Reducing the “Risk” of Chemoprevention: Defining and Targeting High Risk—2005 AACR Cancer Research and Prevention Foundation Award Lecture

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Abstract

Two large-scale, phase III cancer prevention trials, the Breast Cancer Prevention Trial (BCPT) of tamoxifen and Prostate Cancer Prevention Trial (PCPT) of finasteride, concluded with strikingly positive and simultaneously problematic results: reduced cancer risks but a major adverse finding with each agent that prevented its widespread use in the community. For most moderate-risk people, such as those studied in the BCPT and PCPT, the benefit of reduced breast or prostate cancer does not outweigh the major risk of tamoxifen (endometrial cancer in the BCPT) or apparent risk of finasteride (high-grade prostate cancer in the PCPT). Promising interventions with biologically active substances are likely to have adverse, perhaps unforeseen effects, especially with long-term preventive use. Acceptance of such agents will depend heavily on the level of cancer risk of the target population. This article outlines research in molecularly identified high-risk oral intraepithelial neoplasia that creates the clinical opportunity for optimizing the risk-benefit ratio of agents to prevent oral cancer. Two other major research efforts focused on improving preventive agent risk-benefit ratios are molecular-targeted research designed to target away from known adverse signaling pathways and multidisciplinary research based on the PCPT that will develop comprehensive models of prostate cancer risk (especially of aggressive prostate cancer) and pharmacoeogenetic models for identifying high-risk men most likely to benefit from (and not be harmed by) finasteride or similar (5α-reductase inhibiting) agents. Defining and targeting high-risk populations, developing molecular-targeted approaches, and developing accurate pharmacoeogenetic models promise to reduce the risk of chemoprevention and ultimately to reduce the risk and burden of major cancers. (Cancer Res 2006; 66(6): 2893-903)

For decades, the mantra of cancer chemoprevention has been: “Find effective agents with relatively little or no toxicity for preventing cancer in relatively healthy people.” In pursuing this goal, trials big and small of a myriad of agents with relatively less or more toxicity reached at least a temporary plateau with the double-edged results of the Breast Cancer Prevention Trial (BCPT) published in 1998 (1) and Prostate Cancer Prevention Trial (PCPT) published in 2003 (2). Tamoxifen reduced the risk of breast cancer by almost 50% among the 13,388 randomized women (moderately high risk) of the BCPT but also increased these women’s risk of endometrial cancer. Finasteride produced a 25% overall reduction in prostate cancer prevalence among the 18,882 randomized men (ages ≥55 years) of the PCPT but also surprisingly seemed to increase these men’s risk of high-grade prostate cancer. Despite the established preventive effects of tamoxifen and finasteride, the important risks/side effects associated with these agents produced a widespread resistance to their use for preventing breast or prostate cancer.

Important work in the same moderate-risk vein continues, for example, in the Selenium and Vitamin E (prostate) Cancer Prevention Trial (SELECT) involving >35,000 randomized men (≥50 years if African American, ≥55 years if not) and the Study of Tamoxifen and Raloxifene involving >19,000 postmenopausal women at an increased risk of breast cancer (3, 4). Nevertheless, the outcomes of the high-profile, definitive BCPT and PCPT highlight the three major risks of cancer chemoprevention alluded to in the title of this article: drug side effects; the amount of time, money, and effort at risk in chemoprevention trials; and the risk of effective drugs not becoming standard of care. It is critically necessary to identify populations whose high risk of a serious cancer demonstrably outweighs the potential risks and side effects, which now seem virtually inescapable, of taking an effective chemopreventive agent. Defining and then targeting such populations would improve the risk-benefit profile of effective preventive agents, such as tamoxifen and finasteride, and, as an important corollary, would dramatically reduce the risk of exposing people who never would develop cancer to preventive agent side effects. Work in lower-risk populations (or populations at risk of cancer with a good prognosis, such as nonmelanoma skin cancer) will and should continue, as high-risk cancer prevention aims to help individuals with the greatest need of and potential to benefit from active agents.

As chemoprevention research has matured and evolved over recent decades, so has the concept of high risk. For example, women with a Gail model 5-year breast cancer risk of 1.67% (based on age, family history, and other moderately predictive risk factors) generally used to be considered to be at high risk, as were patients with oral leukoplakia (at risk of oral cancer). The identification of truly high risk, such as colorectal cancer risk in familial adenomatous polyposis patients (nearly a 100% cancer risk and a life expectancy of only 40 years) and breast cancer risk in women carrying \( BRCA1 \) or \( BRCA2 \) gene mutations (lifetime risks of 50-85% for breast cancer and 15-45% for ovarian cancer), has been rather rare heretofore, and individuals with these risks also are rare and
difficult to study. Now populations with a Gail model 5-year risk of 1.67%, oral leukoplakia (~10% risk of oral cancer within 10 years), or similar risk factors generally are considered to be at moderate risk as a consequence of the problematic experience of trying to produce effective prevention without undue side effects in such populations. The risk-benefit ratio of tamoxifen clearly improves as breast cancer risk increases (4). For example, tamoxifen has a clear benefit and is generally used in the setting of resected and irradiated ductal carcinoma in situ (DCIS), where the breast cancer risk is 13% to 14% over 5 years. A major current focus of cancer prevention research is the study of genetic, environmental and metabolic factors capable of identifying high-risk populations that would benefit most from cancer prevention trials and, ultimately, standard preventive care. This work is not only designed to identify high cancer risk but also high aggressive cancer risk and thus the populations that would benefit most from specific agents or agent groups with similar mechanisms of action.

Pioneering Translational Chemoprevention in the Retinoid/Oral Intraepithelial Neoplasia Model

The climactic results of the BCPT and PCPT in moderate-risk populations were somewhat foreshadowed in work led by Wun Ki Hong at the M.D. Anderson Cancer Center beginning over 20 years ago with retinoids in oral leukoplakia, or intraepithelial neoplasia (IEN), and other carcinogenesis (or cancers) of the upper aerodigestive tract. Building on the studies in oral IEN, this program provided the proof of principle of human cancer chemoprevention when it showed that a high dose of the retinoid 13-cis-retinoic acid (13cRA) could prevent second primary tumors (SPTs) associated with head and neck cancer (5–7). This high dose was intolerably toxic, however, and a subsequent trial of a low, tolerable dose of 13cRA was not effective SPT prevention (8).

Translational studies in the retinoid/oral IEN model have helped to elucidate the multistep, multifocal nature of oral IEN and to advance our understanding of the molecular effects of agents in carcinogenesis and how to study these effects. The work of Lotan et al. (9), elucidating the role of RAR-β in oral carcinogenesis and its response to retinoids, reflects our initial translational focus on biomarkers of drug efficacy or surrogate end point biomarkers (10). Involving a substantial proportion of nonadvanced IEN cases (hyperplasia or mild dysplasia), this work increasingly revealed the problematic nature of chemoprevention in oral IEN with at most a moderate oral cancer risk (and with a response to retinoids that did not correlate with subsequent cancer development). Therefore, we shifted focus to pharmacogenetics, biomarkers of drug activity, and, especially, defining high-risk oral IEN.

Our pharmacogenetic studies found that cyclin D1 genotype predicted retinoid activity in patients with advanced head and neck IEN (moderate-to-severe dysplasia): the GG genotype marked retinoid sensitivity as indicated by cyclin D1 protein modulation, IEN response, and progression-free survival (11). Cancer development in patients with the GG genotype began ~1 year after stopping the intervention at an annual cancer rate paralleling that of retinoid-resistant patients, who had the AA or AG genotype. This trial (and long-term follow-up of the trial to prevent SPTs with high-dose 13cRA discussed above) contributed clinical evidence for the concept (and benefit) of cancer prevention by delay (12, 13). Other studies of our group have shown that molecular (e.g., genotyopic) aberrations can persist in sites of head and neck IEN that had a complete clinical and histologic response; these studies provide a molecular basis for the cancer delay we have observed in this setting and indicate the importance of molecular confirmation of IEN response (13–15).

We have intensively studied molecular factors signaling the risk of oral cancer or IEN. Margaret R. Spitz and her group identified the first genetic susceptibility marker, or benz[a]pyrene diol epoxide (BPDE)–induced chromosomal sensitivity in peripheral blood lymphocytes, for developing oral IEN (16). Walter N. Hittelman and his group identified polysomy as the first chromosomal instability marker associated with the cancer risk of oral IEN (17), and we developed a statistical model integrating multiple molecular and other markers that could identify lower and higher cancer risk in patients with oral IEN (18). Li Mao et al. identified the first specific molecular alteration associated with the cancer risk of oral IEN (19). This alteration is allelic imbalance [or loss of heterozygosity (LOH)] at chromosomes 3p14 and/or 9p21 and is discussed in Phase III Chemoprevention in High-Risk Oral IEN.

Molecular-targeted drug development in carcinogenesis of the head and neck or any other site has benefited from translational research in the retinoid/oral IEN model, which has helped pioneer rigorous scientific and clinical methodologies, including reliable sampling methods, for clinical and translational studies of oral IEN (9–11, 13, 14, 16–23). This program’s extensive studies of the biology of oral carcinogenesis, agent effects within oral carcinogenesis, and the cancer risk of oral IEN have evolved into a unique opportunity for clinical oral cancer prevention discussed in the following section.

Phase III Chemoprevention in High-Risk Oral IEN

Allelic imbalance/LOH and aneuploidy are molecular markers associated with a high risk of oral cancer in oral IEN patients. Oral IEN with allelic imbalance is an important example of a defined high cancer risk that can be studied in phase III prevention trials. Highly promising approaches for such trials include agents that inhibit cyclooxygenase-2 (COX-2) or epidermal growth factor receptor (EGFR).

Molecular risk. Genetic instability and clonal selection create the risk of cancer development and can be marked by LOH (more specifically) or aneuploidy (more globally). Oral carcinogenesis is a multistep process requiring the accumulation of multiple genetic alterations in epithelial cells. The 3-year oral cancer risk of oral IEN with LOH at 3p14 and/or 9p21 is 25% (19, 24). Genes implicated in this cancer risk include the FHIT tumor suppressor gene (found at 3p14) and the p16/p15/p14 tumor suppressor genes (found at 9p21; refs. 22, 25). The cancer risk increases to at least 35% with the addition of LOH at any other site of a known or candidate tumor suppressor gene (e.g., TRAIL-R1 and TRAIL-R2 at 8p21 and p53 at 17p13). The cancer risk associated with LOH in oral IEN has been confirmed by the consistent results of three independent groups (24, 26–29). LOH at 3p14 and/or 9p21 in IEN associated with curatively treated oral cancer has a 69% risk of a new oral cancer in 3 years (30). Several groups have reported a correlation between aneuploidy and treated cancer risk in oral and laryngeal IEN (31–36). Aneuploidy also has been shown to predict recurrence and poor disease-free and overall survival in early-stage oral cancer (37) and to predict the cancer risk of esophageal, cervical, and other IENs (35, 38).

The practical implications of markers of various levels of cancer risk in oral IEN are illustrated in Table 1 (as related to the trial design depicted in Fig. 1). The oral cancer risk increases with...
independent of COX-2/PGE2; regulation of COX-2/PGE2 and its inhibitor can block tobacco smoke–induced COX-2 expression EGFR ligands and COX-2 (versus nonsmokers), and that an EGFR mucosa of human smokers had significantly higher levels of downstream effectors can be independent of EGFR signaling (48); and there is crosstalk between EGFR and COX-2 pathways (44).

Stimulation of EGFR signaling or enhanced synthesis of COX-2–derived prostanoids can influence several processes that are linked to carcinogenesis, including cell proliferation, apoptosis, angiogenesis, and invasiveness. EGFR or COX-2 expression is increased in oral IEN and has been associated with a poor prognosis in head and neck or lung cancer (49–55). EGFR signaling can lead to increased mitogen-activated protein kinase (MAPK) activity, activator protein-1–mediated induction of COX-2 transcription, enhanced synthesis of PGE2, and inhibited expression of the PGE2-catabolizing enzyme 15-hydroxyprostaglandin dehydrogenase (15-PGDH; refs. 43, 44, 56, 57).

COX-2–derived PGE2 can activate EGFR signaling via matrix metalloproteinase (MMP) activity, cyclic AMP → protein kinase A → cAMP-responsive element binding protein pathway, or an intracellular Src-dependent mechanism (43, 44, 58–61). This crosstalk may influence tumor invasion, metastasis, and the epithelial-mesenchymal transition, which prominently involves down-regulated E-cadherin (62). EGFR and PGE2 can induce Snail to transcriptionally suppress E-cadherin, which (suppression) is associated with MMP activation and dysplasia in oral IEN, a highly aggressive squamous cell cancer phenotype, and a poor prognosis in head and neck and other cancers (63–69). COX inhibition can reverse this phenotype and up-regulate E-cadherin, and increased E-cadherin expression has been correlated with sensitivity to EGFR inhibition (64, 69–71). EGFR inhibitors can inhibit COX-2 expression in head and neck cancer cells and xenografts (72). Besides COX-2, EGFR signaling can stimulate several other procarcinogenic signaling pathways/mechanisms (e.g., involving phosphatidylinositol 3-kinase/Akt, Ras/MAPK, Src, signal transducers and activators of transcription 3, and cyclin D1).

Preclinical data strongly support combined inhibitors targeting both EGFR and COX-2. A dual inhibitor of COX-1/COX-2 combined with an inhibitor of EGFR tyrosine kinase almost completely prevented adenoma development in ApcMin mice (73). A combination of agents targeting EGFR and COX-2 produced significant activity in head and neck cancer in vitro and in xenografts; this activity included additive-synergistic growth inhibition at low doses.

Table 1. Comparative logistics of phase III trials in different IEN risk settings

<table>
<thead>
<tr>
<th>Setting</th>
<th>Cancer risk</th>
<th>Prevalence (%)</th>
<th>Accrual (y)</th>
<th>n</th>
<th>Duration (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk (e.g., all oral IEN)</td>
<td>10% in 10 y</td>
<td>100</td>
<td>5</td>
<td>3,204</td>
<td>10</td>
</tr>
<tr>
<td>Moderate risk (e.g., dysplastic oral IEN)</td>
<td>35% in 10 y</td>
<td>10-15</td>
<td>5</td>
<td>852</td>
<td>10</td>
</tr>
<tr>
<td>Moderate to high risk (e.g., oral IEN with LOH)</td>
<td>35% in 3 y</td>
<td>28</td>
<td>3</td>
<td>580</td>
<td>5</td>
</tr>
<tr>
<td>High risk (e.g., post-cancer oral IEN with LOH)</td>
<td>65% in 3 y</td>
<td>66*</td>
<td>3</td>
<td>300</td>
<td>5</td>
</tr>
</tbody>
</table>

*Prevalence of 3p14 and/or 9p21 LOH in IEN developing in post-treatment oral cancer patients.
that resembled the effect of a high single-agent dose of an EGFR inhibitor in head and neck cancer cells (74–76).

**High risk and phase III clinical trial design.** High cancer risk marked by LOH or aneuploidy makes feasible a phase III clinical trial of promising agents, such as the COX-2 inhibitor celecoxib and/or EGFR inhibitor erlotinib. A schema for such a trial is presented in Fig. 1. Three hundred patients with high-risk oral IEN are randomly assigned in a 2 × 2 factorial design to the following four arms: celecoxib (75 patients), erlotinib (75 patients), celecoxib plus erlotinib (75 patients), and placebo (75 patients). The primary end point is time to oral cancer development. This would be the first trial in oral IEN to select eligible patients based on a molecular marker of high cancer risk or to employ the primary end point of oral cancer. Whereas our earlier work suggested that response of oral IEN (with hyperplasia or dysplasia) did not correlate with cancer development, the cancer end point in this trial would allow a comprehensive assessment of the effect of high-risk oral IEN response to treatment on the development of cancer.

The agents and doses for this trial design (Fig. 1) are based on strong preclinical and clinical data. Celecoxib at 400 mg bid has been studied in four recent clinical/translational trials. A randomized controlled trial of celecoxib at 400 mg bid versus 100 mg bid in familial adenomatous polyposis found that only the 400 mg bid dose had significant activity, a 28% reduction in polyp number, leading to Food and Drug Administration (FDA) approval of celecoxib as adjunctive therapy for this extremely high-risk IEN.

![Figure 2](image-url)

**Figure 2.** The basic design assumptions and estimated effects for phase III chemoprevention with celecoxib and erlotinib in oral IEN with varying risks of oral cancer. The dark blue (treatment group) and dark red (placebo group) lines are the estimated treatment effect on oral cancer incidence in any oral IEN (10% risk in 10 years; A), dysplastic oral IEN (35% risk in 10 years; B), oral IEN with LOH at chromosomes 3p14 and/or 9p21 plus at one other chromosome (35% at 3 years; C), and LOH at 3p14 and/or 9p21 in oral IEN in curatively treated oral cancer patients (65% at 3 years; D).
Celecoxib at 400 mg bid suppressed PGE$_2$ levels in non–small cell lung cancer (NSCLC) and oral IEN tissue (78, 79). Results from a celecoxib trial in NSCLC patients indicate that the reduction in urinary PGE-M (a measure of COX-2 activity) is far greater at 400 mg bid of celecoxib than at 200 or 300 mg bid (80). Furthermore, potentially beneficial COX-2–independent effects of celecoxib (e.g., increased apoptosis) may require higher doses (81–83). Studies of celecoxib in oral IEN are ongoing. Erlotinib at 150 mg/d produces plasma concentrations in patients that are equivalent to active erlotinib concentrations in preclinical head and neck and lung cancer models. Erlotinib abrogates EGFR-dependent induction of COX-2 and suppresses 15-PGDH (56, 57). Suppression of EGFR signaling is active in preclinical and clinical head and neck and lung prevention models (84–86). A limited clinical study in cancers of the head and neck and lung indicated that erlotinib at 150 mg/d produced pathologic responses that correlated with higher tumor tissue concentrations of erlotinib and suppression of cyclin D1 [which is highly associated with oral cancer development, is up-regulated by EGFR, is suppressed by erlotinib in vitro, and can be suppressed in association with oral cancer prevention (11, 13, 87)]. This agent is FDA approved for treating two tobacco-related cancers, including as a single agent in NSCLC. Moreover, there are several relevant trials in head and neck cancer patients, including trials of the EGFR inhibitors gefitinib, cetuximab, and erlotinib as single agents or in combination regimens (88–90), which produced promising safety and efficacy results, suggesting a dose-response

Figure 2  Continued. Modeling of the effect of cardiovascular (CVD) toxicity of celecoxib (added to the cancer risk) based on the same basic trial assumptions and estimated treatment effect in the various oral IEN risk settings is represented by light blue and orange lines.
relationship (91). Erlotinib and celecoxib have distinct, nonoverlapping toxicities and different primary routes of metabolism (i.e., via CYP2C9 for celecoxib and via CYP3A4 for erlotinib).

The main analysis of this trial is to compare the effect of single-agent celecoxib or erlotinib or the two combined versus placebo after a Bonferroni adjustment for multiple comparisons. We assume a risk of 65% for this trial design. We assume that treatment will reduce the cancer rate by 40%, which would lower the 3-year cancer rate from 65% to 39% in the high-risk setting. This lowered 3-year rate corresponds to a treatment hazard ratio of 0.47, which is held constant throughout the comparisons. The sample size of 300 randomized and evaluable patients allows 83% power for any treatment arm comparison with placebo (analyzed by the log-rank test with a two-sided overall type I error rate of 5%).

This phase III design in high-risk oral IEN is useful for illustrating the improved logistics (and feasibility) of prevention trial designs in higher-risk versus lower-risk populations. The improved logistics, or reduced sample size and trial duration, in the highest-risk trial (versus the three other risk settings; Table 1) are based on designs with the same trial assumptions (including the same magnitude of treatment effect), except for different baseline risks for different risk groups. The accrual times in the table assume a likely faster rate of accrual for the more common, lower-risk patients.

The phase III design in high-risk oral IEN also illustrates the important issue of agent risk-benefit profiles in higher-risk versus lower-risk populations. Although a consensus on the long-term toxicity of celecoxib has not been reached, celecoxib has been reported to be associated with the serious side effects of cardiovascular disease (CVD) (92). We can model the influence of these known side effects on the estimated effects of celecoxib within oral IEN patients with various risk levels (Fig. 2), providing a new objective way of evaluating risk-benefit in prevention trials. This modeling involves adding CVD assumptions based on the APC polyp prevention trial of celecoxib (400 mg bid for 3 years) to the

**Figure 3.** Estimated benefit and risk of finasteride for prostate cancer prevention. A, estimates are based largely on primary results of the PCPT and the National Cancer Institute’s Cancer Surveillance Program (unpublished figure used by permission of Leslie G. Ford, Division of Cancer Prevention, National Cancer Institute). For 1,000 men ages 63 years (average; blue men at top) and followed for 7 years, there is a clear advantage of finasteride (bottom right) versus no finasteride (bottom left) in overall prostate cancer (45 versus 60 cases; gray men) and a disadvantage in high-grade prostate cancer (22 versus 18 cases; yellow men). B, objectives of ongoing PCPT biological studies designed to improve the risk-benefit ratio of finasteride. Top, men ages 63 years (average) in the general population. Modeling to identify these men’s risks of any prostate cancer (gray men) or high-grade prostate cancer (yellow men) result in a cohort with very low risks (middle left) or comparatively high risks (middle right). Pharmacoecogenetic modeling in the high-risk cohort to determine who would benefit from finasteride (i.e., decreased risk of overall prostate cancer and no increased risk of high-grade disease) and who would not benefit yields a cohort (bottom right) for whom finasteride is indicated (purple) and one for whom finasteride is not indicated (green) but whose high prostate cancer risk (including of high-grade disease) suggests them as an optimal population for other preventive approaches.
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original trial assumptions indicated above (e.g., that treatment will reduce the 3-year oral cancer rate by 40%). The APC study indicated that CVD risk at 3 years will be 3.5% in the celecoxib arm and 1.0% in the placebo arm.

As shown in Fig. 2A, treatment with celecoxib (400 mg bid) to prevent oral cancer is not beneficial overall in the relatively low-risk setting of any oral IEN. Celecoxib in this lower-risk population actually would be anticipated to be worse than placebo after factoring in potential adverse CVD effects of the drug. Celecoxib becomes beneficial in moderate-risk (35% in 10 years) oral IEN (with dysplasia; Fig. 2B) or relatively high-risk (35% in 3 years) oral IEN (with LOH; Fig. 2C). The potential risk-benefit ratio of celecoxib improves dramatically for patients with the high cancer risk (65% in 3 years) associated with LOH in IEN developing after oral cancer (Fig. 2D). In addition, cardiovascular risk could be lowered or eliminated by using lower doses of the two combined agents or by using a high dose of single-agent erlotinib, the provocative activity of which is described earlier.

This graphical method of calculating overall benefit (cancer reduction) and risk (serious adverse effects) of an intervention could be useful for evaluating the treatment-effect assumptions of future trial designs with celecoxib (or potentially other drugs). Once a feasible and meaningful celecoxib treatment effect is chosen for a future trial designs with celecoxib (or potentially other drugs), trial designers could model the effects of the anticipated treatment effect and the risk of CVD associated with celecoxib in their trial population. If the net benefit shown in the curve of the treatment group has shown that interactions between 15-LOX-1 signaling and GATA-6, protein kinase G, histone deacetylase, and methyltransferase (which are upstream regulators) and PPAR-δ and PPAR-γ (which are downstream mediators) are COX-2–independent mechanisms involved in 15-LOX-1–induced apoptosis and anti-carcinogenic activity (106–111). The important role of 15-LOX-1 in carcinogenesis and as a target for cancer prevention recently has been confirmed by a number of research groups (112–117).

Cancers, CVD, neurodegenerative disorders, and other aging-related diseases can have shared, as well as distinct molecular defects and signaling pathways. Targeting these shared and distinct molecular events/pathways with single or combined agents to prevent multiple diseases may be another approach for improving the risk-benefit ratios of preventive drugs (118, 119).

Cancer Prevention and Therapy Convergence

Phase III cancer prevention with molecular-targeted agents aimed at the EGFR/COX-2 interaction in high-risk oral IEN highlights the growing convergence of cancer prevention with cancer therapy (93). The biology of high-risk IEN shares many targets, such as COX-2 and EGFR, with the biology of cancer (49–55, 94). The distinction between cancer and IEN is blurred in definitively treated oral cancer patients who develop IEN at a very high risk of a new cancer because of LOH (30). Furthermore, it is very difficult to determine if the new cancer developing in these patients is an SPT or a recurrence (39–41, 93–95). We examined patients treated curatively for head and neck cancer and who developed new cancer that was rigorously determined clinically to be either an SPT or recurrence (8). Genetic profiling of the initial and the subsequent cancer in these patients revealed substantial molecular ambiguity regarding the origins of the subsequent cancers (96). For example, >50% of the clinically defined SPTs were molecularly determined to be recurrence (i.e., genetic profiles consistent with clonal spread of the original tumor).

Molecular Targeting and the Risk of Cancer Prevention

In addition to high-risk populations, molecular targeted agents also have great promise for reducing the risk of cancer prevention. Precise targeting of molecular events involved in carcinogenesis and avoiding targets that, if altered, may have undesirable consequences will lower intervention risks overall and may allow for intervening in lower-risk populations. This possibility can be illustrated by the development of COX-2–inhibiting nonsteroidal anti-inflammatory drugs (NSAIDs) for cancer prevention. Blocking PGI2 (prostacyclin) is thought to be one of the major targets and mechanisms involved in the CVD risk associated with these drugs. Other targets of NSAIDs, such as nuclear factor-κB, phosphoinositide-dependent protein kinase-1, protein kinase G, peroxisome proliferator-activated receptors (PPARs), and 15-lipoxygenase-1 (15-LOX-1), may not involve blocking PGI2 (97–99). PGI2 also could be avoided by aiming at COX-2 pathway targets downstream of COX-2 and at the level of PGE2, such as the EP receptor mPGES and 15-PGDH (56–58, 100).

Work of our group led by Imad Shureiqi showed the potential of 15-LOX-1 targeting for avoiding COX-2 and adverse CVD effects. NSAIDs induce 15-LOX-1 in association with apoptosis induction, even in systems involving non–COX-2-inhibiting NSAIDs and non–COX-2-expressing colorectal cancer cells (101). These NSAID/15-LOX-1 findings have been confirmed by two other groups in colorectal cancer (102, 103) and have been extended to other cancers, including esophageal (104) and gastric (105) cancer. Our group has shown that interactions between 15-LOX-1 signaling and GATA-6, protein kinase G, histone deacetylase, and methyltransferase (which are upstream regulators) and PPAR-δ and PPAR-γ (which are downstream mediators) are COX-2–independent mechanisms involved in 15-LOX-1–induced apoptosis and anti-carcinogenic activity (106–111). The important role of 15-LOX-1 in carcinogenesis and as a target for cancer prevention recently has been confirmed by a number of research groups (112–117).

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Reducing the Risk of Chemoprevention

The only known factors associated with prostate cancer risk are older age, family history, and African American ancestry, which are not very predictive alone or in combination. As mentioned earlier, finasteride reduced prostate cancer prevalence by 25% in the PCPT but also increased the apparent risk of high-grade prostate cancer in men at a low-to-moderate overall risk of the disease (2). Consequently, finasteride is not widely used for prostate cancer prevention.

These data have led to an intensive effort to define high prostate cancer risk (especially of aggressive disease), including a National Cancer Institute program project that will develop comprehensive risk models based on genetic, metabolic, and environmental factors influencing prostate cancer risk among men in the PCPT (120). The program will use an invaluable repository of biospecimens and data collected prospectively in the PCPT population to assess the individual and interactive risk associations of many factors assessed in PCPT men. The PCPT ascertained the primary trial end point of cancer via prostate biopsy, regardless of prostate-specific antigen (PSA) or digital rectal examination status. This ascertainment method created a unique set of controls, who had negative biopsies for prostate cancer at the end of study, whereas controls in prior studies have been substantially contaminated (by the presence of cancer) because they were defined at best by low PSA levels (generally <4 ng/mL). Recently reported PCPT data show a substantial prevalence of cancer in men with so-called normal PSA over 7 years (121).
This program project not only will comprehensively assess prostate (including high grade) cancer risk but also will assess the pharmacoeconomic profile of finasteride, or the genetic, metabolic, and environmental factors influencing a man’s outcomes, either beneficial or adverse, associated with finasteride for prostate cancer prevention. Therefore, this program potentially will identify high-risk men most likely to benefit from (and not be harmed by) finasteride for preventing the disease, with potential implications for other active agents as well. The potential of the PCPT program project to identify high risks of prostate cancer and aggressive disease and to improve agent risk-benefit ratios in a high-risk setting is illustrated by Fig. 3. The risks of prostate cancer and high-grade prostate cancer in untreated men (Fig. 3A) potentially will be dramatically increased in populations selected by risk modeling in the new studies (Fig. 3B). The effects of finasteride in reducing these risks (Fig. 3A) potentially will be dramatically improved by pharmacoeconomic modeling in the new studies (Fig. 3B).

Other Chemoprevention Risk-Reducing Approaches

Defining high or moderate cancer risk populations for their risk of a particular agent’s known serious adverse effect(s) could allow targeting individuals with low risk and avoiding those with high adverse risks and thus further reduce the risk of chemoprevention. For example, hemorrhagic stroke (among male smokers with hypertension) is a known adverse effect of vitamin E (122), and SELECT excluded subjects with blood pressure above a certain level (3). Prevention trials of COX-2 inhibitors generally should exclude patients with CVD or certain CVD risk factors (92). Targeting high-risk postmenopausal women with a hysterectomy reduces the major competing risk of endometrial cancer associated with tamoxifen for preventing breast cancer (1, 4). As discussed earlier, finasteride is associated with an apparently increased risk of high-grade prostate cancer, and ongoing molecular epidemiologic (pharmacoeconomic) studies of finasteride are attempting to identify subsets of men at a minimal or no risk of potential finasteride-induced, high-grade disease and thus most likely to benefit from finasteride for prostate cancer prevention (120).

Novel dosing, scheduling, and administration strategies are other ways to potentially reduce chemoprevention risks. For example, lowering the standard dose of tamoxifen has been shown in a 2-year clinical breast cancer prevention trial to substantially retain benefit from finasteride for prostate cancer prevention (120). Analogues or class relatives of effective agents and cancer vaccines [which have shown efficacy against liver cancer (targeting hepatitis B) and cervical cancer (targeting human papilloma virus)] also may help reduce side effects (118, 126). For example, data suggest that raloxifene may be as or more active than its relative tamoxifen in reducing breast cancer risk while avoiding tamoxifen-associated endometrial toxicity (127). A vaccine targeting HER2 for preventing breast cancer (active in an animal breast prevention model; ref. 128) potentially could prevent HER2-associated DCIS and thus avoid chronic dosing toxicities associated with either trastuzumab (cardiac toxicity; ref. 129) or tamoxifen (endometrial toxicity) for chemoprevention in the setting of DCIS patients.

Conclusions

Much of the intense interest in cancer chemoprevention developed decades ago after new therapy approaches substantially stopped improving the morbidity and mortality rates of major cancers (130). Much of the intense interest in defining populations at high cancer risk developed within the past few years after significantly positive phase III chemoprevention trials failed to alter standards of care because the trial agents had unacceptable risk-benefit profiles in moderate-risk populations (1, 2, 4, 118, 131).

Experience has taught us that any promising preventive intervention with biologically active agents is likely to have adverse, perhaps unforeseen effects especially with long-term use (1, 2, 92, 118, 122, 132–136). The risks and side effects of chemopreventive agents must be weighed carefully against the potential cancer preventive benefit, which will depend largely on the magnitude of cancer risk in the target population. This risk-benefit issue applies to cancer preventive drugs currently used for other indications (e.g., NSAIDs for arthritis and finasteride for benign prostatic hyper trophy). Such drugs generally are approved after relatively small and short-term efficacy trials but then can be used in the community for much longer terms. With long terms and large scales, phase III trials (whether for chemopreventing cancer or noncancer, e.g., Alzheimer’s and heart disease) have provided the valuable public service of defining previously unknown risks of some investigational agents in wide standard use in other settings.

Reducing the risk of cancer prevention involves three major directions of study: defining high-risk populations who will better tolerate side effects and risks of active preventive agents; developing agents with fewer side effects and risks due to precise targeting of molecular events involved in the carcinogenesis to be suppressed or prevented; and defining the susceptibility of at-risk individuals to the beneficial and adverse effects of particular agents or agent classes. Successes in these areas of study (and others, e.g., novel dosing and administration) promise to accelerate the ability of cancer prevention to reduce the incidence, morbidity, and mortality of major cancers.

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