PERSPECTIVE

The big C — for Chemoprevention

Drugs to prevent cancer are clearly possible despite some early missteps, says **Michael B. Sporn**. Restoring the cooperative ethos of decades past will help get us there.

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When a complex system starts to dysfunction, it is generally best to fix it early. The alternative often means delaying until the system has degenerated into a disorganized, chaotic mess — at which point it may be beyond repair. Unfortunately, the general approach to cancer has ignored such common sense. The vast majority of cancer research is devoted to finding cures, rather than finding new ways to prevent disease.

The results of these skewed priorities are plain to see: forty years after President Richard Nixon declared war on cancer, the death tolls from most common forms of cancer in the United States have not fallen. It's true that for some cancer types, mortality rates (adjusted for population size) have dropped during these decades, but there are huge, unhappy exceptions: mortality rates for lung and pancreatic cancer have stayed level since 1970, and the total number of US deaths each year from those diseases has doubled[1].

Looking at these discouraging statistics, it is clear that something needs to change. We have been looking at the very nature of cancer in the wrong way. Breast cancer doesn't begin when a lump is first felt or detected by mammogram. All the common epithelial cancers (lung, colorectal, breast, prostate, pancreas and ovary), which account for the majority of deaths, have a long latency period — often 20 years or more. By the time they are clinically detectable, the cells in such carcinomas may harbour hundreds of mutations in different genes[2]. These cells provide no simple, single target for therapy. In contrast, during the long latency period, there is ample opportunity to use multi-functional, multi-targeted preventive drugs that block the development of invasive and metastatic disease.

That's the basic idea of cancer chemoprevention (see First line of defence, page S5): to arrest or reverse the progression of premalignant cells towards full malignancy, using physiological mechanisms that do not kill healthy cells. In experimental animals, it is now possible to prevent the onset of cancer in almost all the common organs in which human carcinoma occurs. Even more importantly, chemoprevention has now been validated in people. One class of drugs, known as selective estrogen receptor modulators (SERMs), can deliver as much as a five-fold reduction in incidence of estrogen receptor-positive breast cancer in women. These compounds — most notably tamoxifen, raloxifene and lasofoxifene — have the added benefit of suppressing osteoporosis[3]. Fenretinide, for which we have 15 years' worth of data, provides significant prevention of breast cancer in premenopausal women[4]. Two anti-androgenic agents, finasteride and

dutasteride, have been shown to be effective at reducing incidence of prostate cancer in long-term clinical trials[5].

And yet we have a paradox: within the world of clinical oncology, chemoprevention of cancer is perceived to be a failure. As a result of some poorly designed and executed clinical trials over the past decade, scepticism abounds about the practicalities of chemoprevention. This harsh assessment is the conventional wisdom among groups as diverse as the pharmaceutical industry, the hospital establishment, the insurance industry, women's advocacy groups and the clinical oncology community itself. Of particular disappointment to many advocates of chemoprevention has been the general lack of enthusiasm from large pharmaceutical firms, as exemplified by the recent decisions of two major companies to curtail further development of lasofoxifene and arzoxifene, another highly promising SERM[6]. Many factors have contributed to this negativity, including difficult regulatory approvals, duration of patent protection and the omnipresent fear of liability in treating supposedly healthy people with drugs.

But attitudes toward chemoprevention need to be re-examined. Most fundamental is the bizarre misperception that people are 'healthy' until they have actual symptoms of invasive cancer, the corollary being that it is unwise and perhaps unethical to give a preventive drug to a healthy person. In reality, however, a person harbouring a premalignant lesion is not healthy, in spite of the absence of symptoms. Many of these people will go on to develop life-threatening cancers. The barn in which hay is smoldering before it bursts into flames is not a safe place.

Another canard is that cancer prevention efforts are not cost-effective. The argument is that the number of lives saved with a preventive drug would be too small with respect to the total number of people who need treatment. But this is a curious perspective. The number of houses destroyed by fire is trivial compared with the total number of houses, and yet almost every homeowner insures against fire. The conceptual problem here is that everyone doesn't die of cancer in a short period; this is a lifetime problem.

There is a simple answer: we should stop doing clinical chemoprevention trials in large populations of people at relatively low risk, and instead focus on cohorts at the highest risk. There are many such groups: women with *BRCA* mutations that can lead to breast and ovarian cancer, people with premalignant pancreatic lesions and those with severe premalignant lung lesions (especially in current or former heavy smokers). Chemoprevention trials on such groups will provide much more definitive results and with much less effort.

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More broadly, the elevation of cancer prevention requires several actions. First, we need a massive educational effort to encourage the general public — not just special interest groups — to support prevention efforts. This has been very successful in cardiology; indeed, the pharmaceutical industry spends huge amounts of money on educational and advertising efforts to promote chemoprevention of cardiovascular disease with statins and anti-platelet agents. Unfortunately, these companies seem unwilling to similarly promote cancer chemoprevention.

In addition, we need to be vigilant about the safety of the preventive drug testing regimen. Thus, we should build in 'rest periods' in clinical chemoprevention trial design. Many drugs used for chemotherapy have severe toxicities if used long term, so rest periods are necessary and routinely used. Although, as a class, chemopreventive drugs are much less toxic, rest periods would make relatively safe drugs even safer. Moreover, drugs need to show extensive efficacy in animal experiments before undergoing human trial — wisdom that was forgotten in the failed clinical trials of beta-carotene, selenium and tocopherol.

Regulatory accommodations will also help. The Food and Drug Administration still forbids the use of two experimental drugs in clinical prevention trials, in spite of the fact that there is overwhelming evidence that combinations can be much safer and more effective than single agents[7]. Further appreciation and understanding of the concept of 'risk' is also essential. For new drugs, the proper comparison is not risk versus benefit but rather risk versus risk[8] — that is, the risk of doing nothing (which may have a deadly outcome), versus the risk of taking a preventive drug for long periods. Oncologists could follow the lead of cardiologists, who have developed a handy scorecard that numerically quantifies a patient's risk[8].

On the basic science front, we must develop new multifunctional drugs that aim at entire networks in the body, rather than single targets[9]. We need further studies on the importance of epigenetics[10] and the tumour microenvironment[8] to develop chemopreventive drugs. The tumour microenvironment, with all of its stromal and inflammatory cells, is an essential part of a carcinoma. Major advances over the past decade in these areas are leading to the development of important new drugs for cancer prevention[8, 10].

So the challenges are numerous and daunting. There is great interest in personalized medicine (a wonderful goal) — but how can we do this successfully if the parameters we assess are exclusively genetic? Our environment, which continually changes, is reflected in epigenetic changes , inflammatory cells and the paracrine mediators they produce, as well as oxidative stress. All of these nongenetic parameters in turn can have profound effects on the structure and function of the genome. The ultimate justification for a preventive approach to control of cancer is that cancer prevention is an opportunity to provide a higher quality of symptom-free and pain-free life to people, rather than waiting until someone has invasive and metastatic cancer with all of its attendant suffering for both patient and family.

We can look to the past for guidance. Fifty years ago, a unique spirit of intense cooperation found cures for acute childhood leukaemia and Hodgkin's disease, two previously fatal conditions. This triumphant work was achieved through highly collaborative efforts that tested multiple combinations of drugs. In the case of leukaemia, it took many years of research at multiple institutions to find the proper mix and dosage of vincristine, amethopterin, 6-mercaptopurine and prednisone (VAMP) that eventually enabled medical researchers Tom Frei and Emil Freireich and their team at the National Institutes of Health (NIH) to find a truly effective combination therapy. This effort involved not only the NIH, but teams at universities, as well as at several major pharmaceutical companies. A similar multigroup effort shortly thereafter led to the conquest of Hodgkin's disease.

Although we still have many cooperative groups for clinical trials, the all-hands-on-deck spirit that promoted the cure of childhood leukemia and Hodgkin's disease has largely disappeared in an increasingly competitive world. Regulatory and legal issues, as well as academic competitiveness and companies' perceived need to protect intellectual property, impede cooperation. To make substantial progress toward cancer prevention, we need to regain this lost ethos. ■

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