British Journal of Nutrition (2009), **102**, 334–336
doi:10.1017/S0007114508199494

Invited Commentary

When good nutrients go bad: can we predict nutrient–drug interactions?

(First published online 23 January 2009)

Classical chemotherapy for cancer and related disorders is associated with wide-ranging toxicities and limited efficacy in a number of clinical settings and relevant animal models. Based on historical use of food as medicine, the field of complementary and alternative medicine has burgeoned over the last decade. The public perception is that drugs are likely to pose significant risk to the patient but that 'natural compounds' are likely to be at worst, safe, and at best, efficacious. It is perhaps not surprising then that a significant proportion of the population are using complementary and alternative medicine (CAM) to ward off diseases such as CVD and cancer and an even greater number begin using CAM with a diagnosis of cancer with or without the knowledge of their primary care physician[1–4].

Whether clinicians should encourage or discourage the use of specific products or include CAM during cancer therapy must be based on reliable scientific evidence. Assumptions of safety and efficacy have often been derived from historical use. However, this approach fails to recognize that the practices have been applied in unique populations with specific lifestyles and cultural practices that may dramatically affect the metabolic handling of the active components. Thus, it is of primary importance to specifically test the individual and combined activity of agents in relevant model systems, before introducing them to patients. This becomes even more complicated when CAM therapies are applied on top of traditional pharmaceuticals with little or no understanding of their interactions.

In addition to potentially participating in the initial development of cancer, nutritional status can also be affected by the disease process itself, or the therapies used to eradicate disease. Weight loss is frequently observed in cancer patients, most notably in those with advanced disease. This can occur because of altered metabolism of nutrients (including protein, lipid, carbohydrate, minerals, vitamins and phytochemicals) or impaired ability of the patient to assimilate nutrients. As well, surgery, radiation and chemotherapy can alter nutritional status for both macro- and micronutrients. In addition to individual differences resulting from genetic polymorphisms that affect nutrient and drug metabolism, and differences between cancer types, sex differences and body compositional differences all affect the incidence of the cancer cachexia/anorexia syndrome or frequency of nutritional deficiencies. Furthermore, there is a growing appreciation for the role that genetic variability plays in both drug and nutrient responses within individuals or populations. Thus the picture becomes even more complicated when one attempts to predict the three-way interaction between nutrients, drugs and genes in patients.

Over the last several years there have been significant advances in our understanding of how the chemicals in foods and herbals interact with natural and synthetic drugs for the treatment/prevention of a myriad of diseases in addition to cancer[5]. Natural health products, foods, supplements, herbals and purified nutrients have all been used either singly or in combination with pharmacological agents in attempts to treat the primary disease itself, to limit drug side-effects, to prevent normal tissue injury or promote rehabilitation of normal tissues, or prevent the development of drug-related nutrient deficiencies. Many of these studies have had positive outcomes in that combinations provided additive or synergistic effects with drugs leading to decreased symptoms of cachexia, improved gastrointestinal function, maintenance of, or improved, immune function, or increased anti-tumour activity[5]. However, a number of combination studies have demonstrated negative effects of specific nutritional compounds on cancer chemotherapy. While one can suggest avoidance of strictly 'antagonistic' components[6,7], what is to be done when specific nutrient–drug combinations appear to have benefit? Can we assume that combining two different nutrients, with individually positive profiles, will improve outcome when combined with the drug of interest? From the results of the article by Xue *et al.*, published in this issue of the *British Journal of Nutrition*[8], it would appear the answer is no. They demonstrate that the apparent beneficial effects of long-chain *n*-3 fatty acids (DHA and EPA) or the amino acid glutamine, on complications associated with tumorigenesis itself, or chemotherapy-related efficacy and toxicity, are primarily ameliorated, and in some cases actually worsen, when used in combination with irinotecan (7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxy-camptothecin; CPT-11)/5-fluorouracil (5-FU) for the treatment of colon carcinoma in an animal model. This negative interaction could not have been predicted based on our current understanding of the individual actions of DHA and EPA or glutamine on tumorigenesis, immune complications and tissue toxicity or the cachexia associated with this class of drugs in this specific tumour model, or in the few clinical trials carried out to date.

Some of the earliest studies examining the benefits of nutritional supplementation in clinical populations focused on decreasing cancer cachexia as this aspect of the disease had a major impact on quality of life, morbidity and mortality. Initial studies largely focused on cancers of the pancreas,

lung, and head and neck as tumours at these sites tend to have poorer prognosis and fewer effective therapies than other solid tumours. More recently, the benefits of supplementation have begun to be examined in a wider variety of tumour types. Both glutamine and long-chain *n*-3 fatty acids have been shown to have anti-cachectic and/or immunomodulatory activity in both animal models and clinical populations[9–14]. Studies have shown that DHA/EPA can improve recovery following surgery, radiation and pre-, post- and during chemotherapy by a number of mechanisms involving changes in mucosal barrier and absorptive function, direct anti-tumour activity or inhibition of tumour progression, changes in drug transport or pharmacokinetics, modulation of inflammatory and other cytokines, and preservation or rehabilitation of the haematopoietic compartment including bone marrow stem cells[15–31]. Similarly, glutamine has been shown to reduce toxicity associated with radiation and chemotherapy and may promote bone marrow survival and repopulation of specific blood cell types[32–34].

Because some of the proposed cellular targets of glutamine and *n*-3 action appear to be overlapping (e.g. immune cells, control of cytokine profiles, enhancement of normal cell proliferation, decreasing muscle proteolysis), one might have imagined that putting the two supplements together with chemotherapy would have additional benefit. If the two agents were acting on exactly the same metabolic pathways, then at worst the combined effect would be the better of *n*-3 + chemotherapy, or glutamine + chemotherapy. This hypothesis was directly tested by Xue *et al.*[8] using the Ward colon tumour model using a typical chemotherapeutic regimen of CPT-11 and 5-FU. This model recapitulates many of the metabolic and haematopoietic changes observed in patients suffering from colon cancer both in the untreated phase and following chemotherapy. In their previous studies they had demonstrated that individually glutamine and *n*-3 fatty acids improved outcomes in the Ward tumour model in response to CPT-11[35,36]. The cancer-related changes in leucocyte counts, including neutrophils, lymphocytes and monocytes, were normalized by either *n*-3 or glutamine in the pre-chemotherapy tumour-bearing animals, and the typical leucocytosis that results following chemotherapy was largely averted. However, animals given chemotherapy and co-supplemented with *n*-3 and glutamine showed the typical leucocyte abnormalities similar to animals given no chemotherapy. Supplementation with either *n*-3 or glutamine also had direct antitumour effects that were enhanced in the presence of chemotherapy (i.e. decreased tumour mass) and also decreased body weight loss, anorexia and muscle wasting associated with CPT-11/5-FU therapy. Combination therapy with both supplements (*n*-3 + glutamine) did not provide added benefit either in the absence or presence of chemotherapy. In fact, the benefits gained with individual treatment (i.e. body weight, food intake, muscle weight and immune parameters) were largely lost in the *n*-3 + glutamine situation.

As Xue *et al.*[8] point out, enteral and parenteral formulas containing *n*-3 fatty acids + glutamine (and often including other nutrients such as nucleosides, arginine and some vitamins) have been used clinically for several years as possible immunomodulatory agents and to improve recovery of trauma, burn and surgery patients[21,37–39]. While possibly efficacious in these specific situations, in fact many of these combinations have not been compared to the individual activities of the components in the mixtures. It is entirely possible that the mixtures are less effective than individual nutrients. Without specifically testing each combination, one simply cannot determine either the safety or efficacy. Couple this with the additional complications posed by a tumour-bearing host and metabolic changes imposed by chemotherapy, and the outcomes become even less predictable. When considering the very large number of nutrients and phytochemicals proposed to have activity in cancer development and possibly in cancer therapy, and the current models available for study, an unmanageable number of combinations to be tested emerge. Therefore, future research needs to focus on the specific molecular targets for each of these agents using genomic, proteomic and metabolomic approaches. Together with computer modelling and bioinformatics this new data may provide the platform for predictions of nutrient–nutrient, nutrient–drug and nutrient–gene interactions essential to the development of efficacious complementary and alternative therapies for cancer and other chronic diseases.

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British Journal of Nutrition