The Future of Molecular-Targeted Cancer Chemoprevention

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Cancer chemoprevention rose and fell on precipitous waves before molecular-targeted research in colorectal neoplasia produced some of the most demoralizing and promising indications for the future of this field. In mid-1990, 2 large-scale, randomized, controlled trials (RCTs) showed that β-carotene actually harmed heavy smokers at risk of lung cancer. We learned in 1998 that tamoxifen reduced breast cancer risk by 50% and in 2003 that finasteride reduced prostate cancer risk by 25%. In both cases, adverse effects ended up overshadowing the positive effects, and neither agent was accepted for standard prevention. Getting back to colorectal research, 1999 results showed that a cyclooxygenase-2 (COX-2)-selective inhibitor (coxib), was significantly active in familial adenomatous polyposis (FAP). This was a seminal finding and promised a bright future for coxibs, which were thought to be safer than aspirin. Then in 2005, large, sporadic, adenoma-prevention RCTs found that celecoxib and rofecoxib had alarming cardiovascular toxicity. This result deepened concerns over the risk–benefit ratio of all chemopreventive agents, darkening the future of cancer chemoprevention despite beneficial preventive effects also evident in the coxib trials.

Events since 2005 have helped to lift the coxib-related pall of cardiovascular toxicity. Serious cardiovascular events subsided in the longer term after stopping celecoxib and apparently were not associated with a low baseline cardiovascular risk. Mixed data on aspirin were clarified by recent data confirming aspirin reductions in colorectal adenoma and cancer risks. A signal advance in combination chemoprevention came with findings that a low-dose, non-coxib combination reduced colorectal adenomas by 70% (>90% for advanced adenomas) with no significantly increased adverse events. New information on tamoxifen and finasteride has lessened concerns about the adverse effects of these active preventive agents. *Helicobacter pylori* antibiotics dramatically reduced stomach cancer risk. Last, raloxifene and human papilloma virus (HPV) vaccine reduced cancer risk, had acceptable side effects, and approved by the US Food and Drug Administration (FDA), with a good chance of widespread community acceptance for prevention.

The future of cancer chemoprevention depends on the continued development of molecular-targeted approaches. This commentary discusses highlights of the biology of preventive molecular targeting, cancer risk modeling, and trials of molecular-targeted agents, all moving toward the development of personalized preventive medicine.

Biology of Molecular-Targeted Cancer Prevention

Chemoprevention began with the fundamental premise that it is possible to intervene within multistep carcinogenesis to prevent the step of invasion. Early prevention biology gave potentially preventive agents unfocused rationales for activity within early, middle, or late stages of multistep premalignancy.[1] Evolving molecular biology has advanced the development of agents capable of targeting specific, rate-limiting events within multistep carcinogenesis.[2,3] Much of the impetus for molecular-targeted chemoprevention came from pioneering biological studies of COX-2, and COX-2 study in FAP is a paradigm for translating targeted research in rare germline disorders to the sporadic setting. FAP is characterized by germline *APC* mutations, which are associated with increased COX-2 levels. Most sporadic adenomas have acquired *APC* mutations, which also are associated with increased COX-2 levels[4,5]; therefore, COX-2 targeting in FAP is relevant to sporadic adenoma prevention (celecoxib and rofecoxib are active in both settings).[6–9] This translation of germline to sporadic biology in the colon–rectum is being extended to other settings such as germline and sporadic *vhl* mutations in renal cancer development.[10] Cardiovascular toxicity of COX-2 inhibitors has stimulated increased interest in targeting events downstream of COX-2 or related pathways, including E-prostanoid (EP) receptors, prostacyclin, 15-LOX-1, peroxisome proliferator-activated receptors, 15-hydroxyprostaglandin dehydrogenase, and the prostaglandin transporter in the colon-rectum, esophagus, lung, and other sites.[5,11–15]

Other areas of biology vital to molecular-targeted chemoprevention include epidermal growth factor receptor (EGFR) signaling, the PI3K/Akt/mammalian target of rapamycin pathway, cMET, bronchioalveolar stem cells (comprising abnormalities in KRAS, Pten, P13K and cyclin-dependent kinase pathways),[16–19] che-

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mokines and the microenvironment[16,19] epigenetics,[20] and promising combinations of molecular-targeted agents. Combined targeting of COX and ornithine decarboxylase (ODC) is highly active in preventing mouse and human colorectal neoplasia, and combined targeting of COX and EGFR is very promising in preventing mouse colorectal neoplasia.[21,22]

Cancer Risk Models

Prevention RCTs with the slow-developing, definitive end point of cancer can have extremely large sample sizes, durations, and costs. A major dilemma has been a lack of surrogate end points (including premalignant lesions and molecular markers that reliably predict cancer) or suitable, high-risk populations, which could substantially reduce RCT logistics.[23,24] Many potential surrogate end points have been studied, but none established.[25] The state of the risk-modeling art has yet to reliably identify truly high-risk populations; most known higher risk populations have a somewhat elevated but still relatively low cancer risk. Fortunately, novel risk modeling with molecular risk factors integrated with clinical and classical epidemiologic factors is moving forward at a rapid pace, and promises to break through the barrier to high-risk identification and lead to substantial breakthroughs (including smaller and shorter definitive trials) in clinical prevention as well (Figure 1).

Risk models based on clinical/classical epidemiologic factors have been developed for several sites and can include established precursor lesions defined by clinical/histologic criteria.[26–28] Such models are being improved by the addition of specific molecular alterations that drive carcinogenesis. For example, in the precursor Barrett esophagus (a well-established but modest predictor of absolute cancer risk), a striking model incorporating a chromosome instability panel of loss of heterozygosity (LOH) and DNA content profiles distinguished between individuals at a high (79% in 6 years) and low (0% in >6 years) cancer risk.[29] LOH profiles (eg, at specific loci in chromosomes 3p and/or 9p)[30,31] substantially increase the relatively low oral cancer risk of oral leukoplakia,[32–34] especially in patients with a previously treated oral cancer.[35] The expression of biomarkers indicating an abrogated response to cellular stress predicts a worse outcome for breast ductal carcinoma in situ (DCIS) patients.[36] A panel of methylation markers in sputum marked a high lung cancer risk in chronic smokers.[37] Germline genetic variations (eg, in the lung and prostate)[38,39] also are promising risk factors for multidimensional models. Recently published lung cancer risk models integrating genomic (somatic gene expression arrays and host DNA repair capacity) and clinical features were more accurate than were clinical models alone.[40,41] Cyclin D1 genotype and expression are associated with a high cancer risk in patients with dysplastic head and neck premalignant lesions.[42] Important molecular risk models are also being designed for the adjuvant setting.[43]

Many molecular risk factors not only improve the accuracy of traditional risk models, but also are steps of carcinogenesis potentially targeted by chemoprevention. Cyclin D1 is a case in point; although no direct cyclin D1 inhibitors are yet in clinical use, several agents inhibit targets (eg, EGFR and mammalian target of rapamycin) upstream of, and thus ultimately could down-regulate, cyclin D1. One such agent, erlotinib, is being tested in a Phase III oral cancer prevention trial in oral leukoplakia patients selected for a high risk owing to the LOH profile mentioned.[44] A Phase II trial of erlotinib is ongoing in intraductal papillary mucinous neoplasms, which are driven by EGFR signaling (Figure 1).[45,46]

Colorectal Neoplasia and Prevention

Several COX inhibitors have been studied in RCTs to prevent colorectal adenomas.[3] Sulindac and celecoxib are effective treatments for adenomas in FAP patients.[6,47] The COX inhibitor aspirin significantly reduced sporadic adenoma risk in 3 relatively short-term RCTs published in 2003.[48–50] Although generally positive, these RCTs were complex, difficult to interpret, and did not lead to the acceptance of aspirin for reducing the risk of sporadic adenomas. Further complicating the interpretation of aspirin, the Physician's Health and Women's Health studies found no protective effect of aspirin on colorectal cancer risk. New 2008 data from the United Kingdom Colorectal Adenoma Prevention study[51] have helped to clarify the mixed results of the previous RCTs by demonstrating that aspirin significantly reduced adenoma risk by 21%. Furthermore, recent pooled analyses of the British Doctors Aspirin Trial and the United Kingdom Transient Ischaemic Attack Aspirin Trial found that aspirin was associated with a significant 26% overall reduction in colorectal cancer risk; the reduction was greatest in people treated with ≥300 mg/d for ≥5 years and did not appear before 10 years.[52] These pooled results are consistent with those of a recent large cohort study from the Health Professionals Followup Study.[53]

Interim cardiovascular event rates were unexpectedly increased in 2 of 3 RCTs, the Adenomatous Polyp Prevention on Vioxx (APPROVe) and Adenoma Prevention with Celecoxib (APC) trials but not a third, the Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP) trial, of selective COX-2 inhibitors (vs placebo) in preventing sporadic adenomas.[54–56] All 3 RCTs were stopped early, and rofecoxib was withdrawn from the world market by the manufacturer because of this serious safety issue, despite significant coxib reductions in adenomas in the trials. These developments cast a dark shadow over cancer prevention. A recent extension anal-