

Editorial**Chemoprevention Clinical Trials: It Is Time to Turn Success into Progress****Powel H. Brown**

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We are at the beginning of an important era in the clinical application of cancer prevention research. Research over the last 20 years has successfully shown the feasibility and promise of chemoprevention, and we are now in position to make such preventive therapy common medical practice. However, because treatment with existing cancer-preventive drugs is associated with risk of bothersome, and sometimes serious, side effects, the promise of chemoprevention has not yet been realized. Major goals now are to develop reliable ways to identify high-risk individuals who would benefit most from preventive therapy and to develop effective cancer prevention drugs with reduced toxicity.

In 1990, Hong et al. (1) showed that it is possible to use medications to prevent the development of head and neck cancers in humans. In addition, over the last few years, results from several phase III clinical cancer prevention trials have confirmed that preventive therapy can reduce the risk of developing precancerous colonic polyps (2-5), invasive and noninvasive breast cancer (6-9), and invasive prostate cancer (10). These studies have conclusively shown that preventive therapy can greatly reduce the risk of cancer in high-risk individuals and provide a firm foundation for further development of cancer-preventive drugs. However, despite the success of these clinical trials, there has been limited progress in using these agents for cancer prevention. It is now time to make progress in this area: to optimally use currently available agents to reduce cancer risk, to efficiently develop more effective and safer cancer-preventive drugs, and to test these new drugs in cancer prevention clinical trials to show their benefits and risks.

Promote Benefit-Risk Analysis to Optimize Use of Available Cancer-Preventive Agents. Antiestrogen drugs such as tamoxifen and raloxifene [selective estrogen receptor modulators (SERM)] have been shown to reduce breast cancer risk by ~50% (6-9, 11). Despite this substantial risk reduction, many women avoid using these medications because of concerns about side effects. Although there are common bothersome side effects (hot flashes, vaginal dryness) and rare serious side effects (increased risk of uterine cancer with tamoxifen and increased risk of thrombosis with both SERMs), women at high risk of breast cancer, particularly those with a very strong family history, and those with noninvasive breast cancer (ductal carcinoma *in situ*) or precancerous lesions (lobular carcinoma *in situ*, or atypical ductal hyperplasia) should discuss the benefits and risks of these drugs with their physicians. Many of these women will accept the risks of

SERM therapy to reduce their high risk. Too few of these women are offered these highly effective cancer-preventive drugs.

To increase the use of currently available cancer-preventive drugs, it will be necessary to continue to promote risk-benefit analysis of these drugs. These agents are approved for high-risk individuals and are not intended to be used routinely in the general population. Although healthy individuals, who are at low risk of cancer, may legitimately be wary of medication with any side effects at all, healthy individuals at high risk of cancer are extremely concerned about that risk and are often willing to accept a certain degree of possible side effects to achieve risk reduction. The demonstration that raloxifene reduced invasive breast cancer risk just as well as tamoxifen, while causing significantly fewer side effects (9), should make this SERM even more acceptable to high-risk women. Thus, it is now important for physicians to discuss routinely the benefits and risks of these cancer-preventive drugs just as they now discuss the benefits and risks of lipid-lowering drugs, antihypertensive drugs, and cancer therapeutic agents. To ensure progress, it will also be necessary to overcome the general misconception that a cancer-preventive drug should be given to the general population and should have no risk. In addition, continued research needs to be conducted to better identify high-risk individuals.

Facilitate Cancer Prevention Drug Development. We are in the midst of a breathtaking expansion of knowledge about cancer biology with advances in genomics, proteomics, and signal transduction. The molecular pathways deranged in cancer cells are being rapidly elucidated and mapped, and drugs that are specifically targeted to each of these pathways are being methodically developed. Such an explosion of information should quickly lead to the development of drugs for the treatment and prevention of cancer. However, although drug development for cancer therapy is occurring at warp speed, the development and testing of drugs for cancer prevention has slowed to a crawl. Pharmaceutical houses have experienced or witnessed huge losses of revenue as drugs such as the Cox-2 inhibitors, previously used for noncancer indications, have been pulled from the market due to rare side effects that are discovered during testing of these agents for cancer-preventive indications. Although rare side effects of such agents would have likely been discovered through other means, the necessity for lengthy clinical trials to test cancer-preventive agents has caused companies to shy away from subjecting current or novel agents to cancer prevention trials. Unfortunately, phase III cancer prevention trials, which have the potential to change medical practice, are now often considered to be a liability to pharmaceutical houses. The expense and length of development and the possibility of discovering potentially serious rare side effects of an existing profitable drug have made drug companies very wary about testing their drugs in this setting. To make progress in this area, it will be necessary to reduce the barriers for pharmaceutical houses to

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develop and profit from cancer-preventive drugs. To make progress in this area, we need to address the complex issues of patent life, regulatory issues, and liability from rare side effects.

Facilitate Testing of Cancer-Preventive Agents in Phase III Clinical Trials. As new drugs become available, it is necessary to test these drugs in clinical trials to show efficacy and safety. Although many agents are currently being tested in phase I and II cancer prevention trials, phase III trials are becoming increasingly difficult. Such trials are, by necessity, expensive and lengthy and often require a large number of subjects (and thus put a large number of individuals at potential risk of unwanted effects). Phase I and II cancer prevention trials enable the early testing of novel preventive therapies and can determine whether novel molecularly targeted agents actually block their expected targets (and possibly other unexpected targets); however, these early trials cannot replace phase III trials. Although surrogate end points have been sought that could make studying the long-term effect on invasive cancer incidence unnecessary, no such surrogate end points have yet been validated. Thus, it is still necessary to conduct phase III cancer prevention studies using invasive cancer as the primary end point.

Although phase III trials are clearly needed to show an effect on the end point of invasive cancer, they are also needed to show the magnitude of the benefit to provide the basis for the critical discussion of benefits and risks. It is these phase III clinical trials that will be the basis for a change in medical practice once they are completed successfully; thus, it is absolutely necessary to devise ways to complete these large scale trials.

The recent concerns over the National Surgical Adjuvant Breast and Bowel Project (NSABP) STELLAR breast cancer prevention trial highlight the difficulties of currently conducting phase III cancer prevention trials. This trial follows the two previously successful NSABP breast cancer prevention trials showing that tamoxifen and raloxifene each reduce the risk of breast cancer in high-risk women by 50% (6, 9). The proposed study would compare raloxifene (considered to be the optimal choice among the SERMs based on having fewer side effects than tamoxifen) with the aromatase inhibitor letrozole. The plan to study the cancer-preventive effect of this aromatase inhibitor was based on the finding that the similar aromatase inhibitor anastrozole was more effective in reducing second primary breast cancers in the ATAC adjuvant breast cancer trial (12). This observation raised great interest in using aromatase inhibitors for breast cancer prevention and led to several prevention trials comparing an aromatase inhibitor to placebo. The proposed NSABP trial differs from these other trials in that it compares two potentially effective agents (the SERM raloxifene with the aromatase inhibitor letrozole) to determine which drug is most effective at preventing breast cancer and which is most tolerable in terms of side effects to high-risk women. It is precisely this comparison that is needed to guide future use of these agents.

Despite the potential of this study to determine which hormonal agent is most effective for breast cancer prevention, concerns about the cost and the acceptance of these drugs for cancer prevention have been voiced (see *Cancer Letter*, March 2 and April 20, 2007). These are legitimate concerns that should be considered for any cancer prevention trial. However, we must find solutions to these problems. Acceptance of medical therapy for cancer prevention will ultimately depend on accurate risk assessment and appropriate use in high-risk individuals. Funding for these expensive but critically important clinical trials will require broad support from all sectors—governmental, industrial, and private. As noted above, pharmaceutical houses are increasingly reluctant to fund or participate in long-term trials of drugs that already have

another indication. We must work to find ways to enable pharmaceutical houses to develop or test these drugs without suffering large financial losses. Similar issues pertain to vaccine development, and novel mechanisms to avoid liability for makers of vaccines are being considered. Analogous solutions need to be found for cancer prevention drug development. In addition, given the current financial constraints of the Federal Government, government funding is increasingly more difficult to obtain for these essential prevention trials. Nonetheless, it is clearly in the public interest to identify the most effective and safest agents for the prevention of cancer, and we must continue to work toward increasing government funding for all areas of cancer research, including cancer prevention clinical trials. It is unacceptable to consider governmental support for cancer research a “fixed pie.” We must work to ensure increased, not decreased, federal spending on cancer research. Finally, we must increase our efforts to harness the potential of the private sector in supporting cancer prevention research. Private philanthropy has been invaluable in advancing AIDS research, vaccine research, and cancer treatment research. We need to increasingly involve cancer research foundations and private philanthropic organizations in supporting cancer prevention research as well. It is our responsibility to work with these organizations to find ways to deliver effective cancer-preventive therapy to those who need it. Therefore, to make progress, we will need to first recognize the critical importance of phase III cancer prevention trials, and then work to develop effective and novel ways to fund these expensive studies using pharmaceutical, governmental, and possibly even private sector support from cancer foundations and philanthropic groups.

It is clear that the barriers to cancer-preventive drug development are substantial. However, the promise of cancer-preventive therapy greatly overshadows these barriers. We have already had much success showing that drug therapy can prevent cancer. We now must do the even more difficult job of turning this success into progress.

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