Cancer Chemoprevention: Successes and Failures

Sherri L. Patterson, Karen Colbert Maresso, and Ernest Hawk

BACKGROUND: Cancer has traditionally been considered a single disease, but it is now known to be far more complex, with an unfolding etiology. In less than 2 centuries, hundreds—if not thousands—of drugs for the treatment of cancer and for palliative care have been developed and tested, with 143 having achieved approval by the US Food and Drug Administration (Medilexicon International; “Cancer Drugs & Oncology Drugs,” http://www.medilexicon.com/drugs-list/cancer.php). Just 13 agents have been approved, however, for treating precancerous lesions or for reducing risk.

CONTENT: Nonsteroidal antiinflammatory drugs, vitamins, food constituents and spice components, antidiabetic drugs, ω-3 fatty acids, and fiber are just a few of the many classes of compounds that have been tested for their cancer-preventive potential. We highlight some of the agents that have been scrutinized by way of randomized clinical trials in humans for their cancer prevention potential. We summarize the major definitive cancer chemoprevention studies that (a) were successful in demonstrating efficacy and ultimately received regulatory approval; (b) were not successful in demonstrating efficacy or had unacceptable toxicities, but from which the field has learned important lessons; and (c) showed compelling efficacy against surrogate end points but failed to achieve regulatory approval because of a lack of consensus regarding the relevance of those end points to clinical benefit.

SUMMARY: Chemopreventive studies have provided new insights into early disease pathogenesis, stimulated new risk assessments and models, fostered important research in end point biomarkers, and led to 13 approved agents. The development of safe and effective chemopreventive agents holds tremendous potential for reducing the burden of cancer.

Stated in the simplest of terms, cancer is the dysregulated proliferation of cells. Causative factors include environmental exposures (e.g., asbestos, ultraviolet radiation), lifestyle choices (tobacco, obesity, physical inactivity), infectious agents [e.g., human papillomavirus (HPV), HIV, hepatitis B virus, Helicobacter pylori], and inherited conditions and mutations [e.g., familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer, and the BRCA13 (breast cancer 1, early onset), and BRCA2 (breast cancer 2, early onset) genes]. The term “chemoprevention,” the inhibition or reversal of the carcinogenic process through the use of drugs or other compounds, became part of the cancer lexicon in the latter half of the 20th century (1). Until then, most efforts to abate the disease were aimed at surgical, radiologic, or chemotherapeutic interventions. With its refined insights into early disease pathogenesis, new risk models, successful risk assessments, and enhanced screening modalities, translational science is leading medicine from disease treatment based on symptoms and loss of normal function to disease prevention based on cellular and molecular insights.

Critical Decisions in the Design of Clinical Prevention Trials

Before providing any meaningful discussion of the successes and failures in cancer prevention trials, it is important to briefly review the most critical elements in trial design, because these elements markedly influence

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the ultimate success or failure of a trial. Although the goals in the design of chemoprevention trials are not unlike those for therapeutic oncology drugs—i.e., build a scientific premise, establish efficacy, explore and/or confirm safety, and achieve regulatory approval—the distinctions to be made between these 2 types of trials are important.

COHORTS
Unlike treatment trials based on patients with a confirmed diagnosis of cancer, prevention trials are most often conducted with asymptomatic, ostensibly healthy individuals, therefore necessitating extra vigilance to avoid harm. Cohorts in prevention trials are typically stratified into 2 main groups: those considered to be at average risk and those at increased risk owing to a genetic predisposition, a personal history of cancer, or evidence of preneoplastic lesions [e.g., colo-rectal adenomas or actinic keratosis (AK)]. Trials based on average-risk cohorts include the Prostate Cancer Prevention Trial (PCPT) and the Selenium and Vitamin E Cancer Prevention Trial (SELECT), both of which enrolled men ≥50 years of age with normal results in the digital rectal examination and the prostate-specific antigen test. Examples of trials based on increased-risk cohorts include the landmark Breast Cancer Prevention Trial (BCPT), which enrolled women with a Gail model score >1.67 [indicating a higher risk for breast cancer compared with the average woman (2)], and the CARET (Beta-Carotene and Retinol Efficacy Trial) and ATBC (Alpha-Tocopherol, Beta-Carotene Cancer Prevention) trials in lung cancer prevention, which enrolled smokers and workers exposed to asbestos (3, 4). The choice of cohort can substantially influence the outcome of a trial by affecting timelines, statistical power, and adherence. Studies of higher-risk cohorts typically offer more power over a shorter time frame, and individuals at increased risk for a disease are often more tolerant of side effects and have more motivation to adhere to a given intervention.

AGENTS
In the context of chemoprevention, “agents” have included nonsteroidal antiinflammatory drugs (NSAIDs) (e.g., aspirin, sulindac, celecoxib), vitamins and their derivatives (e.g., retinoids, selenium, vitamin E), minerals (e.g., calcium), and plant extracts (e.g., wheat bran fiber, tea catechins, flavonoids, berry extracts, curcumin). Before an agent or a combination of agents can be considered for testing in human clinical trials for their cancer prevention properties, they must have demonstrated powerful efficacy in preclinical studies. Optimal doses, duration of treatment, and toxicities should also be defined in early clinical studies before larger and more expensive trials are undertaken. Dosing frequency and route, attendant risks, and acceptable toxicities are broader in the therapeutic setting than in the prevention setting.

END POINTS AND ACHIEVING REGULATORY APPROVAL
Chemoprevention trials are governed by the same regulatory rigor assigned to all clinical studies in humans, but the definition of “clinical benefit” remains a topic of some debate. The US Food and Drug Administration (FDA) drug-approval standards for therapeutic oncology agents include reduction in mortality, improvement in survival, efficacy against an established surrogate end point, or, for accelerated approval, efficacy against a “reasonably likely” surrogate end point (5). The end points or efficacy indicators in cancer prevention studies often rely on biomarkers that serve as surrogates, and although such short-term impacts as reduction in the size and number of colorectal adenomas can be measured, long-term benefits or harms of an intervention can remain unknown for years. Accessibility to the target organ(s) remains an important determinant in trial design as well. An assessment of the end points in trials that have led to the approval of preventive agents reveals that nearly all of the agents have been approved for the treatment of intraepithelial neoplasia, particularly in accessible organs, rather than for cancer prevention per se.

In addition to the choices of cohort, agent(s), and end point, there are a host of other issues that affect cancer chemoprevention trials, including their high costs, difficulties in identifying and recruiting participants, and limited interest and investment from pharmaceutical companies to develop new agents. Nevertheless, 13 agents have achieved regulatory approval for treating precancers or for cancer prevention (Table 1).

Chemoprevention is a rapidly emerging field fueled by great promise, but the field is also tempered by unanticipated disappointments. We outline some of the major successes, as well as studies that demonstrated null or negative results. Of course, negative or null trials are not failures, because they have been invaluable in refining our knowledge and providing critical information to inform future endeavors in the field of cancer chemoprevention.

Demonstrating Efficacy and Achieving Regulatory Approval—Examples of Success

BREAST CANCER
Reports indicating a strong relationship between estrogen and some breast cancers date back almost 100 years (6). Subsequent animal, mechanistic, and observational studies have confirmed the relationship and demonstrated that antiestrogens might play a pivotal
Table 1. FDA-approved agents for treating precancerous lesions or reducing cancer risk in associated cohorts.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Targeted cohort in indication</th>
<th>End point in indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>Women with DCIS* after breast surgery and radiation</td>
<td>Reduce the risk of invasive breast cancer</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Women at high risk for breast cancer (defined as ≥35 years of age with a 5-year predicted breast cancer risk ≥1.67%, as calculated with the Gail model)</td>
<td>Reduce the incidence of breast cancer</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Postmenopausal women at high risk for invasive breast cancer (defined as ≥1 breast biopsy showing lobular CIN or atypical hyperplasia, ≥1 first-degree relatives with breast cancer, or a 5-year predicted risk of breast cancer ≥1.66%, as calculated with the modified Gail model).</td>
<td>Reduction in risk of invasive breast cancer (note: Evista does not eliminate the risk of breast cancer. Patients should have breast exams and mammograms before starting Evista, and after beginning treatment they should continue regular breast exams and mammograms in keeping with good medical practice.)</td>
</tr>
<tr>
<td>HPV vaccine (Cervarix)</td>
<td>Girls and women 9–25 years of age</td>
<td>Prevention of the following diseases caused by oncogenic HPVs 16 and 18:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cervical cancer</td>
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<tr>
<td></td>
<td></td>
<td>• CIN grade ≥2 and AIS</td>
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<tr>
<td></td>
<td></td>
<td>• CIN grade 1</td>
</tr>
<tr>
<td>HPV vaccine (Gardasil)</td>
<td>Girls and women 9–26 years of age</td>
<td>Prevention of the following diseases caused by HPVs included in the vaccine:</td>
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<td></td>
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<td>• Cervical, vulvar, vaginal, and anal cancers caused by HPVs 16 and 18:</td>
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<td>And the following precancerous or dysplastic lesions caused by HPVs 6, 11, 16, and 18:</td>
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<tr>
<td></td>
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<td>• CIN grades 2/3 and cervical AIS</td>
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<td>• CIN grade 1</td>
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<td>• VIN grades 2 and 3</td>
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<td>• VaIN grades 2 and 3</td>
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<td>• AIN grades 1–3</td>
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<tr>
<td>HPV vaccine (Gardasil)</td>
<td>Boys and men 9–26 years of age</td>
<td>Prevention of the following diseases caused by HPVs included in the vaccine:</td>
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<td></td>
<td></td>
<td>• Anal cancer caused by HPVs 16 and 18</td>
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<td></td>
<td></td>
<td>And the following precancerous or dysplastic lesions caused by HPVs 6, 11, 16, and 18:</td>
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<tr>
<td></td>
<td></td>
<td>• AIN grades 1–3</td>
</tr>
<tr>
<td>PDT with Photofrin</td>
<td>Males and females with HGD in Barrett esophagus</td>
<td>Ablation of HGD in Barrett esophagus patients who do not undergo esophagectomy</td>
</tr>
<tr>
<td>Celecoxib b</td>
<td>Males and females &gt;18 years of age with FAP</td>
<td>Reduction in the number of adenomatous colorectal polyps in FAP as an adjunct to usual care (e.g., endoscopic surveillance, surgery)</td>
</tr>
<tr>
<td>BCG</td>
<td>Males and females with CIS of the urinary bladder</td>
<td>Intravesical use in the treatment and prophylaxis of CIS of the urinary bladder and for prophylaxis of primary or recurrent stage Ta and/or Ta papillary tumors after TUR</td>
</tr>
<tr>
<td>Valrubicin</td>
<td>Males and females with BCG-refractory CIS</td>
<td>Intravesical therapy of BCG-refractory CIS of the urinary bladder in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>Males and females with multiple AKs</td>
<td>Topical treatment of multiple AKs</td>
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<tr>
<td>Diclofenac sodium</td>
<td>Males and females with AKs</td>
<td>Topical treatment of AKs</td>
</tr>
<tr>
<td>PDT with 5-aminolevulinic acid</td>
<td>Males and females with AKs of the face or scalp</td>
<td>Topical treatment of minimally to moderately thick AKs of the face or scalp</td>
</tr>
<tr>
<td>Masoprocol c</td>
<td>Males and females with AKs</td>
<td>Topical treatment of AKs</td>
</tr>
<tr>
<td>Ingenol mebutate</td>
<td>Males and females with AKs on the face, scalp, trunk, and extremities</td>
<td>Topical treatment of AKs</td>
</tr>
</tbody>
</table>

* DCIS, ductal carcinoma in situ; CIS, carcinoma in situ; Evista, raloxifene; CIN, cervical intraepithelial neoplasia; AIS, adenocarcinoma in situ; VIN, vulvar intraepithelial neoplasia; VaIN, vaginal intraepithelial neoplasia; AIN, anal intraepithelial neoplasia; PDT, photodynamic therapy; Photofrin, porfimer sodium; HGD, high-grade dysplasia; TUR, transurethral resection.

b FDA labeling voluntarily withdrawn by Pfizer, February 2011.

c Withdrawn from the US market, June 1996.
role in blunting breast cancer development in some women (7).

The landmark BCPT and the follow-up STAR (Study of Tamoxifen against Raloxifene) trials, 2 separate randomized controlled studies, enrolled a total of >32 000 women at risk for breast cancer (2, 8). The BCPT trial demonstrated conclusively that 20 mg/day of tamoxifen, a selective estrogen receptor–modulating agent (SERM), reduced the incidence of invasive breast cancer by 49% and noninvasive breast cancer by 50%, compared with placebo, in women with at least a 1.66% risk of invasive breast cancer over 5 years. Women who took tamoxifen, however, had a significant increase in venous thromboembolic events and a >2-fold increase risk of developing uterine cancer.

The STAR trial compared 2 SERMs, tamoxifen and raloxifene, for preventing breast cancer in postmenopausal women. Although both agents demonstrated similar efficacies (approximately 50% reduction in breast cancers), raloxifene showed fewer adverse effects, including fewer uterine cancers, cases of thrombosis, and hot flashes (8). Despite the improved safety profile of raloxifene, the clinical adoption of either SERM for breast cancer prevention has been slow. Together, the BCPT and STAR trials demonstrated that safety can be improved in iterative generations of agents and trials.

CERVICAL CANCER
A highly successful 2-pronged approach to cervical cancer, the Pap test for early detection and HPV vaccination for prevention, has had a greater impact on reducing both the incidence and the mortality of a single cancer than any other approach to date.

The Pap test, developed in the 1920s and introduced clinically in the 1940s, is a minimally invasive, cost-efficient test in which cells are collected from the cervix to evaluate changes in cellular morphology consistent with preneoplasia or cancer. Early detection offers unprecedented opportunities to apply effective interventions while the disease is at its most curable stage. Deaths from cervical cancer dropped rapidly in the decades following widespread implementation of the Pap test (9).

In 1983, Dürst et al. reported a relationship between an HPV strain (HPV 16) and cervical cancer (10). HPV 16 DNA was identified in >60% of the cervical cancer tissues studied. The following year, the same group identified another oncogenic strain, HPV 18 (11). Together, HPVs 16 and 18 are thought to cause about 70% of all cervical cancers (12). There are >150 types of HPVs, although not all have oncogenic potential. Of the approximately 40 types that can be transmitted sexually, 16 can be considered carcinogenic (13).

Since 2006, the FDA has approved 2 vaccines for use to protect against HPV infections, Gardasil (Merck) and Cervarix (GlaxoSmithKline). Gardasil is a quadrivalent vaccine that protects against 4 HPV types: HPVs 6, 11, 16, and 18. Cervarix is a bivalent vaccine against HPVs 16 and 18. Although these vaccines do not offer protection against all HPV infections and although they cannot prevent the development of all cervical cancers, they can reduce the incidence of cervical cancer by 70% (13).

COLORECTAL CANCER
Single or combined effects of a variety of agents, most notably NSAIDs, have been and continue to be investigated for their effects on colorectal adenomas, early growths that can evolve into cancer if left unchecked. Multiple lines of evidence suggest NSAIDs are active in colorectal adenoma and cancer prevention (14, 15).

In the late 1990s, a small but pivotal study of 83 adults with FAP became the scientific basis for additional research of at-risk cohorts, validated the mechanism-driven approach to cancer prevention, and stimulated private investment in chemoprevention. The participants enrolled in that study were randomized either to placebo or to 1 of 2 celecoxib dosages (100 mg or 400 mg twice a day for 6 months). The adenoma burden was assessed at baseline and again at the end of the treatment period. Patients randomized to the 400-mg celecoxib dosage had a 28% reduction in the number of colorectal adenomas. The study suggested efficacy against adenomas in the small intestine (duodenum) as well (16, 17). This study was the first to demonstrate conclusively the potential of an NSAID for treating adenomas in a high-risk cohort. In 2000, the FDA approved celecoxib under subpart H (accelerated approval) as adjunctive treatment for FAP. A subsequent study of children with FAP found that celecoxib at a dosage of 16 mg/kg per day for 3 months was well tolerated and reduced the number of colorectal polyps by 44% (18). This finding underscores the power of using familial, high-risk cohorts. Unfortunately, because the manufacturer elected not to pursue permanent FDA approval of celecoxib for adjunctive management of FAP, the preliminary approval granted under subpart H was removed in 2011.

SKIN CANCER
Skin cancer, although generally thought of as a single disease, is divided into 2 main types, nonmelanoma skin cancer—i.e., basal cell and squamous cell cancers—and melanoma. Melanoma accounts for <5% of all skin cancer cases, yet it accounts for the vast majority skin cancer deaths (9). Most of the preventive agents the FDA has approved are for AKs, precancerous le-
sions that may progress, if left untreated, to squamous cell skin cancer. Until recently, AKs were treated with local ablative therapies, including photodynamic therapy, cryosurgery, dermabrasion, and/or FDA-approved, self-applied topical treatments (Table 1). The utility and success of ablative therapy have been limited by the long treatment periods, which range from weeks to months; incomplete clearance of AKs; and localized, prolonged skin reactions. In early 2012, the FDA approved a topical gel containing ingenol mebutate (derived from the sap of the Euphorbia peplus plant) for the treatment of AKs. Although the precise mechanism of action is unknown, ingenol mebutate induces programmed cell death (apoptosis), followed by immune reactions in target lesions (19). In 4 randomized, double-blind, and placebo-controlled studies, patients with AKs were randomized either to self-applied ingenol mebutate or to placebo for 2 to 3 days. By day 57, forty-two percent of the patients with face or scalp AKs who had been randomized to the treatment arm experienced complete clearance of their AKs, compared with 3.7% in the placebo arm. Similarly, 34.1% of the participants with AKs on their trunks or extremities experienced complete clearance, whereas only 4.7% of those in the placebo arm had similar results (20). Although there were already a number of established preventive agents for AK, ingenol mebutate offers a substantial improvement over previous agents because of its significantly reduced treatment time. This study again demonstrates the improvement in agents that can be achieved through iterative generations of trials.

BLADDER AND ESOPHAGEAL DYSPLASIA

The use of valrubcin and bacille Calmette–Guérin (BCG) for bladder dysplasia and the use of Photofrin plus photodynamic therapy for esophageal dysplasia were developed largely within the pharmaceutical industry as adjuvant therapies for the treatment of preinvasive neoplastic lesions, rather than for a specific preventive indication. See the article by Sylvester (21) for a recent summary of BCG-related trials and potential future directions regarding its use for bladder dysplasia, the article by Steinberg et al. (22) for more details about valrubcin, and the articles by Overholt et al. (23) and Davila (24) for more information regarding the development and use of Photofrin and photodynamic therapy for esophageal dysplasia.

Null or Negative Trials

Several large studies have investigated vitamins, vitamin precursors, and/or trace minerals to evaluate their cancer-preventive efficacy. Although the intended goals were not met, these studies did provide substantial mechanistic and developmental insights into cancer prevention and thus have served a foundational role for the field.

LUNG CANCER

In the early 1980s, a series of reports suggested a protective role for β-carotene, a precursor to vitamin A, against lung cancer (25–29). These reports formed the basis for the ATBC prevention study, which enrolled >29 000 Finnish male smokers 50–60 years of age, from 1985 to 1993. The men were randomized to one of 4 groups: α-tocopherol (vitamin E), β-carotene (a precursor of vitamin A), both α-tocopherol and β-carotene, or placebo. The participants were followed for 5–8 years (median, 6 years). Men who took β-carotene alone or in combination with vitamin E had an 18% increased incidence of lung cancer and an 8% increase in overall mortality, whereas vitamin E alone had no effect (3).

The CARET trial was a double-blind, placebo-controlled study that enrolled >18 000 male and female smokers, former smokers, and asbestos-exposed workers to study the effects of β-carotene and retinyl palmitate (vitamin E) or placebo on lung cancer and cardiovascular disease. The trial was stopped early after an interim analysis showed a 28% increase in lung cancer incidence and a 17% increase in overall mortality in the treatment group (4).

The ATBC and CARET studies were both based largely on epidemiologic data. These early studies highlighted the importance of preclinical and early-phase work for improving our understanding of mechanisms, confirming preventive activity, evaluating dosing regimens, and minimizing the risk of toxicities, before large and expensive phase III trials are undertaken. Since the close of these trials, chemoprevention trials typically have been built on a converging premise from different lines of evidence, including preclinical, animal, and epidemiologic data.

PROSTATE CANCER

The SELECT trial randomized >35 000 men (≥55 years of age for Caucasians and ≥50 years of age for African Americans) from the US, Puerto Rico, and Canada (30). In the 2 × 2 factorial design, participants were randomized to treatment with vitamin E (400 IU/day), selenium (200 μg/day), vitamin E and selenium together, or placebo. The study was intended to run for 7 to 12 years but was terminated early when an interim analysis revealed the trial’s futility in preventing prostate cancer (30). More controversial was the finding that continued follow-up of study participants actually revealed a 17% increase in prostate cancer risk in healthy men randomized to vitamin E alone (31). This result is important because before the study men used...
selenium off label for this indication in the hope of a prevention benefit and did not suspect harm.

Clinical Efficacy but Lacking Regulatory Approval

PROSTATE CANCER
The PCPT trial, a landmark chemoprevention trial, randomized nearly 19,000 men ≥55 years of age who had normal results in the digital rectal examination and the prostate-specific antigen test either to placebo or to finasteride (5 mg daily) and followed them for 7 years (32). Although finasteride treatment reduced the prevalence of prostate cancer by 23% (33), it failed to achieve regulatory approval for prostate cancer risk reduction. The FDA believed finasteride treatment did not have an acceptable risk–benefit profile, because analyses had indicated that the use of finasteride for prostate cancer prevention would have required the acceptance of 1 high-grade cancer to prevent 3 to 4 potentially clinically relevant lower-grade cancers (34). Although the PCPT trial did not lead to finasteride approval, it did emphasize to the field the FDA’s imperative of appropriately balancing risks and benefits in a chemopreventive setting.

COLON CANCER
In addition to the trials conducted with those at a high risk for colorectal cancer due to inherited mutations, additional studies have been conducted to test the efficacy of celecoxib in reducing sporadic adenomas. A preventive efficacy was confirmed (35), but enthusiasm for the drug was quelled by a significant increase in serious cardiovascular events in the patients who took celecoxib at daily doses of 400–800 mg (36). These studies highlighted the need for broad, sensitive toxicologic and human-safety assessments in chemoprevention trials, particularly in populations at average or moderately increased risk.

Perhaps one of the most exciting and promising cancer prevention studies of patients with previously resected colorectal adenomas to date involved a combination of drugs. This combination consisted of sulindac, which is an older, established antiinflammatory medication, and α-difluoromethylornithine (DFMO), or eflornithine, a failed cancer-therapeutic drug that was later found to be a highly effective depilatory. DFMO blunts the synthesis of polyamines that are key drivers in the formation of some cancers, most notably of the colon and prostate (37). Sulindac was shown in early-phase clinical studies to be efficacious in reducing the colorectal polyp burden (15, 38, 39). Preclinical data with animal models demonstrated that DFMO and sulindac given together functioned synergistically in preventing the growth and viability of human colon cancer cells (40). These results were the basis for the design of a randomized controlled trial of this combination. More than 300 study participants with a history of resected adenomas at least 3 mm in size were randomized either to low-dose sulindac and low-dose DFMO (150 mg daily and 500 mg daily, respectively) or to placebo and were followed for 36 months. Posttreatment colonoscopic examinations revealed a remarkable 70% reduction in recurrent adenomas and a 92% reduction in advanced adenomas (41). Importantly, the side effects from each drug were few, because the drugs were given at doses lower than would be used individually. Confirmatory studies are ongoing. The DFMO/sulindac combination trial demonstrated that synergy between agents can lead to lower doses, improved efficacy, and fewer or less severe toxicities.

Although NSAIDs are one of the most powerful and broadly applicable classes of drugs available and are already in broad clinical use for a variety of conditions, they have well-established gastrointestinal and renal toxicities. Furthermore, at least some members of this class may confer an increased risk of cardiovascular events. Consequently, research efforts are currently directed at improving their risk–benefit balance to enable their use as chemopreventives. Importantly, integrative assessments of the risks and benefits of NSAIDs across multiple diseases (e.g., risks and benefits assessed across cardiovascular disease and cancer) may be needed to tip the risk–benefit ratio in favor of their chemopreventive use (42).

BREAST CANCER
A recent clinical-prevention success that has not yet been evaluated by the FDA is a study of exemestane, an aromatase inhibitor, in 4560 postmenopausal women at increased risk for breast cancer. Participants were randomized to active drug (25 mg) or matched placebo and were administered the drug daily for 5 years. Exemestane reduced the risk of invasive breast cancers by 63% compared with the placebo, without a concurrent increase in reported side effects (43). Currently, the pharmaceutical company has no known plans to pursue approval of exemestane for reducing breast cancer risk.

Summary

The overall goal of chemoprevention is to interrupt the carcinogenic process or to slow the growth of preneoplastic lesions substantially.

In just a few short decades, the field has refined and gained new insights into early disease pathogenesis, developed new risk assessments and models, improved screening modalities, and established the efficacy of 13 approved agents. Identifying chemopreventive agents holds tremendous potential to reduce
the burden of cancer. Previous trials have informed the field substantially, allowing for improved design and conduct of randomized trials. We have learned the importance of iterative generations of trials in improving both an agent’s toxicity profile (from the BCPT and STAR trials) and its treatment regimen (from the ingenol mebutate trial); that there are substantial benefits to the use of germline, familial, or increased-risk cohorts, compared with individuals of average risk, because higher-risk cohorts offer more power over a shorter time frame (from the celecoxib in FAP trial); that repurposing and combining existing agents that blunt different pathways might offer advantages by permitting lower doses of each agent to target more than one mechanistic pathway (from the DFMO and sulindac trial); and that most agents approved to date treat intraepithelial neoplasia (such as colorectal adenomas and AKs), primarily in accessible organs.

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