

CANCER PREVENTION: THE FUTURE FOR ONCOLOGY

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Cancer prevention research seeks to identify the preventable causes of cancer, both positive and negative, and to reduce cancer incidence by effective application of prevention strategies in target populations.(1) Three major approaches to cancer prevention currently exist.

Primary prevention focuses on reducing risk of cancer in normal asymptomatic individuals. Epidemiologic studies provide evidence that environmental factors such as chemicals, viruses, and radiation exposure play an important role in cancer incidence. It is estimated that 70% to 80% of all cancer is attributable to environmental risk factors and that elimination of these factors could have a profound positive effect on cancer incidence and mortality.(2) Cancer prevention strategies that minimize exposure to known causative agents will undoubtedly reduce cancer incidence. Reduction to exposure to carcinogens in tobacco smoke is an example of an effective preventive strategy based on exposure limitation. Similarly, limits placed on occupational exposure to chemical carcinogens such as asbestos or benzene represent an obvious and undoubtedly effective means of reducing cancer incidence. Unfortunately, for the majority of cancers, a single physical or chemical etiologic factor has not been identified, thereby limiting the application of exposure-based prevention strategies.

Another type of exposure-based strategy relies on dietary modification. It is possible to reduce suspected cancer-promoting constituents such as mutagens and fat or to enhance the intake of preventive agents such as fiber and thereby affect cancer incidence.(3) However, due to the influence of countless variables such as bioavailability, me-

tabolism, heredity, lifestyle, and period of exposure, the ability to predict the combined impact of various dietary constituents on cancer risk reduction is limited.(4)

Chemoprevention is an expression coined more than 15 years ago by Sporn and Roberts (5) to describe the novel approach of reducing cancer risk in susceptible individuals by administering a specific natural or synthetic chemical compound to reverse, suppress, or delay the process of carcinogenesis. The definition of chemoprevention does not include food compounds ingested as a normal diet. Chemoprevention has been a successful strategy of primary prevention in some common epithelial cancers, e.g., Tamoxifen for women at risk for breast cancer and Finasteride for men at risk for prostate cancer (see below).

Secondary prevention is utilized to decrease progression of a pre-neoplastic process through screening to accomplish earlier detection or by utilizing chemotherapy to reverse a pre-neoplastic lesion, e.g., endoscopic resection of a villous adenoma or the use of calcium to reduce adenomatous polyps in the large bowel. The natural history of cervical cancer with its long preinvasive stage and the availability of a simple test, the Papanicolaou smear, makes cervical cancer ideal for screening.

Tertiary prevention seeks to decrease morbidity of established disease. The best example is the use of antiestrogen to prevent second breast cancer in women or cis retinoic acid to delay second oral squamous cell cancer in men and women with head and neck cancer.

Tumor Cell Biology

As the understanding of tumor cell biology expands, the development of general approaches to chemoprevention based on broad modification of overall exposure levels or diet is giving way to more refined and potentially more effective pharmacologic interventions. It is this understanding of the cellular transformation systems and the regula-

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tory changes that are associated with abnormal growth and proliferation which form the basis for designing new, effective chemo-prevention agents.(6)

Rather than a single initiating event, multiple changes in the cell genome acting in concert are required for the development of human cancer.(7) Normal cells undergo initiation, promotion, clonal expansion, and progression in a step-wise process to transform into a malignant neoplasm (Fig.1). If the carcinogenic factor is not detoxified or the damaged DNA is inadequately excised, initiation occurs with the conversion of a normal cell to its transformed counterpart. Initiation is a common event, but in the absence of a promoter, most initiated cells remain repressed during an individual's lifetime and never continue further through the subsequent stages of cancer development. The long latency period that characterizes human cancer is probably due to the requirement for multiple initiating or promoting events.

The next step in the multistage process of carcinogenesis is promotion, where repression of the initiated transformed cell is negated and the induction of cellular proliferation and hyperplasia occurs. Increased tumor incidence and/or shortened latency period to tumor appearance are the hallmarks of tumor promotion. Many chemical promoting agents modulate a designated receptor molecule or stimulate a ligand that modifies a specific region of DNA. Protein kinase C is the principal cellular receptor for the tumor promoter 12-O-tetradecanoylphorbol-13 acetate (TPA).(8) Endogenous steroid hormones probably function like tumor promoters over the lifetime in humans. These promoter receptor complexes alter genomic expression and select proliferative capabilities leading to clonal expansion. The number and type of genetic alterations that occur during initiation will influence the probability of initiated cells transforming into malignancy with each repeated cell replication. Promotion does not involve specific molecular changes in DNA structure, but rather affects the expression of the genome. Continued exposure to a promoting agent is necessary for the initiated cell to replicate, undergo clonal expansion, and proceed in-

to the stage of progression. In the unique situation where an onco-genic virus infects the cell by its incorporation of the entire viral genome, the stage of promotion is frequently bypassed with direct entry into the progression process.

Unlike initiation and promotion, which are substantially influenced by events external to the target cell, the factors that drive progression are largely the result of endogenous changes in the expanded clone of preneoplastic cells. Genetic changes in the mutated cells such as inactivation of tumor-suppressor genes and activation of proto-oncogenes result in alterations in growth control, defects in terminal differentiation, enhanced metastatic potential, and resistance to cytotoxicity. (9) The accumulation of genetic alterations that characterize progression from normal to neoplastic tissue has been delineated for colon cancer.(10)

The p53 tumor-suppressor gene is mutated in malignant tumors of the lung, breast, brain, bladder, bowel, and liver. Normal p53 function transiently arrests the cell cycle in G1 or irreversibly results in programmed cell death (apoptosis); loss of p53 activity can provide a distinct selective advantage to human tumors.(11) During tumor progression, angiogenesis allows the tumor to grow beyond 1 to 2 mm in size. Eventually, the tumor cells will metastasize to distant tissues by disseminating through the vascular system.

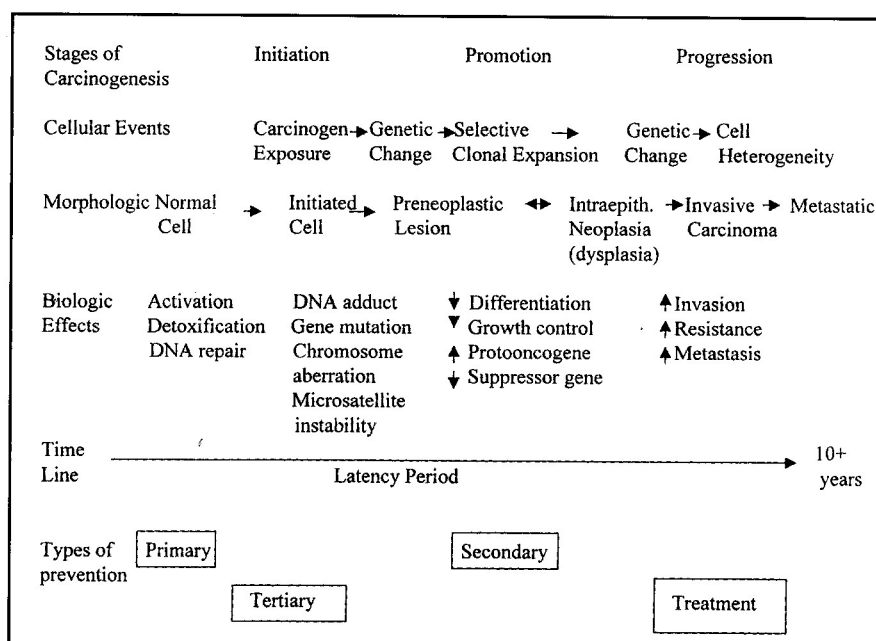


Figure 1. Relationship of Cancer Causality and Biology to Prevention
Based on schemas by Shields & Harris, JAMA, 1991, 7 Meyskens 1988,6 and Weinstein 1991.8

Intraepithelial Neoplasia

Intraepithelial neoplasia (IEN) is a non-invasive lesion that is generally recognized as moderate to severe dysplasia; it is on the causal pathway from normal tissue to cancer. It is characterized by genetic abnormalities, loss of cellular control function, and some of the phenotypic hallmarks of invasive cancer. Cervical intraepithelial neoplasia (CIN) 2-3 is a prototypic example because it is a near-obligate cancer precursor, a risk marker for cancer, and a disease that requires surveillance (PAP smears) and treatment intervention (traditionally surgical excision). (12)

Two of the major factors affecting the rate of progression of intraepithelial neoplasia are the cellular mutation rate, which is enhanced by environmental carcinogens, and the cellular proliferation rate, which is enhanced by agents that include sex hormones, inducers of chronic inflammation, and irritant chemicals that stimulate reactive hyperproliferation. Thus, a possible chemoprevention strategy for intraepithelial neoplasia in humans is to develop drug or drug combinations that will block mutagenic carcinogens and/or prevent epithelial hyperproliferation.

Field Carcinogenesis

In 1953, Slaughter et al (13) described multiple independent premalignant foci progressing concurrently and at different rates to form multiple second primary tumors (SPTs). He coined the term "field cancerization" for this process, which reflects an effect of carcinogen exposure on a large epithelial surface or field. The clinical magnitude of this problem is best illustrated by the 4% to 7% annual incidence of second primary tumors in patients with primary carcinoma of the head and neck and lung.(14) According to field carcinogenesis theory, primary tumors and related SPTs result from progression of commonly initiated, although genetically different, premalignant lesions. Chung et al.(15) analyzed p53 mutations in 31 patients with primary head and neck cancers and related STPs. Molecular support for the independent origin of the tumors is provided by two types of p53 discordance: (1) the occurrence of p53 mutations in one but not the other related primary tumor in 16 cases; and (2) the specifically distinct mutations of p53 in primary tumors and SPTs in five cases.

Markers of carcinogenesis

Biomarkers have been proposed for use as surrogates or intermediate endpoints to the traditional clinical trial endpoints such as clinical response or cancer-related mortality because these traditional endpoints in prevention trials require protracted follow-up.(16) Biomarkers have a number of applications for the management of individuals with cancer or at risk for cancer. A single biomarker or panels of individual biomarkers may be used to provide a clear picture of the state of cancer progression. Biomarker analysis can be used in a variety of other cancer-related applications, including risk or susceptibility assessment, early detection, prognostic determination, and disease progression. Ideally, a suitable biomarker should: (1) be detectable in small tissue specimens that permit serial biopsies of the same site; (2) be expressed differently in normal than in high-risk or premalignant sites and in accordance with carcinogenic changes; (3) be subject to modulation by chemoprevention agents; and (4) have a low rate of spontaneous change.(17)

Table 1 is one classification schema for intermediate end-point biomarkers.(18) Traditionally, precancerous lesions such as polyps, leukoplakia, keratosis, or epithelial tissue dysplasia have served as macroscopic or microscopic evidence of late stages of the carcinogenesis process. Elevated micronuclei in the aerodigestive tract and altered or increased proliferation markers such as PCNA in the colon are consistent findings in high-risk individuals; however, studies to date indicate that measurement of both markers is associated with technical problems, possibly due to sampling error and random or spontaneous marker changes. In an attempt to find more specific markers, investigators are beginning to utilize molecular genetic techniques, such as those described by Fearon and Vogelstein,(10) in the development and progression of dysplastic lesions leading to invasive colon carcinoma. One of these markers, p53 mutation, is associated with an early stage of carcinogenesis in the aerodigestive tract, breast, and skin, but marks later-stage carcinogenesis in the colon and bladder.

A number of specialized biomarkers have been developed as targets for cancer prevention strategies. The lung cancer autocrine growth factor, gastrin-releasing peptide, appears to be critical to human fetal lung development and is found at only low levels of expression in normal individuals but at elevated levels in bronchial secretions and uri-

Table 1
Surrogate Endpoint Biomarkers

Morphologic

Uterine hyperplasia
Colorectal adenoma
Cervical intraepithelial neoplasm
Prostatic intraepithelial neoplasm
Ovarian microadenoma and epithelial invagination
Nuclear morphometry; DNA ploidy
Apoptosis TUNEL

Proliferation

S-phase fraction
Ki 67, MiB-1 Antibody expression
Proliferating Cell Nuclear antigen (PCNA)
Bromdimyundine uptake
DNA cytometry or immunohistochemical labeling

Differentiation

Cell markers, e.g. Keratin 17, vimentin
Altered cell surface antigen expression
Mucin or apomucin
Cytokeratin
Mn antigen

Genetic/Reg

Gene expression, e.g., C-Myc, C-ras
Growth factor t g f-b
Tumor suppressor, e.g., p53
Loss of heterozygosity
Microsatellites, RER
DNA methylation

Biochemical

Hormone level/metabolism
Ornithine decarboxylase activity
PSA
HPV expression (16,18)

Reference: Kelloff, et al., 1996 (16); Szarka, 1994 (58)

ne samples in smokers as well as in patients with resected lung cancers.(19) The activity of the prostaglandin biosynthetic cascade has been used to monitor effects of nonsteroidal anti-inflammatory agents on epithelial tissue.(20) Ornithine decarboxylase (ODC) and polyamine levels are sensitive monitors of difluoro-methylornithine (DFMO) intervention.(21) The activity of the Phase II detoxification enzymes glutathione s-transferase and epoxide hydroxylase has served as an indicator of increased tissue risk for carcinogenesis and also as a model system for the study of anticarcinogens such as oltipraz.(22)

Identification of candidate chemoprevention on agents

The identification of agents with potential chemopreventive capacities is based on epidemiologic studies and laboratory animal studies.(23) The initial agents used in chemoprevention were suggested by epidemiologic studies in which compounds that occur naturally in the diet were shown to be associated with decreased cancer incidence (vitamin A, selenium, and vitamin E, among others).(1) More than 1,000 agents have been reported to inhibit the process of carcinogenesis; however, the number of compounds that have been thoroughly evaluated and advanced to clinical trials is much smaller.

The specific chemopreventive activities and structures are grouped into three general classes: antiproliferation, carcinogen-blocking agents, and antioxidants. Antiproliferatives comprise a diverse group of compounds including DFMO, antihormones, calcium, and retinoids. Decarboxylation of ornithine by the rate-limiting enzyme ODC is required for the biosynthesis of polyamines such as putrescine, spermine, spermidine. Polyamines form noncovalent interactions with macromolecules such as nucleic acids and proteins, suggesting a necessary role in cellular proliferation and differentiation.(24) DFMO alkylates irreversibly block ODC, preventing conversion of ornithine to putrescine. Preclinical studies have established that DFMO has chemopreventive activity in several mouse and rat systems.(25) Clinical studies have established the dose-limiting side effects of DFMO to include diarrhea, anemia, leukopenia, thrombocytopenia, and loss of hearing acuity. However, lower nontoxic doses may produce measurable lowering of polyamine content in the bowel, without the appearance of side effects.(21)

One of the most widely studied antihormonal agents is tamoxifen. Several mechanisms have been postulated for tamoxifen's antitumor effect including: (1) competition with estradiol for receptor sites in the nucleus, thereby leading to estrogen blockade; (2) modulation of the production of transforming growth factor alpha and transforming growth factor beta, which are involved in cell proliferation; and (3) increase in sex hormone-binding globulin, thereby decreasing free-estrogen availability.(26) Based on evidence in adjuvant trials of women with early-stage breast cancer that demonstrated a 38% reduction in new primary breast cancers with tamoxifen in comparison with placebo,(27) the agent was proposed for primary prevention in women at high risk for breast cancer. The Breast Cancer Prevention Trial (P-1), (28) showed that tamoxifen reduced the risk of invasive breast cancer by 49% (43.4 versus 22.0 per 1,000 women in the placebo and tamoxifen groups, respectively $p < 0.00001$). Tamoxifen also reduced the risk of noninvasive breast cancer by 50% (two-sided $p < 0.002$); however, no difference was observed in the occurrence of estrogen-receptor-negative tumors. Secondary endpoints included no change in the annual rate of ischemic heart disease; a reduction in hip, radius, and spine fractures; an increase in endometrial cancer; and an increase in rates of stroke, pulmonary embolism, and deep vein thrombosis. The new NSABP chemoprevention trial, P-2, will compare the toxicity, risks, and benefits of the selected estrogen-receptor modulator (SERM) raloxifen with those of tamoxifen.

Finasteride is a 5- α -reductase inhibitor that blocks the conversion of testosterone to dihydrotestosterone, which in turn is the major androgenic compound within the prostate gland. Preclinical studies have established a beneficial effect in reducing prostatic hypertrophy and in inhibiting human prostate cancer cell lines. In a national trial, finasteride decreased benign prostatic hypertrophy in adult males with minimal or no toxicity.(29) The initial analysis of the randomized double-blind placebo-controlled trial of Finasteride for the prevention of prostate carcinoma shows a 24.8% reduction in prevalence over a seven year period (18.4% occurrence in the Finasteride group vs. 24.4% in the placebo group); however the Finasteride-treated men experienced more tumors of Gleason grade 7, 8, 9 or 10 (37%) than did the placebo group (22.2%). The authors conclude that Finasteride prevents or delays the appearan-

ce of prostate cancer but this possible benefit must be weighted against sexual side effects and the increased risk of high-grade prostate cancer. (30)

The retinoids include natural vitamin A (retinol), and the synthetic derivative fenretinoid. The retinoids control cell growth and differentiation at the level of gene expression through interaction with nuclear receptors.(31)(32) Preclinical studies demonstrate chemopreventive activity with the retinoids in mammary gland, bladder, and skin.(33) Retinoids inhibit the proliferation and progression stages of carcinogenesis.(34) They induce terminal differentiation in selected cells and stimulate intracellular communication and are immunostimulants. Fenretinide (4-HPR) stimulates programmed cell death (apoptosis).(35) However, potential toxicity is associated with the retinoids (i.e., vitamin A and its analogues accumulate in the liver and cause hepatic damage). They can also cause eye damage and they are teratogens. Several clinical trials using retinoids are under way or have been completed. 13-cis-retinoic acid will suppress or reverse oral leukoplakia (36) and second primaries of the upper aerodigestive tract.(37) Topical tretinoin 0.372% will reverse low-grade uterine cervical moderate dysplasia.(38)

The chemopreventive potential of calcium was first shown by its protective effect against proliferation in the colon of patients at high risk for cancer.(39) A total dose of 2,000 mg elemental calcium per day is the likely efficacious and non-toxic dose that can be recommended for people at risk for bowel cancer.(40) A recently completed trial (41) demonstrated that calcium supplement will delay or prevent adenomatous polyp formation in patients with previous colorectal cancer.

Blocking agents act by preventing the conversion of a pro-carcinogen into the active carcinogen. Examples include the inhibition of nitrosocarcinogen formation by ascorbic acid, α -tocopherol, and the phenols.(42) However, the agents with the most potential in this class are agents that enhance carcinogen detoxifying enzymes, especially the Phase II metabolic enzymes including glutathione s-transferases. Tallalay (43) has emphasized the desirability of selecting chemopreventive agents that induce mostly Phase II metabolic enzymes, as opposed to compounds that induce both Phase I mixed-function oxidases and Phase II enzymes. Compounds whose chemopreventive activities fall into this classification include indoles, flavones, phe-

nolic compounds, beta-carotene, ascorbic acid, vitamin E, selenium, oltipraz, and ellagic acid.

The third class of inhibitors are the antioxidants such as beta-carotene, curcumin, N-acetyl-L-cysteine, the nonsteroidal anti-inflammatory drugs (NSAIDs), and polyphenols. These agents directly trap electrophilic sites on activated carcinogens, scavenge oxygen-free radicals, and organic-free radicals, and terminate lipid peroxidation.(44) Agents that enhance the Phase II metabolizing enzymes indirectly elevate the electrophile trapping potential by increased glutathione production and induction of the enzyme glutathione peroxidase. Antioxidant mechanisms may be both antitumorigenic and antiproliferative.(25)

Aspirin and the other NSAIDs inhibit the enzyme cyclooxygenase-2 (COX-2), which catalyzes the first step in conversion of arachidonic acid to the prostaglandins prostacycline and thromboxanes. The primary chemopreventive effect of cyclooxygenase inhibition is thought to be related to changes in tissue levels of these important biologic modifiers that play a role in cell proliferation, neoplasia, and immune response.(45) In animal efficacy screens, the NSAIDs were active in rat colon, rat mammary, mouse bladder, and mouse skin, as well as in 1,2-dimethylhydrazine (DMH)-induced colon tumors in mice.(25) In preliminary clinical studies, Sulindac has shown dramatic effects in causing the total or almost total regression of colorectal adenomatous polyps in patients with familial adenomatous polyposis.(46) Celecoxib is approved by the Federal Drug Administration for the management of adenomas in patients with familial adenomatous polyposis based on a phase III trial reported by Steinbach, et al.(79) Although epidemiologic case-control studies suggest that aspirin or NSAIDs may reduce the risk of death from colon cancer, the only prospectively randomized control study of aspirin in male physicians failed to show an effect on colon cancer incidence and mortality.(48) In clinical trials, beta-carotene has not been effective in preventing skin cancer, (49) bowel polyps,(50) or lung cancer deaths in Finnish smokers.(51)

With a better understanding of tumor cell biology, including an understanding of the changes in cellular genetics and a better understanding of proto-oncogenes and tumor-suppressor genes and their proteins, it may be possible to develop specific agents to target specified steps in the process of carcinogenesis.(52) It may also become possible through the use of molecular genetics to identify the cancer-prone phenotype or genotype and thus target the intervention to those individuals at greatest risk of having the disease develop as well as those likely to respond to the drug in question. For instance, work on glutathione S-transferase μ indicates that people who inherit the null genotype are at greater risk for smoking-related cancers but that they could also be the best candidates for therapy with blocking agents that enhance carcinogen-detoxifying enzymes.(53)

The rationale for using a combination of chemopreventive agents is to increase efficacy and to reduce toxicity. As shown in Figure 2, the carcinogenic process could theoretically be interrupted or influenced by combining agents that affect different pathways, i.e., decrease mutagenesis, increase differentiation, or increase apoptosis.(54) Several combinations have shown synergism, that is, the inhibitory potency of the

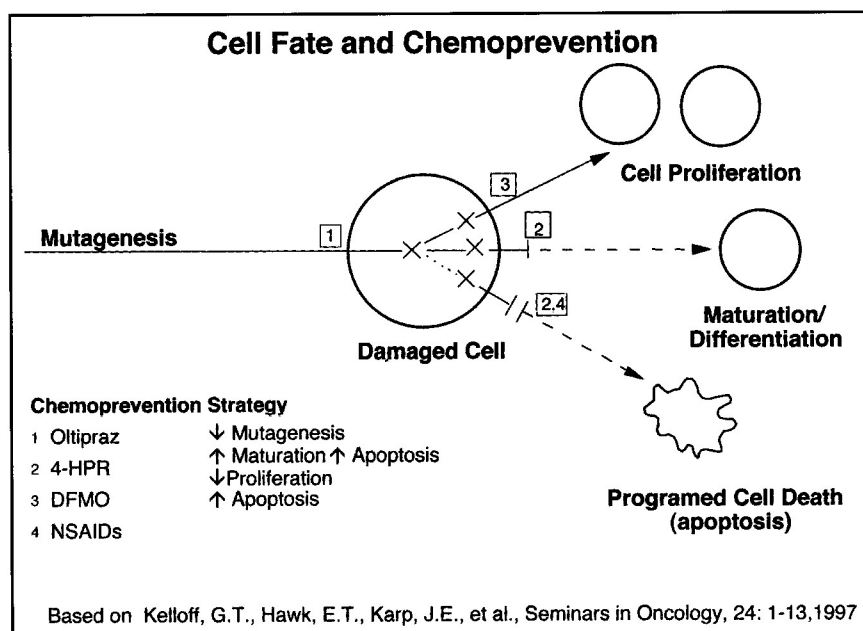


Figure 2. Cell Fate and Chemoprevention Based on Kelloff, *Seminars in Oncology*, 1997.54

No. of

Study Population	Intervention	Subjects	Endpoint	Result	RR(95%C.I.)
High Risk Females	Tam	13,388	BrCa	Pos.	0.51 (0.39-0.66)
Males & Females	ROH	2,297	Skin scc	Pos.	0.74 (0.56-0.99)
Resected Adenoma Pts.	Ca++	930	Colon adenomas	Pos.	0.81 (0.67-0.99)
Elderly Patients	Se	1,312	Skin scc	N.S.	1.10 (0.95-1.20)
Linxian Pop.	ROH + zn	29,584	All Ca	N.S.	1.00 (0.89-1.11)
Male Physicians	BC	22,071	All Ca	N.S.	0.98 (0.91-1.06)
High Risk Males	Fenasteride	18,000	Prostate Ca	Pos.	0.75 (0.64-0.81)
Finnish Smoker	BC	29,133	Lung Ca	Neg.	1.16 (1.02-1.33)
Shipyard Workers/smokers	BC + ROH	18,314	Lung Ca	Neg.	1.28 (1.04-1.57)

Tam = Tamoxifen - ROH = Retinol - Se = Selenium - Zn = Zinc - BC - β -carotene

References: Lippman SM, Lee JJ, Sabicki AL. JNCI 20:1514, 1998 (35), Baron, 1997 (41)

combi-nation of agents is greater than the sum of the potencies of single agents. Synergistic chemopreventive activity has been reported for DFMO and piroxicam in rat colon(55) and 4-HPR and tamoxifen in rat mammary gland.(56)

Chemoprevention trials

As with cancer chemotherapy studies, clinical trials in chemoprevention can be classified as Phase I, II, or III.(57) Phase I trials are primarily toxicity-pharmacokinetic studies of an agent after initial preclinical animal studies indicate useful activity. The objective of this phase is to assess incidence and significance of toxicity and to verify the effect on tissue biomarkers as well as to establish drug pharmacokinetics, tissue distribution, interactions, and metabolism. Phase II studies are conducted to establish activity using intermediate endpoint biomarkers rather than an invasive cancer endpoint. The size of the population for Phase II trials depends on the number of participants necessary to detect a statistically significant change in the study's chosen intermediate endpoint. After short-term activity is established, Phase III trials are conducted to establish long-term efficacy in reducing cancer incidence. Phase III trials typically require thousands of subjects and 5 to 10 years or more to complete.(58)

Table 2 is a list of NCI-sponsored randomized phase III chemoprevention studies.(41, 35, 30, 28)

Promise of Future Success

Clinicians and investigators agree that intraepithelial neoplasia (IEN) has a known probability of leading to cancer.(12) The morphologic changes associated with IEN are part of the cancer process and the lesions of genetic progression manifest themselves as cytologic abnormalities of neoplasia including increased nuclear size, abnormal nuclear shape, increased nuclear stain uptake, variations in cellular size, shape, and stain uptake, increased mitosis, abnormal mitosis, and disordered maturation. Therefore, IEN is a potential surrogate endpoint biomarkers that can accelerate chemoprevention drug development. In the future, molecular markers of carcinogenesis may be validated as Surrogate Endpoint Biomarkers (SEBs) in situ within IEN.(59) It is likely in the not too distant future that patterns of change representing carcinogenesis will be relatively easy to measure. This process should evolve with the progress that is being made in understanding and analyzing systems biology. The molecular pathology within IEN lesions, or even before appearance of these lesions, could also allow better identification of individuals at risk, improved study efficiency, and provide better quantitative estimation of drug efficacy than effects on IEN alone.(60)

Besides the great strides being made in tissue and molecular imaging, functional genomic and proteomic research holds promise for the development of non-invasive

markers. Of great interest are the identification of markers associated with circulating cellular DNA and the in situ imaging of gene expression. Recent work led by Petricoin, et al. in people at risk for prostate and ovarian cancer(61), and by Rosenwald and Staudt in patients with leukemias and lymphoma issues in a new era for molecular oncology.(62) It is possible that peripheral blood cells will serve as initial targets for development of genomic and proteomic profiles for identifying high risk subjects and for monitoring effects of drug interventions in early stages of carcinogenesis. The ability to measure the functional effects

of drug interventions will also be important to chemopreventive drug development.

With rigorous attention to methodology, and to emerging scientific data and new technologies, it is possible that validated markers will improve the efficiency of drug development, while also opening the door to even earlier identification of individuals at risk, i.e., those with predysplastic molecular lesions that occur before intraepithelial neoplasia. To realize this future, there will need to be hard work and proven methodology to assure success for individualized chemoprevention.

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