Progress in Cancer Chemoprevention: Perspectives on Agent Selection and Short-Term Clinical Intervention Trials

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Abstract

The basic cancer-related chemical and biological sciences, pathology, and epidemiology have contributed to the understanding that antimitogenesis and antiproliferation are the important general mechanisms of chemoprevention and to the development of antimutagenic and antiproliferative agents as potential chemopreventive drugs. These disciplines have also provided the biochemical and histopathological bases for identifying intermediate biomarkers that can be used as surrogate end points for cancer incidence in clinical chemoprevention trials and for selecting cohorts for these trials. Particularly important as histological biomarkers of cancer are the cytonuclear morphological and desmiometric changes that define intraepithelial neoplasia (IEN). IEN changes are on the causal pathway to cancer. They may serve as target lesions in Phase II chemoprevention trials and as standards against which other earlier cellular and molecular biomarkers can be evaluated. Strategies for the clinical evaluation of chemopreventive agents have been defined for seven targets—colorectal, prostate, lung, breast, bladder, oral, and cervical cancers. Cohorts have been identified for short-term Phase II trials that investigate the effects of chemopreventive agents on IEN and on earlier biomarkers. Patients with adenomas serve as a cohort for trials in colon. One cohort for Phase II trials in prostate is patients with early stage cancers scheduled for prostatectomy; another is patients with prostatic intraepithelial neoplasia (without prostatic carcinoma). Patients treated for lung cancer are at high risk for bronchiol dysplasia and second cancers; such patients are a cohort for Phase II trials in lung cancer. Presurgical breast cancer patients and patients with ductal or lobular carcinoma in situ are cohorts for studies in breast. Patients with superficial bladder cancers (T1/T2, with or without carcinoma in situ) are cohorts for studies of chemoprevention in bladder, and patients with dysplastic oral leukoplasia are evaluated for chemoprevention of oral cancers. Cervical intraepithelial neoplasia is a prototype IEN, and patients with cervical intraepithelial neoplasia are a cohort for studies of cervical cancer.

Chemoprevention may be defined as the inhibition or reversal of carcinogenesis, a process that starts with cells of normal morphology and ends with invasive cancers. Chemicals that inhibit carcinogenesis become chemopreventive drugs on the successful completion of clinical trials. Chemoprevention is necessarily linked to the mechanisms of carcinogenesis. Several cancer-related scientific disciplines (the basic chemical and biological sciences, pathology, and epidemiology) contribute to understanding how best to interrupt carcinogenesis mechanisms and develop chemopreventive agents most effectively.

Basic Sciences Perspective

The cancer-related basic sciences, including cellular and molecular biology, chemical carcinogenesis, and molecular virology, focus on the series of specific biochemical, cellular, and molecular events in carcinogenesis. These events, which have been reviewed extensively in the literature (e.g., Ref. 1), include formation and activation of carcinogens, induction of genetic damage, stimulation of cell proliferation, and disruption of normal cell growth and differentiation.

Fig. 1 illustrates how chemopreventive agents might work against these events during the various phases of carcinogenesis and what cellular and molecular targets exist for chemoprevention drug development efforts. For example, chemopreventive agents may prevent the genetic damage that results in initiation. In Fig. 1, genetic damage is shown to be a target for chemoprevention from preinitiation to the formation of clinical cancer. As Fearon and Vogelstein et al. (2) have shown in colon, it is likely that genetic damage (mutagenesis) is occurring throughout the premalignant and malignant phases of carcinogenesis. Because inhibition of genetic damage is possible at many sites, antimutagens are good candidates for development as chemopreventive agents. Most of the remaining potential chemoprevention mechanisms depicted in Fig. 1 involve control of cell growth and proliferation; therefore, antiproliferatives, chemicals that exert this control, are also good candidates for development as chemopreventive agents.

The specific biochemical pathways that underlie these mechanisms provide leads to identify potential chemopreventive agents. For example, polyamines are essential to cell growth and proliferation, and polyamine levels are higher in many cancer and other very rapidly proliferating cells than in normal cells. Inhibitors of polyamine synthesis have been designed to slow cell growth. One such agent is DFMO, a specific irreversible inhibitor of ODC, a critical enzyme in polyamine biosynthesis. DFMO prevents growth of tumor cells and has chemopreventive activity in numerous animal models (reviewed in Ref. 3).

The mechanisms suggest that more general pharmacological activities also have chemopreventive potential. An example is compounds that scavenge electrophiles such as activated carcinogens. Dithiothiones and allylic sulfides increase cellular GSH levels, and GSH is known to trap electrophiles and oxygen free radicals (4, 5). Oltipraz, a dithiothione, and allylic sulfides such as dialyl sulfide have well-documented chemopreventive activity (e.g., Ref. 6).

Table 1 is a classification of currently well-known chemopreventive agents listed according to structure or pharmacological effects associated with chemopreventive activity. This classification is presented with the caveat that little is known about chemoprevention, and chemopreventive agents have multiple activities that may obscure the most important mechanisms (note that many of the chemicals listed in Table 1 fall into more than one class). In Table 1, the specific chemopreventive activities and structures are grouped into three general classes. The first general class is carcinogen blocking agents, which are primarily antimutagenic. Carcinogen blocking can be produced, for example, by inhibiting carcinogen activation or enhancing carcinogen detoxification. The second class, antiproliferatives, works through such specific mechanisms as ODC inhibition, protein kinase

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1 The abbreviations used are: DFMO, 2-difluoromethylnornithine; BCG, Bacillus Calmette-Guérin; CIN, cervical intraepithelial neoplasia; CIS, carcinoma in situ; DCIS, ductal carcinoma in situ; EGF, epidermal growth factor; EGF-R, epidermal growth factor receptor; FAP, familial adenomatous polyposis; GSH, glutathione; 4-HPR, all-trans-N-(4-hydroxyphenyl)-retinamide; HPV, human papilloma virus; IEN, intraepithelial neoplasia; LCIS, lobular carcinoma in situ; NKK, 4-(N-methylnitosamino)-1-(3-pyridyl)-1-butanone; NSAID, nonsteroidal antiinflammatory drug; ODC, ornithine decarboxylase; PCNA, proliferating cell nuclear antigen; PIN, prostatic intraepithelial neoplasia; PSA, prostate specific antigen; TCC, transitional cell carcinoma; TGF-ß, transforming growth factor ß; TIS, transitional cell carcinoma in situ; TRUS, transrectal ultrasound.

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Antioxidants

S-allyl-L-cysteine, curcumin, N-acetyl-L-cysteine, NSAIDs, and polyphenols. Antioxidants scavenge reactive oxygen species and organic free radicals. These activities may be either direct or indirect effects of the antioxidant agent. Indirect antioxidant effects include enhancement of the Phase II metabolizing enzymes, thereby increasing intracellular GSH and inducing GSH peroxidase. Antioxidants can be both antimitogenic (7) and antiproliferative (8).

Pathology Perspective

The pathologist views carcinogenesis at the tissue or organ level. Boone et al. (9-11) have described the pathology of epithelial cancer as it relates to chemoprevention. His characterization applies to human and experimental carcinogenesis and presents carcinogenesis as a continuum at the tissue level, i.e., from normal tissue to IEN to cancer. Synonyms for IEN, the stage of neoplasia which appears prior to invasion across the epithelial basement membrane, are dysplasia, precancer, and premalignant or preneoplastic neoplasia. Lesions of the uterine cervix have served as the prototype for IEN, exhibiting mild, moderate, and severe dysplasia, also classified as CIN I, II, and III, respectively. Numerous studies have shown that the vast majority of CIN III patients progress to invasive neoplasia (cancer), and only a few CIN III lesions regress spontaneously (e.g., Refs. 12 and 13).

As addressed later in this paper in the discussion of clinical evaluation strategies, it is highly desirable that early, precancerous lesions (intermediate biomarkers) be identified which can serve as surrogate end points for cancer incidence in chemoprevention trials and, more importantly, as targets for chemoprevention. A significant aspect of the pathologist’s view of carcinogenesis is the observation that IEN can serve as reliable intermediate marker lesions, which can be observed for modulation by chemopreventive agents in a period of months (13), in contrast to the years of observation required by chemoprevention studies that use cancer incidence reduction as the endpoint. IEN thus provide the most promising surrogate end points for cancer incidence and provide standards for validation of other genetic, proliferation, differentiation, and biochemical intermediate biomarkers that are under study as surrogate end points (9-11).

As a result of initiating genetic alterations studied by the basic scientist, the pathologist observes a neoplastic cell population which undergoes a continuous progression of increasingly aberrant morphological changes. These changes are the phenotypic expression of clonal evolution. Each step of the evolutionary process is made up of multiple paths as suggested by Vogelstein and his associates (e.g., Ref. 2). For chemoprevention strategy, the important factor is that carcinogenesis is a continuum of small, randomly occurring mutation/clonal expansion steps within the IEN population that lead to invasiveness, at which point the neoplastic lesion is called cancer. Boone (9-11) reviewed the seven morphological criteria for IEN: increased nuclear size; abnormal nuclear shape; increased nuclear stain uptake; nuclear pleomorphism; increased mitoses; abnormal mitoses; and disordered

C inhibition, and antiestrogenic activity. Antiproliferative agents include retinoids, polyphenols, antihormones, calcium, DFMO, and fluasterone. The third class, antioxidants, includes agents such as S-allyl-L-cysteine, curcumin, N-acetyl-L-cysteine, NSAIDs, and polyphenols. Antioxidants scavenge reactive oxygen species and organic free radicals. These activities may be either direct or indirect effects of the antioxidant agent. Indirect antioxidant effects include enhancement of the Phase II metabolizing enzymes, thereby increasing intracellular GSH and inducing GSH peroxidase. Antioxidants can be both antimitogenic (7) and antiproliferative (8).

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\begin{array}{|l|}
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\text{Table 1 Pharmacological and chemical structural classification of promising chemopreventive agents} \\
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\text{Antimutagens/carcinogen blocking agents} \\
\text{Phase II metabolic enzyme inducers:} \text{ N-Acetyl-L-cysteine, S-} \text{Allyl-L-cysteine,} \\
\text{oltipraz, phenhexyl isothiocyanate} \\
\text{Polyphenols:} \text{ Ellagic acid} \\
\text{Other:} \text{ Curcumin, DHEA,}^{*} \text{ fluasterone (16-fluoro-DHEA)} \\
\hline
\text{Antiproliferatives} \\
\text{Retinoids/carotenoids:} \text{ β-Carotene, 4-HPR, 13-cis-retinoic acid, vitamin} A \\
\text{Antihormones:} \text{ Flutamide, tamoxifen} \\
\text{Antiinflammatories:} \text{ Aspirin, carbonoxolone, curcumin, 18ß-glycyrrhetinic acid,} \\
\text{ibuprofen, piroxicam, sulindac} \\
\text{G6PDH inhibitors:} \text{ DHEA, fluasterone} \\
\text{ODC inhibitors:} \text{ N-Acetyl-L-cysteine, aspirin, carbonoxolone, curcumin, DFMO,} \\
\text{18ß-glycyrrhetinic acid, 4-HPR, ibuprofen, piroxicam, 13-cis-retinoic acid,} \\
\text{sulindac, vitamin} A \\
\text{Protein kinase C inhibitors:} \text{ Carbonoxolone, 18ß-glycyrrhetinic acid, 4-HPR,} \\
\text{tamoxifen} \\
\text{Other:} \text{ Calcium} \\
\hline
\text{Antioxidants} \\
\text{Antiinflammatories: See under “Antiproliferatives”} \\
\text{Antioxidants:} \text{ N-Acetyl-L-cysteine, β-carotene, curcumin, ellagic acid, fumaric acid} \\
\text{Phase II metabolic enzyme inducers: See under “Antimutagens/carcinogen blocking agents”} \\
\text{Thiols:} \text{ N-Acetyl-L-cysteine, S-} \text{Allyl-L-cysteine, oltipraz} \\
\hline
\end{array}
\]

* DHEA, dehydroepiandrosterone; G6PDH, glucose-6-phosphate dehydrogenase.
or absent differentiation. All these characteristics can be considered to be the result of genetic damage, abnormal cell growth and proliferation, or both.

Epidemiology Perspective

The epidemiologist focuses on the major causes of human cancers. It has been estimated from epidemiological studies (14) that tobacco, diet, and hormones are the major causes of human cancers, accounting for 77% of these diseases. Adding those caused by physical damage and viruses accounts for approximately 90% of human cancers. These statistics further verify that the best approach to successful chemopreventive drugs is the development of antimutagens and antiproliferatives. Many chemical compounds that are mutagenic or proliferative have been identified in tobacco smoke (15). Oxidants and high fat content in the diet may lead to lipid peroxidation, which in turn may cause mutations and cell proliferation (16). Likewise, hormones are well-known cell proliferation stimulators (17), and both physical damage and viruses have been associated with increased cell mutation and proliferation rates (1).

Considerations in Design of Clinical Studies

Major obstacles to overcome in designing clinical trials for chemopreventive drugs are the relatively low incidences and long latencies of cancers in the general population, and even in patients considered to be at high risk. To adequately evaluate chemopreventive efficacy with cancer incidence reduction as the end point requires thousands of subjects and decades of time. Such evaluations are too costly and too time consuming to be feasible in drug development. Increased understanding of carcinogenesis has provided a means of addressing these obstacles, namely, by seeking intermediate biomarkers that can be used as surrogate end points for cancer. As described above, critical intermediate biomarkers and targets of chemoprevention are IEN, which are virtually always cancer precursors, in the causal pathway to cancer, or both. Clinical trials for chemoprevention initially may be directed at IEN instead of invasive cancers. Table 2 lists potential cohorts for short-term Phase II chemoprevention trials. Generally, these cohorts provide accessible IEN lesions which can be used for rigorous dose-response studies establishing efficacy. With additional developmental work, results showing reversion, slowed progression, or inhibition of recurrence of the target lesions can be obtained within 3–24 months in such cohorts.

Further, an important component of clinical (and preclinical) studies in chemoprevention is to identify and validate earlier intermediate biomarkers that reflect the important mechanisms of carcinogenesis: proliferative lesions and signals; differentiation signals; and genetic changes such as DNA content and oncogene and tumor suppressor expression (18). Identification of such biomarkers is facilitated by such advanced technology as sophisticated imaging and sampling techniques. The intermediate biomarkers to be evaluated could be very distant developmentally from the cancer; therefore, it is critical that these biomarkers and the methods for measuring and sampling them are standardized and well validated. The reliability of early biomarkers as end points for clinical trials may be improved by using them in batteries. For both single and batteries of markers, standardization and validation are critical aspects of Phase II clinical trials.

Besides direct correlation of their modulation by chemopreventive agents to decreased cancer, major considerations in validation are that the biomarkers are expressed differentially in normal and high risk tissue and that a temporal progression can be shown from normal tissue to intermediate biomarkers to cancer. The sensitivity and specificity of the biomarkers as measures of cancer are also important. They should appear with high frequency in precancerous or high risk tissue. They should be specific for cancer in that they are expressed in high risk tissue, but not in response to other diseases or to conditions such as normal growth or wound healing.

One criterion for selecting cohorts in chemoprevention trials is expectation of a high incidence of the cancer or intermediate biomarker(s) under study within a reasonable time period. For Phase II studies, the study duration should be ≤5 years; and for Phase III trials, it was ≤10 years. Some patients previously treated for cancer are good candidates for chemoprevention trials because of high rates of recurrence or second primary cancers. For example, superficial bladder cancer patients are appropriate subjects for studies of chemoprevention of bladder cancer because the recurrence rate is approximately 50% within 6–12 months (19) and 60%–75% within 2–5 years (20, 21). As discussed under “Strategies for Major Cancers,” high rates of recurrence and new tumors also apply to colon adenomas and to lung and oral lesions. Besides providing end points that shorten the duration of chemoprevention studies, intermediate biomarkers, singly or especially in batteries, should prove useful to identify and refine cohorts for clinical trials. The presence of intermediate biomarkers, along with risk factors (e.g., genetic susceptibility or lifestyle) and exposure biomarkers (e.g., measures of carcinogen exposure, such as carcinogen-DNA adducts and asbestos) could be used to calculate relative risk of cancer development and to distinguish very high risk groups.

Because chemopreventive agents will be administered chronically, it is crucial to determine dosing regimens that provide the greatest efficacy with least risk of adverse effects. This can be accomplished by extensive dose-titration and pharmacokinetic studies in both Phase I and Phase II chemoprevention trials. One strategy that may improve efficacy and lessen toxicity is using combinations of agents. In some combinations of two agents with different presumed mechanisms of activity, synergistic or additive activity may be seen. Such improved activity may allow either or both of the agents to be administered at lower doses, thereby reducing potential toxicity. For example, synergistic activity has been observed in rat colon studies with combinations of DFMO and piroxicam (e.g., Ref. 22) and in rat mammary with 4-HPR and tamoxifen (e.g., Refs. 23, 24). As described below, treatment with these particular combinations of agents is part of the initial strategy for development of chemopreventives in colon and bladder (DFMO with piroxicam) and breast (4-HPR with tamoxifen).

Chemoprevention clinical trials need to be designed around the setting in which the patients are normally seen; this is a challenge for clinical trials science. Chemopreventive treatment and patient monitoring should not interfere with other medication, surgical procedures, and monitoring the patient may be receiving. For example, patients with T1/T2 cancer and TIS form a potential clinical cohort for chemoprevention studies in bladder. Normally the lesions are resected, and the patients are treated with BCG. As described under “Strategies for Major Cancers,” in a chemoprevention trial this normal treatment would be administered and the patients would be started on chemopreventive drugs after completing BCG treatment. Follow-up monitoring of these patients would be conducted on the same schedule as normal follow-up after BCG treatment.
Strategies for Major Cancers

Currently, cancers of seven different organ systems are being targeted for development of chemopreventive agents; colon; prostate; lung; breast; bladder; oral cavity; and cervix. The high incidences and mortality rates of these cancers are well documented (25). In each organ system cancer is associated with earlier, well-defined lesions that may serve as surrogate end points. For each of the seven sites, chemopreventive mechanisms, and potential chemopreventive agents under consideration (see Table 3).

Table 3 Aspects of chemoprevention at major cancer sites

<table>
<thead>
<tr>
<th>Site</th>
<th>Colorectal</th>
<th>Prostate</th>
<th>Lung</th>
<th>Breast</th>
<th>Bladder</th>
<th>Oral</th>
<th>Cervix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agents classified by mechanism</td>
<td>Antiinflammatories (e.g., sulindac, piroxicam, aspirin, ibuprofen)</td>
<td></td>
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<tr>
<td></td>
<td>Antiproliferatives (e.g., DFMO, calcium, curcumin, 18β-glycyrrhetinic acid)</td>
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<tr>
<td></td>
<td>Testosterone 5α-reductase inhibitors (e.g., finasteride)</td>
<td>Retinoids/carotenoids (e.g., vitamin A, 13-cis-retinoic acid, β-carotene)</td>
<td>Antiinflammatories (e.g., sulindac, piroxicam, aspirin, ibuprofen)</td>
<td>Retinoids/carotenoids (e.g., vitamin A, 13-cis-retinoic acid, β-carotene)</td>
<td>Retinoids (e.g., vitamin A, 4-HPR)</td>
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<td>Retinoids (e.g., 4-HPR)</td>
<td>Antiproliferatives (e.g., DFMO)</td>
<td>Antiinflammatories (e.g., 4-HPR)</td>
<td>Antiproliferatives (e.g., DFMO)</td>
<td>Antiproliferatives (e.g., DFMO)</td>
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<td></td>
<td>ras-farnesylation inhibitors (e.g., farnesyl, N-acetyl-l-cysteine)</td>
<td>ras-farnesylation inhibitors (e.g., farnesyl, N-acetyl-l-cysteine)</td>
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<td>ras-farnesylation inhibitors (e.g., farnesyl, N-acetyl-l-cysteine)</td>
<td></td>
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<tr>
<td>Intermediate biomarkers</td>
<td>Adenomas, proliferative indices, aberrant crypts, Lewis blood group, antigens, sialyl-Tn antigen</td>
<td>PIN, PSA, PAP, ^*^ cytotokeratins (loss of 50-64 kDa), vimentin, nuclear, prominent, DNA content</td>
<td>Cellulolypatia/ dysplasia in spumum, bronchial atypical metaplasia/dysplasia, PCNA, blood group antigens, p53</td>
<td>Atypical hyperplasia, DCIS, LCIS</td>
<td>TIS, dysplasia, DNA content, F and G-actins, integrins, loss of heterozygosity (e.g., 9q), blood group antigens, Rh</td>
<td>Dysplastic leukoplakia, keratin expression, GGT</td>
<td>CIN</td>
</tr>
<tr>
<td>Clinical cohorts (Phase II)</td>
<td>Patients with previous adenomas, patients with adenomas &lt;1 cm in diameter</td>
<td>Patients with PIN without prostate adenocarcinoma; patients scheduled for radical prostatectomy</td>
<td>Patients with prostate cancer surgery</td>
<td>Patients with previously resected TIS or T&lt;sub&gt;1&lt;/sub&gt; incidental disease without TIS</td>
<td>Patients with dysplastic leukoplakia</td>
<td>Patients with dysplastic leukoplakia</td>
<td>Patients with HPV-negative cancers with CIN III</td>
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<tr>
<td>Clinical cohorts (Phase II)</td>
<td>Patients with previous adenomas, patients with adenomas &lt;1 cm in diameter</td>
<td>Patients with PIN without prostate adenocarcinoma; patients scheduled for radical prostatectomy</td>
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<td>Patients with previously resected TIS or T&lt;sub&gt;1&lt;/sub&gt;, T&lt;sub&gt;2&lt;/sub&gt; disease without TIS</td>
<td>Patients with dysplastic leukoplakia</td>
<td>Patients with dysplastic leukoplakia</td>
<td>Patients with HPV-negative cancers with CIN III</td>
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<tr>
<td>Clinical cohorts (Phase III)</td>
<td>Subjects at high risk (e.g., family history of adenomas or colorectal cancer, previously treated breast or endometrial cancer)</td>
<td>Subjects at high risk (e.g., family history of adenomas or colorectal cancer, previously treated breast or endometrial cancer)</td>
<td>Subjects at high risk (e.g., family history of adenomas or colorectal cancer, previously treated breast or endometrial cancer)</td>
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<td>Subjects at high risk (e.g., family history of adenomas or colorectal cancer, previously treated breast or endometrial cancer)</td>
<td>Patients with CIN</td>
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| ^*^ PAP, prostatic alkaline phosphatase; GGT, γ-glutamyl transpeptidase.

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activity. Abnormal expression of the Lewis and sialyl-Tn antigens is seen in adenomas and cancers; the pattern of expression corresponds to the size and degree of dysplasia in adenomas (33, 34).

Further, as noted above, sequences and combinations of genetic events seen in adenomatous polyps and colon cancer also have been described elegantly by Vogelstein and coworkers (e.g., Ref. 2). Alterations in the long arm of chromosome 5, DNA hypomethylation, and ras mutations appear to be early lesions. Recent evidence suggests that c-K-ras gene expression may be an important intermediate biomarker. Mutated c-K-ras oncogenes have been identified in 50% of colorectal carcinomas and adenomas >1 cm in diameter; increased frequency of these mutations in adenomas has been associated with increasing degree of dysplasia and lesion size (2, 35). Moreover, ras gene mutations have been found in the very early stages of abnormal proliferation in colon mucosa, i.e., in aberrant crypts in rats (36) and in normal-appearing colon mucosa of rats 15 weeks after treatment with dimethylhydrazine (37).

Not surprisingly, preclinical and clinical studies indicate that anti-inflammatory and other agents that slow proliferative activity have potential as chemopreventive agents in colon. Agents showing chemopreventive activity in animal models, primarily against azoxymethane- or dimethylhydrazine-induced colon cancers in rats and mice, include the NSAIDs sulindac, piroxicam, aspirin, and ibuprofen, as well as compounds such as DFMO, calcium, curcumin, and 18ß-glycyrrhetinic acid (reviewed in Ref. 3). The antiproliferative activity of DFMO was noted above. Calcium inhibits colonic mucosal hyperproliferation (38–40). Curcumin has antioxidant and antiinflammatory activity (41), and 18ß-glycyrrhetinic acid is a well-known antiinflammatory (42). Preliminary clinical studies also support the potential activity of sulindac and aspirin. Sulindac has shown dramatic effects in causing the total or almost total regression of colorectal adenomatous polyposis in patients with FAP and Gardner’s syndrome (43, 44). In a prospective mortality study, aspirin use was found to reduce the relative risk of death from colon cancer (45); and, in patients with previous colorectal adenomas, it reduced the risk of new adenomas (46). The agent combination of DFMO and piroxicam is being evaluated in colon based on synergism observed in animal efficacy screens compared with either agent alone (22).

Patients with a history of adenomatous polyps provide an obvious and feasible cohort for clinical chemoprevention studies, since their risk of developing new adenomas is high. In several studies, new adenomas were seen at rates ranging from 37 to 60% within 1–4 years following polypectomy (29). In the National Polyp Study, a recurrence rate of 29–35% was seen in patients after removal of all synchronous adenomas. Patients with FAP are a special subset of this high-risk group, since they develop many adenomas, some of which inevitably progress to adenocarcinoma (31). Several chemoprevention trials with colorectal adenoma recurrence as the end point are currently in progress in this cohort; the agents being evaluated are sulindac, DFMO, and the combination of β-carotene, vitamin C, and vitamin E (46, 47). A Phase II chemoprevention trial measuring adenoma recurrence is estimated to require 3–6 years and several hundred patients. The high incidence of adenomas in the population suggests that adequate accrual for such studies is possible.

Another promising approach is to determine the effect of potential chemopreventive agents on the growth of adenomas. Hofstad et al. (48) have delineated such a study, which is investigating the chemopreventive activity of a combination of calcium, vitamins A, C, and E; and selenium. The design of the trial is based on two factors described above. The first is the correlation of adenoma size with severity of dysplasia, suggesting that agents which inhibit increases in polyp size also inhibit adenoma progression. The second factor is the negligible risk of malignancy in very small adenomas. Such small lesions may be safely monitored for growth until they reach a diameter of approximately 1 cm. Polyp size is the primary end point of the randomized, placebo-controlled trial; number of polyps and incidence of adenocarcinoma also are monitored. Colonoscopies are to be performed yearly for 3 years. Polyps are counted; those reaching a diameter >9 mm are resected and examined histologically. All smaller polyps are measured in situ without biopsies. At the end of the study period all polyps are to be resected.

From the standpoint of chemoprevention, adenoma development is relatively slow; trials measuring adenoma development and progression are of longer duration than is ultimately desirable in chemoprevention studies. From the viewpoint of the patient, adenomas are difficult to monitor because they require endoscopy. These drawbacks are more than balanced by the knowledge that the adenoma is on the causal pathway to colorectal carcinoma and can be used as a standard against which to evaluate other biomarkers. Rigorous attempts are now being made to validate and standardize the measurement of earlier biomarkers of colon cancer. These efforts, although promising, will require several more years of research before their success can be evaluated. An interesting example of biomarker studies that may lead to both shorter studies and easier monitoring of the target lesion is the recent finding of mutated c-K-ras in stool samples of patients with colorectal cancers and, more significantly, in stool samples of two patients with adenomas (35). This suggests that should ras be validated as an early end point for chemoprevention studies, patients might be monitored by noninvasive analysis of stool samples instead of by more invasive biopsy.

**Prostate.** Prostate cancer is the most common cancer in United States males, accounting for 132,000 (23%) of all new cancers and 34,000 (12%) of cancer deaths in males (25). Etiological and risk factors for prostate cancer include age >50 years, family history, high serum testosterone, high fat diet, prostatitis, and geographical background (prevalence being highest in the United States, Canada, and Northwest Europe). In addition to clinically evident disease, microscopic foci of adenocarcinoma have been found at autopsy in prostates of men who died from other causes. The frequency of such “latent” tumors has been shown to increase with each decade of life from the 50s (5.3–14% incidence) to the 90s (40–80%) (49).

Prostate cancer is slow-growing, often requiring decades to appear as a clinical tumor. Exogenous risk factors seem to contribute more to the disparity between latent and clinical prostate cancer than hereditary factors. For example, the incidence of latent prostate adenocarcinoma does not vary widely among populations (50, 51). In one study, the prevalence of microscopic lesions at autopsy was 20.6, 28.8, and 36.9/100,000 in Japanese, Germans, and African-Americans, respectively. On the other hand, rates of clinical cancer were 2.7, 21.1, and 67.1/100,000, respectively (52). Further, within two generations after immigrating to the United States, the rate of clinical cancer in Japanese approaches that of United States Caucasians (53). These data suggest the presence of a baseline incidence of early microscopic prostatic neoplasia that is subsequently accelerated to different degrees depending on exogenous environmental influences.

Of the agents proposed as chemopreventives in prostate, the best known is finasteride (Proscar), which inhibits the enzyme testosterone 5α-reductase, thereby preventing hyperplasia of prostatic stroma due to this hormone (54). A large Phase III clinical trial of finasteride in chemoprevention of prostate cancer started recently. Experimental data suggest that retinoids such as 4-HPR will be chemopreventive in the prostate (55). ODC is found at high levels in the prostate and prostate neoplasms, so that the ODC inhibitor, DFMO, appears to be a promising chemopreventive agent (56). d-Limonene and related...
compounds are interesting based on data showing they cause programmed cell death in proliferating prostatic cells.⁴

Serum PSA is a potential intermediate biomarker for prostate cancer, since elevated serum levels of PSA have been correlated to the presence of prostatic adenocarcinoma (57). However, PSA is not specific to neoplasia, and the data do not suggest that the level is directly related to degree of neoplastic progression. Recent data indicate that other measurements of PSA, especially density (58) and velocity of PSA rise (57), may correlate better to progression than serum level alone. The validation of PSA as an intermediate biomarker awaits further data, some of which may be obtained in the large National Cancer Institute-sponsored Prostate, Lung, Colorectal, and Ovary Cancer Screening Trial in which PSA will be monitored over several years in more than 30,000 men. Even without further refinement, PSA may prove useful in identifying clinical cohorts at risk as subjects for chemoprevention studies.

The evidence that PIN is a precursor of prostatic adenocarcinoma has been summarized by Bostwick (59). It includes: (a) morphology and cytology similar to those of malignant lesions; (b) presence of carcinoma in foci of PIN; (c) frequent location in the peripheral zone of the prostate, the site at which 70% of prostatic carcinomas occur; (d) proliferative activity similar to that of carcinoma (3-fold that of benign tissue); (e) cytokeratin immunoreactivity, lectin binding, and loss of blood group antigen similar to carcinoma; (f) foci found in 82% of prostates with carcinoma, but in only 43% of normal prostates; and (g) significant increase in the incidence of prostatic carcinoma in patients with PIN.

A potential cohort for a clinical intervention study using high-grade PIN as the surrogate end point would be those individuals with PIN, but without demonstrable prostatic carcinoma. These subjects would be treated with a chemopreventive agent for approximately 2 years and would be evaluated by TRUS-directed biopsy every 3–6 months to determine the modulation of PIN, changes in proliferation indices, and nuclear abnormalities (see Ref. 60 for a listing of possible biomarkers).

Another potential cohort for short-term trials of chemopreventive agents involves patients with newly diagnosed stage B₁/B₂ cancers. Such patients are usually not scheduled for prostatectomy until 3–8 weeks after diagnosis. At diagnosis, treatment with a chemopreventive agent would begin and continue until prostatectomy. At surgery, the removed prostate gland would be analyzed for PIN modulation and other potential biomarkers. Ideally the analysis of PIN could be made more specific by taking sextant TRUS-directed biopsies at diagnosis, primarily from hypocoeic areas, to capture the PIN lesions. These biopsy sites could be marked with fluorescein dye or India ink (the markings will survive 3–4 months) and examined after surgery.

**Lung.** Lung cancer is the second most common cancer in males and the third most common in females in the United States. For 1992, 102,000 cases (18% of all cancers) were estimated for males, and 66,000 cases (12% of all cancers) were estimated for females (25). Thirty-four percent (93,000) of all United States cancer deaths in men and 19% (53,000) of those in women were attributed to lung cancer (23). Lung cancer in heavy smokers exhibits high rates of local recurrence or the associated occurrence of second primary tumors in the upper aerodigestive tract exposed to carcinogens in tobacco smoke. The basis for the high incidence of second primary tumors has been attributed to “field cancerization” (61). This term refers to the fact that the irritation and chronic carcinogenic influence of continuous smoking causes multiple foci of progressing IEN to develop throughout the exposed respiratory epithelial field.

Tobacco use is by far the greatest risk factor in the development of lung cancer (14). The carcinogen NNK, found in tobacco smoke, has been a potent lung carcinogen in animals (62). An animal model using NNK-induced lung cancers in strain A mice is currently being used to investigate the chemopreventive potential of chemicals including arylalkyl isothiocyanates (62, 63).

Vitamin A and other retinoids have been identified as potential chemopreventive agents in lung based on epidemiological data showing inverse correlation of vitamin A blood levels to lung cancer and the role of vitamin A in maintaining differentiation in squamous tissues (64). Most other potential lung chemopreventive agents identified thus far have oxygen radical-scavenging activity. These agents include β-carotene and antioxidants such as N-acetyl-L-cysteine and oltipraz which raise intracellular GSH.

Prominent among ongoing clinical chemoprevention trials is the Phase III, six-center CARET study, which is testing the effect of a combination of 25,000 IU vitamin A and 30 mg β-carotene/day in preventing lung cancer in heavy smokers and workers exposed to asbestos (64). A key factor in the design of this trial is the pilot studies used to determine effective but nontoxic doses of the agents. This work demonstrates the importance and difficulties of dose-titration. It is not yet clear that an effective dose of β-carotene has been found. N-Acetyl-L-cysteine currently is in EUROSCAN, a clinical study sponsored by the European Organization of Research and Treatment of Cancer on chemoprevention of recurring and new primary tumors in patients with previously treated oral, laryngeal, or lung cancer (65). In this 2-year study, N-acetyl-L-cysteine (600 mg/day), vitamin A palmitate (300,000 IU/day in the first year, then 150,000 IU/day in the second year), and both agents together are being evaluated.

Bronchial dysplasia (IEN) has been identified as a premalignant surrogate marker for lung (10). A likely cohort for chemoprevention trials using dysplasia as a surrogate end point biomarker is patients with a history of prior laryngeal carcinoma or stage I lung cancer who have undergone resection. Such patients are at high risk for the presence of dysplasia (also called atypical squamous metaplasia). The rate of second primary tumors in this cohort is of the order of 10–15% over 5 years (66). This cohort would be studied by multiple brushings and biopsies at predetermined sites within the bronchi. Quality control of tissue sampling and marker measurement is especially important in these studies because of concern that biopsy-induced regression may confound results (66).

**Breast.** Breast cancer is by far the most common cancer in United States females, causing 32% (180,000) of total new cancer cases and 19% (46,000) of all cancer deaths estimated for 1992 (25). The risk factors are well known and include family history of breast cancer, Li-Fraumeni syndrome, past history of breast, endometrial or ovarian cancer, atypical hyperplasia of the breast, nulliparity or late age at first full-term pregnancy, early menarche and late menopause, and obesity (67).

Antiproliferation is an important chemopreventive mechanism in breast cancer, demonstrated by agents such as DFMO, retinoids, and antiestrogens. Antiestrogens show potent activities against hormone-sensitive forms of breast cancer. The promise of tamoxifen is widely known; it is now being evaluated as a chemopreventive in a 10-year Phase III clinical trial in women at high risk for breast cancer (68). 4-HPR is also being evaluated in a Phase III clinical trial to prevent recurrence in women previously treated for breast cancer (69). Moreover, synergistic activity in animal studies indicates that the combination of tamoxifen and 4-HPR has potential (23, 24). A limited Phase I study in 12 women with metastatic breast cancer showed that effective doses of the combination produced no significant side effects after up to 14 months of treatment (70). d-Limonene has demonstrated activity against carcinogen-induced mammary tumors in rats (71–73).

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⁴ C. Myers, personal communication.
Agents, such as d-limonene (74) and a more potent related compound perillyl alcohol (75), that inhibit ras protein isoprenylation appear to be good candidates for clinical evaluation.

Much has been accomplished toward understanding the genetic factors that contribute to breast cancer etiology, but reliable precancerous lesions that could serve as end points for chemoprevention trials have not yet been identified. For example, atypical hyperplasia in situ (analogous to human DCIS) to invasive carcinoma is observed, suggesting that this model could be useful in the study of the effects of chemopreventive intervention on this progression.

Patients with CIS, either DCIS or LCIS, are potential cohorts for breast chemoprevention trials. DCIS is considered to be a direct precursor of invasive carcinoma (reviewed in Ref. 79) and accounts for approximately 70% of breast CIS (80). Frequently occurring histological subtypes of DCIS are micropapillary, cribriform, papillary, solid, and comedo carcinoma (79). Comedo-type DCIS exhibits high rates of local recurrence, with progression and microinvasion. In studies summarized by Page and Dupont (76, 81), recurrence of DCIS was 50% within 3 years after treatment by local excision. The absolute risk of developing invasive cancer for women with non-comedo DCIS is approximately 25–30% within 15 years (76). Traditionally DCIS, like invasive cancer, is treated by surgery (76, 79).

LCIS is a risk marker for both ductal and lobular carcinoma occurring anywhere in either breast (e.g., Refs. 76 and 80). The relative risk of LCIS patients for developing cancer has been estimated to be 7–9 times that of the normal population (76), with an absolute lifetime risk of approximately 20% (82). LCIS cohorts appear to be more practical than DCIS cohorts for chemoprevention trials, because the risk is not related to the original biopsy site, but rather to cancer occurring in any location in either breast (81). Further, LCIS is treated less often by mastectomy or other definitive surgery than is DCIS. It has been recommended that LCIS patients be monitored regularly by mammography and physical examination (80). This monitoring period would allow for intervention with and evaluation of chemopreventive agents.

Another possibility, as in the trial designed for presurgical prostate cancer patients, is to administer chemopreventives to patients newly diagnosed with breast cancer and scheduled for surgery. Breast tissue taken at surgery would be used to evaluate the effects of the chemopreventive agent on a variety of molecular and cellular biomarkers and lesions, including hyperplasia and atypical hyperplasia.

Bladder. Bladder cancer is the fourth most common cancer in United States males, estimated for 1992 at 7% (38,500) of new cancer cases and 7% (6300) of cancer-related deaths (25). In United States females, the incidence is much lower, 2.3% (13,000) of new cases and 1% (3,200) of cancer deaths in 1992 (25). Of the 98% of these cancers which are confirmed histologically, 93% are TCC (83). The high recurrence rate was described above under “Considerations in Design of Clinical Studies.” The recurrent lesions are highly unpredictable. Although they may be of the same type as the initial lesions, the subsequent cancers may have progressed in grade or type. The association with environmental and life-style factors suggests that bladder cancer incidence may be modulated by chemopreventive agents. Bladder cancers have been attributed to several such factors including tobacco use and occupational exposure to aromatic amines. Chronic inflammation and infection are also important etiological/risk factors (83).

As in other epithelial mucosa, abnormal proliferation is strongly associated with bladder cancer. As expected, antiproliferatives such as DFMO and differentiating agents such as retinoids, specifically, 4-HPR, have been found to have chemopreventive activity in animal studies. The agents thus far found to have the most profound chemopreventive activity in animal bladder cancer models are NSAIDs. Piroxicam was particularly effective in reducing the incidence of N-butyl-N-(4-hydroxybutyl)nitrosamine-induced TCC in mice (84). As in colon, the combination of DFMO and piroxicam is of interest because of possible synergistic activity.

Recurrence and progression of superficial bladder neoplasia provide important opportunities for evaluating the effects of chemopreventive agents. Koss (85) and Bostwick (86) have discussed two pathways of neoplastic progression in the bladder. One pathway leads to papillary lesions designated by the notation Tp (intrapapillary) and Tp1 (superficially invasive). Initially, 70–80% of TCC present as these superficial tumors with limited potential for invasion (21). The other pathway does not involve papillary excrecences, has a high likelihood of invasion, and leads to TIS. Both intraepithelial lesions are suitable end point biomarkers for chemopreventive studies.

Other intermediate biomarkers have not been well defined and validated in bladder, although several have been implicated. Changes in EGF-R expression and EGF excretion may precede detectable TCC (87). As described above, cells may develop abnormal differentiation patterns during carcinogenesis, resulting in associated changes in cell components. Such effects have been observed in bladder, including altered expression of Lewis’ blood group antigen (88), integrins (89), and F- and G-actins (90). Genetic effects have also been observed, including changes in DNA content (91), loss of heterozygosity (92), and loss Rb gene function (93).

Bladder tumor recurrence and progression suggest using two clinical cohorts to allow relatively short-term Phase II trials of chemopreventive agents in bladder. One cohort is patients with stage Tp/Tp1 disease with TIS (94). This group of patients would receive normal treatment, i.e., resection followed by BCG. After BCG treatment, the patients would be randomized to chemopreventive treatment and placebo groups and monitored for cancer recurrence. The other cohort is patients with stage Tp/Tp1 disease without TIS. Normally, such patients are followed but receive no treatment unless the disease progresses. These patients would be treated with chemopreventive agent and monitored for disease progression. In both cohorts, as many potential intermediate markers as possible would be followed by urine cytology in search of good, validated surrogate end points for further trials. As noted for studies in lung, standardization of analytical techniques would be critical to establish intermediate markers.

Oral Cavity. Cancers of the oral cavity and pharynx have been estimated to account for 4% (20,000) of total new cancer cases in United States males (sixth most common cancer) and 2% (9,700) of cases in U.S. females (eighth most common cancer) (25). These cancers result in an estimated 2% (5,175) of cancer deaths in males and 1% (2,775) in females (25). The oral cavity, like the lung, is subject to field cancerization; thus, these statistics underestimate the severity of the disease, which is reflected by high rates of recurrence and local second primary tumors (95). Extensive morbidity is associated with recurrence and new tumors. The most significant risk factors for disease are tobacco use and tobacco use combined with alcohol consumption (96).

Again, control of cellular proliferation and preservation of normal differentiation have been important strategies in selecting potential chemopreventive agents. Both β-carotene (97, 98) and the retinoid
13-cis-retinoic acid (98, 99) have been shown to reverse oral leukoplakia, which is associated with increased risk of oral cancer and is considered to be a premalignant lesion when dysplasia is present (100).

Oral leukoplakia with dysplasia is a possible end point for rapid evaluation of chemopreventive agents in short-term clinical trials. It is easily accessible and, as noted above, it fits the definition of an intermediate end point biomarker (100, 101) and has been used successfully in chemoprevention trials. The cohort would be patients with biopsy-proved dysplastic leukoplakia but no oral malignancy. Treatment with putative chemopreventive agents for 6 months should be sufficient to determine the ability of the agents to cause regression of the leukoplakia. Because of the ease of tissue sampling, the patients could be followed closely so that any lesion that progressed could be immediately removed surgically. Also, the lesions and surrounding normal tissues can be monitored for modulation of other, possibly earlier, intermediate biomarkers such as those associated with cell proliferation (e.g., EGF and EGF-R, PCNA, TGF-β) and differentiation (e.g., involucrin).

Uterine Cervix. Cervical cancer, despite its high incidence [55,000 new cases of carcinoma in situ, 13,500 new cases of invasive carcinoma, and 4,400 related deaths estimated for 1992 (25)], probably does not present a suitable opportunity for chemoprevention. Early detection and surgical excision have produced a high cure rate for cervical carcinoma except for those very aggressive lesions associated with HPV infection and those that are undetected because of poor medical care. However, as noted above, CIN, the premalignant lesion in cervix, is the prototype IEN, and CIN III is a suitable intermediate end point for studies of chemoprevention. Results obtained in this tissue, e.g., demonstration of agent efficacy and identification of intermediate biomarkers, could be generalized to other cancer sites. Moreover, the cervix is easily and relatively painlessly accessible for biopsy by speculum and for visualization of tissues by colposcopy.

The risk factors for cervical neoplasia are well known. Besides HPV infection, they include early age at first intercourse, multiple sexual partners, race, immunodepression, oral contraceptive use, and smoking (102). As for the other major cancers, the association of incidence with environmental factors indicates that the course of the disease may be modulated. There is also epidemiologic evidence suggesting that vitamin deficiencies may play a role in CIN progression. Vitamin A, carotenoids, folic acid, and vitamin C were thought to prevent progression of CIN to CIS (103); β-carotene has been observed to have a protective effect against invasive cervical carcinoma (104). These epidemiological data on vitamin A suggest that retinoids such as 4-HPR may be particularly good candidates for chemoprevention trials in cervix. Further, since the epidemiological data show that CIN progression may be inhibited, other antiproliferative, such as DFMO, should be good candidates for testing.

The cohorts in short-term chemoprevention trials would be patients with CIN III without HPV infection. Again, modulation of CIN III should be observed within 6 months of treatment. Both normal and dysplastic tissue would be monitored throughout the course of treatment, and at the end of treatment or at any sign of progression, the lesions could be treated definitively by excision. As in the other cancers, multiple intermediate biomarkers would be monitored, including proliferation markers (e.g., PCNA, EGF-R, TGF-α, TGF-β), differentiation markers (e.g., involucrin), and genetic markers (DNA content, ras oncogene expression).

Future Directions

The basic cancer-related chemical and biological sciences, pathology, and epidemiology will continue to be the multidisciplinary framework on which progress in chemoprevention is built. A major tenet derived from these disciplines is that antimitagenesis and antiproliferation are the important general mechanisms of chemoprevention. Efforts will continue to develop chemopreventive drugs with pharmacological activities that are antimitagenic and antiproliferative. These efforts will be carried out in tandem with research directed at developing agents effective at more specific molecular and cellular targets, such as those outlined in Fig. 1. As knowledge in molecular biology and the basic cellular processes in carcinogenesis continues to grow, chemopreventive agents may be designed that are directed to repair or suppress early genetic lesions and to control cellular growth mechanisms (e.g., programmed cell death, angiogenesis). Some of these specific targets may prove to be intermediate biomarkers for cancer, and, hence, viable end points for chemoprevention.

The discussions in this paper make it evident that the identification and validation of intermediate biomarkers to serve, singly or in batteries, as surrogate end points for cancer are the core of applied research in chemoprevention. This research is the primary aspect of Phase II clinical trials. Increased use of advanced technology such as cytomorphometric analysis and the polymerase chain reaction will allow early and rare lesions to be detected and quantified. Coupled with newer sampling techniques (e.g., fine needle aspiration) and imaging systems for biopsies (e.g., colposcopy and TRUS), the lesions may be seen in the context of the tissue and sampled relatively noninvasively. Clearly, stringent validation of these biomarkers is required if they are to serve as surrogate end points in chemoprevention trials. Meticulous attention to developing standardized methods for sampling tissue and measuring the biomarkers is critical.

Two other aspects of the design of chemoprevention clinical trials discussed here should be emphasized. First is the importance of doing dose-titration studies in both Phase I and Phase II trials. Chemopreventive agents will be taken by relatively well subjects over long time periods; thus, determination of safe, optimal doses is necessary. Secondly, chemopreventive treatment should not interfere with or, conversely, be confounded by other treatment and monitoring that the subjects may be receiving. This design aspect is particularly important in trials with cancer patients or high risk subjects already undergoing treatment or monitoring.

A future objective is to extend the approaches for the seven major epithelial cancers described in this paper to other sites and types of cancers. Of particular concern are ovarian and brain cancers and non-Hodgkin’s lymphomas (25). To meet this objective, additional research is required to elucidate the etiology of these cancers and to identify potentially useful premalignant lesions and other intermediate biomarkers.

The progress described in this paper demonstrates the feasibility of clinical chemoprevention. Potential chemopreventive drugs have been identified for each of the seven targets; clinical cohorts (for Phase II, Phase III, or both types of trials) have also been defined. For colorectal, prostate, bladder, oral, and cervix cancers, premalignant lesions exist that may be used as end points in chemoprevention trials, and trials with these end points are planned or in progress. A few drugs have reached Phase II and Phase III trials, e.g., tamoxifen, 13-cis-retinoic acid, 4-HPR, DFMO, aspirin, and calcium. The range of cancer targets against which these agents have promising activity and the high incidence and mortality rates of these cancers are evidence of the potential high positive impact chemoprevention will have on human health.

References


Progress in Cancer Chemoprevention: Perspectives on Agent Selection and Short-Term Clinical Intervention Trials


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