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**Authors**

Kummet, Thomas
Moon, Thomas E
Meyskens, Frank L

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# Reviews

## Vitamin A: Evidence for Its Preventive Role in Human Cancer*

Thomas Kummet, Thomas E. Moon, and Frank L. Meyskens, Jr.

**Abstract**

*Both the provitamin β-carotene and natural vitamin A and its derivatives (the retinoids) are being proposed as potential chemopreventive agents. The biochemistry and pharmacology of vitamin A suggest a number of mechanisms whereby carcinogenesis can be affected. Epidemiologic studies have consistently demonstrated an increased relative risk of cancer for people with low vitamin A intake or low-to-normal serum retinol values. Chemoprevention trials in humans are only now beginning. In the interim, daily consumption of vitamin-A–containing foods may be a "prescription" worth following.*

## Introduction

The relationship between vitamin A and cancer has attracted intense interest from both the medical profession and the lay population[1]. The linking of vitamin A and cancer dates to the early part of this century, when vitamin A deficiency was interpreted to be the cause of certain animal tumors[2]. Research showing a relationship between vitamin A and human cancer was first reported in 1941 by Abels et al.[3], who documented and investigated low vitamin A levels in cancer patients. Since that time, an extensive literature has become available on the role of vitamin A in cancer. Vitamin A and its derivatives are currently considered as promising agents for use in the chemoprevention of cancer[4,5]. In June 1982, the National Research Council released dietary guidelines for reducing the risk of cancer[6]. The report, *Diet, Nutrition, and Cancer,* advised the daily consumption of vegetables rich in vitamin A precursors.

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T. Kummet is affiliated with the University of Texas Health Center, Tyler, TX 75710. T.E. Moon and F.L. Meyskens, Jr., are with the Cancer Center, University of Arizona Health Sciences Center, Tucson, AZ 85724.

This article reviews the relationship between vitamin A and cancer, emphasizing the human studies that have yielded the conclusion that dietary changes can alter cancer risks. In addition, the potential use of pharmacologic doses of retinoids as chemopreventive and therapeutic agents is discussed.

## Physiology

Vitamin A physiology has been extensively reviewed in two recent publications[7,8] and will only be summarized here. *Vitamin A* is a generic term for all substances that possess the biologic properties of retinol, while the term *retinoids* is a designation for the natural forms of vitamin A and their synthetic derivatives.

Vitamin A is present in the diet in two forms. The *provitamins* are the carotenes, most importantly $\beta$-carotene, and are derived from plant sources. Rich sources of provitamins include carrots, squash, spinach, tomatoes, and brussels sprouts. The *preformed vitamins,* which come from animal sources, are retinol, retinal, and retinyl esters. Sources of preformed vitamins are liver, eggs, milk, cream, butter, cheese, and vitamin A pills. The term *retinol equivalent* is used to express the biological potency of various retinoids as a single unit. One $\mu$g of retinol is equal to 6 $\mu$g of $\beta$-carotene. One IU of vitamin A is equal to 0.3 $\mu$g of retinol, 0.6 $\mu$g of $\beta$-carotene, and 1.2 $\mu$g of mixed dietary carotenoids. A dietary intake of 1,000 $\mu$g (3,000 IU) of retinol equivalent per day is recommended as the minimum amount needed to maintain body stores and to meet tissue requirements[9].

Over 80% of ingested preformed vitamin A and up to 200 IU of carotene are absorbed and either excreted rapidly or stored in the liver. The retained vitamin is either released with retinol-binding protein for tissue utilization or excreted into the bile. Vitamin A mobilization from the liver is determined by two factors. First are the peripheral requirements, which equal approximately 1,000 $\mu$g/day. Secondly, vitamin A is excreted from the liver at a rate proportionate to total hepatic stores. Excreted vitamin A may be reabsorbed and recycled, and this may serve to meet some of the daily requirements. Thus, vitamin A is conserved when stores are low, and excreted when stores are high.

$\beta$-carotene is the most important of the over 400 carotenes that are effectively converted to vitamin A (retinyl esters). This compound is well absorbed, but serum measurement reflects only recent dietary intake and is a poor indicator of vitamin A status. Determination of liver retinol reserves is the best monitor of vitamin A status. The liver, with its massive storage capacity, functions to maintain a steady-state serum vitamin A level despite widely varying dietary intake.

Vitamin A metabolism is affected by dietary proteins, fat, vitamin E, and zinc. Protein deficiency results in a decreased conversion of dietary carotenoids to retinyl esters by decreased synthesis and release of proteolytic enzymes and decreased formation of plasma transport proteins. Dietary fat is required for the solubilization of dietary vitamin A. A low fat diet can result in symptomatic vitamin A deficiency, as it is the fat in the diet that causes gall bladder constriction and release of bile salts necessary for micelle formation. Ingested vitamin A is subject to oxidative degradation in the gut; vitamin E functions as a lipid soluble antioxidant to prevent nonenzymatic destruction of vitamin A. Zinc is necessary for protein synthesis and acts indirectly on vitamin A metabolism by its effects on tissue growth. Zinc deficiency results in decreased growth and decreased vitamin A levels.

Serum vitamin A levels are also affected by numerous common conditions. There is a cyclic variation during a woman's menstrual cycle. Oral contraceptives increase levels of serum retinoid-binding proteins and, consequently, retinol levels. Disease states may affect vitamin A levels by decreasing its absorption (chronic pancreatitis, bile acid insufficiency, sprue), increasing its metabolism (hyperthyroidism, febrile conditions), or decreasing its utilization (liver disease, nephrosis).

## Biological Functions

The functions of vitamin A include roles in vision, growth, reproduction, and, most importantly for our understanding of its relationship to malignancy, control of epithelial growth and differentiation[7]. Vitamin A functions to promote the mucus-secreting elements of epithelial tissues and/or to inhibit the keratinizing tendency. Thus, vitamin A deficiency results in an alteration of epithelial tissue to a squamous keratinizing form, with a decrease in the mucus-secreting cell population. The skin becomes hyperkeratotic, and the respiratory, urogenital, and reproductive gland epithelia become cornified. The salivary and pancreatic glands become atrophied and fill with keratinizing cysts. The intestinal mucosa shows a decline in the number of mucus-secreting cells, but shows no squamous differentiation. Different tissues may vary in the number of surface receptors for the retinol-protein complex, and thereby control the cell's position on a spectrum of mucus-to-squamous epithelial differentiation[7].

The relationship of vitamin A, $\beta$-carotene, and other retinoids to neoplasia has been recently reviewed in a number of publications[1,10-12]. Put most simply, vitamin A is necessary for the normal differentiation of tissue. Since cancer can be viewed as a disease of arrested cellular differentiation, vitamin A is proposed to induce normal development in premalignant cells and prevent the progression into frank cancer. The exact biochemical or immunological mechanism(s) by which the vitamin affects carcinogenesis are unknown, but several have been suggested[7,10,13].

A well-accepted model for transformation from benign to malignant phenotype is the two-step model of carcinogenesis[13]. This approach divides the malignant process into two steps: initiation and promotion. Initiation is the irreversible genetic alteration of the target cell by a carcinogen. Promotion results in the phenotypic expression of that genetic alteration. Initiators and promoters may be identical, may vary in dose or frequency of contact with the target cell, or may be entirely different entities. The provitamin $\beta$-carotene (but not the retinoids) may function directly to block initiation by blocking the effects of singlet oxygen, a potentially carcinogenic free radical. The role of the retinoids in this model of carcinogenesis appears to be that of a late-stage antipromoter. In the production of skin cancer in mice, retinoic acid inhibits the induction of the enzyme ornithine decarboxylase[14], a key enzyme in the process of tumor promotion, but not initiation. Alternatively, it has been hypothesized that retinoids may directly compete with promoting agents for control of cellular differentiation[13]. A third possibility is that retinoids inhibit transforming growth factors, polypeptides capable of inducing neoplastic growth in normal cells. Retinoids have been shown to block the effects of a sarcoma-transforming growth factor *in vitro,* and possibly may accomplish this activity by blocking the function of oncogenes[15].

## Epidemiology of Vitamin A and Human Malignancy

Investigations of vitamin A and cancer in human populations can be divided into two main types: dietary recall[16-34], and blood retinol studies[35-45]. Each of these can be further classified as prospective or retrospective investigations. Prospective studies are designed to demonstrate that the presence of a suspected etiologic factor (e.g., low vitamin A) *antedates* the development of a specific end point (e.g., cancer), thereby strengthening the possible cause-and-effect relationship. This type of study presents many more methodologic problems than are usually encountered in retrospective studies, as it requires larger numbers, prolonged follow-up, and significantly more time and money. Retrospective studies are designed to show *an association* (or not) between a suspected etiologic agent and a known end point.

Dietary recall studies done in a prospective manner have consisted of dietary questionnaires administered to large populations. In these studies patients reported the frequency with which various foods were consumed. An index of consumption of various nutrient

categories was calculated by multiplying the frequency with which a specific food was ingested per unit of time by the content of the nutrient in a standard serving of the consumed food. The nutrient category of interest was defined in most studies as a vitamin A index, which included sources of provitamins and preformed vitamins. Some studies separated the vitamin A into β-carotene and "vitamin A" indices. In these prospective studies, subjects were ranked into thirds, quartiles, or quintiles, based on their vitamin A index. A relative risk was calculated by comparing the groups. The retrospective dietary recall investigations were case-control studies in which the dietary intake of cancer patients was compared to that of noncancer patients. Seventeen dietary studies of vitamin A, including both prospective and retrospective studies, have been reported and will be discussed in detail here, as they provide the data for intervention trials. Although there were notable exceptions, statistically significant differences generally were detected only when the lowest intake group was compared to the highest intake group for both prospective and retrospective studies.

Blood retinol studies done in a prospective manner consisted of measuring vitamin A levels in a large group of subjects, and then following the group for the development of malignancies. Retinol levels were compared between the subgroup that developed cancer and the group that did not. Retrospective blood retinol studies compared vitamin A levels of cancer patients to those of a control group.

## Prospective Dietary Studies

This section describes three prospective dietary recall studies (Table 1). The first was published in 1975 by Bjelke et al.[16] and reported data on 8,278 males followed for 5 years, during which time 36 developed lung carcinomas. The vitamin A index was negatively associated with lung cancer incidence at all levels of cigarette smoking. This study was recently updated and expanded, as reported by Kvale at the 1983 Seattle International Cancer Congress[17]. The second prospective study[18] consisted of over a quarter of a million people who filled out a dietary questionnaire during Japan's 1965 census. During 10 years of follow-up, 7,377 of the respondents developed cancer. Daily consumption of vegetables with high levels of β-carotene was reported to decrease the risk of developing cancer of the lung, colon, stomach, prostate, and cervix. The reduced risk for lung cancer held even for ex-smokers, implying an effect of vitamin A late in the carcinogenic process (as an anti-promoter?). A reduced risk for cancer of the cervix showed a dose-response gradient to the calculated carotene index. The third prospective study[19], published in 1981, fol-

| Table 1. Vitamin A and Cancer: Prospective Dietary Studies | | | | | | |
|---|---|---|---|---|---|---|
| Primary author | Location | Tumor type | Cases/ Population | Relative risk | P value | Variable |
| Bjelke[16] | Norway | Lung | 36/8,278 | 3.0 | <0.01 | Total vitamin A index |
| Hirayama[18] | Japan | Lung | 807/265,118 | <2 | Not | Carotene |
| | | Colon | 220/265,118 | <2 | specified | index |
| | | Stomach | 2,917/265,118 | <2 | | |
| | | Prostate | 63/265,118 | <2 | | |
| | | Cervix | 370/265,118 | <2 | | |
| Shekelle[19] | Chicago | Lung | 33/1,954 | 7.0 | .003 | Carotene index: |
| | | | | 5.5 | | Lowest quartile |
| | | | | 3.0 | | to |
| | | | | 1.0 | | highest quartile |
| | | | | (r = .003) | | |

lowed 1,954 men for 19 years. Thirty-three developed cancer of the lung, and an analysis of their dietary intake revealed a significant increased risk with lower intakes of dietary β-carotene. A dose-response gradient was seen both before and after adjusting for smoking. The index for preformed vitamin A was not significantly different. There were 175 other cancers diagnosed during the study period, none of which were associated with carotene or vitamin A intake levels.

### Retrospective Dietary Studies

The first retrospective dietary recall study (Table 2) was published in 1974, also by Bjelke[20]. His case-control studies of patients with gastrointestinal cancers in both Norway and Minnesota revealed that decreased vitamin A intake was associated with an increased risk of cancer of the colon. The relative risk was not specified.

Table 2. Vitamin A and Cancer: Retrospective Dietary Studies

| Primary author | Location | Tumor type | Cases | Relative risk | P value |
|---|---|---|---|---|---|
| Bjelke[20] | Norway & USA | Colon | 421 | Not stated | — |
| Mettlin[22] | Buffalo | Lung | 292 | 2.4 | $\leqslant 0.005$ |
| Mettlin[23] | Buffalo | Bladder | 569 | 2.07 | 0.009 |
| Graham[24] | Buffalo | Larynx | 374 | 2.09 | < 0.005 |
| Mettlin[25] | Buffalo | Esophagus | 147 | 1.28 | 0.03 |
| Graham[26] | Buffalo | Breast | 2,024 | 1.33 | < 0.05 |
| Marshall[27] | Buffalo | Oral | 425 | 2.1 | < 0.05 |
| MacLennan[28] | Singapore | Lung | 184 | 2.2 | < 0.05 |
| Gregor[29] | London | Lung | 100 | 4.8 | < 0.05 |
| Ziegler[30] | Washington, DC | Esophagus | 120 | 1.5 | > 0.05 |
| Modan[31] | Tel Aviv | Gastrointestinal | 406 | 0.94 | > 0.05 |
| Nomura[32] | Japan | Intestinal | 387 | Not stated | 0.017 |
| Smith[33] | Boston | All | 800 | 1.8 | < 0.01 |
| Kolonel[34] | Hawaii | All | — | See text | — |

Roswell Park Memorial Institute has published six articles dealing with vitamin A and cancer incidence[22-27]. All patients admitted to Roswell Park from 1957 to 1965 completed a basic nutritional history, and the data were analyzed for the influence of various nutritional factors on the development of cancer[21]. In 1979, a vitamin A index was derived for the nutritional data base; the major food sources in the Roswell Park vitamin A index were carrots (provitamin) and milk (retinol). Six subsequent articles all reported that decreased intake of vitamin-A–containing foods was associated in a dose-response fashion with an increased risk for the development of cancer. The first article in this series[22] dealt with lung cancer and vitamin A, and showed that the heavier the smoking history, the more pronounced the relative risk associated with low vitamin A intake. Studies for laryngeal[24] and oral[27] cancer were controlled for smoking and also showed effects of low vitamin A intake. A 1982 publication[26] demonstrated a relationship between diet and the development of breast cancer, and singled out low vitamin A intake as the only significant nutritional factor. The investigators found no relationship between cancer incidence and intake of fat, vegetables, or vitamin C in these studies. However, in Roswell Park studies of laryngeal[24], esophageal[25], and oral[27] cancer, vitamin C did have a protective role. Analysis of the data for bladder[23], laryngeal[24], breast[26], and oral cancer showed an increased risk

with a low vitamin A index value, but there was no effect of vegetables alone. The vegetable index in the esophageal cancer patients[25] was inversely related to the disease. Thus, vitamin A was the only nutrient consistently found associated with decreased cancer risk.

There are seven additional retrospective studies of vitamin A intake and human cancer. MacLennan et al.[28] reported in 1977 that infrequent consumption of carotene-containing vegetables resulted in a relative risk for lung cancer of 2.2. In 1980, Gregor et al.[29] reported a case-control study of lung cancer and vitamin A intake in which the group at risk had significantly less intake of preformed vitamin A than did controls[29]. However, for the 22 female patients with lung cancer, the protective benefit for vitamin A did not exist. A third retrospective study[30] examined black males with esophageal cancer. A risk of 1.5 was reported for low vitamin A consumption. Like the Roswell Park esophageal study, a low vitamin C index was a significant risk factor for esophageal cancer (RR 2.1). A 1981 study by Modan[31] compared the vitamin A intake of 406 gastrointestinal cancer cases with that of 812 controls and reported no difference in *total* vitamin A intake, although even here an inverse association between intake of carotene-containing vegetables and cancer was seen.

Three additional retrospective studies used different methodologies in their designs. A Japanese investigation used the preneoplastic condition gastric metaplasia (defined by endoscopic biopsy) as the disease, rather than the (subsequent) gastric carcinoma[32]. The authors showed a significant trend (p = 0.017) for increasing metaplasia with decreasing consumption of vitamin A. In 1978, the Boston Collaborative Drug Surveillance Program specifically addressed the effect of intake of vitamin A supplements on cancer incidence[33]. Of 800 patients with cancer (compared to hospitalized controls with benign disease), men ingesting vitamin A pills had a relative risk of 0.54 (p < 0.01) when compared to non-users. This protective effect was not shown for women. Finally, Kolonel et al.[34] attempted to correlate the cancer incidence rates of the five major racial groups in Hawaii with the dietary intakes of various nutrients (including vitamin A) of a random selection of the population making up those ethnic groups. Using this methodology, they demonstrated no relationship between vitamin A intake and cancer rate.

### Prospective Serological Studies

The first prospective serological study to be reported here was published in October 1980 from the Cancer Epidemiology and Clinical Trials Unit in Oxford, England[35]. Serum from 16,000 London males undergoing a health-screening exam from 1975 to 1978 had been frozen for retinol determinations. By 1980, 90 men had developed cancer. Eighteen cases were lung, 21 gastrointestinal, 25 skin, 8 renal, and 18 other types of cancer. The control group consisted of 172 men without cancer. Overall, the mean serum retinol level of the controls (229 IU/dl) was significantly higher than that of the cases (214 IU/dl). When patients were separated into groups with specific tumor types, only those with lung cancer had a statistically lower level. In addition, there was a suggestion of a dose-response effect, since a significant trend for increasing risk with decreasing levels of retinol was detected. The relative risk in the lowest quintile compared to the highest was 2.2. This association was independent of age and smoking habits.

A second study of similar design appeared in 1981[36]. This study began as a cardiovascular disease investigation in a rural county in Georgia. All residents over 40 years of age were eligible, and 92% cooperated. From 1960 to 1962, serum from 3,102 people was obtained and frozen. By 1974, 92 people had developed cancer. Two age-, race-, and sex-matched controls were selected, and retinol levels were compared. Results showed significantly lower retinol levels in cases than in controls, with the difference greater for males than for females. The authors found no evidence that smoking played a role in the results. They also attempted to control for the misclassification of prevalent cases (at the time of blood sample collection) as incident cases (at the time of diagnosis) by comparing

cases diagnosed in the early years of the study (presumed prevalent cases) with those diagnosed later. There was no difference. While the numbers of any one subtype of cancer were small, the negative association between serum retinol values and cancer incidence held for the squamous cell and adenocarcinoma histologies.

It deserves emphasis that all groups in both studies had serum retinol levels within normal limits, but those in the lowest quintile had over 5 times the relative risk of developing cancer. Table 3 shows the small differences in retinol levels found to be significant in these studies, and the agreement between these two studies.

| Table 3. Vitamin A and Cancer: Prospective Serum Retinol Level Studies | | | | | |
|---|---|---|---|---|---|
| Primary author | Location | Tumor type | Cases | Retinol level (Control minus Case) ($\mu$g/100 ml) | P value |
| Wald[35] | England | All | 86 | 5.0 | < 0.025 |
| Kark[36] | Georgia | All | 85 | 5.59 | 0.003 |

*Retrospective Serological Studies*

Eleven retrospective studies of serum retinol levels in patients with cancer will be discussed (Table 4). The first was published from India in 1962[37]. The authors found that serum vitamin A and carotene were lower in patients with oral leukoplakia than in normal controls, and lower in patients with oral cancer than in those with leukoplakia. They felt that dietary vitamin A deficiency was a factor in the development of oral cancer. The same conclusion was drawn from a 1972 study of nasopharyngeal cancer in Kenya[38], in which serum vitamin A and carotene were lower in the cases compared to an unspecified control group. A study from Pakistan[39] also found a significant decrease in plasma vitamin A and carotene values for a large group of oral cancer patients when compared to an unspecified control group. In a 1974 paper[40], significantly decreased levels of both vitamin A and carotene were reported for patients with gastrointestinal tumors when compared to a control group of patients with chronic benign illnesses. In this English study, there was no difference between cases and controls for the 11 breast cancer cases or for the 6 lung cancer cases. Two years later, however, the same authors expanded the sample of lung cancer cases to 28[41]; the updated analysis showed a significant decrease in plasma vitamin A, with the difference greatest for cases of squamous and small-cell lung cancer. The next publication[42] came from the United States in 1977, and also dealt with lung cancer. The authors measured serum vitamin A in 67 newly diagnosed lung cancer patients. The conclusion of these investigators was that a deficiency of vitamin A was not implicated in pulmonary carcinogenesis. However, they had no control group, and reported only that vitamin A levels were within normal range. Atukorala et al.[43] compared serum vitamin A and carotene levels in 26 cases of newly diagnosed lung cancer with 21 hospitalized controls with nonmalignant conditions. Both vitamin A and carotene levels were lower in the cases, although a statistically significant difference was found only for vitamin A.

Capel and Williams[44] presented data on 245 patients with cancers of the breast, pelvic organs, gastrointestinal tract, and respiratory tract. Although the serum vitamin A of all of the cases and controls was within normal limits, there was a significant difference between the cases and controls of 50 $\mu$g/100 ml, the highest reported difference in any study to date.

Three other studies have been reported in abstract form. In a study from New Orleans[45], only 4 $\mu$g serum vitamin A/100 ml separated 17 lung cancer cases from 17 hospitalized controls. Autopsy-derived values for liver vitamin A stores were also provided. Lung cancer

cases had a mean value of 63 $\mu$g/g, while the mean for the hospitalized control group was 146 and for nonhospitalized controls, 135. A group of "other cancer" patients of the same size ($N = 25$) had a mean of 89. The authors concluded that low serum vitamin A and carotene levels were negatively associated with cancer. In another study[46], the vitamin A levels of esophageal cancer patients ($N = 17$) were compared to those of 12 chronic alcoholics, 10 nonalcoholics with other types of cancer, and 11 nonalcoholics without cancer. The mean values were 33, 53, 43, and 60 $\mu$g/100 ml, respectively. The authors of this report felt that a deficiency of vitamin A might antedate and contribute to the development of esophageal cancer. From the University of Miami and M.D. Anderson Hospital in Houston, a study[47] of 48 oral cancer patients showed a mean retinol level of 57. The control group (type unspecified) had a mean 4 $\mu$g higher. Here, this small difference was statistically significant at p = 0.05.

Thus, of the 11 retrospective serological studies reported here, 10 concluded that low vitamin A levels existed in the cancer population and potentially played a role in its incidence. The one negative study[42] used no controls. *In toto*, both prospective and retrospective investigations suggested that the lower the serum vitamin A level, the greater the cancer risk, *even for levels in the normal range*. The measurement of serum vitamin A levels has improved considerably in the past few years and high pressure liquid chromatographic resolution has allowed separation of vitamin A and metabolites. In future studies, it will be important to certify the stability of vitamin A in the collected serums and to measure metabolites other than retinol.

| Table 4. Vitamin A and Cancer: Retrospective Case-Control Serum Retinol Level Studies | | | | | |
|---|---|---|---|---|---|
| Primary author | Location | Tumor type | Cases | Retinol level (Control minus Case) ($\mu$g/100 ml) | P value |
| Wahi[37] | India | Oral | 555 | 19 | Not reported |
| Clifford[38] | Kenya | Nasopharyngeal | 17 | Not reported | < 0.05 |
| Ibrahim[39] | Pakistan | Oral | 203 | 18 | < 0.01 |
| Basu[40] | England | Gastrointestinal | 11 | 19 | < 0.001 |
| Basu[41] | England | Lung | 28 | 23 | < 0.01 |
| Cohen[42] | Washington, DC | Lung | 67 | No controls | — |
| Atukorala[43] | England | Lung | 26 | 13 | < 0.01 |
| Capel[44] | England | All | 245 | 50 | < 0.05 |
| Lopez-S[45] | New Orleans | Lung | 25 | 4 | — |
| Mellow[46] | Washington, DC | Esophagus | 17 | 28 | < 0.001 |
| Goodwin[47] | Houston | Oral | 48 | 4 | ≤ 0.05 |

## Future Perspectives: Vitamin A as Intervention for Cancer Chemoprevention

The epidemiologic data that have been reviewed here strongly support the hypothesis that vitamin A may protect against cancer. Criteria that indicate a cause-and-effect relationship in epidemiologic studies include biological plausibility, reproducibility, a dose-response relationship, and strength of association. The inverse association between vitamin A and cancer has been documented in both dietary and serological studies from all over the world and for multiple tumor types. A dose-response effect was detected in many of the studies reviewed. The attributable risk of low vitamin A intake or low serum retinol averaged approximately 2. However, considering the multifactorial nature of cancer, it would be unreasonable to expect vitamin A to be the sole or even the major natural deterrent to the development of cancer.

At the present time, vitamin A is the only potential chemopreventive agent with strong and extensive epidemiologic and laboratory evidence favoring its role in cancer prevention. Some other factor associated with vitamin A and carotene intake, such as vitamin C or protease inhibitors, or the reduction of some dietary factor, such as total calories or fat consumption, could be the key element in the anticancer effect. Important questions remain, and it will take controlled experimental trials to provide conclusive evidence as to the factor(s) responsible[1].

The use of pharmacologic doses of retinol for chemoprevention may be limited by undesirable side effects[48]. Symptoms of excess vitamin A include exfoliative dermatitis, dry mucous membranes, headaches, emotional irritability, fatigue, epistaxis, and edema. Because of hepatic vitamin A storage, liver function abnormalities and hepatomegaly may occur. These toxicities have prompted an intensive search for a vitamin A analogue with a better therapeutic ratio[5]. Thus, compounds such as 13-*cis*-retinoic acid have been developed.

If vitamin A is important in cancer prevention, is the carotene or the preformed vitamin responsible for the effect? As the bulk of the dietary studies implicate β-carotene, Peto et al.[1] suggest that the evidence favors β-carotene as being of primary importance. However, the serological studies and most of the *in vitro* laboratory work support retinol and its metabolites and derivatives as the key nutrients. There is no reason that these should be mutually exclusive; some experimental research has shown carotene and not retinol to be an effective anticarcinogen, and other research has shown the opposite. The toxicity of β-carotene may be less, but so may be the benefit.

A key assumption of the review by Peto et al.[1] is that dietary intake does not significantly affect serum levels of retinol. This may not be correct. The serological epidemiology has shown that variations within the normal range of serum retinol vary the relative risk for malignant disease. Indeed, differences from 5 to 20 μg/100 ml have been associated with relative risks from 2 to 5. It has been shown that retinol intake in acne patients can raise serum values by at least that amount, albeit at high doses of retinol (300,000 IU/day)[51]. Similar data have been seen in University of Arizona cancer patients treated on phase I and Phase II retinol protocols (Meyskens and Alberts, unpublished data). It is not inconceivable that long-term ingestion of increased amounts of carotene or retinol would alter serum vitamin A levels, and thus inhibit tumor initiation, promotion, or proliferation.

What then would be a productive intervention trial? Ideally, a large population would be divided into four groups: control, carotene, retinol, and synthetic-retinoid–supplemented, all at various doses. This ideal is unlikely to be achieved in a human population. While these questions and problems are being resolved, the National Research Council's recommendation of frequent consumption of vitamin-A–containing vegetables to decrease cancer risk is reasonable, defensible, and safe. This suggestion deserves the support of the medical community. Equally important, the use of pharmacologic doses of retinoids is to be strongly discouraged except in carefully controlled and monitored trials. These agents have their own toxicity, and some have actually been found to be *in vitro* tumor promoters under certain circumstances[52].

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53. Address correspondence to Dr. Frank L. Meyskens, Jr., Cancer Center, University of Arizona Health Sciences Center, 1501 N. Campbell Avenue, Tucson, AZ 85724.