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PERSPECTIVE

Prevention of Epithelial Cancer: The Challenge for the 21st Century

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Despite apparent declines in incidence and overall mortality rates from cancer,[1] both remain at near all time highs.[2] These trends pale in comparison with the dramatic declines for heart disease and stroke. If current trends continue, cancer is expected to be the leading cause of death in the United States (US) by 2010. A future pandemic of new cancer cases in the USA could be resulted from the aging of the population and the high proportion of new cases in older persons (> 60 years).[3-5] The World Health Organization estimates that worldwide the number of new cancer cases will be increased from 9 million new cases annually now to 20 million cancer cases annually by 2020 and cancer deaths from 5 million to more than 10 million.

Cancer prevention provides excited potential to reduce incidence and cancer mortality. However, despite this potential efficacy, prevention research has received little attention. Prevention funding, despite doubling funding from 1997 to 2001 by the National Cancer Institute (NCI),[6] is still de-emphasized compared with cancer treatment research by the US Federal government[7] (see Table below).

Table. Cancer Research Funding by the National Cancer Institute (NCI) in the USA 2001[6,7]

	Research Funding			
Total Budget (NCI)	Cancer treatment		Cancer prevention	
$ 3.75 billion USD	$ 916	24.4%	$ 427	11.4%

A recent analysis[8] compared the impact of new cancer therapies and cancer prevention on population mortality. Unger and co-workers analyzed eight positive phase III therapeutic trials of the Southwest Oncology Group for in the lung, bladder, stomach, cervix, and renal cancer as well as multiple myeloma and acute myelogenous leukaemia. They estimated how the observed improvements in survival from the new therapies would impact mortality at the population level (utilizing Surveillance, Epidemiology, and End Results data). The researchers compared these results with the impact of the Prostate Cancer Prevention Trial (PCPT). The measure of impact was person-years saved in the first 5 years. The estimated person-years saved data showed that both cancer treatment and cancer prevention have a substantial potential for extending life. However, federal funding for cancer prevention is less than half of that of cancer treatment. Therefore, because of its enormous potential on reducing cancer incidence, prevention warrants increased funding from federal funding agencies.[8]

Private sector -pharmaceutical industry- has little interest on funding prevention research. This lack of interest is related to the fact that compounds in this category are often out of patent or cannot be patented. Selenium, vitamin A, vitamin E, beta-carotene, and Helicobacter pylori eradication treatment have been or are currently being tested for their efficacy in preventing cancer in large prevention trials. Even if the drug can be patented, such as finasteride in the PCPT, healthy persons at low-risk of developing cancer may be less motivated to partake of the prevention regimen, a scenario in stark contrast with the therapeutic setting, where the treatment imperative ensures rigorous compliance with medication. In prevention trials, large cohorts are required to detect potential differences between different prevention regimens. The PCPT enrolled more than 18,000 participants. The Breast Cancer Prevention Trial, randomly assigned 13,388 women to placebo versus tamoxifen to test the efficacy of tamoxifen to reduce the incidence of breast cancer.

Therefore, the prevention of cancer remains the responsibility of public health service. In the US the NCI and in the United Kingdom the British National Health System (NHS) increase support and funding on

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development of effective cancer chemoprevention. The development of successful chemoprevention strategies will have an enormous impact in the world population incidence and mortality.

An important problem however, is how to bridge with evidence-based safety the gab between latest research developments and clinical practice. For example, for breast cancer prevention, concerns about side effects of tamoxifen and its limited ability to prevent estrogen-receptor-negative have strongly curbed its acceptance by the general public for chemoprevention. Several prevention trials are underway and their results, that are awaited with interest, is expected to allow guidelines for advising health care professionals on how to prevent healthy persons, who are at moderate or high risk of developing cancer.

Prevention of inherited cancer

Relatives of a patient with inherited cancer face a very high risk of developing hereditary cancer syndromes if they are carriers of germ-line mutations. For example women with BRCA1 or BRCA2 germ-line mutations have an average risk of breast cancer of approximately 70%. Similarly people with mutations in *CDH1* gene have a 70% risk of developing diffuse gastric cancer. People with inherited familial adenomatous polyposis face a nearly 100% risk of colon cancer. Important advances have been made in preventing these hereditary cancer syndromes through effective prophylactic surgical or nonsurgical interventions. However, germ-line mutation cases account for only 5 to 10% of all cancer cases and interested has been focused on developing effective prevention strategies for the much more often sporadic (noninherited) cancer.

Chemoprevention of sporadic cancer

Chemoprevention research provides strong promise for effective reduction of epithelial cancer incidence. Particularly important will be the impact of effective chemoprevention on population mortality in developing countries. Indeed, the goal of effective treatment in these countries appears unrealistic even in the distant future because early detection due screening programs and both new sophisticated combined targeted therapies and advanced technology for accurate diagnostic staging and outcome prediction are too expensive and not of priority for these countries.

Most common cancers: breast, prostate

Tamoxifen, Finasteride

Few only chemoprevention drugs have completed phase III trials. It is not surprising that tamoxifen and finasteride have completed scientific testing for the most common cancers, breast cancer in female and prostate cancer for men respectively. But despite positive studies, popularity of chemoprevention drugs is increasing slowly.[10]

Aspirin therapy for people at high risk of heart disease may be the ideal model for preventing disease with pharmaceuticals: It is effective, inexpensive, and has few side effects. However, cancer chemoprevention is a newer concept and far more complicated. The drugs tested so far tend to be more expensive and have more serious side effects than aspirin, and their acceptance by doctors and patients has been slow.

In 1998, the National Surgical Adjuvant Breast and Bowel Project (NSABP) completed its P-1 study of tamoxifen for the prevention of breast cancer in women at high risk. The drug was shown to reduce breast cancer incidence by about 50% compared with placebo[9] and was approved by the U.S. Food and Drug Administration for breast cancer prevention later that year. In 2000, celecoxib (Celebrex) was shown to inhibit polyp development in people with familial adenomatous polyposis, a genetic disease that, when left untreated, confers a nearly 100% risk of colon cancer.

In 2003, results from the Prostate Cancer Prevention Trial (PCPT) showed that finasteride reduced biopsy-detected prostate cancer incidence by about 25% compared with placebo.[11]

Side effects reduce wide acceptance

For tamoxifen, users must not only overcome fear of that drug's side effects —which include an increased risk of endometrial cancer, stroke, and pulmonary embolism— but also realize that its first duty was as a cancer drug, and there can be hesitancy in prescribing it for healthy women.

Six years after publication of the NSABP P-1 study, tamoxifen is slowly becoming more popular. In a study that appeared earlier this year, 42% of women who came to the Lynn Sage Breast Program in Chicago and were offered the drug after being deemed eligible decided to take it.[12] An earlier study, published in 2001 in the *Annals of Surgical Oncology*, found that only two of 43 patients who qualified for the drug elected to take it. Fear of the drug's side effects was the most common reason for declining the drug.

Similarly, Finasteride, has been slower to catch on, according to anecdotal evidence. For example, at a recent urology meeting where physicians in the audience at one lecture were asked if they had written a prescription for finasteride for the purpose of prostate cancer prevention, only a few raised their hands, reports Thompson, who led the PCPT.[11]

Thompson attributes the slow uptake of finasteride to its side effects. Besides an increase in sexual side effects, such as decreased sexual potency and loss of libido, the finasteride group in the trial also had a greater number of high-grade tumors. As part of a follow-up study, which is expected to be finished by the end of this year, Thompson and co-workers are examining radical prostatectomy samples from the men diagnosed with high-grade prostate cancer in both the finasteride and placebo groups to see if there are differences in the tumors themselves. High-grade tumors may not be more common in finasteride users, but simply easier to find because the drug shrinks the prostate.

Methodological problems in cancer chemoprevention trials

One important missing piece of the chemoprevention puzzle has been adequate surrogate endpoints for clinical studies. Unlike studies of the prevention of heart disease that can use the well-established surrogate endpoint of cholesterol level for some classes of drugs, in cancer

research, surrogate endpoints—such as cancer incidence or premalignant conditions—do not necessarily correspond to prevention of cancer deaths.

Costs

Price is another barrier to cancer chemoprevention. Unlike aspirin, which costs only pennies per day, these drugs are much more expensive. The average wholesale price for generic tamoxifen is $3.79 per 20 mg pill (the dose tested in the NSABP P-1 trial), according to First Databank, although several studies have concluded that the drug is cost-effective not only because of its health benefits—which include a reduction in hip fractures in addition to the preventive effect on breast cancer—but also because the drug needs to be taken for only 5 years.

For finasteride, however, it is still unknown how long the drug needs to be taken to get the most benefit from it, and it does not fare well in at least one cost-effectiveness analysis. In a poster presentation (SB Zeliadt, Ph.D). at the American Society of Clinical Oncology meeting in June, it was showed the calculated cost-effectiveness of finasteride. Based on a price of $2.22 per pill (as available on drugstore.com; the average wholesale price is higher), finasteride use costs $1,660,000 per life-year gained and $200,000 per quality-adjusted life-year gained. (Researchers generally consider a cost of $50,000 to $100,000 per year gained to be the cutoff for cost-effectiveness (*See Glossary*.

Even when the researchers assumed that there was no effect on high-grade tumors, the drug still cost $290,000 per life-year gained and $130,000 per quality-adjusted life-year gained. The calculations did not approach the cost-effectiveness threshold until the price of the drug was reduced by half.

The numbers were even more staggering when Zeliadt calculated the overall net costs for the entire U.S. population, which take into account both the cost of the drug and the reduction in prostate cancers and benign prostatic hyperplasias. Assuming that about 60% of adult men would be eligible for the drug and about half would take it, Zeliadt calculated that finasteride, at its present price, would cost a total of $2.2 billion per year for men in the United States aged 55 to 64 and an additional $1.2 billion per year for men aged 65 to 80. It's just so expensive to prescribe any preventive intervention, in part because the natural history of cancer is so long and the disease can take decades to develop.

The disconnect between when the drugs are taken by patients and when cancer appears also affects how physicians approach these drugs. Population-based analyses show that this works, but when a physician sits down with a patient there is no guarantee that he needs it.[10]

In addition, disease prevention may not be as ingrained in the medical community as treatment. It is unclear if it's a lack of interest or a lack of expertise in prevention, but it has to change health care delivery system.

Second-generation chemoprevention drugs

But tamoxifen and finasteride are just the first generation of chemoprevention drugs, and there are several other drugs that are now in phase III clinical trials. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is recruiting 32,000 men to test selenium and vitamin E alone and in combination for the reduction of

Glossary	
Cost-effectiveness.	A cost-effectiveness study is a tool for comparing the cost of treatments or interventions, such as chemoprevention. Such a study compares the incremental cost of treatment to the incremental benefit.
Cost per life-year gained.	To determine cost per life-year gained, research will take the cost of the treatment—usually determined in part from the average wholesale price for a drug or data from Medicare or a large health maintenance organization when determining the costs of surgery and other procedures—and compare that with the number of years of life saved by the treatment, while accounting for years lost to side effects from the treatment.
Quality-adjusted life-year	calculations take into account the cost a person associates with a variety of factors, such as taking a pill every day for the rest of a person's life and the side effects of an intervention.
Threshold for cost-effectiveness.	The threshold for cost-effectiveness is often set at either $50,000 or $100,000 per life-year or quality-adjusted life-year. The lower number comes from an analysis of the cost-effectiveness of renal dialysis done for Medicare in the 1970s.
Cost-effectiveness analysis.	Research will often use data from clinical trials in computer models to analyze cost-effectiveness. For each run of the model, sample data from people in both arms of the trial and average the costs incurred by each one are compared.
Comparison	Cost-effectiveness studies are often used to compare one treatment with another for health policy or insurance situations, but they can also help researchers determine where they can reduce costs associated with the intervention, They can see if reducing a drug's cost, toxicity, or dose can improve its cost-effectiveness.
Example.	An analysis of the cost-effectiveness of finasteride showed that the drug could be cost-effective only if the apparent increase in high-grade tumors was proven to be false and if the price of the drug was dramatically reduced.[10]

prostate cancer risk. And in men at high risk of prostate cancer, Merck is testing rofecoxib (Vioxx, a COX-2 inhibitor) and GlaxoSmithKline is testing dutasteride (Avodart, a second-generation version of finasteride).

The Study of Tamoxifen and Raloxifene (STAR), which completed its accrual of more than 19,000 patients this past June, seeks to compare the effectiveness of tamoxifen and raloxifene, an osteoporosis drug that may have fewer side effects than tamoxifen, for prevention of breast cancer in women at elevated risk. And the NSABP has just started recruiting patients who have undergone surgery for stage I colon cancer for their P-3 trial, which will test celecoxib (Celebrex) for the prevention of polyp development.

Chemoprevention is clearly something that is here to stay. The history of medicine certainly tells us that the greatest gains come not from treatment but from prevention."

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