

CANCERS AS SYSTEMIC FUNCTIONAL DISEASES, PART 1: DEFINING THE CANCER DOMAIN

Jeffrey Bland, PhD, FACN, FACB

Jeffrey Bland, PhD, FACN, FACB, is cofounder of the Institute for Functional Medicine, Gig Harbor, Washington. (*Altern Ther Health Med.* 2009;16(2):52-54.)

Cancer represents a very different disease than other chronic diseases in the minds of both health professionals and patients. Even though heart disease is the cause of death for many more people than cancer, it engenders less significant fear and social stigma than cancer does. This is undoubtedly because it is generally felt that we know much less about the origin and treatment of cancer than heart disease and that there is some sense of “personal responsibility” for cancer. Over the past decade, the understanding of the etiology of cancer has started to emerge as in part a systemic functional disorder associated with alteration in cellular biology associated with dedifferentiation, proliferation, angiogenesis, and metastasis.

In the broadest sense, it is now recognized that cancer is really “cancers.” Each person’s cancer has a slightly different molecular and cellular biology associated with it. This makes treatment of cancer via a “one size fits all” therapy virtually impossible, and in a sense, each cancer patient becomes his or her own clinical experiment without a control. To manage cancer more effectively, therefore, it is important to identify common functional characteristics that different cancers share. In this two-part series of articles, the concept of cancer as a systemic functional disorder will be developed, and a general framework of managing disorders associated with malignant cellular proliferation will be described based upon this model. In part 1 of this series, the establishment of a cellular milieu characteristic of cancers will be developed, and in part 2, a clinical approach based on the functional medicine concept of the diathesis of cancer derived from the understanding of its antecedents, triggers, mediators, signs, and symptoms will be described.

There are several systemic functional changes associated with the genesis of cancers, including

- increased DNA damage,
- decreased DNA repair,
- altered epigenetic marks,
- alteration in cell cycle check point integrity,
- alteration in intercellular signal transduction,
- reduced patency of immune surveillance, and
- increased hormonal and chemokine stimulation of mitotic activity.

From this list, which will be discussed in detail in part 2 of this series, it can be seen that cancers are a disturbance of molecular genetics and biology as well as systemic changes in immune defense mechanisms. Historically, it has been thought that cancer goes through several steps, including initiation, propagation, angiogenesis, invasion, and metastasis. The initiating step has been thought to be the result of a mutagenic or carcinogenic cellular insult that can come from either an external or internal initiating event.¹ The recognition that cancer can be initiated by external exposure to a chemical carcinogen goes back to the 19th-century discovery of the correlation between the soot exposure of chimney sweeps and scrotal cancer by Sir Percival Pott. During the early 1900s, it was recognized that exposure to ionizing radiation induced cancers. Later in the 20th century, Denis Parsons Burkitt noted that a form of lymphoma was associated with a specific viral infection, thereby broadening the list of external environmental cancer-inducing agents to include chemicals, radiation, and specific infectious organisms. More recently, Mary-Claire King discovered the BRCA1 and BRCA2 genetic polymorphisms associated with a high prevalence of breast cancer, heralding in the era of cancer genetics.²

From these observations, subsequent research developed the approach to cancer prevention that is now advocated, which is focused on reducing the exposure to known carcinogens in the diet and environment, such as charred meat and polynuclear aromatic hydrocarbons and other chemicals from smoking, respectively. The approach also advocates reducing exposure to radiation from x-rays and to ultraviolet light associated with excess sun exposure as well as limiting activities that would increase the risk for chronic viral, bacterial, and helminth infections.³ The recommendations also include positive behaviors such as regular exercise and appropriate body mass indices; increased intake of dietary fibers, fruits, and vegetables; adequate intake of B-vitamins and minerals and omega-3-containing oils; and inclusion of soy products in the diet.⁴

But beyond these recommendations, there is evidence that other systemic functional factors contribute to the initiation, propagation, tissue invasion, and metastasis of cancers. There is now increasing evidence that the cellular and animal models of carcinogen-induced cancer are not sufficient for understanding the origin of human cancers.⁵ In human cancer, there seems to be no simple relationship between carcinogen exposure and cancer incidence, suggesting that there is more complex interplay

between the exposure to the carcinogen and a several-step process associated with the development of a cancer. This has been called the “two-hit” mechanism and implies that multiple factors must work in combination to convert a normal cell into the systemic disease of cancer. This newer understanding of carcinogenesis raises the opportunity for intervention at several stages along the cascade of cellular and organismic events associated with the development of cancer, including the stage of initiation, the stage of altered intercellular signaling, the propagation of the altered cell, the angiogenic process that is necessary to support the nutrient needs of a growing malignant cellular mass, the invasive process whereby the malignant cells vie for “real estate” in a tissue, and the metastatic events that result in spread of the cancer to distant sites. This multiple-hit progression has resulted in the development of a much more diverse set of therapeutic tools to block cancer growth and progression throughout the various stages of its development.

It is now recognized that every person probably develops a protocancer several times during his or her life but that in most instances, the altered cells are arrested at one of the several check points along the development of the cancer by inherent physiological processes that are cytotoxic to the transformed cells.⁶ This concept opens the door to recognition that certain functional physiological states associated with disturbed metabolism are more conducive to cancer development and progression. The clinical application of this model focuses on the assessment and management of physiological functional states that are associated with increased oncogenic potential.⁷

Common contributors to increased oncogenic potential include but are not limited to

- disturbances in insulin signaling,
- states of chronic inflammation,
- increases in messages triggering cellular cycling,
- increased genomic instability,
- altered mitochondrial bioenergetics associated with oxidant stress,
- altered nucleosome epigenetic methylation patterns, and
- cellular hypoxia.

There is still substantial belief that cancer is predominantly inherited, and therefore, there is little an individual can do to reduce his or her risk of cancer, suggesting that this list of agents that influence oncogenic potential is irrelevant. In 2000, *The New England Journal of Medicine* published a landmark article from a group at the Karolinska Institute in Sweden evaluating the heritability of cancer.⁸ The study of 44 788 pairs of identical twins concluded that “inherited genetic factors make a minor contribution to susceptibility to most types of neoplasms. This finding indicates that the environment has the principal role in causing sporadic cancer.”⁸ Genetics are not a modifiable factor, but the environmental causes of cancer certainly are modifiable if they are recognized and managed. The common contributors to increased oncogenic potential are potentially modifiable factors in cancer etiology. This observation has a direct relationship to

the importance of recognizing in the individual early-stage biomarkers that are indicative of a systemic functional state that is associated with an alteration in cellular function favoring oncogenesis and tumor progression.

There is also the belief that specific therapeutic agents will be discovered to personalize the treatment of cancer based upon the cancer genetics of the tumor. Certainly some progress has been made in this regard with the development of new chemotherapeutic agents that target specific mutated kinases associated with specific tumor types. The problem is that as they advance, cancers change their genetics and undergo monoclonal to polyclonal conversion, which results in “single-hit” drug resistance.⁹ There is now evidence emerging that targeted cancer therapy in advanced disease has not worked for this reason, and the future of chemotherapy is to develop agents whose mechanisms of action have a broader range of activities cutting across many interrelated regulatory steps in cellular signaling.¹⁰ The medical community now more fully recognizes that lifestyle and diet modifications can have this “multi-hit” impact on the processes associated with oncogenesis and thereby slow progression and improve patient outcome. A 2008 controlled clinical trial demonstrated the influence of improving functional physiology in prostate cancer patients by altering the host environment through diet and lifestyle—not by targeting a specific regulatory process, but rather by supporting multiple cellular processes related to the reduction of oncogenic potential.¹¹

It is becoming more clear that many steps along the process are modifiable through changes in the host environment in negotiating the complex path of cancer from the genotype of susceptibility to the phenotype of cancer.¹² In 1983, Bruce Ames pointed out that a complex, minimally processed diet rich in plant-derived nutrients promoted anticarcinogenic outcome by modulation of multiple processes associated with cancer development and progression.¹³ He indicated that our natural diets contain potentially cancer-causing substances, but in their natural state, they also have high levels of anticancer properties. It is the balance between carcinogens and anticarcinogens that determines the potential influence of the environment on susceptibility genes. It is now understood that diet and specific nutrients play important roles in the risk of specific types of cancer.¹⁴ These factors are modifiable and modulate the systemic functional status of the individual, thereby influencing oncogenic potential at all the diverse stages throughout the cancer development process. The Mishio Kushi Macrobiotic Diet is one dietary approach that has been studied for the reduction in oncogenic potential.¹⁵ This approach has developed compelling evidence for the nutritional factors associated with the macrobiotic diet as important in cancer survival and therefore may be of value in the improvement in systemic functional states associated with the development of cancer and its treatment.

It appears that within the various medical subspecialties, the primary care provider (PCP) might be best suited to recommend therapeutic diet and lifestyle programs for patients with altered systemic functional status associated with oncogenic

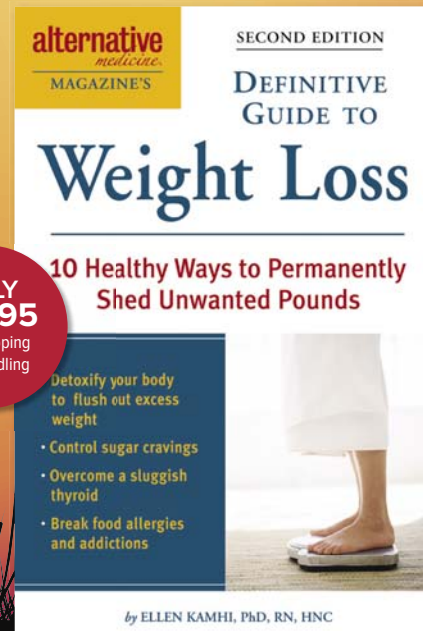
potential. It is most often the PCP that best understands the lifestyles of patients and provides consultation on factors associated with both disease prevention and management of chronic conditions.¹⁶ Studies on home-based diet and exercise programs in cancer survivors that are having their disease managed as a chronic disease have found that PCP-administered functional lifestyle programs resulted in a reduced rate of decline of health.¹⁷ It has also been reported that the impact of PCP-administered prognostic assessment and intervention programs focused on improving systemic functional physiology had a marked positive effect on survival in cancer patients.¹⁸

This article promotes the concept of cancers as systemic functional diseases that can be recognized early through the application of a functional medicine assessment approach and adjunctively managed through a PCP-administered diet, lifestyle, and environment intervention program. The second article in this series will offer a discussion of the prognostic markers to identify systemic functional imbalances associated with oncogenic potential and interventions designed to reduce it.

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