Nutrition Research and Cancer

by Daniel W. Nixon, M.D.

The challenges in oncology nutrition research today are to generate sound experimental evidence in the laboratory, test this evidence in human clinical trials, and then use it to bring effective nutritional strategies to the clinic and the community. Recent scientific advances make these challenges less daunting. The human genome has been mapped, and dramatic advances in genomics and proteomics are increasing our understanding of abnormal cell control mechanisms that may be able to be repaired or blocked.

Researchers are trying to manipulate the abnormal signals from faulty genes that disrupt the nutrition absorption process. Some of these abnormal gene functions may be effective markers of early neoplastic changes and might be able to be used to assess cancer risk and predict the success of preventive and therapeutic interventions. Since the malignancies that are most closely related to diet and nutrition—cancers of the breast, prostate, and gastrointestinal tract—are quite common in Western society, answers from this area of research, if combined with a strong anti-smoking campaign, could save millions of lives. And at long last, some encouraging ways to manage cancer cachexia have appeared.

DIETARY COMPONENTS AND GENES

Huge libraries of proteins and the human genes that produce them are being compiled[1] and are helping us understand the ways genes and their protein products control normal as well as abnormal cell growth. Knowing the nucleic acid sequence of a pertinent gene is not enough. We must also know which proteins the gene produces and how they work inside the cell, since changes in these proteins (and the corresponding changes in cell metabolism) are the cause of most diseases.

Technology is helping scientists study cell proteins more precisely. Two-dimensional gels, protein chips, mass spectroscopy, X-ray crystallography, nuclear magnetic imaging, and powerful bioinformatics software programs that can analyze huge amounts of data are advancing research more quickly than ever before. Nutrition researchers must use these new biological tools to work out the precise interactions between dietary components, genes, and gene products.

We know, for example, that certain dietary polyphenols kill cancer cells in culture by encouraging apoptosis.[2] Oncogene or tumor suppressor gene protein products may lessen this effect in a living organism. It should be possible to determine how polyphenols affect the cell life cycle and encourage cancer cells to die, and to bioengineer food that would enhance this beneficial effect. Once the responsible molecular mechanism behind an antineoplastic substance is discovered, safe, cost-effective, evidence-based clinical trials can follow with well-defined endpoints based on the new molecular markers. Nutrient-derived drugs for treating cancer could be the result.

DIETARY INTERVENTIONS

If certain foods are proven to have antineoplastic effects, when should dietary interventions begin and in whom? For a nutritional strategy to be most effective, intervention should begin very early in the course of the disease (before a tumor becomes invasive) or as a preventive measure before a tumor forms. Dietary manipulation to treat an advanced malignancy is likely to be ineffective. Preventive nutritional strategies are designed for people who have a high risk of developing a particular cancer, people who have premalignant conditions such as oral leukoplakia or adenomatous colon polyps, and people who have a high risk of developing second primary cancers or suffering a recurrence of their first primary cancer. Genetic testing and the discovery of cancer markers in the blood and tissue are helping to identify these populations.

Giving retinoid-based chemopreventives to patients with oral cancer,[3] and other interventions based on known histologic markers, has had substantial positive effects. Patients with adenomatous polyps[4,5,6] who were given calcium and cereal fiber as a preventive measure, and heavy smokers who were given b-carotene to ward off lung cancer,[7] achieved mixed results from these treatments. However, a trial using selenium to prevent skin cancer reported encouraging preliminary data about the mineral's ability to stop prostate cancer from developing, which was a secondary endpoint of the study.[8]

A prevention trial designed to determine dietary fat's influence on breast cancer recurrence has now completed accrual. The trial, known as the Women's Intervention Nutrition Study (WINS),[9] has enrolled nearly 2,500 breast cancer patients

in more than 30 sites around the United States. Subjects who have been treated surgically for cancer and have no known metastatic disease are randomized to a diet of either 30 percent or 15 percent fat calories. The rationale for the trial is that reduced dietary fat could deprive residual tumor cells of stimulatory calories, certain stimulatory fatty acids, or fat-related stimulatory hormones. To date, compliance with the low-fat dietary requirement has been acceptable, so the WINS trial should provide the answer to the important question of dietary fat's influence on breast cancer recurrence.

Elevated dietary fat and obesity play important roles in the development of a variety of common cancers as well as diabetes, hypertension, and cardiovascular disease. If one accepts that the problem of obesity is environmental in nature, caused by poor food choices and lack of physical activity, then reversing obesity is an active way to prevent a number of cancers and chronic diseases from developing. The United States is currently experiencing an epidemic of obesity, affecting all ages and all ethnic groups.[10] Obesity has significant consequences for the health of the entire population, but particularly for children. Type 2 diabetes, for example, is now being seen in children (especially children with minority backgrounds). [11] Overweight children are likely to become overweight adults. The government (via healthier school lunches), educators who can promote disease prevention early in life, medical professionals, and parents must unite to stop this epidemic in our children and ensure that they enter adulthood free of the burden of avoidable chronic disease and the heightened risk of cancer.[12]

NUTRITION AND ADVANCED CANCER

Although patients with breast cancer and some other cancers maintain their weight fairly well and may even experience weight gain,[13] many patients with cancer lose weight. When this weight loss is severe, organs malfunction, infections increase, treatment tolerance decreases, and patients do not live as long.

Cancer-associated weight loss has both disease-related and treatment-related causes. Chemotherapy and radiation treatment can cause mucositis and gastrointestinal dysfunctions that result in poor food intake, and surgery on the mouth and digestive organs can create mechanical and absorption problems. The disease itself can cause anorexia, and current thinking is that this symptom comes from substances produced by the tumor, or by the body in response to the tumor, that circulate in the blood and lymph.[14]

Fully developed cancer cachexia is associated with a number of metabolic derangements that resist effective nutritional and pharmacologic treatment. These problems vary from patient to patient and can include reduced appetite, increased protein breakdown (and the resultant decrease in lean muscle mass), increased hepatic protein synthesis that may be a source of cytokines (which are associated with weight loss), increased glucose turnover and hepatic gluconeogenesis, and increased lypolysis.[14]

The contributions of external (mostly treatment-related) and internal (mostly tumor-related) factors to cachexia are difficult to determine in a cancer patient. Although treatment may shrink tumors, if patients are unable to eat or assimilate nutrients they grow weaker, progressively lose lean body mass, and may die from severe nutritional deficiencies. The process is much more complex than simple starvation.

Initial attempts to combat cancer cachexia with enteral or parenteral delivery of supplemental nutrition have not been very successful.[15] Patients retained water and added fat, but did not build up lean body mass.[16] Pharmacologic interventions have had mixed results.[14,16] Interestingly, no overt increases in tumor growth have been seen with nonvolitional feeding.[14]

The value of newer anti-cachectic strategies, such as glutamine supplementation or omega fatty acid and other lipid supplementation, must be proven in clinical trials. Until such studies are performed, the role of non-volitional nutritional support in advanced cancer remains uncertain.

FUTURE AVENUES FOR NUTRITION RESEARCH

Today, several issues in oncology nutrition remain unresolved. One is the failure of any nutritional program to reverse weight loss in patients with advanced cancer. Traditional nutritional support appears reasonable in the perioperative period, during aggressive chemotherapy and radiation therapy when eating and GI function are compromised, and in post-treatment patients who have discrete, non-tumor-related nutritional problems such as short bowel syndrome, difficulty swallowing, or esophageal obstruction. Yet all members of the health care team should understand that "to date, no intervention has consistently improved weight, strength, quality of life, body composition, and appetite in patients with advanced cancer."[16] Some interventions have increased fat mass but not lean body mass.[16,17] Neither dietary counseling, enteral supplements, nor pharmacologic approaches have reversed cancer cachexia in clinical trials,[17] although some success has been achieved in nutritional programs at specific institutions in the early stages of the disease.

Effective nutritional strategies against cancer cachexia must be based on a detailed knowledge of cachectic mechanisms. Our knowledge of these mechanisms is incomplete, although encouraging preliminary data have been obtained with omega-3 fatty acid supplementation in cachectic pancreatic cancer patients[18] and with adenosine triphosphate (ATP) infusions in advanced non-small cell lung cancer patients.[17] The modulation of acute phase

triphosphate (ATP) infusions in advanced non-small cell lung cancer patients.[16] The modulation of acute-phase responses by omega-3 fatty acid may also be useful.[17,18] The reasons that ATP infusions have positive nutritional effects are not clear, but they appear to replenish both fatty and muscle tissue.[17] Double-blind, placebo-controlled trials of both interventions, perhaps in combination, appear warranted.

Although genetic screening to discover an individual's risk for various diseases may provide useful information for nutrition researchers, the consequences of performing these tests must be considered. Is it wise, for example, to determine someone's risk of developing cancer if you cannot offer an effective intervention? Would a cancer genotype or even an obesity genotype make a person uninsurable? Effective prevention interventions, which now appear most likely to come from dietary or food-related sources, must be developed, and our risk evaluation techniques must be improved before genetic screening is done on a widespread basis. Successful prevention interventions will be achieved only through the concerted efforts of basic scientists, clinical scientists, the professional oncology team, and people who are at risk for developing cancer working together.

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