PROBLEMS AND METHODS IN APPLYING NUTRIENT COMPOSITION DATA TO CURRENT HEALTH ISSUES: VITAMIN A, BETA-CAROTENE AND CANCER

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The role of vitamin A and its precursors in carcinogenesis has been investigated in several experimental and epidemiologic studies during the last ten years. The experimental studies have identified a role of vitamin A in the differentiation of epithelial cells and have shown that a deficiency of vitamin A may increase susceptibility to carcinogenesis in animals (1). From epidemiologic research, there is a growing body of evidence that the risk of particular cancers is inversely related to the consumption of the preformed vitamin (retinol) or the provitamin (carotene). This has been demonstrated in several case-control studies of various sites, such as cancers of the lung (2-4), bladder (5), larynx (6), and others (1), as well as in a few cohort studies (7-9). Of recent interest is the hypothesis that dietary beta-carotene may function as an anti-cancer agent. This was postulated by Peto et al. in 1981 (10) and has led to further testing of the associations of dietary and serum beta-carotene with cancer incidence and to implementation of a few intervention trials.

In planning epidemiologic studies with dietary components, it is essential that the methods of data collection and analysis be considered jointly. The data analysis, in turn, requires an up-to-date relevant set of food composition data that is adequate for testing dietary hypotheses. This should include a comprehensive set of values on the various retinoids and carotenoids on a weight basis, similar to the current procedures used by the U.S. Department of Agriculture for fatty acids and amino acids.

Because of the interrelationship of data collection and analysis, I will review the procedures reported in epidemiologic studies on vitamin A and cancer, discuss some of the problems in these methods, and propose a procedure for estimating the consumption of retinol, beta-carotene and other carotenes prior to the availability of improved analytical food composition data.

Dietary Methods

Most of the investigators collected data on the frequencies of consuming food items that were good sources of retinol, beta-carotene, and probably other carotenoids. As you will note, the procedures for selecting the particular food items and analyzing the dietary intake data were generally not specified.

Cohort Studies. One of the first studies was reported by Bjelke, who sent a mailed questionnaire to a cohort of approximately 8,200 Norwegian males to examine the relationship of vitamin A intake to lung cancer risk (7). Respondents were asked to indicate their current frequencies of consuming 25 selected food items. There were five frequency intervals, ranging from less than once a month to more than 14 times a month. To obtain quantitative data on vitamin A intakes, each food was assigned the vitamin A value of 100 grams of the item. Scores or indices were then estimated by summing the products of frequencies and vitamin A values of the food items. After 5 years, the data analysis revealed an inverse association of vitamin A with the incidence of lung cancer. Subsequently, the cohort was expanded to cover almost 17,000 men and women with more than 11 years of follow-up (11). Mailed questionnaires were again used to obtain frequencies of eating the 25 items, and the negative association of vitamin A with lung cancer risk was again demonstrated.

Hirayama has been following a cohort of 265,000 adults in 25 health districts of Japan since 1965 (8). At that time, interviewers collected information on several demographic and lifestyle characteristics, including the frequencies of consuming various green and yellow vegetables that contained more than 1,000 I.U. of vitamin A per 100 grams. Frequencies were recorded as daily, occasionally, rarely, and never. After 13 years of follow-up, Hirayama reported that daily consumption of these vegetables, as compared to less frequent intakes, was associated with a lower risk of cancer of several sites.

A third prospective study conducted among 2,100 men in Chicago was reported by Shekelle et al. (9). Dietary interviews among these men were conducted in 1958, and food profile scores were developed to record the frequencies of consuming food items in 26 food groups. These scores ranged from 0 to 3 for all groups. Zero always indicated no intake. The ranges in the "1 to 3" scores varied for each group of items. For example, as shown in Table 1, a score of "1" for vegetables was used for a consumption of 1 to 27 units per 28-day period. The ranges were subsequently replaced by a single value, such as "9" for the 1 to 27 units of vegetables. The amount of vitamin A per food unit was estimated by averaging the vitamin A values of all selected items in the food group. For vegetables, this was the mean number of International Units of vitamin A in 100 grams of a variety of items. After computing the individual intakes of vitamin A from each food group, these were combined to form retinol and carotene indices (see Table 1). Nineteen years later analysis of the cancer deaths in this cohort showed no association with the retinol index, but there was a strong inverse association of the carotene index with lung cancer risk. It should be noted that the items in the retinol index also included proportional amounts of carotenoids. Consequently, the finding of a protective association between the "carotene index" and lung cancer risk could be due to factors other than carotene in fruits and vegetables.

A recent paper by Colditz et al. focused on the frequencies of consuming 41 fruits and vegetables among a cohort of 1,271 elderly persons free of cancer (12). From these data, a "green and yellow vegetable score" was derived for each person. (Parenthetically, this term is misleading as the foods also included dried fruits, strawberries and melon.) After five years, the investigators found that persons with the highest "score" had a significantly lower risk of death from cancer than those with lower "scores".

Case-Control Studies. One of the first case-control studies of vitamin A and cancer was conducted among Chinese men and women in Singapore by MacLennan et al. (2). They obtained dietary data on the frequencies of eating eight dark-green leafy vegetables. An index of four of these vegetables was shown to discriminate between cases and controls as well as an index of all eight of these items. Subjects were dichotomized and classified as eating at least two of the four items more than once a week (high) or eating less than two of the items in a week (low). The results showed that persons consuming vegetables less frequently were at higher risk of lung cancer than those consuming them more frequently.

Investigators at Roswell Park Memorial Institute in New York collected dietary data from all patients admitted during the period of 1957 to 1965 (3). Vitamin A intake was estimated from questions concerning the usual frequencies of eating 21 selected foods that were good sources of vitamin A during the months one year before the onset of symptoms. Each item was assigned the vitamin A value of a standard serving as listed in the U.S. Department of Agriculture food composition tables (13), and the estimated individual consumption was the sum of the products of the vitamin A values and the frequencies of the 21 items. Using this method, Mettlin et al. reported inverse associations of vitamin A with lung cancer (3) and with bladder cancer (5). This general procedure has been followed in the analysis of various nutrients and risk of site-specific cancers at Roswell Park (14).

Another case-control study of diet and lung cancer was conducted by Gregor et al. in London (15). Data on the current and past intakes of eggs, butter, margarine, milk, liver, carrots, and green vegetables, as well as vitamin supplements, were obtained by interview. It appears that amounts consumed were estimated and that weekly frequencies were ascertained, although these procedures were not described in the paper. The investigators reported that male cases consumed less vitamin A than controls, due to a lower intake of liver and vitamin pills.

Data from females were inconsistent.

Stehr et al. estimated vitamin A intakes in a case-control study of gastric cancer among proxy informants (16). (Next-of-kin were selected for deceased cases of cancer, and the age and sex-matched control group comprised relatives of deceased heart disease patients.) Similar to the preceding paper, the methodology was described vaguely. Evidently, a vitamin A index based on frequencies of foods that were good sources of vitamin A was derived. Nutrient values were based on standard size servings of the food items. Differences between cases and controls were in the expected direction.

In our first case-control study of vitamin A and lung cancer risk, we selected 84 food items which would account for 85 to 90% of the total vitamin A intakes of the subjects in a usual week (4,17). Amounts consumed were estimated by the subjects from photographs showing three serving sizes of each item. The particular items and the serving sizes were derived from measured three-day food records of 330 persons representative of the study population. Using the frequencies and nutrient values of the portions consumed, we obtained estimates of the usual dietary intakes before symptoms for the cases and the same time period for the age- and sex-matched controls. At that time, vitamin A was listed as "International Units" in our data base, without specific values of the vitamin A components. The published results included data on total vitamin A from foods and supplements, vitamin A from foods only, and vitamin A from retinol precursors or carotenes in foods. The latter comprised the vitamin A in fruits and vegetables and the estimated proportion of provitamin A in eggs, dairy products and a few additional items. Our findings showed that men consuming the highest intakes of vitamin A and particularly provitamin A had a lower risk of lung cancer than men consuming lower intakes of these nutrients. These results were not apparent in women.

Problems in dietary methodology

It is obvious that the reported methods of estimating dietary intakes of vitamin A and beta-carotene in several epidemiologic studies have many limitations. First, the rationale for selecting food items to be included in the questionnaires was generally not stated. Yet, it is important that the particular items are representative of the eating patterns of the study population and account for an estimated 85 to 90% of the vitamin A intakes. This can be derived from accurately measured or recalled food intake data on a similar population.

Second, free-living persons are unlikely to consume 100-gram portions or standard size servings of foods on a regular basis. Such assumptions will lead to inaccurate conclusions.

For example, we recently completed a study to determine if frequency data could be substituted for quantitative intakes in the assessment of dietary histories among a group of 340 men participating in a case-control study of prostate cancer (18). This was tested by converting the frequencies to 100-gram portions or to standard household servings. We found that the frequency methods in both instances failed to yield the same diet-disease associations as did the quantitative method at the individual level.

Third, I question the justification of grouping frequencies of intake into a single value. Considerable information is lost by this process. Such individuality can and should be retained in any research study of diet and disease. Furthermore, the use of average nutrient values for analysis of a diverse group of vegetables or fruits serves no purpose. It also seems unnecessary with the availability of nutrient data banks and computer facilities.

There are other issues to be resolved in planning the data collection and analysis, such as:

1. Wide variation of beta-carotene in leafy green vegetables
2. Difference in fortification levels of breakfast cereals
3. Variation in retinol and carotene contents of soups
4. Effects of seasonal foods on carotene intakes
5. Variation in retinol content of different kinds of liver
6. Difference in serving portions of various vegetables

These factors also point out the need for developing a food composition data base that enables the investigator to analyze the intakes of vitamin A as well as the retinoids and the carotenoids. A number of investigators, including Beecher and his colleagues at the Nutrient Composition Laboratory, U.S. Department of Agriculture are currently refining high pressure liquid chromatography (HPLC) methods to measure these components (19). This research will be extremely useful for future epidemiologic research on vitamin A components and cancer.

Although the data collection issues I raise need to be answered, it should be noted that the reported studies distinguished in a relative manner low and high consumers of sources of vitamin A, and most likely carotene. The negative associations of these nutrients with lung cancer risk certainly suggest a protective role for one or more of these dietary factors.

<u>Recommended procedures for estimating retinol and carotene</u>

After publishing our initial results on diet and lung cancer, we decided to add specific data on retinol, beta-carotene and other carotenes to our data base. We began by reviewing published food composition data such as those of Paul and Southgate (20). However, there were limitations in their data. For example, their values do not distinguish between beta-carotene and other carotenes; the importance of these variations is unknown. Also, because this reference does not include a major portion of the foods consumed in Hawaii, there would need to be considerable imputing of retinol and carotene values. To avoid the use of a diverse array of published data, we followed the procedures recommended by the FAO/WHO Expert Group who published a percentage distribution of vitamin A into retinol, beta-carotene and other carotenes (21). Because all food items could not be classified neatly into the published groupings, we added a few additional categories for mixed dishes by calculating the proportions of the major ingredients in these items. Table 2 shows the food groups of FAO/WHO, and Table 3 includes the food groups with imputed distributions of the components. After computing the I.U. for each component, we utilized the formulas, published by the National Research Council (22), for deriving the micrograms (mcg) of retinol, beta-carotene and other carotenes: 1 I.U. vitamin A = 0.3 mcg retinol, 0.6 mcg beta-carotene, or 1.2 mcg other carotenes.

These derived values are certainly not precise, but they do provide a systematic procedure for estimating the intakes of vitamin A and its components. Until more comprehensive food composition data become available and the roles of these dietary factors in carcinogenesis are elucidated, this method, along with greater attention to data collection, will increase the reproducibility of dietary data and provide further evidence on the roles of vitamin A and beta-carotene in carcinogenesis.

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Table 1

Unit of measurement, vitamin A per unit, and number of units in each food-profile score for food groups forming retinol and carotene indices[a]

Food groups	Unit of measurement	Vitamin A (IU/food unit)	Number of units in food-profile scores		
			1	2	3
Forming the retinol index:					
Whole milk	480 ml	780	1-27 (14)	28 (28)	≥29 (56)
Cream	30 ml	249	1-13 (7)	14-84 (49)	≥85 (168)
Butter	14 g	460	1-27 (14)	28-84 (56)	≥85 (140)
Margarine	14 g	460	1-27 (14)	28-84 (56)	≥85 (140)
Cheese	28 g	400	1-7 (4)	8-16 (12)	≥17 (32)
Ice cream, custard, pudding	120 ml	330*	1-3 (2)	4-12 (8)	≥13 (24)
Eggs	54 g	550	1-11 (6)	12-28 (20)	≥29 (56)
Liver	120 g	52,680	<1 (0.5)	1-2 (1.5)	≥ 3 (4)
Forming the carotene index:					
Vegetables	100 g	2560**	1-27 (9)	28-84 (42)	≥85 (98)
Soup	240 ml	1113***	1-11 (3)	12-28 (16)	≥29 (42)
Fruit	100 g	940****	1-27 (9)	28-84 (42)	≥85 (98)

*Mean value of the 3 items

**Average value of asparagus, green beans, beets, broccoli, cabbage, carrots, cauliflower, corn, eggplant, leafy green vegetables, other green and yellow vegetables, onions, peas and tomatoes

***Value for composite soup

****Average value of avocado, apple, banana, cantaloupe, citrus fruit, other fresh or canned fruit and dried fruit

[a]Data from Shekelle et al. (Ref. 9)

Table 2

Food groups and estimated distribution of vitamin A components*

Food Group	(% from) Retinol	(% from) β-Carotene	(% from other) Carotenoids
Meat and meat organs	90	10	
Poultry	70	30	
Fish and shellfish	90	10	
Eggs and egg products	70	30	
Milk and milk products	70	30	
Animal fats and margarine	90	10	
Grains: corn products		40	60
Other grains and breads		50	50
Legumes, seeds, nuts		50	50
Green vegetables		75	25
Deep-yellow vegetables and tomatoes		85	15
Other vegetables		50	50
Deep-yellow fruits and products		85	15
Other fruits and products		75	25
Vegetable oils		50	50

*Data from FAO/WHO (Ref. 19)

Table 3

Food groups and imputed distributions of vitamin A components

Food Group	(% from) Retinol	(% from) β-Carotene	(% from other) Carotenoids
Mixed entrees with meat, milk, veg. (1/3 each)	53	30	17
Mixed entrees with grains, cheese or eggs, meat or fish (1/3 each)	53	30	17
Soups with meat or fish and veg. (1/3 meat, 1/3 green veg., 1/3 other veg.)	30	45	25
Soups with poultry or milk and veg. (1/3 poultry/milk, 1/3 green veg., 1/3 other veg.)	23	52	25
Other soups		50	50
Soups and sauces with milk or cheese base	70	30	
Fortified breakfast cereals	90	10	
Cakes, cookies, pancakes, waffles	70	30	