REVISTA DE INVESTIGACIÓN CLÍNICA

Contents available at **PubMed**
www.clinicalandtranslationalinvestigation.com

PERMANYER

Rev Inves Clin. 2018;70:136-46 BRIEF REVIEW

Use of Functional Foods and Oral Supplements as Adjuvants in Cancer Treatment

Guadalupe Serna-Thomé[1,§], Denisse Castro-Eguiluz[2§], Vanessa Fuchs-Tarlovsky[3], Miriam Sánchez-López[1], Luis Delgado-Olivares[4], Jaime Coronel-Martínez[1], Eva María Molina-Trinidad[4], Martha de la Torre[5] and Lucely Cetina-Pérez[1*]

[1]Departments of Nutrition, Medical Oncology, and Clinical Research, Instituto Nacional de Cancerología, Mexico City; [2]Consejo Nacional de Ciencia y Tecnología (CONACyT) - Department of Clinical Research, Instituto Nacional de Cancerología, Mexico City; [3]Department of Nutrition, Hospital General de México, Mexico City; [4]Department of Biopharmacy, Universidad Autónoma del Estado de Hidalgo, Pachuca, Hgo., Mexico; [5]Department of Thoracic Oncology, Universidad Nacional Autónoma de México, Mexico City, Mexico.

ABSTRACT

In cancer patients treated with radiotherapy to the abdominopelvic region, dietary modifications and the use of functional foods (fortified food with added ingredients to provide specific health improving benefits, such as antioxidants, omega-3 fatty acids, and glutamine), may contribute to the improvement of the toxic effects of treatment, including nausea, diarrhea, and constipation, among others. With the aim of analyzing which coadjuvant foods benefit these patients, scientific evidence was gathered by a group of experts. For these patients, the authors recommend a diet that includes sufficient foods rich in antioxidants and polyphenols instead of supplements. Docosahexaenoic and eicosapentaenoic acids have proven useful for the management of anorexia/cachexia in pancreatic cancer patients. Probiotics composed of *Lactobacillus* spp. and *Bifidobacterium* spp. are regarded as safe even in patients with neutropenia and have been proven to decrease gastrointestinal symptoms. Several factors should be considered before probiotic supplementation, these include the stage of the disease, radiation dose, and symptomatology of each patient. There is no demonstrated clear benefit to the use of glutamine, so it is not recommended due to its high cost. (REV INVES CLIN. 2018;70:136-46)

Key words: Pelvic Cancer. Radiotherapy. Chemotherapy. Functional Food. Supplement.

Corresponding author:
*Lucely Cetina Pérez
Instituto Nacional de Cancerología
Av. San Fernando, No. 22
Col. Sección XVI, Del. Tlalpan
C.P. 14080, Ciudad de México, México
E-mail: lucelycetina.incan@gmail.com

[§]These authors contributed equally to this work.

Received for publication: 03-03-2018
Accepted for publication: 03-05-2018
doi: 10.24875/RIC.18002527

INTRODUCTION

The concept of functional foods was introduced in Japan in the 1980s with the intention of using foods to decrease the risk of contracting diseases and hence, improve health and quality of life. The definition of functional food, according to the ESPEN guidelines, is "food fortified with additional ingredients or with nutrients or components intended to yield specific beneficial health effects"[1].

On the other hand, food supplements are "food products that supplement the normal diet and which are concentrated sources of nutrients (e.g., vitamins or minerals) or other substances with a nutritional or physiological effect, alone or in combination, marketed in various dose forms: capsules, tablets and similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar oral dosage forms, and liquids and powders designed to be taken in measured small unit quantities"[1].

In general terms, these are foods that are consumed as part of a usual diet and contain biologically active components that decrease the risk of developing various diseases. Some examples include antioxidants, eicosapentaenoic acids (EPA), glutamine, or foods fortified with these components that are not naturally occurring in food or that may be lost in the preparation process. They also refer to the addition of live active microorganisms or probiotics that benefits the body.

Favorably modified foods and lifestyle, in general, may contribute to ameliorate the adverse effects resulting from chemoradiotherapy to the abdominal and pelvic regions, thus promoting the completion of cancer treatment, decreasing expenses to the patient and the health-care institution, and improving patient quality of life.

GLUTAMINE

Glutamine is the most abundant non-essential amino acid in the body, with a blood concentration of 0.6-0.9 mmol/L. It includes an α-amino group, an α-carboxylic acid group and a side chain amide; therefore, it is the most important circulating nitrogen transporter, accounting for 30-35% of all amino acid nitrogen transported in blood. Glutamine serves as a vehicle for ammonia transportation in a nontoxic form[2]. Cancer cells are important consumers of glutamine, and they compete with the host for the circulating molecule. As a consequence, changes in glutamine metabolism have been observed in different organs, as well as glutamine depletion in the host with tumor progression. Glutamine has been shown to be an energy source in cancer cells since it is an oxidation substrate in the mitochondria of neoplastic cells and correlates with increased glutaminase activity. It is also used in nucleotide synthesis. Over time, the tumor becomes the main glutamine consumer, "stealing" up to 50% of circulating glutamine. Furthermore, glutamine has been observed to be synthesized *de novo* by cancer cells, since it is indispensable for cell proliferation and tumor growth. Intestinal glutamine extraction decreases as the tumor grows, and this is associated with a marked drop in mucosal glutaminase activity. Furthermore, the incidence of bacterial translocation increases, suggesting the presence of a defect in the gut mucosal barrier or in the gut immune function[2].

In terms of glutamine supplementation, an efficient dosage must be at least 0.2 g/kg/day, administered for several days; however, some studies in humans suggest that a dosage of 0.5 g/kg/day is safe. Patients supplemented with glutamine present a lower incidence of bacteremia. In general, in critically ill patients, supplementation with glutamine has been proven to improve T-cell response, B-cell, and macrophage function, the function of the intestinal mucosa, and it decreases the infection rate and hospital stay duration[3]. Level of evidence B, strength of recommendation 2.

Several functions of glutamine may play a role in gut protection during radiotherapy. First, glutamine contributes to trophism, since the small intestine is the body's main glutamine consumer. Second, glutamine is the precursor of glutathione, a key molecule in the antioxidant chain. Third, glutamine modulates the inflammatory response in different cells of the immune system and regulates cytokine production. Finally, glutamine protects cells from diverse insults, including heat shock proteins and apoptosis[4]. Therefore, cancer treatment nutritional support with supplemental glutamine has been considered to hasten the healing process of the intestinal injury resulting from

chemoradiotherapy; this is based on the observation that glutamine supplementation reduces the incidence of bacteremia and improves survival. In studies performed in rats, an oral diet enriched with glutamine, administered before abdominal radiation, has been proven effective as a radioprotector. Hence, providing glutamine to patients undergoing abdominopelvic radiotherapy may protect the intestinal mucosa from injury, accelerate the healing process in the irradiated gut, and possibly attenuate the long-term secondary side effects of radiation-induced enteritis[2]. Level of evidence B, strength of recommendation 2.

To determine whether glutamine participates in the prevention of radiation-induced acute enteritis, a randomized clinical trial analyzed patients treated with pelvic radiotherapy and supplemented with glutamine (30 g/day). This intervention group was compared to a control group in which patients received a placebo. Enteritis was diagnosed according to the Radiation Therapy Oncology Group scale; intestinal inflammation was determined with fecal calprotectin, and gut integrity with citrulline. More patients developed enteritis with glutamine than with placebo (55.9% vs. 22%, p = 0.002), with an hazard ratio of 1.59 (95% confidence interval, 0.62-4.05). There were no differences in calprotectin levels, and citrulline levels were also similar between groups. The authors concluded that glutamine did not prevent the development of enteritis during radiotherapy. Therefore, the use of glutamine for the prevention of radiation-induced acute enteritis is not recommended, since it can even promote the development of intestinal toxicity[4]. Level of evidence A, strength of recommendation 1.

In another study, the protective effect of glutamine in radiation-induced diarrhea was evaluated[5]. Patients receiving glutamine (15 g/3 times a day) were compared with patients receiving placebo. The severity of diarrhea was assessed according to the National Cancer Institute Common Toxicity Criteria version 3.0, whereby the need for loperamide, the need for parenteral therapy, and the withdrawal or interruption of treatment due to diarrhea was evaluated. No differences were observed in the incidence of diarrhea between groups. However, when analyzing the severity of diarrhea, none of the patients treated with glutamine had Grade 3 or 4 diarrhea while in the group that received placebo, 69% patients developed Grade 3 or 4 diarrhea. There was no interruption in the cancer treatment of patients receiving glutamine. The authors concluded that glutamine may have a protective effect in the prevention of radiation-induced severe diarrhea[5]. Level of evidence B, strength of recommendation 2.

From the above discussion, it may be concluded that cancer cells exhibit a high rate of anabolic metabolism, similar to that of highly proliferative normal cells, such as mucosal cells in the gut and cells of the immune system. Cancer cells acquire great amounts of glucose and glutamine and use these nutrients to feed the tricarboxylic acid cycle and oxidative phosphorylation, as well as the pentose phosphate pathway for the synthesis of nucleotides, amino acids, and lipids. Together, these pathways generate sufficient cellular components to allow cell proliferation. Increases in the generation of reactive oxygen species in metabolically active cells require the production of adequate levels of antioxidants, including the reduced form of glutathione, that is generated from glutamine by the enzyme glutathione reductase[6].

This metabolic process in cancer cells explains why the tumor acquires most of the available glutamine, as well as the deleterious effects on cells from the intestinal wall and the immune system, since glutamine is scarce. Based on these considerations, it could be expected that glutamine supplementation has a beneficial effect by attenuating radiation-induced enteritis and providing the elements necessary for prompt healing of the intestinal injury. However, a clear benefit supporting glutamine supplementation has yet to be established in patients undergoing radiation. Although studies in rats and mice have demonstrated a protective effect, clinical assays in humans have been contradictory. Therefore, glutamine supplementation is not recommended until further clinical studies are conducted, and a protective effect is consistently demonstrated.

DOCOSAHEXAENOIC ACID (DHA)

DHA is a long-chain polyunsaturated fatty acid from the omega-3 family; it contains a 22-carbon chain and 6 cis double bonds. The concentration of DHA in plasma and tissues is determined mainly by dietary intake. The strongest evidence of the benefit of DHA is related to its unique role in visual and cognitive

development and function. DHA is found at high concentrations in the phospholipids of neural cell membranes, where it serves several physiologic functions, including the regulation of membrane fluidity, the release of neurotransmitters, genetic expression, myelination, and cellular differentiation, and growth[7]. Supplementation with EPA and DHA has been shown to decrease systemic inflammation and oxidative stress and also harbors anti-inflammatory effects. The increase in DHA intake is reflected in its concentration in membrane phospholipids, thus modulating several signaling pathways. This incorporation of DHA into cell membranes leads to the generation of anti-inflammatory lipid mediators involved in the resolution of inflammation, such as resolvins, protectins, and maresins. Clinical trials and observational studies have reported that EPA and DHA seem to be efficient in decreasing inflammation in rheumatoid arthritis, while in inflammatory bowel disease and asthma, results have been inconsistent. Among the beneficial effects observed in cancer, omega-3 fatty acids have been proven to possess anti-neoplastic activity by inducing apoptosis of human cancer cells and increasing their sensitivity to conventional anticancer therapies without affecting normal cells[7].

Some essential fatty acids are selectively toxic to cancer cells, an effect due in part to the production of superoxide. They have a modulatory function in the cellular motility of the tumor, its invasive capacity and metastatic behavior, through regulatory mechanisms mediated by cell adhesion molecules, tumor suppressing molecules, and transduction pathways active in cell motility[8].

Some studies performed *in vitro* and in murine models have demonstrated certain properties that make these fatty acids attractive options in cancer treatment. Among other functions, they modify the cell membrane phospholipids, cellular motility functions, and their invasive potential; they are toxic to cancer cells; they alter the sensitivity of cancer cells to chemotherapeutic agents and radiation. In addition, they exert a protective role in normal tissues exposed to radiation, and they display low toxicity in normal cells[8].

In a case–control study in postmenopausal breast cancer patients, adipose tissue from the gluteus was used as an indicator of exposure to polyunsaturated fatty acids[9]. There was no significant inverse association between n-3 fatty acids and the risk of breast cancer. However, when the balance among different types of polyunsaturated fatty acids was examined, an inverse association was found between the n-3/n-6 ratio and breast cancer. These data support the hypothesis that n-3 fatty acids may inhibit the development of breast cancer, depending on the levels of n-6 fatty acids. It is important to emphasize the importance of considering all lipid components to evaluate their role in cancer[9]. Level of evidence B, strength of recommendation 2.

The importance of lipoperoxidation products must also be recognized. They were considered harmful by toxicologists, but now lipoperoxidation products are recognized as useful metabolites, importantly involved in tumor growth control and tumor sensitization to anticancer treatment. Incorporation of n-3 fatty acids in tissues provides excellent substrates for lipoperoxidation. This selective cytotoxic effect on cancer cells, apparently caused by the loss of efficacy of several antioxidant mechanisms during malignant transformation, is a promising clinical application[9].

Fish oil, rich in DHA, has proven to induce suppression of human breast carcinoma in a nude mice model[10]. In a similar study, the effects of different types of fatty acids were studied (corn oil, butter, beef tallow, or fish oil) in breast cancer tumors in nude mice[11]. Fish oil prevented tumor growth while corn oil permitted the development of the tumor. However, when mice were fed fish oil and Vitamin E, the tumor-suppressing effect was lost, and the tumor grew to a volume similar to that from mice fed corn oil. On the other hand, when mice were fed fish oil and ferric citrate, the lipoperoxidation products increased and the tumor volume decreased. Therefore, it is confirmed that lipid peroxidation in the tumor is responsible for the suppression of tumor growth when the diet is supplemented with n-3 fatty acids[11]. Level of evidence C, strength of recommendation 2.

The cytotoxic mechanism induced by fatty acids does not involve a gradual commitment of the cell to its death; that is, the event that triggers cell death is an oxidative phenomenon that occurs over a short time period, minutes or hours instead of days, since it is completely blocked by Vitamin E[12].

Furthermore, when the cytotoxic potential of other fatty acids containing 2, 4, 5, or 6 double bonds was analyzed, this potential changed with the ability of fatty acids to stimulate the production of superoxide-free radicals. Fatty acids containing 3 or 4 double bonds were the most able to produce free radicals, therefore the most toxic. On the contrary, fatty acids containing 6 double bonds were less effective in producing free radicals, and therefore the least toxic. Iron and copper accelerate cellular death, and Vitamin E inhibits their effect. For this reason, the efficacy of fatty acids in killing cancer cells has been confirmed and is related to the enhancement of lipid peroxidation[13]. Level of evidence C, strength of recommendation 2.

In cervical cancer patients, the effect of n-3 fatty acids has not yet been studied, not even in murine models. Still, *in vitro* assays using human cervical cancer cells (HeLa) have demonstrated that the addition of EPA and DHA is cytotoxic to these cells[14]. Moreover, the addition of several antioxidants to the culture, in particular, Vitamin E, prevented the cytotoxic action of fatty acids. These results confirm that the cytotoxic effect induced by fatty acids is a process that depends on free radicals and lipid peroxidation[14]. Level of evidence C, strength of recommendation 2.

Furthermore, in human colon cancer cells (Caco-2), the addition of a fish emulsion to the cell culture induced apoptosis and arrested cell proliferation in the G2/M stages, in a dose- and time-dependent manner. Joint administration of fish oil and 5-fluorouracil (5-FU) resulted in a significant increase in cell growth inhibition compared to that exhibited by each substance alone. This combined treatment was demonstrated to increase the accumulation of cells in the cell cycle S phase. The combination of fish oil and the chemotherapeutic agent thus results in an additive effect on the inhibition of cellular growth[15]. Level of evidence C, strength of recommendation 2.

Cancer cachexia syndrome is one of the main contributors to morbidity and mortality in patients with advanced malignancy, and it is characterized by massive body weight loss. Although food intake must be incremented in the cachectic patient, lean mass gain is difficult to achieve unless metabolic abnormalities are improved. The mediators responsible for these metabolic changes are produced by the tumor as well as the host and include pro-inflammatory cytokines, neuroendocrine mediators, and some factors specifically produced by the tumor. In addition to its anticancer effects, the omega-3 fatty acid EPA has been proven to possess anti-cachectic properties in a murine colon cancer model. The administration of EPA capsules has been associated with body weight stabilization in patients with advanced pancreatic cancer[16]. These benefits may be related to the anti-inflammatory effects of n-3 fatty acids. To improve the quality of life of cachectic patients, it is necessary not only to stabilize their body weight but also to restore the lean mass consumed during the disease process. For this reason, this study compared the effect of a protein and an energy supplement containing EPA and antioxidants with an isocaloric supplement as a control, in cachectic patients with pancreatic cancer. Weight, body composition, dietary intake, and quality of life were evaluated. The authors found that both supplements stopped weight loss in patients, but only the supplement containing EPA resulted in lean mass gain and improvement in patient quality of life[16]. Level of evidence A, strength of recommendation 1.

Both n-3 fatty acids, EPA and DHA, suppress the production of pro-inflammatory cytokines, increase insulin sensitivity, increase the synthesis of endogenous nitric oxide, increase the concentration of acetylcholine in the brain, and protect neurons from the cytotoxic action of tumor necrosis factor-alpha. The interaction of the aforementioned components suggests that EPA and DHA are useful for the management of anorexia/cachexia induced by cytokines in inflammatory conditions, such as cancer[17]. Level of evidence B, strength of recommendation 1.

Concurrently, the existing evidence suggests that n-3 fatty acids, EPA and DHA, have promising effects due to their cytotoxic action on cancer cells and their anti-inflammatory properties. Even so, clinical trials in cervical cancer patients have not yet been performed, which is why the use of supplements with these fatty acids is not recommended until adjuvant, anti-cachectic and anti-inflammatory effects in cervical cancer patients undergoing concomitant chemoradiotherapy are demonstrated.

ANTIOXIDANTS

During cancer development, a chronic state of oxidative stress is generated due to a decrease in endogenous antioxidant levels, such as superoxide dismutase, glutathione peroxidase, and exogenous antioxidants, including Vitamins C, E, β-carotene, and selenium[18,19]. Oxidative stress may affect several cancer cell functions, including proliferation, genetic instability and mutations, alterations in cellular sensitivity to anticancer agents, invasion, and metastasis. Oxygen radicals increase the production of the angiogenic factors interleukin-8 and vascular endothelial growth factor, and the secretion of matrix metalloproteinase-1; consequently, oxidative stress leads to tumor angiogenesis. In a study in bladder cancer patients, a redox imbalance was observed to correlate with the grade and stage of the disease, on account of a decrease in the levels of antioxidant vitamins and enzymes[18]. Oxidative stress increases during chemoradiotherapy treatment and leads to secondary effects that compromise the patient's quality of life. Hence, supplementation with antioxidants as prophylactic agents has been proposed in cancer prevention and treatment, and they may also attenuate the secondary effects of treatment and improves the patient's quality of life[19]. Still, there is great controversy on the subject, since several clinical trials have obtained different results in favor or against the use of antioxidants during cancer treatment.

A randomized clinical trial analyzed the effects of antioxidant supplementation in women diagnosed with cervical cancer and undergoing chemoradiotherapy. The intervention group received a mixture of antioxidants (200 IU each of Vitamins C and E, 4.8 mg of β-carotene, and 15 mg of selenium) for a period of 6 weeks, and the control group received a placebo. While a significant difference was not observed in lipid oxidative damage, a significant reduction in protein carbonylation and stabilization of hemoglobin levels were described, which appeared to improve the quality of life of patients. Another important finding was that although patients consumed more energy than recommended, they did not fulfill their antioxidant requirements with diet alone[20,21]. Level of evidence A, strength of recommendation 2.

On the other hand, a study analyzed the effect of an antioxidant supplement on the prevention of nephrotoxicity induced by cisplatin in patients with cervical cancer[22]. The supplement contained 4.8 mg of β-carotene, 200 mg of Vitamin C, 200 IU of Vitamin E, 50 μg of selenium, and 15 mg of zinc. No differences were found when compared to control patients who received placebo. This study demonstrated that antioxidant supplementation does not prevent cisplatin-induced nephrotoxicity[22]. Level of evidence A, strength of recommendation 1.

In addition, the meta-analysis reported in the ESPEN guidelines in 2016, analyzed 230,000 cancer patients and reported that the use of β-carotene, Vitamin A or Vitamin E supplements increased the mortality rate[23]. On the other hand, supplementation with 400 IU of Vitamin E and 500 mg of Vitamin C, over a 10 year-period in men 50 years of age or older, had no effect on cancer incidence in the short or long terms[24]. Furthermore, long-term supplementation with 400 IU of Vitamin E and 200 μg of selenium had no beneficial effect on the incidence of prostate cancer[23,24]. Level of evidence A, strength of recommendation 1.

Within the group of antioxidants, polyphenols have been widely studied. Epidemiological studies have revealed that regular consumption of foods rich in polyphenols is associated with a lower risk of developing cancer. In recent years, research has demonstrated that several phenolic compounds, commonly present in some foods and medicinal plants, may exert both effects, chemopreventive and anticancer, due to their unique dual effect on cellular redox regulation. It seems they promote an antioxidant effect that leads to the prevention of carcinogenesis in normal cells, and in cancer cells, they exert a pro-oxidant effect that favors cell death. Some of the mechanisms through which they exert these pro-oxidant actions depend on their high concentration, an elevated pH, and the presence of transition metals; the mechanisms include a temporary decrease in copper, the generation of reactive oxygen species, and alteration in the function of glutathione, and glutathione S-transferase. The chemopreventive effect of antioxidant polyphenols involves their ability to prevent or reduce cellular injury mediated by oxidative stress, and by inducing the expression of genes that encode detoxifying enzymes, among others. However, although several pre-clinical studies have described a potential anticancer activity of diet-derived antioxidants, including selenium, Vitamins E and C,

and β-carotenes, most clinical trials have failed to demonstrate a clear decrease in cancer risk with antioxidant supplementation. Polyphenols such as epigallocatechin gallate (from green tea), curcumin and resveratrol, increase the levels of hydrogen peroxide in cancer cells, promoting apoptosis, and in cervical cancer cells, and autophagy[25]. This effect is prevented with pharmacological treatment attenuating the oxidative stress. Different mechanisms are involved in the cytotoxic effects of polyphenols on cancer cells, including damage to DNA, activation of nicotinamide adenine dinucleotide phosphate oxidase, mitochondrial dysfunction and apoptosis, inhibition of cellular antioxidant defenses and interaction with metal ions. Since polyphenols may act as antioxidants or prooxidants, depending on the cellular target, their administration along with conventional chemo or radiotherapy has been proposed as a promising strategy favoring the selective death of cancer cells, decreasing drug resistance and in the prevention of the deleterious effects of anticancer therapy on normal cells[26,27]. Level of evidence C, strength of recommendation 2.

Based on the evidence generated from clinical trials, it is recommended that cervical cancer patients follow a diet which includes sufficient foods rich in antioxidants and polyphenols. There is no evidence against the use of supplements with 200 IU of Vitamin E, 200 mg of Vitamin C, 4.8 mg of β-carotene, 50 µg of selenium, and 15 mg of zinc, during treatment with chemoradiotherapy. The use of supplements based on high doses of Vitamin A, Vitamin E, and β-carotenes is not recommended, unless a deficiency is present. Due to their pro-oxidant effect, the use of supplements with polyphenols cannot be recommended, but the dietary intake of foods rich in polyphenols is certainly suggested.

PREBIOTICS AND PROBIOTICS

The development of intestinal microflora is the basis for the ability of the intestinal barrier to prevent pathogenic bacteria from invading the gastrointestinal tract. An adequate balance of intestinal microflora and a healthy mucosal immune system confer protection. Quantitatively, the most important bacterial genera are *Bacteroides* and *Bifidobacterium*. Gut-associated lymphoid tissue (GALT) is the most represented in the body. Colonic microflora is the main antigenic stimulus for specific immune responses locally and systemically. Abnormal immune responses to commensal antigens as well as local inflammatory reactions may, as a secondary event, harm intestinal function causing a breach in the intestinal barrier[28].

Probiotics are defined as live organisms pertaining to food ingredients that are beneficial to health. Prebiotics are defined as non-digestible products that, when metabolized by intestinal microorganisms, modulate gut microbiota composition and activity, generating a beneficial physiologic effect on the host; furthermore, fermentation products condition specific changes in the composition and activity of gastrointestinal microbiota, conferring a benefit for the health of the host; they are also known as non-digestible substances in the diet, that selectively stimulate the growth and activity of different bacteria in the colon, benefiting the health of the host[28]. Combinations of prebiotics and probiotics benefit the host by increasing the establishment and survival of live microorganisms in the gut[29]. In terms of their chemical structure, prebiotics are fundamentally fructo- and galacto-oligosaccharides. They are considered non-digestible macromolecules because in humans, enzymes in the gut are unable to hydrolyze them, but they are partially fermented by colonic bacteria. In addition to non-digestible carbohydrates, some peptides and lipids (esters and ethers) are considered prebiotics because they are endogenous bacterial substrates in the colon that provides energy, metabolic substrates, and micronutrients[29,30].

A food ingredient must contain certain properties to be considered a prebiotic: it must be of vegetal origin, form part of a group of complex heterogeneous molecules and not be part of the process of the host's enzymatic digestion[29]. Examples of prebiotics include lactulose, fructans such as inulin, trans-galactooligosaccharides, polydextrose, soy oligosaccharides, lactosucrose, isomalto-oligosaccharides, and glucans among others. Some prebiotics occur naturally in various foods such as leeks, asparagus, chicory, Jerusalem artichoke, garlic, onion, wheat, oatmeal, and soybeans[31].

Probiotics confer protective functions to the digestive system. Their protective effect consists in an

antagonism that hinders pathogen replication and toxin production, due to competition for nutrients or sites of adhesion; they also act on GALT modulation, inducing an increase in immunoglobulin A production, activation of mononuclear cells, activation of lymphocytes, and the production of cytokines[28,29].

A key aspect of probiotics is their ability to exert an effect distant from the site of administration. This may occur through the transfer of organisms, for example, from the intestine to the mammary glands in lactating women, and through the production of molecules that are either absorbed through the intestine or that influence compounds in the host directly or indirectly. Examples include the decrease in blood cholesterol or the decrease in severity and duration of infections in respiratory pathways through immune mediators; another distant effect is observed in the brain, to which the probiotic *per se* does not enter but rather exerts an effect through the molecules they produce, such as neurochemicals. They may also promote their production by the host and reach the brain at least through the vagus nerve system. The most important species of probiotics studied specifically in search of these characteristics have been *Bifidobacterium*, *Lactobacillus*, and *Streptococcus*[32].

Diarrhea has been widely discussed as one of the most damaging secondary effects of treatment with chemoradiotherapy to the abdomen and pelvis; it affects the quality of life of patients and may even lead to the interruption or discontinuation of treatment. Radiotherapy may cause changes in bacterial flora, in the vascular permeability of the mucosa and in intestinal motility. Moreover, chemotherapy disrupts the composition of native intestinal microflora, which is significant to the metabolism of several intestinal enzymes, the regulation of intestinal angiogenesis and immunological functions that maintain the integrity of the intestinal barrier. Some clinical assays have proven the efficacy of probiotics in patients undergoing concomitant pelvic radiotherapy and chemotherapy[33].

In a systematic review, the efficacy and safety of probiotics were evaluated for the prevention of chemoradiotherapy-induced diarrhea in patients with abdominal and pelvic tumors. Probiotics were found to prevent diarrhea caused by chemoradiotherapy; in particular, the incidence of Grade >2 diarrhea is significantly reduced by the use of probiotics. It has also been proven that probiotics rarely cause adverse effects in these patients[33]. Level of evidence A, strength of recommendation 1.

A clinical trial studied the effect of orally administered *Bifidobacterium breve* (the fermented dairy beverage, Yakult) in pediatric patients subjected to chemotherapy, in terms of their ability to resist infections and the composition of their fecal microflora and intestinal environment. The frequency of fever and the need for antibiotics was lower in the group who received the probiotic compared to the placebo group. Furthermore, the use of the probiotic promoted the growth of anaerobic bacteria while disruption of the intestinal microbiota following chemotherapy was more pronounced in the placebo group. Therefore, administration of *B. breve* could be beneficial in immunocompromised patients by improving their intestinal environment[34]. Level of evidence B, strength of recommendation 1.

In patients with colorectal cancer undergoing chemotherapy (5-FU), supplementation with *Lactobacillus rhamnosus* and guar gum decreased the frequency of Grade 3 and 4 diarrhea, patients reported less abdominal distress, fewer patients required hospitalization and warranted fewer dose reductions due to intestinal toxicity, in comparison with patients who received placebo[35]. Level of evidence B, strength of recommendation 2.

A double-blind randomized clinical trial studied the efficacy and tolerability of *L. rhamnosus* in patients with radiation-induced diarrhea. Patients who received probiotics reported better fecal consistency and decreased bowel movements, compared to patients who received placebo. Hence, probiotic supplementation was found to be beneficial[36]. Level of evidence A, strength of recommendation 1.

Giralt et al. studied the effects of the probiotic *Lactobacillus casei* in the prevention of radiation-induced diarrhea in patients with gynecological cancer[37]. In this double-blind study, patients with cervical or endometrial cancer undergoing pelvic radiotherapy were randomly assigned to a probiotic drink containing *L. casei* or placebo. Diarrhea classified as Grade 2 or above and the use of loperamide was no

difference between groups (p = 0.568). However, probiotic intervention had a significant effect on stool consistency (p = 0.04), and the study concluded that *L. casei* did not decrease the incidence of radiation-induced diarrhea[37]. Level of evidence A, strength of recommendation 1.

In a pilot study, Delia et al. analyzed the effect of VSL#3, a high-potency preparation of probiotic lactobacilli, in decreasing the rate and severity of radiation-induced diarrhea during radiotherapy after surgery for abdominal and/or pelvic cancer. Each sachet of VSL#3 contained 450 billion/g of viable lyophilized bacteria, including *L. casei, Lactobacillus plantarum, Lactobacillus acidophilus, Lactobacillus delbrueckii* subsp. *bulgaricus, B. longum, B. breve, B. infantis,* and *S. salivarius subsp. thermophilus.* More patients within the placebo group had radiation-induced diarrhea, compared with the VSL#3 group (p < 0.001), and patients within the placebo group had a more severe disease than those in the probiotic group.

The results from this study indicate that bacteriotherapy with this probiotic preparation may protect patients against the risk of radiation-induced diarrhea. Moreover, it is a safe treatment, even in cancer patients treated with radiotherapy[38].

A subsequent double-blind, placebo-controlled clinical trial conducted by the same author, investigated the efficacy of this high-potency probiotic preparation in the prevention of radiation-induced diarrhea in cancer patients. 490 patients were randomized to receive probiotics (VSL#3) or placebo following adjuvant post-operative radiation therapy; the authors observed that patients within the placebo group had significantly more diarrhea than those who received probiotics (p < 0.001). Furthermore, patients who received the probiotic intervention had significantly less Grade 3 and 4 diarrhea compared with patients to whom placebo was administered (p < 0.001). Probiotic bacteria are a safe and feasible option to protect cancer patients from radiation-induced diarrhea[39]. Level of evidence A, strength of recommendation 1.

Chitapanarux et al. conducted a prospective, double-blind, placebo-controlled, and randomized trial, in which 63 patients with cervical cancer were treated concomitantly with cisplatin and pelvic radiotherapy[40]. Patients were randomized to receive a probiotic containing *L. acidophilus* and *Bifidobacterium bifidum,* or placebo, twice a day during radiotherapy. Grade 2 or 3 diarrhea were observed in 45% of patients who received placebo versus 9% of patients who received probiotics (p = 0.002). In addition, the need for antidiarrheal medication was present in 32% of patients who received placebo versus 9% of patients who received the probiotics (p = 0.03).

The prevalence of liquid stools was 65% in placebo patients, compared to 19% in patients on probiotics (p < 0.001). It thus appears that probiotic supplementation had significant benefits in cervical cancer patients undergoing concomitant chemoradiotherapy[40]. Level of evidence A, strength of recommendation 1.

Randomized clinical trials are not yet sufficiently conclusive to recommend the use of prebiotics; nevertheless, their administration may help improve cancer treatment. Concurrent administration of prebiotics and probiotics may prevent adverse effects from oncology treatments, particularly from pelvic radiotherapy[41].

Probiotics fall in the category of organisms generally recognized as safe. There is concern about the administration of probiotics in cancer patients, on account of the risk of infection and the transfer of antibiotic resistance. That said, randomized clinical trials have not reported a significant increase in the risk of developing adverse effects following probiotic supplementation, when compared to patients who received placebo; on the contrary, probiotics have been proven safe and beneficial in these patients[41].

Current evidence supporting the use of probiotics as joint therapy with concomitant chemoradiotherapy is strong, particularly in cervical cancer patients. Clinical assays vary in terms of the study strain and dosage. Some studies report beneficial effects on certain toxicity manifestations secondary to chemoradiotherapy, particularly the prevention of Grade 3 and 4 diarrhea, and this is consistent in the analyzed studies. In addition, with the available current evidence, the administration of live probiotic microorganisms is considered safe even in cases of neutropenia; hence, probiotic treatment with *Lactobacillus* spp. and *Bifidobacterium* spp. is recommended in cancer patients undergoing pelvic radiotherapy.

CONCLUSIONS

Based on the evidence analyzed, the use of supplements as adjuvants in cancer treatment must be considered carefully. Overall, foods containing functional nutrients are considered a safer option than supplements because of the higher concentration, hence dosage, in the supplement. In addition, foods are composed of a complex variety of nutrients that work synergistically, thus providing an added benefit to the patient. In conclusion, for the cancer patient who receives radiation to the abdominopelvic area, when possible, the authors recommend a diet with sufficient protein, composed of foods rich in omega-3 fatty acids to promote anti-inflammation and prevent cachexia, and importantly, a diet rich in foods containing antioxidants and polyphenols to protect healthy cells from the oxidation derived from cancer treatment. Furthermore, since the use of probiotics has been proven safe for cancer patients, a diet that contains foods with probiotics may confer beneficial effects not only to protect the gastrointestinal tract but also provide an anti-inflammatory environment for the patient.

REFERENCES

1. Cederholm T, Barazzoni R, Austin P, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr. 2017;36:49-64.
2. Souba WW. Glutamine and cancer. Ann Surg. 1993;218:715-28.
3. Uscátegui H. Inmunonutrición: enfoque en el paciente quirúrgico* Immunonutrition: approach on surgical patient. Rev Chil Cirugía. 2010;62:87-92.
4. Vidal-Casariego A, Calleja-Fernández A, de Urbina-González JJ, Cano-Rodríguez I, Cordido F, Ballesteros-Pomar MD. Efficacy of glutamine in the prevention of acute radiation enteritis: a randomized controlled trial. J Parenter Enteral Nutr. 2014;38: 205-13.
5. Kucuktulu E, Guner A, Kahraman I, Topbas M, Kucuktulu U. The protective effects of glutamine on radiation-induced diarrhea. Support Care Cancer. 2013;21:1071-5.
6. Martinez-Outschoorn UE, Peiris-Pagés M, Pestell RG, Sotgia F, Lisanti MP. Cancer metabolism: a therapeutic perspective. Nat Rev Clin Oncol. 2017;14:11-31.
7. Calder R. Docosahexaenoic acid. Adv Nutr. 2016;7:1139-41.
8. Jiang WG, Bryce RP, Horrobin DF. Essential fatty acids: molecular and cellular basis of their anti-cancer action and clinical implications. Crit Rev Oncol Hematol. 1998;27:179-209.
9. Bougnoux P. N-3 polyunsaturated fatty acids and cancer. Curr Opin Clin Nutr Metab Care. 1999;2:121-6.
10. Gonzalez MJ, Schemmel RA, Dugan L Jr., Gray JI, Welsch CW. Dietary fish oil inhibits human breast carcinoma growth: a function of increased lipid peroxidation. Lipids. 1993;28:827-32.
11. Gonzalez MJ, Schemmel RA, Gray JI, et al. Effect of dietary fat on growth of MCF-7 and MDA-MB231 human breast carcinomas in athymic nude mice: relationship between carcinoma growth and lipid peroxidation product levels. Carcinogenesis. 1991;12:1231-5.
12. Ells GW, Chisholm KA, Simmons VA, Horrobin DF. Vitamin E blocks the cytotoxic effect of gamma-linolenic acid when administered as late as the time of onset of cell death–insight into the mechanism of fatty acid induced cytotoxicity. Cancer Lett. 1996;98:207-11.
13. Begin ME, Ells G, Horrobin DF. Polyunsaturated fatty acid-induced cytotoxicity against tumor cells and its relationship to lipid peroxidation. J Natl Cancer Inst. 1988;80:188-94.
14. Sagar PS, Das UN, Koratkar R, et al. Cytotoxic action of cis-unsaturated fatty acids on human cervical carcinoma (HeLa) cells: relationship to free radicals and lipid peroxidation and its modulation by calmodulin antagonists. Cancer Lett. 1992;63: 189-98.
15. Jordan A, Stein J. Effect of an omega-3 fatty acid containing lipid emulsion alone and in combination with 5-fluorouracil (5-FU) on growth of the colon cancer cell line caco-2. Eur J Nutr. 2003;42:324-31.
16. Fearon KC, Von Meyenfeldt MF, Moses AG, et al. Effect of a protein and energy dense N-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomised double blind trial. Gut. 2003;52:1479-86.
17. Das UN, Ramos EJB, Meguid MM. Metabolic alterations during inflammation and its modulation by central actions of omega-3 fatty acids. Curr Opin Clin Nutr Metab Care. 2003;6:413-419.
18. Badjatia N, Satyam A, Singh P, Seth A, Sharma A. Altered antioxidant status and lipid peroxidation in indian patients with urothelial bladder carcinoma. Urol Oncol. 2010;28:360-7.
19. Fuchs-Tarlovsky V. Role of antioxidants in cancer therapy. Nutrition. 2013;29:15-21.
20. Fuchs-Tarlovsky V, Bejarano-Rosales M, Gutierrez-Salmean G, et al. Effect of antioxidant supplementation over oxidative stress and quality of life in cervical cancer. Nutr Hosp. 2011; 26:819-26.
21. Fuchs-Tarlovsky V, Rivera MA, Altamirano KA, Lopez-Alvarenga JC, Ceballos-Reyes GM. Antioxidant supplementation has a positive effect on oxidative stress and hematological toxicity during oncology treatment in cervical cancer patients. Support Care Cancer. 2013;21:1359-63.
22. Fuchs-Tarlovsky V, Gutiérrez-Salmeán G, Casillas MA, Bejarano-Rosales M, Reyes GM. Suplementación con antioxidantes no previene nefrotoxicidad por cisplatino en pacientes con cáncer cérvico uterino avanzado. Rev Venez Oncol. 2011;23;21-5.
23. Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2016;36:11-48.
24. Wang L, Sesso H, Glynn R, et al. Vitamin E and C supplementation and risk of cancer in men: posttrial follow-up in the physicians' health study II randomized trial. Am J Clin Nutr. 2014; 101:915-23.
25. García-Zepeda SP, García-Villa E, Díaz-Chávez J, Hernández-Pando R, Gariglio P. Resveratrol induces cell death in cervical cancer cells through apoptosis and autophagy. Eur J Cancer Prev. 2013;22:577-84.
26. León-González AJ, Auger C, Schini-Kerth VB. Pro-oxidant activity of polyphenols and its implication on cancer chemoprevention and chemotherapy. Biochem Pharmacol. 2015;98:371-80.
27. Trueba GP. Los flavonoides: antioxidantes o prooxidantes. Rev Cuba Investig Biomed. 2003;22:48-57.
28. ILSI. Scientific concepts of functional foods in Europe. Consensus document. Br J Nutr. 1999;81 Suppl 1:S1-S27.
29. Reig AD, Anesto J. Prebióticos y probióticos, una relación beneficiosa. Rev Cuba Aliment Nutr. 2002;16:63-8.
30. Pérez-Conesa D, López G, Ros G. Principales prebióticos y sus efectos en la alimentación humana. An Vet. 2004;20:5-20.
31. Gibson GR, Scott KP, Rastall RA, et al. Dietary prebiotics: current status and new definition. Food Sci Technol Bull Funct Foods. 2010;7:1-19.
32. Reid G. Probiotics: definition, scope and mechanisms of action. Best Pract Res Clin Gastroenterol. 2016;30:17-25.
33. Wang YH, Yao N, Wei KK, et al. The efficacy and safety of probiotics for prevention of chemoradiotherapy-induced diarrhea in people with abdominal and pelvic cancer: a systematic review and meta-analysis. Eur J Clin Nutr. 2016;70:1246-53.
34. Wada M, Nagata S, Saito M, et al. Effects of the enteral administration of *Bifidobacterium breve* on patients undergoing chemotherapy for pediatric malignancies. Support Care Cancer. 2010;18:751-9.
35. Osterlund P, Ruotsalainen T, Korpela R, et al. *Lactobacillus supplementation* for diarrhoea related to chemotherapy of colorectal cancer: a randomised study. Br J Cancer. 2007; 97:1028-34.
36. Urbancsek H, Kazar T, Mezes I, Neumann K. Results of a double-blind, randomized study to evaluate the efficacy and safety of antibiophilus in patients with radiation-induced diarrhoea. Eur J Gastroenterol Hepatol. 2001;13:391-6.

37. Giralt J, Regadera JP, Verges R, et al. Effects of probiotic *Lactobacillus casei* DN-114 001 in prevention of radiation-induced diarrhea: results from multicenter, randomized, placebo-controlled nutritional trial. Int J Radiat Oncol Biol Phys. 2008;71:1213-9.
38. Delia P, Sansotta G, Donato V, et al. Prevention of radiation-induced diarrhea with the use of VSL#3, a new high-potency probiotic preparation [10]. Am J Gastroenterol. 2002;97:2150-2.
39. Delia P, Sansotta G, Donato V, et al. Use of probiotics for prevention of radiation-induced diarrhea. World J Gastroenterol. 2007;13:912-5.
40. Chitapanarux I, Chitapanarux T, Traisathit P, Kudumpee S, Tharavichitkul E, Lorvidhaya V. Randomized controlled trial of live *Lactobacillus acidophilus* plus *Bifidobacterium bifidum* in prophylaxis of diarrhea during radiotherapy in cervical cancer patients. Radiat Oncol. 2010;5:31.
41. Mego M, Holec V, Drgona L, Hainova K, Ciernikova S, Zajac V. Probiotic bacteria in cancer patients undergoing chemotherapy and radiation therapy. Complement Ther Med. 2013;21:712-23.