

# Virtual Mentor

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## STATE OF THE ART AND SCIENCE

### Health Span Extension through Green Chemoprevention

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Prevention of disease is by nature not glamorous. Metrics of success are ephemeral and hard to quantify. An averted death or prolonged good health does not enlist advocates or boost the credibility of health care professionals in the way that curing a potentially fatal or disfiguring disease or eliminating its symptoms does. Only 5 years ago, this journal [commented](#) on health promotion in medicine in the context of physician responsibilities [1]. In the [same issue](#) attention was given to the fact that, in 2002, preventive medicine specialists represented only 0.8 percent of the physician workforce and 0.5 percent of medical school faculty were trained in public health, preventive medicine, or related subspecialties [2].

It is not surprising that disease prevention has garnered such a small fraction of American health care dollars. For example, only 6 percent of the National Cancer Institute's budget is devoted to prevention [3], and the fraction of national health care expenditure devoted to prevention is even smaller [4]. Classically, the primary prevention of disease has involved both active strategies (e.g., vaccination, exercise), and more passive avoidance strategies (e.g., protection from excessive sunlight, tobacco), as well as regulatory or governmental intervention (e.g., attempts to control food- and water-borne carcinogens and pathogens). We discuss herein the rationale for the additional approach of secondary prevention that seeks to impede, block, or reverse the early steps in disease progression, including the molecular steps involved in its initiation.

### The Global Cost of Disease

As the world has changed over the past century, the scourges of starvation and of many infectious diseases have been dramatically reduced in the industrialized nations, and progress is being made on these fronts in the developing world. However, as the lifespans of just a few generations ago are doubling, these conditions are rapidly being replaced by chronic, noncommunicable illnesses such as cardiovascular disease, cancer, chronic obstructive pulmonary disease (COPD) and other respiratory diseases, stroke, obesity, Alzheimer disease, and diabetes. Lifespan is increasing, but health span (the enjoyment of good health, or aging with minimal handicap and near full function for the duration of a vigorous and productive natural life) is not increasing commensurately. The chronic diseases of aging are overwhelming the health care system of the United States. In this country we spend almost \$2.7 trillion on health care annually [5], three-quarters of it on chronic disease treatment [6]. This expenditure represents about 18 percent of our gross domestic

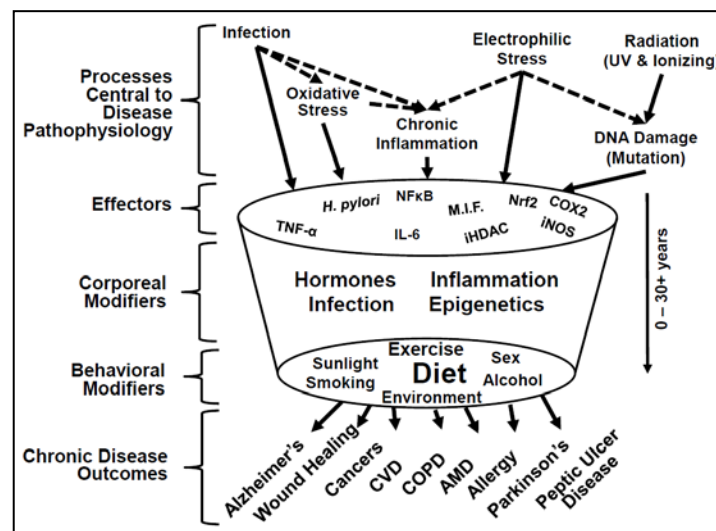
product and about 20 percent of the federal budget [5, 7], but only 4 percent of this figure goes towards public health and prevention programs and policies [4].

Worldwide, there are about 12.7 million new cases of cancer each year, and 7.6 million deaths, at an annual cost (calculated to include years lost from ill health, disability, or early death) of about \$900 billion [8]. This cost exceeds estimates for all other disease costs: heart disease, \$753 billion; cerebrovascular disease, \$298 billion; road accidents, \$204 billion; HIV/AIDS, \$193 billion; lower respiratory infections, \$126 billion; cirrhosis of the liver, \$93 billion; malaria, \$25 billion [8]. Collectively, the cost of these noncommunicable diseases is estimated to represent 48 percent of the global GDP [9]. These, and similar statistics for other chronic diseases (especially the cardiovascular and neurodegenerative diseases), are progressively defining medicine by its ability to deliver long-term health care, but not as a tool for extending health span.

Last year’s United Nations 65th World Health Assembly conference set a goal of reducing the probability of premature mortality from noncommunicable diseases by 25 percent by the year 2025, prompting the fitting reuse of the old aphorism “It’s not just a matter of life and death, it’s more important than that” [10]. It is the prevention of these chronic and degenerative diseases, which have been most closely associated with both affluence and aging, upon which we shall dwell in the next few paragraphs. Most of our examples focus on the prevention of cancers, a suite of diseases the World Health Organization (WHO) estimates will claim 70 percent of its victims in the developing world by 2030 [11].

### The Proximal Common Mechanisms of Chronic Disease

The cellular and physiologic mechanisms by which most of the chronic and degenerative diseases of aging do their damage can be traced in large part back to a very limited number of causal factors: infection with pathogens, inflammation, exposure to electrophilic chemicals, oxidative damage, radiation, and the interaction of one or more of these factors (see figure 1).



**Figure 1.** Protection and prevention with dietary agents.

For prevention to be practical, it is ultimately the intelligent and effective targeting of these factors that we must address. The first of these, infection by pathogens, is estimated by the WHO to be the causative factor in about 22 percent of cancers in low- and middle-income nations (6 percent in high-income nations), with hepatitis B and C viruses, human papilloma virus, *Helicobacter pylori*, and a number of waterborne parasites high on the list of responsible infectious agents [8]. Elimination of infection may directly reduce attributable cancer risk and inflammation, which may add to the protective effect. Though beyond the scope of this article, the mechanisms by which inflammation, electrophile and oxidative damage, and radiation initiate and propagate the disease process continue to be the subject of extensive investigation. (A few general reviews are suggested for the interested reader [12-14].)

### **Making Chemoprevention Green**

*Cancer chemoprevention* refers to the use of drugs or natural compounds (e.g., phytochemicals) to prevent cancer. Michael Sporn, who was instrumental in developing the field of chemoprevention, frames the development of cancer as a continuum, likening its latent, frequently invisible development to a smoldering barn full of hay that, before it bursts into flames, is *not* a safe place to be. In a recent discussion of chemoprevention he describes it as “the arrest or reversal of the progression of premalignant cells towards full malignancy, using physiological mechanisms that do not kill healthy cells” [15]. Stephen Hecht, another pioneer in the field, further suggests that we need to target susceptible individuals for interventions “including chemoprevention using nontoxic or dietary agents with demonstrated efficacy” and avoid “fleeting, flamboyant approaches” in favor of dealing “with lifestyle factors that link cause and prevention” [16]. The last 25 years have provided an abundance of quantifiable evidence to underpin a concept already supported by an ever-more-robust body of epidemiologic evidence—that specific diets can reduce the risks of and protect against cancer and other chronic diseases. The novelty of this approach is rooted in the concept that ingesting certain phytochemicals from specific plants can boost the intrinsic defensive mechanisms of cells that protect against oxidative damage, inflammation, and DNA-damaging chemicals—some of the fundamental causes of chronic disease and aging [17, 18].

We have recently suggested that the practice of “green chemoprevention” begets more frugal medicine and can serve rich and poor alike [19]. We point to the fact that the use of dietary means to deliver protective phytochemicals makes good sense and that chemoprevention by whole foods, or simple extracts of whole foods, presents unprecedented opportunities to solve unmet global problems. It is a frugal and realistic strategy that is economically sustainable in the U.S. and in the underserved and economically deprived populations that are already moving toward more chronic illnesses. And finally, we make the case that proof of the validity of the concept is already available: clinical studies demonstrate the effectiveness of phytochemicals derived from teas (polyphenols), berries (anthocyanins), broccoli sprouts (sulforaphane), garlic (sulfur compounds), and others [19]. Widespread regulatory ambiguities complicate the marketing of green chemoprevention products (e.g.,

should whole food or extracts be regarded as foods, medical foods, dietary supplements, or even drugs?). Large-scale production and standardization of such chemopreventive food products is complex, but clinical studies are currently under way on all of these.

There are a number of questions specific to the target populations that will need to be addressed in delivering these interventions. We have discussed them previously [19-21] but they bear repeating: Are there countervailing health or ecological risks associated with the intervention? What is to be the delivery vehicle (fresh food or processed food or drink products)? Can the food product or intervention be manufactured or grown locally and sustainably? Can farmers or consumers afford the costs? Is the intervention culturally appropriate? Are there any contraindications? Can the actual cost effectiveness be determined as the intervention is implemented? And finally, will people comply? Adoption of healthier diets is of course an uphill battle, and the effect size will likely be small if efforts to encourage more healthy eating are not based on sound science, but progress is being made. Approaches were recently reviewed in a special issue of the journal *Science* [22-24].

A very straightforward starting point for this paradigm shift is for physicians to prescribe preventive diets for their at-risk patients. The food system in the U.S. can readily facilitate the delivery of such diets, but our medical and graduate schools must do a far better job of teaching new physicians and biomedical scientists about human nutrition and the role of diet in disease prevention, and those newly trained professionals must in turn be proactive with their patients and counselees. They must make prevention as much the order of the day as cure. Food—chemopreventive diets—should be, and can be, the daily “multivitamin” of our immediate future.

### **How Much Does Prevention Cost?**

Chemopreventive strategies, in particular dietary approaches, make enormous sense. They are intuitively the most logical, sustainable, ethical, and responsible way to deal with the epidemic of chronic and degenerative disease. They may also be among the most cost-efficient, certainly compared to treatment of frank disease. However, it is very difficult to estimate the true costs and benefits of such approaches, since the impact of preventive measures must be measured over a long time. One must make a number of assumptions about the costs of a dietary prevention strategy, which will most likely involve education, social interventions, and the development of dietary alternatives. One must also make certain assumptions about the degree of protection one can expect to see. In other words—how much of an impact will the intervention have on the disease burden of the target population? And one must assume that even a small risk reduction may have a meaningful impact.

Current methodologies do not enable us to measure reliably the effects of a dietary intervention on future rates of any of the major cancers, but we can measure biomarkers of specific dietary components and of their effects, in particular those that pertain to hepatocellular carcinoma and aflatoxin exposure [20] and air pollutants [25, 26]. Nonetheless, from the perspective of increasing the meager levels

of government funding allocated for this approach, it is incumbent on physicians and scientists to assist policy makers in developing an economic understanding of the road to applied chemoprevention.

The authors of recent studies suggest that economic studies of the cost effectiveness of a core set of strongly recommended preventive services examined in 2006 by the National Commission on Prevention Priorities “consistently report that evidence-based clinical preventive services offer high economic value” [27, 28]. (At its simplest, cost effectiveness is a ratio of the cost of an intervention to a measure of health gain such as quality-adjusted life years [QALY], a metric commonly used by insurers and health care providers). Published calculations for preventive approaches range from \$69 per year of life saved for mandatory seat belt laws [29] to \$12,000 for cervical cancer screening [30] to \$100,000 for automobile airbags [31], when quality of life is not taken into account. It is reasonable to assume that the cost effectiveness of any adequately funded chemoprevention program ought to be comparable to many other widely funded prevention services and most likely under the threshold of \$50,000 per QALY that is often used in cost effectiveness calculations. An adequate level of funding for such a program might be expected to range upwards from the \$55 million spent annually by the CDC on their National Heart Disease and Stroke Prevention Program [32]. Although it is beyond the scope of this short paper to identify the costs of a dietary preventive strategy, we strongly endorse the need for robust and defensible cost calculations with which the efficacy of such strategies can be meaningfully evaluated.

### **Conclusions**

The evidence is mounting and is viewed by many as irrefutable. The challenge for the next decade(s) and for new health professionals is how to convey what has been learned directly to patients and to the general public. Social scientists, the entire spectrum of stakeholders in the food industry (e.g., from farmers to retailers), medical, nursing, and public health schools, government (e.g., regulatory and research branches), and primary and secondary school educators will all need to become invested and involved. The new drivers of this revolution will be not the drug companies but the food and agricultural interests because they will stand to profit greatly from introduction of new foods, new plant cultivars, and the reintroduction of “old foods” into new markets. They should thus be expected to provide a larger share of the funding for chemoprevention research as well as for effective public outreach. The road to longer health span will of course be rocky, but we cannot afford to ignore a strategy of diet-based prevention without putting our health care system in even more severe jeopardy than it already is.

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