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Lifestyle and Dietary Recommendations for Patients with Cancer

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The mainstays of conventional cancer treatment, surgery, chemotherapy, and radiation therapy, while preserving and prolonging the lives of many, present toleration challenges and often lack effectiveness in fully reaching desired goals of remission and survival. An integrative naturopathic approach offers additional adjunctive strategies that can improve both toleration and efficacy of conventional cancer treatment and further improve survival statistics. Fundamental to the naturopathic approach are diet, exercise and stress management.

Diet can be used to assist in recovery from surgery and to improve tolerance to radiation and chemotherapy as specific dietary nutrients offer synergistic antineoplastic actions. Exercise is an effective strategy to both improve tolerance and outcome. Finally, the impact of stress on prognosis is significant, pointing to the important role of stress management during any form of cancer treatment.

Diet

Diet has potential to optimize tolerance to conventional cancer therapies. Notably, there is evidence to suggest that patients who undergo conventional treatments without receiving nutritional support have higher complication rates.[1] Diet can be utilized to support optimal weight, specifically to prevent weight loss during treatment; to support bowel regularity; and to reduce localized areas of inflammation and pain such as headaches, arthralgia and mucositis.[2] While the full arsenal of dietary interventions is beyond the scope of this article, several dietary approaches deserve mention.

Dietary Patterns

Plant-based diets have been shown to be very important in cancer treatments. Fruit, vegetables, and certain components of plant foods, such as fiber and polyphenols, have significant research supporting a protective effect against cancer.[3] The impact of a plant-based diet has also been studied in specific cancer patient populations.

In women diagnosed with early-stage breast cancer and treated with chemotherapy, self-report of hot flashes (HFs) after treatment has been associated with approximately 25% to 30% decreased risk for additional breast cancer events, independent of the subsequent type of antiestrogen therapy. The HFs are associated with, in part, lowered levels of circulating estrogen. With this in mind, the protective effect of a whole foods, vegetable-rich diet might be especially relevant to women without HFs – essentially women with potentially higher circulating estradiol levels and hence a worse prognosis.[4] Specifically, changes in dietary patterns to either decrease energy from fat or to increase fiber intake can alter the enterohepatic recirculation of estrogens, leading to lower circulating estrogen concentrations. A low-fat/high-fiber diet can be expected to reduce serum estradiol by an average of 7.5%,[5] an effect of particular importance to women diagnosed with estrogen receptor positive breast cancer. Although this effect is modest, if it persists over years, this would have biological significance. A secondary analysis of the Women's Healthy Eating and Living (WHEL) Randomized Trial[6] was conducted to determine if HF-negative women gained specific benefit from the study diet that consisted of 5 vegetable servings plus 16 oz of vegetable juice, 3 fruit servings, 30 g of fiber, and limited energy intake from fat to 15% to 20% of total caloric intake.[7] Among women who reported no HFs (therefore presumably with higher estradiol levels and at greater risk) at baseline, there was a 31% lower recurrence rate in the group of women following these dietary recommendations than the HF-negative women in the comparison group (no dietary intervention) over 7.3 years of follow-up. Among HF-negative postmenopausal women, the intervention effect was more significant, with a 47% reduction in risk compared with HF-women assigned to the comparison group.

The beneficial effect of fiber specifically has been noted in other trials. For instance, women diagnosed with breast cancer who, within 12 months of their diagnosis, consumed significant fiber (average consumption of 15.5 g/day of insoluble dietary fiber) experience a 49% reduction in the likelihood of having elevated C-reactive protein (CRP) levels (OR, 0.51; 95% CI, 0.27, 0.95) compared to those who consumed an average of 5.4 g/day (P = 0.053).This suggests an anti-inflammatory effect of fiber consumption which, in turn, improves treatment toleration and is associated with improved survival.[8]

A dietary pattern characterized by significant reduction in the consumption of saturated fat, increased consumption of vegetable proteins with accompanying reductions in animal proteins and dairy

products has been shown to significantly increase PSA-doubling time in men with prostate cancer.[9] The slowed PSA doubling-time reflects decreased prostate cancer progression.

Colon cancer development and progression is also influenced by diet. Frequent consumption of red meat, refined carbohydrates, dairy and eggs is associated with an increased risk for developing colorectal cancer compared to infrequent consumption.[10] There is a significant inverse relationship between total fiber intake and risk of colorectal cancer (OR 0.57, 95% confidence interval 0.47-0.68). Vegetable fiber appears to be more protective than either fruit or grain fiber.[11] In patients with diagnosed colon cancer, a dietary pattern that emphasizes plant foods and minimizes animal sources of protein would be expected to exert a beneficial effect on the colon, perhaps influencing progression risk.

Obesity

It is now estimated that 2.4-3.9% of cancer deaths can be attributed to obesity.[12] The role of obesity in the progression and mortality risk of several cancers including breast, prostate and colorectal cancer is increasingly well defined. In an analysis of 70 clinical trials comprising 80,000 patients with early stage breast cancer, the relative risk of dying from breast cancer was increased by 34% in obese (BMI >30) pre-menopausal women (younger than age 55y) with ER+ tumors.[13] Thus, the absolute 10-year breast cancer mortality for pre-menopausal women with ER-positive disease was 21.5% for obese women compared with 16.6% for non-obese women. Post-menopausal obese women with ER-positive disease had a 6% increased risk of dying from breast cancer. There was no association between obesity and breast cancer death in women with ER negative tumors. Genetic analysis of pretreatment tumor biopsies has identified 121 genes with statistically significant changes in expression between obese and non-obese women.[14] Obesity is often characterized by hyperinsulinemia, estrogen signaling, and inflammation – all of which play important roles in obesity-accelerated breast cancer aggressiveness.

Obesity is also associated with unfavorable outcomes for patients with prostate cancer. Higher BMI (consistent with being overweight and obese) is predictive of a greater likelihood of rising PSA after surgery, indicating prostate cancer recurrence.[15] Furthermore, overweight and obese men experience shorter times to biochemical recurrence after surgery than normal weight men.

Obesity is a known risk factor for the development of colorectal cancer as well as its progression. Obesity related dyslipidemias, increased adipokines and elevated insulin and insulin-like growth factor-1 are collectively associated with both increased colorectal cancer incidence and mortality in both men and women.[16] Obesity also decreases the effectiveness of bevacizumab, a mainstay of conventional colorectal cancer treatment. Bevacizumab is the primary targeted therapy used for inhibiting tumor angiogenesis by blocking the VEGF/VEGF receptor pathway. Obesity is associated with increased levels of vascular endothelial growth factor (VEGF), which could lead to resistance to anti-VEGF bevacizumab therapy. In fact, a prospective clinical trial demonstrated that in patients with metastatic colorectal cancer who were treated with bevacizumab, those who were overweight (BMI >25kg/m^2) experienced significantly shorter time to progression (p = 0.01; HR: 4.37).[17]

Insulin Resistance

A significant driver of malignant behavior in cancer cells of all cancer types, is the increased expression of insulin and IGF-1 receptors.[18] As noted previously, insulin and IGF-1 are direct growth factors in many cancer cells.[19] Insulin and IGF-1 stimulate cellular proliferation in malignant cells via the constitutively "turned on" insulin receptor (IR) and IGF-1 receptors (IGF-1R), which culminate in mTOR activation. Activated mTOR drives proliferation, alters mitochondrial metabolism toward anabolism (aerobic glycolysis), and decreases apoptosis.[20] Some cancers rely exclusively on insulin and IGF-1 for their growth, including an estimated 27% of breast cancers. Approximately 8% of these cases have upregulation of the PIK3/Akt pathway.[21] Additionally, IGF-IR is constitutively activated via autophosphorylation in breast cancer cells with predilection for metastasis to the brain. *In vivo* models demonstrate that experimental deactivation of IGF-IR attenuates the invasive and metastatic potential of these breast cancer cells thereby delaying the development of brain metastases and prolonging survival. These preclinical findings are corroborated by the fact that 25% - 40% of patients with Her2+ and the same percentage of those with triple negative breast cancer have significantly increased risk of brain metastasis. This clinical finding correlates with increased IGF-IR signaling in these breast cancer subtypes.[22]

This concept has clinical application in the dietary advice given to patients. A trial followed 87 women with metastatic breast cancer receiving first line liposomal doxorubicin and cyclophosphamide chemotherapy for a median of 15 months.[23] Of the subjects, 87% had ER+ positive disease and 48% were insulin resistant, with insulin resistance defined as >2.5 HOMA-IR score. (Of note, HOMA-IR can be calculated as fasting serum glucose (mg/dL) x fasting plasma insulin (uU/mL)/405 with a value greater than 2.5 indicative of insulin resistance.) Even after adjusting for other prognostic factors such as age, endocrine status of tumor, visceral disease, and body mass index (BMI), patients with advanced breast cancer and insulin resistance had a statistically significant higher risk of disease progression (P = .035). The median progression-free survival was 8 months in women with insulin resistance, compared with 14 months for those who did not have insulin resistance (P = .04).

The role of insulin resistance is implied in colorectal cancer progression by looking at dietary glycemic load. Dietary glycemic load is positively correlated with insulin, IGF-1 and insulin resistance.[24] A prospective, observational study of 1011 patients with stage III colon cancer reported their dietary intake during and for 6 months after conventional treatment.[25] The median follow-up from the time of completion of adjuvant therapy was 7.3 years. Higher dietary glycemic load was associated with statistically significant decreases

in disease-free, recurrence-free, and overall survival. Specifically, patients with stage III colon cancer who were in the highest quintile of dietary glycemic load experienced an adjusted hazard ratio (HR) for disease recurrence of 1.79 (95% confidence interval [CI] = 1.29 to 2.48), compared with those in the lowest quintile (HR = 1). Increased glycemic load was associated with decreased overall survival. These associations were strongest for overweight patients (BMI > 25; HR 2.26). All of these findings reached statistical significance. These data points support the use of a low glycemic, nutrient dense diet in people diagnosed with colon cancer.

Anti-inflammatory Nutrients

Polyphenols are found in plant foods and spices and possess uniquely potent anti-inflammatory effects. The anti-inflammatory effects of polyphenols are illustrated, for instance in a parallel-designed, placebo-controlled clinical trial of 120 men and women aged 40-74 years that compared the effect of 300 mg of an anthocyanin rich drink isolated from bilberries and black currants to placebo over a three week period.[26] Consumption of the proanthocyanin-containing beverage decreased NF-kappaB-controlled pro-inflammatory chemokines and IFNalpha (an inducer of NF-kappaB activation) by 45% and 40% respectively vs. 20% and 15% in the placebo group (P < 0.050). Another trial assessed the impact of 30 grams of freeze dried vegetables and medicinal herbs mixed into hot water added to the daily diet of five patients with stage I non-small cell lung cancer (NSCLC) in a toxicity study group and 6 patients with stages III and IV NSCLC in a treatment group for up to 24 months.[27] These patients were matched to 13 patients with stages III and IV NSCLC in the control group. The freeze-dried medicinal vegetable soup included soybean, shiitake mushroom, mung bean, red date, scallion, garlic, lentil bean, leek, hawthorn fruit, onion, ginseng, angelica root, licorice, dandelion root, senegal root, ginger, olive, sesame seed, and parsley. All patients were treated with conventional therapies, including radiation, surgery, and/or chemotherapy. Those patients eating the vegetable soup had median survival of 15.5 months compared to a median survival time of 4.5 months in the control group (P<0.01). There was no adverse toxicity in the vegetable/herb group.

There is an emerging body of data which supports specific benefits derived from various flavonoids, members of the polyphenol family of compounds. In a controlled trial, 87 patients, 36 with resected colon cancer and 51 patients after polypectomy, were divided into two groups.[28] One group of 31 patients was treated daily with a flavonoid mixture of 20 mg apigenin and 20 mg epigallocathechin-gallate and compared with a matched control group of 56 patients. Both groups were observed for 3-4 years by surveillance colonoscopy and by questionnaire. Among the 14 patients with resected colon cancer and treated with the flavonoid mixture, there was no cancer recurrence, and one adenoma developed. The cancer recurrence rate of the 15 matched untreated controls was 20% (3 of 15) and adenomas evolved in 4 of those patients (27%). The combined recurrence rate for neoplasia was 7% (1 of 14) in the treated patients and 47% (7 of 15) in the controls (P = 0.027).

In a trial of 26 men with newly diagnosed localized prostate cancer, the subjects were randomized to either 30 mg lycopene or no supplement prior to radical prostatectomy.[29] In the lycopene group, at surgery, 84% had tumors less than 4mL versus 45% in the control group. Additionally, 73% of the lycopene group and only 18% of the control group had clean margins. Prostate intraepithelial neoplasia was present in 67% of the lycopene group compared to 100% of the control group. Finally, PSA decreased by 18% in the lycopene group versus an increase of 14% in the control group.

A pooled analysis of three large prospective trials – the Shanghai Breast Cancer Survival Study (SBCSS), the Life After Cancer Epidemiology (LACE) Study, and the Women's Healthy Eating & Living (WHEL) Study – collectively representing 9514 breast cancer survivors with a mean follow-up 7.4 years, assessed the impact of soy isoflavone.[30] Consumption of over 10 mg isoflavones per day was associated with a 25% reduced risk of recurrence. This inverse association was seen in tamoxifen users, estrogen receptor negative and estrogen receptor positive women.

Polyphenols found in plant foods both down-regulate inflammatory NFkB and up-regulate the transcription factor Nrf2. Nrf2 is normally sequestered in the cytoplasm as an inactive complex with its cytosolic repressor Keap-1. Phytochemicals, specifically polyphenolic flavonoids, activate diverse upstream kinases, which in turn stimulate dissociation of Nrf2 from Keap-1. Once released from Keap-1 repression, Nrf2 translocates to nucleus and binds to promoter region of genes encoding antioxidant and detoxifying enzymes.[31] This effect is synergistic with chemotherapy in so far as intracellular antioxidants are required to preserve the apoptotic cascade initiated by chemotherapy. Additionally, polyphenols directly up-regulate apoptosis the ultimate step in removing aberrant cells. There are many examples of these pro-apoptotic polyphenols such as trans-resveratrol[32] from grapes, peanuts, berries, and red wine. Genistein[33] from soy and curcumin[34] from turmeric, activate apoptosis in cancer cells.

Fasting

A recent and promising approach to improve tolerance of chemotherapy is caloric restriction prior to and during chemotherapy. This approach has gained significant momentum from the research of Valter Longo, PhD. The premise of short term starvation (STS) in an oncology context is twofold. First, when energy is scarce, cells will use energy preferentially for maintenance functions at the price of growth. Furthermore, IGF-1 levels decrease dramatically in response to short-term (36 -120 hours) of starvation. Cells throughout the body respond to IGF-1 as a signal for growth. Thus, fasting results in growth arrest of normal cells. However, most tumor cells have mutations in pTEN, p53, and the PI3K/Akt/mTOR pathway, leading to constitutive upregulation of insulin and IGF-1 initiated proliferation pathway.[35] Thus, in malignant cells, short term starvation and the resultant decrease in IGF-1, does not downregulate the PI3K/Akt/mTOR pathway and therefore does not arrest their growth. This differential effect can be

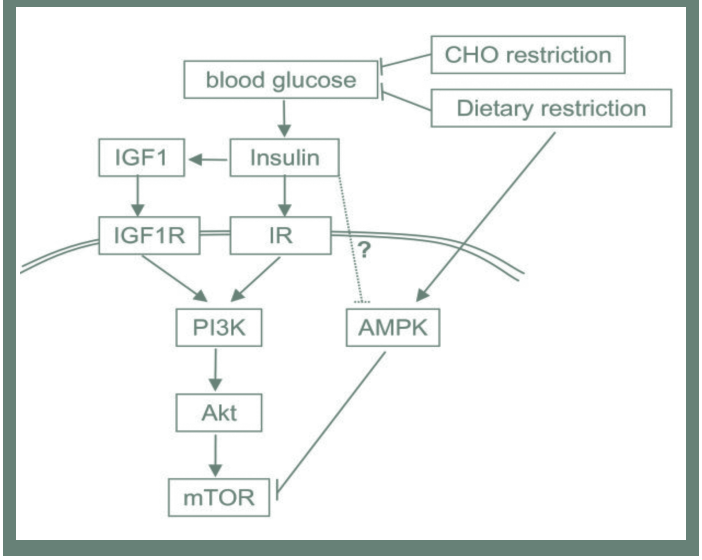
used with chemotherapy to preferentially protect healthy cells that will be in a dormant, non-proliferative state. This state renders these cells somewhat immune to the effects of chemotherapy. Malignant cells continue to proliferate during STS and remain susceptible to chemotherapy.

The effects of STS were demonstrated in case series report of ten patients (7 females and 3 males) with cancer (four with stage IIA breast cancer, two with prostate cancer – stage II and stage IV, one with stage IA ovarian cancer, one with stage IV endometrial cancer, one with stage IV non-small cell cancer of the lung and one with stage IVB esophageal cancer).[36] All patients received chemotherapy and underwent a water-only fast for 48-140 hours pre-chemotherapy and continued for 5-56 hours post chemotherapy. Patients served as their own controls and during fasting cycles they experienced less toxicity even after non-fasted accumulation of toxicity. Patients received an average of 4 cycles of various chemotherapy drugs including docetaxel/cyclophosphamide, docetaxel/carboplatin/±5-FU, carboplatin/paclitaxel, gemcitabine/docetaxel, docetaxel, doxorubicin/cyclophosphamide. Specifically, the chemotherapy received during the water fast resulted in less fatigue, weakness, and gastrointestinal side-effects.

While the benefit and safety of this approach, specifically the impact of fasting on treatment response and survival is still under clinical investigation, it could be considered empirically in patients who experience significant chemotherapy-induced toxicity to a level that is threatening their ability to complete treatment. Of note, preclinical research has indicated that fasting may reduce multidrug resistance in malignant cells,[37] however this needs to be confirmed in human clinical trials. The exact nature of the fasting regimens are under investigation. One fasting protocol under study includes 24, 36, or 48 hour fasts prior to chemotherapy.[38] Another active clinical trial of women with gynecological cancers is studying the impact of modified fasting with daily caloric intake of <400kcal by juices starting 36 to 48 hours before beginning chemotherapy and lasting to 24 hours after ending each chemotherapy.[39]

Although not clinically evaluated, a variation of STS can also be considered between chemotherapy treatments and as a follow-up to conventional treatment. In the absence of active treatment, diet can be used to influence the same constitutively over-active IGF-1 and insulin stimulated PI3K/Akt/mTOR pathway in malignant cells and in individuals with insulin resistance. This proliferation pathway's activity is enhanced in the presence of IGF-1 and insulin, both of which are reduced during caloric and carbohydrate restriction. Furthermore, dietary caloric restriction stimulates AMPk which directly blocks mTOR activation. (see Diagram 1.) The result of down-regulating mTOR is reduced proliferation. Despite the promising theoretical basis for this approach, the clinical data on the impact of caloric and carbohydrate restriction on overall survival and recurrence risk in humans is yet to be determined.

DIAGRAM 1. Dietary restriction and mTOR



Cachexia

Of note, this approach should not be considered for any patient at risk for cachexia, a condition of significant weakness and wasting caused by inflammatory cytokines released by malignant tissue. Certain cancers such as lung cancer, pancreatic cancer and many advanced cancers carry a high risk of cachexia. Protein and essential fatty acid consumption is a clinically validated way to both prevent and delay cachexia.[40] Protein requirements may exceed 80gm/day in people at risk for cachexia. Typically, 0.45 – 0.9g protein/2kg body weight is needed to prevent and manage cachexia. Omega-3 fatty acids, especially eicosapentanoic acid (EPA), at 2gm to 3gm daily is associated with weight gain and improved quality of life. Feeding (increased caloric intake) has not proven to control cachexia.

Exercise

Exercise is a critical component of a lifestyle-based support program during cancer treatment and beyond. Data collected over a median of 23 months post-diagnosis (interquartile range 18–32 months) were pooled in the After Breast Cancer Pooling Project (n = 13,302).[41] The study found that 2.5h (10 MET-hours/week) of moderate intensity physical activity per week was associated with a 27% reduction in all-cause mortality and a 25% reduction in breast cancer mortality compared with women who did not meet the physical activity guidelines (<10 MET-hours/week). In another study, women who engaged in the equivalent of at least two to three hours of brisk walking each week in the year before they were diagnosed with breast cancer were 31% less likely to die of the disease than women who were sedentary before their diagnosis [(HR) = 0.69 (95% CI, 0.45 to 1.06; P = .045)].[42] Women who increased physical activity after diagnosis had a 45% lower risk of death (HR = 0.55; 95% CI, 0.22 to 1.38) when compared with women who were inactive both before and after diagnosis. Conversely, women who decreased physical activity after diagnosis had a four-fold greater risk of death (HR = 3.95; 95% CI, 1.45 to 10.50).

From a cohort of 184,194 adults without colorectal cancer at baseline in 1992-1993, 2,293 participants were diagnosed with invasive, non-metastatic colorectal cancer up to mid-2007.[43] The mean follow-up time from diagnosis to death or end-of-study was 6.8 years. Participants completed detailed questionnaires that included information concerning recreational physical activity and leisure time spent sitting at baseline, before their cancer diagnosis, and again after their cancer diagnosis. The highest pre-diagnosis recreational physical activity category (8.75 or more MET hours per week which was the equivalent of greater than 150 minutes/week) compared with the lowest category (3.5 MET hours per week) was associated with a 28% lower risk of all-cause mortality. The same comparison for post-diagnosis recreational physical activity resulted in a 42% reduced risk of mortality. Additionally, leisure time spent sitting 6 or more hours per day on the pre-diagnosis survey was associated with a statistically significant 36% higher risk of all-cause mortality. Post-diagnosis sitting time was associated with a statistically significant 62% higher risk of colorectal cancer–specific mortality. These studies support recommendations for recreational physical activity and the avoidance of sedentary time among people diagnosed with cancer – throughout the continuum of care.

Stress Management

A third foundational component of lifestyle-based support of people undergoing cancer treatment is stress management. Elevated and prolonged stress hormones, namely cortisol, epinephrine and norepinephrine are associated with the carcinogenic process and shortened survival. The effects of stress on survival was eloquently demonstrated in a prospective trial of 217 participants with newly diagnosed metastatic renal cell cancer, all with life expectancy of greater than 4 months, with good performance status and no major concurrent diseases.[44] All participants completed depression questionnaires, had salivary cortisol levels assessed, and provided blood sample for genomic analysis at baseline and at 4 months. The following factors were associated with decreased survival time: depression, poor quality of life, and flattened diurnal cortisol slope (with elevation of average cortisol). Genomic analyses identified up-regulation of genes involved in inflammation, immune response, and down-regulation of genes that activate programmed cell death (all $p<.0001$) as well as genes involved in cell trafficking, adhesion, oxygen transport, and hemostasis (all $p<.05$).

Based on rodent models of triple negative breast cancer, social isolation causes a heightened stress response that, in turn, increases expression of genes in adipocytes that increase glucose metabolism, lipid synthesis and leptin secretion. These metabolic changes increase the conversion of mammary carcinoma in situ to invasive carcinoma.

Mammary fat, in particular, has heightened sensitivity to stress hormones over visceral fat, making breast tissue especially vulnerable to stress.[45] While the clinical evidence for the negative effects of stress is still developing, early evidence indicates the benefit of stress management on prognosis in people being treated for cancer. Furthermore, a more robust body of data demonstrates the improvement in quality of life that people diagnosed with cancer experience after active stress management.[46-48]

Mindfulness based stress reduction (MBSR) is a particularly well-researched stress management behavior. A meta-analysis of 10 studies showed a significant improvement in psychological and physical quality of life with the practice of MBSR.[49] MBSR has been shown to reduce depression and fear of recurrence in women diagnosed with breast cancer.[50] MBSR lowers cortisol, reduces IL-6, lowers systolic blood pressure and improves NK cell activity – each one of which is correlated with higher quality of life and with better prognosis.[51]

Conclusions

There is ample evidence to support the inclusion of a lifestyle-based approach in people undergoing treatment for cancer. A plant-based diet that is high in polyphenols and has a low in high glycemic load is the foundation of such an approach. Intermittent or continuous caloric restriction may have unique benefits to the improved toleration of treatment and overall survival. Exercise is a potent strategy to increase overall and cancer-specific survival. Finally, stress management has direct impact on reducing the risk of recurrence and in optimizing the quality of daily living.

About the Author

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