a family member or friend who knew the subject well was approached for a proxy interview.

The questionnaire was the same as that administered in all areas that participated in the National Bladder Cancer Study (1). To elicit detailed information on consumption of artificial sweeteners, the questionnaire included items on the use of table-top sweeteners, diet drinks, and diet foods. Information was also obtained on smoking, occupation, coffee consumption, residence, source of water, fluid intake, use of hair dyes, and specific illnesses (i.e., diabetes, bladder, and kidney conditions).

For each hospital control identified for study, all discharge diagnoses listed on the discharge summary were recorded. Discharge diagnoses were coded according to the Eighth Revision of the International Classification of Diseases, Adapted for Use in the United States (15). In the present analysis, we used only the primary discharge diagnosis, which was taken to be the reason for hospitalization. The reason for hospitalization of all hospital controls was reviewed by a physician, and controls hospitalized for conditions potentially related to obesity were identified. This review was conducted without knowledge of the subject's consumption of artificial sweeteners.

Analytic methods

The primary measure of exposure was the proportion of users of any form of artificial sweeteners (i.e., table-top sweeteners, diet drinks, or diet foods). In addition, all analyses were repeated considering each form of artificial sweetener separately. The measure of association between artificial sweetener consumption and the incidence rates of lower urinary tract cancer was the "relative risk" as estimated by the odds ratio. Adjusted relative risks were computed by the maximum likelihood method (16). Initially, the data were stratified by age, smoking, education, and body mass index (17). Adjustment for these factors had virtually no impact on the proportions of users or on the estimates of relative risk; thus, adjustments for these factors were not included in this presentation. In all comparisons, the unexposed group included only subjects who never used any form of artificial sweeteners. "Artificial sweetener use," as referred to in the present analysis, denotes exposure to one or more forms of artificial sweeteners. Artificial sweetener exposure after the starting date of the study was ignored.

TABLE 1

Numbers and percentages of cases of lower urinary tract cancer and controls according to interview outcome, Detroit, Michigan, 1978

	Cases		Total population controls		Total hospital controls	
	No.	%	No.	%	No.	%
Interviewed*	445	79	538	88	347	71
Dead	17	3	2	0	23	5
Disabled	18	3	4	1	26	5
Not located	15	3	16	2	26	5
Physician declined permission to interview patient	24	4	–	–	27	6
Refused to participate	43	8	53	9	41	8
Total identified	562	100	613	100	490	100

* Included interviews with proxy respondents for 45 cases, 16 population controls, and 46 hospital controls.

TABLE 2

Numbers of controls and percentages of controls who ever used artificial sweeteners, by sex and type of control group, Detroit, Michigan, 1978

	Males			Females		
	Total population controls	Total hospital controls	Hospital controls without obesity-related diseases	Total population controls	Total hospital controls	Hospital controls without obesity-related diseases
Total no.	296	234	152	144	71	44
% who ever used:						
Any artificial sweeteners	38	44	38	42	55	55
Table-top sweeteners*	24	29	26	25	42	39
Diet drinks*	24	30	26	28	32	34
Diet foods*	13	16	11	14	18	21

* Subjects included in this category may have used other forms of artificial sweeteners.

TABLE 4

Numbers of cases of lower urinary tract cancer and controls, and relative risks according to history of use of artificial sweeteners, Detroit, Michigan, 1978

Use of artificial sweeteners, by sex	Cases	Total population controls	RR*	Total hospital controls	RR*	Hospital controls without obesity-related diseases	RR*
Males							
Never used	182	183	1.0	132	1.0	95	1.0
Ever used	119	113	1.1	102	0.9	57	1.1
Table-top sweeteners†	83	72	1.2	67	0.9	39	1.1
Diet drinks†	83	70	1.2	70	0.9	39	1.1
Diet foods†	38	38	1.0	37	0.7	17	1.2
Females							
Never used	39	84	1.0	32	1.0	20	1.0
Ever used	51	60	1.8	39	1.1	24	1.1
Table-top sweeteners†	35	36	2.1	30	1.0	17	1.1
Diet drinks†	37	40	2.0	23	1.3	15	1.3
Diet foods†	20	20	2.2	13	1.3	9	1.1

* RR, crude relative risk.
† Subjects included in this category may have used other forms of artificial sweeteners.

Examination II: Answer Guide

(4 pts) 1. D. One case-control study indicated a positive association; four others did not.

(5 pts) 2. Does the use of hospital-based control groups in case-control studies of the relationship between UAS and LUTC substantially bias the results [and can such bias be avoided through elimination from the control group of patients admitted for obesity-related disorders]? [Full credit required recognition of the use of multiple control groups to assess bias as a primary study question. Though the relationship of UAS to LUTC risk was the underlying research question, it was not the primary study question addressed in this article.]

(4 pts) 3. B. To estimate the prevalence of UAS in the population from which the cases of LUTC arose.

(4 pts) 4. D. Gamma may exceed than delta: in a case-control study, the two questions are (1) whether the cases are representative (with respect to their exposure histories) of cases in the target population; and (2) whether the controls are representative (with respect to their exposure histories) of the source population for the cases). Since conditions related to UAS (diabetes, cardiovascular diseases) are more prevalent among hospital patients than in the general population, gamma, the selection probability for exposed controls, will likely be greater than delta, the selection probability for unexposed controls.

(4 pts) 5. B. the observed OR would understate the true OR, since UAS in the population would be overestimated by reliance on the hospital control group. If the answer to the preceding question was incorrect, this question was graded on the basis of that answer and part credit was awarded if the two answers were consistent.

(4 pts) 6. The most compelling reasons for employing a case-control design are the rarity and protracted development of LUTC. (There were only 562 cases in 1978 in all of metropolitan Detroit.) A case-control is therefore more feasible, less costly, more statistically efficient, etc. [Any of these reasons or an equivalently good one receives full credit.]

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(5 pts) 15. Yes: within each category of control group (population controls, total hospital controls, hospital controls without obesity-related illnesses), the proportion of women reporting UAS exceeds the corresponding proportion of men. [Full credit for any relevant support, e.g., hospital controls only.]7.

(4 pts) 16. C. If adjustment for these factors did not change the relative risk estimate, then the factors were not confounders.

(8 pts) 17. Derivation of relative risk for females who have report UAS ever, of any type, based on total population controls:

	UAS	$\overline{\text{UAS}}$
LUTC	51	39
$\overline{\text{LUTC}}$	60	84

$$OR = \frac{ad}{bc} = \frac{(51)(84)}{(39)(60)} = 1.83$$

Point allocation: 2 for layout of table, 2 for correct cells, 2 points for correct formula, 2 points for correct substitution; no points off if arithmetic error is sole problem. [If mistook "relative risk" for CIR, then 2 points off if everything else correct.]

(4 pts) 18. "Use of artificial sweeteners was associated with an 80% increase in risk of developing lower urinary tract cancer [in women]." OR

"Women who used artificial sweeteners were about twice as likely to develop bladder cancer." OR

"The risk of lower urinary tract cancer was increased 1.8 times in women who used artificial sweeteners."

[3 points if almost correct (e.g., "risk of <u>having</u> LUTC" - prevalence - rather than "risk of <u>developing</u> LUTC" - incidence); 2 points if only a general definition of relative risk was given rather than a statement about <u>this</u> relative risk; 2 points if answer stated in terms of UAS in women with LUTC rather than as a relative risk. It should be noted that it is <u>not</u> correct to say that "women with LUTC were 1.8 times as likely to have used artificial sweeteners", since 1.8 is an ratio of <u>odds</u>, not probabilities. The odds ratio estimates the relative risk for the disease since the disease is rare; the odds ratio does <u>not</u> estimate the relative likelihood of the exposure.]

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