Cancer Prevention: Novel Nutrient and Pharmaceutical Developments

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CANCER PREVENTION
NOVEL NUTRIENT AND PHARMACEUTICAL DEVELOPMENTS

Edited by H. Leon Bradlow, Jack Fishman, and Michael P. Osborne

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Introduction

This volume summarizes presentations made at the Strang International Cancer Prevention Conference held on November 13 and 14, 1998, sponsored by the Strang Cancer Prevention Center and the International Society of Cancer Chemoprevention (ISCaC). The title of the meeting was Cancer Prevention: Novel Nutrient and Pharmaceutical Developments.

The educational objectives of this conference were to provide recent information to improve the participants' knowledge of several classes of nutrients and pharmaceutical agents currently believed to be important for tumor inhibition; to review novel preclinical models that facilitate analyzing chemopreventive agent efficacy and mechanisms of gene–nutrient interaction; and to provide current information on recent clinical trials under way studying chemopreventive regimens in the United States, Europe, and Asia.

The conference agenda focused on a limited number of presentations that could best fulfill these objectives and did not attempt to cover all developments emerging in this field. The main sections of the program included a review of many varieties of nutrients and pharmaceutical compounds with tumor-inhibitory properties; current strategies, including preclinical genetic models, for studying chemopreventive agents; recent studies of cyclooxygenase-2 and tumor inhibition; calcium and vitamin D in cancer prevention; an update on breast cancer prevention; and updates from Europe and Asia on cancer chemoprevention studies currently under way.

We would like to acknowledge the contribution of Dr. Michael P. Osborne in developing this program; Ms. Lorraine Bell, with the assistance of Ms. Theresa Di Meola in organizing the conference; and Dr. H. Leon Bradlow in the preparation and editing of this volume for the *Annals of the New York Academy of Sciences*. We are also grateful to the Editorial Department of the Academy, and particularly to Steven Bohall, who shepherded this volume through the press with grace and professionalism, and Stephanie J. Bludau who oversaw production.

MARTIN LIPKIN
ANDREW J. DANNENBERG

Progress in Cancer Chemoprevention

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ABSTRACT: **More than 40 promising agents and agent combinations are being evaluated clinically as chemopreventive drugs for major cancer targets. A few have been in vanguard, large-scale intervention trials—for example, the studies of tamoxifen and fenretinide in breast, 13-*cis*-retinoic acid in head and neck, vitamin E and selenium in prostate, and calcium in colon. These and other agents are currently in phase II chemoprevention trials to establish the scope of their chemopreventive efficacy and to develop intermediate biomarkers as surrogate end points for cancer incidence in future studies. In this group are fenretinide, 2-difluoromethylornithine, and oltipraz. Nonsteroidal anti-inflammatories (NSAID) are also in this group because of their colon cancer chemopreventive effects in clinical intervention, epidemiological, and animal studies. New agents are continually considered for development as chemopreventive drugs. Preventive strategies with antiandrogens are evolving for prostate cancer. Anti-inflammatories that selectively inhibit inducible cyclooxygenase (COX)-2 are being investigated in colon as alternatives to the NSAID, which inhibit both COX-1 and COX-2 and derive their toxicity from COX-1 inhibition. Newer retinoids with reduced toxicity, increased efficacy, or both (e.g., 9-*cis*-retinoic acid) are being investigated. Promising chemopreventive drugs are also being developed from dietary substances (e.g., green and black tea polyphenols, soy isoflavones, curcumin, phenethyl isothiocyanate, sulforaphane, lycopene, indole-3-carbinol, perillyl alcohol). Basic and translational research necessary to progress in chemopreventive agent development includes, for example, (1) molecular and genomic biomarkers that can be used for risk assessment and as surrogate end points in clinical studies, (2) animal carcinogenesis models that mimic human disease (including transgenic and gene knockout mice), and (3) novel agent treatment regimens (e.g., local delivery to cancer targets, agent combinations, and pharmacodynamically guided dosing).**

Cancer chemoprevention is defined as the use of specific chemical compounds to prevent, inhibit, or reverse carcinogenesis.[1,2] In many major cancer targets, human cancer development requires 20–40 years or more,[1] and the scope of chemopreven-

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Editors

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[a]This volume is the result of a conference, entitled **Cancer Prevention: Novel Nutrient and Pharmaceutical Developments,** held in New York City on November 13–14, 1998 by the Strang Cancer Prevention Center, Cornell University Medical College, and the International Society for Cancer Chemoprevention.

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Part IV. Cancer Prevention Updates

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tion encompasses cohorts at all phases of this process—from healthy subjects at normal risk; to populations at intermediate risk from environmental and life style factors, genetic predisposition, and precancerous lesions; and then to previous cancer patients at high risk for second primaries. The identification of efficacious and safe agents, biomarkers of efficacy and risk, and suitable cohorts for clinical intervention are critical to progress in chemoprevention.

PROMISING CHEMOPREVENTIVE AGENTS

Basic research in carcinogenesis has identified many genetic lesions and other cellular constituents associated with the initiation and progression of precancers to invasive disease. Possible mechanisms for chemoprevention involve interfering with the expression and/or activity of these molecules; examples of the mechanisms, their possible molecular targets, and agents that act at these targets are listed in TABLE 1.[1,3,4]

Systematic evaluation of classes of agents acting at molecular targets, such as those listed in TABLE 1, is an important strategy for identifying and characterizing new potential chemopreventive agents.[5] However, many promising agents have multiple chemoprevention-associated molecular activities, some of which are interrelated. Also, a single activity, even if it is the agent's predominant pharmacological activity, may not be the most important or the only one required for chemoprevention. Such may be the case for inhibition of prostaglandin synthase (particularly, cyclooxygenase (COX) activity) by nonsteroidal anti-inflammatory drugs (NSAID). These observations imply that molecular targeting should not be the only approach used to identify potential chemopreventive drugs.[6]

Experimental and epidemiological carcinogenesis studies showing that >90% of cancers are associated with mutagens and mitogens[1,6] suggest a complementary empirical approach—searching for agents that inhibit or reverse cellular processes derived from mutagenesis and mitogenesis: (1) decreased programmed cell death (from senescence; or in response to damage, environmental conditions, such as overpopulation, or hormone withdrawal), (2) decreased maturation or differentiation, and (3) increased proliferation.

Using both approaches, several thousand agents have been reported in the literature to have chemopreventive activity.[7] Since 1987 in the NCI chemoprevention testing program, more than 1,000 agents and agent combinations have been selected and evaluated in preclinical studies of chemopreventive activity, ranging from *in vitro* mechanistic assays[8] and cell-based transformation assays to carcinogen-induced[9] and transgenic animal models. More than 40 promising agents and agent combinations are being evaluated clinically as chemopreventive drugs for major cancer targets (TABLES 2 and 3). A few have been in vanguard, large-scale intervention trials—for example, the studies of tamoxifen[10] and fenretinide in breast,[11] 13-*cis*-retinoic acid in head and neck,[12] vitamin E[13] and selenium in prostate,[14] and calcium [15] in colon. These and other agents are currently in phase II chemoprevention trials to establish the scope of their chemopreventive efficacy and to develop intermediate biomarkers as surrogate end points for cancer incidence in future studies. In this group are fenretinide (bladder, cervix, lung, prostate, oral cavity, and combined with tamoxifen in breast), DFMO (breast, bladder, cervix, oral cavity, prostate, esopha-

TABLE 1. Mechanisms for chemoprevention with possible molecular targets[1]

Mechanism	Possible Molecular Targets	Representative Agents
Antimutagenesis		
Inhibit carcinogen uptake	Bile acids (bind)	Calcium
Inhibit formation/activation of carcinogen	Cytochromes P450 (inhibit)	PEITC, tea, indole-3-carbinol, soy isoflavones
	PG synthase hydroperoxidase, 5-lipoxygenase (inhibit)	NSAID, COX-2 inhibitors, lipoxygenase inhibitors, iNOS[a] inhibitors
	Bile acids (inhibit)	Ursodiol
Deactivate/detoxify carcinogen	GSH/GST (enhance)	Oltipraz, NAC
Prevent carcinogen-DNA binding	Cytochromes P450 (Inhibit)	Tea
Increase level or fidelity of DNA repair	Poly(ADP-ribosyl)transferase (enhance)	NAC, protease inhibitors (Bowman-Birk)
Antiproliferation/Antiprogression		
Modulate hormone/growth factor activity	Estrogen receptor (antagonize)	SERMs, soy isoflavones
	Androgen receptor (antagonize)	Bicalutamide, flutamide
	Steroid aromatase (Inhibit)	Exemestane, vorozole, Arimidex
	Steroid 5α-reductase (inhibit)	Finasteride, epristeride
	IGF-I (inhibit)	SERMs, retinoids
Inhibit oncogene activity	Farnesyl protein transferase (inhibit)	Perillyl alcohol, limonene, DHEA, FTI-276
Inhibit polyamine metabolism	ODC activity (inhibit)	DFMO
	ODC induction (inhibit)	Retinoids, NSAID
Induce terminal differentiation	TGF-β (induce)	Retinoids, vitamin D, SERMs
Restore immune response	COX (inhibit)	NSAID, tea, curcumin
	T, NK lymphocytes (enhance)	Selenium, tea
	Langherans' cells (enhance)	Vitamin E, NSAID
Increase intercellular communication	Connexin 43 (enhance)	Carotenoids (lycopene), Retinoids
Restore tumor suppressor function	p53 (inhibit HPV E6 protein)	—
Induce apoptosis	TGFβ (induce)	Retinoids, SERMs, vitamin D
	RAS Farnesylation (inhibit)	Perillyl alcohol, limonene, DHEA, FTI-276
	Telomerase (inhibit)	Retinoic acid
	Arachidonic acid (enhance)	NSAID, COX-2 inhibitors, lipoxygenase inhibitors
	Caspase (activate)	Retinoids
Inhibit angiogenesis	FGF receptor (inhibit tyrosine kinase)	Soy isoflavones, COX-2 inhibitors
	Thrombomodulin (inhibit)	Retinoids
Correct DNA methylation imbalances	CpG island Methylation (enhance)	Folic acid
Inhibit basement membrane degradation	Type IV collagenase (inhibit)	Protease inhibitors
Inhibit DNA synthesis	Glucose 6-phosphate dehydrogenase (inhibit)	DHEA, fluasterone

[a]Inducible nitric oxide synthase.

TABLE 2. NCI chemoprevention program: promising cancer chemopreventive agents in phase I clinical trials and preclinical toxicology

Agent	Toxicology/Phase I	Target
S-Allyl-L-cysteine	Tox	lung
Curcumin	I	colon, breast
Fluasterone	Tox	breast, colon
Genistein (soy isoflavones)	Tox	breast, prostate, colon
Ibuprofen	I	colon, bladder
Indole-3-carbinol	I	breast
Lycopene	I	prostate
Perillyl alcohol	I	breast, colon
PEITC	I	lung
9-*cis*-Retinoic acid	I	breast, cervix, prostate
Sulindac sulfone	I	colon, breast, prostate
Tea/EGCG[a]	Tox	colon, head and neck, skin
Ursodiol	I	colon
Vitamin D_3 analogues	Tox	breast, colon, prostate
L-Selenomethionine + vitamin E	I	prostate, lung, colon
NAC + DFMO	Tox	breast
DFMO + fenretinide	Tox	breast
DFMO + oltipraz	Tox	bladder, colon
Fenretinide + oltipraz	Tox	breast, bladder
NAC + oltipraz	I	lung

[a]Epigallocatechin gallate.

gus, and colon in combination with Sulindac), and oltipraz (lung, both alone and combined with NAC; liver;[16] skin). NSAID are also in this group because of their colon cancer chemopreventive effects in clinical intervention (aspirin, Sulindac), epidemiological (aspirin), and animal studies (e.g., piroxicam, Sulindac, aspirin).[3] They have also shown high activity against animal bladder cancers.

New agents are continually considered for development as chemopreventive drugs, with selection based on preliminary efficacy data, mechanistic considerations, and potential for improved chemopreventive (therapeutic) index. For example, androgen deprivation has been associated with reduced risk for prostate cancer and therapeutic benefit in treatment of the disease. Preventive strategies with antiandrogens (e.g., flutamide and 5α-reductase inhibitors[17]) are evolving. The selective estrogen receptor modulator (SERM), tamoxifen, has clinically demonstrated chemopreventive potential, but research continues to look for other SERMs that maintain tamoxifen's chemopreventive and bone and heart protective activities, without its side effects (particularly its associated increased risk for uterine cancer). Raloxifene and SERM-3 are examples.[2] Anti-inflammatory agents that selectively inhibit inducible COX-2 are being investigated in colon as alternatives to the NSAID that inhibit both COX-1 and COX-2 and derive their toxicity from COX-1 inhibition.[2,3] Retinoids have shown significant chemopreventive activity with multiple potential mechanisms of action and varied tissue specificity. Mechanisms and efficacy of new generations of retinoids with reduced toxicity, increased efficacy, or both (e.g., 9-*cis*-retinoic acid, which activates both RAR and RXR retinoid receptors, and

TABLE 3. NCI Chemoprevention Program: promising cancer chemopreventive agents in Phase II/III clinical trials

Agent	Phase	Target(s)
Retinoids		
Vitamin A	III	lung
all-*trans*-Retinoic acid	II	cervix
13-*cis*-Retinoic acid	II/III	head and neck, lung, oral cavity
9-*cis*-Retinoic acid	II	cervix
Fenretinide	II/III	bladder, breast, ovary, cervix, lung, oral cavity, prostate
Antiestrogens/antiandrogens		
Tamoxifen	II/III	breast
Fenretinide + tamoxifen	II	breast
Raloxifene	III	breast
Toremifene	II	prostate
Other SERM	II	breast
Exemestane	II	breast
Finasteride	II/III	prostate
Flutamide	II	prostate
DFMO	II	bladder, breast, cervix, colon, Barrett's esophagus, oral cavity, prostate
NSAID		
Aspirin	II/III	colon
Aspirin + calcium	II/III	colon
Aspirin + folic acid	III	colon
Piroxicam	II	colon
Sulindac	II/III	colon, multiple myeloma
DFMO + Sulindac	II	colon
COX-2 Inhibitor	II/III	colon, skin, bladder, Barrett's esophagus
Budesonide	II	lung
Oltipraz	II	liver (DNA adducts), lung
DHEA	II	multiple myeloma
Calcium	II/III	colon
Vitamin D_3	II	colon
Vitamin E	II/III	colon, lung, prostate
L-Selenomethionine	II/III	prostate, skin, colon, esophagus
Folic acid	II/III	cervix, colon
Curcumin	II	oral cavity
Soy isoflavones	II	prostate
Tea	II	skin

Targretin, which selectively activates RXR receptors)[2] are being investigated. A promising and important group of potential cancer chemopreventive drugs, because of their low toxicity and apparent benefit in other chronic diseases (e.g., protection from heart disease), are those derived from natural products, particularly dietary sub-

stances—green and black tea polyphenols,[18] lycopene,[19] soy isoflavones,[20] curcumin,[21] phenethyl isothiocyanate (PEITC),[22] indole-3-carbinol,[23] and perillyl alcohol.[24] Important aspects of developing such agents are careful characterization of the active substance(s) and the technology to ensure reproducible preparations.

The potential of single chemopreventives is limited by potency and, more importantly, toxicity at efficacious doses. Simultaneous or sequential administration of multiple agents can increase efficacy and reduce toxicity. For example, differences in the chemopreventive mechanisms among the agents can provide additive or synergistic efficacy; thus, adequate efficacy may be observed at lower and presumably less toxic doses of the individual agents. Several agent combinations are under development based on their synergistic activity in animal efficacy studies—for example, retinoids (fenretinide, 9-cis-retinoic acid) with antiestrogens (tamoxifen, raloxifene, SERM-3) in breast,[2] and 2-difluoromethylornithine (DFMO) and NSAID (piroxicam, Sulindac) in colon.[4] Also, mechanistic data may suggest the potential synergy of two agents; an example is the enhancement of electrophile-trapping activity (hence, carcinogen detoxifying activity) that might be achieved by combination of an agent, such as *N*-acetyl-L-cysteine (NAC), which provides substrate for glutathione (GSH) synthesis, with an agent, such as oltipraz, which enhances GSH S-transferases (GST). Another possibility is administration of second agents to counter toxicity of potent chemopreventives. Such a strategy has been proposed for NSAID, as a combination of the NSAID with a drug that inhibits associated gastrointestinal toxicity (e.g., misoprostol).[3]

CHEMOPREVENTIVE DRUG DEVELOPMENT STRATEGIES USING INTERMEDIATE BIOMARKERS OF CARCINOGENESIS

NCI's multidisciplinary approach to chemopreventive drug development and collaboration with the Food and Drug Administration to provide consensus guidance for applying this approach have been described previously.[1,3,25] Briefly the approach is an applied drug development science effort that begins with the identification of candidate agents for development and the characterization of these agents in *in vitro* and animal chemopreventive efficacy screens. Promising agents are then further evaluated in animal models to design regimens for clinical testing and use. Agents judged to have potential as human chemopreventives are subjected to preclinical toxicity and pharmacokinetic studies, and then phase I clinical safety and pharmacokinetic trials. The most successful agents then progress to clinical chemoprevention trials.

The impracticality of cancer incidence reduction as an end point is a major challenge in designing chemoprevention efficacy trials. Increased understanding of the molecular and phenotypic progression in carcinogenesis has provided a means of overcoming this obstacle, namely, with intermediate biomarkers that can be validated as surrogate end points for cancer. Primary intermediate biomarkers and targets of chemoprevention are intraepithelial neoplasia (IEN), which are almost always cancer precursors. In the NCI chemopreventive drug development program, phase II and small phase III clinical chemoprevention trials are conducted in patients with current or previous IEN. A primary goal of these studies is characterization and stan-

dardization of quantitative measurements of chemopreventive agent-induced morphometric and cytometric changes in these lesions. Results showing reversion, slowed progression, or inhibition of recurrence of the target lesions can be obtained within 3–24 months in these studies.

Further, an important component of clinical (and preclinical) studies in chemoprevention is identification of earlier intermediate biomarkers in IEN that reflect carcinogenesis/chemopreventive mechanisms—proliferation (e.g., proliferating cell nuclear antigen, MIB-1), differentiation signals (e.g., actins, vimentin, blood group antigens), and genetic/regulatory changes (e.g., apoptosis, DNA methylation, oncogene, and tumor suppressor expression).[26] The early intermediate biomarkers can be very distant developmentally from the cancer; therefore, standardized methods for sampling and measuring them and their validation against IEN are critical. Also, it is anticipated that the reliability of early biomarkers as end points for clinical trials may be improved by using them in batteries that model carcinogenesis.

CONSIDERATIONS IN DEVELOPMENT OF CHEMOPREVENTIVE DRUGS AT FOUR MAJOR CANCER TARGETS: BREAST, COLON, PROSTATE, AND LUNG

For each of four major cancer sites, the following discussion reviews promising agents and specific considerations in the development of chemoprevention strategies in these targets. In breast, the high importance of estrogen modulation is reviewed. In colon, the rationale for using adenomas as a surrogate end point in chemoprevention trials is presented, and the selection and development of antiinflammatories is described. The discussion on prostate reviews new agents under development and looks at the difficulties associated with measuring modulation of prostatic intraepithelial neoplasia (PIN) as a surrogate end point. In lung, the selection of suitable cohorts and the design of a novel local agent delivery system are described.

Breast: Estrogen Modulators as Chemopreventives[2]

Control of estrogen exposure is a key factor in breast cancer chemoprevention strategies. Many of the risk factors for breast carcinogenesis are associated with prolonged cyclical or high levels of estrogen exposure (e.g., early menarche, late menopause, or nulliparity). It is expected that estrogen exposure would couple with genetic predisposition (e.g., BRCA or Li-Fraumeni mutations) and other factors in determining an individual's risk.[6] One strategy for reducing estrogen effects is by treatment with SERMs—agents that modulate estrogen activation estrogen receptors. As noted above, the promise of the antiestrogen, tamoxifen, is widely known based on its success in reducing the risk of breast cancer in women at high risk.[10] Of equal interest is the potential protection SERMs offer against other chronic diseases; depending on the estrogen receptor response elements they affect, protection against cardiovascular disease, bone loss, and brain function are also seen. Newer generation SERMs, which also avoid estrogen agonist toxicity in sites other than breast (e.g., enhanced risk for endometrial cancer) are particularly promising. The second generation SERM, raloxifene, already approved in prevention of osteoporosis and without apparent endometrial toxicity, will be compared with tamoxifen as a breast cancer