

# INTEGRATIVE ONCOLOGY: THE LAST TEN YEARS—A PERSONAL RETROSPECTIVE

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In the last decade, there has been dramatic changes in all areas of integrative patient care. None has been more dramatic than those in the field of cancer care, which has gone from alternative and complementary treatments delivered outside the conventional setting to the integration of many of these approaches into the care of the cancer patient. In many cases, these changes have been driven by patient demand and supported by private funding and out-of-pocket payments by patients themselves. Virtually all major medical centers have departments devoted to integrative patient care—whether true stand-alone centers or departments with a research interest in this area. This is particularly true of the major cancer centers, many of which—including Memorial Sloan Kettering Cancer

Center, New York; M.D. Anderson Cancer Center, Houston, Tex; Johns Hopkins University, Baltimore, Md; Duke University, Durham, NC; and the Dana Farber Cancer Institute, Boston, Mass—have developed integrative cancer programs. In addition, programs such as the Cancer Treatment Centers of America have inpatient and outpatient programs with teams of practitioners, including medical oncologists, surgeons, and radiation therapists, as well as credentialed naturopathic doctors, nutritionists, mind-body specialists and other integrative practitioners. Despite the increased interest in developing integrative approaches to cancer, many medical oncologists remain skeptical about the value of these modalities. (*Altern Ther Health Med.* 2007;13(1):56-64.)

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The growing interest in integrative therapies has been paralleled by the increasing number of articles appearing in peer-reviewed journals in the last 10 years. In 1994, the *Journal of Clinical Oncology* published only 1 article on complementary and alternative medicine (CAM)-related therapies. In contrast, in 2004, there were 27 articles on various CAM topics, including acupuncture, trials on various support group approaches to cancer care, and review articles on topics such as herbal therapy and cancer, antioxidant treatment in cancer care, and the use of coenzyme Q10 with cancer therapy. The journal *Alternative Therapies in Health and Disease* has continued to publish important studies in cancer care. In the last 5 years, several new journals with an emphasis on integrative cancer care have appeared, including *Integrative Cancer Therapies* and the *Journal of the Society for Integrative Oncology* (formerly the *Journal of Cancer Integrative Medicine*). Both of these peer-reviewed journals serve as valuable conduits for the growing research in this field. A new organization, the Society of Integrative Oncology, was created recently. It held an inaugural meeting in New York City in 2004 and meets annually each November. These meetings are evidence of the

growing interest in researching the role of natural compounds, including botanical and Chinese herbal products in the treatment of a variety of cancers as well as the increasing research base supporting the use of many adjunctive modalities, including acupuncture, massage, and meditation. The Center for Mind-Body Medicine at Georgetown University, under the directorship of James Gordon, MD, has been on the forefront of efforts to educate both medical professionals and patients about the value of integrative cancer care. They run the annual CancerGuides™ Program and a periodic Integrative Cancer Care Symposium, which involve many leaders in this field, including David Rosenthal, MD; Keith Block, MD; Ralph Moss, PhD; Mark Hyman, MD; Donald Yance, ND; and Henry Dreher, MS.

As Michael Lerner, PhD, contends in his important book, *Choices in Healing: Integrating the Best of Conventional and Complementary Approaches*, nutrition, physical modalities, and mind-body approaches comprise the heart of integrative approaches to cancer.<sup>1</sup> Many integrative and CAM practitioners in the field of cancer care have come to this field from a variety of backgrounds, some through personal experience and training in traditional Chinese medicine and acupuncture, some because of training in naturopathic medicine or nutrition, and others after attending a conventional medical school. My own background in many ways mirrors the evolution of integrative therapy over the past decade. After obtaining an undergraduate degree in Evolutionary Biology from Cornell University, I spent 4 years in graduate school at the Columbia University Institute of Human

Nutrition, under the Directorship of Myron Winick, MD, where I pursued graduate work in nutritional biochemistry. I developed a strong grounding in nutrition, biochemistry, and particularly endocrinology. In addition, I was fortunate to work with early leaders in the field of obesity and diabetes at St Luke's-Roosevelt Hospitals, including Xavier Pi-Sunyer, MD, and Ted Van Itallie, MD. In my subsequent years at Cornell medical school, I was surprised to have only 1 hour of instruction in nutrition, and to receive virtually no training in nutrition throughout my internship and internal-medicine residency. My subsequent oncology training at The New York Hospital-Cornell Medical Center and Memorial Sloan Kettering Cancer Center was largely devoted to training in conventional chemotherapeutic approaches to cancer, which included almost no mention of nutritional influences on cancer. Little time was devoted to the psychological aspects of cancer. During my residency, I had the opportunity to spend 6 months working in a Cambodian refugee camp, where I experienced the value of traditional healing approaches as well as conventional care in the treatment of numerous maladies of the refugee population.

In my early clinical practice years, I was encouraged by my patients to pursue the role of nutrition in cancer. My earliest interest was an attempt to reconcile the growing body of information from large ecological and epidemiologic studies on nutrition in cancer prevention with a rational nutritional approach to cancer care, moving beyond the issue of cancer-related weight loss and cachexia, an extremely important but more limited problem within a general oncology practice. In a patient population that was well educated and anxious to make major lifestyle changes, one challenge was developing safe and appropriate nutritional interventions in early-stage breast, prostate, and other solid tumors. I later explored more broadly the role of complementary therapies in cancer, discovering the vastly different worlds inhabited by cancer patients, their family members, and medical oncology professionals.

In 1998, as a result of my growing interest and experience in complementary medicine, I founded the Program in Integrative Medicine at Greenwich Hospital-Yale New Haven Health System, where I continue to serve as medical advisor. The culmination of my experiences and commitment to practicing medicine in an integrative environment ultimately led to the establishment of The Boyd Center for Integrative Health in Greenwich, Conn, where we tend to the mind, spirit, and physical needs of patients and their caregivers.

#### EPIDEMIOLOGY OF CANCER AND NUTRITION

As a result of early epidemiologic studies connecting high fat intake to breast cancer,<sup>2</sup> high fruit and vegetable intake to a variety of cancers,<sup>3,5</sup> high fiber intake to colon cancer,<sup>6</sup> and other similar studies,<sup>7</sup> reductionist approaches seeking the crucial nutrient mediating these effects became common in the cancer-prevention research field, leading to the concept of "chemoprevention." Many integrative nutrition practitioners have embraced similar approaches, using a variety of nutraceutical

and supplement interventions. Beta-carotene has extensive epidemiology supporting its role in reducing lung cancer risk in smokers, and the well-defined biology of vitamin A and carotenoids in epithelial health suggests its potential role in lung cancer prevention. Unfortunately, 2 randomized trials, the Carotene and Retinol Efficacy Trial (CARET) in US smokers with a history of asbestos exposure and the  $\alpha$ -tocopherol and  $\beta$ -carotene trial (ATBC) in Finnish male smokers demonstrated an increase in lung cancer risk.<sup>8,9</sup> Similarly, high-fiber diets in almost all large ecological studies and several very small randomized trials strongly favored the value of fiber in colon cancer prevention, with multiple, plausible biological explanations for this effect; however, several large, randomized trials failed to confirm an association between high fiber intake and reduction in colonic polyps,<sup>10,11</sup> though they have been criticized because of short follow-up and an uncertain effect on the risk of polyp transformation into cancer.

More recently, vitamin E (as  $\alpha$ -tocopherol), which had been initially linked to a reduction in prostate cancer risk in the ATBC trial,<sup>9</sup> has been shown not to lower cardiovascular risk,<sup>12</sup> and more recently, has been found to potentially increase the risk of earlier second cancers as well as recurrences in patients with head and neck cancer. In this randomized trial,<sup>13</sup> patients with newly diagnosed head and neck cancer, treated with primary radiation therapy as a curative modality, were given at the initiation of radiation either a placebo or 400 units of vitamin E. The vitamin E was continued beyond radiation for an additional 3 years. Patients receiving vitamin E had an increase in incidence of both recurrent and new primary tumors during the supplementation period. In the post-intervention years of the study, however, patients receiving placebo had a higher risk of cancer, so that by the end of the study, the total incidence of recurrent and primary tumors was essentially similar in both groups. The study suggested that the intake of vitamin E did not directly cause malignant change but reduced the benefit of radiation, resulting in earlier recurrence risk in this population.

A recent review of vitamin E in primary prevention of both cardiovascular disease and cancer—The Women's Health Study, a randomized trial of vitamin E vs placebo—failed to show a significant benefit in cancer reduction with 600 units of vitamin E daily.<sup>14</sup> Somewhat more surprisingly, recent prospective cohort studies have called into question the relationship between fruit and vegetable intake and reduced breast and colon cancer risk, despite the widespread assumption of benefit.<sup>15,16</sup>

There is a need to reconcile the seeming contradictions between the early epidemiologic studies and the common-sense understanding of the role of phytonutrients in reducing both cancer incidence and prognosis, with these more recent trials' failure to show benefit. As many in the field of integrative oncology appreciate, these trials often fail to understand the critical role of nutrient synergy in influencing the malignancy process. Administration of a single  $\alpha$ -tocopherol supplement may miss the critical interaction of multiple antioxidants, including gamma and other tocopherol isomers, ascorbate, carotenoids, selenium, and myriad

other important antioxidant phytonutrients and the potential for unbalancing this antioxidant network with a single high-dose nutrient. Administration of a single supplement may also miss the critical role of the timing of intervention in influencing cancer development, with the growing recognition that malignancy is a decades-long process. Nutrient interventions may occur too late to influence the early initiation phase of cancer. Of interest is the study of cruciferous vegetable intake in prostate cancer risk from the Health Professionals Follow-up Study.<sup>17</sup> Surprisingly, intake of these vegetables had a limited influence on the development of prostate cancer when measured during the period of study. It was only when the level of vegetable intake was assessed years before individuals were enrolled in the trial that it was found to have an inverse relationship with cancer. This suggests that these interventions are of greatest importance in the earliest phases of cancer, when the particular influence of a rich phytonutrient diet may limit genotoxicity, both from its antioxidant properties and its enhanced activation of detoxifying enzyme systems. While these activities are important throughout the evolution of cancer, they play a particularly key role in the earliest stages of cancer, often in late adolescence or very early adulthood and decades before the appearance of clinical cancer. In contrast, the importance of promotional factors, often hormonal or endocrinologic, may supersede the role of single or limited phytonutrients in influencing the later stages of cancer.

My own focus in integrative cancer care and nutrition has been on the crucial role of these hormonal factors, particularly insulin and IGF-1.<sup>18</sup> I believe that the insulin-resistant state that influences these factors is a plausible explanation for the role of nutrition status, weight, and diet on cancer etiology as well as long-term cancer outcomes. The evidence that this system of interactions plays a crucial role in mediating the role of diet, exercise, and even mind-body approaches on the clinical outcome of a wide variety of cancers continues to grow. This also may explain the discrepancies between the epidemiologic data and the intervention and prospective trials that I noted earlier. Frank Meyskens, MD, a medical oncologist from the University of California, Irvine, in explaining the discrepancy between the epidemiologic data and the failure of early chemoprevention trials to show benefit, has described what he calls the “biological action package”—that is, it is not any single nutrient, but the totality of nutritional and lifestyle influences that may play a crucial role in reducing cancer risk.<sup>19</sup> This reflects the failure of the reductionist approach to account for the true synergistic influences of all of these factors on cancer outcomes, a crucial tenet of integrative cancer approaches. Though there have been exceptions that appear to be clinically important, such as lycopene in reducing prostate cancer incidence<sup>20</sup> and selenium in reducing the incidence of a variety of cancers,<sup>21</sup> single nutrient interventions appear not to be as promising as once had been hoped. This also reaffirms the early study of Doll and Peto, which looked at the role of various influences on cancer incidence in America and recognized that between 30% and 70% of cancers are caused by “lifestyle changes,” including diet and physical activity.<sup>22</sup>

Another key to this discrepancy is being provided by research in nutrigenomics. Several recent case-controlled studies have demonstrated the importance of genetic polymorphisms in endogenous antioxidant systems in influencing the role of dietary antioxidants in cancer prevention. Manganese superoxide dismutase (MnSOD), a critical enzyme in reactive oxygen species (ROS) scavenging, along with catalase and glutathione peroxidase, plays a critical role in tumorigenesis.<sup>23</sup> Many tumor cells have deletions in MnSOD, which has been implicated as a tumor suppressor, highlighting the importance of adequate antioxidant defenses. In several important studies, the presence of the AA allele of MnSOD, reducing its activity, has been shown to interact with plasma antioxidant levels to affect risk of both prostate and breast cancer. Men in the Physicians’ Health Study with the AA variant who had high antioxidant levels as measured by plasma selenium, lycopene, and  $\alpha$ -tocopherol levels, had up to a 10-fold lower risk of both overall prostate cancer and histologically aggressive prostate cancers than AA carriers with low antioxidant levels.<sup>24</sup> Similarly, in the Western New York Breast Cancer Study, women with the AA allele had a 4-fold increase in breast cancer risk that was present with lower fruit and vegetable intake and negligible in those with a rich intake of antioxidant foods.<sup>25</sup> Thus, there is a critical intersection between genotype and nutrient status that may influence the benefit of phytonutrients in small subpopulations that may be obscured when evaluated within the general population.

### Insulin and Cancer

As noted earlier, over the past 8 years, I have focused on the role of insulin and the insulin-resistant state in cancer development and progression. As a consequence of the growing obesity epidemic, more than 30% of adults in Western countries appear to have evidence of insulin resistance. The consequence of insulin resistance is not only persistent and significant hyperinsulinemia and its metabolic consequences, but also the associated pro-inflammatory state, accompanied by high levels of C-reactive protein, interleukin-6, and other cytokines associated with this state. There is growing evidence of the influence of insulin resistance on systemic inflammation and the recognition that this inflammatory state is strongly correlated with poor outcomes in cancer.<sup>26</sup>

The American Cancer Society recently published a long-term prospective study of adults with cancer following almost 1 million people over a period of 7 to 8 years.<sup>27</sup> This study revealed a striking and broad effect of increasing weight on poor cancer outcomes, suggesting that obesity reduces survival from virtually every cancer, except lung and bladder cancer. The most parsimonious explanation for this broad effect of obesity is likely to be factors such as insulin resistance and the up-regulation of the insulin-IGF system, along with concurrent increases in other hormonal tumor promoters, such as estrogen. Insulin itself is a relatively weak direct promoter of tumor cell proliferation.

In the insulin-resistant state, however, there is an accompanying increase in the level of free IGF-1, a potent stimulus to

tumor cell proliferation. In addition, hyperinsulinemia is accompanied by an increased level of the insulin-IGF-1 hybrid receptor. This receptor is frequently expressed at high levels in tumor cells, and is a particularly sensitive proliferative signaling pathway in the presence of local IGF-1 levels. Thus, chronic hyperinsulinemia can lead to a high level of signal activation through the IGF-1 system, both enhancing cell proliferation and reducing apoptosis. Importantly, IGF signaling in breast cancer may impair the response to a variety of chemotherapy agents such as daunorubicin and paclitaxel as well as reduce responsiveness both to hormone therapy in estrogen receptor-positive cancers and to trastuzumab inhibition via the HER-2-neu pathway.<sup>28-30</sup> Thus, increased body weight, particularly with abdominal-visceral obesity and accompanying insulin resistance, through increased insulin-IGF-1 signaling, may impair response to treatment and adversely affect tumor outcomes.

The importance of insulin as a prognostic factor in breast cancer has been confirmed by Pamela Goodwin, MD, at the University of Toronto.<sup>31</sup> Women with breast cancer who were in the highest fifth of fasting insulin levels at diagnosis had a significant increase in risk of recurrence of breast cancer, in contrast to those with the lowest level of insulin. The study controlled for typical prognostic factors such as tumor size and lymph node status, suggesting the important role of hyperinsulinemia on recurrence and survival of breast cancer.

The early results of the Diabetes Prevention Program have shown that simple lifestyle changes such as diet and exercise, even with only modest weight reduction, reduce the insulin resistant state and the progression of these at-risk patients to frank diabetes and other adverse outcomes.<sup>32</sup> That lifestyle changes may have a similar influence on the outcome of cancer, and not just the quality of life, has been confirmed by 2 very important "lifestyle" studies in women with breast cancer. The Women's Intervention Nutrition Study (WINS) trial evaluated the role of dietary fat reduction in women with early-stage breast cancer.<sup>33</sup> These women were randomized between a low-fat diet and a control diet in addition to conventional adjuvant systemic therapy. Strikingly, the authors found a 56% reduction in breast cancer recurrence in women whose breast cancer was estrogen and progesterone receptor-negative. Surprisingly, while those who were estrogen receptor-positive had a benefit, it was not as significant as that in the hormone receptor-negative patients. This is in contrast to the assumption that hormone sensitivity would increase the benefit of nutritional input via a reduction in circulating estrogen. This may represent the effect of the moderate weight loss in this group, with its significant reduction in insulin levels and a consequent reduction in breast cancer recurrence. This is the first adjuvant cancer trial to show that a broad nutritional approach can influence cancer outcomes, not simply prevent the development of cancer. Similarly, in a study that evaluated the influence of physical activity on outcomes in early breast cancer, Holmes et al reported that women who exercised 4 to 5 hours weekly had a marked reduction in breast cancer recurrence.<sup>34</sup>

Recently, 2 prospective observational studies revealed a

reduction of more than 50% in recurrence and mortality in early stage colorectal cancer with increased physical activity.<sup>35,36</sup> It is worth noting that in these studies, lifestyle change had a significant therapeutic effect on cancer recurrence—equivalent to chemotherapy. In the case of colon cancer, the benefit of exercise was much greater than that of the accompanying adjuvant chemotherapy. Many medical oncologists have dismissed the idea that nutrition, exercise, and other lifestyle changes can have any impact on cancer outcomes. This attitude may reflect a failure to appreciate the potential mechanisms of these effects, the lack of physician training in nutrition, and the focus on traditional pharmaceutical approaches to cancer.

These studies have altered our understanding of the value of both lifestyle interventions and an integrative approach to cancer. Nutrition and exercise can influence not only the quality of life of cancer patients, but also have the potential to significantly increase cancer survival. These studies also show the need for research on nutrients such as n-3 fatty acids, gamma-linolenic acid (GLA) and conjugated linoleic acid, and phytonutrients that may target insulin resistance and the accompanying inflammatory state and ultimately influence cancer outcomes.

#### Nutrients and Botanicals in Cancer Care

Recently, there has been a convergence between conventional cancer research focused increasingly on bioactive botanical and phytonutrient compounds and the growing exploitation of the resulting data in the integrative care of cancer patients. Many naturopathic doctors, as well as some allopathic physicians with an interest in cancer care, use a variety of supplements as an adjunct to or, on occasion, as an alternative to conventional care, often drawing on research from *in vitro* and animal studies as well as selected human trials in cancer research publications. There is an urgent need to assess the safety and efficacy of such multi-nutrient interventions. Typical placebo-controlled randomization approaches often are inadequate to assess the complexity of these interventions. Hopefully, a cooperative effort using an outcomes-based assessment can help answer these questions. This issue highlights the value of a truly integrated team of physicians, trained naturopathic doctors, medical nutritionists, and other integrative practitioners in designing and carrying out this critical research.

One target of great interest is the transcription regulator nuclear factor kappa B (NFκB), a group of protein dimers that bind a common sequence motif known as the κB site.<sup>37</sup> This complex appears to act as a central regulator of inflammation and is activated by oxidative stress, cytokines such as tumor necrosis factor-α (TNF-α), and infection. It is critical as a mediator of inflammation-related cancers and in turn is induced by many cancer therapies, leading to resistance to chemotherapy-induced apoptosis (programmed cell death), increased angiogenesis, enhanced tumor cell proliferation, and metastases.<sup>38</sup> Interestingly, it also appears to be an important intermediate in the inflammation associated with insulin resistance<sup>39</sup> as well as a mediator of cyclooxygenase-2 (COX-2)-related effects. Increasing

research has documented the potential of multiple drug and dietary interventions to inhibit NFκB activity and other promising molecular targets with the possibility of enhanced chemotherapy efficacy.<sup>40,41</sup> These have included thalidomide, nonsteroidal anti-inflammatory drugs (NSAIDs) and salicylates, flavopiridol, genistein, resveratrol, curcumin, epigallocatechin gallate (EGCG), lycopene, parthenolides, n-3 fatty acids, and indole-3-carbinol. There is also growing interest in the ability of macrolide antibiotics, such as rapamycin, to inhibit NFκB.

Over the past 8 years, my practice has been following advanced (stage IIIB and IV) non-small cell (NSC) lung cancer populations using an integrative approach including conventional induction chemotherapy followed by varying maintenance regimens based on tumor response (using chemo-sensitivity testing when feasible), and nutritional interventions including increased n-3 and gamma-linolenic fatty acid intake, selenium, and celecoxib. An important adjunct to this regimen has been clarithromycin. This regimen, as with all medical therapies, is administered only after we have discussed it with patients and obtained their informed consent. It is given once daily beginning at diagnosis and continuing throughout the patient's course unless contraindicated or not tolerated. Its addition was based on an extensive Japanese experience with numerous *in vitro* and animal studies documenting potential mechanisms and several human studies showing prolonged survival in randomized, placebo-controlled settings.<sup>42-47</sup> To date, no US studies of clarithromycin and lung cancer have been initiated. In an unpublished retrospective review of our experience, patients have been found to have a significant increase in median survival compared to those in trials in advanced stage NSC lung cancer using the same or similar chemotherapy regimens (30 vs 10-14 months). The range of patient survival (14 to 76 months) also exceeds the experience with many conventional therapies in NSC lung cancer. Of interest is the recent evidence from infectious disease research that clarithromycin is a potent inhibitor of NFκB and significantly limits lung inflammation in the setting of various pulmonary infections, suggesting a potential explanation for this response.<sup>48,49</sup> This series is subject to multiple critiques, including an absence of a control arm, the bias typical in a small trial size, and the addition of other integrative interventions, including several nutrients and the effect of careful attention by numerous integrative practitioners. Though this treatment cannot yet be recommended to lung cancer patients, it is an example of how an integrative, multi-intervention approach may function as a hypothesis generator, potentially leading to larger randomized trials that can assess these interventions in a multi-institutional setting.

### **Stress and Cancer**

Another important focus in integrative oncology is the role of stress in cancer incidence and outcome and the role of mind-body approaches such as meditation, support group interventions, and other integrative modalities in limiting stress. The role of stress in cancer causation remains speculative. A recent study

in women demonstrated a reduction in breast cancer risk among women with higher self-described stress.<sup>50</sup> The authors speculated that stress-induced amenorrhea might have resulted in reduced ovarian estrogen production and therefore reduced breast cancer risk.

There has been significant interest in improved outcomes and quality of life in cancer patients through a variety of stress-reduction interventions. In 1989, the seminal study by David Spiegel, MD, showed that supportive-expressive group therapy in women with metastatic breast cancer had a significant effect not only on quality of life but on survival when compared with historical controls.<sup>51</sup> These results were a powerful motivation in the field of integrative oncology and were valuable in highlighting the need for psychosocial support for the cancer patient. Numerous smaller studies have assessed the value of stress reduction on cancer outcomes and have emphasized the influence of stress on the immune response as an explanation for these effects.<sup>52,53</sup> However, a large randomized controlled trial by Goodwin et al<sup>54</sup> that replicated Spiegel's small study failed to confirm the influence of group support on cancer survival. This study has been the subject of much criticism. In the current era of cancer care, it is difficult to limit a control group in terms of support, given the recognition of its role in improved quality of life and the widespread availability of supportive networks in helping cancer patients. More importantly, it fails to recognize the biological nature of stress and its influence on the cancer process. Many patients, though experiencing "stress," may not have the biologically significant stress that can influence cancer processes. Self-described stress is ubiquitous in the cancer population and even in the general population of healthy people. Careful psychological screening using measures such as the Mental Adjustment to Cancer score (MAC) and the Hospital Anxiety and Depression Scale (HADS) may detect the presence of manifestations of significant stress, such as high levels of depression and anxiety.<sup>55,56</sup> These measures also have limitations, and true physiologic measures of stress are crucial in determining important biological manifestations within an individual. These include influences on autonomic sympathetic drive as well as long-term alterations in the hypothalamic-pituitary-adrenal (HPA) axis. Sephton et al noted that women with metastatic breast cancer who have abnormalities in the diurnal rhythm of cortisol as measured by serial salivary cortisol levels—a possible measure of chronic stress—have a significant reduction in survival in contrast to women with a normal diurnal cortisol pattern.<sup>57</sup> Similar studies have confirmed the crucial importance of a normal circadian cortisol rhythm and the adverse effect of alterations in the HPA axis in colon cancer.<sup>58</sup>

My focus has been in exploring the biologic basis for alterations in the HPA axis and how they can influence cancer. The traditional view among professionals and the public is that stress-related neuroendocrine changes influence the immune response, leading to cancer progression. This has remained the dominant research paradigm in explaining the influence of stress reduction on cancer outcomes, and immune measures are rou-

tinely assessed in many mind-body cancer interventions. When critically evaluated, however, the true influence of immune surveillance on cancer outcomes may be more limited,<sup>59,60</sup> particularly when viewed from an evolutionary biology perspective.

Recent discoveries about the role of the regulatory component of the immune system suggest additional limits of natural anti-tumor immune responses.<sup>61</sup> Natural selection favors retention of adaptations that enhance the reproductive success of individuals in a population. This critical period includes early childhood, the reproductive years, and the period of childrearing, ending in the fifth decade in pre-modern populations. Most solid tumors, such as breast, colon, and prostate, disproportionately affect older members of the population, with peak mortality in the sixth and seventh decades. The incidence of these cancers has increased significantly in the last 100 years. In contrast, for the majority of human history, infectious disease and trauma have represented the greatest challenges to survival. The immune response has thus evolved to control infectious disease and simultaneously limit the risk of autoimmunity.

The benefit of an effective anti-tumor response may be outweighed by the accompanying increase in risk of autoimmunity.<sup>59</sup> As is well known, patients who are immunosuppressed, either innately or through acquired immunodeficiency states (eg, human immunodeficiency virus [HIV], post-transplant) are at a significant risk for increased malignancy. The majority of these malignancies are viral in origin, however, including Epstein-Barr virus (EBV) in high-grade lymphoma; human papilloma virus (HPV)-related epithelial cancers, such as anogenital and cervical; and herpes virus 8 in Kaposi's sarcoma.<sup>62</sup> In fact, despite the profound immunodeficiency associated with HIV, a recent study in the post-Highly Active Anti-Retroviral Therapy (HAART) era has demonstrated that the only malignancies clearly linked to HIV-related immune suppression appear to be herpes-8 related Kaposi's sarcoma and the EBV-related lymphoid malignancies.<sup>60</sup> Furthermore, only Kaposi's sarcoma and lymphoma have declined significantly in incidence with an improvement in immune function. Similarly, patients who are post-transplant are particularly at risk for these diseases.<sup>63</sup> Interestingly, research has indicated that the immunosuppressed state may be associated with a reduction rather than an increase in the incidence of solid tumors such as prostate, breast, and colon cancer, suggesting the paradoxical concept that the immune response may enhance the risk of cancer.<sup>64</sup>

The recent discovery of the regulatory immune response capable of suppressing immunity may provide an explanation for this paradox. This regulatory system, including CD4 lymphocytes expressing IL-2 r (CD-25), so-called T-reg cells, has been shown to be critical in preventing autoimmune disease.<sup>65</sup> In the presence of excessive tissue inflammation, the T-reg cell population (CD-4, CD-25) is up-regulated. These cells will suppress both cytotoxic CD-8 T-cells and natural killer cells, reducing the risk of autoimmunity. Removal of this subfraction of T-cells from laboratory animals leads to a widespread disseminated and fatal autoimmune illness, including thyroiditis, diabetes, dermatitis, and inflamma-

tory bowel disease.<sup>66</sup> Numerous studies have documented the presence of increased levels of T-cells in peripheral blood, draining lymph nodes and tumor in a wide variety of cancers accompanied by a suppression of any antitumor immune response.<sup>67,73</sup>

There is growing evidence that both the innate and adaptive immune systems may enhance rather than decrease cancer progression through their influence on pro-inflammatory, pro-angiogenic, and anti-apoptotic mechanisms. There is evidence that both neutrophils and macrophages may enhance tumor progression positively through the release of a variety of cytokines, such as macrophage inhibitory factor-1.<sup>74</sup> This may partially explain the important role of anti-inflammatory compounds (eg, COX-2 inhibitors, n-3 fatty acids) in reducing malignant progression. Similarly, T-cells, B-cells, and natural killer cells may paradoxically contribute to tumor progression.<sup>75-77</sup>

Of concern, however, despite its widespread acceptance, is the inadequacy of the immune surveillance theory in explaining the influence of stress in and the potential benefits of stress reduction for cancer patients. An alternative and highly plausible explanation is the growing recognition that both increased sympathetic drive and, most importantly, alterations in the HPA axis have been linked to the development of visceral obesity and insulin resistance.<sup>78,79</sup> The presence of the pro-inflammatory state associated with hyperinsulinemia and the increased drive of the IGF-insulin pathway are powerful tumor promoters that can increase tumor progression. With enhanced cell proliferation, there is a high risk of more rapid and earlier acquisition of a more malignant phenotype, leading to high risk of disease progression and more adverse outcomes. Alterations in the circadian rhythm of not only cortisol and other humoral mediators but of sleep-associated abnormalities typically seen in severe stress also have been linked to the development of visceral obesity and insulin resistance.<sup>80</sup> This is of interest in light of the growing recognition that impaired sleep and alterations in diurnal secretion of melatonin due to light disruption may have adverse effects on outcomes of breast, colon, and other cancers.<sup>81-83</sup> Though reduced melatonin levels may be a potential mediator of this effect, the change in sleep rhythm and accompanying circadian rhythm abnormalities may lead to an increase in abdominal and visceral obesity, leading to an increase in the risk of insulin resistance and its associated tumor-promoting humoral environment.

In addition to the influence of stress on visceral obesity and insulin, there is increasing evidence that chronic stress can influence tumor growth through up-regulation in angiogenesis.<sup>84,85</sup> These studies suggest that stress increases vascular endothelial growth factor (VEGF) production by tumor cells via activation of  $\beta$ -adrenergic receptors in the presence of increased circulating catecholamines. This leads to enhanced tumor vessel density and tumor growth rate, an effect inhibited by  $\beta$ -adrenergic blockers such as propranolol. This again raises the intriguing possibility of an anti-cancer effect of a non-cancer-related medication.

### **An Integrative Cancer Care Practice**

Over the last 4 years, I have attempted to integrate many of

these concepts into my practice. At the heart of our program is the partnership between patients and their family members. In addition, it is of crucial importance that treatment is delivered in a safe, nurturing environment. The development of my practice has been assisted by constant input from my patients, many of whom have brought important ingredients to the program and actively participated in its evolution.

Our nutritionist evaluates patients before treatment begins and sees them at regular intervals during therapy to provide dietary and supplement guidelines. During treatment, we follow serial changes in patients' initial metabolic profiles with attention to weight gain, a well-known side effect and adverse prognostic factor after adjuvant therapy and an indicator of insulin resistance.

The critical role of metabolic growth promoters is reflected in our approach to both early-stage cancers and advanced cancer. In the adjuvant approach to breast, colon, and prostate cancer, before the initiation of conventional therapy, we obtain a detailed assessment of these mediators, including measures of insulin resistance, inflammation, and hyperlipidemia, as well as careful anthropometric assessment of body mass index and body composition. During chemotherapy and radiation, high-dose antioxidants generally are avoided, though evidence suggests both a reduction in antioxidant status in patients undergoing chemotherapy<sup>86</sup> and a reduction in chemotherapy-related side effect with some antioxidant supplements.<sup>87-89</sup> Taking other important supplemental nutrients is encouraged, however. During chemotherapy, we incorporate essential fatty acid supplements, including eicosapentaenoic acid, docosahexaenoic acid, and gamma-linolenic acid. In addition to their well known anti-inflammatory effects, n-3 fatty acids result in reductions in insulin resistance, improved chemotherapeutic efficacy, and lower toxicity. Patients are individually assessed for measures of stress and encouraged to participate in our individual and group support programs. They are encouraged to work with our traditional Chinese medicine practitioners, who can provide in-office acupuncture with chemotherapy. To reduce anxiety and stress, guided imagery is offered to our patients before chemotherapy and invasive procedures. Patients can participate in our group exercise program, Breathwalk, a walking meditation exercise that is based on the work of Gurucharan Kalsa Singh<sup>90</sup> and that induces the relaxation response and provides aerobic exercise. This program is extremely popular and enhances patients' compliance with our exercise recommendations.

In addition to standard post-adjuvant treatment follow-up, we focus on issues that are critical to cancer survivors, in whom integrative therapies are particularly important. There is growing evidence of persistent post-therapy-related fatigue, often accompanied by a rise in inflammatory mediators, altered diurnal cortisol rhythms, and sleep disturbance.<sup>91,92</sup> We are actively studying interventions with exercise, acupuncture, and Chinese medicine and following changes in inflammatory markers (C-reactive protein, Interleukin-1 and 6), cortisol rhythm, and measures of fatigue. The post-treatment period is a critical time when cancer patients often feel they have "fallen off the cliff," losing the fre-

quent contact they had with health professionals during treatment. This is a time of heightened anxiety about recurrence and an opportunity for integrative interventions to reduce not only fatigue and other post-treatment-related effects but reinforce the importance of nutrition and exercise on general health outcomes, including cardiovascular disease, hypertension, and diabetes.

In patients with advanced cancer, we have numerous studies ongoing that reflect integrative principles and recognize the important convergence of a new understanding of tumor biology, including gene array analysis, the role of multiple signal transduction pathways in control of cell proliferation and apoptosis, and the growing interest in angiogenesis. A new concept in cancer biology, the interactome, recognizes the complexity of tumor cells in 4 dimensions.<sup>93</sup> The concept of the interactome, using computer modeling, recognizes that all cells, including tumor cells, have many simultaneously active metabolic pathways accompanied by critical protein-protein interactions that change over time. In malignant cells, they activate cell growth and proliferation while enhancing treatment resistance. This modeling may provide the opportunity for new, synergistic approaches to anticancer therapy. This also suggests a potential role for simultaneously targeting multiple overlapping signaling pathways, such as the estrogen receptor (ER), the epidermal growth factor-receptor (EGF-R), and the insulin-like growth factor-1 receptor (IGF-1 R), while also targeting downstream activators such as NFκB. This is in contrast to the conventional and often ineffective approach of administering one drug or treatment at a time.

The recent introduction of bevacizumab has increased interest in anti-angiogenesis approaches to cancer and has statistically, though marginally, improved the response and survival of metastatic colon cancer when combined with the standard regimen, FOLFOX.<sup>94</sup> Similar results have been demonstrated for advanced lung and breast cancer. There is potential opportunity for the introduction of additional angiogenesis inhibitors, such as tetrathiomolybdate,<sup>95</sup> the copper chelating agent thalidomide, antibiotics such as doxycycline, and numerous phytonutrients that have antiangiogenesis activity, as well as for innovative uses of conventional chemotherapeutic approaches, such as low-dose cyclophosphamide and low-dose, continuous-infusion paclitaxel.<sup>96</sup>

Similarly, the understanding that regulatory T-cells actively suppress the anti-tumor immune response has profoundly influenced newer anti-tumor immune approaches. New adoptive cell therapy<sup>97</sup> and dendritic vaccine approaches<sup>98</sup> have been introduced pre-treatment with immunosuppressive high-dose chemotherapy, in part to reduce the regulatory T-cell population and allow the tumor-specific immune response to be "unmasked." The critical importance of this was brought home to me by a patient with metastatic breast cancer who is currently in my care. After failing conventional chemotherapy, she developed progressive hepatic metastases and was entered into a vaccine trial with a limited anti-tumor response. After my initial evaluation, we chose a low-dose daily oral cyclophosphamide dose as a metronomic anti-angiogenesis strategy coupled with celecoxib

and followed her over the next 6 months. By her 6-month follow-up visit, her markers had normalized and her positron emission tomography (PET) scan showed resolution of her liver metastases. On re-evaluation, there was a marked reduction in her regulatory T-cells and an increase in her cytotoxic T-cell population. New evidence from the Tumor Immunology Laboratory at the National Cancer Institute suggesting that low-dose cyclophosphamide is an effective inhibitor of both T-reg number and activity<sup>99</sup> reinforces our suspicion that our patient's remission was a result of the "unmasking" of her anti-tumor immune response and provides insight into a safer strategy to enhance the benefit of immune therapies with low-dose chemotherapy.

The future holds exciting opportunities for a truly integrative approach to cancer care. Challenges include the need for a collaborative effort aimed at assessing the multi-intervention approach typical of integrative cancer care in contrast to conventional cancer care. This need is heightened when one considers that a high percentage of participants in phase 1 cancer trials already use numerous complementary interventions,<sup>100</sup> often without the investigators' knowledge and potentially affecting trial outcomes. In addition, efforts to broaden insurance coverage for effective supportive modalities such as acupuncture must be sought if these treatments are to be offered to the cancer community, particularly underserved minority communities that do not have access to these critical services. Lastly, a growing number of integrative practitioners are recognizing their obligation to address critical, parallel issues such as the role of environment in health and the need to partner with environmental organizations to bring these issues to the public at large. An example of this is the growing network Collaboration on Health and the Environment (CHE), which was founded by Michael Lerner and involves academic and research institutions and individuals as well as a broad array of advocacy groups that are dedicated to exploring critical issues in environmental health. The collaborative spirit of integrative medicine will bring changes in conventional medical care and increase physicians' passion for their work and mission.

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