

*Editorial***The Critical Role of Risk-Benefit Assessments in Cancer Prevention**

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Controversy is building around agent development for cancer prevention. The withdrawal of rofecoxib (Vioxx, Merck) from the market and safety concerns raised by studies of other cyclooxygenase-2-selective inhibitors and an over-the-counter nonsteroidal anti-inflammatory drug have alarmed patients, physicians, and regulatory authorities. Evidence of nonsteroidal anti-inflammatory drug-associated cardiovascular toxicity—of relatively low frequency but significant magnitude—reminds us of the critical role that risk-benefit assessments play in agent development for cancer prevention. The placebo-controlled design of cancer prevention trials explains in part why these toxicities came to light only recently. Although this could dampen industry's willingness to commit resources to cancer prevention, it also has the potential to stimulate creativity in clinical research and transform regulatory oversight in productive and meaningful ways. Our response to this challenge will dictate the pace of progress in cancer prevention research.

Safety. The tension between assuring patient safety—our main concern in investigational trials—and proving agent efficacy for cancer prevention poses distinct developmental challenges. Safety assessments are inherently difficult in cancer prevention, which must balance the risk-benefit ratio in a specific group at a presumed—although still probabilistic—risk of cancer. Positive trials of compounds, such as tamoxifen, finasteride, and aspirin, illustrate these developmental challenges. Although tamoxifen reduces the risk of invasive and noninvasive breast cancer by ~50%, it is rarely used owing to concerns regarding treatment-related uterine cancers and thrombotic events. Finasteride was shown to reduce the period prevalence of prostate cancer by 25%, but it was also associated with an increase in higher-grade cancers. Aspirin reduces recurrent colorectal adenomas, but it conveys hemorrhagic risks. Even nutritional compounds that were once considered benign interventions have checkered profiles. For example, β -carotene was actually shown to increase the risk of lung cancer incidence and mortality among smokers. More recently, a meta-analysis of trials with vitamin E suggested increased mortality among people using high doses of a subset of vitamin E supplements.

Efficacy. In addition to safety issues, clinical prevention trials are subject to varying interpretations of their short-term and long-term significance. This uncertainty derives from the probabilistic nature of carcinogenesis and the length of time it takes to observe "hard" clinical end points. Ironically, these and other obstacles limit commercial interest and investment in cancer prevention at a time when the demand for chemoprevention is growing. Nonetheless, increasing understanding of molecular carcinogenesis and growing numbers of individuals that are at risk for cancer are creating exciting new opportunities for chemoprevention.

Intervention trials are typically designed to show a significant difference in the number of events over time within a particular group (i.e., before versus after investigational treatment) or across different groups (e.g., investigational treatment versus standard care). In order to identify differences in efficacy and safety that might be ascribed to the experimental regimen, researchers exploit the three cardinal elements of trial design: participants, end points, and agents. Among these three elements, a focus on participants and end points offers the greatest likelihood of accelerating near-term progress in cancer prevention.

Study Participants. Participants in clinical prevention trials include persons at risk for cancer owing to endogenous and/or exogenous risk factors. Preliminary trials focused on the biology of neoplastic initiation or progression in high-risk individuals are critical to detecting early signals of agent efficacy and prioritizing lead compounds for testing in larger and longer-term trials. For example, investigational agents tested in individuals with germ line mutations that place them at high risk for cancer may achieve clinical goals with fewer than 100 participants in as little as a few months. By contrast, demonstration of agent efficacy in more heterogeneous or lower-risk groups typically requires thousands of participants and years of observation. These broad-scale trials may better reflect the general population and represent our long-term goal but require an exceptionally high level of justification. The costs (i.e., staff, infrastructure, available participants, research opportunities, and, perhaps our most valuable resource, time) of conducting these studies prematurely are extraordinarily high. In an environment of increasing research opportunities and limited funding, massive trials in heterogeneous or low-risk groups preclude the execution of many smaller trials involving more homogeneous or higher-risk groups. The growing number of competing hypotheses and concerns over agent safety demand renewed commitment to trials informed by biological principles. In addition, we must insist on more from our largest trials. For example, reviewers should require the development of tissue banks for the exploration of intermediate end points that might improve our understanding of cancer biology and permit iterative improvements in agent identification and validation.

End Points. Long follow-up times provide an effective, although costly and cumbersome, approach to acquiring the requisite number of neoplastic events. Alternative approaches exist, but they probably require new or different infrastructures than those in current use. For example, rather than waiting for clinical declaration of disease, we should use sensitive technologies (e.g., endoscopy) to detect disease earlier during carcinogenesis whenever possible. In addition, within-person (rather than between-person) comparisons provide important efficiencies because they control for issues of disease susceptibility and heterogeneity, thereby reducing trial costs. Finally, realistically validated intermediate end points, such as intra-epithelial neoplasia, offer important clinical insights and

efficiencies. Although the significance of intraepithelial neoplasia end points remains a surprisingly contentious issue, certain of these biologically mature lesions have been definitively established as the focus of screening, intervention, and medical reimbursement in many settings. Indeed, >10 drugs have been approved for the treatment of intraepithelial neoplasia, most within the last 5 years.

Conclusion. Associations between early and late neoplastic events are probabilistic at best. Therefore, useful chemopreventives can only be expected to have relative and partial effects, and toxicities are inevitable. Nevertheless, effective agents will contribute to either of chemoprevention's dual objectives: medical prevention and public health. The proximal goal, medical prevention, largely concerns individuals at greater than average risk who are typically identified by screening. The distant goal of public health involves gains against cancer incidence and mortality at the population level.

Compelling evidence argues for implementing today's technologies while recognizing their limitations, in each instance guided by serious consideration of their risks and benefits. This approach to medical prevention recognizes that certain transitional tools offer valuable, albeit incomplete, solutions. Other disciplines have cleared this hurdle by implementing realistically validated technologies rather than waiting for reductions in late events. Clinical prevention in

cardiovascular disease is the classic demonstration of this principle. By employing progressively better tools for the treatment of risk factors for late-stage events (e.g., myocardial infarction, cerebrovascular accidents, and myocardial infarction- or cerebrovascular accident-related death) rather than exclusively treating late events, researchers successfully shifted emphasis from treatment to prevention and ultimately achieved the anticipated public health benefits. Indeed, through appropriate adoption of emerging technologies, risk factors, such as hypertension, hyperlipidemia, and asymptomatic stages of atherosclerosis, became accepted as subclinical diseases worthy of identification, intervention, and reimbursement in and of themselves. Cardiovascular mortality has been dropping ever since this approach was broadly adopted a decade ago. Although the distinction between cancer prevention and treatment may blur at the extremes (as do concepts of risk and disease), prevention is clearly an achievable goal on a par with, if not preferable to, cancer treatment.

The central tenet of the Hippocratic oath—"first, do no harm"—is generally assumed to refer to action; however, it clearly applies to inaction as well. This principle is most readily evident in clinical practice; however, it also applies to the research enterprise. Incremental insights into carcinogenesis and advances in cancer prevention technology compel careful appraisal of our trial designs and developmental strategies for the next generation of clinical research.