

A Review of Epidemiologic Evidence that Carotenoids Reduce the Risk of Cancer¹

REGINA G. ZIEGLER

Environmental Epidemiology Branch, Epidemiology and Biostatistics Program, Division of Cancer Etiology, National Cancer Institute, Bethesda, MD 20892

ABSTRACT The epidemiologic evidence that carotenoids are involved in cancer etiology is evaluated. Low intake of vegetables and fruits and carotenoids is consistently associated with an increased risk of lung cancer in both prospective and retrospective studies. In addition, low levels of serum or plasma β -carotene are consistently associated with the subsequent development of lung cancer. The simplest explanation is that β -carotene is indeed protective. Since retinol is not related in a similar manner to lung cancer risk, β -carotene seems to play a role that does not require its conversion into vitamin A. However, the importance of other carotenoids, other constituents of vegetables and fruits, and other nutrients whose levels in the blood are partially correlated with those of β -carotene has not been adequately explored. In addition, smoking, a powerful risk factor for lung cancer, is associated with reduced intake of carotenoids and lowered blood levels of β -carotene and has not always been adequately controlled in these analyses. Prospective and retrospective studies suggest that carotenoids may reduce the risk of certain other cancers; however, too few studies have looked at these sites to examine the consistency of the evidence. Although clinical trials of the efficacy of β -carotene in cancer prevention are underway, it is still necessary and prudent to continue well-designed prospective and retrospective studies of the carotenoid hypothesis. *J. Nutr.* 119: 116–122, 1989.

INDEXING KEY WORDS:

- β -carotene • carotenoids • cancer
- vitamin A • smoking

In the early 1980s the idea emerged that β -carotene might reduce the risk of cancer through a mechanism that did not require its conversion into vitamin A (1). Previously attention had been focused on vitamin A and the chemically similar retinoids. Preliminary support for an independent role for β -carotene derived from 1) the responsiveness of serum β -carotene levels to β -carotene intake, a relationship not seen for vitamin A in adequately nourished populations, and 2) several epidemiologic studies demonstrating inverse associations

between cancer risk and consumption of vegetables and fruits, the primary source of carotenoids in the diet. Recently cancer epidemiologists have begun to treat β -carotene and vitamin A as distinct exposures to be evaluated separately. This approach is feasible because carotenoids are estimated to contribute only 25% of dietary vitamin A in the United States (2) and other Western countries and because serum levels of β -carotene and vitamin A are not highly correlated. This review will focus on the epidemiologic evidence that β -carotene and other carotenoids are directly involved in cancer etiology.

Two types of epidemiologic studies of diet and cancer will be considered: prospective and retrospective. In a prospective study dietary information and/or blood samples are collected from a healthy group of people, and the cohort followed over time. When a sufficient number of cancer diagnoses or deaths have occurred, the data collected earlier are compared for the cases and either all the non-cases in the cohort or a subset of the cohort matched to the cancer cases. In a retrospective study patients with a particular cancer are identified, and comparable controls selected. Then information about usual diet prior to signs and symptoms of disease, blood samples, or both are collected and compared for the cases and controls. In this review the results of the studies will be evaluated by examining whether there is an association between carotenoids and cancer, its direction, its statistical significance, and whether there is a graded response to increasing exposure and the statistical significance of the trend. Associations and trends can be biologically meaningful without being statistically significant; studies with small numbers may lack the power to attain statistical significance.

¹Presented as part of the symposium, "Biological Actions of Carotenoids," given at the 72nd annual meeting of the Federation of American Societies for Experimental Biology, Las Vegas, NV, May 2, 1988, and supported by grants from the BASF Corporation, Hoffmann-LaRoche Inc., and the National Dairy Council.

TABLE 1
Prospective studies of dietary carotenoids and cancer

| Authors, date | Study population | Exposure evaluated | Cancer site | No. of cases ¹ | Evidence of association ² |
|--------------------------------|--|--|-----------------------|---------------------------|--------------------------------------|
| Hirayama, 1979, 1985 (3, 4) | Japan Men, women | Green-yellow vegetables | All cancer | 14,740 | tr, neg (M, F) |
| | | | Stomach | 5,247 | tr, neg (M, F) |
| | | | Lung | 1,917 | tr, neg (M only) |
| | | | Cervix | 589 | +, neg |
| Shekelle et al., 1981 (5) | Western Electric Co. employees Chicago, IL Men | Carotenoids in vegetables, fruits, and soups | All cancer | 208 | — |
| | | | Non-melanoma skin | 36 | — |
| | | | Lung | 33 | +, tr, neg |
| | | | Prostate | 29 | — |
| | | | Colon | 29 | — |
| | | | Rectum | 20 | — |
| | | | Bladder | 19 | — |
| | | | Epidermoid head, neck | 14 | (+), neg |
| Kvale et al., 1983 (6) | Norway Men | Vegetables (excl. potatoes) Fruits, berries | Lung | 70 | (+), neg |
| | | | | | — |
| Colditz et al., 1985 (7) | Elderly MA residents Men, women | 6 vegetables and fruits | All cancer | 42 | +, tr, neg |
| | | | | | |
| Paganini-Hill et al., 1987 (8) | Leisure World, CA residents Men, women | Carotenoids | All cancer | 638 | (tr), neg (M) (+), neg (F) |
| | | | Breast | 123 | (+), neg (F) |
| | | | Colon | 110 | — |
| | | | Prostate | 92 | — |
| | | | Bladder | 58 | (tr), neg (M) tr, neg (F) |
| | | | Lung | 55 | — |

¹Refers to the number of cancer cases used to evaluate a relationship with carotenoids. This number may be less than the cancer incidence or mortality within the cohort because of missing information on diet and potential confounders.

²A statistically significant association; e.g., a significant difference in dietary intake between cases and non-cases or a significant difference in cancer rates between subgroups of the cohort stratified by dietary intake is indicated by +; (+) indicates an apparent association that is not statistically significant; tr indicates a statistically significant test for trend in cancer rates or rate ratios with changes in dietary intake; (tr) indicates an apparent trend that is not statistically significant; neg implies a decreased risk of cancer with increased intake.

Five prospective studies have looked at the relationship between carotenoid intake and cancer (Table 1). Three of the studies followed persons for cancer incidence (5, 6, 8); two, cancer mortality (3, 4, 7). One study, the only one to utilize an interview developed after emergence of the β -carotene hypothesis, asked about most of the major dietary sources of carotenoids and formed a quantitative index of carotenoid intake using food composition tables (8). At present food composition tables reflect the content of β -carotene, α -carotene, β -cryptoxanthin, lycopene, and possibly several other carotenoids.² A second study had to rely on derived rather than original data in forming an approximate carotenoid index (5).³ The other three studies used the frequency of consumption of selected vegetables and fruits (3, 4, 6, 7).

In three of the four studies that examined all cancers combined, risk was inversely related to vegetable and fruit or carotenoid intake (3, 4, 7, 8). The two studies that analyzed men and women separately noted the inverse relationship with all cancer in both sexes (3, 4, 8). Lung was the cancer site most frequently involved;

decreased risk with increased intake was seen in three of the four studies that evaluated this site (3–6). Cancer at several other sites (stomach, cervix, epidermoid head and neck, breast, bladder) was reported in a single study to be reduced with increased intake of vegetables and fruits or carotenoids. However, only two studies systematically evaluated cancer at different sites (5, 8). In addition, the less common cancers would not have oc-

²The method approved by the Association of Official Analytical Chemists for separating and quantifying the carotenoid precursors of vitamin A does not resolve β -carotene from α -carotene, β -cryptoxanthin, lycopene, and other chemically similar hydrocarbon carotenoids. However, other common carotenoids, specifically the xanthophylls such as lutein and zeaxanthin, are separated. The U.S. Department of Agriculture, in conjunction with the National Cancer Institute, is now measuring the content of β -carotene and other specific carotenoids in selected vegetables and fruits with HPLC.

³Indices of nutrient and food group intake were directly calculated from the 28-d diet histories, which were not saved. A carotenoid index was not formed. One was later derived from information about vitamin A and food group consumption.

curred in sufficient numbers in these cohorts to be analyzed. The single study that used a quantitative measure of carotenoid intake rather than an approximate measure found a non-significant inverse association with all cancer but no association with lung cancer, and a significant inverse association with bladder cancer alone (8).

It is not easy or especially meaningful to compare the strength of the associations noted in these studies. Different measures of exposure were evaluated, different constellations of cancer sites were investigated, and different statistical approaches were employed.

In general, these studies did not demonstrate in their published reports that smoking was adequately controlled. Since intake of vegetables and fruits and thus carotenoids is decreased among smokers (9), uncontrolled confounding by smoking might generate an apparent protective effect for diet in studies of lung cancer and other smoking-related cancers, such as head and neck, cervix, and bladder. Most of the studies adjusted for smoking intensity (cigarettes/d). One study (5) recognized that duration of smoking, which is a stronger predictor of lung cancer risk than smoking intensity (10), might be inversely proportional to vegetable and fruit intake and need to be controlled in analysis. Also, some of these studies were limited in their ability to adjust tightly for smoking because of the small numbers of lung and other specific cancers.

Only one of these studies systematically investigated the relationship of dietary intake of all the major nutrients to risk of cancer (5). Carotenoid intake alone was significantly associated with risk of lung cancer. No increase in risk of lung cancer with low retinol (preformed vitamin A) consumption was noted in this study or a second study (8) although results of a third study did suggest such a relationship (6). Retinol occurs in dairy products, eggs, liver, many fortified cereals, and most multivitamin supplements and is the major source of vitamin A in the U.S. diet. Finding a reduction in cancer risk with consumption of carotenoids but not retinol, as in (5) and (8), strongly suggests that the active carotenoids do not first have to be metabolized into vitamin A (retinol) to be protective.

As mentioned previously, three studies evaluated intake of selected vegetables and fruits and did not form a carotenoid index (4, 6, 7). The vegetables and fruits considered were not all high in carotenoids and could have been protective because of some other constituent such as fiber, vitamin C, calcium, indoles, or phenols.

Prospective epidemiologic studies have looked not only at carotenoid intake prior to the onset of cancer, as in the studies presented in Table 1, but also at serum or plasma levels of carotenoids prior to disease. These studies are presented in Table 2. Dietary intake and nutrient levels in blood are not equivalent measures of exposure. Blood levels of carotenoids may respond to other dietary factors than just the carotenoids and may reflect individual metabolic patterns as well as dietary

intake. In addition, current food composition tables list for carotenoid content a composite value which measures a number of hydrocarbon carotenoid species including β -carotene, each at a somewhat different efficiency.⁴ But with HPLC the major carotenoids in serum or plasma can be separated and individually quantitated.

In five prospective studies, blood that had been collected and frozen prior to the diagnosis of cancer has been assayed either for total carotenoids or β -carotene (Table 2). In each study controls matched to the cancer cases were selected from the cohort so that a limited number of stored blood samples would need to be thawed and an aliquot taken. Four of the studies used cancer incidence; one, cancer mortality (13). Three of the studies systematically tested for associations with each of the common cancers in their population (11, 13, 14), and a fourth study is currently doing so (15, 16).

The earliest study, which measured total carotenoids spectrophotometrically, did not find an inverse association with all cancer or any specific cancer of those investigated (11). However, the studies that measured serum or plasma β -carotene levels by HPLC did detect some effects. Each of the three studies that compared blood β -carotene levels in those that subsequently developed lung cancer and in their controls noted statistically significant reductions in risk at high levels (13-15). Two of these studies calculated relative risks and found that among those individuals with serum β -carotene levels in the lowest quintile, risk of lung cancer was 2.2 times that of individuals in the highest quintile (14, 15). Stomach cancer was reduced at high blood β -carotene levels in the two studies that examined that site, but the reduction in risk was not as pronounced as for lung cancer (13, 14). Finally, breast cancer was inversely related to blood β -carotene levels in one study (12).

Although these studies do suggest a role for blood β -carotene, other compounds whose levels in the blood might be partially correlated with β -carotene levels were not investigated to determine if they might be even more strongly associated with reduced risk of cancer. For example, the other common carotenoids were not analyzed. Other nutrients concentrated in vegetables and fruits, such as vitamin C and folacin, were not studied since they had not been protected from degradation during storage of the blood samples. Vitamins A and E were the only other nutrients routinely assayed along with β -carotene. Among the five studies, strong or consistent associations were not seen for vitamin A. However, in two studies, one of lung cancer (15) and one of breast cancer (12), inverse associations as strong as those for β -carotene were seen for vitamin E levels in the blood.

⁴Food composition tables actually list the vitamin A content of food in IU and RE, and the carotenoid content must be calculated from these values.

TABLE 2

Prospective studies of serum or plasma carotenoids and cancer

| Authors, date | Study population | Exposure evaluated | Cancer site | No. of cases, controls ¹ | Evidence of association ² |
|----------------------------|---|--------------------|--------------------|-------------------------------------|--------------------------------------|
| Willett et al., 1984 (11) | 14 U.S. centers in hypertension study Men, women | Total carotenoids | All cancer | 111, 210 | — |
| | | | Lung | 17, 28 | — |
| | | | Breast | 14, 31 | — |
| | | | Leukemia, lymphoma | 11, 23 | +, pos |
| | | | Gastro-intestinal | 11, 22 | — |
| | | | Prostate | 11, 21 | — |
| | | | Breast | 39, 78 | (+), (tr), neg |
| Wald et al., 1984 (12) | Guernsey, Eng. Women | β -carotene | Breast | 39, 78 | (+), (tr), neg |
| Stahelin et al., 1984 (13) | Chemical co. employees, Basel, Sw. Men | β -carotene | Lung | 35, 102 | +, neg |
| | | | Stomach | 19, 37 | (+), neg |
| | | | Large bowel | 14, 33 | — |
| | | | Other cancers | 47, 136 | — |
| Nomura et al., 1985 (14) | Japanese in Honolulu Heart Program, HI Men | β -carotene | Colon | 81, 302 | (+), neg |
| | | | Lung | 74, 302 | +, tr, neg |
| | | | Stomach | 70, 302 | (+), neg |
| | | | Rectum | 32, 302 | — |
| | | | Bladder | 27, 302 | — |
| | | | Lung | 99, 196 | +, tr, neg |
| Menkes et al., 1986 (15) | Washington County, MD Men, women | β -carotene | Lung | 99, 196 | +, tr, neg |
| Colon | | | 72, 143 | — | |
| Schober et al., 1987 (16) | | β -carotene | Colon | 72, 143 | — |

¹Refers to the number of cases and matched controls selected from the cohort that were used to evaluate a relationship with carotenoids.

²A statistically significant association, e.g., a significant difference in blood nutrient levels between cases and controls or a significant difference in relative risks between subgroups of the study population stratified by blood nutrient levels is indicated by +; (+) indicates an apparent association that is not statistically significant; tr indicates a statistically significant test for trend in relative risks with changes in blood nutrient levels; (tr) indicates an apparent trend that is not statistically significant; pos implies an increased risk of cancer with increased intake; neg implies a decreased risk of cancer with increased intake.

In all of the studies in Table 2 that investigated a smoking-related cancer, such as lung cancer, smoking status was controlled in design by matching controls to cases (11, 15) or in data analysis (11, 13–15). However, as in the studies in Table 1, it was not always demonstrated in the published reports that control was adequate. Adequate control of smoking is critical since smoking reduces carotenoid levels in the blood in two ways. First, as already discussed, cigarette smokers include fewer carotenoid-rich vegetables and fruits in their diet than non-smokers. In a recent study the carotenoid intake of male smokers was reported to be 80–90% that of male non-smokers; the comparable range for females was 70–80% (9). Second, plasma levels of β -carotene rise less sharply with increasing intake of carotenoids in smokers than in non-smokers. In the same study men and women who smoked 1 pack/d had, on the average, 72 and 79%, respectively, of the plasma β -carotene levels of non-smokers consuming a similar amount of carotenoids in the diet (9).

As discussed before, blood β -carotene levels may have determinants other than β -carotene consumption. Four of these studies measured serum or plasma cholesterol, and all found that β -carotene or total carotenoids was

moderately correlated ($r = 0.20$ – 0.25) with cholesterol (11, 13, 14, 16). Willett et al. (11) adjusted their serum carotenoid levels for serum cholesterol in order to generate a better measure of carotenoid intake, while Menkes et al. (15) chose not to do so because they felt the absolute value of β -carotene in the serum reflected biologic availability at a site of tumorigenesis. Both approaches are reasonable and represent a difference of opinion as to whether dietary intake or physiologic status is the more basic exposure.

Four of these prospective studies stored frozen serum or plasma samples for extended periods prior to analyzing for total carotenoids or β -carotene, and all four reported significant degradation.⁵ To correct for loss, these studies matched controls to cases by length of storage (11, 15, 16) or standardized for storage interval in analysis (11, 12). β -Carotene loss seemed to range from 23% (15) to 60% (14) during -70°C storage for

⁵The fifth study measured β -carotene immediately after collection in all the blood samples (13). Most investigators prefer to conserve the blood by freezing it and using only the samples from persons that ultimately develop cancer and from a limited number of matched controls.

approximately 10 yr and appeared to be even higher during -20°C storage with repeated thawings (12). These estimates of degradation are very approximate, but they do indicate a serious obstacle to prospective studies of blood carotenoids and cancer.⁶ If degradation leads to a more imprecise measure of exposure, then the power of the study to detect associations is diminished. If degradation is more extensive in stored blood samples from the cases because of repeated thawings, then the cases will appear to have lower β -carotene levels than the controls.

In addition to the prospective studies just reviewed, a number of retrospective studies of carotenoids and specific cancers have been conducted. Usually cases and controls are asked to recall typical dietary patterns prior to any signs of disease in a structured interview. However, in several retrospective studies attempts have been made to incorporate a biochemical component. Blood for nutrient determinations is drawn either close to the time of diagnosis prior to any treatment or several months after completion of all treatment when appetite, diet, and metabolism have had an opportunity to revert to normal.

Lung has been the site studied most frequently in retrospective studies and will be the only site reviewed here because of space limitations. In addition, for most of the other sites too few retrospective studies of the role of carotenoids have been conducted to evaluate the consistency of the evidence. The nine retrospective studies of carotenoid intake and lung cancer are summarized in Table 3. Retrospective studies of blood carotenoid levels and lung cancer are not included. The severity of this particular cancer and its treatment suggests that diet and metabolism would be altered and makes such studies difficult to interpret.

All nine of the studies of diet and lung cancer showed a decreased risk with increased intake of carotenoids or green or yellow-orange vegetables. In all the studies either the inverse associations or the tests for trend were statistically significant. In seven of the studies most of the carotenoid-rich vegetables and fruits had been included in the dietary interview (18-22, 24-26). Then frequencies of consumption of individual foods had been weighted by carotenoid densities from food composition tables and combined into a carotenoid index. One study compared the frequencies of dark green and dark yellow-orange vegetable consumption with the carotenoid index and found more pronounced decreases in lung cancer risk with the two food group measures (20). Two explanations are possible. These two food groups, rich in β -carotene and probably other specific carotenoids, might be better measures of intake of β -carotene or another protective carotenoid than an approximate index of the hydrocarbon carotenoids. Alternatively, the protective agent might be a constituent of vegetables and fruits other than the carotenoids. Determining the β -carotene content of the common vegetables and fruits would help to distinguish the two possibilities.

Other dietary factors concentrated in vegetables and fruits were rarely investigated in these studies. Inverse associations with risk of lung cancer were noted for vitamin C in two studies (18, 24) and for dietary fiber in one study (24), but the associations were weaker than with carotenoids. Non-nutrient constituents of vegetables and fruits, such as indoles and phenols, were not evaluated. However, retinol intake was considered in seven studies and seemed unrelated to lung cancer risk (18-22, 24-26).

In most of these retrospective studies, as in the prospective studies discussed earlier, it was not clear that the carotenoid-lung cancer associations were adequately adjusted for smoking. Emphasis was placed on adjusting for smoking intensity even though duration of smoking may have been a more potent confounder.

Five of the studies used general population (18-21) or neighborhood (22, 24) controls, rather than hospital controls. This approach eliminates the possibility that the dietary patterns that predispose toward many chronic diseases and thus characterize many hospitalized individuals may generate dietary differences between controls and cases.

More detailed results from the five studies that used a carotenoid index and population or neighborhood controls can be compared. All of the studies conducted in men (18-21, 24) detected a decrease in risk of lung cancer with high carotenoid intake. Two observed the same relationship in women (21, 22); two did not (18, 24). One study included whites and Hispanics and found the protective effect of dietary carotenoids restricted to whites (21). Reduction in risk with carotenoid intake was noted in all histologic subtypes of lung cancer (squamous, small cell, and adenocarcinoma) in the three studies that investigated this issue (20, 22, 24). Two studies reported that the protection was primarily among smokers who had quit (21, 24), but a third study found it predominantly among current smokers (20). When the populations under study were divided into quartiles or tertiles, the smoking-adjusted relative risks of lung cancer among the lowest carotenoid consumers, compared to the highest consumers, ranged from 1.3 (20) and 1.5 (21) to 1.8 (24) and 2.2 (18). The lowest relative risk was seen in the study that controlled most rigorously for smoking duration (20) and may reflect a more valid estimate of the underlying association. Nonetheless, these relative risks suggest that the levels of vegetable and fruit intake characteristic of about 30% of a typical community may be sufficient for a noticeable reduction (22-55%) in lung cancer risk.

In summary, low intake of vegetables and fruits and carotenoids is consistently associated with an in-

⁶The Centers for Disease Control, in conjunction with the National Cancer Institute, are now conducting precise studies of the stability of the major carotenoids during long-term storage at -70°C .

TABLE 3

Retrospective studies of dietary carotenoids and lung cancer

| Authors, date | Study population | Exposure evaluated | Cases, controls Type of controls | Evidence of association ¹ |
|-------------------------------------|---|---|--|--------------------------------------|
| MacLennan et al., 1977 (17) | Singapore Chinese Men, women | 8 vegetables (6 green leafy vegs.) | 233, 300 Hospital | +, neg |
| Hinds et al., 1984 (18) | Oahu, HI Multiethnic Men, women | Carotenoids | M: 261, 444 F: 103, 183 Population | +, tr(?), neg tr(?), pos |
| Ziegler et al., 1984, 1986 (19, 20) | New Jersey Men | Carotenoids Dark green vegs. Dark yellow-orange vegs. | 763, 900 Population | (tr), neg tr, neg tr, neg |
| Samet et al., 1985 (21) | New Mexico Men, women | Carotenoids | 447, 759 Population | +, (tr), neg |
| Wu et al., 1985 (22) | Los Angeles, CA Women | Carotenoids | 220, 440 Neighborhood | +, tr(?), neg |
| Pisani et al., 1986 (23) | Lombardy, Italy Men, women | Carrots Leafy green vegs. | 417, 849 Hospital | tr, neg tr, neg |
| Byers et al., 1987 (24) | Upstate New York Men, women | Carotenoids | M: 296, 587 F: 154, 315 Neighborhood | +, tr, neg — |
| Bond et al., 1987 (25) | Chemical company employees, Texas Men | Carotenoids | 734 ² Cohort ³ | +, tr(?), neg |
| Pastorino et al., 1987 (26) | Milan, Italy Women | Carotenoids | 47, 159 Hospital | +, neg |

¹A statistically significant association, e.g., a significant difference in dietary intake between cases and controls or a significant difference in relative risks between subgroups of the study population, stratified by dietary intake is indicated by +; tr indicates a statistically significant test for trend in relative risks with changes in dietary intake; (tr) indicates an apparent trend that is not statistically significant; tr(?) implies an apparent trend that was not tested for statistical significance; pos implies an increased risk of cancer with increased intake; neg implies a decreased risk of cancer with increased intake.

²Represents the combined number of cases and controls participating in the study. Separate numbers of cases and controls were not given.

³Controls matched to the cases were selected from the cohort.

creased risk of lung cancer in both prospective and retrospective studies. In addition, low levels of serum or plasma β -carotene are consistently associated with the subsequent development of lung cancer. The simplest explanation is that β -carotene is indeed protective. Since retinol is not related in a similar manner to lung cancer risk, β -carotene seems to play a role that does not require its conversion into vitamin A. However, the importance of other carotenoids, other constituents of vegetables and fruits, and other nutrients whose levels in the blood are partially correlated with those of β -carotene has not been adequately explored. In addition, smoking, a powerful risk factor for lung cancer, is associated with reduced intake of carotenoids and lowered blood levels of β -carotene and has not always been adequately controlled in these analyses.

Prospective and retrospective studies suggest that carotenoids may reduce the risk of certain other cancers; however, too few studies have looked at these sites to evaluate the consistency of the evidence. A number of clinical trials of the efficacy of β -carotene in cancer prevention are underway. Nonetheless, it is still necessary and prudent to continue well-designed

prospective and retrospective studies of the β -carotene hypothesis to examine the strength of the association, the cancer sites and histologies involved, the role of other carotenoids, the importance of related dietary factors and nutrient levels, and the generalizability to population subgroups.

LITERATURE CITED

- PETO, R., DOLL, R., BUCKLEY, J. D. & SPORN, M. B. (1981) Can dietary beta-carotene materially reduce human cancer rates? *Nature* 290: 201-208.
- COMMITTEE ON DIETARY ALLOWANCES, FOOD AND NUTRITION BOARD (1980) *Recommended Dietary Allowances*, 9th rev. ed., pp. 58, National Academy of Sciences, Washington, D.C.
- HIRAYAMA, T. (1979) Diet and cancer. *Nutr. Cancer* 1: 67-81.
- HIRAYAMA, T. (1985) A large scale cohort study on cancer risks with special reference to the risk reducing effects of green-yellow vegetable consumption. *Int. Symp. Princess Takamatsu Cancer Res. Fund* 16: 41-53.
- SHEKELLE, R. B., LEPPER, M., LIU, S., MALIZA, C., RAYNOR, W. J., JR., ROSSOF, A. H., PAUL, O., SHYROCK, A. M. & STAMLER, J. (1981) Dietary vitamin A and risk of cancer in the Western Electric Study. *Lancet* 2: 1185-1190.

6. KVALE, G., BJELKE, E. & GART, J. J. (1983) Dietary habits and lung cancer risk. *Int. J. Cancer* 31: 397-405.
7. COLDITZ, G. A., BRANCH, L. G., LIPNICK, R. J., WILLETT, W. C., ROSNER, B., POSNER, B. M. & HENNEKENS, C. H. (1985) Increased green and yellow vegetable intake and lowered cancer deaths in an elderly population. *Am. J. Clin. Nutr.* 41: 32-36.
8. PAGANINI-HILL, A., CHAO, A., ROSS, R. K. & HENDERSON, B. E. (1987) Vitamin A, beta-carotene, and the risk of cancer: A prospective study. *JNCI* 79: 443-448.
9. STRYKER, W. S., KAPLAN, L. A., STEIN, E. A., STAMPFER, M. J., SOBER, A. & WILLETT, W. C. (1988) The relation of diet, cigarette smoking, and alcohol consumption to plasma beta-carotene and alpha-tocopherol levels. *Am. J. Epidemiol.* 127: 283-296.
10. DOLL, R. & PETO, R. (1978) Cigarette smoking and bronchial carcinoma: Dose and time relationships among regular smokers and lifelong nonsmokers. *J. Epidemiol. Commun. Hlth.* 32: 303-313.
11. WILLETT, W. C., POLK, B. F., UNDERWOOD, B. A., STAMPFER, M. J., PRESSEL, S., ROSNER, B., TAYLOR, J. O., SCHNEIDER, K. & HAMES, C. G. (1984) Relation of serum vitamins A and E and carotenoids to the risk of cancer. *N. Engl. J. Med.* 310: 430-434.
12. WALD, N. J., BOREHAM, J., HAYWARD, J. L. & BULBROOK, R. D. (1984) Plasma retinol, beta-carotene, and vitamin E in relation to the future risk of breast cancer. *Br. J. Cancer* 49: 321-324.
13. STAHELIN, H. B., ROSEL, F., BUSS, E. & BRUBACHER, G. (1984) Cancer, vitamins, and plasma lipids: Prospective Basel Study. *JNCI* 73: 1463-1468.
14. NOMURA, A. M. Y., STEMMERMAN, G. N., HEILBRUN, L. K., SALKELD, R. M. & VUILLEUMIER, J. P. (1985) Serum vitamin levels and the risk of cancer of specific sites in men of Japanese ancestry in Hawaii. *Cancer Res.* 45: 2369-2372.
15. MENKES, M. S., COMSTOCK, G. W., VUILLEUMIER, J. P., HELSING, K. J., RIDER, A. A. & BROOKMEYER, R. (1986) Serum beta-carotene, vitamins A and E, selenium, and the risk of lung cancer. *N. Engl. J. Med.* 315: 1250-1254.
16. SCHOBER, S. E., COMSTOCK, G. W., HELSING, K. J., SALKELD, R. M., MORRIS, J. S., RIDER, A. A. & BROOKMEYER, R. (1987) Serologic precursors of cancer I. Prediagnostic serum nutrients and colon cancer risk. *Am. J. Epidemiol.* 126: 1033-1041.
17. MACLENNAN, R., DACOSTA, J., DAY, N. E., LAW, C. H., NG, Y. K. & SHANMUGARATNAM, K. (1977) Risk factors for lung cancer in Singapore Chinese, a population with high female incidence rates. *Int. J. Cancer* 20: 854-860.
18. HINDS, M. W., KOLONEL, L. N., HANKIN, J. H. & LEE, J. (1984) Dietary vitamin A, carotene, vitamin C and risk of lung cancer in Hawaii. *Am. J. Epidemiol.* 119: 227-237.
19. ZIEGLER, R. G., MASON, T. J., STEMHAGEN, A., HOOVER, R., SCHOENBERG, J. B., GRIDLEY, G., VIRGO, P. W., ALTMAN, R. & FRAUMENI, J. F., JR. (1984) Dietary carotene and vitamin A and risk of lung cancer among whites in New Jersey. *JNCI* 73: 1429-1435.
20. ZIEGLER, R. G., MASON, T. J., STEMHAGEN, A., HOOVER, R., SCHOENBERG, J. B., GRIDLEY, G., VIRGO, P. W. & FRAUMENI, J. F., JR. (1986) Carotenoid intake, vegetables, and the risk of lung cancer among white men in New Jersey. *Am. J. Epidemiol.* 123: 1080-1093.
21. SAMET, J. M., SKIPPER, B. J., HUMBLE, C. G. & PATHAK, D. R. (1985) Lung cancer risk and vitamin A consumption in New Mexico. *Annu. Rev. Respir. Dis.* 131: 198-202.
22. WU, A. H., HENDERSON, B. E., PIKE, M. C. & YU, M. C. (1985) Smoking and other risk factors for women. *JNCI* 74: 747-751.
23. PISANI, P., BERRINO, F., MACALUSO, M., PASTORINO, U., CROSIGNANI, P. & BALDASSERONI, A. (1986) Carrots, green vegetables, and lung cancer: A case-control study. *Int. J. Epidemiol.* 15: 463-468.
24. BYERS, T. E., GRAHAM, S., HAUGHEY, B. P., MARSHALL, J. R. & SWANSON, M. K. (1987) Diet and lung cancer risk: Findings from the Western New York Diet Study. *Am. J. Epidemiol.* 125: 351-363.
25. BOND, G. G., THOMPSON, F. E. & COOK, R. R. (1987) Dietary vitamin A and lung cancer: Results of a case-control study among chemical workers. *Nutr. Cancer* 9: 109-121.
26. PASTORINO, U., PISANI, P., BERRINO, F., ANDREOLI, C., BARBIERI, A., COSTA, A., MAZZOLENI, C., GRAMEGNA, G. & MARUBINI, E. (1987) Vitamin A and female lung cancer: A case-control study on plasma and diet. *Nutr. Cancer* 10: 171-179.