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Authors
Bertram, J S
Kolonel, L N
Meyskens, F L, Jr

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Rationale and Strategies for Chemoprevention of Cancer in Humans

John S. Bertram, Laurence N. Kolonel, and Frank L. Meyskens, Jr.

Basic Science Program [J. S. B.] and Epidemiology Program [L. N. K.], Cancer Research Center of Hawaii, University of Hawaii, Honolulu, Hawaii 96813, and Department of Internal Medicine and Cancer Prevention and Control Program, Arizona Cancer Center, Tucson, Arizona 85724 [F. L. M.]

Abstract

The potential for chemical intervention (chemoprevention) as a means of halting or delaying the process of carcinogenesis is assessed as a strategy for reducing the incidence of human cancer. The process of carcinogenesis is dissected into its constituent steps, thereby exposing sites for intervention. These sites are then critically discussed with regard to (a) the existence of chemicals active at these sites using data gained from the laboratory and from epidemiological studies, (b) intrinsic problems or advantages associated with intervention at specific sites in the carcinogenic process, and (c) practical aspects of intervention in humans. The design and potential long-term positive and negative consequences of chemoprevention clinical trials are critically discussed, with the objective of exposing the major differences that exist between clinical trials in cancer chemoprevention and those in cancer chemotherapy. Results of completed prevention trials and details of ongoing trials are presented and discussed.

Based on the laboratory, epidemiological, and clinical evidence presented, it is concluded that chemoprevention offers excellent prospects as a means of reducing cancer incidence. Among currently available agents, the retinoids possess the best combination of properties. However, much more research is needed to optimize drugs and protocols and to develop interim end points for assessing response. The authors finally caution that overambitious claims for the prospects for chemoprevention may lead to reduced emphasis on the need for changes in life-style (principally in smoking and diet) that are viewed as having the greatest potential for reducing cancer incidence.

Scope

The concept of the chemoprevention of cancer as originally proposed referred to the prevention of cancer by the use of pharmacological agents to inhibit or reverse the process of carcinogenesis (1). In this article we have maintained this narrow definition and have thus excluded dietary aspects of cancer that cannot be specifically attributed to the consumption of defined chemicals that can be shown to decrease cancer incidence. Likewise excluded from consideration are strategies for primary cancer prevention designed to decrease cancer risk through removal or avoidance of diverse factors such as fat, tobacco, or UV radiation where exposure is positively correlated with risk. We have instead concentrated on those agents which have the potential for secondary prevention, defined here as intervention to prevent the consequences of carcinogen exposure, and for tertiary prevention, defined as intervention to arrest or reverse a premalignant lesion. Agents having the potential for use in humans have been critically evaluated in the context of their mode of action and likely side effects. Finally, we discuss in detail the special problems of, and requirements for, the application of this knowledge to the design of chemoprevention trials.

Rationale behind the Concept of Cancer Prevention

The goal of individuals engaged in cancer research and of governmental and other agencies that fund this research is to reduce the morbidity and mortality associated with this disease. This can be achieved by prevention or cure. How can we best approach the ambitious goal of the National Cancer Institute of a 50% reduction in cancer mortality by the year 2000 (2)? Clearly, with approximately 930,000 new cases of cancer expected next year in the United States alone (3), excluding nonmelanotic skin cancer, one cannot escape the need for continued efforts to increase cure rates of existing tumors either by early detection and treatment prior to dissemination or by improved therapeutic strategies. However, the growing body of evidence demonstrating heterogeneity among primary and metastatic tumor cell populations (4), the rapid evolution of tumor cells towards new phenotypes (5), and the lack of past success in developing therapies that can eradicate disseminated solid tumors responsible for most cancer mortality in the United States have led to some pessimism regarding this approach to the control of cancer in the near future (6, 7). It is hoped that advances in newer areas of treatment research, such as biological response modifiers, will make these concerns unwarranted. Nevertheless one cannot fail to be humbled by the challenge of totally eradicating 10^8 tumor cells without also destroying sensitive host stem cell populations.

There are, of course, two ways to avoid the problem of advanced cancer: the early detection of tumors when their mass is small and when dissemination has not occurred; or the prevention of tumor development. Early detection has decreased morbidity and mortality for accessible sites, such as the uterine cervix, but severe problems exist in the early detection of tumors at inaccessible sites such as the lung. One aspect of the second approach to the control of cancer, that of chemoprevention, is the subject of this paper.

What is the evidence that chemoprevention offers a realistic promise of reducing the incidence of human cancer? As will be evident in the following sections, cancer epidemiology provides the most compelling evidence that primary prevention is possible and that chemopreventive agents exist naturally in our diet. However, in order to effectively study cancer chemopreventive agents in a laboratory setting, we cannot wait for the rare spontaneous development of tumors in an aging animal population; instead, malignancies are induced by exposure to known chemical or physical carcinogens and drug effects on these induced tumors are monitored. The validity of these model carcinogenesis systems relies heavily upon how closely human cancer induction matches these experimental models. If, for example, most human cancer were genetically determined, the mechanisms might be expected to be quite dissimilar from those operative in carcinogen-exposed rodents. Thus, the rodent model might be quite inadequate to study human carcinogenesis. However, epidemiological data from both descriptive and analytical studies, particularly on temporal trends in incidence and on changing risks in migrant populations (8–10),

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1 A position paper of the American Association for Cancer Research, Inc., commissioned by the Association’s Scientific and Public Affairs Committee. Reprint requests for both individual and bulk orders should be addressed to American Association for Cancer Research, Inc., Temple University School of Medicine, West Building, Room 301, Philadelphia, PA 19140. Supported by Grants CA 39947 (J. B.), CA 33619 (L. N. K.), and CA 27502 and CA 23074 (F. L. M.)
strongly support the conclusion that the majority of human cancers in the most commonly involved organs is induced by exogenous agents and thus is preventable if the cause can be identified and eliminated. Since many of these exogenous agents induce cancer in rodents, the use of rodent models for the study of human carcinogenesis is rational.

Estimates have been made of the extent to which exogenous factors can account for the total cancer burden in humans. Higginson and Muir (11) and Knudsen (12) concluded that not more than 2% of all human cancer is attributable to purely genetic or congenital factors. Of particular importance is the contribution of diet to this total. Doll and Peto (13) suggested that perhaps 35% of all cancer mortality in the United States (range, 10–70%) could be attributable to dietary factors, while Wynder and Gori (14) offered the figures of 40% in men and nearly 60% in women.

In order to discuss chemoprevention, it is important to understand the etiology of human cancer, a subject that is addressed by the disciplines of cancer epidemiology and carcinogenesis. Fortunately, major advances have been made in these two areas in the last decade, and while specific details remain to be unraveled, major concepts have emerged which allow a systematic approach to this question.

Carcinogenesis and Its Prevention

Overview of the Carcinogenic Process

What is known of the processes by which these exogenous agents induce human cancer? Necessarily, most of our knowledge derives from studies on cancer induction or its modulation in experimental animal systems. While we cannot as yet confidently extrapolate from laboratory studies of carcinogenesis to human risk because of problems of dose, metabolism, and physiology, there is nevertheless overwhelming evidence that, at the cellular level, humans by and large do not differ qualitatively from experimental animals in their response to carcinogens. Furthermore, processes operative in humans that lead to cancer induction are also operative in rodent systems. For example, many carcinogens active in animals were initially discovered because of industrial exposure and carcinogenesis in humans [e.g., benzo(a)pyrene, β-naphthylamine, asbestos] (13), and it has recently been demonstrated that the putative genotoxic lesions induced in the DNA of rodents by major classes of carcinogens are also induced in human cells by these same agents (15–17). Furthermore, similar classes of oncogenes are found to be activated in tumors of rodent and human origin (18), implying that not only are the chemical lesions identical in human and experimental animal test systems, but also some of the biological consequences of lesion formation (19) will bear close resemblance.

In order to discuss the process of carcinogenesis and its potential for inhibition, it is useful to categorize known chemopreventive agents into chemical class or according to locus of action. We have chosen this latter system of classification. Although epidemiological evidence seldom addresses mechanisms, we have integrated the epidemiological data, since this scheme offers useful insights into the complexities of the carcinogenic process and the potential for intervention.

Let us first present an overview so that individual steps may be seen in their proper context and potential sites for intervention can be identified. This overview is necessarily a simplified version of an incompletely understood process, which excludes special cases such as asbestos and hormonally induced cancers. As seen in Fig. 1, the steps may be separated mechanistically and temporally. Metabolic activation of a carcinogen to chemically reactive products and their reaction with cellular targets (DNA bases) occurs within a few hours of exposure. Many tissues have the ability to repair this chemical damage over a time period of days or weeks. Current evidence suggests that this chemical damage is converted to a stable biological lesion during DNA replication. This requirement may in part explain the high frequency of neoplasms in proliferating tissues and leads to the conclusion that intervention to prevent initiation (Fig. 1, Steps 1–4) must occur prior to or shortly after exposure. By contrast, the conversion of an initiated cell to a premalignant or fully malignant cell, either spontaneously or induced by tumor promoters, is a prolonged process lasting decades in humans. Inhibition of this process at any time prior to the onset of frank malignancy can be expected to delay the onset of disease. Thus, intervention can be started after exposure or during continuous exposure. The final site for intervention is the progression of premalignant cells to malignant cells of increasing virulence (Fig. 1, Step 5). For many epithelial tissues early pathological changes appear to be reversed by agents such as the retinoids; however, there is no evidence yet that this reversal is permanent. The ability to block the progression of malignant cells to cells with increasing invasive or metastatic properties has to our knowledge not yet been demonstrated.

Sites for Potential Chemoprevention

Carcinogen Formation

Experimental Studies. Major suspects in the etiology of gastric cancer are nitrosamines, either preformed in foods or formed endogenously in the stomach from the reaction of nitrite with amines (20). Ascorbic acid is an effective scavenger of nitrite ions; it will inhibit nitrosamine formation under in vivo conditions (21) and will reduce the mutagenicity of human gastric juice as determined by the Ames test (22). Most human feces also contain mutagenic compounds, the presence of which is associated with diets conferring high risks of colon cancer (23). Coadministration of ascorbic acid and α-tocopherol can cause a major reduction in mutagen content (24); however, the individual contribution of ascorbic acid was not determined.

Other studies of the chemopreventive action of ascorbic acid...
in experimental animals not involving nitrosamines are fragmentary and inconclusive. Part of the difficulty is that rodents normally utilized for research endogenously synthesize ascorbic acid. Two studies in guinea pigs, which like humans require exogenous ascorbic acid, showed either a slight enhancing effect of high dose ascorbate on 3-methylcholanthrene-induced sarcomas (25) or no effect (26). In the 10T½ cell culture system which is widely utilized to study carcinogens and chemopreventive agents, ascorbate was reported to strongly inhibit 3-methylcholanthrene-induced transformation and to cause reversion of some neoplastic cell lines to normality (27).

Epidemiological Studies. Table 1 summarizes the epidemiological findings on vitamin C or the consumption of foods, especially fresh fruits, which are major dietary sources of this nutrient. Several case-control investigations of this vitamin have been reported, but only two groups of investigators have yet reported on the relationship of vitamin C to cancer based on cohort data (28-30). As seen in Table 1, most of the positive evidence relates specifically to two cancer sites, the esophagus and stomach, which is consistent with the hypothesis that gastric cancer results from the endogenous production of nitrosamines (51, 52). The decline in gastric cancer incidence over the past 50 years (53) parallels the increasing availability of fresh fruits and vegetables. The contribution of vitamin C supplements to total intake and to cancer risk has not been adequately studied. Some recent studies which included supplement use have reported negative findings (43, 48), but these were not investigations of either gastric or esophageal cancer. The overall evidence is strongly suggestive of a role for ascorbate in the prevention of cancer of the digestive tract, particularly the esophagus and stomach.

**Interference with the Metabolic Activation of Chemical Carcinogens**

Most chemical carcinogens do not themselves produce damage to cellular targets presumed to be DNA but require activation to chemically reactive species capable of covalent modification of DNA bases. It is these modified bases that during DNA replication are believed to result in DNA perturbations which ultimately cause neoplastic transformation.

Thanks to the pioneering work of Miller and Miller (54), there now exists a good understanding of the essential role played by drug-metabolizing enzymes in the production of biologically reactive intermediates (for review see Ref. 55). The metabolism of carcinogens is complex; for a review of the metabolism of the ubiquitous environmental carcinogen BP, see Ref. 56. Any protocol causing preferential metabolism at sites not resulting in chemically reactive species (Step 2) or providing competing substrates for reaction with the ultimate carcinogen (Fig. 1, Step 3) will decrease the amount of DNA damage resulting from a fixed exposure to a carcinogen. This can be expected to decrease the ultimate carcinogenic consequence of that exposure. What is the potential for such intervention? We will deal with interference with metabolic activation first.

**Experimental Evidence for Modulation of Metabolic Activation.** Enzymes having as a major function the metabolism of xenobiotics to more water-soluble excretable forms are found in many organs of the body. The major reactions are of hydroxylation and subsequent conjugation. Although these mechanisms work well for most compounds, carcinogens become activated to reactive forms when metabolism occurs at critical sites. Prospects for chemoprevention depend upon the existence of alternative routes of metabolism that result in detoxification of most carcinogens. Thus, a shift from epoxidation of BP to 3-hydroxylation of BP induced by BHT (57) has the effect of reducing the carcinogenicity of this compound, while many flavones, which under appropriate circumstances will block metabolism of polycyclic aromatic hydrocarbons, will also effectively block two-stage carcinogenesis in mouse skin induced by DMBA. This topic has been reviewed recently by Wattenberg (58) and by Slaga and Digiovanni (59) to whom the reader is referred for detailed references.  

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**Table 1** *Summary of epidemiological studies on vitamin C and cancer risk*

<table>
<thead>
<tr>
<th>Finding</th>
<th>Cancer site</th>
<th>Refs. showing the association</th>
<th>Refs. not showing the association</th>
<th>Specific nature of the association</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Correlational studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inverse relationship between cancer rates and vitamin C intake</td>
<td>Esophagus</td>
<td>31, 32</td>
<td></td>
<td>Vitamin C</td>
</tr>
<tr>
<td></td>
<td>Stomach</td>
<td>33</td>
<td></td>
<td>Vitamin C</td>
</tr>
<tr>
<td>Lower intake of vitamin C by cases than by controls</td>
<td>Esophagus</td>
<td>34, 36, 37</td>
<td>35</td>
<td>Fresh fruits</td>
</tr>
<tr>
<td></td>
<td>Stomach</td>
<td>38</td>
<td>39</td>
<td>Fresh fruits</td>
</tr>
<tr>
<td></td>
<td>Colorectum</td>
<td>28</td>
<td>39</td>
<td>Fresh fruits</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>40</td>
<td>42-44</td>
<td>Vitamin C</td>
</tr>
<tr>
<td></td>
<td>Oral cavity</td>
<td>41</td>
<td></td>
<td>Vitamin C</td>
</tr>
<tr>
<td></td>
<td>Larynx</td>
<td>45</td>
<td></td>
<td>Vitamin C</td>
</tr>
<tr>
<td></td>
<td>Cervix</td>
<td>46</td>
<td></td>
<td>Vitamin C; association with cervical dysplasia</td>
</tr>
<tr>
<td></td>
<td>Breast</td>
<td>47</td>
<td>48-50</td>
<td>Vitamin C; risk is actually increased</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Case-control studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower intake of vitamin C by cases than by controls</td>
<td>Stomach</td>
<td>29</td>
<td></td>
<td>Fresh fruits</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>28</td>
<td></td>
<td>Vitamin C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>Vitamin C</td>
</tr>
<tr>
<td>Lower prediagnostic serum vitamin C in cases than in noncases</td>
<td>Stomach</td>
<td>29</td>
<td></td>
<td>Vitamin C</td>
</tr>
</tbody>
</table>

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2 The abbreviations used are: BP, benzo(a)pyrene; BHT, butylated hydroxytoluene; DMBA, dimethylbenzanthracene; TPA, tetradecanoylphorbol acetate.
The experimental evidence clearly demonstrates the effectiveness of intervention at this stage, although the epidemiological data are incomplete. Although in principle this is an attractive means of inhibiting the consequences of carcinogen exposure, there are, however, several drawbacks which make implementation in humans impractical. Not only is modulation of enzyme activity dose, chemical, and time schedule dependent, but one must also consider the diversity of the human genetic background, the exposure of humans to many carcinogens, and the diverse routes by which carcinogens are activated (e.g., hydroxylation of nitrosamines, N-hydroxylation of aromatic amines, ring epoxidation of aromatic hydrocarbons, etc.). How can we ensure that protection against one carcinogen is not accompanied by potentiation of the effects of others? Furthermore, agents may have multiple effects, not all of which may be beneficial. Thus, selenium supplementation of deficient animals may increase the detoxifying enzyme glutathione peroxidase (64), but it may also alter sites of metabolic conversion of carcinogens, which in some cases may enhance metabolic activation (65). Because of these considerations, intervention at this point in the carcinogen process appears feasible only in groups exposed to a dominant carcinogenic stimulus such as tobacco, although the situation here is complex, involving multiple carcinogens and promoters. A special case that might be mentioned is the accepted treatment of radioactive fallout victims with iodide to prevent the uptake (metabolic activation) of 

Inhibition of the Promotional Phase of Carcinogenesis

This phase is the least understood, has the longest duration, and yet is the phase with the most potential for human intervention. This potential stems from several separate lines of evidence: (a) since this phase is of many years duration in humans, it is possible, unlike the case for antiinitiation therapy, to begin treatment long after carcinogen exposure; (b) since late stages of carcinogenesis are affected, it should be possible to detect results in a few years rather than the decades required to demonstrate effectiveness of antiinitiation therapy; (c) from the results of animal studies and from epidemiological evidence, drugs are available which alter the potential for activity without appreciable side effects. A major disadvantage of drugs active in this phase is that studies in both animals and cell culture show that inhibition of promotion is reversible, requiring continuous treatment for continuous effect. Thus, although clinical efficacy be unequivocally demonstrated, the ethics of discontinuing therapy in clinical trial volunteers will require careful consideration.

Compounds Blocking Reaction of the Proximal Carcinogen with Tissue Nucleophiles

Because most, if not all, activated carcinogens are highly reactive electrophiles, chemical specificity can be expected to be less rigorous for chemopreventive compounds capable of intercepting the proximal or ultimate carcinogenic form of a carcinogen; any nucleophilic compound can be expected to show activity. With few exceptions, results of studies utilizing agents of this type have been disappointing when conducted in whole animals. The reason for lack of activity may imply that in most cases metabolic activation takes place within the target cell and that in order to be effective in blocking reaction with DNA, the compound must penetrate the proximal carcinogen, probably within milliseconds of formation, and must compete with available tissue nucleophiles for covalent binding. In view of the high concentration of tissue nucleophiles and the extremely low concentration of proximal carcinogens to be expected in human tissues, this may be an unrealistic goal.

Experimental Studies. In spite of the problems discussed above, this mode of chemoprevention presents exciting possibilities, since the elimination of powerful electrophiles (i.e., proximal carcinogens) can be expected to be universally beneficial. Early work demonstrated the potential of this approach, when nucleophilic sulfhydryl groups present in cysteine were shown to be capable of reducing the toxicity of alkylating carcinogens (66). While sulfhydryl groups can be expected to compete for binding to all electrophiles, apparently greater specificity for reaction with a proximal carcinogen has been shown with the plant phenol ellagic acid, which undergoes rapid covalent binding with the activated form of BP. This compound has been shown to decrease the in vitro mutagenic effects of BP-diol epoxide (67). Ellagic acid will also inhibit the induction of lung tumors in newborn mice; however, this requires the i.p. administration of ellagic acid just prior to carcinogen injection at the same site. Tumorigenesis by the parent carcinogen BP was not inhibited, indicating that sufficiently high concentrations of ellagic acid did not reach sites of distal metabolism of BP (68).

Epidemiological Studies. To our knowledge no studies have suggested activities of sulfhydryl groups or ellagic acid in human populations. It is possible that the antioxidants \( \beta \)-carotene and \( \alpha \)-tocopherol may also act by this mechanism. Their activities are summarized in a later section of this review.

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It should be noted that with the clear exception of tobacco, what contribution exogenous tumor promoters make to human cancer incidence is not known; nor is it clear if the activity of agents such as phenobarbital, which promote liver carcinogenesis in rodents, has direct relevance to humans. The situation is further complicated by the observation that repeated exposure to so-called “complete” carcinogens can, in the mouse skin, substitute for promoter. Thus, in some situations, inhibition of chronic initiating events may influence tumor yields comparatively to inhibition of promotion.

The biochemical mode of action of tumor promoters is poorly understood; however, recent work has identified a Ca++, phospholipid-dependent protein kinase as a receptor for the potent promoter TPA (71) and has shown that normal products of membrane degradation also activate this kinase (72). The consequences of kinase activation involve multiple regulatory pathways (72, 73), including prostaglandins. Inhibition of prostaglandin synthesis can inhibit experimental promotion (74).

Because of the formation of promoters as normal end products of membrane degradation, “spontaneous” promotion in humans may be very similar mechanistically to experimental promotion in mouse skin induced by the phorbol ester tumor promoters.

**Vitamin A: The Retinoids and Carotenoids**

The intense interest in this group of compounds stems from a number of epidemiological studies which demonstrate an inverse correlation between dietary intake or blood level of vitamin A or carotenoids and cancer risk at several epithelial sites and from an even greater number of experimental studies demonstrating the anticarcinogenic effects of these compounds.

Although these substances have been grouped together for the purposes of this report, it is important to realize that these compounds are not equivalent. Vitamin A (a) functions as a visual pigment, (b) maintains reproductive capacity in both males and females, and (c) allows normal growth and epithelial differentiation. Only retinaldehyde and retinol and its esters can serve all these functions of vitamin A and these compounds are freely interconvertible in the body. Reproduction, growth, and epithelial differentiation, but not vision, can be maintained by retinoic acid, a natural metabolite of retinol. The retinoids, a term coined to describe the natural and synthetic analogues of retinol, are generally inactive in maintaining vision but will maintain normal growth and epithelial differentiation; they are in general, therefore, more like retinoic acid than like retinol. The carotenoids are plant pigments, some of which can be broken down in the small intestine to retinaldehyde and then converted to retinol. Some carotenoid is absorbed unchanged. The most important carotenoid in the diet is believed to be β-carotene. Although the carotenoids have no known direct vitamin A-like activity, much recent epidemiological evidence supports the contention, first raised by Peto et al. (75), that the β-carotene component of the diet is more important in preventing cancer than the preformed retinol-retinol ester component. The entire field of retinoid research has been recently reviewed (76).

**Experimental Evidence.** The retinoids have been tested as inhibitors of experimental carcinogenesis by many investigators using many models and many organ and tissue sites. Key observations are listed in Table 2. These studies have been reviewed recently elsewhere (77) and the reader is referred there for the discussion that space does not permit here. It is clear from the studies that some sites fairly consistently (but not always) show reductions in tumor incidence with retinoid treatment; other sites, in contrast, usually fail to respond to retinoid therapy. Those sites at which retinoids strongly suppress experimental carcinogenesis are the mammary gland (78), the urinary bladder (79), and the skin in the classical two-stage system (80) but not, as detailed below, using a complete carcinogenesis protocol. Less consistent effects have been reported for the prevention of lung, liver, and oral tumors. These inconsistent results may be the consequence of inappropriate choice of retinoid, the dose used, the species tested, or the initiating carcinogen.

There is considerable debate about whether the vitamin A precursors derived from plant sources are active per se, possibly due to their antioxidant properties (92), or are activated by virtue of their conversion to retinoids. In experimental animal studies in which β-carotene has either chemopreventive (93–95) or antitumor (96) activity, the extent and possible significance of its conversion to retinol were not determined. In the one in vitro study, β-carotene reduced the number of DMBA-induced lesions in mouse mammary explants; however, the authors did not satisfactorily demonstrate whether this activity was due to β-carotene itself or was dependent upon its conversion to retinoids (97). However, it is clear that for UV-induced skin tumors in mice, the protective effect of β-carotene is not solely due to its provitamin A activity, since canthaxanthine, a carotenoid which cannot be converted to vitamin A, is also active (95). The effects of β-carotene on systems other than UV-induced skin cancer have not been adequately investigated.

**Epidemiological Studies.** Many epidemiological studies have now reported on the association of vitamin A and cancer (summarized in Table 3). Some of these studies identified only food groups known to be rich sources of vitamin A, while others estimated actual vitamin A intake from the dietary information. A large number of these studies pertain to lung cancer, the site first associated with this nutrient (98). As shown in Table 3, all of the cohort studies and the great majority of those case-control studies which determined dietary intakes of vitamin A itself found a protective effect. Most of the studies which looked only at food items also found this inverse association, although one must recognize that such analyses do not distinguish vitamin A from other constituents of these foods (including non-

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**Table 2 Inhibition of experimental carcinogenesis by retinoids**

<table>
<thead>
<tr>
<th>Organ/tissue</th>
<th>Species</th>
<th>Carcinogen</th>
<th>Response</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammary gland</td>
<td>Rat</td>
<td>DMBA</td>
<td>D*</td>
<td>78, 81</td>
</tr>
<tr>
<td>Mammary gland</td>
<td>Rat</td>
<td>NMU</td>
<td>D</td>
<td>82</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Rat</td>
<td>NMU</td>
<td>D</td>
<td>79</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Mouse</td>
<td>BBN</td>
<td>D</td>
<td>83</td>
</tr>
<tr>
<td>Skin</td>
<td>Mouse</td>
<td>DMBA (2-stage)</td>
<td>D</td>
<td>80</td>
</tr>
<tr>
<td>Liver</td>
<td>Rat</td>
<td>Aflatoxin B1</td>
<td>D*</td>
<td>84</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>Hamster</td>
<td>DMBA</td>
<td>D</td>
<td>86</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>Hamster</td>
<td>DMBA</td>
<td>D</td>
<td>87</td>
</tr>
<tr>
<td>Esophagus/fore-stomach</td>
<td>Hamster</td>
<td>BP</td>
<td>D</td>
<td>88</td>
</tr>
<tr>
<td>Colon</td>
<td>Rat</td>
<td>NMU</td>
<td>N</td>
<td>89</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Hamster</td>
<td>Azaserine</td>
<td>D</td>
<td>90</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Hamster</td>
<td>BOP</td>
<td>N</td>
<td>91</td>
</tr>
</tbody>
</table>

* D, decrease in tumor incidence over carcinogen-only treated controls; NMU, N-nitrosomethylurea; BBN, butyl-4-hydroxybutynitrosamine; DAB, dimethylaminolevulinate; BOP, N-nitrosobis(2-oxypoly)amine; N, no decrease in tumor incidence.
nutritive components) that may actually be responsible for the observed effect. The mixed results of the analyses based on blood measurements may reflect any of several methodological biases, including: (a) the effects of the disease process itself on serum levels in those patients whose samples were collected after diagnosis; (b) nonrepresentative results based on single samples collected at only one point in time; (c) homeostasis [especially with regard to retinol (139)]; and (d) degradation of the vitamin during long-term storage.

Unfortunately, many of the earlier studies did not attempt to separately analyze the data for retinol and carotenes. Of those which have done this, a growing number have found the protective effect to be specific for carotenes (29, 43, 101–103, 116, 123, 131) as first suggested by Peto (75). No study which separately analyzed for retinol and carotenes has found retinol but not carotene protective, although some have found both (29, 44, 121). There has been little effort yet to further refine the association with carotenes. Although β-carotene is a major dietary component, many other carotenes are present in foods and could be responsible for the effect.

A significant opposite finding is a positive association between dietary vitamin A intake and prostate cancer, based on three recent reports (48–50). If confirmed, this association could reflect an effect of vitamin A on cell proliferation in the prostate (140) or an interaction of the vitamin with zinc, which is highly concentrated in the prostate and may play a role in prostatic carcinogenesis (141). Enhancement of carcinogenesis by vitamin A or its analogues has been demonstrated experimentally (142). Treatment with retinoids may be associated with an increased risk for prostate cancer (143). Enhancement of carcinogenesis by vitamin A or its analogues has been demonstrated experimentally (142). Treatment with retinoids may be associated with an increased risk for prostate cancer (143).

**Table 3 Summary of epidemiological studies on vitamin A and cancer risk**

<table>
<thead>
<tr>
<th>Finding</th>
<th>Cancer site</th>
<th>Refs. showing the association</th>
<th>Refs. not showing the association</th>
<th>Specific nature of the association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower intake of vitamin A by cases than controls</td>
<td>Lung</td>
<td>Vegetables</td>
<td>99</td>
<td>Lower intake of vitamin A by cases than controls</td>
</tr>
<tr>
<td></td>
<td>Oral cavity</td>
<td>Total vitamin A</td>
<td>42, 44, 100, 101</td>
<td>Total vitamin A and carotene</td>
</tr>
<tr>
<td></td>
<td>Larynx</td>
<td>Total vitamin A</td>
<td>43, 102, 103</td>
<td>Total vitamin A</td>
</tr>
<tr>
<td></td>
<td>Esophagus</td>
<td>Vegetables and dairy products</td>
<td>37</td>
<td>Total vitamin A</td>
</tr>
<tr>
<td></td>
<td>Stomach</td>
<td>Vegetables and/or milk</td>
<td>61, 105–107</td>
<td>Total vitamin A</td>
</tr>
<tr>
<td></td>
<td>Pancreas</td>
<td>Vegetables</td>
<td>108</td>
<td>Total vitamin A</td>
</tr>
<tr>
<td></td>
<td>Colorectum</td>
<td>Vegetables and/or milk</td>
<td>110</td>
<td>Total vitamin A</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal tract combined</td>
<td>Retinol and carotene</td>
<td>28, 62</td>
<td>Retinol and carotene</td>
</tr>
<tr>
<td></td>
<td>Bladder</td>
<td>Total vitamin A</td>
<td>113</td>
<td>Total vitamin A</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
<td>Liver and carrots</td>
<td>114</td>
<td>Total vitamin A; risk is actually increased</td>
</tr>
<tr>
<td></td>
<td>Breast</td>
<td>Total vitamin A</td>
<td>48</td>
<td>Total vitamin A</td>
</tr>
<tr>
<td></td>
<td>Cervix</td>
<td>Total vitamin A and carotene; association with cervical dysplasia and carcinoma in situ</td>
<td>115</td>
<td>Total vitamin A</td>
</tr>
<tr>
<td></td>
<td>Ovary</td>
<td>Carotenes</td>
<td>116</td>
<td>Carotenes</td>
</tr>
<tr>
<td></td>
<td>General</td>
<td>Vitamin A supplements</td>
<td>117</td>
<td>Vitamin A supplements</td>
</tr>
<tr>
<td>Lower serum or plasma vitamin A levels in cases than controls</td>
<td>Lung</td>
<td>Retinol</td>
<td>118, 119</td>
<td>Lower serum or plasma vitamin A levels in cases than controls</td>
</tr>
<tr>
<td></td>
<td>Esophagus</td>
<td>Retinol</td>
<td>120</td>
<td>Retinol</td>
</tr>
<tr>
<td></td>
<td>Bladder</td>
<td>Retinol and carotene</td>
<td>121</td>
<td>Retinol and carotene</td>
</tr>
<tr>
<td>Lower intake of vitamin A by cases than by noncases</td>
<td>Lung</td>
<td>Vegetables</td>
<td>122</td>
<td>Lower intake of vitamin A by cases than by noncases</td>
</tr>
<tr>
<td></td>
<td>Total vitamin A</td>
<td>30, 98</td>
<td>Total vitamin A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carotene</td>
<td>123</td>
<td>Total vitamin A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stomach</td>
<td>Vegetables</td>
<td>124</td>
<td>Total vitamin A</td>
</tr>
<tr>
<td></td>
<td>Colorectum</td>
<td>Total vitamin A</td>
<td>28</td>
<td>Total vitamin A</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
<td>Vegetables</td>
<td>125</td>
<td>Total vitamin A</td>
</tr>
<tr>
<td></td>
<td>General</td>
<td>Vegetables</td>
<td>126</td>
<td>Total vitamin A</td>
</tr>
<tr>
<td>Lower prediagnostic serum vitamin A in cases than in noncases</td>
<td>Lung</td>
<td>Retinol</td>
<td>127</td>
<td>Lower prediagnostic serum vitamin A in cases than in noncases</td>
</tr>
<tr>
<td></td>
<td>Total vitamin A</td>
<td>29, 131</td>
<td>Total vitamin A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>β-carotene</td>
<td>129, 130</td>
<td>Total vitamin A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stomach</td>
<td>Retinol</td>
<td>29, 128</td>
<td>Retinol</td>
</tr>
<tr>
<td></td>
<td>Breast</td>
<td>Retinol</td>
<td>132</td>
<td>Retinol</td>
</tr>
<tr>
<td></td>
<td>General</td>
<td>β-carotene</td>
<td>127, 133, 134</td>
<td>β-carotene</td>
</tr>
<tr>
<td></td>
<td>Retinol</td>
<td>129</td>
<td>Retinol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carotene</td>
<td>129</td>
<td>Carotene</td>
<td></td>
</tr>
<tr>
<td>Decrease in precursor lesions in treated group</td>
<td>Oral cavity</td>
<td>Formation of micronuclei in buccal mucosal cells of betel nut chewers decreased after retinol and β-carotene supplementation</td>
<td>136, 137</td>
<td>Decrease in precursor lesions in treated group</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Esophageal dysplasia not affected by retinol (plus riboflavin and zinc) supplementation</td>
<td>138</td>
<td>Esophageal dysplasia not affected by retinol (plus riboflavin and zinc) supplementation</td>
<td></td>
</tr>
</tbody>
</table>
Epidemiological data indicate that a wide range of cancer sites may be influenced by these compounds. Unfortunately, no single agent has yet been identified as responsible for the effect. The carotenoids as a group appear more likely to be responsible than retinol, although the active agent may not be β-carotene.

The naturally occurring retinoids are rapidly sequestered by the liver in the form of fatty acid esters. This results in difficulty in achieving elevated tissue levels except after very high doses. To overcome this drawback, synthetic retinoids have been developed which cannot be esterified by the liver; they achieve high tissue levels and, in some cases, have enhanced therapeutic ratios (156). It should be noted that pronounced species and organ site differences exist in the chemopreventive action of these synthetic retinoids, and it is not known whether these differences relate to changes in pharmacokinetics or drug distribution, or to other more subtle biochemical differences. For example, while both N-(2-hydroxypropyl)retinamide and N-(3-hydroxypropyl)retinamide are active in in vitro assays, only the former is an effective inhibitor of carcinogen-induced bladder carcinoma in mice (142). Species differences have also been observed; thus, 4-hydroxyphenyllretinamide is highly effective in inhibiting rat mammary adenocarcinomas induced by DMBA (81) but fails to influence DMBA-induced adenocarcinomas in the mouse mammary gland (143). Because we cannot yet confidently predict activity in a particular species or organ, in extrapolating to humans we must be prepared for some initial disappointments.

Retinoids are active in the promotional phase of carcinogenesis. In the experimental animal studies, retinoids demonstrate activity when administered after exposure to the carcinogen; indeed, a delay of up to 9 weeks after cessation of bladder tumor induction in the mouse (144) or 16 weeks after mammary tumor induction in the rat (82), still allowed strong preventive activity. In most cases retinoids have little effect on the growth of tumors themselves; their effects are seen as delay in tumor onset, i.e., an extension of the latent period. This knowledge is of importance in designing intervention trials in humans, particularly in high risk groups, since a significant number of preclinical tumors may already exist in these patients and be unresponsive to retinoid therapy. For this reason retinoid effects on premalignant cells may be evident only after outgrowth of these preexisting tumors. An exception to this statement is that retinoids clearly cause regression of some squamous and basal cell carcinomas (see Table 8).

The chemopreventive actions of retinoids are reversible upon drug withdrawal. This has been demonstrated in both in vivo studies (82) and transformation studies in vitro (145). Therefore, in human intervention trials, continuous treatment will be required for continuous effect, since the underlying pathology is not being cured but rather its progression retarded.

In some experimental situations, including UV-induced skin carcinogenesis, retinoids may enhance tumor incidence (Table 4). These observations are of sufficient concern to have prompted a Food and Drug Administration warning against UV exposure and retinoid therapy (148) and will require close monitoring of human subjects.

Both natural and synthetic retinoids are toxic compounds that can cause acute effects, including elevated intracranial pressure and desquamation of the skin, as well as chronic effects, including bone remodeling, hepatic toxicity, and skin erythema. The retinoids are also highly teratogenic, producing multiple malformations. Their use must therefore be carefully controlled; even overzealous use of readily available vitamin supplements can produce severe effects, particularly in the young. (For review see Ref. 155.)

The Antioxidants: Selenium and α-Tocopherol

Selenium

Experimental Studies. The inhibitory effects of selenium on experimentally induced tumors are well documented; however, the requirements for activity are complex, and effective levels are generally close to toxic levels (Table 5). Thus, in the majority of studies, protective effects of selenium were noted only at dietary concentrations of 2 ppm or above, while toxic symptoms, usually weight loss, were generally manifest with dietary levels above 5 ppm, underlining the fine line between an effective and a toxic concentration of this element. In only two studies have the effects of a deficiency of selenium been evaluated. In both instances, supplementation led to decreased tumorigenesis (158, 159). The data of Ip and Sinha are of interest for two reasons: (a) selenium replenishment of a deficient diet at the level of 0.1 ppm, which is the usual concentration in animal food, led to a decreased incidence of DMBA-induced tumors; (b) the enhancement of tumor yield caused by selenium deficiency was pronounced only in animals fed a high polysaturated fat diet of 25% corn oil (158). This interplay of fat and selenium, if it occurs in humans, will complicate epidemiological studies.

Mechanisms of selenium inhibition of carcinogenesis appear complex and are poorly understood. Some studies have suggested that selenium inhibits the initiation phase of carcinogenesis (64, 65, 157, 166, 167), while others have demonstrated effects when given postcancerogen (161, 163). The suggestion that selenium owes its effects to a decrease in proliferation rate of target cells (168) would satisfy effects on both initiation and promotion phases of carcinogenesis and would explain the close correspondence between anticarcinogenic doses and those caus-

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Table 4  Enhancement of carcinogen-induced neoplasia by retinoids

<table>
<thead>
<tr>
<th>Organ</th>
<th>Species</th>
<th>Retinoid</th>
<th>Route</th>
<th>Carcinogen</th>
<th>Ref.</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Mouse</td>
<td>Retinoic acid</td>
<td>Topical</td>
<td>UV</td>
<td>149, 150</td>
<td>a</td>
</tr>
<tr>
<td>Bladder Cheek pouch</td>
<td>Rat</td>
<td>HER</td>
<td>p.o.</td>
<td>BBN</td>
<td>142</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>Hamster</td>
<td>Retinyl palmitie</td>
<td>Topical</td>
<td>DMBA</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Mammary gland</td>
<td>Mouse</td>
<td>Retinyl acetate</td>
<td>p.o.</td>
<td>Hormone</td>
<td>152</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>Rat</td>
<td>Retinyl palmitie</td>
<td>p.o.</td>
<td>MNNG</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>10T½ fibroblast</td>
<td>Mouse</td>
<td>Retinoid acid</td>
<td>Topical</td>
<td>in vitro</td>
<td>MCA</td>
<td>154</td>
</tr>
</tbody>
</table>

* Enhancement associated with repeated exposure to carcinogen; retinoids will inhibit 2-stage carcinogenesis (Table 2).
* HER, 2-hydroxyethylretinamide; BBN, butyl-4-hydroxybutylnitrosamine; MNNG, N-ethyl-N-nitro-N-nitrosoguanidine; MCA, 3-methylcholanthrene.
* Could result from local irritation since p.o. 13-cis-retinoic acid will inhibit at this site (86).
* Enhancement seen only in mice fed initially toxic dose of retinoid.
* Hormone-induced tumors; retinoid-treated groups showed enhanced hormone response of uterus and adrenals.
/ Low tumor incidence, vitamin A-free group consumed less and weighed less than retinoid-treated groups; caloric restriction itself may reduce incidence in control group.
ing reduction in weight gain. This mechanism would also serve to explain how selenium is capable of also inhibiting viral carcinogenesis and the growth rate of some transplanted tumors (for review see Ref. 169).

Epidemiological Studies. Although the epidemiological literature on selenium and cancer is not extensive, recent interest in the anticancer potential of this trace element has led to a number of reports which are summarized in Table 6. Most of the correlational studies found inverse associations between selenium and cancer of a variety of sites, although there was some evidence for positive associations as well (173,180). These studies were somewhat limited by the indirect nature of the measurements in certain instances (170–173, 180) and by the difficulty in establishing meaningful values for intakes of this element. The case-control data are also suggestive of a protective effect, but the numbers of cases to date preclude meaningful conclusions for specific cancer sites. Such analyses are also limited, however, by variations over time in the serum levels within individuals and by the effects of other trace minerals, particularly zinc (179), on selenium levels.

α-Tocopherol (Vitamin E)

Experimental Studies. Few studies have been conducted to evaluate the role of this lipid phase antioxidant in experimental carcinogenesis. Its potential role is, however, supported by the hypothesis that cellular damage produced by active oxygen contributes to the promotional phase of carcinogenesis (188) and that antioxidants such as α-tocopherol can protect against this damage (189). Additionally, α-tocopherol has been shown to inhibit endogenous nitrosation reactions leading to the formation of carcinogenic nitrosamines (for review see Refs. 190 and 191), implying that if nitrosation is a determinant of human cancer, then α-tocopherol should be protective. Additional suggestive evidence for the protective role of α-tocopherol in human malignancy comes from the observation that administration of α-tocopherol and ascorbic acid to volunteers on Western diets causes dramatic reductions in fecal mutagenicity (24). Several pilot studies to test the association between fecal mutagens and subsequent colon cancer as influenced by these
antioxidants are currently under way (see Table 9).

Early reports of inhibitory actions of this compound on tumors induced by polycyclic aromatic hydrocarbons (192, 193) have not, in general, been substantiated by later studies (for review see Ref. 194), although a recent report has shown that topical application to DMBA-treated hamster buccal mucosa can lead to a reduction in tumor yield (195). In the DMBA rat mammary carcinoma model, while α-tocopherol was not active alone, it was shown to potentiate the antitumor effects of selenium. Treatment was accompanied by a decrease in the lipid peroxidation state of the target mammary tissue and liver (166). A study of dimethylyldrazine-induced colon carcinomas in rats concluded that a diet high in α-tocopherol reduced the number but not the incidence of tumors (196).

Epidemiological Evidence. Because vitamin E is an antioxidant, there is growing interest in its potential to inhibit carcinogenesis. To date, few epidemiological investigations of the role of this nutrient in the risk for cancer have been reported. Vitamin E is widely distributed in foods, particularly in vegetable oils, the consumption of which is difficult to quantify by the diet history method. Thus, it is not surprising that the reports on this nutrient are all based on assays of vitamin E levels in serum. As seen in Table 7, most of these studies are based on prospective cohort data and the results are mixed. Of the five cohort studies, three found no association of vitamin E serum levels with any of the sites examined (29, 129, 131), and one of the two which did find an inverse relationship reported opposite results for men and women (134). Since vitamin E is carried in the lipid fraction of the blood and shows significant correlations with lipid levels (29), some of these discrepancies may reflect inadequate control for blood lipid levels. Further, both Willett et al. (177) and Salonen et al. (134) have found that low levels of vitamins A and E appear to enhance the risk associated with low levels of selenium, suggesting that results based on assessments of any of these nutrients alone could be misleading.

Other Antioxidants

There is considerable evidence that liberation or generation of activated oxygen species [hydrogen peroxide, superoxide anions (O$_2^-$), hydroxyl radicals ('OH), etc.] within the cell is highly damaging and may directly (by DNA base modification) or indirectly (by lipid peroxidation among other mechanisms) contribute to carcinogenesis (for a review see Ref. 188). Agents which can act as alternative substrates (e.g., synthetic antioxidants such as BHT, dietary antioxidants such as β-carotene, ascorbic acid, or α-tocopherol) can experimentally reduce cancer incidence. Furthermore, it can also be shown that the enzymatic conversion of the superoxide anion to water protects against carcinogenesis. However, the experimental systems are in general highly defined, and the use of antioxidants or of procedures reducing oxidative damage has shown only limited usefulness in whole body studies.

It is not clear in many instances, however, if these compounds are indeed acting as antioxidants. Thus, the phenolic antioxidants BHT and butylated hydroxyanisole appear to inhibit carcinogenesis by an alteration in metabolic activation, not by their antioxidant properties (57, 58). β-Carotene, which figures prominently in the epidemiological literature as a negative modulator of carcinogenesis, could owe much of its effects to its provitamin A activity rather than its properties as an antioxidant, while ascorbic acid has been well established as a chemopreventive agent only in the special case of blocking nitrosamine formation. Its effects in a defined in vitro system of mouse fibroblasts were on late stages of carcinogenesis (27), possibly by virtue of its effects on fibroblast differentiation.

The experimental and epidemiological evidence for the role of antioxidants in the prevention of cancer shows numerous inconsistencies, making it difficult to draw firm conclusions for their potential as chemotherapeutic agents. Nevertheless, there is a strong rationale for their potential protective effect. It may be that these agents act by common mechanisms and that analysis of single agents may be misleading, as is suggested by the apparent interactions of selenium and α-tocopherol in both animal and human studies.

Other Potential Chemopreventive Agents

Antiinflammatory Agents. Both steroidal and nonsteroidal antiinflammatory agents are potent inhibitors of two-stage (DMBA-TPA) tumorigenesis of mouse skin. The potency of steroids as tumor inhibitors parallels their potencies as antiinflammatory agents, implying a mechanistic linkage (74). Indomethacin has been reported to reduce the incidence of carcinoma in carcinogen-treated rat colon (197); however, the activity of these agents at other sites has received little attention. Because of these limitations, the lack of epidemiological data that might suggest activity, and the appreciable side effects expected of these agents, human studies are not, to our knowledge, specifically planned. It should be noted that the United States physician study of β-carotene was integrated into a study of low dose aspirin as a protective agent against cardiovascular disease. The study design will allow any cancer chemopreventive effects of aspirin to be evaluated.

Protease Inhibitors. Protease inhibitors will inhibit two-stage carcinogenesis in mouse skin by an effect on the promotional phase (198) and will also inhibit neoplastic transformation induced by chemical and physical agents in 10T½ cells, again during the promotional phase of carcinogenesis (199). In other studies, diverse natural and synthetic protease inhibitors will partially inhibit dimethylyldrazine-induced colon cancer (200) and spontaneous liver cancer (201) in mice.

The mode of action of these compounds is not well understood. Their action in vivo has been proposed to be due to a decrease in the utilization of protein due to impaired digestion (198), but clearly this cannot explain the in vitro results. The

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**Table 7 Summary of epidemiological studies of vitamin E and cancer risk**

<table>
<thead>
<tr>
<th>Findings</th>
<th>Cancer site</th>
<th>Refs. showing the association</th>
<th>Refs. not showing the association</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower serum vitamin E levels in cases than in controls</td>
<td>Lung</td>
<td>130</td>
<td>29, 131</td>
<td>Male subjects only</td>
</tr>
<tr>
<td>Cohort studies</td>
<td>Stomach</td>
<td>130</td>
<td>29, 131</td>
<td></td>
</tr>
<tr>
<td>Lower prediagnostic serum vitamin E levels in cases than in noncases</td>
<td>Lung</td>
<td>130</td>
<td>29, 131</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stomach</td>
<td>127</td>
<td>131</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Colorectum</td>
<td>134</td>
<td>134</td>
<td>Male subjects only</td>
</tr>
<tr>
<td></td>
<td>Bladder</td>
<td>134</td>
<td>134</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Breast</td>
<td>134</td>
<td>134</td>
<td></td>
</tr>
<tr>
<td></td>
<td>General</td>
<td>134</td>
<td>134</td>
<td></td>
</tr>
</tbody>
</table>

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3020
toxicity of these compounds has received little attention, though they have been shown to be potent inhibitors of protein synthesis (for review see Ref. 202), and to inhibit liver lysosomal protein degradation (203). If the in vivo effects depend upon effects other than inhibition of protein utilization, which can be achieved more efficiently by diet, then it would appear likely that inhibition of protein degradation would be accompanied by significant toxicity that would mitigate against their use in humans.

No epidemiological studies have specifically addressed the role of protease inhibitors in cancer. However, the suggestion has been made that the low cancer risk demonstrated in vegetarians who consume diets rich in seeds, a major source of protease inhibitors, could be due to this component of the diet (204). Clearly, however, there are many other variables distinguishing this population group.

Clinical Aspects of Chemoprevention

Considerations for Clinical Research in Chemoprevention

In this section we will examine criteria for epidemiological, laboratory, and clinical data which should be considered during the planning stage of a chemoprevention trial. Because the conduct and design of an interventional trial contrast markedly with those of a therapeutic trial and because interventional trials are of recent introduction, we will also discuss the major components of such a trial, as well as the practical and ethical issues that must be confronted prior to commencement.

As discussed in the previous section of this paper (see Tables 1, 3, 6, 7), numerous epidemiological studies suggest that dietary factors are important in cancer pathogenesis, although the specific components responsible have not clearly been identified (13, 205). Also discussed were certain general principles of carcinogenesis and the large number of laboratory studies with defined agents which have clearly demonstrated that the carcinogenic process can be blocked both in vitro and in vivo. An important but often neglected implication of these findings is that carcinogens and inhibitors of carcinogenesis are species, tissue, organ, dose, and timing specific. This observation implies that even if laboratory studies are highly suggestive of a beneficial effect, only intervention trials in humans with specific pathological alterations will provide definitive answers.

A number of different types of prevention studies can be considered, a topic which we have discussed in detail elsewhere (206, 207). These include primary, secondary, and tertiary interventions. As defined here, primary intervention corresponds to primary prevention in the classical sense: prevention of exposure before it occurs. Examples would include “don’t smoke,” “use sunscreen,” “lower fat in your diet,” are generally prescriptive in nature and would not involve active chemoprevention. Secondary intervention involves the use of an agent to prevent neoplasia resulting from carcinogen exposure or, in the case of ascorbic acid, from carcinogen formation. Familiar examples would include use of an inhibitor (e.g., retinoids) or dietary supplement (e.g., β-carotene, vitamins A and C) in smokers, asbestos workers, or aniline dye workers. Tertiary intervention corresponds to use of an agent in individuals with already established preneoplasia, who do not yet have cancer. These include individuals with such conditions as dysplasia of the bladder, cervix, esophagus, or lung or adenomatous colonic polyps. There is a narrow distinction between intervention in preneoplasia and adjuvant therapy of early or residual disease with antiproliferative agents, such as antiestrogens in breast cancer. On mechanistic grounds, we have excluded these latter agents from consideration.

The simplest and most commonly used definition of preneoplasia includes only those conditions for which classical histological changes for a precursor can be shown. Preneoplastic conditions or tendencies can be defined for most tissues. Easily measured and well-known examples include cervical dysplasia, leukoplakia of the oral cavity, squamous metaplasia of the lung, and adenomatous polyps of the colon. A (chemo)prevention definition of preneoplasia is considerably broader and, in addition to histologically abnormal tissues, probably should include tissues which appear completely normal but which are altered in some way predisposing them to neoplasia (e.g., a hereditary change, or exposure to an initiator). With advances in molecular and cell biology, earlier and earlier stages of preneoplasia are being defined. With time, we may well actively intervene at the genetic level using “molecular prevention.” Preneoplasia represents a spectrum of increasing risk in which the incidence of cancer transformation increases and the potential success for preventive intervention decreases.

Different groups of individuals can be considered for intervention trials and the choice will markedly affect the design of that trial. For example, a chemoprevention trial for patients with a genetic or familial predisposition, at high risk for subsequent serious cancer (e.g., familial polyposis, dysplastic nevus syndrome), will be considerably different than a trial for patients at low risk for subsequent cancer (e.g., one prior colonic polyp in a middle aged individual, or a certain number of sun exposure hours). A potent agent which may be appropriate on theoretical and scientific grounds for both high and low risk individuals may well not be acceptable for low risk individuals after practical and ethical issues are considered because of the potential for side effects.

Criteria for Proposing an Intervention Trial

In addition to consistent and supportive epidemiological and laboratory evidence, a number of other specific items also should be considered in the development of a particular trial. These include (a) choice and dose of agent and alternative therapies, (b) the general feasibility of the trial and risk reduction estimates, (c) design of the trial, (d) feasibility of recruitment of the required numbers of subjects, (e) follow-up and compliance, (f) unexpected side effects, (g) measurement(s) of outcome (primary, secondary, and tertiary), and (h) risk/benefit to the individual and cost/benefit to society.

Choice and Dose of Agent. The choice of agent for a particular intervention may appear obvious from laboratory and epidemiological studies. However, extrapolation to the human situation may be much more difficult than initially postulated. For example, as discussed earlier, epidemiological data suggest that “vitamin A” or “carotenoid” content of the diet may be inversely related to the incidence of many cancers, particularly lung cancer. This finding suggests that supplementation with β-carotene or vitamin A would be reasonable. However, the important factor may not be “vitamin A” or “carotenoid” at all, but some other factor associated with it in foods.

The choice of a proper dose is even more difficult. In a trial in which the effect on preneoplasia is measured, it would seem reasonable that limited, closely monitored cancer control phase II toxicity and efficacy studies be performed before a large randomized trial is pursued, an approach which has been carefully undertaken for cervical dysplasia, where pathological assessment can be performed (208–210). The choice of a dose for
intervention trials in which changes in an intermediate end point cannot be measured is even more difficult. The dose probably should be just below that at which side effects (i.e., a measure of biological effect) occur. Choosing a dose which produces no evidence of short-term biological or side effects would seem to risk dooming a study to certain failure unless significant elevations of the compound can be measured in the serum or target tissue. On the other hand, failure to adequately test an agent for side effects before use in large scale trials invites disaster. A recent example was the planned study of a new clinically untested retinoid (4-hydroxyphenylretinamide) for the prevention of human bladder and breast cancer, based on a limited number of promising animal studies (81, 211, 212), but no human toxicity. Just before these large trials were to begin, potentially severe and unexpected cutaneous toxicities were detected in patients receiving the compound for acne, and the prevention studies have been postponed indefinitely.

**Trial Feasibility and Risk Reduction Estimates.** A large number of different trials have been proposed, but only a few will prove to be practically feasible because of the large number of cases required. Approximations of risk reduction are frequently overestimated; therefore, initial accrual of subjects into the study may be unrealistically low, assuring no definitive results, very long trials, or both. Kuller (213) has recently provided a particularly useful review of some obvious problems with risk reduction estimates in prevention trials. These include an overestimation of the cancer incidence rate in the control group, because both groups will tend to improve their diet and reduce undesirable behaviors (e.g., smoking) that contribute to cancer risk, and an unexpectedly long lag period to reduction in risk from start of therapy. Since all risk reduction estimates for intervention trials are necessarily based on insufficient data (which are very crude at best), the actual number of subjects entering a trial should probably be at least twice the worst case estimate. A recent instructive situation has been the planned trial of reduction in dietary fat and its effect on breast cancer. Initial estimates 3 years ago indicated that 6,000–10,000 subjects would be required; current projections suggest 18,000–27,000 subjects as the target.3

**Design of the Trial.** Because chemoprevention protocols, particularly those involving vitamins or micronutrients, are essentially nontoxic, the design of a chemoprevention trial may be very different from the usual design of a chemotherapy trial. A number of design options need to be considered, a subject particularly well discussed by Prentice (214). In addition to randomized Phase III investigations and Phase II randomized trials in controlled populations, the case-control-within-a-cohort approach and utilization of factorial designs have considerable advantages. Factorial design, whereby two or three agents may be evaluated separately and in combination (215), is widely utilized in biological research as an efficient method of asking multiple questions with limited resources.

**Feasibility of Recruitment.** Once the number of subjects required has been chosen for the trial, feasibility of accrual to the study should next be shown. The general sense of the study should be considered first. A study of skin cancer prevention in the Southwestern or Southeastern United States would appear reasonable; however, such a study in Alaska would probably take forever. More difficult decisions surround more subtle issues, such as with the use of a compound to reduce the risk for developing lung cancer in smokers. Identification and accrual of these patients into a prevention study would seem to be easy. This has not been the case, and considerable thought must go into recruitment to assure success (213, 216).

Unlike approximations of risk reduction, projected patient accrual can be accurately estimated using careful planning. The general approach to determine whether an adequate number of individuals exists for a trial has been to perform a pilot or simulated recruitment. Potential subjects are identified from insurance company roles, physicians' records, directed public relations campaigns, or other sources. Initially, potential subjects are anonymously contacted, interest is determined, and questionnaires are sent to determine eligibility. Subjects are then contacted, detailed eligibility and exclusion checklists are completed, and (optimally) the eligible subjects are given consent forms. From various studies, only 10–25% of potentially available (and expected) subjects will actually be eligible and choose to enter into a prevention trial.

**Follow-up and Compliance.** Compliance (or adherence) presents the next serious obstacle to a successful trial. Short-term and long-term compliance present serious problems for the investigator, both of which can be measured by the use of pill packs (blistered), questionnaires, or measurement of relevant fecal, urine, or serum metabolites. The problem of short-term noncompliance can be minimized by the use of a 3-month run-in period, in which all participants are placed on placebo before randomization occurs. In general, 10–15% of subjects fail to comply and are lost to the study. However, they are lost before randomization; therefore, power estimates are unaffected. Long-term noncompliance presents a much more serious problem for data analysis, because subjects have already been randomized. Thus, all reasonable attempts must be utilized to assure compliance, a subject for which the cardiovascular literature provides many useful guidelines (217). Long-term compliance should be considerably better for a group of subjects at very high risk for a serious internal malignancy taking a benign agent than for a group at very low risk for cutaneous cancer taking an agent with many side effects.

**Unexpected Long-Term Consequences.** Interactions of the trial itself on its outcome should be expected. Important lessons from the MRfit (Multiple Risk Factor Intervention Trial) study should be applied to cancer prevention (218–221). In this trial, subjects were identified by the presence of smoking, hypertension, or hypercholesterolemia and classified for risk for coronary heart disease. Patients were randomized to a usual care group, in which only annual follow-up was done, and to a special intervention group in which risk reduction education and intervention were given. At the end of the trial, there was a significant risk reduction in both groups, but there was no significant difference between the two groups for coronary heart disease events. Surprisingly, in the usual care group, smoking, blood pressure, and cholesterol levels were all decreased from base line. Of great interest was that the use of antihypertensives in the control group had increased from 19 to 47%. These results were attributed to three basic retrospectively identified factors: Factor 1, the behavior of the usual care group was favorably altered, probably due to increased awareness by both the subjects and their physicians; Factor 2, some aspects of the intervention program had a deleterious effect on mortality; and Factor 3, the statistical methods were not appropriate. Factor 1 will almost certainly have an impact on cancer prevention studies which use compounds readily available to the public; these include all studies which use vitamins, micronutrients, fiber, or changes in diet as an intervention strategy. Whether some agents will adversely affect outcome in chemoprevention studies is not known, but we must be alert to the possibility.

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3 P. Greenwald, personal communication.
Measurements of Outcome. Assessment of results may be prolonged and difficult. In only a few situations in which the incidence of cancers is measured will enough of these primary end points be generated to make possible conclusions as to the success or failure of the intervention within 5–10 years. For diseases in which the fate of a precancerous lesion can be easily followed (e.g., oral leukoplakia or cervical dysplasia), regression of the lesion can be considered an important secondary intermediate end point and preliminary results can be obtained rapidly. However, most primary end points may well take decades to reach, so it is important that intermediate end points be identified and quantitated. In this report, we define the primary end point in cancer chemoprevention trials as a reduction in cancer incidence, the secondary end point as a reduction in incidence or severity of a precancerous lesion, and the tertiary end point as a change in a biological factor predisposing to cancer. Some examples are discussed here for colon cancer.

A valid secondary end point related to colon cancer is the appearance of adenomatous colon polyps, for which there is considerable evidence that this lesion is a true precursor (222). Since close to 50% of individuals over 50 years old eventually develop polyps, the incidence of this lesion would be sufficient to obtain risk reduction estimates in a meaningful time frame. If subjects are selected who have had an adenomatous colon polyp removed within the prior 12 to 24 months, the subsequent recurrence of polyps can be followed as a convenient end point. Since the incidence of precancerous lesions is high, decisions about the efficacy of an intervention on a number of potential tertiary end points could also be measured. These include fecal mutagens, stool composition, and stool weight. Whether changes in these tertiary parameters will accurately predict the subsequent development of cancer is unknown and would be tested in the trial. The development and assessment of such markers will be extremely important for the design and long-term success of chemoprevention studies in human cancer.

Risk/Benefit Ratios. The risk and benefit to the individual will need to be considered in light of the disease being prevented and the side effects of the agent being used. Certainly, trials using low doses of vitamin A and C will be of low risk and potentially of great benefit to patients with familial polyposis. The use of these compounds at high doses in subjects with one prior polyp may or may not be warranted and may need to be carefully considered even in patients with familial polyposis and even if the subjects are followed carefully and/or efficacy was demonstrated in a Phase II trial. Many other examples of different at-risk populations can be given.

Economic Aspects of Cancer Prevention

Weinstein (223) has considered cost-effective priorities for cancer prevention in detail elsewhere. In his analysis, the cost to society per life saved for the bioassay for carcinogenic potency of a widely used but untested chemical, p-dichlorobenzene, was compared to the cost of the current intervention trial with β-carotene. Assuming both tests were positive, i.e., p-dichlorobenzene is determined to be carcinogenic and is partially removed from the marketplace and β-carotene is found to reduce cancer rates by 15%, it was calculated that the cost per life saved for the β-carotene study was only about 1% of the cost per life saved from implementing the results of the carcinogenesis assay. This calculation furthermore ignored the economic costs of removing or replacing p-dichlorobenzene. Similar calculations showed that the cost of active prevention in the general population would compare favorably with currently accepted costs of health care screening.

There seems little doubt that, if chemopreventive intervention works, it will be highly cost effective and ethically a far more desirable means of reducing mortality than treatment. However, we have no proof as yet that intervention will work in practice, and many problems lie in the way of effective implementation and require research. Not least among these is the daunting cost of detailed toxicity monitoring required in the initial trials. In a time of limited resources, how do we most effectively and humanely allocate our efforts?

Innumerable specific questions can be asked about cost-effective priorities for cancer prevention. Some include: Should research support for the treatment of advanced non-small cell lung and other untreatable cancers be reallocated to prevention of these diseases? Should prevention trials target well-defined precancerous condition existing in small populations at high risk or large populations at low risk? How do we educate to change behavior? Do we emphasize prevention and health and concentrate on children or do we advocate prescriptive practices for adults? We have known for over 20 years that smoking is harmful, and yet society has not dealt effectively with this problem. If we determine that fiber is a good preventive addition, and fat contributes to cancer risk, can we deal effectively with the meat, dairy, and restaurant industry? If fiber supplementation is widely adopted, will society be willing to double our sewage capacity? Can we afford to? What will be the continued source of funding for these investigations which may last 5 to 20 years? Can they survive the usual peer review? Is it ethical to interrupt a major clinical trial in the middle because of lack of funds? These issues cannot be resolved in this article but clearly emphasize that cancer prevention and control efforts will require active input from a wide variety of disciplines usually not involved in cancer research, including nutritionists, communications experts, behavioral scientists, and health policy decision makers.

Review of Past Trials

A listing of completed trials or early results on trials which have been reported is given in Table 8. In general, these studies were reports on a small number of patients or were preliminary results of larger studies. Nevertheless, a review of these results is informative.

Skin cancer has been the subject of most studies (238–243). Four trials have been performed in patients with single or multiple actinic keratoses. The randomized trial of Moriarty et al. (242) using p.o. etretinate is particularly encouraging, since regression in 37 of 44 patients with actinic keratoses was demonstrated in the treatment group and in only 2 of 42 controls. Six trials of synthetic retinoids against established basal cell carcinomas have been reported (238, 243). For all lesions, a complete response of 18% was recorded in 316 lesions, with an additional 61% of lesions showing a partial response. These studies in toto indicate that retinoids are effective in suppressing known precursors and low-grade skin lesions, thereby establishing a good clinical basis for intervention trials for nonmelanomatous skin cancer in a prevention setting. A substantial number of studies have examined the effect of oral and topical retinoids on preneoplastic and proliferative conditions of the oral cavity (231–237). Two Phase II studies of topical isotretinoin showed regression of leukoplakia in 10 of 16 subjects (231, 232). In a larger randomized study (but without a control group) trans-retinoic acid, isotretinoin, and etretinate all produced regression of leukoplakia, which per-
sisted for several months (233, 234). A well-designed double-blind trial of oral isotretinoin showed regression in the majority of patients with leukoplakia compared to only a small percentage in the control (235), a result which was highly significant. In a unique placebo-controlled Phase III study, both vitamin A and β-carotene but not canthaxanthine, a carotenoid without provitamin A activity, reduced micronuclei in exfoliated cells from chronic betel nut chewers (137). These studies clearly indicate that retinoids can suppress or reverse preneoplastic lesions in the oral cavity. Two Phase II studies of oral isotretinoin against laryngeal papillomatosis also showed that this lesion can be significantly suppressed and a prolonged response obtained in 50% of patients (236, 237).

Two groups are currently studying the effect of topical retinoids against cervical dysplasia. One group has used trans-retinoic acid delivered via a cervical cap and has performed Phase I and II studies (208–210). In the latter study, complete regression of cervical dysplasia was demonstrated in 10 of 18 patients. Topical retinyl acetate has also been tested and has been found feasible to apply, but no efficacy data have yet been reported (227).

A Phase II study in normal subjects indicates that ascorbic acid plus α-tocopherol can reduce fecal mutagens if they are elevated before therapy (24). Two studies of intervention therapy for precursors to colon cancer have been reported (228, 229). In 8 patients with familial polyposis, ascorbic acid produced complete regression of lesions in 2 patients and a partial response in 3, although the durability of the responses was not recorded (228). A randomized double-blind trial of ascorbic acid (3 g/day) in 49 patients with polyposis coli demonstrated a reduction in polyp area after 9 months of treatment, although no therapeutic benefit was apparent (229).

In 1981, Newmark et al. (245) hypothesized that calcium played an important role in colon cancer development. In a 19-year prospective study in men, risk of colorectal cancer was inversely correlated with dietary vitamin D and calcium (246), although a more recent study utilizing a different study population failed to show this association (247). Preclinical studies suggest that adequate calcium is necessary for suppression of proliferation (248). A study of the frequency and distribution of proliferating epithelial cells lining colonic crypts in 10 subjects at high risk for colon cancer indicates that oral calcium supplementation induces a quiescent state, similar to that observed in subjects at low risk (249). These observations provide a considerable rationale for an intervention trial of calcium supplementation in patients with colonic polyps.

The effects of etretinate on the recurrence of bladder cancers have been studied in two Phase II investigations (224, 225). In
one trial, therapy was only for 4 to 8 months and no differences due to the outgrowth of nonresponsive preclinical tumors, as discussed earlier. In a second study, therapy was continued indefinitely, and after 8 months, there was a highly significant difference in complete plus partial recurrence rate in control versus treated groups (225).

In an unusual trial, the effect of etretinate was measured on bronchial metaplasia in actively smoking individuals (231). Using a "metastatic index" derived from the results of serial biopsies, the authors found that etretinate significantly reduced the incidence of metaplasia. Confirmation of these results will obviously be important. In a controlled double-blind study of α-tocopherol, no difference was demonstrated in mammary dysplasia between the control versus treated group (226). However, therapy was continued for only 2 months.

The initial "prevention" studies indicate that nonmelanoma
tous cutaneous cancers and oral cavity lesions are responsive to retinoids. Definitive large-scale carefully stratified, randomized, double-blind Phase III studies are needed to confirm these intriguing observations. Trials in other organ sites are too limited for conclusions and indicate that more Phase II studies are needed. These investigations do suggest, however, that prolonged therapy may be necessary for success.

Review of Current Trials

A symposium on issues germane to the development of cancer chemoprevention trials has recently been published (250). A listing of current major intervention trials is provided in Table 9; follow-up has been too short to allow even preliminary conclusions. Two trials are directed to general cancer prevention, while the remaining 21 studies concentrate on 5 major target sites. Different inhibitory agents are being used. Nine of these would be considered as dietary supplements and include β-carotene, vitamins A (retinyl palmitate or retinol), B6, B12, C, E, folic acid, selenium, and wheat bran. Only all-trans- and 13-cis-retinoic acids can be considered synthetic, although small amounts of the compounds are found naturally. The rationale behind the use of wheat bran was considered outside the scope of this paper, while data supporting the use of vitamin B6, B12, and folic acid were considered too preliminary for inclusion. The studies in collaboration with the Chinese involve individu
al contaminated with multiple dietary deficiencies and were also considered outside the scope of this paper. Although for the most part the studies are randomized, a major confounding issue for studies involving dietary components is the potentially increasing use of these compounds by the control group.

Future Prospects

Absent from organ sites targeted for additional chemopreven
tion are several sites for which data suggest that intervention would be worthwhile. Epidemiological and experimental evidence suggest that retinoids would be effective against carcino
mas of the bladder and head and neck. Results of small clinical trials support this view. Experimental studies of dietary antioxidants in mammary carcinogenesis and limited clinical studies with calcium in the colon also support the further evaluation of these agents at these sites. An orderly sequence of development for new chemopreventive agents is under de
velopment. Potential in vitro and animal in vivo models have been proposed and a chemoprevention drug discovery network has been established. The results do, however, clearly indicate that preclinical studies will only be generally and not specifically applicable to humans. Whether these differences are intrinsic or represent pharmacological or pharmacokinetic differences remains to be determined. One strategy which should be pur
sued is the identification of in vitro human preneoplastic model systems (e.g., polyps, dysplasias from various sites). Another approach that might be developed would include the testing of promising agents against preneoplastic or metaplastic disease in a number of easily monitored sites (e.g., cervix, oral cavity, skin). A positive result would encourage further development.

Table 9 Current clinical chemoprevention intervention studies

<table>
<thead>
<tr>
<th>Target site/organ</th>
<th>Target risk/group</th>
<th>Inhibitory agents</th>
<th>Cancer control phase</th>
<th>Location</th>
<th>Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>Cervical dysplasia</td>
<td>trans-Retinoic acid</td>
<td>III</td>
<td>U/Arizona, AZ</td>
<td>E. Surwit</td>
</tr>
<tr>
<td>Cervix</td>
<td>Cervical dysplasia</td>
<td>Folic acid</td>
<td>III</td>
<td>Hutchinson, WA</td>
<td>J. Chu</td>
</tr>
<tr>
<td>Colon</td>
<td>Familial polyposis</td>
<td>Vitamins C and E and wheat bran</td>
<td>III</td>
<td>Memorial, NY</td>
<td>J. DeCosse</td>
</tr>
<tr>
<td>Colon</td>
<td>Familial polyposis</td>
<td>Calcium carbonate</td>
<td>III</td>
<td>U/Illinois, IL</td>
<td>M. Lipkin</td>
</tr>
<tr>
<td>Colon</td>
<td>Adenomatous polyps</td>
<td>β-Carotene</td>
<td>I (epidemiology)/III</td>
<td>Dartmouth, NH</td>
<td>E. Greenberg</td>
</tr>
<tr>
<td>Colon</td>
<td>Adenomatous polyps</td>
<td>β-Carotene, vitamins C and E</td>
<td>III</td>
<td>Dartmouth, NH</td>
<td>T. Colacchio</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Dysplasia patients</td>
<td>β-Carotene, Centrum</td>
<td>III</td>
<td>NCI, MD; Chinese Academy</td>
<td>J. Li/P. Taylor</td>
</tr>
<tr>
<td>Esophagus</td>
<td>General population/high risk</td>
<td>Multiple vitamins, minerals</td>
<td>III</td>
<td>NCI, MD; Chinese Academy</td>
<td>J. Li/P. Taylor</td>
</tr>
<tr>
<td>Lung</td>
<td>Chronic smokers</td>
<td>Vitamin B12, folic acid</td>
<td>III</td>
<td>U/Alabama, AL</td>
<td>D. Heimburger</td>
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<tr>
<td>Lung</td>
<td>Asbestososis</td>
<td>β-Carotene, retinol</td>
<td>III</td>
<td>Hutchinson, WA</td>
<td>G. Ommen</td>
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<tr>
<td>Lung</td>
<td>Cigarette smokers</td>
<td>β-Carotene, retinol</td>
<td>III</td>
<td>Hutchinson, WA</td>
<td>M. Henderson/G. Goodman</td>
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<tr>
<td>Lung</td>
<td>Middle age smoking males</td>
<td>β-Carotene, vitamin E</td>
<td>III</td>
<td>NCI, MD; Finland</td>
<td>NCI</td>
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<tr>
<td>Lung</td>
<td>Smoking males</td>
<td>β-Carotene</td>
<td>II (feasibility)</td>
<td>U/Pittsburgh, PA</td>
<td>L. Kuller</td>
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<tr>
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<td>III</td>
<td>Hutchinson, TX</td>
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<td>Albino (basal cell carcinoma)</td>
<td>β-Carotene</td>
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<td>III</td>
<td>Memorial, NY</td>
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<td>β-Carotene</td>
<td>III</td>
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<td>III</td>
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<tr>
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<td>III</td>
<td>U/Azria, AZ</td>
<td>F. Meykens/L. Levine</td>
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<tr>
<td>Skin</td>
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<td>13-cis-retinoic acid</td>
<td>III</td>
<td>NCI, MD</td>
<td>J. Tangrea</td>
</tr>
<tr>
<td>All sites</td>
<td>Physicians</td>
<td>β-Carotene</td>
<td>III</td>
<td>Peter Bent Brigham, MA</td>
<td>C. Hennekens</td>
</tr>
<tr>
<td>All sites</td>
<td>Dentists/nurses</td>
<td>Retinyl palmitate, sodium selenite, vitamins B6 and E</td>
<td>II (feasibility)</td>
<td>Peter Bent Brigham, MA</td>
<td>C. Hennekens</td>
</tr>
</tbody>
</table>

* U/, University of; NCI, National Cancer Institute; Memorial, Memorial Sloan-Kettering Cancer Center.
Summary and Conclusions

Prospects for Chemoprevention

We have discussed the evidence that the majority of human cancer is produced by exogenous factors to which we are exposed as a consequence of life-style, including diet, and that the initial and subsequent biochemical changes induced by these agents in human cells are qualitatively similar, if not identical, to changes induced in rodent cells by experimental carcinogens. In these rodent cells, the process of carcinogenesis can be prevented or arrested by a variety of compounds, many of which are natural components of the human diet. That cancer may also be prevented in humans is supported by epidemiological studies which have demonstrated an association between consumption of some of these compounds, particularly those with vitamin A or provitamin A activity, and decreased cancer risk. These separate lines of evidence provide strong support for the concept that the chemoprevention of cancer in humans is a realistic goal with the potential of causing significant reductions in cancer rates.

Laboratory studies have divided the process of carcinogenesis into 2 distinct phases, initiation and promotion. Antiinitiation therapy offers the greatest potential for the prevention of human cancer, since biological damage is prevented. However, many practical limitations stand in the way of implementation of laboratory findings. The opportunity to use antiinitiators in clinical trials would appear to be limited to two situations: (a) where carcinogenesis is known to be a consequence of a known major source (e.g., tobacco). This may, unfortunately, encourage tobacco use; (b) after disasters where many individuals are exposed to high-level chemical or physical carcinogens.

In contrast, the use of antipromoters in clinical trials has many advantages and represents the major thrust of current efforts. Extensive laboratory and epidemiological studies support the use of the retinoids as antipromoters in chemoprevention studies.

Extensive laboratory studies have provided us with detailed information about the process of carcinogenesis. These experimental approaches have clearly established the important principle that carcinogenesis and its inhibition is carcinogen, anticarcinogen, dose, route, schedule, tissue, and species specific. This important conclusion must not be ignored in the planning of chemoprevention trials, and while general principles of carcinogenesis apply to humans, a specific intervention derived from animal models may not have the desired effect in a clinical trial. Only carefully designed studies in humans will provide definitive information about the usefulness of a particular chemopreventive agent.

The design and implementation of a chemoprevention trial is a complex task. Careful consideration should be given to a number of factors before implementation of the trial: choice and dose of agent; experimental design; general feasibility and recruitment; risk reduction estimates; follow-up and compliance; unexpected long-term consequences; measurement of benefit and risk/benefit to the individual; and cost/benefit to society. The choice of chemopreventive agent must be matched to the particular study group. It seems necessary to study both selected populations at high risk for a specific cancer (e.g., individuals with oral leukoplakia) and large populations at overall low risk (e.g., United States physicians). In the former case, it appears ethical, as in current trials, to use a drug such as a synthetic retinoid which has a strong likelihood of efficacy but also has strong likelihood of causing appreciable side effects. In the latter case, we are limited to using drugs and doses which offer a high margin of safety. In doing so, we are most probably also limiting our chances of successful intervention.

Recommendations

The experimental data presented above and the results of early chemoprevention trials lead to the conclusion that the secondary prevention of cancer by pharmacological intervention offers an excellent potential for reducing cancer incidence. At the present state of knowledge, the retinoids possess the best combination of properties. However, in our view, significant reductions in cancer rates will ultimately depend more on primary prevention (i.e., as defined here, the elimination of exposure) than on chemoprevention per se. Thus, the public must not be lulled into complacency by overambitious claims for the prospect of chemoprevention. Modifications of lifestyle, particularly smoking cessation and dietary change, as recently recommended by several prestigious national organizations (251–254), must continue to receive the major emphasis in public awareness programs.

Little is known of the pharmacokinetics of chemopreventive agents and whether differences in tissue distribution or metabolic disposition can explain the differences in organ and species response observed. Research in this area should increase our confidence in the applicability of experimental drugs to humans and should also result in the development of drugs with improved therapeutic ratios. In this same context, additional laboratory models of carcinogenesis are required which more closely reflect human carcinogenesis, especially preneoplastic conditions.

The mode of action of demonstrated chemopreventive agents needs elaborating at the biochemical level. Success would almost certainly identify other sites for intervention and lead to improved drugs. Rational development of novel chemopreventive drugs should be encouraged and may best be achieved as a consequence of the current revolution in our understanding of oncogenes and of the carcinogenic process. Such knowledge should benefit both the prevention and the treatment of cancer.

Additional epidemiological/laboratory studies on the role of dietary fat, antioxidants, and their interactions are needed in order that more confident dietary recommendations and interventional strategies may be formulated.

Because of the protracted nature of chemoprevention trials, reliable interim end points of response need development.

Chemoprevention studies are justified when laboratory and epidemiological studies provide strong supportive evidence of a beneficial effect with minimal risk to the individual and when a coherent strategy can be developed. Examples of additional human trials which may be warranted in the near future, if current evidence is supported by the results of further research, include: bladder cancer reduction with synthetic retinoids; breast cancer reduction with antioxidants such as α-tocopherol; and colon cancer reduction with calcium.

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RATIONALE AND STRATEGIES FOR CHEMOPREVENTION OF CANCER


RATIONALITIES AND STRATEGIES FOR CHEMOPREVENTION OF CANCER


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Rationale and Strategies for Chemoprevention of Cancer in Humans

John S. Bertram, Laurence N. Kolonel and Frank L. Meyskens, Jr.


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