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Critical Review

Nutrition in Cancer: Evidence and Equality

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Abstract

Purpose: Poor nutrition is highly implicated in the pathogenesis of cancer and affects the survival of patients during and after completion of definitive therapies. Mechanistic evidence accumulated over the last century now firmly places dysregulated cellular energetics within the emerging hallmarks of cancer. Nutritional intervention studies often aim to either enhance treatment effect or treat nutritional deficiencies that portend poor prognoses. Patients living within food priority areas have a high risk of nutritional need and are more likely to develop comorbidities, including diabetes, hypertension, renal disease, and cardiovascular risk factors. Unfortunately, there is currently a paucity of data analyzing the impact of food priority areas on cancer outcomes.

Methods: Therefore, we performed a review of the literature focusing on the molecular and clinical interplay of cancer and nutrition, the importance of clinical trials in elucidating how to intervene in this setting and the significance of including citizens who live in food priority areas in these future prospective studies.

Conclusions: Given the importance of nutrition as an emerging hallmark of cancer, further research must be aimed at directing the optimal nutrition strategy throughout oncologic treatments, including the supplementation of nutritious foods to those that are otherwise unable to attain them

Introduction

Cancer remains the second leading cause of death in the United States,[1] and 30% to 40% of cancers are estimated to be preventable by a healthy diet, adequate physical activity, and maintaining a normal body habitus.[2] According to recent estimates, 80,000 cancer cases per year could be prevented with an adequate diet alone.[3] The importance of nutrition is broadly implicated in cancer incidence, outcomes, and mitigation of long-term comorbidities after treatment.[3-5] Unfortunately, nutrition recommendations in oncology remain vague and often contradictory.[6] Epidemiologic studies throughout the 20th and 21st centuries associate high-calorie diets and obesity with the incidence of many types of cancer. Indeed, morbidities of obesity, including insulin resistance and diabetes mellitus type 2, are both independently recognized to increase cancer risk.[7,8]

Initial intervention studies illustrating the link between tumor growth and caloric intake span back to the early

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1900s.[9] Mechanistically, studies have revealed that the chronic consumption of excess calories promotes an increase in the insulin-like growth factor-1 (IGF-1) mammalian target of rapamycin (mTOR) signaling pathway, which is paramount to nutrient sensing and subsequent cell growth.[7] Various methods of dietary interventions to mitigate this pathway are under active exploration, including caloric restriction, intermittent-fasting, and specific macronutrient restriction.

Prospective, interventional studies are currently limited; however, there are data correlating poor nutrition in patients with cancer with reduced quality of life, increased toxicities from standard-of-care therapies, and inferior overall survival.[10-15] Countering these findings, attempts to combat weight loss in patients undergoing concurrent chemoradiation for head and neck cancer was associated with worse local control and overall survival.[16] Furthermore, definitive cancer treatment using chemotherapy and radiation therapy can accelerate the aging process, impacting long-term physical and mental quality of life in cancer survivors.[17,18] Survival rates after cancer treatment continue to increase; thus, mitigating other comorbidities that pose a significant risk to longevity, such as cardiovascular disease and diabetes, is critical. Unfortunately, patients with cancer experience both of these preventable diseases at rates significantly higher than the general population.[19]

In 2019, cancer topped cardiovascular disease as the most common cause of death in several high-income and upper-middle-income countries around the world.[20] In the United States, death rates vary by affluence. For example, Americans living in the poorest counties are twice as likely to die of cervical cancer and 40% more likely to die of lung cancer.[1] Multiple factors contribute to disparities in cancer mortality, including smoking, cancer screening, access to affordable health care, and nutrition status. Approximately 10% of Americans live in low-income areas that have poor access to nutritious meals and the resources needed to attain them.[21] Therefore, nutrition is one factor amenable to intervention, disproportionate in access, and backed by maturing data that may help improve outcomes in patients with cancer from diagnosis through treatment and during the survivorship period.

Epidemiology

Population-based studies over the last several decades have attempted to quantify cancer incidence and mortality based on dietary patterns. Numerous study results indicate that overall healthy lifestyle habits decrease the risk of cancer incidence and mortality by 10% to 60%, including but not limited to avoidance of tobacco and maintaining a normal weight through a healthy diet and physical activity.[22,23] The assessment of specific dietary patterns and health-related outcomes proves difficult owing to the wide-range of lifestyle variables that interact with each other and mortality in epidemiologic studies. Furthermore, most nutrition data are gathered using food surveys aimed at analyzing adherence to specific diets or eating within different macronutrient or micronutrient profiles. Owing to the intrinsic heterogeneity encountered within such studies, results are often mixed and generally considered fundamentally biased, resulting in inconsistent findings.[24] Furthermore, intervention bias plagues many of these analyses.

A recent meta-analysis including 31 studies reported that patients who followed diets that scored high on the Dietary Approaches to Stop Hypertension, the Alternative Healthy Eating Index, and the Healthy Eating Index had significantly decreased cancer incidence, mortality, and all-cause mortality.[25] Adherence to a Mediterranean diet was also inversely associated with cancer mortality, including significant risk reductions in colorectal, breast, gastric, liver, head and neck, and prostate cancers, which the authors attributed to higher intakes of fruit, vegetables, and whole grains.[26] However, data evaluating vegetarian diets on cancer incidence and mortality are inconsistent. A large analysis of 96 vegetarian and vegan studies showed a significant decrease in the incidence of cancer (relative risk: 0.92; confidence interval, 0.87-0.98), but not cancer mortality.[27] Yet another meta-analysis that included 9 studies of vegetarian diets and evaluated the subsequent risk of breast, colorectal, and prostate cancers found no significant association between diet and cancer risk.

Studies analyzing macronutrient profiles, such as dietary fat intake and cancer risk, also relay conflicting conclusions. In one meta-analysis, total dietary cholesterol intake was significantly associated with lung cancer risk among 37,000 participants in a case-control series, but no association was found in 243,000 participants from cohort reviews,[28] making the results difficult to interpret. On the other hand, total intake of dietary fat was not associated with risk of breast cancer-specific death or all-cause mortality,[29] and trended with decreased risk in several studies.[30,31]

Epidemiologic studies have the advantage of large participant numbers tracked over a long period of time. The results of these studies can be hypothesis-generating, but care should be taken when extrapolating to generalized dietary recommendations. Inaccuracies in survey data collection and food frequency questionnaires, the challenges of isolating single variables from complex dietary patterns, and healthy user bias are several of many factors that contribute to the difficulty in deducing specific nutrient guidelines from these type of analyses.[32] Hence, prospective dietary intervention studies are necessary to confirm or disprove findings. As such, although we can conclude from these data that healthy diets are associated with a decrease in the incidence and mortality from cancer, the benefits of specific dietary interventions remain ambiguous.

Metabolism and Cancer

Dietary intake is likely to affect carcinogenesis through metabolic mechanisms and inflammatory processes. Indeed, deregulated cellular energetics is an emerging hallmark of cancer.[33] Rampant cell growth in rapidly dividing tumors requires significant energetic and anabolic inputs. In normal physiologic cellular environments, in the presence of oxygen, glucose is predominantly taken through glycolysis to the mitochondria for aerobic respiration to generate adenosine triphosphate. In 1930, Otto Warburg published the first data showing that tumors revert to anerobic glycolysis, even in the presence of oxygen, instead of shunting glucose to lactate.[34] The increased flux of glucose through glycolysis is the basis of the positron emission tomography scan, which uses radiolabeled glucose (^{18}F-fluorodeoxyglucose) to visualize tumor location.

Why a dividing tumor cell prefers a less efficient energetic pathway remains uncertain. In 2009, Vander Heiden et al proposed that the increased glucose flux provides carbon sources for biomass production.[35] Adenosine triphosphate requirements for anabolic inputs may never be limiting; therefore, dividing cells preferentially shunt glucose and glutamine to the production of nicotinamide adenine dinucleotide phosphate, nucleotide, amino acid, and fatty acid synthesis. Well-described oncogene activations and tumor suppressor losses are tightly linked to glucose metabolism. The activation of the phosphoinositide 3-kinase (PI3k)/AKT/mTOR pathway upregulates multiple glycolytic enzymes with the net effect to increase glycolytic flux. For example, glucose transporter-1 and hexokinase-2 are upregulated and facilitate glucose uptake.[35-37] Acting in opposition, 5' adenosine monophosphate-activated protein kinase and tumor protein p53 signaling both decrease glycolytic flux; therefore, their losses are likely to maintain anerobic glycolysis.[35-37]

Many tumors are associated with obesity and metabolic syndrome, suggesting a dietary link. Elevated body mass index scores, higher glucose, and insulin resistance are correlated with increasing incidence and mortality from cancer.[7,8] The phenotype between metabolic dysregulation from obesity overlaps with the deregulated cellular energetic hallmark of cancer. The chronic excitation of the insulin/IGF-1 pathway leading to PI3k activation induces a similar increase in glycolytic flux, and chronic IGF-1 elevation in humans is associated with an increased risk of breast, colorectal, and lung cancer.[38-40] Therefore, novel interventions aim to manipulate host metabolic inputs via caloric restriction, time-restricted feeding, and nutrient restriction[41] to enhance cancer treatment.

Treatment Enhancement

Calorie restriction (CR) is often defined as a daily reduction in energy intake by 20% to 60%.[37,42] Initial studies using CR in oncology date back to 1909 when a German scientist showed that a stepwise reduction in total calories slowed transplanted sarcoma growth.[9] These studies were replicated and consistently showed slowed tumor growth of transplanted tumors in animals experiencing deprivation.[43,44] The rate of spontaneous tumorigenesis was also stunted by CR in models of sarcoma, skin, mammary, and lung cancer, and increased the lifespan of the host.[43,45-47] Some early studies also attempted specific macronutrient deprivation, or dietary restriction, compared with pure caloric restriction. In the late 1930s, Bischoff and Long showed that the replacement of formulated dietary chow with either Crisco or pure starch did not impede cancer growth, and the effect was indeed from CR alone.[44] Tannenbaum performed numerous experiments in the 1940s and 1950s, looking at both CR and macronutrient deprivation. Some experiments provided evidence that dietary carbohydrate restriction alone is the most effective at inhibiting tumor formation.[48] Other experiments that showed fat intake, specifically polyunsaturated oils, despite a lower total caloric intake, was associated with higher carcinogenesis.[48] Overall, the conclusion from these early works was that the degree of caloric restriction predicted the degree of both spontaneous and induced tumor inhibition, with no consensus on macronutrient effects.[45-47]

More recent studies in the 1990s to early 2000s replicated the findings of CR in the reduction of incidence and growth of cancer. Decreased growth was found in additional rodent models of glioma, prostate, colon, and mammary cancers.[49-52] One recent study in primates randomized 72 rhesus monkeys to 30% caloric restriction versus standard feed and found a significant reduction in the onset of age-related diseases, including a 50% reduction in the lifetime development of cancer.[53] However, the mechanism for tumor inhibition remains poorly understood. In a glioma model, 40% CR significantly decreased vascularity and increased apoptosis within the tumor and significantly decreased intracerebral growth.[49,54] These effects were accompanied by systemic reductions in both IGF-1 and glucose.[49] CR also reduced the growth of prostate cancer accompanied by reduced levels of IGF-1.[50] IGF-1 appears to mediate this mechanism, at least in part by decreasing proto-oncogene signaling downstream of PI3k.[55] Indeed, Sabatini et al. found that multiple cancer cell lines grown in mice are highly sensitive to CR and become resistant only with a gain of function PI3k mutations.[56] However, of note, all animal studies suffer from potential bias because experimental mice are generally overweight and medically morbid; thus, questioning whether the dietary mechanisms are providing profound antitumor effects or merely offsetting the resulting sequalae from a previous overfed state.[57]

Despite the beneficial mechanistic changes that accompany caloric restriction, long-term calorie

restriction is likely not feasible in the oncology clinic. Many studies show that patients who lose significant weight during cancer treatment have poorer outcomes and a reduced quality of life.[4,13,58] These effects are multifactorial. The development of cachexia, defined as skeletal muscle loss with or without anorexia and not reversible with nutritional intervention, portends a poor prognosis.[59] Cachexia is poorly understood, likely resulting from a mixture of systemic inflammation, increased resting energy expenditure, and decreased protein synthesis.[58-60] Therefore, the potential benefits of caloric restriction while preventing the incidence of cachexia are difficult to glean. In addition, long-term caloric restriction was shown to decrease immune function in animal models.[37]

Given these challenges, time-restricted feeding, which includes short-term fasting, intermittent fasting, and short-term extreme caloric restriction, have been studied. Cellular adaptions to starvation, conserved from yeast to mammals, repeatedly show increases in stress resistance by reducing nutrients and growth signals, such as IGF-1, and thus downregulating the PI3k/AKT/mTOR pathway.[61,62] Reductions in IGF-1 signaling have been shown to induce cell cycle arrest as normal cells partition cellular processes toward survival while tumor cells are largely immune to this regulation.[55,63] This difference, termed differential stress resistance,[63] allows normal but not tumor cell survival in response to high doses of chemotherapeutic agents.[55,64] Indeed, short-term fasting in just 48 to 72 hours induced a 70% reduction in circulating IGF-1 levels and protected mice to lethal doses of chemotherapeutic agents.[55] Cycles of fasting proved effective at delaying cancer progression in multiple tumor mouse models, reducing toxicities to chemotherapy and promoting long-term survival, particularly when combined with chemotherapy.[65,66] In humans, short-term fasts have been shown to be safe and may decrease chemotherapeutic side effects.[67,68] Additional studies are ongoing and promising.

Finally, other dietary interventions under active investigation in oncology aim to restrict specific nutrients. The ketogenic diet (KD), defined by the presence of ketone bodies in systemic circulation, aims to restrict both carbohydrates and protein. The KD was originally developed in the 1920s as a treatment for intractable pediatric epilepsy.[69] At very low carbohydrate intakes, such as those with fasting, the liver produces beta-hydroxybutyrate from fatty acids, which is a ketone body that is able to cross the blood-brain barrier and provide an additional energy source for the brain. The KD may provide a selective advantage against cancer cells because beta-hydroxybutyrate bypasses the Warburg metabolism while providing adequate energy via the tricarboxylic acid cycle in normal tissues. In addition, the KD induces significant reductions in both insulin and IGF-1,[70,71] and acts as signaling molecules to inhibit histone deacetylase and gene expression.[72] Preclinical studies show that the KD significantly slowed tumor growth, sensitized tumor cells to both chemotherapy and radiation therapy, decreased cachexia, and increased survival.[73-78] Preliminary clinical studies show the safety and feasibility of the KD in the clinic,[64,70,79-82] and current clinical trials are ongoing.

Nutritional Support and Equality

Oncologic outcomes and treatment-related toxicities have been closely correlated to nutrition status before, during, and after definitive therapies for multiple cancer sites. For example, the effects of nutritional deficits in head and neck cancers have been extensively studied, where malnutrition can have a negative impact on morbidity, quality of life, and cancer-specific mortality. Indeed, patients with head and neck cancer are frequently considered malnourished before starting any definitive therapy,[83] and the receipt of curative chemoradiation often exacerbates nutritional insufficiencies secondary to known side effects, such as mucositis, dysphagia, xerostomia, nausea/vomiting, and other acute toxicities.[84] Continued poor nutrition in these patients with cancer can have detrimental effects on cure rates and increase the likelihood of posttreatment complications.[83,85] Furthermore, in patients with lung cancer, skeletal muscle depletion,[5] clinical weight loss,[85,86] and malnutrition[87] have all been associated with a poorer cancer prognosis. Retrospective data showed an association between elevated body mass index and improved overall survival in patients with non-small cell lung cancer (NSCLC) who were diagnosed with locally advanced disease.[86] Remarkably, the median survival for patients with stage III NSCLC who were obese before starting chemoradiation was significantly improved (29 vs 17 months) compared with patients considered underweight.[86] Improvement in lung cancer survival with pretreatment obesity was sustained for years after the completion of definitive therapy, even after accounting for patient demographic, tumor, and treatment characteristics.[86] The survival benefit in this study most likely reflects the ability for patients to undergo aggressive, uninterrupted therapy for an otherwise devastating malignancy and perhaps counters the poorer prognosis in cachectic individuals.

Nutritional deficiencies have been linked with prognosis in multiple other cancer sites besides lung or head and neck tumors, including breast, gynecologic, gastrointestinal, and genitourinary malignancies.[85] Nutrition is not only essential to tolerate definitive therapy in these disease sites, which can ultimately dictate cure, but sustaining a high-quality diet can mitigate many of the problems cancer survivors often face. Cancer treatment frequently accelerates aging, which can increase the risk

of patients acquiring multiple comorbidities, such as diabetes, cardiovascular disease, and osteoporosis.[18,88] Physical deconditioning and fatigue, both common long-term side effects in cancer survivors, lead to reduced physical activity and loss of muscle mass, promoting sarcopenic obesity.[88] Cancer survivors with sarcopenic obesity, which is the replacement of muscle mass with fat, are at a high risk for posttreatment mortality.[89] Therefore, maintaining a healthy, nutritious diet at all timepoints during cancer care is critical, especially in cancer survivors who received curative treatment.

As such, 1 in 3 patients with cancer inquire about dietary intake. Unfortunately, current recommendations from National Comprehensive Cancer Network–designated cancer institutions remain vague.[6] From the aforementioned investigational interventions, the preferred diet from an oncologic perspective is uncertain. Yet, there is a role for nutritional intercession as can be deduced from the data discussed. Despite the potential benefits of dietary changes in all patients with cancer, the greatest advantage would most likely be observed in those who have little access to healthy, nutritious foods. One in 10 Americans live within a food priority area (FPA), defined as an area encompassing low quantity and quality of grocers, and adequate transportation to get there.[21,90] In some inner cities, the proportion increases to 1 in 4 Americans.[91] Although the effects of residence within a FPA on various health issues, such as diabetes,[92] hypertension,[93] renal disease,[94] and cardiovascular risks,[95] have been well-characterized in the literature, data reporting the effects of residing in FPAs on cancer treatment and outcomes is nonexistent.

A recent population-based analysis using a comparative risk model estimated the association of diet with cancer risk in American citizens. From this study, middle-aged men and minorities (ie, black/Latinos) had the highest proportion of diet-associated cancer burden than any other group.[3] Thus, health care centers that cater to an underserved population not only care for patients at an increased risk to develop malignancies, but may also treat patients who lack the nutritional resources necessary to withstand aggressive therapy and live healthy as survivors. To make nutritional interventions impactful in all cancer communities, further research should characterize the nutritional needs of patients with cancer residing in FPAs and strategize how best to include them in future clinical trials.

Conclusions

Population-based analyses demonstrate that many cancers are significantly associated with lifestyle factors and a number of cases may be prevented with adequate nutrition alone. Epidemiologic studies, although plagued with confounding variables, suggest that some dietary strategies may be helpful in both the prevention and treatment of cancer. However, prospective, dietary intervention studies are required to establish specific nutritional guidelines. These strategies may include caloric or dietary restriction aimed at enhancing antitumor effects while recognizing that patients have to be appropriately selected given the risk of cachexia and malnutrition commonly found at the time of diagnosis. Other dietary strategies involve decreasing cardiovascular and metabolic comorbidities in cancer survivors, in part by eating healthy, nutritious meals. Optimal dietary interventions may decrease both morbidity and mortality in patients with cancer before, during, and after definitive therapy. Low-income patients with poor access to nutritional foods, such as those who reside in FPAs, may have the most to gain from such approaches. Future studies should not only focus on optimizing oncologic dietary strategies, but also elucidate the impact of poor access to food on cancer incidence, outcomes, and morbidity. Such research will allow for optimal nutritional strategies to all patients with cancer, particularly those at risk for suboptimal care.

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