An Update on Cancer Chemoprevention

By Tammy Chernin, RPh

INTRODUCTION

Cancer chemoprevention is an innovative area of pharmaceutical cancer research that focuses on the prevention of cancer through pharmacological, nutritional, or endocrinologic intervention. The challenge rests in identifying agents that are efficacious, but of low or no toxicity.

More than 50 promising agents and agent combinations are currently being clinically evaluated for chemopreventive activity against major cancer targets.[1] Four classes of preventive agents have shown particular promise in clinical trials and are considered priority substances for study by the National Cancer Institutes' Prevention and Control Programs. These include selective estrogen receptor modulators (SERMS) and other hormonal agents, nonsteroidal anti-inflammatory drugs (NSAIDS), calcium compounds, and retinoids (chemical cousins of vitamin A).[2]

CHEMOPREVENTION STRATEGIES

Over the past decade, advances in understanding carcinogenesis have made possible the identification of candidate chemoprevention agents that are being developed to hit key molecular targets.[3-5] Drug development strategies involve modulation of the activities occurring at the cellular and tissue level of carcinogenesis that are characterized by mutagenesis and proliferation. The initiation and progression of precancers to invasive disease has been linked with many enzymes, genetic lesions, and other cellular constituents. Table 1 summarizes many of the cellular chemopreventive mechanisms, molecular targets for inhibiting these mechanisms, and corresponding agents/agent classes currently being explored for chemopreventive efficacy.

An essential issue in the development of chemoprevention agents is the role of markers, also called surrogate endpoint biomarkers (SEBMs), intermediate markers, and sometimes even tumor markers.[6] Intermediate biomarkers of cancer are the phenotypic, genotypic, and molecular changes that occur during carcinogenesis. Many are potentially SEBMs for cancer incidence and understanding their interrelationship is very important to chemoprevention.

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 (Table 2).

CHEMOPREVENTIVE AGENTS

Selective Estrogen-Receptor Modulators

The SERMs are a relatively new promising class of agents. In November, 1998, following the impressive results of the first fully completed prospective, randomized Breast Cancer Prevention Trial (BCPT), tamoxifen received approval for the reduction of breast cancer incidence in women at high risk.[7] Tamoxifen citrate, which inhibits the action of estrogen on breast tissue, improves disease-free survival among women who have estrogen-receptor positive breast cancer and reduces the risk of contralateral breast cancer.[8] The BCPT reported that tamoxifen reduced breast cancer risk by about 50% among women who had a high risk of cancer because of age (older than 60 years) or a combination of other risk factors. However, most breast cancers occur in women who are not identified to be at increased risk (see Table 3). In addition to increased rates of endometrial cancers in the tamoxifen group, rates of stroke, pulmonary embolism, and deep-vein thrombosis were also elevated, which may limit its use for primary prevention of breast cancer.[9]

To have a substantial impact on breast cancer reduction in the whole population, a preventive agent needs to be safe and effective for long periods and to be acceptable for use in women who have an average or low risk of breast cancer.

Raloxifene hydrochloride is a SERM, chemically distinct from tamoxifen and estradiol, that binds to estrogen receptors to competitively block estrogen-induced DNA transcription in the breast and endometrium. Raloxifene was evaluated in the multicenter, randomized, double-blind Multiple Outcomes of Raloxifene Evaluation Trial (the MORE trial) for prevention of fracture. Participants were also monitored for the occurrence of breast cancer, a secondary endpoint of the trial. Raloxifene reduced the risk of newly diagnosed invasive cancer by 76% during a median of 40 months of treating postmenopausal women for osteoporosis. Women with osteoporosis have a lower risk of breast cancer, presumably because of lower endogenous estrogen levels, so the women who entered the MORE trial were not comparable to those entering BCPT. Raloxifene did not increase the risk of endometrial cancer during the first 3 years of the MORE trial treatment, but the total number of cases was small. Raloxifene, tamoxifen and estrogen increase the risk of venous thromboembolic disease to a similar degree.

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TABLE 1. MECHANISMS FOR CHEMOPREVENTION: POSSIBLE MOLECULAR TARGETS AND PROMISING AGENTS

Mechanism	Possible molecular targets	Representative agents
Antimutagenesis		
Inhibit carcinogen uptake	Bile acids (bind)	Calcium
Inhibit formation/activation of carcinogen	Cytochromes P450 (inhibit) PG synthase hydroperoxidase 5-lipooxygenase (inhibit) Bile acids (inhibit)	PEITC, tea, indole-3-carbinol, soy isoflavones NSAIDs, COX-2 inhibitors, lipoxygenase inhibitors, iNOS inhibitors, glucocorticoids Ursodiol
Deactivate/detoxify carcinogen	GSH/GST (enhance)	Oltipraz, NAC, sulforaphane
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) Androgen receptor (antagonize) Steroid aromatase (inhibit) Steroid 5a-reductase (inhibit) IGF-I (inhibit) AP-1 (inhibit) Peroxisome proliferator Activated receptor (activate)	SERMs, soy isoflavones Bicalutamide, flutamide Exemestane, vorozole, arimidex Finaseride, epristeride SERMs, retinoids Retinoids Retinoids, NSAIDs
Inhibit oncogene activity	Farnesyl protein transferase (inhibit)	Perillyl alcohol, limonene, DHEA, FTI-276
Inhibit polyamine metabolism	ODC activity (inhibit) ODC induction (inhibit)	DFMO Retinoids, NSAIDs
Induce terminal differentiation	TGFβ (induce)	Retinoids, vitamin D, SERMs
Restore immune response	COX (inhibit) T, NK lymphocytes (enhance) Langerhans cells (enhance)	NSAIDs, COX-2 inhibitors, tea, curcumin Selenium, tea, NSAIDs, COX-2 inhibitors Vitamin E, NSAIDs, COX-2 inhibitors
Increase intercellular communication	Connexin 43 (enhance)	Cartenoids (lycophene), retinoids
Restore tumor suppressor function	p53 (inhibit HPV E6 protein)	—
Induce apoptosis	TGFβ (induce) RAS farnesylation (inhibit) Arachidonic acid (enhance) Caspase (activate) Guanosine monophosphate diesterase (inhibit)	Retinoids, SERMs, vitamin D Perillyl alcohol, limonene, DHEA, FTI-276 Retinoic acid, NSAIDs, COX-2 inhibitors, lipoxygenase inhibitors Retinoids NSAIDs, sulindac, sulphone
Inhibit angiogenesis	FGF receptor (inhibit tyrosine kinase) Thrombomodulin (inhibit)	Soy isoflavones, COX-2 inhibitors Retinoids
Correct DNA methylation imbalances	CpG island methylation (enhance)	Folic acid
Inhibit basement membrane degradation	Type IV collagenase (inhibit)	Protease inhibitors (Bowman-Birk)
Inhibit DNA synthesis	Glucose 6-phosphate dehydrogenase (inhibit)	DHEA, fluasterone

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PEITC=phenethylisothiocyanate; PG=Prostaglandins; NSAIDs=nonsteroidal anti-inflammatory drugs; COX=cycloxygenase; iNOS=inducible nitric acid synthase; GSH=glutathione; GST=glutathione-s-transferase; NAC=N-acetyl-l-cysteine; SERMs=selective estrogen receptor modulators; IGF-I=insulin-like growth factor-1; AP-1=(transcription) activator-protein-1; DHEA=dehydroepiandrostenedione; ODC=ornithine decarboxylase; DFMO=2-difluromethylornithine; TGFβ=tumor growth factor beta; NK=natural killer cells; HPV=human papilloma virus; FGF=fibroblast growth factor; CpG=cytosine-guanosine.

Since metastatic breast cancers can develop resistance to tamoxifen after long-term exposure it is important to determine the long-term effects of raloxifene and other SERMs. The effectiveness of tamoxifen for prevention of primary breast cancer beyond 5 years of treatment is uncertain.

The Study of Tamoxifen and Raloxifene (the STAR trial) will randomize 22,000 postmenopausal women to tamoxifen vs raloxifene, without a placebo group, to compare the two agents in reducing the incidence of breast cancer in women who are at increased risk at developing the disease. Tamoxifen and raloxifene may be useful preventive therapies for women who have an increased risk of estrogen receptor-positive breast cancer and vertebral fractures. The MORE trial is continuing to assess the effectiveness and safety of long-term use of raloxifene.

TABLE 2. SUMMARY OF PHASE II AND III TRIALS DIRECTED AT 12 MAJOR CANCER TARGETS

Target	Agent
Breast	Fenretinide, DFMO Fenretinide with tamoxifen and exemestane
Prostate	Antiandrogens Antiestrogens Soy proteins Fenretinide
Colon	Ursodiol Calcium alone and with Vitamin D DFMO alone and with sulindac Sulindac Piroxicam Celecoxib
Head and neck	13-cis-retinoic acid with interferon and vitamin E Fenretinide DFMO Curcumin
Esophagus	DFMO Selective COX-2 inhibitor
Lung	Fenretinide Oltipraz Anethole trithione Aerosolized budesonide (pilot study)
Bladder	Fenretinide DFMO Selective COX-2 inhibitor
Cervix	DFMO Retinoids
Skin	DFMO Fenretinide Selective COX-2 inhibitor Topical tea polyphenols
Liver	Oltipraz
Multiple myeloma	DHEA and Biaxin

Adapted from National Cancer Institute. 1998 Annual Report.[27]

Hormonal Therapy

A multicenter study of women at high risk of developing breast cancer is underway testing the effects of a combination of hormones administered as a nasal spray.[10] The spray, which contains deslorelin (a compound that inhibits production of estrogen by the ovaries), estradiol (a type of estrogen), and testosterone, stops the ovaries from releasing eggs, as well as hormones. The spray induces hormonal changes similar to menopause, and may provide an alternative to prophylactic mastectomy. "The goals of this study are to reduce breast density, reduce the risks of breast and ovarian cancers, preserve the reproductive organs, and improve the quality of life for women who are at high risk for developing breast cancer," according to Jeffrey N. Weitzel, MD, director of the Department of Clinical Cancer Genetics and the Cancer Screening and Prevention Program for the City of Hope Comprehensive Cancer Center in Duarte, California, one of the researchers working on the study. "There is clear need for the development of safe and effective chemoprevention options," Dr. Weitzel added.

"Chemoprevention studies are and will most likely continue to be an important part of breast cancer research in the future," said Debbie Saslow, PhD, director of breast and cervical cancer for the American Cancer Society.

NSAIDs and Cox-2 Inhibitors

In the United States the lifetime incidence of colorectal cancer is about 6%, and it is the second most common cause of cancer death.[11] About 75% of patients diagnosed with colorectal cancer have no special risk factors for the disease with 15% to 20% having a family history. The remainder suffer from hereditary nonpolyposis colorectal cancer (3–8%), familial adenomatous polyposis (FAP)(1%), or ulcerative colitis (1%). Most colorectal cancers develop from adenomatous polyps or adenomas. Over 5 to 10 years, about 5% of adenomatous polyps become malignant.[12] Surgery and chemotherapy are not very effective for advanced forms of colorectal cancer making the quest for early detection and preventive measures very important.

According to a report in the August 1999 issue of Gastroenterolgy, results of previous studies have suggested that NSAIDs reduce the risk of colorectal cancer and indicated that this antineoplastic effect may be mediated through cyclooxygenase inhibition.[13] But the potential benefit of conventional NSAIDs in the prevention of colorectal cancer is offset by the risk of toxicity, particularly NSAID-induced gastritis.

Evidence suggests that NSAIDs reduce the risk of colorectal cancer through the inhibition of cycloxygenase (COX), the enzyme that catalyzes the rate-limiting step in the conversion of arachidonic acid to prostaglandins. Cyclooxygenase exists in two forms, COX-1 and COX-2. COX-1 is produced constitutively in tissues throughout the body including platelets, the gastric mucosa, and the kidneys. The production of COX-2 is primarily induced at sites of inflammation.[14] COX-2 has also been found in tissues from colon, breast (*HER-2/neu*-positive), and head and

neck cancers. High levels have also been found in the blood vessels that supply tumors (see Table 4).

In animals models of FAP, COX-2 inhibitors appeared more effective than traditional NSAIDs at preventing polyp formation.[15] The results of a 6-month clinical trial evaluating celecoxib, a selective COX-2 inhibitor, reported an 11.9% decrease in the rate of precancerous polyps with 100 mg daily and a 28% decrease with 400 mg daily.[16]

Whether NSAIDs decrease the risk of colorectal cancer by inhibiting cyclooxygenase and inhibiting PG synthesis is not entirely clear. Recent research suggests that the induction of apoptosis ("programmed cell death") is an important component underlying the action of a number of diverse chemopreventive agents including sulindac and other NSAIDs.

In August, 1999, the Food and Drug Administration (FDA) granted GD Searle a 6-month priority review of celecoxib for the treatment of colorectal adenomatous polyps in patients with FAP, and in December, 1999, accelerated approval was granted.[17,18] Nearly 100% of patients with FAP will develop colon cancer by the age of 40 years unless some intervention is provided.[19]

Patients with FAP need to continue to be monitored according to the usual guidelines, and surgery be performed when indicated. The approved dose of 400 mg bid is higher than for the other indications with celecoxib and should be taken with food to help increase absorption.

Research programs for chemoprevention of colorectal cancer are also in progress for rofecoxib, aspirin, and sulindac. A derivative of sulindac called exisulind appears to inhibit polyp formation without inhibiting COX-2 and has received a priority review by the FDA for the treatment of colorectal adenomatous polyps in patients with FAP.

The efficacy and potential application of these agents in the inhibition of colon carcinogenesis continues to be studied and, most likely, more potent inhibitors will be designed based on the molecular structure of COX-2. And if COX-2 inhibition is shown to be related to the chemopreventive effects of NSAIDs it may suggest that inhibition of

TABLE 3. PERSONAL FACTORS INFLUENCING INCIDENCE OR RELATIVE RISK OF BREAST CANCER

Factor	Condition	Incidence	Relative risk
Age-annual incidence by 5-year group (female only)	35–39 years	0.06%	
	40–44 years	0.12%	
	45–49 years	0.20%	
	50–54 years	0.25%	
	60–64 years	0.35%	
	65–69 years	0.41%	
	70–74 years	0.46%	
	75–79 years	0.48%	
	80–84 years	0.47%	
	85+ years	0.42%	
	lifetime	12.0%	
Genetics (lifetime risk)	BRCA1 or BRCA2 (+)(found in 1/800 women)		56-80%
Number of primary relatives with breast cancer (lifetime risk)	0	12%	
	1 (dx>50 years)	12%	
	1 (dx<50 years)	13-21%	
	2 (dx>50 years)	11-24%	
	2 (dx <50 years)	25-48%	
Radiation to breast (lifetime risk)	age <16 (for Hodgkin's disease)	35% by age 40	
	Chest x-ray	12%	
Age of menarche	<12 years		1.3
Age of menopause	>55 years		1.5–2.0
	<45 years		0.77
Age of first live birth	25–29 years		1.5
	After 30 years		1.9
	After 35 years		2.0–3.0
	Nulliparous		1.4 –3.0
Breast Disease			
Nonproliferative	cysts, fibrosis, fibroadenoma, etc.		1.0
Proliferative	hyperplasia, papilloma		1.5–2.0
Atypia	atypical Hyperplasia		4.0–5.0
Carcinoma in situ			6.9–12.0
Alcohol intake	3–9 drinks per week		1.3

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this isoenzyme may be broadly effective in the chemoprevention of colorectal cancer.

Retinoids

Scientists are studying both natural and synthetic retinoids alone and in combination with other compounds in the prevention of cervical cancer, lung cancer, cancers of the head and neck, and skin cancer.

Waun Ki Hong, professor of medicine and chair of the department of head and neck and thoracic medical oncology at the University of Texas M.D. Anderson Cancer Center in Houston, is a world-renowned expert in the use of retinoids as chemoprevention for development of malignancies in the aerodigestive tract. The main hypothesis underlying all of Dr. Hong's work in this area has been that by understanding the early molecular events, which lead to the induction of tumors in the aerodigestive tract, strategies can be designed to prevent malignant transformation.

Retinoic acid is known to be important in the control of cellular proliferation in the epithelium.[20] Six retinoic acid receptor subtypes have been identified of which the beta-retinoic acid (RAR-beta) appears to be the key marker. In normal tissues, all six receptor subtypes are expressed. However, in patients with leukoplakia, a precancerous, slowly developing change in the normal tissue of a mucus membrane, the beta-subtype is essentially not expressed in those lesions. Patients with oral leukoplakia have a high chance of developing malignancies in the area of the leukoplakia. After 3 months of retinoic acid therapy, Dr. Hong's clinical study reported an upregulation of RAR-beta in these patients, which corresponded to regression of the lesion. This suggests that RAR-beta can be used as a biomarker for successful therapy with retinoic acid as a chemopreventative.

In Dr. Hong's original study, "high-dose" 13 cis-retinoic acid was used but considerable toxicity was noted. In a subsequent study, a lower dose was used and approximately 60% of patients with lesions of leukoplakia showed complete reversal of these lesions. Forty percent, however, are de novo resistant to the retinoic acid derivative, and of the 60% who originally responded, approximately 50% go on to become resistant and redevelop leukoplakia. To overcome primary resistance, Dr. Hong's group developed a combination approach using retinoic acid, interferon, and vitamin E as a combined chemopreventative regimen. Vitamin E is used for its ability to decrease the retinoic acid side effects and is believed to be chemopreventative in and of itself. Interferon was synergistic in reversing premalignant lesions when used with retinoic acid. In the 31 patients evaluable on this trial, there was a disparity in response based on the site of leukoplakia. 50% of patients whose larynx tissue was primarily affected showed good resolution of the premalignant lesions but only 1% with oral lesions showed any reversal. Dr. Hong's group continue to make strides in the prevention of second primary head and neck cancers and is currently conducting a very large trial in which he is looking at 13-cis-retinoic acid as a chemopreventative in well over 1,000 patients treated for primary head and neck cancers. The hope is that a better understanding of the salient molecular events will lead to better chemopreventative strategies.

TABLE 4. SUMMARY OF PHASE II AND III TRIALS DIRECTED AT 12 MAJOR CANCER TARGETS

Location	COX-1	COX-2
Chondrocyte	X	X
Gastrointestinal tract	X	
Platelets	X	
Endothelial cells	X	
Renal medulla	X	
Renal cortex		X
Brain		X
Synovial tissue		X
Colorectal tumors		X
Breast cancer		X
Lung		X
Liver	X	
Spleen	X	

Adapted from Hawkey CJ. Cox-2 inhibitors. *Lancet* [29]; Cada DJ. Celecoxib. *Hosp Pharm* [30]; GD Searle and Co. Celecoxib package insert.[31]

Calcium

Calcium compound studies focus on colon cancer prevention mainly in individuals previously diagnosed with colon polyps or cancer. During a 4-year study period, 31% of the individuals taking two 600 mg tablets of calcium each day developed at least one polyp, compared with 38% of those taking the placebo.[21] The calcium group also had fewer polyps per person than the placebo group. "If you can prevent polyps from forming, you can prevent the cancer," said Gabriel Feldman, MD, director of colon and prostate cancer for the American Cancer Society. The study authors, led by J.A. Baron, MD, of Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire, recommend more research be conducted to clarify risks and benefits of calcium in various groups. Older men should be especially cautious about taking calcium supplements to reduce their risk of colon cancer because of recent research suggesting a diet high in calcium may increase the risk of prostate cancer. More studies are underway involving a variety of calcium compounds.

FUTURE RESEARCH

Newer and future research on chemopreventative agents will include pharmacodynamic modeling, which is the topical application of a chemopreventive agent to target tissue to avoid systemic metabolism and toxicity. The approach has particular promise for the lung, but is applicable to

several target organs. Retinoids formulated and delivered by this means could well improve efficacy without toxicity.

A recent example of pharmacodynamic modeling confirmed the chemopreventive potential of aerosolized steroids.[22] A pilot study, currently in progress, is looking at the potential for locally-administered budesonide in patients with precancerous lesions in the bronchus.

One strategy to improve efficacy and reduce toxicity is agent combinations. In some combinations of two agents with different presumed mechanisms of activity, synergistic or additive activity may be seen. For example, synergistic activity has been observed in rat colon studies with combinations of alpha-difluoromethylornithine (DFMO; a specific inhibitor of polyamine biosynthesis) and the NSAID piroxicam[23] and in rat mammary and prostate cancers with combinations of retinoids and antiestrogens.[24-26] Thus, the identification and evaluations of potentially effective agent combinations will be an ongoing research effort for chemoprevention.

The Prostate Cancer Prevention Trial is designed to see whether taking the drug finasteride (used to treat patients with benign prostatic hyperplasia) can prevent prostate cancer in men ages 55 and older. The drug reduces levels of dihydrotestosterone (DHT), a male hormone that plays a key role in benign prostate enlargement and is also believed to be involved in the development of prostate cancer. The trial has completed recruitment of 18,500 men, and results are expected in 2001.

In addition, certain other chemopreventive compounds are under investigation. These include oltipraz (which can change the way in which people respond to a cancer-causing agent produced by a fungus that contaminated certain foods), selenium, vitamin E, and N-acetylcysteine.

PUBLIC HEALTH IMPACT

Proof of chemopreventive drug efficacy based on cancer incidence reduction can require up to 45,000 subjects over a period of more than 10 years depending on the risk of the population under study. The impracticality of conducting such large human intervention trials, due partly to high dollar cost and the scarcity of eligible and willing patients, emphasizes the importance of more accurately predicting an individual's risk and identifying surrogate endpoint biomarkers. A challenge for the future is to define this process which will potentially reduce the size and duration of some cancer incidence trials to as few as 500 to 1,000 patients over a period of 3 years. Besides reducing the cancer burden, it is hypothesized that chemoprevention drugs could improve the quality of life for some high-risk patients who may otherwise undergo invasive screening procedures or surgical treatments.

Safety evaluation in humans is performed incrementally and often begins in individuals at high risk, and thus at greater potential for benefit. As these drugs are found to be efficacious for these high-risk patients, the public health impact of chemopreventive drug intervention will also develop incrementally since they will be justifiably qualified for use in lower-risk populations. As we develop more sophisticated evaluations to calculate those at risk a clearer picture will develop defining subsets of the population most likely to benefit from drug intervention.

CONCLUSION

The past 2 decades have seen a tremendous increase in media coverage, publications (both trade and publication), and educational programs on disease prevention, which are directed at the general population. A future challenge is educating the population on the potential additional benefits of active intervention, whether it is by prescribed drug or specific dietary substances.

The focus of chemoprevention research in the next millennium will include defining the functional and histological changes during carcinogenesis, the cancer risk conferred by these changes, their modulation in preclinical experimentation and randomized clinical trials by chemopreventive drugs, dietary agents and regimens and treatments resulting from early detection. The large number of chemoprevention research programs now ongoing ensures that the promise of chemoprevention will continue to be realized in the future.

REFERENCES

1. Kelloff GJ, Sigman CC, Greenwald P. Cancer chemoprevention: progress and promise. *Eur J Cancer.* 1999;35(13):1755-1762.
2. National Cancer Institute. Highlights of NCI's Prevention and Control programs. Available at www.graylab.ac.uk:80/cancernet/600045.html. Accessed February 20, 2000.
3. Kelloff GJ, Hawk ET, Crowell JA, et al. Strategies for identification and clinical evalulation of promising chemopreventive agents. *Oncology (Huntington).* 1996;10:1471-1484.
4. Kelloff GJ, Hawk ET, Karp JE, et al. Progress in clinical chemoprevention. *Semin Oncol.* 1997;24:241-252.
5. Hong WK, Sporn MB. Recent advances in chemoprevention of cancer. Science. 1997;278:1073-1077.
6. Meyskens FL. Principles of human chemoprevention. *Hematol Oncol Clin North Am.* 1998;12(5):935-941.
7. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst.* 1998;90(18):1371-1388.
8. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. *JAMA.* 1999;281(23):2189-2197.
9. Cobleigh M. Breast cancer prevention: raloxifene's role still being studied. American Society of Clinical Oncology 35th Annual Meeting May 18,1999. Available at www.medscape.com/medscape/cno/1999/ASCO/Story.cfm?/story_id=663. Accessed February 21, 2000
10. American Cancer Society. Hormonal chemoprevention for women at high risk. 1999. Available at http://www2.cancer.org/ezineCFML/dsp_storyIndex.cfm?fn=/002_05271999_0.html. Accessed February 21, 2000.
11. PDQ Screening and Prevention—Health Professionals. Prevention of colorectal cancer. Available at http://cancernet.nci.nih.gov/clinpdq/Screening_for_colorectal_cancer_Physician.html. Accessed February 22, 2000.

12. Midgley R, Kerr D. Colorectal cancer. *Lancet.* 1999;353:391-399.
13. Sinicrope FA, Lemoine M, Xi L, et al. Reduced expression of cyclooxygenase 2 proteins in hereditary nonpolyposis colorectal cancers relative to sporadic cancers. *Gastroenterology.* 1999;117(2):350-358.
14. Frolich JC. A classification of NSAIDs according to the relative inhibition of cyclooxygenase isoenzymes. *Trends Pharmacol Sci.* 1997;18:30-34.
15. Taketo MM. Cyclooxygenase-2 inhibitors in tumorigenesis (part II). *J Natl Cancer Inst.* 1998;90:1609-1620.
16. Burton TM. Monsanto's Celebrex may treat cancer. *Wall Street Journal.* September 24, 1999:B3.
17. GD Searle. Celebrex to get priority review for colorectal polyps. Press release. August 31, 1999.
18. Anon. Celebrex data requested by FDA may clarify cancer risk reduction potential. F-D-C Reports- "The Pink Sheet" January 3, 2000.
19. King J, Dozois R, Lindor N, et al. Care of patients and their families with familial adenomatous polyposis. *Mayo Clin Proc.* 2000;75:57-67.
20. Herman TS. Understanding molecular events and better chemopreventative strategies for the next millennium. American Society for Therapeutic Radiology and Oncology's 41st Annual Meeting. November 2, 1999. Accessed at http://oncology.medscape.com/Medscape/CNO/1999/ASTRO/Story.cfm?story_id=864. Accessed February 18, 2000.
21. American Cancer Society. Protective Powers of Calcium Supplements. Available at http://www2.cancer.org/ezineCFML/dsp_storyIndex.cfm?fn=002_03011999_0.html. Accessed February 24,2000.
22. Wattenberg LW, Wiedmann TS, Estensen RD, et al. Chemoprevention of pulmonary carcinogenesis by aerosolized budesonide in female A/J mice. *Cancer Res.* 1997;57:5489-5492.
23. Reddy BS, Nayini J, Tokumo K, et al. Chemoprevention of colon carcinogenesis by concurrent administration of piroxicam, a nonsteroidal anti-inflammatory drug with D,L-a-difluoromethylomithine, an ornithine decarboxylase inhibitor, in diet. *Cancer Res.* 1990;50:2562-2568.
24. Anzano MA, Byers SW, Smith JM, et al. Prevention of breast cancer in the rat with 9-cis-retinoic acid as a single agent and in combination with tamoxifen. *Cancer Res.* 1994;54:4614-4617.
25. Anzano MA, Peer CW, Smith JM, et al. Chemoprevention of mammary carcinogenesis in the rat: combined use of raloxifene and 9-cis-retinoic acid. *J Natl Cancer Inst.* 1990;88:123-125.
26. Lucia MS, Anzano MA, Slayter MV, et al. Chemopreventive activity of tamoxifen, N-(4-hydroxyphenyl)retinamide, and the vitamin D analogue Ro24-5531 for androgen-promoted carcinomas of the rat seminal vesicle and prostate. *Cancer Res.* 1995;55:5621-5627.
27. National Cancer Institute. 1998 Annual Report: Cancer Prevention Research Program. Available at http://dcp.nci.nih/gov/CB/AR98.htm. Accessed February 21, 2000.
28. Adams V. Breast cancer prevention with tamoxifen. Drug Store News. Available at http://secure.1f.com/drug/ce/99_5_lesson.htm. Accessed February 29, 2000.
29. Hawkey CJ. Cox-2 inhibitors. *Lancet.* 1999;353:307-314.
30. Cada DJ. Celecoxib. *Hosp Pharm.* 1999;34:560-576.
31. GD Searle and Co. Celecoxib package insert. Chicago, IL, May 1999.