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.

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. 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. Fenretinide, for which we have 15 years’ worth of data, provides significant prevention of breast cancer in premenopausal women. Two anti-androgenic agents, finasteride and
dutasteride, have been shown to be effective at reducing incidence of prostate cancer in long-term clinical trials. 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, skepticism 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. 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. The conceptual problem here is that everyone doesn’t die of cancer in a short period; this is a lifetime problem. The conceptual problem here is that everyone doesn’t die of cancer in a short period; this is a lifetime problem.

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CANCER PREVENTION OUTLOOK

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