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SUPPLEMENT ARTICLE

The relevance of nutrition to pediatric oncology: A cancer control perspective

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Abstract

It is indisputable that adequate and appropriate nutrition is fundamental to the health, growth, and development of infants, children, and adolescents, including those with cancer. Nutrition has a role in most of the accepted components of the cancer control spectrum, from prevention through to palliation. The science of nutrigenomics, nutrigenetics, and bioactive foods (phytochemicals), and how nutrition affects cancer biology and cancer treatment, is growing. Nutritional epigenetics is giving us an understanding that there are possible primary prevention strategies for pediatric cancers, especially during conception and pregnancy, which need to be studied. Primary prevention of cancer in adults, such as colorectal cancer, should commence early in childhood, given the long gestation of nutritionally related cancers. Obesity avoidance is definitely a target for both pediatric and adult cancer prevention, commencing in childhood. There is now compelling evidence that the nutritional status of children with cancer, both overweight and underweight, does affect cancer outcomes. This is a potentially modifiable prognostic factor. Consistent longitudinal nutritional assessment of patients from diagnosis through treatment and long-term follow-up is required so that interventions can be implemented and evaluated. While improving, there remains a dearth of basic and clinical nutritional research in pediatric oncology. The perspective of evaluating nutrition as a cancer control factor is discussed in this article.

KEYWORDS

cancer control, childhood cancer, malnutrition, nutrigenomics, nutrition

1 | INTRODUCTION

Awareness of the relevance of nutrition to children with cancer and research on cancer in children is increasing. This is changing the clinical care of these children and the understanding of the biology of their cancers. Nutritional oncology is an interdisciplinary field in which cancers are investigated as both systemic and local diseases originating by changes in the genome and progressing through a multistep process that may be modified by nutritional factors. These points of nutritional preemption are fundamental for the prevention of cancer, the quality of life of cancer patients, and the reduction in cancer recurrence.[1] The growing knowledge of the gene-nutrient interaction is altering how we view the biology and approach to treatment of cancer and other chronic diseases.[1,2] Nutritional status—both underweight and overweight—impacts cancer clinical outcomes and thus is a modifiable prognostic factor[3-8] A recent review in the Lancet documents that the problem of both underweight and overweigh is a dual scourge in developing counties.[3]

Nutrition is essential to well-being from conception through adulthood. That optimal nutrition is essential to the well-being of children during stages of growth is obvious and well documented.[2] Fundamentally, what makes the clinical practice of pediatrics different from that of adult medicine is that the fetus, child, and adolescent are all going through a process of growth and development. During this period, the spectrum of diseases and their pathology is different from that observed in adulthood. This is also manifest in the different prevalence and biology of cancers presenting in newborns, infants, children, and adolescents. Inappropriate/inadequate nutrition results in being underweight, overweight, and/or micronutrient depleted. This may occur in children with cancer prior to diagnosis, at diagnosis, during therapy, and after treatment.[4-8] The causes of cancer cachexia in children are multifactorial, including low socioeconomic status, tumor

Abbreviations: ALL, acute lymphoblastic leukemia; BSA, body surface area; DNA, deoxyribonucleic acid; HIC, high-income country; LIC, low-income country; LMIC, low-middle-income country; WCRF, World Cancer Research Fund.

type and stage, host factors, and intensity of treatment, resulting in inadequate/inappropriate nutrition. Malnutrition, both underweight and overweight, can result in increased infections, organ dysfunction, altered pharmacokinetics, poor quality of life, and other comorbidities. Unfortunately, the literature has a dearth of clinical and basic research on the impact of nutrition within the pediatric oncology domain. In recent years, there has been the promise that nutritional research in pediatric oncology is improving. A background and history of activities in nutrition and pediatric oncology is given in the article by Barr and Stevens.[6]

Deficiencies of macro and micronutrients give rise to well-described clinical pathological morbidities such as kwashiorkor (protein deficiency), marasmus (energy/protein deficiency), rickets (vitamin D deficiency), blindness (vitamin A deficiency), anemia (iron, folate and B12 deficiency), and many more nutritional-related pathologies.[2] There is a spectrum of nutritional status that spans that of significant deficiency with overt clinical signs, insufficiency without overt signs but a degree of physiological impairment, nutritionally replete, overconsumption leading to obesity due to excess calories, and clinical toxicity due to excess use of supplements, e.g., excess vitamin A resulting in encephalopathy or excess iron and hemochromatosis.[2]

Micronutrient insufficiency can affect optimal physiological function with subclinical manifestations, e.g., impaired immune status associated with zinc, vitamin C or D depletion, and impaired cognitive development due to protein, iron, or iodine insufficiency. Nutritional-related pathologies can add to both the morbidity and risk of mortality of an acute or chronic disease, including cancer.[2-9] This is most evident in low income countries.[6,7]

The impact of inappropriate/ inadequate nutrition on the individual pediatric cancer patient and their underlying disease can be evaluated from the perspective of cancer control. This article and the other articles in this supplement highlight this perspective and the considerable relevance of nutrition to pediatric cancer control.

The conventional perspective of cancer control is that it encompasses the complete spectrum of the cancer journey plus the understanding of the biology and pathology of different cancers.[10-13] Cancer control may involve a national or regional strategy for cancer care and prevention and may also encompass a comprehensive research strategy within a specific jurisdiction. It is arguable that, for pediatric and adolescent oncology, a separate cancer control strategy is required or at least the recognition of the distinct differences from adult oncology.

As defined by the American Cancer Society,[11] "Cancer control focuses on reducing the number of people who get cancer, have complications from it, and die from it. It uses approaches that have been tested through research to control the number of cancer cases as well as the effects of cancer. Cancer control programs work to find and use the most effective ways to prevent cancer, reduce the risk of cancer, find cancer earlier, improve cancer treatments, help more people survive cancer, and improve the quality of life for people who have cancer."

The National Cancer Institute in the United States states that[12] "Cancer control science is the conduct of basic and applied research in the behavioral, social and population sciences to create or enhance interventions that independently or in combination with biomedical approaches will reduce the burden of cancer."

Using the above understanding of cancer control, it should be recognized that all of the components, i.e., cancer prevention, epidemiology, biology, response to therapy, supportive care, toxicity of therapy, quality of life, delayed effects, survivorship and palliative care can be impacted by nutrition. The quantity and quality of food and nutritional supplements that are consumed by an individual, in the past and present, may affect the pathogenesis and biology of cancer, response to treatment, side effects of therapy and quality of life.[1,2,5,6]

2 | CANCER PREVENTION

Primary prevention of malignancies that occur in infancy, childhood, and adolescence is generally considered to be of minimal benefit, if not impossible. Research into primary prevention for this cohort of cancer patients has been minimal to date. There is some evidence that maternal factors may be of importance, especially during pregnancy. A maternal diet high in its content of fruits and vegetables or supplemented with folic acid appears to reduce the risk of ALL, neuroblastoma, and tumors of the central nervous system.[14,15] Breast feeding may be associated with a decreased prevalence of childhood cancers.[16] There is also some correlation between both maternal obesity and high birthweight with an increased prevalence of childhood cancers.[17-19] These observations require evaluation of intervention strategies to improve nutrition and health behaviors before conception and during pregnancy.[20]

Early prevention of cancers that occur later in life, such as colorectal cancer, should be an accepted practice during the formative years. Given that many carcinomas in adults are generally slow growing,[1] it is arguable that the most effective strategy is to start nutritional preventive practices as early as possible, i.e., in childhood, as difficult as that may be. Avoidance of food preservatives such as nitrates, limitation of red meat consumption while adopting a diet high in vegetables and fruits, and promoting reduction of obesity are some nutritional cancer prevention strategies advocated by the World Cancer Research Fund (WCRF). Their latest report on preventative strategies is as relevant to children as it is for adults.[21] The WCRF states that a third of the most common adult cancers could be prevented by a healthy diet, being physically active and maintaining a normal body weight. These cancers that could be prevented include those of the esophagus, mouth, pharynx, larynx, colon, rectum, and breast.[21] The recent observation that colorectal cancers are occurring at younger ages is possibly related to poor nutrition and other life style-related factors, but causation in adolescents and young adults (AYAs) remains an enigma.[22,23] The correlation of obesity and increased incidence of cancers in adults, such as breast cancer and colorectal cancer, plus poorer prognosis of those cancers in obese patients, is added reason to prevent obesity in childhood.[24-26] Obese children will usually become obese adults. The role of carcinogens, anticarcinogens, and calorie reduction is being studied, but the role of diet choices and food preparation starting early in life deserves more attention.[27]

Secondary prevention usually refers to the practice of cancer screening and early detection of a cancer. Cancer screening is not an accepted practice in children and adolescents, except in those with heritable tumors. However, screening school-age children for dietary intake of quantity and quality could be a public health policy that may have preventive benefits for a number of chronic diseases, including adult cancers. Numerous publications have documented the poor quality of diets in both high-income countries (HICs) and low- and middle-income countries (LMICs) in children and adolescents, and observed in survivors of childhood cancer.[28-31] Adult survivors of adolescent and young adult cancer have also been shown in a literature review to have poor diets and require interventions.[32] Unfortunately, this kind of policy is not sufficiently researched to assess its potential benefit as a preventive strategy.

It is noteworthy that research and funding for cancer prevention strategies, or clinical and basic research to explore correlations that may lead to preventive intervention studies, is woefully inadequate in pediatrics, especially compared with that expended on therapeutic studies. The NIH spends less than 5% of its research budget on nutrition research and little of that on nutrition prevention research. The cliché of "prevention is better than cure" is not heeded sufficiently in young people.

3 | NUTRITION AND EPIDEMIOLOGY/ CANCER BIOLOGY

Case–control studies in nutritional epidemiology are difficult to conduct, expensive, time consuming and frequently controversial, as the recent discussion on red meat consumption exemplifies. However, there is still a role for them, as alluded to above in the evaluations of foods and supplements during pregnancy.

The basic premises of nutritional cancer epidemiology in childhood are to evaluate[1,33]

- The nutritional status of children who develop cancer to understand the relationship of nutrition and nutritional therapies to the prevalence of cancer in children.
- Parental nutrition to understand its relationship to the incidence of cancer in offspring, especially maternal nutrition during conception and pregnancy.
- The nutritional status of children undergoing cancer therapy to understand the role of nutrition during cancer treatment and how it affects outcomes.
- Nutritional therapies that have been utilized by various cultures to treat cancer.

The effect of nutrition on human health has been studied for centuries. Investigations that were conducted in the 20th century mainly examined the role of nutrition on overall health. However, with the advent of the digital age and more sophisticated analytical methods, researchers are able to analyze specific effects of various nutrient elements and nutritional profiles on the human genome, its expression machinery, metabolic effects, and the pathogenesis of cancer.(Figure 1). Molecular epidemiology evaluates specific gene-nutrient interactions and correlations are now being made.[1,2]

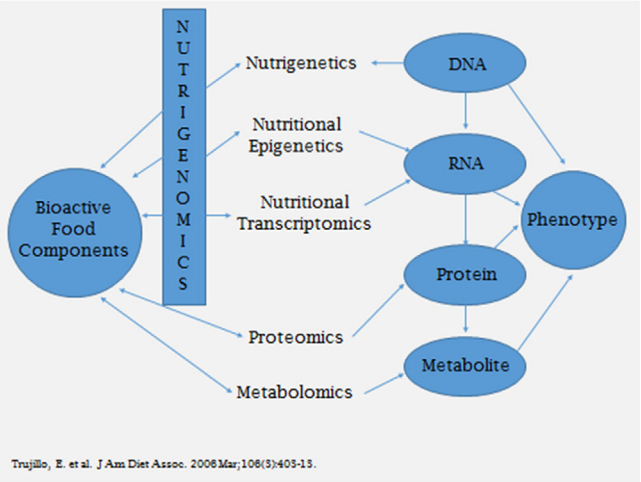

FIGURE 1 Bioactive foods and nutrigenomics

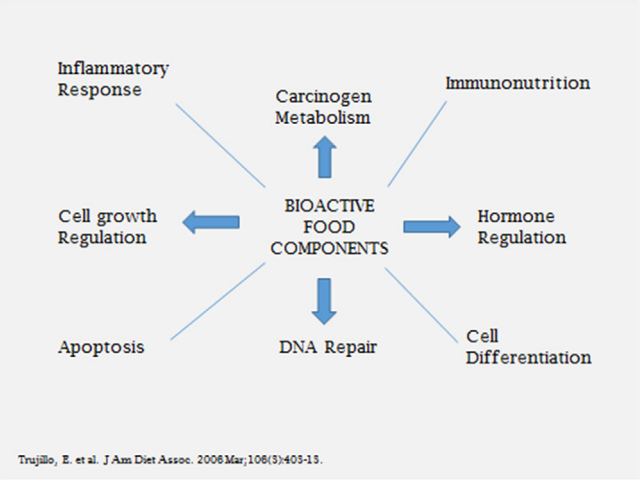

FIGURE 2 Bioactive food and cancer biology

It is recognized that thousands of bioactive substances exist in our diet.[1,2,33,34] This is especially apparent in the phytochemicals available in fruits and vegetables. These substances may function in many different biological mechanisms, such as on the immune system, cell division, apoptosis etc. (Figure 2). This has spawned the relatively new science of nutritional genetics subdivided into nutrigenomics and nutrigenetics.[35-39] Nutrigenomics is the scientific study of the dynamic, yet regulated manner in which bioactive food components interact with specific genes. Nutrigenomics aims at elucidating the relationship between various nutrients and genome regulation and expression, and how genotoxic diets lead to disease pathogenesis.

The nutrigenomics premises are as follows: [1,2,35-39]

- Diet and dietary components can alter the risk of disease development by modulating multiple processes involved with onset, incidence, progression, and/or severity of diseases.

- Food components can act on the human genome, either directly or indirectly, to alter the expression of genes and gene products.
- Diet could potentially compensate for or accentuate effects of genetic polymorphisms.
- The consequences of a diet are dependent on the balance of health and disease states and on an individual's genetic background.

Nutrigenetics evaluates the impact that our genes have on our body's response to nutrition.[1,2,36,37] This is the same perspective as that of pharmacogenetics in which single-nucleotide polymorphisms within specific genes can alter the pharmacokinetics, pharmacodynamics, and prevalence and degree of drug side effects.

One of the main roles of the body is to maintain genome stability, especially in stem cells that are destined to differentiate and contribute to normal physiology, including tissue architectural integrity, organ functioning, and immunity.[1,2,36-39] The genome itself is prone to damage and mutations, and thus the body has developed elaborate surveillance and repair mechanisms to counter such threats and maintain normalcy. Recently, mounting evidence from nutrigenomic studies suggest that micro- and macronutrients play significant roles in genome stability, and that the development of diseases is intimately correlated with inappropriate nutrient intake.[1,2,36-39] Micronutrients are vital in the normal functioning of life. Many serve as substrates or cofactors that supplement important enzymes responsible for genome maintenance, expression, and repair.

Epigenetics is the mechanism by which genes can be expressed.[1,2,35,40-43] Genes can be regulated up or down, without intrinsic changes to the DNA of the gene. This includes oncogenes. There is growing evidence that epigenetic changes due to nutritional intake and or nutritional status, as measured by altered methylation or histone acetylation, may affect specific gene expression.[1,40-44] Bioactive or functional foods can affect the phenotype of the individual and possibly that of the cancer phenotype

The Agousti mouse model highlights the different physical effects on the offspring due to two different maternal diets which changed the epigenome.[43,44] Thus, studying the maternal diet and its effects on the epigenome of children and correlation to childhood cancers is a promising area of research.

4 | OTHER "OMICS"

Proteomics: This is the study of proteins and their functions. That protein production can be affected by nutritional intake is established.[1,2,35,40,45] Cancer changes the proteome in complex ways. Proteomic changes are described in childhood CNS tumors.[45] Functional variations of a protein are known as proteoforms. Linking past and present diet to proteoforms and the biology of childhood cancer and response to therapy is yet to be established, but worthy of basic research.

Metabolomics: This is the broad profiling of metabolites at the cellular, tissue, and circulating levels. Metabolite profiles are the final result of cellular function driven by genomic, transcriptomic, proteomic, and environmental factors inclusive of nutrition.[1,46] Metabolomics, it could be argued, allows an assessment of the patient closest to their current physiological state and offers opportunities for advancement in nutritional cancer epidemiology.

Transcriptomics[1,47]: This is the study of the transcriptome—the complete set of RNA transcripts that are produced by the genome, under specific circumstances or in a specific cell. Studying the role of nutrition on producing the transcriptome is also in its infancy.

5 | PERSONALIZED NUTRITION

At the 2017 annual meeting of the American College of Nutrition, plenary sessions were presented on "Personalized Nutrition in Disrupting Cancer.[48] The 2018 meeting expanded on personalized nutrition under the topic of "Translate the Science of Nutrigenomics into Practice." This approach is not yet embraced in pediatric oncology and is a challenge for our basic and clinical scientists.

5.1 | Nutritional assessment

This is an essential component of clinical care, especially during active therapy and after the completion of treatment. Surveys in both HICs and LMICs have shown that most institutions are inadequately and inconsistently undertaking nutritional assessments at diagnosis and longitudinally during and after therapy.[49-51] Nutritional assessments should include the ABCD components, i.e., anthropometric, biochemical, clinical, and dietary, including assessments of body composition. This is discussed in the article by Viani et al.[51]

5.2 | Nutritional interventions

Based on appropriate nutritional assessment, nutritional interventions, when needed, should be undertaken to maintain growth and development and to enhance the quality of life of children with cancer. As has been surveyed, there is no consistent approach being undertaken to interventions in both HICs and LMICs.[49,50] Using an algorithm to aid decisions on interventions is recommended.[52] The use of numerous supplements by families is common. There is concern that these may affect the efficacy of both radiation therapy and some chemotherapeutic agents. This concern is probably greatest with respect to antioxidants.[53,54] In general, if oral intake is adequate and appropriate, supplements should not be given. If there is overt insufficiency, it is clinically appropriate to supplement, e.g., vitamin D, especially in temperate latitudes.[55,56] Nutritional interventions are discussed by Trehan et al.[57] and integrative therapies by Diorio et al.[58]

5.3 | Nutrition, pharmacokinetics, pharmacodynamics, drug-food interactions

Nutritional status, being under or overweight, does affect how drugs are metabolized and distributed.[59,60] Thus, nutritional status can affect both pharmacokinetics and pharmacodynamics. This raises the

dilemma of whether dosage of chemotherapy based on BSA is the most appropriate calculation in these circumstances.[60,61] Currently, basing dose on BSA in patients at either end of the malnutrition spectrum may result in underdosing or overdosing. Standard dosing in severely undernourished patients does lead to increased drug toxicity.

Drug-food interactions are well known, such as grapefruit affecting the plasma levels of some drugs used in oncology. Knowledge of drug-drug interactions is well taught, and pharmacists are certainly aware of that concern, but drug-food interactions are frequently ignored. The article by Wiernikowski et al. discusses this topic.[62]

5.4 | Nutritional status and effect on cancer outcomes

The prevalence of malnutrition and its effect on outcomes in children with cancer in different countries has been documented over the last decade.[4-8,63-66] Among children who are undernourished, increased frequency and severity of infection, reduced quality of life, and poor neurodevelopmental and growth outcomes have been reported consistently. The risks associated with undernutrition are more threatening to children diagnosed with cancer and are best exemplified by epidemiologic data from LMICs in which children often present with overt undernutrition at diagnosis.[4-8] After controlling for stage of disease, these studies have found that poor nutritional status correlates with reduced adherence to therapy and impaired survival in children and adolescents. Remediation of undernutrition in LMICs has been one of many strategies leading to improved survival rates for children and reducing abandonment of therapy. These studies underscore the importance of directing attention and resources toward managing, and ideally preventing undernutrition so as to ensure maintenance of adequate growth and development, plus provide children with cancer the best prospects for cure. Being overweight or obese is also associated with poorer survival rates. This is significant in both ALL and acute myeloid leukemia.[63-66] There is a link between poor nutrition and increased toxicity of therapy, especially that of increased infections. Micronutrient deficiencies are likely to add to the severity of side effects. The article by Barr and Stevens documents compelling evidence of the influence of nutritional status on pediatric oncology outcomes.[6]

5.5 | CAM and integrative therapies

Oncologists are well aware that some form of CAM therapies is frequently utilized by patients and their parents.[67-70] Integrative approaches are being employed and studied. Due to the huge market in supplements, Google searches, and alternative advice frequently given to our patients and parents, there is often confusion as to what parents should do. Nutritional interventions are among these integrative therapies employed. Nutrition and supplements are among the few things that parents feel they can control in the care of their children with cancer.

There are many products sold as "Nutraceuticals," such as immunonutrition products and other natural products, to decrease toxicity and side effects.[69] The nutraceutical market is unregulated, and its impact on outcomes largely unknown. The naturopath is gaining ever-increasing influence as an adjuvant caregiver who frequently recommends nutritional products or bioactive food substances. That some of these products may be useful is possible, but it requires research to verify both safety and efficacy. This topic is discussed by Diorio et al.[58] in this *PBC* supplement.

5.6 | Nutrition and survivors

Long-term follow-up of survivors of malignant disease in children and adolescents is now routine in most pediatric oncology programs, but is resource dependent. Most long-term follow-up guidelines are risk based, dependent on the risk of long-term side effects from the underlying disease and therapy. Nutritional evaluation and guidance should be incorporated from a perspective of ameliorating side effects when possible, e.g., minimizing cardiovascular side effects and metabolic syndrome associated with obesity.[72,73] There is the opportunity for potential second cancer prevention by education on nutrition and life style modification.[74] Survivors of cancers in adolescents and young adults should be nutritionally evaluated and interventions offered when appropriate.[32] This subject is discussed and referenced in the article by Cohen et al. in this *PBC* supplement.[74]

5.7 | Nutrition and palliative care

The major perspective in this phase of the cancer journey is usually symptom control and overall well-being of the patients. How, what, when, and if to offer nutritional support is generally individualized, but can be a source of conflict between parents and caregivers. There are guidelines with respect to nutritional support as well as some ethical questions that arise at this stage.[75,76] However, these guidelines are consensus opinions, and there is little research to guide what we do with respect to nutrition in the palliative care setting for children and adolescents with cancer.

6 | CONCLUSION

That nutrition plays a role in cancer biology, possible prevention, treatment, outcomes, supportive care, and the well-being of our patients is becoming ever more evident. A seminal review article by Mauer et al. over three decades ago brought our attention to the role of nutrition in our patients, but our response to investigating nutrition has been underwhelming.[77]

The advancing field of nutritional genetics offers promise of a personalized approach to nutrition in clinical practice.[48] There is a paucity of the basic and clinical research required to understand the impact of nutrition on cancer biology (especially gene-nutrient interactions) and what interventions are required.[1,2] Given the complexity of the many components in studying the impact of nutrition on patient physiology and tumor biology, the use of "big data" analysis is needed.[78] Nutritional research is not a priority within pediatric cancer cooperative clinical groups.[79,80] However, the recent publication of a *JNCI* monograph from the COG is encouraging.[28,78,81]

Nutrition is frequently viewed only through the narrow prism of supportive care and not the expanded cancer control perspective. There are other exciting avenues of research, such as the diet-microbiome-inflammation axis, which are likely also relevant to cancer biology and the well-being of children.[82,83] It is our desire to advance basic nutrition science, to study the gene-nutrient interaction in pediatric oncology, embed nutritional biology questions in cooperative group therapeutic clinical trials, continually observe nutritional status and its impact on all cancer clinical outcomes, and employ nutritional interventional questions in those studies. The advent of a personalized approach to the nutritional care and interventions for our patients, due to the expanding knowledge of nutrigenomics, nutrigenetics, and the microbiome, is a vision to be embraced.

This *PBC* supplement is compiled to educate on important aspects of nutrition for the pediatric oncology community and promote the necessity of a more robust approach to nutrition research within the entire cancer control spectrum.

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