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ypes: A model for
e Rand Corporation,
California.

tility of fixed-
ssing human exposure to
he Specialty Conference on
easurement, Air Pollution
w Orleans, Louisiana.

1980. Exposure estimation
-14.4 presented at the
ion Control Association,

hods for discrete event
random numbers. IBM
ornia, 25 March.

ome-to-work trips
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:hnique for measuring
:ide concentrations
: of Civil Engineering,
ornia.

:eria for siting air
Control Assoc. 27(6):

:rpreting urban carbon
computerized blood
Assoc. 28(9):911-16.

J. TOXICOL.-CLIN. TOXICOL., 21(1&2), 129-150 (1983-84)

ASSESSING DIET IN CASE-CONTROL STUDIES OF CANCER

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There are several ways to assess diet and nutritional status used in field studies that evaluate the relationship of diet and nutritional status to cancer. In the 24-hour recall method, an interviewer asks a person in great detail about his or her diet over a 24-hour period. The interviewer not only asks about all the types of foods that were eaten, but also about the quantities consumed, the way the food was cooked, any add-ons like butter or salad dressing, and recipes for any special dishes that were prepared. Obviously, a 24-hour recall is not the type of instrument that can be easily administered by a novice interviewer because there is no fixed list of questions to be followed. The interviewer needs to have a sense of dietary patterns.

A second type of dietary interview is the food diary or food record. The subject is asked to jot down what he or she eats for a defined period, perhaps three days, seven days, or even a month. A food record can involve approximate weights or volumes

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of each food item, or exact weights or volumes that are measured by the subject. Obviously this type of interview requires the willing cooperation of the subject because he or she has to do all the work.

A third way of assessing diet by interview is a simplified method involving food frequencies. The interviewer asks the subject how often he or she usually eats hot dogs, or carrots, or green beans, or skim milk, or whatever. The emphasis is on the frequency of consumption of distinct food items. The basic assumption of this technique is that the major source of variation in dietary intake within a population is the choice of foods, not the amount of each food consumed or the exact method of preparation. This assumption is more valid for certain nutrients than for others. If vitamin A or carotene or vitamin C is of interest, then the choice of foods and how often specific foods are consumed is probably the most important factor in determining nutrient intake. If, on the other hand, cholesterol or fat or polyunsaturated fat is of interest, the quantity of each food item consumed and the method of cooking play an important role; and simple food frequencies provide less reliable estimates of nutrient intake.

Generic questions can be utilized to complement food frequencies and to increase their reliability in assessing intake of such nutrients as cholesterol and fat. Examples of generic questions about cooking are

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- How do you usually cook poultry--do you broil it, fry it, or take the skin off?
- To what extent do you trim the fat from beef before you eat it?
- How do you usually cook green vegetables--do you eat them raw, steam them, or saute them in butter?

A useful question for assessing overall nutritional status is to ask how many meals are usually eaten per day. Asking how often meals are eaten at a fast food establishment gives an estimate of how an individual feels about including food additives and highly processed foods in his or her diet.

Frequently neglected methods of assessing diet are anthropometric, or physical, measurements. Height, weight, weight adjusted for height, and skinfold thickness can reveal nutritional status. Many studies of malnutrition in developing countries have depended upon height and weight adjusted for height as indicators of protein-calorie malnutrition in young children. Height is an indicator of long-term dietary adequacy, whereas weight adjusted for height is a measure of recent dietary adequacy. Age at menarche is a good inverse indicator of the affluence or Westernization of the diet. In international comparisons the younger the age at menarche, the higher the percent of total calories from fat, and the higher the risk of breast cancer.

Finally, biochemistry is another way of assessing nutritional status. For example, vitamins A, C, and E and trace materials can be measured in the serum. A number of the B vitamins can be quantitated in the urine, and trace minerals can be detected in toenail clippings. Total mutagenic activity can be measured in feces with the Ames test.

Unfortunately, biochemical techniques do not directly reveal dietary patterns. For example, lowered serum vitamin A levels are associated with an increased risk of cancer; but paradoxically, the consumption of foods rich in vitamin A does not raise serum levels of vitamin A dramatically in a population as well-fed as that in the United States. It may be that consumption of carotene, one of the precursors of vitamin A, affects serum vitamin A levels and the risk of cancer. Or cholesterol or other fats may be involved in the effective absorption of vitamin A that may affect the risk of cancer. It is possible that individuals with low serum vitamin A are distinct genetically, but not distinct in terms of diet. Even though we know what biochemical measure is associated with risk of cancer, we still do not understand the mechanisms of the association.

The advantages and disadvantages of the interview methods for assessing dietary intake are important to consider. Obviously, a 24-hour recall and a food diary or food record, which include information on processing, cooking, and portion size, collect much more detail than a series of food frequencies. However, the food diaries and records are limited in representativeness because dietary patterns are recorded for only a short interval of time.

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frequencies are required and are phrased--How often during your usual adult life did you eat a tomato (or beef, or cold cereal)? For certain foods, like fruits and vegetables that may be eaten on one day and not eaten again for several days or weeks, it is necessary to focus on a long period of time to get a stable estimate of intake. However, for fruits and vegetables, the 24-hour recall has a seasonal bias, depending on whether the subject was interviewed in the summer or winter. To circumvent this potential bias, the subject can be asked how often he or she usually eats a particular food item while in season, and how often while out of season. For infrequently consumed foods, like pickled or smoked foods, which some believe to be associated with risk of certain cancers, again a food frequency format is desirable because such foods will not be eaten frequently enough to be noted in 24-hour recalls or even in 7-day food diaries.

If the questions about diet are to be directed back to a period of time prior to disease, which is essential in a case-control study, food frequencies again offer an advantage. The diet on the day of a 24-hour recall might well be influenced by the ravages of the disease itself, or by the treatment, or simply by the person being restricted to hospital food for an extended period. In a case-control study, although not in a prospective cohort study, it is necessary to employ an interviewing technique that can refer back to usual adult dietary patterns prior to disease.

Another advantage of food frequencies is that if the questionnaire is to be oriented towards a particular hypothesis, only those food items that are sources of the nutrient(s) of interest need to be included. For example, if one is interested in vitamin A, carotene, and lung cancer, a concise interview can be designed to focus on liver, dairy products, fruits, and vegetables, which are the major sources of vitamin A and carotene. This simplifies the interview for the interviewer, the subject, and the committee that has to approve the study design and the interview format.

As mentioned before, extensive interviewer training is necessary for 24-hour recalls and extensive subject cooperation is necessary for food diaries or food records. Generally, within the Environmental Epidemiology Branch of the National Cancer Institute, food frequencies questions are used for many of the reasons mentioned and are complemented with appropriate generic questions.

Dietary patterns can seem very amorphous and unpredictable. Ultimately, the validity of dietary information cannot be tested because there is no touchstone of truth that can be used as a comparison. What if a subject were asked to record very carefully what he or she eats over an extended period. Anyone who has ever participated in one of these studies knows that automatically a person's diet starts to change. For example, the salad bar is avoided if all ten items that go on the plate need to be described. The candy bar that serves as an afternoon snack just might be skipped if someone else will be evaluating the

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dietary information recorded. Therefore, any self-recorded dietary information tends to be biased. It might be possible to surreptitiously monitor a subject for 24 hours and see whether his or her diet actually resembled what was reported in a 24-hour recall. However, when dietary information is to be collected for a month or a year, there is no way of testing validity of the information.

When frequencies of consumption of a number of food items are known, we generally do not simply calculate relative risks for each individual food item. A typical questionnaire consists of 40-80 food items. A problem of multiple comparisons will arise. If 95 percent confidence limits are placed on each estimate of risk, then by chance alone, 1 out of every 20 food items is going to be associated with risk at a level of statistical significance.

But a more basic problem is that many interested in diet and cancer do not believe the choice of individual foods is that critical, with a few exceptions, (e.g., the proposed relationship between peanuts, aflatoxin, and liver cancer). In general, it does not seem that specific items, such as string beans or beef, cause cancer. Food groups or nutrients or other biochemical constituents of a number of foods are what are likely to be positively or negatively associated with risk. Therefore, we analyze dietary information in terms of basic food groups and nutrients.

Food groups include the traditional groupings used by dieticians, like green vegetables, leafy green vegetables, citrus fruits, red meats, and dairy products. Also included are more contemporary groupings, like nitrite-containing foods and highly processed and refined foods. Food groups are important because they form the basis for the way people design their diets. A homemaker goes to the supermarket to shop for her or his family and will perhaps select a meat, a starch, and vegetable for every dinner, but the individual food items may vary from week to week. Food groups provide more stable estimates of dietary patterns than single food items. Another advantage of using food groups is that with them hypotheses can be systematically generated in an exploratory study. There are a finite number of food groups, and whether there is either a positive or negative association between cancer risk and any food group can be evaluated.

It is important to realize that delineating a relationship between intake of a food group and risk of disease is adequate for public health recommendations, even though the precise etiology of the disease may still be unknown. For example, if it were demonstrated that high fruit and vegetable intake consistently reduces the risk of certain types of cancers, that would be sufficient for a public health recommendation, even if it were not known whether fruits and vegetables affected the risk of cancer via their content of fiber, carotene, vitamin C, or trace minerals.

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cholesterol, polyunsaturated fat, fiber, etc.) intake provide another way of analyzing dietary exposures. To convert food frequencies into a nutrient index, several other pieces of information are needed: a usual portion size for each of the food items; some information about the usual way of preparing a food item, if the method of preparation could alter the nutrient content; and exactly how much of each nutrient of interest exists in a fixed quantity of each food item.

There are two good ways of getting the usual portion size and the usual method of preparation for any one food item. One is to ask an experienced dietician or nutritionist for estimates based on the traditional assumptions. There are empirical tables of usual portion sizes for different food items. Perhaps a more sophisticated way would be to develop descriptive statistics from either the U.S. Department of Agriculture's (USDA) Food Consumption Survey or the National Center for Health Statistics's Health and Nutrition Examination Study. Both of these studies collect detailed dietary information from a reasonably representative sample of the population and can provide usual portion sizes and cooking patterns for people of any particular age, race, and sex. For example, if cheese is of interest, these surveys can be assessed to find out how often the cheese of choice is parmesan, or cheddar, or Swiss. More and more frequently, these data bases will be used for these types of calculations.

The nutrient content of a fixed quantity of each food item can be obtained from USDA Handbook No. 8. Some other tabulations of nutrient composition data are generally derived from Handbook No. 8, with supplementary data from industries and private groups. The USDA is currently updating and revising its food consumption data bank, and there will be values for many more nutrients than before. For example, there will be values for cholesterol, polyunsaturated fat, vitamin B-6, folacin, fiber, and zinc, all of which are of current interest.

It is often assumed that in this compendium of food composition data the values are absolutely true. However, some of the laboratory work that produced these values was done several decades ago, and some was done more recently. Different types of assays have been used for calculating the nutrient content of different food items. For example, sometimes carotenoids were separated by chromatography, individually measured chemically, and the quantities totaled. Sometimes the total biologic activity of all the carotenoids present was measured. The chemical and biologic assays give somewhat different results. I am not implying that food consumption data are the weakest link in assessing diet, but they are often incorrectly assumed to be absolutely trustworthy.

Once food frequencies have been combined into measures of food group consumption and nutrient indices, the relative risks for different levels of intake can be evaluated. Most nutritional epidemiologists argue that the population should be split into just a few groups and that the risk associated with low, middle,

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and high consumption should be estimated. Dietary information is not sufficiently precise to stratify the population much further. The population should not necessarily be grouped on the basis of the Recommended Dietary Allowances. Each RDA is set high enough so that 97.5 percent of the population's needs will be met with respect to clinical deficiency. It is not clear that clinical deficiency is related to cancer risk. Intakes of nutrients higher than those required for correcting clinical deficiency might be optimal.

Generally, we divide the population into tertiles or quartiles. One advantage of dividing all the dietary exposures--whether food items, food groups, or micronutrient indices--into tertiles is that it is then easy to ask which exposure has the strongest association with risk. The relative risk between extremes of one exposure cannot be compared with the relative risk between broader groupings of another exposure.

As already discussed, there is no perfect way to test the absolute validity of dietary assessment. However, there are some simple ways of ascertaining relative validity, two of which will be described here (1). One frustration is that there are not many studies that have validated the dietary assessment methods appropriate for large-scale field studies.

One way to assess the validity of dietary information is to compare the answers given by a subject and his or her spouse. The premise is that if both the subject and spouse, independently in two separate interviews without having been forewarned that both will be interviewed, give the same frequency of consumption for a particular food item, then the common answer must be approximately correct.

This type of analysis was presented by Marshall et al. (2). (The major table from the paper is presented here as Table 1.) The authors used 70 food frequency questions to interview 158 pairs of subjects and spouses in upstate New York. They measured to what extent there was relative, but not necessarily exact, concordance of answers. Specifically, they divided the range of answers into 5-7 times a week, 1-4 times a week, 1-3 times a month, and less than once a month and asked to what extent the spouse and subject gave answers that fell in the same category.

For each food item, 60 to 80 percent of the respondent pairs agreed exactly on the category. More than 90 percent of the pairs agreed within one category of each other. Radical disagreements were extremely rare. Less than 2 percent of the individuals had, for any one food item, the maximum category picked by the subject and the minimum category picked by the spouse, or vice versa. The authors concluded that food frequencies were replicable enough to assess the relationship of dietary patterns to cancer.

The authors make the intriguing point that when smoking and alcohol use were assessed in the same way, the reproducibility between subject and spouse was comparable. For at least the past decade, smoking and alcohol information obtained by interview has

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been accepted as sufficiently valid for epidemiologic studies. Actually, it is not known just how accurate data really need to be in order to identify underlying associations. If the underlying association with cancer is strong, then the data need not be as replicable to demonstrate the association. If it is a very weak association, more reproducible data are needed. It is not known how strong the underlying associations between diet and cancer really are.

Another way of deciding whether nutritional assessment is adequate is to judge the nutrition-related results of a particular study according to the standard epidemiologic criteria for causality. The criteria include strength of association, dose-response relationship, specificity, internal consistency, independence of other associations, no evidence of bias, biologic plausibility, and consistency with other epidemiologic studies. Results that meet these criteria would be quite compelling.

Several of my colleagues and I (3) recently completed a case-control study of esophageal cancer, and we evaluated our findings by these criteria. Our study was based in Washington, D.C., because it is the United States metropolitan area with the highest esophageal cancer mortality rate for nonwhite males. The next of kin of 120 black males who died of esophageal cancer during 1975-1977 and of 250 black males who died of other causes were interviewed. The usual adult frequencies of consumption of 31 food items were obtained. Food groups and nutrient indices were formed. All the dietary measures were divided into high,

TABLE 1
Agreement Between Estimates of Food Consumption Frequency by 158 Male Respondents and Spouses in the Western New York Study of Cancer Epidemiology

Food	Exact Agreement (percent)	Within One Category of Agreement (percent)	Food	Exact Agreement (percent)	Within One Category of Agreement (percent)
Vegetables					
Asparagus	57.1	92.3	Lettuce	61.7	92.9
Beets	63.2	96.1	Lima beans	63.4	93.5
Broccoli	66.7	95.5	Onions	52.3	83.5
Brussels sprouts	71.8	96.2	Peas	54.3	92.1
Cabbage	61.5	96.8	Potatoes	73.4	96.8
Carrots	55.6	91.5	Radishes	62.3	86.1
Cauliflower	64.1	94.2	Rice	58.4	91.6
Celery	60.4	85.7	Spinach	66.7	97.4
Cole slaw	54.8	89.8	Summer squash	62.9	87.4
Corn	62.4	92.6	Sweet potatoes	73.3	96.7
Cucumbers	59.1	87.7	Tomatoes	53.7	91.3
Green beans	53.7	92.0	Turnips	74.2	94.7
Green peppers	62.5	90.1	Yellow wax beans	54.3	87.4
Hot peppers	84.8	93.4			
Fruits					
Apples	52.8	87.4	Melons	52.6	83.6
Bananas	59.6	87.4	Oranges/tangerines	49.0	88.6
Berries	51.8	82.0	Peaches	45.2	84.9
Cherries	53.9	83.6	Pears	46.2	77.3
Grapefruit	60.3	86.3	Plums	59.7	79.2
Grapes	56.7	84.0			
Meats					
Bacon	57.0	90.1	Pepperoni	75.8	94.6
Bologna	59.6	93.2	Pickled fish	98.7	100.0

Celery	60.4	85.7	Spinach	66.7	97.4
Cole slaw	54.8	89.8	Summer squash	62.9	87.4
Corn	62.4	92.6	Sweet potatoes	73.3	96.7
Cucumbers	59.1	87.7	Tomatoes	53.7	91.3
Green beans	53.7	92.0	Turnips	74.2	94.7
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Cherries	53.9	83.6	Pears	46.2	77.3
Grapefruit	60.3	86.3	Plums	59.7	79.2
Grapes	56.7	84.0			
Meats					
Bacon	57.0	90.1	Pepperoni	75.8	94.6
Bologna	59.6	93.2	Pickled fish	98.7	100.0
Canned fish	57.2	94.1	Pickled meats	98.0	98.0
Canned ham	79.7	92.8	Pork chops	58.8	94.8
Canned meats	84.3	97.4	Pork roast	69.5	95.5
Corned beef	76.0	96.7	Poultry	59.3	96.0
Hamburger	74.7	97.4	Roast beef	58.4	97.4
Hot dogs	53.9	88.3	Salami	67.3	91.3
Lamb	84.4	98.7	Sausage	50.0	90.3
Liver	61.0	97.4	Shellfish	77.9	95.5
Meat spreads	91.4	98.7	Smoked fish	96.7	99.3
Other cold cuts	45.8	82.4	Smoked meats	93.3	98.0
Other fresh fish	61.4	93.5	Steak	61.7	92.2
Other ham	53.3	90.3	Veal	73.3	95.3
Other Foods			Alcoholic Beverages		
Cheese	56.2	85.0	Beer	66.0	88.0
Milk	59.4	83.2	Cocktails	82.9	95.0
Other bread	50.7	88.8	Long drinks	70.9	92.2
White bread	64.5	88.2	"On the rocks"	83.8	95.1
			Straight drinks	75.7	86.4
Cigarettes	69.1	98.7	Wine	67.6	87.3

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middle, and low levels of consumption. Relative risk was calculated in terms of food items, then food groups, then nutrient indices. The results for the food groups and the nutrients are shown in Table 2.

Dairy products and eggs, fruits and vegetables, and fresh or frozen meat and fish were each inversely associated with risk of esophageal cancer. In each case, the relative risk was about 2 when low consumers were compared to high consumers. Each of these associations showed a dose-response relationship. For example, with fruits and vegetables relative risk went from 1.0 to 2.1 to 2.4. The associations were specific. Even though these three particular food groups were inversely associated with risk, such food groups as carbohydrates and what we called cheap meat and fish, which included processed sandwich meats and luncheon meats, were not associated with risk at all. Furthermore, internal consistency was noted within the data. Food items within a specific food group tended to bear the same association to risk.

When indirect measures of diet, such as relative weight (weight/height^2) and meals per day, were formed, the patterns found paralleled those already noted. The fewer the nutritionally vital food groups that were eaten, the higher the risk. The less the relative weight, the higher the risk; and the fewer meals eaten per day, the higher the risk. As shown in Table 3, an overall measure of nutritional status was formed by combining the three nutritionally vital food groups. When the people that

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TABLE 2
RR of Esophageal Cancer by Consumption of Food Groups and Micronutrients

Nutrition Index[b]	RR by Consumption Level[a]			RR Adjusted for Ethanol by Consumption Level[a]		
	High	Moderate	Low	High	Moderate	Low
Food Groups						
Meat, fish, eggs, and cheese	1.0	1.7	1.1	1.0	1.7	1.3
Meat and fish	1.0	1.3	0.9	1.0	1.3	1.2
Dairy products and eggs	1.0	1.6	2.0†	1.0	1.7	1.9†
Fruits and vegetables	1.0	2.1	2.4§	1.0	1.7	2.0†
Vegetables	1.0	1.7	1.8†	1.0	1.5	1.6*
Green vegetables	1.0	1.2	1.5*	1.0	1.0	1.3
Yellow vegetables	1.0	1.0	1.2	1.0	1.0	1.7
Fruits	1.0	2.8	2.4§	1.0	2.4	2.0†
Carbohydrates	1.0	1.1	1.2	1.0	1.1	1.2
Bread	1.0	1.1	1.2	1.0	1.1	1.1
Fresh or frozen meat and fish	1.0	1.5	2.1†	1.0	1.6	2.2†
Precooked or processed meat and fish	1.0	0.9	0.8	1.0	0.9	0.9
Nitrite-containing foods	1.0	1.1	0.8	1.0	1.1	1.0
Micronutrients						
Vitamin A	1.0	1.4	1.5	1.0	1.5	1.5
Carotene	1.0	1.4	1.6*	1.0	1.3	1.3
Vitamin C	1.0	1.3	2.1§	1.0	1.2	1.8†
Thiamin	1.0	1.2	1.1	1.0	1.2	1.2
Riboflavin	1.0	1.1	1.6*	1.0	1.0	1.7†

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[a] Statistical significance of trend: *--P<0.10; †--P<0.05; §--P<0.01.

[b] Includes all food groups and micronutrients analyzed.

TABLE 3
RR of Esophageal Cancer by an Overall Measure of Food Consumption Patterns

Food Consumption Pattern[a]	Number of Cases	Number of Controls	RR[b] (95% confidence interval)	RR, Adjusted for Ethanol[b,c]
HHH	2	20	1.0	1.0
HHM HMM	24	65	3.7 (0.8-17.0)	3.8
HHL MMM HML HLL	32	68	4.7 (1.0-21.4)	4.5
MML MLL	36	46	7.8 (1.7-35.7)	6.7
LLL	11	8	13.8 (2.5-76.4)	15.0

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[a] Concurrent level of consumption of fresh or frozen meat and fish, fruits and vegetables, and dairy products and eggs, each rated as high (H), moderate (M), or low (L). For example, HML indicates high consumption of one of the three food groups, moderate consumption of a 2d, and low consumption of a 3d.

[b] All risk relative to those consuming high quantities of all three food groups (HHH).

[c] The categories of ethanol consumption were 0-5.9 and 6.0-80.0 fluid ounces of hard liquor equivalents/day.

3
y an Overall Measure
ion Patterns

RR[b] (95% confidence interval)	RR, Adjusted for Ethanol[b,c]
1.0	1.0
3.7 (0.8-17.0)	3.8
4.7 (1.0-21.4)	4.5
7.8 (1.7-35.7)	6.7
3.8 (2.5-76.4)	15.0

·esh or frozen meat and fish, lucts and eggs, each rated as For example, HML indicates food groups, moderate consump- a 3d.

high quantities of all

were 0-5.9 and 6.0-80.0 fluid
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were low in consumption of all three food groups were compared with those that were high in consumption of all three, the risk went progressively from 1.0 to 15, which is, for nutritional epidemiologic studies, an unusual and impressive gradient.

The dietary associations found were independent of other exposures, specifically alcohol, smoking, and socioeconomic status. The independence of diet and socioeconomic status is important because it indicates that as yet unidentified aspects of lifestyle were not generating the dietary associations noted.

We were concerned about bias. The cases would probably be eating less of a number of food items at the time of interview because of the effects of esophageal cancer, and what they remembered about their usual adult diet might be affected. But biased recall seemed not to be the case. Even though the cases reported that they ate less than the controls of 8 of the food items, they reported that they ate more of 11 of the food items and equal amounts of the 12 other food items.

The interpretation presented for this study, that a general micronutrient deficiency increases the risk of esophageal cancer, is biologically plausible. I will not discuss the research that corroborates this hypothesis, but there are many biochemical and animal studies that indicate that riboflavin, niacin, thiamin, vitamin C, vitamin A or carotene might be necessary for epithelial integrity, and might reduce the risk of carcinogenesis.

The results of this study are consistent with those of other epidemiologic studies. In general, high rates of esophageal cancer are noted in areas with limited diets and impoverished agriculture, specifically parts of Iran, South Africa, China, and the USSR. In addition, other case-control studies have reported results similar to ours. Thus the criteria that an epidemiologist generally demands for causality were met in this one particular study of dietary exposures and cancer risk.

Nutritional epidemiology is an embryonic discipline. It is just emerging. The people entering it display a certain amount of audacity. No one really knows how extensively nutritional assessment can be refined in order to identify risk factors for chronic diseases, but it is clear that nutritional assessment has not yet been pushed to its limits. I personally feel that when experts, such as the National Academy of Sciences, claim that 30 percent of the cancers in men and 40 percent to 60 percent of the cancers in women are related, at least in part, to nutrition, it is crucial to see how far nutritional assessment can be pushed in evaluating risk factors for cancer.

REFERENCES

1. Block, G. 1982. A review of validations of dietary assessment methods. Am. J. Epidemiol. 115:492-505.

2. Marshall, J., R. Priore, B. Haughey, T. Rzepka, and S. Graham. 1980. Spouse-subject interviews and the reliability of diet. Am. J. Epidemiol. 112:675-83.

3. Ziegler, R.G., L.E. Morris, W.J. Blot, L.M. Pottern, R.H. Hoover, and J.F. Fraumeni, Jr. 1981. Esophageal cancer among black men in Washington, D.C. II. Role of nutrition. J. Nat. Cancer Inst. 67:1199-1206.

DISCUSSION

David J. Wagstaff, Food and Drug Administration: I would like to point out that some of the interpretations of food intake data and some of the food-disease relationships are open to question. For example, on the seasonal effect of fruits and vegetables, Dr. Jack Smith, University of Nebraska, has said that in his analyses of data--I think he was particularly working with the HANES data--he found no significant effect of season on intake of fruits and vegetables. I think that surprising.

The second point is that there are others who view some of these things differently--you mentioned aflatoxin and peanuts as a cause of liver cancer. I would like to point out that for some of the studies on which this conclusion is based, the data are rather skimpy.

Finally, I am very agnostic on this matter of relating esophageal cancer to intake of nutrients and whether it might be confounded with lifestyle. I see that you have controlled for ethanol and things like that, but that is a tough one. What we eat is really related to our lifestyle very much, and I, for one, think we need a little more work on that.

Dr. Ziegler: The first question was about the influence of season on fruit and vegetable intake. First of all, if it turns out that season does not alter fruit and vegetable intake, the interview is simplified. We will ask about consumption both in and out of season; but if people eat apples or oranges as frequently in the summer as in the winter, we will simply get similar frequencies. Dr. Linda Pickle and I are also analyzing the HANES data and are evaluating the impact of season, along with other parameters, on dietary patterns.

I think the second point you brought up was the aflatoxin and peanuts issue. I tried to concentrate on methodology, not etiology, in this talk. If I said that aflatoxin and contaminated peanuts were a cause of liver cancer, I did not mean to phrase it quite that positively. I was trying to give some hypotheses about diet and cancer as illustrations. The data on that particular issue could be discussed at great length, and that was not what I intended to do in this talk.

Finally, you asked about esophageal cancer and micronutrient deficiency. We did try to see whether some lifestyle pattern might be the underlying cause of esophageal cancer that was generating our apparent associations with diet. We specifically evaluated tobacco and alcohol and found the dietary associations to be independent of these other risk factors. If you read the paper we wrote on the subject, I think you will see that we analyzed this particular issue in depth. I don't believe that some unidentified aspect of lifestyle generated the dietary associations we reported.

Samuel Shapiro, Boston University School of Medicine: I would just like to comment that I think that the trends that are now developing in nutritional epidemiology are very encouraging ones, and what Dr. Ziegler has presented today is entirely in line with those trends. For a long time, studies in nutritional epidemiology have been inhibited by the view that the topic cannot be studied unless you can place the nutritionist with the household and the nutritionist snoops around with a book and records every single item of diet that is consumed over a period of a week, or even longer.

This approach of using frequencies, I think is highly promising, and I would agree that confounding from lifestyle in any rigorously conducted epidemiologic study, has to be fairly rigorous before it is going to eliminate the relative risk of 13.8 shown in one of these tables. Even if one takes the lower boundary in that table, which is 2.5, it seems to me that you would have to think of some great difference in lifestyles, other than alcohol and cigarettes, to explain that away.

The developments that are occurring right now in relation to vitamin A and its precursors, vitamin C, and micronutrients in relation to cancer risk, I think are among the most exciting that have taken place in the last decade, and they hold great promise.