Importance of nutrition in pediatric oncology

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Abstract
A nutritional perspective within pediatric oncology is usually just related to the supportive care aspect during the management of the underlying malignancy. However, nutrition has a far more fundamental importance with respect to a growing, developing child who has cancer as well as viewing cancer from a nutritional cancer control perspective. Nutrition is relevant to all components of cancer control including prevention, epidemiology, biology, treatment, supportive care, rehabilitation, and survivorship. This article briefly describes this perspective of nutrition within a cancer control context and is a summary of the presentation at the "1st International SIOP-PODC Workshop on Nutrition in Children with Cancer" held in Mumbai.

Key Words: Nutrition, nutrigenomics, nutritional genomics, pediatric oncology

Introduction
As all pediatricians know, optimal nutrition for the growing, developing child is essential to maximize health status. This is no different if a child or adolescent has cancer. If we consider nutrition from a cancer control perspective for pediatric oncology, we have to recognize the relevance of nutrition within many components of the cancer control spectrum. Accepted definitions of comprehensive cancer control are:

• Decrease the incidence and mortality of cancer, to enhance the quality of life of those affected by cancer, through an integrated and coordinated approach directed to primary prevention, early detection, treatment, rehabilitation, palliation, and an understanding of the epidemiology and biology of the cancers

• A national cancer control plan is a public health program designed to reduce the number of new cases and deaths and improve the quality of life of cancer patients, through systematic and equitable implementation of evidence-based strategies for prevention, early detection, diagnosis, treatment, and palliation, making the best use of available resources

• Nutrition does have a role in prevention, epidemiology, biology, supportive care, the effect on the toxicity of therapy, quality of life, delayed effects, and survivorship. This article summarizes some of these cancer control concepts from a pediatric nutritional perspective.

Cancer Prevention/Epidemiology/Cancer Biology
Case-control studies of childhood cancer indicate that folate during conception and early pregnancy may be important in mitigating risk of some pediatric cancers. Studies have evaluated the importance of fruits and vegetables, prenatal vitamin supplementation, especially folic acid, during times of conception, and fetal development. A meta-analysis of seven studies reported that multivitamins with folic acid had a protective effect against neuroblastoma, leukemia, and central nervous system (CNS) tumors. Although primary prevention of pediatric cancers is currently not a high priority, it is important from a national basis that folic acid supplementation be recommended to all women who expect to conceive. There are other well-documented health benefits of folic acid during pregnancy such as a reduction of neural tube defects. Primary prevention of several adult cancers begins in childhood, of which reduction in the incidence of obesity is one of the most important.

Cancer epidemiology and molecular epidemiology related to nutrition are a growing area of study. We need to evaluate the nutritional status of children who develop cancer to understand the relation of nutrition to the prevalence of cancer in children. We need to evaluate enteral nutrition to understand its relation to the incidence of cancer in offspring, especially maternal nutrition during conception pregnancy and early infancy. We need to evaluate the nutritional state of children undergoing cancer therapy to understand the role of nutrition during cancer treatment and how it may affect outcomes. We need to evaluate nutritional therapies that may have been used by various cultures to treat cancer.

Molecular epidemiology biologists are studying the potential contribution of bioactive food substances on genetic and epigenetic risk factors to the etiology of cancers. Nutritional Genomics or Nutrigenomics, is the study of how foods affect the expression of genetic information in an individual and how an individual’s genetic make-up metabolizes and responds to bioactive nutrients. Bioactive food components can affect the expression and function of DNA, RNA, protein, and metabolites that may ultimately affect the phenotype of the host and/or cancer. Nutritional epigenetics may be especially important. This is the study of heritable changes of DNA not involving changes in DNA sequence but may regulate gene expression. The major mechanism of epigenetic regulation is on methylation patterns which are involved in cancer development. These disturbances in methylation of imprinted genes can predispose individuals to cancer, including pediatric cancers. Folic acid is a necessary nutrient in the DNA methylation process and is the most studied nutrient with respect to this. There are other dietary factors that are known to modify...
DNA methylation and may be relevant to maternal and infant diet. These include selenium, Vitamin A, Vitamin B12, thiamine, Vitamin B6, and zinc.[4]

It has been observed that changes in activity or expression of specific genes reflect the availability of certain nutrients. There are over 30,000 bioactive food components in fruits and vegetables which may affect a variety of cancer processes, for example, DNA repair, apoptosis, cell differentiation, inflammation, etc.[4,5]

The conceptual basis of this new branch of genomic research can best be described by five tenants:

• Common dietary chemicals acting directly or indirectly on the genome may alter gene structure or expression
• Diet can be a risk factor for cancer and other chronic diseases to some individuals under certain circumstances
• Some diet-regulated genes and their variants are likely to play a role in disease initiation, progression, and severity
• The genetic makeup of an individual can influence the degree by which diet affects the balance between health and disease
• Diet recommendations based on knowledge of nutritional requirements, nutritional status, and genotype, termed “customized or personalized nutrition,” can be used to prevent, mitigate or cure chronic disease.

We as pediatric oncology health care providers need to be aware that nutrition potentially plays a role in the pathogenesis of pediatric malignancies, as well as the subsequent evolution of adult cancers due to the influence of nutrition over a lifetime. The cancer control components of prevention, epidemiology, and biology of the disease may all be well influenced by what infants, children and adolescents eat, as well as what their mothers ate during pregnancy.

Food/Drug Interactions

We are well-aware that there are interactions between drugs that are administered to our children. There can also be interactions between food and food supplements affecting the metabolism and efficacy of drugs. The best known of this is the grapefruit juice affect which can influence cytochrome P450 pathways.[6] Food substances that interfere with the cytochrome pathways may result in inhibition of drug metabolism leading to a longer time of drug clearance and possible increases in toxicity. It may also inadvertently affect metabolism with shorter clearance and thus decreased efficacy.

Nutritional status during chemotherapy may well affect the pharmacokinetics and pharmacodynamics of several of the drugs that are utilized in the treatment of pediatric malignancies.[7-10] At both ends of the spectrum of malnutrition, that is, protein energy malnutrition and being underweight and stunted, or being overweight or obese, can influence how drugs are cleared. This has been well-described for methotrexate when undernutrition decreases drug clearance and associated with the increased toxicity. Obesity also affects clearance of ifosfamide, cyclophosphamide, and doxorubicin.

Cancer Cachexia

Cancer patients presenting as undernourished, or who during therapy become undernourished, are well-described.[10-13] The causes of cancer cachexia are multifactorial and may be related to the disease, host phenotype, socioeconomic status of the patient, as well as the treatment that is, used.[10-13] The disease-related effects may be due to mechanical obstruction, effects on absorption of nutrients, appetite suppressing factors, paraendocrine, or cytokine production. There may be psychological and CNS components with decreased appetite, anorexia, alterations in taste and smell, and stress factors such as anticipatory nausea and vomiting. Host-related factors may be due to altered metabolism, increased growth requirements and other co-morbidities such as parasite infestations. Treatment-related effects on nutrition are those of chemotherapy, radiation, and surgery. The systemic treatment modalities are frequently associated with gastrointestinal complications such as mucositis anywhere in the gastrointestinal tract, ileus, nausea and vomiting, abdominal pain and changes in absorption of nutrients. All these interrelated factors can result in increased needs, increased loses, and decreased intake of nutrients. Subsequently, there may be a protein energy deficit and/or micronutrient deficits which result in poor growth, poor quality of life, and deterioration of specific organ function (especially the immune system) with increased risk of systemic infections and potentially add to overall increased treatment-related morbidity and mortality.

Survivorship

Long-term complications in survivors of pediatric cancers due to original cancer or its treatment are well-documented. These include malnutrition, either under or overweight.[10,13,14] Malnutrition can affect survivor’s quality of life as well as predispose them to other chronic conditions related to obesity such as cardiovascular disease, type 2 diabetes, metabolic syndrome, and increased predisposition to other cancers such as breast and colorectal.[15] There is an onus on long-term follow-up clinics to include longitudinal nutritional assessment in order for interventional strategies to be implemented. Promoting healthy lifestyles with respect to both nutrition and exercise is both a primary and secondary prevention strategy to ameliorate long-term health morbidities.

Conclusion

Nutrition affects most components of the cancer control perspective within pediatric oncology. The above is a brief overview of that concept.

That nutritional status can affect outcomes both in respect to morbidity and possibly mortality and is well-described.[10-13,16] This cancer control component is further discussed in other articles within this journal and was presented at the SIOP POGO Nutritional Conference in Mumbai. The consequences of malnutrition (both undernutrition and obesity) and inadequate support or intervention during therapy is an important aspect of supportive care, which unfortunately is too frequently
ignored due to the focus on treating the underlying malignancy. The quote from van Eys should not be ignored, “Nutrition should be viewed for what it is, supplying the most basic needs of children. No child has died from being fed appropriately, but may die of starvation. The practice of pediatric oncology should not contribute to that statistic.”[17]

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References