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Tailoring Cancer Chemoprevention Regimens to the Individual

Allan H. Conney*

Susan Lehman Cullman Laboratory for Cancer Research, Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854-8020

Abstract The present article, which is a tribute to the memory of Dr. Edward Bresnick, emphasizes the importance of environmental and life-style factors for cancer causation in the human population and points out approaches to cancer prevention. These approaches include vaccinations for the prevention of cancers that are caused by infectious agents as well as the use of cancer chemopreventive agents. The use of tamoxifen and letrozole to prevent breast cancer, finasteride to prevent prostate cancer, sunscreens or topical applications of 5-fluorouracil to prevent sunlight-induced skin cancer, and aspirin or calcium to prevent colon cancer are a few examples of cancer chemoprevention in high risk individuals and in the general population. An underdeveloped area of cancer chemoprevention is the use of combinations of agents that work by different mechanisms. It was pointed out that animal studies indicate that many cancer chemopreventive agents inhibit carcinogenesis under one set of experimental conditions but enhance carcinogenesis under another set of experimental conditions. These observations suggest that tailoring the chemopreventive regimen to the individual or to groups of individuals living under different environmental conditions or with different mechanisms of carcinogenesis may be an important aspect of cancer chemoprevention in human populations. How to tailor cancer chemoprevention regimens to the individual is an important challenge for the future. J. Cell. Biochem. 91: 277–286, 2004.
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Key words: cancer chemoprevention; cancer causation; carcinogenesis

Edward Bresnick

Ed Bresnick received his PhD degree in 1958 from Fordham University, and he joined the Wellcome Research Laboratories (Tuckahoe, NY) in 1959 to work with George Hitchings. I joined the Wellcome Research Laboratories in 1960 to work with John Burns and became good friends with Ed during these early days. We talked about science and about the affairs of the day, and we also enjoyed getting together socially on weekends—Ed with his wife Etta and me with my wife Diana. Ed's research was supervised rather closely by Gertrude Elion and George Hitchings (future Nobel prize winners), and Ed wanted a more independent position. In 1961, Ed accepted an Assistant Professor position in Harris Busch's biochemistry department at Baylor, where he rose to the rank of full Professor. In 1971, Ed went to the Medical College of Georgia as chairman of the Department of Cell and Molecular Biology, and he later chaired Departments of Biochemistry or Pharmacology at the University of Nebraska, the

Abbreviations used: TPA, 12-*O*-tetradecanoylphorbol-13-acetate; DMBA, 7,12-dimethylbenz[a]anthracene; PhIP, 2-amino-1-methyl-6-phenylimidazo(4,5-*b*)pyridine; UVB, ultraviolet B light.

This article is dedicated to the memory of Dr. Edward Bresnick—a good friend and an outstanding research scientist and teacher. A portion of this article was published earlier [Conney, 2003].

Allan H. Conney is the William M. and Myrle W. Garbe Professor of Cancer and Leukemia Research.

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*Correspondence to: Dr. Allan H. Conney, PhD, Susan Lehman Cullman Laboratory for Cancer Research, Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, 164 Frelinghuysen Road, Piscataway, NJ 08854-8020.
E-mail: aconney@rci.rutgers.edu

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University of Vermont and the Dartmouth Medical School. He also served as Director of the Eppley Institute in Omaha, Director of the Norris Cotton Cancer Center at Dartmouth, and Vice Chancellor for Research at the University of Massachusetts. In later years, Ed relinquished his administrative responsibilities and returned to the Dartmouth Medical School to work with Alan Eastman—a former student. Ed (as an Adjunct Professor at Dartmouth) would boast that he was probably the oldest postdoc in the nation.

Ed was an outstanding teacher as well as an outstanding judge and advocate of good science. He would evaluate presentations and research proposals in a critical but helpful way so as to enhance the quality of the science and of the presentation. Ed had a distinguished career as a scientist and teacher, and he also served the cancer research community and our nation as President of the American Association for Cancer Research and on many advisory and review committees for the National Cancer Institute and for other groups. Ed has done much to help in the development of young scientists and to improve our nation's cancer research program. Although Ed is greatly missed, his spirit lives on through his own research contributions, through his contributions to the cancer research community, and because of the many lives that he has touched.

Cancer Causation: Importance of Environment/Life-Style Factors

Inherited genetic mutations have been shown to have a major role in the etiology of skin cancer in individuals with xeroderma pigmentosum (mutations in the *XP* gene in combination with exposure to sunlight), in about 10% of breast cancer patients (mutations in the *BRCA 1* or *BRCA 2* gene), in retinoblastoma patients (mutations in the *Rb* gene), and in several other cancers. Environmental and life-style factors, however, are believed to play the major role in the etiology of most human cancers. Ultimately, it is the interaction between genes and environment that determine an individual's cancer risk.

Early studies. The first mention of environmental causes of cancer was by John Hill and his colleagues who described an association of the use of tobacco snuff with cancer of the nasal sinuses in 1761 [see Redmond, 1970]. This was followed a few years later by the observation of the British physician, Percivall Pott indicating a high incidence of scrotal cancer in chimney sweepers [Pott, 1775]. The recommendation by the Danish Chimney Sweepers' Guild that their members take a bath after working in chimneys resulted in a marked decrease in the risk of scrotal cancer, and this behavioral change was probably the earliest example of a cancer preventive regimen.

In the mid-1900s Richard Doll, Ernst Wynder, and their colleagues demonstrated that cigarette smoking was the major cause of lung cancer in humans, and efforts to curtail cigarette smoking were initiated and are continuing. Although these programs have met with some success, there is a need to do more to discourage cigarette smoking.

In 1981, Richard Doll and Richard Pitot estimated that about one-third of human cancer in the United States was related to tobacco smoking, another one-third to dietary factors, and about one-tenth to infectious agents [Doll and Peto, 1981]. These estimates, based on epidemiological studies available at the time, are generally in accord with more recent estimates although the proportion of cancers thought to be associated with infectious agents has increased to almost 20% worldwide (e.g., hepatitis B virus, human papilloma virus, helicobacter pylori, and others). The use of vaccines to prevent cancers caused by infectious agents has been encouraging and may be used on a broad scale in future years. Evidence for the importance of environmental/life-style factors for the majority of human cancers is given below.

Studies in migrant populations. In earlier years, people living in Japan had a high risk of stomach cancer and a low risk of colon, breast, and prostate cancer whereas people in the United States had a low risk of stomach cancer but a high risk of colon, breast, and prostate cancer. When the Japanese moved to the United States, their cancer risk became similar to that in the United States. As Japan is becoming more Westernized, its population is developing the same kinds of cancers that occur in the United States.

Changes in cancer deaths in the United States during the past 70 years. In 1930, stomach cancer was the major cause of cancer-related death in the United States whereas lung cancer deaths were rare. During subsequent years, the risk for stomach cancer decreased and the risk for lung cancer increased drama-

tically and was associated with increases in the smoking of cigarettes. About 90% of lung cancer in the United States can be attributed to cigarette smoking. The reason(s) for the dramatic decrease in stomach cancer during the past 70 years is not known with certainty but may be related to refrigeration, less need for salt as a preservative, and greater access to fresh fruit and vegetables. The marked changes in age-adjusted cancer deaths in different organs in males and females in the United States between 1930 and 1999 are shown in Figures 1 and 2. Between 1993 and 1999, the overall death rate from cancer has dropped about 6% in the United States and the cancer incidence has stabilized from 1995 to 1999 [Edwards et al., 2002]. Because of the projected future size and aging of the United States population, it is anticipated that the overall number of cancer cases in the United States will double by 2050 if the current age-adjusted incidence rate remains stable [Edwards et al., 2002]. These projections point out the urgency for identifying suitable strategies for cancer prevention.

Studies in monozygotic and dizygotic twins. In a large study on the concordance of cancer in monozygotic and dizygotic twins, it was concluded that 60–70% of the risk of breast, prostate, and colorectal cancer was related to environmental factors, and similar conclusions were reached for several other types of cancer (e.g., pancreas, bladder, stomach, and others) [Lichtenstein et al., 2000]. The percentage of monozygotic twins that developed the same kind of cancer as his/her corresponding twin by age 75 was only 13% for breast cancer, 18% for prostate cancer, and 11% for colorectal cancer (Table I). The percentage of dizygotic twins that developed the same kind of cancer as his/her corresponding twin by age 75 was 9% for breast cancer, 3% for prostate cancer, and 5% for colorectal cancer (Table I). Although the studies by Lichtenstein et al. [2000] indicated the importance of inherited/genetic factors in cancer

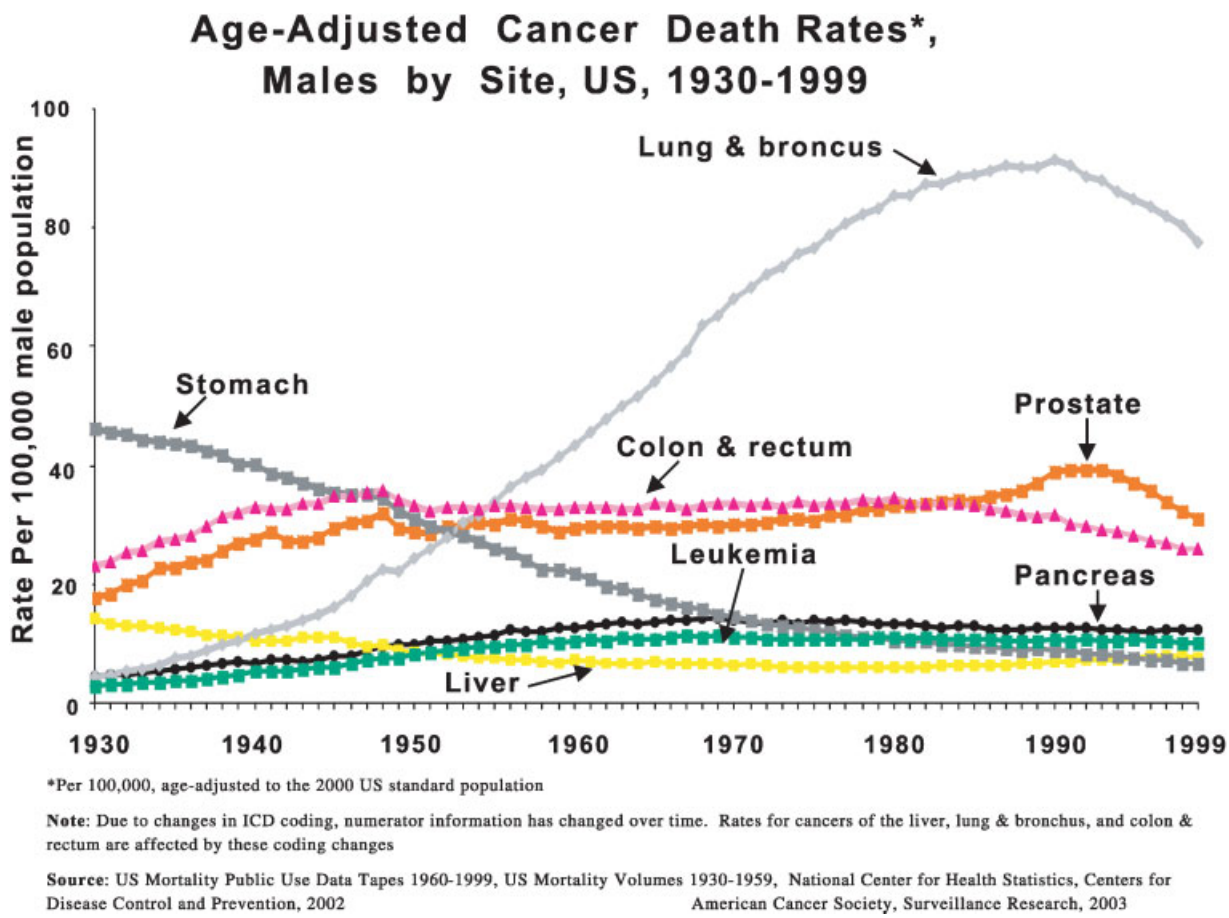

Fig. 1. Age-adjusted cancer death rates for males by site in the United States from 1930 to 1999. Obtained from the American Cancer Society, Surveillance Research, 2003.

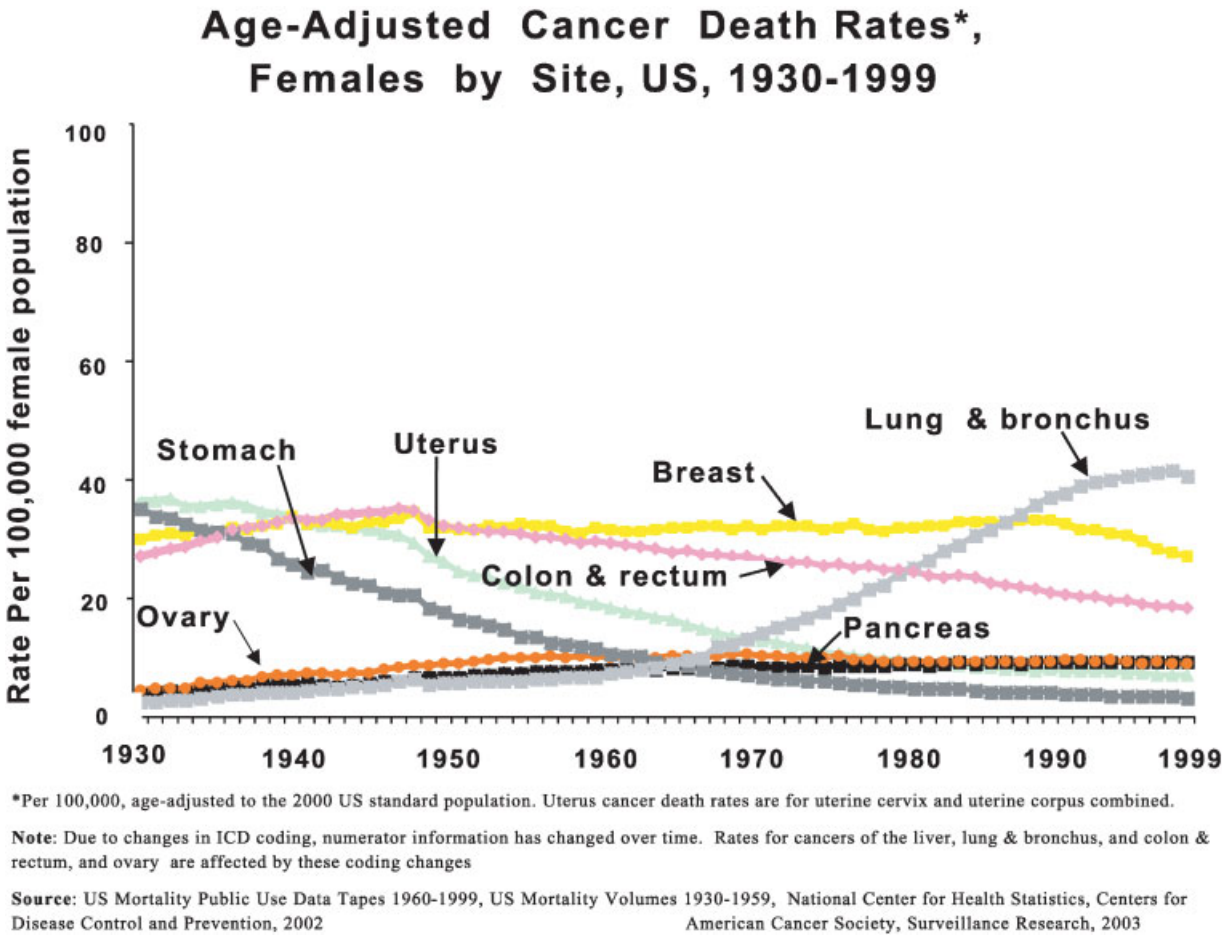

Fig. 2. Age-adjusted cancer death rates for females by site in the United States from 1930 to 1999. Obtained from the American Cancer Society, Surveillance Research, 2003.

causation, it was concluded that environmental factors are considerably more important for cancer causation in most individuals. Since both inherited genes and environmental factors play a role in cancer etiology, the importance of gene-environment interactions in cancer causation is receiving increasingly greater attention. The important role of environmental/life-style factors for the majority of human cancer provides great encouragement because it gives us the opportunity of preventing a large fraction of human cancer.

TABLE I. Absolute Risks of Colorectal, Breast, and Prostate Cancer (Concordance Rates) in Twins of an Affected Person up to the Age of 75 Years

Site of cancer	Monozygotic twins	Dizygotic twins
Colorectum	0.11	0.05
Breast (in women)	0.13	0.09
Prostate	0.18	0.03

Taken from Lichtenstein et al. [2000].

Research on Cancer Chemoprevention

The use of tamoxifen and letrozole to prevent breast cancer, finasteride to prevent prostate cancer, sunscreens or topical applications of 5-fluorouracil to prevent sunlight-induced skin cancer, and aspirin or calcium to prevent colon cancer are a few examples of cancer chemoprevention in high risk individuals and in the general population. An underdeveloped area of cancer chemoprevention is the use of combinations of agents that work by different mechanisms. Combinations of chemopreventive agents that work by different mechanisms have the potential for synergistic effects and effective action at lower dose levels and with less side effects than when single agents are used. Combinations of drugs are in wide-spread

use for antibacterial therapy, antiviral therapy, and for cancer chemotherapy. It is likely that combinations of chemopreventive agents will be used more extensively for cancer prevention in the future.

Inhibitors of Carcinogenesis in One Experimental Model may Stimulate Carcinogenesis in Another Experimental Model

Although many compounds have been shown to exert substantial chemopreventive activity in experimental animals under one set of experimental conditions, some of these compounds can enhance carcinogenesis under another set of experimental conditions. Some examples are given below.

Studies with decaffeinated green tea. Although oral administration of moderate dose levels of regular green tea or decaffeinated green tea inhibited UVB-induced carcinogenesis in DMBA-initiated mice [Wang et al., 1994], only regular green tea inhibited complete UVB-induced carcinogenesis in the absence of DMBA pretreatment [Huang et al., 1997] (Tables II and III). Oral administration of moderate dose levels of decaffeinated green tea had little or no effect on UVB-induced complete carcinogenesis, and high dose levels of decaffeinated green tea unexpectedly enhanced UVB-induced complete carcinogenesis [Huang et al., 1997] (Table III).

Studies with caffeine. Although many studies indicated inhibitory effects of caffeine administration on carcinogenesis in animals [Rothwell, 1974; Nomura, 1976, 1980, 1983; Theiss and Shimkin, 1978; Zajdela and Latarjet, 1978; Perchellet and Boutwell, 1981; VanderPloeg and Welsch, 1991; Huang et al., 1997; Hagiwara et al., 1999; Lou et al., 1999; Lu et al., 2002], some studies showed a stimulatory effect of caffeine administration on carcinogenesis [Hiroshino and Tanooka, 1979; Minton et al., 1983; Welsch et al., 1983, 1988; Nagasawa and Konishi, 1988; Hagiwara et al., 1999]. It was found that topical applications of caffeine inhibited TPA-induced tumor promotion and cigarette smoke condensate-induced tumorigenesis in mouse skin [Rothwell, 1974; Perchellet and Boutwell, 1981], and that oral or topical administration of caffeine also inhibited UVB-induced carcinogenesis in mouse skin [Zajdela and Latarjet, 1978; Huang et al., 1997; Lou et al., 1999; Lu et al., 2002]. In addition, subcutaneous injections of caffeine immediately after administration of urethane or 4-nitroquinoline-1-oxide inhibited the formation of lung tumors in mice [Nomura, 1976, 1980, 1983], and the i.p. injection of caffeine three-times a week inhibited the formation of spontaneous or urethane-induced pulmonary adenomas in strain A mice [Theiss and Shimkin, 1978]. In other studies, treatment of GR mice with caffeine in the drinking water (0.5 mg/ml) inhibited ovarian hormone-induced breast tumorigenesis [VanderPloeg and Welsch, 1991] and 0.1% caffeine in the drinking fluid inhibited the formation of PhIP-induced mammary tumors in rats [Hagiwara et al., 1999].

In contrast to the inhibitory effects of caffeine on carcinogenesis described above, administration of caffeine in the drinking water (0.25–0.50 mg/ml) increased spontaneous or DMBA-induced breast tumorigenesis in mice [Nagasawa and Konishi, 1988; Welsch et al., 1988]. In addition, treatment of rats with caffeine in the drinking water enhanced DMBA-induced breast carcinogenesis [Minton et al., 1983; Welsch et al., 1983] and PhIP-induced colon carcinogenesis [Hagiwara et al., 1999]. It was also observed that multiple topical applications

TABLE II. Inhibitory Effects of Oral Administration of Green and Black Tea on the Formation of UVB-Induced Keratoacanthomas and Squamous Cell Carcinomas in DMBA-Initiated SKH-1 Mice

Treatment	Tea solids (mg/ml)	% Mice with keratoacanthomas	No. of keratoacanthomas per mouse	% Mice with carcinomas	No. of carcinomas per mouse
Water control		97	6.33	33	0.60
Green tea	4.0	43	1.37	7	0.07
Black tea	4.4	35	1.35	4	0.04
Decaf green tea	3.6	77	1.90	17	0.17
Decaf black tea	3.9	67	1.73	17	0.20

Female SKH-1 mice (30/group) were treated topically with 200 nmol of DMBA. One week later the mice were treated with gradually increasing concentrations of tea leaf extracts as drinking fluid for 6 days and full-strength teas (1.25 g tea leaves/100 ml hot water; ~4 mg tea solids/ml) for an additional 8 days prior to and during treatment with UVB (30 mJ/cm^2) twice weekly for 31 weeks. Taken from Wang et al. [1994].

TABLE III. Effect of Oral Administration of Green Tea, Decaffeinated Green Tea, or Caffeine on UVB-Induced Complete Carcinogenesis

Experiment	Treatment	Tea solids (mg/ml)	Number of keratoacanthomas per mouse	Number of carcinomas per mouse
1	Water	—	5.75 ± 1.04	1.58 ± 0.32
	Green tea	4.0	2.21 ± 0.46[a]	0.86 ± 0.23[b]
	Decaf. green tea	3.6	4.58 ± 0.64	1.66 ± 0.30
	Caffeine	0.36	1.81 ± 0.44[a]	1.00 ± 0.20[c]
	Decaf. green tea + caffeine	4.0	2.53 ± 0.43[a]	0.57 ± 0.12[a]
2	Water	—	0.89 ± 0.24	0.93 ± 0.28
	Green tea	9.0	0.29 ± 0.09[a]	0.19 ± 0.09[a]
	Decaf. green tea	9.0	2.37 ± 0.46[a]	1.44 ± 0.24[c]

In experiment 1, female SKH-1 mice were treated with UVB (30 mJ/cm^2) twice weekly for 40 weeks, and the animals were killed 4 weeks later. Water, tea leaf extracts (1.25 g tea leaf/100 ml hot water; ~4 mg tea solids/ml) and caffeine (0.36 mg/ml) were administered as the drinking fluid until the animals were sacrificed. Each value is the mean ± SE from 24–30 mice. In experiment 2, female SKH-1 mice were treated with UVB (30 mJ/cm^2) twice weekly for 45 weeks. Lyophilized teas (9 mg tea solids/ml) were administered as the drinking fluid. Each value is from 27 to 30 mice. Values that are statistically different from the corresponding water group are indicated. Taken from Huang et al. [1997].
[a]$P < 0.01$.
[b]$P < 0.05$.
[c]$P < 0.10$.

of caffeine together with 4-nitroquinoline-1-oxide increased the tumorigenic effects of 4-nitroquinoline-1-oxide in mice pretreated with a single application of β-radiation [Hiroshino and Tanooka, 1979]. The results of these studies indicate that the effects of caffeine on carcinogenesis are complex, and whether caffeine inhibits or stimulates carcinogenesis depends on the experimental model utilized. More detailed mechanistic studies are needed to determine why caffeine inhibits carcinogenesis in some animal models and stimulates carcinogenesis in others. It is possible that ingestion of caffeine inhibits carcinogenesis in some individuals and stimulates carcinogenesis in others.

Studies with phenobarbital and indole-3-carbinol. Although chronic administration of phenobarbital together with 2-acetylaminofluorene, inhibits its hepatocarcinogenicity by enhancing metabolic detoxification, when phenobarbital is administered chronically after a short exposure to 2-acetylaminofluorene, phenobarbital is a promoting agent that enhances the formation of liver tumors [Peraino et al., 1971]. Similarly, administration of indole 3-carbinol prior to or together with certain carcinogens inhibits their carcinogenic activity [Wattenberg and Loub, 1978; Grubbs et al., 1995; Dashwood, 1998], but chronic administration of indole 3-carbinol after a hepatocarcinogen functions as a tumor promoter and enhances the formation of liver cancer [Bailey et al., 1987; Dashwood et al., 1991; Kim et al., 1997; Dashwood, 1998; Oganesian et al., 1999; Xu et al., 2001; Stoner et al., 2002]. Although epidemiology studies indicate the lack of hepatocarcinogenicity for phenobarbital in the general population, the effects of chronic phenobarbital administration during dietary exposure to a liver carcinogen such as alfatoxin B_1 or after cessation of exposure to the carcinogen may differ.

Studies with vitamin E. Although some epidemiological studies suggest that low levels of vitamin E are associated with an increased risk of cancer and supplemental vitamin E may have cancer chemopreventive effects [Knekt, 1991; Knekt et al., 1991; Gridley et al., 1992; Blot et al., 1993], other studies have failed to find an inhibitory effect of administration of vitamin E on cancer formation in human populations [Willett, 1998]. In animal studies, topical applications of vitamin E inhibited DMBA-induced complete carcinogenesis in the hamster buccal pouch [Odukoya et al., 1984], DMBA-induced tumor initiation in mouse skin [Slaga and Bracken, 1977], TPA-induced tumor promotion in mouse skin [Perchellet et al., 1985], and UV-induced carcinogenesis in mouse skin [Gensler and Magdaleno, 1991]. Although α-tocopherol was an effective inhibitor of UV-induced carcinogenesis, α-tocopherol acetate and α-tocopherol succinate were inactive [Gensler et al., 1996]. In contrast to the inhibitory effects of vitamin E on carcinogenesis described above, feeding high levels of vitamin E to rats stimulated 1,2-dimethylhydrazine-induced intestinal tumors when compared with rats fed a low level

of vitamin E [McIntosh, 1992], and topical applications of vitamin E exerted tumor promoting activity in DMBA-initiated mice [Mitchel and McCann, 1993]. In additional unpublished studies in our laboratory, topical applications of α-tocopherol 5 days a week to initiated high risk mice previously treated with UVB for 5 months enhanced the formation of skin tumors. In addition, the growth of tumors transplanted into mice, rats, or chickens was stimulated when the animals received multiple injections of vitamin E [Kline and Sanders, 1989; Nitta et al., 1991].

Studies with estrogen. Many animal studies indicate that estradiol and other estrogens are carcinogenic in the uterus and mammary gland, but administration of estradiol inhibits intestinal carcinogenesis in the mouse [Weyant et al., 2001]. In accord with these observations, an extensive intervention study indicated that administration of estrogen and progestin to postmenopausal women enhanced breast and endometrial cancer, but colon cancer was reduced [Beral et al., 2002; Writing Group for the Women's Health Initiative Investigators, 2002].

Studies with cigarette smokers. Cigarette smoking has an antiestrogenic effect, and cigarette smokers have a decreased risk of endometrial cancer and an increased risk of osteoporosis (an estrogen deficiency disease). In an earlier study, cigarette smokers in an aflatoxin B_1-contaminated area of China were reported to have a decreased risk of liver cancer—possibly because of enhanced metabolic detoxification of aflatoxin B_1 [Lin et al., 1991]. Since cigarette smoking greatly increases the risk for lung and other cancers and for pulmonary and cardiovascular disease, all efforts to stop people from smoking should continue. However, it may be possible to isolate safe anticancer substances from tobacco smoke that would inhibit the formation of endometrial and liver cancer in individuals with a high risk of developing these cancers.

Studies with all-trans retinoic acid (RA) and 1α,25-dihydroxyvitamin D_3 (VD_3). Topical applications of all-trans RA or VD_3 strongly inhibited tumor promotion by TPA in mice previously initiated with DMBA [Verma et al., 1979; Wood et al., 1983; Conney et al., 1997]. However, when all-trans RA or VD_3 was administered topically twice a week together with DMBA using a complete carcinogenesis protocol, a markedly enhanced tumor response was observed [Verma et al., 1982; Wood et al., 1985; Conney et al., 1997]. These data are shown in Table IV.

Studies with β-carotene. Because β-carotene can inactivate singlet oxygen and is present in fruits and vegetables associated with reduced cancer risk, it was tested as a potential chemopreventive agent in a population with a high risk of developing lung cancer. In contrast to expectations, it was found that daily supplementation with 20–30 mg of β-carotene (a precursor of vitamin A and all-trans RA) increased the risk of lung cancer in smokers (exposed to polycyclic aromatic hydrocarbons and other carcinogens) but not in nonsmokers [see Omenn, 1998]. These results, observed in

TABLE IV. Effect of VD_3 and All-trans RA on Tumor Promotion by TPA or Tumor Formation in Mouse Skin Induced by Chronic Twice Weekly Treatment With DMBA

Experiment	Treatment	% Tumor-bearing animals	Tumors/mouse (mean ± SEM)
1	TPA	92	20.0 ± 2.5
	TPA + VD_3 (0.5 nmol)	63	3.9 ± 1.0
	TPA + RA (2.0 nmol)	33	1.3 ± 0.5
2	TPA	88	8.61 ± 1.09
	TPA + VD_3 (0.5 nmol)	59	3.39 ± 0.91
3	DMBA	63	1.20 ± 0.26
	DMBA + VD_3 (0.5 nmol)	100	5.67 ± 0.76
	DMBA + RA (0.5 nmol)	80	2.57 ± 0.43
	DMBA + RA (25 nmol)	93	8.40 ± 1.13

In Experiment 1, female CD-1 mice previously initiated with 200 nmol of DMBA were treated topically with the indicated dose of all-trans RA or VD_3 together with 5 nmol of TPA twice a week for 15 weeks. In Experiment 2, female mice previously initiated with 50 nmol of DMBA were treated with solvent vehicle or VD_3 in vehicle 1 h before 16 nmol of TPA twice a week for 16 weeks. In Experiment 3, animals were treated with the indicated compounds or solvent vehicle 1 h prior to treatment with 50 nmol of DMBA twice a week for 16 weeks. Mice treated twice weekly with solvent, VD_3, or all-trans RA in the absence of DMBA did not develop any tumors. Data from Experiment 1 were taken from Conney et al. [1997]. Data from Experiments 2 and 3 were taken from Wood et al. [1983] and Wood et al. [1985].

the lungs of smokers treated with β-carotene, may be analogous to the stimulatory effect of all-trans RA treatment on complete carcinogenesis by the polycyclic hydrocarbon DMBA on mouse skin (Table IV) and may not have occurred in people who had stopped smoking. It is of interest that the stimulatory effects of β-carotene on lung cancer formation in smokers occurred to a greater extent in smokers who were also alcohol drinkers. Additional analysis of data from individuals in the CARET trial taking 30 mg of β-carotene and 25,000 IU of retinyl palamate indicated that consumption of rosaceae fruit and vegetables decreased the risk of lung cancer in the placebo arm of the trial but daily supplementation with 30 mg of β-carotene and 25,000 IU of retinyl palmitate prevented the beneficial effects of fruit and vegetables [Neuhouser et al., 2003].

In contrast to the adverse effects of β-carotene in smokers described above, in subjects who neither smoked or drank alcohol, daily supplementation with 25 mg of β-carotene inhibited the recurrence of colorectal adenomas [Baron et al., 2003]. However, β-carotene administration increased the risk for the recurrence of colorectal adenomas in people who smoked and drank alcoholic beverages [Baron et al., 2003]. These studies point out the complexities of cancer chemoprevention studies in human populations and indicate some potential confounders. These studies also point out that β-carotene may be a cancer chemopreventive agent in one group of individuals (people with recurrent colorectal adenomas who don't smoke or drink alcoholic beverages) but that β-carotene enhances carcinogenesis in another group of individuals (smokers who also drink alcoholic beverages).

Tailoring Cancer Chemopreventive Regimens to Individual Needs

Studies during the past decade have identified potential risk factors and molecular targets for cancer chemopreventive agents as well as potential early biomarkers of cancer risk and early predictors of the effectiveness of cancer chemopreventive agents [Lippman and Hong, 2001, 2002; Potter et al., 2003; Sabichi et al., 2003]. More extensive research in these areas is badly needed. Enhanced research on genetics and molecular epidemiology as well as a better understanding of gene–environment interactions will help guide research that will aid in establishing and individualizing appropriate cancer chemopreventive regimens.

As indicated above, some compounds may be extremely effective cancer chemopreventive agents in one experimental setting but enhance carcinogenesis in another experimental setting. It is likely that an optimal cancer chemopreventive regimen for smokers will be different from an optimal cancer chemopreventive regimen for former smokers or for people exposed to specific dietary carcinogens such as heterocyclic amines in broiled meat and fish or aflatoxin B_1 in mold contaminated foods. Greater efforts should be made to understand mechanisms of cancer chemoprevention and to determine whether a potential chemopreventive agent is useful in many experimental settings or whether it is only useful in a limited number of experimental settings. There is a need to better understand genetic, environmental, and life-style factors that influence carcinogenesis in humans and to use this information to help in the selection of an appropriate cancer chemopreventive regimen in individuals with a high cancer risk. In many instances, it may be possible to tailor cancer chemopreventive agents to individual subjects with known carcinogen exposures or to individuals at high risk for cancer with mechanistically understood pathways of carcinogenesis so that chemopreventive regimens can be customized to the individual and selected on a more rational basis.

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